

Connectivity of the pedunculopontine nucleus in parkinsonian freezing of gait

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Parkinson's disease (PD) may involve sudden unintended arrests in gait or failure to initiate gait, known as gait freezing. Deep brain stimulation of the pedunculopontine nucleus (PPN) has been found to be an effective therapy for this phenomenon. In this study, we characterized the connectivity of the PPN freezing of gait (FOG) patients, compared with non-FOG PD and healthy controls using diffusion tensor imaging techniques. Differences in PPN connectivity profiles of the study groups were shown in the cerebellum and pons. The PPN showed connectivity with the cerebellum in controls and non-FOG PD. FOG patients showed absence of cerebellar connectivity, and increased visibility of the decussation of corticopontine fibres in the anterior pons. The findings suggest that corticopontine projections, which cross at the pons are increased in gait freezing, highlighting the importance

Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder, which is prevalent among 1% of the population above the age of 60 years [1]. Sudden unintended arrests in gait of PD patients and failure to initiate gait, known as gait freezing, becomes more common and severe as the disease duration increases. However, there is a certain subtype of PD patients who early in the stages of the disease exhibit gait freezing and postural imbalance as their predominant symptoms. This is not only extremely debilitating, but also places the patients at increased risks of falls and consequent injuries. Gait freezing usually responds poorly to levodopa therapy [2]. It also occurs in other movement disorders such as progressive supranuclear palsy [3]. This may suggest that the pathophysiology of gait freezing is not entirely because of progressive dopamine depletion, but rather a separate pathophysiological process may be the mechanism in part of this phenomenon. Deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) has been found to be an effective therapy for PD patients who exhibit such gait freezing as their predominant symptom. Diffusion tensor imaging (DTI) allows the study of neuronal integrity and connectivity, and macroscopic axonal organization in the brain [4]. We characterized the connectivity of the PPN freezing of gait (FOG) patients, compared with non-FOG PD and healthy controls.

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Methods

Ten PD patients who had been referred for DBS to our functional neurosurgery unit were enrolled prospectively. Two patients were diagnosed with primary gait freezing showing few other parkinsonian symptoms on clinical examination and Unified Parkinson's Disease Rating Scale. Eight patients had PD without gait freezing. Their symptoms consisted primarily of tremor, rigidity, or bradykinesia. All patients before DBS underwent neuropsychological evaluation and multidisciplinary clinical review, and neuro-imaging studies.

Data acquisition

Diffusion weighted data was acquired for all patients and 17 randomly selected controls on a Philips Achieva 1.5T magnet (Best, The Netherlands) using echo planar imaging. DTI images used 32 directions of diffusion weightings ($b_{\max} = 1200 \text{ s/mm}^2$) and two nondiffusion weighted volumes (echo time 65 ms, repetition time 9390 ms, reconstructed matrix = $128 \times 128 \times 45$, reconstructed voxel size $2.5 \times 2.5 \times 2.5 \text{ mm}$).

Image analysis

Images were analyzed using tools from The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library V4.1.4 (www.fmrrib.ox.ac.uk/fsl/). Diffusion data was analyzed using the FMRIB diffusion toolbox as detailed earlier [5]. This included correction of eddy current distortion, local fitting of diffusion tensors, and Bayesian estimation of diffusion parameters obtained

The study was carried out at the Department of Neurosurgery, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK.

using Markov Chain Monte Carlo sampling to build up distributions on diffusion parameters at each voxel. Finally, probabilistic tractography as implemented by FMRIB diffusion toolbox was performed which repetitively samples from the distributions on voxel-wise principal diffusion directions, computing a probabilistic streamline through samples. The structural MRI data was registered to the DTI using the FMRIB's linear registration tool. DTI image data was transformed into MNI 152 standard space, and one seed voxel was placed at each PPN location. We use DTI fractional anisotropy (FA) mapping in the stereotactic targeting of the PPN [6]. This technique was applied to place seed voxels in the PPN, using the FA and first eigenvector (V1) map in which the superior cerebellar decussation and medial lemnisci could be clearly visualized (using RGB modulation) and used to precisely identify the location of the PPN. In the coregistered DTI structural MRI–MNI 152 image, seed voxel location was confirmed using each modality. Probabilistic tractography was performed in each patient and healthy controls for both seed voxels. The final results were averaged and placed onto the MNI 152 standard brain template (Montreal Neurological Institute, Canada, UK) for analysis.

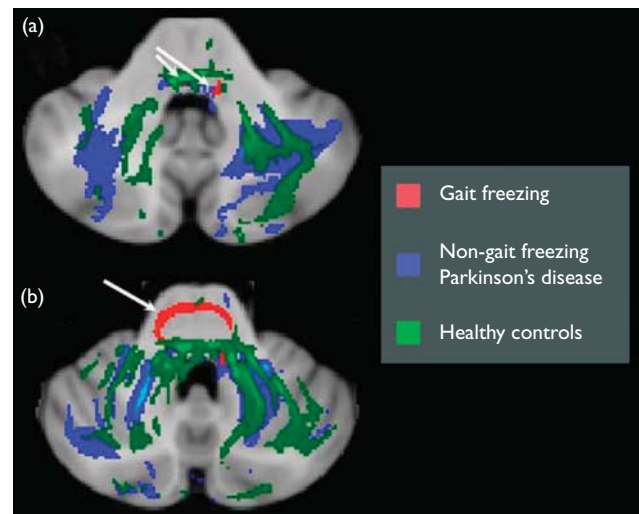
Results

Two FOG patients with PD were treated with bilateral PPN DBS at low frequency. Tremor, rigidity and bradykinesia were evident in these patients. Non-FOG PD patients ($n = 8$) were treated with bilateral subthalamic nucleus (STN) stimulation at high frequency. There has been much discussion regarding the anatomic location of the PPN and its visibility on MRI. We use DTI FA mapping in the stereotactic targeting of the PPN [6]. For this study, we have calculated the centroid (centre-of-mass) of the effective site of stimulation in each of the four PPN electrodes. Cartesian coordinates of the stimulation centroids were used as seed voxels for probabilistic tractography. Probabilistic tractography showed similar connectivity profiles for all study groups of the PPN with the cerebral cortex. Considerable differences of connectivity profiles of the study groups were shown in the cerebellum and pons. FOG patients showed absence of PPN connectivity to any part of the cerebellum, whereas non-FOG PD patients displayed significant connectivity with the cerebellum, similar to, although not completely overlapping with healthy normal controls (Fig. 1a). In contrast, FOG patients showed increased connectivity with the PPN in the anterior pons at the level of the mid-section of the fourth ventricle. This was not seen in non-FOG PD or controls (Fig. 1b).

Discussion

The choice of the target for DBS in PD depends primarily on the symptomatology of the patient. Ventral intermediate thalamic nucleus stimulation arose as an alternative to thalamotomy, and is usually applied to treat PD tremor.

Fig. 1



Probabilistic tractography displayed on the MNI152 standard brain. (a) Axial section through the upper pons and cerebellum. In FOG patients (red) connectivity with the cerebellum is absent, whereas non-FOG PD patients show similar connectivity to control subjects. (b) Axial section through the mid-pons and cerebellum. FOG patients (red) showed anterior pontine connectivity (arrow) which was absent in non-FOG PD patients and controls.

However, neither other dyskinesias, akinesia nor freezing improve with stimulation of this target [6,7]. Stimulation of the STN and globus pallidus internus (GPi) can improve tremor, rigidity and bradykinesia. DBS of the GPi seems to improve the on-drug symptoms of PD [8,9]. Some regard high-frequency stimulation of the STN as optimal for PD as it also has a positive effect on gait and postural stability [10]. However, even though both STN and GPi stimulation can improve gait freezing in L-3,4-dihydroxyphenylalanine (L-DOPA) responsive patients, this effect is often only short lived (4–5 years) [8]. Low-frequency stimulation of the PPN has been introduced as a new and effective treatment for gait freezing, and shows promising results [8]. How stimulation of the PPN achieves the observed improvements in gait freezing is unclear. Takakusaki *et al.* [11] have pointed to the role of the basal ganglia and brainstem systems in the aetiology of gait freezing. PPN stimulation shows promising results even in patients not responding to L-DOPA. PPN stimulation may be effective in L-DOPA-resistant FOG because the PPN is 'downstream' from the dopaminergic networks of the basal ganglia, and connects directly with the locomotor control centres in the brainstem and cerebellum [12]. Stimulating PPN neurons at low frequency may thus bypass the impaired basal ganglia and activate locomotor and postural control centres more directly.

Our results raise two major issues. First, they highlight the possible role of the cerebellum in the pathophysiology of gait freezing. PPN connectivity with the cerebellum was significantly reduced in FOG patients, whereas non-FOG

PD patients showed similar, although not identical connectivity as healthy controls. Aravamuthan *et al.* [13] demonstrated using diffusion tractography that the human PPN exhibits connections with the cerebral cortex, basal ganglia, cerebellum and spinal cord. This study was performed in eight healthy adult controls. The observed cerebellar connections were throughout the declive and folium regions of the cerebellum. Our findings confirm that the cerebellar connections are in healthy state and in the non-FOG PD state. But this cerebellar connectivity was much reduced in the two FOG patients. In contrast, connectivity of the PPN across the anterior pons was pronounced in the FOG patients but not in either the non-FOG PD or controls. Corticopontine fibres travel through the cerebral peduncles to synapse with the pontine nuclei in the ventral part of the pons. The pontine nuclear axons then decussate in the anterior pons and project through the contralateral middle cerebellar peduncle as mossy fibres to the cerebellar cortex. They form part of the corticoponto-cerebellar pathways [14]. We found that in FOG patients, connectivity through the middle cerebellar peduncle with the cerebellum was reduced. Cortico-pontine fibres may become 'overactive' in FOG and thus their decussation becomes more visible in the anterior pons. In contrast, there may be more cortical input to correct for the reduced input from the PPN to the cerebellum. This is speculative at present and will need to be tested physiologically in more patients.

Conclusion

Our findings show that the PPN exhibits connectivity with the cerebellum in the healthy adult. The non-FOG PD patients also show connectivity with the cerebellum through the middle cerebellar peduncle, although these are not identical to the normal healthy adult. Data from the FOG patients suggests no such connectivity with the cerebellum. In addition FOG patients show a visible crossing of fibres in the anterior pons connecting with the PPN, a phenomenon not observed in either healthy controls or non-gait freezing PD, suggesting that the corticopontine projections, which cross at this level, are

increased in gait freezing. This highlights the importance and role of corticopontine-cerebellar pathways.

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Conflicts of interest: none declared.

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