The effect of Pedunculopontine nucleus deep brain stimulation on postural sway and vestibular perception

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Abstract

Purpose: Deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) reduces the number of falls in patients with Parkinson's disease (PD). We hypothesised that enhanced sensory processing contributes to this PPN-mediated gait improvement.

Methods: Four PD patients (and eight matched controls) with implanted bilateral PPN and subthalamic nucleus DBS electrodes were assessed on postural (with/without vision) and vestibular perceptual threshold tasks.

Results: PPN ON stimulation (compared to OFF) lowered vestibular perceptual thresholds but there was a disproportionate increased in the normal sway increase on going from light to dark.

Conclusions: The disproportionate increased sway with PPN stimulation in the dark may paradoxically improve balance function since mechanoreceptor signals rapidly adapt to continuous pressure stimulation from postural akinesia. Additionally, the PPN-mediated vestibular signal enhancement also improves the monitoring of postural sway. Overall, PPN stimulation may improve sensory feedback and hence balance performance.
**Introduction**

Parkinson’s disease (PD) standard medical (L-Dopa) and surgical therapy (subthalamic nucleus Deep Brain Stimulation or ‘STN DBS’), are effective in reducing patients’ bradykinesia, rigidity and rest tremor but is less successful in controlling postural dysfunction [1]. Recent data suggest that pedunculopontine nucleus (PPN) DBS may improve balance function in PD [2]. Recent single-neurone primate data suggests the PPN is highly vestibular-responsive [3]. We hypothesized that PPN-related postural improvement may relate to improved sensory processing.

**Methods**

Four PD patients (table 1) with simultaneously implanted bilateral PPN and STN electrodes (males, mean age 61.5 ± 3 years), and eight healthy age matched controls (mean age 65 ± 10 years) were recruited. The patients were part of a double-blind randomised controlled trial comparing the effect of simultaneous STN and PPN deep brain stimulation to that of STN alone. The average location of the active PPN contacts were: 4.5 ± 2.3mm lateral (perpendicular to midline), -0.1 ± 1.9 mm AP (in relation to PC) and Vertical -17.5 ± 1.9 mm (perpendicular to AC-PC plane [4]). Written informed consent was obtained from all participants and the experimental protocol approved by the local Research Ethics Committee. Participants’ performed a balance and a vestibular threshold task in in counterbalanced order. Patients carried out each task once with PPN stimulation OFF and once with PPN stimulation ON. Patients were blinded to their stimulation setting and the order of PPN stimulation was randomized. Patients remained on STN stimulation and normal dopaminergic medication throughout.

We used a previously described vestibular threshold task [5]. Patients sat in a motorized rotating chair in darkness with white noise masking, and were required to indicate their direction of motion (left/right). An automated staircase algorithm determined subjects’ perceptual threshold. An average of four trials was obtained.
A force plate (OR6-5-1, AMTI, MA, USA, 91 × 61 × 17 cm, sampling rate 1000Hz and calibrated using a 10.2Kg weight on two locations) assessed postural sway by detecting the amount of pressure applied by each foot, under two conditions for 120s: Eyes open (EO) and eyes closed (EC) in counterbalanced order. Participants were told to stand with their arms hanging loosely by their sides with their heels 8 cm apart.

Differences between groups were tested using t-tests (at significance level 0.05), however, due to the small number of patients (n=4), we did not perform statistical tests within this group. We calculated the Romberg coefficient (RC=Sway EO/Sway EC) for participants. An RC=1 indicates that vision does not affect sway whereas RC<1 indicates a visual influence on sway since there is greater sway in the dark (EC).

**Results**

When PPN stimulation was off, patients had significantly worse (i.e. higher) vestibular thresholds (t(10) = -2.355, p = 0.04) compared to controls (Figure 1A). PPN stimulation lowered vestibular thresholds such that the difference compared to controls was no longer significant (t(10) = -2.136, p = 0.06).

Patients displayed significantly more sway compared to controls with eyes open both ON (t(10) = -3.069, p = 0.012) and OFF (t(10) = -3.599, p = 0.005) stimulation (Figure 1B) and with eyes closed ON (t(10) = -2.584, p = 0.027) and OFF (t(10) = -3.016, p = 0.0013) stimulation (Figure 1C). Interestingly, with EO, sway was no different whether PPN stimulation was ON or OFF (Figure 1B), whereas with EC, sway increased with stimulation ON compared to OFF (Figure 1C).
In all groups, RC<1 indicating more sway with EC (Figure 1D). OFF stimulation, patients’ RCs were not different from controls (t(10) = 1.171, p = 0.269), however, ON stimulation, patients’ RCs which were lower than controls (t(10) = 4.870, p = 0.001). Thus when PPN stimulation is ON compared to OFF, patients swayed disproportionately more with EC, but there was little change in sway with EO when PPN was ON or OFF.

**Discussion**

We hypothesised that PPN DBS improves postural control in PD patients by enhancing sensory processing.

We found that in four patients with PD, PPN DBS improved vestibular perceptual thresholds, supporting recent primate data showing that PPN neurones are vestibular-responsive. Our patients always had STN stimulation ON and this may support the idea that simultaneous STN and PPN stimulation act synergistically as suggested recently [6]. Hence if PPN is a brainstem centre for vestibular processing, its stimulation may improve postural function in PD patients by modulating vestibular signalling

Despite its purported beneficial effects upon postural control, PPN stimulation paradoxically increased sway in the dark, which could imply worse postural control. However, cutaneous mechanoreceptors in the glabrous skin of the foot, which play a role in postural control [7] are rapidly adapting [8]. Hence, excessive rigidity as in the OFF condition, will lead to a loss of input from these cutaneous receptors. This mechanoreceptor adaptation can be avoided by increasing sway. It follows that increasing sway above an excessively rigid baseline in PD patients (e.g. with PPN DBS) will maintain mechanoreceptor input for postural control. That we found improved vestibular thresholds, indicating a more reliable vestibular signal, may also enable better monitoring by the postural system, of the body’s position-in-space relative to gravity. This improvement in vestibular
signalling may thus enable the postural system to safely accommodate any PPN-related increased sway. Finally, increased sway will provide additional input to the vestibular system, and further reduce the uncertainty regarding the estimate of body-in-space position.

In conclusion, the improved reliability of the vestibular signal function with PPN stimulation may facilitate a strategy of increased postural movement which further improves sensory feedback by enhancing somatosensory signalling. This prediction of enhancing somatosensory signalling will require specific testing.

Conflicts of interest:

None

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References:


**Figure 1:** (A) Box plot of vestibular thresholds for the patients and controls. Bar plot of overall sway in the eyes open (B) and eyes closed (C) conditions (EO and EC). (D): Romberg coefficient (EO/EC) is shown to compare sensory conditions directly.

**Table 1:** Patient demographics, including gender age and UPDRS scores for the activities of daily living section (II) and the motor examination (III) on and off PPN stimulation. *As, one patient was unable to complete assessment with PPN OFF, scores when all stimulation was OFF are shown.*
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<th>Weight (kg)</th>
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<th>III</th>
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<th>III</th>
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