CHAPTER

79

Deep Brain Stimulation of the Pedunculopontine Tegmental Nucleus Improves Static Balance in Parkinson's Disease

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OUTLINE

INTRODUCTION

Postural instability is a severe symptom in Parkinson's disease (PD) and atypical Parkinsonisms that causes falls and postural deformities (Doherty et al., 2011; Koller et al., 1989; Playfer, 2001; Visser et al., 2003). The treatment of postural instability in PD with antiParkinsonian drugs is unsatisfactory, and frequent falls occur in patients who experience good pharmacological control of other motor disabilities (Bloem et al., 1996; Horak et al., 1996; Johnson et al., 2015; Baston et al., 2016; Curtze et al., 2015).

The origin of this postural instability that leads to falling is unclear. It has been hypothesized that postural instability in PD patients may result from dysfunctions of processing and integration of sensory signals and deficits in motor adjustment processes and muscle tone regulation. Correct sensory processing requires the integration of visual, vestibular, and somatosensory signals, so that motor adjustments can be executed in the presence of proper basic muscle tone. In normal subjects control mechanisms occur in a normal fashion, and visual cues play an essential role in overall balance control. In contrast, in PD patients one or all of these control systems is affected (Jobst et al., 1997), and balance becomes highly dependent on visual cues.

Deep brain stimulation (DBS) of basal ganglia nuclei has been applied in an attempt to improve postural instability in L-dopa-resistant PD and other Parkinsonian syndromes. The subthalamic nucleus (STN) and globus pallidus internus (GPi) have been the most common targets for DBS (Bleuse et al., 2011; Colnat-Coulbois et al., 2005; Maurer et al., 2003; Rocchi et al., 2002, 2004; St George et al., 2012; Visser et al., 2008a,b) in an attempt

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to improve postural control in PD. The results of these and other related studies were the object of a recent comprehensive review (Collomb-Clerc and Welter, 2015). In brief, unsatisfactory results for STN DBS and GPi DBS on balance disorders have been reported in PD patients, and even aggravation of imbalance has been observed in some patients. Also, a combination of L-dopa with DBS has yielded unsatisfactory results, in particular when medication has been used with STN DBS.

In the last decade, in patients with PD who were poorly responsive to pharmacological and/or surgical therapies, the pedunculopontine tegmental nucleus (PPTg) has emerged as a promising DBS target (Ferraye et al., 2010; Mazzone et al., 2005, 2013, 2016; Moro et al., 2010; Wilcox et al., 2011; Goetz et al., 2016a,b). Besides the fact that stimulation of this structure has been found to elicit locomotion in animals, interest in the PPTg has been raised by the possibility that it may serve as a basal ganglia output to motor spinal cord mechanisms, bypassing both the thalamocortical route and dopaminergic nigrostriatal mechanisms (Garcia-Rill, 1991; Scarnati et al., 2011; Skinner et al., 1990; Takakusaki et al., 2003), and facilitating arousal and reward mechanisms that might increase patient attention in the production of voluntary movements (Garcia-Rill et al., 2004, 2015a,b; Skinner et al., 2004; Goetz et al., 2016b; Florio et al., 1999; Schultz, 2016; Thompson et al., 2016; Florio et al., 1999; Hong and Hikosaka, 2014; Okada and Kobayashi, 2013; Pan and Hyland, 2005; Thompson et al., 2016; Gut and Winn, 2016). In addition, it has been shown that PPTg DBS may modulate somatosensory evoked potentials, suggesting that it could also affect integration and processing of sensory signals (Insola et al., 2014, 2016).

The relatively low number of PPTg DBS patients does not allow one to draw definitive conclusions concerning the role of PPTg in motor control, but improvement of freezing of gait and a reduction of falls have been consistently reported, despite some inconsistencies in gait parameters that are likely due to patient selection, stage of disease, and precise site of stimulation. In a previous study (Mazzone et al., 2014) we reported that PPTg DBS improved gait initiation and specific spatio–temporal and kinematic parameters during unconstrained walking, suggesting that the improved gait initiation may help overcome the block of preparation for movement that is present in gait freezing.

Given these premises, the aim of our study was to assess the effects of unilateral PPTg stimulation on postural balance in patients who were previously subjected to gait analysis (Mazzone et al., 2014). Postural balance was assessed by evaluating fluctuations in the center of pressure (CoP) during upright stance. We used the CoP to assess postural balance because it represents a reliable index of the point location of the ground reaction force vector, reflecting the sway of the body and the forces used to maintain the center of gravity within the support base.

METHODS AND MATERIALS

Patients

Ten male PD patients who completed 1 year of follow-up were studied. All patients gave informed written consent, and the protocol was approved by the local ethics committee. Surgical procedures and details for targeting, implanting, and stimulating the PPTg have been previously described (Mazzone et al., 2013). Briefly, all patients were implanted under general anesthesia with the 3389 DBS lead (Medtronic Neurological Division, Minneapolis, MI, USA). The PPTg targeting was planned on the basis of stereotactic angio computed tomography (CT) scans, using the pontomesencephalic junction line and the obex as reference points. In the midsagittal slice we identified the axial level for the determination of the z plane, corresponding in the patient's anatomy to the PPTg. The x and y coordinates were calculated by overlapping the axial CT scans with slides +31 to +36 mm from the obex of Paxinos and Huang's atlas (1995), in which the PPTg is reported. A three-dimensional virtual surgery system allowed us to reproduce the surgical procedure exactly and follow an angled trajectory, which proved to be avascular, intraparenchymal, and extraventricular. In this way surgery was tailored according to the patient's anatomy, thus overcoming the issue of large differences that occur in the brainstem from patient to patient. Intraoperative monitoring of somatosensorial-evoked potentials, recorded through the electrode contacts, allowed us to evaluate the correct position of the stimulating electrode (Insola et al., 2014, 2016).

The demographic characteristics of patients, stimulation parameters, and drug treatment are given in Table 79.1. An overview of electrode position in the studied patients is reported in Fig. 79.1. The electrode implantation was contralateral to the most disabled hemisoma, thus nine patients were implanted on the right side and one on the left side.

Stabilometry and Postural Instability

A stabilometric platform (Global Postural System, GPS 400, Chinesport SpA, Udine, Italy) was used to evaluate the displacement of the CoP and variation of the confidence ellipse area (i.e., the area in which consecutive positions of the CoP were included), with eyes either open or closed. To measure postural sway, the barefoot patients were instructed to maintain an upright standing position on the platform with arms unfolded at their sides. According to international standard procedures, patients were first asked to remain with head straight and eyes open, and instructed to maintain their gaze on a fixed point 90 cm in front of them that was placed at eye level for each patient (Gagey and Weber, 2005;

TABLE 79.1 Demographic and Clinical Data of the Patients, and Stimulation Parameters; One Year of Follow-Up (Data is Given as Mean ± SD)

Total Studied Patients	10
Age	60.2 ± 7.4 years
Sex	Male
Disease duration	10.8 ± 9.5 years
Preoperative UPDRS part III items 27–30	5.3 ± 3.0
Postoperative UPDRS part III items 27–30	2.8 ± 0.9
Preoperative Hoehn and Yahr scale	3.5 ± 0.6
Postoperative Hoehn and Yahr scale	2.6 ± 0.8
Preoperative levodopa equivalent daily dose	1050.1 ± 397.9 mg
Postoperative levodopa equivalent daily dose	350.0 ± 275.8 mg
Stimulus amplitude	2.5–3.0 V
Stimulus pulse width	60 μs
Stimulus rate	40 Hz

Tjernstrom et al., 2015). Feet were kept at an angle of 30 degrees and the distance between the heels was 2 cm. Before starting the platform recording, the tendency of patients to fall was evaluated using the pull test, according to Hunt and Sethi (2006).

During the stabilometric evaluation, four treatments were tested: drugs-off/DBS-off (off/off), drugs-on/DBS-off (on/off), drugs-off/DBS-on (off/on), and drugs-on/DBS-on (on/on). Ten age-matched healthy subjects were used as controls. Treatments were tested in the following order.

1. Off/off (medication and DBS were suspended 12 h and 20 min before stabilometry, respectively).
2. On/off (stimulation was switched off 20 h before stabilometry). This time interval was chosen on the basis of the observation that the effects of PPTg DBS decline within 20 h of ceasing stimulation (Mazzone et al., 2016).
3. Off/on (medication was suspended 12 h before stabilometry).
4. On/on (stabilometry was performed 2–3 h after the first daily medication dose).

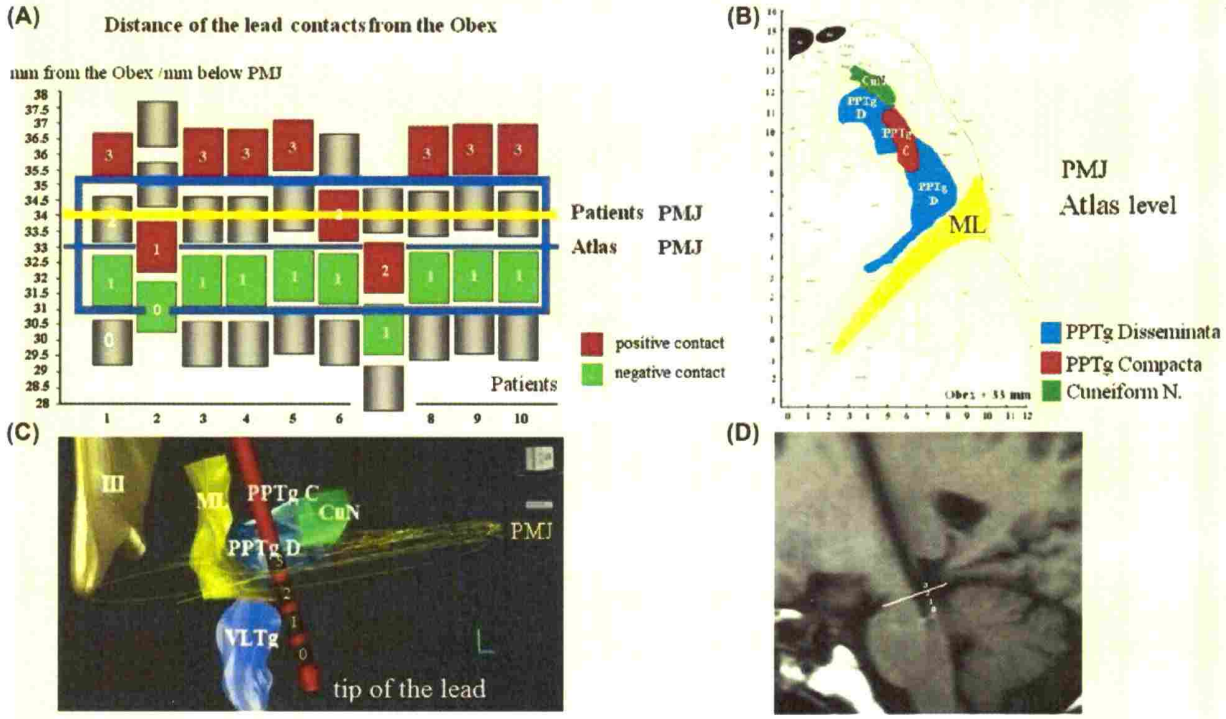

FIGURE 79.1 Representation of the position of the stimulating lead in each of the patients enrolled in the study. In (A) the rectangle bordered by the thick blue line indicates the surgical region in which the PPTg was targeted according to Paxinos and Huang (1995). The *blue line* in the middle of the rectangle represents the pontomesencephalic junction line (PMJ) as inferred in plate +33 of Paxinos and Huang's atlas indicated in (B), while the thick *yellow line* represents the real PMJ line of patients as inferred from their MRI. Note that the negative contact of the stimulating contact pair was deeply located in the pontine extension of the PPTg. The stimulating electrode was medial to the medial lemniscus, as represented in (C). A representative MRI with indications of the PMJ and electrode contacts is given in (D). *III*, third ventricle; *CuN*, cuneiform nucleus; *ML*, medial lemniscus; *PPTgC*, pars compacta; *PPTgD*, pars disseminata; *VLTg*, ventrolateral tegmental nucleus.

The evaluation of CoP variations was performed during a standard task using three parameters.

1. The sway ellipse (SE, mm^2), which corresponds to the area that contains 90% of the positions of the sampled CoP values.
2. The total length (TL, mm) of oscillations, which corresponds to the sum of the distances between each position of the CoP.
3. The mean velocity (MV, mm/ms) of CoP displacement, which corresponds to the average velocity of the CoP calculated by dividing the TL of the CoP trajectory by the recording time.

Ten minutes after the first task, a second session was performed to evaluate the Romberg's index (RI). For this purpose patients were requested to repeat the stabilometric test, but this time with their eyes closed. Thus the RI was calculated as the ratio [(SE) or (TL) (eyes closed)/(SE) or (TL) (eyes open)] × 100.

Statistics

One-way or two-way ANOVA for repeated measures was used to compare the postural parameters across the four treatments and the two eye conditions (open vs. closed). Post hoc comparison with a Newman–Keuls test was used to compare means across treatments. The statistical package software STATISTICA 8.0 (Statsoft Inc., Tulsa, OK, USA) was used. Values are given as mean ± standard deviation (SD)

RESULTS

Fig. 79.1 illustrates the position of the stimulating electrode in each operated patient as inferred from magnetic resonance imaging (MRI). Note that the negative contact of the active pair was always located in the pontine extension of the PPTg, clearly below the pontomesencephalic junction.

Fig. 79.2 shows that a significant increase in the number of falls in the pull test occurred in the off/off state when compared to controls. Falls were significantly reduced in patients under on/off, off/on, and on/on treatments when compared to patients in the off/off state. On/on was the most effective combination of all those tested. This means that a synergistic effect of drug and DBS had occurred, improving the patient's ability to respond with an appropriate postural adjustment to the sudden retropulsive movement induced by the examiner (pull).

Fig. 79.3 shows that, as far as the SE was concerned, there was a significant increase in on/off when comparing controls in the two eye states. However, there was a trend of DBS to reduce SE, irrespective of the eye state,

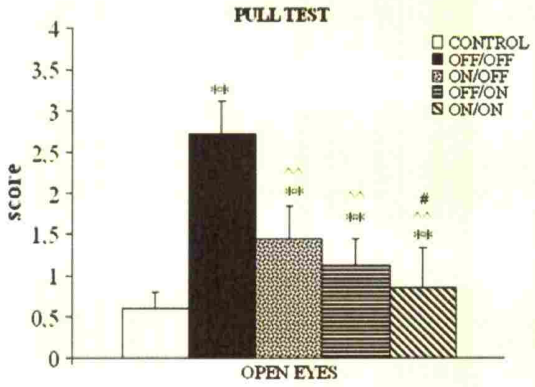

FIGURE 79.2 Effects of different combinations of drugs/DBS treatments on falls during the pull test. $^{**}P < .001$ controls versus each condition; $^{\wedge\wedge}P < .001$ off/off versus on/off, off/on, and on/on; $^{\#}P < .001$ on/off versus on/on. One-way ANOVA followed by Newman–Keuls test.

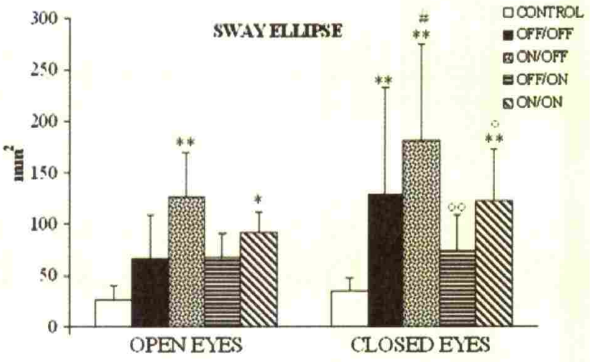

FIGURE 79.3 Modifications of the SE according to eye state and combinations of drugs/DBS treatments. $^{*}P < .05$ open eye controls versus on/on; $^{**}P < .001$ open eye controls versus on/off and closed eye controls versus off/off, on/off, and on/on; $^{\circ}P < .05$ closed eye on/off versus on/on; $^{\circ\circ}P < .001$ closed eye on/off versus off/on; $^{\#}P < .05$ closed eye off/off versus on/off. ANOVA for repeated measures followed by Newman–Keuls test.

which became statistically significant when comparing on/off versus off/on when patients kept their eyes closed. There was also a synergistic effect to combining drug and DBS which resulted in a significant increase of SE when comparing controls versus on/on, regardless of eye state.

Fig. 79.4(A) shows that a significant increase occurred in TL in each of the experimental conditions when compared with controls independent of eye state, with the effect being more evident when the eyes were closed. In regard to MV (Fig. 79.4B), there was a significant increase in off/off when comparing this treatment with controls, while a significant decrease occurred by comparing off/on versus off/off in both eyes open and eyes closed conditions. Thus this data supports the idea that in the absence of visual input, the ability of patients to

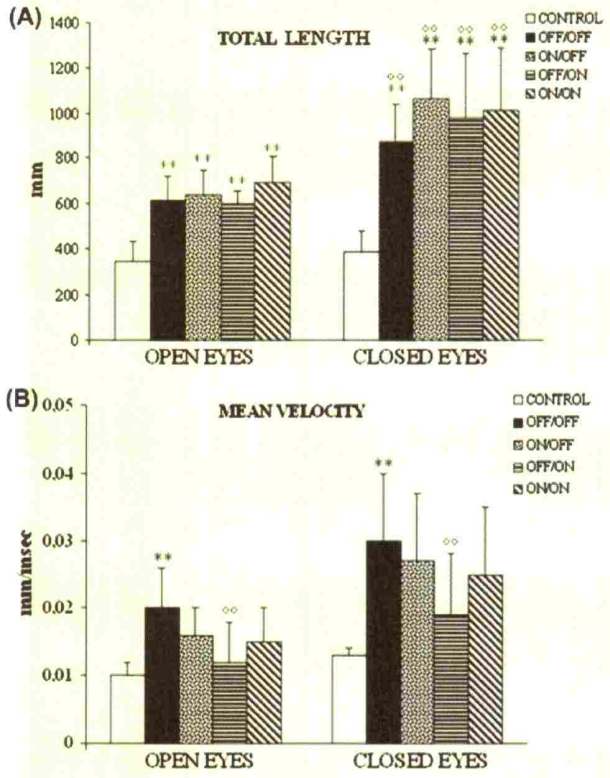

FIGURE 79.4 Modifications of TL of oscillations (A) and MV of CoP displacement (B) according to eye state and combinations of drugs/DBS treatment. (A) $^{**}P < .001$ open and closed eye controls versus each condition; $^{\circ\circ}P < .001$ open eyes versus closed eyes in the four experimental conditions. (B) $^{**}P < .001$ open and closed eye controls versus off/off; $^{\circ\circ}P < .001$ open and closed eye off/off versus off/on. Two-way ANOVA for repeated measures followed by Newman–Keuls test.

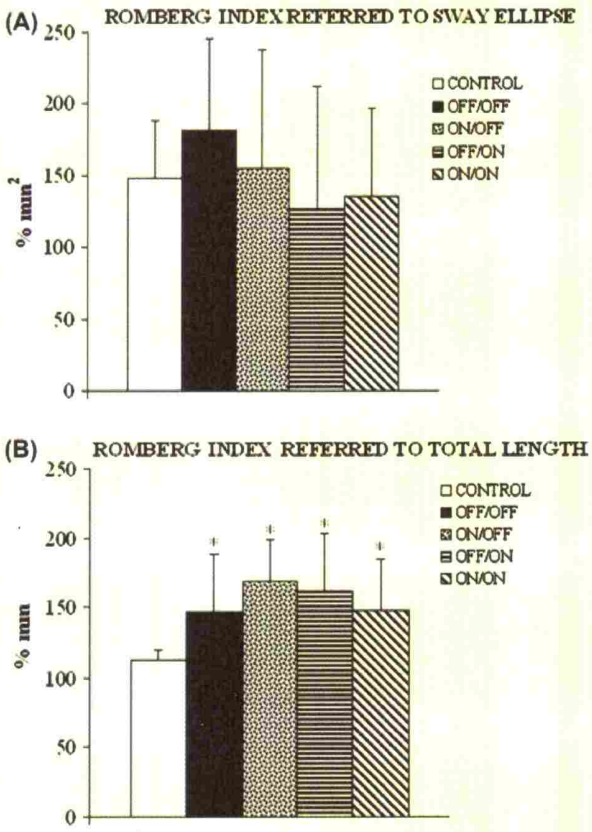

FIGURE 79.5 Modifications of the RI referred to SE (A) and TL (B). Differences were significant only in TL comparisons: $^{*}P < .05$ controls versus each condition. One-way ANOVA followed by Newman–Keuls test.

maintain their balance was worsened to the point that neither medication, nor stimulation, nor their combination was effective in restoring normal postural control.

Fig. 79.5 shows that in the RI referred to SE there was a trend to reach values recorded in controls when both off/on and on/on treatments were compared versus each of the studied treatments, although the differences did not reach significance. In contrast, the values of RI referred to TL were significantly higher when comparing controls versus each of the four treatments.

Fig. 79.6 illustrates CoP trajectories and posturographic values in a representative PD patient with eyes either open or closed in the four investigated treatments. Both TL and SE measurements were higher when the patient was medicated and kept the eyes closed. Irrespective of eye state, the values decreased when DBS was applied. When drug and DBS were simultaneously applied, the CoP displacement showed a tendency to reach values similar to those recorded under medication.

DISCUSSION

Balance disorders in PD are generally considered to arise from a combination of disrupted transmission of proprioceptive signals and alterations in their central integration. The evaluation of posturography performance in these patients allows us to evaluate objectively the real efficacy of treatments designed to improve global postural stability and/or any of several parameters of postural control. The administration of drugs such as L-dopa has been reported to increase SE and TL values, likely inducing a reduction of rigidity, but without inducing a substantial postural recovery that could be further worsened by dyskinetic side-effects of the drug (Armand et al., 2009; Brotchie et al., 2005). In addition, L-dopa does not satisfactorily improve automatic postural adjustments and kinesthetic and proprioceptive deficits occurring in PD patients (Jobst et al., 1997; Baston et al., 2016).

The increase in SE in PD patients is worsened by a number of factors, including the severity of the disease,

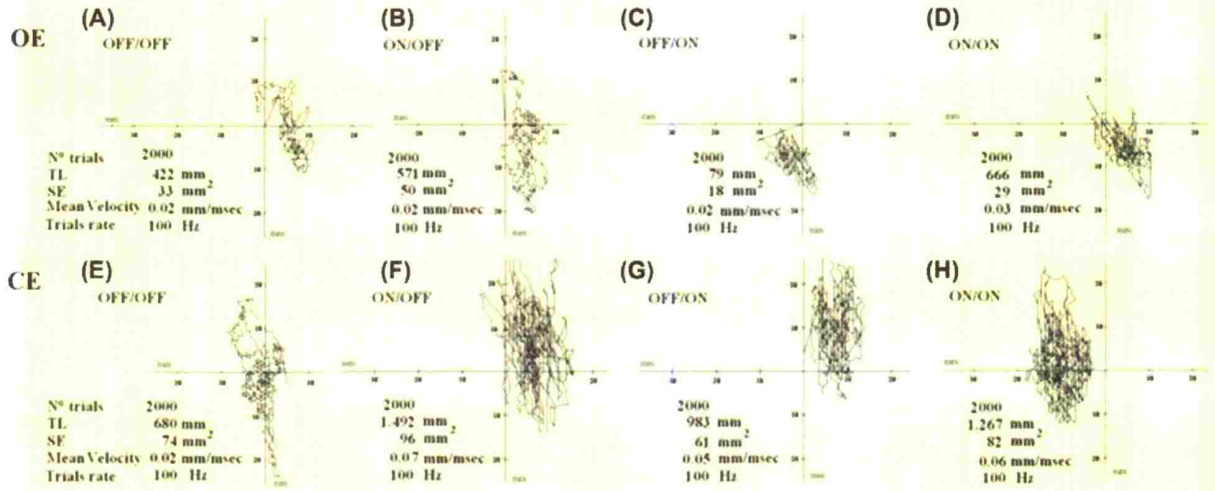

FIGURE 79.6 A representative patient with Parkinson's disease in the four tested treatments. Panels (A–D): open eyes (OE); panels (E–H) closed eyes (CE). In on/off condition (B and F) the administration of L-dopa increased both SE and TL but postural control was not restored, as explained in the text. Under DBS alone (off/on—C and G) both SE and TL were reduced compared to off/off, but the patient recovered postural control. In on/on (D and H) L-dopa reduced the action of PPTg DBS, and there was an increase of both SE and TL. However, the action of L-dopa in the absence of DBS (on/off) was less effective than in the presence of DBS (on/on), and postural control was still maintained. This effect was more pronounced when patients kept their eyes closed.

the medication, and poor self-perception of balance (Baston et al., 2016). Given the unsatisfactory efficacy of dopaminergic drugs, DBS of the basal ganglia nuclei has been proposed as an alternative technique to drug treatment for controlling postural imbalance. To date, studies of DBS in PD have been largely focused on stimulation of traditional targets, such as the STN and GPi (Rocchi et al., 2002, 2004; Collomb-Clerc and Welter, 2015; Johnson et al., 2015), but its effectiveness in postural performance is still controversial (Burchiel et al., 1999). On the basis of results reported in some of these studies (Rocchi et al., 2002, 2004), it has been proposed that nondopaminergic pathways from basal ganglia to brainstem structures may be responsible for improvements in balance (Rocchi et al., 2002). The evaluation of the Unified Parkinson Disease Rating Scale (UPDRS) concerning parameters strictly linked to motor functions integrated in the brainstem (items 27–30) has shown that both STN and GPi DBS, when compared to L-dopa, have markedly favorable effects in static posturography, such that the administration of L-dopa alone is poorly effective and may even worsen postural sway abnormalities (Rocchi et al., 2004; Bejjani et al., 2000; Johnson et al., 2015). Moreover, it has been reported that UPDRS evaluation may not be predictive of the sway area and velocity of oscillations owing to a lack of correlation between UPDRS scores, root mean square distance, and mean velocity (Rocchi et al., 2002).

Furthermore, L-dopa has different effects on postural control when combined with either STN DBS or GPi DBS, and the sole use of the UPDRS may not be sufficient to highlight differences revealed by objective instrumental evaluation. Adverse side-effects of L-dopa have been reported to be less severe when medication was used in association with STN DBS rather than with GPi DBS, perhaps because following STN DBS a lower amount of medication is required when compared to GPi DBS (Rocchi et al., 2004). When combining STN DBS and L-dopa, the unfavorable side-effects of L-dopa alone on postural, sway were attenuated (Bejjani et al., 2000). Thus according to this data L-dopa should be carefully dosed if an optimal effectiveness of DBS on axial and postural signs is required. This concept is in line with the hypothesis that in advanced stages of PD other neurotransmitter systems besides the dopaminergic system, such as the cholinergic brainstem systems that include the PPTg, may be critically involved in postural and gait signs (Baston et al., 2016; Bohnen et al., 2013; Karachi et al., 2010; Muller and Bohnen, 2013; Rocchi et al., 2002, 2004).

We have extended the study of basal ganglia DBS and its combination with L-dopa to include DBS of the PPTg, a brainstem structure that may act at the interface between the basal ganglia, brainstem, and spinal cord mechanisms related to postural control. We previously showed that mandibular movements, specific parameters of gait initiation and performance were improved in PD patients by PPTg DBS. As a follow-up of that study, we investigated the effects of PPTg DBS on static posturography in the same cohort of patients previously evaluated for mandibular movements and gait.

Our results substantially confirm what has been previously reported following DBS of the STN and GPi associated with L-dopa. Thus the suggestion arises that L-dopa administration might be of limited utility when DBS is applied to any of the basal ganglia nuclei considered in PD patients suffering from severe L-dopa-resistant gait and axial disturbances. In this regard, it is noteworthy that our patients subjected to PPTg DBS were also poorly responsive to L-dopa, specifically in gait and posture subitems 27–30 of the UPDRS. These results are consistent with those found in patients, selected on the basis of absence of tremor and dyskinesias, previously investigated by other authors using STN and GPi stimulation (Baston et al., 2016; Rocchi et al., 2002, 2004).

As stated above, postural disturbances might arise from disruption of central functions that require an appropriate integration of proprioceptive, vestibular, visual, and kinesthetic information. The structures involved in the ventrolateral pontine tegmentum, in which the PPTg is embedded, are surrounded by three major ascending sensory pathways, i.e., the medial lemniscus, the spinothalamic tract, and the superior cerebellar peduncle (Mazzone et al., 2013, 2016). This means that DBS of the ventrolateral pontine tegmentum might help to facilitate brainstem integration of ascending sensory signals travelling in these pathways, improving the ability to maintain posture, reducing the number of freezing and falling episodes, and favoring gait performance (Ferraye et al., 2010; Mazzone et al., 2014; Moro et al., 2010; Thevathasan et al., 2011). In this context, an important role might be played by the cerebellum, since recent findings have shown that the cerebellum is influenced by stimulation of the PPTg (Scarnati et al., 2016; Vitale et al., 2016). However, the lack of clinical studies regarding the role of PPTg DBS on cerebellar functions does not allow us to pursue this hypothesis farther.

The bilateral effects of unilateral stimulation of the PPTg are in line with previous clinical and physiological observations (Insola et al., 2014; Mazzone et al., 2012, 2014). We used unilateral stimulation knowing that positive results in our patients are found using a single DBS electrode (Mazzone et al., 2013) and the effects of unilateral stimulation are bilaterally distributed, resulting in bipedal gait being restored in unilaterally PPTg-stimulated PD patients (Caliandro et al., 2011; Mazzone et al., 2014). The bilateral distribution of the effects of PPTg DBS is in agreement with the fact that PPTg neurons also project contralaterally to their basal ganglia and cortical targets (Lavoie and Parent, 1994; Aravamuthan et al., 2007). Thus it is reasonable that unilateral stimulation may produce bilateral effects without necessarily requiring bilateral implantation.

When comparing the postural responses in the on/on treatment with those responses reported in the same condition but stimulating traditional targets (Rocchi et al., 2004), two results arise: there is a higher effectiveness of PPTg stimulation when compared to stimulation of traditional targets; and there is a greater response to PPTg when compared to L-dopa. These results may explain the reason why our patients in the on/on state, although manifesting increased oscillations under L-dopa treatment (Fig. 79.5), had better postural control under PPTg DBS, especially when their eyes were closed. It is noteworthy that these patients received a daily dose of L-dopa (450 ± 325 mg/day) that was not particularly disabling for posture. Indeed, these patients were considered eligible for PPTg DBS because they showed gait and axial disturbances that were not considered to depend on dopaminergic mechanisms (Bonnet et al., 1987; Grimbergen et al., 2009; Karachi et al., 2010).

Balance performance, assessed by postural and vestibular perceptual tasks, has also been recently reported by Yousif et al. (2016) to be improved in patients with bilateral PPTg and STN electrodes. However, when considering the sole effects of PPTg DBS, their data must be interpreted cautiously, since their patients always received STN stimulation plus medication, and the RI was unconventionally expressed as the ratio sway, eyes open/sway, eyes closed, in contrast to other reports in the literature (Gagey and Weber, 2005; Tjernstrom et al., 2015).

Our data, which is in line with our previous observations reported on gait and oromandibular movements (Mazzone et al., 2012, 2014) in the same 10 patients and observations reported by other authors (Baston et al., 2016; Rocchi et al., 2002, 2004; Yousif et al., 2016), supports the notion that there is a major effect of unilateral PPTg DBS, which may be due to functional recovery of brainstem mechanisms involved in postural control. However, a number of critical issues remain to be solved before one can truly determine the long-term stability of PPTg DBS. Consequently, there are limitations to our study.

A first and glaring limitation is that the study was restricted to a 1-year follow-up in a relatively low number of patients ($n = 10$). Thus this study did not allow us to establish the long-term benefits of PPTg-DBS, if any, nor what is particularly advisable for ensuring the long-term maintenance of these benefits. In this regard we are conducting evaluations in a larger number of patients. However, if we consider that in the same short follow-up period we also instrumentally evaluated oromandibular movements and gait performance, the results do point to a general improvement of motor abilities. Interestingly, in a recent, long-term, double-blinded study that evaluated gait-related items of UPDRS part

II and the Movement Disorder Society-UPDRS part III, benefits of PPTg DBS in nine unilaterally implanted PPTg patients were appreciated at 2 years postoperatively, while at 4 years in some patients benefits had begun to wane (Mestre et al., 2016). In dealing with this data it should be kept in mind that PPTg DBS should be primarily intended to modulate or restore motor brainstem mechanisms and not to block the progression of neuronal degeneration that likely continues to evolve in the brain of patients. Thus it is not surprising that effects may decline from patient to patient at different degrees as time elapses, and the concept arises that better results should be expected in younger patients. In addition, the position that was used to target the PPTg in the patients included in the above study does not coincide with the position that we have adopted according to both Paxinos and Huang's atlas (1995) and recent revisitations of brainstem nuclei (Mazzone et al., 2013; Paxinos et al., 2012) (Fig. 79.1). Thus comparison with our data is of limited value. Undoubtedly, the low number of patients implanted to date in the PPTg, the lack of appropriate long-term studies, the dyshomogeneity in patient selection, and inconsistencies in the precise site of stimulation adopted by different groups are the main issues that need to be overcome in the future, to determine truly the stability of PPTg DBS. In this regard, it is important to stress the fact that in our practice the best clinical results were obtained by placing the negative contact of the active pair of contacts markedly below the pontomesencephalic junction (Fig. 79.1). Other authors mainly target the mesencephalic portion of the nucleus, and the scanty MRI documentation that accompanies their papers does not allow a reliable comparison of targeted sites.

A second limitation of our study may be seen in the design of the intervals that we adopted for stimulation and medication arrest in the off/off condition. Such a condition may be harmful for patients, and posture analysis may be compromised, if not impossible, if postural instability is severe. Thus in the off-DBS condition we cannot exclude that incomplete cessation of stimulation effects occurred. Such a consideration may be also made in regard to L-dopa withdrawal. In regard to these considerations, we prefer not to wait too long after PPTg stimulation is switched off and/or the drug discontinued, so we start posture evaluations when postural instability begins to be felt by patients.

Overall, from the body of data presented and discussed, a crucial role of brainstem ascending and descending pathways appears to be involved in the pathogenesis and progression of L-dopa-resistant motor symptoms, which to date have mainly been attributed to basal ganglia nuclei. Thus the effectiveness of PPTg DBS for the control of postural deficits in motor disorders such as PD adds new insights into the role of central mechanisms that control posture and movement, and suggests an improved therapeutic approach to Parkinsonian disorders.

HIGHLIGHTS

- Parkinsonian patients show L-Dopa-resistant postural and gait abnormalities
- The pedunculopontine tegmental nucleus is a surgical target for these motor signs.
- Deep brain stimulation of this target in PD patients improves static balance
- The results help to understand the stimulation of brainstem nuclei on motor control

Acknowledgments

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References

Aravamuthan, B.R., Muthusamy, K.A., Stein, J.F., Aziz, T.Z., Johansen-Berg, H., 2007. Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei. Neuroimage 37, 694–705.

Armand, S., Landis, T., Sztajzel, R., Burkhard, P.R., 2009. Dyskinesia-induced postural instability in Parkinson's disease. Park. Relat. Disord. 15, 359–364.

Baston, C., Mancini, M., Rocchi, L., Horak, F., 2016. Effects of levodopa on postural strategies in Parkinson's disease. Gait Posture 46, 26–29.

Bejjani, B.P., Gervais, D., Arnulf, I., Papadopoulos, S., Demeret, S., Bonnet, A.M., et al., 2000. Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. J. Neurol. Neurosurg. Psychiatry 68, 595–600.

Bleuse, S., Delval, A., Blatt, J.L., Derambure, P., Destee, A., Defebvre, L., 2011. Effect of bilateral subthalamic nucleus deep brain stimulation on postural adjustments during arm movement. Clin. Neurophysiol. 122, 2032–2035.

Bloem, B.R., Beckley, D.J., van Dijk, J.G., Zwinderman, A.H., Remler, M.P., Roos, R.A., 1996. Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. Mov. Disord. 11, 509–521.

Bohnen, N.I., Frey, K.A., Studenski, S., Kotagal, V., Koeppe, R.A., Scott, P.J., et al., 2013. Gait speed in Parkinson disease correlates with cholinergic degeneration. Neurology 81 (18), 1611–1616.

Bonnet, A.M., Loria, Y., Saint-Hilaire, M.H., Lhermitte, F., Agid, Y., 1987. Does long-term aggravation of Parkinson's disease result from nondopaminergic lesions? Neurology 37, 1539–1542.

Brotchie, J.M., Lee, J., Venderova, K., 2005. Levodopa-induced dyskinesia in Parkinson's disease. J. Neural Transm. (Vienna) 112, 359–391.

Burchiel, K.J., Anderson, V.C., Favre, J., Hammerstad, J.P., 1999. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. Neurosurgery 45, 1375–1382.

Caliandro, P., Insola, A., Scarnati, E., Padua, L., Russo, G., Granieri, E., et al., 2011. Effects of unilateral pedunculopontine stimulation on electromyographic activation patterns during gait in individual patients with Parkinson's disease. J. Neural Transm. 118, 1477–1486.

Collomb-Clerc, A., Welter, M.L., 2015. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: a systematic neurophysiological review. Neurophysiol. Clin. 45, 371–388.

Colnat-Coulbois, S., Gauchard, G.C., Maillard, L., Barroche, G., Vespignani, H., Auque, J., et al., 2005. Bilateral subthalamic nucleus stimulation improves balance control in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 76, 780–787.

Curtze, C., Nutt, J.G., Carlson-Kuhta, P., Mancini, M., Horak, F.B., 2015. Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease. Mov. Disord. 30, 1361–1370.

Doherty, K.M., van de Warrenburg, B.P., Peralta, M.C., Silveira-Moriyama, L., Azulay, J.P., Gershanik, O.S., et al., 2011. Postural deformities in Parkinson's disease. Lancet Neurol. 10, 538–549.

Ferraye, M.U., Debu, B., Fraix, V., Goetz, L., Ardouin, C., Yelnik, J., et al., 2010. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 133, 205–214.

Florio, T., Capozzo, A., Puglielli, E., Pupillo, R., Pizzuti, G., Scarnati, E., 1999. The function of the pedunculopontine nucleus in the preparation and execution of an externally-cued bar pressing task in the rat. Behav. Brain Res. 104, 95–104.

Gagey, P.M., Weber, B., 2005. Posturologie, third ed. Elsevier-Masson.

Garcia-Rill, E., 1991. The pedunculopontine nucleus. Prog. Neurobiol. 36, 363–389.

Garcia-Rill, E., Homma, Y., Skinner, R.D., 2004. Arousal mechanisms related to posture and locomotion: 1. Descending modulation. Prog. Brain Res. 143, 283–290.

Garcia-Rill, E., Luster, B., D'Onofrio, S., Mahaffey, S., Bisagno, V., Urbano, F.J., 2016. Implications of gamma band activity in the pedunculopontine nucleus. J. Neural Transm. (Vienna) 123, 655–665.

Garcia-Rill, E., Luster, B., D'Onofrio, S., Mahaffey, S., Bisagno, V., Urbano, F.J., 2015b. Pedunculopontine arousal system physiology - deep brain stimulation (DBS). Sleep Sci. 8, 153–161.

St George, R.J., Carlson-Kuhta, P., Burchiel, K.J., Hogarth, P., Frank, N., Horak, F.B., 2012. The effects of subthalamic and pallidal deep brain stimulation on postural responses in patients with Parkinson disease. J. Neurosurg. 116, 1347–1356.

Goetz, L., Piallat, B., Bhattacharjee, M., Mathieu, H., David, O., Chabardes, S., 2016a. On the role of the pedunculopontine nucleus and mesencephalic reticular formation in locomotion in nonhuman primates. J. Neurosci. 36, 4917–4929.

Goetz, L., Piallat, B., Bhattacharjee, M., Mathieu, H., David, O., Chabardes, S., 2016b. The primate pedunculopontine nucleus region: towards a dual role in locomotion and waking state. J. Neural Transm. (Vienna) 123, 667–678.

Grimbergen, Y.A., Langston, J.W., Roos, R.A., Bloem, B.R., 2009. Postural instability in Parkinson's disease: the adrenergic hypothesis and the locus coeruleus. Expert Rev. Neurother. 9, 279–290.

Gut, N.K., Winn, P., 2016. The pedunculopontine tegmental nucleus-A functional hypothesis from the comparative literature. Mov. Disord. 31, 615–624.

Hong, S., Hikosaka, O., 2014. Pedunculopontine tegmental nucleus neurons provide reward, sensorimotor, and alerting signals to midbrain dopamine neurons. Neuroscience 282, 139–155.

Horak, F.B., Frank, J., Nutt, J., 1996. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. J. Neurophysiol. 75, 2380–2396.

Hunt, A.L., Sethi, K.D., 2006. The pull test: a history. Mov. Disord. 21, 894–899.

Insola, A., Padua, L., Mazzone, P., Scarnati, E., Valeriani, M., 2014. Low and high-frequency somatosensory evoked potentials recorded from the human pedunculopontine nucleus. Clin. Neurophysiol. 125, 1859–1869.

Insola, A., Mazzone, P., Valeriani, M., 2016. Dorsal column nuclei evoked activity recorded from the human pedunculopontine nucleus. Neurophysiol. Clin. 46, 315–317.

Jobst, E.E., Melnick, M.E., Byl, N.N., Dowling, G.A., Aminoff, M.J., 1997. Sensory perception in Parkinson disease. Arch. Neurol. 54, 450–454.

Johnson, L., Rodrigues, J., Teo, W.P., Walters, S., Stell, R., Thickbroom, G., et al., 2015. Interactive effects of GPI stimulation and levodopa on postural control in Parkinson's disease. Gait Posture 41, 929–934.

Karachi, C., Grabli, D., Bernard, F.A., Tande, D., Wattiez, N., Belaid, H., et al., 2010. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J. Clin. Investig. 120, 2745–2754.

Koller, W.C., Glatt, S., Vetere-Overfield, B., Hassanein, R., 1989. Falls and Parkinson's disease. Clin. Neuropharmacol. 12, 98–105.

Lavoie, B., Parent, A., 1994. Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. J. Comp. Neurol. 344, 210–231.

Maurer, C., Mergner, T., Xie, J., Faist, M., Pollak, P., Lucking, C.H., 2003. Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease. Brain 126, 1146–1163.

Mazzone, P., Lozano, A., Stanzione, P., Galati, S., Scarnati, E., Peppe, A., et al., 2005. Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. Neuroreport 16, 1877–1881.

Mazzone, P., Padua, L., Falisi, G., Insola, A., Florio, T.M., Scarnati, E., 2012. Unilateral deep brain stimulation of the pedunculopontine tegmental nucleus improves oromotor movements in Parkinson's disease. Brain Stimul. 5, 634–641.

Mazzone, P., Sposato, S., Insola, A., Scarnati, E., 2013. The clinical effects of deep brain stimulation of the pedunculopontine tegmental nucleus in movement disorders may not be related to the anatomical target, leads location and setup of electrical stimulation. Neurosurgery 73, 894–906.

Mazzone, P., Paoloni, M., Mangone, M., Santilli, V., Insola, A., Fini, M., et al., 2014. Unilateral deep brain stimulation of the pedunculopontine tegmental nucleus in idiopathic Parkinson's disease: effects on gait initiation and performance. Gait Posture 40, 357–362.

Mazzone, P., Vilela, F.O., Viselli, F., Insola, A., Sposato, S., Vitale, F., et al., 2016. Our first decade of experience in deep brain stimulation of the brainstem: elucidating the mechanism of action of stimulation of the ventrolateral pontine tegmentum. J. Neural Transm. (Vienna) 123, 751–767.

Mestre, T.A., Sidiropoulos, C., Hamani, C., Poon, Y.Y., Lozano, A.E., Lang, A.E., et al., 2016. Long term double blinded unilateral pedunculopontine area stimulation in Parkinson's disease. Mov. Disord. 31, 1570–1574.

Moro, E., Hamani, C., Poon, Y.Y., Al-Khairallah, T., Dostrovsky, J.O., Hutchison, W.D., et al., 2010. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. Brain 133, 215–224.

Muller, M.L., Bohnen, N.I., 2013. Cholinergic dysfunction in Parkinson's disease. Curr. Neurol. Neurosci. Rep. 13, 377.

Okada, K., Kobayashi, Y., 2013. Reward prediction-related increases and decreases in tonic neuronal activity of the pedunculopontine tegmental nucleus. Front. Integr. Neurosci. 7, 36.

Pan, W.X., Hyland, B.I., 2005. Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. J. Neurosci. 25, 4725–4732.

Paxinos, G., Huang, X.F., 1995. Atlas of the Human Brainstem. Academic Press, San Diego.

Paxinos, G., Huang, X., Sengul, G., Watson, C., 2012. Organization of brainstem nuclei. Hum. Nerv. Syst. 260–327.

Playfer, J.R., 2001. Falls and Parkinson's disease. Age Ageing 30, 3–4.

Rocchi, L., Chiari, L., Horak, F.B., 2002. Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 73, 267–274.

Rocchi, L., Chiari, L., Cappello, A., Gross, A., Horak, F.B., 2004. Comparison between subthalamic nucleus and globus pallidus internus stimulation for postural performance in Parkinson's disease. Gait Posture 19, 172–183.

Scarnati, E., Florio, T., Capozzo, A., Confalone, G., Mazzone, P., 2011. The pedunculopontine tegmental nucleus: implications for a role in modulating spinal cord motoneuron excitability. J. Neural Transm. 118, 1409–1421.

Scarnati, E., Vitale, F., Capozzo, A., Mazzone, P., 2016. Cholinergic input from the pedunculopontine nucleus to the cerebellum: implications for deep brain stimulation in Parkinson's disease. Neural Regen. Res. 11, 729–730.

Schultz, W., 2016. Reward functions of the basal ganglia. J. Neural Transm. (Vienna) 123, 679–693.

Skinner, R.D., Kinjo, N., Henderson, V., Garcia-Rill, E., 1990. Locomotor projections from the pedunculopontine nucleus to the spinal cord. Neuroreport 1, 183–186.

Skinner, R.D., Homma, Y., Garcia-Rill, E., 2004. Arousal mechanisms related to posture and locomotion: 2. Ascending modulation. Prog. Brain Res. 143, 291–298.

Takakusaki, K., Habaguchi, T., Ohtinata-Sugimoto, J., Saitoh, K., Sakamoto, T., 2003. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. Neuroscience 119, 293–308.

Thevathasan, W., Coyne, T.J., Hyam, J.A., Kerr, G., Jenkinson, N., Aziz, T.Z., et al., 2011. Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. Neurosurgery 69, 1248–1253.

Thompson, J.A., Costabile, J.D., Felsen, G., 2016. Mesencephalic representations of recent experience influence decision making. eLife 5.

Tjernstrom, F., Bjorklund, M., Malmstrom, E.M., 2015. Romberg ratio in quiet stance posturography–test to retest reliability. Gait Posture 42, 27–31.

Visser, M., Marinus, J., Bloem, B.R., Kisjes, H., van den Berg, B.M., van Hilten, J.J., 2003. Clinical tests for the evaluation of postural instability in patients with parkinson's disease. Arch. Phys. Med. Rehabil. 84, 1669–1674.

Visser, J.E., Allum, J.H., Carpenter, M.G., Esselink, R.A., Limousin-Dowsey, P., Honegger, F., et al., 2008a. Effect of subthalamic nucleus deep brain stimulation on axial motor control and protective arm responses in Parkinson's disease. Neuroscience 157, 798–812.

Visser, J.E., Allum, J.H., Carpenter, M.G., Esselink, R.A., Speelman, J.D., Borm, G.F., et al., 2008b. Subthalamic nucleus stimulation and levodopa-resistant postural instability in Parkinson's disease. J. Neurol. 255, 205–210.

Vitale, F., Mattei, C., Capozzo, A., Pietrantoni, I., Mazzone, P., Scarnati, E., 2016. Cholinergic excitation from the pedunculopontine tegmental nucleus to the dentate nucleus in the rat. Neuroscience 317, 12–22.

Wilcox, R.A., Cole, M.H., Wong, D., Coyne, T., Silburn, P., Kerr, G., 2011. Pedunculopontine nucleus deep brain stimulation produces sustained improvement in primary progressive freezing of gait. J. Neurol. Neurosurg. Psychiatry 82, 1256–1259.

Yousif, N., Bhatt, H., Bain, P.G., Nandi, D., Seemungal, B.M., 2016. The effect of pedunculopontine nucleus deep brain stimulation on postural sway and vestibular perception. Eur. J. Neurol. 23, 668–670.