**Pedunculopontine nucleus region deep brain stimulation in Parkinson disease: surgical techniques, side effects and postoperative imaging**

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The pedunculopontine nucleus (PPN) region has been used in clinical studies as a target for deep brain stimulation (DBS) in Parkinson disease (PD). These have yielded variable results but the overall trend is that of an improvement in falls and freezing in many of the treated patients. It remains unclear whether the variability in published data is related to patient selection, stimulation parameter or differences in surgical technique. It is also likely that multiple other factors may influence outcomes. We have analyzed data on surgical anatomy and terminology of the PPN region in a companion manuscript. Here we focus on issues concerning surgical technique, side effects of surgery, and postoperative imaging.

**Materials and Methods**

A Movement Disorders Society (MDS) working group was encharged of reviewing data relevant to PPN surgery. Questions were formulated in the framework of a consensus conference and distributed to the co-authors of the manuscript A PubMed database was searched using the following key words: pedunculopontine nucleus; deep brain stimulation; anatomy; physiology; surgery. Specific topics were assigned to groups of authors, and this work was reviewed and edited by the Executive Committee of the working group.

Here, we investigate issues relevant to surgical techniques: unilateral versus bilateral implantation of DBS electrodes; combining PPN with other targets; stereotactic targeting; microelectrode recording; intraoperative test stimulation; the type of electrode; and local field potentials. The group reviewed reports of intraoperative and early postoperative complications, and addressed the relevance and importance of postoperative imaging studies.

**Results**

**Rationale for bilateral versus unilateral PPN DBS**

***Preclinical Data.*** Semba and Fibiger showed in rodents that the PPN input from the brainstem reticular formation, the lateral hypothalamus, the zona incerta, the midbrain central grey, the ventral tegmental area, the substantia nigra pars compacta (SNc) and the substantia nigra pars reticulata (SNr) is primarily bilateral, but with an ipsilateral predominance1. In contrast to those findings, other reports in rodents 2 and primates 3 have demonstrated that nucleus subthalamicus (STN) projections to the PPN were exclusively ipsilateral.

Kita and Kita quantified the lateralization of projections from the PPN to the STN in rats 4. They observed that only 10% of projections were cholinergic with a five-fold predominance of ipsilateral versus contralateral fibers. The predominance of ipsilateral to contralateral projections in the remaining non-cholinergic projections was close to three-fold.

In summary, projections from the basal ganglia and other structures to the PPN in rodents were predominantly unilateral. Those between PPN and the STN appeared to be bilateral, with a stronger ipsilateral representation. Alhough no data exist in humans, precalinical findings suggest that, even though unilateral surgery may influence both sides of the body, it may likely have a stronger impact on the contralateral side.

***Clinical Data.*** Clinical insight into the safety and efficacy of unilateral versus bilateral PPN stimulation has been limited. Unilateral DBS has been carried out in two series with 6 5 and 13 patients 6 treated in different centers. In contrast, bilateral DBS was conducted in various other trials. After an initial study with two individual patients 7, two series of 6 subjects were reported in which bilateral PPN DBS was delivered along with STN DBS 8, 9. Another series of 5 patients was reported with bilateral PPN DBS administered in tandem with DBS in the caudal zona incerta (cZi) 10.

Imaging studies in PD patients suggest that unilateral PPN DBS increases cerebral blood flow bilaterally into the central thalamus and cerebellum 11. Formal comparisons between unilateral and bilateral PPN DBS, however, tend to support bilateral DBS 12. Khan and colleagues showed that on-medication UPDRS motor scores improved by 5.7% with unilateral DBS and by 18.4% with bilateral PPN DBS in a series of 5 PD patients 12. Similarly, improvement in UPDRS axial subscores (items 27-30) after unilateral PPN DBS was 22% and after bilateral DBS 36%.

In an experimental study to measure the spatiotemporal characteristics of gait during PPN DBS, Thevathasan and colleagues compared the effects of unilateral versus bilateral stimulation in a blinded fashion 13. The authors found that improvement in freezing after bilateral stimulation of the caudal PPN in the off medication condition was approximately twice as high as that recorded after unilateral stimulation.

***Conclusions.***  Both unilateral and bilateral PPN DBS were found to have an impact on gait and axial symptoms. Only one clinical trial and one study on gait compared the effects of bilateral vs unilateral PPN DBS directly. In both, bilateral stimulation proved to be superior, particularly for controlling freezing of gait. These findings, nevertheless need to be corroborated by additional studies including a higher number of patients prior to specific recommendations.

**Combination with other targets**

While few PD patients present with a predominant gait disorder or freezing refractory to medical treatment, the majority of patients in whom DBS is considered suffer also from other parkinsonian symptoms. Chronic stimulation of the PPN has been combined with stimulation of other targets, including the STN, the globus pallidus internus (GPi), and the cZi. There has been a different rationale for choosing each target with some evidence suggesting that target combinations may be superior to PPN DBS alone. Combined stimulation poses a series of challenges for the assessment of the effects of DBS in each target, as well as for unlocking the understanding of the complex relationship between medication and stimulation. A particular problem is the fact that, in general, most groups use low frequency stimulation for the PPN and high frequency stimulation in other targets. This regimen requires complex programming or the use of an additional pulse generator.

In their initial trial, Stefani and colleagues implanted 6 PD patients with bilateral PPN and STN electrodes. This combined approach was selected to tailor DBS according to the patients’ symptoms – that is- those typically controlled by STN DBS and those considered as being STN stimulation-refractory 8. Overall, the results showed a synergistic effect between targets. In a study from Grenoble, PPN DBS was added to STN DBS in 6 patients with advanced PD 14. The addition of PPN DBS reduced the duration of freezing episodes under the off-drug condition. Moreover, it reduced falls related to freezing. Total UPDRS scores, however, did not significantly change.

In another report, in three PD patients PPN DBS was combined with GPi DBS with the rationale to treat off dystonia as well gait features 6. In a more recent study, it was demonstrated that low frequency PPN DBS combined with high frequency GPi DBS in a patient with advanced PD had a marked impact on gait ignition and freezing of gait. In contrast, isolated PPN or GPi DBS yielded only mild effects with the patient being blinded in each condition and by using a computerized gait analysis system 15.

Khan and colleagues observed that the effects of combined PPN and cZI DBS in seven patients were superior to those of single target 10, 16. When both PPN and cZI electrodes were bilaterally activated, motor scores improved by 41.8%. When receiving bilateral PPN and cZI DBS, UPDRS axial subscores improved by 58.3%.

***Conclusions.***  Only a few trials have studied the effects of combining PPN DBS with stimulation of the STN, GPi or cZI. Furthermore, the small number of patients in each study limits the interpretation of the data.

**Stereotactic targeting**

***Target site within the PPN.*** There is no consensus on the optimal target site within the PPN region. There remains uncertainty as to whether electrodes should be implanted in the rostral PPN (at the level of the inferior colliculus (IC)) or caudal PPN (in a region about 4mm below IC). Given the murkiness of the available data and since the PPN is oriented along the long axis of the brainstem, a reasonable approach would be to have contacts in both rostral *and* caudal PPN region.

It should be noted, however, that in animal studies of PPN stimulation-induced locomotion, the activation of the posterior *pars compacta* was efficacious while stimulation of anterior PPN was not 17, 18. A recent study on an animal model of PD showed that stimulation of the anterior PPN induced freezing and worsened gait, but gait was improved by posterior PPN stimulation 19.

***Targeting of PPN across different groups.*** Below, we wsummarize the methods used by different investigators to target the PPN. Stereotactic imaging consisted of either MRI alone or combined with CT 10, 16.

*Bristol, UK* 7, 20. MRI T2-weighted and proton density sequences were used. The PPN was defined on an axial plane acquired parallel to that formed by the upper border of the pons and the midbrain collicular point. In that section, the PPN was localized between the decussation of the superior cerebellar peduncle and the medial lemniscus. The nucleus was suggested to extend approximately 5 mm caudal to that point, running parallel to the fourth ventricle and to the cerebral aqueduct.

*Toronto, Canada*  21, 22. T1- and T2-weighted MRI sequences were obtained. The target region was defined as being 4–5 mm below the caudal aspect of the inferior colliculus, 2–3 mm posterior to the limit between the base and tegmentum of the pons in the anteroposterior axis, and 3–4 mm medial to the lateral edge of the brainstem. The final coordinates were modified according to individual anatomical variations and by intraoperative findings.

*Oxford, UK* 23, 24. Patients underwent echo planar and diffusion weighted MR data acquisition and diffusion tensor imaging (DTI). This allowed visualization of the superior cerebellar decussation and medial lemniscus. In addition, a stereotactic CT scan of the whole head at 1.0 mm contiguous slices was acquired. Using planning software, the pre-operatively acquired T2-weighted MRI scan was volumetrically fused to the stereotactic CT. The target chosen was the one delineated by DTI. A trajectory was chosen along the long axis of the brainstem, from a level just below the red nucleus to the inferior colliculus, incorporating the seeded target site along the axis of implantation.

*London, UK* 25-27. Zrinzo and colleagues used information derived from MRI sequences to obtain an optimized visualization of the PPN and adjacent brainstem structures (Fig. 1). The rostral pole of the PPN was identified at the mid-inferior collicular level, whereas the caudal pole was suggested to lie in the rostral pons. Altogether, the authors suggested that the PPN spans for a distance of 5mm. The authors characterized fourth ventricular landmarks, including the fastigial point (F), a line tangential to the floor of the fourth ventricle along the median sulcus (VFL), and a line perpendicular to VFL passing through the fastigium. The intersection between these lines determined the base point (B). The axial plane to target the PPN was perpendicular to VFL (Fig. 2).

T1-weighted images were used to identify the landmarks and proton density images to provide contrast within the brainstem. On axial proton density images reformatted with respect to fourth ventricular landmarks, the rostral PPN was characterized as a region of intermediate signal intensity bounded laterally by the medial lemniscus, spinothalamic tract and lateral lemniscus, anteromedially by the decussation of the superior cerebellar peduncle and posteromedially by the central tegmental tract. On more caudal proton density axial images (5mm inferior to the mid-inferior collicular level), the gray matter between the lemniscal system and the superior cerebellar peduncle was compressed to a narrow boomerang shape structure and it was suggested that the caudal pole of the PPN occupies this slender gray matter region. Stereotactic images from 12 patients undergoing DBS of other brain targets were analysed. Mean (SD) coordinates for the visualized poles of the PPN in relation to the base point–fastigial (B–F) plane were derived. The rostral pole of the PPN was found to be 6 (0.5) mm lateral to the midline, and 4.2 (0.8) mm anterior, and 19.3 (1.4) mm rostral to the base point. The caudal pole was 6.8 (0.5) mm lateral, 4.4 (0.5) mm anterior to B, and 14.3 (1.4) mm rostral to the B–F plane.

Mean (SD) coordinates of the MRI-localized PPN poles in relation to AC-PC were as follows: rostral pole 6.0 (SD 0.5) mm lateral and 3.0 (1.1) mm posterior to PC, and 9.0 (1.1) mm caudal to the AC–PC plane. The caudal pole was 6.8 (0.5) mm lateral and 4.0 (1.1) mm posterior to PC, and 13.9 (1.2) mm caudal to the AC–PC plane. Coordinates of the PPN midpoint were 6.4 (0.5) mm lateral, 3.5 (1.0) mm posterior, and 11.4 (1.2) mm caudal to the posterior commissure. The authors indicated that there was considerable variation in the location of the PPN in relation to both third and fourth ventricular landmarks. They also pointed out that atlas-based coordinates would be useful in providing an estimate of PPN localization, but that further refinement by MR imaging would be needed.

*Rome, Italy* 28, 29. CT sections corresponding to an axial plane located 5 mm below the ponto-mesencephalic junction were obtained. The target was then located at a point within that section that was 7 mm in front of (lateral to) the wall of the pontine tegmentum.

Investigators in Rome also used: 1) ventriculography ; 2) angio-CT scans (axial planes); and 3) three-dimensional (3D) reconstructions of brainstem atlases. As the trajectory was preferably extra-ventricular, the angles most commonly used ranged from 8° to 11° in the coronal plane and 25° in the sagittal plane, being as parallel as possible to the floor of the IVth ventricle.

*Grenoble, France* 30. In Grenoble, investigators used ventriculography and MRI though there were changes in methodology which evolved over several years. Average coordinates of the tentative target were 1.5 mm posterior to PC, 13 mm below the AC-PC line and 6mm lateral from the midline. The tentative trajectory was parallel to the floor of the fourth ventricle.

In the first 6 patients, the PPN was targeted based on bi-orthogonal televentriculographic images, which allowed the localization of ventricular landmarks (AC, PC and aqueduct/ floor of the fourth ventricle). These were fused with T1- and T2-weighted 1.5 T MR scans. A central trajectory was chosen to be parallel to the floor of the fourth ventricle, passing through PC with a 14◦-20◦mediolateral angle. The target depth was set at 13 mm below PC, and 6 mm from the midline. A second trajectory was defined 2 mm posterior to the central one. A third trajectory was occasionally performed 2 mm anterior or lateral to the central trajectory.

In the next 5 patients, a target was chosen that was 2 to 3 mm posterior to PC, 6 mm from the midline, at the level of the PMJ, with an angle adapted to the brainstem orientation. Targeting was supported by using a Brainstem Normalized Coordinate System (BCNS) that accounted for the PMJ and its width as the craniocaudal and anteroposterior references, respectively.

*San Francisco, USA* 31. This group targeted the PPN based on MRI at a point superolateral to the decussation of the superior cerebellar peduncles on T2 weighted fast spin echo images.

Average coordinates were 6 to 7.5 mm lateral, 13 to 15 mm inferior and 15 to 17 mm posterior to the midcommissural point. With respect to brainstem-based coordinate systems, target coordinates weree 6 to 7.5 mm lateral, 3 to 5 mm anterior to B and 13 to 16 mm rostral to the B–F plane. When appropriate, the target was adjusted so that it would be 2 to 3 mm away from the lateral edge of the brainstem, at the level of the PMJ.

*Brisbane, Australia* 32. After CT/MRI fusion, the PPN was targeted on MRI in stereotactic space with the concomitant use of reconstructions from brainstem atlases. The PPN was identified lateral to the superior cerebellar decussation at the level of the inferior colliculus. Trajectories were parallel to the axis of the brainstem and fourth ventricle, passing through the subthalamic region posterior to the red nucleus.

*Hannover, Germany* 15. In Hannover, targeting was conducted based on T1 and T2 weighted MRI images fused with a stereotactic CT. A combination of three different methods was used: 1. Image-guided indirect determination of the PPN after the visualization of neighbouring structures (decussation of the superior cerebellar peduncles and medial lemniscus). 2. Preliminary definition of the midpoint of the PPN in relation to AC-PC: 6 – 7 mm lateral, 3 – 4 mm posterior to PC, and 11 – 13 mm below the AC-PC plane. 3. Preliminary definition of the rostral and the caudal poles of the PPN according to the method of Afshar (rostral pole: 6mm lateral and 4mm anterior to the base point (B), 16 mm rostral to the base point–fastigial (B–F) plane; caudal pole: 7 mm lateral and 4 mm anterior to B, 11 mm rostral to the B–F plane. The coordinates obtained by all three methods were then compared and adapted. The final target for the lowest electrode contact was the caudal pole of the PPN.

***Conclusions.*** Most authors advocate T2 and proton density sequences for direct visualization of landmarks in the PPN region. The PPN target lies medial to the medial lemniscus, close to the lateral edge of the superior cerebellar commissure and lateral to the central tegmental tract. In the rorstrocaudal axis, it straddles the PMJ with its rostral pole located at the level of the mid-inferior colliculus.

Most groups choose trajectories parallel to floor of the fourth ventricle. According to some investigators, an appropriate dorsoventral landmark for placing the tip of the electrodes is a region 5 mm below the inferior edge of the inferior colliculus (immediately inferior to the transition between midbrain and pons). The B-F system can be used for targeting but has only been validated by a few groups.

There is general agreement that indirect targeting based on AC-PC only is problematic. Nevertheless, the reported average coordinates relative to AC-PC are the following: 6 to 7.5 mm lateral, 13 to 15 mm inferior and 15 to 17 mm posterior to the AC-PC midpoint (or 1.5 mm posterior to PC). A few authors also advocate that, in the medial lateral plane the electrode tip should be placed in a region 2-4 mm medial to the lateral edge of the brainstem. Since the caudal extent of the PPN is unclear, some authors suggest placing the tip of the electrode 4 mm below the PMJ.

In conclusion, a variety of imaging protocols were used to approach the PPN. Although the target appears to be similar across studies, there is no consensus as to which protocol would be most appropriate.

**Microelectrode recording**

***Electrophysiological features of the PPN region and target localization.*** Several groups reported the findings of microelectrode recording in the PPN region. The findings are summarized below.

*Toronto, Canada* 22. In the study by the Toronto group, neurons were classified according to the width and polarity of their action potentials. Three populations were described: 1. Units that fired randomly at 17 Hz (most cells); 2. Neurons suggested as being cholinergic based on the characteristics of their action potentials (16% of the total number of cells- firing at 9 Hz); and 3. Units with positive action potentials that fired regularly at a mean of 67 Hz (7% of cells).

Most neurons (57%) fired randomly while 21% exhibited a bursty firing pattern. Above and below the PPN, the proportion of bursting neurons was smaller (11 and 19% respectively) while more neurons exhibited random firing (65 and 75% respectively). Overall, 36% of the neurons responded to at least one type of passive or voluntary limb movement. Changes in firing rate were mostly excitatory (about 80%).

*Grenoble, France* 33, 34. Among 21 cells recorded, 14 (67%) fired irregularly and seven (33%) exhibited a burst-like pattern. The mean firing rate of all neurons was 28 Hz. During locomotor tasks, 57% of cells modified their firing. Of interest, two patients were asked to mimic stepping movements in the operating room. In those individuals, 7 cells showed an increase of firing during mimicked gait.

*San Francisco, USA* 31. The mean spontaneous discharge rate for neurons presumably within the PPN or dorsal to it was 23Hz and 35Hz, respectively. Bursting discharge was more prevalent in the PPN compared to more dorsal regions. Wide action potential neurons were seen in the region dorsal to PPN, and in the dorsal part of PPN itself, but not in caudal regions. In the region dorsal to the PPN, 44% of neurons had significant oscillatory activity, while this was only observed in 19% of cells within the PPN. Oscillation frequencies within PPN tended to be higher than those recorded in dorsal regions. Responses to contralateral movements of the limbs were observed in 43% of units in the PPN region. Most units responded to passive movements with phasic increases in discharge.

*Brisbane, Australia 35.* In a study from Brisbane, 686 cells were recorded from 11 patients (10 with PD and 1 with PSP). Neurons were divided in narrow (87%) or wide-spike units (13%). Mean firing rates in both populations was 12-13Hz. In narrow units, 16% of firing occurred in bursts, versus 46% in wide firing units. Wide units were more prominent in the caudal PPN and suggested to be cholinergic. Although around half of the cells recorded in this study were movement-responsive, most units showed a decrease in firing (in contrast to other reports in the field). Interestingly, certain cells were inhibited during imaginary gait.

***Conclusions.***  Most neurons in the PPN region seem to fire in a range between 12-30Hz in patients with PD. There are however, subpopulations that fire at lower (9Hz- possible cholinergic cells) and higher rates (60-70Hz). Most cells fire randomly. Around 20-30% of units fire in bursts, which are more commonly recorded in the presumed PPN than dorsal to it.

Around 35-45% (perhaps more) of cells in the PPN region respond to passive or active movements. Some cells respond to movements that mimic gait patterns. The phenotype of cells recorded is unclear and the exact nuclear region where the cells were recorded has laso been difficult to pinpoint (PPN, cuneiform, or subcuneiform).

**Intraoperative test stimulation**

***Electrodes, stimulation parameters, effects and side effects.*** According to published data most groups do not use microstimulation to assess thresholds for possible side effects induced by electrical stimulation.

Based on the Grenoble experience in awake patients 34, stimulation induced no effect on akinesia, rigidity or tremor. Furthermore, no effects were observed during a task in which patients were asked to pedal while in the supine position. However, microstimulation was used to delineate neighbouring structures*.* Stimulation was applied every 3mm from -5mm to -15mm below the AC-PC plane. Stimulation parameters were: frequencies of 25 and 130Hz, a pulse width of 0.06 ms, and current intensities of 0.1 up to 4mA. Stimulation induced the following effects depending on frequency: mono and binocular movements (such as eye deviation or trembling vision) at both 25 and 130Hz, mostly present when stimulation was delivered at the rostral level of the inferior colliculus; myoclonic movements/muscular vibratory-like sensations at 25Hz; paresthesias, mainly at 130Hz, when stimulation was delivered laterally, around 6 to 7 mm from the midline.

Sites in which monocular deviation and paresthesias were recorded at 25Hz at a low amplitude were avoided for lead implantation. Best clinical outcomes were obtained when 130Hz microstimulation induced only transient paresthesias on the contralateral face and upper limb and when 25Hz induced myoclonic movements/muscular vibration like sensations at the PMJ level. Some authors have suggested that this could be a possible target signature.

The Brisbane group reported stimulation-induced sleep when current was delivered at 100-130 Hz to the rostral PPN 36. Other side effects included disturbances with ocular pursuit and saccades, with reports of shimmering in the visual fields.

***Conclusions.*** Reported stimulation-induced effects in the operating room include oscillopsias, paresthesias and myoclonic movements.

**What type of DBS electrode to implant?**

Both the Medtronic 3387 and the Medtronic 3389 DBS electrodes have been used (Medtronic Inc., Minneapolis). The advantage of the 3387 is that, with a wider span of the contacts, a broader anatomical coverage is possible. Since the PPN is partially degenerated in PD (and more so in PSP), one may advocate that smaller spaced electrodes might be preferable. Given the length of the PPN region and the uncertainty about the optimal stimulation site, the Oxford group favors the 3387 electrode. Since the Brisbane group concentrated on the more caudal region of the PPN, the 3389 model was used.

***Conclusions.*** To date, there is no data suggesting that one electrode is better than the other for stimulating the PPN region.

**Local field potentials**

Several studies have explored local field potentials (LFP) in the PPN region, intraoperatively from microelectrodes 22, 31 or postoperatively from externalized DBS electrodes 36, 37. Overall results have been heterogeneous with patients showing peaks in the theta, alpha or beta frequency bands 22, 31, 36, 37. One study suggested that this variability could be related to electrode location, with alpha and beta activity being more marked in the caudal and rostral PPN, respectively 36. The San Francisco group demonstrated that, as the electrode was advanced, the percentage of power in the low beta range (13–21 Hz) increased from 35.2% to 40.8% at rest, and from 11.1% to 29.8% during movement 22, 31. In a few studies, local field potentials were shown to respond to limb movement 31, 37 and to correlate with gait (e.g. alpha band) 36. Changes in electrophysiological activity were observed after L-Dopa administration 38 and related to movement initiation 37. Tattersall et al 35 has recently demonstrated that alpha power was significantly higher relative to beta power in caudal PPN. These authors have also found an increase in both alpha and beta power (alpha/beta power ratio) during limb movements. Relatively less attention has been paid to gamma band activity 39.

Additionally, somatosensory evoked potentials were recorded from implanted PPN electrodes 28, 40-42. Yeh and colleagues recorded somatosensory evoked potentials after median nerve stimulation 43. These were triphasic or biphasic potentials with latencies to the largest negative peak in the order of 16.8 and 18.7 milliseconds. There was no difference in SEP amplitude and latency between on and off medication states. High frequency oscillations could be identified after the contralateral median nerve was stimulated.

As part of the reticular activating system, the PPN may also respond directly to sensory inputs 18. In humans, the midlatency auditory evoked P50 potential recorded at the vertex has been proposed to be generated by the PPN 44, but such studies have not been carried out in PD patients 45.

***Conclusions.***  Frequency bands in the alpha, beta and theta ranges and movement-related potentials were all recorded from the PPN region. In the off medication condition, beta desynchronization occured during movement in a small study. In the on medication condition, oscillations in the 7-11Hz range were recorded. Beta related synchronization occurred during pre-movement phases and theta related desynchronization occurred with movement.

It may be important to develop a standard set of resting and movement related intraoperative LFPs that might help to optimize PPN targeting. One problem is that the alpha band activity correlating with gait may not be evident when patients are lying supine.

**Intraoperative and early postoperative complications**

***Adverse effects and management.*** There are no reports of serious adverse events either intraoperatively or in the early postoperative period after PPN DBS in more than 100 published patients. No symptomatic bleeding wasreported on postoperative imaging. No permanent neurologic deficits were described. This suggests that PPN DBS surgery has a safety profile that is similar to other targets which are being used in PD, however it should be noted that these findings may be underestimated and due to a reporting bias.

Stimulation-induced adverse events in the early postoperative period included oscillopsia, paresthesias, burning sensations, myoclonus, and sleep induction 30, 36, 46. These phenomena were time-locked with stimulation, they were frequency dependent,and were reversible when stimulation was reduced or ceased.

***Conclusions.*** Available evidence suggests that surgery for implantation of electrodes in the PPN is relatively safe and well tolerated.

**Postoperative imaging**

Examination of postoperative figures from many publications reveals that in most studies electrodes were implanted in the same anatomic region although many studies do not provide much detail. When assessing coordinates and the exact numbers, it is difficult to reach uniform conclusions. Some studies reported the location of the tip of the electrodes, while others described the position of contacts 0 or 2. Further, studies have used different landmarks when assessing their data, including the AC-PC or the B-F system. Another issue is that, even when electrodes were placed in the same brainstem region, patients were stimulated through different contacts (some in the caudal PPN, others in the rostral PPN) 7, 20;8, 15, 47, 48; 6, 11, 21, 23, 26, 28-31, 33, 38, 49, 50

Some MR sequences produce large lead artifacts and only poor internal tissue contrast within the brainstem. This may limit accurate determination of the localization of the lead (Fig 3). 14. Nevertheless, MR imaging is currently the most useful method to localize and to confirm electrode placement in the PPN region as well as to document its variability (Figs 4a and b) 34, 36.

***Conclusions:*** A wide variety of techniques were employed to document lead location following PPN DBS. CT imaging cannot account for individual anatomical variability and requires co-registration with atlases or MR images. Although most authors used MRI, sequences often were not reported in detail. Poor tissue contrast within the region of interest appears to be a general problem and this adds to the difficult in identifying internal anatomical landmarks. Stereotactic MRI using proton density sequences seems to be of value for documenting lead placement in the PPN region postoperatively.

**Discussion**

PPN DBS is a relatively novel intervention in PD. There are a number of important challenges to be resolved such as identification of the optimal target, surgical approach, surgical technique, intraoperative confirmation of the target, and postoperative validation of the electrode position. There is considerable variabilty across groups, the overall experience with PPN DBS is still limited, and there is lack of controlled trials. Despite these challenges the procedure appears to provide benefit to some patients and appears to be relatively safe.

By systematically reviewing the published data, we hope to identify challenges so that future studies can be designed to better address this controversial issue. We also hope that this publication may facilitate the development of surgical protocols for PPN DBS.

**Legends to Figures**

**FIG. 1.** Axial sections perpendicular to the long axis of the brainstem. Row I: level of rostral PPN and mid inferior colliculi (IA and IB: 36 mm rostral to obex; IC and ID: 16 mm rostral to BF plane). Row II: through middle of PPN (IIA and IIB: 33 mm rostral to obex; IIC and IID: 13 mm rostral to BF plane). Row III: sections taken through caudal PPN (IIIA and IIIB: 31 mm rostral to obex; IIIC and IIID: 11 mm rostral to BF plane). Columns A and B: adapted from Paxinos et al 51. Column A presents negative photographs of sections stained with cresyl violet and acetylcholinesterase: white matter appears dark, gray matter appears light. Line drawings presented in column B show the outline of fibre tracts and nuclei. The ventricular system is solid black, a number of structures relevant to the PPN have been assigned a colour. Columns C and D: taken from Afshar et al 52. Column C presents photomicrographs of modified Mulligan stain sections; white matter tracts appear light, gray matter is dark. Column D: stereotactic drawings based upon probability data acquired from multiple hemi brainstems (see text and note superimposed stereotactic grid). Major structures are labelled but the PPN is not amongst them. Surrounding structures have been assigned the same colour scheme as in column B. Columns E and F: MRI images from a representative patient in the study acquired using the specifically modified proton density sequence described in the text. White matter appears hypointense and gray matter relatively hyperintense. Planning software was used to reconstruct axial images at a plane perpendicular to the midline of the fourth ventricular floor. Column F: interpretation of the structural arrangement of brainstem structures within the MR image assisted by the inherent image contrast as well as an understanding of the regional anatomy. The PPN can be directly localized within the gray matter lying lateral to the SCP and its decussation (green) and CTT (blue) and medial to the lemniscal systems (yellow) and is represented by a red circle. Note: atlas photographs and drawings reproduced here were originally published in conventional anatomical representation (anterior surface of the brainstem towards the bottom of the page). These images were purposefully rotated through 180° to make their orientation analogous to the axial radiological imaging convention that is more familiar to clinicians. CTT/ctg, central tegmental tract; LL/ll, lateral lemniscus; ML, medial lemniscus; PPN, pedunculopontine nucleus; PPTgC, PPN pars compacta; PPTgD, PPN pars diffusa; SCP/scp, superior cerebellar peduncles; STT/spth, spinothalamic tract. Illustrations in columns A and B reprinted from Paxinos G, Huang XF: Atlas of the Human Brainstem. San Diego: Academic Press; 1995 51. Illustrations in columns C and D reprinted from Afshar et al, 1978 52.

Adapted from Zrinzo et al. 27, with permission.

**FIG. 2.** Atlas-based landmarks of the fourth ventricle as defined in Afshar's stereotactic atlas of the human brainstem and cerebellum. Variability in the angle of the mesencephalic flexure (a) may lead to increased variability of the spatial relationship of brainstem structures to the traditional AC-PC line. Brainstem structures may therefore enjoy a more constant relationship with fourth ventricular landmarks. A line is drawn tangential to the floor of the fourth ventricle in the midline (VFL); a second line passes through the fastigium, perpendicular to the first. The intersection of these two lines (B) and the fastigial point (F) define two points in a new reference plane in a similar manner to that defined by the more traditional AC-PC points. Extensions of the VFL and the AC-PC line subtend an angle a: the mesencephalic angle.

Adapted from Zrinzo et al. 27, with permission.

**FIG. 3**. Location of DBS electrodes in the PPN region in a patient from the Grenoble group. (**a**) Sagittal fusion imaging of the final intra-operative teleradiography with the preoperative MRI, showing how the coordinates of the tip of the distal contacts of the electrodes were measured. h: distance (in mm) to the pontomesencephalic (PM) line, defined as the line connecting in the anterior-posterior direction the pontomesencephalic junction to the caudal end of the quadrigeminal plate, measured on the midline; AC: anterior commissure; PC: posterior commissure. d: orthogonal distance in mm to the line prolonging the fourth ventricle line. V4: fourth ventricle. (**b**) 3D T1-weighted magnetic resonance imaging in the axial plane parallel to the bicommissural plane, at the level of contacts 1 and 5 of the electrodes. Those contacts delivered cathodic current and the contact depth of the right and left electrodes was symmetrical. (**c**) Atlas adaptation onto patient' s MRI. Superior posterior view of the 3D image with the pedunculopontine nucleus in pink, the medial lemniscus in white and the four electrode contacts in blue. Note that in this patient the electrode is located posterior to the pedunculopontine nucleus.

Adapted from Ferraye et al. 14, permission pending.

**FIG 4**. Location of active stimulation sites within the PPN region mapped on a sagittal T1-weighted MR scan.

Adapted from Thevathasan et al., Brain 2012, with permission.

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