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Connectivity of the human pedunculopontine nucleus region and diffusion tensor imaging in surgical targeting

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Object. The pedunculopontine nucleus (PPN) region of the brainstem has become a new stimulation target for the treatment of gait freezing, akinesia, and postural instability in advanced Parkinson disease (PD). Because PD locomotor symptoms are probably caused by excessive γ-aminobutyric acidergic inhibition of the PPN, low-frequency stimulation of the PPN may overcome this inhibition and improve the symptoms. However, the anatomical connections of this region in humans are not known in any detail.

Methods. Diffusion weighted magnetic resonance (MR) images were acquired at 1.5 teslas, and probabilistic tractography was used to trace the connections of the PPN region in eight healthy volunteers. A single seed voxel ($2 \times 2 \times 2$ mm) was chosen in the PPN just lateral to the decussation of the superior cerebellar peduncle, and the Diffusion Toolbox of the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain was used to process the acquired MR images. The connections of each volunteer's PPN region were analyzed using a human brain MR imaging atlas.

Results. The PPN region was connected with the cerebellum and spinal cord below and to the thalamus, pallidum, subthalamic nucleus, and motor cortex above. The regions of the primary motor cortex that control the trunk and upper and lower extremities had the highest connectivity compared with other parts of motor cortex.

Conclusions. These findings suggest that connections of the PPN region with the primary motor cortex, basal ganglia, thalamus, cerebellum, and spinal cord may play important roles in the regulation of movement by the PPN region. Diffusion tensor imaging tractography of the PPN region may be used preoperatively to optimize placement of stimulation electrodes and postoperatively it may also be useful to reassess electrode positions.
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Key Words • diffusion tensor imaging • diffusion tractography • Parkinson disease • pedunculopontine nucleus

It has long been known that the PPN region plays an important role in locomotion.[49,57] Many other functions have also been associated with the PPN, such as control of the sleep/wake cycle, muscle tone, incentive motivation, biting and gnawing, antinociception, gating of the startle reflex, and cognitive and auditory processing.[13,20,45,54,58] Understanding the role of the PPN region in locomotion and control of muscle tone has been mainly based on studies in rodents and cats. Findings from recent studies in primates, however, have suggested that the PPN region is also important in voluntary movements[1,28,33,34,39,41] and in the akinesia of PD.[22,29,38] These reports strongly support the conclusion that the PPN region is an important relay in the basal ganglia circuitry that controls locomotor function.

In recent years, interest in this region has increased because it has become a potential new target for the treatment of advanced PD, especially in patients with akinesia or freezing symptoms.[35,44] Treatment by electrical stimulation of the thalamus, STN, or GPI using deep brain stimulating electrodes usually fails to alleviate the gait freezing, akinesia, and postural instability of advanced PD.[27] This may be because akinesia in PD is caused by excessive GABAergic inhibition of the PPN that is not affected by deep brain stimulation in conventional targets. However, in monkeys rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Aziz's group[22,38,39] showed that microinjection of the GABA receptor A antagonist, bicuculline, into the PPN, or low-frequency stimulation of the same region, can overcome the inhibition of PPN neurons and significantly improve akinesia.

Despite these encouraging results, data on the connectivity of the primate PPN region are sparse. In the human brain, the PPN is bound on its lateral side by fibers of the medial lemniscus and on its medial side by fibers of the superior cerebellar peduncle and its decussation.[14,40] Rostrally, the anterior aspect of the PPN contacts the dorsomedial aspect of the posterolateral SN, whereas the retrorubral field

Abbreviations used in this paper: BDA = biotinylated dextran amine; DT = diffusion tensor; FMRIB = Oxford Centre for Functional Magnetic Resonance Imaging of the Brain; GABA = γ-aminobutyric acid; GP = globus pallidus; GPI = GP internus; HRP = horseradish peroxidase; MR = magnetic resonance; PD = Parkinson disease; PPN = pedunculopontine nucleus; SN = substantia nigra; STN = subthalamic nucleus.

borders it dorsally. The most dorsal aspect of the PPN is bound caudally by the pontine cuneiform and subcuneiform nuclei and ventrally by the pontine reticular formation. The most caudal pole of the PPN is adjacent to neurons of the locus coeruleus.

Diffusion weighted imaging is a noninvasive method of brain imaging that characterizes the self-diffusion properties of water molecules.[2] In the white matter of the brain, which has directional organization, diffusion varies in different directions, and in areas of coherent fiber organization the principal diffusion direction corresponds to the underlying fiber direction.[3,4] Therefore, by following estimates of the principal direction of diffusion it is possible to reconstruct estimated fiber pathways.[9,25,37] Conventional approaches to tract tracing, however, can typically only trace pathways in areas of high anisotropy—that is, within white matter bundles—where the estimate of fiber direction is more certain. By contrast, probabilistic tractography approaches[6] take into account the uncertainty associated with estimates of fiber direction and are, therefore, able to trace fibers to and from gray matter.[5] Probabilistic approaches yield confidence boundaries on a particular pathway between gray matter structures in the brain and have been previously used, for example, to investigate the cortical connectivity of the human thalamus[5,24] and periventricular–periaqueductal gray region.[51]

In this study, we have used probabilistic diffusion tractography to investigate the connectivity of the PPN region. In the context of our findings, we also review the anatomical basis underlying the role of the PPN as a target for electrical stimulation in advanced PD in which akinesia, freezing, and postural instability are predominant features.

Materials and Methods

Diffusion weighted MR imaging was performed in eight healthy control volunteers (four men and four women, age range 21–34 years), who gave informed written consent in accordance with our approval from the Oxford Research Ethics committee.

Diffusion Weighted Imaging Acquisition

Images were acquired on a 1.5-tesla Siemens MR imaging unit (echo planar imaging, field of view 256 × 208 mm, matrix 128 × 10^4, slice thickness 2 mm, in-plane resolution 2 × 2 mm, TR 15 seconds, TE 106.2 msec). The diffusion weighting was isotropically distributed along 60 directions, using a b-value of 1000 seconds/mm^2. For each set of diffusion weighted imaging data, five volumes with no diffusion weighting were acquired at points throughout the acquisition. For each volunteer, three sets of diffusion weighted data were acquired for subsequent averaging to improve the signal to noise ratio. The total imaging time for the diffusion weighted imaging protocol was approximately 30 to 45 minutes.

High-resolution T1-weighted structural images were also obtained with a 3D fast low-angle shot sequence (TR 12 msec, TE 5.6 msec, flip angle 19°, with elliptical sampling of k-space, giving a voxel size of 2 × 2 × 2 mm in 5.05 minutes).

Probabilistic Tractography

The Diffusion Toolbox from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl/) was used to process the acquired MR images. Non–brain tissue was extracted using the Brain Extraction Tool.[52] The Diffusion Toolbox tractography (using ProbTrack Probabilistic tracking) was run from single seed voxels (measuring 2 × 2 × 2 mm, which represent the most definite point of pedunculopontine nucleus as defined earlier by Olszewski and Baxter[40]) by using 5000 samples per seed voxel. Registration of a single seed voxel in the PPN region is shown in Fig. 1. The resulting brain image was then linearly transformed onto the Montreal Neurological Institute standard and structural brain template of 152 averaged brains by using FMRIB's Linear Registration Tool.[23] The connectivity maps for each PPN were placed at a threshold to include those voxels through which at least 5% (that is, 250/5000) of samples passed. The connection targets of the PPN were determined using a human brain MR imaging atlas.[11] The number of volunteers in whom a particular connection was observed was recorded. The connectivity maps placed at a threshold were translated into binary code and summed across volunteers. The resulting connectivity maps for eight volunteers (16 PPNs) were placed at a threshold to include only those voxels for which a connection was present in at least 50% of volunteers for illustration.

Results

Connections Below the PPN

Two main connections were found below the PPN region. In 75% of the patients studied, connections between the PPN and cerebellum via the superior cerebellar peduncle were shown (Fig. 2A). Also, in all patients PPN connections with the spinal cord were noted. These are consistent with several other reports in which neuroanatomical techniques have been used,[16,18,19,46,53] which thus support the validity of this tractography technique.

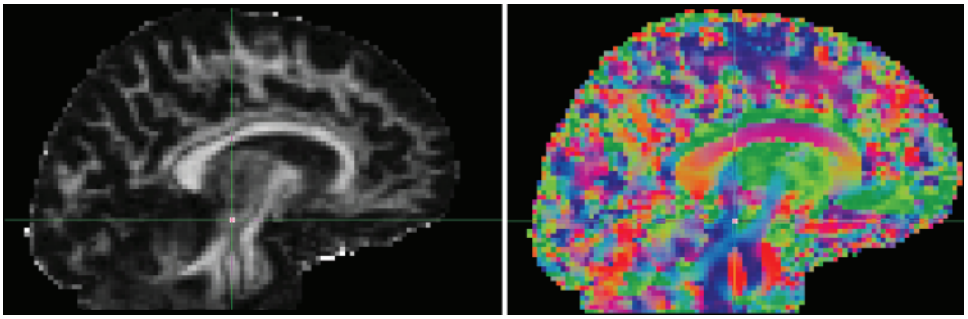

FIG. 1. Registration of a single seed voxel on a fractional anisotropy map *(left)* and on a red-green-blue image representing the principal diffusion direction (*red* indicates the x axis; *green*, the y axis; and *blue*, the z axis *[right]*) in the PPN region viewed in sagittal section. The seed location is indicated by the *white pixel* at the *cross-hairs*. The superior cerebellar peduncle is visible as a region of high fractional anisotropy *(bright areas, left)*, with diffusion predominantly in the y, z direction *(blue and green areas, right)*, located just inferior and posterior to the seed point. The images show that the placement of the seed voxel is not within the superior cerebellar peduncle. Therefore, it is likely that tracked fibers originate within the PPN itself, and that the contribution of nearby crossing or collateral fibers to the cerebellum is minimal.

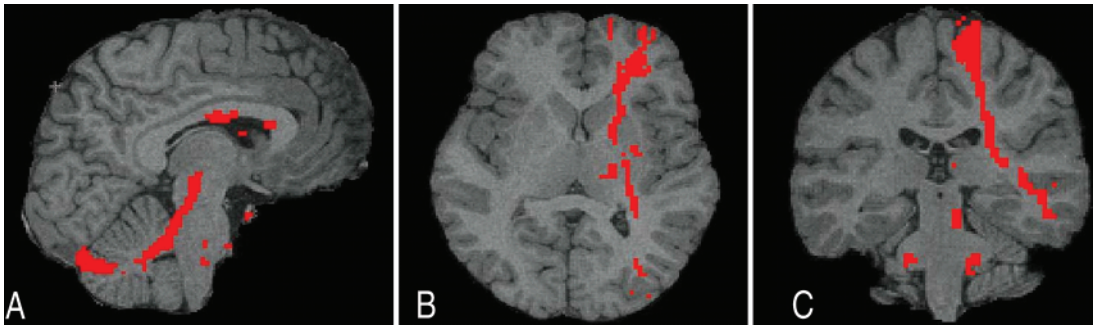

FIG. 2. Ascending tracts from the PPN region. Example tracts from seeding a voxel in the PPN region in a single healthy volunteer are shown registered on T1-weighted structural MR images. The tracts *(red areas)* were found to innervate the cerebellum target via the superior cerebellum peduncle (A), the basal ganglia structures (thalamic nucleus, pallidum, and STN) and the prefrontal cortex (B), and the primary motor cortex (trunk, upper/lower extremity, and orofacial region, C). The connectivity to the motor cortex region was observed passing through the posterior limb of the internal capsule.

Connections Above the PPN

The PPN connections to basal ganglia, thalamus, and cortex were more variable among the volunteers. The basal ganglia were most strongly connected with the PPN region; 87.5% of the patients showed connections between the PPN and the thalamus, pallidum, and STN (Fig. 2B).

The connections between the primary motor cortex and PPN region were more variable. The upper extremity representation connected with the PPN in 87.5% of patients, the lower extremity region in 62.5%, the trunk region in 56.25%, and the orofacial region in only 12.5% of patients. The premotor cortex and frontal lobe connected with the PPN in 62.5% of the patients. All these connections passed via the posterior limb of the internal capsule (Fig. 2C).

The connections averaged across all eight volunteers (16 PPNs) are shown in Table 1. The connectivity of the PPN region across the eight volunteers is shown in Fig. 3. The 3D rendered images of common connectivity of the PPN region across the eight volunteers are shown in Fig. 4.

Discussion

The findings from our study demonstrate that diffusion tractography can be used successfully to characterize the

TABLE 1

*Results of tracts studied in eight volunteers (16 PPNs)**

Case No. & Laterality	Motor Cortex Region				Premotor Cortex	Frontal Cortex	Thalamus	Pallidum	STN	Cerebellum	Spinal Cord
	UE	Trunk	LE	Orofacial							
1											
rt					+		+	+	+	+	+
lt	+	+	+		+	+		+			+
2											
rt	+	+	+		+	+	+	+	+	+	+
lt	+	+	+		+	+		+	+		+
3											
rt	+		+			+	+	+	+	+	+
lt	+	+	+				+	+	+	+	+
4											
rt	+	+	+				+		+	+	+
lt						+	+				+
5											
rt	+		+		+	+	+	+	+	+	+
lt	+		+		+	+	+	+	+	+	+
6											
rt	+					+	+	+	+		+
lt	+	+		+	+	+	+	+	+	+	+
7											
rt	+	+			+		+	+	+	+	+
lt	+				+		+	+	+	+	+
8											
rt	+	+	+		+	+	+	+	+	+	+
lt	+	+	+	+			+	+	+	+	+
total	14	9	10	2	10	10	14	14	14	12	16
mean (%)	87.5	56.25	62.5	12.5	62.5	62.5	87.5	87.5	87.5	75.0	100

* LE = lower extremity; UE = upper extremity; + = tracts present.

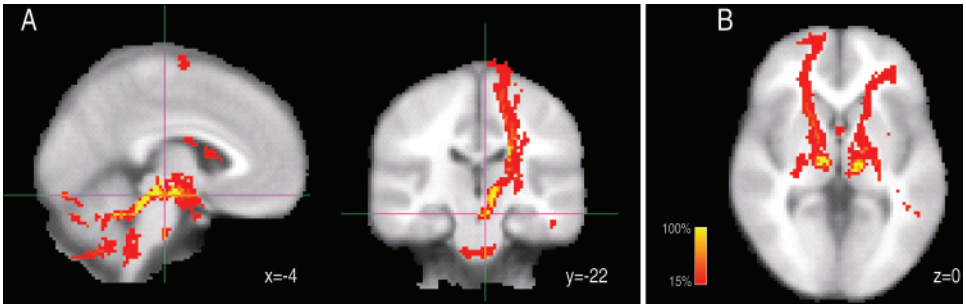

FIG. 3. Connectivity of the PPN region across a group of eight volunteers. Probabilistic tractography was performed from a single seed of the PPN region. The resulting connectivity distributions from each volunteer were registered into standard space, and an average was generated, which is shown here in standard space based on the Montreal Neurological Institute brain. *Yellow areas* represent connectivity common to all the volunteers and *red areas* represent connectivity common to 15% of the volunteers. These tracts were reproducibly found to course through both descending tracts and ascending tracts. A: Sagittal and coronal images showing connectivity of right side seed in the PPN region. Note the connectivity to cerebellum and motor cortex. Similar tracts were found on the left side. B: Connectivity for both right and left seeds in the PPN with an axial slice. Note the strong connectivity to basal ganglia and frontal areas including the orbitofrontal cortex. The x, y, and z values represent the distance in millimeters from 0.

connectivity of the PPN region in humans. This technique is an effective noninvasive method for examining anatomical connections of clinically important structures in the human nervous system. Although the results from our investigation of diffusion weighted imaging in humans in general agree with those of previous studies based on tracer studies in nonhuman primates, it is nevertheless important to demonstrate directly the existence of homologous pathways in the human brain.

One important connection below the PPN region is from the cerebellum, which passes via the superior cerebellar peduncle (Fig. 1 *left*). The cerebellar deep nuclei are known to send efferent collateral axons to the PPN region on their way to the thalamus in monkeys.[18] Thus DT imaging confirms the existence of this pathway in humans that supports the function of the cerebellum helping to control of movement, coordination, and posture.[47,48,55]

A second important connection of the PPN region is with the spinal cord. This connection has been extensively reported in rodents[16,46] and cats.[19] The PPN region probably functions as a relay station between the cerebral cortex and the spinal cord, acting as a brainstem control center for interlimb coordination in locomotion and bimanual motor behavior.[32]

The PPN was also found to connect with the GP, thalamus, and STN, confirming in humans the results of numerous studies previously conducted in animals.[7,8,15,17,21,41] In nonhuman primates, the pallidum provides the major input to the PPN,[50] whereas the STN is the major output target of the PPN.[31] The ventrolateral thalamus also receives efferent fibers from deep nuclei of cerebellum both directly and via the PPN.[18] However, in rodents most of the inputs to the PPN are from the SN pars reticulata.

It was interesting to see that the primary motor cortex has extensive connections with the PPN region in humans. Authors of several reports have described a similar but smaller connection in nonprimates.[10,30,36] In rodents cortical projections are seen from premotor and supplementary motor areas to the PPN.[41] In primates Matsumura et al.[32] showed projections from the macaque motor cortical areas to PPN, namely from motor cortex, the supplementary and presup-

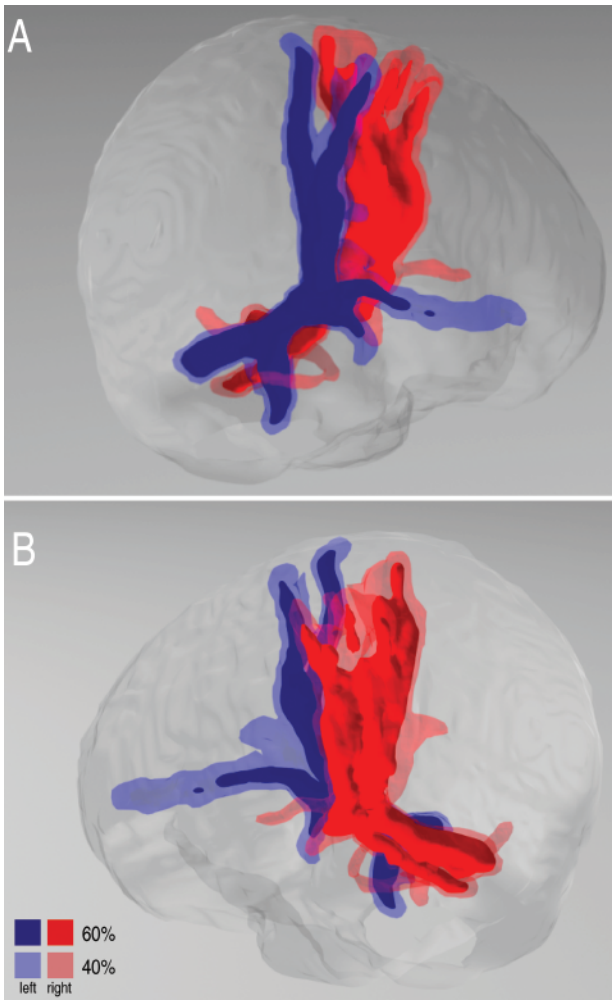

FIG. 4. Three-dimensional rendered images of common connectivity of the PPN region across a group of eight volunteers. The *red* represents the probabilistic tracts from the seed in the right PPN and the *blue* the tracts from the seed in the left PPN. The *darker areas* represent connectivity common to 60% of the volunteers and the *lighter areas* represent connectivity common to 40% of the volunteers.

TABLE 2

*Summary of PPN connectivity in previous studies in which authors used neural tracing methods**

Authors & Year	Study Group	Neural Tracing Methods	Connectivity Tracts to PPN														
			MC	TL	GP	STN	C & P	SN	CB	SC	EN	PFN	PRF	SI	HT	NB & A	NA
Jackson & Crossman, 1983	rat	HRP	+		+	+		+		+	+	+	+				
Swanson et al., 1984	rat	fluorescent tracer (SITS & True Blue) & PHA-L								+				+	+		
Hallanger & Wainer, 1988	rat	WGA/HRP & PHA-L													+	+	
Spann & Grofova, 1989	rat	HRP, HRP/WGA & fluorescent tracer								+							
Chivileva & Gorbachevskaya, 2005	dog	HRP					+										+
Gorbachevskaya & Chivileva, 2006	dog	HRP			+†						+						
Kim et al., 1976	monkey	tritiated amino acids (L-leucine, L-proline, L-lysine)			+‡												
Carpenter et al., 1981	monkey	HRP injections			+‡	+		+									
DeVito & Anderson, 1982	monkey	radioactive amino acids			+‡												
Parent & De Bellefeuille, 1982	monkey	fluorescent tracers (EB & DP)		+	+‡												
Hazrati & Parent, 1992	monkey	anterograde tracer (biocytin)		+					+								
Lavoie & Parent, 1994	monkey	anterograde tracing method (leucine & PHA-L)		+	+‡	+		+									
Shink et al., 1997	monkey	anterograde tracing method (BDA)			+‡												
Matsumura et al., 2000	monkey	BDA & HRP/WGA	+														
present study	humans	DT imaging	+	+	+	+			+	+							

* CB = cerebellum; C & P = caudate & putamen; DP = 4′6-diamidino-2-phenylindole–primuline; EB = Evans blue; EN = entopeduncular nucleus; HRP/WGA = wheat germ agglutinin–conjugated HRP; HT = hypothalamus; MC = motor cortex; NA = nucleus accumbens; NB & A = nucleus basalis and amygdala; PFN = parafascicular nucleus; PHA-L = phaseolus vulgaris–leukoagglutinin; PRF = pontine reticular formation; SC = spinal cord; SI = substantia innominata; SITS = 4-acetamido-4′-isothiocyanatostilbene-2,2′-disulfonic acid; TL = thalamus.

† Both GPI and GP external.

‡ The GPI only.

plementary motor areas, and from the dorsal and ventral divisions of the premotor cortex. They used anterograde axonal tracing by injecting BDA and wheat germ agglutinin–conjugated HRP into the motor cortical areas. In these monkeys, bundles of anterogradely labeled fibers were seen to descend ipsilaterally through the internal capsule and then in the cerebral peduncle at the levels of the forebrain and midbrain. At the pontine level, some of these fibers left the cerebral peduncle to terminate in the PPN. In humans these descending connections seem to be even more prominent, and they were seen in all our volunteers with the aid of tractography (Fig. 3). There is no reason to suppose, based on studies conducted in animals, that the PPN projects reciprocally back to either the motor cortex or to the striatum; but unfortunately DT imaging tractography cannot show the direction of any of the connections identified. A summary of previous studies in which neural tracing methods have been used are shown in Table 2. Thus the current study provides anatomical evidence that the human PPN receives direct cortical inputs from multiple motor-related areas in the frontal lobe. As elsewhere these connections are likely to be excitatory, but their size in humans suggests that they are particularly important for activating the PPN.

It has been well documented that the PPN has strong links with basal ganglia and it receives inhibitory, GABAergic inputs primarily from the GPI and substantia nigrata pars reticulata.[10,12,26,42,43,50] On the other hand, the PPN sends excitatory outputs predominantly to the SN pars compacta, STN, and the intralaminar thalamic nuclei.[12,31]

There are several methodological issues that need to be addressed in the interpretation of diffusion tractography results. First, it is not possible to differentiate afferent from efferent pathways in diffusion data. Second, tractography picks up mainly large-fiber pathways; smaller pathways, or those through regions of fiber crossing or interrupted by synapses may not be detected with the methods used here. This may, for example, explain the relatively low detection of fiber to the orofacial region of motor cortex. Fibers going to the lateral portion of the motor strip are difficult to track as they have to cross longitudinally oriented pathways. Third, the brainstem contains a high level of susceptibility artifacts that can interfere with tract tracing. We acquired our diffusion data using a 1.5-tesla system, as in many previous brainstem studies.[56] Last, because the anatomy of the brainstem is complex, the PPN cannot be directly visualized on structural images. Its location must be deduced by reference to identifiable adjacent structures, such as the superior cerebellar peduncle and its decussation. By placing just a single seed voxel in this region, we increase our confidence in identifying the PPN exclusively, but we cannot entirely rule out the possibility that pathways to and from nearby structures could influence our PPN tractography due to partial volume effects. Future studies using higher resolution diffusion data should help to confirm the specificity of our results.

Conclusions

From the results of our study we were able to establish that the PPN region has connections with frontal motor cortical areas and subcortical motor control loops involving thalamus, basal ganglia, cerebellum, and spinal cord. Diffusion tensor imaging tractrography of the PPN region can be used as preoperative tool to localize the electrode place-

ment site, and it may also be useful as a postoperative tool to reassess electrode positions.

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