**Pedunculopontine nucleus region deep brain stimulation in Parkinson disease: surgical anatomy and terminology**

Clement Hamani, Tipu Aziz, Bastiaan R. Bloem, Peter Brown, Stephan Chabardes, Terry Coyne, Kelly Foote, Edgar Garcia-Rill, Etienne Hirsch, Andres M. Lozano, Paolo A. M. Mazzone, Elena Moro, Michael S. Okun, William Hutchison, Peter Silburn, Ludvic Zrinzo, Mesbah Alam, Laurent Goetz, Erlick Pereira, Anand Rughani, Wesley Thevathasan, Joachim K. Krauss

Clement Hamani, Anand Rughani, William Hutchison and Andres M. Lozano

Division of Neurosurgery, Toronto Western Hospital, University of Toronto, Toronto, Canada

Tipu Aziz and Erlick Pereira

Department of Neurosurgery, University of Oxford, John Radcliffe Hospital, Oxford, UK

Bastiaan R. Bloem

Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands

Peter Brown

Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Oxford, UK

Stéphan Chabardès and Laurent Goetz

Grenoble Institute of Neurosciences-INSERM U836 CEA-UJF-CHU, Grenoble, France

University Joseph Fourier, Grenoble, France

Department of Neurosurgery-CHU, Grenoble, France

Kelly Foote

Department of Neurosurgery, University of Florida, Gainesville, USA

Edgar Garcia-Rill

Department of Anatomy and Neurobiology, University of Arkansas for Medical Sciences, Little Rock, USA

Etienne C. Hirsch

Inserm, U 1127, F-75013, Paris, France

CNRS, UMR 7225, F-75013, Paris, France

Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127, F-75013, Paris, France

Institut du Cerveau et de la Moelle épinière, ICM, F-75013, Paris, France

Paolo A. M. Mazzone

OU for Stereotactic and Functional Neurosurgery

ASLRMC – CTO Hospital, Roma, Italia

Michael S. Okun

University of Florida Center for Movement Disorders, Departments of Neurology and Neurosurgery, Gainesville, USA

Peter Silburn and Terry Coyne

Centre for Clinical Research, University of Queensland, Brisbane, Australia

Ludvic Zrinzo

Department of Neurosurgery, Queens Square, London, UK

Elena Moro

University Joseph Fourier, Grenoble, France

Department of Neurology-CHU, Grenoble, France

Mesbah Alam and Joachim K. Krauss

Department of Neurosurgery, Medical School Hannover, Hannover, Germany

Wesley Thevathasan

Melbourne Brain Centre, Department of Medicine, University of Melbourne, Melbourne, Australia

Gait disorders, which are frequently progressive, are a major source of disability in patients with movement disorders. The anatomical basis and pathophysiology is poorly understood and there is a need to draw more attention to this area.

The possible relevance of the pedunculopontine nucleus (PPN) region for movement disorders has been outlined by independent groups of investigators who have demonstrated that there are degenerative changes in patients with advanced akinetic disorders such as Parkinson’s disease (PD), progressive supranuclear palsy (PSP) and multiple systems atrophy (MSA)1-3. Recent data indicates that cholinergic denervation due to degeneration of PPN neurons may underlie dopamine-nonresponsive gait and balance impairment in PD 4, 5.

Several lines of evidence over the last few years have been important in ascertaining that the PPN area could be considered as a potential target for deep brain stimulation (DBS) to treat freezing and other problems as part of a spectrum of gait disorders in Parkinson’s disease(PD). In a metabolic study, Mitchell et al. showed increased 2-deoxyglucose uptake reflecting increased synaptic activity in the PPN region of a primate rendered parkinsonian after (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (MPTP) injections6. The PPN receives GABAergic projections from the medial pallidum7, 8, and therefore it has been assumed that PPN activity was reduced in the parkinsonian brain 7, 9. Yet, this concept has been challenged by the known pathophysiology that the subthalamic nucleus (STN), which is excitarory and hyperactive in PD also projects to the PPN. This later pathway might account for the hyperactivity of PPN neurons projecting to STN in rats with unilateral lesion of the substantia nigra10. In normal primates, high frequency stimulation, radiofrequency and excitotoxic PPN lesions induced akinesia11-15. In MPTP-treated parkinsonian primates, however, low frequency stimulation (25Hz) and microinjections of bicuculline, a GABA antagonist, into the PPN reversed akinesia15-18. Recording of the midlatency auditory evoked P50 potential in PD patients concluded that the PPN was overactive in PD, and that bilateral pallidotomy normalized PPN output 19, 20.

Since the introduction of the PPN area as a target for DBS in PD, a variety of studies have been published. Most indicate improvements in freezing and falls in patients that are severy affected by these problems. The results across patients, however, have been variable, perhaps reflecting patient selection, heterogeneity in target selection and differences in surgical methodology. Here we provide a thorough review of several issues relevant to targeting and surgical technique. The aim of this manuscript is to gain more insight into the reasoning for choosing specific techniques and to discuss shortcomings of vailable studies. Finally, this set of data is intended to form a foundation for developing a core protocol to be used in PPN DBS surgery.

**Materials and Methods**

A working group was encharged of reviewing data relevant to PPN surgery. Questions were formulated during a consensus conference and were 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 outline both the accumulated knowledge and the domains of uncertainty in surgical anatomy and terminology. Issues relevant for surgical technique, side effects and postoperative imaging will be addressed in a companion manuscript.

**Results**

**Anatomy and function of the PPN area**

The PPN, sub-cuneiform and cuneiform nuclei (CnF) comprise the mesencephalic locomotor region (MLR)21-23. This is a functional region from which electrical stimulation induces coordinated locomotion in decerebrate mammals21, 22.

The PPN projects and receives projections from the STN, globus pallidus internus (GPi), and substantia nigra reticulata (SNr) and compacta (SNc) 24-26. Further, it has afferent and efferent connections with the cerebellum, thalamus, cerebral cortex, and the spinal cord7, 21. The PPN is also connected to catecholaminergic systems in the brainstem, such as the noradrenergic locus coeruleus21, 27 and to serotonergic neurons of the dorsal raphe nucleus28-30.

On the basis of its cytoarchitectural organization, the PPN has been subdivided into a pars dissipata (pdPPN) and a pars compacta (pcPPN) (Fig. 1). Triple in situ hybridization studies determined that the profile of PPN neurons varies across its extent 31. The pdPPN is located throughout the rostrocaudal extent of the PPN region and contains mainly small to medium sized GABAergic neurons. The pcPPN is located in the caudal half of the nucleus and contains mostly cholinergic and glutamatergic cells7, 9, 21, 32, 33. In addition cholinergic neurons of the PPN are also known as the Ch5 cholinergic cell group according to the classification of Mesulam 34. Similar to the PPN, the sub-cuneiform and cuneiform nuclei do not contain homogenous neuronal populations. Neurons of the CnF are mainly comprised of nitrinergic and GABAergic cells. These nuclei have no clear boundaries. This has led to some confusion concerning the overlap of functionally or anatomically defined regions in this area.

Experimental studies have shown that the PPN receives dopaminergic input from the substantia nigra compacta (SNc) and ventral tegmental area (VTA) 28, 35, 36. Such inputs are modulated by NMDA, AMPA and GABAB receptors.

The PPN output controls the striatal loop, i.e., STN, GPi, and SNc. Other projections reach the intralaminar nuclei of the thalamus and nuclei of the lower brainstem. As such, the PPN occupies a strategic position between the limbic and striatal loops and while it is mainly involved in locomotor activity7, 9, 21, 32, 37-40, and it is also potentially relevant in other domains including cognition and sleep. Together with the thalamic intralaminar nuclei, the PPN is part of the “ascending reticular activating system” 7, 21, 41.

Both PPN and CnF have been suggested to influence muscle tone during the initiation of locomotion 42, 43. Rodent studies have shown that MLR injections of the GABAA agonist muscimol completely abolish stepping. Because muscimol solely acts on neuronal cell bodies and not on passing axons, these results suggest that cells around the injection site (i.e. CnF and PPN) may be responsible for MLR-induced stepping 39. A recent rodent study has shown that stimulation of the MLR markedly improves hind limb function in rats with incomplete spinal cord injury 44.

**Considerations about the terminology used in PPN anatomy**

Since the description of the PPN by Jacobsohn in 1909 45, the terminology used to label this nucleus has varied continuosly. For instance, it has been labelled as “Nucleus tegmenti pedunculopontinus” 45, “Pedunculo-pontine tegmental nucleus” 46, “Nucleus reticularis pedunculopontinus” 47, “Nucleus pedunculopontinus” 48, “Nucleus tegmenti pedunculopontinus” 49, 50, “the Area U” 50-52, “the n’ nucleus ” 53, and “the PPTn of Kolliker” 49(the latter must be distinguished from the Kolliker-Fuse nucleus which now refers to a subnucleus of the parabrachialis nucleus). Since there are so many differences in nomenclature, the terminology used across studies has not been consistent.

**Anatomical localization of the PPN on brainstem atlases**

There is variabilitiy concerning the exact anatomical localization of the PPN across different brainstem atlases, in particular with regard to its borders 46, 47, 49, 50, 54. It is commonly accepted, that the PPN is bordered medially by the superior cerebellar peduncle (and its decussation) as well as the central tegmental tract (Fig. 2). Anterior and lateral to the PPN is the lemniscal system, and caudal and rostral are the retrorubral field and SNr, respectively. The posterior aspect of the PPN is contiguous with the lateral portion of the CnF.

Considering the cytoarchitectural characteristics of the pontomesencephalic reticular formation, the precise anatomical distinction between pontine and mesencephalic structures has always been open to debate. As a result, to define the rostro-caudal extent of the PPN some investigators have relied on the pontomesencephalic junction (PMJ), a line that connects the inferior aspect of the quadrigeminal plate (frenulum veli) posteriorly with the *foramen caecum* of the interpeduncular fossa anteriorly.

Reviewing different brainstem atlases with a focus on the PMJ as well as on the orientation of the slices in the transverse plane may provide a landmark for the rostro-caudal extent of the PPN in the human brainstem.

***Cytoarchitecture of the Human Brain Stem: Olszewski and Baxter.*** This atlas of brainstem structures provides an accurate description of the PPN and its subregions 49. Caveats from a surgical perspective include that it is not based on stereotactic coordinates and that the transverse angle of sections is not exactly parallel to the PMJ. Two sub-divisions of the PPN are distinguished: the pars dissipata and pars compacta. The PMJ slice is in plate n◦ XXVIII (cross section n◦ 801) with no reference made to the PPN or the CnF. The next plate consists of a section 3 mm or 150 slices rostral (plate n◦ XXX; cross section n◦ 651) that crosses the brainstem at the mid-portion of the inferior colliculus (IC) (Fig. 3). In this section, the PPN pars dissipata and CnF are clearly delineated. Of interest, plate n◦ XXXI (cross section n◦ 601), located 1 mm (50 slices) rostral to plate n◦ XXX and 4 mm rostral from the PMJ, contains the PPN pars compacta and dissipata, which is in contact with the CnF posteriorly. In this atlas, the PPN extends for 8 mm in the rostrocaudal axis, reaching the level of the caudal border of the red nucleus (plate n◦ XXXIV - Cross section n◦ 401). The CnF and its subnuclei are represented as a large structure that extends from the PMJ (or just above it) to the level of the red nucleus.

***Atlas of the Human Brainstem:* *Paxinos and Huang.*** Plates in this brainstem atlas are numbered based on distance from the obex 46. The PMJ is represented in Figures 48 (Obex +31 mm) and 49 (Obex +32 mm), which contain the nucleus of the trochlear nerve, fibers of the trochlear nerve, their decussation, and the frenulum veli, just caudal to the infra-collicular recess. The caudal aspect of the PPN pars dissipata is shown in Figure 48 (Obex +31 mm). The pars compacta is shown in Figure 50 (Obex +33mm), which also shows the pars dissipata at the level of IC. According to the atlas, pars compacta extends 4 mm rostrally but does not extend beyond the level of IC. The PPN extends to the rostral pole of IC (Obex +36mm). Just above the PMJ, the CnF is located posterior to the PPN and extends to the caudal aspect of the superior colliculus. We note that in recent work, the authors have considerably changed this nomenclature 55.

***Atlas for Stereotaxy of the Human Brain: Schaltenbrand and Wahren.*** In this atlas, the PPN is labelled as the Nucleus tegmenti pedunculopontinus (Tg.pdpo) 50. It is represented in coronal slices perpendicular to the anterior-posterior commissural (AC-PC) plane at the level of the superior aspect of the superior cerebellar peduncle (plate 29). Axial slices of the rostral brainstem are presented in plate 57. The PPN *per se* is not labelled in those plates. Nevertheless, it may be included in the diffuse area labelled as griseum circumflexum brachii conjunctivi (Gr.cf.b.cj), which extends from the caudal mesencephalon to a region 5 mm below the PMJ.

***Duvernoy’s Atlas of the Human Brain Stem and Cerebellum: Naidich et al.*** This book consists of a multimodal atlas of the brainstem based on magnetic resonance imaging 47. The PPN and CnF are described in several axial slices (P 84-89 ; P 329-330). Assumptions on the rostrocaudal extent of the PPN are difficult to conclude since the sections are not parallel to the PMJ.

The fact that most atlases rely on cytoarchitectural features may underestimate the extent of the PPN, which is in general a diffuse nucleus with indistinct borders. Using choline-acetyltransferase (ChAT) immunohistochemistry, for example, Mesulam and colleagues studied the extent of PPN cholinergic cells 56. They indicated that the caudal aspect of the PPN extends far below the level of the inferior colliculus, whereas PPNc could be observed as rostral as the decussation of the superior cerebellar peduncle. These findings were confirmed in a later study which provided more detail about the cholinergic cell group Ch5 within the PPN 1.

Two post mortem human studies found that sagittal sections were the most reliable for identifying the PPN in three dimensions. Labelling of cholinergic neurons showed that the pars compacta was located immediately dorsal to the brachium conjunctivum, with cells of the pars dissipata scattered within the brachium conjunctivum. The pars compacta was localized anterior/ventral to the posterior half of the IC, while the pars dissipata extended posteriorly and anteriorly below PPNc 57, 58.

**Discussion**

In conclusion, the anatomy and the function of the PPN area will require further clarification. The extent of both PPN and the CnF does not exactly coincide when different brainstem atlases and atlas slices are compared. It is difficult to provide a precise delineation between the PPN pars dissipata and the CnF, as these two structures partially overlap in the MRF.

The lack of consensus in the field is an important overall limitation to PPN anatomy, particularly for PPN DBS surgery. This lack of clarity contibutes to the difficulty in targeting and determining the exact localization of the electrodes implanted in human subjects suffering from neurodegenerative disorders.

**Legends to Figures**

**FIG. 1.** The PPN region at the level of the decussation of the superior cerebellar peduncles and the inferior colliculus (**A**) and at the level of the trochlear nucleus and the intercollicular area (**B**). The main nuclei are labeled on the left and the long fiber tracts on the right side. STT, spinothalamic tract; CA, cerebral aqueduct; CN, cuneiform nucleus; CTT, central tegmental tract; Dec SCP, decussation of the superior cerebellar peduncles; LC, locus coeruleus; LL, lateral lemniscus; ML, medial lemniscus; MLF, medial longitudinal fasciculus; NRD, nucleus raphé dorsalis; PAG, periaqueductal gray; PN, pontine nuclei; PPNc, pedunculopontine nucleus pars compacta; PPNd, pedunculopontine nucleus pars dissipata; SNc, substantia nigra pars compacta; RST, rubrospinal tract; IV, trochlear nucleus; V, mesencephalic nucleus of the trigeminal nerve.

Adapted from Fournier-Gosselin et al.33 with permission from John Wiley and Sons.

**FIG. 2.** Functional mapping of PPN region: correlations between the structures in the vicinity of the PPN and their potential stimulation effects. An electrode positioned lateral to the PPN might be revealed by buzzing sounds (lateral lemniscus), unpleasant painful sensation and/or change in temperature sensation (spinothalamic tract), or paresthesias (medial lemniscus) when trial stimulation is applied. An anteromedial position could elicit the sensation of contralateral facial pulling or blinking (rubrobulbar tract) and/or mood changes (substantia nigra). A mediodorsal location could lead to oscillopsia, diplopia, or ocular deviation toward the side stimulated (medial longitudinal fascicle and trochlear nucleus) mandating careful inspection of extraocular movements. An electrode positioned dorsally could lead to a sensation of discomfort (PAG), mandating that the stimulation be done with caution in the vicinity of the PPN. A dorsally placed electrode could also be noticed by jaw movements subjectively felt as pulling of masticatory muscles (mesencephalic nucleus of the trigeminal nerve). Nonspecific altered level of alertness (locus coeruleus) might also be observed. PPN, pedunculopontine nucleus; Dec SCP, decussation of the superior cerebellar peduncles; SNc, substantia nigra pars compacta.

Adapted from Fournier-Gosselin et al.33, with permission from John Wiley and Sons.

**FIG. 3.** Plates XXX and XXXI of Cytoarchitecture of the human brain stem published by J. Olszewski and D.Baxter. The PPN pars dissipata is labelled as Tg. ds and PPN pars compacta is labelled as Tg. cm. CNf is labelled as Cun (a) Plate XXX: representation of the cross section 651. The plate contains the most caudal aspect of the PPN observable in the atlas. The posterior aspect of the brainstem is clearly located in the mesencephalon due to the presence of the inferior colliculus. According to the distances between cross-sections, the posterior aspect is located 3mm rostral the PMJ (Plate XXVIII in cross section 801). (b): photomicrograph of cross section 601 located 1 mm rostral to the plate XXX. The plate contains the PPN pars compacta. (a) and (b).

Reprinted from Olszewski and Baxter 49, with permission from Karger.

**References**

1. Manaye KF, Zweig R, Wu D, et al. Quantification of cholinergic and select non-cholinergic mesopontine neuronal populations in the human brain. Neuroscience 1999;89(3):759-770.

2. Zweig RM, Jankel WR, Hedreen JC, Mayeux R, Price DL. The pedunculopontine nucleus in Parkinson's disease. Ann Neurol 1989;26(1):41-46.

3. Zweig RM, Whitehouse PJ, Casanova MF, Walker LC, Jankel WR, Price DL. Loss of pedunculopontine neurons in progressive supranuclear palsy. Ann Neurol 1987;22(1):18-25.

4. Grabli D, Karachi C, Folgoas E, et al. Gait disorders in parkinsonian monkeys with pedunculopontine nucleus lesions: a tale of two systems. J Neurosci 2013;33(29):11986-11993.

5. Karachi C, Grabli D, Bernard FA, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest 2010;120(8):2745-2754.

6. Mitchell IJ, Cross AJ, Sambrook MA, Crossman AR. Neural mechanisms mediating 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine-induced parkinsonism in the monkey: relative contributions of the striatopallidal and striatonigral pathways as suggested by 2-deoxyglucose uptake. Neurosci Lett 1986;63(1):61-65.

7. Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain 2000;123 ( Pt 9):1767-1783.

8. Shink E, Sidibe M, Smith Y. Efferent connections of the internal globus pallidus in the squirrel monkey: II. Topography and synaptic organization of pallidal efferents to the pedunculopontine nucleus. J Comp Neurol 1997;382(3):348-363.

9. Hamani C, Stone S, Laxton A, Lozano AM. The pedunculopontine nucleus and movement disorders: anatomy and the role for deep brain stimulation. Parkinsonism Relat Disord 2007;13 Suppl 3:S276-280.

10. Orieux G, Francois C, Feger J, et al. Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the subthalamic nucleus in a rat model of Parkinson's disease. Neuroscience 2000;97(1):79-88.

11. Kojima J, Yamaji Y, Matsumura M, et al. Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. Neurosci Lett 1997;226(2):111-114.

12. Aziz TZ, Davies L, Stein J, France S. The role of descending basal ganglia connections to the brain stem in parkinsonian akinesia. Br J Neurosurg 1998;12(3):245-249.

13. Munro-Davies L, Winter J, Aziz TZ, Stein J. Kainate acid lesions of the pedunculopontine region in the normal behaving primate. Mov Disord 2001;16(1):150-151.

14. Nandi D, Liu X, Winter JL, Aziz TZ, Stein JF. Deep brain stimulation of the pedunculopontine region in the normal non-human primate. J Clin Neurosci 2002;9(2):170-174.

15. Jenkinson N, Nandi D, Muthusamy K, et al. Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus. Mov Disord 2009;24(3):319-328.

16. Jenkinson N, Nandi D, Miall RC, Stein JF, Aziz TZ. Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. Neuroreport 2004;15(17):2621-2624.

17. Nandi D, Aziz TZ, Giladi N, Winter J, Stein JF. Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. Brain 2002;125(Pt 11):2418-2430.

18. Nandi D, Jenkinson N, Stein J, Aziz T. The pedunculopontine nucleus in Parkinson's disease: primate studies. Br J Neurosurg 2008;22 Suppl 1:S4-8.

19. Teo C, Rasco L, Skinner RD, Garcia-Rill E. Disinhibition of the sleep state-dependent p1 potential in Parkinson's disease-improvement after pallidotomy. Sleep Res Online 1998;1(1):62-70.

20. Teo C, Rasco L, al-Mefty K, Skinner RD, Boop FA, Garcia-Rill E. Decreased habituation of midlatency auditory evoked responses in Parkinson's disease. Mov Disord 1997;12(5):655-664.

21. Garcia-Rill E. The pedunculopontine nucleus. Prog Neurobiol 1991;36(5):363-389.

22. Garcia-Rill E, Houser CR, Skinner RD, Smith W, Woodward DJ. Locomotion-inducing sites in the vicinity of the pedunculopontine nucleus. Brain Res Bull 1987;18(6):731-738.

23. Garcia-Rill E, Simon C, Smith K, Kezunovic N, Hyde J. The pedunculopontine tegmental nucleus: from basic neuroscience to neurosurgical applications: arousal from slices to humans: implications for DBS. J Neural Transm 2011;118(10):1397-1407.

24. Edley SM, Graybiel AM. The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. J Comp Neurol 1983;217(2):187-215.

25. Lavoie B, Parent A. Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. J Comp Neurol 1994;344(2):210-231.

26. Aravamuthan BR, McNab JA, Miller KL, et al. Cortical and subcortical connections within the pedunculopontine nucleus of the primate Macaca mulatta determined using probabilistic diffusion tractography. J Clin Neurosci 2009;16(3):413-420.

27. Reese NB, Garcia-Rill E, Skinner RD. The pedunculopontine nucleus--auditory input, arousal and pathophysiology. Prog Neurobiol 1995;47(2):105-133.

28. Steininger TL, Rye DB, Wainer BH. Afferent projections to the cholinergic pedunculopontine tegmental nucleus and adjacent midbrain extrapyramidal area in the albino rat. I. Retrograde tracing studies. J Comp Neurol 1992;321(4):515-543.

29. Honda T, Semba K. Serotonergic synaptic input to cholinergic neurons in the rat mesopontine tegmentum. Brain Res 1994;647(2):299-306.

30. Kayama Y, Koyama Y. Control of sleep and wakefulness by brainstem monoaminergic and cholinergic neurons. Acta Neurochir Suppl 2003;87:3-6.

31. Wang HL, Morales M. Pedunculopontine and laterodorsal tegmental nuclei contain distinct populations of cholinergic, glutamatergic and GABAergic neurons in the rat. Eur J Neurosci 2009;29(2):340-358.

32. Inglis WL, Winn P. The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. Prog Neurobiol 1995;47(1):1-29.

33. Fournier-Gosselin MP, Lipsman N, Saint-Cyr JA, Hamani C, Lozano AM. Regional anatomy of the pedunculopontine nucleus: relevance for deep brain stimulation. Mov Disord 2013;28(10):1330-1336.

34. Mesulam MM, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). Neuroscience 1983;10(4):1185-1201.

35. Ichinohe N, Teng B, Kitai ST. Morphological study of the tegmental pedunculopontine nucleus, substantia nigra and subthalamic nucleus, and their interconnections in rat organotypic culture. Anat Embryol (Berl) 2000;201(6):435-453.

36. Semba K, Fibiger HC. Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. J Comp Neurol 1992;323(3):387-410.

37. Inglis WL, Olmstead MC, Robbins TW. Pedunculopontine tegmental nucleus lesions impair stimulus--reward learning in autoshaping and conditioned reinforcement paradigms. Behav Neurosci 2000;114(2):285-294.

38. Winn P, Brown VJ, Inglis WL. On the relationships between the striatum and the pedunculopontine tegmental nucleus. Crit Rev Neurobiol 1997;11(4):241-261.

39. Garcia-Rill E, Skinner RD, Fitzgerald JA. Chemical activation of the mesencephalic locomotor region. Brain Res 1985;330(1):43-54.

40. Mena-Segovia J, Bolam JP, Magill PJ. Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? Trends Neurosci 2004;27(10):585-588.

41. Rye DB. Contributions of the pedunculopontine region to normal and altered REM sleep. Sleep 1997;20(9):757-788.

42. Alam M, Schwabe K, Krauss JK. The pedunculopontine nucleus area: critical evaluation of interspecies differences relevant for its use as a target for deep brain stimulation. Brain 2011;134(Pt 1):11-23.

43. Mori S. Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. Prog Neurobiol 1987;28(2):161-195.

44. Bachmann LC, Matis A, Lindau NT, Felder P, Gullo M, Schwab ME. Deep brain stimulation of the midbrain locomotor region improves paretic hindlimb function after spinal cord injury in rats. Sci Transl Med 2013;5(208):208ra146.

45. Jacobsohn LU. Über die Kerne des menschlichen Hirnstamms: (Medulla oblongata, Pons, und Pedunculus cerebri). Preuss, Akad d. Wiss, 1909.

46. Paxinos G, Huang XF. Atlas of the human brainstem. San Diego: Academic Press, 1995.

47. Naidich TP, Duvernoy HM, Delman BM, Sorensen AG, Kollias SS, Haacke EM. Duvernoy's Atlas of the Human Brain Stem and Cerebellum. Wien, New York: Springer, 2007.

48. Nieuwenhuys R, Voogd J, van Huijzen C. The Human Central Nervous System: A Synopsis and Atlas. 4th ed. Berlin, Heidelberg, New York: Springer, 2007.

49. Olszewski J, Baxter D. Cytoarchitecture of the human brain stem. Basel, New York: Karger, 1982.

50. Schaltenbrand G, Wahren W. Atlas for stereotaxy of the human brain. : Year Book Medical Publishers, Incorporated, 1978.

51. Riley HA. An Atlas of the Basal Ganglia, Brain Stem and Spinal Cord. . Baltimore: Williams & Wilkins, 1943.

52. Ziehen GT. Makroskopische und mikroskopische Anatomie des Gehirn.1903.

53. Kolliker A. Handbuch der Gewebclchre des Menschcn1896.

54. Afshar F, Watkins ES, Yap JC. Stereotaxic atlas of the human brainstem and cerebellar nuclei. New York: Raven Press, 1978.

55. Paxinos G, Huang X, Sengul G, Watson C. Organization of brainstem nuclei. The Human Nervous System. Amsterdam: Elsevier Academic Press, 2012:260-327.

56. Mesulam MM, Geula C, Bothwell MA, Hersh LB. Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons. J Comp Neurol 1989;283(4):611-633.

57. Karson CN, Garcia-Rill E, Biedermann J, Mrak RE, Husain MM, Skinner RD. The brain stem reticular formation in schizophrenia. Psychiatry Res 1991;40(1):31-48.

58. Garcia-Rill E, Biedermann JA, Chambers T, Skinner RD, Mrak RE, Husain M, Karson CN. Mesopontine neurons in schizophrenia. Neuroscience 1995;66(2):321-335.