Anatomy, Physiology, and Pathophysiology of the Pedunculopontine Nucleus

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ABSTRACT

The pedunculopontine nucleus is composed of cholinergic and non-cholinergic neurones and is located in the caudal pontomesencephalic tegmentum. Evidence suggests that the nucleus plays a role in the production and control of movement. The nucleus has dense interconnections with the basal ganglia, as well as with other areas of the brain associated with motor control. Electrical stimulation of the pedunculopontine nucleus in the decerebrate cat or rat produces organized locomotor movements. Physiological studies show that the pedunculopontine nucleus modulates its activity in response to locomotion, as well as voluntary arm and eye movements. Degeneration of the pedunculopontine nucleus is seen in post-mortem brains in humans with Parkin- son's disease and Parkinsonian syndromes. In animal

models of Parkinson's disease, metabolic changes are seen in the pedunculopontine nucleus, and chemical inhibition or mechanical disruption of the nucleus can produce an akinetic state in animals and man. In this paper we review the literature in support of the suggestion that some of the symptoms of Parkinson's disease are caused by dysfunction of the pedunculopontine nucleus. In accordance with this view, direct stimulation of the nucleus can ameliorate some symp- toms of the disease, as demonstrated in both experimental animals and man.

Keywords: PPN; pedunculopontine; Parkinson's disease; anatomy; physiology

INTRODUCTION

Interest in the pedunculopontine nucleus (PPN) has increased in recent years. A simple search for the term ''pedunculopontine'' in Pubmed produces no articles in 1977, 12 in 1987 and 38 in 2007, and 25 already this year as this article goes to press. Much of the interest over the last decade has been generated by the increasing awareness that the PPN might be involved in the genesis of some motor disorders, in particular Parkinson's dis- ease. This is not to say that the PPN is not involved in other functions. It has long been known that the PPN plays a role in the regulation of cortical activity, and the sleep-wake cycle. There is also increasing evidence that the PPN is involved in attention, reward and learning. These aspects of PPN function are beyond the scope of this review, and readers who wish to learn more of them as well as the PPNs role in motor function should look to one of the excellent reviews already published1–7. Our review will concentrate on the anatomy and physiology of the PPN that implicate it in motor control and the experimental evidence that suggests that dysfunction of the PPN is at least, in part, responsible for the symptoms of some movement disorders.

PEDUNCULOPONTINE NUCLEUS ANATOMY

The pedunculopontine nucleus (PPN) is formed by an ensemble of cholinergic and noncholinergic neurones located in the caudal pontomesencephalic tegmentum. Its rostral end begins just below the red nucleus, dorsal to the substantia nigra, continuing caudally to the level of the locus coeruleus. The PPN is bounded medially by the fibres of the brachium conjunctivum, lateral and ventrally by the medial lemniscus and dorsally by the nucleus cuneiformis and subcuneiformis.

Classically, in the human, the PPN has been split into two parts: the pars compacta (PPNc) and the pars dissipatus (PPNd). Olszewski and Baxter[8] defined these two subdivisions under the light microscope due to the size and density of the neurones that they contain. The PPNc is only seen in the caudal half of the nucleus and is made up of large neurones. These neurones are densely arranged in the dorsolateral portion of the nucleus. The PPNd is present throughout the rostro-caudal axis of the nucleus and is made up of small and medium sized cells seen among the fibres of the brachium conjunctivum and tractus tegmentalis centralis. These distinctions are also seen in other primates[9,10] though such obvious boundaries seem to become more difficult to see in lower species, which have been used for the majority of studies on the nucleus (Fig. 1).

The PPN is largely made up of cholinergic neurones, though the proportions differ between the two subnuclei. Mesulam states that 80 to 90% of neurones in the human PPNc stain positively for choline acetyltransferase (ChAT). The PPNd shows a more varied cholinergic population where 25 to 75% of the neurones can be CHaT positive depending on their position within the subnucleus.11These figures have been disputed, with more recent studies finding the percentages of cholinergic neurones in PPNc and PPNd to be 58% and 16 to 25%, respectively[12]. These authors

admit, however, that the discrepancy in these estimates may be due to the ill-defined boundaries of the PPN.

Though the majority of cells in the PPN express acetylcholine, many cells exist within the PPN that utilize other neurotransmitters. These include the excitatory neurotransmitter glutamate,[13,14] the inhibitory amino acid GABA[15] and dopamine[16]. To complicate matters further, subpopulations of the cholinergic neurones are found to express other neurochemical markers as well as those for ACh. Cholinergic neurones have been seen to co-express the transmitters glutamate,[17] GABA,[18] signalling molecules such as nitric oxide,[19] as well as neuropeptides such as Substance P[20]. Unfortunately, an underlying pattern to this lavish expression of neuro-chemicals has yet to be discerned.

CONNECTIONS

Since Jacobsohn first described the PPN in 1909,[117] it remained an obscure collection of cells in the mesencephalon. Even in their classic 1954 cytoarchitectonic description of the human brainstem Olszewski and Baxter[8] classified the nucleus as having "unknown connections." However, the discovery that the PPN receives a large converging input from the basal ganglia brought it to the attention of anatomists[21]. Up to this point no direct descending pathway to the lower motor nuclei from the basal ganglia had been demonstrated, despite their obvious involvement in motor control. This was surprising as it had been known for some time that the basal ganglia's influence on movement remained even after the destruction of the cortex[22]; it was generally accepted, therefore, that the basal ganglia could exert their control via lower motor centers. Following early degeneration experiments by Wilson[23] in 1914 it was thought for many years that this control was exercised via a direct pathway from the medial pallidum (GPm) to the red nucleus. Later this pathway was

discounted as insignificant[24,25]. But the discovery of connections between the basal ganglia and PPN provided a plausible substrate for this hitherto theoretical connection.

As well as receiving projections from the basal ganglia, the PPN has ascending and descending, afferent and efferent connections to almost all other parts of the central nervous system. Ascending projections out- weigh the descending ones. Ascending connections are in the main part concentrated on the basal ganglia and the nonspecific nuclei of the thalamus. Descending fibres are directed to the spinal cord and the medullary and pontine reticular formations. The PPN also has connections with the contralateral PPN.

Nauta and Mehler made small lesions in the structures comprising the lentiform nucleus of monkeys and found that following lesions of the GPm there was dense degeneration in the PPN[21]. The findings were quickly replicated in the monkey[26,27] as well as the rat and cat using anatomical tracing[28–30] as well as electrophysiological stimulation and recording methods[31,32]. Though the pathway is observed in all the species mentioned, there are differences in the size and distribution of the innervation. In the monkey, between 87 and 94% of cells in the GPm are activated antidromically by stimulation of the PPN[33,34] In the cat, similar studies have yielded inconclusive results with between 8 and 76% of the neurones activated[31,33–35] Efferent fibres from the GPm in the monkey terminate in the PPN in a much more constricted pattern than those in the sub-primate PPN, probably reflecting the more diffuse composition of the PPN in the lower species[36–39]. The PPN in turn returns projections to the GP[40]. There is also a small ipsilateral projection from the PPN to the striatum, with an even smaller contra- lateral component. These terminals are spread through- out the caudate nucleus and putamen[41,42].

Another basal ganglia nucleus with which the PPN has strong connections is the substantia nigra (SN). This is seen in the human43and monkey,[26] as well as the rat [41,44,45] and cat[46]. Glutaminergic and cholinergic cells project from the PPN mainly to the compacta division of the SN (SNc)[11,47–49]. The cholinergic projection has a strong influence on the dopaminergic cells in the SNc, where the terminals are seen to make multiple contacts on the dendritic arbors of dopaminergic cells[18,43,50]. The anatomy suggests that the PPN has a strong modulatory effect on the dopaminergic cells of the midbrain[51,52]. In turn, the substantia nigra pars reticularis sends GABAergic projections to the PPN[53].

The PPN also projects to the subthalamic nucleus (STN) in the various species studied[26,38,54–57]. In the monkey, the afferent fibres are distributed uniformly throughout the STN and the axons do not make close contact with single STN neurones, but seem to make enpassant contact with several cells in the nucleus[42]. PPN fibres innervating the STN are cholinergic, glutamatergic, and GABAergic[58].The STN sends a smaller reciprocal projection to the PPN, which has been shown to be glutaminergic in the rat[57,59–62]. Thus, the PPNs major targets in the basal ganglia are the SN and STN, with a relatively smaller projection to the pallidum. In all cases there is a profuse ipsilateral innervation of these nuclei with a much smaller contralateral element

Apart from the aforementioned reciprocal connections with the basal ganglia, the other major ascending pathway originating in PPN is to the thalamus. The ascending reticular activating system[63] influences the cortex via cholinergic input to the thalamus. The most important and largest of these thalamopetal cholinergic inputs originates in the cholinergic cells of the PPN[64,65]. The projection is mainly to the nonspecific nuclei of the thalamus and has a role in producing the fast cortical-oscillatory activity associated with arousal and REM sleep[66]. The PPN also receives direct cortical afferents, with fibres

arising in the primary, supplementary, presupplementary, dorsal and ventral premotor cortex, as well as frontal eye fields. There is a much smaller unilateral projection from the ipsilateral PPN to the same areas of cortex originating from large cells of the PPN[30,67,68].

As well as sending ascending axons to the basal ganglia and above, the PPN has descending connections, though ascending fibres outnumber the descending ones around five times[69]. The PPN has cholinergic connections with mesencephalic and medullary reticular formation. These connections are again thought to play a pivotal role in the control of arousal and the sleep-wake cycle and many are collaterals of axons ascending to the thalamus[70,71]. The PPN also sends connections directly to the spinal cord. Though the descending projections of the PPN in the monkey have yet to be explored, in the rat, anatomical tracer injections have shown that the PPN projects to the sacral, cervical spine, and the lumbar enlargements, while receiving inputs from the cervical, thoracic and lumbar dorsal horns. The origins of these projections are areas of the PPN that also receive direct afferents from the basal ganglia. The PPN also projects indirectly to the spinal cord via the medulla[69,72–74] and receives input from the red nucleus[75]. In addition to providing a gateway to lower motor neurons, the PPN may also be a unique point of interaction for the two principal motor systems of the brain, namely the cerebellum and basal ganglia. The PPN receives an impressive input from the deep cerebellar nuclei, suggesting the intriguing idea that the PPN is an area where the basal ganglia and the cerebellum can interact[75–77]. Many of the major connections above have been confirmed in the human brain using diffusion tractography78,79(Fig. 2).

Given its impressive array of reciprocal connections with basal ganglia nuclei, motor cortices and its descending influence on spinal cord motor neurons, it is obvious why the PPN is of interest to motor neuro- scientists. Wilson[23] had originally

proposed that the red nucleus was the gateway from the basal ganglia to lower motor centres; it seems he may have only been wrong by a few millimetres.

PPN PHYSIOLOGY

Membrane Properties Intracellular recordings in slice preparations have identified at least three types of cells according to their intrinsic electrical membrane properties,[80] though some authors only describe two types[81]. Type I cells exhibit low-threshold spikes, which give rise to bursting patterns of action potentials following long duration depolarizing currents. The neurones also fire bursts of spikes after the offset of a hyperpolarizing current[80]. Type II cells display a transient outward current (A-current). Type II cells do not inherently fire in bursts. Type III cells possess both low threshold calcium currents as well as a transient outward current. These properties are seen in cells that express ChAT as well as those that do not, suggesting that the cholinergic and noncholinergic populations of cells in the PPN share similar electrical membrane properties[82].

Single Unit

In cats and rats, two types of neurone have been identified in vivo by their firing properties[83,84]. One type exhibits low but regular spontaneous activity in a wide tri-phasic waveform. The second type displays a shorter bi-phasic waveform, and fires in a highly spontaneous irregular pattern. Experiments from Garcia-Rill's laboratory have laid foundation to our understanding of the role of the PPN in locomotion. They demonstrated that stimulation of areas in and around the PPN elicits organized locomotor programs. Single pulses of stimulation of the PPN do

not induce locomotion. Rather, stepping is recruited by high frequency (20—60 Hz) stimulation given in long trains of several seconds before movement is induced. Current is slowly increased during stimulation, which first induces in- creased muscle tone bilaterally before movement is initiated. If the amplitude of the current is not increased gradually the stimulation will cause a prominent startle reflex in the animal, which can be followed by stepping or turning movements. Because of its role in locomotion the PPN has been included as a part of the mesencephalic locomotor region (MLR). The MLR is an area of the mesencephalon from which it is possible to elicit locomotor activity in the de-corticate cat or rat. The absolute anatomical location of the MLR remains unclear, but it does include areas outside the PPN.

Cells within the PPN itself modulate their firing during locomotion. Single cell recordings in the decerebrate cat by Garcia-Rill et al. revealed three distinct populations of cell activity in response to locomotion[72,85–87]. Some cells increase their tonic firing rate for as long as locomotion takes place; others decrease their firing rate over the same period. These cells were described as “on” and “off” cells, respectively. Other cells respond to the locomotor cycle by firing in phase with it, these cells were called “bursters.”[86]. The cells behave in this manner regardless of changes to peripheral input i.e., restraint of the limbs, or application of local anaesthetic to the joints. The authors suggest that the “on” and “off” cells might be regarded as modulating the duration of a given stepping period, whereas the ”burster” cells were involved in controlling the frequency of stepping,1though their exact function remains unclear. Injection of L-dopa into neonate rats causes the pups to make stepping motions that are very similar to spontaneous locomotion. C-Fos immunoreactivity in such animals is seen to be elevated in the PPN indicating an increase in activity in the nucleus associated with the locomotive behavior[88].

More recent *in vivo* studies have been conducted in trained animals. In cats trained to make a lever-release movement, two kinds of firing activity were detected intermingled within the PPN[83]. Neurones with brief spikes were seen to fire very early before the onset of movement. It is assumed by the authors - with supporting indirect evidence - that these neurones are non-cholinergic and project to the STN. The other population of cells fire at a slow rate and have a broad spike profile. These cells are in the majority in the dorsal PPN and are thought to be cholinergic. The cells fire later than the other population, at a time when the animal was expecting a reward or when the behavioural reinforcement was delivered, in this case a food pellet.

In experiments where monkeys were trained in a similar task two comparable populations of cells were observed: one of tonically firing low frequency cells with a wide waveform, and another of high frequency low phasically active cells with a short spike duration. In contrast to the findings in cats, there was no evidence that the former population was in the majority in the dorsal PPN of monkeys. Here, neurones responded to voluntary movements of either the contralateral or ipsilateral arm. The response started before the movement (less than 200 ms) and lasted throughout the movement, and could be either an increase or a decrease in firing rate. A change in firing rate was seen in almost half the cells encountered, usually an increase[89]. It is not only movement of the limbs that modulates activity in the PPN. Changes in firing rates were also seen during voluntary saccades, with some cells phasically increasing or decreasing their firing rate just before the initiation of the saccade and others increasing their firing rate tonically during fixation[90,91]. Other cells were seen to increase their firing rate around the time of the reward presented for the execution of a correct saccade.

A very recent study where microelectrode recordings were made in the human corroborates many of the qualities of the neuronal responses in the PPN described earlier. Analysis of the spike shape and duration revealed three types of neurone. Two types could be discriminated by their firing pattern: as in the animal studies one fires at a high rate with a long duration spike and one fires at a lower rate with a short spike duration. The study also described cells in the human that are seen in experimental animals that fire in a "burster" like fashion. PPN neurones were found that modulated their firing rates with active or passive movement of the contralateral arm[92]. The small number of ipsilateral arm movements that were tested were not associated with changes in firing rate in the PPN, though further testing will be required to confirm this observation (Weinberger, personal communication). Although the results reflect a cell population that is very similar to that found in the animal literature, we should bear in mind that the patients in the study either had Parkinson's disease or progressive supranuclear palsy and probably do not represent the normal physio- logical state. A recent paper from Peter Brown's group demonstrates this. They recorded local-field potentials in the PPN of patients undergoing surgery for deep brain stimulation (DBS) of the PPN. They found that when the patients were on L-dopa medication there was an increase in 7 to 11 Hz synchronized oscillatory activity in the PPN. The activity was coupled with cortical EEG in the same patients. The results suggest that there is altered activity in the PPN of patients with Parkinson's disease[93].

Taken as a whole, the anatomical connections and physiological properties of the PPN suggest that the nucleus is in a position to influence the control of movement. The PPN has direct control of the muscles via direct and indirect connections to the spinal cord, and also has massive influence on the basal ganglia via the large reciprocal connections it has with many of its nuclei. Such influence however may come at a price. Evidence suggests

that dysfunction of the PPN, caused either directly by damage to the nucleus or by aberrant input is the cause of some of the most debilitating symptoms of Parkinson's disease and related disorders.

PATHOPHYSIOLOLOGY

Postmortem Studies

The PPN degenerates in humans with Parkinson's disease and parkinsonian syndromes. Staining histological sections for cholinergic cells, Hirsch et al. found that there was a marked decrease in the amount of stained neuropil in the PPN in the brains of patients with Parkinson's disease who came to postmortem[94]. The loss of staining was accompanied by a loss of cholinergic neurones specifically in the PPN, with no loss of other cholinergic cell populations in the mesencephalon. The loss of cells is even greater in the Parkinsonian syndrome, progressive supranuclear palsy[94–96]. In idiopathic Parkinson's disease, there is a relationship between the amount of cell loss that has taken place in the PPN and the severity of Parkinsonian symptoms,[97,98] the relationship has been shown to be correlated specifically to the loss of cholinergic cells[98]. Furthermore, a patient with hydrocarbon-induced Parkinsonism that resembled an "akinetic form of Parkinson's disease" showed a degeneration of the PPN that was more complete than that typically seen in idiopathic Parkinson's disease[99]. Similarly, severe akinetic symptoms have been seen in humans after small infarcts in the mesencephalon that destroy the PPN[100]. The post-mortem evidence that damage to the PPN is observational, but these reports are consistent with our suspicion that the akinetic symptoms of Parkinson's disease may be especially related to the integrity of the PPN (see animal studies below).

Animal Models

As discussed earlier, it has been suggested that some of the symptoms of Parkinson's disease are at least in part due to the loss of function that follows degeneration of the PPN. To examine this possibility several investigators have altered the normal function of the PPN in experimental animals. Injection of the excitotoxin kainic acid into the PPN unilaterally in a monkey produces marked motor symptoms, notably hypokinesia and rigidity on the contralateral side that were similar to those seen in Parkinson's disease[101] with the effects abating over 1 to 2 weeks. The level of motor dysfunction and the amount of time taken for the symptoms to subside were proportional to the size of injection of the excitotoxin. Histology of the animals revealed a marked reduction in cholinergic cells in the lesioned side compared to the non-lesioned side. Unilateral radio frequency lesions of the PPN in the monkey also pro- duced a hypokinesia in monkeys that resembled Par- kinson's disease. Again animals with unilateral thermal lesions recovered over a period of around a week. If an animal with a unilateral lesion were subjected to a second lesion on the contralateral side the animal dis- played a similar profound paucity and slowness of movement, this time without recovery. Similar motor deficits with no recovery were found if an animal received simultaneous bilateral PPN lesions[102]. These results were also seen when using excitotoxic lesions instead of thermal lesions[103].

Intriguingly lesions of the PPN in the rat produce less clear-cut results. The old literature places the PPN in the mesencephalic motor region, and lesions here produced motor deficits. However, recent studies elegantly demonstrate that careful excitotoxic lesions of the whole PPN, produce effects relating to attention, reward and learning but without changes in motor behavior[104,105]. A new study from Winn's laboratory has shed fresh light on this paradox. Lesions of dorsal PPN had no effect on spontaneous locomotion, whereas lesions in the

anterior PPN substantially decreased spontaneous locomotion. Exactly how a partial lesion of the PPN produces an effect on locomotion where a full lesion does not is unclear. But the authors stress the possibility of a dissociation of function between the anterior and posterior PPN[106].

As well as direct damage to the PPN, changes in other parts of the diseased brain may influence PPN function. In Parkinson's disease, the GPm is overactive. The GPm provides the major input to the PPN, which is GABAergic and therefore inhibitory (see above). In a unilateral MPTP primate model of Parkinson's disease, regional patterns of 2-DG uptake indicate an increase in synaptic activity in the PPN[107]. Metabolic markers of neuronal activity are also down regulated in the PPN in the MPTP primate, alongside a decrease in ACh and Substance P synthesis[108]. However, it is unclear how the increased inhibitory input affects the firing rate of neurones in the PPN. Some reports in the 6-hydroxy dopamine model of Parkinson's disease in the rat describe a decrease in firing, whereas others see an increase[109]. It may be that the overactive (excitatory) pathway from the STN plays a part in modulating at least some of the neurones of the PPN. Regardless, inhibiting the PPN by direct injection of the GABA agonist muscimol in a normal monkey significantly decreases the motor activity of the animal. In the same animal made severely Parkinsonian with MPTP, injection of the GABA antagonist bicuculine into the PPN, which blocks the influence of the descending inhibition from the GPm, alleviated the Parkinsonian symptoms. The amount of recovery due to injection of bicuculine was equivalent to that of L-dopa therapy[110]. High frequency stimulation and lesioning the GPm alleviate the symptoms of Parkinson's in both the human and the monkey, it may be that this is in part due to the removal of the pathological input to the PPN from the GPm. The behavioural changes that are brought about by manipulating the PPN with GABA agonists and antagonists or altering the input from the GPm suggest that inhibition of

the PPN is of significant functional consequence and is responsible for some of the symptoms of Parkinson's disease. Electrical stimulation of the PPN can also alleviate the symptoms of Parkinson's disease. We implanted a miniature DBS electrode into a monkey, and produced stimulation by an implanted pulse generator, which was programmed through the skin by a radio frequency programmer. We found that the results were frequency dependent. High frequency stimulation caused akinesia, whereas low frequency stimulation increased motor activity.111In the Parkinsonian (MPTP) monkey, low frequency stimulation (<10 Hz) of the PPN was again pro-kinetic and successfully ameliorated the Parkinsonian symptoms.111In this study stimulation of the PPN at low frequency was as efficient as oral L-dopa in relieving the motor deficits, though this amount of symptomatic relief has not been translated to clinical practice. When stimulation was used in combination with L-dopa therapy the effect was even greater, returning the animal to motor activity levels equal to those seen before the animal was made Parkinsonian[112]. It is conceivable that this additive effect reflects in some way the pathological processes underlying the different motor symptoms of Parkinson's dis- ease. The effects of L-dopa treatment may be independent, and upstream from the PPN, whereas stimulating the PPN might be affecting other more direct pathways that induce movement, and may even produce these effects at least in part via a non-dopaminergic pathway.

Given the evidence above it is not surprising that direct manipulation of the PPN has been suggested as an intervention for Parkinson's disease[7,103,110,113]. Following the demonstration that Parkinsonian symptoms can be reduced by stimulation of the PPN with DBS in the MPTP model of Parkinson's disease in the primate[111,112] several functional neurosurgical centres worldwide have successfully targeted the PPN with DBS in humans with persuasive results[114–116]. However, the potential benefits are

restricted by our limited understanding of the PPN. Further basic neuroscientific investigations of the PPN and its relationship with the basal ganglia will help deep brain stimulation of the PPN evolve, and translate into clinical benefit.

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REFERENCES

1. Garcia-Rill E. The pedunculopontine nucleus. Prog Neurobiol 1991;36:363–389.

2. Winn P. How best to consider the structure and function of the pedunculopontine tegmental nucleus: evidence from animal studies. J Neurol Sci 2006;248(1–2):234–250.

3. Winn P, Brown VJ, Inglis WL. On the relationships between the striatum and the pedunculopontine tegmental nucleus. Crit Rev Neurobiol 1997;11:241–261.

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

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

6. Mena-Segovia J, Ross HM, Magill PJ, Bolam JP. The pedunculopontine nucleus: towards a functional integration with the basal ganglia. Springer: 2005.

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

8. Olszewski J, Baxter D. Cytoarchitecture of the human brain stem, 1st ed. Philadelphia: Lippencott; 1954.

9. Geula C, Schatz CR, Mesulam MM. Differential localization of nadph-diaphorase and calbindin-d(28k) within the cholinergic neurons of the basal forebrain, striatum and brain-stem in the rat, monkey, baboon and human. Neuroscience 1993;54:461– 476.

10. Noback CR. Brain of a gorilla. II. Brain stem nuclei. J Comp Neurol 1959;111:345–385.

11. 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: 611–633.

12. Manaye K, Zweig R, Wu D, et al. Quantification of cholinergic and select non-cholinergic mesopontine neuronal populations in the human brain. Neuroscience 1999;89:759–770.

13. Clements JR, Grant S. Glutamate-like immunoreactivity in neurons of the laterodorsal tegmental and pedunculopontine nuclei in the rat. Neurosci Lett 1990;120:70–73.

14. Lavoie B, Parent A. Pedunculopontine nucleus in the squirrel monkey: distribution of cholinergic and monoaminergic neurons in the mesopontine tegmentum with evidence for the presence of glutamate in cholinergic neurons. J Comp Neurol 1994;344: 190–209.

15. Ford B, Holmes CJ, Mainville L, Jones BE. GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. J Comp Neurol 1995;363:177– 196.

16. Rye DB, Saper CB, Lee HJ, Wainer BH. Pedunculopontine tegmental nucleus of the rat: cytoarchitecture, cytochemistry, and some extrapyramidal connections of the mesopontine tegmentum. J Comp Neurol 1987;259:483—528.

17. Bevan MD, Bolam JP. Cholinergic, gabaergic, and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. J Neurosci 1995;15:7105—7120.

18. Charara A, Smith Y, Parent A. Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: Phaseolus vulgaris-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry. J Comp Neurol 1996;364:254—266.

19. Vincent SR, Satoh K, Armstrong DM, Panula P, Vale W, Fibiger HC. Neuropeptides and NADPH-diaphorase activity in the ascending cholinergic reticular system of the rat. Neuroscience 1986;17:167—182.

20. Vincent SR, Satoh K, Armstrong DM, Fibiger HC. Substance P in the ascending cholinergic reticular system. Nature 1983;306: 688—691.

21. Nauta WJ, Mehler WR. Projections of the lentiform nucleus in the monkey. Brain Res 1966;1:3—42.

22. Forman D, Ward J. Responses to electrical stimulation of caudate nucleus in cats in chronic experiments. J Neurophysiol 1957;20:230—244.

23. Wilson SAK. An experimental research into the anatomy and physiology of the corpus striatum. Brain 1914;36:427—492.

24. Ranson SW, Ranson M. The Pallidofugal fibres in the monkey. AMA Arch Neuro Psychiatr 1939;42:1059—1067.

25. Verhaart WJC. A comparison between the corpus striatum and the red nucleus as subcortical centra of the cerebral motor system. Psychiatry neurol 1938;32:676.

26. Carpenter MB, Carleton SC, Keller JT, Conte P. Connections of the subthalamic nucleus in the monkey. Brain Res 1981;224:1—29.

27. Kim R, Nakano K, Jayaraman A, Carpenter MB. Projections of globus pallidus and adjacent structures—autoradiographic study in monkey. J Comp Neurol 1976;169:263—290.

28. Nauta HJ. Projections of the pallidal complex: an autoradiographic study in the cat. Neuroscience 1979;4:1853—1873.

29. Carter DA, Fibiger HC. The projections of the entopeduncular nucleus and globus pallidus in rat as demonstrated by autoradiography and horseradish peroxidase histochemistry. J Comp Neurol 1978;177:113—123.

30. Moonedley S, Graybiel AM. Connections of the nucleus tegmenti pedunculopontinis, pars compacta (tpc) in cat. Anat Rec 1980;196:a129—a129.

31. Filion M, Harnois C. A comparison of projections of entopeduncular neurons to the thalamus, the midbrain and the habenula in the cat. J Comp Neurol 1978;181:763—780.

32. Larsen M, Bjarkam CR, Ostergaard K, West MJ, Sorensen JC. The anatomy of the porcine subthalamic nucleus evaluated with immunohistochemistry and design-based stereology. Anat Embryol 2004;208:239—247.

33. Harnois C, Filion M. Pallidal neurons branching to the thalamus and to the midbrain in the monkey. Brain Res 1980;186:222— 225.

34. Harnois C, Filion M. Pallidofugal projections to thalamus and midbrain: a quantitative antidromic activation study in monkeys and cats. Experimental brain research 1982;47:277—285.

35. Larsen KD, Sutin J. Output organization of the feline entopeduncular and subthalamic nuclei. Brain Res 1978;157:21—31.

36. 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;382:348—363.

37. Larsen KD, McBride RL. The organization of feline entopenduncular nucleus projections: anatomical studies. J Comp Neurol 1979;184:293—308.

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

39. Parent A, De Bellefeuille L. Organization of efferent projections from the internal segment of globus pallidus in primate as revealed by fluorescence retrograde labeling method. Brain Res 1982;245:201—213.

40. DeVito JL, Anderson ME, Walsh KE. A horseradish peroxidase study of afferent connections of the globus pallidus in Macaca mulatta. Exp Brain Res 1980;38:65—73. 41. Saper CB, Loewy AD. Projections of the pedunculopontine tegmental nucleus in the rat: evidence for additional extrapyramidal circuitry. Brain Res 1982;252:367—372.

42. 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;344:210—231.

43. Mesulam MM, Mash D, Hersh L, Bothwell M, Geula C. Cholinergic innervation of the human striatum, globus pallidus, subthalamic nucleus, substantia nigra, and red nucleus. J Comp Neurol 1992;323:252—268.

44. Beckstead RM, Domesick VB, Nauta WJ. Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Res 1979;175:191—217.

45. Jackson A, Crossman AR. Nucleus tegmenti pedunculopontinus: efferent connections with special reference to the basal ganglia, studied in the rat by anterograde and retrograde transport of horseradish peroxidase. Neuroscience 1983;10:725—765.

46. Nomura S, Mizuno N, Sugimoto T. Direct projections from the pedunculopontine tegmental nucleus to the subthalamic nucleus in the cat. Brain Res 1980;196:223—227.

47. Mesulam MM, Mufson EJ, Levey AI, Wainer BH. Atlas of cholinergic neurons in the forebrain and upper brainstem of the macaque based on monoclonal choline acetyltransferase immunohistochemistry and acetylcholinesterase histochemistry. Neuroscience 1984;12:669—686

48. Spann BM, Grofova I. Cholinergic and non-cholinergic neurons in the rat pedunculopontine tegmental nucleus. Anat Embryol 1992;186:215—227.

49. Lavoie B, Parent A. Pedunculopontine nucleus in the squirrel monkey: cholinergic and glutamatergic projections to the substantia nigra. J Comp Neurol 1994;344:232—241.

50. Bolam JP, Francis CM, Henderson Z. Cholinergic input to dopaminergic neurons in the substantia nigra: a double immunocytochemical study. Neuroscience 1991;41(2—3):483—494.

51. Maskos U. The cholinergic mesopontine tegmentum is a relatively neglected nicotinic master modulator of the dopaminergic system: relevance to drugs of abuse and pathology. British jour- nal of pharmacology 2008;153(Suppl 1):S438—S445.

52. Mena-Segovia J, Winn P, Bolam JP. Cholinergic modulation of midbrain dopaminergic systems. Brain Res Rev 2008; Epub ahead of print.

53. Childs JA, Gale K. Neurochemical evidence for a nigrotegmental GABAergic projection. Brain Res 1983:258;109—114.

54. Graybiel AM. Direct and indirect preoculomotor pathways of brain-stem—autoradiographic study of pontine reticular-formation in cat. J Comp Neurol 1977;175:37—78.

55. Nauta HJ, Cole M. Efferent projections of the subthalamic nucleus: an autoradiographic study in monkey and cat. J Comp Neurol 1978;180:1—16.

56. Hammond C, Rouzaire-Dubois B, Feger J, Jackson A, Crossman AR. Anatomical and electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus tegmenti pedunculopontinus in the rat. Neuroscience 1983;9:41—52.

57. Jackson A, Crossman AR. Subthalamic projection to nucleus tegmenti pedunculopontinus in the rat. Neurosci Lett 1981;22: 17—22.

58. Bevan MD, Francis CM, Bolam JP. The glutamate-enriched cortical and thalamic input to neurons in the subthalamic nucleus of the rat: convergence with GABA-positive terminals. J Comp Neurol 1995;361:491—511.

59. Kita H, Kitai ST. Efferent projections of the subthalamic nu-in the rat: light and electron microscopic analysis with the PHA-L method. J Comp Neurol 1987;260:435—452.

60. Moriizumi T, Nakamura Y, Tokuno H, Kitao Y, Kudo M. Topographic projections from the basal ganglia to the nucleus tegmenti pedunculopontinus pars compacta of the cat with special reference to pallidal projection. Experimental brain research 1988;71(2):298—306.

61. Granata AR, Kitai ST. Intracellular analysis of excitatory subthalamic inputs to the pedunculopontine neurons. Brain Res 1989;488(1—2):57—72.

62. Smith Y, Hazrati LN, Parent A. Efferent projections of the subthalamic nucleus in the squirrel monkey as studied by the PHA-L anterograde tracing method. J Comp Neurol 1990;294:306—323.

63. Morruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949;1:455—473.

64. Pare D, Smith Y, Parent A, Steriade M. Projections of brain-stem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. Neuroscience 1988; 25:69—86.

65. Steriade M, Pare D, Parent A, Smith Y. Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque mon- key. Neuroscience 1988;25:47—67.

66. Steriade M. Acetylcholine systems and rhythmic activities during the waking—sleep cycle. Prog Brain Res 2004;145:179—196.

67. Kuypers HG, Lawrence DG. Cortical projections to the red nucleus and the brain stem in the Rhesus monkey. Brain Res 1967;4:151—188.

68. Matsumura M, Nambu A, Yamaji Y, et al. Organization of somatic motor inputs from the frontal lobe to the pedunculopontine tegmental nucleus in the macaque monkey. Neuroscience 2000;98:97—110.

69. Spann BM, Grofova I. Origin of ascending and spinal pathways from the nucleus tegmenti pedunculopontinus in the rat. J Comp Neurol 1989;283:13—27. 70. Sugimoto T, Hattori T. Direct projections from the globus pallidus to the paraventricular nucleus of the thalamus in the rat. Brain Res 1984;323:188—192.

71. Semba K. Aminergic and cholinergic afferents to REM sleep induction regions of the pontine reticular formation in the rat. J Comp Neurol 1993;330:543—556.

72. Skinner RD, Kinjo N, Henderson V, Garcia-Rill E. Locomotor projections from the pedunculopontine nucleus to the spinal cord. Neuroreport 1990;1(3—4):183—186. 73. Semba K, Fibiger HC. Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and anterograde transport and immunohistochemical study. J Comp Neurol 1992;323:387—410.

74. Rye DB, Lee HJ, Saper CB, Wainer BH. Medullary and spinal efferents of the pedunculopontine tegmental nucleus and adjacent mesopontine tegmentum in the rat. J Comp Neurol 1988;269:315—341.

75. Hazrati LN, Parent A. Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey. Brain Res 1992;585(1—2):267—271.

76. 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;321:515—543.

77. Ruggiero DA, Anwar M, Golanov EV, Reis DJ. The pedunculopontine tegmental nucleus issues collaterals to the fastigial nucleus and rostral ventrolateral reticular nucleus in the rat. Brain Res 1997;760(1—2):272—276.

78. Aravamuthan BR, Muthusamy KA, Stein JF, Aziz TZ, Johansen-Berg H. Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei. Neuroimage 2007;37:694—705.

79. Muthusamy KA, Aravamuthan BR, Kringelbach ML, et al. Connectivity of the human pedunculopontine nucleus region and diffusion tensor imaging in surgical targeting. J Neurosurg 2007;107:814—820.

80. Kang Y, Kitai ST. Electrophysiological properties of pedunculo- pontine neurons and their postsynaptic responses following stimulation of substantia nigra reticulata. Brain Res 1990;535: 79—95.

81. Takakusaki K, Shiroyama T, Kitai ST. Two types of cholinergic neurons in the rat tegmental pedunculopontine nucleus: Electro-physiological and morphological characterization. Neuroscience 1997;79:1089—1109.

82. Saitoh K, Hattori S, Song W, Isa T, Takakusaki K. Nigral GABAergic inhibition upon cholinergic neurons in the rat pedunculopontine tegmental nucleus. Eur J Neurosci 2003;18: 879—886.

83. Dormont JF, Conde H, Farin D. The role of the pedunculopontine tegmental nucleus in relation to conditioned motor performance in the cat. I. Context-dependent and reinforcement-related single unit activity Experimental brain research 1998;121:401— 410.

84. Scarnati E, Proia A, Di Loreto S, Pacitti C. The reciprocal electrophysiological influence between the nucleus tegmenti pedunculopontinus and the substantia nigra in normal and decorticated rats. Brain Res 1987;423(1—2):116—124.

85. Garcia-Rill E, Skinner RD, Fitzgerald JA. Activity in the mesencephalic locomotor region during locomotion. Exp Neurol 1983;82:609—622.

86. Garcia-Rill E, Skinner RD. Modulation of rhythmic function in the posterior midbrain. Neuroscience 1988;27:639—654.

87. Skinner RD, Kinjo N, Ishikawa Y, Biedermann JA, Garcia- Rill E. Locomotor projections from the pedunculopontine nucleus to the medioventral medulla. Neuroreport 1990;1(3—4): 207—210.

88. Staup MA, Stehouwer DJ. Ontogeny of L-DOPA-induced locomotion: Expression of c-Fos in the brainstem and basal ganglia of rats. Brain Res 2006;1068:56—64.

89. Matsumura M, Watanabe K, Ohye C. Single-unit activity in the primate nucleus tegmenti pedunculopontinus related to voluntary arm movement. Neurosci Res 1997;28:155—165.

90. Kobayashi Y, Inoue Y, Yamamoto M, Isa T, Aizawa H. Contribution of pedunculopontine tegmental nucleus neurons to performance of visually guided saccade tasks in monkeys. J Neurophysiol 2002;88:715—731.

91. Kobayashi Y, Saito Y, Isa T. Facilitation of saccade initiation by brainstem cholinergic system. Brain Dev-Jpn 2001;23(Suppl 1):S24—S27. 92. Weinberger M, Hamani C, Hutchison WD, Moro E, Lozano A, Dostrovsky JO. Pedunculopontine nucleus microelectrode recordings in movement disorder patients. Exp Brain Res 2008; Epub ahead of print.

93. Androulidakis AG, Mazzone P, Litvak V, et al. Oscillatory activity in the pedunculopontine area of patients with Parkinson's disease. Exp Neurol 2008;211:59—66.

94. Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc Natl Acad Sci USA 1987;84:5976—5980.

95. Zweig RM, Whitehouse PJ, Casanova MF, Walker LC, Jankel WR, Price DL. Loss of putative cholinergic neurons of the pedunculopontine nucleus in progressive supranuclear palsy. Ann Neurol 1985;18:144—144.

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

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

98. Rinne JO, Ma SY, Lee MS, Collan Y, Roytta M. Loss of cholinergic neurons in the pedunculopontine nucleus in Parkinson's disease is related to disability of the patients. Parkinsonism Relat Disord 2008; Epub ahead of print.

99. Pezzoli G, Strada O, Silani V, et al. Clinical and pathological features in hydrocarbon-induced parkinsonism. Ann Neurol 1996;40:922—925.

100. Kuo SH, Kenney C, Jankovic J. Bilateral pedunculopontine nuclei strokes presenting as freezing of gait. Mov Disord 2008;23:616— 619.

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

102. Aziz TZ, Davies L, Stein JF, France S. The role of descending basal ganglia connections to the brain stem in parkinsonian aki- nesia. Br J Neurosurg 1998;12:245—249.

103. Munro-Davies L, Winter J, Aziz TZ, Stein JF. The role of the pedunculopontine region in basal-ganglia mechanisms of akine- sia. Exp Brain Res 1999;129:511—517.

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

105. Keating GL, Winn P. Examination of the role of the pedunculo- pontine tegmental nucleus in radial maze tasks with or without a delay. Neuroscience 2002;112:687—696.

106. Alderson HL, Latimer MP, Winn P. A functional dissociation of the anterior and posterior pedunculopontine tegmental nucleus: excitotoxic lesions have differential effects on locomotion and the response to nicotine. Brain Struct Funct 2008; Epub ahead of print.

107. Mitchell IJ, Clarke CE, Boyce S, et al. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine. Neuroscience 1989;32:213—226.

108. Gomez-Gallego M, Fernandez-Villalba E, Fernandez-Barreiro A, Herrero MT. Changes in the neuronal activity in the pedunculopontine nucleus in chronic MPTP-treated primates: an *in situ* hybridization study of cytochrome oxidase subunit I, choline acetyl transferase and substance P mRNA expression. J Neural Transmission (Vienna, Austria: 1996) 2007;114:319—326.

109. Breit S, Martin A, Lessmann L, Cerkez D, Gasser T, Schulz JB. Bilateral changes in neuronal activity of the basal ganglia

in the unilateral 6-hydroxydopamine rat model. J Neurosci Res 2008;86:1388—1396.

110. 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(Part 11):2418—2430.

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

112. Jenkinson N, Nandi D, Oram R, Stein JF, Aziz TZ. Pedunculopontine nucleus electric stimulation alleviates akinesia independently of dopaminergic mechanisms. Neuroreport 2006;17:639—641.

113. Jenkinson N, Nandi D, Aziz TZ, Stein JF. Pedunculopontine nucleus: a new target for deep brain stimulation for akinesia. Neuroreport 2005;16:1875—1876.

114. Plaha P, Gill SS. Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. Neuroreport 2005; 16:1883—1887.

115. Stefani A, Lozano A, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130:1596—1607.

116. Mazzone P, Lozano A, Stanzione P, et al. Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. Neuroreport 2005;16:1877—1881

117. Jacobsohn L. Uber die Kerne des menschlichen Hirnstamms: (Medulla oblongata, Pons, und Pedunculus cerebri). Anhang zuden Abhandlungen der Kgl. Preuss, Akad d. Wiss: 1909.

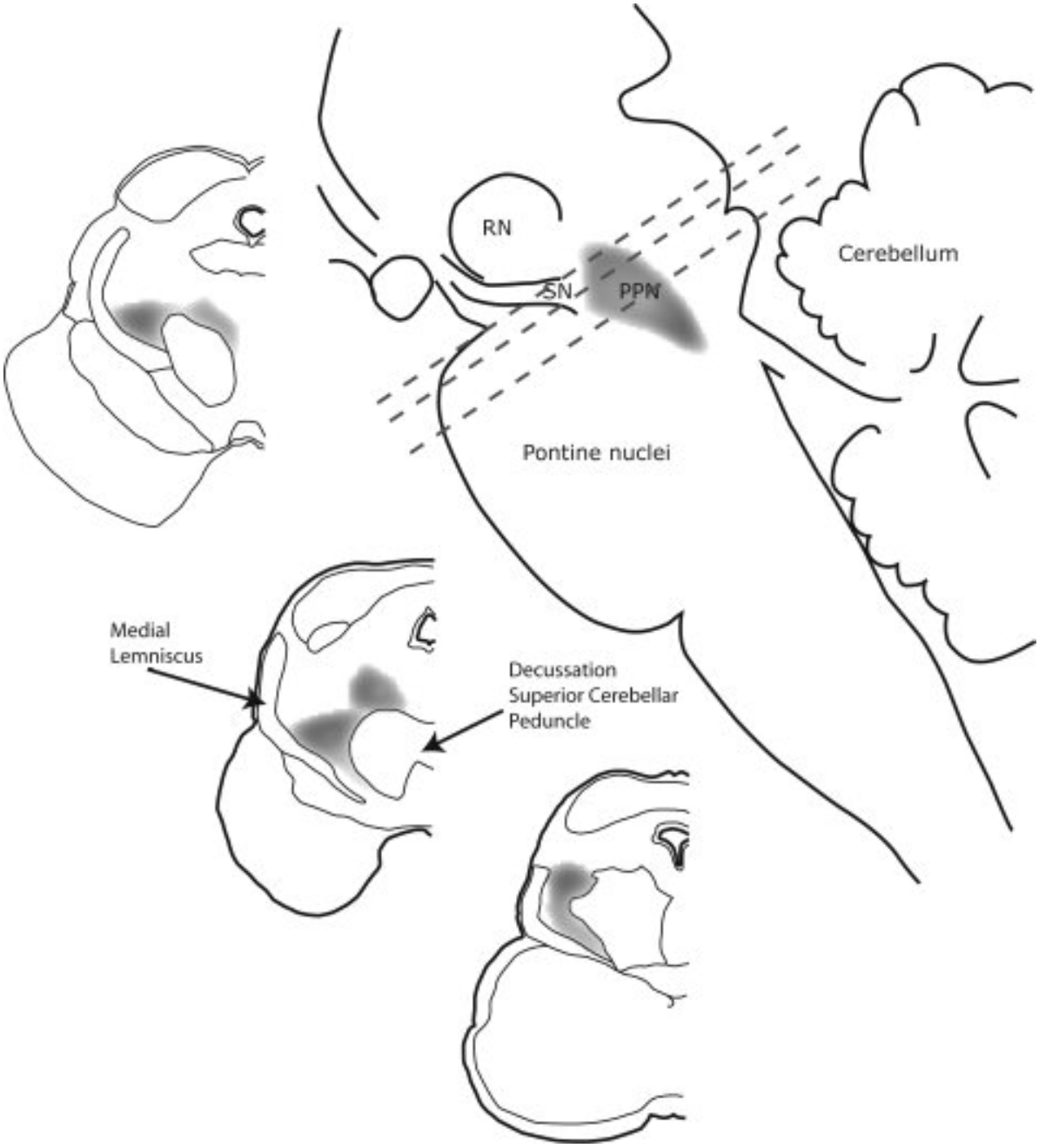

FIG. 1. Three axial sections through the human brainstem showing the position of the pedunculopontine nucleus. The level of the three sections is indicated by the dashed lines in the para-sagital cartoon of the brainstem and midbrain. RN, Red Nucleus; PPN, Pedunculopontine Nucleus; SN, Substantia Nigra. Adapted from Olszewski and Baxter (1954).

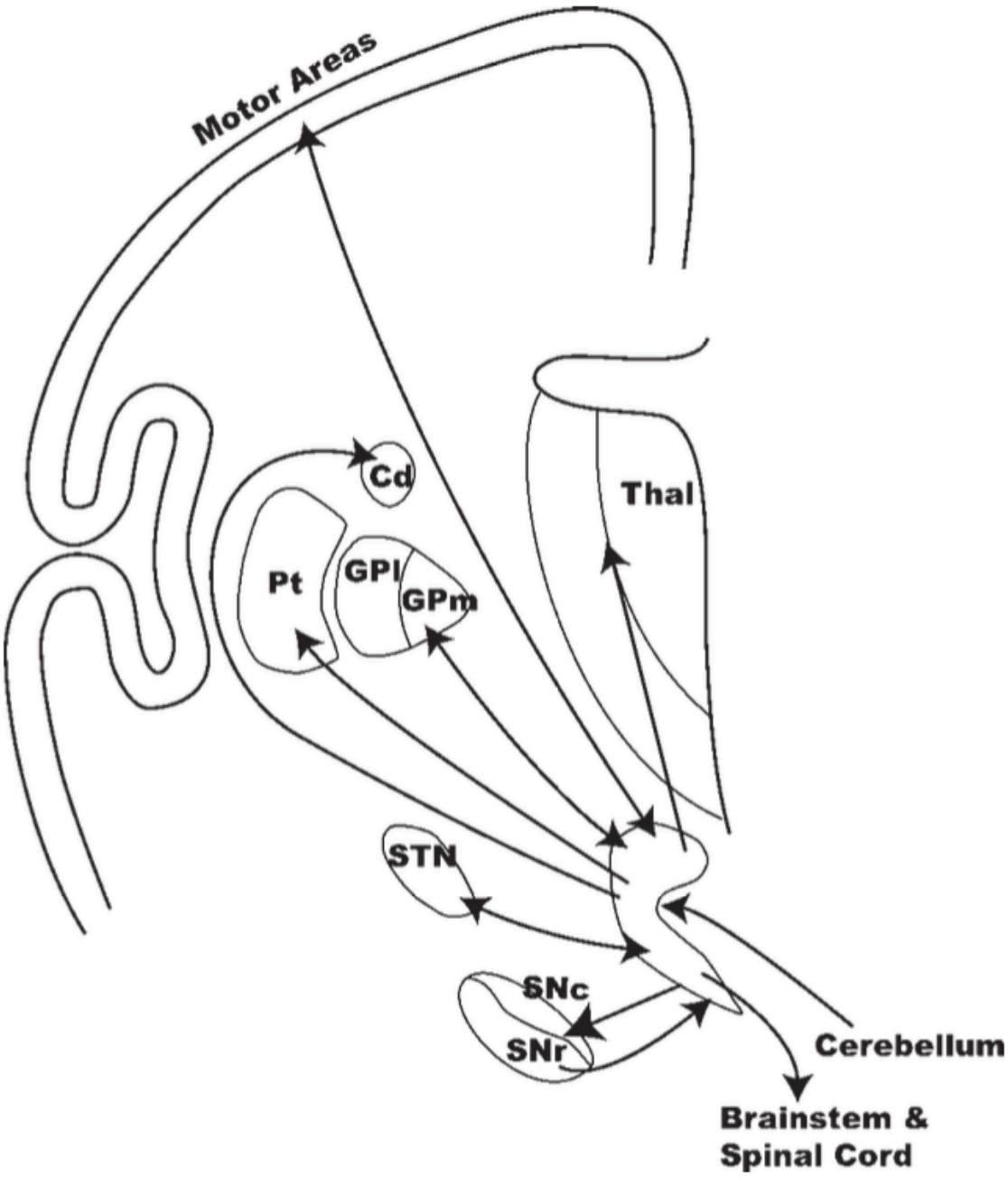

FIG. 2. The major efferent and afferent pathways of the PPN to the basal ganglia and other motor structures (see text for details; abbrevi- ations as in text).