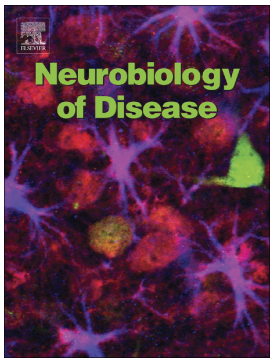
Accepted Manuscript



Pedunculopontine nucleus: An integrative view with implications on Deep Brain Stimulation

Andreas Nowacki, Salvatore Galati, Janine Ai-Schlaeppi, Claudio Bassetti, Alain Kaelin, Claudio Pollo

PII:	S0969-9961(18)30487-X
DOI:	doi:10.1016/j.nbd.2018.08.015
Reference:	YNBDI 4256
To appear in:	*Neurobiology of Disease*
Received date:	2 February 2018
Revised date:	22 June 2018
Accepted date:	24 August 2018

Please cite this article as: Andreas Nowacki, Salvatore Galati, Janine Ai-Schlaeppi, Claudio Bassetti, Alain Kaelin, Claudio Pollo , Pedunculopontine nucleus: An integrative view with implications on Deep Brain Stimulation. Ynbdi (2018), doi:10.1016/j.nbd.2018.08.015

Pedunculopontine nucleus: an integrative view with implications on Deep Brain Stimulation

Andreas Nowacki[1], Salvatore Galati[2], Janine Ai-Schlaeppi[1], Claudio Bassetti[3], Alain Kaelin[2], Claudio Pollo[1]

[1]Department of Neurosurgery, Inselspital, University Hospital Bern and University of Bern, Bern, Switzerland

[2]Department of Neurology, Ospedale Regionale di Lugano. Lugano, Switzerland

[3]Department of Neurology, Inselspital, University Hospital Bern and University of Bern, Bern, Switzerland

Financial disclosure/Conflict of interest: There are no conflicts of interest to be declared.

Funding: There are sources of funding for the study.

Corresponding author:

Andreas Nowacki,

Department of Neurosurgery,

Inselspital, University Hospital Bern, and University of Bern,

Bern, Switzerland

Telephone: (+)41 316320014

e-mail address: neuro.nowacki@gmail.com

Abstract:

The pedunculopontine nucleus (PPN) is a reticular nucleus located in the mesencephalic and upper pontine tegmentum. Initially, characterized by its predominant cholinergic projection neurons, it was associated with the "mesencephalic locomotor region" and "reticular activating system". Furthermore, based on histopathological studies, the PPN was hypothesized to play a role in the manifestation of symptoms in movement disorders such as Parkinson`s disease (PD). Since axial symptoms represent unmet needs of PD treatments, a series of pioneering experiments in Parkinsonian monkeys promoted the idea of a potential new target for deep brain stimulation (DBS) and much clinical interest was generated in the following years leading to a number of trials analysing the role of PPN for gait disorders. This review summarizes the historical background and more recent findings about the anatomy and function of the PPN and its implications in the basal ganglia network of the normal as well as diseased brain. Classical views on PPN function shall be challenged by more recent findings. Additionally, the current role and future perspectives of PPN DBS in PD patients shall be outlined.

Keywords: Deep Brain Stimulation, Gait disorders, Pedunculopontine, nucleus, Review

Introduction:

Several independent findings based on animal models as well as in humans have indicated a role of the pedunculopontine nucleus (PPN) in motor function over the past few decades. The PPN is located in the mesencephalic and upper pontine tegmentum and was classically identified by its predominant cholinergic neurons. Based on its widespread connections to other areas of the brain and spinal cord, the PPN is involved in a variety of functions. Most importantly with regard to clinical implications, altered PPN function in a parkinsonian model of non-human primates promoted the idea of this nucleus to be a possible new target for treating motor symptoms in Parkinson`s disease (PD) as early as 1989 (Mitchell et al., 1989). Consecutive primate studies supported the concept that PPN plays a crucial role in motor function. Particularly, high-frequency stimulation of the PPN was reported to reduce motor activity in the intact non-human monkey and low-frequency PPN-DBS could successfully improve motor activity in a primate model of PD (Jenkinson et al., 2004; Nandi et al., 2002b). Based on these and other pioneering findings, the PPN was targeted in humans in order to treat predominantly gait disturbances associated with Parkinson`s disease or other movement disorders (Pereira et al., 2008; Stefani et al., 2007). However, initial enthusiasm about this promising new target was dampened by mixed outcome results of PPN DBS reported by different centers in the course of the following years (Hamani et al., 2011). Parallel to clinical studies analysing the effect of PPN-DBS, a tremendous number of animal studies has refined our understanding of the PPN and its involvement in many neurophysiological processes beyond motor function such as regulation of the sleep-wake-cycle, involvement in reward circuits and influence of behavioural decision-making (Mena-Segovia and Bolam, 2017; Winn, 2006). This review article aims to give a brief historical background and to report on more recent findings about the anatomy and function of the PPN and its implications in the basal ganglia network of the normal as well as diseased brain. Furthermore, the current and future role of PPN-DBS in humans shall be discussed.

Anatomical considerations

The PPN is an evolutionary highly conserved structure which is found in almost every species that has so far been studied including fish, amphibians and vertebrates (Brantley and Bass, 1988; Honda and Semba, 1995; Marin et al., 1997; Rye et al., 1987). The PPN was first described by Jacobson in 1909 based on neuroanatomical studies in humans (Jacobson, 1909). However, the first systematic approach to characterize the PPN dates back to 1954 when Olszewski and Baxter published their classic cytoarchitectonic study of the human PPN based on light microscopic analysis (Olszewski and Baxter, 1954). The PPN is located in the upper brainstem tegmentum at the junction of the midbrain and pons at the level of the inferior colliculus (Figure 1). In humans, the PPN is located just below the red nucleus dorsally to the substantia nigra (SN) and extends caudally approximately 5-10 mm to the level of the locus coeruleus (Hamani et al., 2016a). The PPN lies medial and posterior to the lemniscus medialis and lateral to the decussating cerebellar fibers (brachium conjunctivum) and central tegmental tract. The functionally similar subcuneiform and cuneiform nucleus are located just dorsally to the PPN. According to Olszewski and Baxter the PPN was divided into two parts referring to the size and density of neurons: a pars compacta which is located in the caudal half of the nucleus and a pars dissipata which extends throughout the rostrocaudal axis of the PPN (Olszewski and Baxter, 1954). However, due to the fact, that the PPN is a reticular nucleus, definition of the exact borders seems arbitrary and since its initial description, different human brain atlases have described different rostrocaudal extents of the PPN based on cytoarchitectonical features (summarised in Hamani et al. 2016 (Hamani et al., 2016a)). More recently, some authors have considered the division of the PPN into a pars compacta and reticulata as outdated with reference to a neurochemical and functional point of view (Mena-Segovia and Bolam, 2017). The reasons for this shall be discussed briefly. The PPN contains numerous cholinergic neurons giving rise to intense immunoreactivity to choline acetyltransferase (ChAT) and which correspond to the Ch5 group in the classification of Mesulam (Mesulam et al., 1989; Mesulam et al., 1983). Thus, based on immunostaining, the PPN boundaries can be clearly described and the distribution of cholinergic neurons within the PPN follows the concept of a subdivision of the nucleus into a pars compacta and pars reticulata: cholinergic neurons are estimated to make up 58 to 90% in the pars compacta and 16 to 75% in the pars reticulata subregion (Manaye et al., 1999; Mesulam et al., 1989). However, the PPN is a neurochemically heterogenous

structure that contains at least two other interdigitated projection neurons: GABAergic and glutamatergic (Wang and Morales, 2009). The relative frequencies of these neurochemically distinct cell types vary considerably between the subregions of the PPN and do not follow the same distribution of the cholinergic neurons. GABAergic neurons are densely located in the rostral part of the PPN, some extending to the substantia nigra pars reticulata (SNr) (Mena-Segovia et al., 2009). Glutamatergic neurons are predominantly found in the caudal PPN (Clements and Grant, 1990). Thus, the distribution of different populations of neurons based on their expression of neurotransmitters does not equally follow the principle segregation of the PPN nucleus into two parts. Moreover, cholinergic neurons have been found to co-express a variety of neuropeptides such as substance P and atrial natriuretic peptide as well as nitric oxide (NO) but the exact co-expression patterns still need to be discerned (Moga and Saper, 1994; Vincent et al., 1983; Vincent et al., 1986). Furthermore, the principle segregation into a pars reticulata and pars compacta does not go along with functional aspects which seem to be arranged according to another topographical distribution (to be discussed below).

Besides the classification of different neurons within the PPN according to the microscopic phenotype and the neurotransmitters that they express, in-vitro electrophysiological studies of the rat PPN have identified different cell types based on the membrane characteristics and the firing patterns. Morphologically small type I neurons were characterized by low-threshold Ca-spikes and bursting activity. Type II neurons displayed a transient outward potassium current with no bursting activity. A third type was described that revealed both of these current types and firing patterns (Kamondi et al., 1992; Luebke et al., 1992). All cell types were immunopositive for choline acetyltransferase at least to a certain degree. However, the exact neurochemical identity of each of the electrophysiologically distinct cell types remains unclear. Different cell types according to their firing patterns have also been found by microelectrode recording during PPN-DBS in humans. Cells could be classified according to random or burst-like activity patterns and according to low-frequency (8-35 Hz) and high-frequency (60-70 Hz) firing patterns (Tattersall et al., 2014; Weinberger et al., 2008; Wilcox et al., 2011). Similar to the results of in-vitro models, the underlying phenotype of the different electrophysiological cell types remains unsolved.

The PPN has numerous afferent and efferent connections to virtually all parts of the central nervous system (CNS). Figure 2 summarizes important afferent and efferent connections of the PPN. Listing these numerous afferent and efferent connections can be tedious, however, they can be easier appreciated and memorized when they are related to function. Although the functional aspects of the PPN are described in more detail below, some coarse principles shall already be mentioned here, that help categorize afferent and efferent connections of the PPN according to the functionally and anatomically partly overlapping networks into which the PPN is integrated. First, the PPN is integrated into the subcortical cerebello-thalamo-cortical and basal ganglia-thalamo-cortical networks regulating motor function (Garcia-Rill, 1991). Not surprisingly, the PPN receives input from the deep cerebellar nuclei and is highly interconnected with parts of the basal ganglia such as the striatum, internal pallidal segment (GPi), the subthalamic nucleus (STN) and SN and sends efferent fibers to the spinal cord and ventral tegmental area (VTA). Second, the PPN is involved in arousal and regulation of the sleep-wake-cycle (Garcia-Rill et al., 2015). Therefore, it is highly interconnected with parts of the reticular formation and brain stem nuclei, and sends widespread efferent fibers to the hypothalamus, thalamus and basal forebrain. With this concept in mind, many of the afferent and efferent connections that are systematically listed in the following paragraphs can be allocated to one of these functional networks.

Most of our knowledge about the connectivity of the PPN comes from tracing studies of rats and other mammals with only some of them based on primates. It is important to mention, that the majority of analyses of efferent innervation patterns of the PPN is based on tracing studies and reconstruction of cholinergic neurons and much less is known about the connectivity of the non-cholinergic neurons, which, however, are estimated to outnumber cholinergic neurons by factor five at least in the rat (Mena-Segovia et al., 2009; Wang and Morales, 2009). One important principle that has been demonstrated is that a single cholinergic neuron innervates concomitantly different target structures by means of numerous axon collaterals (Mena-Segovia et al., 2008a; Mena-Segovia et al., 2008b). Both ascending and descending connections have been described and can further be divided (Mena-Segovia and Bolam, 2017). (i) *Ascending ventral* axon collaterals innervate parts of the basal ganglia, amygdala, the basal forebrain and septum region as well as the lateral hypothalamus (Dautan et al., 2016a; Lavoie and Parent, 1994b; Mena-Segovia et al.,

2004; Semba and Fibiger, 1992; Semba et al., 1988; Woolf and Butcher, 1986). In addition, intense efferent connections with dopaminergic neurons of the SNc and VTA as well as to the STN have been demonstrated by tracing experiments in rats and monkeys (Beninato and Spencer, 1987; Bevan and Bolam, 1995; Gould et al., 1989; Lavoie and Parent, 1994a; Oakman et al., 1995). (ii) *Ascending dorsal* axon collaterals innervate the superior colliculi and widespread parts of the reticular, limbic, motor, sensory and associative thalamus (Ainge et al., 2004; Hallanger and Wainer, 1988; Holmstrand and Sesack, 2011; Motts and Schofield, 2009; Pare et al., 1988; Smith et al., 1988; Steriade et al., 1988). (iii) Descending fibers have been demonstrated to innervate the pontine and medullary reticular formation, the motor trigeminal nucleus, serotonergic cells of the ascending reticular activating system **(**ARAS**)** as well as the pontine oralis and gigantocellular nucleus (Fay and Norgren, 1997a; Fay and Norgren, 1997b; Martinez-Gonzalez et al., 2014; Mitani et al., 1988; Nakamura et al., 1989; Rye et al., 1987; Skinner et al., 1990b). Furthermore, efferent connections to the spinal cord have been described (Skinner et al., 1990a). There is still uncertainty about the extent of ascending and descending fibers that cross to the contralateral side. At least there is evidence of contralateral projections to the thalamus, but whether or not this example constitutes a general principle remains unclear (Usunoff et al., 1999). In summary, different widespread targets are innervated by PPN cholinergic neurons along separate parallel streamlines. If there is a somatotopical organization of cholinergic neurons within the PPN in terms of anatomically segregated neuron assemblies that innervate distinct targets remains an interesting hypothesis. First evidence in favour of this premise comes from optogenetic and recording studies in rats, which have shown that cholinergic neurons in the rostral part primarily innervate the dorsolateral striatum whereas cholinergic neurons within the caudal PPN innervate limbic dopaminergic neurons in the VTA (Dautan et al., 2014; Dautan et al., 2016b).

Contrary to cholinergic neurons, non-cholinergic cells are less arbored and less is known about their connectivity patterns although the few findings that have been made point towards a considerable overlap with targets reached by cholinergic cells. According to tracing studies in monkeys and rats, glutamatergic neurons innervate the SNc, STN, VTA and thalamus (Barroso-Chinea et al., 2011; Bevan and Bolam, 1995; Charara et al., 1996). Similarly, GABAergic PPN neurons have been demonstrated to send their axons to the STN and hypothalamus (Bevan and Bolam,

1995; Ford et al., 1995). As far as the STN is concerned, some evidence supports the concept that PPN strongly influences the activity of STN neurons. For instance, lesion of the PPN promoted a significant increase of STN firing discharge in Parkinsonian rats (Breit et al., 2006). Of note, during 25 Hz PPN-DBS the large majority of STN neurons change their activity in terms of firing rate and burst activity (Galati et al., 2008).

Furthermore, important inputs to the PPN arise from the basal ganglia. Initial findings by Nauta and Mehler, that lesions of the GPi induced degeneration of the PPN in the monkey pointed already towards a connection between these structures that was later confirmed by tracing studies in rats, cats and monkeys (Carter and Fibiger, 1978; Groenewegen et al., 1993; Nauta, 1979; Nauta and Mehler, 1966). Another nucleus of the basal ganglia which is interconnected with the PPN is the SN. While extensive efferent connections exist from the PPN to the SNc, the PPN receives strong input from the SNr (Spann and Grofova, 1991). Similarly, intense reciprocal connections exist between the STN and the PPN (Steininger et al., 1992). Besides intense reciprocal connections with different nuclei of the basal ganglia, tracer experiments in the rat and squirrel monkey have shown that the PPN receives input from the deep cerebellar output nuclei and red nucleus (Hazrati and Parent, 1992; Ruggiero et al., 1997). Furthermore, the PPN receives input from the motorcortex, premotor cortex as well as frontal eye fields in a somatotopically organized way, but this somatotopy overlapped to some considerable extent (Matsumura et al., 2000; Matsumura et al., 1997). Furthermore, tracer experiments in rats indicate that the PPN receives input from the extended amygdala (Zahm et al., 2001). Based on retrograde tracing experiments in rats, the PPN has been further demonstrated to receive inputs from widespread brainstem areas such as the superior colliculi, periaqueductal gray, central tegmental field, dorsal raphe nucleus, superior raphe nucleus and zona incerta among others (Steininger et al., 1992).

The diversity of electrophysiological cell types and neurochemicals involved in PPN signalling as well as the numerous and widespread afferent and efferent connections hint already at the tremendous complexity of PPN function that shall be discussed in the following section.

Functional considerations

It is remarkable that initial studies from separate groups investigating different fields of neuroscience have indicated that the PPN is involved in two fundamental but apparently independent behavioural processes: arousal and locomotion. Arousal defines a brain state of increased sensory information processing that enables adequate behavioural responses, or in simple terms, it corresponds to what we can observe as wakefulness. In a first series of experiments by Moruzzi and Magoun, electrical stimulation of the reticular formation led to a conversion of the pattern of the electroencephalogram (EEG) from slow, high-voltage oscillations to fast, low-voltage activity known as “desynchronization” marking the transition from sleep to wakefulness (Moruzzi and Magoun, 1949). Thus, the term “reticular activating system” (RAS) was proposed to constitute the underlying neural substrate of arousal. The concept of the RAS was further developed over the next decades by findings that activation of thalamic cholinergic cells contributed to arousal (Steriade et al., 1991a; Steriade et al., 1991b; Steriade et al., 1988). Based on current models, the neurobiological substrate of arousal constitutes a complex subcortical network with a number of different neurotransmitters involved. The locus coeruleus (LC) plays a key role in mediating arousal and maintaining wakefulness through wide-spread noradrenergic transmissions to the amygdala, hippocampus, hypothalamus, thalamus, basal forebrain and neocortex (Jones et al., 1977; Jones and Moore, 1977; Jones and Yang, 1985; Loughlin et al., 1986; Osaka and Matsumura, 1994; Seguela et al., 1990). On the level of the hypothalamus, GABAergic neurons in the ventrolateral preoptic area (VLPO) of the hypothalamus are active during slow-wave and rapid eye movement (REM) sleep while silent during wakefulness whereas orexin neurons of the lateral hypothalamus are active during arousal and wakefulness. Noradrenergic transmission from LC to the hypothalamus and dorsal thalamus promotes arousal by inhibiting the VLPO neurons and changing the thalamic firing pattern to the single spiking mode which is associated to the wakeful state with increased thalamocortical transmission (McCormick et al., 1991; Osaka and Matsumura, 1994; Szymusiak et al., 1998). Furthermore, reciprocal connections between the LC and the serotonergic dorsal raphe nucleus (DR) have been associated with regulation of the sleep-wake cycle (Kim et al., 2004; McGinty and Harper, 1976). As outlined before, intense efferent cholinergic and non-cholinergic projections from the PPN were demonstrated to reach the thalamus and lateral hypothalamus as well as the nucleus basalis of Meynert illustrating a possible link to

PPN involvement in arousal (Semba and Fibiger, 1992; Semba et al., 1988). The PPN projections to the thalamus are widespread including thalamocortical and thalamostriatal relay nuclei such as the ventral lateral thalamus and lateral geniculate nucleus as well as the nonspecific intralaminar nuclei such as parafascicular nucleus (Ainge et al., 2004; Erro et al., 1999; Kolmac and Mitrofanis, 1998). This hypothetical role was confirmed by findings that cells within the PPN had higher firing rates during wakefulness and REM sleep and the role of the PPN as a component of the RAS and a modulator of arousal as well as REM sleep was adopted (Boucetta et al., 2014; Garcia-Rill et al., 2013; Steriade et al., 1991a; Steriade et al., 1991b). However, lesions of cholinergic cells within the PPN failed to demonstrate an impairment of the waking state and the overall sleep-wake-cycle including REM sleep (Deurveilher and Hennevin, 2001) questioning the significance of PPN cholinergic contribution to modulation of the sleep-wake-cycle and arousal. More recent findings in the field have indicated that cholinergic neurons might help mediate brain state changes, as their firing rate increases transiently during the transition from sleep to wakefulness and after sensory stimulation before returning to baseline (Petzold et al., 2015). Additionally, PPN cholinergic cells have been indicated to play a role in mediating REM sleep, although their activation may not be a necessary prerequisite for REM sleep to occur (Grace et al., 2014; Van Dort et al., 2015). The intricate mechanism and the putative role of the PPN in mediating or modulating REM sleep is beyond the scope of this article and we refer to other elaborate reviews that have been published before (Garcia-Rill et al., 2015; Rye, 1997).

Parallel to and independent of the discovery of a probable involvement of the PPN in arousal and regulation of the sleep-wake-cycle, the PPN was associated with locomotion. PPN has been considered in many aspects a sort of “functional portion” of basal ganglia since it establishes extensive and reciprocal connections with several basal ganglia structures as above mentioned. Furthermore, PPN participates to at least two critical pathways: first, it is part of the so-called mesencephalic locomotor region (MLR) through direct projections to the spinal cord. Thus, PPN should concur to provide a sort of additional locomotor release, well documented in cats and rodents (Garcia-Rill et al., 1987; Skinner et al., 1990a). Second, it contributes to ascending cholinergic projection towards the thalamic complex nuclei and other relay nuclei of the well-known direct or indirect pathways of the basal ganglia. In particular, one of the more prominent PPN-fugal output directly impinges

GPi and STN and it has been hypothesized the likely involvement of a “dysfunctional” PPN in the physiopathology of akinesia. For instance, microinjection of GABA receptor antagonist bicuculline, into the PPN of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys were followed by significant improvement of akinesia similar to what observed with oral administration of L-3,4-dihydroxyphenylalanine (L-DOPA) (Nandi et al., 2002a).

Classically, the PPN and adjacent nuclei such as the cuneiform and subcuneiform nucleus have been suggested to comprise the MLR (Garcia-Rill, 1991). The MLR is a theoretical construct that was defined to help explain the findings of induction of movement in decerebrate cats after electrical stimulation of the pontomesencephalic reticular formation, especially the PPN and its associated nearby structures (Garcia-Rill et al., 1987; Mori et al., 1978; Skinner et al., 1990b). These pioneering findings have engaged considerable controversies regarding PPN function in locomotion in the course of the following years with numerous studies presenting partly conflicting findings. For instance, unilateral lesioning of the PPN in the non-human primate induced marked motor symptoms with hypokinesia and rigidity on the contralateral side that endured for one to two weeks until recovery whereas bilateral lesions of the monkey PPN led to persistent paucity and slowness of movement (Aziz et al., 1998; Kojima et al., 1997; Munro-Davies et al., 1999). Similarly, high-frequency stimulation of the PPN caused a significant decrease in motor activity and loss of postural control in the macaque monkey (Pereira et al., 2008). Further evidence of the concept that the PPN is involved in locomotor function comes from recording experiments of macaques that have shown increased or decreased neuronal activity during arm movements and different phasic or tonic discharge patterns of PPN and cuneiform nucleus during locomotion on a treadmill. Of note, locomotion-responding neurons were located throughout the rostro-caudal extent of the PPN and cuneiform nucleus in both studies (Goetz et al., 2016; Matsumura et al., 1997). On the other hand, initial studies failed to demonstrate impaired spontaneous locomotion after lesioning the PPN in the rat (Inglis et al., 1994a; Inglis et al., 1994b; Keating and Winn, 2002; Steiniger and Kretschmer, 2004). Interestingly, more recent experiments in rats found that lesions of the posterior (caudal) PPN had no effect on spontaneous locomotion whereas lesions of the anterior PPN decreased spontaneous motor activity as measured by spontaneous locomotion in a red-light illuminated photocell cages. This finding emphasizes a functional dissociation within the PPN (Alderson et al., 2008).

But how can these apparently conflicting results be explained and integrated into a comprehensive theory of the PPN`s role in locomotor function?

As outlined above, the PPN is interconnected with many core nuclei of the basal ganglia which are involved in motor control, such as the SNr and SNc, the GPI and the STN. Furthermore, it receives input from the cerebellar output nuclei and the motor and premotor cortex and it projects to the brain stem and spinal cord where it might influence direct motor output. Thus, based on its connectivity, the PPN is located in a core position to modulate key structures within the motor network. Numerous studies have shed a light on the intricate mechanisms how the PPN might be involved in motor functions. Electrophysiological studies have pointed towards opposite roles of cholinergic and glutamatergic neurons in movement. In experiments with decerebrate cats, PPN stimulation induced an acetylcholine mediated decrease in muscle tone and inhibition of motorneurons, while stimulation of the dorsal part, which contains more glutamatergic neurons elicited activity in the nucleus pontis oralis that was accompanied by increased muscle tone and motor activity (Takakusaki et al., 2016). This dichotomous role of the PPN with different influences of glutamatergic and cholinergic cells on locomotion has been confirmed by recent optogenetic experiments that demonstrated elicitation of locomotion after activation of PPN glutamatergic neurons, while optogentic activation of cholinergic neurons in mice had no such clear direct influence on locomotion (Roseberry et al., 2016). Of note, activation of the cholinergic neurons of the PPN improved motor symptoms such as gait, forelimb akinesia and overall general motor activity in freely moving Parkinsonian rat (Pienaar et al., 2015). A further mechanism by which the PPN exerts effects on behaviour and locomotion might be mediated through its extensive projections to the mesencephalic dopaminergic neurons comprising the SNc and VTA (Gould et al., 1989). Efferent projections to dopaminergic neurons originate from all three cholinergic, glutamatergic and GABAergic subtypes in a somatotopically organized manner with rostral PPN cells projecting predominantly to the SNc and caudal PPN neurons innervating the VTA and SNc (Charara et al., 1996; Dautan et al., 2016b; Gould et al., 1989; Oakman et al., 1995). Remarkably, the PPN and laterodorsal tegmental nucleus constitute the only cholinergic input to midbrain dopaminergic neurons (Dautan et al., 2016b). That this anatomical connectivity has an impact on behaviour and locomotion has been demonstrated in several independent studies. First evidence of cholinergic influence on nigrostriatal

dopaminergic cells came from electrophysiological studies in anaesthesized rats demonstrating marked changes in the firing properties of dopaminergic cells after stimulation of acetylcholine receptors (Lichtensteiger et al., 1982). On a behavioural level, nicotine (acetylcholine receptor agonist) administration to VTA neurons was observed to enhance drug-seeking behaviour in rats (Volkow and Morales, 2015). Furthermore, intra-VTA infusion of nicotine increases locomotion (Panagis et al., 1996). The neurons of the caudal PPN (Ch5 group according to Mesulam) are the main source of cholinergic innervation of the VTA. Interestingly, lesions of the cholinergic posterior PPN in rats (caudal PPN in humans, cholinergic neurons containing part) but not anterior PPN lesions changed the locomotor response to nicotine. Thus, the caudal PPN seems to modulate at least in part locomotor activity by mediating cholinergic transmission to the VTA (Alderson et al., 2008; Panagis et al., 1996). Furthermore, optogenetic activation of cholinergic axons in the VTA increases locomotor activity in freely moving rats (Dautan et al., 2016b). Additionally, several lines of evidence indicate the PPN to play a role in dopamine mediated behaviours such as motivational behaviour, reinforcement and learning (Okada et al., 2009; Pan and Hyland, 2005). For instance, distinct subpopulations of PPN neurons in monkeys have been demonstrated to respond differentially to predicted and actual reward values and further experiments in rats point towards a role of PPN neurons in detecting reward-prediction errors and in signalling action-outcome associations (Leblond et al., 2014; Okada et al., 2009; Thompson et al., 2016; Tian et al., 2016). Thus, several lines of evidence based on electrophysiological studies and behavioural tasks suggest that the PPN is involved in reinforcement learning and reward circuits. By its modulatory effect on mesencephalic dopaminergic neurons, the PPN is believed to influence behavioural decision-making by direct and indirect regulation of striatal activity (Mena-Segovia and Bolam, 2017). However, the underlying mechanisms by which the PPN receives sensory input about behaviourally relevant stimuli remain unclear and need to be further investigated. Furthermore, the role that different neuronal subpopulations within the PPN play in these processes need to be elucidated.

It is possible that the diversity and partly conflicting results obtained by different groups and in different species are due to lesions and recordings of different PPN sectors during the diverse experimental set-ups as well as the different outcome measures used to determine motor activity. Nevertheless, growing evidence

suggests, that the PPN seems to have numerous and complex effects on the control of behaviour and locomotion depending on the cell type and location within the PPN. Whereas descending cholinergic fibers seem to decrease motor activity in the brain stem nuclei and spinal cord inhibiting ongoing movement, ascending projections mediated by acetylcholine and glutamate might promote goal-directed behaviour by increasing dopamine transmission to the striatum. Furthermore, the PPN is densely interconnected with the STN, which itself exerts powerful excitatory control on the GPi, the main inhibitory output nucleus of the basal ganglia. Whether the PPN determines if the STN breaks ongoing basal ganglia activity remains to be investigated (Gillies and Willshaw, 1998).

The role of the PPN in movement disorders

Apart from studies on decerebrate vertebrates, the vast amount of the above presented studies are based on animal models with a healthy, non-diseased brain and therefore indicate a crucial contributory role of the PPN in attention, motivation and goal-directed behaviour as well as locomotion in the normally functioning brain. Another important line of evidence suggested that the PPN may be involved in the pathophysiology of degenerative movement disorders such as PD, progressive supranuclear palsy and multisystem atrophy. In 1987, Hirsch and colleagues reported that the cholinergic Ch5 cell group corresponding to the PPN undergoes degeneration in idiopathic PD and in the parkinsonian syndrome of progressive supranuclear palsy (Hirsch et al., 1987). The authors already hypothesized that certain symptoms of these movement disorders have their genesis in the pathology of these cholinergic neurons. These results were confirmed by findings of Zweig and coworkers and the loss of cholinergic cells within the PPN was later shown to be correlated with the severity of Parkinsonian symptoms (Rinne et al., 2008; Zweig et al., 1989; Zweig et al., 1987).

The potential role of the PPN in the pathophysiology of degenerative movement disorders was further characterized in animal models of non-human primates. The discovery that the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces parkinsonism in humans led to its application in primate models of PD for research purposes which has been proven to be a powerful animal model of PD which exhibits main features of human PD such as resting tremor and drug-induced

dyskinesias (Burns et al., 1983; Langston et al., 1983; Langston et al., 2000). In 1989, Mitchell and colleagues investigated MPTP-treated monkeys and found an altered pattern of abnormal neuronal activity in basal ganglia circuitry with increased activity in neurons of the medial segment of the globus pallidus (GPi) projecting to the pedunculopontine nucleus (Mitchell et al., 1989). Furthermore, metabolic markers are downregulated in the PPN in the MPTP treated monkey accompanied by decreased synthesis of acetylcholine (Gomez-Gallego et al., 2007). Given the fact that the main output of the internal pallidal segment is mediated by the inhibitory neurotransmitter GABA, it was hypothesized that chronic inhibition of the PPN driven by an overactive GPi contributed to the pathophysiological process underlying motor symptoms of PD such as bradykinesia and gait control. In support of this idea, direct injection of the GABA-agonist muscimol into the PPN in a normal monkey reduced significantly the motor activity of the animal whereas injection of the GABA antagonist bicuculine into the PPN of a MPTP-treated monkey reversed akinesia (Nandi et al., 2002a). Findings that unilateral lesioning of the PPN led to temporary Parkinsonian symptoms on the contralateral side in monkeys, whereas bilateral lesions led to marked persistent akinesia further supported the concept that the PPN is involved in the pathophysiology of PD and associated movement and gait disorders (Aziz et al., 1998).

Motivated by these findings that pointed towards a potential new target for neuromodulation therapy, a number of stimulation experiments in primates were conducted in the following period. Stimulation after bilateral implantation of DBS leads into the PPN of an intact macaque under ventriculographic guidance led to motor effects that were frequency-dependent. Whereas low-frequency stimulation (5-10 Hz) caused tremor on the contralateral side, high-frequency stimulation (45-100 Hz) caused reduced motor activity and impaired postural control of the animal (Nandi et al., 2002b). On the other hand, in the MPTP-treated monkey low-frequency stimulation of bilaterally implanted DBS leads into the PPN improved motor activity, a finding that was interpreted as a proof-of-principle of DBS to treat Parkinson`s disease and gait disorders (Jenkinson et al., 2005; Jenkinson et al., 2004; Jenkinson et al., 2006).

Deep brain stimulation of the PPN in humans

The theoretical background and the encouraging stimulation experiments of the PPN in Parkinsonian monkeys at the beginning of the millennium prompted the first application attempts of PPN-DBS in patients with PD and the first two case reports by Plaha et al and Mazzone et al. were published as early as 2005 (Mazzone et al., 2005; Plaha and Gill, 2005). In both cases low-frequency stimulation of 10-25 Hz after bilateral PPN electrode implantation were reported to alleviate predominantly PD axial symptoms and no major side-effects were observed. These observations led the authors to conclude that the PPN might be a new target to treat axial symptoms, that otherwise only respond poorly to dopaminergic therapy and DBS of the STN and GPi. Since these first reports on successful DBS implantation of the PPN, a number of other case reports and studies including a small number of patients have been published leading to fewer than 100 cases of PPN-DBS so far (Thevathasan et al., 2017). The first enthusiasm about this potential new target was soon dampened by the mixed and sometimes disappointing outcomes found between different and even within single centers (Morita et al., 2014). However, more than 10 years of experience with PPN-DBS have certainly broadened the understanding of the complexity of the issue. Reviewing the literature enables us to identify which patients might profit from PPN-DBS and to appreciate what can be expected and what cannot be expected from PPN-DBS in terms of outcome. Furthermore, factors that might have an impact on the success of PPN-DBS are about to be elucidated.

PPN-DBS study results in humans: motor outcome

A heterogeneous dataset including case reports, open label series, double-blinded single time point assessments, and longer term double-blinded studies have been published so far. Table 1 summarizes key studies with at least 5 subjects. These studies define the basis upon which first conclusions about the clinical effectiveness of PPN-DBS can be drawn. Before discussing the findings of the studies, it is important to acknowledge the limitations and confounds from these studies: table 1 points to a pivotal issue that makes the interpretation of the results challenging if not impossible due to the heterogeneous study designs, different outcome measures used to assess freezing of gait (FOG), falls and postural instability as well as the variability of the DBS settings including unilateral PPN-DBS, lone bilateral PPN-DBS and combined bilateral PPN-DBS with other targets such as the caudal Zona incerta

(cZI) or Subthalamic nucleus (STN). Furthermore, the targeting strategy and stimulation site within the PPN varies considerably between studies. For instance, active contact positions were distributed throughout the rostro-caudal axis between studies. Additionally, the differences between the exact stimulation site and costimulation with other targets are accompanied by varying stimulation parameters (Ferraye et al., 2010; Khan et al., 2012; Khan et al., 2011; Mestre et al., 2016; Moro et al., 2010; Stefani et al., 2007; Thevathasan et al., 2011a; Thevathasan et al., 2012; Welter et al., 2015). Despite this inhomogeneity, table 1 shows a clear trend towards a reduction in axial symptoms of PD patients especially towards an improvement FOG and falls in the majority of patients. This mean reduction in postural instability, FOG and the number of falls was recently confirmed by two meta-analyses, although the inhomogeneity of study designs, stimulation paradigms and stimulation sites as well as confounders of co-stimulation necessitates very cautious interpretation of compound data. Furthermore, these positive effects on postural stability and gait are variable between studies and even within studies. It seems that some patients profit while others do not.

There are different possible explanations for the inconsistency of results. First of all, it is difficult to assess and quantify axial PD signs such as postural instability, FOG and falls. For instance, the “pull test” item of the Unified Parkinson´s Disease Ranking Scale (UPDRS) is the only method used by most studies to assess postural instability. However, it is poorly reliable and highly depends on the examiner. On the other hand, to assess FOG and falls, most studies relied on questionnaires which are prone to recall bias (Ferraye et al., 2010; Thevathasan et al., 2011a). Other studies used objective laboratory methods to analyse spatiotemporal gait patterns (Peppe et al., 2010; Stefani et al., 2007; Thevathasan et al., 2012). However, the fluctuating quality of FOG and its propensity for disappearing under observation restrict the validity of such elaborate methods. Second, the stimulation site differed between studies. While some studies targeted the caudal PPN, active contact position was distributed along the rostrocaudal axis in other studies (summarized in table 1). From anatomical and functional considerations based on animal experiments, the PPN is not a homogenous structure but seems to have different, anatomically and functionally segregated parts (Alderson et al., 2008; Dautan et al., 2016b; Takakusaki et al., 2016). In line with this premise, first evidence from neurophysiological studies in humans confirmed such a somatotopy: oscillations in the alpha band measured in

the caudal part of the PPN were found to correlate with gait and freezing whereas beta band oscillations in the rostral part of the PPN did not (Tattersall et al., 2014; Thevathasan et al., 2012). Thus, very limited data points towards the hypothesis that stimulation of the caudal PPN is clinically more effective in reducing FOG than stimulation of the rostral PPN (Thevathasan et al., 2012). However, there are still controversies about this (Hamani et al., 2016b).

Contrary to axial symptoms and FOG, other symptoms such as tremor, akinesia and rigidity do not seem to respond to PPN-DBS. The great majority of the studies found no significant reduction in the overall motor UPDRS part III (Ferraye et al., 2010; Moro et al., 2010; Thevathasan et al., 2011a; Thevathasan et al., 2012; Welter et al., 2015). Positive effects of PPN-DBS on the total motor UPDRS III score were only repeatedly reported by open-label studies of one group including 1 to 7 patients and by one prospective double-blind study of 6 patients (Khan et al., 2012; Khan et al., 2011; Plaha and Gill, 2005; Stefani et al., 2007). Furthermore, in contrast to DBS of the STN for PD, PPN-DBS enabled no reduction of dopaminergic therapy in all those studies reporting on L-DOPA equivalent doses (Moro et al., 2010; Thevathasan et al., 2011a; Welter et al., 2015).

Another important feature of PPN-DBS with reference to its motor effects is the long latency for clinical benefits to occur. Unlike stimulation of the STN, there are no immediate observable effects after switching on and off the neurostimulator in case of PPN-DBS. Furthermore, some centres described carry-over effects after chronic stimulation lasting for days to weeks (Ferraye et al., 2010). This does not only have theoretical implications for the study design when incorporating stimulation-on and stimulation-off phases to evaluate clinical effects, but also for clinical purposes and stimulation parameter adjustment. The unpredictable, fluctuating nature of gait freezing and the long latencies of stimulation parameter adjustments makes DBS programming of the PPN a complex and time-consuming procedure (Thevathasan et al., 2017). All studies found that low-frequency stimulation of the PPN was optimal to alleviate motor symptoms (see table 1). However, the frequencies varied considerably between studies and ranged from 15-70 Hz depending on the co-stimulation with other targets. Again, the inhomogeneity between studies in terms of stimulation paradigms prevents from drawing further conclusions about the optimal stimulation parameters.

PPN-DBS study results in humans: side effects and non-motor impact

Clinical application of bilateral PPN-DBS has been demonstrated to be clinically safe. Though, when it comes to the most dreaded complication in DBS, namely a surgery-related haemorrhage, the impact can be disastrous and lead to permanent dependency of the patient (Welter et al., 2015). Side effects, which are stimulation-dependent can be explained by current-spread and consecutive activation of the neighbouring anatomical structures. These encompass contralateral paraesthesia, that typically habituate over seconds to minutes and which are explained by current spread to the medial lemniscus (Ferraye et al., 2010; Stefani et al., 2007). Painful sensations may reflect activation of the more posterior located spinothalamc fiber tract (Hazrati et al., 2012). Oscillopsia is another regularly described phenomenon that clinically goes along with ipsilateral nystagmus and has been attributed to stimulation of the cerebellothalamic fibers within the superior cerebellar peduncle (Jenkinson et al., 2012). Stimulation of the latter has been further associated with limb myoclonus (Ferraye et al., 2010). Urge incontinence attributed to stimulation of the pontine micturition centre was described in one patient (Aviles-Olmos et al., 2011). Further investigation into this phenomenon with urodynamic testing found no detrimental effects on urodynamic filling parameters and detrusor activity but a slight increase in maximal bladder capacity (Roy et al., 2017).

That the cholinergic transmission originating from the PPN may play a role in mediating brain state changes and mediate arousal, attention and REM-sleep control was outlined above. The question if stimulation of the PPN as part of the so-called RAS also has clinical implications has been addressed, especially because gait deficits and falls are at least in part attributable to attentional deficits (Giladi and Hausdorff, 2006). To date, there is no evidence of impaired cognitive function after PPN DBS, on the contrary, some studies found a positive effect on frontal lobe function and reaction time (Ferraye et al., 2010; Thevathasan et al., 2011b; Thevathasan et al., 2010; Welter et al., 2015). Moreover, the possible impact of PPN stimulation on sleep in patients with PD was addressed by three studies. These studies found that PPN DBS affected the switching between sleep stages and promoted REM sleep (Alessandro et al., 2010; Arnulf et al., 2010; Lim et al., 2009). Using polysomnography in 5 PD patients undergoing unilateral PPN-DBS Lim and

co-workers demonstrated a near doubling of nocturnal REM sleep episodes between the DBS "off" and DBS "on" states, without significant changes in other sleep states. This is particularly noteworthy as REM sleep disorders are a common symptom in PD patients (Bassetti and Bargiotas, 2018; Di Fabio et al., 2013). However, it remains unclear if these observations of PPN-DBS induced increases in the frequency of REM sleep episodes have any clinical significance.

Missing or weak effects of PPN stimulation due to the complex intrinsic functional and anatomical segregation of the small nucleus on the one hand and induction of side effects due to current spread to the surrounding fiber pathways on the other hand might be improved by future applications of electrodes with an altered design. Smaller electrodes and current steering technologies might increase the specification of stimulation in this area, similarly to what has been demonstrated in other target structure such as the STN(Contarino et al., 2014; Pollo et al., 2014; Steigerwald et al., 2016).

Targeting strategies of the PPN

Similar to the differences in study designs and co-stimulation with other targets, there is considerable variability in the targeting strategies used by different groups. Targeting methods include both *direct targeting* strategies based on identification of the target structure based on landmarks depictable on the patient`s MRI or *indirect targeting* strategies based on coordinates derived from human brain atlases. Thus methodology ranged from sole T2-weighted MRI-based direct targeting under general anaesthesia, combination of MRI-based and stereotactic CT-based targeting as well as loan stereotactic CT- or ventriculography-based targeting incorporating information from a stereotactic atlas of the human brain stem (Ferraye et al., 2010; Plaha and Gill, 2005; Stefani et al., 2007; Thevathasan et al., 2011a; Weinberger et al., 2008). Some groups used intraoperative microelectrode recording for target confirmation, while others did not (Ferraye et al., 2010; Khan et al., 2012; Thevathasan et al., 2011a). A detailed discussion about the different targeting approaches and results of microelectrode recordings is beyond the scope of this review and can be found in other excellent reviews (Hamani et al., 2016a; Hamani et al., 2016b). Only a few points shall be highlighted in the context of this review: as already outlined above, there is considerable variability of the exact location and borders of the PPN between different brainstem atlases. This might be attributed to

the fact that the PPN is a reticular nucleus with indistinct boundaries and has important implications on atlas-based targeting and further contributes to the difficulty to exactly localize implanted electrodes. With respect to direct targeting based on MRI, the PPN can be detected (indirectly) in the context of surrounding structures: lateral to the cerebellar peduncle and medial to the medial lemniscus at the level of the pontomesencephalic junction. By applying T1- and Proton-weighted sequences, Zrinzo and colleagues compared atlas-based coordinates and MRI images of 12 patients and found significant differences between the predicted PPN coordinates based on atlases and the PPN position found on MRI (Zrinzo et al., 2008). These differences were especially pronounced in the rostro-caudal axis. This study underlines the high individual variability of the exact anatomical location of the PPN and the shortcomings of atlas-based targeting technique not to account for this variability. However, the MRI borders of the PPN and nearby structures also cannot be delineated with certainty in many cases especially in patients with degenerative processes of the PPN (Mazzone et al., 2016; Yelnik, 2007). More recently, diffusion tensor imaging has been proposed to help guide targeting by better visualizing the neighbouring fiber tracts (Alho et al., 2017). If DTI-based targeting strategies improve accuracy and outcome, has to be shown in future studies.

PPN-DBS in humans: who can profit?

Despite more than 10 years of clinical experience with DBS of the PPN, the number of implanted patients remains limited and outcome varies to a considerable extent. Attributable factors have been discussed and include high variability of clinical methodology, difficulties of outcome assessment as well as distinct underlying patient characteristics throughout different studies. Despite these numerous limitations of current data, there is a clear trend that PPN has the potential to improve FOG and reduce falls in some patients. Factors that may predict outcome are currently not known. On the other hand, PPN-DBS does not seem to improve other aspects of PD such as tremor, rigor and akinesia and does not allow a reduction of dopaminergic medication. Gathering the available information, there are two PD patient profiles that might best respond to PPN-DBS. First, patients with early-onset and severe medication resistant gait freezing are candidates for sole PPN-DBS (Giladi and Hausdorff, 2006). This unusual subgroup only consists of around 5% of patients with PD. Patients suffering from medication-responsive gait freezing and motor fluctuations, however, qualify for classical STN and GPi DBS (Deuschl et al., 2006; Follett et al., 2010). Patients with PD who develop therapy-resistant gait freezing despite STN and GPi DBS can be candidates for co-stimulation with PPN (Ferraye et al., 2010; Khan et al., 2012; Stefani et al., 2007; Thevathasan et al., 2011a).

Concluding remarks

The classical ideas about the PPN which was primarily associated with the key words “mesencephalic locomotor region” and the “reticular activating system” have been refined to a considerable extent over the past few decades. The PPN has been appreciated as an inhomogeneous reticular nucleus of the pontomesencephalic tegmentum that features intricate neuroanatomical, neurochemical and neurophysiological properties. Its intense anatomical connectivity with key components of the basal-ganglia, cerebellum, thalamus, midbrain dopaminergic nuclei, brainstem motor nuclei and spinal cord puts it into a central position to modulate a variety of functions such as reward prediction error coding, motivational and goal-directed behaviour, locomotion, attention and regulation of the sleep-wake-cycle. The overall complexity which is condensed into a comparatively small neuronal assembly of a few millimetres in diameter needs to be acknowledged if we intend to

modulate subcomponents of its many functions by applying DBS to treat gait disorders in PD patients. Certainly more details about the intricate organization of the PPN and ways to target more accurately clinically effective subterritories of the PPN must be found out until we can appreciate its full clinical potential. Notwithstanding these constraints, the clinical findings that early-onset gait disturbances as well as therapy resistant gait freezing despite STN/GPi-stimulation may benefit from additional low-frequency stimulation of the PPN shall motivate for the conduct of future research and clinical trials. The latter ones have to take account of the difficulties for proper targeting as well as meaningful assessment of clinical outcome. Improvement of imaging, down-scaling and steering of the stimulation area by use of directional leads in order to improve the therapeutic window as well as utilization of a dedicated scale to assess gait disturbances and freezing might be important and encouraging future factors to help disentangle the complex and ambitious enterprise to understand and achieve clinically relevant effects of PPN-DBS.

References

Ainge, J. A., et al., 2004. Induction of c-fos in specific thalamic nuclei following stimulation of the pedunculopontine tegmental nucleus. Eur J Neurosci. 20**,** 1827-37.

Alderson, H. L., et al., 2008. 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. 213**,** 247-53.

Alessandro, S., et al., 2010. Non-motor functions in parkinsonian patients implanted in the pedunculopontine nucleus: focus on sleep and cognitive domains. J Neurol Sci. 289**,** 44-8.

Alho, A., et al., 2017. Magnetic resonance diffusion tensor imaging for the pedunculopontine nucleus: proof of concept and histological correlation. Brain Struct Funct. 222**,** 2547-2558.

Arnulf, I., et al., 2010. Sleep induced by stimulation in the human pedunculopontine nucleus area. Ann Neurol. 67**,** 546-9.

Aviles-Olmos, I., et al., 2011. Urinary incontinence following deep brain stimulation of the pedunculopontine nucleus. Acta Neurochir (Wien). 153**,** 2357-60.

Aziz, T. Z., et al., 1998. The role of descending basal ganglia connections to the brain stem in parkinsonian akinesia. Br J Neurosurg. 12**,** 245-9.

Barroso-Chinea, P., et al., 2011. Glutamatergic and cholinergic pedunculopontine neurons innervate the thalamic parafascicular nucleus in rats: changes following experimental parkinsonism. Brain Struct Funct. 216**,** 319-30.

Bassetti, C. L., Bargiotas, P., 2018. REM Sleep Behavior Disorder. Front Neurol Neurosci. 41**,** 104-116.

Beninato, M., Spencer, R. F., 1987. A cholinergic projection to the rat substantia nigra from the pedunculopontine tegmental nucleus. Brain Res. 412**,** 169-74.

Bevan, M. D., Bolam, J. P., 1995. Cholinergic, GABAergic, and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. J Neurosci. 15**,** 7105-20.

Boucetta, S., et al., 2014. Discharge profiles across the sleep-waking cycle of identified cholinergic, GABAergic, and glutamatergic neurons in the pontomesencephalic tegmentum of the rat. J Neurosci. 34**,** 4708-27.

Brantley, R. K., Bass, A. H., 1988. Cholinergic neurons in the brain of a teleost fish (Porichthys notatus) located with a monoclonal antibody to choline acetyltransferase. J Comp Neurol. 275**,** 87-105.

Breit, S., et al., 2006. Lesion of the pedunculopontine nucleus reverses hyperactivity of the subthalamic nucleus and substantia nigra pars reticulata in a 6-hydroxydopamine rat model. Eur J Neurosci. 24**,** 2275-82.

Burns, R. S., et al., 1983. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci U S A. 80**,** 4546-50.

Carter, D. A., Fibiger, H. C., 1978. The projections of the entopeduncular nucleus and globus pallidus in rat as demonstrated by autoradiography and horseradish peroxidase histochemistry. J Comp Neurol. 177**,** 113-23.

Charara, A., et al., 1996. 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. 364**,** 254-66.

Clements, J. R., Grant, S., 1990. Glutamate-like immunoreactivity in neurons of the laterodorsal tegmental and pedunculopontine nuclei in the rat. Neurosci Lett. 120**,** 70-3.

Contarino, M. F., et al., 2014. Directional steering: A novel approach to deep brain stimulation. Neurology. 83**,** 1163-9.

Dautan, D., et al., 2016a. Extrinsic Sources of Cholinergic Innervation of the Striatal Complex: A Whole-Brain Mapping Analysis. Front Neuroanat. 10**,** 1.

Dautan, D., et al., 2014. A major external source of cholinergic innervation of the striatum and nucleus accumbens originates in the brainstem. J Neurosci. 34**,** 4509-18.

Dautan, D., et al., 2016b. Segregated cholinergic transmission modulates dopamine neurons integrated in distinct functional circuits. Nat Neurosci. 19, 1025-33.

Deurveilher, S., Hennevin, E., 2001. Lesions of the pedunculopontine tegmental nucleus reduce paradoxical sleep (PS) propensity: evidence from a short-term PS deprivation study in rats. Eur J Neurosci. 13, 1963-76.

Deuschl, G., et al., 2006. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 355, 896-908.

Di Fabio, N., et al., 2013. Sleepwalking, REM sleep behaviour disorder and overlap parasomnia in patients with Parkinson's disease. Eur Neurol. 70, 297-303.

Erro, E., et al., 1999. Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. Exp Brain Res. 127, 162-70.

Fay, R. A., Norgren, R., 1997a. Identification of rat brainstem multisynaptic connections to the oral motor nuclei in the rat using pseudorabies virus. II. Facial muscle motor systems. Brain Res Brain Res Rev. 25, 276-90.

Fay, R. A., Norgren, R., 1997b. Identification of rat brainstem multisynaptic connections to the oral motor nuclei using pseudorabies virus. I. Masticatory muscle motor systems. Brain Res Brain Res Rev. 25, 255-75.

Ferraye, M. U., et al., 2010. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain. 133, 205-14.

Follett, K. A., et al., 2010. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 362, 2077-91.

Ford, B., et al., 1995. GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. J Comp Neurol. 363, 177-96.

Fournier-Gosselin, M. P., et al., 2013. Regional anatomy of the pedunculopontine nucleus: relevance for deep brain stimulation. Mov Disord. 28, 1330-6.

Galati, S., et al., 2008. Deep brain stimulation promotes excitation and inhibition in subthalamic nucleus in Parkinson's disease. Neuroreport. 19, 661-6.

Garcia-Rill, E., 1991. The pedunculopontine nucleus. Prog Neurobiol. 36, 363-89.

Garcia-Rill, E., et al., 1987. Locomotion-inducing sites in the vicinity of the pedunculopontine nucleus. Brain Res Bull. 18, 731-8.

Garcia-Rill, E., et al., 2013. Coherence and frequency in the reticular activating system (RAS). Sleep Med Rev. 17, 227-38.

Garcia-Rill, E., et al., 2015. Pedunculopontine arousal system physiology - Implications for insomnia. Sleep Sci. 8, 92-9.

Giladi, N., Hausdorff, J. M., 2006. The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. J Neurol Sci. 248, 173-6.

Gillies, A. J., Willshaw, D. J., 1998. A massively connected subthalamic nucleus leads to the generation of widespread pulses. Proc Biol Sci. 265, 2101-9.

Goetz, L., et al., 2016. On the Role of the Pedunculopontine Nucleus and Mesencephalic Reticular Formation in Locomotion in Nonhuman Primates. J Neurosci. 36, 4917-29.

Gomez-Gallego, M., et al., 2007. 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 Transm (Vienna). 114, 319-26.

Gould, E., et al., 1989. Cholinergic projections to the substantia nigra from the pedunculopontine and laterodorsal tegmental nuclei. Neuroscience. 28, 611-23.

Grace, K. P., et al., 2014. Endogenous cholinergic input to the pontine REM sleep generator is not required for REM sleep to occur. J Neurosci. 34, 14198-209.

Groenewegen, H. J., et al., 1993. Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. Neuroscience. 57, 113-42.

Hallanger, A. E., Wainer, B. H., 1988. Ultrastructure of ChAT-immunoreactive synaptic terminals in the thalamic reticular nucleus of the rat. J Comp Neurol. 278**,** 486-97.

Hamani, C., et al., 2016a. Pedunculopontine Nucleus Region Deep Brain Stimulation in Parkinson Disease: Surgical Anatomy and Terminology. Stereotact Funct Neurosurg. 94**,** 298-306.

Hamani, C., et al., 2016b. Pedunculopontine Nucleus Region Deep Brain Stimulation in Parkinson Disease: Surgical Techniques, Side Effects, and Postoperative Imaging. Stereotact Funct Neurosurg. 94**,** 307-319.

Hamani, C., et al., 2011. The pedunculopontine nucleus as a target for deep brain stimulation. J Neural Transm (Vienna). 118**,** 1461-8.

Hazrati, L. N., Parent, A., 1992. Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey. Brain Res. 585**,** 267-71.

Hazrati, L. N., et al., 2012. Clinicopathological study in progressive supranuclear palsy with pedunculopontine stimulation. Mov Disord. 27**,** 1304-7.

Hirsch, E. C., et al., 1987. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc Natl Acad Sci U S A. 84**,** 5976-80.

Holmstrand, E. C., Sesack, S. R., 2011. Projections from the rat pedunculopontine and laterodorsal tegmental nuclei to the anterior thalamus and ventral tegmental area arise from largely separate populations of neurons. Brain Struct Funct. 216**,** 331-45.

Honda, T., Semba, K., 1995. An ultrastructural study of cholinergic and non-cholinergic neurons in the laterodorsal and pedunculopontine tegmental nuclei in the rat. Neuroscience. 68**,** 837-53.

Inglis, W. L., et al., 1994a. An investigation into the role of the pedunculopontine tegmental nucleus in the mediation of locomotion and orofacial stereotypy induced by d-amphetamine and apomorphine in the rat. Neuroscience. 58**,** 817-33.

Inglis, W. L., et al., 1994b. Outflow from the nucleus accumbens to the pedunculopontine tegmental nucleus: a dissociation between locomotor activity and the acquisition of responding for conditioned reinforcement stimulated by d-amphetamine. Neuroscience. 62**,** 51-64.

Jacobson, L., 1909. Über die Kerne des menschlichen Hrinstamms: (Medulla oblongata, Pons, und Pedunculus cerebri). Anhang zu den Abhandlungen der Kgl. Preuss. Akad. d. Wiss.

Jenkinson, N., et al., 2012. On the origin of oscillopsia during pedunculopontine stimulation. Stereotact Funct Neurosurg. 90**,** 124-9.

Jenkinson, N., et al., 2005. Pedunculopontine nucleus: a new target for deep brain stimulation for akinesia. Neuroreport. 16**,** 1875-6.

Jenkinson, N., et al., 2004. Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. Neuroreport. 15**,** 2621-4.

Jenkinson, N., et al., 2006. Pedunculopontine nucleus electric stimulation alleviates akinesia independently of dopaminergic mechanisms. Neuroreport. 17**,** 639-41.

Jones, B. E., et al., 1977. Ascending projections of the locus coeruleus in the rat. I. Axonal transport in central noradrenaline neurons. Brain Res. 127**,** 1-21.

Jones, B. E., Moore, R. Y., 1977. Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. Brain Res. 127**,** 25-53.

Jones, B. E., Yang, T. Z., 1985. The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. J Comp Neurol. 242**,** 56-92.

Kamondi, A., et al., 1992. Membrane properties of mesopontine cholinergic neurons studied with the whole-cell patch-clamp technique: implications for behavioral state control. J Neurophysiol. 68**,** 1359-72.

Keating, G. L., Winn, P., 2002. Examination of the role of the pedunculopontine tegmental nucleus in radial maze tasks with or without a delay. Neuroscience. 112**,** 687-96.

Khan, S., et al., 2012. Clinical outcomes from bilateral versus unilateral stimulation of the pedunculopontine nucleus with and without concomitant caudal zona incerta region stimulation in Parkinson's disease. Br J Neurosurg. 26**,** 722-5.

Khan, S., et al., 2011. Outcomes from stimulation of the caudal zona incerta and pedunculopontine nucleus in patients with Parkinson's disease. Br J Neurosurg. 25**,** 273-80.

Kim, M. A., et al., 2004. Reciprocal connections between subdivisions of the dorsal raphe and the nuclear core of the locus coeruleus in the rat. Brain Res. 1026, 56-67.

Kojima, J., et al., 1997. Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. Neurosci Lett. 226, 111-4.

Kolmac, C. I., Mitrofanis, J., 1998. Patterns of brainstem projection to the thalamic reticular nucleus. J Comp Neurol. 396, 531-43.

Langston, J. W., et al., 1983. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 219, 979-80.

Langston, J. W., et al., 2000. Investigating levodopa-induced dyskinesias in the parkinsonian primate. Ann Neurol. 47, S79-89.

Lavoie, B., Parent, A., 1994a. Pedunculopontine nucleus in the squirrel monkey: cholinergic and glutamatergic projections to the substantia nigra. J Comp Neurol. 344, 232-41.

Lavoie, B., Parent, A., 1994b. Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. J Comp Neurol. 344, 210-31.

Leblond, M., et al., 2014. The role of pedunculopontine nucleus in choice behavior under risk. Eur J Neurosci. 39, 1664-70.

Lichtensteiger, W., et al., 1982. Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology. 21, 963-8.

Lim, A. S., et al., 2009. Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. Ann Neurol. 66, 110-4.

Loughlin, S. E., et al., 1986. Efferent projections of nucleus locus coeruleus: topographic organization of cells of origin demonstrated by three-dimensional reconstruction. Neuroscience. 18, 291-306.

Luebke, J. I., et al., 1992. Serotonin hyperpolarizes cholinergic low-threshold burst neurons in the rat laterodorsal tegmental nucleus in vitro. Proc Natl Acad Sci U S A. 89, 743-7.

Manaye, K. F., et al., 1999. Quantification of cholinergic and select non-cholinergic mesopontine neuronal populations in the human brain. Neuroscience. 89, 759-70.

Marin, O., et al., 1997. Distribution of choline acetyltransferase immunoreactivity in the brain of anuran (Rana perezi, Xenopus laevis) and urodele (Pleurodeles waltl) amphibians. J Comp Neurol. 382, 499-534.

Martinez-Gonzalez, C., et al., 2014. Divergent motor projections from the pedunculopontine nucleus are differentially regulated in Parkinsonism. Brain Struct Funct. 219, 1451-62.

Matsumura, M., et al., 2000. Organization of somatic motor inputs from the frontal lobe to the pedunculopontine tegmental nucleus in the macaque monkey. Neuroscience. 98, 97-110.

Matsumura, M., et al., 1997. Single-unit activity in the primate nucleus tegmenti pedunculopontinus related to voluntary arm movement. Neurosci Res. 28, 155-65.

Mazzone, P., et al., 2016. Progress in deep brain stimulation of the pedunculopontine nucleus and other structures: implications for motor and non-motor disorders. J Neural Transm (Vienna). 123, 653-654.

Mazzone, P., et al., 2005. Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. Neuroreport. 16, 1877-81.

McCormick, D. A., et al., 1991. Actions of norepinephrine in the cerebral cortex and thalamus: implications for function of the central noradrenergic system. Prog Brain Res. 88, 293-305.

McGinty, D. J., Harper, R. M., 1976. Dorsal raphe neurons: depression of firing during sleep in cats. Brain Res. 101, 569-75.

Mena-Segovia, J., Bolam, J. P., 2017. Rethinking the Pedunculopontine Nucleus: From Cellular Organization to Function. Neuron. 94, 7-18.

Mena-Segovia, J., et al., 2004. Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? Trends Neurosci. 27, 585-8.

Mena-Segovia, J., et al., 2009. GABAergic neuron distribution in the pedunculopontine nucleus defines functional subterritories. J Comp Neurol. 515, 397-408.

Mena-Segovia, J., et al., 2008a. Cholinergic brainstem neurons modulate cortical gamma activity during slow oscillations. J Physiol. 586, 2947-60.

Mena-Segovia, J., et al., 2008b. Cholinergic modulation of midbrain dopaminergic systems. Brain Res Rev. 58, 265-71.

Mestre, T. A., et al., 2016. Long-term double-blinded unilateral pedunculopontine area stimulation in Parkinson's disease. Mov Disord. 31, 1570-1574.

Mesulam, M. M., et al., 1989. Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons. J Comp Neurol. 283, 611-33.

Mesulam, M. M., et al., 1983. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). Neuroscience. 10, 1185-201.

Mitani, A., et al., 1988. Cholinergic projections from the laterodorsal and pedunculopontine tegmental nuclei to the pontine gigantocellular tegmental field in the cat. Brain Res. 451, 397-402.

Mitchell, I. J., et al., 1989. 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. 32, 213-26.

Moga, M. M., Saper, C. B., 1994. Neuropeptide-immunoreactive neurons projecting to the paraventricular hypothalamic nucleus in the rat. J Comp Neurol. 346, 137-50.

Mori, S., et al., 1978. Controlled locomotion in the mesencephalic cat: distribution of facilitatory and inhibitory regions within pontine tegmentum. J Neurophysiol. 41, 1580-91.

Morita, H., et al., 2014. Pedunculopontine Nucleus Stimulation: Where are We Now and What Needs to be Done to Move the Field Forward? Front Neurol. 5, 243.

Moro, E., et al., 2010. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. Brain. 133, 215-24.

Moruzzi, G., Magoun, H. W., 1949. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol. 1, 455-73.

Motts, S. D., Schofield, B. R., 2009. Sources of cholinergic input to the inferior colliculus. Neuroscience. 160, 103-14.

Munro-Davies, L. E., et al., 1999. The role of the pedunculopontine region in basal-ganglia mechanisms of akinesia. Exp Brain Res. 129, 511-7.

Nakamura, Y., et al., 1989. Monosynaptic nigral inputs to the pedunculopontine tegmental nucleus neurons which send their axons to the medial reticular formation in the medulla oblongata. An electron microscopic study in the cat. Neurosci Lett. 103, 145-50.

Nandi, D., et al., 2002a. Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus. Brain. 125, 2418-30.

Nandi, D., et al., 2002b. Deep brain stimulation of the pedunculopontine region in the normal non-human primate. J Clin Neurosci. 9, 170-4.

Nauta, H. J., 1979. Projections of the pallidal complex: an autoradiographic study in the cat. Neuroscience. 4, 1853-73.

Nauta, W. J., Mehler, W. R., 1966. Projections of the lentiform nucleus in the monkey. Brain Res. 1, 3-42.

Oakman, S. A., et al., 1995. Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra differs significantly from those projecting to ventral tegmental area. J Neurosci. 15, 5859-69.

Okada, K., et al., 2009. Different pedunculopontine tegmental neurons signal predicted and actual task rewards. J Neurosci. 29, 4858-70.

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

Osaka, T., Matsumura, H., 1994. Noradrenergic inputs to sleep-related neurons in the preoptic area from the locus coeruleus and the ventrolateral medulla in the rat. Neurosci Res. 19, 39-50.

Pan, W. X., Hyland, B. I., 2005. Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. J Neurosci. 25, 4725-32.

Panagis, G., et al., 1996. Nicotine injections into the ventral tegmental area increase locomotion and Fos-like immunoreactivity in the nucleus accumbens of the rat. Brain Res. 730, 133-42.

Pare, D., et al., 1988. Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. Neuroscience. 25, 69-86.

Peppe, A., et al., 2010. Deep brain stimulation of the pedunculopontine tegmentum and subthalamic nucleus: effects on gait in Parkinson's disease. Gait Posture. 32, 512-8.

Pereira, E. A., et al., 2008. Deep brain stimulation of the pedunculopontine nucleus in Parkinson's disease. Preliminary experience at Oxford. Br J Neurosurg. 22 Suppl 1, S41-4.

Petzold, A., et al., 2015. Decoding brain state transitions in the pedunculopontine nucleus: cooperative phasic and tonic mechanisms. Front Neural Circuits. 9, 68.

Pienaar, I. S., et al., 2015. Pharmacogenetic stimulation of cholinergic pedunculopontine neurons reverses motor deficits in a rat model of Parkinson's disease. Mol Neurodegener. 10, 47.

Plaha, P., Gill, S. S., 2005. Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. Neuroreport. 16, 1883-7.

Pollo, C., et al., 2014. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain. 137, 2015-26.

Rinne, J. O., et al., 2008. Loss of cholinergic neurons in the pedunculopontine nucleus in Parkinson's disease is related to disability of the patients. Parkinsonism Relat Disord. 14, 553-7.

Roseberry, T. K., et al., 2016. Cell-Type-Specific Control of Brainstem Locomotor Circuits by Basal Ganglia. Cell. 164, 526-37.

Roy, H. A., et al., 2017. Effects of pedunculopontine nucleus stimulation on human bladder function. Neurourol Urodyn.

Ruggiero, D. A., et al., 1997. The pedunculopontine tegmental nucleus issues collaterals to the fastigial nucleus and rostral ventrolateral reticular nucleus in the rat. Brain Res. 760, 272-6.

Rye, D. B., 1997. Contributions of the pedunculopontine region to normal and altered REM sleep. Sleep. 20, 757-88.

Rye, D. B., et al., 1987. Pedunculopontine tegmental nucleus of the rat: cytoarchitecture, cytochemistry, and some extrapyramidal connections of the mesopontine tegmentum. J Comp Neurol. 259, 483-528.

Seguela, P., et al., 1990. Noradrenaline axon terminals in adult rat neocortex: an immunocytochemical analysis in serial thin sections. Neuroscience. 35, 249-64.

Semba, K., Fibiger, H. C., 1992. 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. 323, 387-410.

Semba, K., et al., 1988. Brainstem afferents to the magnocellular basal forebrain studied by axonal transport, immunohistochemistry, and electrophysiology in the rat. J Comp Neurol. 267, 433-53.

Skinner, R. D., et al., 1990a. Locomotor projections from the pedunculopontine nucleus to the spinal cord. Neuroreport. 1, 183-6.

Skinner, R. D., et al., 1990b. Locomotor projections from the pedunculopontine nucleus to the medioventral medulla. Neuroreport. 1, 207-10.

Smith, Y., et al., 1988. Cholinergic and non-cholinergic projections from the upper brainstem core to the visual thalamus in the cat. Exp Brain Res. 70, 166-80.

Spann, B. M., Grofova, I., 1991. Nigropedunculopontine projection in the rat: an anterograde tracing study with phaseolus vulgaris-leucoagglutinin (PHA-L). J Comp Neurol. 311, 375-88.

Stefani, A., et al., 2007. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain. 130, 1596-607.

Steigerwald, F., et al., 2016. Directional deep brain stimulation of the subthalamic nucleus: A pilot study using a novel neurostimulation device. Mov Disord. 31, 1240-3.

Steiniger, B., Kretschmer, B. D., 2004. Effects of ibotenate pedunculopontine tegmental nucleus lesions on exploratory behaviour in the open field. Behav Brain Res. 151, 17-23.

Steininger, T. L., et al., 1992. Afferent projections to the cholinergic pedunculopontine tegmental nucleus and adjacent midbrain extrapyramidal area in the albino rat. I. Retrograde tracing studies. J Comp Neurol. 321, 515-43.

Steriade, M., et al., 1991a. Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: cortically induced synchronization and brainstem cholinergic suppression. J Neurosci. 11**,** 3200-17.

Steriade, M., et al., 1991b. Fast oscillations (20-40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. Proc Natl Acad Sci U S A. 88**,** 4396-400.

Steriade, M., et al., 1988. Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. Neuroscience. 25**,** 47-67.

Szymusiak, R., et al., 1998. Sleep-waking discharge patterns of ventrolateral preoptic/anterior hypothalamic neurons in rats. Brain Res. 803**,** 178-88.

Takakusaki, K., et al., 2016. Brainstem control of locomotion and muscle tone with special reference to the role of the mesopontine tegmentum and medullary reticulospinal systems. J Neural Transm (Vienna). 123**,** 695-729.

Tattersall, T. L., et al., 2014. Imagined gait modulates neuronal network dynamics in the human pedunculopontine nucleus. Nat Neurosci. 17**,** 449-54.

Thevathasan, W., et al., 2011a. Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. Neurosurgery. 69**,** 1248-53; discussion 1254.

Thevathasan, W., et al., 2017. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: A clinical review. Mov Disord.

Thevathasan, W., et al., 2011b. A block to pre-prepared movement in gait freezing, relieved by pedunculopontine nucleus stimulation. Brain. 134**,** 2085-95.

Thevathasan, W., et al., 2012. Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. Brain. 135**,** 148-60.

Thevathasan, W., et al., 2010. The impact of low-frequency stimulation of the pedunculopontine nucleus region on reaction time in parkinsonism. J Neurol Neurosurg Psychiatry. 81**,** 1099-104.

Thompson, J. A., et al., 2016. Mesencephalic representations of recent experience influence decision making. Elife. 5.

Tian, J., et al., 2016. Distributed and Mixed Information in Monosynaptic Inputs to Dopamine Neurons. Neuron. 91**,** 1374-1389.

Usunoff, K. G., et al., 1999. Nitric oxide synthase-containing projections to the ventrobasal thalamus in the rat. Anat Embryol (Berl). 200**,** 265-81.

Van Dort, C. J., et al., 2015. Optogenetic activation of cholinergic neurons in the PPT or LDT induces REM sleep. Proc Natl Acad Sci U S A. 112**,** 584-9.

Vincent, S. R., et al., 1983. Substance P in the ascending cholinergic reticular system. Nature. 306**,** 688-91.

Vincent, S. R., et al., 1986. Neuropeptides and NADPH-diaphorase activity in the ascending cholinergic reticular system of the rat. Neuroscience. 17**,** 167-82.

Volkow, N. D., Morales, M., 2015. The Brain on Drugs: From Reward to Addiction. Cell. 162**,** 712-25.

Wang, H. L., Morales, M., 2009. Pedunculopontine and laterodorsal tegmental nuclei contain distinct populations of cholinergic, glutamatergic and GABAergic neurons in the rat. Eur J Neurosci. 29**,** 340-58.

Weinberger, M., et al., 2008. Pedunculopontine nucleus microelectrode recordings in movement disorder patients. Exp Brain Res. 188**,** 165-74.

Welter, M. L., et al., 2015. PPNa-DBS for gait and balance disorders in Parkinson's disease: a double-blind, randomised study. J Neurol. 262**,** 1515-25.

Wilcox, R. A., et al., 2011. Pedunculopontine nucleus deep brain stimulation produces sustained improvement in primary progressive freezing of gait. J Neurol Neurosurg Psychiatry. 82**,** 1256-9.

Winn, P., 2006. How best to consider the structure and function of the pedunculopontine tegmental nucleus: evidence from animal studies. J Neurol Sci. 248**,** 234-50.

Woolf, N. J., Butcher, L. L., 1986. Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. Brain Res Bull. 16**,** 603-37.

Yelnik, J., 2007. PPN or PPD, what is the target for deep brain stimulation in Parkinson's disease? Brain. 130**,** e79; author reply e80.

Zahm, D. S., et al., 2001. Ventral mesopontine projections of the caudomedial shell of the nucleus accumbens and extended amygdala in the rat: double dissociation by organization and development. J Comp Neurol. 436**,** 111-25.

Zrinzo, L., et al., 2008. Stereotactic localization of the human pedunculopontine nucleus: atlas-based coordinates and validation of a magnetic resonance imaging protocol for direct localization. Brain. 131**,** 1588-98.

Zweig, R. M., et al., 1989. The pedunculopontine nucleus in Parkinson's disease. Ann Neurol. 26**,** 41-6.

Zweig, R. M., et al., 1987. Loss of pedunculopontine neurons in progressive supranuclear palsy. Ann Neurol. 22**,** 18-25.

Table 1: cZI, caudal Zona incerta; FOG, freezing of gait; GFQ, gait and falls questionnaire; PDQ-39, Parkinson`s disease Quality of Life; RSGE, rating scale for gait evaluation

Study: Auhtor, Date, Centre	Number of patients	Targets	Stimulation site	Stimulation parameters	Study design	Follow-up time	Outcome measures	Conclusions
Stefani et al.; 2007; Rome	6	bilat. STN + PPN	Caudal and rostral PPN	25 Hz, 60µs, 1.5-2.0 V	Double-blind	6 months	UPDRS II and III ADL sclae	- Bilat. PPN + STN superior to STN alone in UPDRS III axial subscore reduction in ON-med as well as ADL scores
Ferraye et al.; 2010; Grenoble	6	bilat. STN + PPN (consecutively)	Caudal and rostral PPN	15-25 Hz, 60-90 µs, 1.2-3.8 V	Double-blind (6 months) Open-label (12 months)	6 months and 12 months	UPDRS, FOGQ, PDQ-39	- no changes of UPDRS in double-blind phase - improvement of gait (2 of 6) at 1 year - improvement of FOG (4 of 6) at 1 year
Khan et al.; 2011 and 2012; Bristol	7	bilat. cZI + PPN	PPN (not specified)	60 Hz; 60 µs; 2.6 V	Open-label	12 months	UPDRS III; PDQ-39	- PPN + cZI significantly improved UPDRS III axial subscore compared to PPN and cZI alone in ON-med
Thevathasan et al.; 2011a; Brisbane	5	bilat. PPN	Caudal PPN	35 Hz; 60 µs; 3.5 V	Open-label	24 months	UPDRS; GFQ	- GFQ scores improved in all patients; fewer falls - Off-med UPDRS

								axial scores improved
Thevathasan et al.; 2012; Oxford, London	7	bilat. PPN	Caudal PPN	35-40 Hz, 60 µs; 1.8-3.5 V	Single-session double blind	2-30 months	UPDRS II + III; GFQ	- GFQ score improved significantly
Welter et al.; 2015; Paris	6	bilat. PPN	Cuadal and rostral PPN	20-40 Hz; 60 µs; 1.3-3.1 V	Double-blind	6 months	RSGE, UPDRS II and III composite gait score, PDQ-39	- brainstem hemorrhage in 1 patient - reduced FOG in 3 of 4 patients - PDQ-39 improved significantly
Mestre et al.; 2016; Toronto	9	unilat. PPN	Caudal and rostral PPN	50-70 Hz; 60-120 µs; 1-3.5 V	Double-blind	24-48 months	UPDRS II and III axial scores	- Improvement in falls and freezing in 5-6/8 patients

Figure legends

Figure 1: Schematic (**A, B**) and corresponding ChAT-immunostained microscopical (**C, D**) views of the Pedunculopontine nucleus and its anatomical relationship in the midbrain tegmentum at the level of the inferior colliculus (A, C) and at the level of the trochlear nucleus and intercollicular area (B, D). The ChAT-immunostained microscopical images demonstrate the subdivision of the nucleus into a compact and reticular part with its weakly defined boundaries. The curved arrows point to some of the interstitial ChAT-positive neurons in the diffuse part of Ch5 (Ch5d).
CA, cerebral aqueduct; cg = central grey; Ch5c = compact part of group 5 cholinergic neurons; Ch5d = dense part of group 5 cholinergic neurons; Ch6 = group 6 cholinergic neurons; CN/nc = cuneiform nucleus; ctt/CTT = central tegmental tract; Dec SCP = decussation of the superior cerebellar peduncles; dr/NRD = dorsal raphe nucleus; LC = locus coeruleus; LL = lateral lemniscus; ML = medial lemniscus; MLF = medial longitudinal fasciculus; PAG = periaqueductal gray; PN = pontine nuclei; ppc/PPNc = compact part of the pedunculopontine nucleus; PPNd = pedunculopontine nucleus pars dissipata; scp = superior cerebellar peduncle; SNc = substantia nigra pars compacta; STT = spinothalamic tract; RST = rubrospinal tract; tn/IV = trochlear nucleus; V = mesencephalic nucleus of the trigeminal nerve; v IV= 4th ventricle.
(*Figure 1 A,B is adapted from Fournier-Gosselin et al. 2013 (Fournier-Gosselin et al., 2013), Figure 1 C, D is adapted from Mesulam et al. 1989 (Mesulam et al., 1989) with kind permission of the authors*).

Figure 2: Connectivity map of the Pedunculopontine nucleus. Afferent connections are displayed in black, efferent cholinergic connections are displayed in blue, efferent GABAergic connections are displayed in yellow, efferent glutamatergic connections are displayed in red. The connectivity map represents current knowledge and is not intended to be exhaustive. Ach = acetylcholine; AMY = amygdale; GABA = gamma-aminobutyric acid; Glu = glutamate; Gig cell = Gigantocellular nucleus; GP = Globus pallidus; PAG = periaqueductal grey matter; Pon. ora. = Pontinus oralis nucleus; PPN = Pedunculopontine nucleus; Raphe nucl. = Raphe nuclei; SNc = substantia nigra compacta; SNr = substantia nigra reticulata; STN = Subthalamic nucleus; sup. Coll. = superior colliculus; VTA = ventral tegmental area.

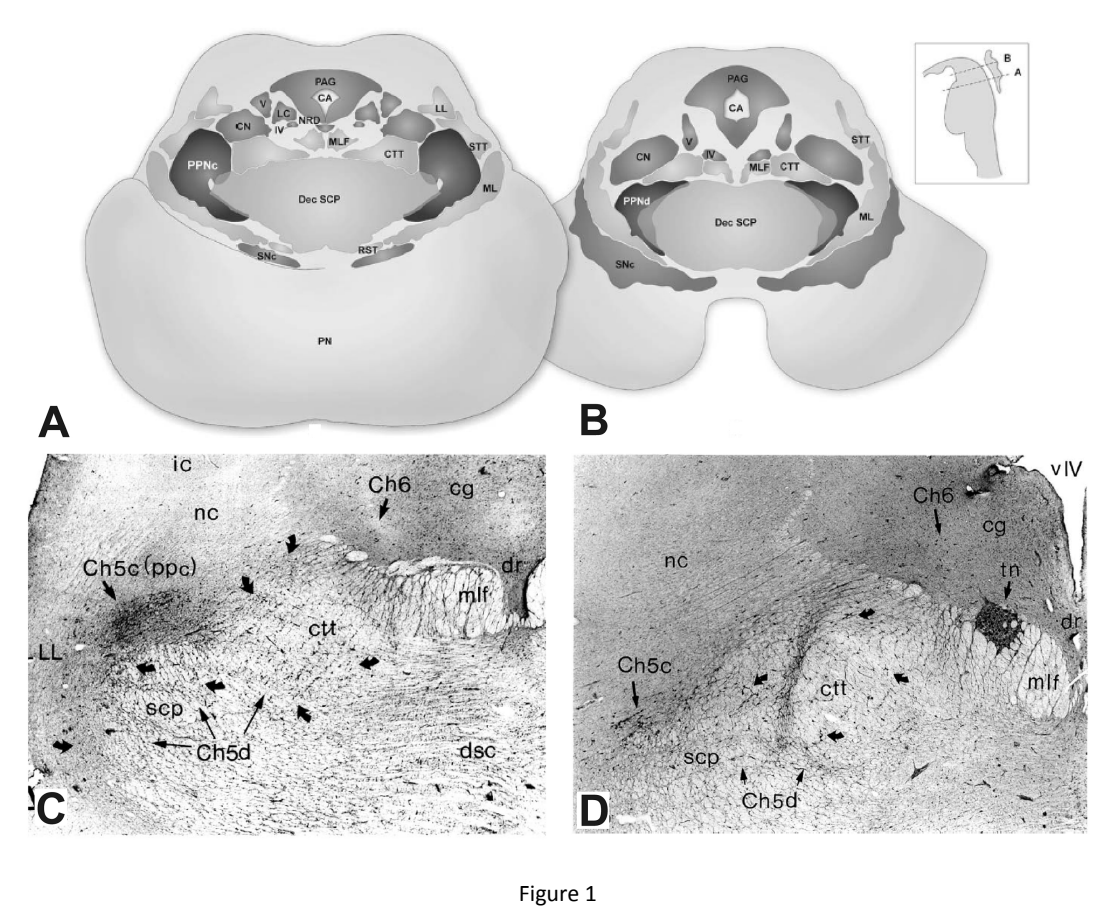

PAG
CA
V
LC
NRD
CN
IV
MLF
CTT
LL
STT
PPNc
ML
Dec SCP
SNc
RST
PN
A
PAG
CA
V
CN
IV
MLF
CTT
STT
PPNd
ML
Dec SCP
SNc
B
B
A
ic
nc
Ch6
cg
Ch5c (ppc)
dr
mlf
ctt
LL
scp
Ch5d
dsc
C
vlV
Ch6
cg
nc
tn
dr
Ch5c
ctt
mlf
scp
Ch5d
D

Figure 1

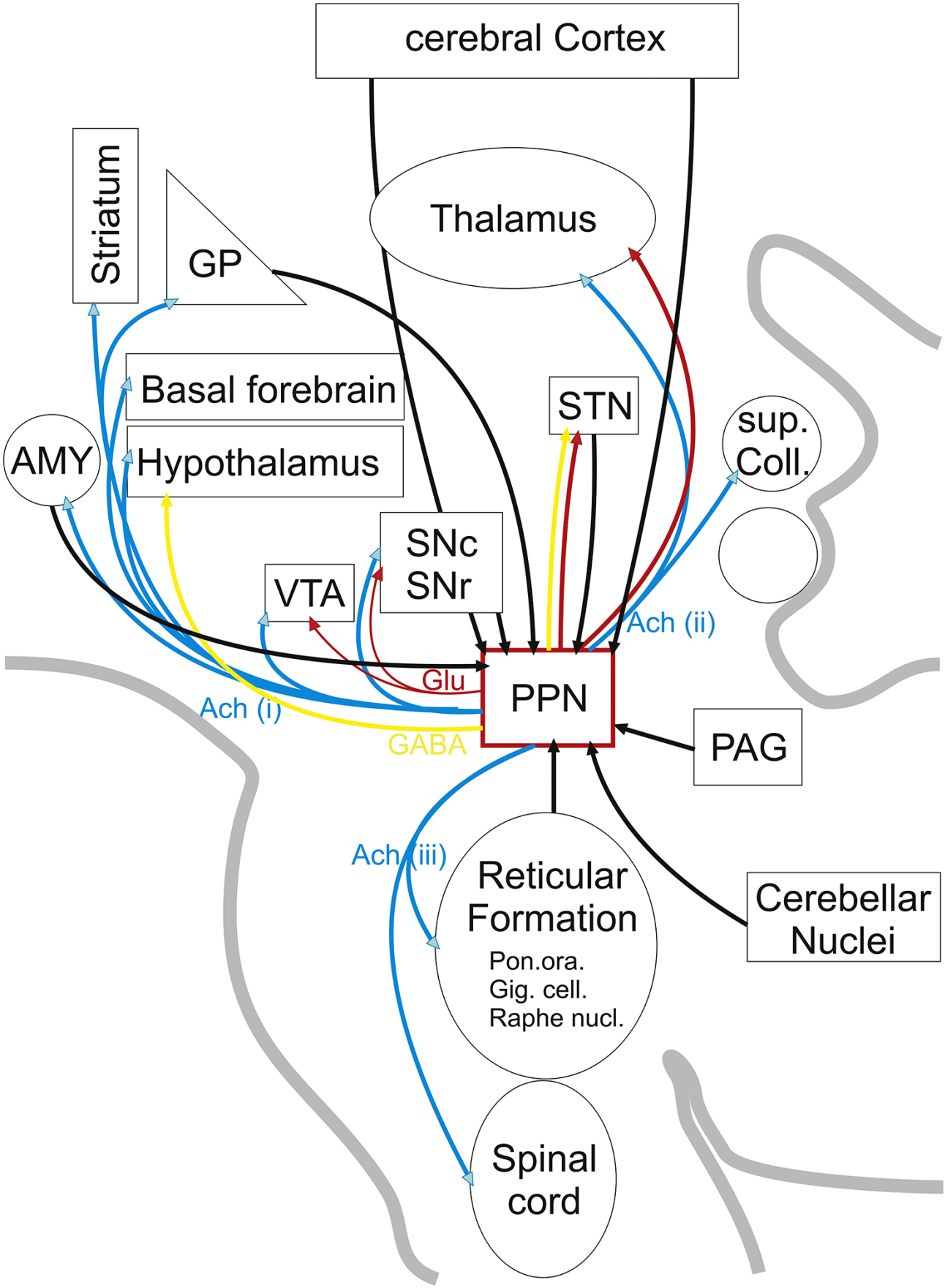

cerebral Cortex
Striatum
GP
Thalamus
Basal forebrain
Hypothalamus
AMY
STN
sup.
Coll.
SNc
SNr
VTA
Ach (ii)
Glu
PPN
Ach (i)
GABA
PAG
Ach (iii)
Reticular
Formation
Pon.ora.
Gig. cell.
Raphe nucl.
Cerebellar
Nuclei
Spinal
cord

Figure 2