Neurobiology of Disease 128 (2019) 3–8

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

The pedunclopontine nucleus and Parkinson's disease

Cecilia Tubert[1], Daniel Galtieri[1], D. James Surmeier*

Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

ABSTRACT

In the last decade, scientific and clinical interest in the pedunculopontine nucleus (PPN) has grown dramatically. This growth is largely a consequence of experimental work demonstrating its connection to the control of gait and of clinical work implicating PPN pathology in levodopa-insensitive gait symptoms of Parkinson's disease (PD). In addition, the development of optogenetic and chemogenetic approaches has made experimental analysis of PPN circuitry and function more tractable. In this brief review, recent findings in the field linking PPN to the basal ganglia and PD are summarized; in addition, an attempt is made to identify key gaps in our understanding and challenges this field faces in moving forward.

1. The PPN is a functionally heterogenous brainstem region

Historically defined as a population of cholinergic neurons in the rostral brainstem, the pedunculopontine nucleus (PPN) is now known to be not only neurochemically heterogenous but functionally complex. In addition to cholinergic neurons, the PPN is populated by glutamatergic and GABAergic neurons (Clements and Grant, 1990; Clements et al., 1991; Ford et al., 1995; Lavoie and Parent, 1994b). Cholinergic neurons, which express choline acetyltransferase (ChAT) and NADPH (Clements and Grant, 1990), have medium to large fusiform, triangular, multipolar or round somas (20–40 μm in diameter) with 2 to 6 primary dendrites (Honda and Semba, 1995; Ichinohe et al., 2000; Rye et al., 1987). Glutamatergic neurons, which express type 2 vesicular glutamate transporter (VGlut2), have a smaller somata (< 20 μm) with 2 to 4 primary dendrites (Clements and Grant, 1990; Ichinohe et al., 2000; Jia et al., 2003; Wang and Morales, 2009). GABAergic neurons, which express the 67 KD isoform of glutamate decarboxylase (GAD67), are similar in size to glutamatergic neurons (Clements and Grant, 1990; Ichinohe et al., 2000; Jia et al., 2003; Wang and Morales, 2009).

Despite its original classification as a cholinergic nucleus, cholinergic neurons constitute only 25–30% of the total number of neurons in the PPN. Glutamatergic neurons constitute the largest fraction (40–45%) of PPN neurons, with GABAergic neurons being about as common as cholinergic neurons (Wang and Morales, 2009). There also appears to be a small group of glycinergic neurons in the PPN (Pienaar et al., 2013). The three principal neuronal populations are unevenly distributed in the PPN. In the rostral, par dissipata portion of the PPN, cholinergic neurons are sparse. Whereas, in the caudal, pars compacta region, cholinergic neurons are considerably more abundant. Glutamatergic neurons also increase in density along the rostro-caudal axis, whereas GABAergic neurons have the opposite gradient, being most abundant in the pars dissipata (Wang and Morales, 2009). Although there is some controversy about the co-expression of different neurotransmitters, the prevailing view is that there is essentially no co-expression and these three populations are truly distinct (Clements et al., 1991; Jia et al., 2003; Lavoie and Parent, 1994a; Wang and Morales, 2009).

This neurochemical diversity in the PPN is partially paralleled by physiological diversity. Based upon in vitro electrophysiological studies with intracellular sharp electrodes, Takakusaki and Kitai (1997) classified PPN neurons into two groups (Type I and Type II). Type I neurons had low threshold spikes (LTS) and sub-threshold voltage oscillations that were sensitive to the Na^+ channel blocker tetrodotoxin. They were spontaneously active, spiking in irregular or bursting patterns at up to 18 spikes per second. Type II neurons also were spontaneously active (3–16 Hz), but their spiking was more regular than Type I neurons. These neurons also had a prominent slow ramp to the first spike after a hyperpolarizing step, indicating the presence of a robust population of Kv4 K^+ channels; another hallmark of these cells was a prominent spike after-hyperpolarization, which like the Kv4 channels served to regularize spiking. Another distinguishing feature of Type II neurons was the presence of Ca^{2+} and Ca^{2+}- dependent sub-threshold oscillations. This description also is consistent with work by Scarnati et al. (1987).

What is less clear is the relationship between Type I and II neurons and the transmitter phenotype of PPN neurons. A little more than half of Type II neurons were found to have histochemical markers of cholinergic neurons, while all of the Type I neurons lacked these markers (Takakusaki and Kitai, 1997). Using a similar post hoc immunocytochemical approach to identify recorded neurons, Petzold et al. (2015) found that PPN cholinergic neurons had a stronger spike

* Corresponding author at: Department of Physiology, Feinberg School of Medicine, Northwestern University, 303 E. Chicago Ave., Chicago, IL 60611, USA.
E-mail address: j-surmeier@northwestern.edu (D.J. Surmeier).

[1] C.T. and D.G. contributed equally to this work.

https://doi.org/10.1016/j.nbd.2018.08.017
Received 2 April 2018; Received in revised form 22 June 2018; Accepted 26 August 2018
Available online 29 August 2018
0969-9961/

frequency adaptation and a lower overall firing frequency than their non-cholinergic counterparts – consistent with the conclusions of Takakusaki et al. (2016). More recently, genetic approaches have been used to label cholinergic and GABAergic PPN neurons with fluorescent reporters allowing directed sampling of these populations (Bordas et al., 2015). These studies have largely confirmed previous work suggesting that cholinergic neurons have the Type II phenotype and gone on to suggest that the expression of Kv7 (KCNQ) K^+ channels by cholinergic neurons not only contributes to the previously described properties of Type II neurons but also endows them with resonance properties in the 20 Hz range.

2. Functional connectivity of the PPN

Both the afferent and efferent connectomes of the PPN are complex. Although monosynaptic rabies virus techniques (Wall et al., 2010; Wickersham et al., 2007) have not been used to generate quantitative, unbiased maps of the regions making synaptic connections with each of the PPN subtypes, conventional anatomical approaches have shown that the basal ganglia and a wide variety of other structures provide a rich innervation of the PPN. In particular, GABAergic neurons in the internal part of the globus pallidus (GPi) and the subtantia nigra pars reticulata (SNr) robustly innervate the PPN (Shink et al., 1997); glutamatergic neurons of the subtalamic nucleus (STN) also innervate the PPN (Granata and Kitai, 1989; Hammond et al., 1983; Jackson and Crossman, 1983; Kita and Kitai, 1987; Steininger et al., 1992). The PPN also receives excitatory innervation from the cerebral cortex, including frontal motor regions and primary auditory cortex (Schofield and Motts, 2009; Semba and Fibiger, 1992; Sesack et al., 1989). The deep cerebellar nuclei, laterodorsal tegmental nucleus, superior and inferior colliculi, dorsal raphe, and locus coeruleus also innervate the PPN (Hazrati and Parent, 1992; Jones and Yang, 1985; Redgrave et al., 1987; Satoh and Fibiger, 1986; Semba and Fibiger, 1992; Steininger et al., 1992, 1997) (Fig. 1). Again, what remains is to clearly determine whether there is cellular specificity to the afferent connectome.

The efferent connectome of the PPN also is diffuse. The longest ranging PPN projections arise from the cholinergic neurons, which as a population, send both ascending projections to the thalamus, basal ganglia, and limbic structures and descending projections to other brainstem nuclei (Dautan et al., 2016; Dautan et al., 2014; Lavoie and Parent, 1994c; Mena-Segovia et al., 2008; Semba and Fibiger, 1992; Takakusaki et al., 1996)(Fig. 1). In contrast, the GABAergic and glutamatergic neurons appear to largely target neighboring areas within the midbrain and brainstem (Bevan and Bolam, 1995; Ford et al., 1995; Mena-Segovia et al., 2008; Ros et al., 2010)(Fig. 1). These projections are somewhat topographically organized – neurons within the caudal PPN project primarily to limbic structures, including the dopaminergic neurons within the ventral tegmental area (VTA), while neurons in the rostral portions of the PPN primarily send projections to motor structures such as the dorsal striatum and substantia nigra pars compacta (SNc) (Dautan et al., 2014; Inglis and Winn, 1995; Jackson and Crossman, 1983; Lavoie and Parent, 1994c; Martinez-Gonzalez et al., 2011; Oakman et al., 1995; Winn, 2006).

One of the most studied targets of the PPN is the SNc. The PPN is well established as one of the primarily sources of excitatory synapses on SNc dopaminergic neurons. Electrical stimulation in the PPN in ex vivo slices produces excitatory post-synaptic potentials in SNc neurons (Futami et al., 1995), while in vivo studies have shown that PPN activation produces an increase in spike discharge rate in SNc neurons (Di Loreto et al., 1992; Scarnati et al., 1986, 1987). As expected from these results, PPN stimulation increases dopamine release in the nucleus accumbens (Floresco et al., 2003). Putting this result into a functional context, inhibition of activity in the PPN blunts the response of SNc dopaminergic neurons to salient behavioral cues, arguing that this key feature of SNc dopaminergic neurons is controlled by the PPN (Pan and Hyland, 2005).

What is more controversial is the type of PPN neuron responsible for excitation of SNc dopaminergic neurons. Recent studies examining the PPN cholinergic projection to SNc dopaminergic neurons have produced conflicting results (Estakhr et al., 2017; Xiao et al., 2016). Despite clear behavioral effects associated with cholinergic activation, Xiao et al. (2016) found that a large fraction of SNc dopaminergic neurons failed to respond to optogenetic activation PPN cholinergic neurons when antagonists for glutamatergic synaptic transmission were present, suggesting that the effects of cholinergic stimulation on SNc activity were largely, if not entirely, mediated by indirect, network based signaling. In contrast, there is little doubt that glutamatergic PPN neurons provide a robust excitatory innervation of SNc dopaminergic neurons. Early in vivo studies found that the excitatory effects of PPN stimulation on SNc discharge rate were dramatically attenuated by antagonists of ionotropic glutamate receptors (Di Loreto et al., 1992; Scarnati et al., 1986; Scarnati et al., 1987). More recently, it has been shown that selective, optogenetic activation of PPN glutamatergic neurons excites ventral tegmental area (VTA) dopaminergic neurons and that mice will lever press for optical stimulation (Yoo et al., 2017). In agreement with these findings, recent work from our group found that PPN glutamatergic neurons made monosynaptic synapses on the proximal dendrites of SNc dopaminergic neurons near the spike-generating axon initial segment, allowing PPN synapses to effectively drive single spikes and bursts of spikes (Galtieri et al., 2017).

3. PPN and the symptoms of PD

One of the most compelling motivations to study PPN cholinergic neurons was the recognition that nearly half of them are gone in late stage PD patients (Hirsch et al., 1987; Shinotoh et al., 1999; Zweig et al., 1989). Given that the PPN appears to be part of the reticular activating system and the mesencephalic locomotor region, it was natural to hypothesize that the sleep and gait symptoms of PD – neither of which are levodopa-responsive – were caused by PPN degeneration (Muslimovic et al., 2008; Sethi, 2008; Zweig et al., 1987). This clinical motivation has been buttressed by work showing a correlation between PD patient falls and the reduction in acetycholine release in the thalamus, which was presumably due to the loss of PPN cholinergic

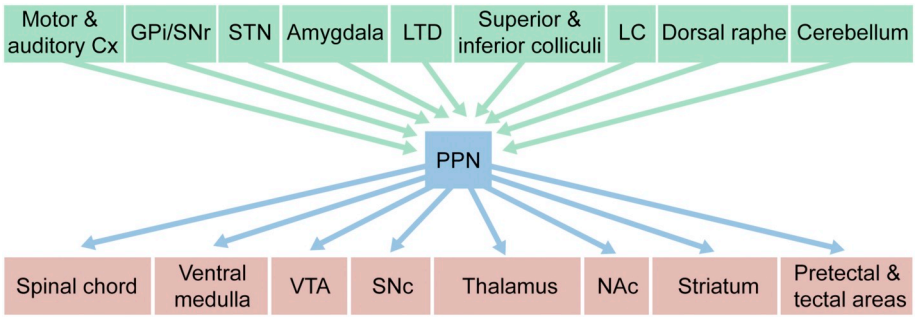

Fig. 1. Summary of the afferent and efferent connectivity of PPN.
Abbreviations: Cx: Cortex; GPi: internal Globus pallidus; SNr: Subtantia Nigra pars reticulata; STN: Subthalamic nucleus; LTD: Laterodorsal tegmental nucleus; LC: Locus coeruleus; VTA: Ventral tegmental area; SNc: Subtantia Nigra pars compacta; NAc: Nucleus accumbens.

neurons (Bohnen et al., 2009; Bohnen et al., 2012). In support this conclusion, functional MRI work has shown that in healthy human subjects PPN activity increases during imagined walking (Karachi et al., 2010).

A number of animal studies have supported the connection between PPN cholinergic neurons and gait control. Karachi et al. (2010) reported that selectively lesioning PPN cholinergic neurons with urotensin II-conjugated diphtheria toxin induced gait and postural deficits in monkeys. They also found that MPTP treatment induced a significant loss of PPN cholinergic neurons, similar to that observed in PD patients. Selectively increasing the excitability of PPN cholinergic neurons with a chemogenetic strategy reportedly ameliorated gait and postural disturbances in a rat model of PD (Pienaar et al., 2015).

However, the connection between PPN cholinergic neurons and gait is far from resolved. Pioneering work done by Garcia-Rill and colleagues (1991) (Garcia-Rill and Skinner, 1987a, 1987b, 1988; Kinjo et al., 1990; Skinner et al., 1990), show that the input from the PPN, in relation to the activation of locomotion, to the ventral medulla and the spinal chord is mainly non-cholinergic. Based on their work, Pahapill and Lozano (2000) speculated that the PPN glutamatergic neurons, which they suggest provide the main PPN output to the spinal chord and the ventral medulla, are critical for the initiation of programed movements and gait, whereas PPN cholinergic neurons relay sensory information about movement back to the basal ganglia and thalamus, helping to maintain gait. This hypothesis has been supported by two compelling, high profile studies using optogenetic approaches, both of which show that PPN glutamatergic neurons – not cholinergic neurons –control gait and locomotion (Caggiano et al., 2018; Roseberry et al., 2016).

A closely related question is the nature of the pathophysiology that might underlie a gait disturbance. Clearly, frank loss of PPN cholinergic could result in dysregulation of target neuronal populations, one of which is likely to be PPN glutamatergic neurons. But, electrophysiological studies in animal models of PD have not yielded a clear picture of what this pathophysiology might be. Some studies have found an increase in the firing rate of unidentified PPN neurons (Aravamuthan et al., 2008; Breit et al., 2001; Geng et al., 2016; Zhang et al., 2008), others have reported decreased spiking (Florio et al., 2007; Gomez-Gallego et al., 2007) while others found no change (Mena-Segovia et al., 2005; Heise and Mitrofanis, 2006). Frankly, these studies, which have all relied upon the use of toxins to create a model of PD, are difficult to interpret for a variety of reasons. One is that the PPN is very close to the SNc, where toxin models induce inflammation, creating a potential artifact. Another concern is that none of the animal PD models faithfully reproduce the pattern of pathology in human PD patients, particularly that seen outside of the SNc in the brainstem (Surmeier et al., 2017a). As PPN receives a convergent input from many of these structures, it could very well be the case that PPN pathophysiology will never be recapitulated in a PD model that only targets the SNc.

In PD patients, there is very little relevant data. It has been reported that there is a decrease in alpha oscillations in the field potentials (Tattersall et al., 2014; Thevathasan et al., 2012) or a synchronization between alpha and beta oscillations (Lau et al., 2015) during the imagined gait. But how this translates to pathological activity patterns in identified cell types is completely unclear. Given the differences in the functional roles played by these different groups of PPN neuron, this is a critical question.

Another key question that remains unanswered is the relationship between gait disturbances and falls. Several studies have implicated basal forebrain cholinergic systems, rather than those of the PPN, in fall frequency in PD patients (Kucinski and Sarter, 2015; Sarter et al., 2014).

In spite of all this uncertainty, the clinical importance of gait and balance disturbances in PD patients have motivated an attempt to use deep brain stimulation (DBS) of the PPN region as a palliative treatment. Unfortunately, these studies have yielded conflicting results (Ferraye et al., 2010; Stefani et al., 2007; Thevathasan et al., 2012; Thevathasan et al., 2018). In a recent review, Thevathasan et al. (2018) conclude that despite this inconsistency, PPN DBS has the potential to improve gait and reduce falls in PD patients. They also conclude that the bilateral PPN DBS has better outcomes than the unilateral DBS. Of course, given the complexity of the PPN and neighboring structures linked to gait, this is not surprising. In agreement with an earlier review (Stefani et al., 2013), recent work by Takakusaki et al. (2016) suggests that one issue is the location of the DBS electrode. They argue that the caudal portions of the PPN and the neighboring cuneiform nucleus, which is closely linked to the mesencephalic locomotor region, are the most effective targets for gait disturbances in PD patients; in contrast, stimulation of the more rostral portions of the PPN produced an inhibition of brain stem motor regions and concomitant muscle atonia. In relation to this, Gut and Winn (2015), in a mice model of PD, described that an anterior PPN DBS worsened gait, but posterior PPN DBS mildly improved it, wich emphasize the importance of the DBS location inside the PPN.

The effects of PPN DBS appear not to be limited to movement. Sleep and cognition may also be affected by PPN DBS in PD patients (Alessandro et al., 2010; Ceravolo et al., 2011; Costa et al., 2010; Peppe et al., 2012; Romigi et al., 2008). In particular, bilateral, low frequency PPN-DBS has been reported to improve sleep quality and architecture (Alessandro et al., 2010; Peppe et al., 2012; Romigi et al., 2008). Verbal fluency, long-term memory, and executive functions might also be improved by PPN DBS (Ceravolo et al., 2011). Studies reporting alleviation of non-motor symptoms in PD patients have consistently targeted the caudal PPN, where cholinergic neurons are more abundant.

Frankly, given the complexity of the PPN region, it seems unlikely that the indiscriminate electrical stimulation afforded by DBS is ever likely to yield reliable clinical outcomes, even its role in PD symptoms is resolved. Rather, optogenetic or chemogenetic targeting of genetically defined PPN (or neighboring) neurons is much more likely to be clinically useful. To make this happen, cell-specific promoters that would allow targeted gene delivery [e.g., (Roseberry et al., 2016)] need to be developed for human use.

4. PPN and PD pathogenesis

Another set of questions for which there are no clear answers has to do with PD pathogenesis, rather than symptomology. There are two specific questions that merit discussion in this regard. First, why do PPN neurons die in PD patients? Second, does PPN pathology contribute to the loss of SNc dopaminergic neurons and the cardinal motor symptoms of PD?

Although the initial description of PPN pathology in PD patients focuse on cholinergic neurons (Hirsch et al., 1987; Shinotoh et al., 1999; Zweig et al., 1989), more recent work has suggested that neuronal loss is not limited to this population but includes GABAergic and glycinergic neurons as well (Pienaar et al., 2013). In rodent toxin and proteostasis inhibition models of PD, neuronal loss in the PPN also includes non-cholinergic neurons (Elson et al., 2016; Pienaar and van de Berg, 2013). It is not clear whether loss extends to glutamatergic neurons implicated in gait control.

What remains to be determined is why any of these neurons die. One possibility is that mitochondrial dysfunction is a culprit, as in the SNc (Surmeier et al., 2017b). Pienaar et al. (Pienaar et al., 2016) suggest that alterations in nitric oxide (NO) signaling triggers mitochondria-mediated cell arrest and apoptosis of cholinergic neurons. Another possibility is that the loss of PPN cholinergic neurons is induced by pathophysiology elsewhere in the brain. Bensaid et al. (2016) suggest that there is a reciprocity between SNc dopaminergic neurons and PPN cholinergic neurons, such that when one dies, the other does as well. Precisely why this would be the case is unclear and it must be noted that this hypothesis is based upon acute lesion studies. Although

inflammation seems not to be a factor in the results of Bensaid et al. (2016), there is a clear need to show that slow, progressive, non-toxin-induced loss of SNc dopaminergic neurons has the same effect as acute, toxin-induced loss.

Another possibility is that the loss of PPN cholinergic neurons is the consequence of alpha-synuclein pathology. Given the large axonal field and abundance of presynaptic release sites of PPN cholinergic neurons, it is likely that they express high levels of alpha-synuclein, which functions in the vesicular release of neurotransmitter. As calcium promotes the aggregation of alpha synuclein (Lautenschlager et al., 2018; Llinas et al., 1992; Nielsen et al., 2001; Schneggenburger and Neher, 2000), the combination of elevated expression of alpha-synuclein and high intracellular calcium, which presumably exists in Type II cholinergic neurons, could promote alpha synuclein pathology and ultimately neuronal death. Another possibility that has received a great deal of attention is that PPN cholinergic neurons are vulnerable to propagated alpha synuclein pathology (Braak et al., 2004; Dijkstra et al., 2014). The robust synaptic connectivity of PPN cholinergic neurons with brainstem nuclei that manifest Lewy pathology is consistent with this idea (Surmeier et al., 2017a). That said, this model has difficulty explaining the selectivity of the PPN loss, as PPN glutamatergic neurons, which appear to be resistant to PD pathology, also are richly connected with the same brainstem regions. Clearly, more study is needed on this point.

A related question is whether PPN pathology contributes to the loss of SNc dopaminergic neurons. One of the earliest theories about PD pathogenesis was that it was driven by glutamatergic *N*-methyl-D-aspartate (NMDA) receptor-mediated, excitotoxicity (Beal, 1998; German et al., 1992; Meredith et al., 2009; Obeso et al., 2008). NMDA receptor antagonists, are neuroprotective in toxin models of PD (Armentero et al., 2006; Calabresi et al., 2013). Lesioning the STN, a source of glutamatergic innervation of to SNc dopaminergic neurons, also is neuroprotective in toxin models (Piallat et al., 1996; Wallace et al., 2007). Given the potent glutamatergic innervation of SNc dopaminergic neurons by the PPN (Galtieri et al., 2017), it is possible that elevated activity in these neurons could drive excitotoxicity. However, this could all be an artifact of toxin models that produce local inflammation and activation of astrocytes and microglia, leading to impaired glutamate homeostasis. Indeed, in ex vivo brain slices from toxin models, extracellular glutamate is elevated in the SNc even though it has been cut off from the glutamatergic neurons innervating it – clearly implicating deficits in astrocytic regulation of extracellular glutamate (Meredith et al., 2009).

5. Conclusions

The PPN is a complex region from a variety of standpoints. Although it is clearly implicated in movement control, its specific role in gait and posture is unclear, as is its role in arousal, sleep and cognition. Even with refinements in electrode placement, attempts to target this region using DBS are likely to yield inconsistent results because of the complexity of the region. Alternative strategies using optogenetic or chemogenetic approaches are more likely to produce consistent clinical outcomes. It also remains to be resolved why PPN neurons are lost in PD and how this loss affects pathology in other regions, including the SNc.

Acknowledgement

This work was supported by NIH (NS047085 to DJS), the JPB Foundation (DJS) and the Flanagan Scholars program (CT).

References

Alessandro, S., Ceravolo, R., Brusa, L., Pierantozzi, M., Costa, A., Galati, S., ... Peppe, A., 2010. Non-motor functions in parkinsonian patients implanted in the pedunculopontine nucleus: focus on sleep and cognitive domains. J. Neurol. Sci. 289 (1–2), 44–48. https://doi.org/10.1016/j.jns.2009.08.017.

Aravamuthan, B.R., Bergstrom, D.A., French, R.A., Taylor, J.J., Parr-Brownlie, L.C., Walters, J.R., 2008. Altered neuronal activity relationships between the pedunculopontine nucleus and motor cortex in a rodent model of Parkinson's disease. Exp. Neurol. 213 (2), 268–280. https://doi.org/10.1016/j.expneurol.2008.05.023.

Armentero, M.T., Fancellu, R., Nappi, G., Bramanti, P., Blandini, F., 2006. Prolonged blockade of NMDA or mGluR5 glutamate receptors reduces nigrostriatal degeneration while inducing selective metabolic changes in the basal ganglia circuitry in a rodent model of Parkinson's disease. Neurobiol. Dis. 22 (1), 1–9. https://doi.org/10.1016/j.nbd.2005.09.010.

Beal, M.F., 1998. Excitotoxicity and nitric oxide in Parkinson's disease pathogenesis. Ann. Neurol. 44 (3 Suppl 1), S110–S114.

Bensaid, M., Michel, P.P., Clark, S.D., Hirsch, E.C., Francois, C., 2016. Role of pedunculopontine cholinergic neurons in the vulnerability of nigral dopaminergic neurons in Parkinson's disease. Exp. Neurol. 275 (Pt 1), 209–219. https://doi.org/10.1016/j.expneurol.2015.11.004.

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 (11), 7105–7120.

Bohnen, N.I., Muller, M.L., Koeppe, R.A., Studenski, S.A., Kilbourn, M.A., Frey, K.A., Albin, R.L., 2009. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology 73 (20), 1670–1676. https://doi.org/10.1212/WNL.0b013e3181c1ded6.

Bohnen, N.I., Muller, M.L., Kotagal, V., Koeppe, R.A., Kilbourn, M.R., Gilman, S., ... Frey, K.A., 2012. Heterogeneity of cholinergic denervation in Parkinson's disease without dementia. J. Cereb. Blood Flow Metab. 32 (8), 1609–1617. https://doi.org/10.1038/jcbfm.2012.60.

Bordas, C., Kovacs, A., Pal, B., 2015. The M-current contributes to high threshold membrane potential oscillations in a cell type-specific way in the pedunculopontine nucleus of mice. Front. Cell. Neurosci. 9, 121. https://doi.org/10.3389/fncel.2015.00121.

Braak, H., Ghebremedhin, E., Rub, U., Bratzke, H., Del Tredici, K., 2004. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 318 (1), 121–134. https://doi.org/10.1007/s00441-004-0956-9.

Breit, S., Bouali-Benazzouz, R., Benabid, A.L., Benazzouz, A., 2001. Unilateral lesion of the nigrostriatal pathway induces an increase of neuronal activity of the pedunculopontine nucleus, which is reversed by the lesion of the subthalamic nucleus in the rat. Eur. J. Neurosci. 14 (11), 1833–1842.

Caggiano, V., Leiras, R., Goni-Erro, H., Masini, D., Bellardita, C., Bouvier, J., ... Kiehn, O., 2018. Midbrain circuits that set locomotor speed and gait selection. Nature 553 (7689), 455–460. https://doi.org/10.1038/nature25448.

Calabresi, P., Di Filippo, M., Gallina, A., Wang, Y., Stankowski, J.N., Picconi, B., ... Dawson, T.M., 2013. New synaptic and molecular targets for neuroprotection in Parkinson's disease. Mov. Disord. 28 (1), 51–60. https://doi.org/10.1002/mds.25096.

Ceravolo, R., Brusa, L., Galati, S., Volterrani, D., Peppe, A., Siciliano, G., ... Stefani, A., 2011. Low frequency stimulation of the nucleus tegmenti pedunculopontini increases cortical metabolism in parkinsonian patients. Eur. J. Neurol. 18 (6), 842–849. https://doi.org/10.1111/j.1468-1331.2010.03254.x.

Clements, J.R., Grant, S., 1990. Glutamate-like immunoreactivity in neurons of the laterodorsal tegmental and pedunculopontine nuclei in the rat. Neurosci. Lett. 120 (1), 70–73.

Clements, J.R., Toth, D.D., Highfield, D.A., Grant, S.J., 1991. Glutamate-like immunoreactivity is present within cholinergic neurons of the laterodorsal tegmental and pedunculopontine nuclei. Adv. Exp. Med. Biol. 295, 127–142.

Costa, A., Carlesimo, G.A., Caltagirone, C., Mazzone, P., Pierantozzi, M., Stefani, A., Peppe, A., 2010. Effects of deep brain stimulation of the peduncolopontine area on working memory tasks in patients with Parkinson's disease. Parkinsonism Relat. Disord. 16 (1), 64–67. https://doi.org/10.1016/j.parkreldis.2009.05.009.

Dautan, D., Huerta-Ocampo, I., Witten, I.B., Deisseroth, K., Bolam, J.P., Gerdjikov, T., Mena-Segovia, J., 2014. A major external source of cholinergic innervation of the striatum and nucleus accumbens originates in the brainstem. J. Neurosci. 34 (13), 4509–4518. https://doi.org/10.1523/JNEUROSCI.5071-13.2014.

Dautan, D., Hacioglu Bay, H., Bolam, J.P., Gerdjikov, T.V., Mena-Segovia, J., 2016. Extrinsic sources of cholinergic innervation of the striatal complex: a whole-brain mapping analysis. Front. Neuroanat. 10, 1. https://doi.org/10.3389/fnana.2016.00001.

Di Loreto, S., Florio, T., Scarnati, E., 1992. Evidence that non-NMDA receptors are involved in the excitatory pathway from the pedunculopontine region to nigrostriatal dopaminergic neurons. Exp. Brain Res. 89 (1), 79–86.

Dijkstra, A.A., Voorn, P., Berendse, H.W., Groenewegen, H.J., Rozemuller, A.J., van de Berg, W.D., 2014. Stage-dependent nigral neuronal loss in incidental Lewy body and Parkinson's disease. Mov. Disord. 29 (10), 1244–1251. https://doi.org/10.1002/mds.25952.

Elson, J.L., Yates, A., Pienaar, I.S., 2016. Pedunculopontine cell loss and protein aggregation direct microglia activation in parkinsonian rats. Brain Struct. Funct. 221 (4), 2319–2341. https://doi.org/10.1007/s00429-015-1045-4.

Estakhr, J., Abazari, D., Frisby, K., McIntosh, J.M., Nashmi, R., 2017. Differential control of dopaminergic excitability and locomotion by cholinergic inputs in mouse substantia Nigra. Curr. Biol. 27 (13), 1900–1914. e1904. https://doi.org/10.1016/j.cub.2017.05.084.

Ferraye, M.U., Debu, B., Fraix, V., Goetz, L., Ardouin, C., Yelnik, J., ... Pollak, P., 2010. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 133 (Pt 1), 205–214. https://doi.org/10.1093/brain/awp229.

Floresco, S.B., West, A.R., Ash, B., Moore, H., Grace, A.A., 2003. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine

transmission. Nat. Neurosci. 6 (9), 968–973. https://doi.org/10.1038/nn1103.
Florio, T., Scarnati, E., Confalone, G., Minchella, D., Galati, S., Stanzione, P., ... Mazzone, P., 2007. High-frequency stimulation of the subthalamic nucleus modulates the activity of pedunculopontine neurons through direct activation of excitatory fibres as well as through indirect activation of inhibitory pallidal fibres in the rat. Eur. J. Neurosci. 25 (4), 1174–1186. https://doi.org/10.1111/j.1460-9568.2007.05360.x.
Ford, B., Holmes, C.J., Mainville, L., Jones, B.E., 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 (2), 177–196. https://doi.org/10.1002/cne.903630203.
Futami, T., Takakusaki, K., Kitai, S.T., 1995. Glutamatergic and cholinergic inputs from the pedunculopontine tegmental nucleus to dopamine neurons in the substantia nigra pars compacta. Neurosci. Res. 21 (4), 331–342.
Galtieri, D.J., Estep, C.M., Wokosin, D.L., Traynelis, S., Surmeier, D.J., 2017. Pedunculopontine glutamatergic neurons control spike patterning in substantia nigra dopaminergic neurons. elife 6. https://doi.org/10.7554/eLife.30352.
Garcia-Rill, E., Skinner, R.D., 1987a. The mesencephalic locomotor region. I. activation of a medullary projection site. Brain Res. 411 (1), 1–12.
Garcia-Rill, E., Skinner, R.D., 1987b. The mesencephalic locomotor region. II. Projections to reticulospinal neurons. Brain Res. 411 (1), 13–20.
Garcia-Rill, E., Skinner, R.D., 1988. Modulation of rhythmic function in the posterior midbrain. Neuroscience 27 (2), 639–654.
Garcia-Rill, E., 1991. The pedunculopontine nucleus. Prog. Neurobiol. 36 (5), 363–389.
Geng, X., Xie, J., Wang, X., Wang, X., Zhang, X., Hou, Y., ... Wang, M., 2016. Altered neuronal activity in the pedunculopontine nucleus: an electrophysiological study in a rat model of Parkinson's disease. Behav. Brain Res. 305, 57–64. https://doi.org/10.1016/j.bbr.2016.02.026.
German, D.C., Manaye, K.F., Sonsalla, P.K., Brooks, B.A., 1992. Midbrain dopaminergic cell loss in Parkinson's disease and MPTP-induced parkinsonism: sparing of calbindin-D28k-containing cells. Ann. N. Y. Acad. Sci. 648, 42–62.
Gomez-Gallego, M., Fernandez-Villalba, E., Fernandez-Barreiro, A., Herrero, M.T., 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 (3), 319–326. https://doi.org/10.1007/s00702-006-0547-x.
Granata, A.R., Kitai, S.T., 1989. Intracellular analysis of excitatory subthalamic inputs to the pedunculopontine neurons. Brain Res. 488 (1–2), 57–72.
Gut, N.K., Winn, P., 2015. Deep brain stimulation of different pedunculopontine targets in a novel rodent model of parkinsonism. J. Neurosci. 35 (12), 4792–4803. https://doi.org/10.1523/jneurosci.3646-14.2015.
Hammond, C., Rouzaire-Dubois, B., Feger, J., Jackson, A., Crossman, A.R., 1983. Anatomical and electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus tegmenti pedunculopontinus in the rat. Neuroscience 9 (1), 41–52.
Hazrati, L.N., Parent, A., 1992. Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey. Brain Res. 585 (1–2), 267–271.
Heise, C.E., Mitrofanis, J., 2006. Fos immunoreactivity in some locomotor neural centres of 6OHDA-lesioned rats. Anat. Embryol. (Berl.) 211 (6), 659–671. https://doi.org/10.1007/s00429-006-0130-0.
Hirsch, E.C., Graybiel, A.M., Duyckaerts, C., Javoy-Agid, F., 1987. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proc. Natl. Acad. Sci. U. S. A. 84 (16), 5976–5980.
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 (3), 837–853.
Ichinohe, N., Teng, B., Kitai, S.T., 2000. Morphological study of the tegmental pedunculopontine nucleus, substantia nigra and subthalamic nucleus, and their interconnections in rat organotypic culture. Anat. Embryol. (Berl.) 201 (6), 435–453.
Inglis, W.L., Winn, P., 1995. The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation. Prog. Neurobiol. 47 (1), 1–29.
Jackson, A., Crossman, A.R., 1983. 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 10 (3), 725–765.
Jia, H.G., Yamuy, J., Sampogna, S., Morales, F.R., Chase, M.H., 2003. Colocalization of gamma-aminobutyric acid and acetylcholine in neurons in the laterodorsal and pedunculopontine tegmental nuclei in the cat: a light and electron microscopic study. Brain Res. 992 (2), 205–219.
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 (1), 56–92. https://doi.org/10.1002/cne.902420105.
Karachi, C., Grabli, D., Bernard, F.A., Tande, D., Wattiez, N., Belaid, H., ... Francois, C., 2010. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J. Clin. Invest. 120 (8), 2745–2754. https://doi.org/10.1172/JCI42642.
Kinjo, N., Atsuta, Y., Webber, M., Kyle, R., Skinner, R.D., Garcia-Rill, E., 1990. Medioventral medulla-induced locomotion. Brain Res. Bull. 24 (3), 509–516.
Kita, H., Kitai, S.T., 1987. Efferent projections of the subthalamic nucleus in the rat: light and electron microscopic analysis with the PHA-L method. J. Comp. Neurol. 260 (3), 435–452. https://doi.org/10.1002/cne.902600309.
Kucinski, A., Sarter, M., 2015. Modeling Parkinson's disease falls associated with brainstem cholinergic systems decline. Behav. Neurosci. 129 (2), 96–104. https://doi.org/10.1037/bne0000048.
Lau, B., Welter, M.L., Belaid, H., Fernandez Vidal, S., Bardinet, E., Grabli, D., Karachi, C., 2015. The integrative role of the pedunculopontine nucleus in human gait. Brain 138 (Pt 5), 1284–1296. https://doi.org/10.1093/brain/awv047.
Lautenschlager, J., Stephens, A.D., Fusco, G., Strohl, F., Curry, N., Zacharopoulou, M., ... Schierle, G.S.K., 2018. C-terminal calcium binding of alpha-synuclein modulates synaptic vesicle interaction. Nat. Commun. 9 (1), 712. https://doi.org/10.1038/s41467-018-03111-4.
Lavoie, B., Parent, A., 1994a. Pedunculopontine nucleus in the squirrel monkey: cholinergic and glutamatergic projections to the substantia nigra. J. Comp. Neurol. 344 (2), 232–241. https://doi.org/10.1002/cne.903440205.
Lavoie, B., Parent, A., 1994b. 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. 344 (2), 190–209. https://doi.org/10.1002/cne.903440203.
Lavoie, B., Parent, A., 1994c. Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. J. Comp. Neurol. 344 (2), 210–231. https://doi.org/10.1002/cne.903440204.
Llinas, R., Sugimori, M., Silver, R.B., 1992. Microdomains of high calcium concentration in a presynaptic terminal. Science 256 (5057), 677–679.
Martinez-Gonzalez, C., Bolam, J.P., Mena-Segovia, J., 2011. Topographical organization of the pedunculopontine nucleus. Front. Neuroanat. 5, 22. https://doi.org/10.3389/fnana.2011.00022.
The pedunculopontine nucleus. In: Mena-Segovia, J., Ross, H.M., Magill, P.J., Bolam, J.P. (Eds.), The Basal Ganglia VIII. Advances in Behavioral Biology. 56 Springer, Boston, MA.
Mena-Segovia, J., Sims, H.M., Magill, P.J., Bolam, J.P., 2008. Cholinergic brainstem neurons modulate cortical gamma activity during slow oscillations. J. Physiol. 586 (12), 2947–2960. https://doi.org/10.1113/jphysiol.2008.153874.
Meredith, G.E., Totterdell, S., Beales, M., Meshul, C.K., 2009. Impaired glutamate homeostasis and programmed cell death in a chronic MPTP mouse model of Parkinson's disease. Exp. Neurol. 219 (1), 334–340. https://doi.org/10.1016/j.expneurol.2009.06.005.
Muslimovic, D., Post, B., Speelman, J.D., Schmand, B., de Haan, R.J., Group, C. S, 2008. Determinants of disability and quality of life in mild to moderate Parkinson disease. Neurology 70 (23), 2241–2247. https://doi.org/10.1212/01.wnl.0000313835.33830.80.
Nielsen, M.S., Vorum, H., Lindersson, E., Jensen, P.H., 2001. Ca2+ binding to alpha-synuclein regulates ligand binding and oligomerization. J. Biol. Chem. 276 (25), 22680–22684. https://doi.org/10.1074/jbc.M101181200.
Oakman, S.A., Faris, P.L., Kerr, P.E., Cozzari, C., Hartman, B.K., 1995. Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra differs significantly from those projecting to ventral tegmental area. J. Neurosci. 15 (9), 5859–5869.
Obeso, J.A., Marin, C., Rodriguez-Oroz, C., Blesa, J., Benitez-Temino, B., Mena-Segovia, J., ... Olanow, C.W., 2008. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Ann. Neurol. 64 (Suppl. 2), S30–S46. https://doi.org/10.1002/ana.21481.
Pahapill, P.A., Lozano, A.M., 2000. The pedunculopontine nucleus and Parkinson's disease. Brain 123 (Pt 9), 1767–1783.
Pan, W.X., Hyland, B.I., 2005. Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. J. Neurosci. 25 (19), 4725–4732. https://doi.org/10.1523/JNEUROSCI.0277-05.2005.
Peppe, A., Pierantozzi, M., Baiamonte, V., Moschella, V., Caltagirone, C., Stanzione, P., Stefani, A., 2012. Deep brain stimulation of pedunculopontine tegmental nucleus: role in sleep modulation in advanced Parkinson disease patients: one-year follow-up. Sleep 35 (12), 1637–1642. https://doi.org/10.5665/sleep.2234.
Petzold, A., Valencia, M., Pal, B., Mena-Segovia, J., 2015. Decoding brain state transitions in the pedunculopontine nucleus: cooperative phasic and tonic mechanisms. Front. Neural Circ. 9, 68. https://doi.org/10.3389/fncir.2015.00068.
Piallat, B., Benazzouz, A., Benabid, A.L., 1996. Subthalamic nucleus lesion in rats prevents dopaminergic nigral neuron degeneration after striatal 6-OHDA injection: behavioural and immunohistochemical studies. Eur. J. Neurosci. 8 (7), 1408–1414.
Pienaar, I.S., van de Berg, W., 2013. A non-cholinergic neuronal loss in the pedunculopontine nucleus of toxin-evoked parkinsonian rats. Exp. Neurol. 248, 213–223. https://doi.org/10.1016/j.expneurol.2013.06.008.
Pienaar, I.S., Elson, J.L., Racca, C., Nelson, G., Turnbull, D.M., Morris, C.M., 2013. Mitochondrial abnormality associates with type-specific neuronal loss and cell morphology changes in the pedunculopontine nucleus in Parkinson disease. Am. J. Pathol. 183 (6), 1826–1840. https://doi.org/10.1016/j.ajpath.2013.09.002.
Pienaar, I.S., Harrison, I.F., Elson, J.L., Bury, A., Woll, P., Simon, A.K., Dexter, D.T., 2015. An animal model mimicking pedunculopontine nucleus cholinergic degeneration in Parkinson's disease. Brain Struct. Funct. 220 (1), 479–500. https://doi.org/10.1007/s00429-013-0669-5.
Pienaar, I.S., Vernon, A., Winn, P., 2016. The cellular diversity of the pedunculopontine nucleus: relevance to behavior in health and aspects of Parkinson's disease. Neuroscientist. https://doi.org/10.1177/1073858416682471.
Redgrave, P., Mitchell, I.J., Dean, P., 1987. Descending projections from the superior colliculus in rat: a study using orthograde transport of wheatgerm-agglutinin conjugated horseradish peroxidase. Exp. Brain Res. 68 (1), 147–167.
Romigi, A., Placidi, F., Peppe, A., Pierantozzi, M., Izzi, F., Brusa, L., ... Stefani, A., 2008. Pedunculopontine nucleus stimulation influences REM sleep in Parkinson's disease. Eur. J. Neurol. 15 (7), e64–e65. https://doi.org/10.1111/j.1468-1331.2008.02167.x.
Ros, H., Magill, P.J., Moss, J., Bolam, J.P., Mena-Segovia, J., 2010. Distinct types of non-cholinergic pedunculopontine neurons are differentially modulated during global brain states. Neuroscience 170 (1), 78–91. https://doi.org/10.1016/j.neuroscience.2010.06.068.
Roseberry, T.K., Lee, A.M., Lalive, A.L., Wilbrecht, L., Bonci, A., Kreitzer, A.C., 2016. Cell-type-specific control of brainstem locomotor circuits by basal ganglia. Cell 164 (3), 526–537. https://doi.org/10.1016/j.cell.2015.12.037.
Rye, D.B., Saper, C.B., Lee, H.J., Wainer, B.H., 1987. Pedunculopontine tegmental nucleus

of the rat: cytoarchitecture, cytochemistry, and some extrapyramidal connections of the mesopontine tegmentum. J. Comp. Neurol. 259 (4), 483–528. https://doi.org/10.1002/cne.902590403.
Sarter, M., Albin, R.L., Kucinski, A., Lustig, C., 2014. Where attention falls: increased risk of falls from the converging impact of cortical cholinergic and midbrain dopamine loss on striatal function. Exp. Neurol. 257, 120–129. https://doi.org/10.1016/j.expneurol.2014.04.032.
Satoh, K., Fibiger, H.C., 1986. Cholinergic neurons of the laterodorsal tegmental nucleus: efferent and afferent connections. J. Comp. Neurol. 253 (3), 277–302. https://doi.org/10.1002/cne.902530302.
Scarnati, E., Proia, A., Campana, E., Pacitti, C., 1986. A microiontophoretic study on the nature of the putative synaptic neurotransmitter involved in the pedunculopontine-substantia nigra pars compacta excitatory pathway of the rat. Exp. Brain Res. 62 (3), 470–478.
Scarnati, E., Proia, A., Di Loreto, S., Pacitti, C., 1987. The reciprocal electrophysiological influence between the nucleus tegmenti pedunculopontinus and the substantia nigra in normal and decorticated rats. Brain Res. 423 (1–2), 116–124.
Schneggenburger, R., Neher, E., 2000. Intracellular calcium dependence of transmitter release rates at a fast central synapse. Nature 406 (6798), 889–893. https://doi.org/10.1038/35022702.
Schofield, B.R., Motts, S.D., 2009. Projections from auditory cortex to cholinergic cells in the midbrain tegmentum of guinea pigs. Brain Res. Bull. 80 (3), 163–170. https://doi.org/10.1016/j.brainresbull.2009.06.015.
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 (3), 387–410. https://doi.org/10.1002/cne.903230307.
Sesack, S.R., Deutch, A.Y., Roth, R.H., Bunney, B.S., 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J. Comp. Neurol. 290 (2), 213–242. https://doi.org/10.1002/cne.902900205.
Sethi, K., 2008. Levodopa unresponsive symptoms in Parkinson disease. Mov. Disord. 23 (Suppl. 3), S521–S533. https://doi.org/10.1002/mds.22049.
Shink, E., Sidibe, M., Smith, Y., 1997. 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. 382 (3), 348–363.
Shinotoh, H., Namba, H., Yamaguchi, M., Fukushi, K., Nagatsuka, S., Iyo, M., ... Irie, T., 1999. Positron emission tomographic measurement of acetylcholinesterase activity reveals differential loss of ascending cholinergic systems in Parkinson's disease and progressive supranuclear palsy. Ann. Neurol. 46 (1), 62–69.
Skinner, R.D., Kinjo, N., Ishikawa, Y., Biedermann, J.A., Garcia-Rill, E., 1990. Locomotor projections from the pedunculopontine nucleus to the medioventral medulla. Neuroreport 1 (3–4), 207–210.
Stefani, A., Lozano, A.M., Peppe, A., Stanzione, P., Galati, S., Tropepi, D., ... Mazzone, P., 2007. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 130 (Pt 6), 1596–1607. https://doi.org/10.1093/brain/awl346.
Stefani, A., Peppe, A., Galati, S., Bassi, M.S., D'Angelo, V., Pierantozzi, M., 2013. The serendipity case of the pedunculopontine nucleus low-frequency brain stimulation: chasing a gait response, finding sleep, and cognition improvement. Front. Neurol. 4, 68. https://doi.org/10.3389/fneur.2013.00068.
Steininger, T.L., Rye, D.B., Wainer, B.H., 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 (4), 515–543. https://doi.org/10.1002/cne.903210403.
Steininger, T.L., Wainer, B.H., Blakely, R.D., Rye, D.B., 1997. Serotonergic dorsal raphe nucleus projections to the cholinergic and noncholinergic neurons of the pedunculopontine tegmental region: a light and electron microscopic anterograde tracing and immunohistochemical study. J. Comp. Neurol. 382 (3), 302–322.
Surmeier, D.J., Obeso, J.A., Halliday, G.M., 2017a. Parkinson's disease is not simply a prion disorder. J. Neurosci. 37 (41), 9799–9807. https://doi.org/10.1523/jneurosci.1787-16.2017.
Surmeier, D.J., Obeso, J.A., Halliday, G.M., 2017b. Selective neuronal vulnerability in Parkinson disease. Nat. Rev. Neurosci. 18 (2), 101–113. https://doi.org/10.1038/nrn.2016.178.
Takakusaki, K., Kitai, S.T., 1997. Ionic mechanisms involved in the spontaneous firing of tegmental pedunculopontine nucleus neurons of the rat. Neuroscience 78 (3), 771–794.
Takakusaki, K., Shiroyama, T., Yamamoto, T., Kitai, S.T., 1996. Cholinergic and non-cholinergic tegmental pedunculopontine projection neurons in rats revealed by intracellular labeling. J. Comp. Neurol. 371 (3), 345–361. https://doi.org/10.1002/(SICI)1096-9861(19960729)371:3<345::AID-CNE1>3.0.CO;2-2.
Takakusaki, K., Chiba, R., Nozu, T., Okumura, T., 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 (7), 695–729. https://doi.org/10.1007/s00702-015-1475-4.
Tattersall, T.L., Stratton, P.G., Coyne, T.J., Cook, R., Silberstein, P., Silburn, P.A., ... Sah, P., 2014. Imagined gait modulates neuronal network dynamics in the human pedunculopontine nucleus. Nat. Neurosci. 17 (3), 449–454. https://doi.org/10.1038/nn.3642.
Thevathasan, W., Cole, M.H., Graepel, C.L., Hyam, J.A., Jenkinson, N., Brittain, J.S., ... Brown, P., 2012. A spatiotemporal analysis of gait freezing and the impact of pedunculopontine nucleus stimulation. Brain 135 (Pt 5), 1446–1454. https://doi.org/10.1093/brain/aws039.
Thevathasan, W., Debu, B., Aziz, T., Bloem, B.R., Blahak, C., Butson, C., ... Functional, N., 2018. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: a clinical review. Mov. Disord. 33 (1), 10–20. https://doi.org/10.1002/mds.27098.
Wall, N.R., Wickersham, I.R., Cetin, A., De La Parra, M., Callaway, E.M., 2010. Monosynaptic circuit tracing in vivo through Cre-dependent targeting and complementation of modified rabies virus. Proc. Natl. Acad. Sci. U. S. A. 107 (50), 21848–21853. https://doi.org/10.1073/pnas.1011756107.
Wallace, B.A., Ashkan, K., Heise, C.E., Foote, K.D., Torres, N., Mitrofanis, J., Benabid, A.L., 2007. Survival of midbrain dopaminergic cells after lesion or deep brain stimulation of the subthalamic nucleus in MPTP-treated monkeys. Brain 130 (Pt 8), 2129–2145. https://doi.org/10.1093/brain/awm137.
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 (2), 340–358. https://doi.org/10.1111/j.1460-9568.2008.06576.x.
Wickersham, I.R., Finke, S., Conzelmann, K.K., Callaway, E.M., 2007. Retrograde neuronal tracing with a deletion-mutant rabies virus. Nat. Methods 4 (1), 47–49. https://doi.org/10.1038/nmeth999.
Winn, P., 2006. How best to consider the structure and function of the pedunculopontine tegmental nucleus: evidence from animal studies. J. Neurol. Sci. 248 (1–2), 234–250. https://doi.org/10.1016/j.jns.2006.05.036.
Xiao, C., Cho, J.R., Zhou, C., Treweek, J.B., Chan, K., McKinney, S.L., ... Gradinaru, V., 2016. Cholinergic mesopontine signals govern locomotion and reward through dissociable midbrain pathways. Neuron 90 (2), 333–347. https://doi.org/10.1016/j.neuron.2016.03.028.
Yoo, J.H., Zell, V., Wu, J., Punta, C., Ramajayam, N., Shen, X., ... Hnasko, T.S., 2017. Activation of pedunculopontine glutamate neurons is reinforcing. J. Neurosci. 37 (1), 38–46. https://doi.org/10.1523/JNEUROSCI.3082-16.2016.
Zhang, Q.J., Liu, J., Wang, Y., Wang, S., Wu, Z.H., Yan, W., ... Ali, U., 2008. The firing activity of presumed cholinergic and non-cholinergic neurons of the pedunculopontine nucleus in 6-hydroxydopamine-lesioned rats: an in vivo electrophysiological study. Brain Res. 1243, 152–160. https://doi.org/10.1016/j.brainres.2008.09.028.
Zweig, R.M., Whitehouse, P.J., Casanova, M.F., Walker, L.C., Jankel, W.R., Price, D.L., 1987. Loss of pedunculopontine neurons in progressive supranuclear palsy. Ann. Neurol. 22 (1), 18–25. https://doi.org/10.1002/ana.410220107.
Zweig, R.M., Jankel, W.R., Hedreen, J.C., Mayeux, R., Price, D.L., 1989. The pedunculopontine nucleus in Parkinson's disease. Ann. Neurol. 26 (1), 41–46. https://doi.org/10.1002/ana.410260106.