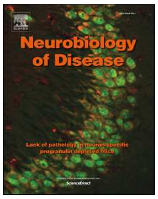
Neurobiology of Disease 128 (2019) 19–30

Contents lists available at ScienceDirect

Neurobiology of Disease

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



Review

Neurophysiology of the pedunculopontine tegmental nucleus

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ARTICLE INFO

Keywords:
Basal ganglia
Cerebellum
Movement
Neurodegeneration
Parkinson's disease
Spinal cord
Substantia Nigra

ABSTRACT

The interest in the pedunculopontine tegmental nucleus (PPTg), a structure located in the brainstem at the level of the pontomesencephalic junction, has greatly increased in recent years because it is involved in the regulation of physiological functions that fail in Parkinson's disease and because it is a promising target for deep brain stimulation in movement disorders. The PPTg is highly interconnected with the main basal ganglia nuclei and relays basal ganglia activity to thalamic and brainstem nuclei and to spinal effectors. In this review, we address the functional role of the main PPTg outputs directed to the basal ganglia, thalamus, cerebellum and spinal cord. Together, the data that we discuss show that the PPTg may influence thalamocortical activity and spinal motoneuron excitability through its ascending and descending output fibers, respectively. Cerebellar nuclei may also relay signals from the PPTg to thalamic and brainstem nuclei. In addition to participating in motor functions, the PPTg participates in arousal, attention, action selection and reward mechanisms. Finally, we discuss the possibility that the PPTg may be involved in excitotoxic degeneration of the dopaminergic neurons of the substantia nigra through the glutamatergic monosynaptic input that it provides to these neurons.

1. Introduction: Morphofunctional properties of the pedunculopontine tegmental nucleus neurons

The pedunculopontine tegmental nucleus (PPTg) is located in the pontomesencephalic tegmentum and is characterized by a complex and peculiar pattern of input–output relationships that permit it to participate in a variety of functions. For example, it may affect arousal, consciousness, cognition, sleep-waking cycles and sensory integration via fibers directed to non-motor thalamic nuclei. At the same time, it may also participate in motor control, being strictly involved in locomotion, and in the regulation of muscle activity through fibers directed to the lower brainstem and spinal cord.

Interest in the PPTg originated in the 1980s, after it was shown that it receives basal ganglia (BG) efferents. In monkeys, the PPTg is located in the pontine tegmentum between the caudal pole of the red nucleus and the parabrachial nucleus, extending posteriorly to the pontomesencephalic junction. The cytoarchitecture of its neurons suggests that it is homologous to the nucleus that was originally defined in the human brainstem by Jacobsohn (1909). Different neuronal densities characterize its subdivisions, the subnucleus dissipatus and the subnucleus compactus, in the human brain (Olszewski and Baxter, 1982; Paxinos and Huang, 1995). These subnuclei are less distinct in lower species, but cytological analogies with the human brain are preserved.

Interest in the PPTg was further stimulated by anatomopathological investigations showing that PPTg neurons degenerate to variable extent in neurodegenerative disorders. The neuronal loss was found to more severe in progressive supranuclear palsy (75%–80%) than in Parkinson's disease (PD) (43%–57%). Degeneration of the PPTg also occurs in patients with both Alzheimer's disease and Lewy body dementia, where the neuronal loss was found to occur to a lower extent (e.g. 25%–34%) (Hirsch et al., 1987; Jellinger, 1988; Karachi et al., 2010; Rinne et al., 2008; Zweig et al., 1989).

PPTg neurons participate to a neuronal network that is similar across mammalian species (Alam et al., 2011; Stephenson-Jones et al., 2012); however, the strength of some connections varies. PPTg output fibers that are rostrally directed form a compact bundle that courses in the mesopontine tegmentum and splits into ventromedial and dorsolateral bundles directed to BG and thalamic nuclei, respectively. The substantia nigra (SN) and the subthalamic nucleus (STN) are the most densely innervated structures among the BG targets. In the SN, PPTg fibers arborize and contact the dopaminergic neurons of the pars compacta. Several fibers also reach the pallidal complex where they mainly end in the inner segment of the globus pallidus (the entopeduncular nucleus in rodents). In the striatum, PPTg fibers innervate the putamen and the caudate nucleus, while they are virtually absent in the ventral striatum (Dautan et al., 2014; Lavoie and Parent, 1994c).

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https://doi.org/10.1016/j.nbd.2018.03.004
Received 8 December 2017; Received in revised form 9 February 2018; Accepted 6 March 2018

Other structures innervated by PPTg fibers include the lateral hypothalamus, the ventral tegmental area, amygdaloid and thalamic nuclei (i.e. anterior, reticular, mediodorsal, centromedian, centrolateral, posterior, lateral geniculate and habenula), septal regions (dorsal and lateral), tectal nuclei (pretectal and superior colliculus), cranial nerve nuclei (V,VII and XII), and frontal cortical areas (Edley and Graybiel, 1983; Jackson and Crossman, 1983; Lavoie and Parent, 1994c; Rye et al., 1987; Saper and Loewy, 1982; Woolf and Butcher, 1989). In turn, PPTg neurons are innervated by nigral, subthalamic and entopeduncular fibers. Concerning nigral afferents, at first considered to originate from pars reticulata only (Edley and Graybiel, 1983; Spann and Grofova, 1991), they also include dopaminergic fibers from pars compacta as shown by recent data (Ryczko et al., 2016b). Thus, the PPTg is linked to the BG by three major reciprocating circuits involving the SN, STN and globus pallidus. It is noteworthy that the PPTg also receives fibers from areas four and six of the motor cortex and from the deep cerebellar nuclei. Limbic, hypothalamic and raphe inputs to the PPTg have also been reported (Edley and Graybiel, 1983; Erro and Gimenez-Amaya, 1999; Rye et al., 1987).

In addition to ascending fibers, the PPTg provides descending axons that run through the ventromedial branch of Probst's tract to innervate the gigantocellular tegmental field, the pontine reticular nuclei oralis and caudalis and the ventromedial portions of the gigantocellular reticular nucleus. This establishes a route to influence spinal cord motor mechanisms as well as motor and autonomic functions of some cranial nerves. Other targets for descending PPTg fibers include pontine, vestibular, and deep cerebellar nuclei, the spinal cord and the rostral ventrolateral medulla (Grofova and Keane, 1991; Jackson and Crossman, 1983; Lavoie and Parent, 1994c; Ruggiero et al., 1997; Ryczko et al., 2016a; Rye et al., 1988; Woolf and Butcher, 1989; Xiang et al., 2013).

The PPTg has complex cytochemical and electrophysiological properties. It was initially considered to be cholinergic being analogous to the CH_5 cholinergic cell group (Mesulam et al., 1983; Mizukawa et al., 1986), consequently all its functions were believed to be mediated by acetylcholine (ACh). However, a serious limitation to this view is that a consistent number of choline acetyltranferase-(ChAT, the enzyme synthesizing ACh)-negative cell bodies were also observed in other investigations (Beninato and Spencer, 1987; Beninato and Spencer, 1988).

The number of ACh neurons on one side of the human brain has been estimated to be approximately 6000 in the PPTg pars compacta and 12000 in the pars dissipata of the PPTg in subjects aged 28–60 years. Other studies have estimated 1200–1300 ACh neurons in the PPTg (one side) of subjects who died aged 20–50. A continuous nonlinear decrease of ACh neurons has been observed with age in individuals who died at 28–70 years, and a stable low count of ACh neurons has been measured between 80 and 91 years (a –40% decrease with age). In some centenarians, counts have been found to be comparable with those of subjects who died aged 34–65 (Karachi et al., 2010; Manaye et al., 1999; Ransmayr et al., 2000).

Today, it is known that the neuronal population of the PPTg is heterogeneous as separate subpopulations express ACh, glutamate (GLU) or gamma-aminobutyric acid (GABA) (Lavoie and Parent, 1994b; Martinez-Gonzalez et al., 2012; Wang and Morales, 2009). Studies in both monkeys and rats have also shown the presence of PPTg neurons in which ACh is co-localized with either GLU or GABA (Lavoie and Parent, 1994a; Lavoie and Parent, 1994b; Martinez-Gonzalez et al., 2012; Wang and Morales, 2009); however, the neurons expressing this colocalization have been found not exceed 5% of all PPTg neurons in the rat (Wang and Morales, 2009). With the exception of the aforementioned data on cholinergic neurons, no data is available concerning the distribution of other PPTg neuronal subpopulations in the healthy human brain or in neurodegenerative disorders.

The PPTg fibers innervating lower brainstem structures and the spinal cord are of particular interest given the effects of PPTg stimulation on locomotion and muscle tone. These fibers originate largely from nonACh neurons (Goldsmith and van der Kooy, 1988; Rye et al., 1988) and recent investigations have suggested the involvement of glutamatergic neurons (Ryczko et al., 2016a).

A further level of complexity in the heterogeneity of PPTg neurons is that they contain the corticotropin-releasing hormone or substance P, atriopeptin and nitric oxide synthase co-localized with ACh. Only noncholinergic PPTg neurons have been reported to express the calcium-binding D28k protein, while the cholinergic neurons of the PPTg together with those of the laterodorsal tegmental nucleus (LDTN) have been distinguished from those of the basal forebrain based on their high levels of NADPH diaphorase activity and nitric oxide synthase (Austin et al., 1995; Cote and Parent, 1992; Dawson et al., 1991; Edley and Graybiel, 1983; Geula et al., 1993; Standaert et al., 1986; Wanaka et al., 1990; Woolf et al., 1989). Finally, additional neurochemical features that have helped to localize the PPTg from surrounding basal forebrain structures are the high density of fibroblast growth factor receptors in the area in which the PPTg is located and the lack of nerve growth factor receptors in the cholinergic PPTg neurons. In fact, fibroblast growth factor, and not nerve growth factor, was shown to be the survival factor for PPTg ACh neurons (Garcia-Rill et al., 1991).

The heterogeneity of PPTg neurons has been also confirmed by their electrophysiological properties. We identified three types of PPTg neurons in anesthetized rats in an electrophysiological study: Type I (40% of the recorded neurons), with a slow and regular discharge rate (1.7 ± 0.2 imp/s) and a regular distribution of interspike intervals (ISIs); Type II, (another 40% of the recorded neurons), with a high and irregular discharge rate (11.7 ± 0.7 imp/s), a positivelyskewed distribution of ISIs and the presence of bursts of impulses; and Type III (20% of the recorded neurons), with multisecond discharge oscillations of 3–10 s, a discharge rate of 5.8 ± 1.2 imp/s, a positively-skewed or symmetric distribution of ISIs and the presence of bursts. Many Type III neurons displayed a large triphasic impulse waveform lasting 3–5 ms (Scarnati et al., 1987).

Subsequent intracellular studies have confirmed the presence of three distinct types of PPTg neurons and provided details of their intrinsic membrane properties. In *in-vitro* recordings Type I neurons were found to express low threshold spikes mediated by T-type calcium channels; Type II neurons expressed an I_A current delaying action potentials after membrane hyperpolarization; and Type III neurons expressed both T-type and I_A currents (Kang and Kitai, 1990; Leonard and Llinas, 1990). Further data have been provided by electrophysiological recordings coupled with immunostaining for ChAT: Type I neurons responded to depolarizing currents with bursting discharges. They were small-tomedium sized, fusiform or triangular neurons having 3–5 primary dendrites, and were likely glutamatergic. Type II neurons responded to depolarizing currents with a non-bursting pattern (tonic). They were medium-to-large sized, polygonal neurons, had 5–7 primary dendrites and 50% were immunopositive for ChAT. Type III neurons had mixed characteristics and were not considered to be cholinergic (Takakusaki et al., 1996; Takakusaki et al., 1997; Takakusaki and Kitai, 1997).

Single-unit recordings in awake patients have provided some insight into the discharge patterns of neurons recorded in the PPTg region in PD. The discharge rate varied from 9 to 70imp/s; but most neurons discharged at 12–13 imp/s and were characterized by a randomly-distributed or a burst firing activity (Lau et al., 2015; Piallat et al., 2009; Tattersall et al., 2014; Weinberger et al., 2008). Classification of these neurons has been based on the shape (di- or triphasic) and duration (narrow or wide) of their impulse waveform. It could not be excluded that impulses travelling in passing fibers contributed to the observed activity, as impulses lasting < 0.5–1 ms are more typical of fibers than neurons (Nowak and Bullier, 1998; Ranck Jr, 1975). The utility of these data for secure identification of the PPTg is debatable, as the activity recorded in the PPTg region of PD patients varied greatly from patient to patient, likely depending on the extent of neuronal degeneration in both the SN and the PPTg. In addition, these characteristics did not allow the identification in patients of the three different types of neurons recorded in vitro or in vivo studies, thus the presumed cholinergic nature of neurons with a triphasic wide action potential in the human PPTg remains speculative. It should be also considered that neuronal activity in these investigations was recorded in a pathological state, therefore it is not possible to say how PPTg neurons discharge in the normal condition. Despite these limitations, the discharge rate of 20 imp/s recorded in human PPTg deserves particular attention. Indeed, in monkeys performing an eye-movement task, PPTg neurons showed a basic firing rate of 19 ± 0.5 imp/s (mean ± SD) (Okada and Kobayashi, 2015). This firing was regular since the coefficient of variability (CV) of the ISIs distribution of neuronal activity was low (< 1). When the monkey performed a conditioned eye movement, neuronal firing tonically increased to 23.6 ± 0.7 imp/s. while the CV remained low. This suggests that during the execution of the conditioned eye movement firing frequency increased but the tonic pattern of discharge was preserved. This increased activity likely encoded the waiting phase that preceded an upcoming event or the acquisition of the reward as scheduled in the behavioral paradigm (discussed later in the chapter). Burst activity did not appear to be a striking characteristic in the electrical activity of PPTg neurons recorded under basic conditions in behaving monkeys. This suggests that burst activity found in the PPTg in PD patients may represent a pathological discharge.

2. The PPTg and the reticular activating system (RAS)

The PPTg, together with chemospecific neuronal systems originating from the SN, locus coeruleus, LDTN, cuneiform nucleus and raphe nuclei, is part of a rhythmogenic complex that participates in both arousal and movement. Its deregulation is involved in sleep disturbances, attention deficits, movement disorders, epilepsy, coma, schizophrenia and depression (Garcia-Rill, 2015).

The functional importance of this region was first suggested by data from behavioral studies. Following the injection of cholinomimetics into the medial pontine reticular formation, rats entered a state very similar to rapid eye movement sleep (REM or paradoxical sleep). REM sleep induced by intracerebral injection of cholinergic agonists and natural REM sleep were accompanied by increased ACh release in the gigantocellular tegmental field, one of the rostral targets of PPTg and LDTN. In agreement with this finding, electrical stimulation of the PPTg enhanced the release of ACh in the gigantocellular tegmental field, while simultaneously depressing respiration, similar to what occurred in the ACh-induced REM sleeplike state (Bringmann, 1995; Kleiner and Bringmann, 1996; Lydic and Baghdoyan, 1993; Lydic and Baghdoyan, 1994; Mitani et al., 1988). Thus, cholinergic projections from the PPTg to the gigantocellular tegmental field may be important for the induction and maintenance of normal REM sleep and cortical activity. This effect may be exerted by PPTg neurons via the suppression of the bursting pattern of thalamic neurons involved in slow-wave sleep (SWS) and via the maintenance of single-spike activity linked to REM sleep and awake (Domich et al., 1986; Marks and Roffwarg, 1993; Weyand et al., 2001).

PPTg neurons have been found to selectively change their activity during the transition from non-rapid eye movement (NREM) sleep to wakefulness or to REM sleep. Some neurons that were tonically active during waking increased their firing up to 25–50 Hz (i.e. at frequencies in the gamma band) during locomotor movements in monkeys (Goetz et al., 2016b). In contrast, alpha oscillations have been recorded in the PPTg at rest and during gait in PD patients (Thevathasan et al., 2012b). This may indicate that a failure in the brainstem mechanisms generating gamma oscillations occurs in PD.

High-threshold calcium channels in the PPTg are thought to mediate the generation of gamma band activity, and the different types of these channels may serve distinct functions; for example, P/Q-type channels preferentially modulate waking whereas N-type channels maintain REM sleep (Garcia-Rill, 2015; Kezunovic et al., 2011; Urbano et al., 2014). Significantly, three types of PPTg cells were described. Those with both N and P/Q type channels comprising about 50% of neurons, those with only N-type (30%), and those with only P/Q type (20%) (Luster et al., 2016). It remains to be determined if these cells correspond to the *in-vivo* classifications of “Wake-REM-on” that are cells active during both waking and REM sleep, “REM-on” cells that are active during REM sleep only, and “Wake-on cells that are active only during waking. The longer the PPTg activation is prolonged by activation of calcium channels, the more thalamic and lower brainstem PPTg targets should receive relayed gamma band activation.

ACh is likely to be involved in the above processes, as it is released during active states when gamma oscillations appear in thalamic and cortical neurons (Brucke et al., 2013; Garcia-Rill et al., 2016; Howe et al., 2017; Sarter et al., 2016). The modulation of thalamocortical gamma oscillations by the PPTg cholinergic neurons may also influence thalamic processing of sensory information. The loss of this function in PD may disrupt the integration of postural sensory signals at thalamic levels and, consequently, weaken postural control in PD patients (Muller et al., 2013).

Whether the cholinergic, GABAergic and glutamatergic PPTg neurons selectively change their firing patterns in different physiological states is a matter of incertitude. That said, cholinergic neurons of the PPTg have been described to rhythmically discharge in the gamma band in phase with slow cortical oscillations in rats under deep anesthesia (Mena-Segovia et al., 2008). In contrast, non-cholinergic neurons that discharged in phase with cortical activity were found to increase their activity in the opposite phase respect to the cholinergic neurons, independently of nested gamma oscillations. These data suggest that cortical gamma activity may be naturally modulated by PPTg neurons, taking for granted that anesthesia-induced slow cortical oscillations are similar to those recorded during sleep.

In a study carried out in spontaneously-sleeping-waking head-fixed rats, PPTg cholinergic neurons were found to be maximally active in correlation with fast cortical activity and muscle tone during waking and REM sleep. In the same study many GABAergic and glutamatergic neurons similarly modulated their discharge as cholinergic neurons, while others showed different discharge profiles depending on waking and REM sleep, and in positive or negative correlation with muscle tone (Boucetta et al., 2014). The maintenance of gamma band activity is considered essential to support consciousness (Garcia-Rill, 2015).

Together with the LDTN, the PPTg is also considered to be important for the generation of ponto-geniculo-occipital (PGO) waves (Lim et al., 2007). These field potentials, which are characteristic of the transition from SWS to REM sleep, may be recorded in several brain regions, including the mesopontine tegmentum. PPTg neurons have been found to fire in bursts prior to, or in correspondence, with spontaneous PGO waves. The inhibitory GABAergic input from SN pars reticulata is crucial for the generation of PGO waves. This input could drive the membrane potential of PPTg neurons to a level that allows them to discharge in bursts so that PGO waves may occur. Accordingly, some GABAergic neurons of SN pars reticulata were described to be active before the onset of PGO waves (Datta et al., 1991; Datta, 2009; Datta and Siwek, 2002).

The discharge profiles of GABAergic and glutamatergic neurons in the PPTg are poorly understood. In rats most of the presumed glutamatergic neurons that did not fire in correlation with muscle tone, have been found to be active during waking and REM sleep, while others were minimally active during waking and maximally active during REM sleep. However, other presumed glutamatergic neurons that were maximally active during waking and minimally active during REM sleep modulated their firing in correlation with the level of muscle tone (Boucetta et al., 2014).

Thus, according to the different profiles of neuronal activity that have been found in its neuronal populations, it is possible to state that the PPTg promotes waking and REM sleep and modulate cortical activation and muscle tone during these states.

3. The PPTg participates in cognitive and sensorimotor functions

There is convincing evidence that the PPTg participates in higher functions of the brain; for example, lesions or chemical inactivation of the PPTg have been reported to disrupt reward-related responses, attention and stimulus–reward associations. The execution of conditioned reinforcement paradigms was consequently compromised, but movement, per se, was preserved and subtle motor deficits were evident only if tasks were particularly demanding. The extent to which specific subsets of PPTg neurons were responsible for the above deficits remains unclear, thus, one may ask through which pathways the PPTg operates in such functions.

A considerable number of PPTg cholinergic fibers innervate the centromedian-parafascicular complex (CM-Pf), which in turn innervates the cerebral cortex (Erro et al., 1999; Jackson and Crossman, 1983; Kobayashi and Nakamura, 2003; Rye et al., 1987; Saper and Loewy, 1982; Sugimoto and Hattori, 1984). The projections from the CM-Pf complex to the cerebral cortex increase progressively through evolution, reaching their maximal level in humans. Thus, the parafascicular (Pf) nucleus allows the PPTg to gain access to different cortical functions and to several high-order functions of the brain, including attention, action selection, learning, memory, spatial perception, control of impulsivity and decision-making. PPTg neurons may also participate in these functions through their axons ending in the striatum, where they synapse onto medium spiny neurons and cholinergic interneurons (Lapper and Bolam, 1992).

The loss or disruption of function that occurred following PPTg lesions confirms this viewpoint. For example, the acquisition of active and passive avoidance and of a place-learning task were impaired, whereas retention and retrieval of acquired avoidance behaviors were unimpaired in rats with PPTg lesions (Fujimoto et al., 1989; Fujimoto et al., 1992). Learning was also impaired when lesioned animals performed mnemonic motor tasks, such as an eight-arm radial maze-working memory task and a place-navigation water-maze task (Dellu et al., 1991) or when engaged in reversal learning in a spatial discrimination task (Syed et al., 2016). The integrity of the PPTg was also necessary for the development of morphine-induced place preference (Bechara and van der Kooy, 1992a). In contrast to the above results, no marked functional deficit was detected in PPTg lesioned rats engaged in a delayed non-matching to position accuracy task (Steckler et al., 1994). Furthermore, PPTg lesioned rats were not impaired in cocaine or heroin self-administration, or in the development of cocaine or heroin-conditioned place preferences (Parker and van der Kooy, 1995; Steidl et al., 2014).

Stimulus-reward association learning and attentional performance were disrupted in rats with PPTg lesion engaged in specific behavioral paradigms (Cyr et al., 2015; Florio et al., 1999; Inglis et al., 2000; Inglis et al., 2001).

Rats with ibotenate-induced loss of PPTg neurons, or a selective loss of ACh neurons induced by diphtheria toxin conjugated to urotensin-II, showed no deficits in learning or performance during fixed- or variable-ratio reinforcement paradigms (MacLaren et al., 2016). Acquisition of bar pressing for self-stimulation and amphetamine or morphine was prevented by *N*-methyl-D-aspartate (NMDA)–induced lesions of the PPTg while a reduction of bar pressing rate was found if the lesion was made after acquisition of self-stimulation (Lepore and Franklin, 1996). However, the performance in bar-pressing tasks depends on different subregions of the PPTg (Wilson et al., 2009). Indeed, when the posterior part of the PPTg was inactivated by microinjection of the GABA antagonist muscimol, the rats maintained their learned bar pressing rate for food reward but were unable to update their actions as the probability to earn a reward decreased (MacLaren et al., 2013).

The correct performance of the animal in many of the above tasks might have required intense activation of PPTg neurons driving, in turn, the activity of PF neurons. In agreement with this hypothesis, PPTg and Pf neurons discharged in the gamma band if the task was particularly demanding. The presence of high-threshold calcium currents in these neurons assured that the gamma band was effectively induced by the Pf and relayed to the cortex (Hyde et al., 2013; Kezunovic et al., 2011; Kezunovic et al., 2012).

The flow of information from the PPTg to the Pf neurons is rapid, as shown by the short-latency activation of Pf neurons in response to PPTg microstimulation (Capozzo et al., 2003). It is reasonable to propose that this activation was due to the activation of a direct pathway from PPTg to Pf, as these responses were still present following the destruction of cerebellar nuclei or after interruption of BG circuitry (i.e. in the absence of structures that could be co-activated by PPTg stimulation).

The neuronal circuitry involving the CM-Pf complex and the BG is also important for behavioral flexibility (i.e. in switching behavior in accordance with changes in the context in which a given action must be executed). In particular, the glutamatergic Pf neurons innervated by the PPTg cholinergic fibers and projecting to the dorsomedial striatum, may have a crucial role in this function. Indeed, these fibers may modulate the activity of the striatal cholinergic interneurons, which act in specific attention and sensory processes that are required for proper selection of motor responses to behavioral stimuli. As short-latency (< 80 ms) phasic activation was observed in PPTg neurons in response to the presentation of visual and acoustic stimuli of behavioral significance (Dormont et al., 1998; Norton et al., 2011; Pan and Hyland, 2005; Thompson and Felsen, 2013), the striatum may process behavior-related signals rapidly transmitted via the PPTg–Pf pathway. The short-latency of PPTg responses (< 80 ms) suggest a direct access to PPTg from early components of auditory, visual and somatosensory pathways, i.e. before access via multisynaptic pathways involving the superior colliculus, cerebral cortex and basal ganglia (Grunwerg et al., 1992; Krauthamer et al., 1995; Schofield, 2010; Schofield et al., 2011).

Since the PPTg and thalamic intralaminar nuclei, including the Pf, are reduced in PD (Halliday, 2009; Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1989), the disruption of sensory integration in the PPTg and the loss of the fast-conducting sensory input to the striatum via the PPTg–Pf pathway may decrease sensory responsiveness to external cues in PD patients. As a consequence of this loss, difficulties in the selection and/or execution of suitable motor actions in response to sensory information that usually drive movement or may occur in PD patients.

4. Motor functions of the PPTg

The integrity of the PPTg is important for reaching movements and in dopaminergic drug-stimulated orofacial activities (i.e. biting and licking) but not in spontaneous or drug-induced locomotion in the rat (Dunbar et al., 1992; Gut and Winn, 2015; Inglis et al., 1994; Muller and Klingberg, 1986; Olmstead and Franklin, 1994; Swerdlow and Koob, 1987).

However, being a part of the mesencephalic locomotor region, the PPTg is one of the locomotion-inducing sites of the midbrain. Indeed, its microstimulation elicited locomotion on a treadmill in decerebrate rats and cats. In addition, single-unit recordings in the PPTg region identified the presence of rhythmic patterns of neuronal activity synchronized to actual spontaneous locomotion (Garcia-Rill et al., 1983; Goetz et al., 2016a; Goetz et al., 2016b; Skinner and Garcia-Rill, 1984). PPTg neurons also displayed tonic and cyclic patterns of activity during spontaneous fictive locomotion. These electrophysiological data suggest that PPTg neurons contribute to the generation of rhythmic activity by the mesencephalic locomotor region. A recent study in mice has also provided evidence supporting a role of glutamatergic PPTg neurons in setting locomotor speed and gait selection (Caggiano et al., 2018).

Microrecordings from presumed PPTg neurons in PD patients showed that they discharged in relation to limb movements and in locomotor imagery tasks (Lau et al., 2015; Tattersall et al., 2014). This latter finding suggests that the PPTg, besides being involved in motor execution, also participates in motor programming and allows an integrated regulation of locomotor rhythm and postural muscle tone during locomotion (Takakusaki et al., 2016). Limb movement may therefore occur smoothly in the presence of optimal muscle tone. The reticulospinal system, arising from the pontomedullary reticular formation and descending in the neuraxis from the cervical to the lumbosacral segments, would allow synergistic action of the neck, trunk and limb muscles while modulating the central pattern generators in the spinal cord. In addition, projections to the superior colliculus and cranial nerve nuclei (V,VII and XII) would allow the PPTg to contribute to a wide range of motor activities, including saccadic eye movements, eye-head coordination and oro-pharyngolaryngeal movement.

Postural tone may be modulated by PPTg neurons projecting to the brainstem structures and spinal cord (Garcia-Rill et al., 2001; Garcia-Rill and Skinner, 1987a; Garcia-Rill and Skinner, 1987b; Kelland and Asdourian, 1989; Scarnati et al., 2011; Skinner et al., 1990a; Skinner et al., 1990b; Takakusaki et al., 2016). In particular, the PPTg could act through the reticulospinal system whose neurons, located in dorsal and ventral regions of the pontomedullary reticular formation, may induce, if activated, muscular atonia or hypertonia, respectively. Stimulation of the PPTg region in animals, and PPTg DBS in PD patients, has been shown to produce short-latency excitation of hindlimb motoneurons. This excitation was investigated by stimulating the L6 dorsal root in rats and recording the monosynaptic reflex response (H-reflex) (Baldissera et al., 1994; Scarnati et al., 2011). This response was strongly facilitated when a low-intensity conditioning stimulus was applied in the PPTg region prior (1–2 ms) to L6 dorsal root stimulation. This facilitation suggested that a descending PPTg pathway facilitated the excitability of spinal alpha-motoneurons. Accordingly, when a single stimulus was applied to the PPTg region, a descending volley was recorded in the medullary midline (in the region of the medial longitudinal fascicle), from the spinal cord surface at the thoracic and lumbar levels and from dorsal (sensory) and ventral (motor) roots. The latency of the descending volley along the neuraxis and spinal roots indicated that hindlimb motoneurons were activated via a disynaptic pathway with a relay in the brainstem. The spinal and muscle responses disappeared when neurons in the PPTg region were destroyed by ibotenic acid microinjection or when a discrete electrolytic lesion was placed in the medial longitudinal fascicle. This suggested that the effects of PPTg stimulation could be mediated via the reticulospinal pathways. A similar facilitation was observed in PD patients when investigating the effect of PPTg DBS on the soleus-H-reflex (Pierantozzi et al., 2008). Stimulation of the PPTg caused a net decrease of the threshold to evoke the H-reflex, whereas STN-DBS was less effective and L-Dopa ineffective. That the PPTg may modulate reticulospinal pathways is also supported by its participation in the acoustic startle response, i.e. in the fast skeletal muscle contraction that occurs in response to a sudden loud stimulus (MacLaren et al., 2014; Yeomans et al., 2006).

Improvements in posture and gait freezing have been consistently reported in PD patients subjected to PPTg DBS, while the effects on gait are debatable (Ferraye et al., 2010; Mazzone et al., 2014; Mazzone et al., 2016; Moro et al., 2010; Thevathasan et al., 2011a; Wilcox et al., 2011). Improvements in gait initiation, stride length and cadence have been found in most of our patients (Mazzone et al., 2014). The inconsistencies pertaining to gait may have originated from factors such as patient selection criteria, the different degree of degeneration in the SN between patients and other central structures, the precise stimulation site and stimulation parameters. Regarding parameters, the best clinical impact on gait in our patients was obtained with stimuli delivered at 40 Hz, 2–4 V and with a pulse duration of 60 μs. Similar parameters were successfully adopted in other studies and induced locomotion in animals (Orlovskii et al., 1966; Skinner and Garcia-Rill, 1984; Thevathasan et al., 2012a; Wilcox et al., 2011).

The motor role of the PPTg is also supported by studies on stroke. Indeed, freezing of gait and ataxia have been reported in patients affected by vascular accidents confined to the PPTg region (Bhidayasiri et al., 2003; Kuo et al., 2008). In addition, a diffusion tensor imaging investigation of the functional changes of the PPTg in chronic stroke patients showed that the neuronal activity of the PPTg in the affected hemisphere increased only in patients who were able to walk (Yeo et al., 2011). Interestingly, in a recent study, rats that underwent photothrombotic stroke of the right sensorimotor cortex exhibited deficits in dynamic and static gait parameters in a walking test. The rats regained the ability to walk and improved in several dynamic gait parameters when subjected to stimulation of the region involving the PPTg (Fluri et al., 2017). Thus, the integrity of the PPTg may be also crucial for recovery of walking after stroke.

5. The PPTg output to the dopaminergic neurons of the substantia nigra

As mentioned previously, the existence of a direct PPTg projection to the SN pars compacta has been established in rodents, felines and non-human primates. Following the discovery of ChAT-containing PPTg output neurons, several authors considered that the PPTg projection to the SN pars compacta was cholinergic. This view was corroborated by the presence of other markers in the SN that were indicative of a cholinergic input, such as the presence of ACh postsynaptic receptors, ChAT-immunoreactive terminals and acethylcholinesterase (the ACh degrading enzyme) (Bolam et al., 1991; Clarke and Pert, 1985; Henderson and Greenfield, 1987; Lacey et al., 1991; Martinez-Murillo et al., 1989). In contrast, electrophysiological data from our laboratory indicated the presence of PPTg excitatory fibers innervating the SN pars compacta and using GLU as a neurotransmitter. This conclusion was reached after finding that electrical microstimulation of the PPTg produced a brief activation in nigrostriatal neurons. This orthodromic response appeared at a variable latency of 2–3 ms, followed high-frequency activation (up to 300 Hz) and was still present in animals with lesions in structures that could give rise to fibers co-activated by PPTg stimulation, or which could relay polysynaptic pathways linking the PPTg to the SN (Scarnati et al., 1984; Scarnati et al., 1987). Results from electron-microscopy studies supported these conclusions. Indeed, following a discrete electrolytic lesion of the PPTg, degenerating terminals containing round vesicles and making asymmetric synaptic contacts with dendrites of SN pars compacta neurons were observed in both rat and cats (Scarnati et al., 1988b; Tokuno et al., 1988; Usunoff, 1984). The morphology of these contacts was indicative of an excitatory input and, given the electrophysiological characteristics of the PPTg-evoked excitation of nigral neurons, GLU was thought to be involved in the PPTg-SN pars compacta pathway.

We investigated this possibility considering that despite the location of the PPTg in the CH_5 cholinergic mesopontine cell group and the presence of nicotinic and muscarinic ACh receptors in SN pars compacta neurons, some authors reported inconsistencies in the effects of ACh iontophoretically applied onto SN pars compacta neurons or even failed to demonstrate ACh participation in the PPTg-SN pars compacta pathway (Collingridge and Davies, 1981; Dray et al., 1976; Lacey et al., 1991; Lichtensteiger et al., 1982). The effects of excitatory aminoacid antagonists, as well as cholinergic receptor antagonists, administered by iontophoresis onto nigrostriatal neurons that were orthodromically activated by stimulation of the PPTg region were tested (Di Loreto et al., 1992). Cholinergic receptor antagonists failed to suppress the orthodromic response whereas both NMDA and non-NMDA antagonists of GLU receptors were effective. Iontophoretic application of the competitive antagonist of non-NMDA receptors 6-cyano-2, 3-dihydroxy-7-nitroquinoxaline, onto nigral neurons was the most effective at simultaneously suppressing the PPTg-evoked excitation and the activation induced by iontophoretically-applied specific non-NMDA agonists.

The monosynaptic nature of this GLU-mediated response was subsequently confirmed in in vitro slice preparations (Futami et al., 1995) and also shown by neuroanatomical investigations in the monkey. After injecting anterograde tracers in the PPTg, thin and varicosed labeled terminals were found in the SN. These terminals arborized almost exclusively in the pars compacta, where they closely surrounded the soma and proximal dendrites of dopaminergic neurons (Lavoie and Parent, 1994c). In addition, injection of *Phaseolus vulgaris* leucoagglutinin as an anterograde tracer into the primate PPTg labeled glutamate-positive terminal boutons that established asymmetrical contacts with dendritic shafts of SN dopaminergic neurons (Charara et al., 1996; Parent et al., 1999). A recent investigation has shown that in mouse PPTg axons establish glutamatergic synapses on the soma and proximal dendrites of SN pars compacta neurons (i.e. in an ideal position to influence spike generation) (Galtieri et al., 2017). It is noteworthy that orthodromic activation very similar to that recorded in SN pars compacta neurons was observed in entopeduncular and STN neurons (Hammond et al., 1983; Scarnati et al., 1988a). Therefore, the PPTg could also influence simultaneously its main BG targets through fast-conducting excitatory fibers.

In brain slice preparations from mice both NMDA and non-NMDA receptors were found at PPTg synapses. Optogenetic stimulation of PPTg axons showed that SN pars compacta neurons faithfully followed burst stimulation, even in the presence of NMDA antagonists (Galtieri et al., 2017).

However, in another study NMDA and non-NMDA antagonists partially suppressed the monosynaptic excitatory postsynaptic potentials (EPSP) evoked in identified DA neurons of the pars compacta via stimulation of the PPTg, while the GLU antagonist-resistant EPSPs were blocked by cholinergic antagonists (Futami et al., 1995). Thus, both GLU and ACh are involved in the pathway from the PPTg to the SN pars compacta; however, the GLU component was more effective in activating nigral neurons than the ACh component. The existence of this glutamatergic pathway establishing synapses preferentially onto pars compacta neurons is in agreement with the effects of chemical manipulation of the pontine tegmentum on striatal dopamine metabolism. For example, kainic acid (an excitotoxin) infusion in the PPTg sharply increased dopamine turnover in the striatum and produced cell death in the SN (Hernandez-Lopez et al., 1992; McGeer and McGeer, 1984; Niijima and Yoshida, 1988). Striatal dopamine efflux was also found to be stimulated by the injection of cholinergic agonists in the SN pars compacta; however, this effect was influenced by the integrity of the PPTg (Blaha and Winn, 1993; Forster and Blaha, 2003). This latter effect demonstrates once again the crucial role of PPTg fibers in modulating the activity of the dopaminergic nigrostriatal pathway.

6. The role of the PPTg in predictive reward information and reward-based learning

The formation of stimulus–reward associations requires the integrity of the PPTg. The PPTg consolidates the association between the stimulus and behavioral-response selection and is crucial for the execution of goal-directed behavior and in eliciting and reinforcing approach behavior (Cyr et al., 2015; Dellu et al., 1991; Florio et al., 1999; Inglis et al., 2000; Inglis et al., 2001; Lepore and Franklin, 1996; Syed et al., 2016; Wilson et al., 2009; Yeomans et al., 1993). In addition, cholinergic neurons in the PPTg appear to be critical for mediating the reinforcing effects of opiates and stimulants, including morphine, amphetamine and nicotine (Bechara and van der Kooy, 1989; Bechara and van der Kooy, 1992b; MacLaren et al., 2016; Olmstead and Franklin, 1994; Steidl et al., 2014). Given the existence of a PPTg monosynaptic excitatory input to SN pars compacta neurons, one may ask if PPTg neurons may influence the responsiveness of the dopaminergic nigrostriatal system to rewarding stimuli. SN pars compacta neurons phasically respond to reward-related sensory cues or to the reward itself, whereas striatal neurons increase their firing during the expectancy of forthcoming stimuli in behavioral paradigms, including the delivery of the reward (Schultz, 1986; Schultz et al., 1992; Schultz, 1997; Schultz, 2016b).

Mesencephalic dopaminergic neurons may transform a reward-related sensory signal into an internal variable encoded by changes in their discharge pattern. These neurons respond with a phasic discharge to reward-related signals. The early component of this response, which precedes behavioral action and has a latency and duration of < 100 ms, may serve to detect stimuli and reflect their salience. The late component, which appears at approximately 250 ms, encodes information about the value of the reward. If the reward is not given, or if its value differs from what is expected, a prediction error response arises (Schultz, 2016a; Schultz, 2016b).

PPTg neurons may participate in this process because of their responsiveness to reward-related sensory stimuli and to the reward itself, and because of the robust monosynaptic excitatory input that they provide to SN pars compacta neurons. However, the participation of PPTg neurons is not restricted to the incentive aspects of rewarded motor acts, but also concerns the detection of the sensory cues involved in behavioral paradigms. For example, PPTg neurons in mice, rats and cats were also reported to exhibit short-latency responses to behavioral sensory cues (Dormont et al., 1998; Norton et al., 2011; Pan and Hyland, 2005; Thompson et al., 2016; Thompson and Felsen, 2013). In agreement with the functional link between the PPTg and SN dopaminergic neurons, the responses recorded in PPTg neurons at the presentation of behavioral cues were of shorter latency than those of the dopaminergic neurons and the responsiveness of these latter neurons to sensory cues was suppressed by inactivation of the PPTg (Pan and Hyland, 2005).

In a visually-guided saccade task a monkey was requested to fixate on a central fixation target and a reward was delivered after the monkey made a saccade at the presentation of a cue that indicated the position of the saccade target. It was possible to inform the monkey about a large or a small upcoming reward by presenting different shapes of the central fixation target. Therefore, it was possible to investigate whether differences in predicted and actual reward magnitude would affect neuronal responses (Okada and Kobayashi, 2013; Okada and Kobayashi, 2014; Okada and Kobayashi, 2016). Tonic or phasic reward-related modulation of neuronal activity occurred in different classes of PPTg neurons in correspondence with, or during, the expectation of the behavioral events of the paradigm. The tonic response consisted of a sustained increase or a sustained depression of discharge. Most of the sustained increase developed from the onset of the initial fixation target until the reward delivery, and the magnitude of the response was higher when the shape of the fixation target cued the animal to expect a large reward. Thus the level of activity reflected the predicted reward amount. The sustained activity also continued if the reward delivery was delayed and sharply decreased once the reward was gained. However, if the target cue was maintained after the reward delivery, some PPTg neurons showed sustained activity, thus indicating that the monkey continued to fixate on the saccade target even after reward delivery. This may indicate the existence of PPTg neurons that sustain attention toward the task event rather than toward the reward. If the animals were cued at the start of a trial by a fixation point that preceded the presentation of the fixation target, PPTg neurons increased their discharge rate at the presentation of the cue that signalled the start of the trial, and this activity was sustained until the end of the trial. The fact that the magnitude of the tonic activation reflected the predicted reward amount undoubtedly supports the reward nature of this response. From these data it appears that the reward target was the pivotal sensory cue driving the monkey's attention. If something unusual happened (i.e. the target signal was not switched off), the monkeys maintained their attention to this cue. Overall, the tonic responses may be considered to be specifically involved in the prediction of the upcoming reward and reflect the sustained attentional and motivational state of the monkey.

The results from a task in which monkeys performed a saccade toward a rewarded or not rewarded target showed that PPTg neuronal responses were comparable to those described above (Hong and Hikosaka, 2014). In this study, separate groups of PPTg neurons were phasically excited by reward-related cues, tonically discharged from cue to reward release, or phasically discharged when the reward was delivered. In a paradigm where the reward was not given, a phasic depression of activity was observed at the presentation of the cue not linked to the reward. Many of these neurons were electrophysiologically identified as projecting to SN pars compacta. The participation of PPTg neurons in the computation of the reward prediction error was also supported by data from a two-valued reward visually-guided task, in which the shape of the fixation target at the start of each trial informed the animal to expect large or small rewards. In this paradigm, reward information was carried by two distinct groups of neurons, those that tonically discharged between the onset of the fixation target and the reward delivery, or those that phasically discharged after the reward delivery. In tonically discharging neurons, the level of activity was associated with the magnitude of the expected reward. In phasically discharging neurons, the level of activity reflected the actual value of the reward. Thus, the activity of separate populations of PPTg neurons may encode predicted and actual reward values.

Major differences in the responsiveness to reward-related stimuli were observed when comparing PPTg neurons with nigral dopaminergic neurons. For example, contrary to dopamine neurons, different populations of PPTg neurons encode different reward- and event-related properties, and no phasic depression was reported if the reward was omitted.

The maintenance of sustained arousal and attention is a fundamental prerequisite for enhanced performance in any behavioral paradigm. In the paradigms discussed above, sustained arousal and attention could be assured by the tonic increase of activity that occurs from the presentation of the reward-related cue to the reward delivery, and by the increased activity that persists during the presentation of paradigm events. It is noteworthy that neurons that changed their activity during the behavioral paradigm and during intertrial intervals exhibited a periodic discharge activity at approximately 35 Hz and reached frequencies of up to 100 Hz (i.e. in the gamma-band activity range that is typical of intense arousal) (Okada and Kobayashi, 2015).

Local field potential oscillations synchronized at alpha frequency and coupled with similar activity in the cerebral cortex were reported in PD patients during L-Dopa therapy and during self-paced joystick movements (Androulidakis et al., 2008). Oscillatory rhythms in local field potentials in locomotor-inducing mesencephalic sites, including the PPTg, were reported to synchronize at theta frequencies (6–12 Hz) in the rat (Noga et al., 2017). However, the appearance of alpha oscillations in neuronal discharge and in field potentials must be cautiously interpreted as: (1) some studies recorded during resting conditions when the nucleus fires at low frequencies, and (2) PPTg neurons degenerate in neurodegenerative diseases. In spite of these limitations, the oscillations observed in pathological states may be indicative of profound alterations in the functional properties of PPTg neurons, to the point that they do not show sustained gamma-band activity as suggested by the associated monkey studies.

Finally, there are analogies in the responses of PPTg and striatal neurons to behavioral signals and rewards (Apicella et al., 1991; Apicella et al., 1992; Apicella, 2002; Apicella, 2007). Thus, the PPTg and the striatum may share common profiles of neuronal responses in relation to the presentation and expectation of predictable behavioral events, including reward.

If the neuronal circuitry in which the PPTg is involved in reward is considered it could also be hypothesized that the PPTg may rapidly convey information to mesencephalic dopaminergic neurons via the monosynaptic excitatory PPTg–SN pathway. It may also influence striatal neurons both indirectly, via intralaminar thalamic nuclei, and directly, by its neurons innervating the striatum.

7. Does the cerebellum play a role in mediating PPTg influence on cerebral cortex?

Although cerebellum and BG are separate neuronal systems, they share common structures in the neuronal circuits in which they are involved. For example, PPTg fibers are directed to deep cerebellar nuclei, and disynaptic pathways link the dentate nucleus to the striatum via thalamic nuclei (Hazrati and Parent, 1992; Hoshi et al., 2005; Jaarsma et al., 1997; Newman and Ginsberg, 1992; Ruggiero et al., 1997; Woolf and Butcher, 1989). The STN is robustly innervated by PPTg fibers and is in turn linked to the cerebellar cortex via pontine nuclei (Bostan et al., 2010; Bostan et al., 2013). Recent tractographic studies also showed a PPTg–cerebellum projection in the human brain, and altered or even absent PPTg connectivity in the corticopontine-cerebellar pathways was found in PD patients with freezing of gait (Aravamuthan et al., 2007; Schweder et al., 2010; Wang et al., 2016; Wu et al., 2011; Youn et al., 2015). Cholinergic fibers that originate in the PPTg diffusely innervate both cerebellar cortex and cerebellar nuclei, where they establish asymmetric synaptic contacts on small- and medium-sized dendrites of cortical and nuclear neurons. These cholinergic fibers may modulate the excitability of cerebellar neurons in relation to arousal and rhythmic activity of thalamocortical neurons (Jaarsma et al., 1997; McCormick, 1989).

We investigated the effects of PPTg microstimulation on cerebellar nucleus neurons in intact rats and in rats with an induced loss of PPTg neurons (Vitale et al., 2016). The main response in fastigial, interpositus and dentate nuclei was a short-latency, brief activation. This activation followed short trains of stimuli delivered up to 200 Hz and likely resulted from the activation of a direct input from the PPTg. The percentage of neurons activated from the PPTg significantly decreased when PPTg neurons degenerated, suggesting that the recorded excitatory response in intact rats was mainly due to the stimulation of PPTg neurons rather than activation of passing fibers. Dentate nucleus neurons were the most responsive to PPTg stimulation, therefore, further investigation of the properties of the PPTg-evoked response was performed in these neurons. Their activation was shown to be mediated by ACh. Indeed, iontophoretic application of atropine or mecamylamine onto dentate neurons while stimulating the PPTg reduced, if not completely abolished, the evoked responses.

Results suggested that the PPTg may influence the medial cerebellum via the fastigial and interpositus nuclei. PPTg may also participate in cerebello-cortical mechanisms via the dentate nucleus. Thus, the lateral cerebellum may act in synergy with the Pf to ensure the most appropriate level of BG and cortical activity required for motor selection in response to stimuli having a precise behavioral significance. Therefore, reward and reinforcement learning information are elements that the BG could provide to the cerebellum.

The influence of the PPTg on the medial cerebellum via the fastigial and interpositus nuclei may be involved in gait deficits and postural instability in advanced PD. These patients are unresponsive to L-Dopa treatment but may benefit from low-frequency (20–40 Hz) PPTg DBS (Ferraye et al., 2010; Mazzone et al., 2016; Moro et al., 2010; Ostrem et al., 2010; Thevathasan et al., 2011a). This led some authors to consider gait and axial disturbances in PD as consequences of ACh disruption in the brainstem rather than disruption of the nigrostriatal dopaminergic system. In addition, the severity of these motor disabilities was directly related to the degree of ACh neuronal loss in the PPTg (Bohnen et al., 2013; Bohnen and Albin, 2011; Karachi et al., 2010; Muller et al., 2013). However, as discussed previously, other neurotransmitters (i.e. GLU) are thought to be involved in fibers descending from the PPTg to the spinal cord and the lower brainstem motor structures. Thus, further investigations are needed to clarify the nature of the neurotransmitters involved in PPTg descending fibers that contribute to gait and muscle tone.

8. Conclusions: The PPTg and PD, facts and perspectives

The wealth of evidence that we have discussed suggests that, in addition to being involved in motor control, the PPTg also participates in the formation and selection of appropriate motor responses prior to the execution of a goal-directed movement. These phases would require proper functioning of arousal, attention, and motivation (i.e. functions in which the PPTg has a role).

PPTg DBS may relieve a block of a pre-prepared movement (Thevathasan et al., 2011b), and improve postural sensory integration (Mazzone et al., 2018; Muller et al., 2013) so that gait may proceed smoothly. It is also possible that the arousal increase following PPTg stimulation may cause some patients to be more attentive to what they are doing or what they are about to do. This would facilitate their actions while simultaneously and automatically adjusting their postural tone because of the restoration of PPTg influence on descending motor pathways.

Garcia-Rill suggested that PPTg DBS may provide a maintained level of gamma band activity (Garcia-Rill et al., 2016).

In agreement with this view, and with the central role of the PPTg in promoting arousal and REM sleep, patients subjected to PPTg DBS showed improvements in daytime sleepiness and REM sleep. Their cognitive functions also improved as shown by their enhanced performance in delayed recall, executive functions and verbal fluency paradigms (Costa et al., 2010; Lim et al., 2009; Peppe et al., 2012; Zanini et al., 2009). These improvements were accompanied by bilateral increased glucose utilization in the prefrontal and frontal cortical areas and in the ventral striatum (Stefani et al., 2010). However, the number of investigated patients remains low. Therefore, further controlled studies are required in larger and more homogeneous cohorts, with similar surgical procedures, target implantation methods, and stimulation parameters.

The data discussed in this review highlight the crucial role of the PPTg, both in the translation from motivation to action, and in the facilitation of brainstem motor mechanisms that are required for the correct execution of purposive movements. Except for the cholinergic neurons involved in arousal and REM sleep, it is not clear to what extent the different neuronal populations that are present in the PPTg are selectively involved in the different functions of the PPTg that we have discussed.

The existence of GLU neurons in the pathway from the PPTg to the SN is the rationale behind the assumption of GLU-mediated excitotoxic degeneration of DA-containing neurons in the SN pars compacta. It is known that injections of excitotoxic compounds in the mesopontine tegmentum induce degeneration of pars compacta neurons (McGeer and McGeer, 1984). This neuronal death could result from over-excitation of NMDA and non-NMDA GLU receptors located on dopamine neurons, which consequently disrupt intracellular calcium homeostasis. In support of this possibility, the GLU receptor antagonist MK80I was reported to prevent the neurotoxic effect of MPTP on pars compacta DA neurons, and to alleviate experimental parkinsonism (Klockgether et al., 1991; Turski et al., 1991). The neuronal loss in the SN could be also modulated by the cholinergic component of the PPTg SN pathway. In agreement with this hypothesis, stimulation of nicotinic ACh receptors was reported to be neuroprotective for dopaminergic nigral neurons. In agreement with this neuroprotective effect, specific destruction of PPTg cholinergic neurons was found to be associated to a loss of nigral dopaminergic neurons (Bensaid et al., 2016).

If one considers the staging of PD, the pathology in the initial stages I-II is confined to the medulla oblongata, the pontine tegmentum and anterior olfactory structures, while in the successive stages III-IV spreads 1 to the midbrain and the forebrain (Braak et al., 2003; Braak et al., 2006). Thus, PPTg may be affected in PD before SN and abnormal activity of PPTg neurons may damage nigral dopaminergic neurons. Interestingly, a study of the P50 midlatency auditory evoked potential suggested that in the initial stages of PD PPTg neurons may be overactive (Teo et al., 1997).

The results of several *in-vivo* and *in-vitro* studies point firmly to the fact that neuronal degeneration in the mammalian central nervous system may result from excessive stimulation of GLU receptors and indicate antagonists of NMDA and non-NMDA receptors as a drug therapy to counteract or to slow the neuronal degeneration occurring in PD and other disorders (Ikonomidou and Turski, 1996; Lange and Riederer, 1994; Willard and Koochekpour, 2013).

The existence of GLU in the PPTg–SN pars compacta pathway, the presence of GLU receptors on dopaminergic nigral neurons and the intriguing results from animal studies suggest that dopaminergic neurons might degenerate through an excitatory aminoacid-induced mechanism in which the PPTg could be involved. Therefore, the role of GLU input from the PPTg may be even more relevant than it appears at first glance, as GLU is colocalized with other neurotransmitters in addition to being the sole neurotransmitter of a subpopulation of PPTg neurons. Finally, the question arises as to whether such an excitotoxic mechanism occurs in PD. The experimental evidence suggests this hypothesis feasible; however, additional studies on GLU neurotransmission in the pontine tegmentum of PD patients would clarify this issue.

Conflict of interest

The Authors declare no conflict of interest.

Acknowledgements

The Authors wish to thank two anonymous referees for their constructive criticism and Prof. Edgar Garcia-Rill for his critical reading of the manuscript. The work has been supported by grants from University of L'Aquila (small RIA 2017), EU Biomed 2 overheads, and by a Medtronic donation (investigator-initiated trial 2016).

References

Alam, M., Schwabe, K., Krauss, J.K., 2011. The pedunculopontine nucleus area: critical evaluation of interspecies differences relevant for its use as a target for deep brain stimulation. Brain 134, 11–23.

Androulidakis, A.G., Mazzone, P., Litvak, V., Penny, W., Dileone, M., Gaynor, L.M., Tisch, S., Di Lazzaro, V., Brown, P., 2008. Oscillatory activity in the pedunculopontine area of patients with Parkinson's disease. Exp. Neurol. 211, 59–66.

Apicella, P., 2002. Tonically active neurons in the primate striatum and their role in the processing of information about motivationally relevant events. Eur. J. Neurosci. 16, 2017–2026.

Apicella, P., 2007. Leading tonically active neurons of the striatum from reward detection to context recognition. Trends Neurosci. 30, 299–306.

Apicella, P., Ljungberg, T., Scarnati, E., Schultz, W., 1991. Responses to reward in monkey dorsal and ventral striatum. Exp. Brain Res. 85, 491–500.

Apicella, P., Scarnati, E., Ljungberg, T., Schultz, W., 1992. Neuronal activity in monkey striatum related to the expectation of predictable environmental events. J. Neurophysiol. 68, 945–960.

Aravamuthan, B.R., Muthusamy, K.A., Stein, J.F., Aziz, T.Z., Johansen-Berg, H., 2007. Topography of cortical and subcortical connections of the human pedunculopontine and subthalamic nuclei. NeuroImage 37, 694–705.

Austin, M.C., Rice, P.M., Mann, J.J., Arango, V., 1995. Localization of corticotropin-releasing hormone in the human locus coeruleus and pedunculopontine tegmental nucleus: an immunocytochemical and in situ hybridization study. Neuroscience 64, 713–727.

Baldissera, F., Di Loreto, S., Florio, T., Scarnati, E., 1994. Short-latency excitation of hindlimb motoneurons induced by electrical stimulation of the pontomesencephalic tegmentum in the rat. Neurosci. Lett. 169, 13–16.

Bechara, A., van der Kooy, D., 1989. The tegmental pedunculopontine nucleus: a brainstem output of the limbic system critical for the conditioned place preferences produced by morphine and amphetamine. J. Neurosci. 9, 3400–3409.

Bechara, A., van der Kooy, D., 1992a. A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived rats but not in deprived rats. Behav. Neurosci. 106, 351–363.

Bechara, A., van der Kooy, D., 1992b. Lesions of the tegmental pedunculopontine nucleus: effects on the locomotor activity induced by morphine and amphetamine. Pharmacol. Biochem. Behav. 42, 9–18.

Beninato, M., Spencer, R.F., 1987. A cholinergic projection to the rat substantia nigra from the pedunculopontine tegmental nucleus. Brain Res. 412, 169–174.

Beninato, M., Spencer, R.F., 1988. The cholinergic innervation of the rat substantia nigra: a light and electron microscopic immunohistochemical study. Exp. Brain Res. 72, 178–184.

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.

Bhidayasiri, R., Hathout, G., Cohen, S.N., Tourtellotte, W.W., 2003. Midbrain ataxia: possible role of the pedunculopontine nucleus in human locomotion. Cerebrovasc. Dis. 16, 95–96.

Blaha, C.D., Winn, P., 1993. Modulation of dopamine efflux in the striatum following cholinergic stimulation of the substantia nigra in intact and pedunculopontine tegmental nucleus-lesioned rats. J. Neurosci. 13, 1035–1044.

Bohnen, N.I., Albin, R.L., 2011. The cholinergic system and Parkinson disease. Behav. Brain Res. 221, 564–573.

Bohnen, N.I., Frey, K.A., Studenski, S., Kotagal, V., Koeppe, R.A., Scott, P.J., Albin, R.L., Muller, M.L., 2013. Gait speed in Parkinson disease correlates with cholinergic degeneration. Neurology 81, 1611–1616.

Bolam, J.P., Francis, C.M., Henderson, Z., 1991. Cholinergic input to dopaminergic neurons in the substantia nigra: a double immunocytochemical study. Neuroscience 41, 483–494.

Bostan, A.C., Dum, R.P., Strick, P.L., 2010. The basal ganglia communicate with the cerebellum. Proc. Natl. Acad. Sci. U. S. A. 107, 8452–8456.

Bostan, A.C., Dum, R.P., Strick, P.L., 2013. Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn. Sci. 17, 241–254.

Boucetta, S., Cisse, Y., Mainville, L., Morales, M., Jones, B.E., 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, 4708–4727.

Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211.

Braak, H., Muller, C.M., Rub, U., Ackermann, H., Bratzke, H., de Vos, R.A., Del Tredici, K., 2006. Pathology associated with sporadic Parkinson's disease–where does it end? J. Neural Transm. Suppl. 89–97.

Bringmann, A., 1995. Different functions of rat's pedunculopontine tegmental nucleus are reflected in cortical EEG. Neuroreport 6, 2065–2068.

Brucke, C., Bock, A., Huebl, J., Krauss, J.K., Schonecker, T., Schneider, G.H., Brown, P., Kuhn, A.A., 2013. Thalamic gamma oscillations correlate with reaction time in a go/noGo task in patients with essential tremor. NeuroImage 75, 36–45.

Caggiano, V., Leiras, R., Goni-Erro, H., Masini, D., Bellardita, C., Bouvier, J., Caldeira, V., Fisone, G., Kiehn, O., 2018. Midbrain circuits that set locomotor speed and gait selection. Nature 553, 455–460.

Capozzo, A., Florio, T., Cellini, R., Moriconi, U., Scarnati, E., 2003. The pedunculopontine nucleus projection to the parafascicular nucleus of the thalamus: an electrophysiological investigation in the rat. J. Neural Transm. 110, 733–747.

Charara, A., Smith, Y., Parent, A., 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, 254–266.

Clarke, P.B., Pert, A., 1985. Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Res. 348, 355–358.

Collingridge, G.L., Davies, J., 1981. The influence of striatal stimulation and putative neurotransmitters on identified neurones in the rat substantia nigra. Brain Res. 212, 345–359.

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, 64–67.

Cote, P.Y., Parent, A., 1992. Calbindin D-28k and choline acetyltransferase are expressed by different neuronal populations in pedunculopontine nucleus but not in nucleus basalis in squirrel monkeys. Brain Res. 593, 245–252.

Cyr, M., Parent, M.J., Mechawar, N., Rosa-Neto, P., Soucy, J.P., Clark, S.D., Aghourian, M., Bedard, M.A., 2015. Deficit in sustained attention following selective cholinergic lesion of the pedunculopontine tegmental nucleus in rat, as measured with both post-mortem immunocytochemistry and in vivo PET imaging with [(1)(8)F]fluoroethoxybenzovesamicol. Behav. Brain Res. 278, 107–114.

Datta, S., 2009. Regulation of neuronal activities within REM sleep-sign generators. Sleep 32, 1113–1114.

Datta, S., Siwek, D.F., 2002. Single cell activity patterns of pedunculopontine tegmentum neurons across the sleep-wake cycle in the freely moving rats. J. Neurosci. Res. 70, 611–621.

Datta, S., Curro, D.R., Pare, D., Oakson, G., Steriade, M., 1991. Substantia nigra reticulata neurons during sleep-waking states: relation with ponto-geniculo-occipital waves. Brain Res. 566, 344–347.

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, 4509–4518.

Dawson, T.M., Bredt, D.S., Fotuhi, M., Hwang, P.M., Snyder, S.H., 1991. Nitric oxide synthase and neuronal NADPH diaphorase are identical in brain and peripheral tissues. Proc. Natl. Acad. Sci. U. S. A. 88, 7797–7801.

Dellu, F., Mayo, W., Cherkaoui, J., Le Moal, M., Simon, H., 1991. Learning disturbances following excitotoxic lesion of cholinergic pedunculo-pontine nucleus in the rat. Brain Res. 544, 126–132.

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, 79–86.

Domich, L., Oakson, G., Steriade, M., 1986. Thalamic burst patterns in the naturally sleeping cat: a comparison between cortically projecting and reticularis neurones. J. Physiol. 379, 429–449.

Dormont, J.F., Conde, H., Farin, D., 1998. The role of the pedunculopontine tegmental nucleus in relation to conditioned motor performance in the cat. I. Context-dependent and reinforcement-related single unit activity. Exp. Brain Res. 121, 401–410.

Dray, A., Gonye, T.J., Oakley, N.R., 1976. Caudate stimulation and substantia nigra activity in the rat. J. Physiol. 259, 825–849.

Dunbar, J.S., Hitchcock, K., Latimer, M., Rugg, E.L., Ward, N., Winn, P., 1992. Excitotoxic lesions of the pedunculopontine tegmental nucleus of the rat. II. Examination of eating and drinking, rotation, and reaching and grasping following unilateral ibotenate or quinolinate lesions. Brain Res. 589, 194–206.

Edley, S.M., Graybiel, A.M., 1983. The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. J. Comp. Neurol. 217, 187–215.

Erro, E., Gimenez-Amaya, J.M., 1999. Pedunculopontine tegmental nucleus. Anatomy, functional considerations and physiopathological implications. An. Sist. Sanit. Navar. 22, 189–201.

Erro, E., Lanciego, J.L., Gimenez-Amaya, J.M., 1999. Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. Exp. Brain Res. 127, 162–170.

Ferraye, M.U., Debu, B., Fraix, V., Goetz, L., Ardouin, C., Yelnik, J., Henry-Lagrange, C., Seigneuret, E., Piallat, B., Krack, P., Le Bas, J.F., Benabid, A.L., Chabardes, S., Pollak, P., 2010. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 133, 205–214.

Florio, T., Capozzo, A., Puglielli, E., Pupillo, R., Pizzuti, G., Scarnati, E., 1999. The function of the pedunculopontine nucleus in the preparation and execution of an externally-cued bar pressing task in the rat. Behav. Brain Res. 104, 95–104.

Fluri, F., Malzahn, U., Homola, G.A., Schuhmann, M.K., Kleinschnitz, C., Volkmann, J., 2017. Stimulation of the mesencephalic locomotor region for gait recovery after stroke. Ann. Neurol. 00, 000.

Forster, G.L., Blaha, C.D., 2003. Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat. Eur. J. Neurosci. 17, 751–762.

Fujimoto, K., Yoshida, M., Ikeguchi, K., Niijima, K., 1989. Impairment of active avoidance produced after destruction of pedunculopontine nucleus areas in the rat. Neurosci. Res. 6, 321–328.

Fujimoto, K., Ikeguchi, K., Yoshida, M., 1992. Impaired acquisition, preserved retention and retrieval of avoidance behavior after destruction of pedunculopontine nucleus areas in the rat. Neurosci. Res. 13, 43–51.

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, 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, 30352.

Garcia-Rill, E., 2015. Waking and the Reticular Activating System in Health and Disease. Elsevier-Academic Press, Amsterdam.

Garcia-Rill, E., Skinner, R.D., 1987a. The mesencephalic locomotor region. I. Activation of a medullary projection site. Brain Res. 411, 1–12.

Garcia-Rill, E., Skinner, R.D., 1987b. The mesencephalic locomotor region. II. Projections to reticulospinal neurons. Brain Res. 411, 13–20.

Garcia-Rill, E., Skinner, R.D., Fitzgerald, J.A., 1983. Activity in the mesencephalic locomotor region during locomotion. Exp. Neurol. 82, 609–622.

Garcia-Rill, E., Davies, D.L., Skinner, R.D., Biedermann, J.A., McHalffey, C., 1991. Fibroblast growth factor-induced increased survival of cholinergic mesopontine neurons in culture. Brain Res. Dev. Brain Res. 60, 267–270.

Garcia-Rill, E., Skinner, R.D., Miyazato, H., Homma, Y., 2001. Pedunculopontine stimulation induces prolonged activation of pontine reticular neurons. Neuroscience 104, 455–465.

Garcia-Rill, E., Luster, B., D'Onofrio, S., Mahaffey, S., Bisagno, V., Urbano, F.J., 2016. Implications of gamma band activity in the pedunculopontine nucleus. J. Neural Transm. (Vienna.) 123, 655–665.

Geula, C., Schatz, C.R., Mesulam, M.M., 1993. Differential localization of NADPH-diaphorase and calbindin-D28k within the cholinergic neurons of the basal forebrain, striatum and brainstem in the rat, monkey, baboon and human. Neuroscience 54, 461–476.

Goetz, L., Piallat, B., Bhattacharjee, M., Mathieu, H., David, O., Chabardes, S., 2016a. On the role of the Pedunculopontine nucleus and mesencephalic reticular formation in locomotion in nonhuman Primates. J. Neurosci. 36, 4917–4929.

Goetz, L., Piallat, B., Bhattacharjee, M., Mathieu, H., David, O., Chabardes, S., 2016b. The primate pedunculopontine nucleus region: towards a dual role in locomotion and waking state. J. Neural Transm. (Vienna) 123, 667–678.

Goldsmith, M., van der Kooy, D., 1988. Separate non-cholinergic descending projections and cholinergic ascending projections from the nucleus tegmenti pedunculopontinus. Brain Res. 445, 386–391.

Grofova, I., Keane, S., 1991. Descending brainstem projections of the pedunculopontine tegmental nucleus in the rat. Anat. Embryol. (Berl) 184, 275–290.

Grunwerg, B.S., Krein, H., Krauthamer, G.M., 1992. Somatosensory input and thalamic projection of pedunculopontine tegmental neurons. Neuroreport 3, 673–675.

Gut, N.K., Winn, P., 2015. Deep brain stimulation of different pedunculopontine targets in a novel rodent model of parkinsonism. J. Neurosci. 35, 4792–4803.

Halliday, G.M., 2009. Thalamic changes in Parkinson's disease. Parkinsonism Relat. Disord. 15 (Suppl. 3), S152–S155.

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, 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, 267–271.

Henderson, Z., Greenfield, S.A., 1987. Does the substantia nigra have a cholinergic innervation? Neurosci. Lett. 73, 109–113.

Hernandez-Lopez, S., Gongora-Alfaro, J.L., Martinez-Fong, D., Aceves, J., 1992. A cholinergic input to the substantia nigra pars compacta increases striatal dopamine metabolism measured by in vivo voltammetry. Brain Res. 598, 114–120.

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, 5976–5980.

Hong, S., Hikosaka, O., 2014. Pedunculopontine tegmental nucleus neurons provide reward, sensorimotor, and alerting signals to midbrain dopamine neurons. Neuroscience 282, 139–155.

Hoshi, E., Tremblay, L., Feger, J., Carras, P.L., Strick, P.L., 2005. The cerebellum communicates with the basal ganglia. Nat. Neurosci. 8, 1491–1493.

Howe, W.M., Gritton, H.J., Lusk, N.A., Roberts, E.A., Hetrick, V.L., Berke, J.D., Sarter, M., 2017. Acetylcholine release in prefrontal cortex promotes gamma oscillations and Theta-gamma coupling during cue detection. J. Neurosci. 37, 3215–3230.

Hyde, J., Kezunovic, N., Urbano, F.J., Garcia-Rill, E., 2013. Visualization of fast calcium oscillations in the parafascicular nucleus. Pflugers Arch. 465, 1327–1340.

Ikonomidou, C., Turski, L., 1996. Neurodegenerative disorders: clues from glutamate and energy metabolism. Crit. Rev. Neurobiol. 10, 239–263.

Inglis, W.L., Dunbar, J.S., Winn, P., 1994. 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.

Inglis, W.L., Olmstead, M.C., Robbins, T.W., 2000. Pedunculopontine tegmental nucleus lesions impair stimulus–reward learning in autoshaping and conditioned reinforcement paradigms. Behav. Neurosci. 114, 285–294.

Inglis, W.L., Olmstead, M.C., Robbins, T.W., 2001. Selective deficits in attentional performance on the 5-choice serial reaction time task following pedunculopontine tegmental nucleus lesions. Behav. Brain Res. 123, 117–131.

Jaarsma, D., Ruigrok, T.J., Caffe, R., Cozzari, C., Levey, A.I., Mugnaini, E., Voogd, J., 1997. Cholinergic innervation and receptors in the cerebellum. Prog. Brain Res. 114, 67–96.

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, 725–765.

Jacobsohn, L., 1909. Uber die kerme des menschlichen hirnstamms. Verlag der konigl akademie der Wissennschaften, Berlin.

Jellinger, K., 1988. The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 51, 540–543.

Kang, Y., Kitai, S.T., 1990. Electrophysiological properties of pedunculopontine neurons and their postsynaptic responses following stimulation of substantia nigra reticulata. Brain Res. 535, 79–95.

Karachi, C., Grabli, D., Bernard, F.A., Tande, D., Wattiez, N., Belaid, H., Bardinet, E., Prigent, A., Nothacker, H.P., Hunot, S., Hartmann, A., Lehericy, S., Hirsch, E.C., Francois, C., 2010. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J. Clin. Invest. 120, 2745–2754.

Kelland, M.D., Asdourian, D., 1989. Pedunculopontine tegmental nucleus-induced inhibition of muscle activity in the rat. Behav. Brain Res. 34, 213–234.

Kezunovic, N., Urbano, F.J., Simon, C., Hyde, J., Smith, K., Garcia-Rill, E., 2011. Mechanism behind gamma band activity in the pedunculopontine nucleus. Eur. J. Neurosci. 34, 404–415.

Kezunovic, N., Hyde, J., Simon, C., Urbano, F.J., Williams, D.K., Garcia-Rill, E., 2012. Gamma band activity in the developing parafascicular nucleus. J. Neurophysiol. 107, 772–784.

Kleiner, S., Bringmann, A., 1996. Nucleus basalis magnocellularis and pedunculopontine tegmental nucleus: control of the slow EEG waves in rats. Arch. Ital. Biol. 134, 153–167.

Klockgether, T., Turski, L., Honore, T., Zhang, Z.M., Gash, D.M., Kurlan, R., Greenamyre, J.T., 1991. The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. Ann. Neurol. 30, 717–723.

Kobayashi, S., Nakamura, Y., 2003. Synaptic organization of the rat parafascicular nucleus, with special reference to its afferents from the superior colliculus and the pedunculopontine tegmental nucleus. Brain Res. 980, 80–91.

Krauthamer, G.M., Grunwerg, B.S., Krein, H., 1995. Putative cholinergic neurons of the pedunculopontine tegmental nucleus projecting to the superior colliculus consist of sensory responsive and unresponsive populations which are functionally distinct from other mesopontine neurons. Neuroscience 69, 507–517.

Kuo, S.H., Kenney, C., Jankovic, J., 2008. Bilateral pedunculopontine nuclei strokes presenting as freezing of gait. Mov. Disord. 23, 616–619.

Lacey, M.G., Calabresi, P., North, P.A., 1991. Cholinergic excitation of A9 and A10 dopaminergic neurons in vitro through both nicotinic and muscarinic receptors. In: Bernardi, G., Carpenter, M.B., Di Chiara, G., Morelli, M., Stanzione, P. (Eds.), The Basal Ganglia III. Plenum Press, New York, pp. 463–470.

Lange, K.W., Riederer, P., 1994. Glutamatergic drugs in Parkinson's disease. Life Sci. 55, 2067–2075.

Lapper, S.R., Bolam, J.P., 1992. Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. Neuroscience 51, 533–545.

Lau, B., Welter, M.L., Belaid, H., Fernandez, V.S., Bardinet, E., Grabli, D., Karachi, C., 2015. The integrative role of the pedunculopontine nucleus in human gait. Brain 138, 1284–1296.

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

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, 190–209.

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, 210–231.

Leonard, C.S., Llinas, R.R., 1990. Electrophysiology of mammalian pedunculopontine and laterodorsal tegmental neurons in vitro: implications for the control of REM sleep. In: Steriade, M., Biesold, D. (Eds.), Brain Cholinergic Systems. Oxford Science, Oxford, pp. 205–223.

Lepore, M., Franklin, K.B., 1996. N-methyl-D-aspartate lesions of the pedunculopontine nucleus block acquisition and impair maintenance of responding reinforced with brain stimulation. Neuroscience 71, 147–155.

Lichtensteiger, W., Hefti, F., Felix, D., Huwyler, T., Melamed, E., Schlumpf, M., 1982. Stimulation of nigrostriatal dopamine neurones by nicotine. Neuropharmacology 21, 963–968.

Lim, A.S., Lozano, A.M., Moro, E., Hamani, C., Hutchison, W.D., Dostrovsky, J.O., Lang, A.E., Wennberg, R.A., Murray, B.J., 2007. Characterization of REM-sleep associated ponto-geniculo-occipital waves in the human pons. Sleep 30, 823–827.

Lim, A.S., Moro, E., Lozano, A.M., Hamani, C., Dostrovsky, J.O., Hutchison, W.D., Lang, A.E., Wennberg, R.A., Murray, B.J., 2009. Selective enhancement of rapid eye movement sleep by deep brain stimulation of the human pons. Ann. Neurol. 66, 110–114.

Luster, B.R., Urbano, F.J., Garcia-Rill, E., 2016. Intracellular mechanisms modulating gamma band activity in the pedunculopontine nucleus (PPN). Phys. Rep. 4.

Lydic, R., Baghdoyan, H.A., 1993. Pedunculopontine stimulation alters respiration and increases ACh release in the pontine reticular formation. Am. J. Phys. 264, R544–R554.

Lydic, R., Baghdoyan, H.A., 1994. The neurobiology of rapid eye-movement sleep. In: Saunders, N., Sullivan, C. (Eds.), Sleep and Breathing, 2nd ed. Marcel Dekker, New York, pp. 47–77.

MacLaren, D.A., Wilson, D.I., Winn, P., 2013. Updating of action-outcome associations is prevented by inactivation of the posterior pedunculopontine tegmental nucleus. Neurobiol. Learn. Mem. 102, 28–33.

MacLaren, D.A., Markovic, T., Clark, S.D., 2014. Assessment of sensorimotor gating following selective lesions of cholinergic pedunculopontine neurons. Eur. J. Neurosci. 40, 3526–3537.

MacLaren, D.A., Wilson, D.I., Winn, P., 2016. Selective lesions of the cholinergic neurons within the posterior pedunculopontine do not alter operant learning or nicotine sensitization. Brain Struct. Funct. 221, 1481–1497.

Manaye, K.F., Zweig, R., Wu, D., Hersh, L.B., De Lacalle, S., Saper, C.B., German, D.C., 1999. Quantification of cholinergic and select non-cholinergic mesopontine neuronal populations in the human brain. Neuroscience 89, 759–770.

Marks, G.A., Roffwarg, H.P., 1993. Spontaneous activity in the thalamic reticular nucleus during the sleep/wake cycle of the freely-moving rat. Brain Res. 623, 241–248.

Martinez-Gonzalez, C., Wang, H.L., Micklem, B.R., Bolam, J.P., Mena-Segovia, J., 2012. Subpopulations of cholinergic, GABAergic and glutamatergic neurons in the pedunculopontine nucleus contain calcium-binding proteins and are heterogeneously distributed. Eur. J. Neurosci. 35, 723–734.

Martinez-Murillo, R., Villalba, R., Montero-Caballero, M.I., Rodrigo, J., 1989. Cholinergic somata and terminals in the rat substantia nigra: an immunocytochemical study with optical and electron microscopic techniques. J. Comp. Neurol. 281, 397–415.

Mazzone, P., Paoloni, M., Mangone, M., Santilli, V., Insola, A., Fini, M., Scarnati, E., 2014. Unilateral deep brain stimulation of the pedunculopontine tegmental nucleus in idiopathic Parkinson's disease: effects on gait initiation and performance. Gait Posture 40, 357–362.

Mazzone, P., Vilela, F.O., Viselli, F., Insola, A., Sposato, S., Vitale, F., Scarnati, E., 2016. Our first decade of experience in deep brain stimulation of the brainstem: elucidating the mechanism of action of stimulation of the ventrolateral pontine tegmentum. J. Neural Transm. (Vienna) 123, 751–767.

Mazzone, P., Vitale, F., Capozzo, A., Viselli, F., Scarnati, E., 2018. Deep brain stimulation of the pedunculopontine tegmental nucleus improves static balance in Parkinson's disease. In: Krames, E., Hunter Peckham, P., Rezai, A. (Eds.), Neuromodulation. Academic Press Elsevier, New York, pp. 967–976.

McCormick, D.A., 1989. Cholinergic and noradrenergic modulation of thalamocortical processing. Trends Neurosci. 12, 215–221.

McGeer, E.G., McGeer, P.L., 1984. Substantia nigra cell death from kainic acid or folic acid injections into the pontine tegmentum. Brain Res. 298, 339–342.

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, 2947–2960.

Mesulam, M.M., Mufson, E.J., Wainer, B.H., Levey, A.I., 1983. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). Neuroscience 10, 1185–1201.

Mitani, A., Ito, K., Hallanger, A.E., Wainer, B.H., Kataoka, K., McCarley, R.W., 1988. Cholinergic projections from the laterodorsal and pedunculopontine tegmental nuclei to the pontine gigantocellular tegmental field in the cat. Brain Res. 451, 397–402.

Mizukawa, K., McGeer, P.L., Tago, H., Peng, J.H., McGeer, E.G., Kimura, H., 1986. The cholinergic system of the human hindbrain studied by choline acetyltransferase immunohistochemistry and acetylcholinesterase histochemistry. Brain Res. 379, 39–55.

Moro, E., Hamani, C., Poon, Y.Y., Al-Khairallah, T., Dostrovsky, J.O., Hutchison, W.D., Lozano, A.M., 2010. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. Brain 133, 215–224.

Muller, K., Klingberg, F., 1986. Lesions in the mesencephalic part of pedunculopontine nuclei modify goal-directed behaviour. Biomed. Biochim. Acta 45, 1159–1165.

Muller, M.L., Albin, R.L., Kotagal, V., Koeppe, R.A., Scott, P.J., Frey, K.A., Bohnen, N.I., 2013. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease. Brain 136, 3282–3289.

Newman, D.B., Ginsberg, C.Y., 1992. Brainstem reticular nuclei that project to the cerebellum in rats: a retrograde tracer study. Brain Behav. Evol. 39, 24–68.

Niijima, K., Yoshida, M., 1988. Activation of mesencephalic dopamine neurons by chemical stimulation of the nucleus tegmenti pedunculopontinus pars compacta. Brain Res. 451, 163–171.

Noga, B.R., Sanchez, F.J., Villamil, L.M., O'Toole, C., Kasicki, S., Olszewski, M., Cabaj, A.M., Majczynski, H., Slawinska, U., Jordan, L.M., 2017. LFP oscillations in the mesencephalic locomotor region during voluntary locomotion. Front Neural Circuits. 11, 34.

Norton, A.B., Jo, Y.S., Clark, E.W., Taylor, C.A., Mizumori, S.J., 2011. Independent neural coding of reward and movement by pedunculopontine tegmental nucleus neurons in freely navigating rats. Eur. J. Neurosci. 33, 1885–1896.

Nowak, L.G., Bullier, J., 1998. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. Exp. Brain Res. 118, 477–488.

Okada, K., Kobayashi, Y., 2013. Reward prediction-related increases and decreases in tonic neuronal activity of the pedunculopontine tegmental nucleus. Front. Integr. Neurosci. 7, 36.

Okada, K., Kobayashi, Y., 2014. Fixational saccade-related activity of pedunculopontine tegmental nucleus neurons in behaving monkeys. Eur. J. Neurosci. 40, 2641–2651.

Okada, K., Kobayashi, Y., 2015. Rhythmic firing of Pedunculopontine tegmental nucleus neurons in monkeys during eye movement task. PLoSOne 10, e0128147.

Okada, K.I., Kobayashi, Y., 2016. Reward and behavioral factors contributing to the tonic activity of monkey Pedunculopontine tegmental nucleus neurons during saccade tasks. Front. Syst. Neurosci. 10, 94.

Olmstead, M.C., Franklin, K.B., 1994. Lesions of the pedunculopontine tegmental nucleus block drug-induced reinforcement but not amphetamine-induced locomotion. Brain Res. 638, 29–35.

Olszewski, J., Baxter, D., 1982. Cytoarchitecture of the Human Brainstem, 2nd ed. Basel, Karger, pp. 192.

Orlovskii, G.N., Severin, F.V., Shik, M.L., 1966. Locomotion induced by stimulation of the mesencephalon. Dokl. Akad. Nauk SSSR 169, 1223–1226.

Ostrem, J.L., Christine, C.W., Glass, G.A., Schrock, L.E., Starr, P.A., 2010. Pedunculopontine nucleus deep brain stimulation in a patient with primary progressive freezing gait disorder. Stereotact. Funct. Neurosurg. 88, 51–55.

Pan, W.X., Hyland, B.I., 2005. Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. J. Neurosci. 25, 4725–4732.

Parent, A., Parent, M., Charara, A., 1999. Glutamatergic inputs to midbrain dopaminergic neurons in primates. Parkinsonism Relat. Disord. 5, 193–201.

Parker, J.L., van der Kooy, D., 1995. Tegmental pedunculopontine nucleus lesions do not block cocaine reward. Pharmacol. Biochem. Behav. 52, 77–83.

Paxinos, G., Huang, X.F., 1995. Atlas of the Human Brainstem. Academic Press, San Diego.

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, 1637–1642.

Piallat, B., Chabardes, S., Torres, N., Fraix, V., Goetz, L., Seigneuret, E., Bardinet, E., Ferraye, M., Debu, B., Krack, P., Yelnik, J., Pollak, P., Benabid, A.L., 2009. Gait is associated with an increase in tonic firing of the sub-cuneiform nucleus neurons. Neuroscience 158, 1201–1205.

Pierantozzi, M., Palmieri, M.G., Galati, S., Stanzione, P., Peppe, A., Tropepi, D., Brusa, L., Pisani, A., Moschella, V., Marciani, M.G., Mazzone, P., Stefani, A., 2008. Pedunculopontine nucleus deep brain stimulation changes spinal cord excitability in Parkinson's disease patients. J. Neural Transm. (Vienna) 115, 731–735.

Ranck Jr., J.B., 1975. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res. 98, 417–440.

Ransmayr, G., Faucheux, B., Nowakowski, C., Kubis, N., Federspiel, S., Kaufmann, W., Henin, D., Hauw, J.J., Agid, Y., Hirsch, E.C., 2000. Age-related changes of neuronal counts in the human pedunculopontine nucleus. Neurosci. Lett. 288, 195–198.

Rinne, J.O., Ma, S.Y., Lee, M.S., Collan, Y., Roytta, M., 2008. Loss of cholinergic neurons in the pedunculopontine nucleus in Parkinson's disease is related to disability of the patients. Parkinsonism Relat. Disord. 14, 553–557.

Ruggiero, D.A., Anwar, M., Golanov, E.V., Reis, D.J., 1997. The pedunculopontine tegmental nucleus issues collaterals to the fastigial nucleus and rostral ventrolateral reticular nucleus in the rat. Brain Res. 760, 272–276.

Ryczko, D., Auclair, F., Cabelguen, J.M., Dubuc, R., 2016a. The mesencephalic locomotor region sends a bilateral glutamatergic drive to hindbrain reticulospinal neurons in a tetrapod. J. Comp. Neurol. 524, 1361–1383.

Ryczko, D., Cone, J.J., Alpert, M.H., Goetz, L., Auclair, F., Dube, C., Parent, M., Roitman, M.F., Alford, S., Dubuc, R., 2016b. A descending dopamine pathway conserved from basal vertebrates to mammals. Proc. Natl. Acad. Sci. U. S. A. 113, E2440–E2449.

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, 483–528.

Rye, D.B., Lee, H.J., Saper, C.B., Wainer, B.H., 1988. Medullary and spinal efferents of the pedunculopontine tegmental nucleus and adjacent mesopontine tegmentum in the rat. J. Comp. Neurol. 269, 315–341.

Saper, C.B., Loewy, A.D., 1982. Projections of the pedunculopontine tegmental nucleus in the rat: evidence for additional extrapyramidal circuitry. Brain Res. 252, 367–372.

Sarter, M., Lustig, C., Berry, A.S., Gritton, H., Howe, W.M., Parikh, V., 2016. What do phasic cholinergic signals do? Neurobiol. Learn. Mem. 130, 135–141.

Scarnati, E., Campana, E., Pacitti, C., 1984. Pedunculopontine-evoked excitation of substantia nigra neurons in the rat. Brain Res. 304, 351–361.

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, 116–124.

Scarnati, E., Di Loreto, S., Proia, A., Gallie, G., 1988a. The functional role of the pedunculopontine nucleus in the regulation of the electrical activity of entopeduncular neurons in the rat. Arch. Ital. Biol. 126, 145–163.

Scarnati, E., Hajdu, F., Pacitti, C., Tombol, T., 1988b. An EM and Golgi study on the connection between the nucleus tegmenti pedunculopontinus and the pars compacta of the substantia nigra in the rat. J. Hirnforsch. 29, 95–105.

Scarnati, E., Florio, T., Capozzo, A., Confalone, G., Mazzone, P., 2011. The pedunculopontine tegmental nucleus: implications for a role in modulating spinal cord motoneuron excitability. J. Neural Transm. (Vienna) 118, 1409–1421.

Schofield, B.R., 2010. Projections from auditory cortex to midbrain cholinergic neurons that project to the inferior colliculus. Neuroscience 166, 231–240.

Schofield, B.R., Motts, S.D., Mellott, J.G., 2011. Cholinergic cells of the pontomesencephalic tegmentum: connections with auditory structures from cochlear nucleus to cortex. Hear. Res. 279, 85–95.

Schultz, W., 1986. Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. J. Neurophysiol. 56, 1439–1461.

Schultz, W., 1997. Dopamine neurons and their role in reward mechanisms. Curr. Opin. Neurobiol. 7, 191–197.

Schultz, W., 2016a. Dopamine reward prediction-error signalling: a two-component response. Nat. Rev. Neurosci. 17, 183–195.

Schultz, W., 2016b. Reward functions of the basal ganglia. J. Neural Transm. (Vienna) 123, 679–693.

Schultz, W., Apicella, P., Scarnati, E., Ljungberg, T., 1992. Neuronal activity in monkey ventral striatum related to the expectation of reward. J. Neurosci. 12, 4595–4610.

Schweder, P.M., Hansen, P.C., Green, A.L., Quaghebeur, G., Stein, J., Aziz, T.Z., 2010. Connectivity of the pedunculopontine nucleus in parkinsonian freezing of gait. Neuroreport 21, 914–916.

Skinner, R.D., Garcia-Rill, E., 1984. The mesencephalic locomotor region (MLR) in the rat. Brain Res. 323, 385–389.

Skinner, R.D., Kinjo, N., Henderson, V., Garcia-Rill, E., 1990a. Locomotor projections from the pedunculopontine nucleus to the spinal cord. Neuroreport 1, 183–186.

Skinner, R.D., Kinjo, N., Ishikawa, Y., Biedermann, J.A., Garcia-Rill, E., 1990b. Locomotor projections from the pedunculopontine nucleus to the medioventral medulla. Neuroreport 1, 207–210.

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, 375–388.

Standaert, D.G., Saper, C.B., Rye, D.B., Wainer, B.H., 1986. Colocalization of atriopeptin-like immunoreactivity with choline acetyltransferase- and substance P-like immunoreactivity in the pedunculopontine and laterodorsal tegmental nuclei in the rat. Brain Res. 382, 163–168.

Steckler, T., Keith, A.B., Sahgal, A., 1994. Lesions of the pedunculopontine tegmental nucleus do not alter delayed non-matching to position accuracy. Behav. Brain Res. 61, 107–112.

Stefani, A., Pierantozzi, M., Ceravolo, R., Brusa, L., Galati, S., Stanzione, P., 2010. Deep brain stimulation of pedunculopontine tegmental nucleus (PPTg) promotes cognitive and metabolic changes: a target-specific effect or response to a low-frequency pattern of stimulation? Clin. EEG. Neurosci. 41, 82–86.

Steidl, S., Wang, H., Wise, R.A., 2014. Lesions of cholinergic pedunculopontine tegmental nucleus neurons fail to affect cocaine or heroin self-administration or conditioned place preference in rats. PLoSOne 9, e84412.

Stephenson-Jones, M., Ericsson, J., Robertson, B., Grillner, S., 2012. Evolution of the basal ganglia: dual-output pathways conserved throughout vertebrate phylogeny. J. Comp. Neurol. 520, 2957–2973.

Sugimoto, T., Hattori, T., 1984. Organization and efferent projections of nucleus tegmenti pedunculopontinus pars compacta with special reference to its cholinergic aspects. Neuroscience 11, 931–946.

Swerdlow, N.R., Koob, G.F., 1987. Lesions of the dorsomedial nucleus of the thalamus, medial prefrontal cortex and pedunculopontine nucleus: effects on locomotor activity mediated by nucleus accumbens-ventral pallidal circuitry. Brain Res. 412, 233–243.

Syed, A., Baker, P.M., Ragozzino, M.E., 2016. Pedunculopontine tegmental nucleus lesions impair probabilistic reversal learning by reducing sensitivity to positive reward feedback. Neurobiol. Learn. Mem. 131, 1–8.

Takakusaki, K., Kitai, S.T., 1997. Ionic mechanisms involved in the spontaneous firing of tegmental pedunculopontine nucleus neurons of the rat. Neuroscience 78, 771–794.

Takakusaki, K., Shiroyama, T., Yamamoto, T., Kitai, S.T., 1996. Cholinergic and noncholinergic tegmental pedunculopontine projection neurons in rats revealed by intracellular labeling. J. Comp. Neurol. 371, 345–361.

Takakusaki, K., Shiroyama, T., Kitai, S.T., 1997. Two types of cholinergic neurons in the rat tegmental pedunculopontine nucleus: electrophysiological and morphological characterization. Neuroscience 79, 1089–1109.

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, 695–729.

Tattersall, T.L., Stratton, P.G., Coyne, T.J., Cook, R., Silberstein, P., Silburn, P.A., Windels, F., Sah, P., 2014. Imagined gait modulates neuronal network dynamics in the human pedunculopontine nucleus. Nat. Neurosci. 17, 449–454.

Teo, C., Rasco, L., al-Mefty, K., Skinner, R.D., Boop, F.A., Garcia-Rill, E., 1997. Decreased habituation of midlatency auditory evoked responses in Parkinson's disease. Mov.

Disord. 12, 655–664.

Thevathasan, W., Coyne, T.J., Hyam, J.A., Kerr, G., Jenkinson, N., Aziz, T.Z., Silburn, P.A., 2011a. Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. Neurosurgery 69, 1248–1253.

Thevathasan, W., Pogosyan, A., Hyam, J.A., Jenkinson, N., Bogdanovic, M., Coyne, T.J., Silburn, P.A., Aziz, T.Z., Brown, P., 2011b. A block to pre-prepared movement in gait freezing, relieved by pedunculopontine nucleus stimulation. Brain 134, 2085–2095.

Thevathasan, W., Cole, M.H., Graepel, C.L., Hyam, J.A., Jenkinson, N., Brittain, J.S., Coyne, T.J., Silburn, P.A., Aziz, T.Z., Kerr, G., Brown, P., 2012a. A spatiotemporal analysis of gait freezing and the impact of pedunculopontine nucleus stimulation. Brain 135, 1446–1454.

Thevathasan, W., Pogosyan, A., Hyam, J.A., Jenkinson, N., Foltynie, T., Limousin, P., Bogdanovic, M., Zrinzo, L., Green, A.L., Aziz, T.Z., Brown, P., 2012b. Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. Brain 135, 148–160.

Thompson, J.A., Felsen, G., 2013. Activity in mouse pedunculopontine tegmental nucleus reflects action and outcome in a decision-making task. J. Neurophysiol. 110, 2817–2829.

Thompson, J.A., Costabile, J.D., Felsen, G., 2016. Mesencephalic representations of recent experience influence decision making. elife 5, e16572.

Tokuno, H., Moriizumi, T., Kudo, M., Nakamura, Y., 1988. A morphological evidence for monosynaptic projections from the nucleus tegmenti pedunculopontinus pars compacta (TPC) to nigrostriatal projection neurons. Neurosci. Lett. 85, 1–4.

Turski, L., Bressler, K., Rettig, K.J., Loschmann, P.A., Wachtel, H., 1991. Protection of substantia nigra from MPP+ neurotoxicity by N-methyl-D-aspartate antagonists. Nature 349, 414–418.

Urbano, F.J., D'Onofrio, S.M., Luster, B.R., Beck, P.B., Hyde, J.R., Bisagno, V., Garcia-Rill, E., 2014. Pedunculopontine nucleus gamma band activity-preconscious awareness, waking, and REM sleep. Front. Neurol. 5, 210.

Usunoff, K.G., 1984. Tegmentonigral projection in the cat: electron microscopic observations. Adv. Neurol. 40, 55–61.

Vitale, F., Mattei, C., Capozzo, A., Pietrantoni, I., Mazzone, P., Scarnati, E., 2016. Cholinergic excitation from the pedunculopontine tegmental nucleus to the dentate nucleus in the rat. Neuroscience 317, 12–22.

Wanaka, A., Johnson Jr., E.M., Milbrandt, J., 1990. Localization of FGF receptor mRNA in the adult rat central nervous system by in situ hybridization. Neuron 5, 267–281.

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, 340–358.

Wang, M., Jiang, S., Yuan, Y., Zhang, L., Ding, J., Wang, J., Zhang, J., Zhang, K., Wang, J., 2016. Alterations of functional and structural connectivity of freezing of gait in Parkinson's disease. J. Neurol. 263, 1583–1592.

Weinberger, M., Hamani, C., Hutchison, W.D., Moro, E., Lozano, A.M., Dostrovsky, J.O., 2008. Pedunculopontine nucleus microelectrode recordings in movement disorder patients. Exp. Brain Res. 188, 165–174.

Weyand, T.G., Boudreaux, M., Guido, W., 2001. Burst and tonic response modes in thalamic neurons during sleep and wakefulness. J. Neurophysiol. 85, 1107–1118.

Wilcox, R.A., Cole, M.H., Wong, D., Coyne, T., Silburn, P., Kerr, G., 2011. Pedunculopontine nucleus deep brain stimulation produces sustained improvement in primary progressive freezing of gait. J. Neurol. Neurosurg. Psychiatry 82, 1256–1259.

Willard, S.S., Koochekpour, S., 2013. Glutamate signaling in benign and malignant disorders: current status, future perspectives, and therapeutic implications. Int. J. Biol. Sci. 9, 728–742.

Wilson, D.I., MacLaren, D.A., Winn, P., 2009. Bar pressing for food: differential consequences of lesions to the anterior versus posterior pedunculopontine. Eur. J. Neurosci. 30, 504–513.

Woolf, N.J., Butcher, L.L., 1989. Cholinergic systems in the rat brain: IV. Descending projections of the pontomesencephalic tegmentum. Brain Res. Bull. 23, 519–540.

Woolf, N.J., Gould, E., Butcher, L.L., 1989. Nerve growth factor receptor is associated with cholinergic neurons of the basal forebrain but not the pontomesencephalon. Neuroscience 30, 143–152.

Wu, T., Wang, L., Hallett, M., Chen, Y., Li, K., Chan, P., 2011. Effective connectivity of brain networks during self-initiated movement in Parkinson's disease. NeuroImage 55, 204–215.

Xiang, H.B., Zhu, W.Z., Guan, X.H., Ye, D.W., 2013. The cuneiform nucleus may be involved in the regulation of skeletal muscle tone by motor pathway: a virally mediated trans-synaptic tracing study in surgically sympathectomized mice. Brain 136, e251.

Yeo, S.S., Ahn, S.H., Choi, B.Y., Chang, C.H., Lee, J., Jang, S.H., 2011. Contribution of the pedunculopontine nucleus on walking in stroke patients. Eur. Neurol. 65, 332–337.

Yeomans, J.S., Mathur, A., Tampakeras, M., 1993. Rewarding brain stimulation: role of tegmental cholinergic neurons that activate dopamine neurons. Behav. Neurosci. 107, 1077–1087.

Yeomans, J.S., Lee, J., Yeomans, M.H., Steidl, S., Li, L., 2006. Midbrain pathways for prepulse inhibition and startle activation in rat. Neuroscience 142, 921–929.

Youn, J., Lee, J.M., Kwon, H., Kim, J.S., Son, T.O., Cho, J.W., 2015. Alterations of mean diffusivity of pedunculopontine nucleus pathway in Parkinson's disease patients with freezing of gait. Parkinsonism Relat. Disord. 21, 12–17.

Zanini, S., Moschella, V., Stefani, A., Peppe, A., Pierantozzi, M., Galati, S., Costa, A., Mazzone, P., Stanzione, P., 2009. Grammar improvement following deep brain stimulation of the subthalamic and the pedunculopontine nuclei in advanced Parkinson's disease: a pilot study. Parkinsonism Relat. Disord. 15, 606–609.

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, 41–46.