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REVIEW ARTICLE

The pedunculopontine nucleus area: critical evaluation of interspecies differences relevant for its use as a target for deep brain stimulation

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Recently, the pedunculopontine nucleus has been highlighted as a target for deep brain stimulation for the treatment of freezing of postural instability and gait disorders in Parkinson's disease and progressive supranuclear palsy. There is great controversy, however, as to the exact location of the optimal site for stimulation. In this review, we give an overview of anatomy and connectivity of the pedunculopontine nucleus area in rats, cats, non-human primates and humans. Additionally, we report on the behavioural changes after chemical or electrical manipulation of the pedunculopontine nucleus. We discuss the relation to adjacent regions of the pedunculopontine nucleus, such as the cuneiform nucleus and the subcuneiform nucleus, which together with the pedunculopontine nucleus are the main areas of the mesencephalic locomotor region and play a major role in the initiation of gait. This information is discussed with respect to the experimental designs used for research purposes directed to a better understanding of the circuitry pathway of the pedunculopontine nucleus in association with basal ganglia pathology, and with respect to deep brain stimulation of the pedunculopontine nucleus area in humans.

Keywords: pedunculopontine nucleus; basal ganglia; mesencephalic locomotor region; deep brain stimulation; Parkinson; gait disturbance

Abbreviations: MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Introduction

Clinical studies have shown that deep brain stimulation of the pedunculopontine nucleus is safe and partially effective in ameliorating specific symptoms of Parkinson's disease, in particular gait and posture (Pierantozzi *et al*., 2008; Moro *et al*., 2010). There are, however, also clinical data that demonstrate that the outcome of pedunculopontine nucleus deep brain stimulation can be quite variable (Ferraye *et al*., 2010).

Fundamental and basic principles regarding neuronal control of locomotion or gait function have been remarkably preserved during evolution. The mechanism of gait of bipedal humans, however, is fundamentally different from that of quadrupedal animals (rats or cats). The differences in the organization and the functional connections within and between the basal ganglia with respect to the pedunculopontine nucleus can be explained by the phylogenetic expansion and differentiation of the neocortex in the primate, cat and rodent brain. Likewise, there is evidence that the role of basal ganglia in locomotor behaviour is different in higher primates and non-primate mammals (Murer and Pazo, 1993; Dybdal *et al*., 1997; Dybdal and Gale, 2000). Anatomical data also reveal that there are functional differences between the

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basal ganglia of primates and non-primates, which must be considered when extrapolating between species.

Human bipedal locomotion is distinct from all other bipedal mammals, which is in accordance with modern hierarchical change in evolution. Animal studies in rodents or monkeys revealed that the evolution from quadrupedal to bipedal locomotion did not affect the principal anatomical structures, but that the connectivity among the different nuclei may differ between species (Barton and Harvey, 2000; Courtine *et al*., 2005; Onodera and Hicks, 2009). With respect to the pedunculopontine nucleus, the topography and morphological structure are probably similar in most mammals, but the circuitry distribution of cholinergic, glutamatergic or GABA-ergic neurons within this region and the degree of afferent and efferent fibres may vary, which could account for species-dependent outcome of behaviour in experimental settings. Other differences may be related to differences of the normal versus the parkinsonian state.

There have been several recent reviews on the pedunculopontine nucleus, concentrating on various aspects including its connectivity to the basal ganglia (Mena-Segovia *et al*., 2004), its function in Parkinson's disease (Pahapill and Lozano, 2000), and its integrative role according to animal studies (Winn, 2006, 2008). The present review concentrates on comparative interspecies aspects according to anatomical, physiological and behavioural studies, which indicate—that at least partially—the action of deep brain stimulation might not only be mediated through modulation of the pedunculopontine nucleus but also through modulation of the adjacent cuneiform or subcuneiform nuclei. Furthermore, the review intends to provide background information that can be used to judge the internal and external validity of experimental studies that are used as an argument to support the role of the pedunculopontine nucleus area in human locomotion.

The pedunculopontine nucleus

Terminology

One source of confusion about the pedunculopontine nucleus has been the variable terminology used. Most often it has been described as pedunculopontine nucleus, but the abbreviation PPTg (Pedunculopontine tegmental nucleus) has also been used in both the human and the rodent atlas of Paxinos and colleagues (Paxinos and Huang, 1995; Paxinos and Watson, 1998). The abbreviation Tg.pdpo (nucleus tegmenti pedunculopontinus) has been used in the human brain atlas of Schaltenbrand and Wahren (1977). Moreover, in some cases, confusion arose when the peripeduncular nucleus was used for the pedunculopontine nucleus (Mazzone *et al*., 2005, 2009; Stefani *et al*., 2007) since the peripeduncular nucleus is a distinct region separated from the pedunculopontine nucleus by the medial lemniscus (Yelnik, 2007; Zrinzo *et al*., 2007).

Anatomical localization

The pedunculopontine nucleus occupies a strategic position within the core of the brainstem tegmentum, at the crossroad of several major fibre systems. It receives direct input from the cerebral cortex and is reciprocally connected with several basal ganglia components and limbic areas, and gives further rise to ascending projections to the thalamus (Steininger *et al*., 1992; Matsumura *et al*., 2000). It is also directly connected to other motor nuclei in the brainstem and spinal cord (Garcia-Rill *et al*., 2001; Takakusaki *et al*., 2004, 2008). Additionally, clinical and experimental investigations have established that the basal ganglia and the cerebellum are concerned with complementary aspects of body posture and motor functions and interesting anatomical analogies have been made between these two sets of structures (Mehler and Nauta, 1974). The pedunculopontine nucleus may therefore act as an integrative interface between these structures. It is also possible that the cerebellum may influence the function of various basal ganglia components and the entire thalamus via a relay in the pedunculopontine nucleus (Hazrati and Parent, 1992). The pedunculopontine nucleus is, together with the cuneiform and the subcuneiform nucleus, the major component of the mesencephalic locomotor region. Both the mesencephalic locomotor region and the mesencephalic reticular formation comprise a population of different types of neurons with different physiological functions that extend from the meso-diencephalic junction down to the medulla oblongata, just above the junction to the spinal cord, as first described by August Forel (1877). Therefore, it would be more appropriate to name specific areas within the mesencephalic locomotor region or mesencephalic reticular formation. Confusion arises with respect to the naming of the localization and implantation zones in deep brain stimulation. The terms mesencephalic reticular formation or mesencephalic locomotor region could be used to avoid over generalization as this nomenclature has been adopted in animal studies of lesioning or stimulation of the cuneiform or pedunculopontine nucleus (Steeves *et al*., 1975; Garcia-Rill *et al*., 1987*b*; Skinner *et al*., 1990).

The pedunculopontine nucleus forms a cluster of cells that is located in the caudal mesencephalic tegmentum, extending from the caudal border of the red nucleus to the parabrachial nucleus. In mammals, including humans, the pedunculopontine nucleus is bordered medially by fibres of the superior cerebellar peduncle and the peduncular decussation and laterally by the medial lemniscus. Rostrally, the anterior portion of the pedunculopontine nucleus contacts the substantia nigra and is adjacent to the retrorubral field; the most dorsal aspect of the pedunculopontine nucleus is bound caudally by the cuneiform and subcuneiform nuclei and ventrally by the pontine reticular formation. The most caudal pole of the cuneiform is adjacent to neurons of the locus coeruleus (Pahapill and Lozano 2000). The whole pedunculopontine nucleus is encircled by the mesencephalic locomotor region; however, its exact boundaries are disputable. Those that propound an extended localization of the pedunculopontine nucleus (Garcia-Rill, 1991) expand the nucleus from the posterior end of the substantia nigra to the laterodorsal tegmental nucleus, which is caudally adjacent to the pedunculopontine nucleus within the central grey matter. The laterodorsal tegmental nucleus is bordered medially by the dorsal tegmental nucleus of Gudden, rostrally by the dorsal raphe nucleus, and laterally by the locus coeruleus. Similar to the pedunculopontine nucleus, it contains cholinergic neurons intermingled with non-cholinergic (mainly glutamatergic) neurons

(Monti and Monti, 2000). Some of the cholinergic neurons in the pedunculopontine nucleus and laterodorsal tegmental nucleus contain α_1- and α_2-adrenoceptors, which have been proposed to be active during waking and are excited by noradrenaline from the locus coeruleus acting at α_1-adrenoceptors (Hou *et al*., 2002).

Overall, the anatomical and morphological structure of the pedunculopontine nucleus is similar in rodents, cats, non-human primates and humans (Figs 1–4). However, architecture or circuitry distribution of cholinergic, glutamatergic or GABA-ergic neurons seems to vary, as well as the phylogenetic distribution of afferent and efferent projections. Cytoarchitecturally the pedunculopontine nucleus consists of two parts: a compact part, pars compacta with a higher density of cholinergic neurons dorsolaterally; and a diffuse part, pars dissipata with glutamatergic, cholinergic and other neuron types, situated at the rostrocaudal axis of the pedunculopontine nucleus (Inglis and Winn, 1995).

Interspecies differences in afferent and efferent connections

Anatomical aspects

With respect to afferent and efferent connections, phylogenetically related differences exist in the pallidotegmental pathway in rats and cats as compared with monkeys and humans. In rats, the pedunculopontine nucleus receives most of its afferents from the substantia nigra (Moon-Edley and Graybiel, 1983; Steininger *et al*., 1992). However, in the monkey the pedunculopontine nucleus receives its most extensive afferents from the globus pallidus medialis (De Vito *et al*., 1980; De Vito and Anderson, 1982). Additionally, retrograde axonal tracing studies showed that efferents of the globus pallidus medialis target a broader area of the pedunculopontine nucleus than efferents from the entopeduncular nucleus, i.e. the equivalent to the primate globus pallidus internus in rodents or cats (Lee *et al*., 2000). Some authors have even suggested that the entopeduncular nucleus is not linked with the pedunculopontine nucleus, but rather with a brainstem region located just medial to it, which they referred to as the 'midbrain extrapyramidal area' (Rye *et al*., 1987; Lee *et al*., 1988; Steininger *et al*., 1992). Similar to rats, projections of the entopeduncular nucleus appear to be less in cats than in monkeys (Vilensky *et al*., 1985).

The distribution of dopaminergic nerve terminals of the thalamus is markedly denser and more widespread in primates as compared with the rat (Garcia-Cabezas *et al*., 2009). Likewise, it has been reported that feline pallidothalamic projections are more restricted than those of primates (Larsen and McBride, 1979). Instead, the differentiation of afferent and efferent projections of substantia nigra pars reticulata to the pedunculopontine nucleus is more distinct in the monkey than in the rat. Additionally, the spatial relationship and morphological features of substantia nigra pars reticulata efferent cell populations exhibit a pattern in the monkey that does not compare well with that seen in the rat (Beckstead and Frankfurter, 1982). It has also been observed that in the rat there is a great overlap in the nigrotectal, nigrotegmental and nigrothalamic projecting neurons, with as many as 50% of the cells projecting to the thalamus and tectum (Deniau *et al*., 1978; Bentivoglio *et al*., 1979). In contrast, little overlap in these projection cells exists in the monkey substantia nigra pars reticulata (Parent *et al*., 1983), which allows a greater topographical discrimination of distinct output behaviour in different species.

Physiological aspects

In line with this, physiological experiments have suggested that the pathway from the globus pallidus to the pedunculopontine nucleus may be larger in the monkey than in the cat. Antidromic activation experiments in the cat suggest that 8% (Larsen and Sutin, 1978; Larsen and McBride, 1979) to 50% (Filion and Harnois, 1978) of the entopeduncular nucleus neurons project to the pedunculopontine nucleus, whereas >80% of globus pallidus internus neurons that project to the pedunculopontine nucleus send axon collaterals to the ventrolateral nucleus of the thalamus in monkeys (Harnois and Filion, 1982; Parent and De Bellefeuille, 1982). With respect to efferent connections, electrical stimulation of the pedunculopontine nucleus in rats increases the firing rates of neurons in the entopeduncular nucleus (Scarnati *et al*., 1988), suggesting a strong efferent connection to this nucleus. Instead, in the monkey the pedunculopontine nucleus-efferent fibres to the subthalamic nucleus and substantia nigra pars reticulata are much larger than those to the pallidal complex (Lee *et al*., 2000).

Behavioural aspects

The subthalamic nucleus exerts diverse behavioural output, either directly or via projection of the pedunculopontine nucleus. There is evidence that the connectivity of neurons in the subthalamic nucleus differs between monkeys and rats. For example, the response to stimulation and blockade of GABA receptor antagonists in the monkey subthalamic nucleus is not predicted by the neural circuitry model derived from studies in cats or rats. While in rats unilateral microinjection of a $GABA_A$ receptor agonist into the subthalamic nucleus produced a site-dependent contralaterally directed postural asymmetry without locomotor activation (Dybdal and Gale, 2000; Périer *et al*., 2002), in cats microinjections of the $GABA_A$ receptor agonist muscimol into the subthalamic nucleus elicited circling behaviour to the contralateral side, while the $GABA_A$ receptor antagonists bicuculline and picrotoxin produced ipsilateral turning (Murer and Pazo, 1993). Additionally, inhibition of the subthalamic nucleus using focal injection of the GABA agonist muscimol was without effect in the monkey (Dybdal *et al*., 1997). On the other hand, a recent study has shown that microinjections of muscimol in the subthalamic nucleus induced movement disorders such as hemiballism and laterocollis (Karachi *et al*., 2009), whereas blockade of GABA inhibition in the subthalamic nucleus by focal application of bicuculline evoked dyskinetic and postural responses similar to those evoked by inhibition of the substantia nigra (Crossman *et al*., 1984; Dybdal *et al*., 1997; Dybdal and Gale, 2000). This suggests that, unlike the rat subthalamic nucleus, the monkey subthalamic nucleus may exert a net inhibitory influence on the substantia nigra either directly or via projection of the globus pallidus or pedunculopontine nucleus.

Diffusion tractography aspects

Recently, probabilistic diffusion tractography image tracing showed differences in the organization of connectivity in the pedunculopontine nucleus between humans and monkeys. This study has confirmed the connection between the pedunculopontine nucleus and substantia nigra in monkeys, but lends credence to the surprising finding that the human pedunculopontine nucleus does not have a strong connection with the substantia nigra. Further, the cerebellum and spinal cord are more strongly connected in humans compared with monkeys (Aravamuthan *et al*., 2009). These organizational differences might be important to understand the electrophysiological output of spiking in connection with the pathology of gait in rodent, monkey and human patients.

The pedunculopontine nucleus area in clinical and animal studies

Lesion studies in humans

In human Parkinson's disease, the destruction of cholinergic neurons in the pedunculopontine nucleus parallels the progression of the destruction of dopaminergic neurons in the substantia nigra pars compacta, but there is no evidence for the destruction of GABA-ergic neurons in the pedunculopontine nucleus. Additionally, a previous study of human autopsies in patients with Parkinson's disease showed a significant reduction in the total number of substance P-neurons in the pedunculopontine nucleus (decrease of 43%), which was corroborated by findings in the laterodorsal tegmental nucleus (decrease of 28%) and the oral pontine reticular nucleus (decrease of 41%), as well as in the median raphe nucleus (decrease of 76%; Gai *et al*., 1991).

Clinical case reports have shown that lesions or subacute infarctions in the midbrain region primarily present with gait instability and support the view that the mesencephalic locomotor region plays an important role in locomotion control in humans. Because of these reports, it was hypothesized that pedunculopontine nucleus damage can lead to gait disorders (Masdeu *et al*., 1994; Bhidayasiri *et al*., 2003; Hathout and Bhidayasire, 2005; Kuo *et al*., 2008). Clinical evidence hypothesizes the involvement of the mesencephalic locomotor region, in particular the pedunculopontine nucleus, in gait ataxia (Hathout and Bhidayasire, 2005) or in gait disturbances of patients with dystonia. The pedunculopontine nucleus, cuneiform and the periaqueductal grey may be involved in dystonia (McNaught *et al*., 2004; Shashidharan *et al*., 2005; Holton *et al*., 2008; Loher and Krauss, 2009). These studies provide a complex association between the pedunculopontine nucleus and transmitters in the brainstem and basal ganglia that are involved in the regulation of motor function and gait disturbance.

Lesion in non-human primates

Animal studies in non-human primates have shown that unilateral radiofrequency lesions of the pedunculopontine nucleus cause a temporary akinesia, and bilateral lesions of the pedunculopontine nucleus result in sustained akinesia (Aziz and Stein 1997; Munro-Davies *et al*., 1999). Additionally, studies in monkey have shown that unilateral excitotoxic lesions of the pedunculopontine nucleus with kainic acid produce hemiparkinsonism, which was characterized by relatively mild levels of flexed posture and hypokinesia in the contralateral limbs (Kojima *et al*., 1997; Matsumura and Kojima, 2001). A recent study has shown that in the monkey, bilateral preferential lesions in the pedunculopontine nucleus resulted in a significant and reproducible gait and posture instability, which could not be ameliorated by treatment with the dopaminergic agonist apomorphine (Karachi *et al*., 2010). This result is concomitant with the observation that gait and postural instability of late stage Parkinson's disease or symptoms of progressive supranuclear palsy in humans do not respond to treatment with dopaminergic agonists, possibly because these symptoms are due to advanced destruction of cholinergic neurons in the pedunculopontine nucleus.

Lesion studies in rodents

Disturbed motor function, such as akinesia or gait disturbances i.e. deficits related to Parkinson's disease, have not been found after lesioning the pedunculopontine nucleus in rodents, whereas in monkeys or in humans, degeneration or lesion of the pedunculopontine nucleus may cause akinesia or gait disturbance. In rodents, however, mostly non-motor behaviour has been investigated after local manipulation of the pedunculopontine nucleus. The function of the pedunculopontine nucleus has been associated with sensorimotor gating, execution of externally cued reward motor, or place preference context and reinforcement, but not locomotion as such (Dellu *et al*., 1991; Koch *et al*., 1993; Inglis *et al*., 1994; Olmstead and Franklin, 1994). Local injection of the excitotoxin ibotenic acid in the pedunculopontine nucleus produced deficient sensorimotor gating, increased anxiety and disturbed working memory (Koch *et al*., 1993; Steiniger and Kretschmer, 2004). Another study has observed a reduction in anxiety-like behaviour after bilateral electrolytic lesions in the pedunculopontine nucleus (Homs-Ormo *et al*., 2003). Regional differences in the extent of damage to the pedunculopontine nucleus or to surrounding structures, or the differences in the degree of damage to cholinergic versus non-cholinergic cells, could be responsible for the contradictory results reported. Notably, these studies did not find changes in spontaneous ambulatory behaviour. On the other hand, it is remarkable that injection of GABA antagonist into the pedunculopontine nucleus abolishes haloperidol-induced catalepsy in rats (Miwa *et al*., 1996).

Although most of the studies that completely lesioned the pedunculopontine nucleus in rodents indicated no motor impairment (Winn, 2006), one study has shown that lesion within a restricted portion of the anterior part of the pedunculopontine nucleus or (pedunculopontine nucleus pars dissipata in rats) do produce motor deficits (Alderson *et al*., 2008). These results are consistent with the hypothesis that the anterior pedunculopontine nucleus, which is analogous to the pedunculopontine nucleus pars dissipata in rodents, has functions related to the motor process, while the posterior pedunculopontine nucleus or pedunculopontine nucleus pars compacta is less concerned with motor control processes (Olszewski and Baxter, 1954).

Interspecies differences and animal models

Rodent and monkey studies have accumulated data about the involvement of the pedunculopontine nucleus in the development of Parkinson's disease. Experimental studies using the 6-hydoxydopamine lesion rat model have shown higher neuronal firing activity in the pedunculopontine nucleus (Breit *et al.*, 2001, 2005; Jeon *et al*., 2003). On the other hand, unilateral lesions of the pedunculopontine nucleus have been shown to induce hemiparkinsonism in monkeys (Kojima *et al*., 1997; Aziz *et al*., 1998; Munro-Davies *et al*., 1999; Matsumura, 2001), which shows that in monkeys, hypoactivity of the pedunculopontine nucleus causes Parkinson's disease-like symptoms. This may be explained by a lesioning-induced hypoactivity of substantia nigra pars compacta neurons that leads to the appearance of parkinsonian motor symptoms. Neuronal metabolic activity in the pedunculopontine nucleus provides further evidence in favour of underactivation of pedunculopontine nucleus neurons in the Parkinson model of basal ganglia in monkeys (Gomez-Gallego *et al*., 2007). Therefore realization of the differences between species and differences in animal models needs to be taken into account when explaining the pathophysiology of movement disorders and the role of the pedunculopontine nucleus (Vilensky *et al*., 1985).

The different results of electrophysiological studies in rodent, non-human primate and human patients with Parkinson's disease may be explained on the basis of variable afferent and efferent connectivity to the basal ganglia nuclei. It is conceivable that degeneration of the pedunculopontine nucleus in Parkinson's disease in humans causes overactivity of the glutamatergic efferent projection from the subthalamic nucleus and disinhibits the GABA-ergic interneurons in the pedunculopontine nucleus, which in turn might decrease the outflow in both ascending and descending circuitries of the basal ganglia (Pahapill and Lozano, 2000; Mena-Segovia *et al*., 2004).

Validity of the 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine models for studying the role of the pedunculopontine nucleus

It should be noted that the two validated animal models that are used mostly for Parkinson's disease therapeutic experimental research, namely the 6-hydroxydopamine induced lesion in rodents and the chronic or acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model, only show the pathology of dopaminergic destruction in the basal ganglia, but not the destruction of the pedunculopontine nucleus, even though the depletion of dopamine has a profound indirect and direct effect on the pedunculopontine nucleus (Karachi *et al*., 2010). Therefore the question remains open as to whether electrophysiological findings in the pedunculopontine nucleus are truly comparable.

To produce gait disorders or akinesia in rodents, the modulation of both dopaminergic neurons in the substantia nigra pars compacta and cholinergic and non-cholinergic neurons in the pedunculopontine nucleus, which are involved in the pathology of Parkinson's disease or progressive supranuclear palsy in humans, might be necessary. A previous study has proposed that, in order to show a sufficiently pronounced motor deficient behaviour in quadrupedal animals (rodents), it requires 50–70% dopamine depletion in the striatum, which resembles up to 50% of dopamine loss in the substantia nigra pars compacta (Fearnley *et al*., 1991). While acute or chronic lesions of dopaminergic neurons in the substantia nigra pars compacta by 6-hydroxydopamine or MPTP toxin apparently do not affect the integrity of the pedunculopontine nucleus in rodents, a recent study has shown that MPTP treatment in aged monkeys destroyed cholinergic neurons of the pedunculopontine nucleus (Karachi *et al*., 2010).

Chronic treatment with the environmental toxin rotenone in rodents produces a hypokinetic syndrome, postural instability and unsteady gait, which is accompanied by destroyed cholinergic neurons in the pedunculopontine nucleus and the presence of Lewy bodies in the striatum and substantia nigra pars compacta (Betarbet *et al*., 2000; Alam and Schmidt, 2002; Höglinger *et al*., 2003). This rodent model may therefore be more suitable to investigate the role of pedunculopontine nucleus stimulation on disturbed parkinsonian gait and other Parkinson's disease symptoms.

On the other hand, observation of gait disturbance by lesioning the pedunculopontine nucleus in rodents cannot be fully elucidated in the activity box or from the catalepsy test. So far, exploratory behaviour in the activity box (a dynamic test) and catalepsy (a static test) have been investigated, but the kinetics of gait disturbance are a mixture of both static and dynamic motor behaviour (Alam *et al*., 2009). Therefore, in most studies that have investigated gait disturbance after pedunculopontine nucleus lesion in rodents, the appropriate behavioural assessment, such as rotarod or stepping assessment, was not used.

The cuneiform and the subcuneiform nucleus

There is controversy and considerable confusion concerning the role of the pedunculopontine nucleus in the initiation of locomotion. Some experiments have related the effect of stimulation, drug injection or lesion on initiation of movement on the pedunculopontine nucleus, but their results may have involved activation in adjacent structures of the mesencephalic locomotor region, especially the cuneiform (Milner and Mogensen, 1988; Brudzynski *et al*., 1993). Histological verification of sites for electric stimulation and injection in cats, rats and guinea pigs has shown that these sites were invariably located in and around the cuneiform nucleus (Amemiya and Yamaguchi, 1984; Brudzynski *et al*., 1986; Milner and Mogenson, 1988; Coles *et al*., 1989).

The cuneiform nucleus is ventrally demarcated by the decussation of the superior cerebellar peduncle and the pedunculopontine nucleus. At caudal levels, it is dorsally bordered by the external cortex of the inferior colliculus, laterally by the dorsal nucleus of the lateral lemniscus and ventrally by the superior cerebellar peduncle (Fig. 1). Similar to the pedunculopontine nucleus, the cuneiform is not a homogeneous population of cells. It consists of two different types of cells, i.e. GABA-ergic and nitrergic neurons (Pose *et al*., 2000).

The pedunculopontine nucleus and the cuneiform nucleus are both important sites in the mesencephalic locomotor region and have been suggested to facilitate muscle tone during initiation of

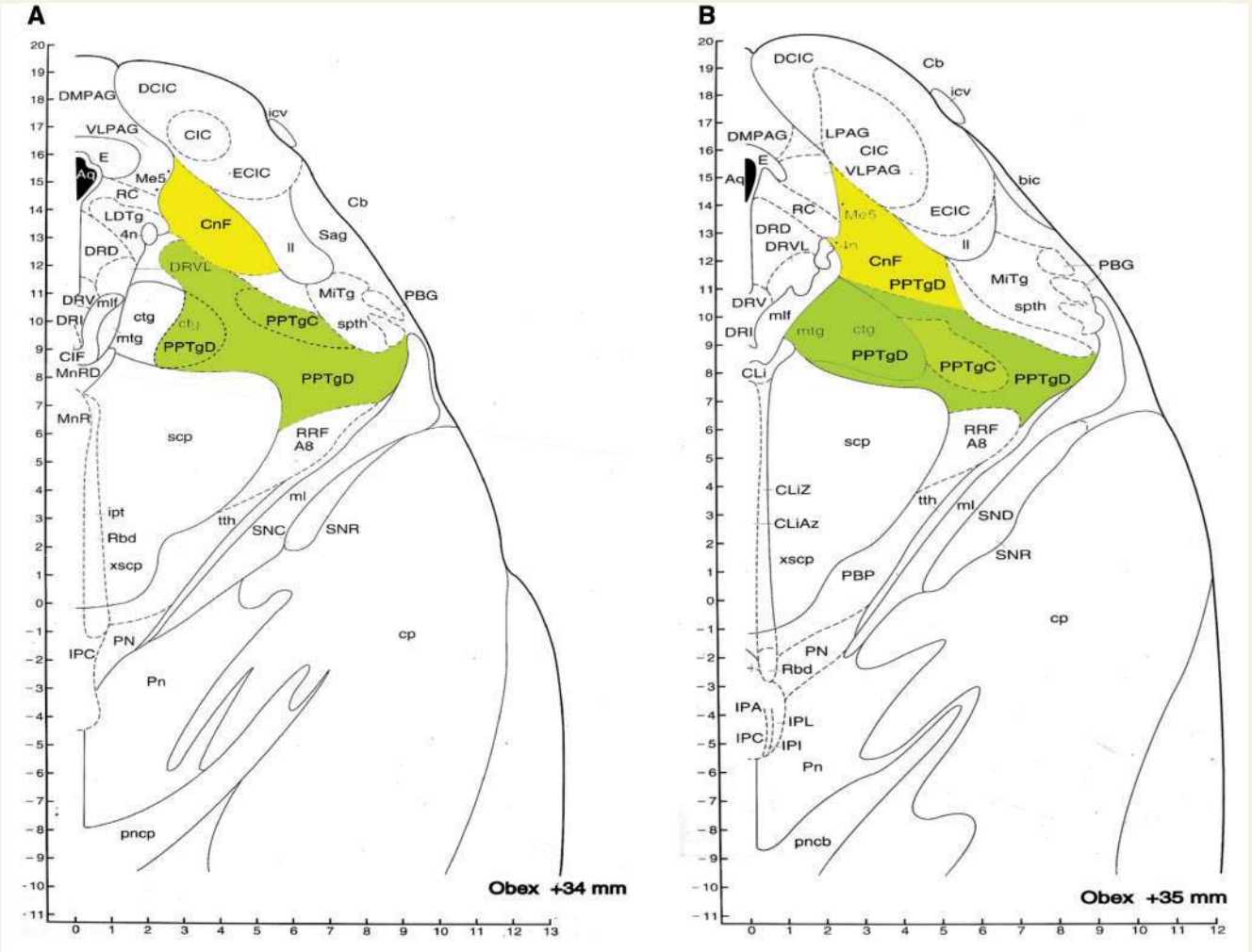

Figure 1 Location of the human pedunculopontine nucleus pars compacta (PPTgC), pedunculopontine pars dissipata (PPTgD) and the cuneiform nucleus (CnF) and major surrounding structures along the axis of the brainstem. (**A**) 34 mm and (**B**) 35 mm rostral to the obex. (Reprinted from Paxinos and Huang, 1995, with kind permission from Elsevier.)

locomotion (Mori *et al*., 1987). Some human atlases further differentiate between cuneiform and subcuneiform nucleus, however, without giving a precise anatomical boundary of both the cuneiform and subcuneiform nucleus (Olszewski and Baxter, 1954). Clinical studies have suggested that the most suitable targets are in the subcuneiform nucleus, which is located slightly posterior to the pedunculopontine nucleus pars compacta, probably in the ventral part of the cuneiform nucleus since stimulation-induced locomotion has been reported in animals at this location (Takakusaki *et al*., 2003; Piallat *et al*., 2009; Ferraye *et al*., 2010). However, in most animal studies the subcuneiform nucleus is seen as an integral part of the cuneiform and not specifically outlined. Cholinergic neurons of the pedunculopontine nucleus extend dorsally to the classic pedunculopontine nucleus pars compacta, i.e. in the so-called subcuneiform. Neuronal populations in fact partly overlap in this region and a sharp delineation of separate individual regions does not reflect the exact reality correctly.

Effective sites for chemically evoked locomotion in freely moving rats appear to be located predominantly in the cuneiform and not in the pedunculopontine nucleus as defined by Milner and Mogenson (1988). However, lesions of the cuneiform in rats do not show differences in locomotion behaviour as compared with sham lesion (Allen *et al*., 1996), while electrical stimulation of the cuneiform nucleus elicited suppression of muscular tone and somatic reflexes (Mileikovsky *et al*., 1989, 1990; Mileikovsky and Nozdrachev, 1997). These effects may be mediated by premotor inhibitory neurons within the ventromedial medulla (Morales *et al*., 1999), which is one of the principal targets of cuneiform fibres. It is possible that cuneiform terminals modulate the activity of premotor neurons, since the cuneiform is related to modulation of both the sensory and the motor system (Zemlan and Behbehani, 1988). However, the cuneiform and the pedunculopontine nucleus are close in proximity and perhaps the effect of electrical stimulation or local drug injection always attribute to one or the other (Garcia-Rill and Skinner, 1987*a*, *b*; Garcia-Rill *et al*., 1991).

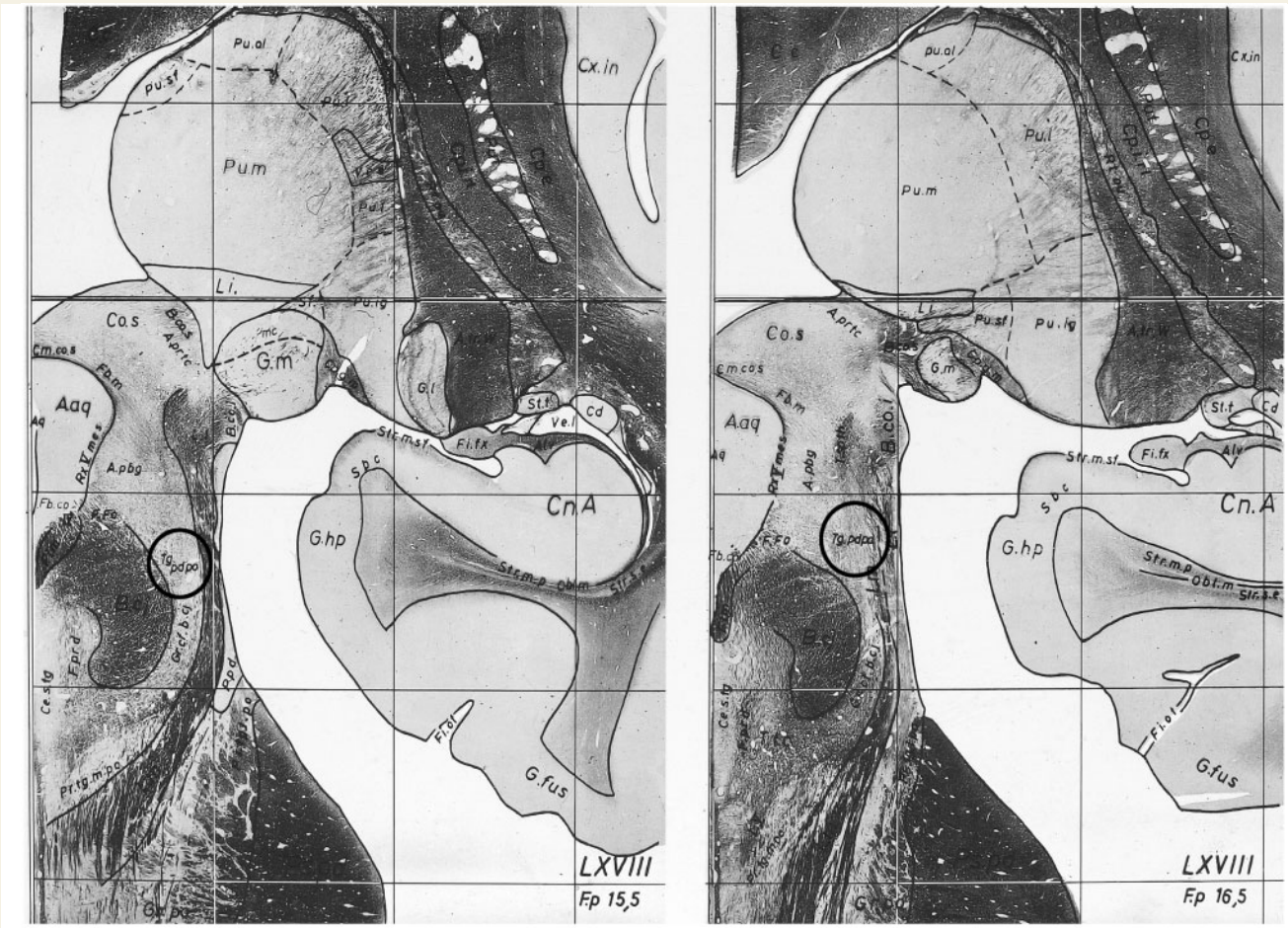

Figure 2 The coronal sections which are 15.5 mm (**A**) and 16.5 mm (**B**) posterior to the midcommissural point (3.5 and 4.5 mm posterior to the posterior commissure) in a human brain show the pedunculopontine nucleus, which has been marked with a circle. The anatomical abbreviation in the Schaltenbrand-atlas is tagged as Tg.pdpo (nucleus tegmenti pedunculopontinus). (Reprinted from Schaltenbrand and Wahren, 1977, with kind permission from Thieme.

The peripeduncular nucleus

The peripeduncular nucleus is bordered on its ventral aspect by the substantia nigra pars compacta and the cerebral peduncle, and on its dorsal aspect by the parvocellular and the magnocellular nucleus of the medial geniculate body. Both are in the immediate vicinity of the brachium colliculi inferioris, the principal conducting pathway from the inferior colliculus to the medial geniculate body (Maiskii *et al*., 1984).

In rodents, cytochemical tracing suggests that the peripeduncular nucleus is connected with limbic, motor, auditory, dorsal and ventral nuclei of the lateral lemniscus and non-specific diencephalic and mesencephalic centres including the pedunculopontine nucleus, cuneiform and laterodorsal tegmental nucleus (Arnault and Roger, 1987). It also has a reciprocal connection with the ventromedial nucleus of the hypothalamus. Autoradiographically it has been shown that the peripeduncular nucleus is a powerful source of projections into the amygdaloid complex (Jones *et al*., 1976). Studies in rodents show that it projects to the rostral zones of the amygdaloid complex. In monkeys, however, it projects to the basolateral zone of the amygdaloid complex (Jones *et al*., 1976; Turner and Herkenham, 1981). The paramedian and medial parts of the peripeduncular nuclei in monkey seem to be the essential components in the prefrontopontine connection (Schmahmann and Pandya, 1997).

The peripeduncular nucleus apparently plays an important role in the neuroendocrine control of male and female copulatory behaviour in rodents, as well as in the regulation of the milk ejection reflex (Tindal and Knaggs, 1975; Hansen and Köhler, 1984; Lòpez and Carrer, 1985; Factor *et al*., 1993; Szabo *et al*., 2010). Additionally, in Alzheimer's disease, neurofibrillary tangles have been shown in the peripeduncular nucleus among several subcortical nuclei and cortical regions (German *et al*., 1987). However, to our knowledge, no study has related the peripeduncular nucleus to movement.

Deep brain stimulation of the pedunculopontine nucleus

Non-human primate studies have shown that both blocking GABA-ergic inhibition with bicuculline or direct electrical

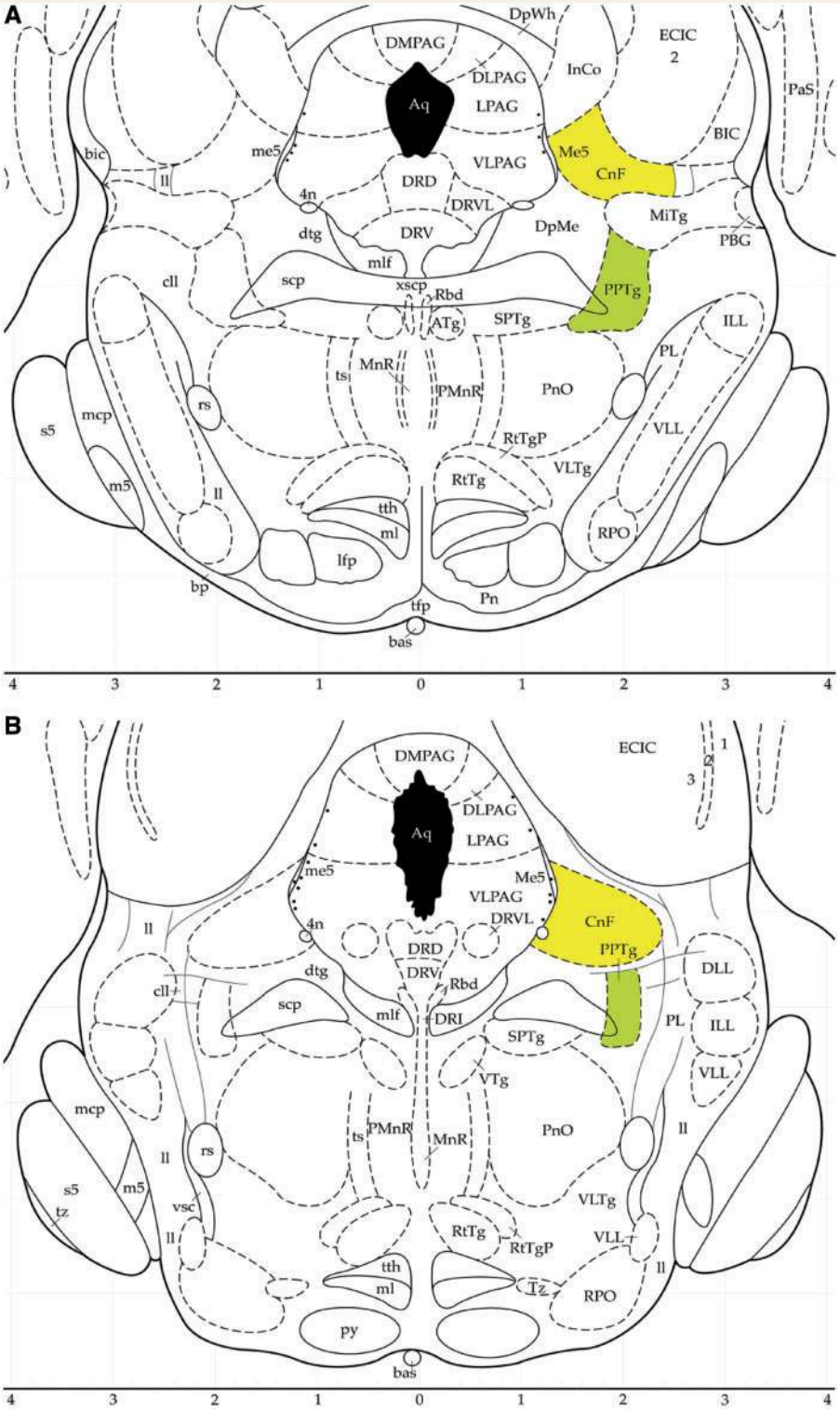

Figure 3 Anatomical location of pedunculopontine tegmental nucleus (PPTg) and cuneiform nucleus (CnF) in rat midbrain region. **3A** and **3B** are a Schematic coronal plane of rat brainstem shown at −8.00 to −8.30 posterior to bregma, 1.8–2 mm lateral to the midline and 6.8–7.4 mm ventral to the skull surface according to Paxinos and Watson (1998).

stimulation of the pedunculopontine nucleus at low frequencies (10–30 Hz), reliably increased motor activity. Instead, high frequency stimulation decreased movement, which is consistent with the idea that parkinsonian akinesia is, in part, caused by over-inhibition of the pedunculopontine nucleus by descending afferents from the basal ganglia. Electrical stimulation of the pedunculopontine nucleus at low frequencies is thought to be effective by disinhibition or by driving the inhibited cholinergic

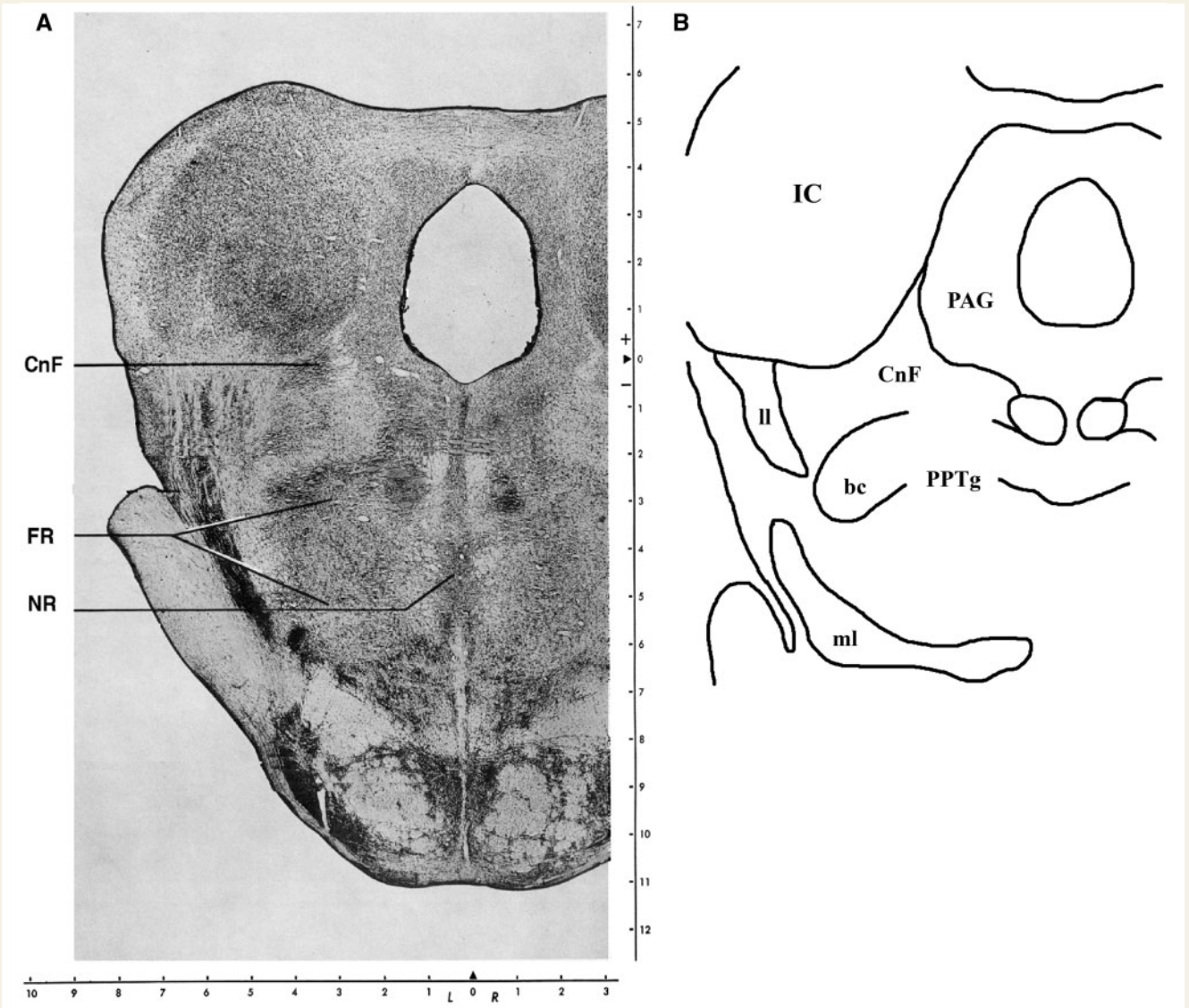

Figure 4 Anatomical location of reticular formation (FR) and nucleus raphe (NR) in cat midbrain region. (**A**) Schematic coronal planes of the cat brainstem, where cuneiform nucleus (CnF) and pedunculopontine (PPTg) are lying in the coordination P 2.0, LR 3 to 4 mm H 0.5 to −5, according to sterotaxic atlas of the cat brain by Snider and Niemer, 1970. (**B**) Sketch of **A**, showing the position of PPTg.

and glutamatergic neurons (Nandi *et al*., 2002; Jenkinson *et al*., 2004).

Clinical studies have shown that both unilateral and bilateral deep brain stimulation of the pedunculopontine nucleus at low frequency (20–25 Hz) have a beneficial effect on gait in Parkinson's disease and probably less so in patients with progressive supranuclear palsy (Mazzone *et al*., 2009). This is in line with previous studies that have found that high frequency stimulation of the MPTP-treated monkey pedunculopontine nucleus deep brain stimulation with 100 Hz produced adverse effects, whereas 2.5, 5 and 10 Hz with a pulse width of 120 ms enhanced movement (Jenkinson *et al*., 2004). A recent study, which used frequencies of 5, 20, 50, 70 and 130 Hz with a pulse width of 60 ms for chronic stimulation, showed improvement of falls in patients with Parkinson's disease at 50–70 Hz stimulation of the pedunculopontine nucleus (Moro *et al*., 2010). Interestingly, a recent rodent study of deep brain stimulation in the pedunculopontine nucleus has shown that both low (25 Hz) and high frequency (130 Hz) stimulation in the 6-hydroxydopamine rat model of Parkinson's disease improved the time of descent latency in the pole test and total distance travelled in the open field (Rauch *et al*., 2010). Therefore, both clinical and animal studies indicate that the issue of the optimal frequency and pulse width remains to be determined.

There is great controversy, however, whether the optimal site for stimulation is situated in the pedunculopontine nucleus or adjacent areas. For a number of reasons, including individual variability regarding brain anatomy and variations among the brainstem atlases, variations in target determination are evident.

Reliance on atlas-based localization of the pedunculopontine nucleus might be expected to lead to anatomical targeting errors in a number of patients. The simultaneous implications of a systematic approach of using several atlases linked to multimodal neuroimaging techniques could be validated, which would lead to more reliable and reproducible surgical planning (Zrinzo and Zrinzo, 2008; Zrinzo *et al*., 2008). Also, spiking characteristics of different zones in the pedunculopontine nucleus, cuneiform or subcuneiform might be useful to further delineate the final site for chronic stimulation (Piallat *et al*., 2009; Shimamoto *et al*., 2010).

Since the pedunculopontine nucleus is partially damaged in patients with Parkinson's disease it remains arbitrary how the optimal site for deep brain stimulation would be determined. As outlined above, the pedunculopontine nucleus has close proximity to the cuneiform and laterodorsal tegmental nucleus, which contain cholinergic, glutamatergic, GABA-ergic and substance P populations of neurons, and which also have afferent and efferent connections to the basal ganglia. The stimulating contact may possibly affect these adjacent regions to the pedunculopontine nucleus. This is especially likely since the various neuronal populations of this brainstem region partly overlap.

A clinical study in patients with Parkinson's disease has shown the best effects on gait with active contacts located slightly posterior to the pedunculopontine nucleus, i.e. in the cuneiform and subcuneiform nuclei (Ferraye *et al*., 2010). In addition, the same group showed that imagination of gait results in increased tonic firing of subcuneiform neurons (Piallat *et al*., 2009). As noted above, in rats, cats and monkeys, similar findings were thought to correspond to the cuneiform (Shik *et al*., 1966; Eidelberg *et al*., 1981; Garacia-Rill *et al*., 1983; Coles *et al*., 1989). Additionally, it has been shown that the combination of pedunculopontine nucleus stimulation with either subthalamic nucleus or globus pallidus internus may have superior effects than stimulation of either region alone (Mazzone *et al*., 2009; Schrader *et al*., 2010).

Conclusion

The pedunculopontine nucleus integrates both sensory and motor information via ascending and descending pathways. With respect to research concerning the function of this region, however, interspecies anatomical and physiological differences need to be taken into account. The efficacy of deep brain stimulation in Parkinson's disease and possibly progressive supranuclear palsy is most likely unrelated to dopaminergic dysfunction but may be mediated by modulation of cholinergic neurons in the pedunculopontine nucleus region. It is important to note that the effect of deep brain stimulation might not be mediated by the pedunculopontine nucleus proper but also by neighbouring structures such as the cuneiform and subcuneiform nucleus. These issues need to be taken into account when using animal models to examine the effect of pedunculopontine nucleus deep brain stimulation for Parkinson's disease.

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