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Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family?

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The basal ganglia are more highly interconnected with the pedunculopontine tegmental nucleus (PPN) than with any other brain region. Regulation and relay of basal ganglia activity are two key functions of the PPN. The PPN provides an interface for the basal ganglia to influence sleep and waking, and the two structures are similarly implicated in learning, reward and other cognitive functions. Perturbations of basal ganglia activity have consequences for the PPN and vice versa, exemplified by their interdependencies in motor function and Parkinson's disease. Thus, close anatomical and physiological links between the PPN and basal ganglia make it increasingly difficult to consider the two as separate functional entities.

The pedunculopontine tegmental nucleus (PPN), often considered synonymous with the cholinergic cell group Ch5 [1], is a rostral brainstem structure that is thought to be part of the 'ascending reticular activating system' because of its ascending cholinergic projections to the thalamus that modulate cortical activation [2] (Figure 1). Indeed, it has long been known that the PPN is a crucial element in the generation and maintenance of the rapid rhythms in the cortex that are associated with wakefulness and REM sleep. In addition to its regulatory function in the sleep–wake cycle, the PPN is involved in control of movement and constitutes the central part of the 'mesencephalic locomotor region' [3]; this role in movement is likely to be subserved by direct projections from the PPN to the spinal cord [4]. More recent research has suggested that the PPN might be involved in a wider variety of psychological and behavioural processes.

The PPN establishes reciprocal connections with the basal ganglia. The degree of reciprocity is unique when compared with the other targets of the basal ganglia, and a clear, but complex, physiological interdependence is now apparent. Furthermore, emerging evidence from studies on Parkinson's disease and its models shows that this reciprocal relationship is crucial for the normal function of both the basal ganglia and the PPN. As such, a better understanding of the PPN is vital for a full appreciation of basal ganglia function.

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Structural considerations

Other cell groups exist with the cholinergic neurons in the PPN, including glutamatergic [5], GABAergic [6], peptidergic [7] and dopaminergic [8] neurons. Furthermore, various neurochemical markers frequently colocalize with markers of cholinergic neurons in the PPN. Thus, populations of cholinergic neurons have been shown to coexpress glutamate [9], GABA [10], NADPH-diaphorase [11] and, to a lesser extent, various Ca^{2+}-binding proteins [12,13]. The importance of the non-cholinergic cells has been emphasized on the basis of interactions between different populations of PPN neurons [14] and their physiological properties [15]. Moreover, many inputs to the PPN preferentially establish synaptic contact with the non-cholinergic cells in this region [16,17], further indicating the importance of these cell groups. Despite this neurochemical complexity, and the fact that cholinergic neurons could represent as little as 50% of the total cell population [18], experimental work on the PPN has focused on the cholinergic cells, leading to proposals that it is this cell group that is primarily responsible for the varied functions of the PPN [19–21].

The PPN might be better defined on the basis of connections than solely on the distribution of the cholinergic cells. In support of this idea, several tracer studies have shown that, on the basis of connectivity, the boundaries of the PPN do not necessarily fit within the limits of the cholinergic cell group [16,17,22]. Thus, according to both afferent and efferent connections, and the presence of non-cholinergic cells with proven functional significance, the borders of the PPN seem to extend dorsally and medially from the cholinergic population.

Similarities in function

The basal ganglia have many features in common with the PPN. Their anatomical relationship seems to be maintained across species, from ancestral tetrapods to humans [23]. When considered as a whole, the basal ganglia and PPN have a similar pattern of inputs and outputs, including cortex, thalamus, superior colliculus, amygdala and brainstem. Indeed, Winn and colleagues have proposed that the anatomical organization and electrophysiological characteristics of the PPN closely resemble those of the substantia nigra, including features reminiscent of

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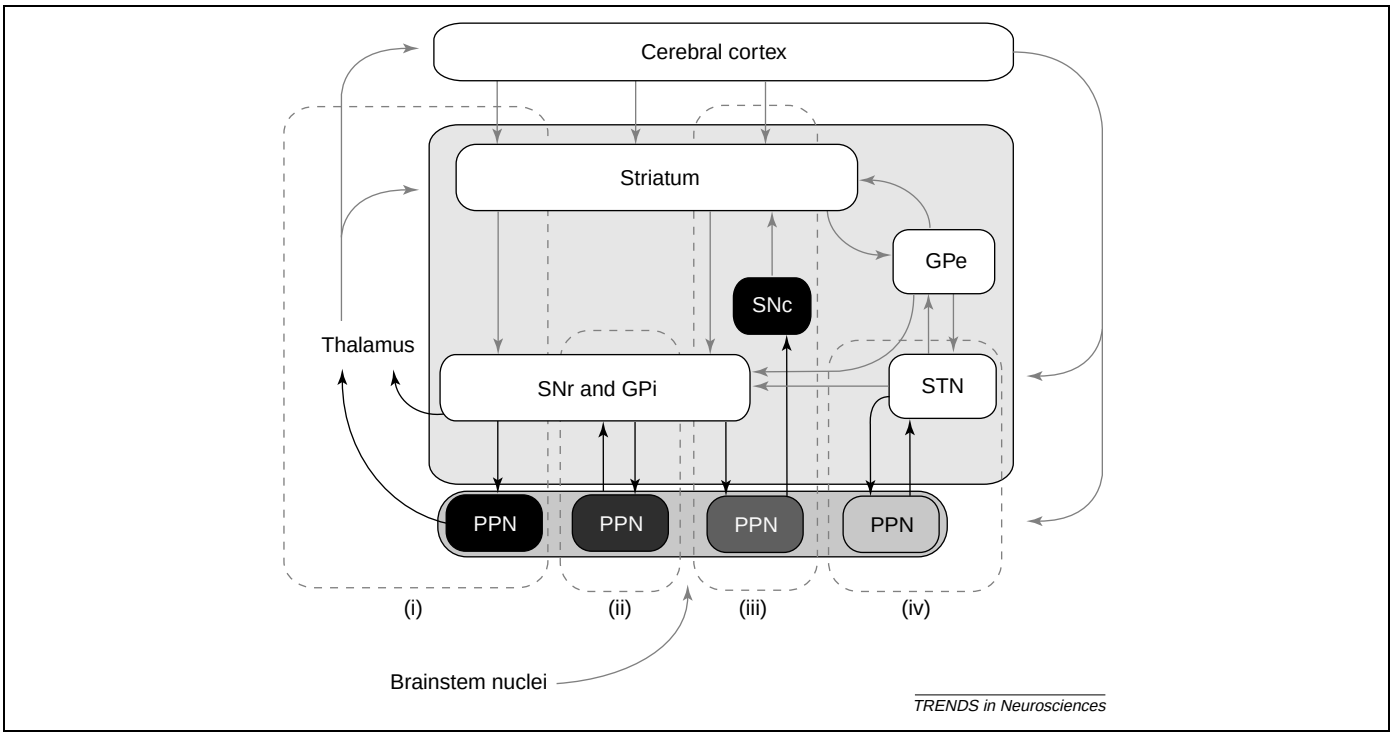

Figure 1. Interconnections between the basal ganglia and the pedunculopontine tegmental nucleus (PPN). There are several possible circuits by which the basal ganglia and PPN interact, some of which are highlighted by the dashed rectangles and the different shades of gray in the PPN boxes. Here, we consider only the major routes by which the basal ganglia and PPN are interconnected. From left to right: (i) the PPN sends projections to the thalamic cells that project to the striatum [64]; (ii) there are reciprocal connections between the PPN and the basal ganglia output nuclei [substantia nigra pars reticulata (SNr) and internal globus pallidus (GPi)], the latter nuclei providing a dense inhibitory projection to PPN; (iii) a substantial projection from the PPN innervates dopaminergic neurons of the substantia nigra pars compacta (SNc), which in turn modulate striatonigral and striatopallidal pathways; and (iv) a reciprocal, putative excitatory loop is formed between the PPN and the subthalamic nucleus (STN). The extents of convergence and divergence of these interconnections are unknown, as is the relative importance of different types of PPN neurons. These complex interconnections imply that the PPN has a profound and widespread influence over basal ganglia activity and, similarly, that the basal ganglia are in a position to modulate PPN activity at many different levels.

both the pars reticulata and pars compacta [24,25]. In line with the similarities in anatomy and physiology, the basal ganglia and PPN are involved in a common set of functions. Early work on the motor function of PPN showed that low-threshold electrical stimulation within the PPN elicited locomotion [26], leading to the now widely held proposal that the PPN is an important relay nucleus between the basal ganglia and the spinal cord [27]. Recent studies have shown that the PPN controls postural muscle tone [27] and that it is involved in saccades [28]. Although the common involvement of the basal ganglia and PPN in movement has long been known, recent findings suggest that the PPN is more than a simple relay for the basal ganglia. Indeed, these structures share functions beyond motor control and there is some degree of interdependence of function. Thus, the basal ganglia play a role in regulation of the sleep–wake cycle [29], which depends on their interconnections with the PPN [30,31] but is separate from motor function. In addition, the basal ganglia and PPN seems to play similar roles in attention [32] and in reward and learning [33], suggesting that, in common with the basal ganglia, the PPN is a limbic–motor interface (for detailed reviews, see Refs [24,34]). Indeed, the multifarious functions of the PPN have been implicated in a learning pathway for reward prediction [35], a function that is also traditionally associated with the basal ganglia.

Interconnections between the PPN and basal ganglia

These shared, or at the very least closely related, functions raise the question of what underlies such commonality. Does this arise as a consequence of the common pattern of connectivity with other brain areas, or could it be due to the remarkable level of interconnectivity between the PPN and the basal ganglia? The basal ganglia are more highly interconnected with the PPN than with any other region of the brain (Figure 1). Thus, there are reciprocal connections between the PPN and the striatum, substantia nigra pars reticulata (SNr), substantia nigra pars compacta (SNc), internal globus pallidus (GPi), external globus pallidus (GPe) and subthalamic nucleus (STN) [36–39]. The complexity and importance of these relationships can be best illustrated by the connections of the PPN with the basal ganglia output nuclei, the GPi and SNr, and with the STN. The SNr sends a prominent GABAergic projection to the PPN that innervates both cholinergic and glutamatergic neurons [17]. This nigral output inhibits the activity of cholinergic [40–42] and non-cholinergic [41] neurons of the PPN. In turn, the PPN sends back a mixed cholinergic and glutamatergic projection to the SNr and GPi, as well as to the SNc and GPe [39,43–45], and these projections are functionally relevant in physiological [46,47] and behavioral experiments [48,49]. The STN provides

glutamatergic innervation of the PPN which, in turn, sends cholinergic, glutamatergic and GABAergic projections back to the STN [50,51]. Electrophysiological studies have shown the importance of GABAergic and glutamatergic inputs for regulation of PPN activity [42,52], and predict how disruption of these inputs could alter normal activity of PPN neurons and consequently motor functions, as was proposed [19] and then observed in Parkinson's disease and its models [53].

The fact that the basal ganglia output nuclei and the STN have reciprocal connections with the PPN has implications relating to our understanding, and possibly the treatment, of Parkinson's disease. According to the direct and indirect pathways model, one would predict that in Parkinson's disease or its models there would be both increased inhibitory input to PPN from basal ganglia output nuclei and increased excitatory input from STN. Indeed, experimental studies support these predictions [54–58]. Thus, increased inhibition would lead to suppression of activity in the PPN, which, because the PPN is thought to facilitate movement, would in turn produce a state of motor hypoactivity. In agreement with this, pharmacological blockade of the inhibitory input to PPN markedly attenuates akinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of Parkinson's disease [54]. By contrast, PPN neurons also exhibit increased activity in models of Parkinson's disease [55–57]; this depends on STN [57] and thus presumably relates to the hyperactivity of STN neurons that occurs after chronic loss of dopamine [59,60]. The importance of the PPN is further highlighted by the pathological changes that occur in this region in Parkinson's disease [61,62]. Interestingly, altered activity of PPN neurons has also been proposed to contribute, at least in part, to dopamine neuron death [63]. Clearly, it is crucial to establish which PPN cell types increase their firing in response to increased input from STN, and which cell types decrease their firing in response to increased input from SNr and GPi. Doing so would bring an understanding of the relevance of various inputs from the basal ganglia for the functions of different types of PPN neurons, thus aiding the development of new therapeutic approaches to Parkinson's disease.

Concluding remarks

It is evident that the PPN and the basal ganglia are more intimately connected than traditionally believed; the PPN is more than a simple relay of basal ganglia output that merely subserves the role of the latter in locomotor function. Indeed, the PPN is in a position to influence activity in the whole of the basal ganglia; their interconnections form complex feedback and feedforward circuits that are likely to cause opposing effects on basal ganglia output nuclei. It has become increasingly difficult to extricate the varied functions of the PPN from many of those of the basal ganglia. Taken together, these characteristics suggest that the relationship between the basal ganglia and PPN is unique when compared with the other targets of the basal ganglia. Thus, should we consider the PPN as part of the basal ganglia?

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