

## Targeting the Pedunculopontine Nucleus in Parkinson's disease: Time to Go Back to the Drawing Board

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Subthalamic or pallidal Deep Brain Stimulation (DBS) are effective treatments for selected Parkinson disease (PD) patients. The effectiveness of subthalamic nucleus (STN) or pallidal DBS led logically to efforts to employ DBS in other brain regions to treat aspects of PD lacking adequate medical treatments. Gait and balance deficits unresponsive to dopamine replacement therapy are major problems in more advanced PD patients. The absence of satisfactory medical treatments for these problems led to human clinical experiments deploying DBS in the region of the pedunculopontine nucleus (PPN) with the goal of alleviating crippling gait and balance problems. The fundamental rationale was that low frequency DBS in the PPN would increase the activity of a critical group of PPN neurons. The clinical experience with PPN DBS was reviewed recently<sup>1</sup>. In this Viewpoint, we discuss the scientific rationale for PPN DBS and argue that our present understanding of the PPN, surrounding regions, and their potential roles in locomotion does not provide a good scientific rationale for conventional PPN DBS in PD.

### **Original Rationale for PPN DBS**

The origins of the scientific rationale for PPN DBS lies in the 1960's when investigators in the Soviet Union discovered that the region of the mesopontine junction is important in controlling locomotion and posture. These investigators found that low intensity electrical stimulation in this region induced locomotion in decerebrate cats.<sup>2</sup> This electrophysiologically defined region was called the Mesencephalic Locomotor Region (MLR). Subsequent work by Garcia-Rill and colleagues suggested that the MLR is centered around the PPN, which is populated by cholinergic neurons.<sup>3,4</sup> Garcia-Rill and colleagues suggested a model in which MLR-PPN neurons projected to a region of the ventromedial medulla (VMM) connected to spinal central pattern generators

responsible for locomotion.<sup>4</sup> Because cholinergic neurons were a prominent part of the PPN, it was widely inferred that they were critical mediators of forebrain inputs regulating locomotion, though retrograde tracing data from Garcia-Rill and colleagues strongly implicated non-cholinergic PPN neurons as the major source of PPN to VMM projections.<sup>5</sup>

The PPN is a heterogeneous region composed of cholinergic, glutamatergic, GABAergic, and probably glycinergic neurons.<sup>6,7,8</sup> These different neuron types are not distributed uniformly within the PPN. Cholinergic neurons are denser in the caudal than in the rostral portion of the PPN, glutamatergic neuron density increases along the rostral to caudal axis, while the GABAergic neurons show the opposite pattern.<sup>6,8</sup> The connectome of these populations is heterogeneous. Oakman and coworkers<sup>9</sup>, for example, found that substantia nigra pars compacta (SNc) neurons receive cholinergic innervation mainly from the rostroventral and medial PPN, while ventral tegmental area (VTA) neurons receive cholinergic inputs principally from caudal PPN. The cytological and connective heterogeneity of the PPN is in marked contrast to relatively homogeneous STN and GPi. This has potential implications for PPN DBS as a variation in DBS electrode position is likely to modulate different circuitry with differing effects on motor behavior.

Several observations subsequently suggested that PPN cholinergic neurons were involved in gait and balance problems in PD and related disorders. Hirsch et al. described loss of cholinergic PPN neurons in PD and Progressive Supranuclear Palsy.<sup>10</sup> The magnitude of cholinergic PPN neuron

loss was described as greater in PD subjects with a history of falls, consistent with a critical role for cholinergic PPN neurons in gait and balance control.<sup>11</sup> Positron emission tomography imaging studies of cholinergic terminal integrity performed by some of us (NIB, MM, RLA) supported this inference.<sup>12,13,14</sup> Subsequent work, however (see below), showed that there also is loss (albeit not as great) of other PPN neuronal populations in PD patients.

Karachi et al. moved beyond correlative studies with experiments in non-human primates to assess whether loss of PPN cholinergic neurons could be causally linked to gait and posture deficits. First, they showed that lesioning cholinergic PPN neurons caused gait, balance, and posture deficits. Second, they showed that with MPTP lesions, loss of PPN cholinergic neurons exacerbated dopamine insensitive gait, balance, and posture deficits<sup>11,15</sup>. More recently, pharmacogenetic stimulation of PPN cholinergic neurons was reported to reverse gait and postural abnormalities in a rat toxin PD model.<sup>16</sup>

In addition, some studies suggested the emergence of pathophysiological PPN activity in rodent PD toxin models.<sup>17,18,19</sup> Breit et al. described increased activity and bursting of PPN neurons after 6-OHDA lesions. Although it was unclear which PPN neuron subpopulations was contributing to the pathophysiology, it established a parallel with the pathophysiology observed in STN of PD patients and the hypothesis that DBS might ameliorate symptoms. Breit et al. also described relative normalization of PPN neuron activity in animals with joint 6-OHDA SNc lesions and ibotenic acid STN lesions.<sup>18</sup> The PPN receives a number of afferent projections from the basal

ganglia,<sup>6,7</sup> and it is plausible that basal ganglia dysfunction would result in PPN-MLR dysfunction, providing an additional rationale for DBS targeting of the PPN in PD.

### **Recent Studies Contradicting the Original Rationale**

Results of other experiments, however, contradict the idea that cholinergic PPN neurons are critical for gait. Neither indiscriminate excitotoxic lesions of PPN neurons nor selective lesions of cholinergic PPN neurons produced marked abnormalities in gait in rodents. Selective lesions of PPN cholinergic neurons did not worsen gait impairments resulting from basal forebrain cholinergic and striatal dopamine lesions.<sup>20,21</sup>

In part, discrepant results may be a consequence of the poorly defined anatomy of the operationally-defined MLR. As mentioned above, the MLR was defined on the basis of the motoric response to electrical stimulation – an approach that alone cannot be used to precisely define the somatodendritic location of the obligate neurons. Work by Takakusaki in decerebrate cats suggests that the cuneiform nucleus, which is rostral to the PPN, is essential for stimulation-induced locomotion<sup>22</sup>. Lu and colleagues' experiments in rats have implicated a group of neurons ventral to the PPN that project directly to the spinal cord pattern generators.<sup>23,24</sup> In fact, work with newer tools or tool combinations suggests that the key node for locomotion may not be the PPN.

Studies using optogenetic methods to selectively activate neuron subpopulations within the MLR shed further doubt on the centrality of PPN cholinergic neurons for locomotion and highlight the complexity of MLR functional anatomy. Roseberry et al. attempted to stimulate cholinergic neurons, GABAergic neurons, and glutamatergic neurons in this region.<sup>25</sup> For technical reasons, it was difficult to stimulate cholinergic neurons adequately. In resting mice, stimulation of glutamatergic neurons elicited locomotion. In locomoting mice, stimulation of glutamatergic PPN neurons significantly accelerated locomotion and stimulation of GABAergic PPN neurons slowed locomotion. This work is consistent with a role for the PPN in the MLR but suggest that cholinergic PPN neurons are not the critical population for locomotion. These results are consistent with the older Garcia-Rill group model. In older tract-tracing studies, the PPN-VMM projection identified as the key descending pathway for gait activation was found to consist mainly of non-cholinergic neurons. Also consistent with the MLR to VMM model, Capelli et al. recently described caudal brainstem circuits controlling locomotor velocity.<sup>26</sup> This group traced MLR efferents to the caudal medulla and found that they originated in both PPN and cuneiform nuclei glutamatergic neurons. Caggiano et al. describe both PPN and cuneiform nucleus glutamatergic neurons as important for gait control in mice with complex interactions (including direct interconnections) between these two nuclei influencing gait speed and gait modes.<sup>27</sup>

While the original conception of the role of cholinergic PPN neurons focused on regulation of brainstem control of locomotion, these neurons have a major rostral projection to the thalamus, suggesting a role in modulation of sensory information.<sup>6,7</sup> This concept is supported by research

in PD subjects indicating a role for these projections in sensory integration to maintain normal posture and detection of salient external cues.<sup>28,29</sup>

PPN glutamatergic neurons also project rostrally. A recent study demonstrated that PPN glutamatergic neurons robustly activate SNc dopaminergic neurons, creating yet another way in which these neurons might initiate movement.<sup>30</sup> By comparison, optogenetic activation of PPN cholinergic neurons evokes much smaller responses that are weakly linked to changes in SNc DA neuron spiking.<sup>31</sup>

### **Lessons from Human Studies**

These results may explain data from some human PPN DBS studies. Two studies report significant improvement in gait parameters with PPN DBS in the OFF medication state, but not in the ON medication state.<sup>32,33</sup> It is plausible that in the OFF medication state, PPN activation of dopaminergic neurons produces enough incremental striatal dopamine to make a difference in locomotion. In the ON medication state, however, this modest effect may be obscured by the effects of dopamine replacement treatment. In contrast, Stefani and coworkers found that PPN DBS stimulation improved gait and posture both in OFF and ON states.<sup>34</sup> Further clouding interpretation of the clinical outcome data, some PD subjects receiving PPN DBS also underwent DBS at conventional targets such as the STN.<sup>1</sup> In their recent review, Thevathasan et al. conclude that despite the variation in outcomes, when properly positioned, PPN DBS has the potential to reduce falls and improve gait in PD patients.<sup>1</sup> Thevathasan et al. are appropriately cautious about



the existing clinical outcome data and stress that the effect of PPN DBS on the quality of life of PD patients remains unproven.<sup>1</sup> Efforts at meta-analysis of individual subject data support these conclusions.<sup>35-37</sup>

In spite of some beneficial outcomes in PD patients, the uncertainties surrounding the nature of the MLR and the neuronal heterogeneity of the mesopontine region pose significant theoretical obstacles to the use of PPN DBS. Is the PPN the appropriate target? Given the small sizes of the involved nuclei and their considerable heterogeneity, the electric fields generated by standard DBS electrodes are likely to modulate the activity of multiple nuclei at the mesopontine junction.<sup>3</sup> In their pioneering studies of rostral human brainstem cholinergic neurons, Mesulam et al. emphasize that the distribution of mesopontine cholinergic neurons does not follow clear nuclear boundaries and that their dendrites interpenetrate a number of surrounding structures.<sup>38</sup> This is likely true for other PPN neuronal populations as well. As shown by the optogenetic experiments, there is considerable functional heterogeneity within this region. The mesopontine region is characterized also by the presence of a number of important white matter tracts, increasing the risk of significant side effects of stimulation. The challenges of developing accurate stereotaxic targeting algorithms and correlating electrode placement, clinical outcomes, and underlying anatomy in the rostral brainstem underscores these concerns.<sup>39</sup> Even if DBS electrode actions could be restricted to one of these nuclei, different and likely contradictory effects will result from indiscriminate effects of conventional DBS. Consistent with this concern, rats with combined

toxin lesions of the substantia nigra and PPN were reported to exhibit worsening gait performance upon receiving a PPN DBS analogue.<sup>20</sup>

In addition, there is conflicting information about the effects of dopamine depletion on PPN neuronal activity. In non-human primates and in PD patients, data suggest that the PPN activity is suppressed in PD; pharmacological disinhibition improves motor behavior in parkinsonian MPTP-lesioned primates.<sup>40</sup> In contrast, rodent studies suggest either PPN activity is elevated<sup>18,41,42</sup>, suppressed<sup>41,43</sup>, or not changed<sup>45,46</sup> after dopamine depletion. A recent, small non-human primate study did not find a change in PPN activity in MPTP lesioned non-human primates.<sup>47</sup> These discrepancies have yet to be resolved but are likely to stem from the heterogeneity in cell types and circuit complexity.

Another issue is that many PPN neurons degenerate in PD. This includes not only cholinergic PPN neurons, but also GABAergic and glycinergic neurons.<sup>48</sup> How this pathology affects the response of neurons to electrical stimulation is unclear. If the goal is to boost the activity of PPN neurons that are compromised, then low frequency stimulation, near the normal autonomous rate of cholinergic PPN neurons, should be more effective than higher frequency stimulation which is likely to drive neurons into depolarization block. Indeed, low frequency – but not high frequency – PPN stimulation has been reported to improve akinesia in parkinsonian monkeys.<sup>49</sup>

## **Summary**

In summary, what we have learned about the PPN and MLR over the past few years undermines the simplistic model that underpins the rationale for PPN DBS. Our understanding of the relevant circuitry remains rudimentary. Further, much of what we know about these circuits is based on studies in rodents and felines. While it is likely that critical features of posture and locomotion control are phylogenetically conserved, additional non-human primate experiments are needed. Even if we understood the relevant motor circuits in detail, the small sizes of these structures, and the considerable heterogeneity of neurons within the PPN and surrounding structures, indicates that conventional DBS is too blunt an instrument to selectively target the relevant neurons. Finally, manipulating sick neurons adds an additional element of uncertainty. In the context of these facts, it is not surprising that the clinical results of PPN DBS are largely unimpressive.<sup>1</sup> Technical refinements in conventional DBS targeting or technology are unlikely to overcome these obstacles.

While basic research revealed significant obstacles to manipulating mesopontine neuronal populations, it also indicates circuits in this region are important in gait and balance, and likely relevant to PD. It is plausible that cell type specific manipulations in this region with optogenetic or chemogenetic methods might be useful.<sup>50</sup> That said, deploying these technologies in well-designed clinical experiments face a number of hurdles, not the least of which is a much firmer grasp of the neural circuitry controlling gait and posture is required. We need also as well to know how this circuitry is disrupted in PD.<sup>51</sup> At this point in time, human experimentation with PPN DBS should be reconsidered. Efforts should focus on sorting out precisely how the

PPN/MLR and their afferent and efferent connections work, on what dysfunctions are characteristic of PD, and on developing the technologies needed to rectify these dysfunctions in PD patients.

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