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Editorial

PPN-DBS: A utopic vision or a realistic perspective?

A special issue focusing on the pedunculopontine nucleus (PPN), also known as PPTg, a term advocated by the neurosurgeon who performed the first PPN implantation in a patient with PD (Mazzone et al., 2005), today, might appear as a dated topic. Nevertheless, the same goal has inspired our current efforts just as it did at the beginning of our pioneering attempts at the turn of the 21st century (Stefani et al., 2007), i.e., to answer the unmet needs of patients with Parkinson's disease (PD) (Galati and Stefani, 2015).

Boldness must be part of the job for a clinical scientist, and the initial evidence on the role of the PPN in the pathophysiology of gait in PD was enough to explore the safety of PPN implantation and the effects of its subsequent stimulation in humans (Galati et al., 2008; Mazzone et al., 2005; Stefani et al., 2007, 2012).

In fact, basic and clinical research on the PPN is still vibrant today. This observation emerges simply from looking at the trend of indexed papers in PubMed covering recent literature on the PPN's role in movement disorders: there have been approximately 200 papers in the last 5 years alone. It is beyond the scope of this SI to tackle them all; however, here, we highlight several studies that address fundamental issues. One important investigation by Caggiano et al. (2018) provides fresh evidence of brainstem control of locomotion adapted to behavioral needs in which glutamatergic neurons in the PPN, together with those in the cuneiform nucleus, support explorative locomotion and speed/gait selection. Interestingly, Bury et al. (2017) show increased mtDNA deletion levels in PPN cholinergic neurons from postmortem aged controls and PD patients.

Of course, promising data from experimental settings do not always translate into meaningful clinical successes. As a matter of fact, the PPN has yet to become a competitive target for stereotactic neurosurgery worldwide, and there appear to be no strategic investments or large ongoing trials. Thus, the PPN as a clinical target remains “experimental” even for atypical parkinsonism, such as progressive supranuclear palsy and despite its midbrain atrophy (Doshi et al., 2015).

Surprisingly, the basic role of the PPN has been under debate. For several years, the PPN was considered to be a critical cholinergic station. As outlined by Surmeier in this SI, one of the most compelling motivations to study PPN cholinergic neurons was the recognition that nearly half of these neurons may degenerate in patients before the onset of late stage PD (i.e., Hirsch et al., 1987). At present, the anatomy and function of the elongated PPN appears peculiarly complex (see Nowicki et al., this SI, synthesizing its proteiform afferent/efferent connections). From the molecular anatomy to the behavioral function, such complexity underlies the difficulties in explaining the implications of the PPN in the basal ganglia network of both the normal as well as the diseased brain.

Indeed, complex functional anatomy, which encompasses individual phenotypes, might explain conflicting clinical outcomes. Specifically, the host status (meaning cholinergic or glutamatergic or even GABAergic brainstem efficiency in any PD patient) might be the relevant factor that dictates the procedure's success or failure.

Our intention was neither to answer fully all the questions surrounding PPN-mediated influences on motor and nonmotor aspects of PD nor was it to fuel the crucial debate raised by the distinguished neurosurgical team in the UK (Zrinzo et al., 2008). When we assembled this SI, we aimed to focus on fundamental neurobiological questions. To this end, we have encouraged some prestigious colleagues, opinion leaders in either the clinics or laboratories studying the functions of the basal ganglia, to offer their insight. The 10 papers presented herein envision a modern interpretation of the PPN's role inside a functioning network and an impaired network augmented by DBS. Above all, those who remain anchored to the archaic vision based upon the dichotomy of the direct/indirect pathway, excluding pontine structures and extra-BG networks, will be left behind modern neuroscience.

On the other hand, current studies such as the presentation by Vitale and coauthors explore the participation of PPN neurons in the computation of reward prediction error with a new focus on the functional neuroanatomy of the glutamatergic connection between the cerebellum and the PPN. Likewise, the elegant contribution of Di Giovanni and colleagues investigates the nondopaminergic pathways, particularly the noradrenaline role and accounts for the observed placebo-like response and arousal-like PPN-mediated effects (Stefani et al., 2007). Further, the group led by Mena Segovia corroborates once more the critical influence subserved by PPN subregions on either motor or cognitive functions.

In addition to the conflicting findings on patients with advanced PD who display uncertain modulation of gait and postural balance (Thevathasan et al., 2017), the low-frequency stimulation of PPN caudal subregions is likely to stimulate residual output fibers and induce a positive sensation of “well-being” (Stefani et al., 2007); more alertness; sleep architecture benefits (Stefani et al., 2013); and some cognitive impairment amelioration. Morgante has brilliantly recapped this evidence (in this SI) with an updated review.

That said, Moro and coauthors authoritatively address this issue, here, elevating some warnings. They emphasize that i) low frequency PPN DBS could disinhibit PPN network activity in PD, improving gait freezing in a subcohort of PD patients; ii) alpha band activity is prominent in local field potentials recorded from PPN electrodes during PPN DBS, thus enhancing the allocation of attention; hence, iii) the pathophysiology of gait freezing may partly reflect impaired release of preprogrammed adjustments to locomotion; and finally iv) pre-programmed movement is impaired in gait freezing and improves with PPN DBS.

In other words, PPN DBS could facilitate attentional ‘switching’ between locomotion and pre-programmed adjustments. However, the

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considerable neurodegeneration of the PPN in the most advanced stages might impede such an effective DBS.

Therefore, targeting PPN regions should represent an alternative or add-on target in select cohorts such as those PD patients featuring postural instability at the onset; those “early-stim patients” developing severe nonresponding postural deficit after STN-DBS treatment; or, further, those patients with tau-related “parkinsonisms” including axial predominating signs and a relatively preserved pontine tegmentum.

We hope our SI piques your interest and curiosity. Possibly, it might raise some provocative questions, such as the following:

1 Does electrophysiological evidence always transpose into behavioral counterparts? The PPN has a constant interplay with the BG, affecting STN electrophysiological discharge including Beta band prominence (see Galati this SI and Galati et al., 2008). However, does this interplay reverberate into consistent changes of clinical score? Hard to define, but unlikely.

2 Are routine rodent PD models reliable? Alternatively, are the use of toxins in creating a model of PD implicitly biased? The PPN is very close to the substantia nigra pars compacta (SNc), where “toxin models induce inflammation, creating a potential artifact”. Furthermore, none of the animal models “faithfully reproduce the pattern of pathology in human PD patients”, particularly that seen outside of the SNc in the brainstem (Surmeier et al., 2017). It could be that PPN pathophysiology will never be recapitulated in a non-primate animal model of PD that only targets the SNc. Hence, seminal research on primates in this context (i.e., Nandi et al., 2002, Goetz et al., this SI) is needed.

3 Are available electro-catheters for DBS suited to selectively stimulate specific neuropils and demonstrate significant correlations with specific clinical items? Is it possible that the disappointing results obtained in PD patients reflect not the variability of the surgical approach or targeting but, instead, the individual pathology that any given PD patient bears? In this regard, some authors have begun suggesting alternative strategies using optogenetic or chemogenetic approaches that are more likely to produce consistent clinical outcomes. To this end, cell-specific promoters that would allow targeted gene delivery (e.g., Roseberry et al., 2016) need to be developed for human use.

A utopic vision or a realistic perspective?

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