Where and what is the PPN and what is its role in locomotion?

This scientific commentary refers to ‘The integrative role of the pedunculopontine nucleus in human gait’, by Lau et al. (doi:10.1093/brain/awv047).

Parkinson’s disease is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity and tremor, and dopamine replacement with levodopa remains the mainstay of treatment. In recent years, deep brain stimulation of the subthalamic nucleus (STN) has been widely used to treat tremor, rigidity and akinesia (Benabid et al., 2009). However as the disease progresses, axial symptoms such as postural instability and gait disturbances often emerge, in particular freezing of gait (FOG). These gait disturbances are poorly responsive to dopamine therapy and to deep brain stimulation of the STN (Ferraye et al., 2010). FOG is very debilitating, often leading to falls and having a severe impact on quality of life. Patients describe FOG as ‘like having feet that are glued to the floor’ and a 2010 workshop on FOG described it as ‘brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk’. Moreover, these disturbances of gait are responsive to sensory stimuli. For example, FOG is accentuated when approaching doorways and can be alleviated by the availability of targets for stepping. In this issue of Brain, Lau et al. (2015) explore the effects of deep brain stimulation on performance of a locomotor imagery task in patients with Parkinson’s disease, and reveal distinct roles for the STN and a second structure, the pedunculopontine nucleus (PPN), in the control of gait.

Gait is a complex motor behaviour that is controlled by networks of neurons in the spinal cord (Grillner, 2006). These are in turn modulated by brainstem centres responsible for gait initiation and control (Karachi et al., 2010). Of these the mesencephalic locomotor region, consisting of the PPN, the cuneiform and subcuneiform nuclei, is the most important. In animal models, stimulation of the PPN induces spontaneous locomotion, and lesions of the PPN result in gait deficits (Karachi et al., 2010). As a result, low frequency stimulation of the PPN is evolving as an intervention to control FOG and postural instability in late Parkinson’s disease.

While the results of stimulation and lesion studies are consistent with the role of the mesencephalic locomotor region in control of locomotion, how mesencephalic locomotor region activity controls locomotion and why gait is responsive to sensory stimulation remain unclear. In this issue of Brain, Lau et al. address these questions by making extracellular recordings from the PPN in six patients undergoing implantation of electrodes for the management of gait dysfunction. They compare these recordings with those from eight patients undergoing implantation in the STN. During imagined gait in a computer-generated task, strong increases are seen in single unit activity in the PPN. Postoperatively, field potential recordings reveal increases in alpha and beta power, with this activity beginning before the onset of imagined gait. By contrast, relatively fewer neurons in the STN respond to imagined gait. These findings are consistent with the emerging idea that PPN activity is not only engaged in control of gait, but is likely to be involved in motor planning or gait initiation. They also show that the PPN and STN have fundamentally different roles in gait control.

The results of Lau and co-workers are in general agreement with recent data that suggest that PPN activity is likely involved in motor planning (Jahn et al., 2008; Karachi et al., 2010; Tattersall et al., 2014). However, there are also key differences. Lau et al. appear to have explored only the rostral PPN (around the level of the inferior colliculus), limiting comparisons with previous studies that have explored a more longitudinally extensive region extending to the caudal PPN (around 4 mm below the pontomesencephalic line) (Thevathasan et al., 2012; Tattersall et al., 2014). The exact location of the
PPN is controversial. Moreover, the PPN is not a closed structure with demarcated boundaries, and is thus elusive to clinically available MRI (Zrinzo et al., 2008). Stereotactic atlases generally rely on cytoarchitectural techniques that identify only the rostral component containing the pars compacta. These atlases have guided many surgical centres to implant only the rostral PPN (Zrinzo et al., 2008; Ferraye et al., 2010). However, it is clear from studies using immunohistochemistry that PPN cholinergic neurons of the pars dissipata [revealed by staining with choline-acetyltransferase antibodies (ChAT5)] extend far more caudally (Mesulam et al., 1989). While it has not been established whether deep brain stimulation in the rostral and caudal PPN differ in efficacy for gait disorders, several studies have suggested that the caudal PPN may be a more effective site for relief of FOG (Thevathasan et al., 2012; Fu et al., 2014). The lack of clinical outcome data in patients implanted with PPN electrodes in the study by Lau et al. makes it difficult to evaluate the clinical relevance of the region they have explored.

Previous studies on the potential of deep brain stimulation in the PPN to improve gait disturbances have obtained widely varying results. An early study found limited benefit from PPN stimulation (Ferraye et al., 2010), whereas another group reported that PPN stimulation was very effective in managing FOG (Thevathasan et al., 2012). What accounts for these different conclusions? As discussed above, the PPN cannot be clearly identified in MRI scans, and target selection is clearly different for different groups. This variability makes it difficult to compare findings between groups in human subjects. This extends not only to the physiological response of the PPN, but also to the clinical response to stimulation. There is clearly a need for an agreement on the definition of the PPN as a clinical target for deep brain stimulation and for an anatomical definition of its boundaries.

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References

New criteria for Alzheimer’s disease: which, when and why?

This scientific commentary refers to ‘Prevalence and prognosis of Alzheimer’s disease at the mild cognitive impairment stage’ by Vos et al. (doi:10.1093/brain/awv029).

Until relatively recently, a clinical diagnosis of Alzheimer’s disease could only be made when an individual had acquired sufficient memory and other cognitive impairments to interfere with activities of daily living, and no more likely cause for their cognitive impairment was apparent. The prospect of targeted disease-modifying therapies predicted to have maximum effects when given early required diagnostic criteria that would both allow earlier disease detection, and be specific for Alzheimer pathology. The former led to the designation of ‘mild cognitive impairment’ (MCI) in individuals