populations? A clinical and polysomngraphic case-control study. Sleep Med 2013; 14: 788–94.
Luca G, Haba-Rubio J, Dauvilliers Y, Lammers GJ, Overeem S, Donjacour CE, et al. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. J Sleep Res 2013; 22: 482–95.
Manni R, Ratti PL. Terzaghi M. Secondary 'incidental' REM sleep behavior disorder: do we ever think of it? Sleep Med 2011; 12: S50–3.
Mayer G, Bitterlich M, Kuwert T, Ritt P, Stefan H. Ictal SPECT in patients with rapid eye movement sleep behavior disorder. Brain 2015; 138: 1263–70.
Mysliwiec V, O'Reilly B, Plochinski J, Kwon HP, Germain A, Roth BJ. Trauma associated sleep disorder: a proposed parasomnia emcompassing disruptive nocturnal behaviors, nighmares, and REM without atonia in trauma survivors. J Clin Sleep Med 2014; 10: 1143–8.
Postuma RB, Gagnon JF, Tuineaig M, Bertrand JA, Latreille V, Desjardins C, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? Sleep 2013; 36: 1579–85.
Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in *Sleep*. Sleep 2002; 25: 120–30.
Wing YK, Lam SP, Zhang J, Leung E, Ho CL, Chen S, et al. Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. Neurology 2015; 84: 516–522.

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, beta and gamma 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.

Francois Windels,[1] Wesley Thevathasan,[2] Peter Silburn[1] and Pankaj Sah[1]

1 *Queensland Brain Institute, The University of Queensland, Queensland 4072, Australia*

2 *Melbourne Brain Centre, Department of Medicine, Royal Melbourne Hospital, University of Melbourne and the Bionics Institute, Melbourne, Australia*

Correspondence to: Pankaj Sah,
E-mail: pankaj.sah@uq.edu.au

doi:10.1093/brain/awv059

References

Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009; 8: 67–81.

Ferraye MU, Debu B, Fraix V, Goetz L, Ardouin C, Yelnik J, et al. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. Brain 2010; 133 (Pt 1): 205–14.

Fu RZ, Naushahi MJ, Adams A, Mehta A, Bain PG, Pavese N, et al. Sub-caudal pedunculopontine nucleus (PPN) deep brain stimulation (DBS) best predicts improvements in freezing of gait questionnaire (FOGQ) scores in Parkinson's disease patients. Mov Disord 2014; 29 (Suppl 1): 1193.

Grillner S. Biological pattern generation: the cellular and computational logic of networks in motion. Neuron 2006; 52: 751–66.

Jahn K, Deutschlander A, Stephan T, Kalla R, Wiesmann M, Strupp M, et al. Imaging human supraspinal locomotor centers in brainstem and cerebellum. Neuroimage 2008; 39: 786–92.

Karachi C, Grabli D, Bernard FA, Tande D, Wattiez N, Belaid H, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest 2010; 120: 2745–54.

Lau B, Welter M-L, Belaid H, Fernandez-Vidal S, Bardinet E, Grabli D, et al. The integrative role of the pedunculopontine nucleus in human gait. Brain 2015; 138: 1284–96.

Mesulam MM, Geula C, Bothwell MA, Hersh LB. Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons. J Comp Neurol 1989; 283: 611–33.

Tattersall TL, Stratton PG, Coyne TJ, Cook R, Silberstein P, Silburn PA, et al. Imagined gait modulates neuronal network dynamics in the human pedunculopontine nucleus. Nat Neurosci 2014; 17: 449–54.

Thevathasan W, Cole MH, Graepel CL, Hyam JA, Jenkinson N, Brittain JS, et al. A spatiotemporal analysis of gait freezing and the impact of pedunculopontine nucleus stimulation. Brain 2012; 135 (Pt 5): 1446–54.

Zrinzo L, Zrinzo LV, Tisch S, Limousin PD, Yousry TA, Afshar F, et al. Stereotactic localization of the human pedunculopontine nucleus: atlas-based coordinates and validation of a magnetic resonance imaging protocol for direct localization. Brain 2008; 131 (Pt 6): 1588–98.

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