REM sleep behaviour disorder: a window on the sleeping brain

This scientific commentary refers to ‘Ictal SPECT in patients with rapid eye movement sleep behaviour disorder’, by Mayer et al. (doi:10.1093/brain/aww042).

REM sleep behaviour disorder (RBD) continues to serve as an increasingly instructive window on the sleeping brain. The identification of RBD in humans in 1986 was predicted by Michel Jouvet’s 1965 feline model produced by bilateral perilocus coeruleus lesions and subsequently replicated in the rat (Schenck et al., 2002).

Initially, human RBD was felt to be a curious and fascinating experiment in nature resulting in the isolated absence of atonia during REM sleep, permitting the ‘acting out of dreams’ (or, the ‘dreaming out of acts’). As more diverse groups of patients were studied, and as patients with RBD were followed over time, a number of interesting facts and correlations emerged. One of these was that the overwhelming majority (up to 90%) of patients with what initially appeared to be ‘idiopathic’ RBD would eventually develop a neurodegenerative disease (often following a delay of decades), particularly one of the synucleinopathies (Parkinson’s disease, dementia with Lewy bodies, or multiple system atrophy) (Iranzo et al., 2014). Furthermore, waking motor manifestations of bradykinesia and hypophonia in patients with comorbid Parkinson’s disease and RBD were markedly improved during movements and vocalizations within episodes of RBD (De Cock et al., 2007). Similar findings were reported for RBD associated with multiple system atrophy (De Cock et al., 2011), with enhanced facial expression, improved speech and faster/stronger movements in REM sleep compared to wakefulness. These improvements were unlikely to be due to enhanced dopamine transmission because patients with multiple system atrophy are poorly responsive to levodopa, suggesting that the movements in RBD are not influenced by extrapyramidal regions (i.e. they bypass the basal ganglia). In this issue of Brain, Mayer et al. use ‘ictal’ SPECT to study the pathways of RBD in vivo, and confirm that the basal ganglia are not activated during behavioural events in REM sleep (Mayer et al., 2015).

Because both RBD and narcolepsy/cataplexy are examples of state dissociation, RBD was sought, and duly found, in patients with narcolepsy/cataplexy. Indeed, a recent large study established that ~50% of patients with these conditions also show RBD (Luca et al., 2013). This association led to the identification of other similarities between narcolepsy and Parkinson’s disease including hyposmia, depression, constipation, and hyperechogenicity of the substantia nigra (Mayer et al., 2015). There is also the neuropathological suggestion of a higher-than-expected prevalence of Alzheimer’s disease and Parkinson’s disease in patients with narcolepsy, along with the clinical suggestion of an increased prevalence of Parkinson’s disease.

To study the pathways of RBD in vivo, Mayer et al. performed ‘ictal’ SPECT in two patients with idiopathic RBD, one with Parkinson’s disease with RBD, and two with narcolepsy/cataplexy with RBD. The ‘ictal’ SPECT activation pattern was identical in all patients irrespective of the underlying aetiology: activation of the bilateral premotor areas, the interhemispheric cleft, the peri-aqueductal area, the dorsal and ventral pons, and the anterior lobe of the cerebellum. The basal ganglia were spared in all these patients (in contrast to the involvement of the basal ganglia during wakefulness in Parkinson’s disease).

The most striking findings of Mayer et al. are: (i) the phenotypic expression of RBD in the ‘ictal’ SPECT activation pattern across a broad spectrum of REM sleep behaviours (simple, complex, aggressive, violent, sleep-talking and shouting) is largely identical in narcolepsy-, Parkinson’s disease-, and idiopathic RBD, despite the different underlying neurotransmitter abnormalities (hypocretin/orexin in narcolepsy; predominantly dopaminergic in Parkinson’s disease, although incomplete hypocretin cell loss has also been documented in Parkinson’s disease); (ii) the sparing or bypassing of the basal ganglia during REM sleep-related movements in patients with Parkinson’s disease and RBD explains the lack of hypokinesia during episodes of the sleep disorder—providing evidence for state dissociation of motor activity (which should serve as a reminder that motor phenomena in Parkinson’s disease may be exquisitely state-dependent); and (iii) the existence...
of a previously unsuspected overlap between narcolepsy/cataplexy and neurodegenerative disorders.

Despite the impressive findings, it should be noted that this initial study by Mayer et al. had a small sample size and a major gender discrepancy (75% female). Further studies are therefore needed with larger sample sizes and greater male representation—especially as idiopathic RBD and RBD with Parkinson’s disease are both male-predominant—across idiopathic and symptomatic subgroups (e.g. medication-induced, precipitated by neurological disorders). Also, the duration of illness (RBD, and any associated neurological disorder) should be considered in the data analyses, as different stages of disease progression could affect the pattern of neural circuitry activation in the ‘ictal’ SPECT scan, and in the other imaging methods advocated by Mayer and co-workers. The same SPECT scan methodology should also be used to examine REM sleep in controls in at least one study. Nevertheless, if future studies reveal the same pattern of brain activation, then the findings of Mayer et al. can be considered to represent a robust ‘brain signature’ of RBD. As stated by the authors, ‘investigations identifying neurotransmitters involved in the activation of this neural network need to be performed in the future’. This may be especially pertinent to antidepressant-induced RBD.

What more might be learned from RBD?

(i) There are a number of individuals without clinical manifestations of RBD who demonstrate REM sleep without atonia during polysomnographic studies. Therefore REM sleep without atonia is necessary but not sufficient to generate the full-blown RBD syndrome. What is, or are, the additional necessary lesions? This issue was addressed for the experimental feline model by the Morrison group (Schenck et al., 2002).

(ii) In support of the previous point, the two medications used most frequently to treat RBD (clonazepam and melatonin) do not restore normal REM sleep muscle atonia (although there is some suggestion that melatonin may do so partially). This raises the still-open question of the mechanism of action of these drugs in controlling the clinical features of RBD.

(iii) Antidepressant medications, particularly selective serotonin reuptake inhibitors and venlafaxine, may either cause or unmask REM sleep without atonia, and RBD. It has recently been shown that major depression per se (possibly as an early manifestation of a neurodegenerative disorder) may be a risk factor for RBD (Lam et al., 2013), and also that development of RBD symptoms among patients with major depressive disorder may represent an early phase of a-synucleinopathy neurodegeneration instead of being merely an antidepressant-induced condition (Wing et al., 2015). This provides four possible explanations for the medication/RBD association: the medication per se; the depression for which the medication was prescribed; both prior explanations (Postuma et al., 2013); or an underlying synucleinopathy predisposing both to RBD and to depression, with antidepressant medication precipitating overt RBD. Therefore, the mechanisms for drug- and depression-associated RBD remain to be fully elucidated.

(iv) There is growing evidence of a relationship between RBD and post-traumatic stress disorder (Manni et al., 2011). A recently described condition in which RBD-like behaviours begin acutely or subacutely following emotional trauma has been termed ‘trauma associated sleep disorder’ (Mysliwiec et al., 2014). What is the mechanism of RBD induced by psychic trauma?

(v) Do RBD behaviours represent ‘the acting out of dreams’ or, rather, ‘the dreaming out of acts’? In other words, to what extent is activation of the cerebral cortex and/or activation of brainstem motor pattern generators—with simultaneous ascending projections to the cortex and descending projections to the alpha spindle motor neurons—responsible for the dreams that are enacted or, conversely, the actions that are concurrently represented in the dreams?

(vi) Why the male predominance for those with RBD who progress to Parkinson’s disease?

(vii) What role, if any, does the cerebellum play in the underlying neurobiology and clinical manifestations of RBD? The findings from the Mayer et al. study, and in the literature cited by these authors, suggest that there is cerebellar involvement. This topic needs further investigation.

Clinical observations and experimental research findings add pieces to the puzzle of the nature of sleep and wakefulness, and underscore the value of close collaboration between clinicians and basic science researchers. The authors should be commended for having identified a most important piece of the puzzle.

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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 responses 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 laterally 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