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Ictal SPECT in patients with rapid eye movement sleep behaviour disorder

Yves Dauvilliers ¹ and Philippe Peigneux ²

1 Centre de Référence Nationale Maladie Rare – Narcolepsie et Hypersomnie Idiopathique, Département de Neurologie, Hôpital Gui-de-Chauliac, Inserm U1061, Montpellier, France

2 UR2NF - Neuropsychology and Functional Neuroimaging Research Unit at CRCN - Centre de Recherche Cognition et Neurosciences and UNI - ULB Neurosciences Institute, Université Libre de Bruxelles, Belgium

Correspondence to: Pr Yves Dauvilliers,
Service de Neurologie,
Hôpital Gui-de-Chauliac,
80 avenue Augustin Fliche,
34295 Montpellier cedex 5,
France
E-mail: ydauvilliers@yahoo.fr

Sir,
We have read with great interest the article entitled 'Ictal SPECT in patients with rapid eye movement sleep behaviour disorder' published March 2015 by Mayer et al. (2015) in *Brain*. In this article, the authors evidence brain regions activated during an episode of rapid eye movement (REM) sleep behaviour disorder (RBD) using ictal single photon emission tomography (SPECT). Four patients were included in this study: one with idiopathic RBD, one with RBD and Parkinson's disease and two with RBD and narcolepsy. Ictal SPECT in an RBD episode as compared to wakefulness revealed RBD-related activations in the bilateral premotor areas, the interhemispheric cleft, the periaqueductal area, the dorsal and ventral pons and the anterior lobe of the cerebellum in all patients, thus bypassing the basal ganglia. The authors also claim this to be the first study to report results with ictal SPECT in patients with idiopathic RBD, or associated with Parkinson's disease or narcolepsy. We here dispute this claim.

Indeed, in 2011 we published the first SPECT recording during a well-documented and controlled RBD episode associated with multiple system atrophy, in which we demonstrated a selectively increased perfusion in the supplementary motor area (Dauvilliers et al., 2011). We used the same technique as Mayer et al. (2015), i.e. ictal SPECT immediately (14 s) after the onset of a long (2-min duration) and complex RBD episode in a 54-year-

old right-handed man with a 3-year history of probable multiple system atrophy-cerebellar (predominance of cerebellar ataxia) (Dauvilliers et al., 2011). Dream-enacting behaviours were particularly frequent and violent in this patient, and confirmed by video-polysomnography that documented profound REM sleep disturbances with only 8% of REM sleep with atonia. Additionally, and at variance with the study of Mayer et al., we scanned in similar conditions two healthy control subjects matched for age and gender in both normal REM sleep (i.e. without RBD) and during wakefulness. In these controls, we found no perfusion changes in the supplementary motor area in REM sleep as compared to wakefulness. However, a higher perfusion was found in the anterior cingulate cortex both in the RBD and normal REM sleep states, a finding mostly related to the decreased perfusion in this area during wakefulness time. No perfusion changes were found in the brainstem. To sum up, both our own and the recent Mayer et al. studies have underlined a neural fingerprint (i.e. the activation of the cortical premotor supplementary area) associated with the generation of movements during an RBD episode, whether idiopathic or comorbid with Parkinson's disease, multiple system atrophy or narcolepsy (Dauvilliers et al., 2011; Mayer et al., 2015). Noticeably, another study previously reported decreased perfusion in the frontal lobe and in the pons in patients with idiopathic RBD scanned during symptomatic, but not

EEG-controlled RBD episodes, and without providing details on the methodology used (Shirakawa et al., 2002).

Other SPECT studies recording brain activity at wake time in idiopathic RBD reported increased perfusion in the pons, putamen and right hippocampus, together with decreased perfusion in fronto-temporo-parietal cortices (Mazza et al., 2006). Moreover, abnormal perfusion in the hippocampus was a predictor for the conversion risk to neurodegenerative disorders such as Parkinson's disease in these patients (Dang-Vu et al., 2012). Increased activity in a Parkinson's disease-related metabolic network was found in idiopathic RBD, especially in patients who converted to a progressive neurodegenerative syndrome during follow-up (Holtbernd et al., 2014). Finally, a specific RBD-related metabolic network was recently characterized during wakefulness using PET, showing increased activity in the pons, thalamus, medial frontal and sensorimotor areas, hippocampus, supramarginal and inferior temporal gyri, and posterior cerebellum, and decreased activity in occipital and superior temporal regions (Wu et al., 2014). These abnormal metabolic networks provided valuable markers of idiopathic RBD during wakefulness to identify patients at higher risk to develop neurodegenerative parkinsonism.

The current (Mayer et al., 2015) and our preceding (Dauvilliers et al., 2011) studies have emphasized a common motor pathway in RBD. They also both localized the motor generator responsible for dream-enacting behaviour in the supplementary motor area by bypassing the basal ganglia. Although the muscle atonia during REM sleep is induced by brainstem centres and more precisely by the sublaterodorsal tegmental nucleus REM-on neurons, recent evidence also suggests that descending projections of neurons from the motor cortex are involved in phasic activation (i.e. muscle twitches) and potentially complex and severe movements (i.e. RBD) during REM sleep (Du Beau et al., 2012; Luppi et al., 2013). The supplementary motor area is a key structure for behavioural planning, coordination, execution and speech production, and may subtend complex actions that are under internal control, such as the performance for a sequence of movements from memory, as opposed to movements guided by visual cues (Picard et al., 2003).

To conclude, involvement of the supplementary motor area as one of the key neural generators for abnormal movement production during RBD, whether comorbid or not, is turning out to be a major finding. This highlights a functional role of high-order motor cortical areas in generating movements during enacted dreams in RBD, when tonus inhibition is no longer efficient, and we are glad to see here with this new publication a confirmation of our previously published results (Dauvilliers et al., 2011).

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