Neuromelanin-sensitive imaging correlates of idiopathic rapid eye movement sleep behavior disorders

Mickael Ehrminger[1], Alice Latimier[2], Daniel Garcia-Lorenzo[3], Smaranda Leu-Semenescu[4], Marie Vidailhet[5], Isabelle Arnulf[4], and Stephane Lehericy[6]

[1]Ecole Normale Superieure, Paris, France, [2]Service des pathologies du sommeil, ICM - Institut du Cerveau et de la Moelle, Paris, France, [3]CENIR - Centre for NeuroImaging Research, ICM - Institut du Cerveau et de la Moelle, Paris, France, [4]Service des pathologies du sommeil, Hopital Pitie-Salpetriere, Paris, France, [5]Service de Neurologie, ICM - Institut du Cerveau et de la Moelle, Paris, France, [6]CENIR - Center for NeuroImaging Research, ICM - Institut du Cerveau et de la Moelle, Paris, France

Purpose. Rapid eye movement (REM) sleep behavior disorders (RBD) are non-dopaminergic symptoms of nocturnal violence that occur in isolation in patients with idiopathic RBD (iRBD). RBD is also a premotor sign of parkinsonism as it can precede the occurrence of motor signs by several years. RBD is thought to result from damage of the locus subcoeruleus, which controls muscle atonia during REM sleep in animal models [1]. The locus coeruleus/subcoeruleus complex (LCSC) contains glutamatergic, GABAergic and catecholaminergic neurons. Catecholaminergic neurons contain a pigment, neuromelanin, which presents paramagnetic T1-shortening effects resulting in bright signal in T1-weighted (T1-w) images [2]. Recently, the neuronal origin of RBD was related to damage of the LCSC in patients with Parkinson's disease (PD) [3]. Here we studied the role of the LCSC using neuromelanin-sensitive MRI in iRBD.

Materials & Methods. Fifteen patients with iRBD (age: 67.9 ± 7.2) and 16 age- and sex-matched healthy controls (age: 65.9 ± 4.8) were included in this study. All subjects gave written informed consent and the local ethics committee approved the study. A complete neurological and neuropsychological examination was performed. Sleep and nocturnal movements were monitored during a single night and the percentage of REM sleep without atonia (a progressive marker of RBD) was measured.

MR acquisitions were performed using a 3T TRIO 32-channel TIM system (Siemens, Germany) with a 32-channel receive head coil. Brain anatomical scans were acquired using a sagittal three-dimensional (3D) T1-w MPRAGE acquisition (TR/TE/TI: 4.18/2300/900 ms, 1 average, voxel size, 1×1×1 mm^3) and neuromelanin-sensitive (NST1) images that were acquired using two-dimensional axial turbo spin echo images (TR/TE/flip angle: 900ms/15ms/180°, NEX=3, voxel size: 0.4x0.4x3mm^3).

NST1 images were processed as described in [3]. The 3D T1-w images were corrected for intensity inhomogeneity and non-linear transformations towards the new ICBM template were estimated [4]. NST1 images were rigidly registered to the 3D T1-w volume. To calculate the signal intensity in the LCSC area, three regions were manually defined on the ICBM template. Combining rigid and non-linear transformations, the three regions were resampled onto the NST1 images. The first region was defined in the pontine tegmentum and was used as reference region to linearly normalize the slice-intensity to remove the inter-slice and inter-patient variability. The other two regions (one for each side) were defined as large boxes to ensure that the LCSC was included but avoiding any other structure that could be considered as "bright" in the NST1 images, such as the substantia nigra. Inside these boxes, we considered that the brightest region of 10-connected voxels found in this 3D region corresponded to the LCSC. We considered the intensity of the LCSC as the average of the intensities of the 10-connected voxel region. Values of the left and right LCSC were averaged to increase the SNR.

Results. iRBD patients showed a significant decrease in signal intensity compared to healthy volunteers (Kruskal-Wallis test, $p<0.01$) (Figures 1 and 2). In patients, we found a negative correlation between the intensity of the LCSC and the percentage of REM sleep without atonia ($r = -0.4652$, $df = 28$, $p < 0.01$) that remains significant after controlling for gender and age (Figure 3).

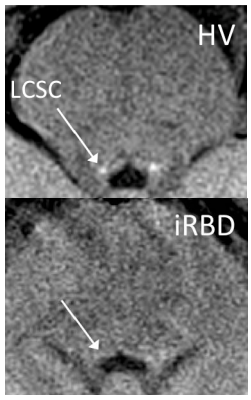

Figure 1. Axial 2D NST1 image at the level of the LCSC in a healthy volunteer (HV, up) and a patient with iRBD (down).

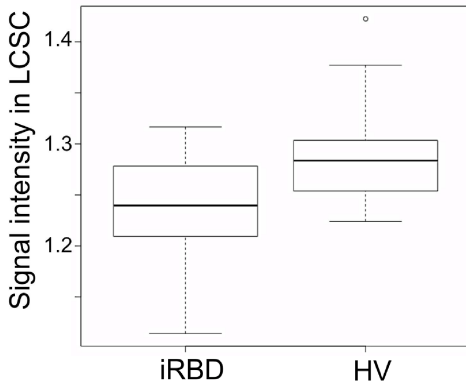

Figure 2. Box plot of the LCSC signal intensity in healthy volunteers (HV) and iRBD patients.

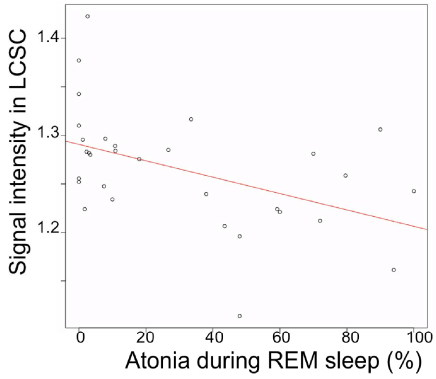

Figure 3. Correlation between Atonia during REM sleep and LCSC intensity in iRBD

Conclusion. Using neuromelanin-sensitive MRI techniques and careful clinical evaluation combined with sleep and video monitoring, we found evidence that the locus coeruleus/subcoeruleus complex is involved in the pathophysiology of iRBD and the control of atonia during REM sleep as already observed in patients with PD. Damage to the substantia nigra will be studied in these patients using R2* relaxometry. Longitudinal studies will help better understand the dynamics of degenerative changes from iRBD to Parkinsonism.

References [1] Luppi Sleep Medicine Reviews 2011;15:153-163 ; [2] Sasaki et al., Neuroreport, 2006;17:1215-1218 ; [3] Garcia-Lorenzo et al., Brain 2013;136:2120-2129 ; [4] Fonov et al. Neuroimage 2011; 54: 313–27

Acknowledgements. This work was supported by NRJ-12 Institut de France and the Investissements d'Avenir, IHU-A-ICM, Paris Institute of Translational neuroscience ANR-10-IAIHU-06.