Neuromelanin-sensitive imaging correlates with rapid eye movement sleep behavior disorders in Parkinson's disease

Daniel García-Lorenzo[1,2], Clarisse Longo Dos Santos[3,4], Cecile Gallea[1,2], Claire Ewenczyk[2,5], Habib Benali[6], Cyril Poupon[3,4], Smaranda Leu-Semenescu[2,7], Isabelle Arnulf[2,7], Marie Vidailhet[2,5], and Stephane Lehericy[1,2]

[1]CENIR, Institut du Cerveau et de la Moelle épinière - ICM, Paris, France, [2]Université Pierre Marie Curie, UMR-S975; Inserm U975; CNRS UMR 7225, Paris, France, [3]NeuroSpin, CEA, Gif-sur-Yvette, France, [4]IFR49, Gif-sur-Yvette, France, [5]Fédération de Neurologie, Pitié-Salpêtrière, Paris, France, [6]Université Pierre Marie Curie, Inserm U678, Paris, France, [7]Service des pathologies du sommeil, Pitié-Salpêtrière, Paris, France

Purpose. In Parkinson's disease (PD), rapid eye movement (REM) sleep behavior disorders (RBD) are early, non-dopaminergic symptoms of nocturnal violence that can precede the occurrence of parkinsonism by several years. The exact neuronal origin of RBD in PD is not precisely known, but the locus subcoeruleus controls muscle atonia during REM sleep in animal models. Recently, diffusion MRI changes were localized in the midbrain tegmentum, rostral pons and pontine reticular formation in patients with idiopathic RBD [1]. Neurons of the locus coeruleus/subcoeruleus complex (LCSC) are noradrenergic neurons that contain a pigment, neuromelanin, which presents paramagnetic T1-shortening effects. In patients with Parkinson's disease, loss of neuromelanin-containing neurons was detected in the LCSC area using neuromelanin-sensitive imaging [2]. Here we studied the relation between the intensity of the LCSC and RBD in PD patients.

Materials & Methods. Forty-one patients with PD (age: 60.3 ± 9.7) and 22 age- and sex-matched healthy volunteers were included in this study. All subjects gave written informed consent and the study was approved by the local ethics committee. A complete neurological and neuropsychological examination was performed. Sleep and nocturnal movements were monitored during a single night in the sleep unit in order to determine the presence or absence of RBD and measure the percentage of REM sleep without atonia (a progressive marker of RBD).

MR acquisitions were performed using a 3T TRIO 32-channel TIM system (Siemens, Germany) with a 12-channel receive head coil. Brain anatomical scans were acquired using a sagittal 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 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). This acquisition was repeated twice using the exact same parameters. Five patients and three control subjects were removed from this study due to severe movement during the acquisition.

Each neuromelanin-sensitive T1-weighted (NST1) image was processed independently. The 3D T1-weighted images were corrected for intensity inhomogeneity and non-linear transformations towards the new ICBM template [3] were estimated. Each NST1 image was rigidly registered to the 3D MPRAGE T1-weighted volume. To calculate the signal intensity in the LCSC area, 3 regions were manually defined on the ICBM template. Combining rigid and non-linear transformations, the 3 regions were resampled onto the 2D NST1 images (Figure 1). 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.

Results. No significant difference was found between the intensities in the first and the second scans (paired t-test p=0.83). A strong correlation was found between the intensities of the left and right LCSC (r = 0.76, p<1e-10). We averaged, left and right values from the two scans to increase the SNR of the LCSC intensity. RBD patients showed a significant decrease in signal intensity compared to both healthy controls and non-RBD patients (kruskal-wallis test corrected using the tukey-kramer method, p<0.05). There was no difference in LCSC mean intensity between the non-RBD patients and the healthy controls. In patients, we found a negative correlation between the intensity of the LCSC and the percentage of REM sleep without atonia (-0.41, p <0.05), which remains significant after controlling for gender and age.

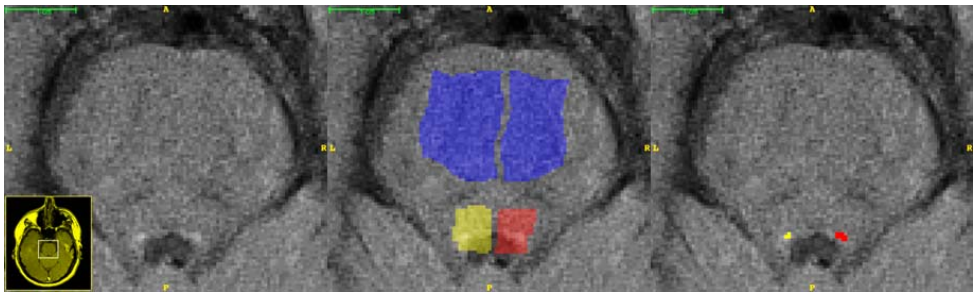

Figure 1. Left: axial 2D spin echo image passing at the level of the LC. Middle: regions of interest used to calculate signal intensity within the LC area: region for the slice normalization (blue), bounding box for maximum search in the left (red) and right (yellow) LC. Right: voxels of maximum signal intensity in the left (red) and right (yellow) LC area.

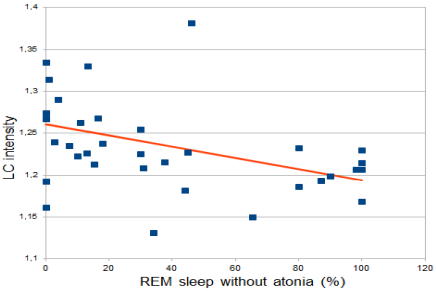

Figure 2. Correlation between REM sleep without atonia and LCSC intensity for the PD group

Conclusion. Using neuromelanin-sensitive MRI techniques and careful clinical evaluation combined with sleep and video monitoring, we found clear evidence that the locus coeruleus/subcoeruleus complex is involved in the pathophysiology of RBD and control of atonia during REM sleep. This technique should be now tested in idiopathic RBD for predicting PD. Refinement of the technique may help distinguish the locus coeruleus and subcoeruleus.

References. [1] Scherfler et al. 2010 Ann Neurol 69:400-407 ; [2] Sasaki et al., 2006,Neuroreport, 17:1215-1218 ; [3] Fonov 2011 Neuroimage 54(1):313-327

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