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Longitudinal follow-up of brain metabolism in rat models of progressive Parkinson's disease using Magnetic Resonance Spectroscopy Imaging.

C. Chassain¹, C. Melon², G. Pages³, Y. Le Fur⁴, P. Salin², L. Kerkerian-Le Goff², F. Durif^{5,6}.

Purpose / Introduction

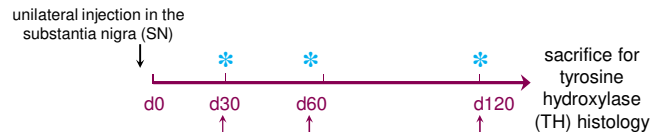
Parkinson's disease (PD) is characterized by: **i)** selective and progressive loss of nigral dopamine (DA) neurons, **ii)** unilateral to bilateral evolution pattern and **iii)** late appearance of motor deficits ($\geq 50\%$ of DA neurons have degenerated).

The development of animal models mimicking these features has opened new possibilities to study the disease's evolution. Here, longitudinal **magnetic resonance spectroscopy imaging** was used to **follow up metabolites distribution** in key basal ganglia components in two rat models of progressive PD.

Objective: provide novel insights onto the pathological alterations associated with the progression of the neurodegenerative process.

Subjects and Methods:

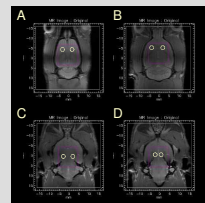
❖ Experimental design:



- n=7 rats in each group
- Group 1: injection of the substrate inhibitor of excitatory amino acid transporters (EAATs) = PDC (300 nmol)¹
- Group 2: injection of α -synuclein (1 μ L of the recombinant adeno-associated virus vectors (1.5x10¹³ vg/mL))
- Group 3: sham= injection of the vehicle
- in vivo MRSI:**
 - 11.7 T (Bruker BioSpec 117/16 Ultra Shielded Refrigerated system)
 - circular polarized ¹H RF coil for excitation and a head rat surface coil for signal reception.
- * Behavior test = cylinder test
- analysis of the symmetry/asymmetry of their forepaw use during 5 min.

❖ NMR experiments:

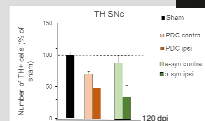
- Coronal images = fast spin echo T_2 -weighted RARE; 256x256; 2 mm slice thickness
- MRSI acquisition = CSI with a semi-LASER voxel volume selection (dimensions in mm: FOV 32x32x2, voxel size = 10x10x2, image size = 20x20, resolution = 1.6x1.6x2, TR = 2000ms, TE = 24ms, VAPOR for water suppression).



T2 coronal MRI slices covering the motor cortex (Cx), the dorsal striatum (STR), subthalamic nucleus (STN) and substantia nigra (SN) in A, B, C and D respectively. CSI voxels are in purple. Yellow circles are voxels for each structure at right and left.

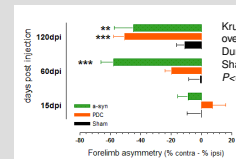
Results

TH immunohistochemistry in SN of an α -syn rat.



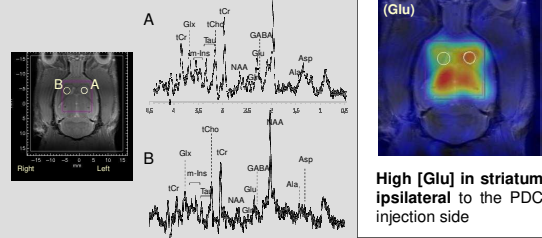
Kruskal-Wallis ANOVA, overall $P < 0.0001$, and Dunn's post-hoc test vs Sham: PDC ipsi $P = 0.0025$ and α -syn ipsi $P = 0.0008$.

Cylinder test.

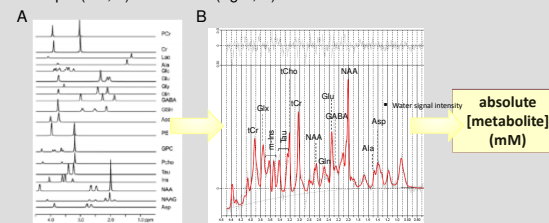


Kruskal-Wallis ANOVA, overall $P < 0.0001$, and Dunn's post-hoc test vs Sham: PDC ipsi $P < 0.01$ and α -syn ipsi $P < 0.001$.

MRSI example: acquisition on striata of a PDC PD rat model

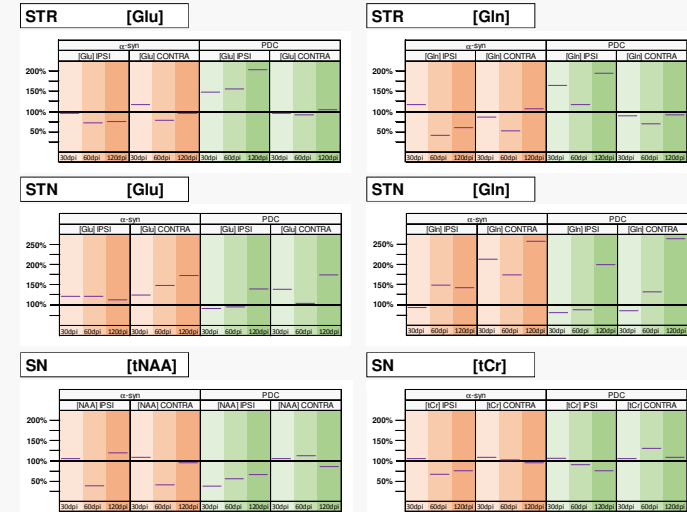


MRSI data are processed under CSIAP0². A metabolite map is generated. Spectra from ipsi (left, A) and contra (right, B) striata of the side of lesion are extracted.



- (A). Decomposition basis set to fit the NMR spectra in LCModel³.
- (B). Top: residual signal between the experimental and fitted spectra. Bottom: overlap of the experimental (grey) and fitted spectra (red). The thin signal under the experimental spectrum is the baseline spline estimate.

Illustration of the evolution of selected metabolite concentrations (as % of SHAM):



Conclusions

- ❖ MRSI = useful technique for **longitudinal characterization of metabolite profiles** in animal models of PD.
- ❖ **specificities** of the neurochemical changes within key basal ganglia components in the two PD rat models: the well-established α -synuclein and a new one, the PDC model.
- ❖ Uni- to bilateral progression of neurodegeneration in the PDC model: involvement of the **subthalamic nucleus contralateral** to the PDC injection side.

1. Assous et al. Neurobiol. 2014;65:69-81
2. Le Fur et al. Magn Reson Mater Phys. 2010;23(1):23-30.
3. Provencher. Magn Reson Med. 1993;30(6):672-679.

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