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

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Purpose / Introduction

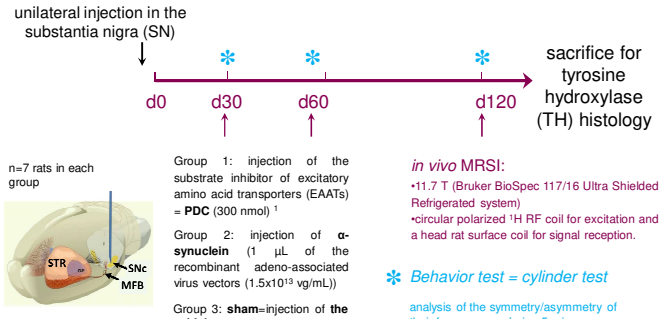
Parkinson's disease (PD) is characterized by: **i)** selective and progressive loss of nigral dopamine (DA) neurons, **ii)** unilateral to bilateral evolution pattern and **iii)** late appearance of motor deficits (≥50% of DA neurons have degenerated).

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:



Group 1: injection of the substrate inhibitor of excitatory amino acid transporters (EAATs) = **PDC** (300 nmol) [1]

Group 2: injection of **α-synuclein** (1 µL of the recombinant adeno-associated virus vectors (1.5x10[13] vg/mL))

Group 3: **sham**=injection of **the vehicle**

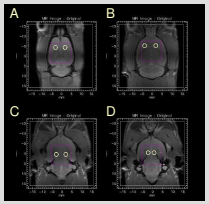
in vivo MRSI:
- 11.7 T (Bruker BioSpec 117/16 Ultra Shielded Refrigerated system)
- circular polarized ^{1}H RF coil for excitation and a head rat surface coil for signal reception.

✻ *Behavior test = cylinder test*

analysis of the symmetry/asymmetry of their forepaw use during 5 min.

❖ NMR experiments:

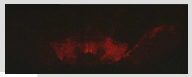
- Coronal images = fast spin echo T_2-weighted RARE; 256x256; 2 mm slice thickness
- MRSI acquisition = CSI with a semi-LASER voxel volume selection (dimensions in mm: FOV 32x32x2, voxel size = 10x10x2, image size = 20x20, resolution = 1.6x1.6x2, TR = 2000ms, TE = 24ms, VAPOR for water suppression).

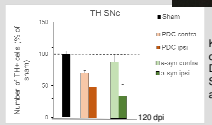


T2 coronal MRI slices covering the motor cortex (Cx), the dorsal striatum (STR), subthalamic nucleus (STN) and substantia nigra (SN) in A, B, C and D respectively.
CSI voxels are in purple. Yellow circles are voxels for each structure at right and left.

Results

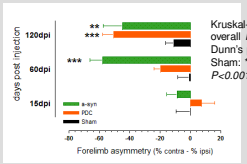
TH immunohistochemistry in SN of an α-syn rat.





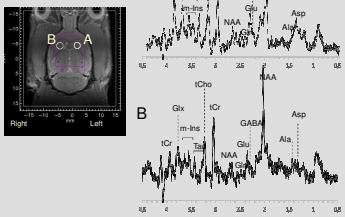
Kruskal-Wallis ANOVA, overall *P<0.0001*, and Dunn's post-hoc test vs Sham: PDC ipsi *P=0.0025* and α-syn ipsi *P=0.0008*.

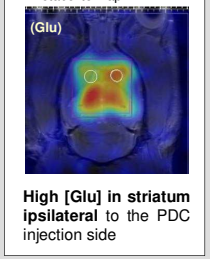
Cylinder test.



Kruskal-Wallis ANOVA, overall *P<0.0001*, and Dunn's post-hoc test vs Sham: ** *P<0.01* and *** *P<0.001*.

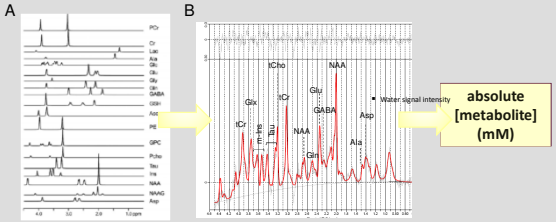
MRSI example: acquisition on striata of a PDC PD rat model





High [Glu] in striatum ipsilateral to the PDC injection side

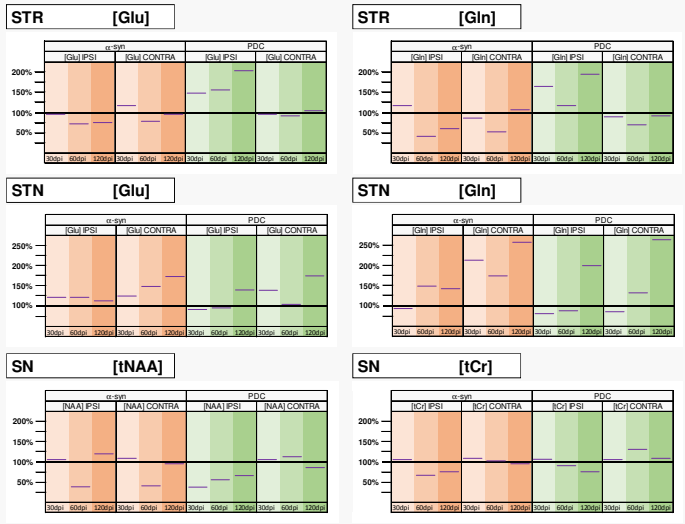
MRSI data are processed under CSIAPO[2]. A metabolite map is generated. Spectra from ipsi (left, A) and contro (right, B) striata of the side of lesion are extracted.



(A). Decomposition basis set to fit the NMR spectra in LCModel [3].

(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 Phy. 2010;23(1):23–30.
3. Provencher. Magn Reson Med. 1993;30(6):672–679.

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