# Longitudinal voxel-wise mapping of alpha-synuclein-induced brain pathology in a mouse model of Parkinson's Disease

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## Introduction

The mechanisms underlying Parkinson's Disease (PD) pathology have not yet been elucidated. Recent evidence suggests aggregated misfolded alpha-synuclein (a primary component of Lewy bodies, [aSyn]), may propagate in a prion-like manner, mediating the spread of pathology and contributing to PD progression. Using an aSyn propagation mouse model of PD, with a known locus of pathology, we longitudinally examined voxel-wise aSyn-induced changes in anatomy using magnetic resonance imaging (MRI).

## Methods

### Study Design

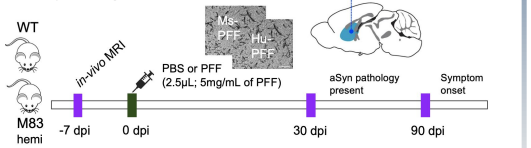


**Figure 1.** 11-week old wild-type (WT) and hemizygous M83 aSyn$^{A53T}$ transgenic mice (Giasson et al. 2002) received an injection of either mouse [Ms-] or human [Hu-] preformed fibrils [PFF] of aSyn, or phosphate buffered saline (PBS; control group) in the right striatum (n~10 mice per group per genotype per sex). T1-weighted MRI images (FLASH (Fast Low Angle SHot),TR/TE 20 ms/4.5 ms, 100 µm isotropic voxels, scan time= 14 min, flip angle=20°on a Bruker 7T preclinical scanner with 30 cm bore with AVANCE electronics) were acquired at -7, 30 and 90 days post-injection.

### MRI-derived atrophy: Deformation-based Morphometry (DBM)

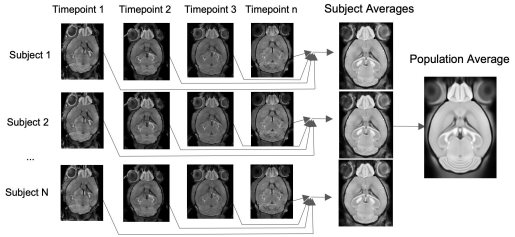


**Figure 2.** Brain atrophy was assessed using DBM to measure nonlinear differences between groups (Lerch et al., 2011). Mice brains are registered together through a series of linear and nonlinear registration steps to create a group-wise average. The deformation fields map the minimum deformation required at a voxel-level to map each subject to the average neuroanatomy of the group. Jacobian determinants are used to measure local anatomical differences; either expansions or contractions, and are dependent of the magnitude of the deformation at each voxel. Subject-level and population averages obtained with 2-level model building (https://github.com/cobralab/twolevel_ants_dbm).

## Results

### 1) Effect of aSyn PFF-induced pathology in M83 mouse model

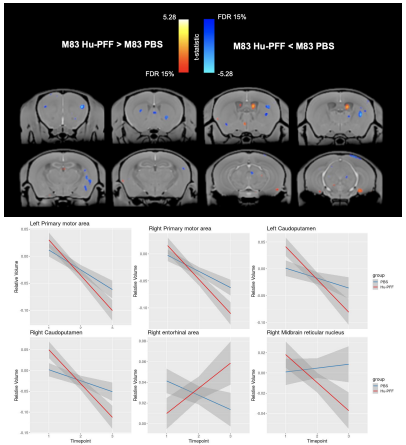


**Figure 3.** Widespread atrophy occurring for M83 Hu-PFF compared to M83 PBS injected mice; warmer colors describe voxels that are larger for the Hu-PFF mice compared to the saline controls, whereas cooler colours describe voxel decreases. Hu-PFF induced atrophy was observed for the injection site as well as connecting regions (red lines represent M83 Hu-PFF and blue lines represent M83 PBS-injected mice).

### 2) Is Ms-PFF sufficient to cause pathology? → WT Ms-PFF vs WT PBS

(no significant differences survive FDR correction)

#### a) Effect of mouse inoculum on genotype

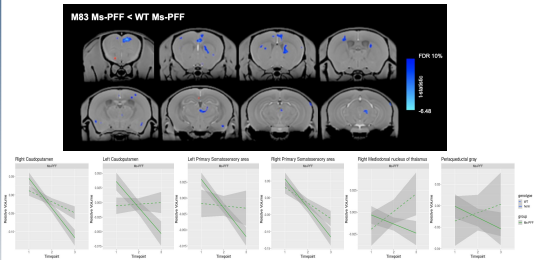


**Figure 4.** Atrophy as a result of having endogenous pathological aSyn (ie having the mutated A53T transgene) for Ms-PFF injected mice was observed for the injection site as well as connecting regions. Green lines represent Ms-PFF injected mice such that the dotted lines represent WT and solid lines represent M83 mice.

#### b) Effect of mouse inoculum in PD model

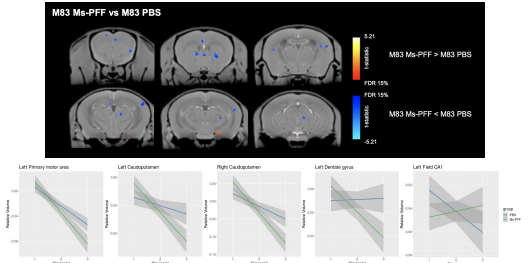


**Figure 5.** Widespread volume decreases were observed for M83 Ms-PFF injected mice compared to M83 PBS mice, occurring beyond the injection site, with volume increases observed for voxels in the contralateral field CA1 region. Green lines represent M83 Ms-PFF injected and blue lines represent M83 PBS-injected mice.

### 3) Effect of aSyn species (Hu- vs Ms-PFF) on the starting material (ie genotype)

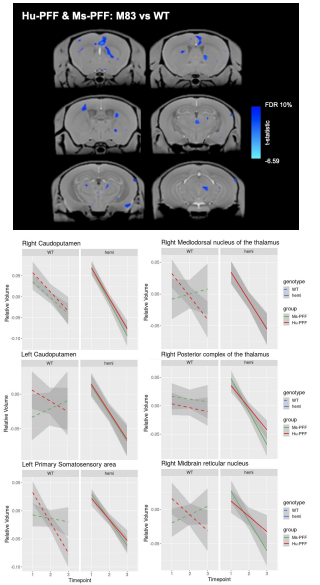


**Figure 6.** Effect on Hu- vs Ms-PFF on M83 model. While we do not observe any significant differences between M83 Ms- vs Hu-PFF, significant differences between M83 and WT mice, regardless of the source of the PFF were observed, such that the M83 mice that received either Ms- or Hu-PFF exhibited more atrophy compared to their WT counterparts.

## References


- Giasson et al. (2002). Neuronal α-synucleinopathy with severe movement disorder in mice expressing A53T human α-synuclein. *Neuron*
- Lerch et al. (2011). MRI phenotyping of genetically altered mice. In Magnetic Resonance Neuroimaging (pp. 349-361). *Humana Press.*
- Luk et al. (2012a). Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. *Journal of Experimental Medicine*
- Luk et al. (2012b). Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science*


## Summary of Results

- The inoculation of PFFs gives rise to widespread patterns of PFF-induced brain atrophy, particularly involving regions that project to, or receive input from the injection site.
- The presence of the mutation appears to further instigate the observed degeneration.
- Whole brain network patterns of aSyn PFF-induced brain atrophy along with cellular markers of pathology are currently being performed to characterize a signature of network spreading and disease progression.


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