Sex specific disease progression patterns in a mouse model of synucleinopathy

Stephanie Tullo[1,2], Daniel Gallino[2], Janice Park[2], Megan Park[2], Kristie Mar[2], Esther del Cid-Pellitero[3], Edward A. Fon[3], M. Mallar Chakravarty[1,2,4,5]

[1]Integrated Program in Neuroscience, McGill University, Montreal, Canada; [2]Douglas Research Center, Verdun, Canada; [3]Montreal Neurological Institute, Montreal, Canada; [4]Department of Biological & Biomedical Engineering, McGill University, Montreal, Canada; [5]Department of Psychiatry, McGill University, Montreal, Quebec, Canada

Introduction

While sex-related differences in Parkinson's disease (PD) are well-described, with prevalence and PD onset significantly higher and earlier in men compared to women, these differences remain poorly understood. While clinical profile of symptomatology also seems to differ among the sexes, there is little information on sex differences in the patterns of neurodegeneration, and findings are mixed on sex differences related to disease progression.

Methods

1) Experimental Design

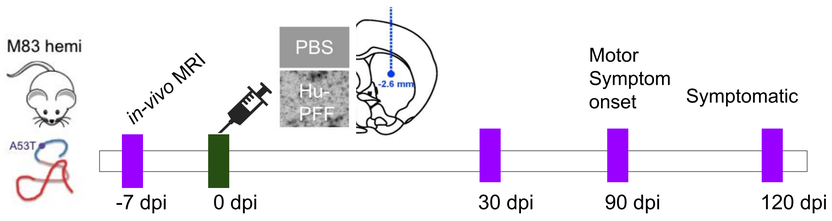
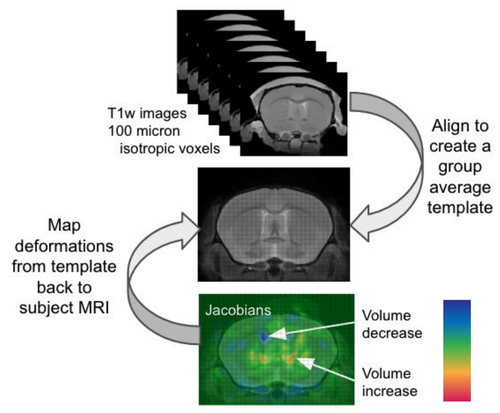


Figure 1. Hemizygous M83 aSynA53T transgenic mice (Giasson et al., 2002) received an injection of human alpha-synuclein (aSyn) preformed fibril (Hu-PFF) or phosphate buffered saline (PBS; control group) in the right dorsal striatum (n~8 mice/group/sex/time point).

90 dpi			
	PBS	Hu-PFF	Total
M	21	23	44
F	23	20	43

120 dpi			
	PBS	Hu-PFF	Total
M	9	5	14
F	9	8	17

2) Pathology measures: Deformation-based Morphometry (DBM)



3) Pathology brain patterns: Non-negative matrix factorization

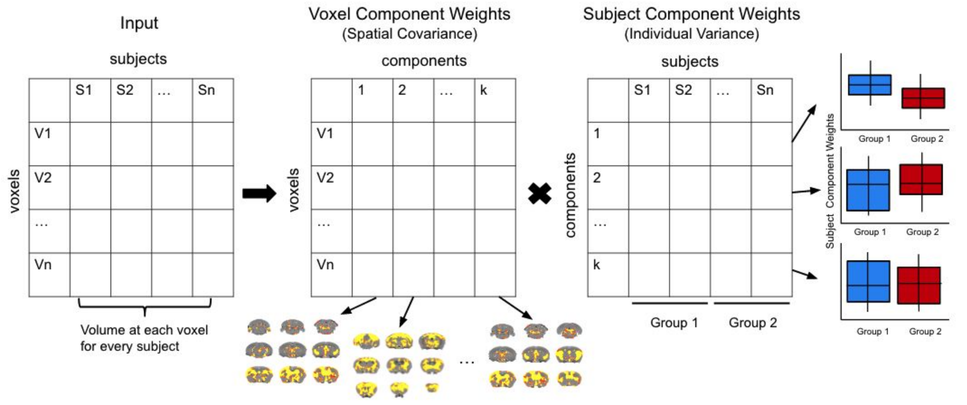


Figure 3. Voxel-wise whole brain patterns were obtained using orthogonal projective NMF (Patel et al., 2020). NMF decomposes an input matrix (composed of the ratio values and Jacobians (volumes) at each voxel for each subject) into two matrices; 1) component weights (k=6), which describes clusters of voxels sharing a covariance pattern, and 2) subject weights, which describes how each subject loads onto each pattern. The spatial pattern of voxel scores for each component were plotted onto the average template. Injection group differences in subject weights for each component metric were assessed using general linear models.

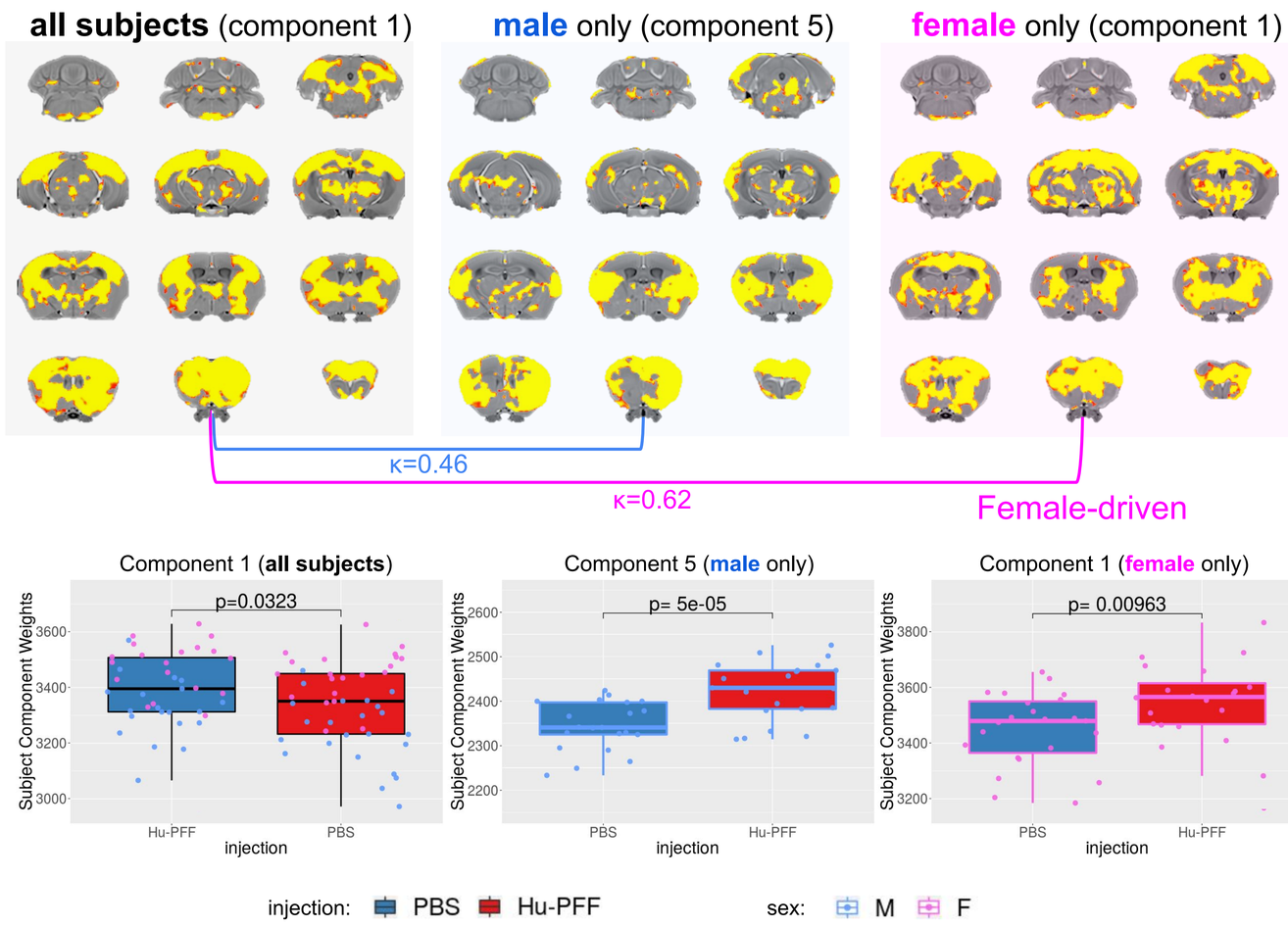
Figure 2. Voxel-wise volume measures were derived from deformation based morphometry of T1-weighted MRI images (100 μm^3 isotropic voxels; Bruker 7T) acquired at 30, 90 and 120 days post-injection (dpi). Mice brains are registered together through a series of linear and nonlinear registration steps to a group template. The deformation fields map the minimum deformation required at a voxel-level to map each subject to the average neuroanatomy of the group. These alterations could either be expansions or contractions and are dependent of the magnitude of the deformation at each voxel.

Results

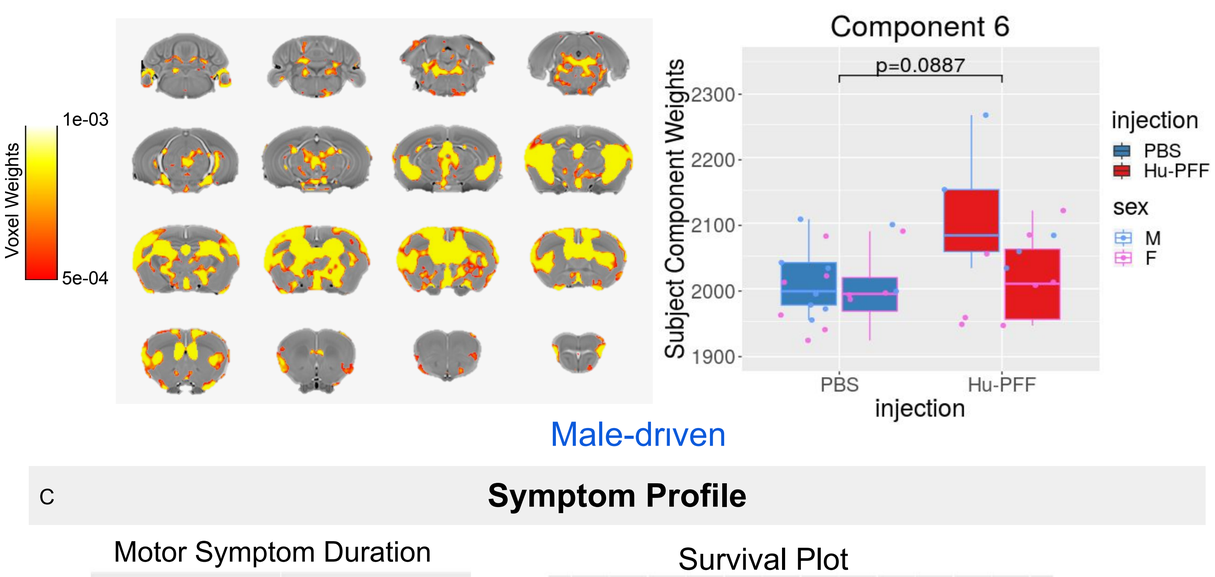
Across disease progression

Figure 4. Sex differences in PFF-induced brain pathology examined using voxel-wise volumetric trajectories over time. [A] Coronal slices of the mouse brain (from anterior to posterior from top left to bottom right) with t-statistical map overlay demonstrating the effects of injection and sex in M83 hemizygous mice. Colour map describes the slope (injection by sex interaction). [B] Plot of relative volume change (mm^3) over the four time points (-7, 30, 90 and 120 days post-injection) for a peak voxel in the injection site (right striatum); solid line for PBS-injected mice, dashed line for human PFF-injected mice, blue for male and red for female mice. Volumetric decline observed for Hu-PFF injected mice (compared to PBS injected mice), with steepest rate of decline for male PFF-injected mice (blue dashed line).interaction was observed whereby male Hu-PFF-injected mice had lower survival rates (p=0.0015; not shown).

A Pre-motor symptomatology (90 dpi)



B Post-motor symptom onset (120 dpi)



C Symptom Profile

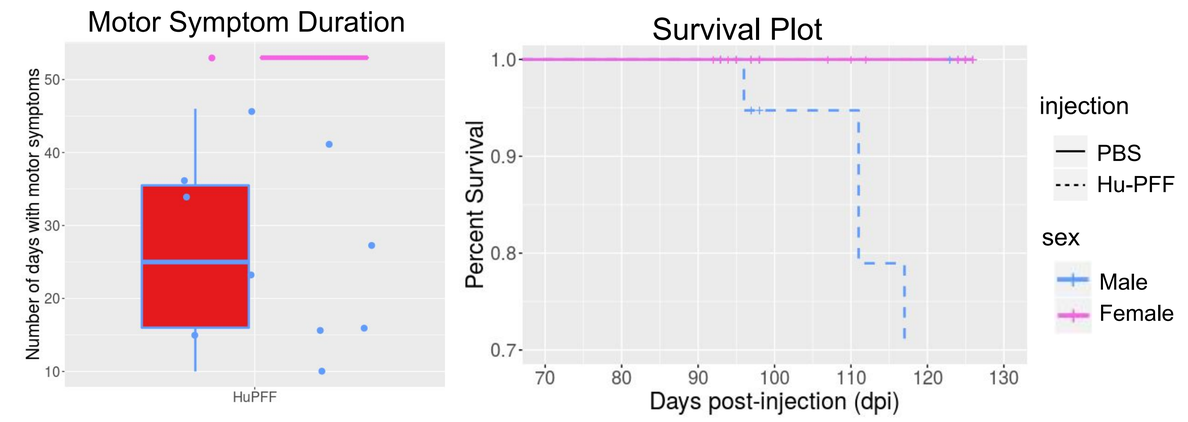


Figure 5. Sex specific disease progression patterns at pre- and post-motor symptom onset. [A] NMF decomposition at 90 dpi (pre-motor symptom onset) for three separate NMFs (all subjects (n=87) versus males only (n=44) versus females only (n=43)); k=6 components. Significant group differences in subject component weights were observed for only one of six components for each of the three NMF runs (component 1, 5, and 1 respectively). The spatial pattern of voxel weights (denoted by the colour map) plotted onto the mouse brain, depicts patterns of voxels sharing a similar covariance pattern. Dice-kappa overlay score was used to examine the spatial similarity between the three spatial patterns; higher kappas denote greater overlap. The greatest overlap with the all subject NMF component was with the female-only spatial component (κ=0.62), thus suggesting that the all subject component is predominantly female driven, although observing no statistical significance of injection group by sex interaction for the subject weights for the all subject component 1. [B] NMF decomposition at 120 dpi (post-motor symptom onset) (k=6 components; n=32; component 6). Plot of subject weights shows marginal significance of injection and sex (p=0.088) for the subject weights of the male PFF-injected mice (red filled with blue outline boxplot). [C] Sex differences in terms of duration of motor symptoms (from first day to endpoint day) for M83 Hu-PFF mice (red boxplots; blue outline for male and pink outlined for female mice). Percent survival of the mice plotted across the days post-injection (dpi). Almost 30% of the male Hu-PFF-injected mice (blue dashed line) succumbed to their disease progression a couple days prior to the 120 dpi time point (group by sex interaction; male Hu-PFF-injected mice had lower survival rates; p=0.0015).

Summary of Results

Differential impact of sex on clinical features of synucleinopathies:

- PFF-injected **females** showing a more benign phenotype while displaying greater and more accelerated neurodegeneration at early stages, prior to symptomatology/peri- symptom onset.
- Post-symptom onset, **males** developed widespread pathology accompanied by a more severe disease phenotype.
- PFF-injected **males** succumbed to their symptoms at significantly higher and faster rates than their female counterparts.

These findings support the idea that PD development may involve different mechanisms, yielding distinct prognosis between the sexes, which may have implications for research into neuroprotection and sex-specific analyses in pre-clinical drug trials.

References

- Giasson et al. (2002). Neuronal α-synucleinopathy with severe movement disorder in mice expressing A53T human α-synuclein. *Neuron*, 34(4), 521-533.
- Jurado-Coronel et al. (2018). Sex differences in Parkinson's disease: features on clinical symptoms, treatment outcome, sexual hormones and genetics. *Frontiers in neuroendocrinology*, 50, 18-30.
- Luk et al. (2012). Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. *Journal of Experimental Medicine*, 209(5), 975-986.
- Patel et al. (2020). Investigating microstructural variation in the human hippocampus using non-negative matrix factorization. *Neuroimage*, 207, 116348.

Funding Sources

HEALTHY BRAINS FOR HEALTHY LIVES
Fonds de recherche Santé Québec
CIHR IRSC
NSERC CRSNG

Contact Info

stephanie.tullo@mail.mcgill.ca
@stephanie_tullo
>CoBrALab