

# Progress Toward an Animal Model of PSP

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# Why do we need an Animal Model?

- **Drug Discovery**

- Reverse/Stop Protein Aggregation (Tauopathy)
  - improve longevity
- Symptomology → improve quality of life

- **Progressive Model**

- Examine the Spread of Disease within the Brain
  - understand disease progress
- Early Indicators (Biomarkers) → early detection

# What should this Model Look Like?

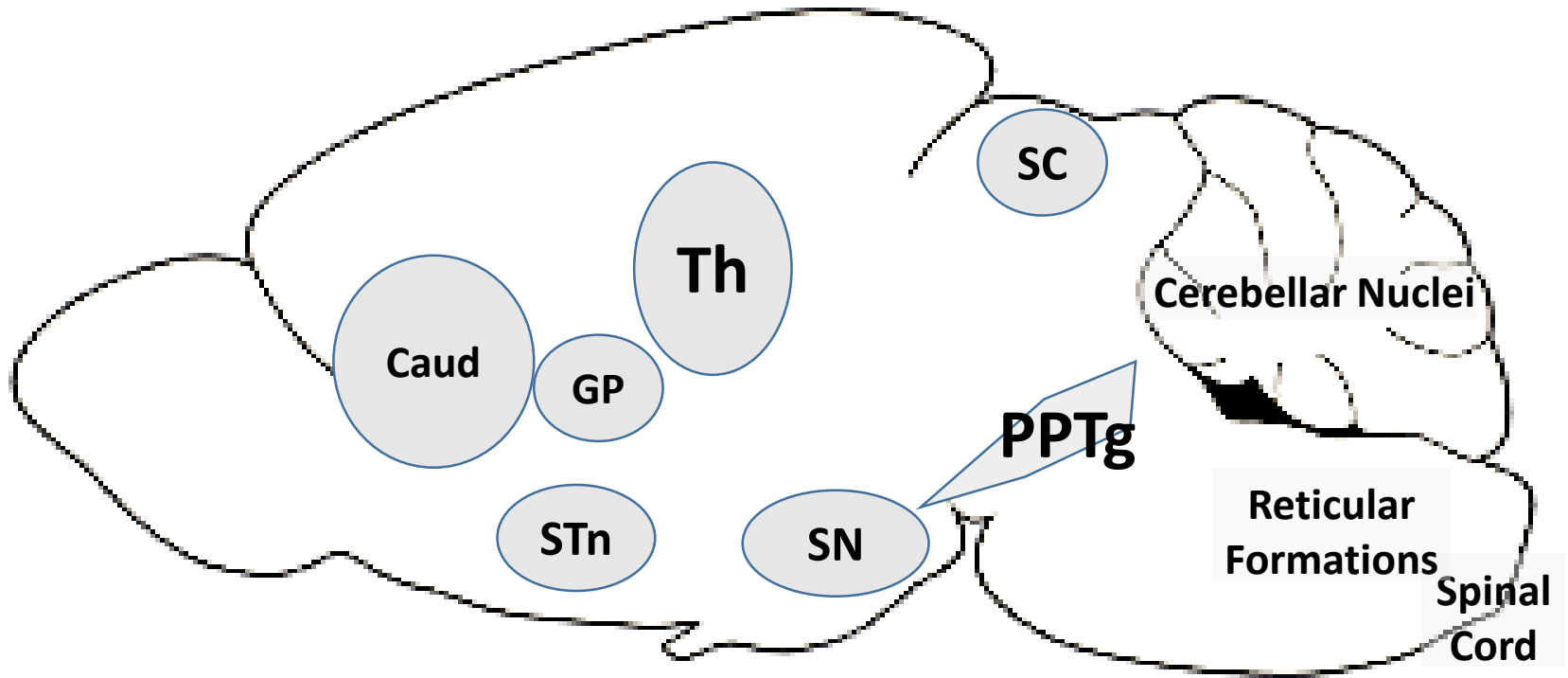
## **Postmortem Brain Characteristics:**

- Pedunculopontine Tegmentum Loss
- Ventricular Enlargement
- Substantia Nigra Loss
- Abnormal Protein Aggregates (Tauopathy)

## **Behavioral:**

- Startle Deficits
- Motor Deficits
- Cognitive Deficits

# Hypothesized Spread of Tau in PSP



Caud = Caudate

GP = Globus Pallidus

PPTg = Pedunculopontine Tegmentum

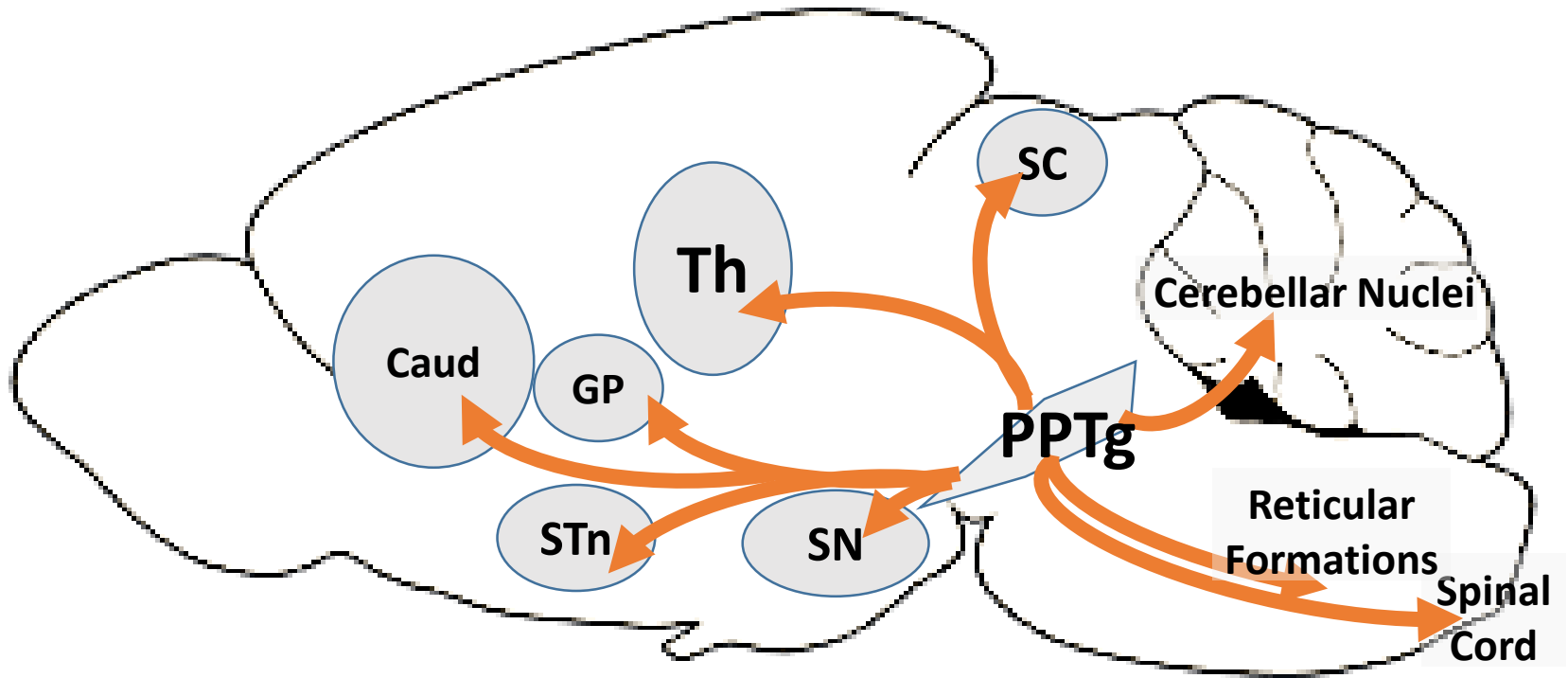
SC = Superior Colliculus

SN = Substantia Nigra

STn = Subthalamic Nucleus

Th = Thalamus

# Hypothesized Spread of Tau in PSP



**Neurons in the PPTg that make direct contacts with all these brain structures are degenerated in PSP.**

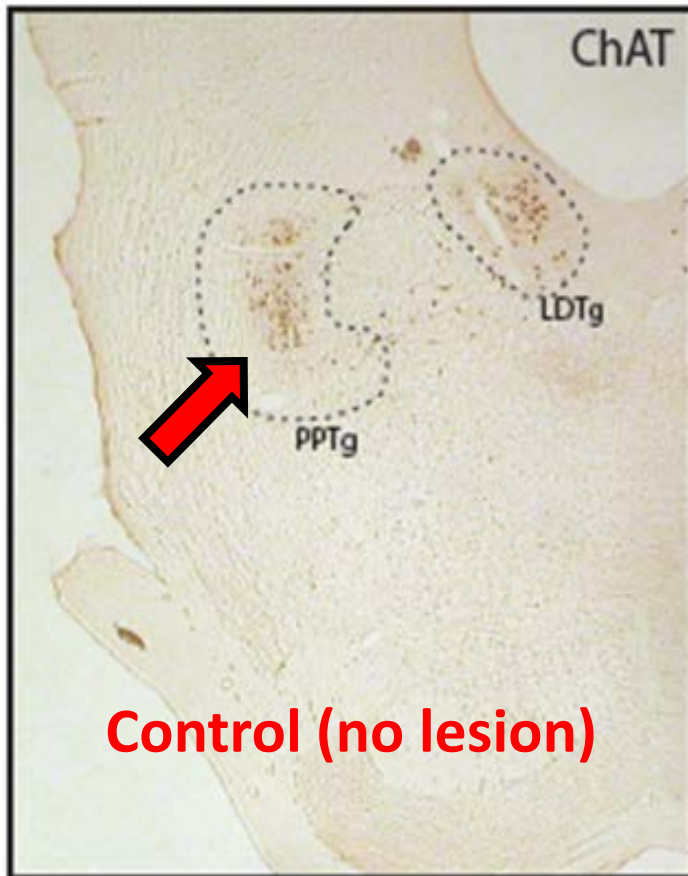
Williams et al., 2007 (Brain)

Hirsch et al., 1987 (PNAS); Mazere et al., 2012 (Radiology); Brandel et al., 1991 (Neuroscience)

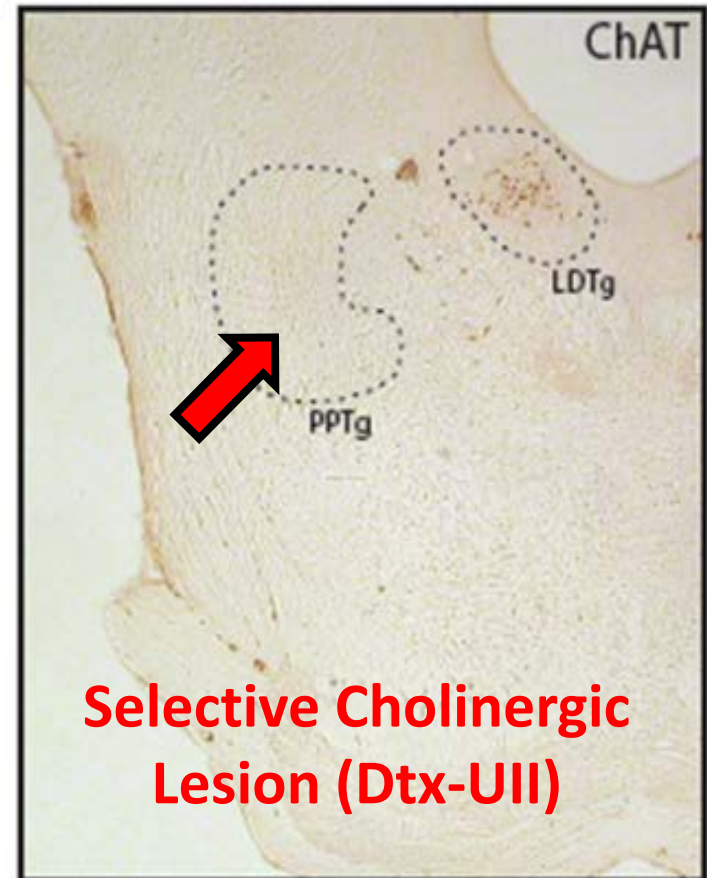
# Selectively Remove the PPTg Neurons in Rats

Hirsch et al. (1987) report that cholinergic PPTg neurons are nearly abolished in PSP.

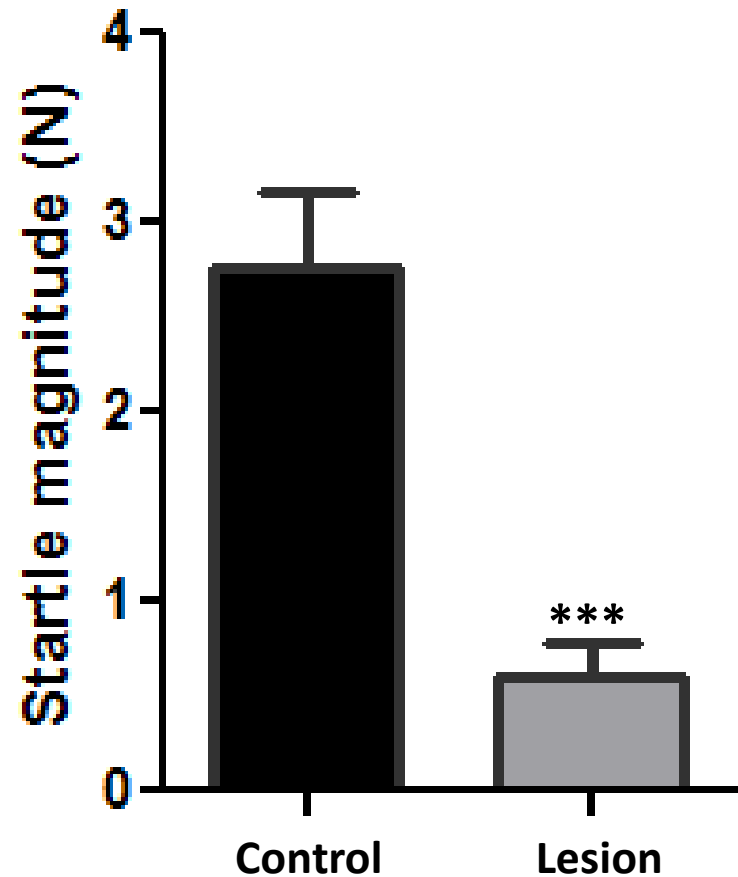
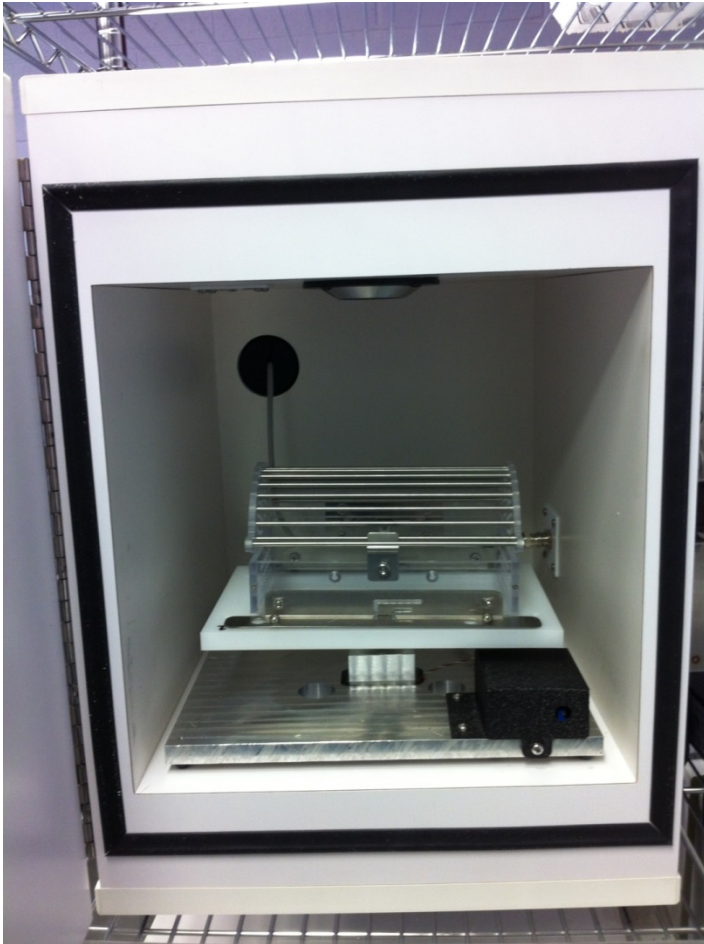
Normal



PSP-like



# Blunts Acoustic Startle Response



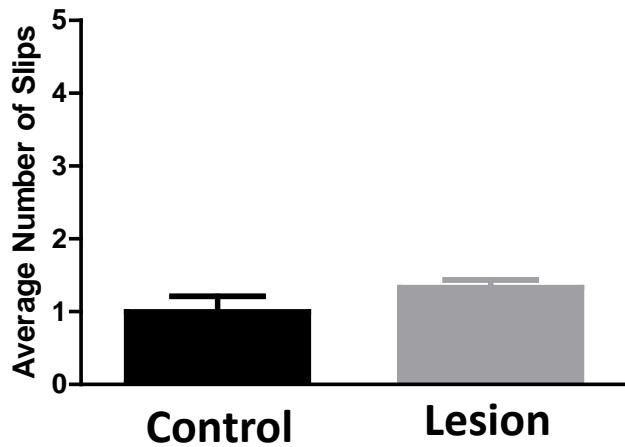
Kofler et al., 2001 (Mov Disord) & Williams et al., 2008 (J Neurol) reported that PSP patients have a blunted response to repeated loud stimuli.

# Motor Deficits: Horizontal Ladder

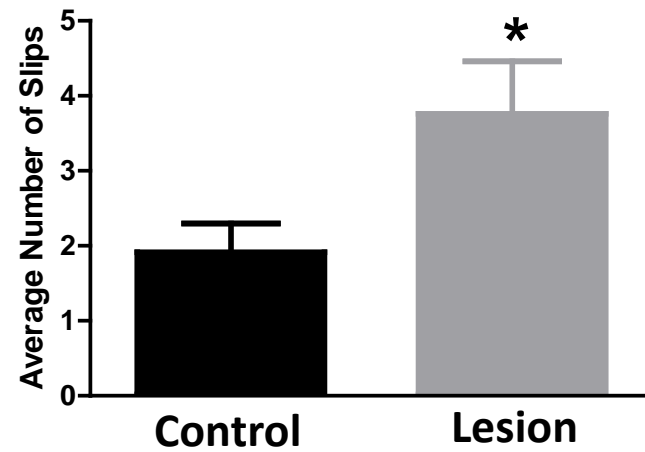


## 14 Months Post-Lesion

### Front Paw Slips



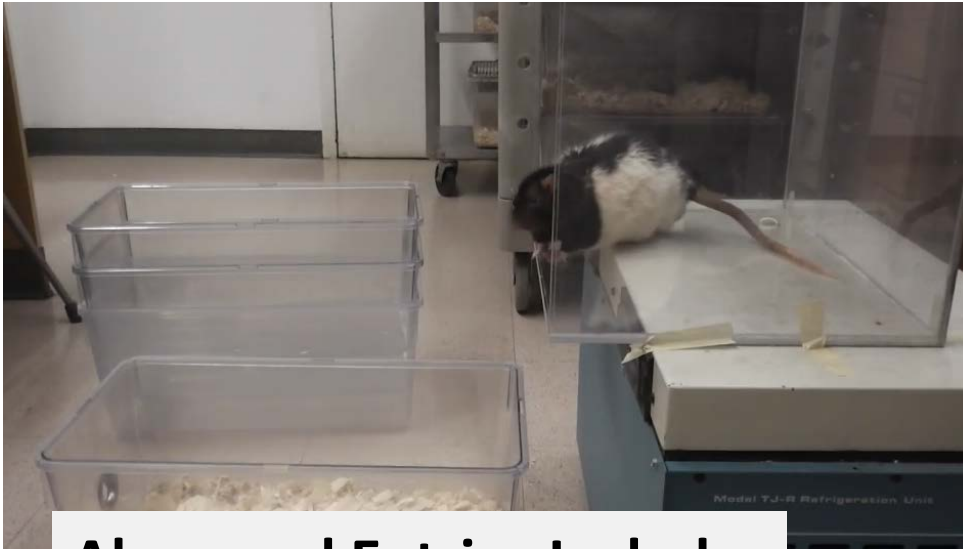
### Back Paw Slips



\* = 0.02

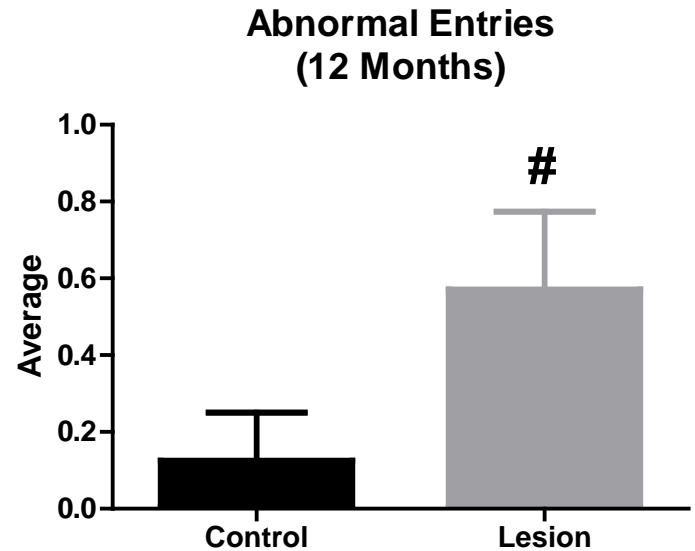


# Motor Deficits: Vertical Descent Paradigm



## Abnormal Entries Include:

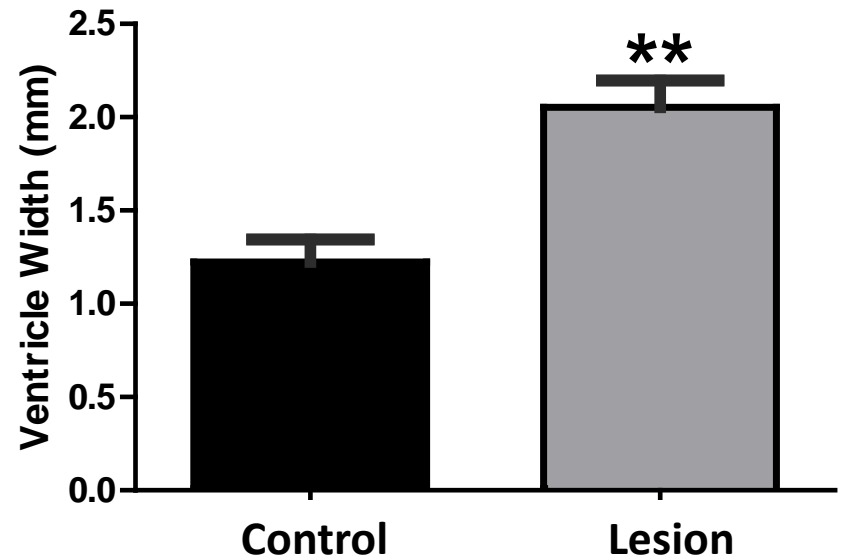
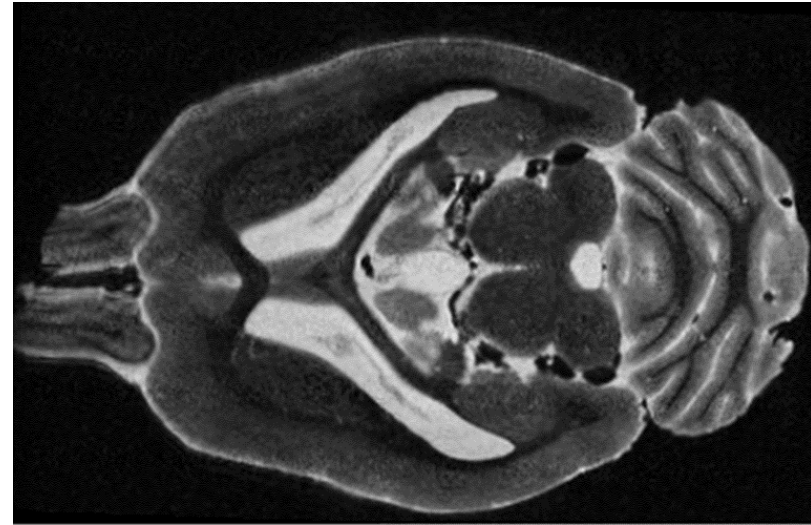
- Falling into cage
- Uncoordinated jumps
- Flipping in the air
- Falling backwards



# = 0.09

# Ventricular Enlargement

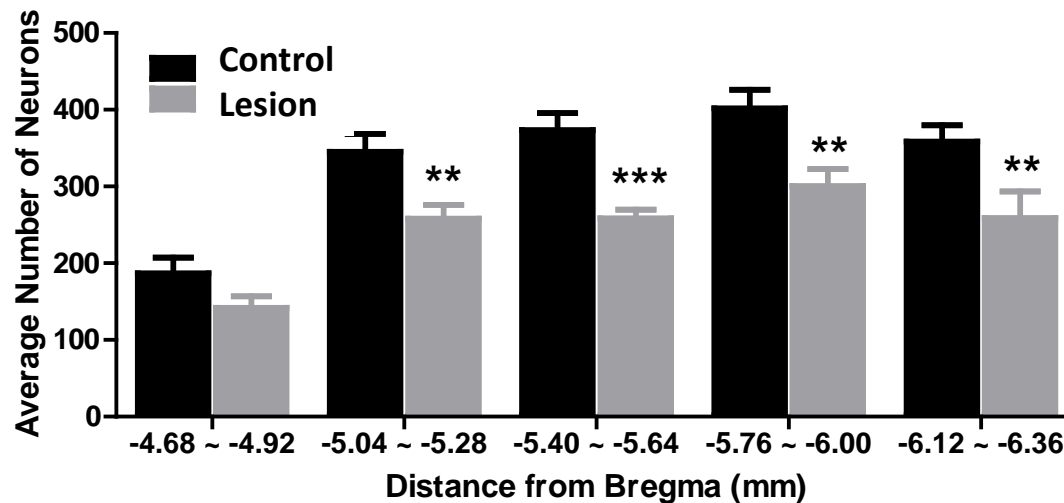
Yekhlef, et al. (2003) reported that ventricular enlargement (MRI) was a reliable criteria to differentiate Parkinson's Disease and PSP.



# Substantia Nigra Loss

One point of the overlapping brain damage between PSP and Parkinson's Disease is a loss of neurons in the Substantia Nigra (SN).





## TH-positive cells in the SN (14 months)



**Overtime, PPTg lesions produce a significant loss of SN neurons. Although at 14 months post-lesion, the loss is not to the degree seen in PSP.**

# What should this Model Look Like?

## Pathological:

- Pedunculo-pontine Tegmentum Loss 
- Ventricular Enlargement 
- Substantia Nigra Loss 
- Abnormal Protein Aggregates (Tauopathy)   
→ may need better model

## Behavioral:

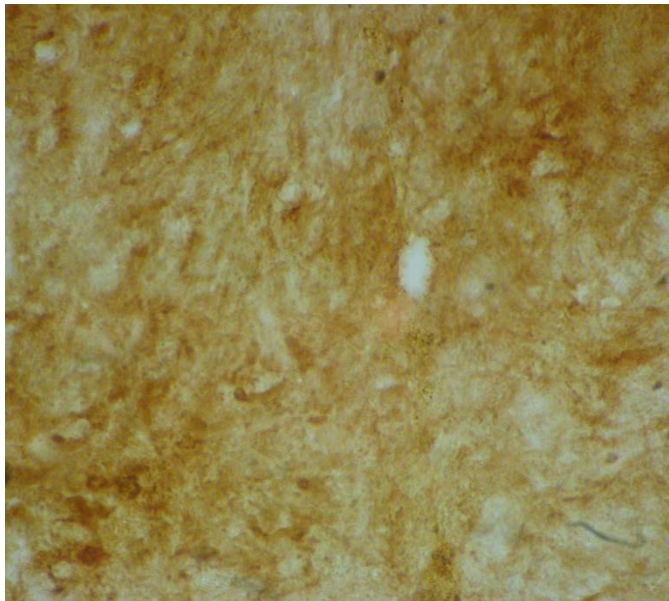
- Startle Deficits 
- Motor Deficits 
- Cognitive Deficits → in progress

# Infect PPTg Neurons with hTau-Viruses

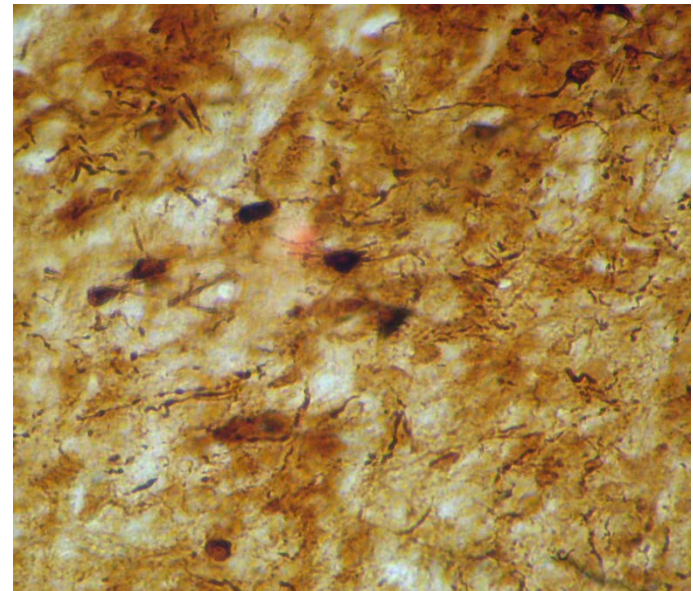
- 1) Kill Cholinergic Neurons – to get same as the lesion
- 2) Produce abnormal Tau and its Spread
- 3) Accelerate the Progression of Deficits

**Neurons filled with abnormal tau in rat PPTg**

**Control Virus**



**hTau Virus**



**Antibody AT8 – detects phosphorylated tau (human and rat)**

# Future Directions

**A) Complete Tau characterization of both Lesion and hTau-virus models**

**B) Initiate screening drugs to:**

- decrease symptom severity**
- slow degeneration progression**

# Acknowledgements

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# Targeting hTau to Cholinergic PPTg Neurons in Rats

To mimic PET data, PPTg pathology, and to produce behavioral deficits.

