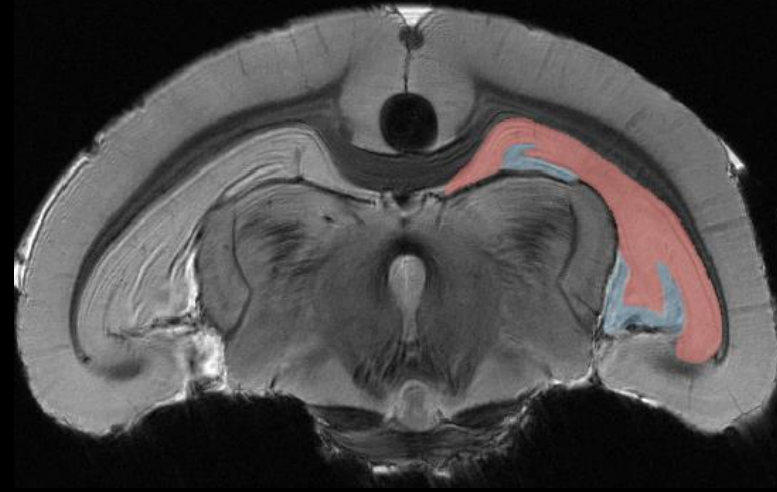
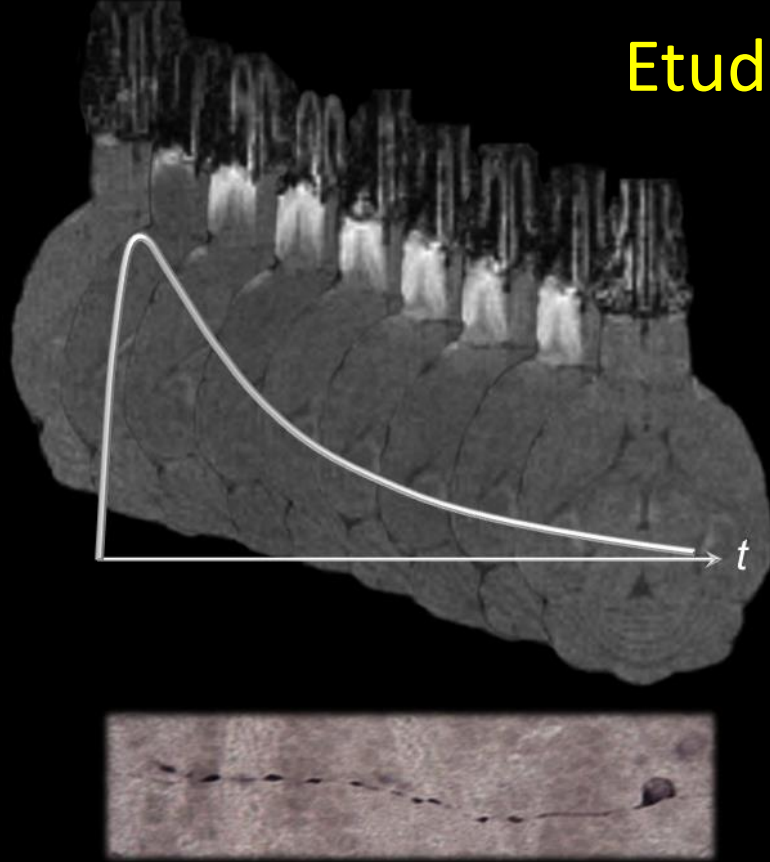


# Etude morphologique et fonctionnelle par IRM à très haut champ de modèles animaux de la maladie d'Alzheimer



Anne Bertrand

Directeurs de thèse : Marc Dhenain, Youssef Wadghiri

*URA CEA-CNRS 2210, MIRCen, Fontenay-Aux-Roses*

*NeuroSpin, CEA, Saclay*

*Center for Biomedical Imaging, NYULMC, New York*

# Maladie d'Alzheimer

# Maladie d'Alzheimer

IRM 7T

Maladie d'Alzheimer

IRM 7T

Modèles animaux

# Maladie d'Alzheimer

Imagerie  
morphologique

IRM 7T

Primate

Modèles animaux



Marc Dhenain  
MIRcen, CEA, Fontenay-Aux-Roses

Micro-MRI of cerebral aging in mouse lemur primates

MEMRI study of neuronal transport in mouse models of tauopathy and amyloidosis

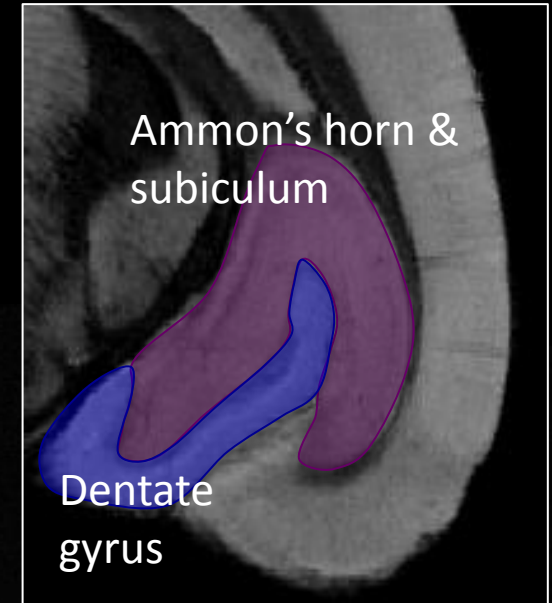
# Rationale

- Non-human primate model of aging
  - Cognitive alterations *Bachevalier 1991*
  - Age-related atrophy *Peters 1996*
  - Spontaneous A $\beta$  deposits *Struble 1985*
  - Spontaneous tauopathy, *Selkoe 1987*
- Small size and relatively fast aging



# Study design

- **12 formalin-fixed mouse lemur brains**
  - 6 young (<5 years) and 6 old (>5 years)
  - Ex vivo staining by Gd-DOTA soaking
- **Ex vivo MRI**
  - 7T clinical magnet
    - Neurospin, CEA*
  - 3D Gradient Echo, 6h
  - TR=200 ms, TE=20s
  - Res. = 31x31x120 $\mu$ m

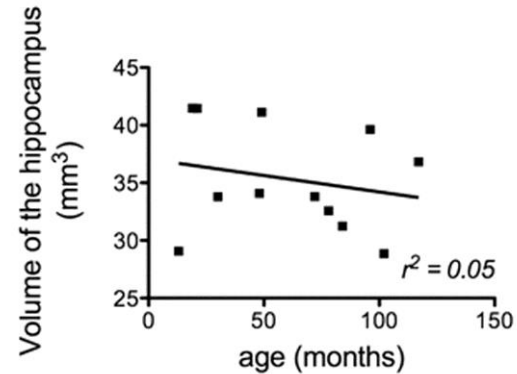




During aging in  
microcebus:

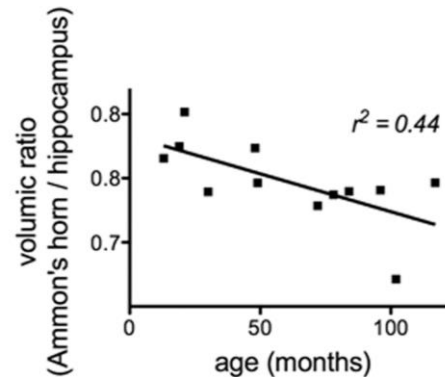
- No significant decrease of hippocampal volume
- **Decrease** in normalized **Ammon's horn + subiculum** volume
- **Increase** in normalized **dentate gyrus** volume

Correlation between age and total hippocampal volume



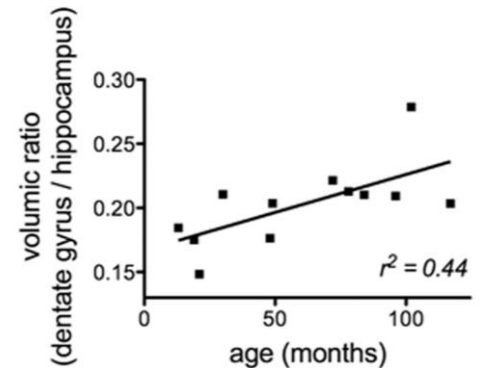
*n.s.* (Pearson correlation coefficient)

Correlation between age and normalized Ammon's horn volume



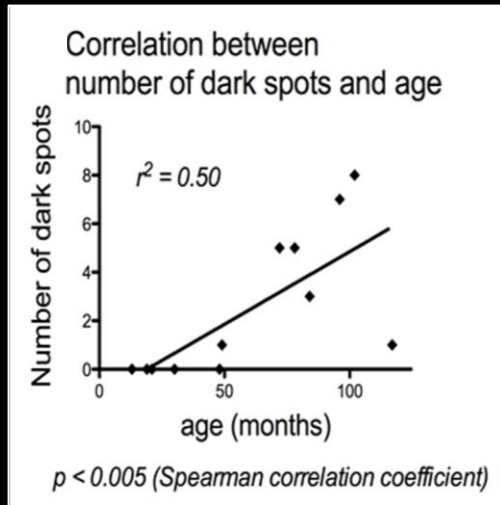
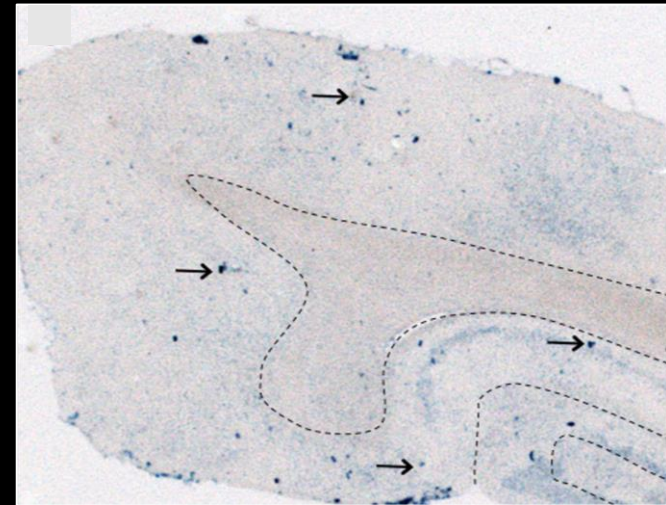
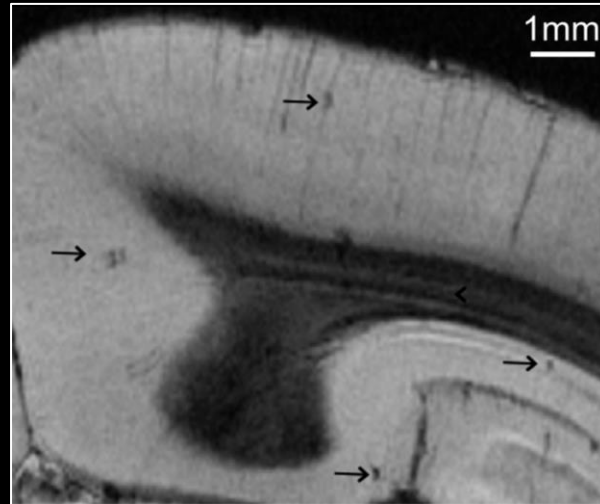
$p < 0.05$  (Pearson correlation coefficient)

Correlation between age and normalized dentate gyrus volume



$p < 0.05$  (Pearson correlation coefficient)

# Side results: MRI detects hypointense spots in the brain of mouse lemurs



# Better characterization of the mouse lemur as a model of aging and Alzheimer's pathology

- **Age-related growth of the dentate gyrus**
  - Not reported in humans and primates
  - Linked to local neurogenesis ?
- **Cerebral microhemorrhages**
  - Not reported in other primates
  - Reminiscent of human microbleeds associated with aging
- Spontaneous A $\beta$  deposits of mouse lemurs **can be detected by MRI**
  - Low incidence (1 among 6 old animals) : coherent with the literature
  - Step towards detection of spontaneous A $\beta$  deposits in humans

# Maladie d'Alzheimer

Imagerie  
morphologique

IRM 7T

Primate

Modèles animaux



Marc Dhenain  
MIRcen, CEA,  
Fontenay-Aux-Roses

# Maladie d'Alzheimer

Imagerie  
morphologique

IRM 7T

Imagerie  
fonctionnelle

Primate

Modèles animaux

Souris  
transgénique



Marc Dhenain  
MIRcen, CEA,  
Fontenay-Aux-Roses

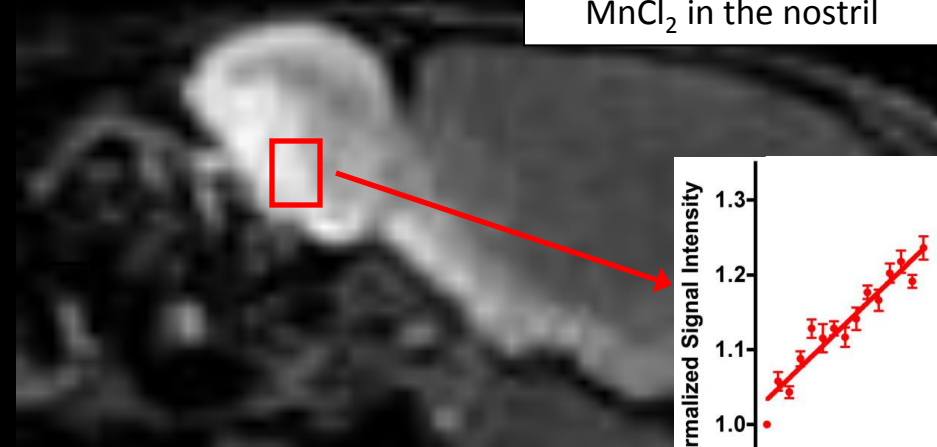
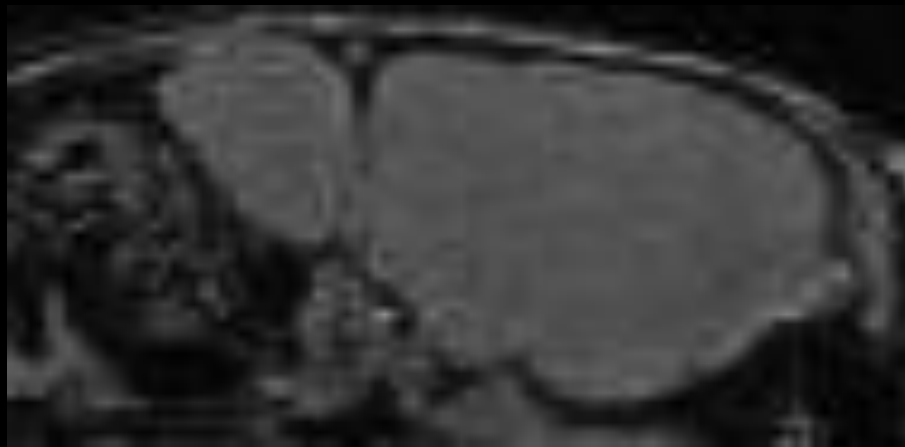
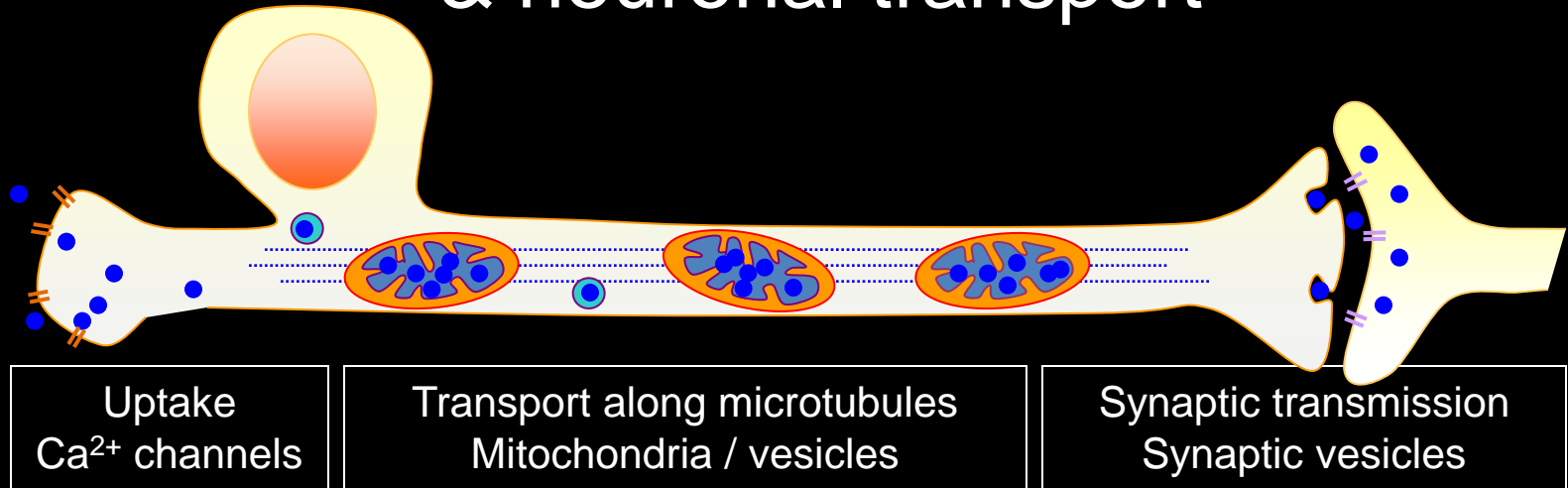


Youssef Z Wadghiri  
NYULMC  
New York ,NY, USA

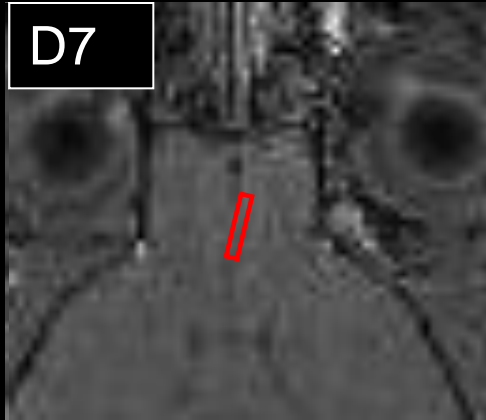
Micro-MRI of cerebral aging in mouse lemur primates

MEMRI study of neuronal transport in mouse models of tauopathy and amyloidosis

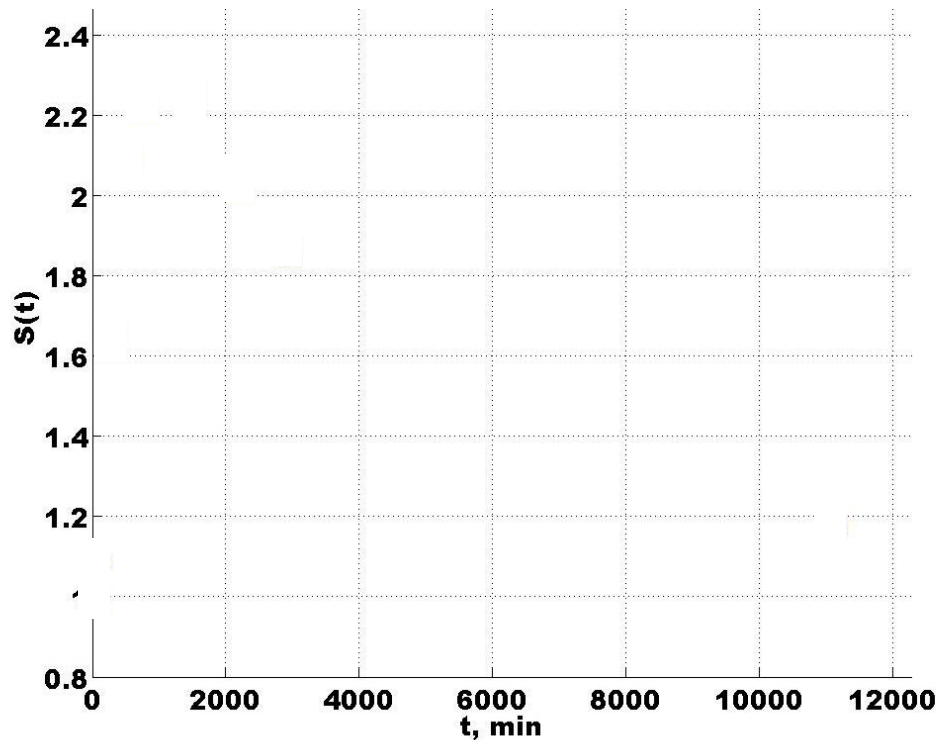
# Manganese-enhanced MRI & neuronal transport



# Analysis of signal intensity curves



Normalized signal intensity as a function of time

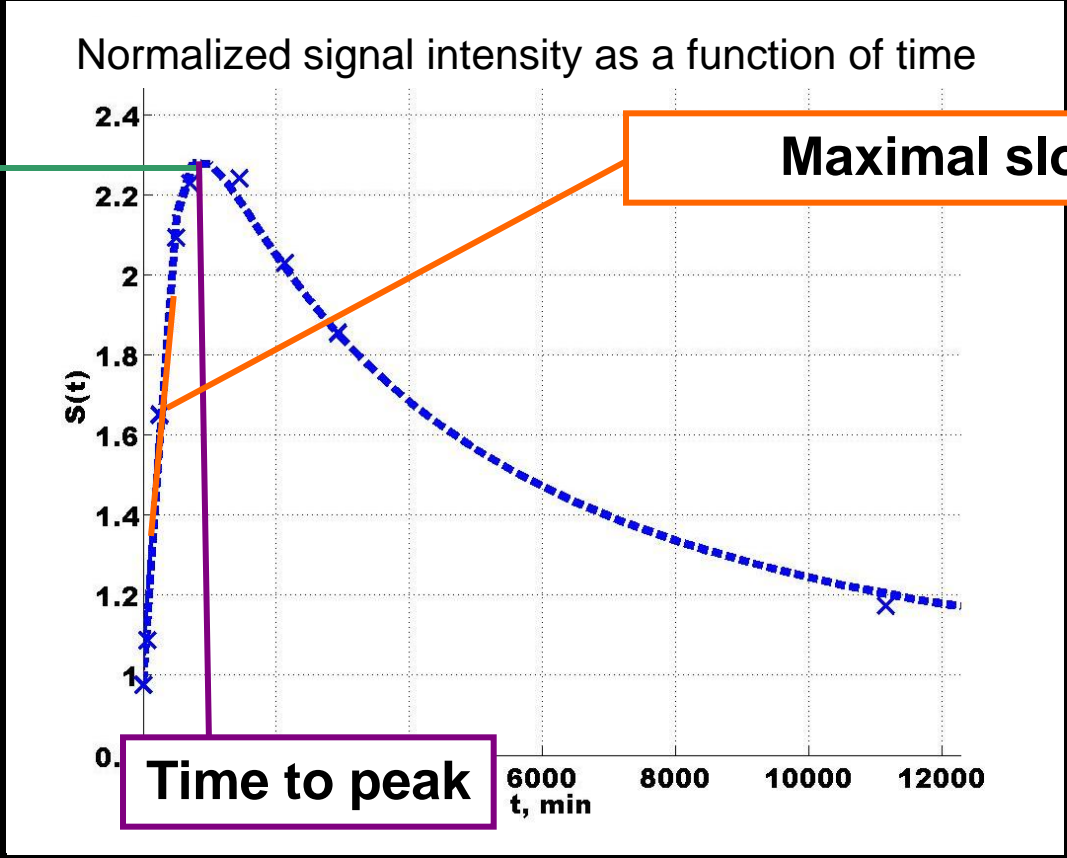




# Analysis of signal intensity curves

Peak value

Maximal slope



Time to peak

Drift-diffusion model

Cross Neuroimage 2008

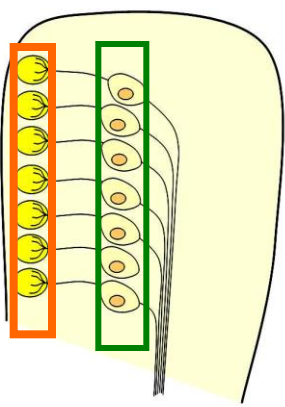
Micro-MRI of cerebral aging in mouse lemur primates

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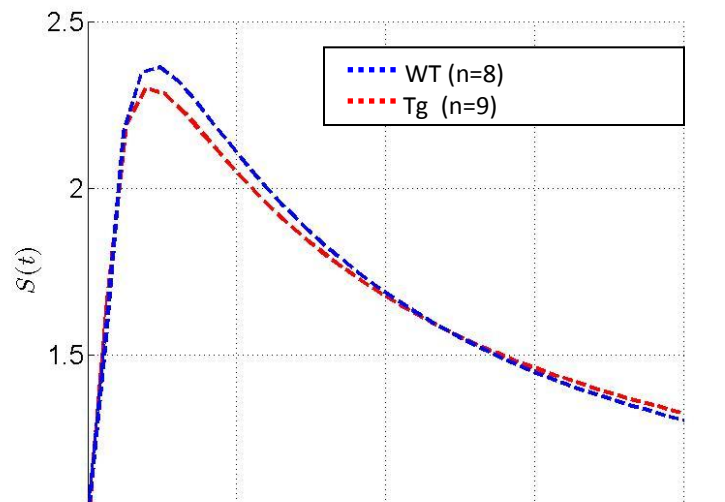
- the JNPL3(P301L) line: a model of tauopathy

# Curve profiles

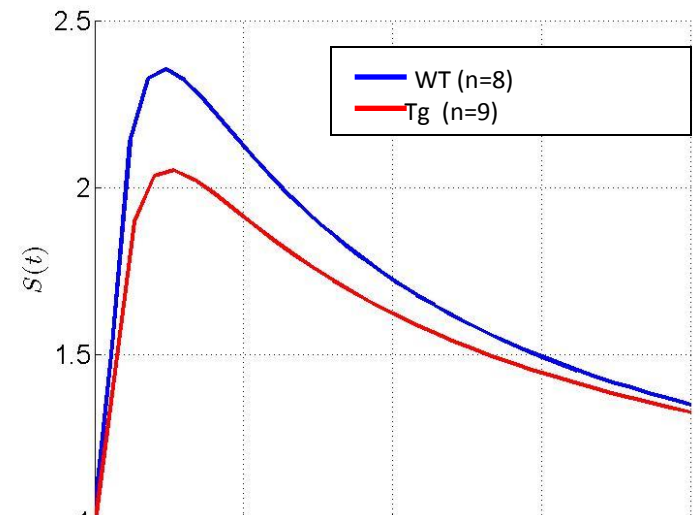
Glomerular layer



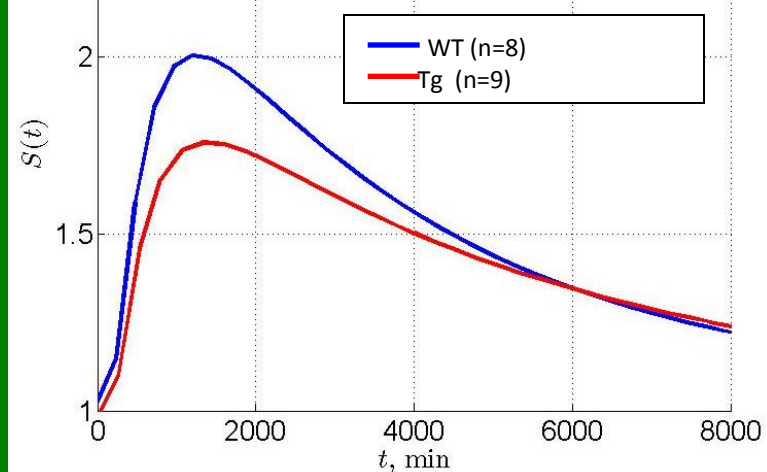
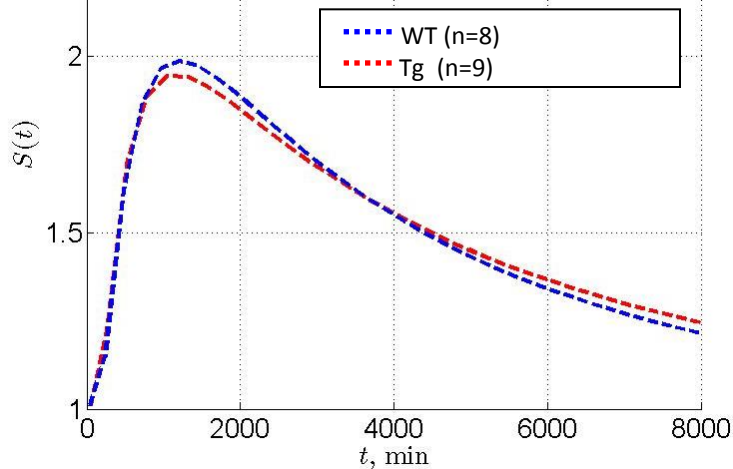
Mitral cell layer



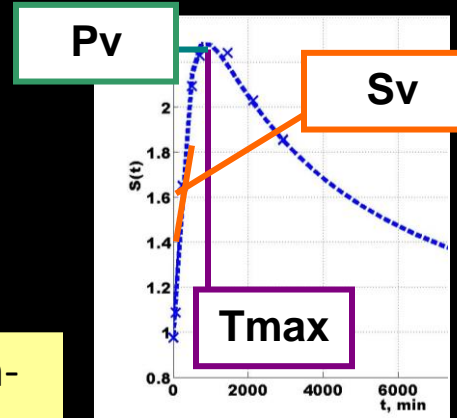
At 3 month-old, curves of Tg and WT mice are similar



At 6 month-old (same mice) curves of Tg and WT mice differs

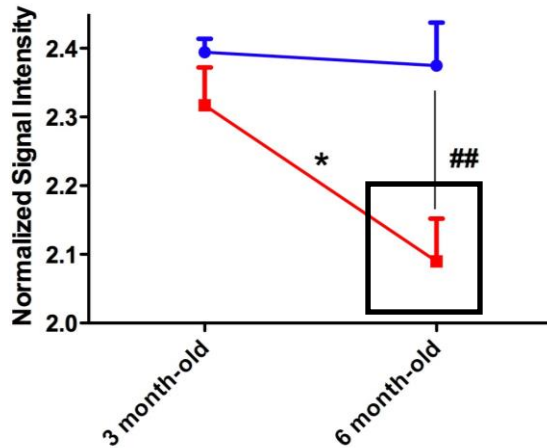


# Parameter analysis



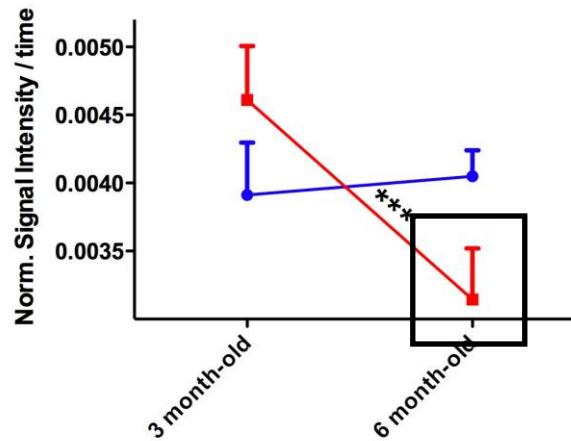
Parameters are all significantly affected in 6 month-old Tg mice

### Pv is decreased



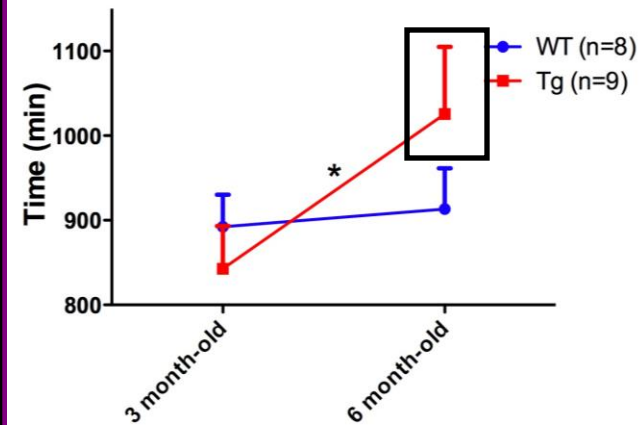
\*:  $p < 0.05$  (Wilcoxon signed rank test); ## :  $p < 0.01$  (t-test)

### Sv is decreased



\*\*\*  $p < 0.001$  (paired t-test).

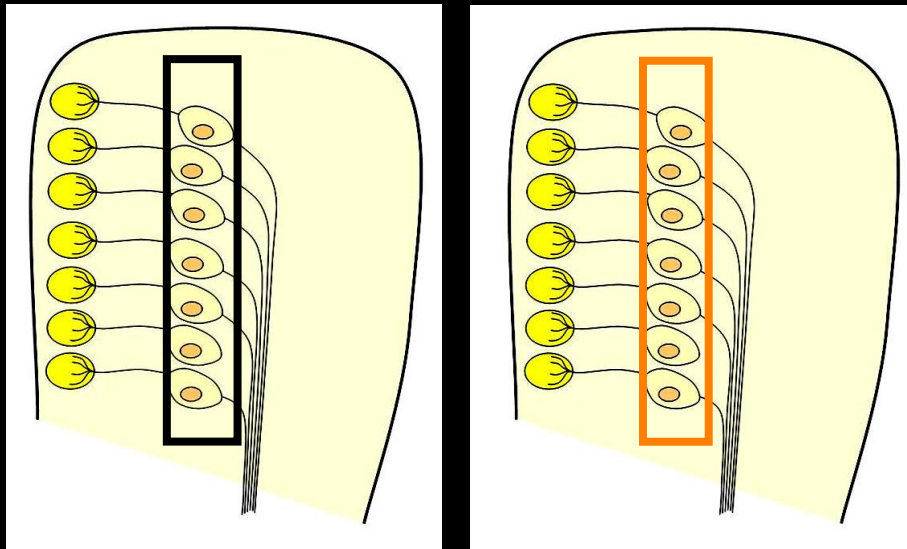
### Tmax is delayed



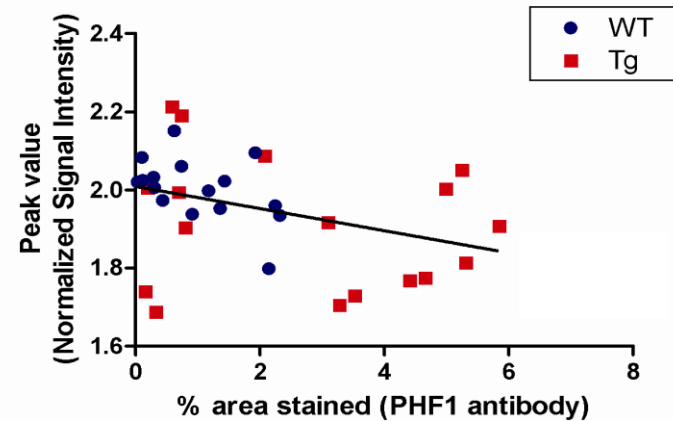
\*  $p < 0.05$  (paired t-test).

# MEMRI parameters correlates with levels of tauopathy

MEMRI ↔ Histology

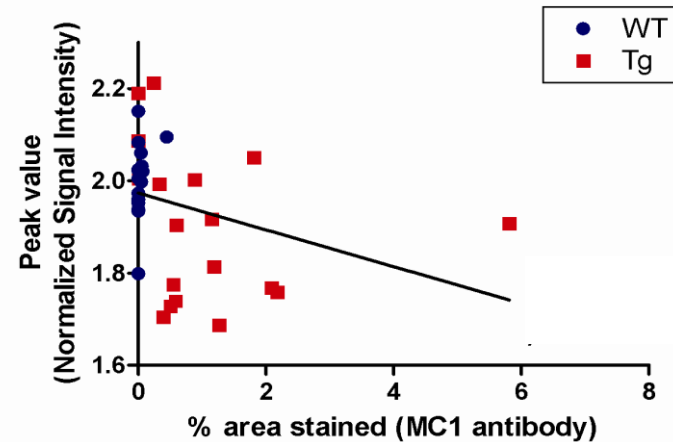


**A. Peak value correlates with somatic tau pathology (PHF1 antibody)**



Correlation:  $r = -0.38$  and  $p < 0.05$  (Spearman correlation coefficient).

**B. Peak value correlates with somatic tau pathology (MC1 antibody)**



Correlation:  $r = -0.46$  and  $p < 0.01$  (Spearman correlation coefficient).

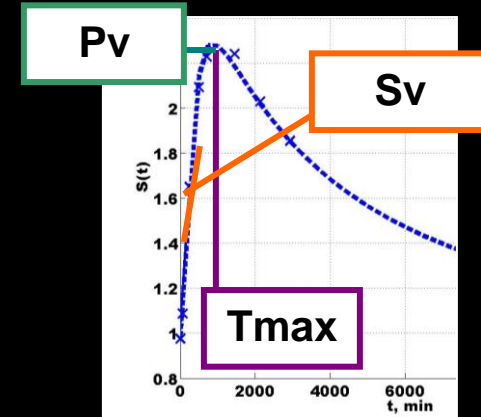
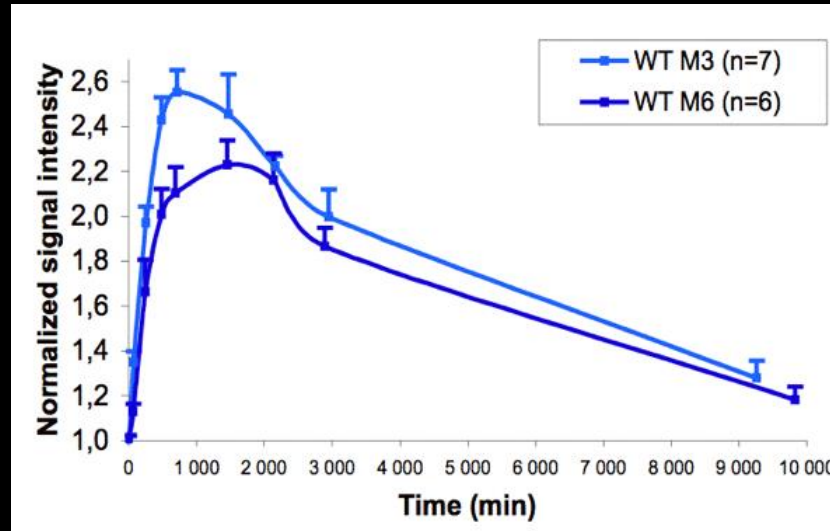
- ***In vivo* detection of neuronal transport impairment** related to the expression of human-mutated tau in mice
- **Correlation** between MEMRI parameters and abnormal tau expression
- **MEMRI can be used as a preclinical biomarker of tauopathy**

Micro-MRI of cerebral aging in mouse lemur primates

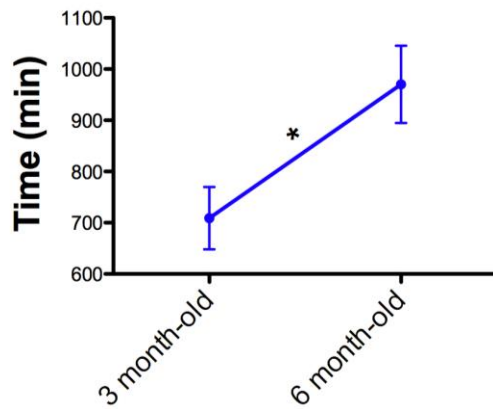
MEMRI study of neuronal transport in mouse models of tauopathy and amyloidosis

- the JNPL3(P301L) line: a model of tauopathy
- the 5XFAD line: an accelerated model of amyloidosis

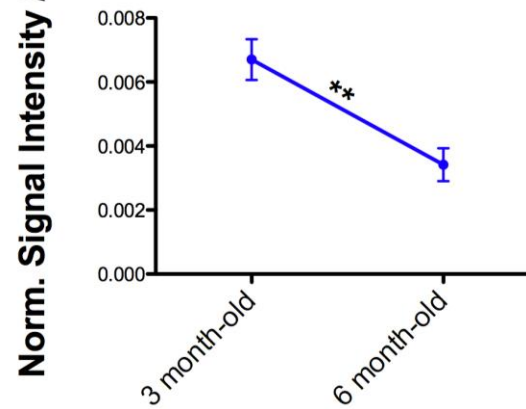
# WT- 5XFAD



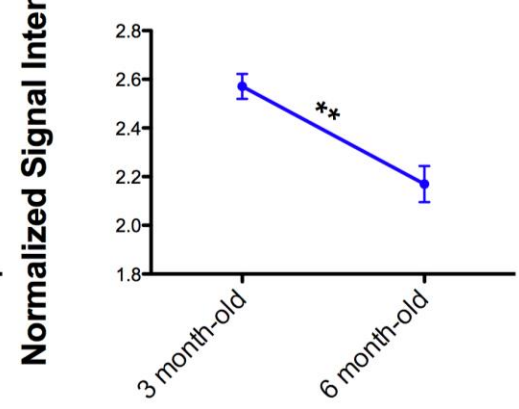
Tmax is delayed



Pv is decreased



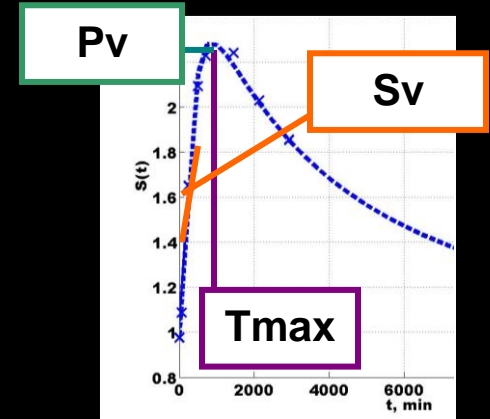
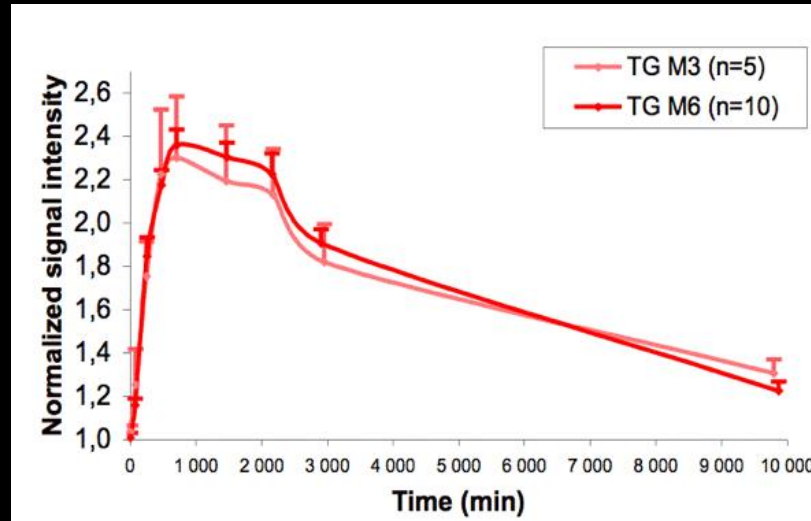
Sv is decreased



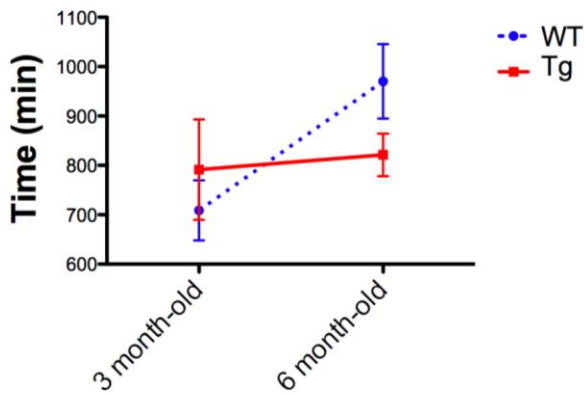
\*:  $p < 0.05$ ; \*\*:  $p < 0.01$ , Mann Whitney test



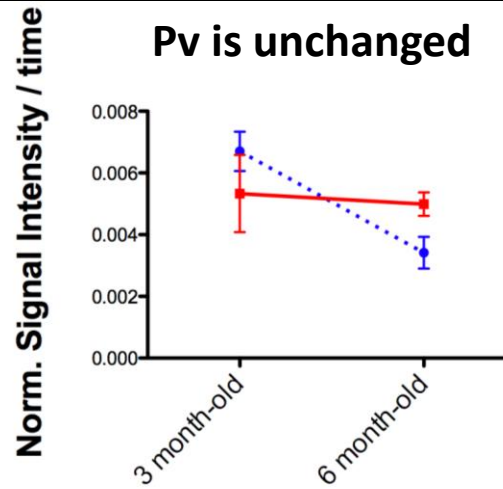
# Tg – 5XFAD



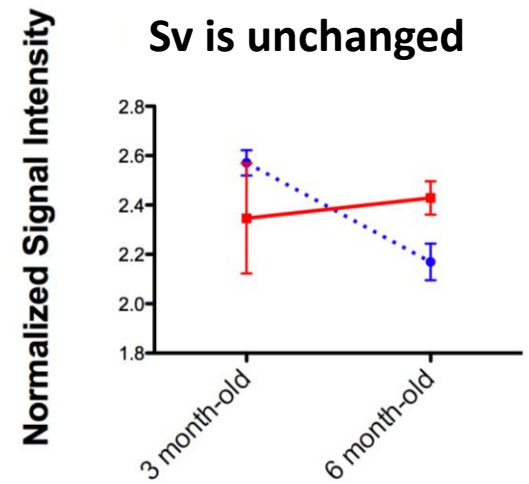
**Tmax is unchanged**



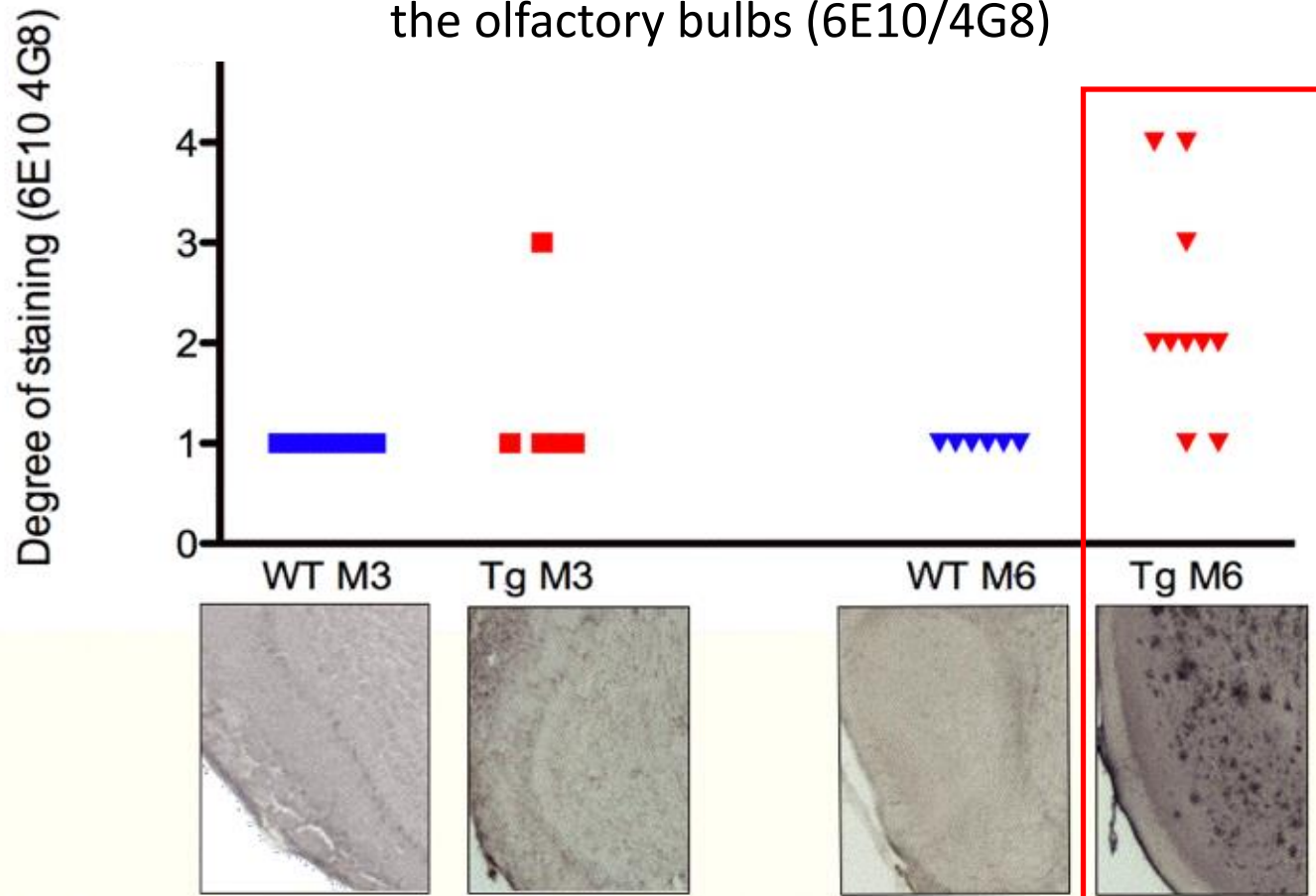
**Pv is unchanged**



**Sv is unchanged**



# Semi-quantitative estimation of the amyloid load in the olfactory bulbs (6E10/4G8)



- Age-related impairment of neuronal transport in WT mice

- Observed in aging rats, not mice

*Frolkis 1997, Cross 2008*

- Absence of neuronal transport impairment in 5XFAD mice

- True acceleration ?
- Excitotoxicity ?

*Itoh Neuroscience 2008*

*Gobbo 2012*

# Understanding the mechanisms of Alzheimer's disease

Differences between AD lesions:

- *In vivo* neuronal transport is altered in the presence of tauopathy
- *In vivo* neuronal transport is apparently increased in an accelerated mouse model of amyloidosis
  - True acceleration ?
  - Excitotoxicity ?

# Understanding the mechanisms of normal aging

- First report of a growth of the dentate gyrus during aging
  - Higher resistance to aging process ?
  - Active neurogenesis ?
- First report of an age-related impairment of neuronal transport in WT mice

# Acknowledgments



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