(In vivo) Imaging modalities for investigation of CNS (endo)phenotypes with a focus on Alzheimer's disease

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URA CEA CNRS 2210 – MIRCen - Fontenay aux Roses

Multimodal Imaging
of Neurodegenerative Diseases and Therapies

Alzheimer's Disease Group:
Modelization, Biomarkers, Preclinical Imaging

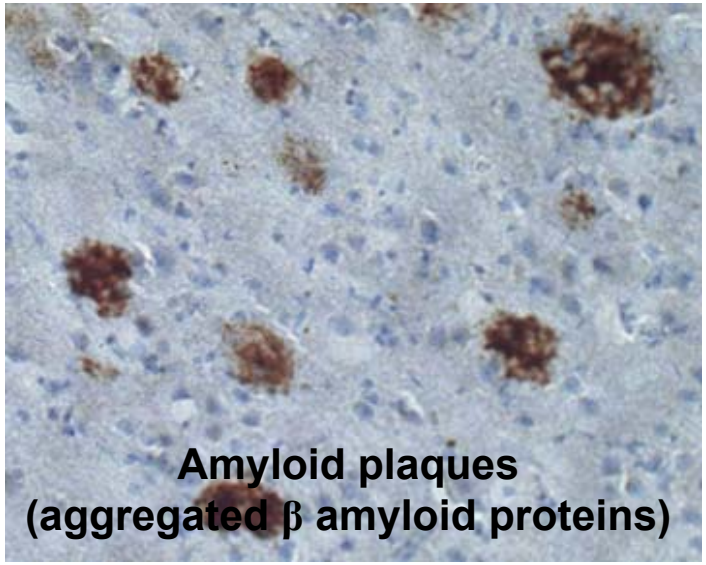
Presentation available on: http://mamobipet.free.fr/Teaching/Teaching.html

Outline

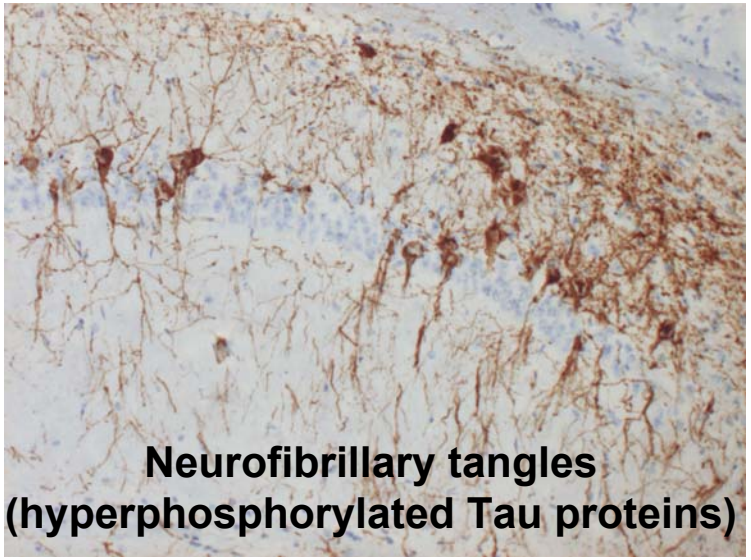
- Neurodegenerative disease and preclinical research (example of Alzheimer's disease)
  - Disease overview
  - Concepts of targets, endophenotypes and biomarkers
  - Concepts of animal models
  - Biomarkers in animal models
- Cerebral atrophy
- Functional imaging
  - Cerebral metabolism
  - Perfusion
  - Neuronal transportation
- Amyloid plaque imaging
- Toxicity

Alzheimer's disease (AD)

- Severe dementia
- Most common neurodegenerative disease
  - 22 million people worldwide
- Two main microscopic lesions



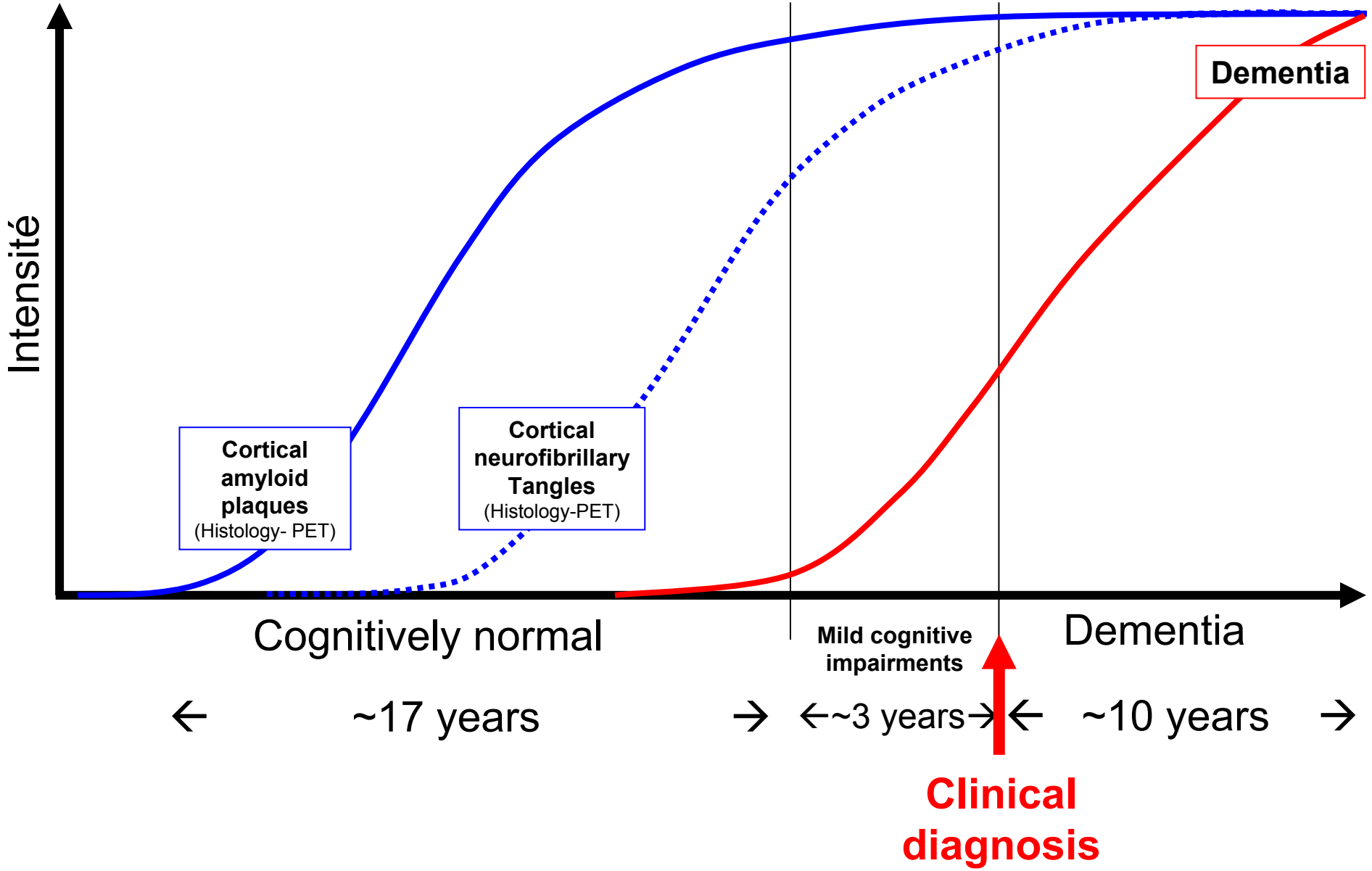
Amyloid plaques (aggregated β amyloid proteins)



Neurofibrillary tangles (hyperphosphorylated Tau proteins)

- No curative treatment

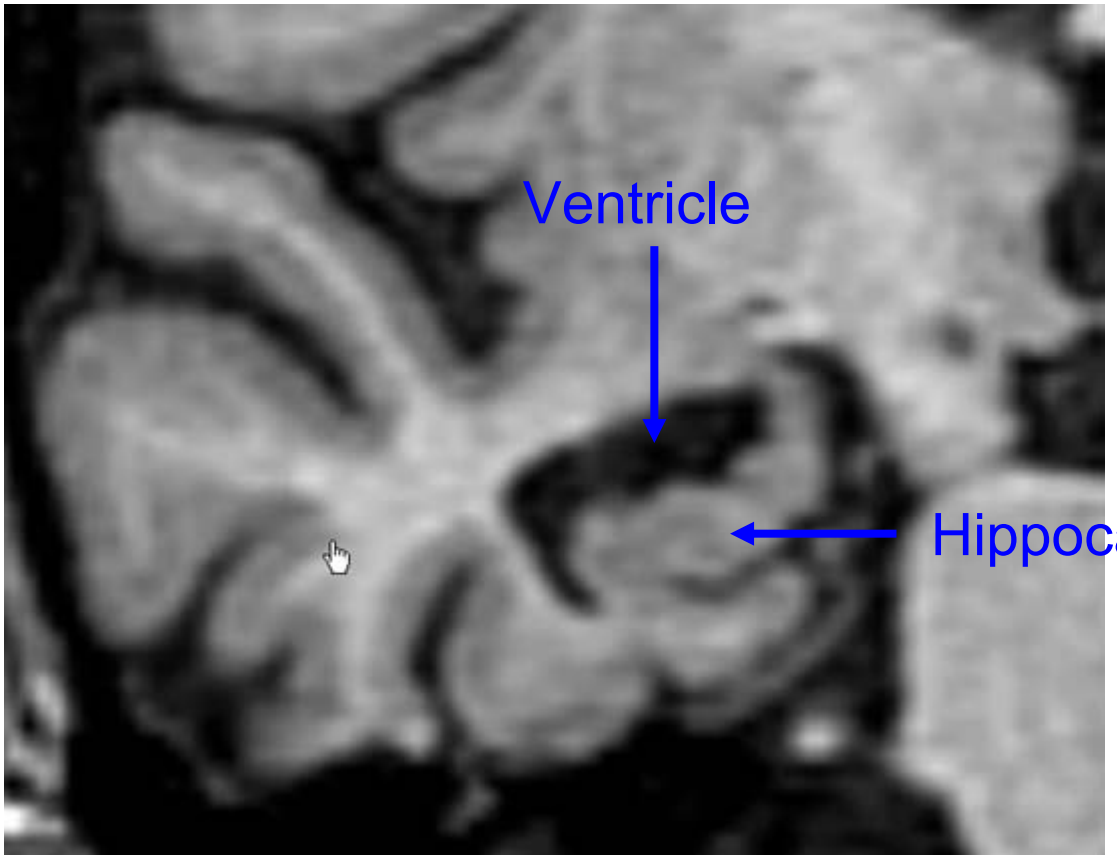
Natural history of Alzheimer's disease



Jack et al, 2013

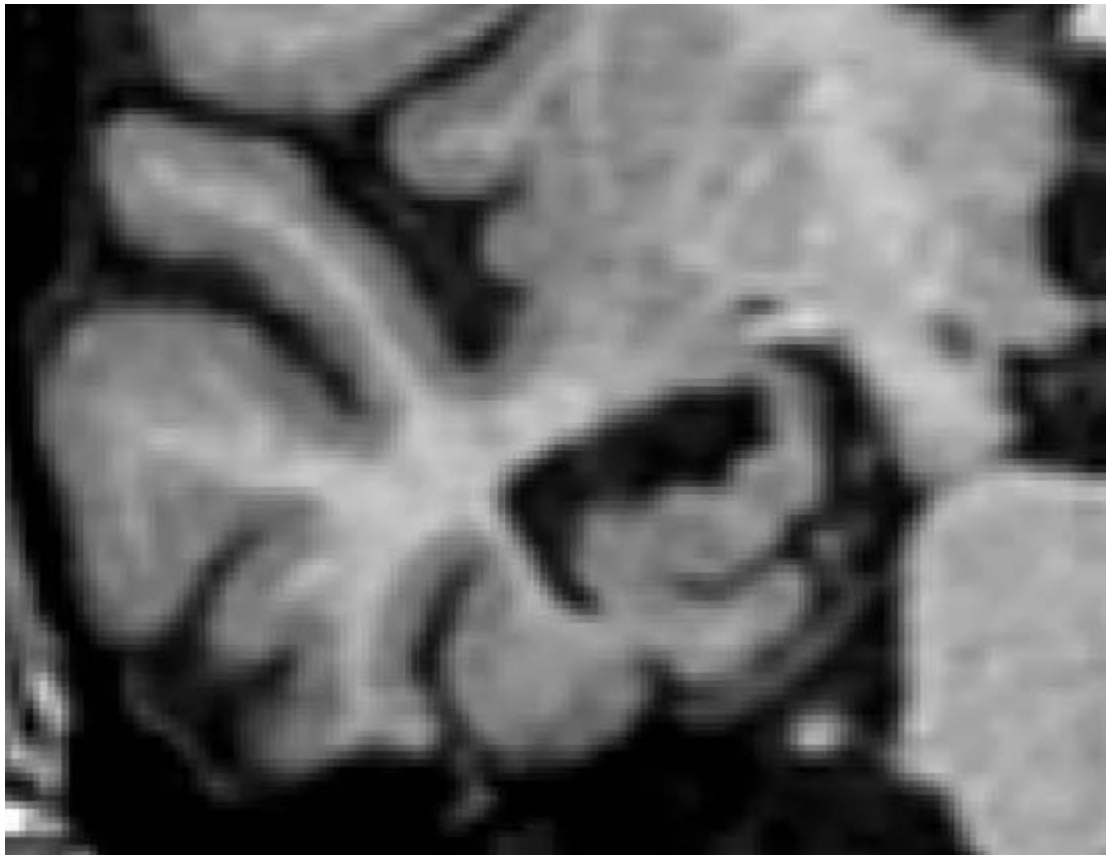
Cerebral atrophy

Progression of cerebral atrophy during 10 years



Clifford Jack, ISMRM, 2008

Progression of cerebral atrophy during 10 years



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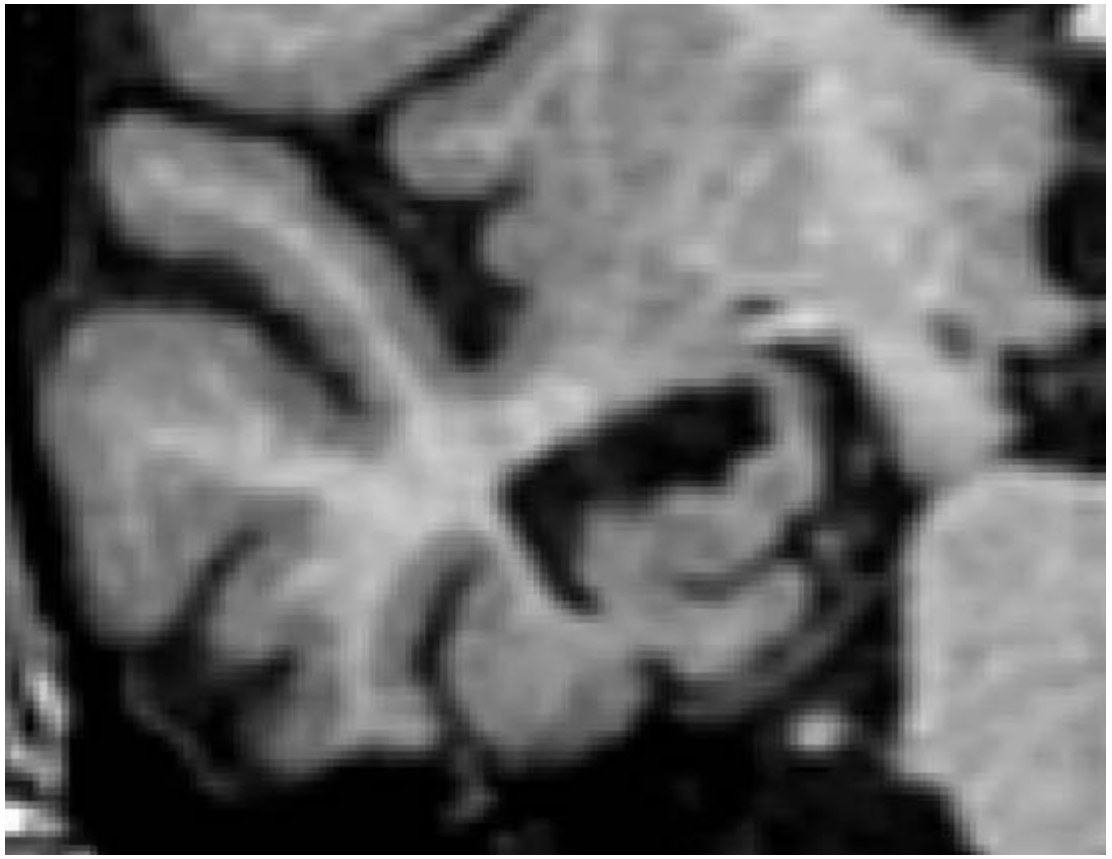

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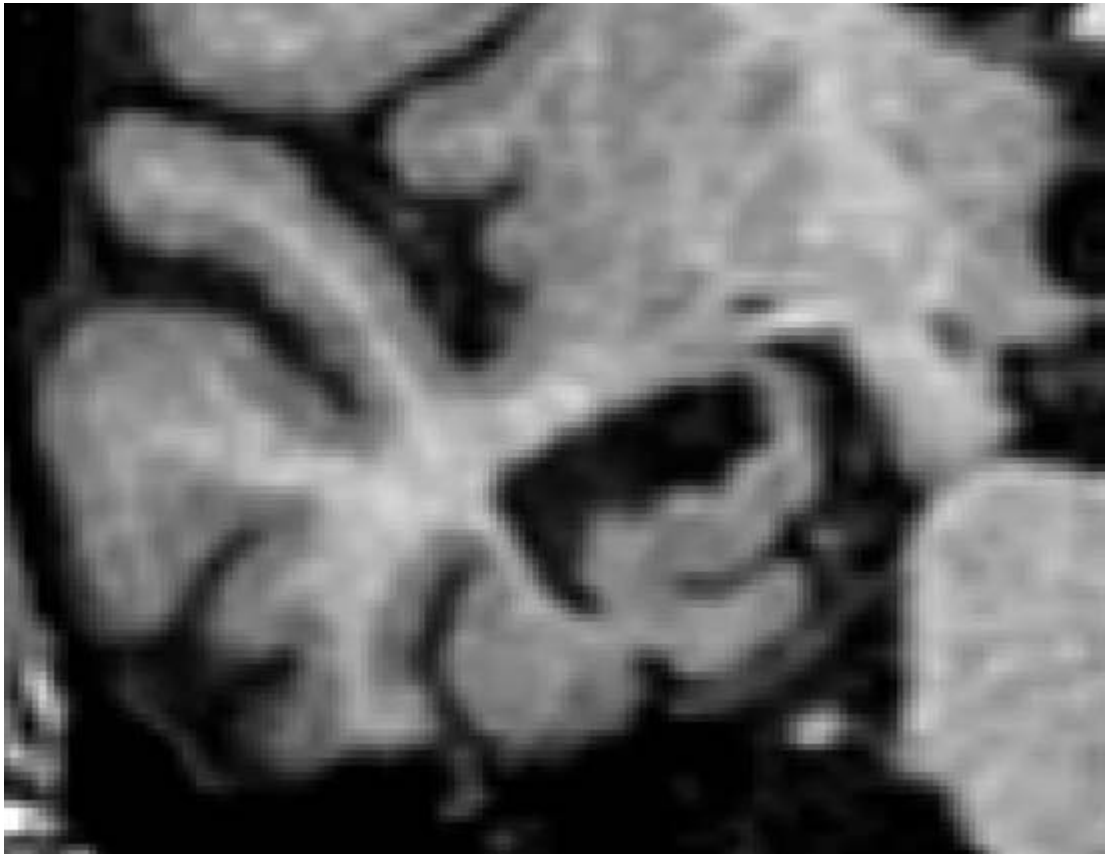

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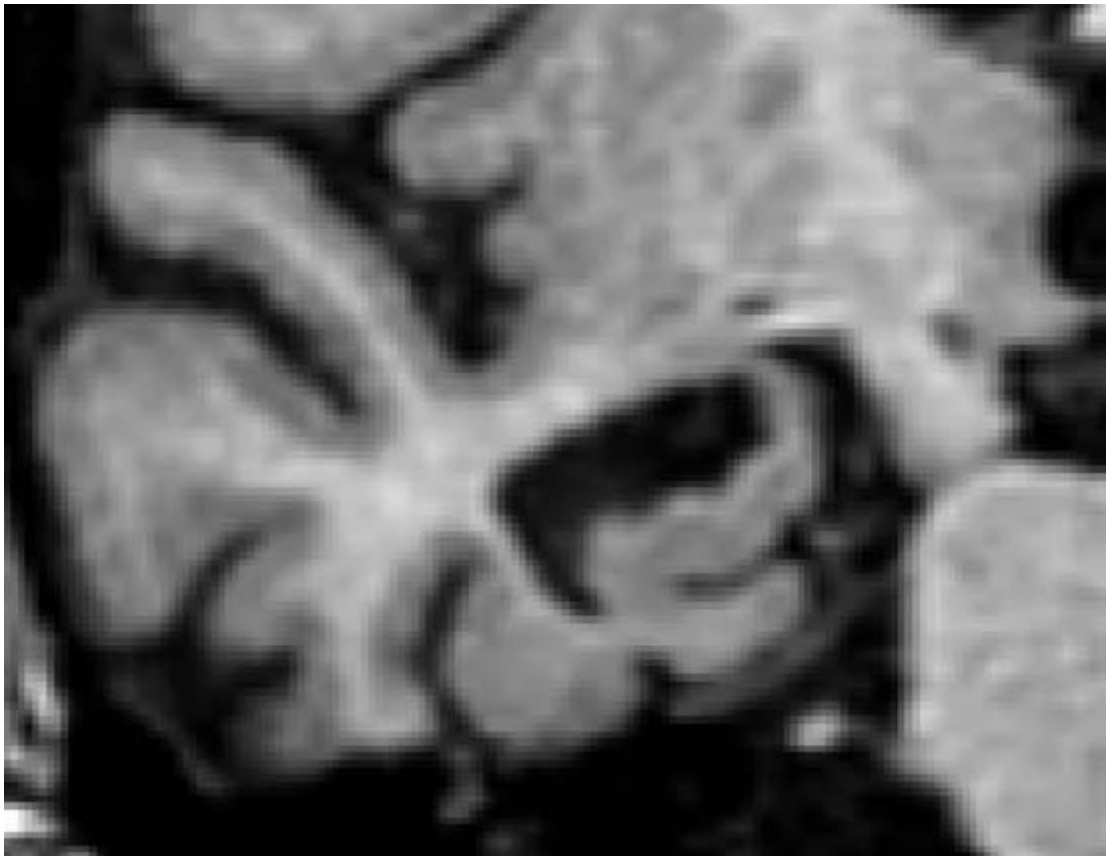

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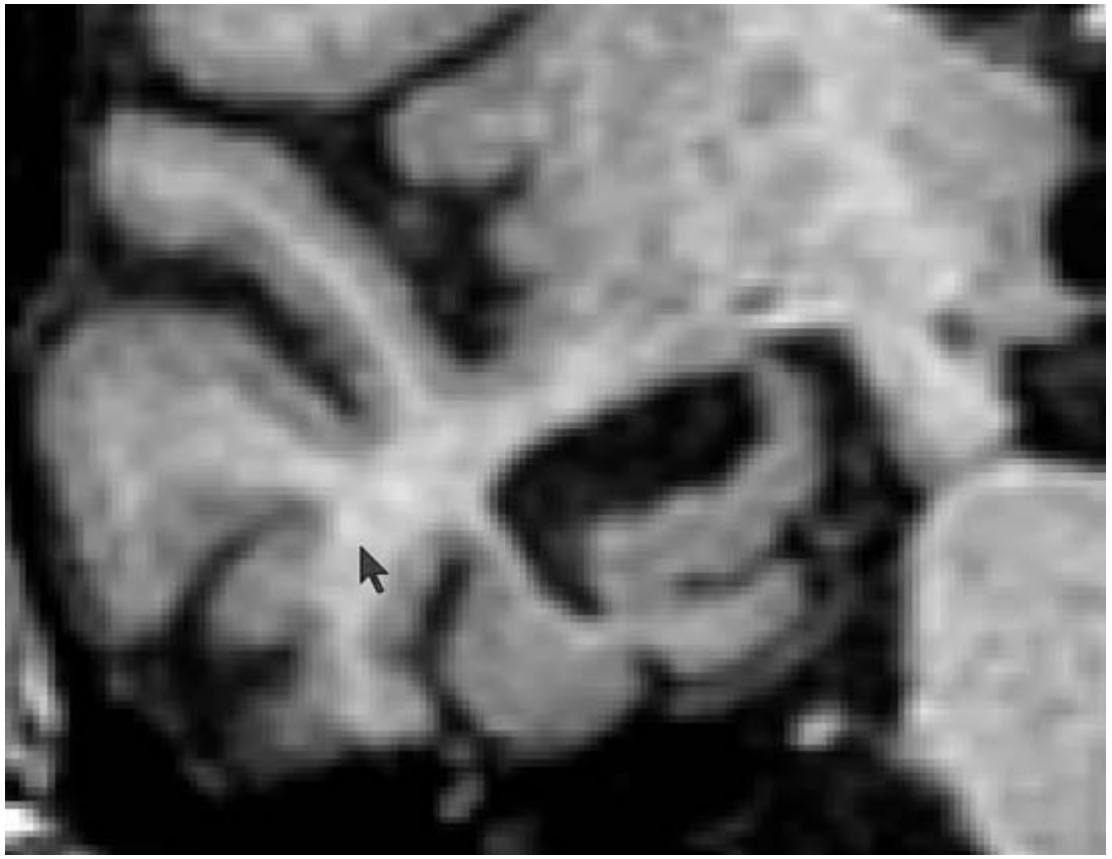

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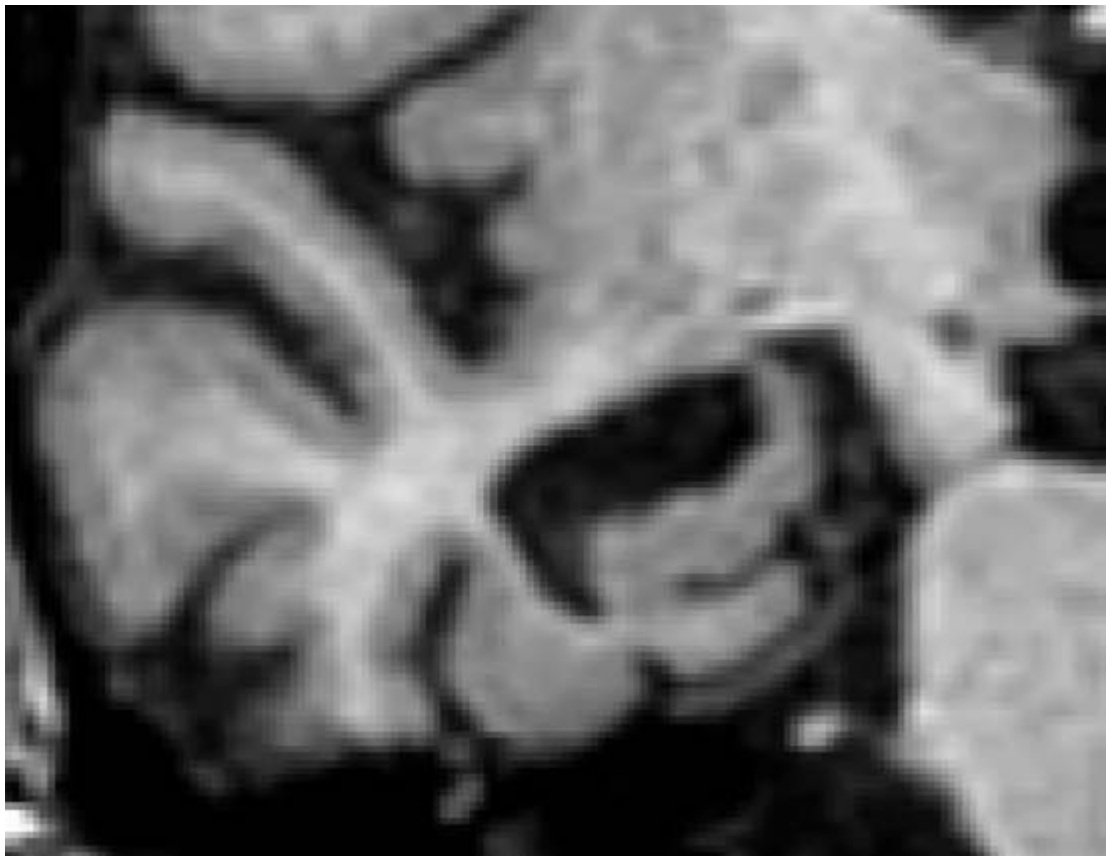
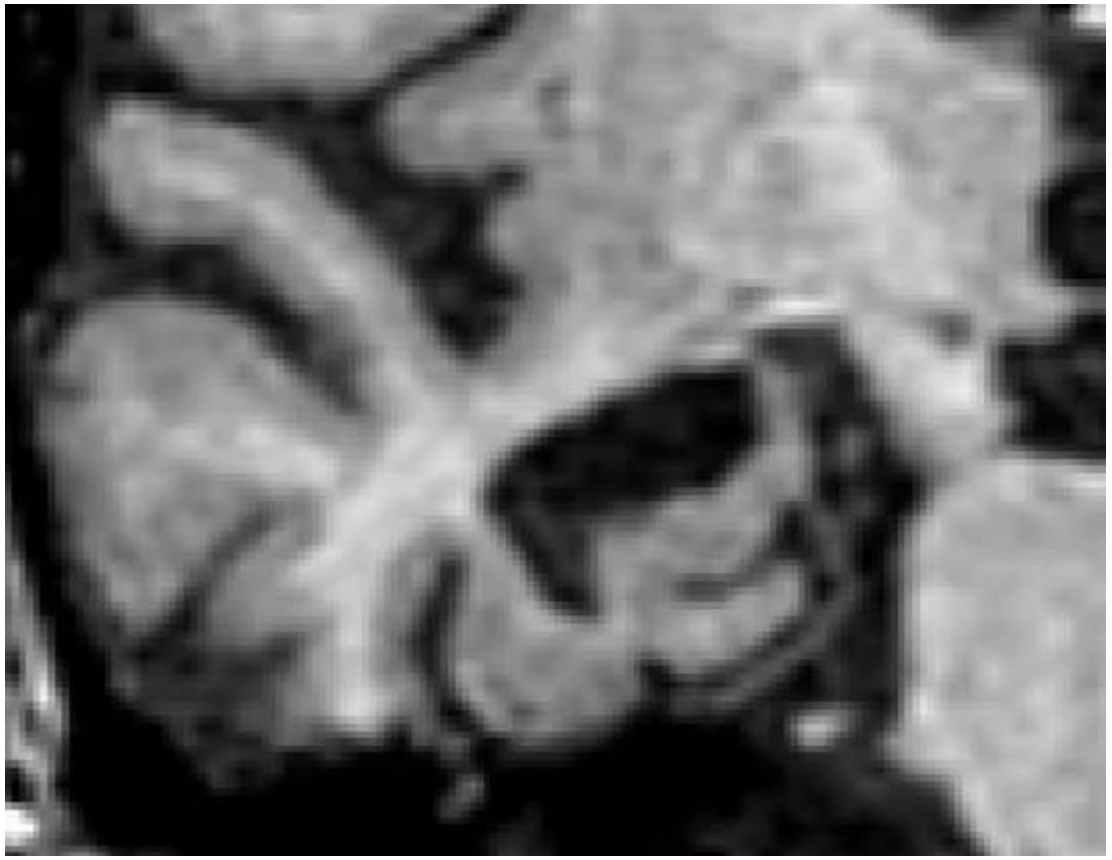
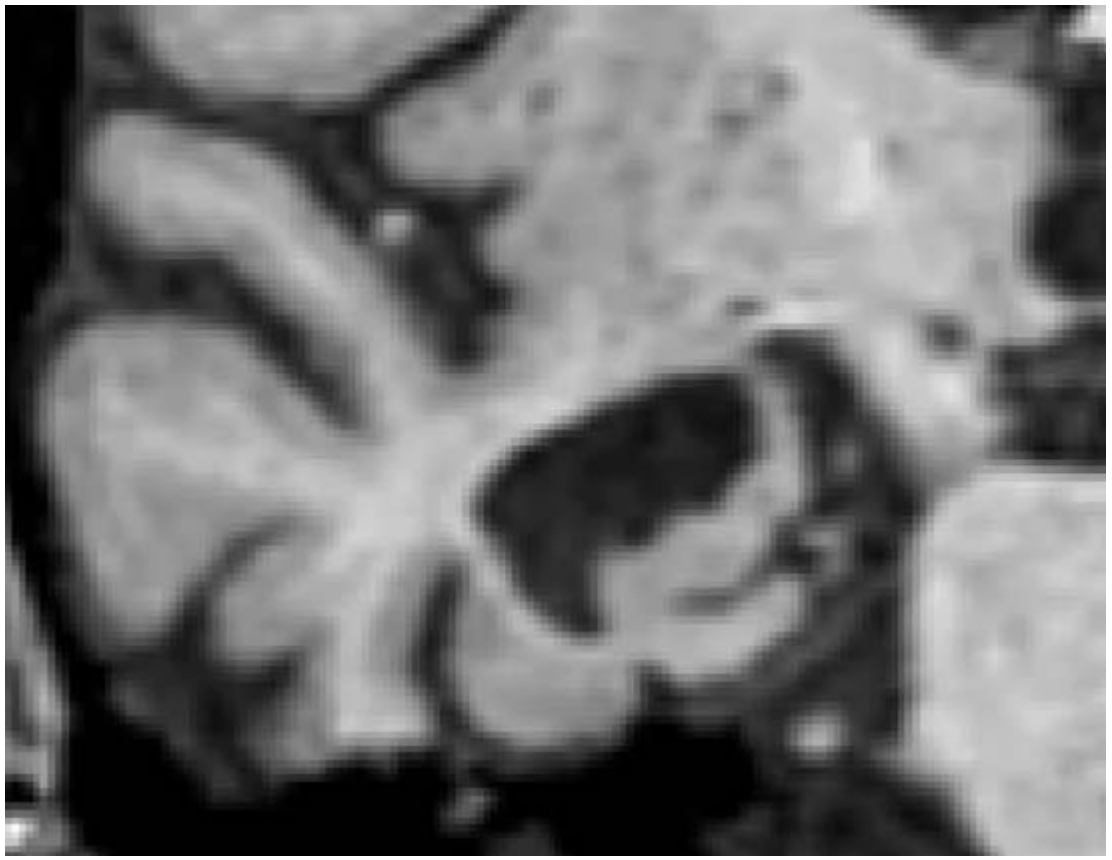


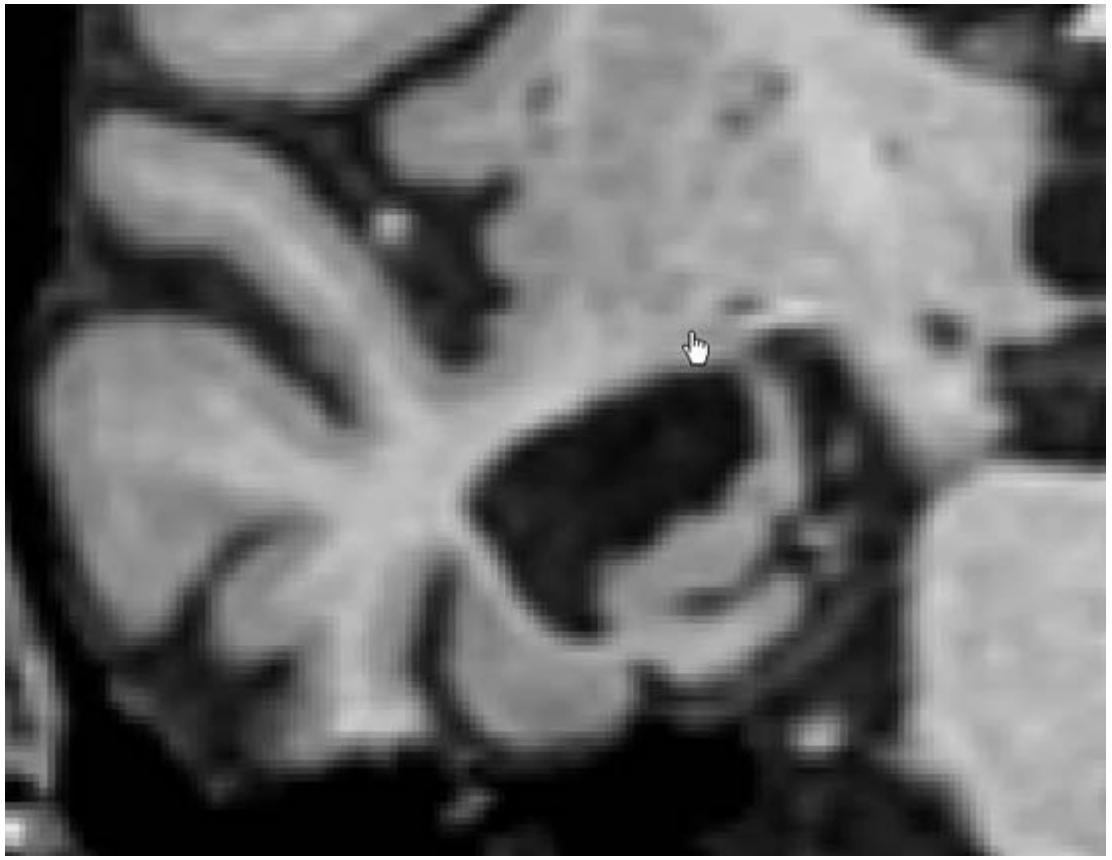
Progression of cerebral atrophy during 10 years



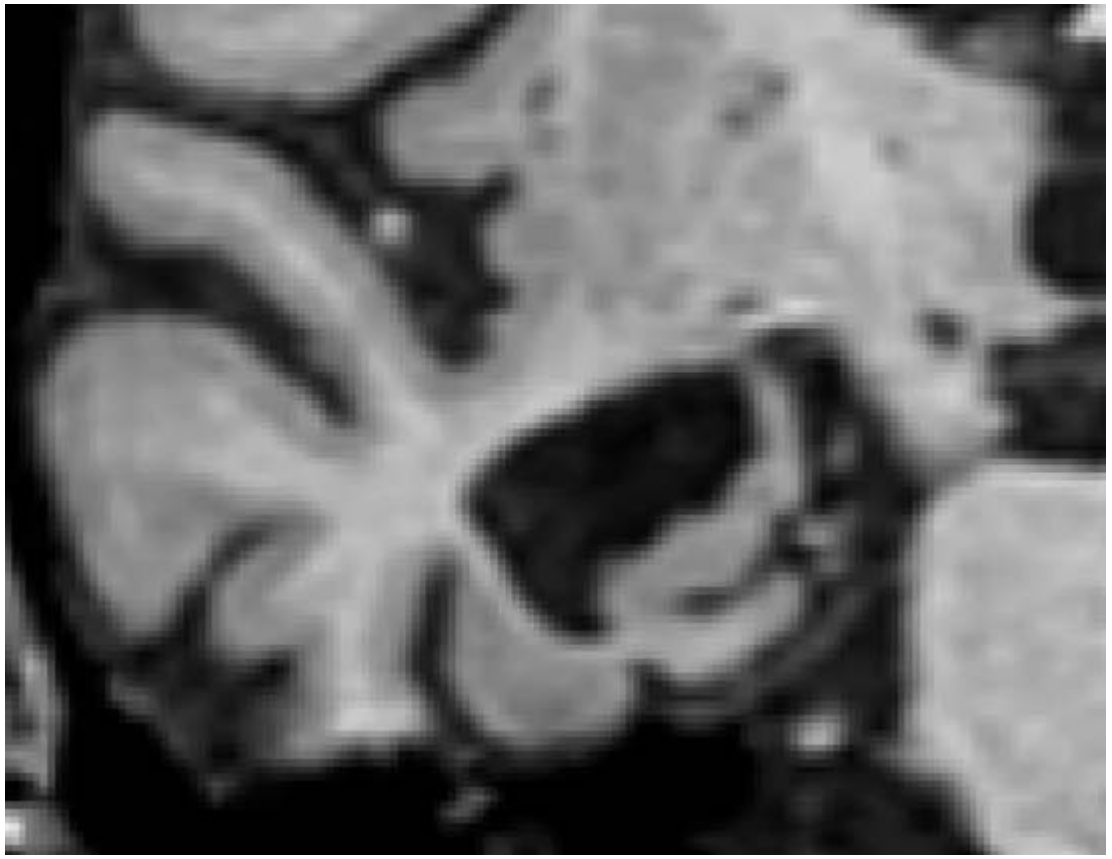
Progression of cerebral atrophy during 10 years



Progression of cerebral atrophy during 10 years



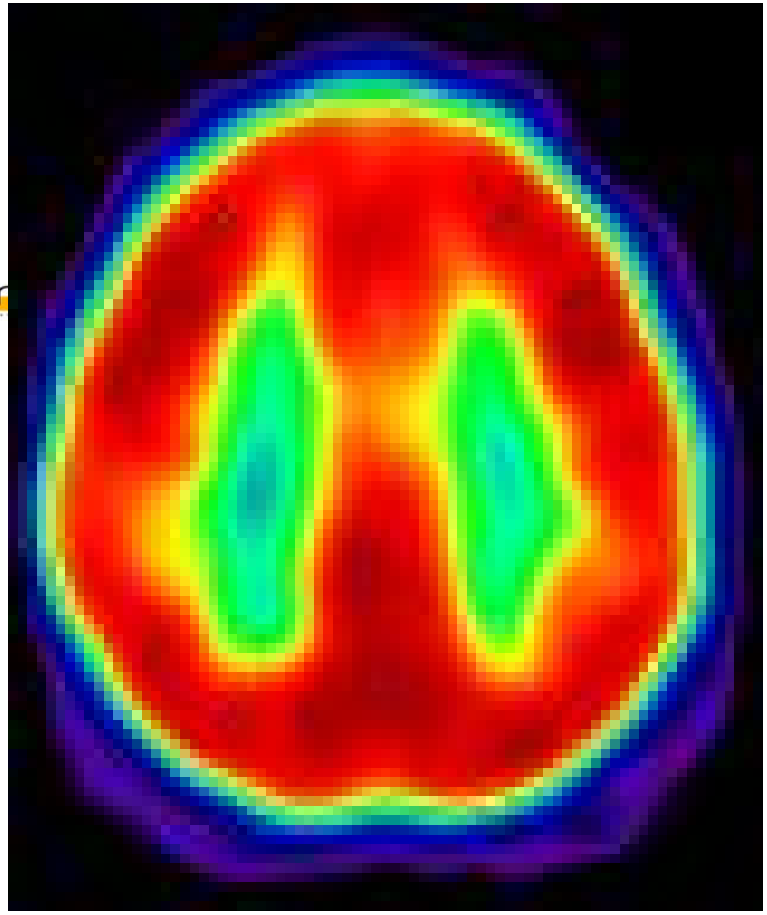
Progression of cerebral atrophy during 10 years

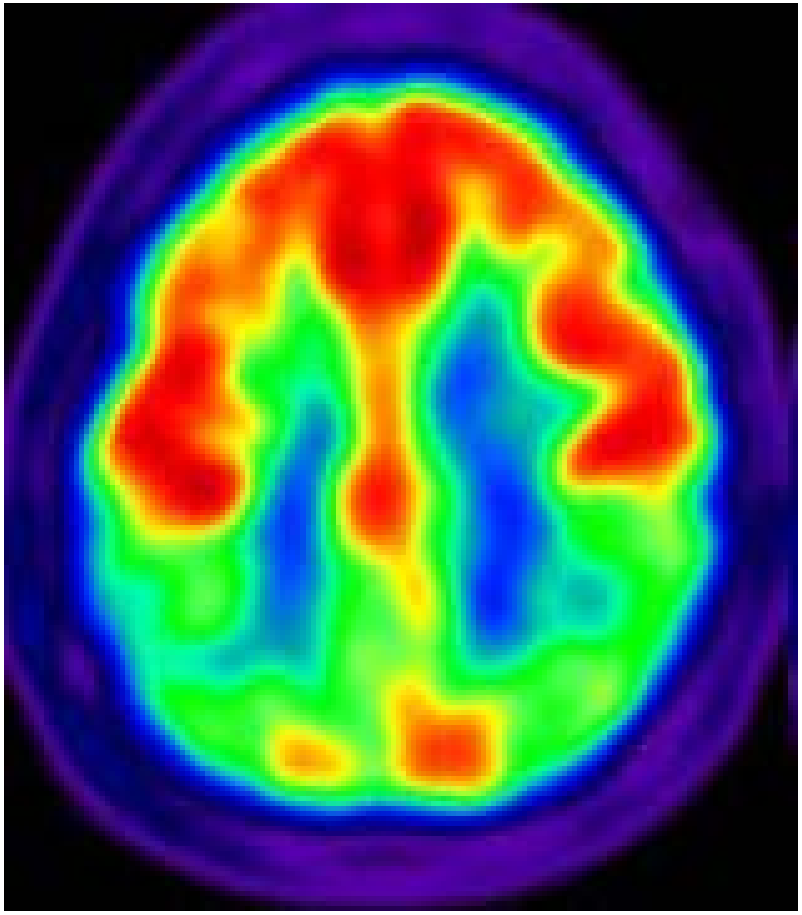


Reduced cerebral metabolism

Normal

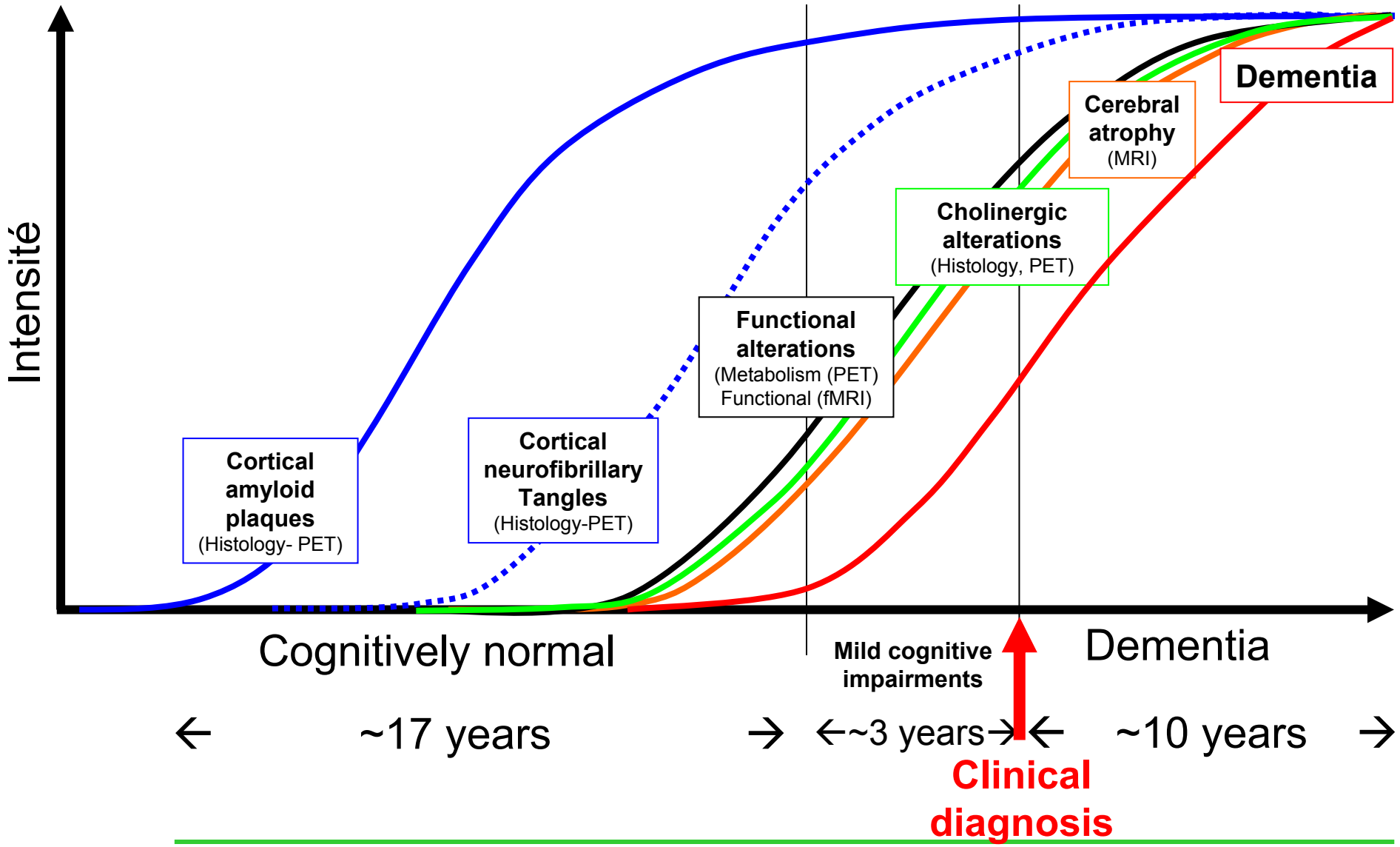
Alzheimer





Measured by PET imaging

Natural history of Alzheimer's disease



Jack et al, 2013

Strategies to modify the clinical outcome?

Disease → Clinical outcome (Phenotype)

Ex. Cognitive alterations
Death, etc…

Validation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Strategies to modify the clinical outcome?

Disease

Therapy

Clinical outcome (Phenotype)

Ex. Cognitive alterations
Death, etc…

Validation

EUROPEAN MEDICINES AGENCY
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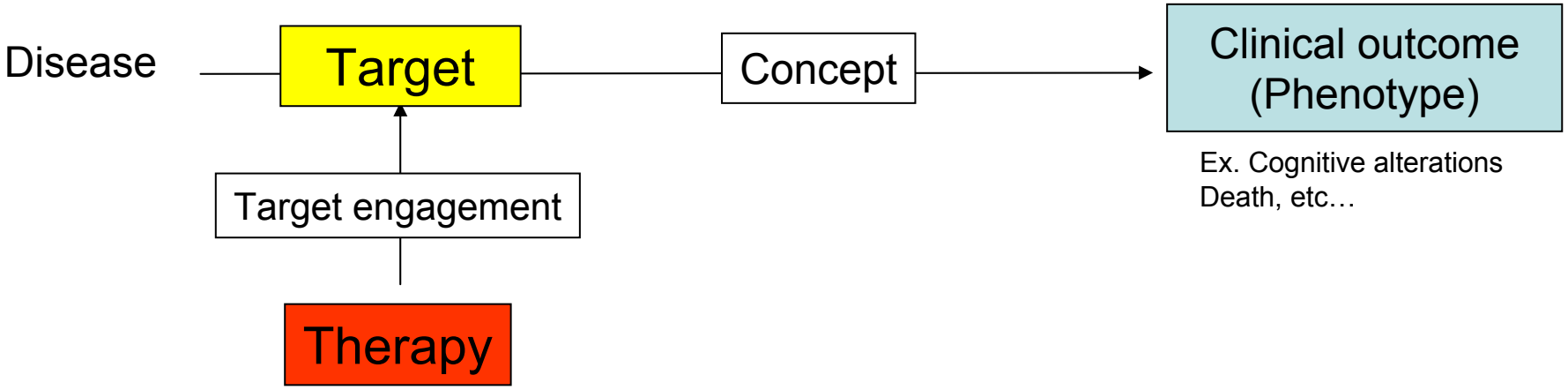
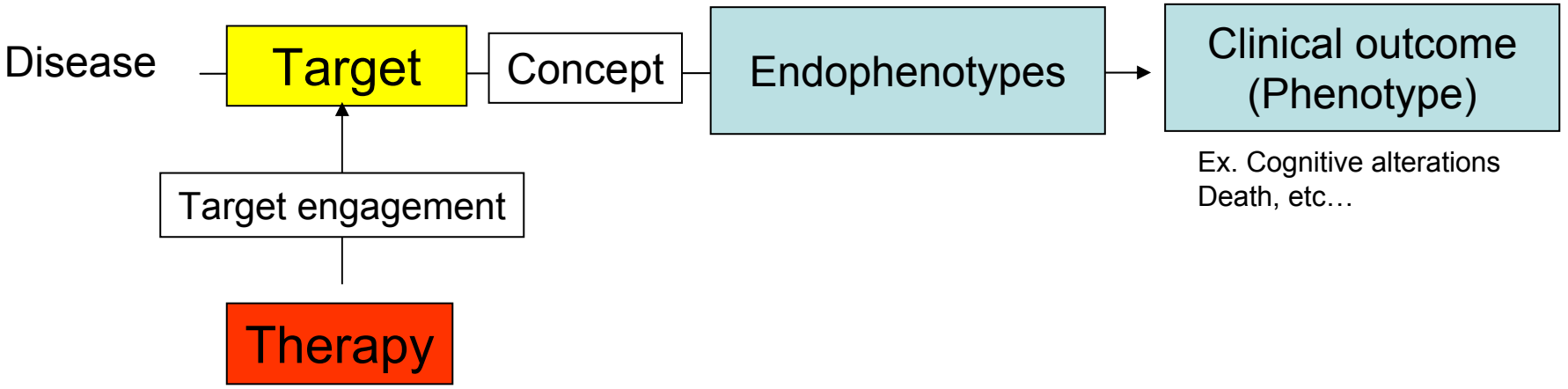
Empiric approaches: Is my drug treating the disease ?

Isolate a target



- Two critical questions
  - Is my therapy modifying/reaching the target ?
    - Target engagement, proof of mechanims (POM)
  - If I modify the target, do I modify the clinical outcome ?
    - Proof of concept (POC)

Natural history of the disease and endophenotypes



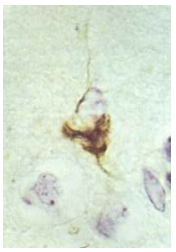
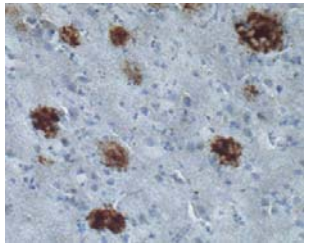
- ***Endophenotypes***
  - Intermediate phenotypes with a manifestation closer to the process at the origin of the disease (as compared to phenotypes)
    - Gottesman & Gould. Am J Psychiatry, 2003, 160: 636-45.
    - Reitz & Mayeux. Neuroscience, 2009, 164: 174-90. (for AD)
  - Their identification allows to
    - Perform more powerful analysis of the therapy efficacy
    - Define milestone in the evaluation of chronic diseases
    - Stratify patients during clinical studies

Evaluation of endophenotypes: markers and biomarkers

Disease → Target → Endophenotypes → Clinical outcome (Phenotype)

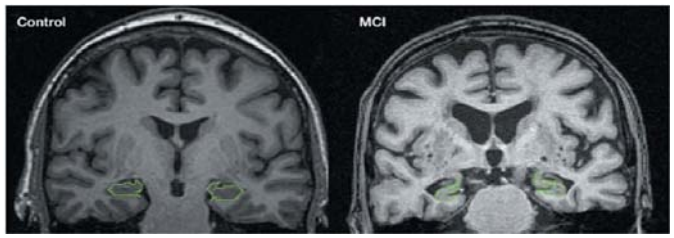
Ex. Cognitive alterations
Death, etc…

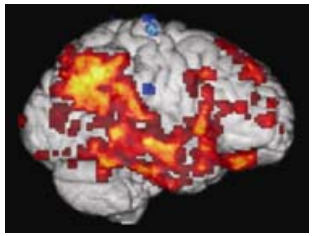
Markers


Biomarkers

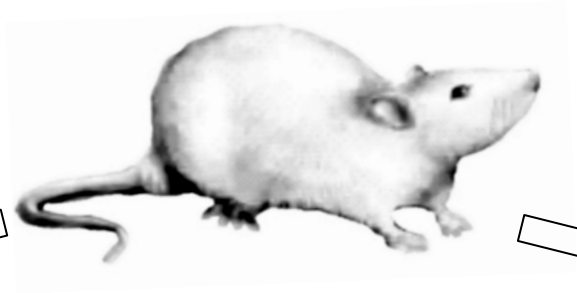
Diagnostic | Longitudinal | Functional



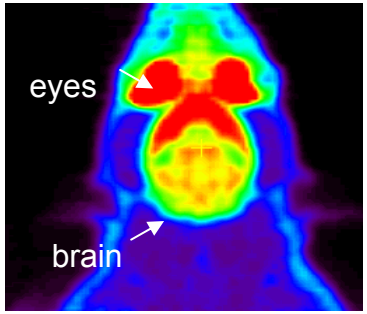


Understand the disease

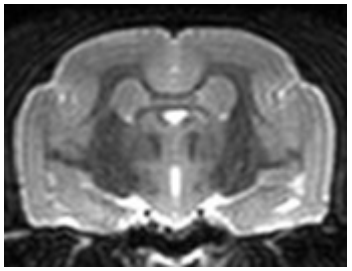
In vivo imaging techniques available for small animals



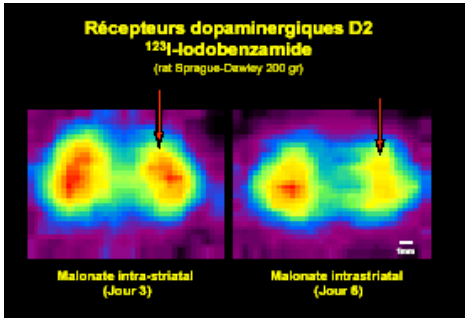
µPET



MRI/µMRI

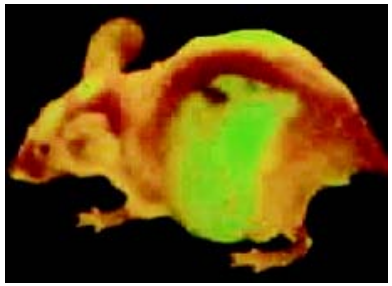


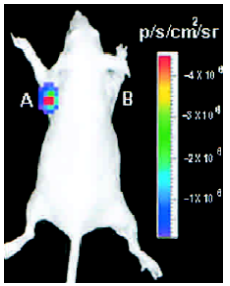
SPECT



Optical

(fluorescence & bioluminescence)

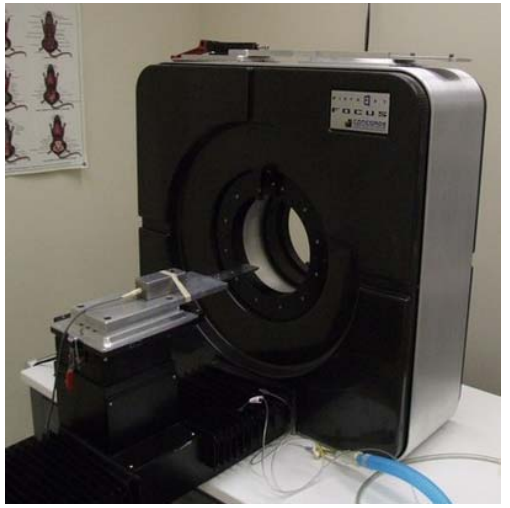




BIOLOGICAL IMAGING MODALITIES

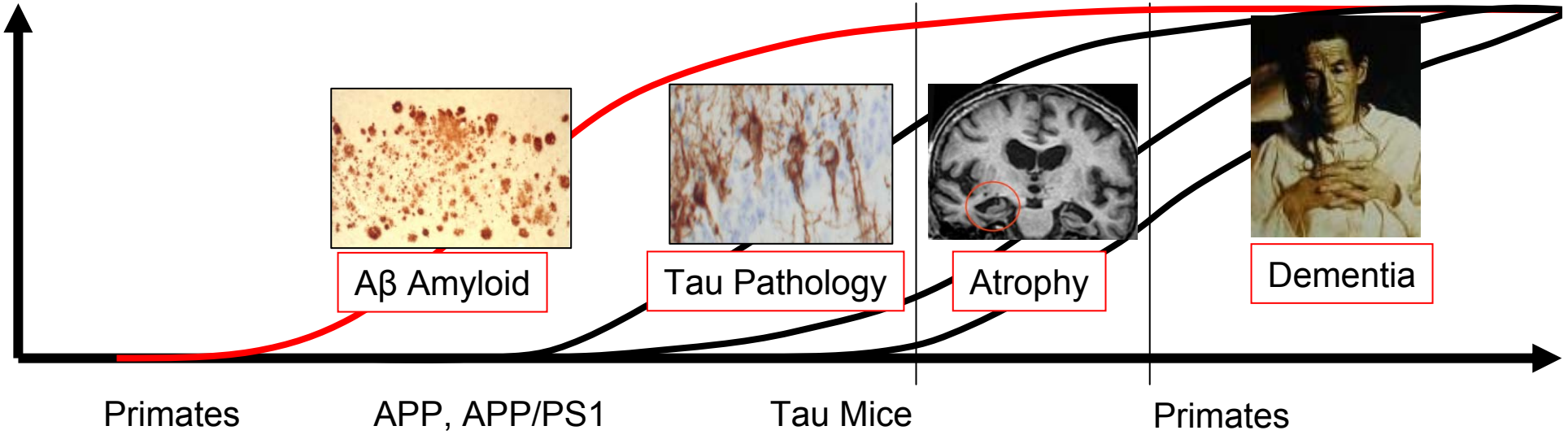
MODALITY	PARAMETERS	RESOLUTION	SENSITIVITY	APPLICATIONS
MRI	Spontaneous contrast or contrast agents T_1 & T_2 relaxation	0.1 mm 40 µm	0.1 µmole ^{1}H	Anatomy Blood Flow
PET	Radiotracer Concentration µCi/ml	SPECT: 5 mm PET: 2-3 mm µPET: 1 mm	10^{-6} µmole	Metabolism, PK/ADME Blood flow/volume, Perfusion Receptor concentration Gene expression

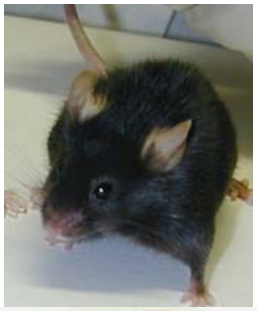
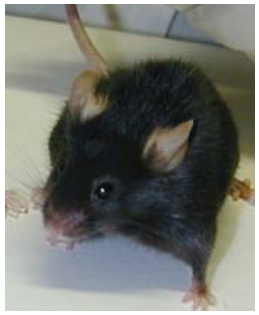
MRI

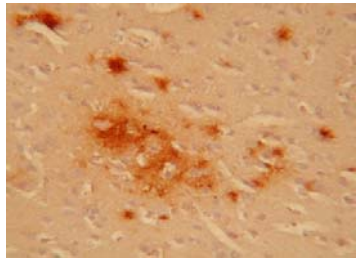
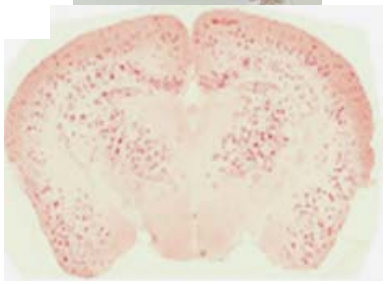
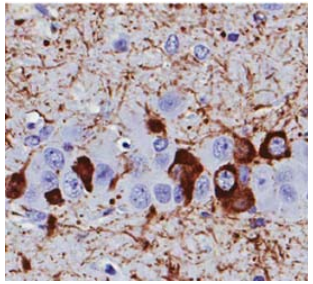
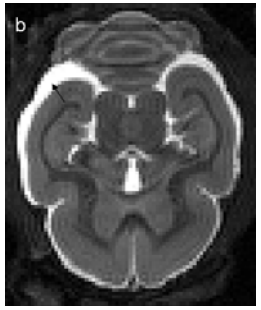


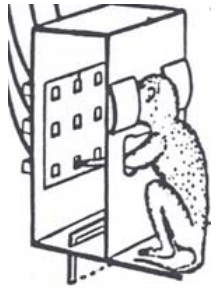
PET

Which animal model ?



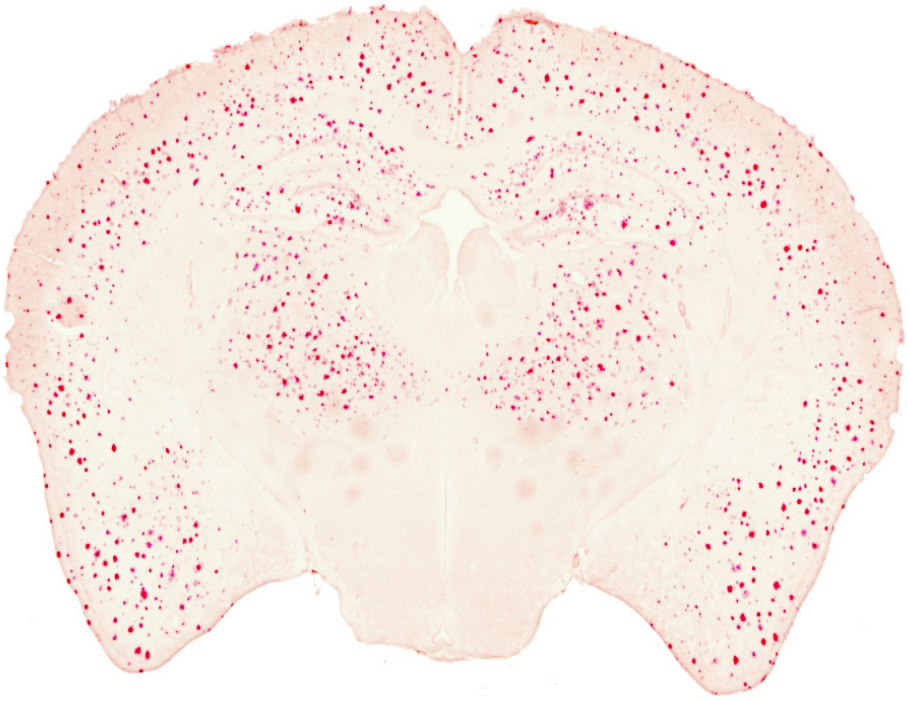






Amyloid mice

APP/PS1



Model of amyloidosis
→ Evaluation of anti-amyloid drugs

Tau mice

ex. Tau(P301L)

Model of Tau pathology
→ Evaluation of anti-Tau drugs

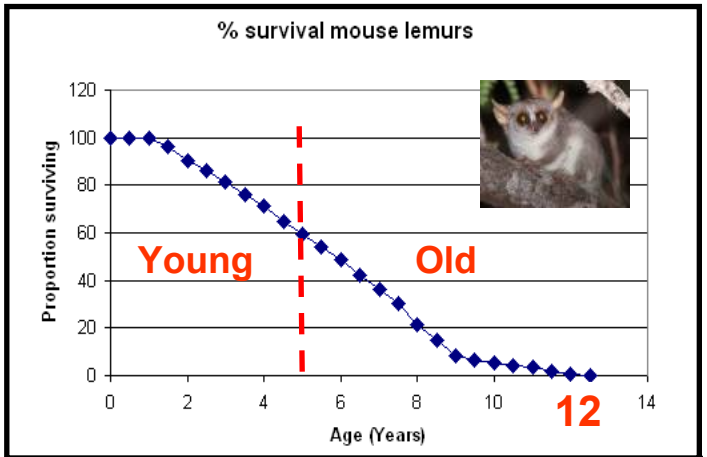
Mouse lemur

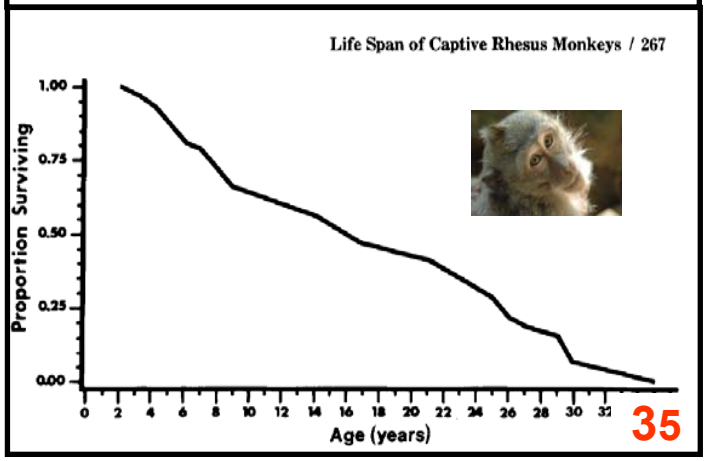
Primate

Phylogenic proximity with humans

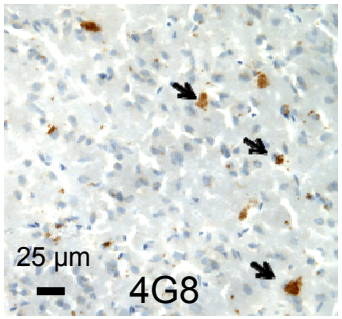
Small size/ smallcost

Short life span

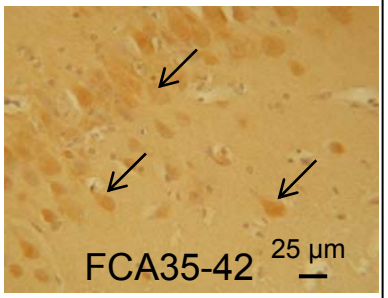




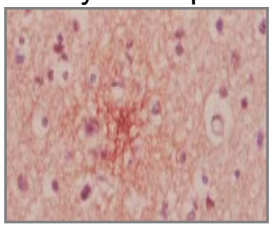
Intracell APP



Intracell Abeta

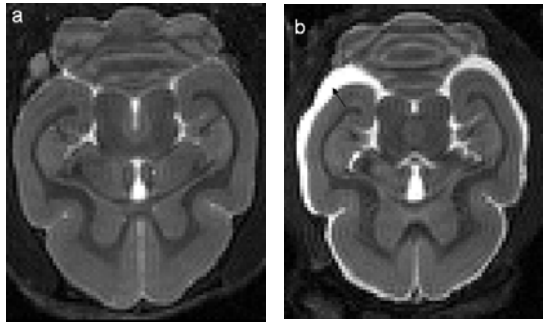


Diffuse amyloid deposits (rare)



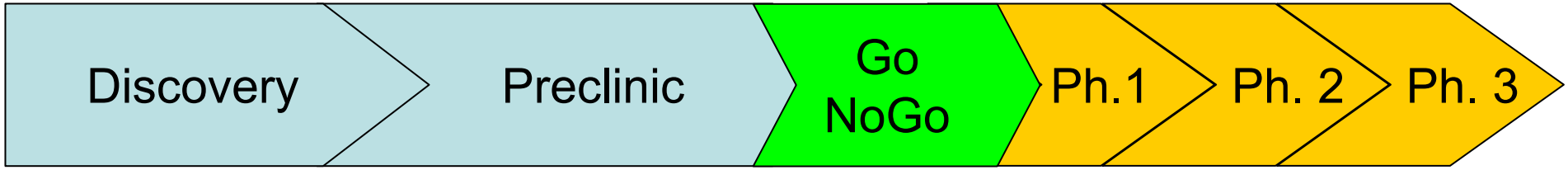
Bons et al., Neurobiology of aging, 1991

Cerebral atrophy correlated to cognitive alterations

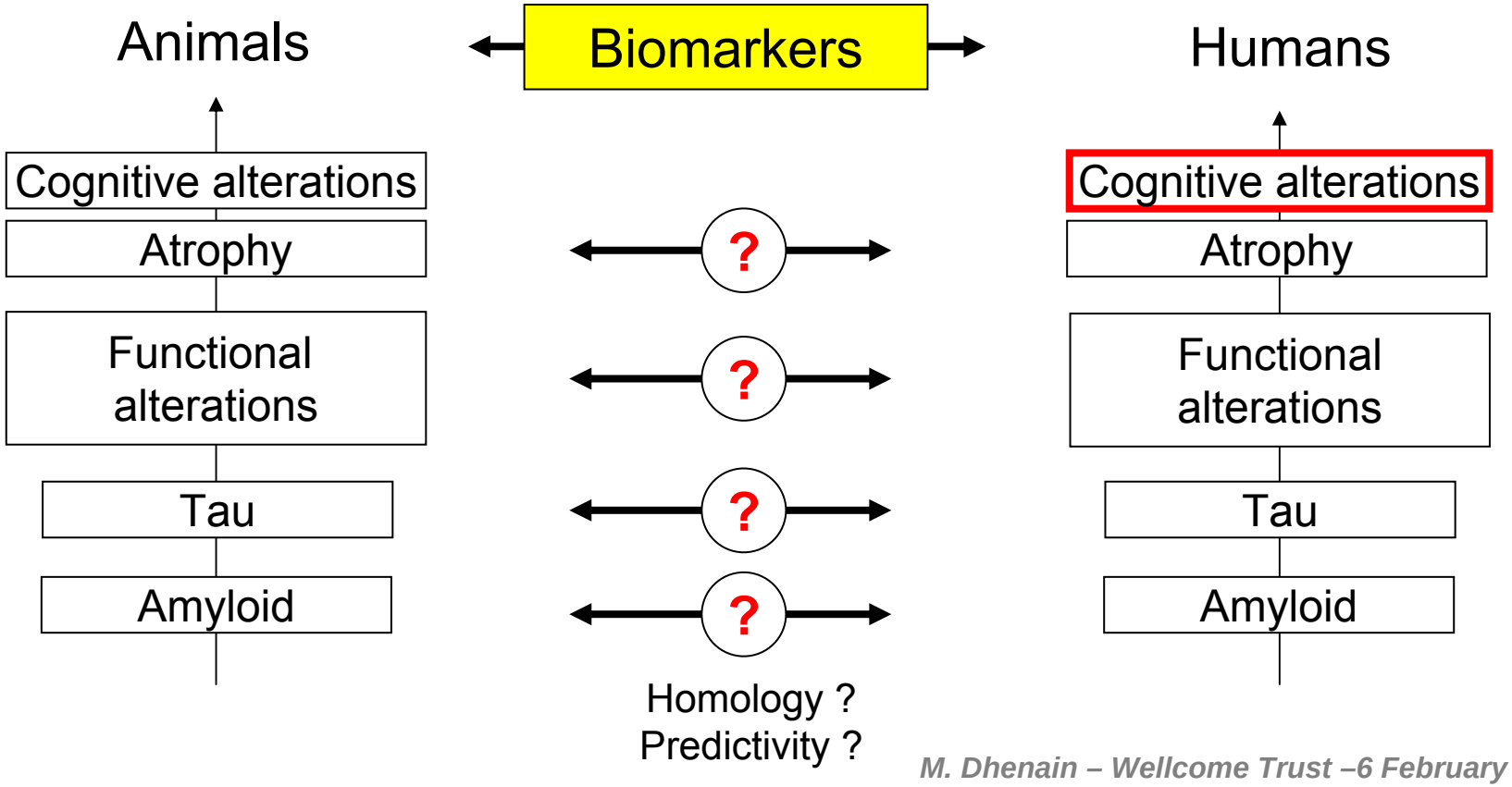


Proposed framework

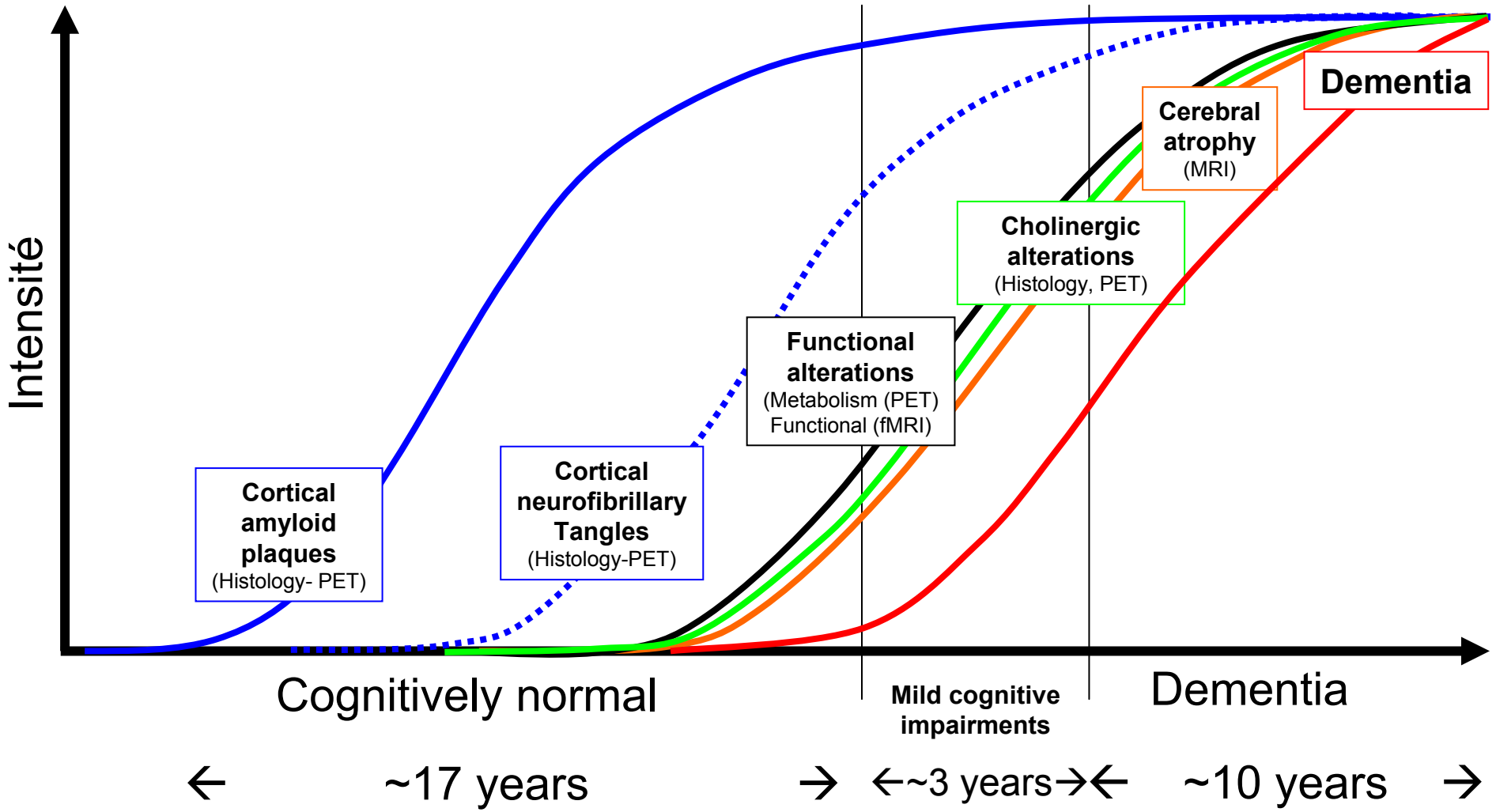
- Classical approach



- Proposed approach

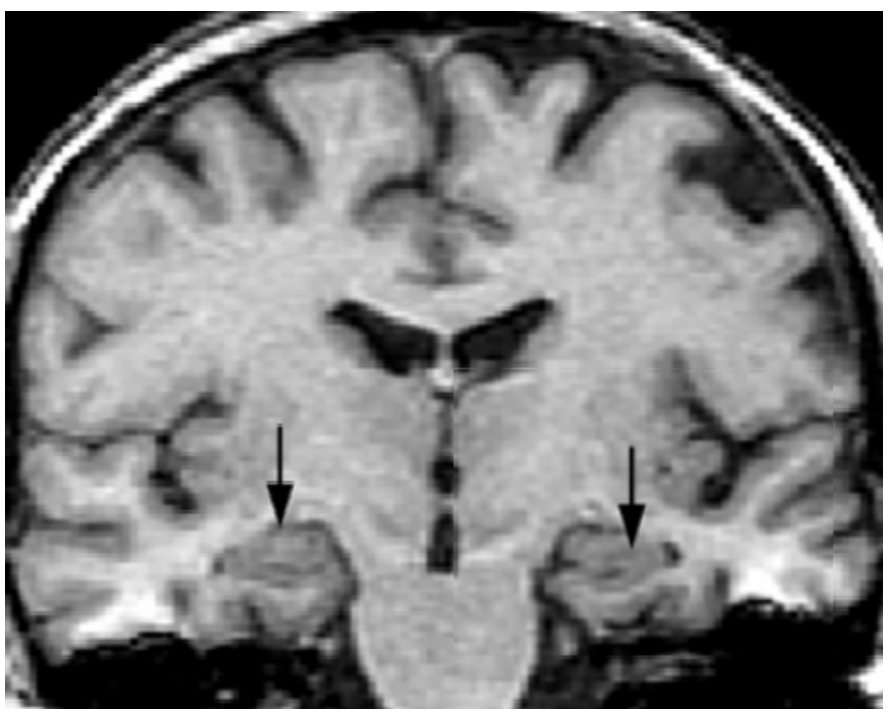


Cerebral atrophy

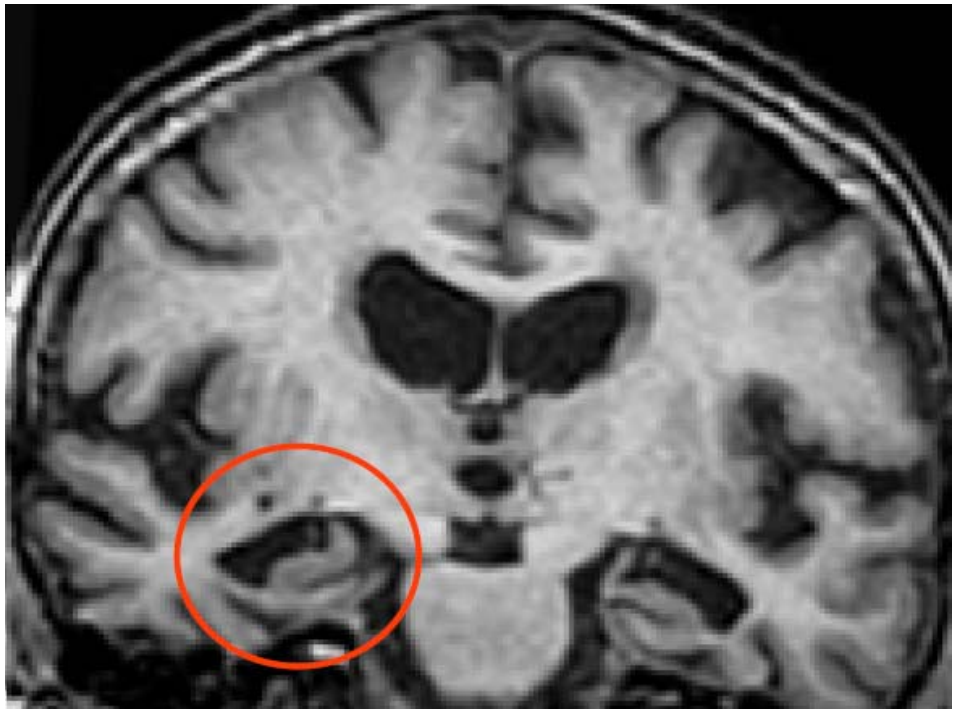


Jack et al, 2013

Cerebral atrophy in humans with Alzheimer



Normal aging



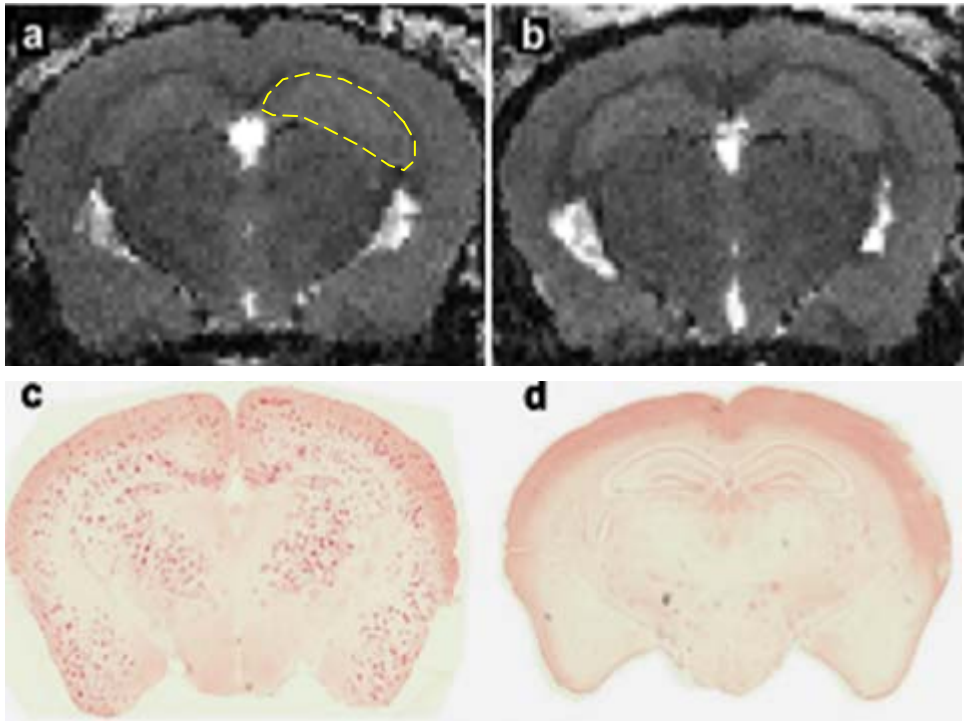
Alzheimer

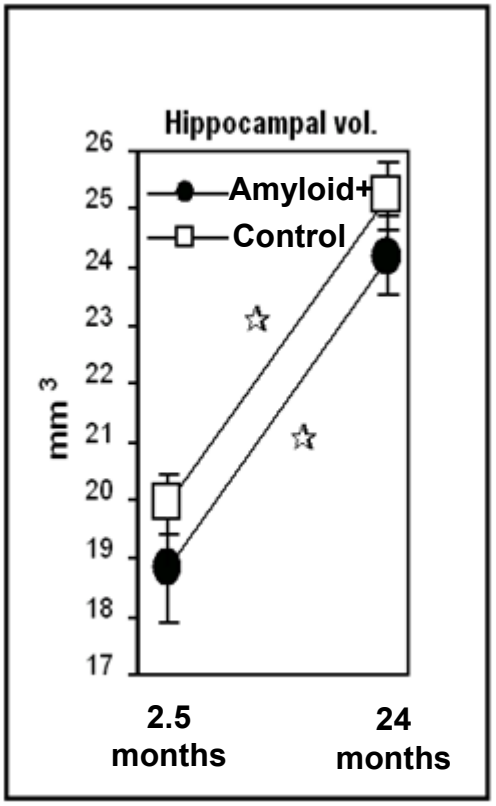
Starts in the hippocampus then spreads all over the brain

Evaluation of cerebral atrophy in animal models of AD

Images provided by Dr. S. Lehericy

No atrophy in mouse model of amyloidosis

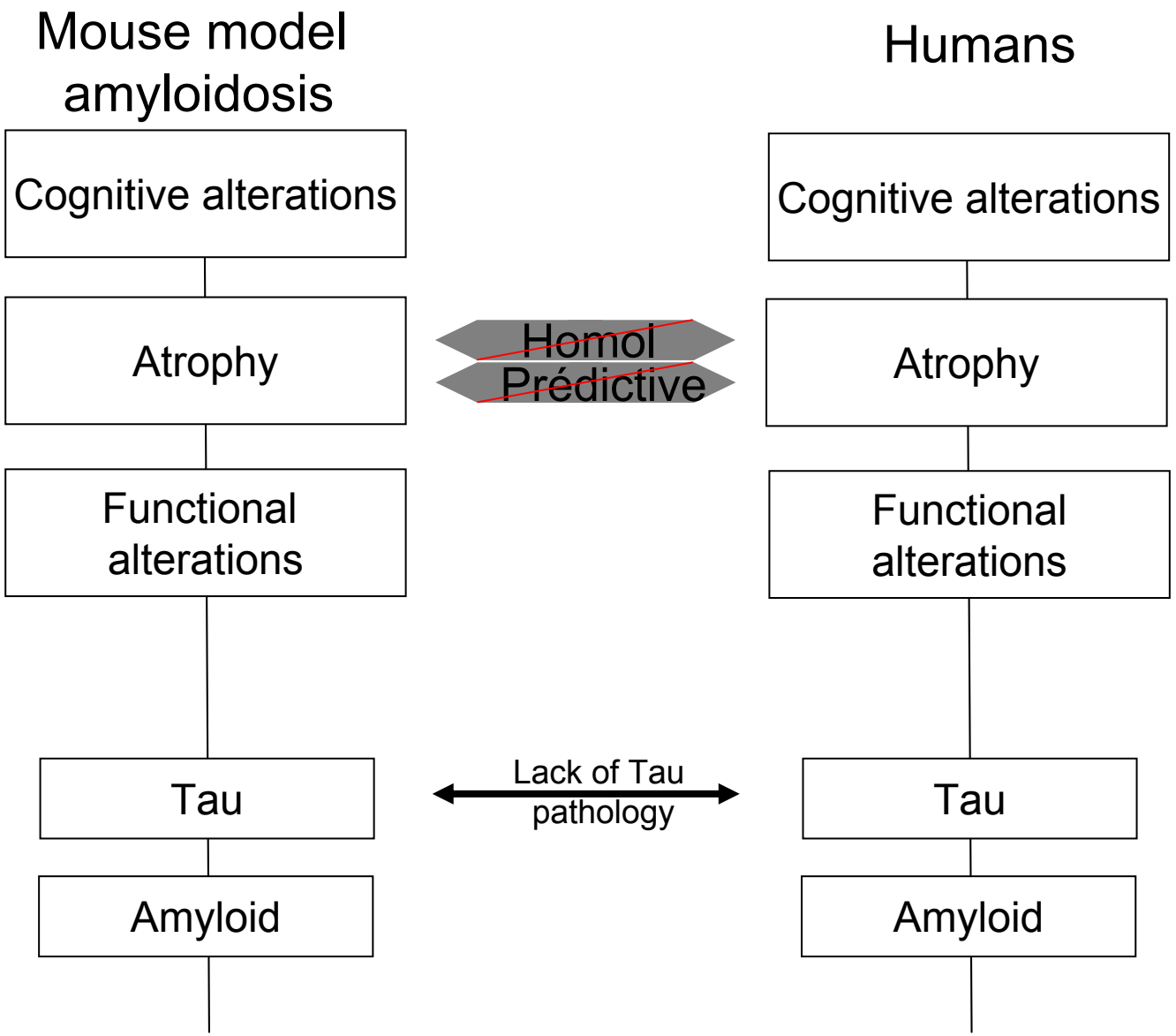




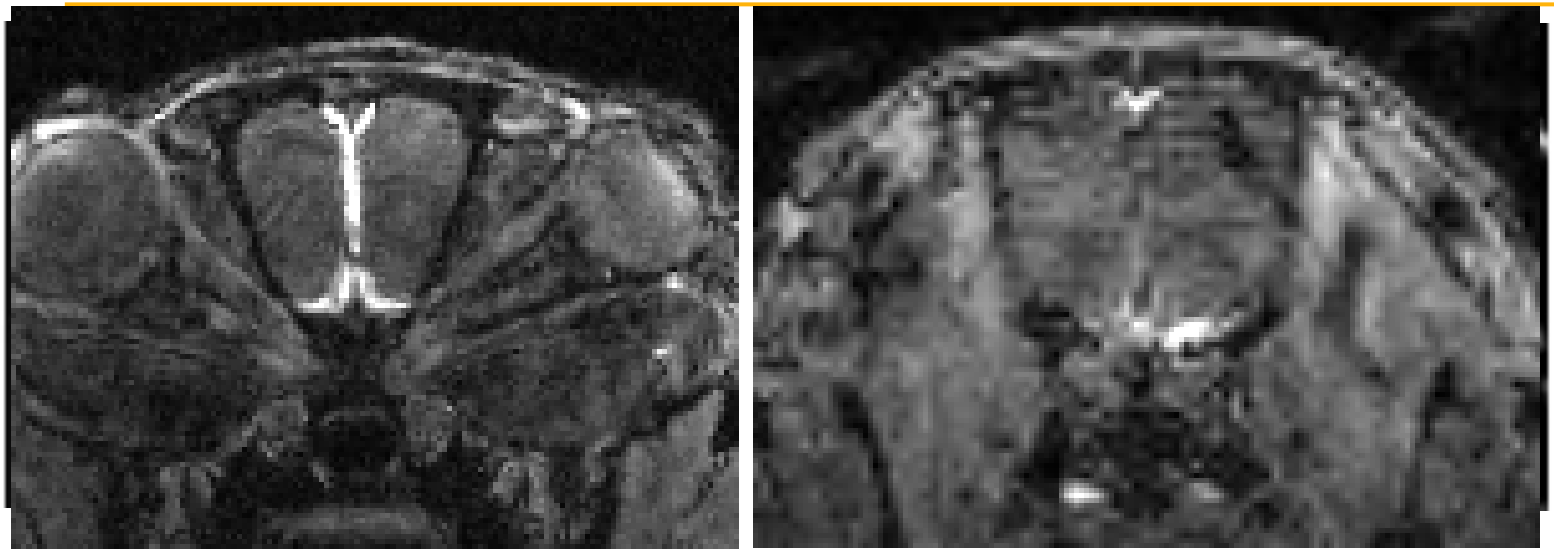
Brain and hippocampal growth
even in the presence of amyloid deposits…

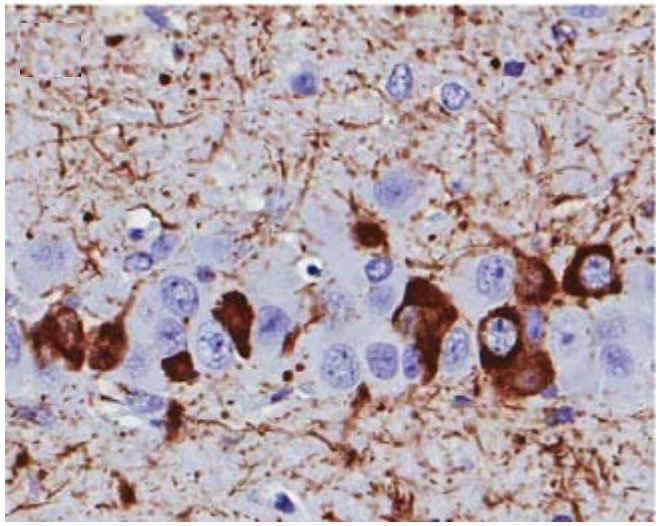
Delatour B. et al.. Neurobiol Aging, 27(6), 835-847; 2006.

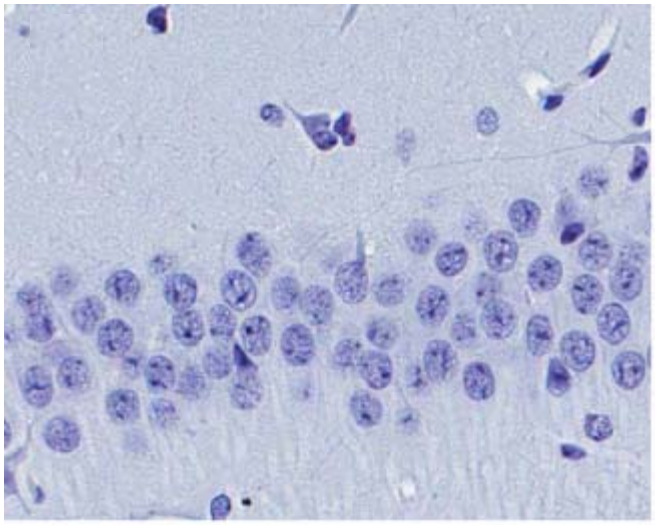
MRI biomarkers in models of amyloidosis



Cerebral atrophy in Tau mice



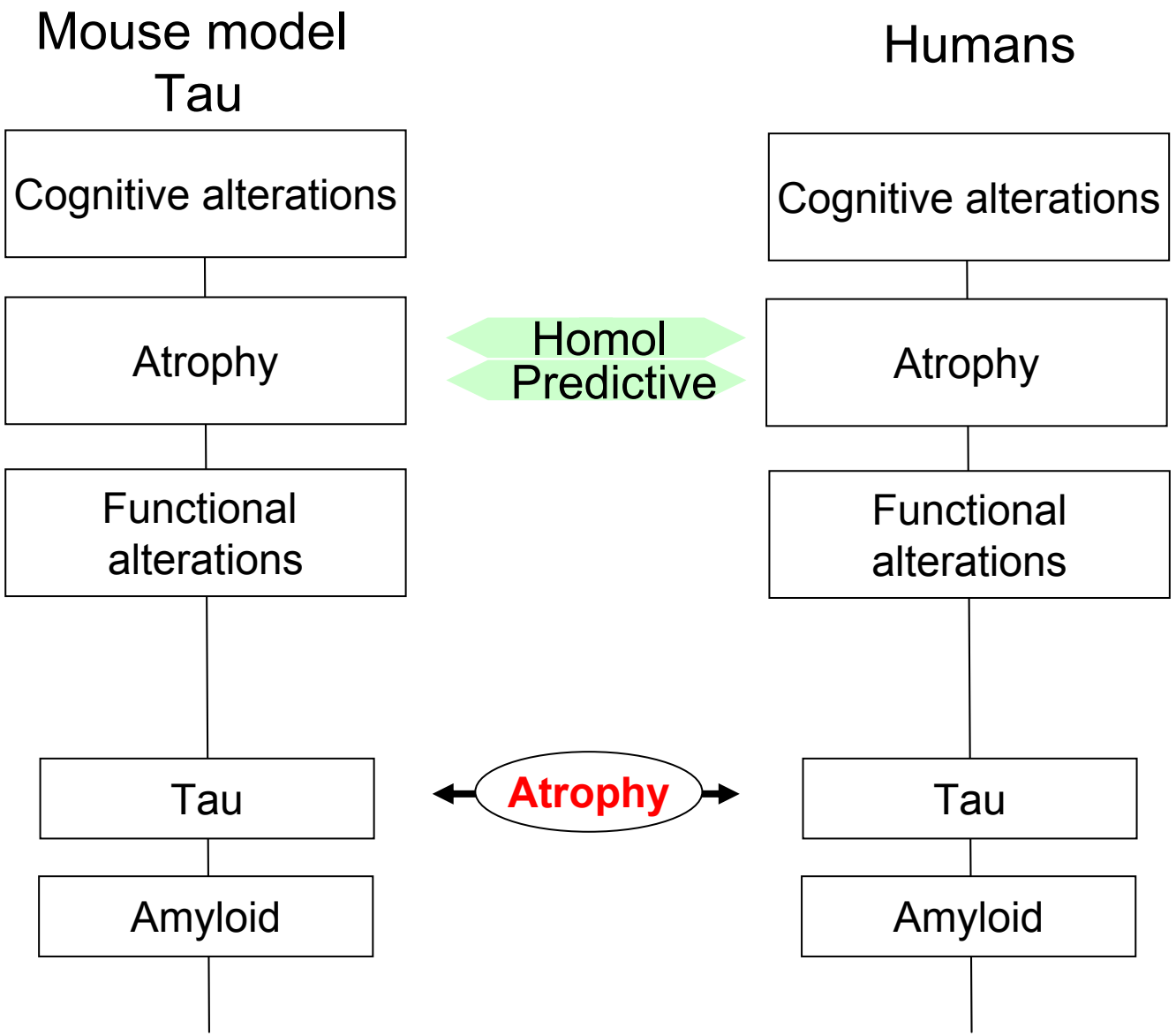




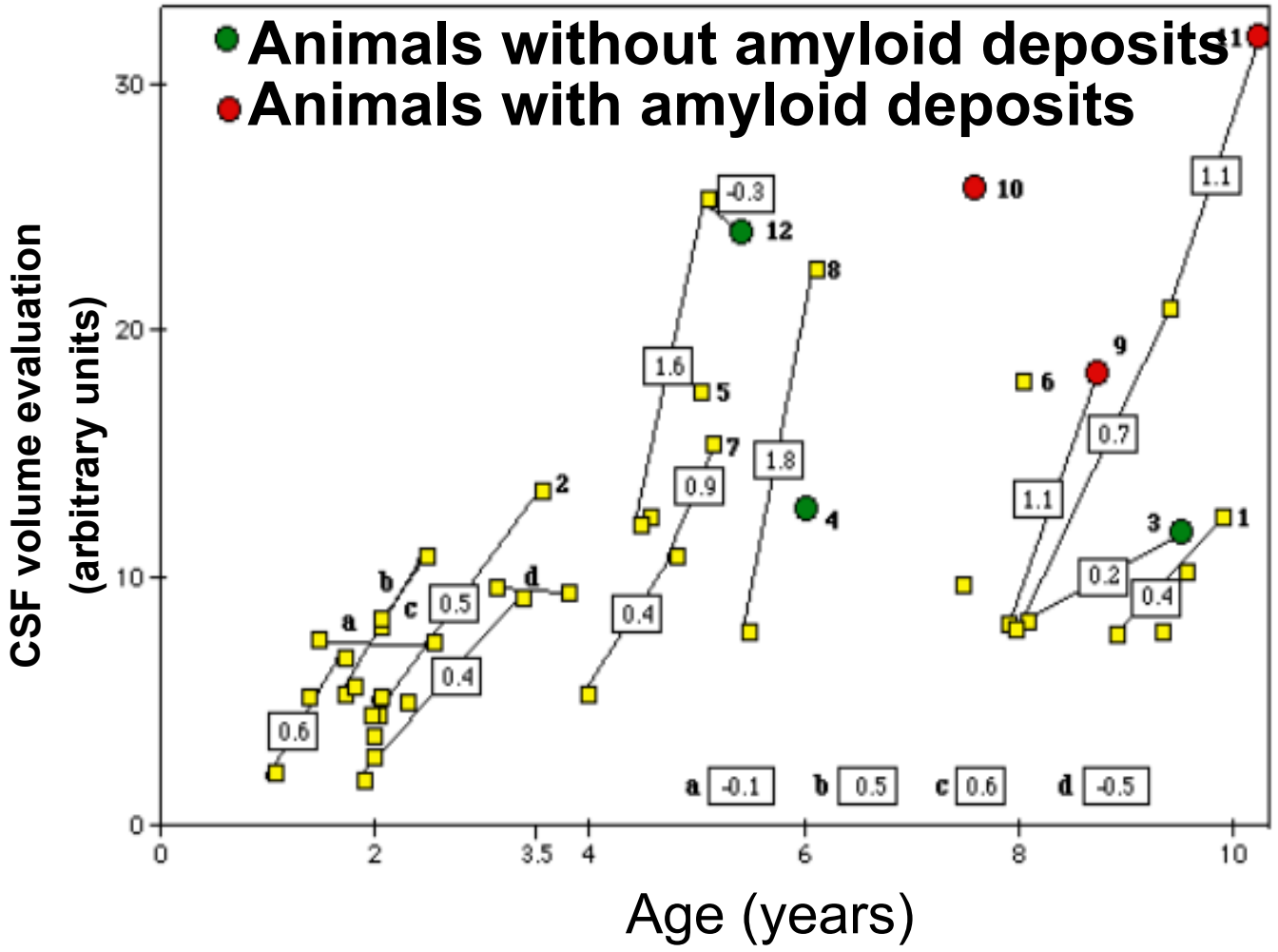
Suggests that atrophy is a marker of Tau pathology

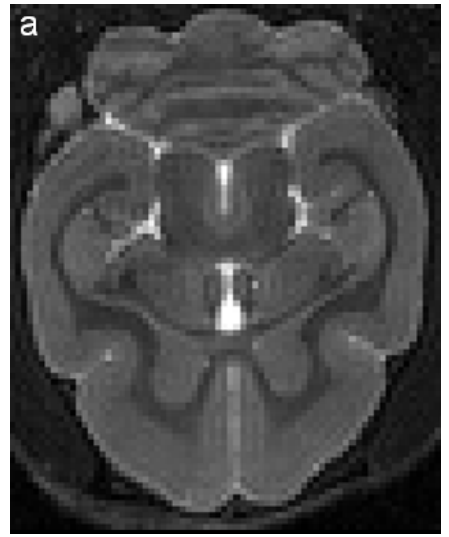
Yang D et al. Neuroimage, 2011 (rTg4510 = P301L mice)

MRI biomarkers in models of Tau pathology



Cerebral atrophy in mouse lemurs



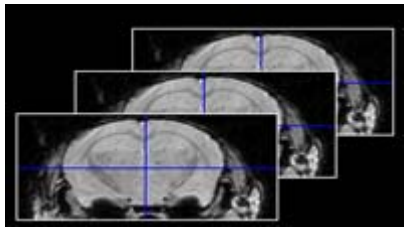


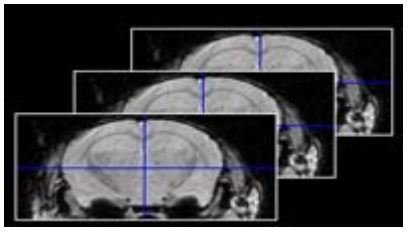
Correlation with cognitive alterations

Dhenain et al. Neurobiol Aging. 2000; Picq et al. Neurobiol Aging. 2013

Group analysis

Voxel based analysis (VBA) methods

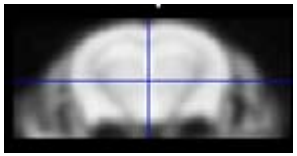




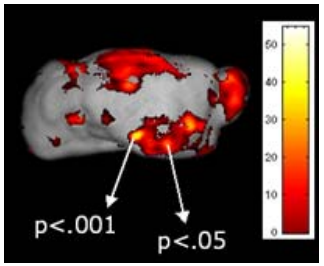
Group 1: X animals (young)

Group 2: X animals (old)

Is there a significative difference between the images from the group 1 versus the group 2 animals ?



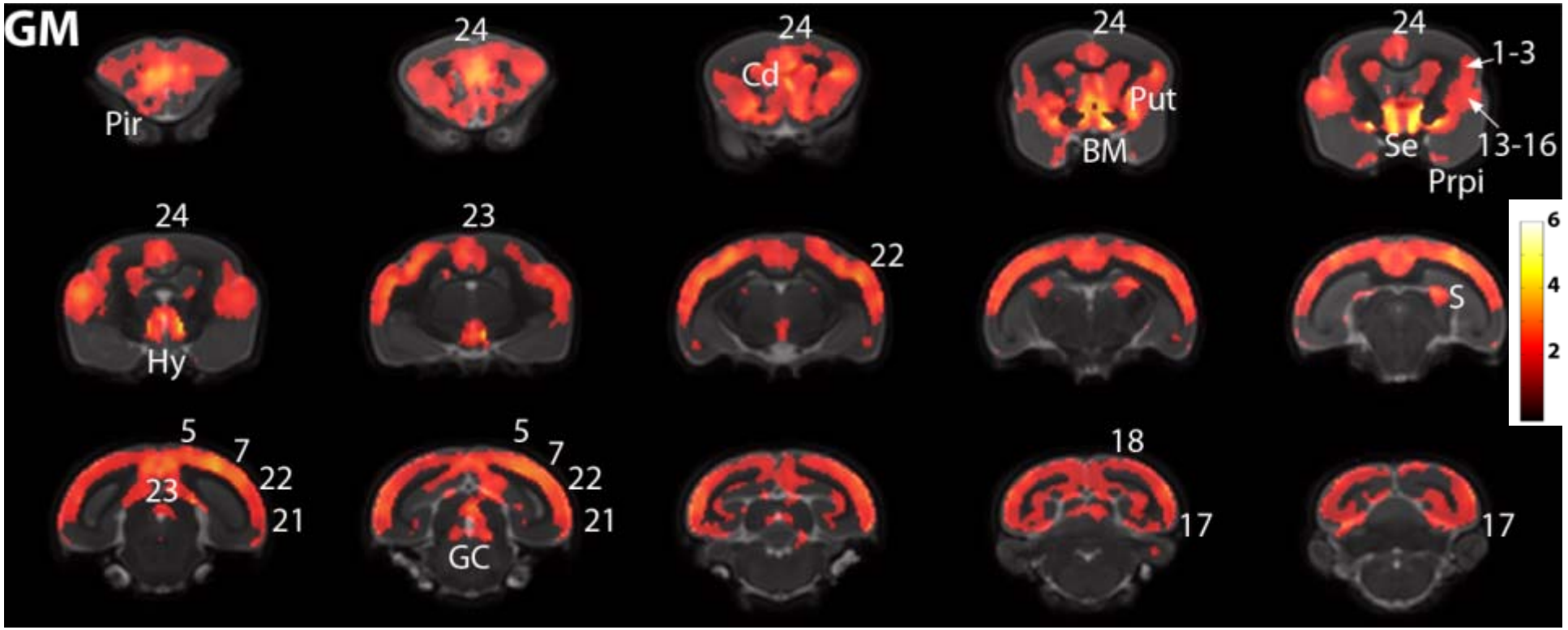
Spatial normalisation on a template
Statistical analysis



Statistical maps showing regions of significative differences

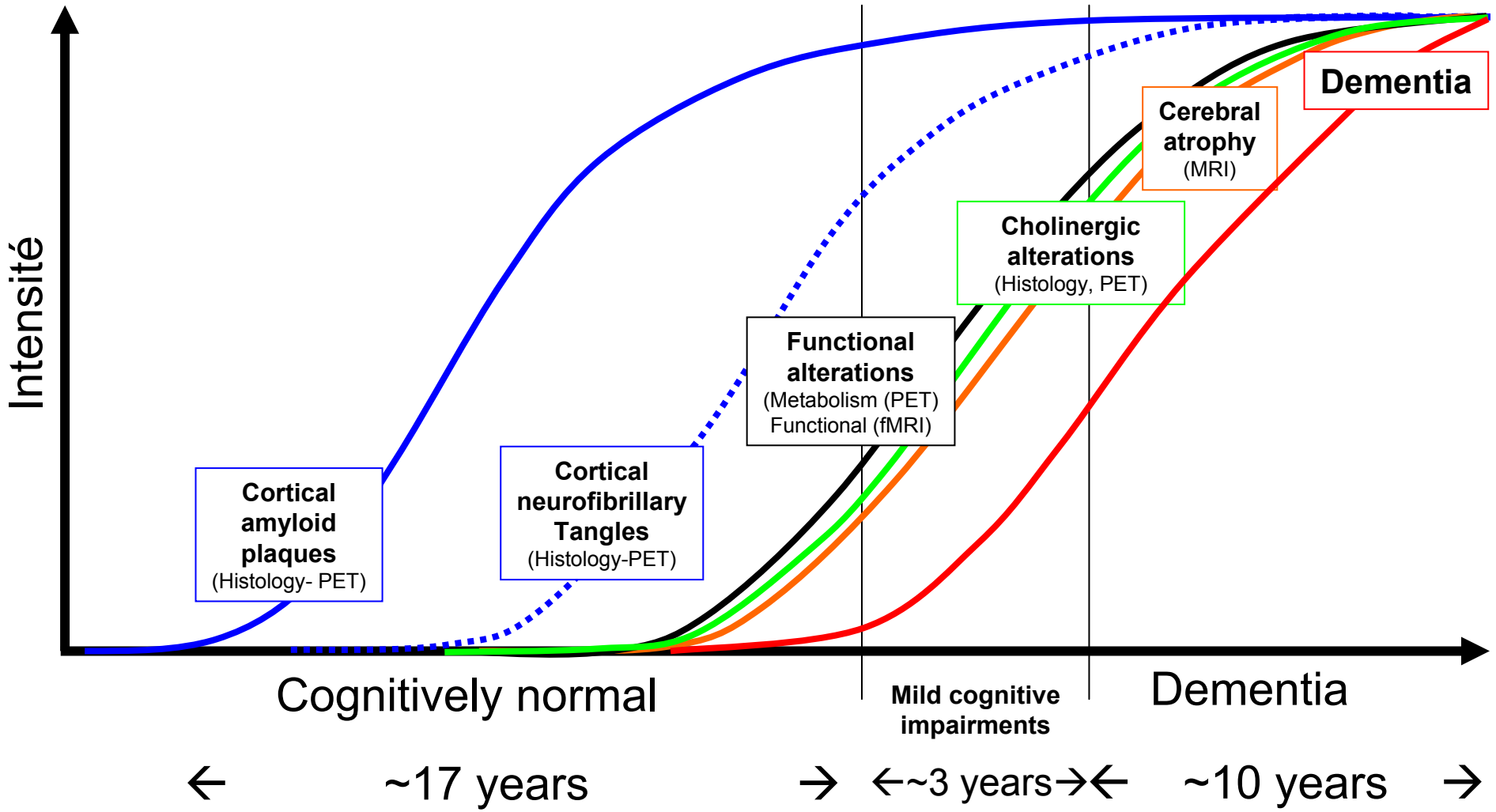
Quantification of cerebral atrophy (in lemurs)

- Voxel based methods



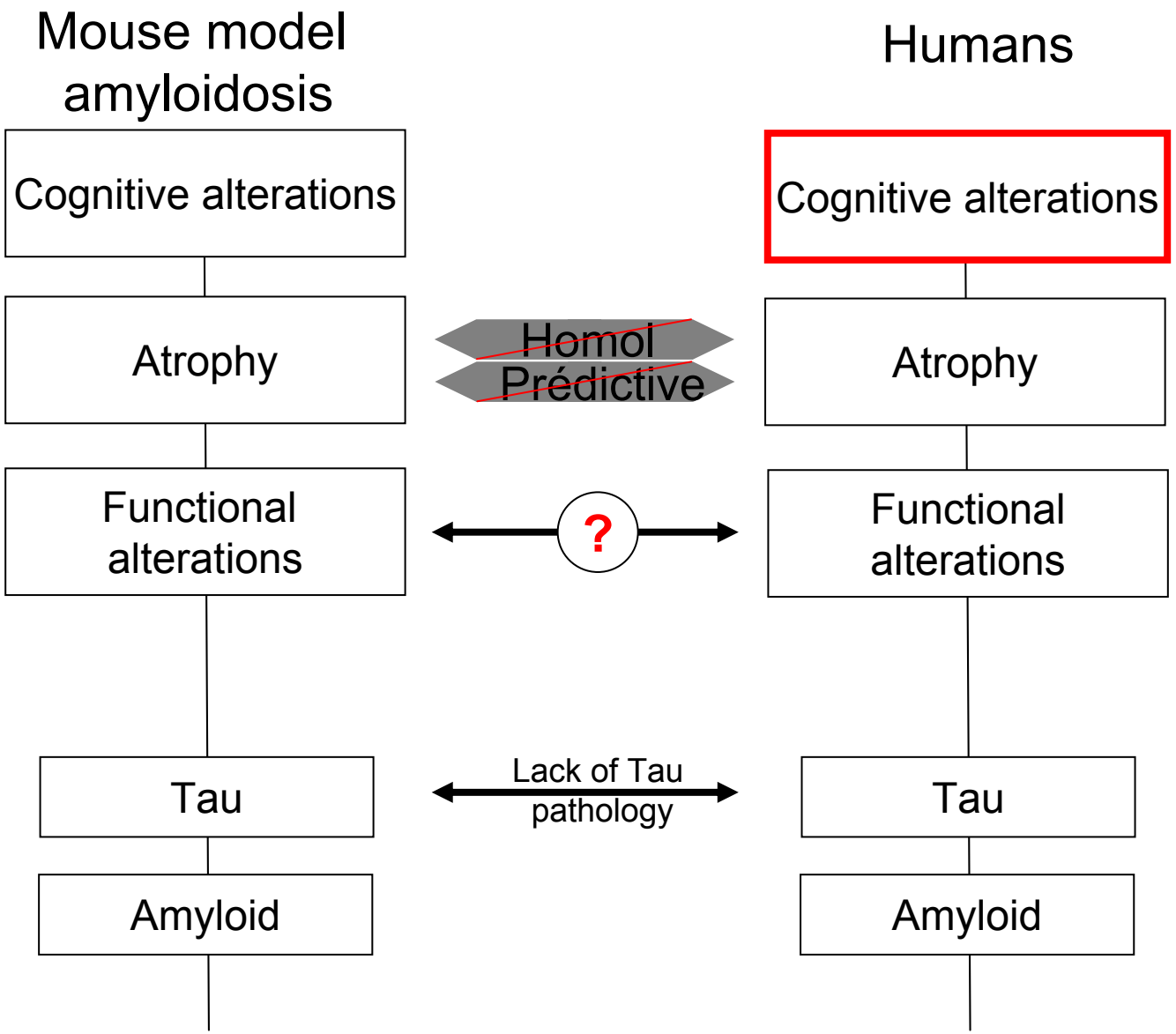
Sawiak et al., Submitted

Functional alterations

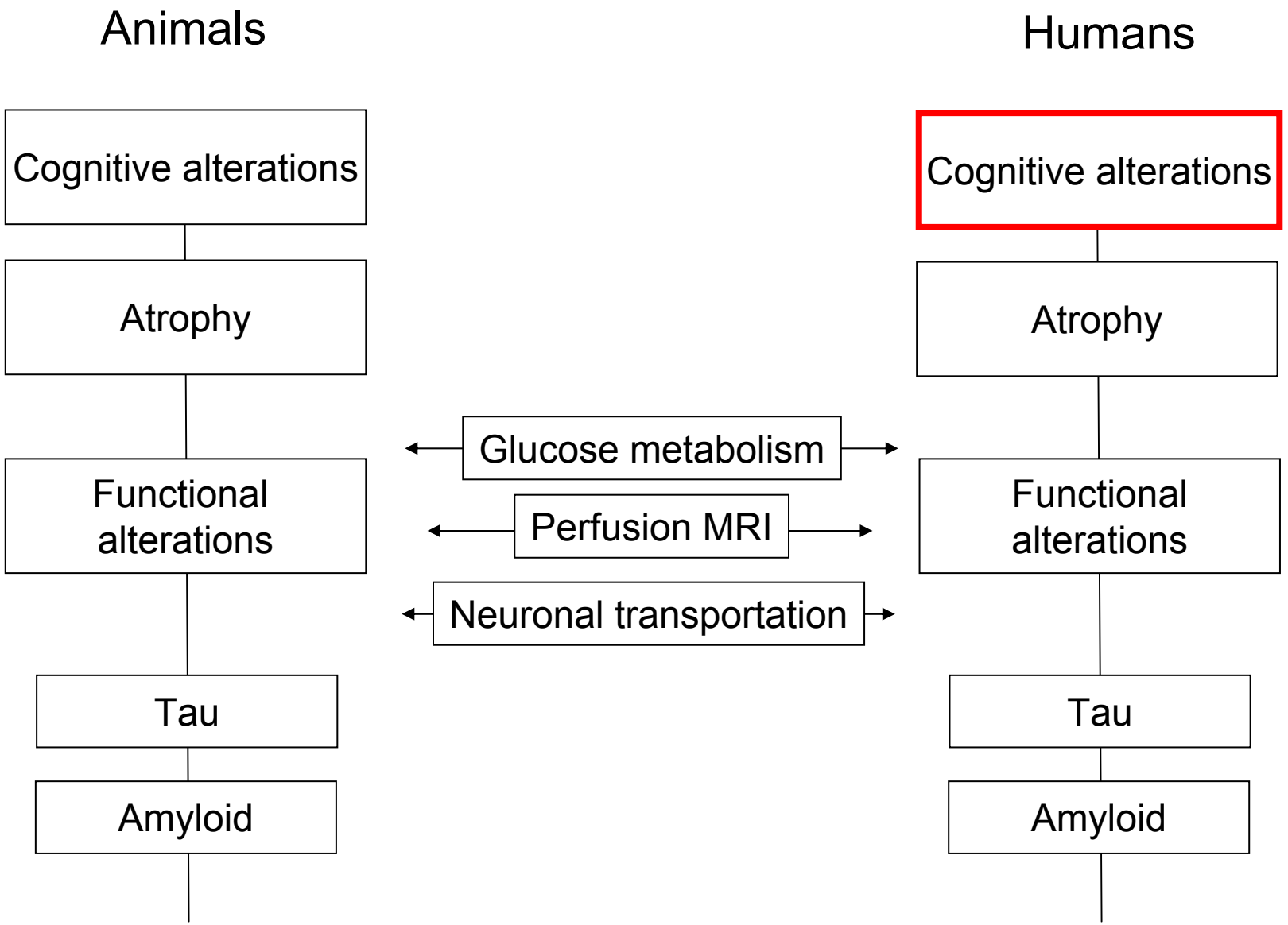


Jack et al, 2013

Biomarkers in models of amyloidosis



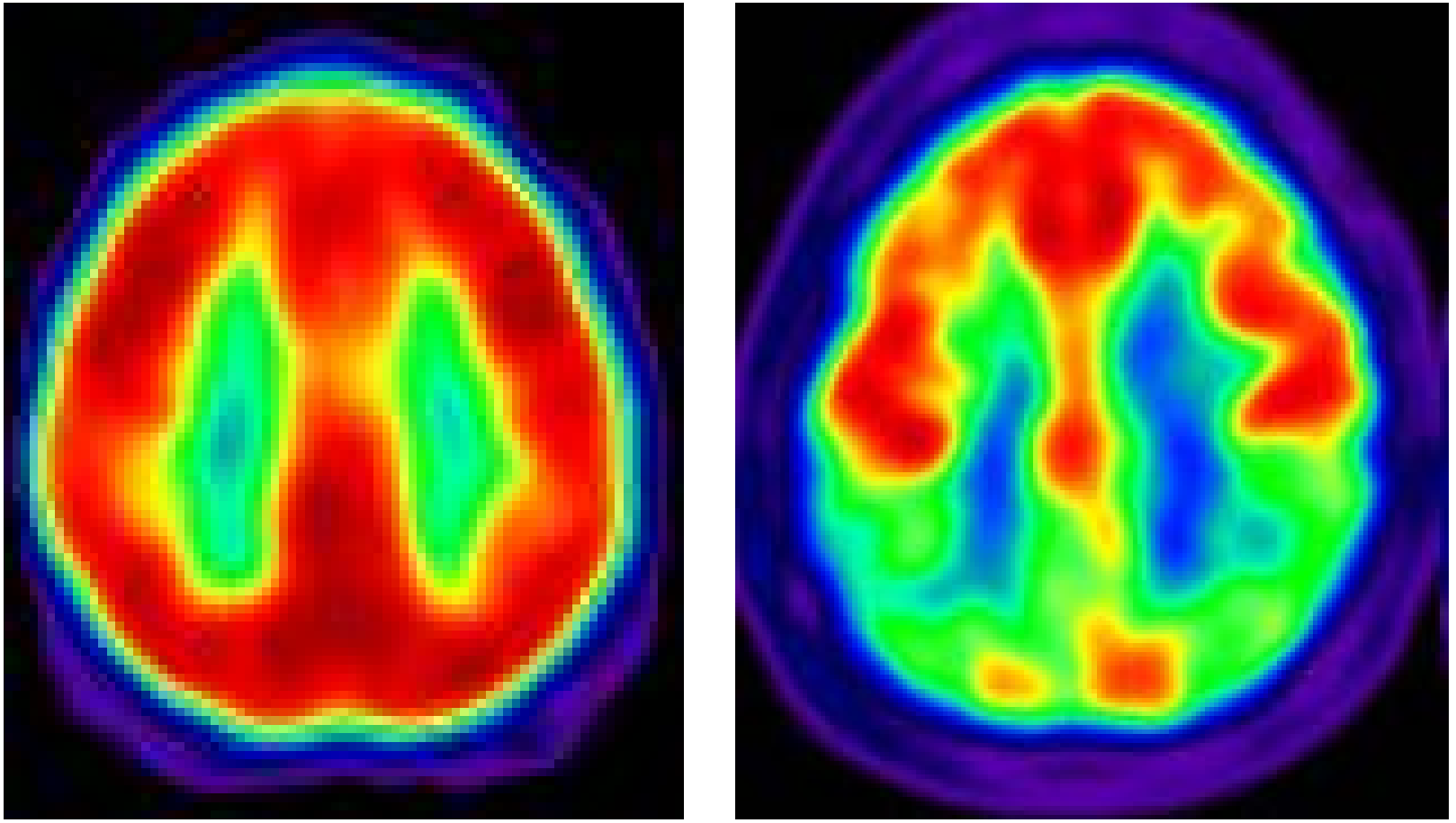
Functional alterations



Reduced cerebral metabolism

Normal

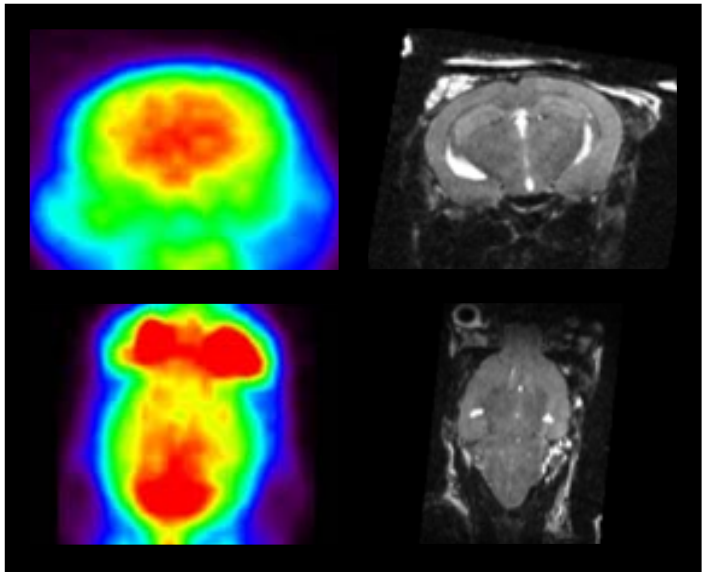
Alzheimer

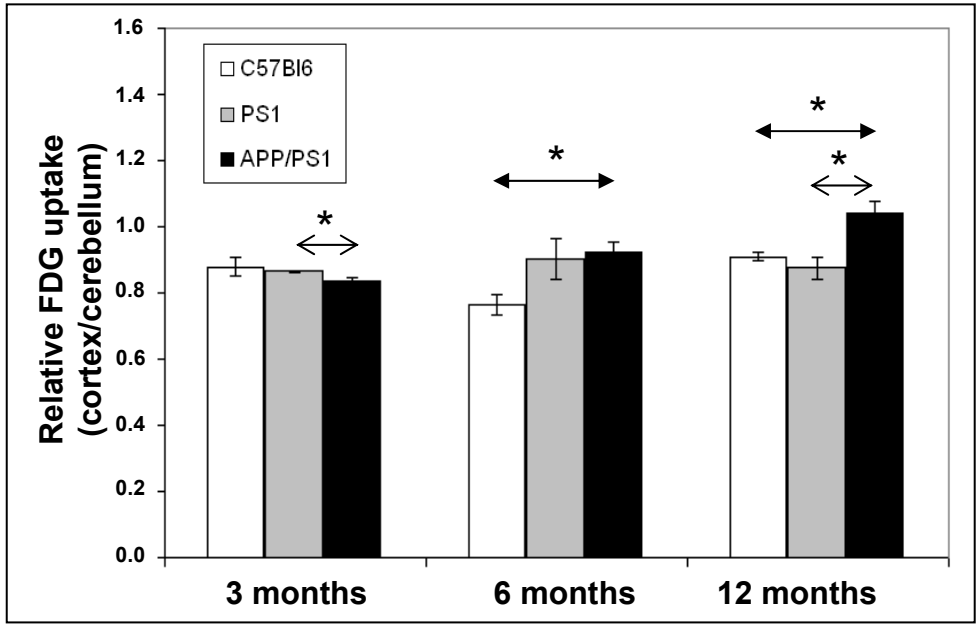


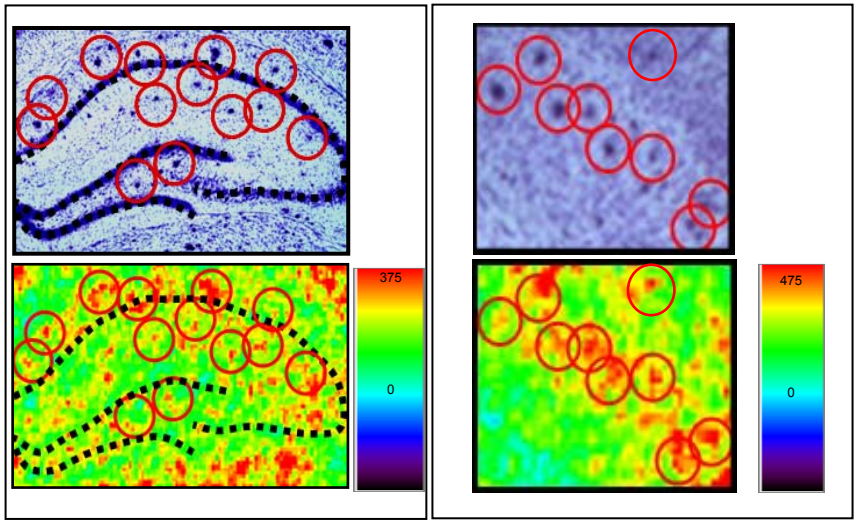
18F-fluorodesoxyglucose (PET-FDG)

Increased glucose uptake in amyloid mice

FDG-PET



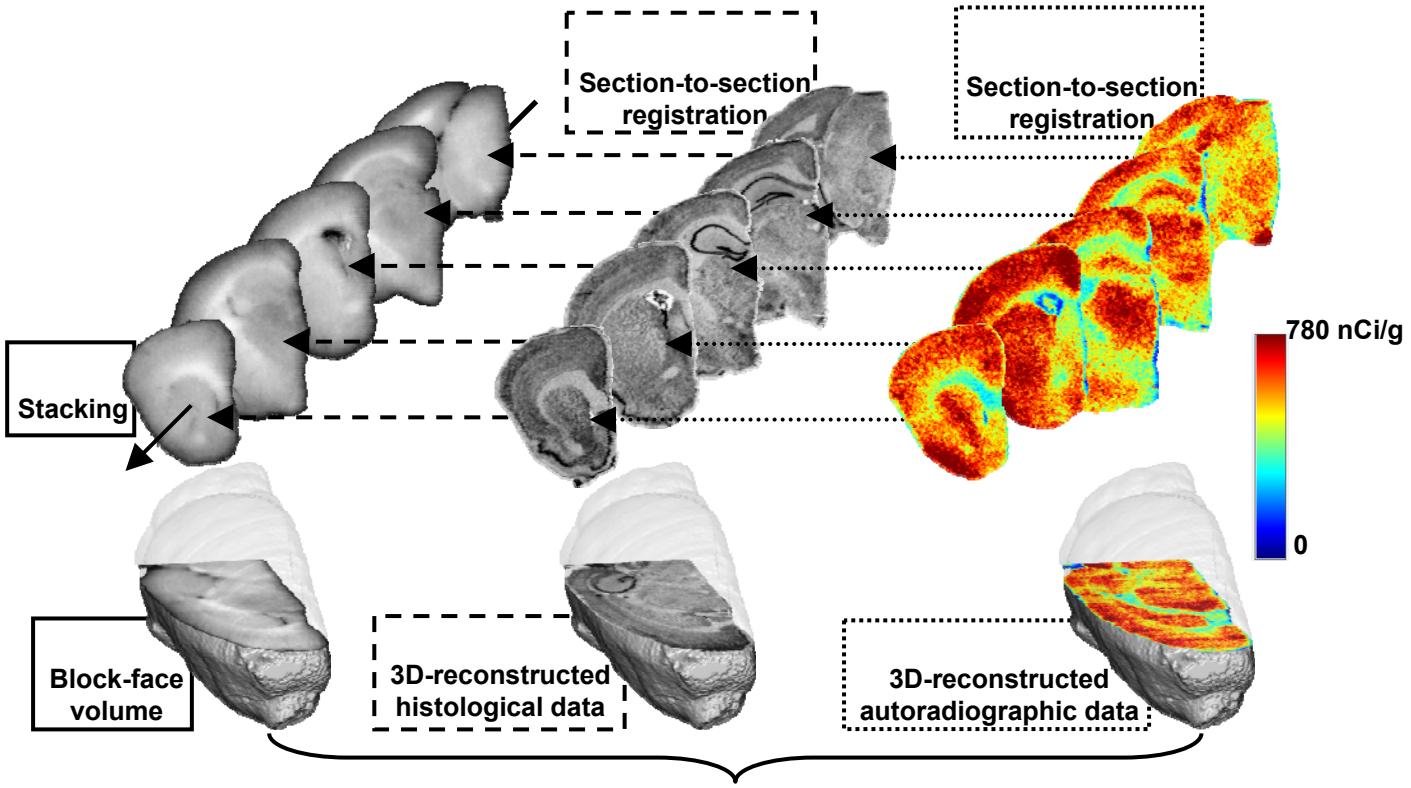




2DG autoradiography

G. Poisnel et al, Neurobiology of Aging, 2012

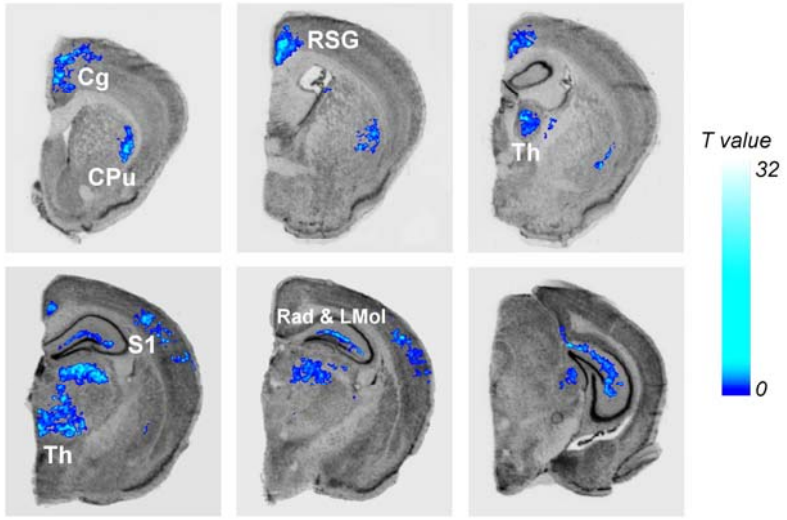
Localized study of glucose uptake thanks to 3D-histology



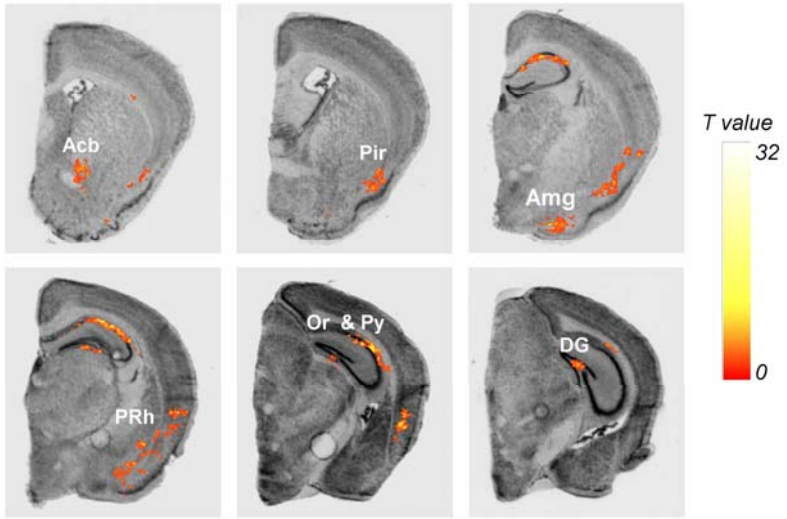
Lebenberg *et al.*, Neuroimage 2010

Voxel-wise analysis of glucose uptake thanks to 3D-autoradiography

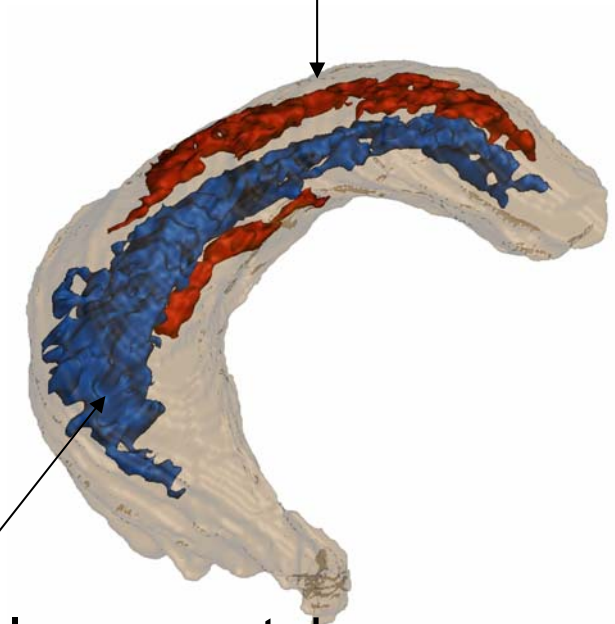
Areas of decreased glucose uptake in APP/PS1 relative to PS1 mice



Areas of increased glucose uptake in APP/PS1 relative to PS1 mice



High glucose uptake

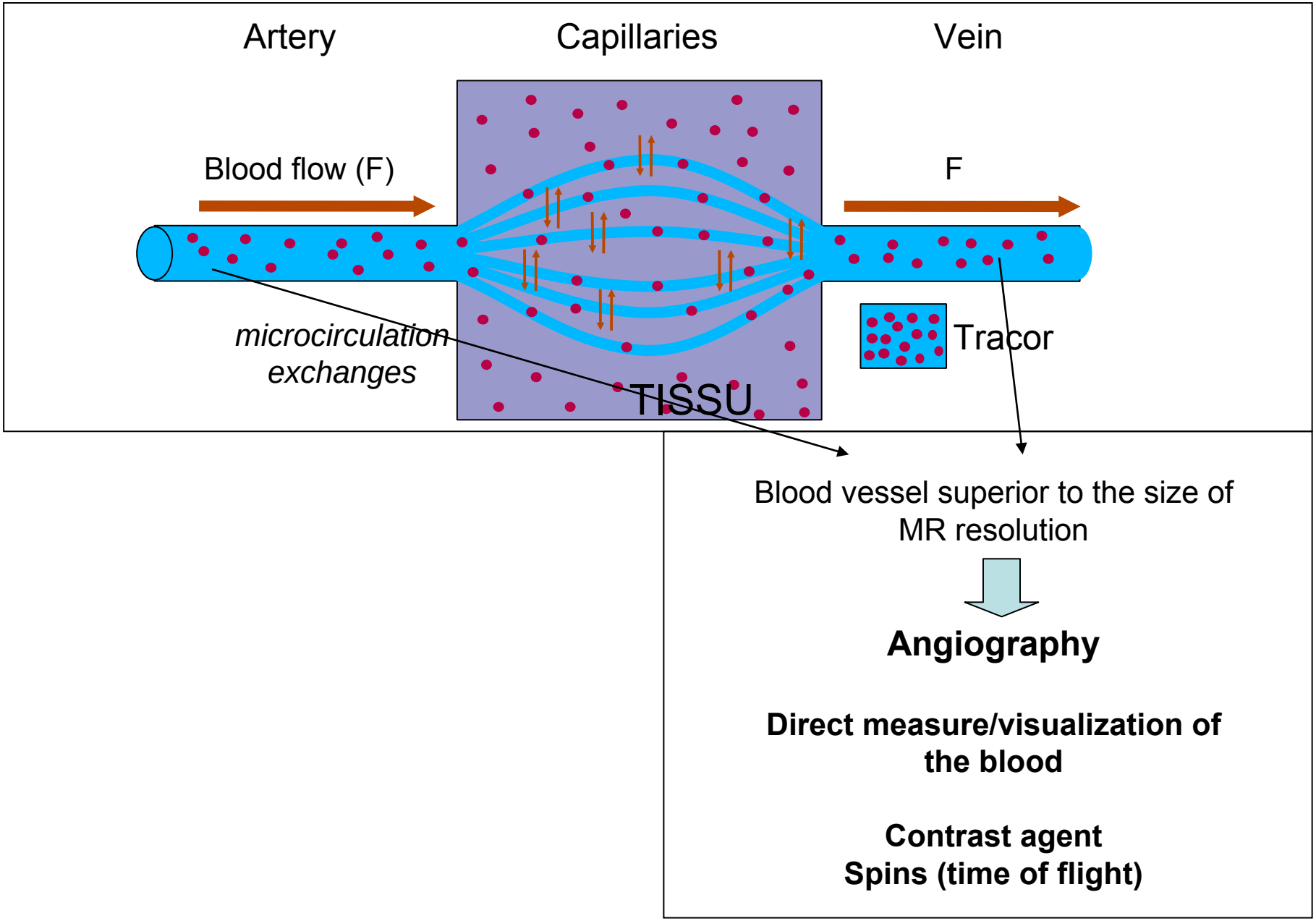


Low glucose uptake

3-D Hippocampus

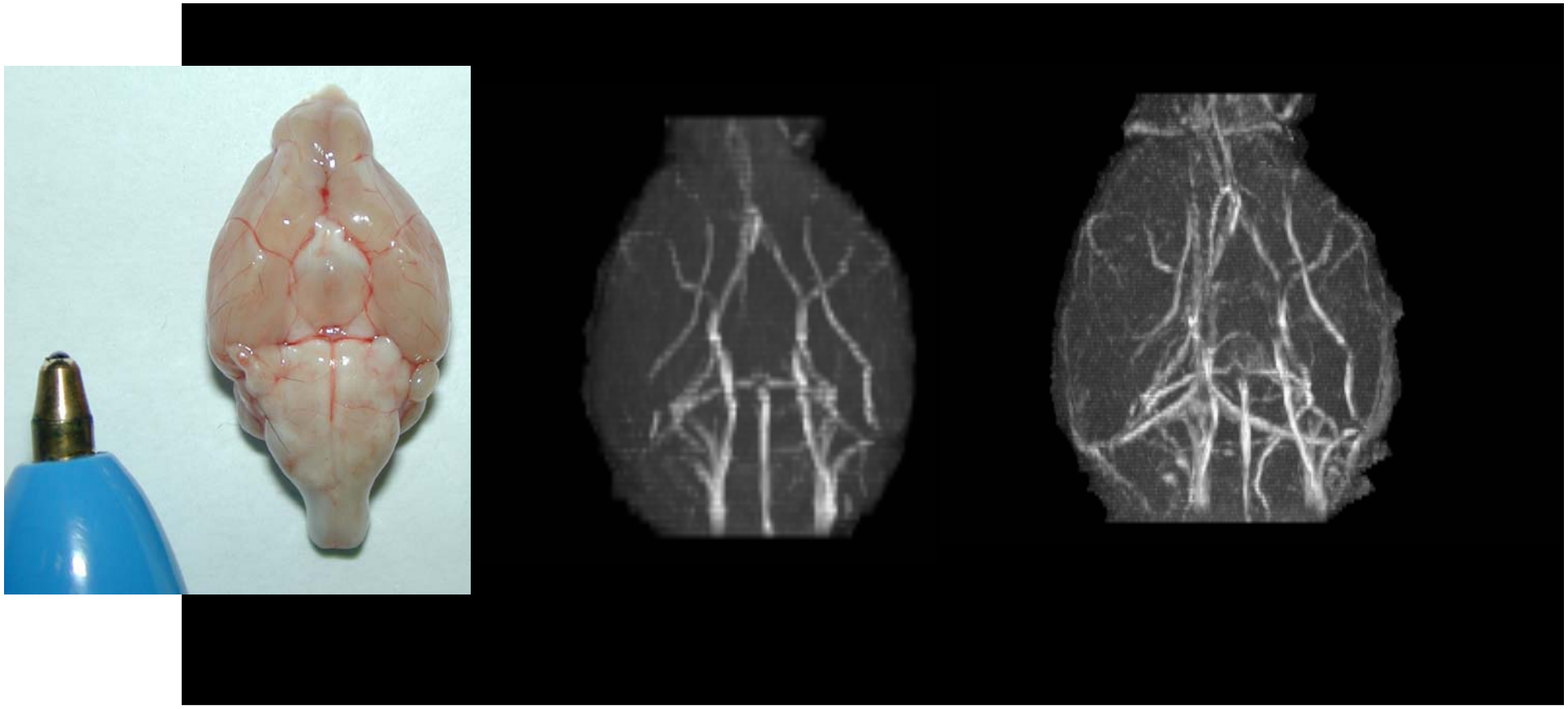
Dubois *et al*
Neuroimage, 2010

Evaluation of the vascular function from MRI

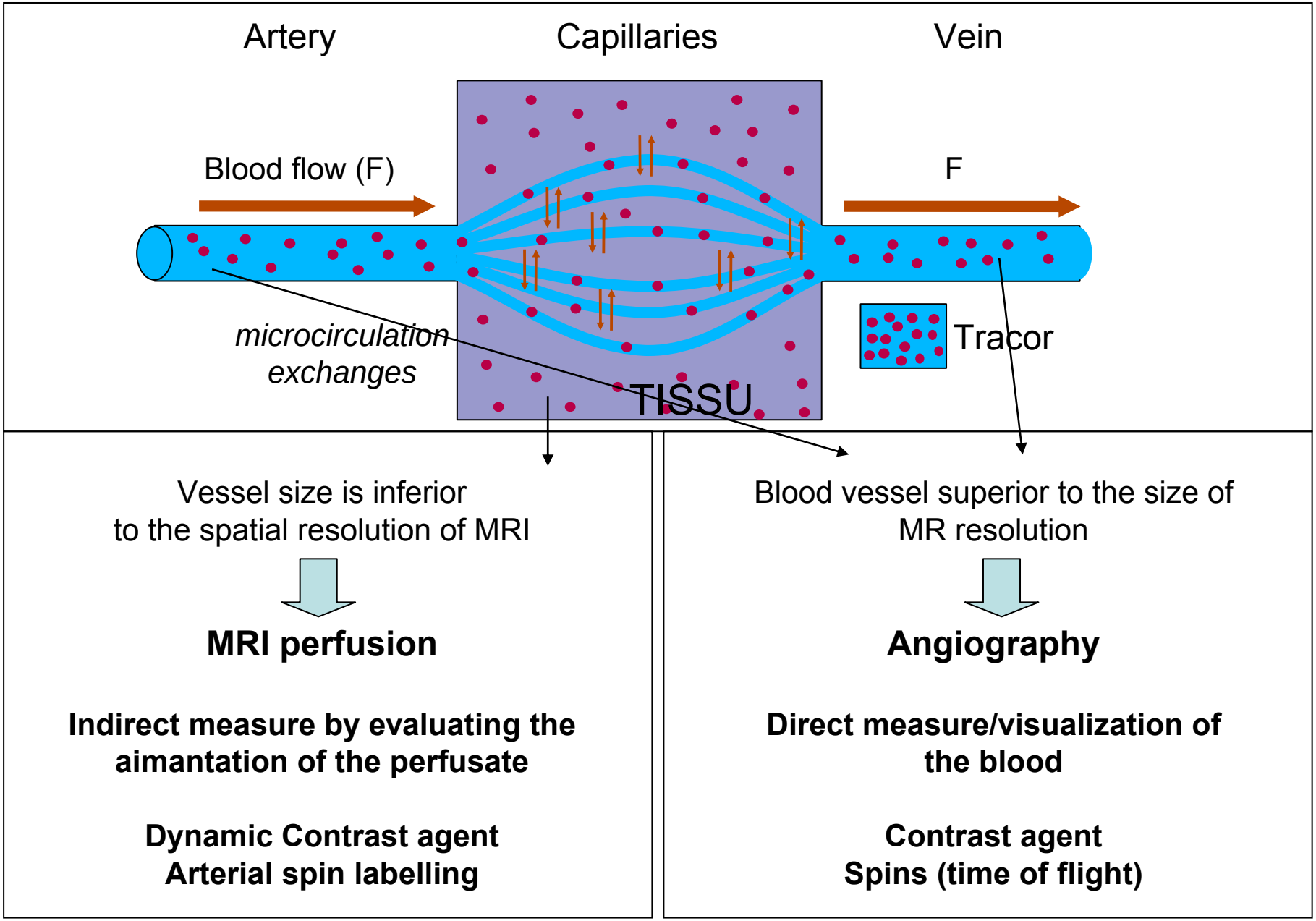

Artery
Capillaries
Vein
Blood flow (F)
F
microcirculation
exchanges
TISSU
Tracor
Blood vessel superior to the size of
MR resolution
Angiography
Direct measure/visualization of
the blood
Contrast agent
Spins (time of flight)

MR Angiography

Without contrast agents With contrast agents

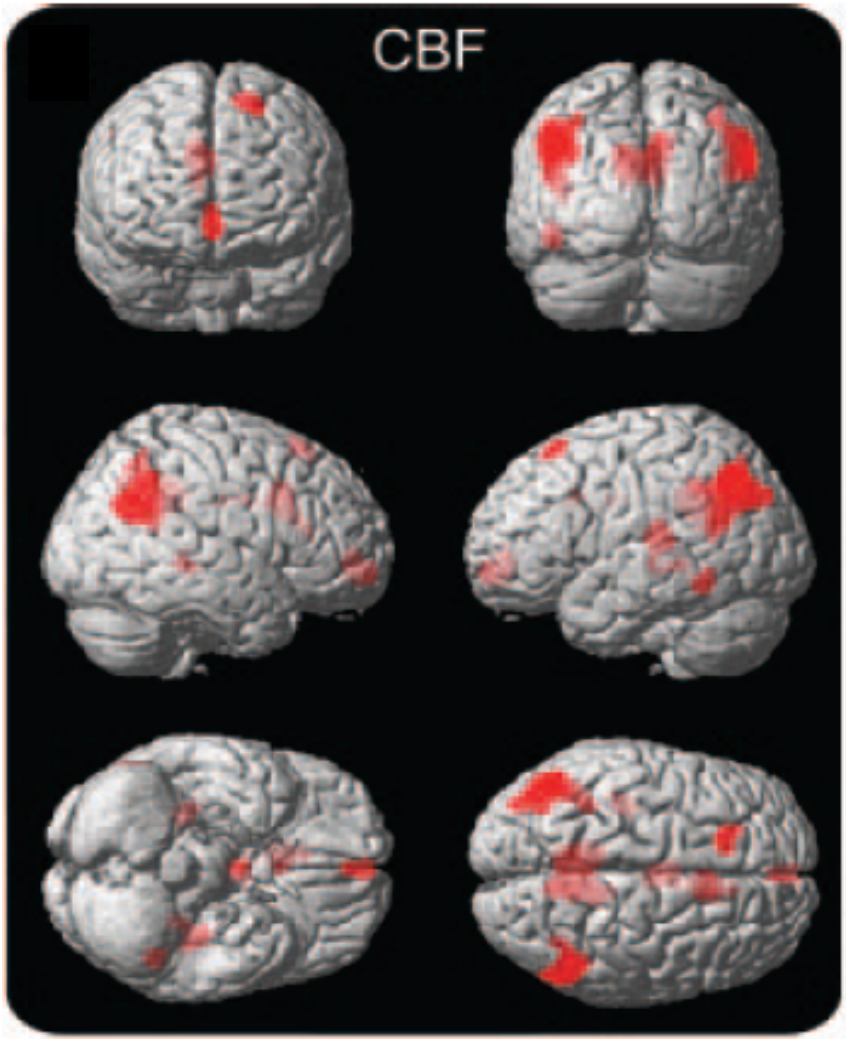


El Tannir El Tayara N, Delatour B, Volk A, Dhenain M. Detection of vascular alterations by in vivo magnetic resonance angiography and histology in APP/PS1 mouse model of Alzheimer's disease. *MAGMA*, 2010, 23: 53-64

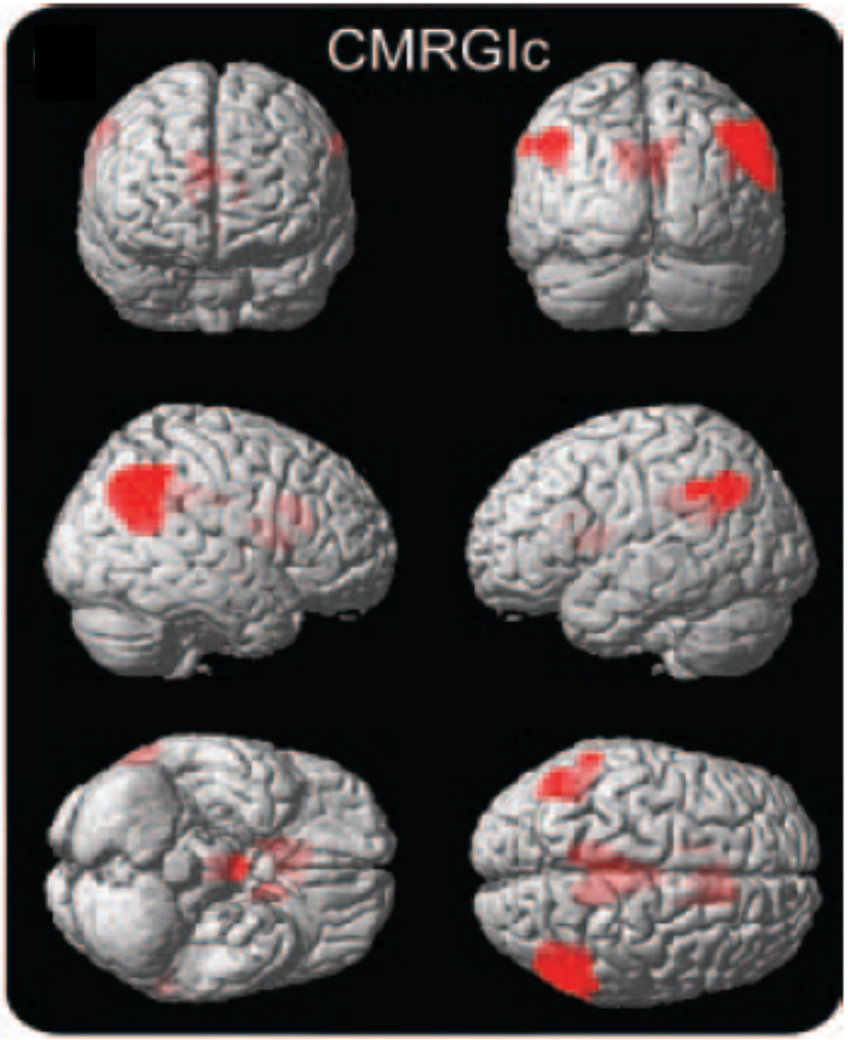

Artery
Capillaries
Vein
Blood flow (F)
F
microcirculation
exchanges
TISSU
Tracor
Vessel size is inferior
to the spatial resolution of MRI
MRI perfusion
Indirect measure by evaluating the aimantation of the perfusate
Dynamic Contrast agent
Arterial spin labelling
Blood vessel superior to the size of MR resolution
Angiography
Direct measure/visualization of the blood
Contrast agent
Spins (time of flight)

Perfusion measurements from MRI

ASL-MRI provides overlapping information with FDG-PET



ASL-MRI

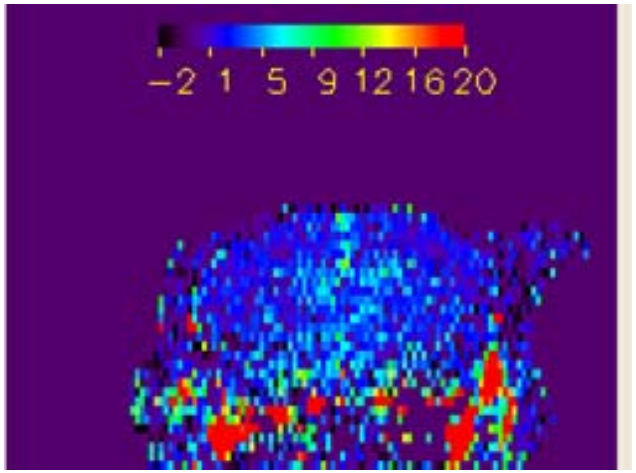


FDG-PET

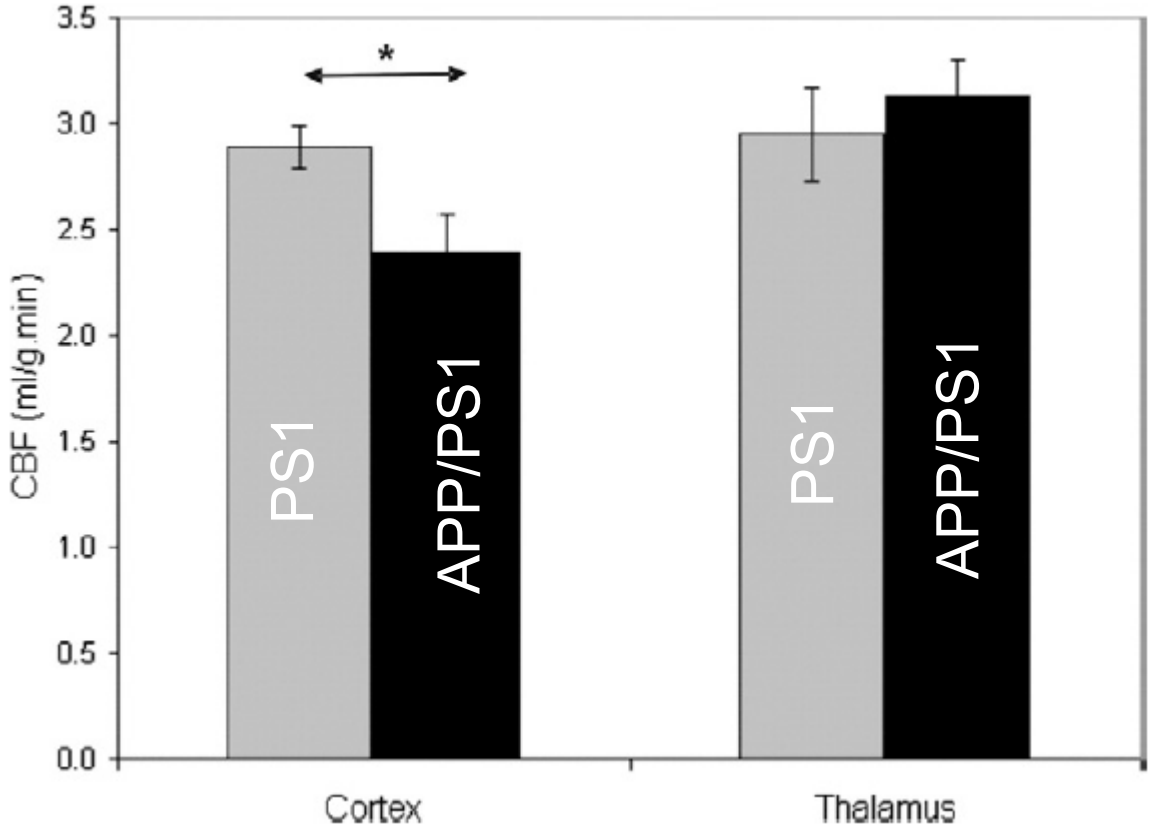
Chen Y et al. Neurology 77, 1977-85; 2011.

Effects of amyloid on cerebral perfusion?

Perfusion map



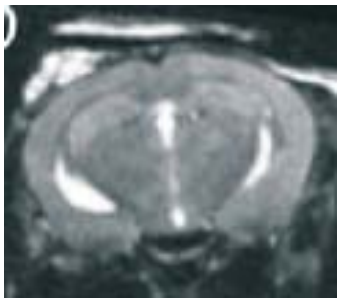
FAIR technique

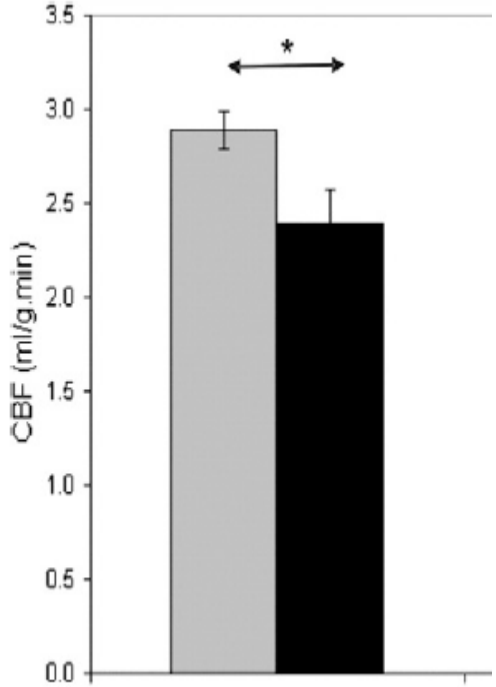


Amyloid induces cortical hypoperfusion

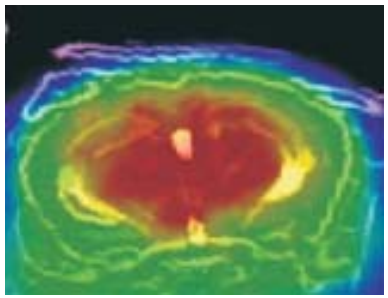
Poisnel et al, Neurobiology of Aging, 2012

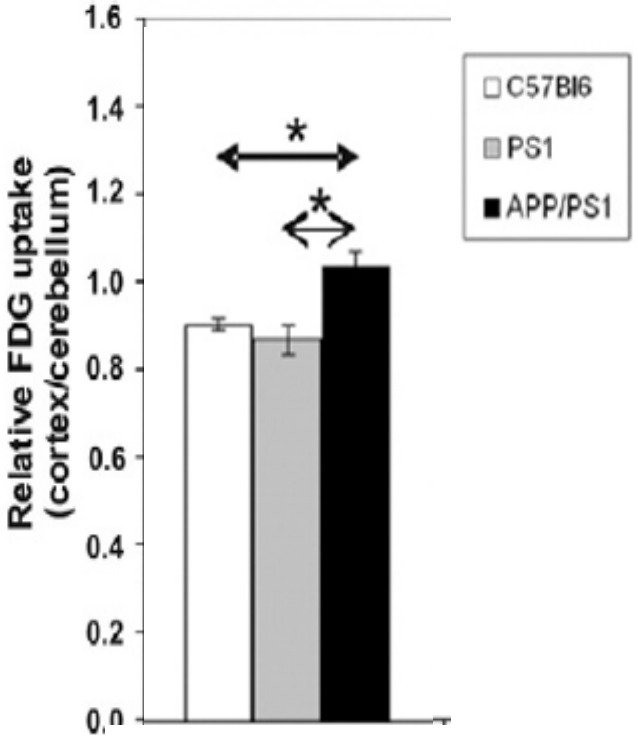
Dissociation between perfusion and glucose uptake in mouse models of amyloidosis





Perfusion

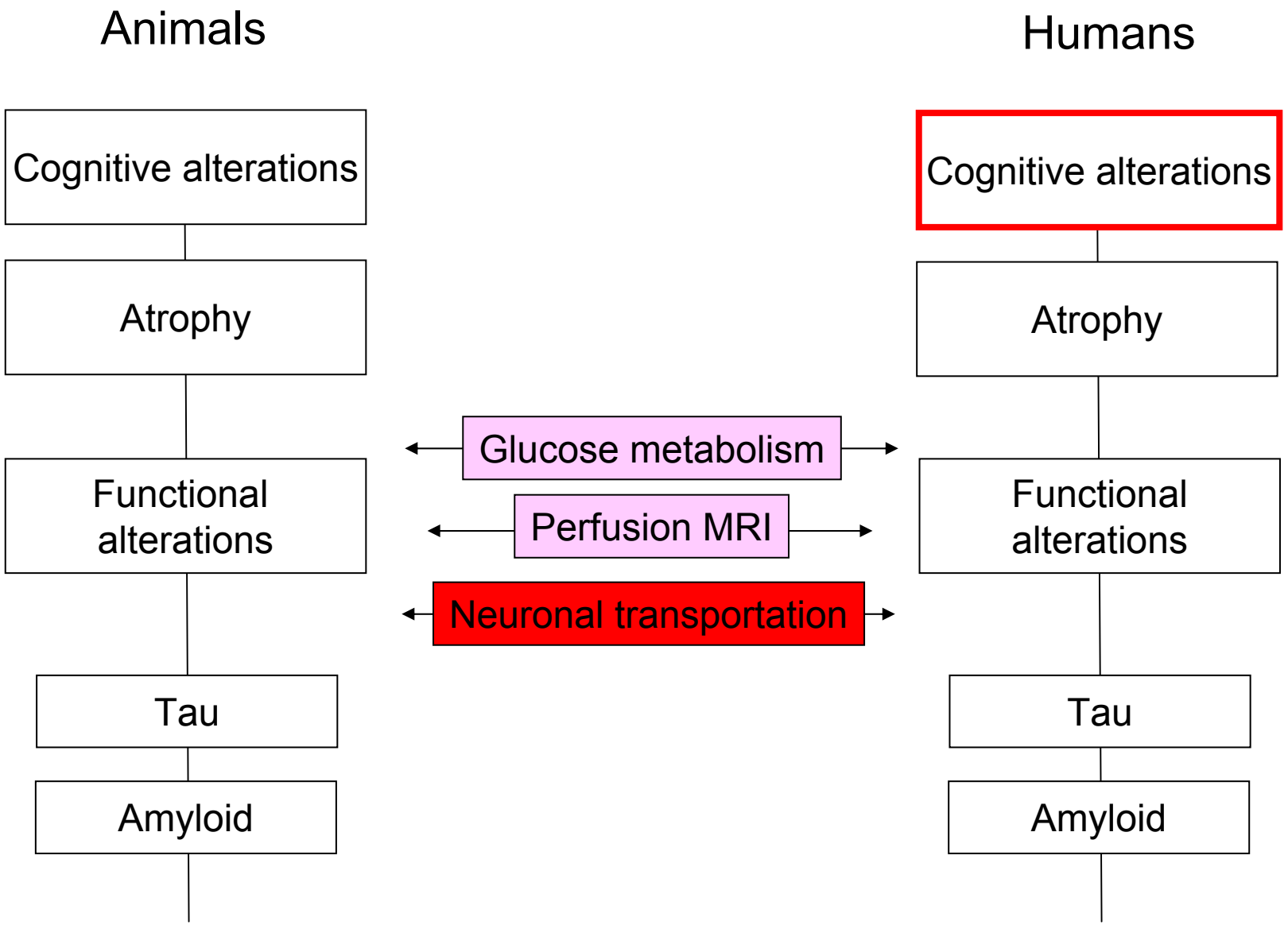




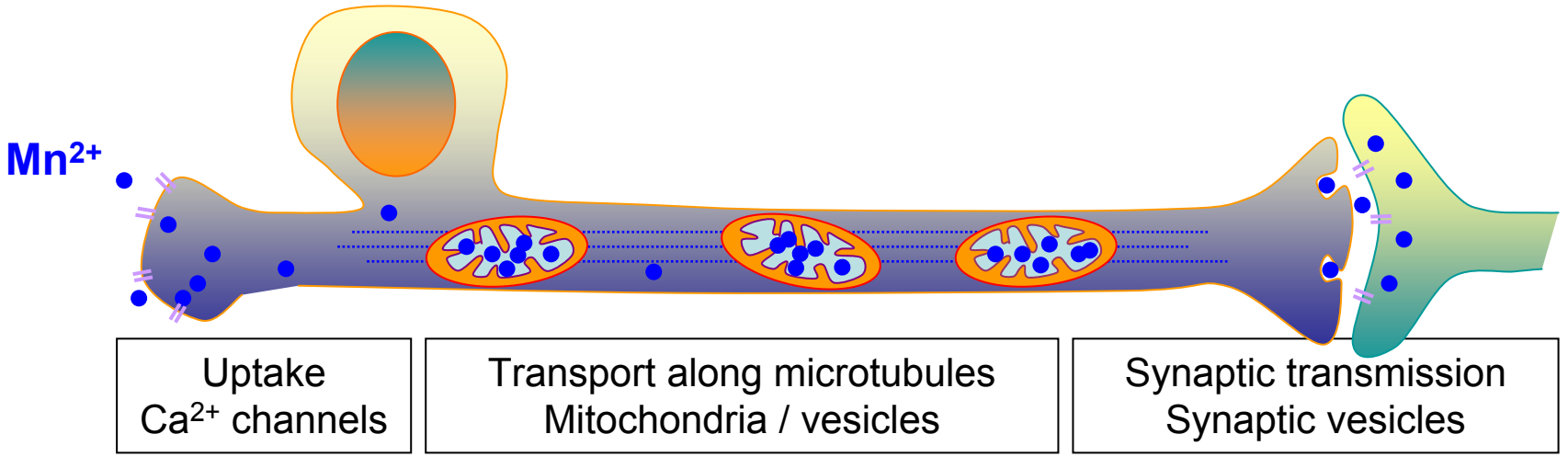
Glucose uptake

Poisnel G et al. Neurobiology of Aging. 2012.

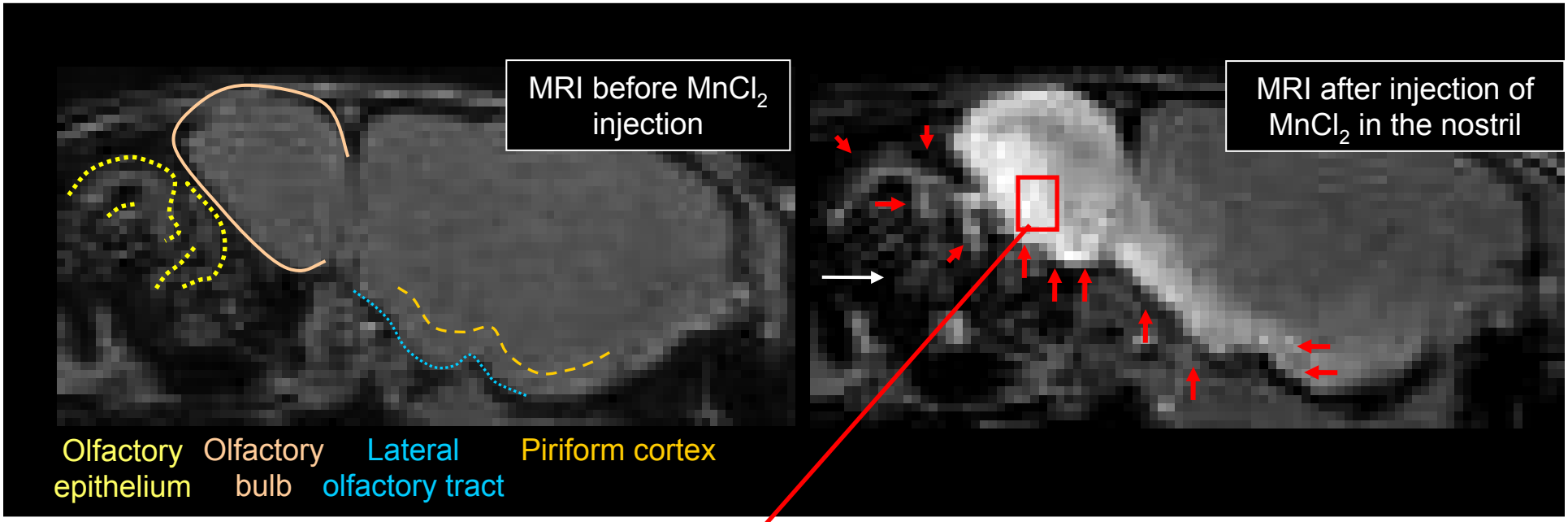
Functional alterations

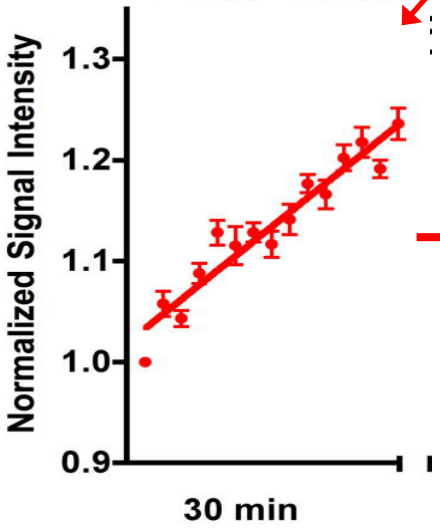


Manganese-enhanced MRI (MEMRI) & neuronal transport



MEMRI & neuronal transport



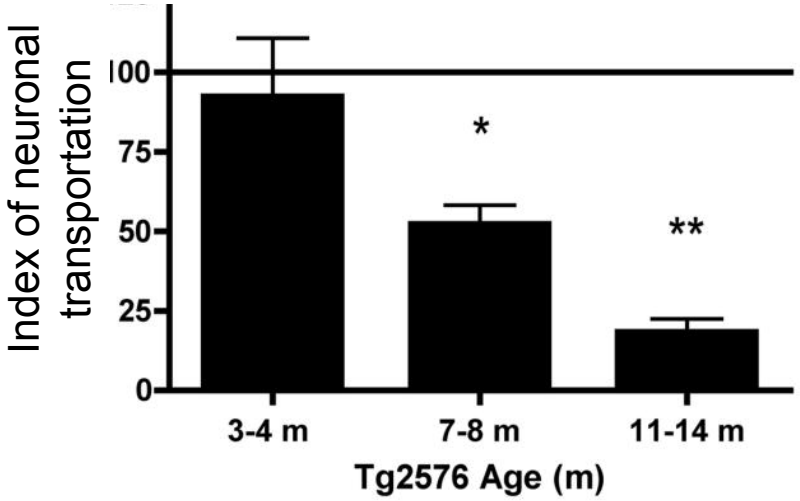


Index of the speed of neuronal transportation

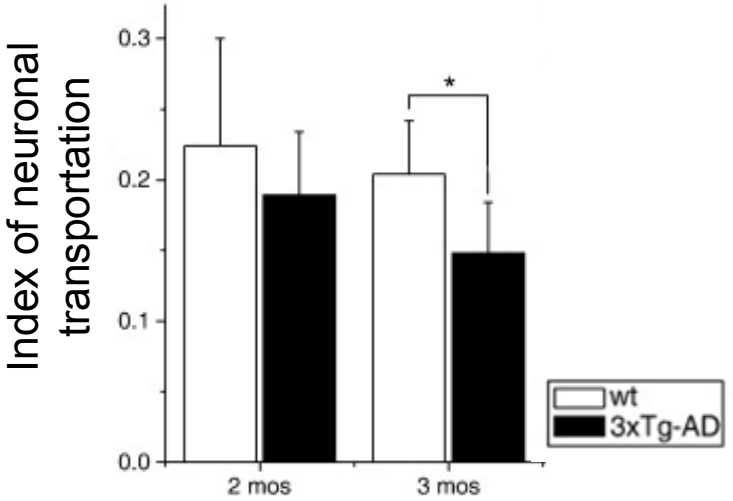
Smith KD et al.
Neuroimage. 2007

Alteration of neuronal transport in animal models of Alzheimer's disease

Amyloid	Tau + Amyloid
APP_{Swe}	$PS1_{M146V}$ + APP_{Swe} + Tau_{P301L}

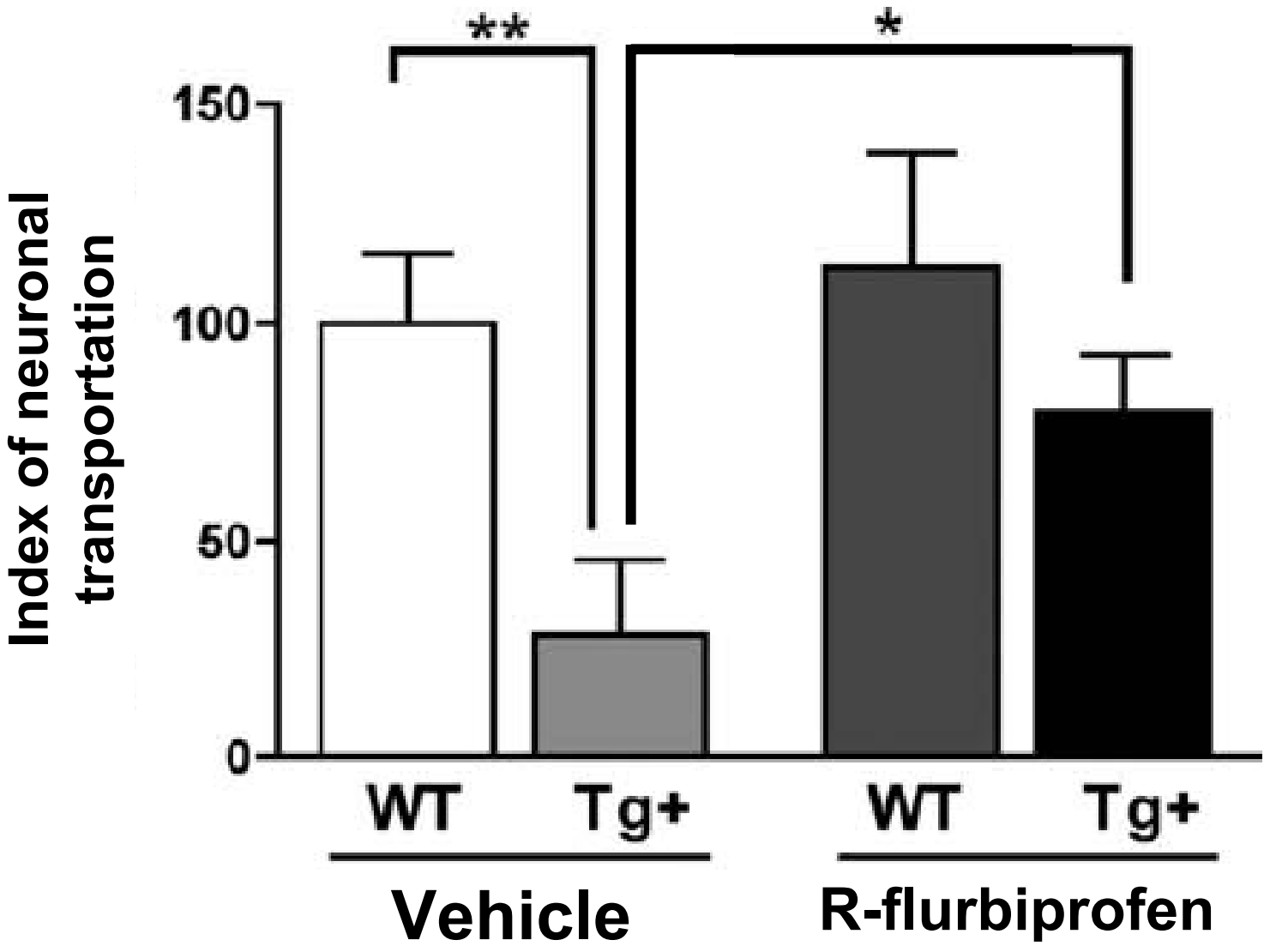


Smith KD et al. Neuroimage *2008*



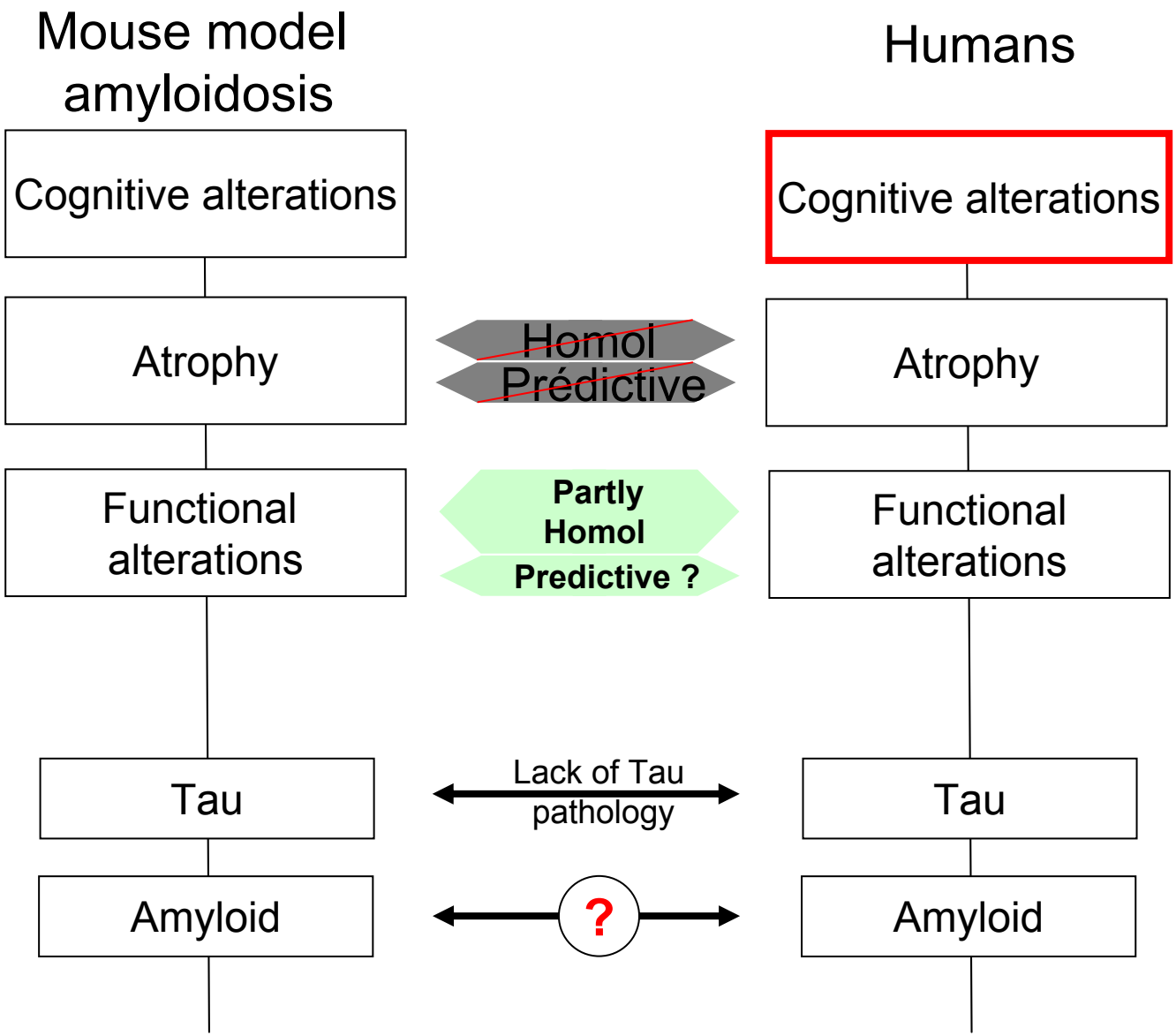
Kim J et al. Neuroimage 2011

MEMRI studies and therapeutic evaluations

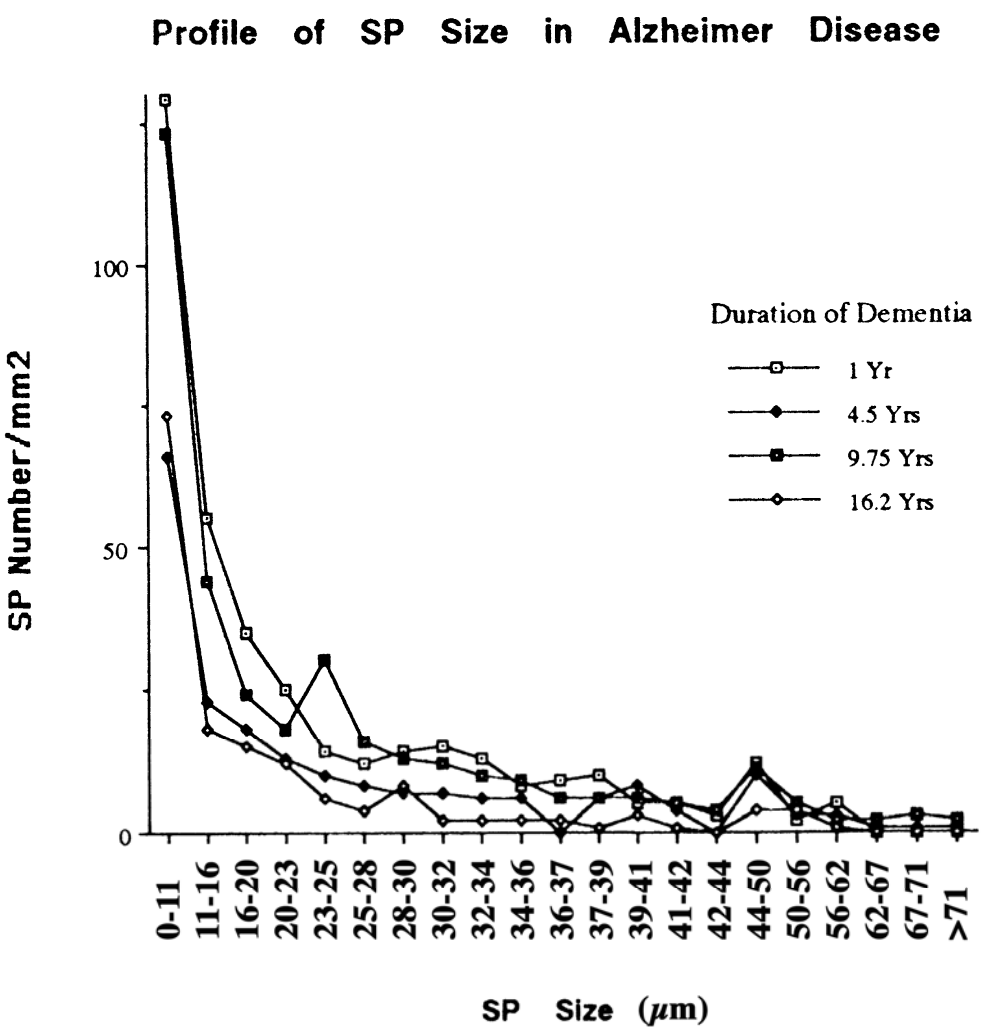


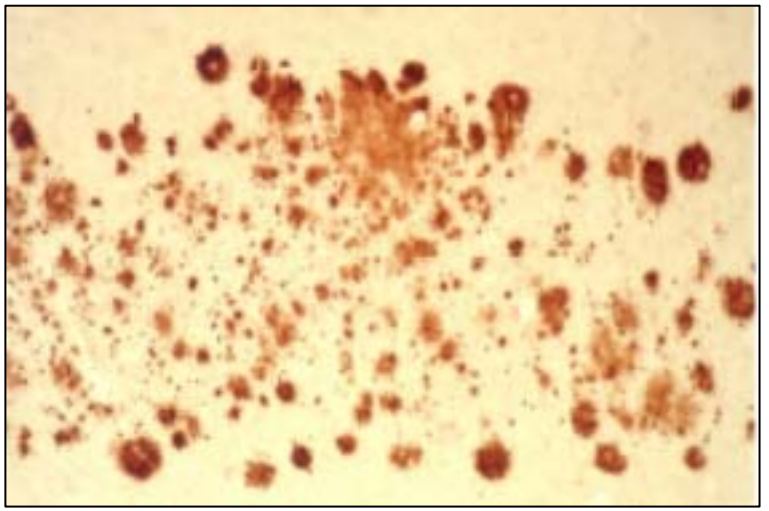
Smith KD et al. Magn Reson Med 65, 1423-9; 2011

Biomarkers in models of amyloidosis



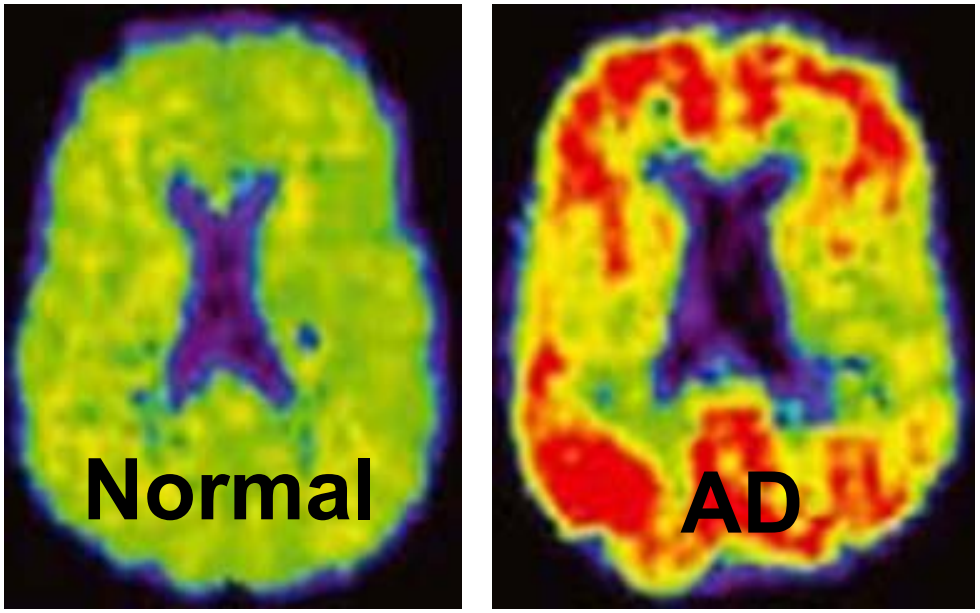
Amyloid plaques





Modified from Hyman BT et al. Journal of Neuropathology and Experimental Neurology 1993;52(6):594-600.

Imaging amyloid plaques in humans: PET



PIB

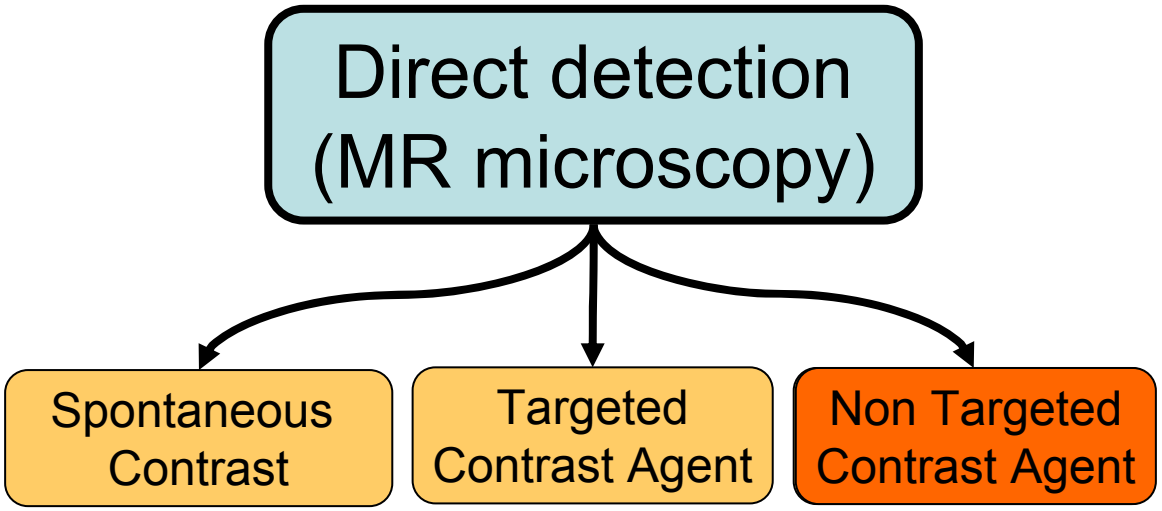
Klunk WE et al. Ann Neurol, 2004

AV45

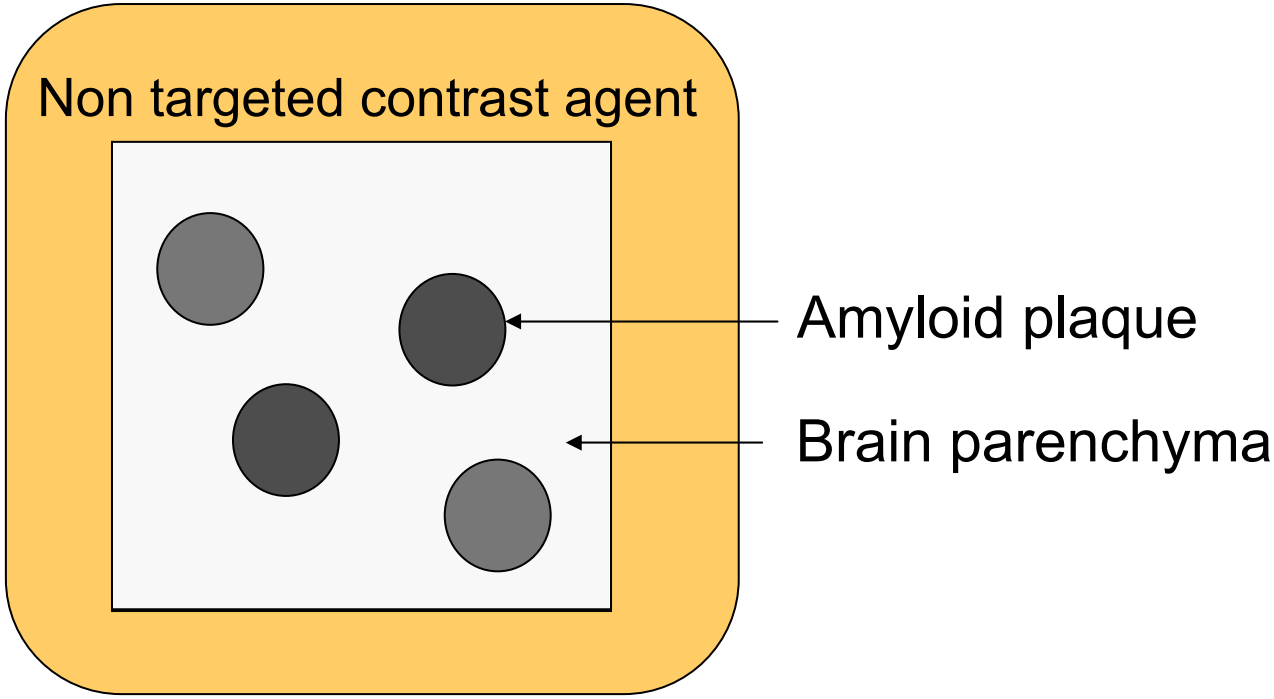
Approved by the FDA in April 2012

Other ligands available

Imaging amyloid plaques in animals: MRI

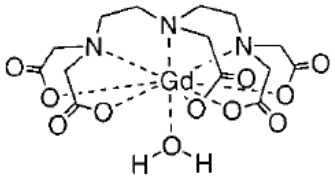


Detection of amyloid plaques thanks to non targeted contrast agents

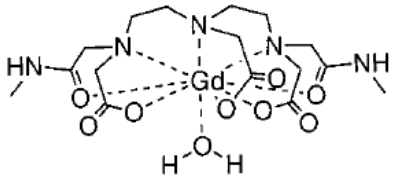


- Increases the signal and contrast in the brain

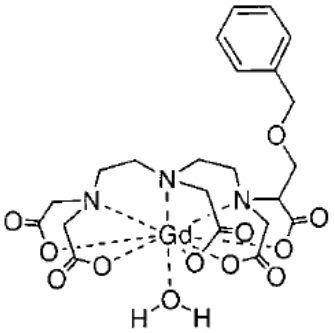
Use of clinically approved MR contrast agents



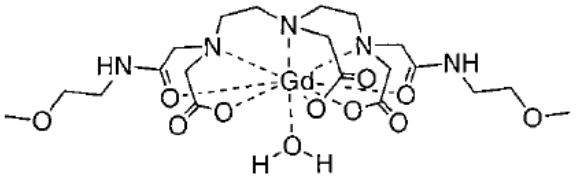
$[Gd(DTPA)(H_2O)]^{2-}$ (Magnevist™)



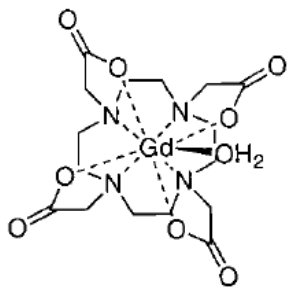
$[Gd(DTPA\text{-}BMA)(H_2O)]$ (Omniscan™)



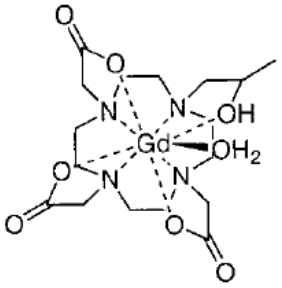
$[Gd(BOPTA)(H_2O)]^{2-}$ (MultiHance™)



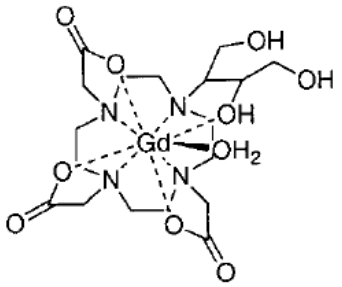
$[Gd(DTPA\text{-}BMEA)(H_2O)]$ (OptiMARK™)



$[Gd(DOTA)(H_2O)]^-$ (Dotarem™)



$[Gd(HP\text{-}DO3A)(H_2O)]$ (ProHance™)



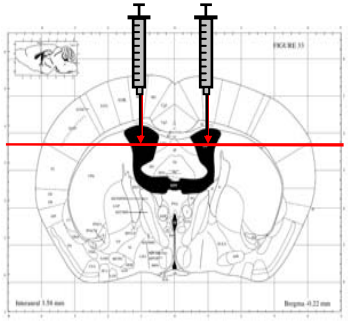
$[Gd(DO3A\text{-}butrol)(H_2O)]$ (Gadovist™)

37 million exams, in 70 different countries

Caravan P. et al. *Chem Rev* **1999**, *99*, 2293-352.

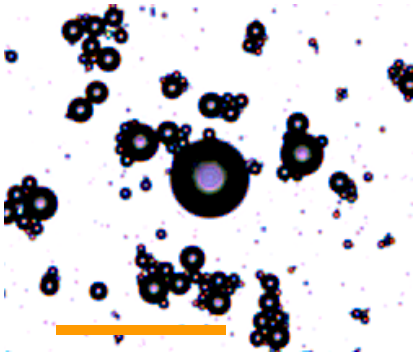
In vivo Gadolinium-Staining methods

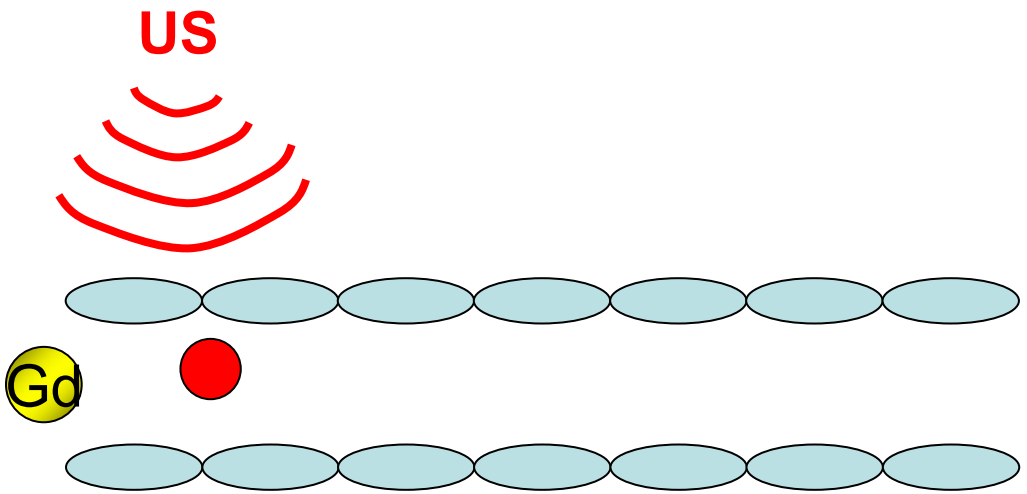
- Intra-cerebro-ventricular (ICV) administration of Gadolinium contrast agent
  - Commonly used procedure in experimental research



- Opening of the blood brain barrier thanks to ultrasounds and microbubbles (*Hynynen K. Radiology 2001)*

Clinically approved microbubbles



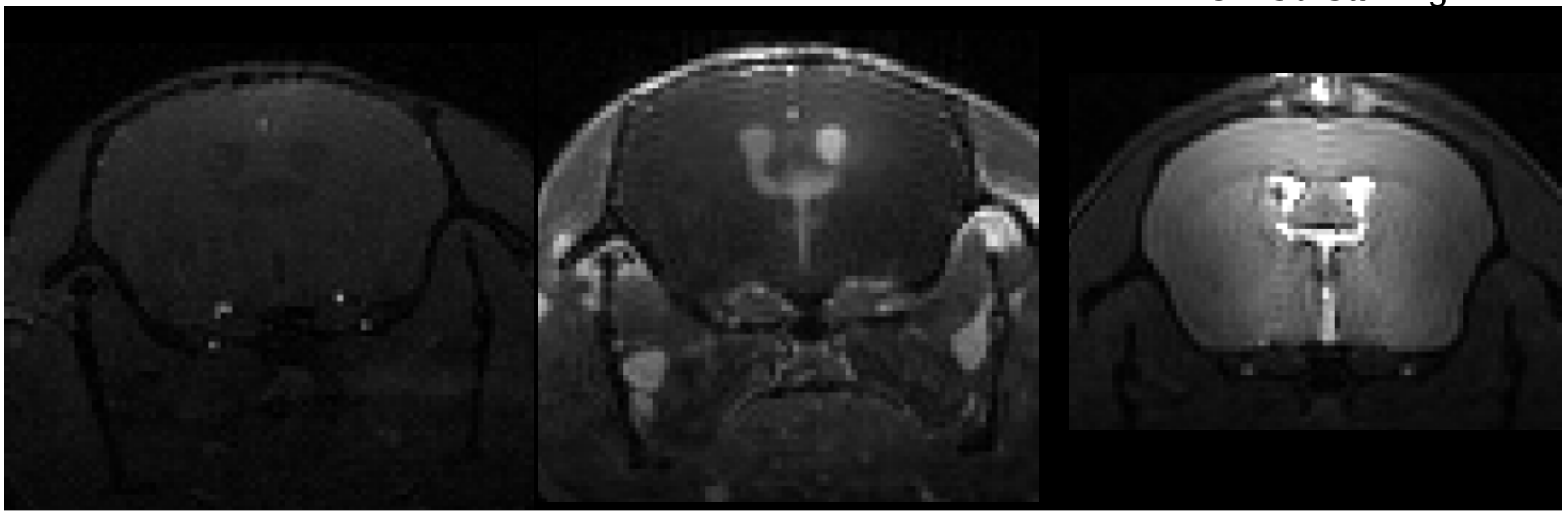


Penetration of the Gd in the brain

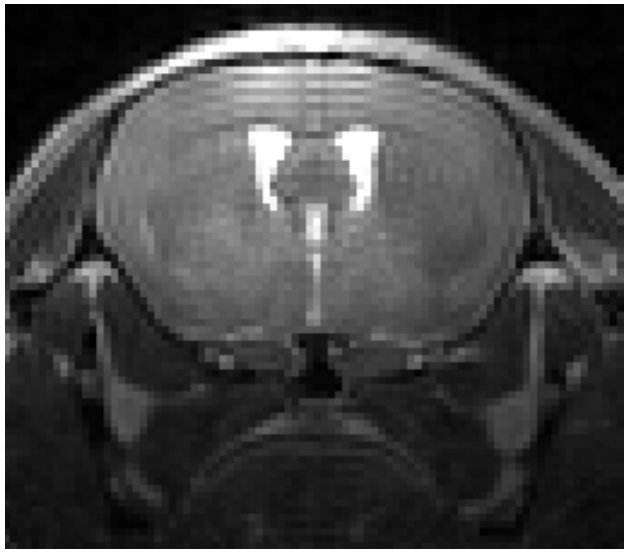
Control

Gadolinium – Intra-Venous

ICV-Gd-Staining



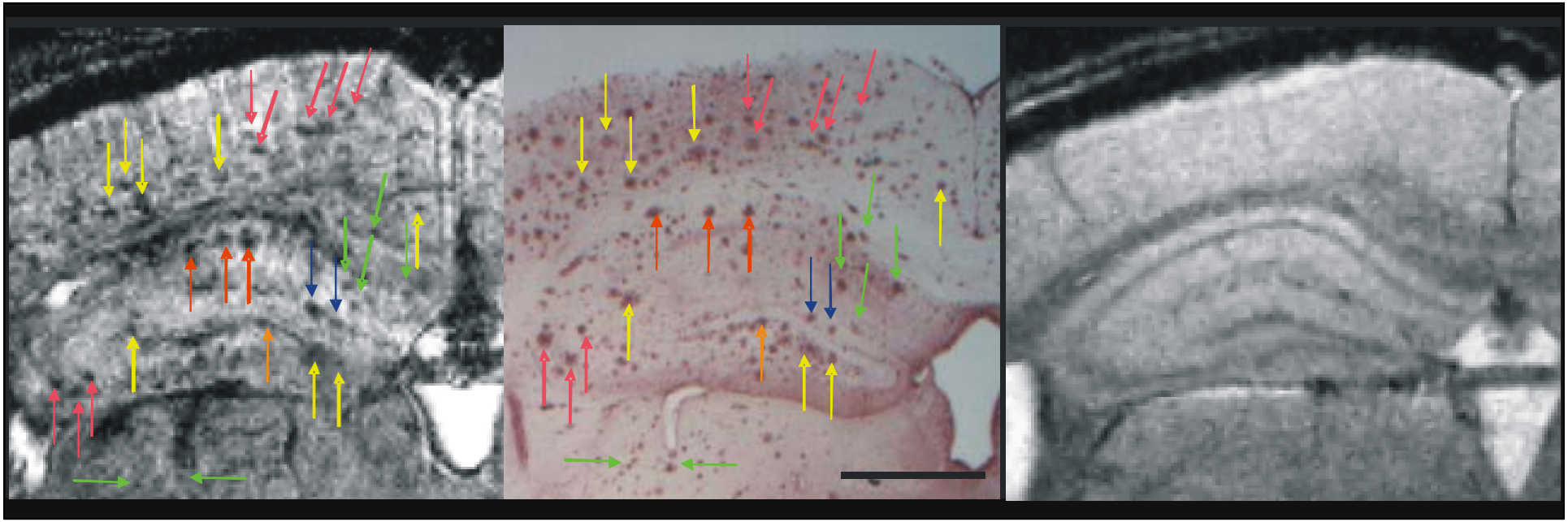
US-Gd-Staining



Gradient echo 3D low resolution
156*156*203 μm^3

Petiet et al. Neurobiol Aging 2012
Santin et al. NeuroImage 2013

Amyloid plaques detection by in vivo MR microscopy



Amyloid mouse

Control

29*29*117 μm^3
Acquisition time: 32 min

Santin et al. NeuroImage 2013; Petiet et al. Neurobiol Aging, 2012

Amyloid plaques detection by in vivo MR microscopy

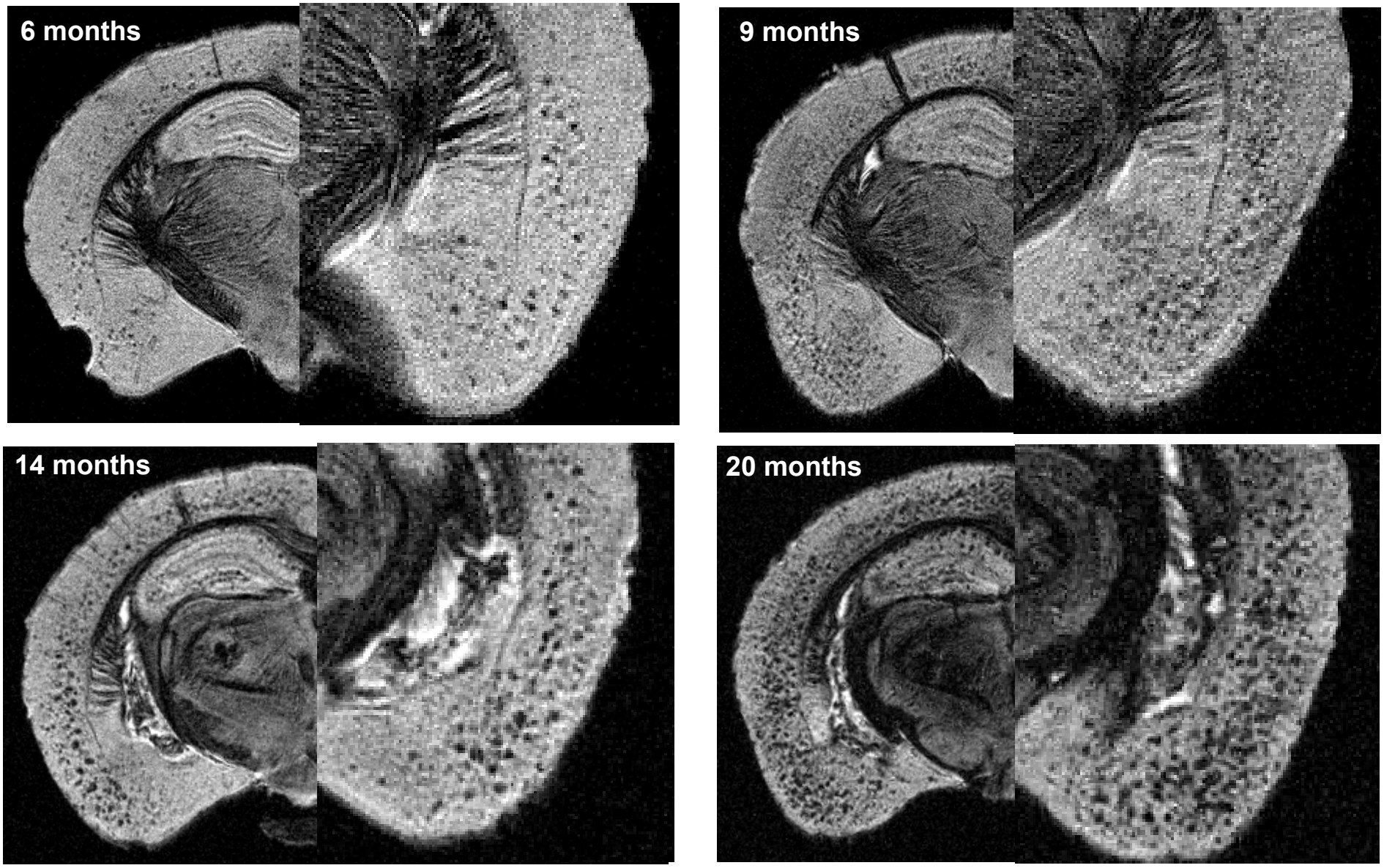
Detection of amyloid plaques by "*In-vivo* Gadolinium staining"

Amyloid

Control

29*29*117 μm^3
Acq Time 32 min

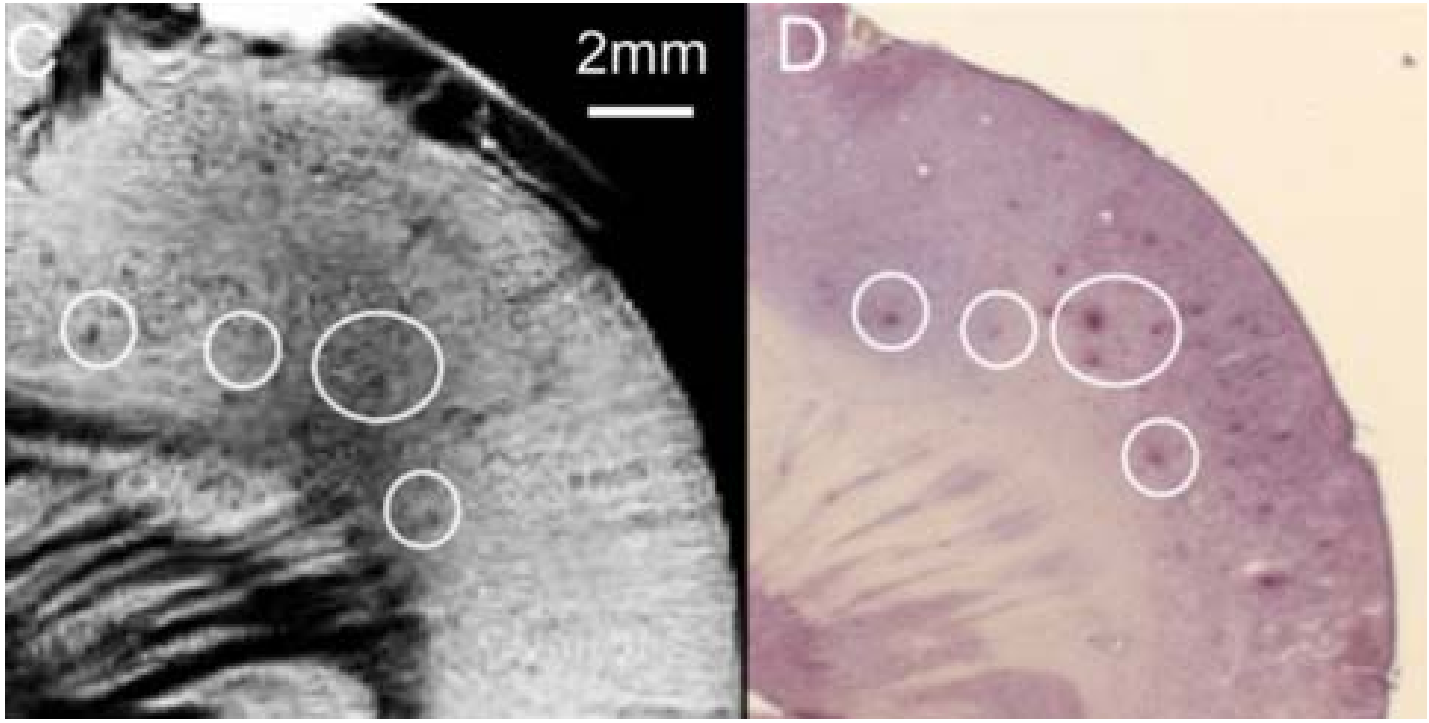
Detection of amyloid plaques by MR microscopy



Petiet A. et al. Neurobiology of Aging, 2012, 33 - 1533-1544

Amyloid imaging in mouse lemur primates

Model of neurodegenerative process



Bertrand et al, PlosOne 2013

Detection of amyloid plaques by MRI

Detect amyloid plaques

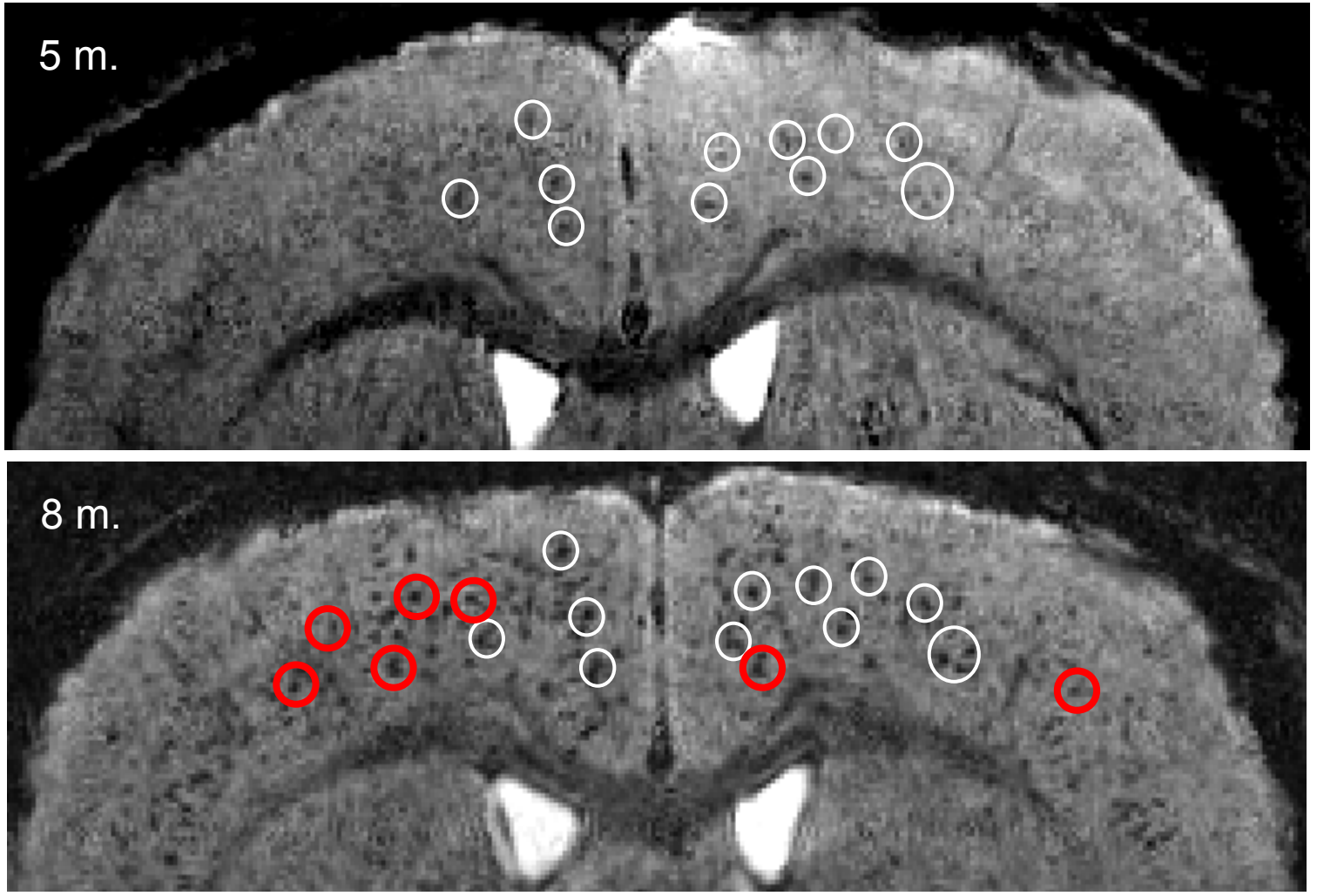
- Non Targeted contrast agent
- Without contrast agent
- Targeted contrast agent
- Relaxometry

Quantify amyloid plaques

- Manual Analyses (Regions of interest)
- Automatic quantifications (Segmentation)
- Automatic analyses (VBM, DBM)

Use for therapeutic evaluations

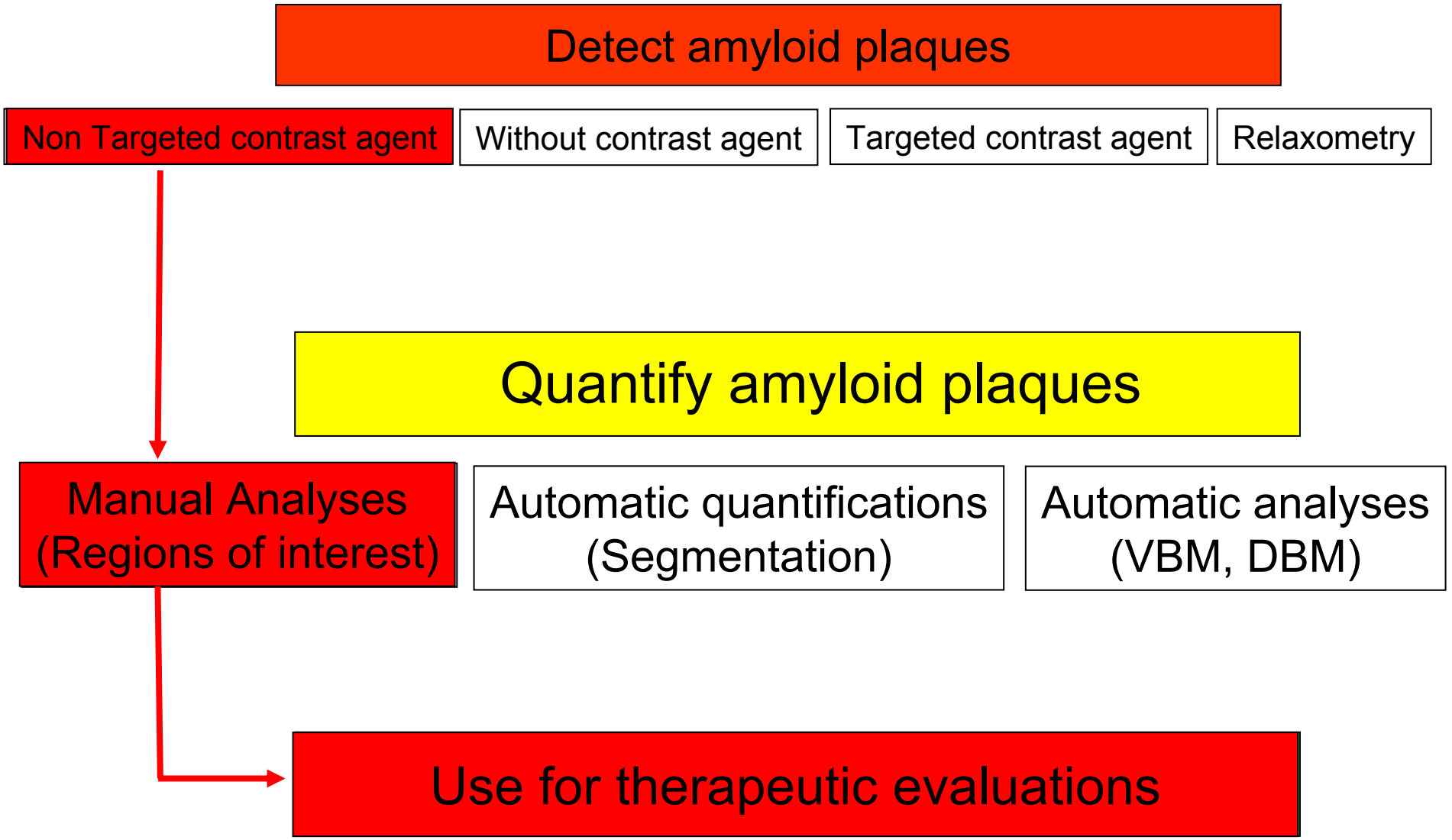
In-vivo longitudinal follow-up of amyloid plaques



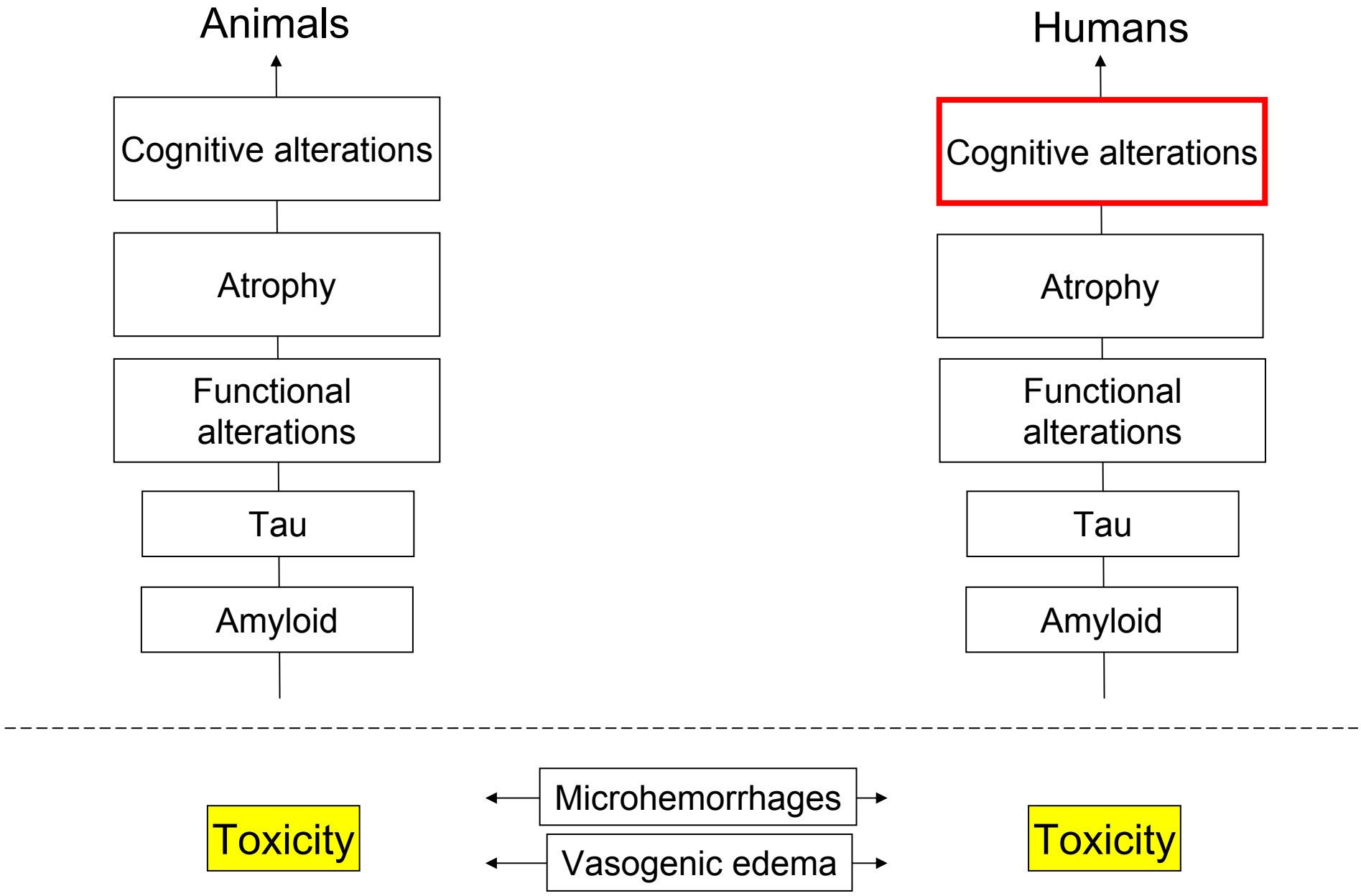
→ A tool for preclinical therapeutic evaluation

Santin M et al., in preparation., ISMRM 2012, 923

Detection of amyloid plaques by MRI: Summary



Evaluation of toxicity



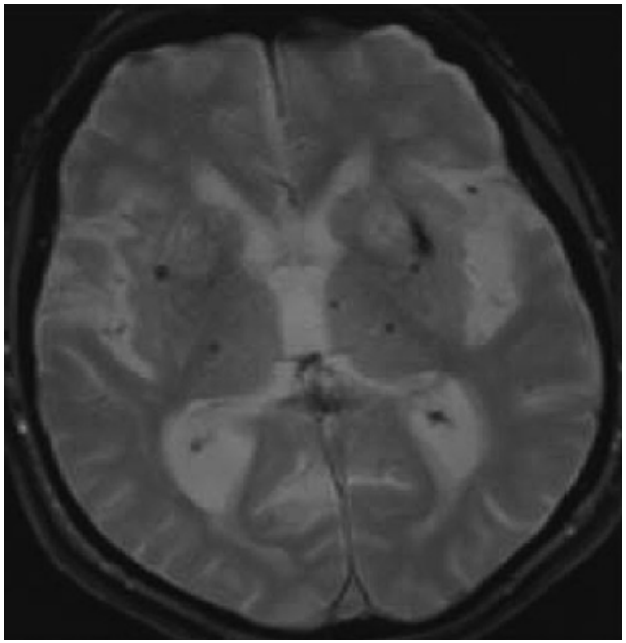
Imaging biomarkers of Toxicity
Example of the immunotherapy

Severe side effects detected in human studies

Meningoencephalitis

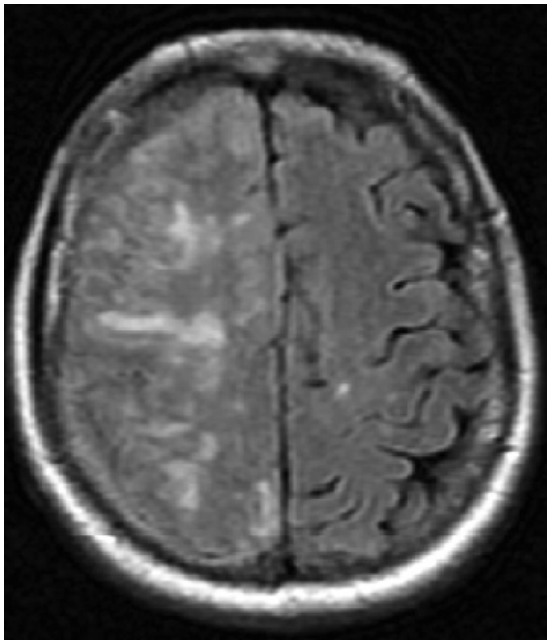
Orgogozo JM et al.
Neurology, 2003

ARIA-H
Microhemorrhages



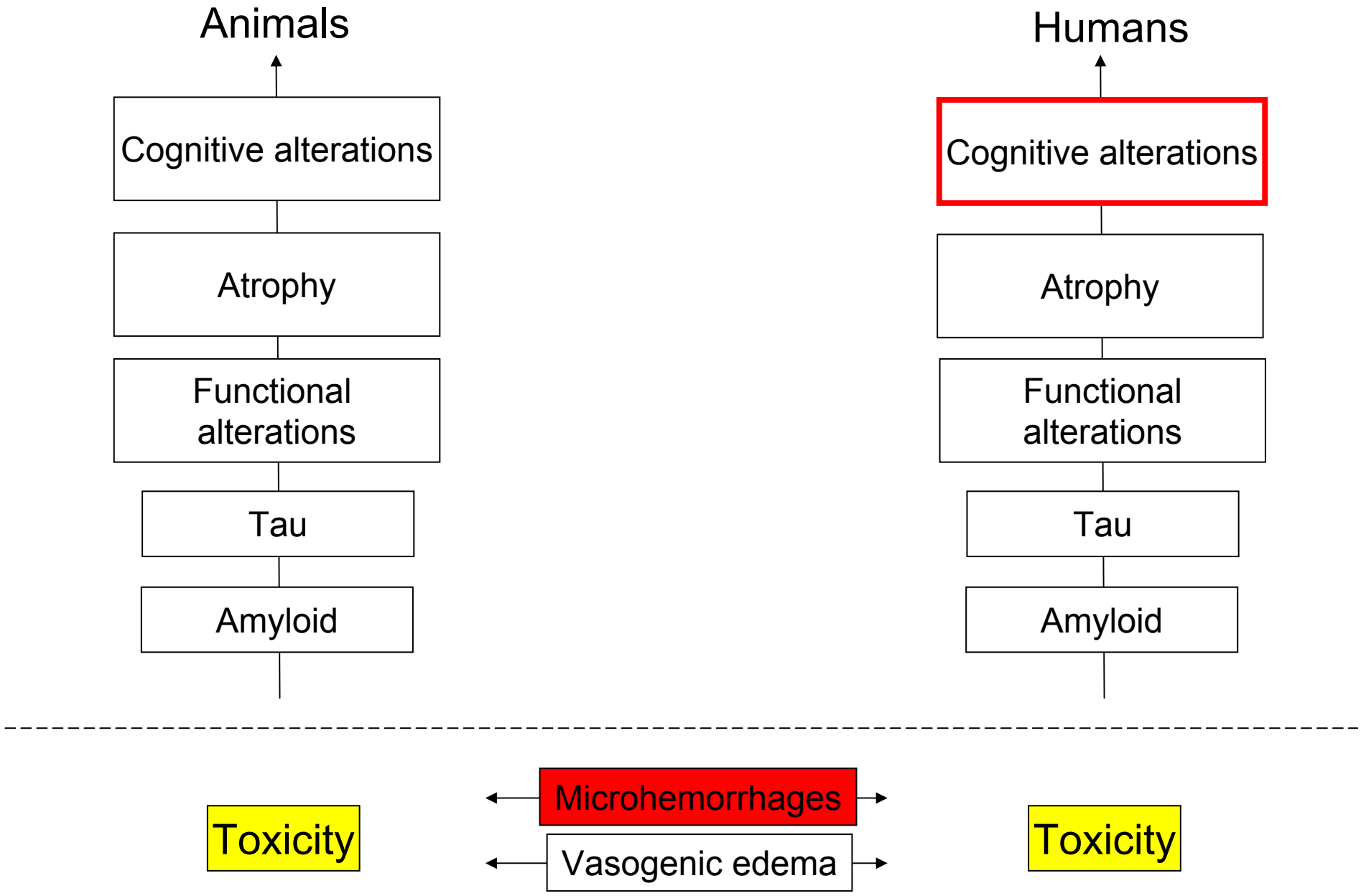
Ferrer I et al.
Brain Pathol, 2004

ARIA-E
Vasogenic edema

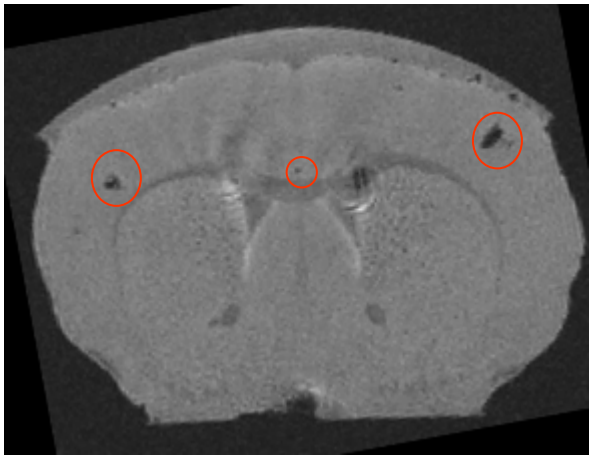


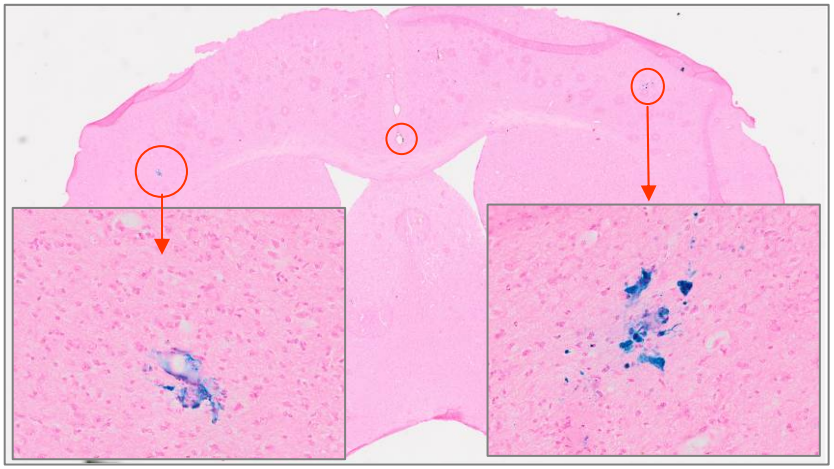
Salloway S et al.
Neurology, 2009

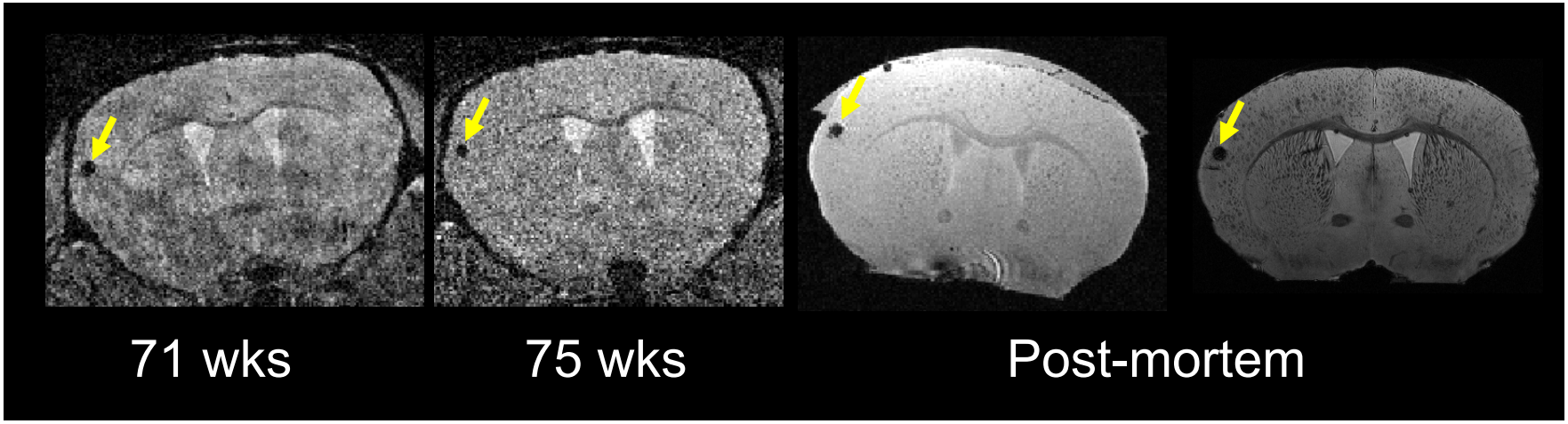
Evaluation of toxicity



Detection of ARIA-H by MRI

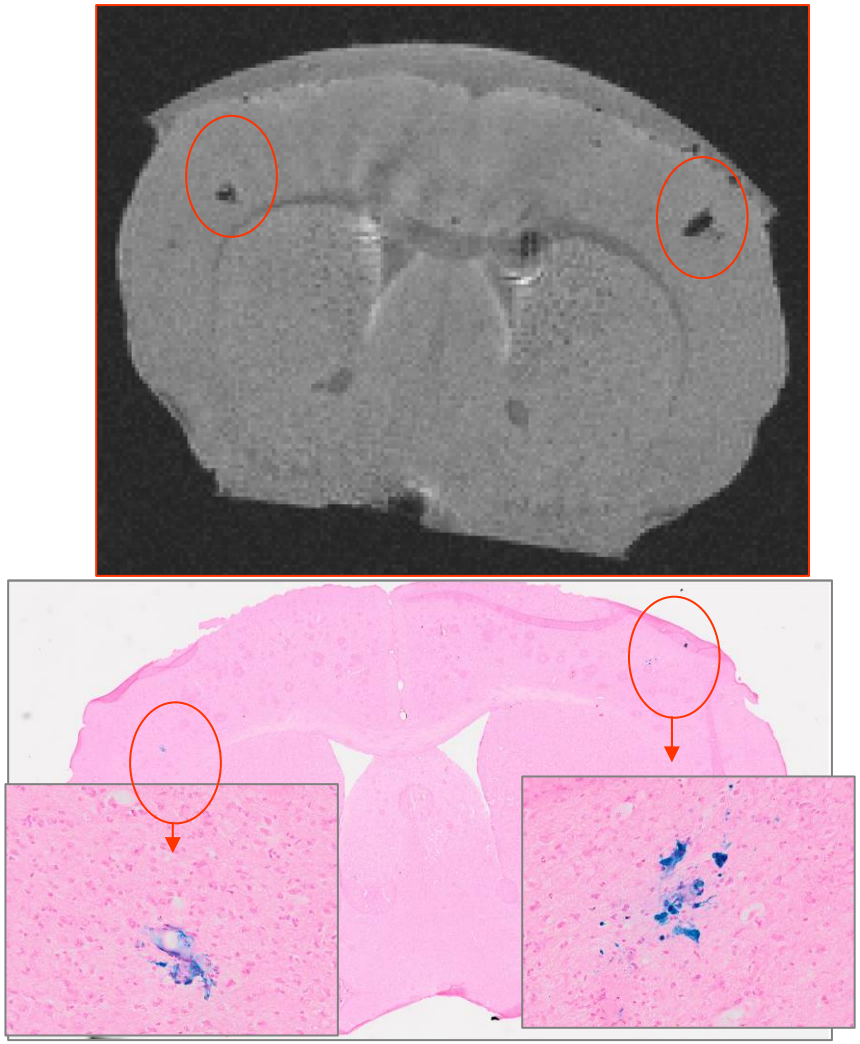




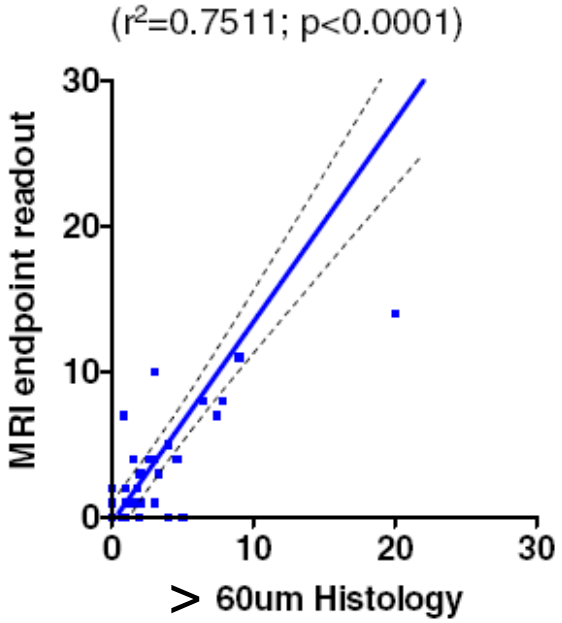


ARIA-H (Immunotherapy - Mouse)

Validation of microhemorrhage detection



Registration between MRI and histological sections

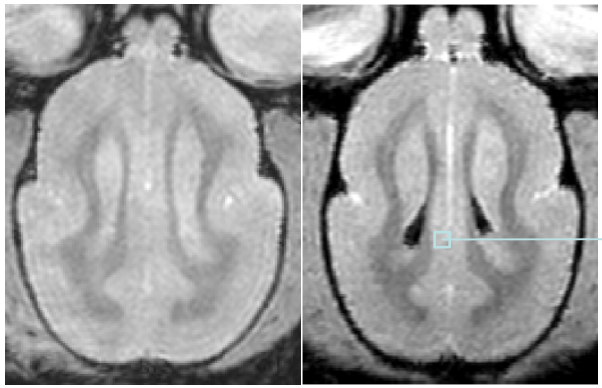


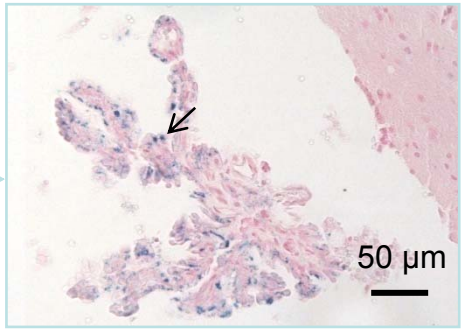
Luo F et al. JPET, 2010

Comparison of counting in MRI and histological sections

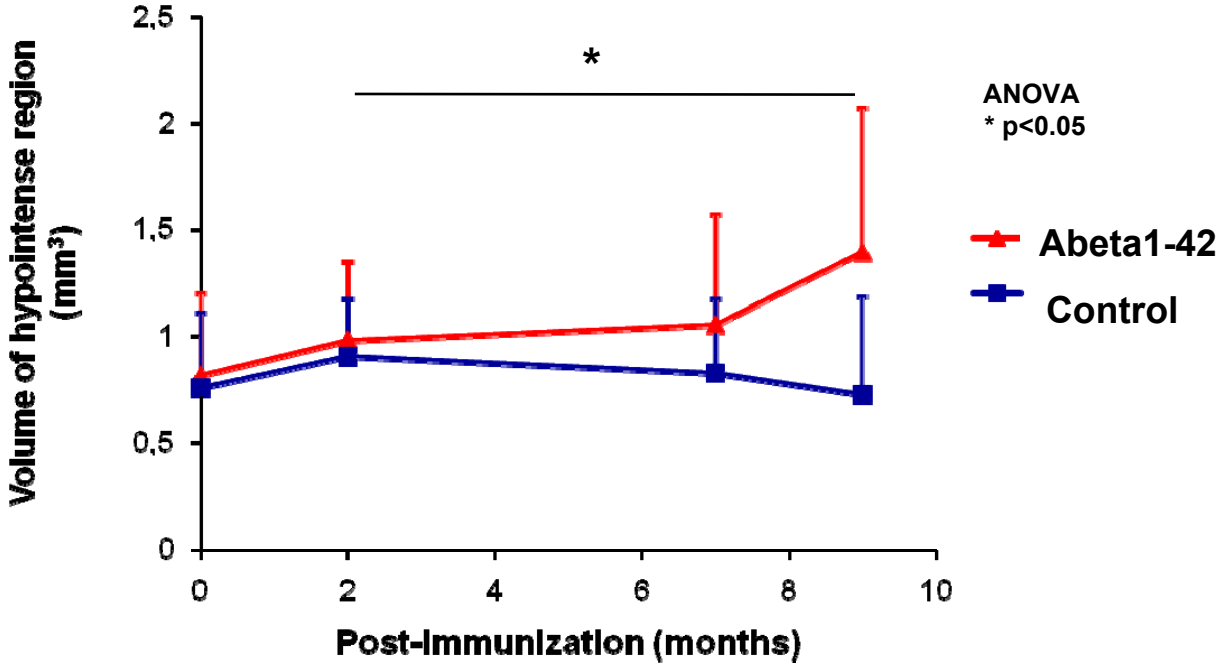
Iron accumulation in the choroid plexus

Mouse lemur





Perls iron sections



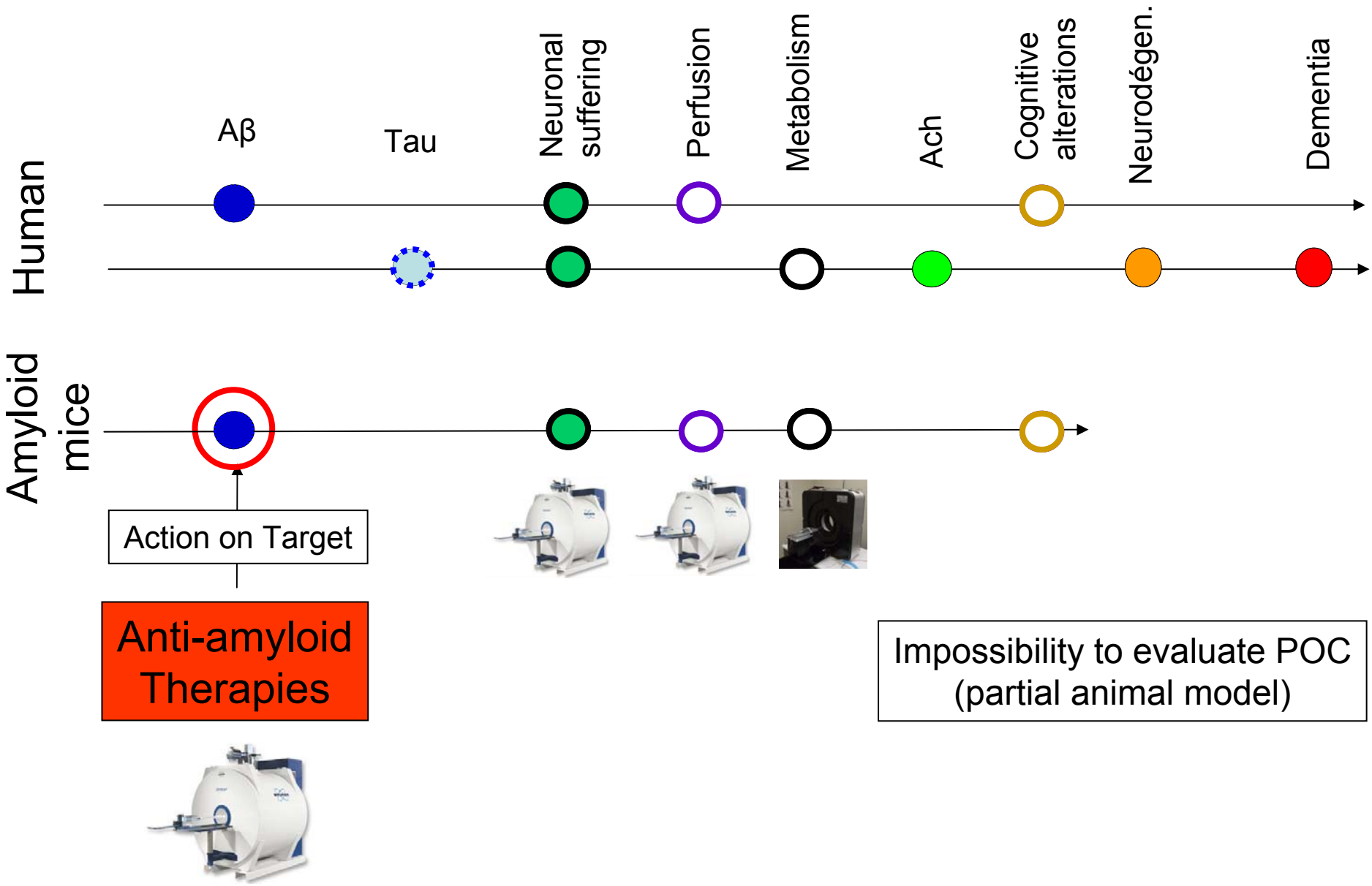
Joseph-Mathurin
Neurobiol Aging
2013

Immunisation with Aβ1-42 increases iron accumulation In the choroid plexus

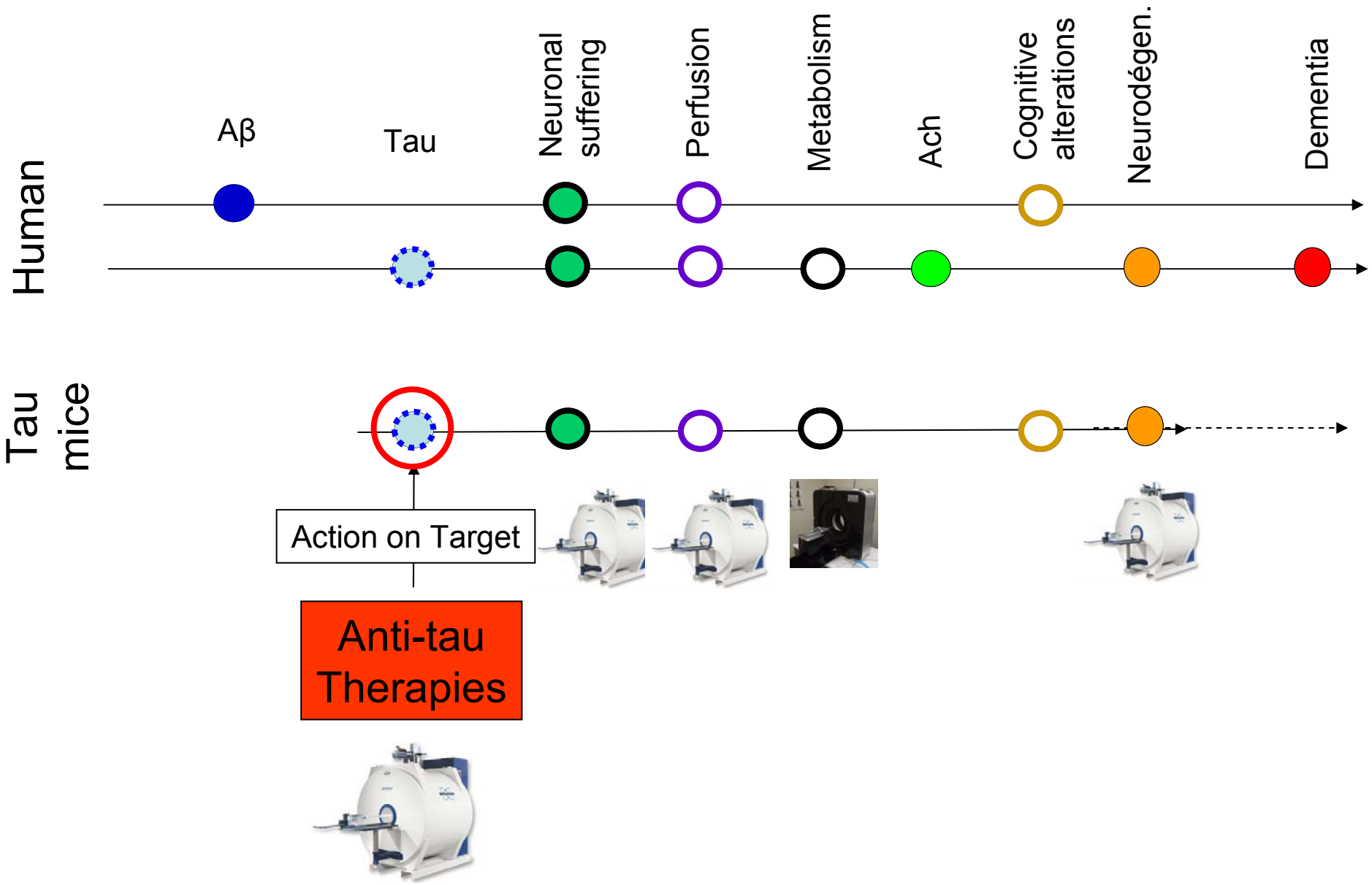
Conclusions

- Imaging biomarkers are used to evaluate
  - Amyloid load
  - Cerebral atrophy (probably linked to Tau pathology)
  - Glucose uptake/metabolism
  - Angiography
  - Perfusion
  - Neuronal health
  - Microhemorrhages associated to immunotherapies
- Many other parameters can be assessed by MRI
  - Perfusion associated to pharmacologic stimulation
  - Blood brain barrier alterations
  - Diffusion
  - Spectroscopy
- Multimodal imaging (especially with MRI)
- Longitudinal follow-up

What can we study in amyloid mice



What can we study in Tau mice



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- Medicen (Pole de compétitivité Ile de France)

- NIH

- Programme longévité du CNRS 2009

- Fondation de Coopération Scientifique Maladie d'Alzheimer et maladies apparentées

- France Berkeley