Quantification & Validation of Imaging Biomarkers in Preclinical Models of Alzheimer's Disease

(Applications for Therapy Development)

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URA CEA CNRS 2210 – MIRCen - Fontenay aux Roses
Alzheimer's Disease Group:
Modelization, Biomarkers, Preclinical Imaging

Declaration of Conflict of Interest or Relationship

Conflict of Interest

"I have no conflicts of interest to disclose with regard to the subject matter of this presentation"

Slides are available from:
http://marc.dhenain.free.fr/Diaps/ISMRM.pdf

Outline

- Alzheimer's disease and preclinical research
  - Concepts of preclinical biomarkers
  - Concepts of animal models
  - Concepts of biomarkers in animal models
- Amyloid plaque imaging
- Cerebral atrophy
- Functional imaging: Perfusion
- Functional Imaging: Neuronal transportation
- Evaluation of toxicity

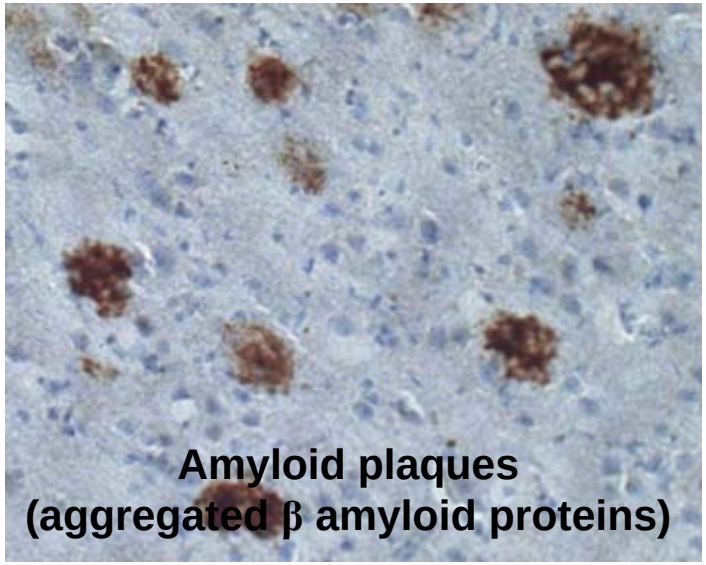
http://marc.dhenain.free.fr/Diaps/ISMRM.pdf

Alzheimer's disease (AD)

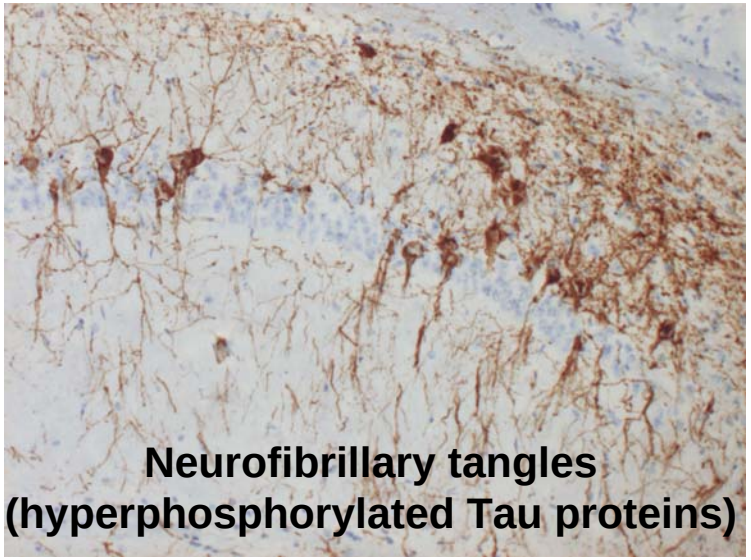
- Severe dementia

- Most common neurodegenerative disease
  - 22 million people worldwide
  - 34 million people in 2025

- Two main microscopic lesions



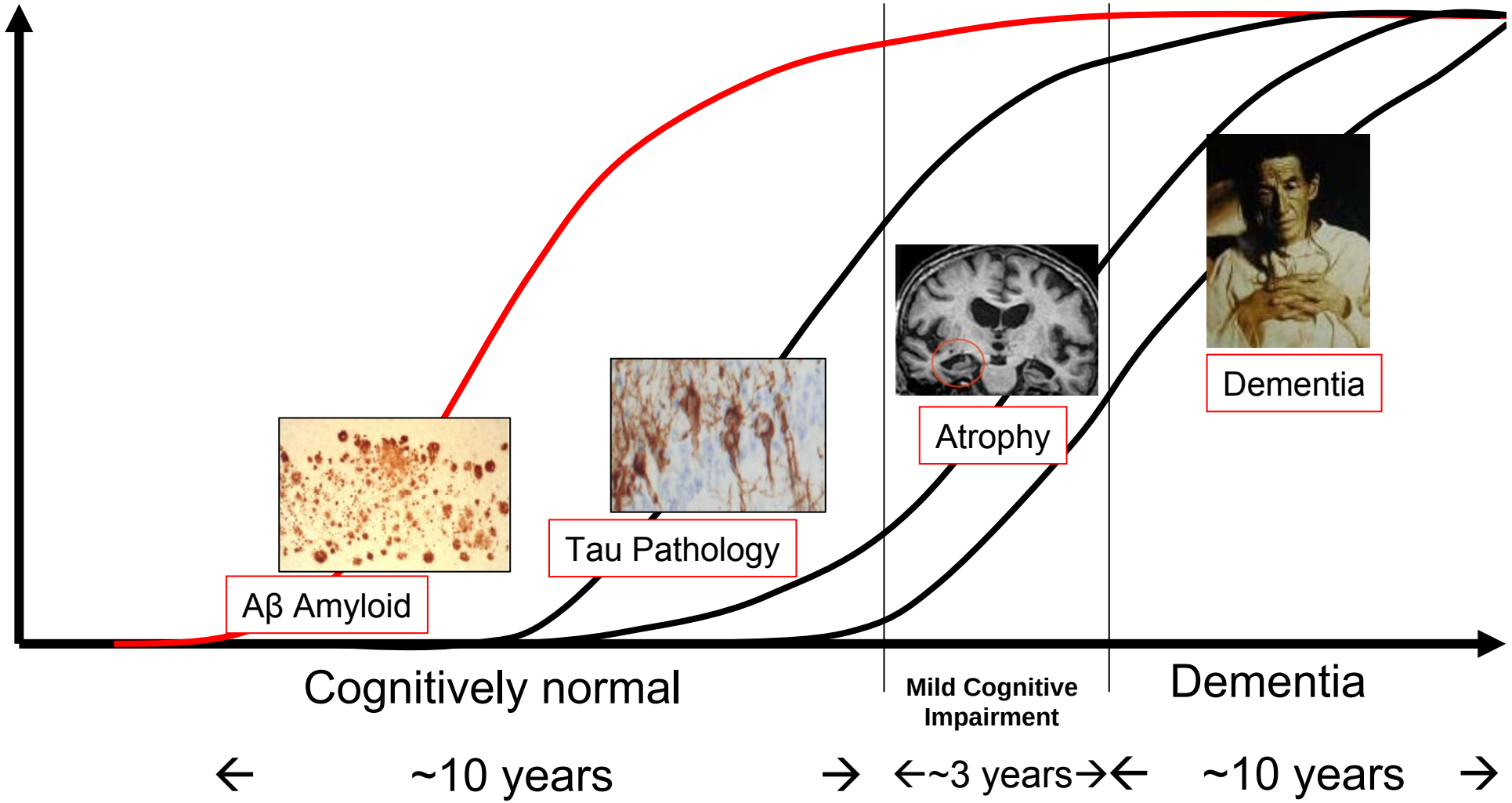
Amyloid plaques (aggregated β amyloid proteins)



Neurofibrillary tangles (hyperphosphorylated Tau proteins)

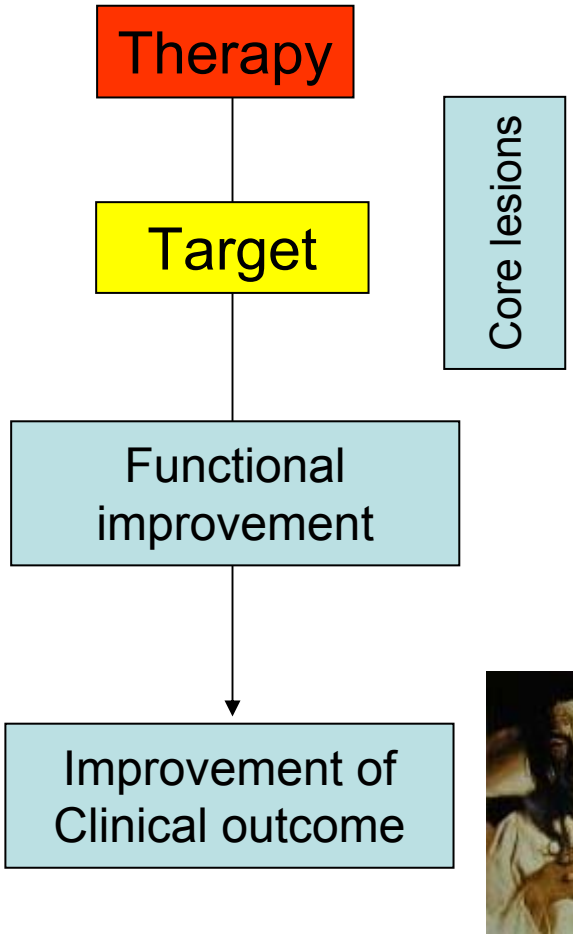
- No curative treatment

A slowly evolving disease

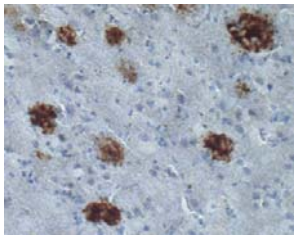


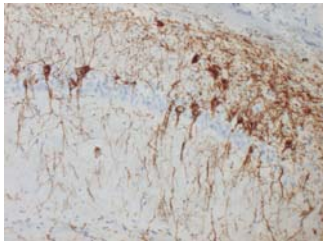
Jack CR Jr et al. (2010). Lancet Neurol 9:119-128.

Critical questions during drug discovery



• Is the therapy active on core lesions ?





• Is the therapy modifying disease evolution ?

• Improvement of brain function ?

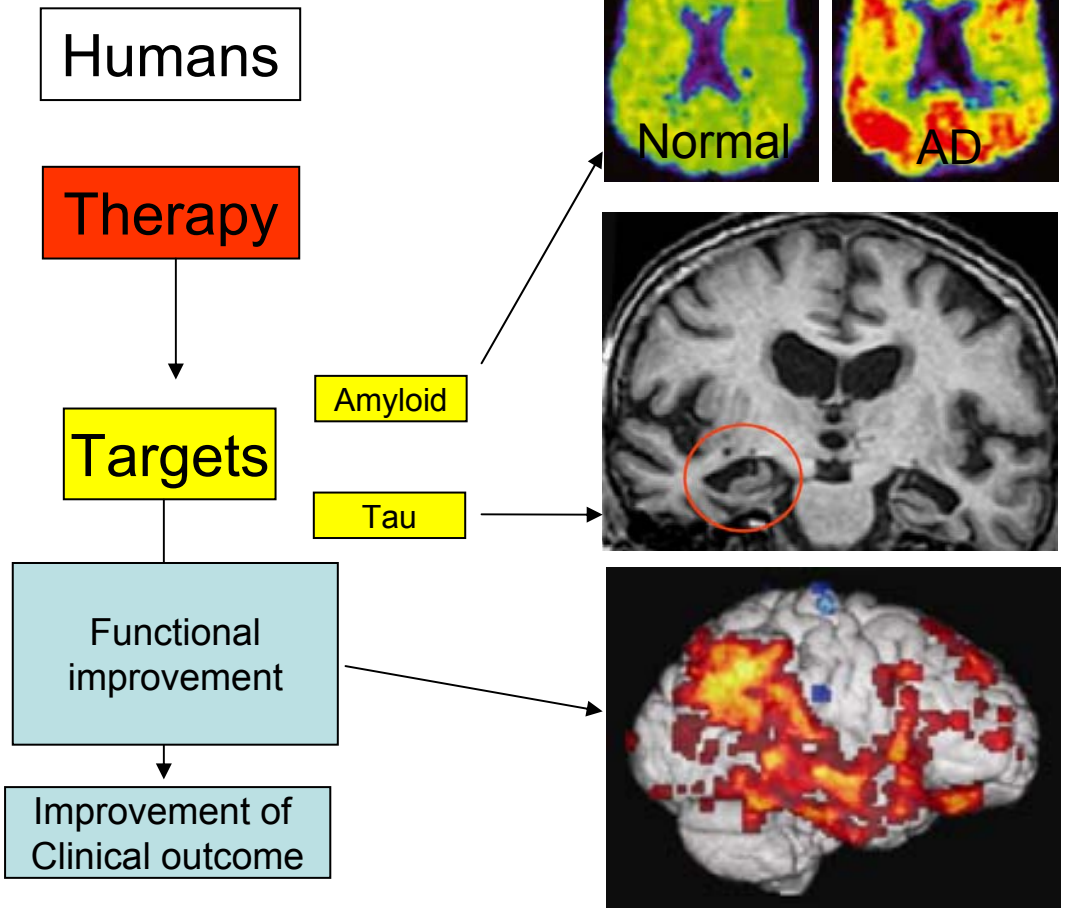
• Is the therapy modifying the clinical outcome ?

Ex. Cognitive alterations

Toxicity

• Is the therapy toxic ?

Biomarkers are widely used in human studies



Amyloid plaque imaging (PET)
PIB
Klunk WE et al. Ann Neurol, 2004
Amyvid (AV45)
FDA approved April2012

Cerebral atrophy (MRI)
Jack CR Jr et al.
Neurology, 1999

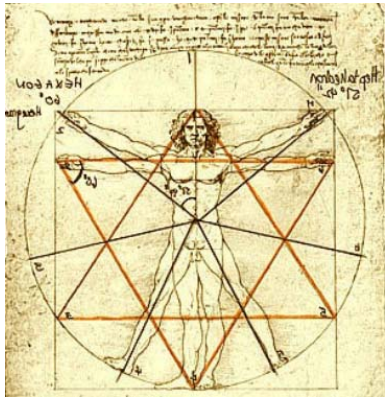
Glucose metabolism (PET)
Edison P et al.
Neurology, 2007

Meningoencephalitis (MRI)
Orgogozo JM et al.
Neurology, 2003

Animal models are critical in the process of drug development

Disease characterization

- Diagnostic
- Natural history of the disease



Preclinical research

- Basic mechanisms
- Drug discovery

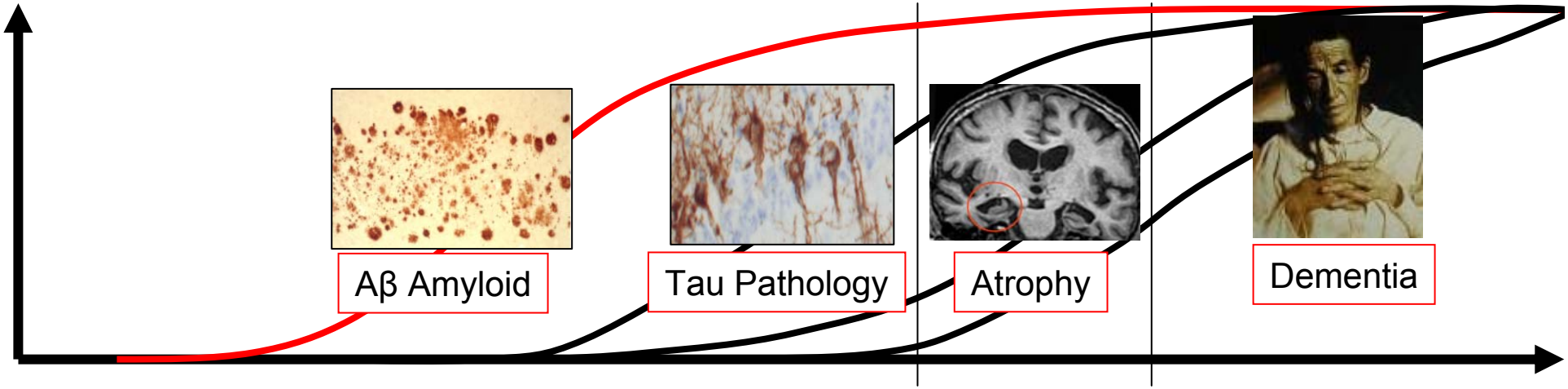
Toxicity/Safety

- Small animals
- Large animals

Clinical trials

- Phase 1 – Pharmacokinetic
  - 10 volunters
- Phase 2 – Safety
  - 20-40 volunters
- Phase 3 - Safety/Efficacy
  Targeted population
  5000/50 000 persons

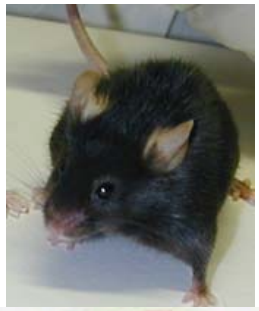
Which animal model ?

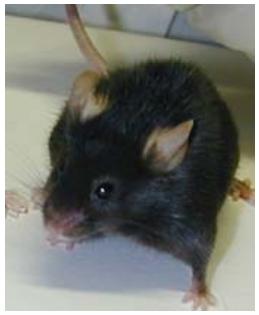


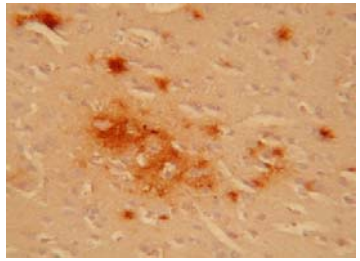
Mouse lemur Primates

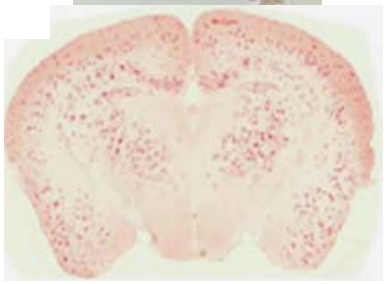
APP, APP/PS1 Mice

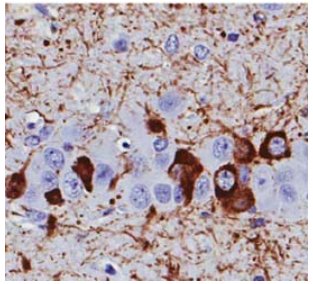
Tau Mice



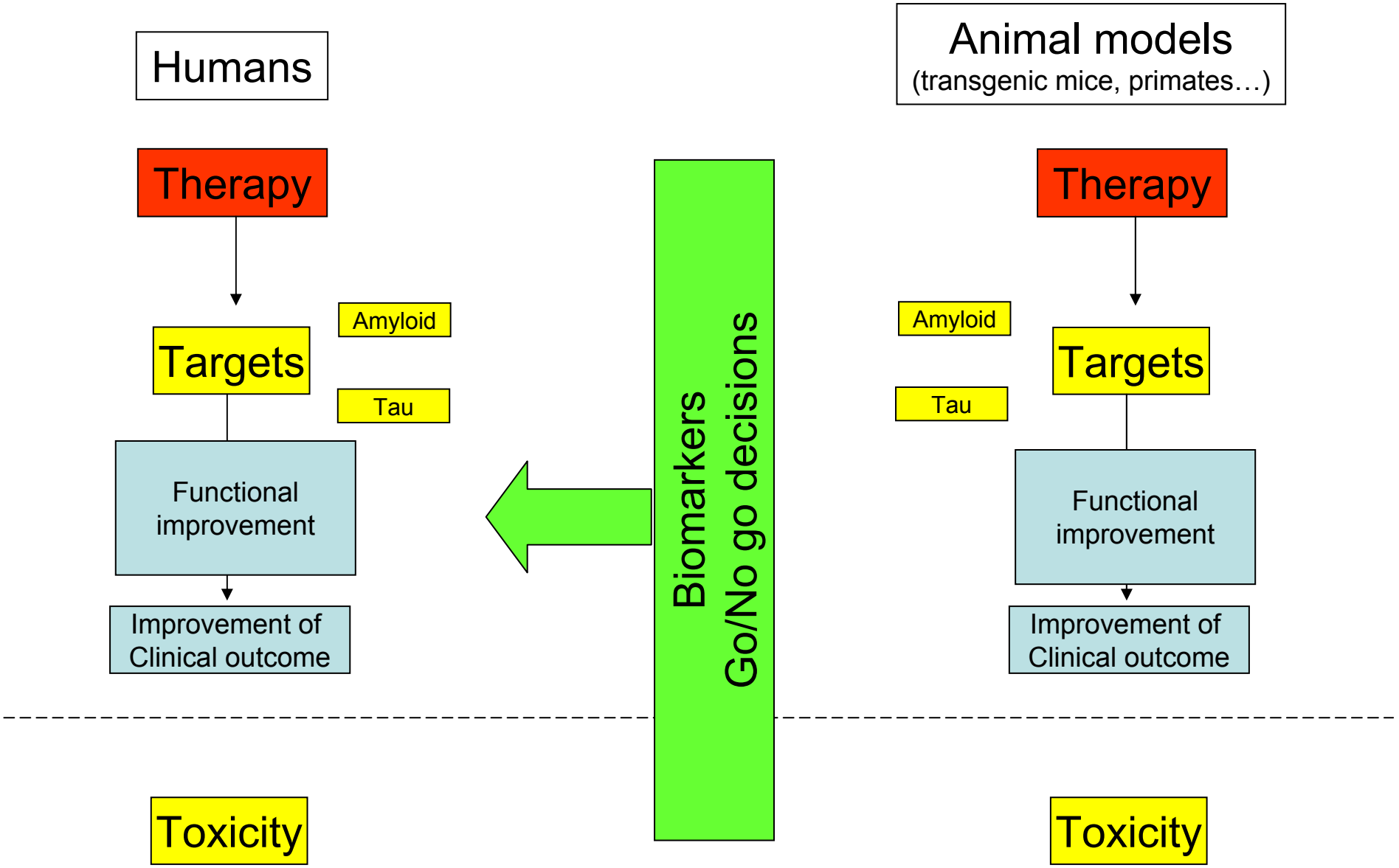




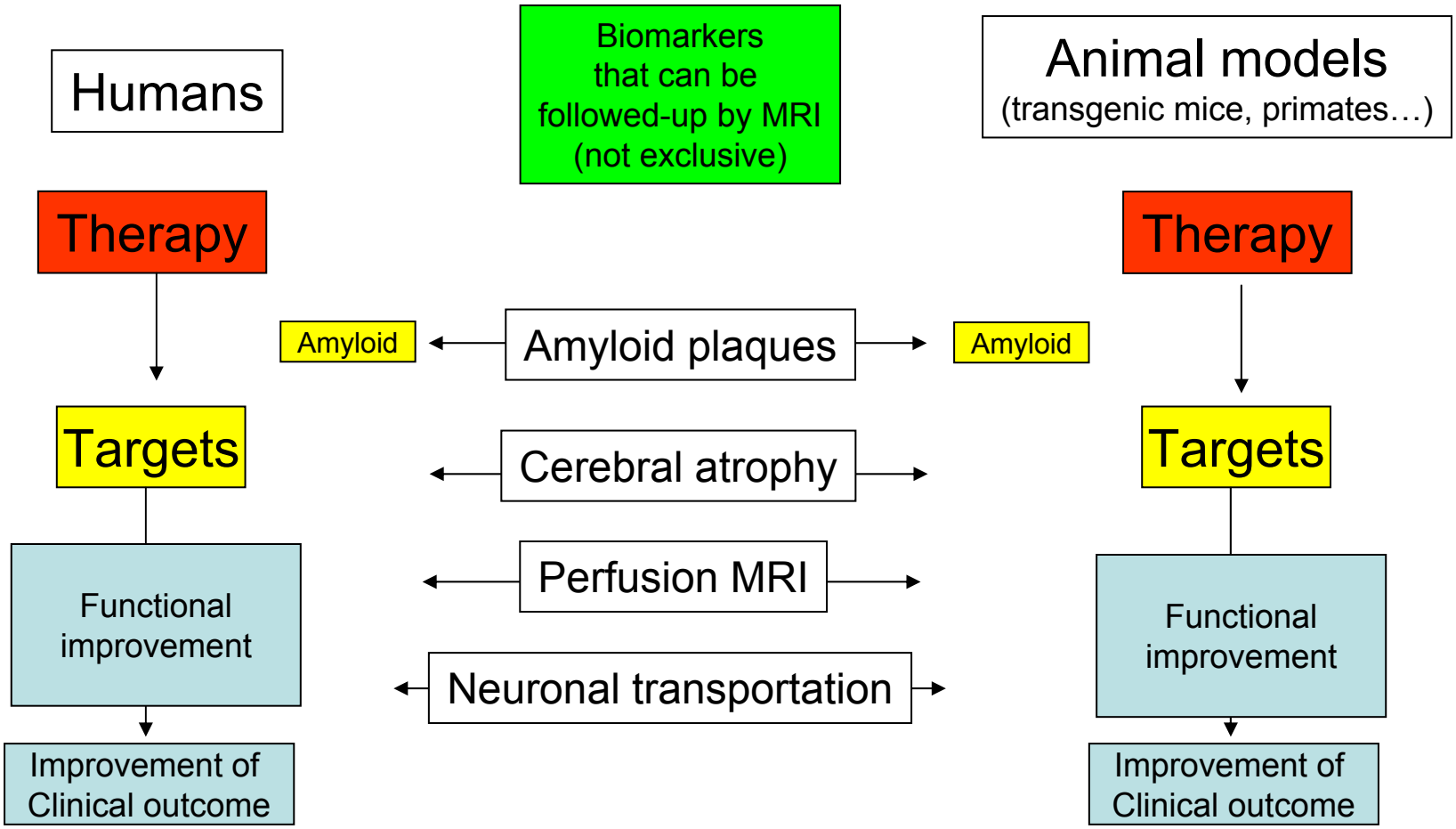




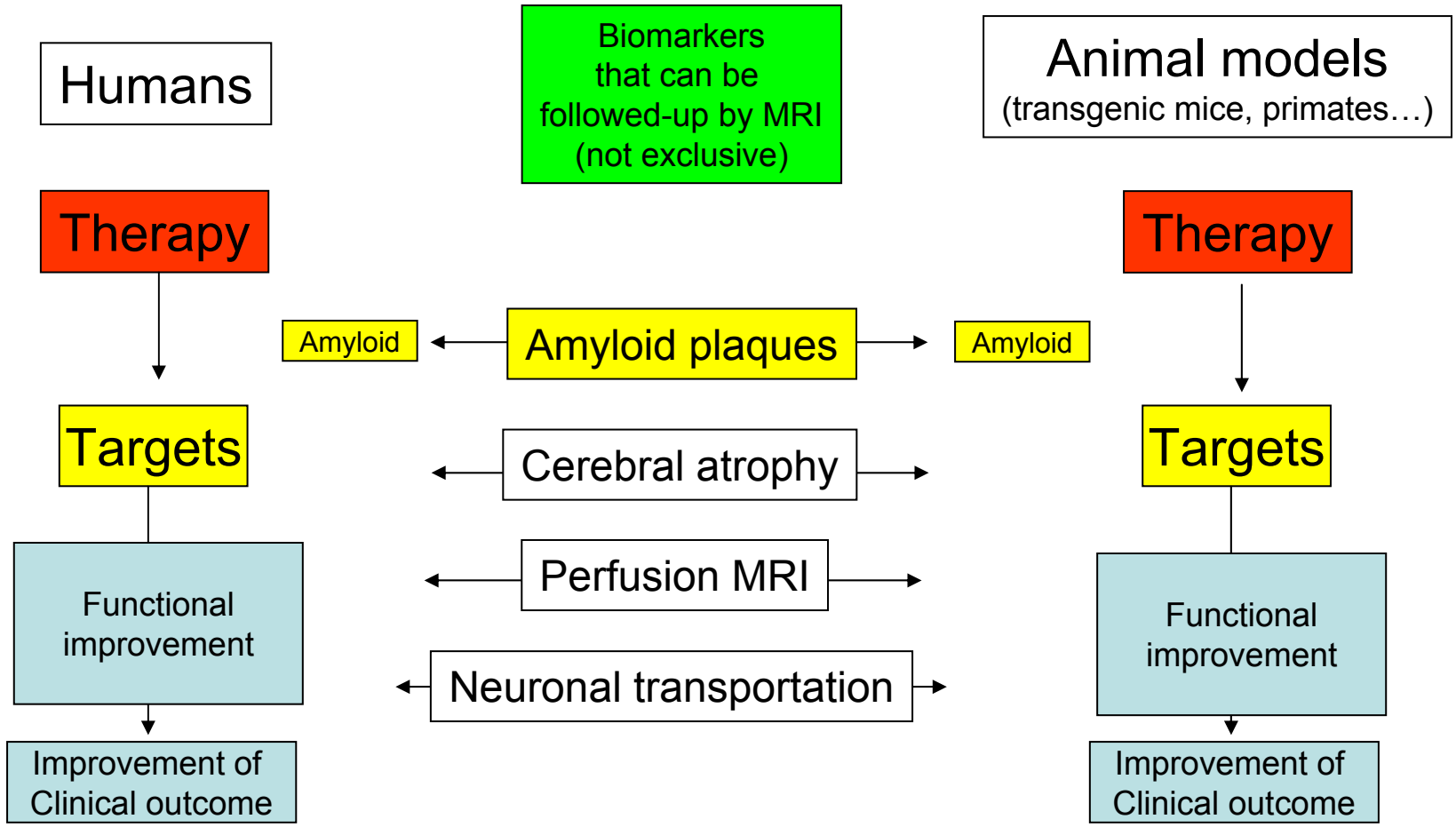
Preclinical studies and Biomarkers



MRI biomarkers



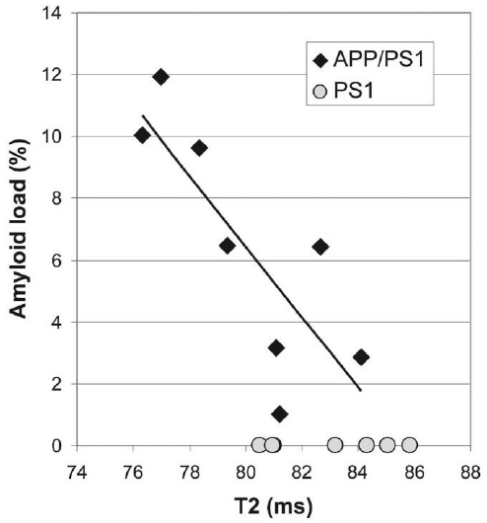
MRI biomarkers



Imaging amyloid plaques by MRI

Indirect detection

Relaxivity (T2 decrease)



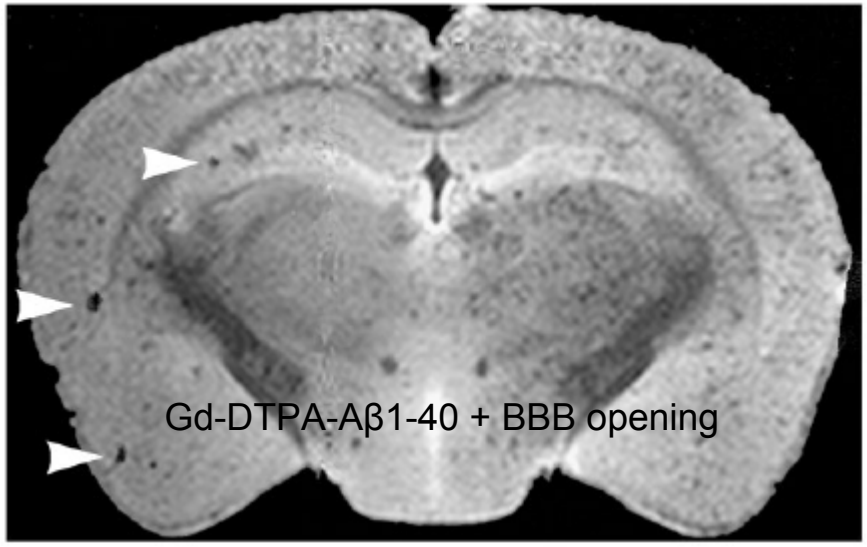
El Tannir El Tayara N et al. MRM, 2007
Helpern J et al. MRM, 2004

Direct detection (MR microscopy)

Spontaneous contrast

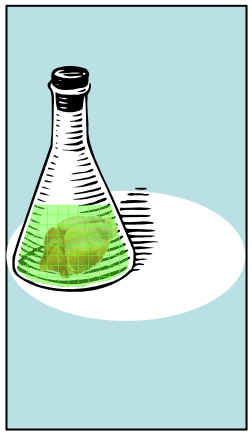
Targeted Contrast agent

Non targeted Contrast agent



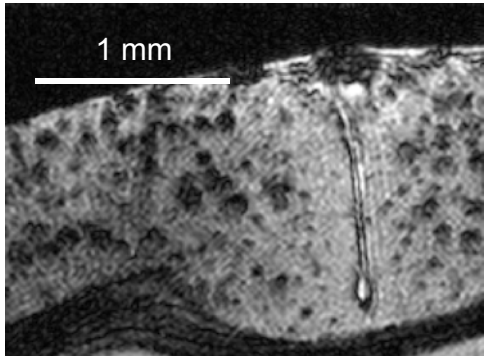
Zaim Wadghiri Y et al. MRM, 2003

Development of Gadolinium Staining method



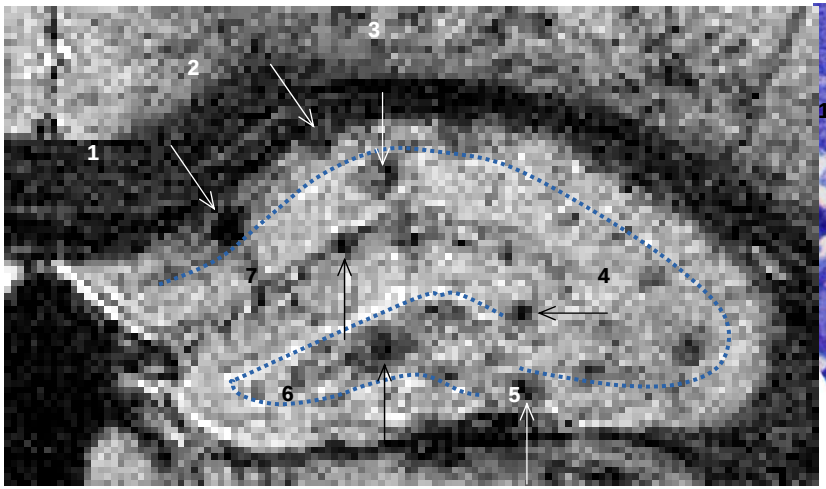
Passive staining
Gd:PBS > 24 hrs

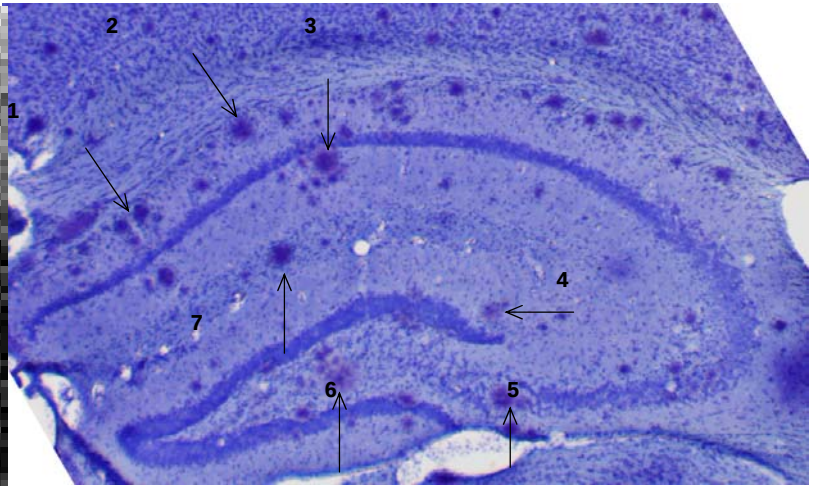
Dotarem, Guerbet, France



16*16*100µm^3

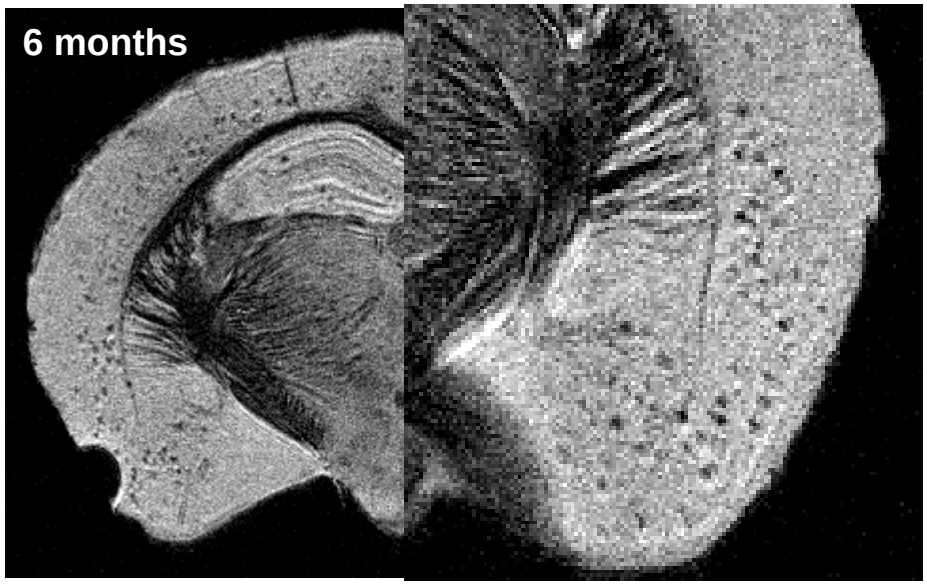
"Passive Gadolinium staining" method

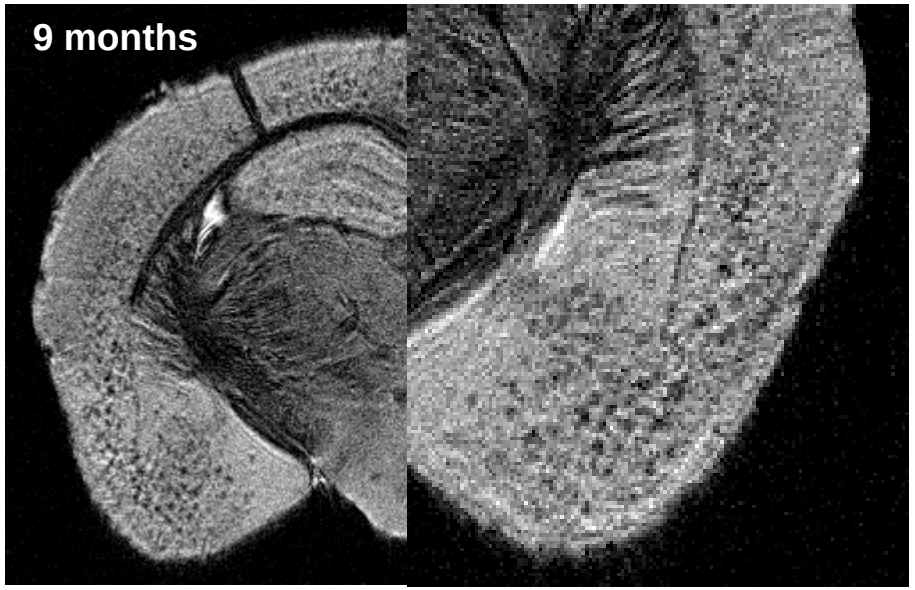


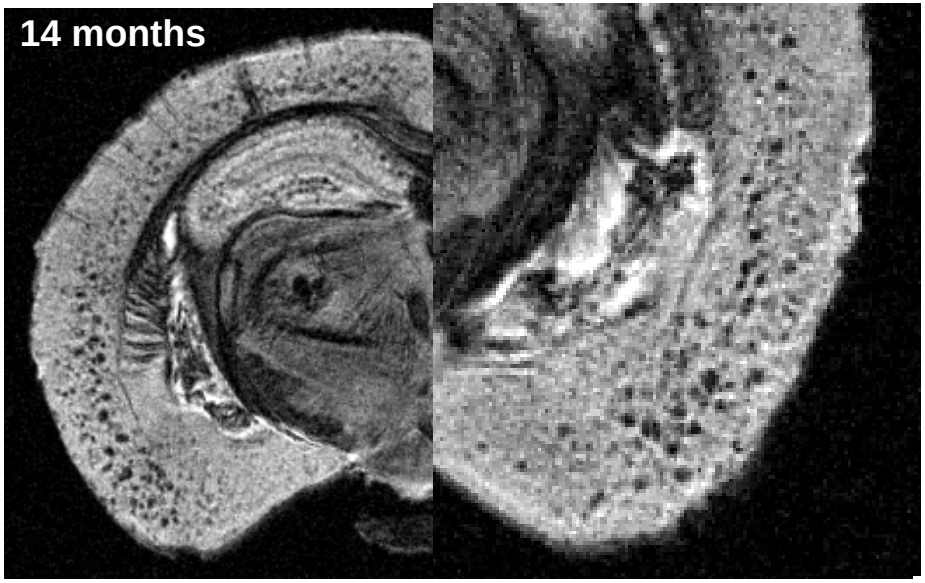


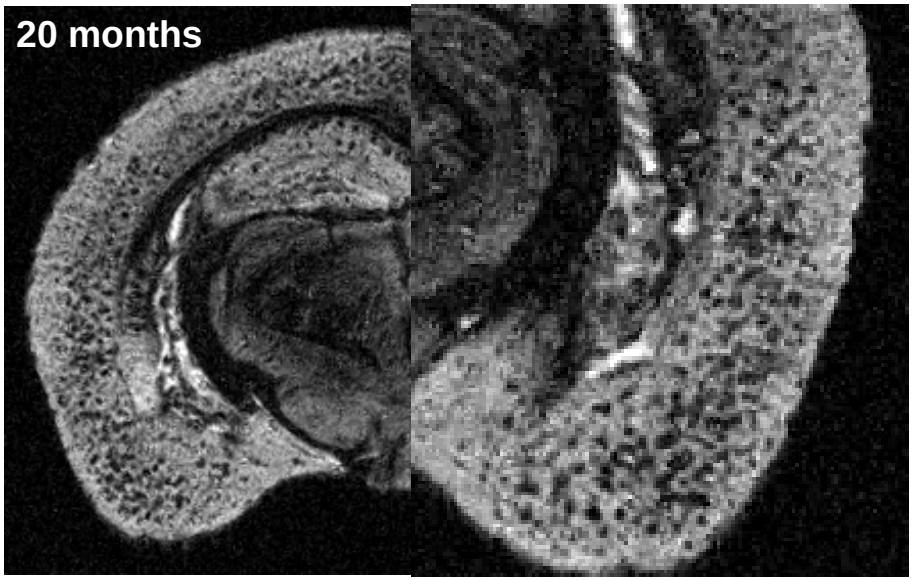
Petiet A et al. Neurobiology of Aging, Ahead of Print.

Detection of amyloid plaques by MR microscopy



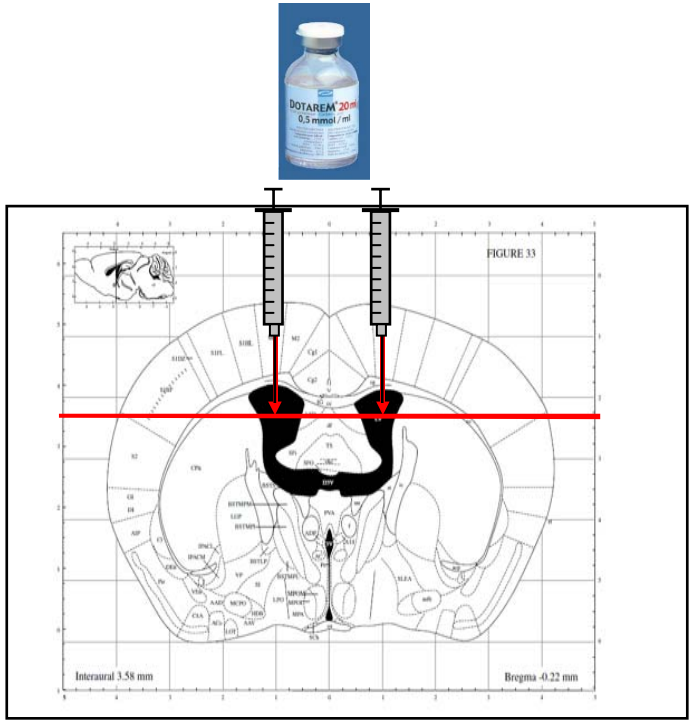




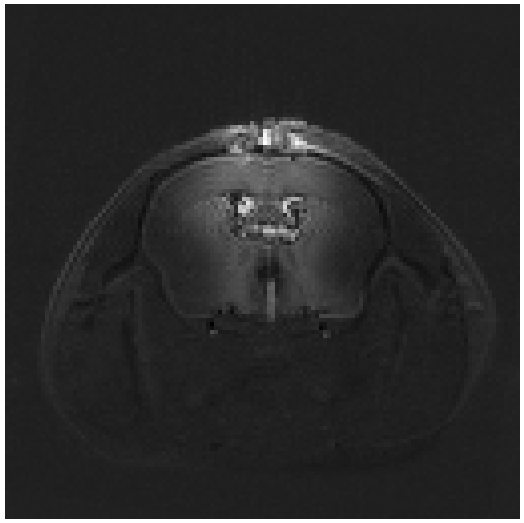


Petiet A et al. Neurobiology of Aging, Ahead of Print.

In-vivo intra-cerebroventricular injection of Gadolinium



Movie from
30 min to 2 hours
post Gd injection



→ Diffusion of Gadolinium in the brain

"*In-vivo* Gadolinium staining" method

In-vivo follow-up of amyloid load

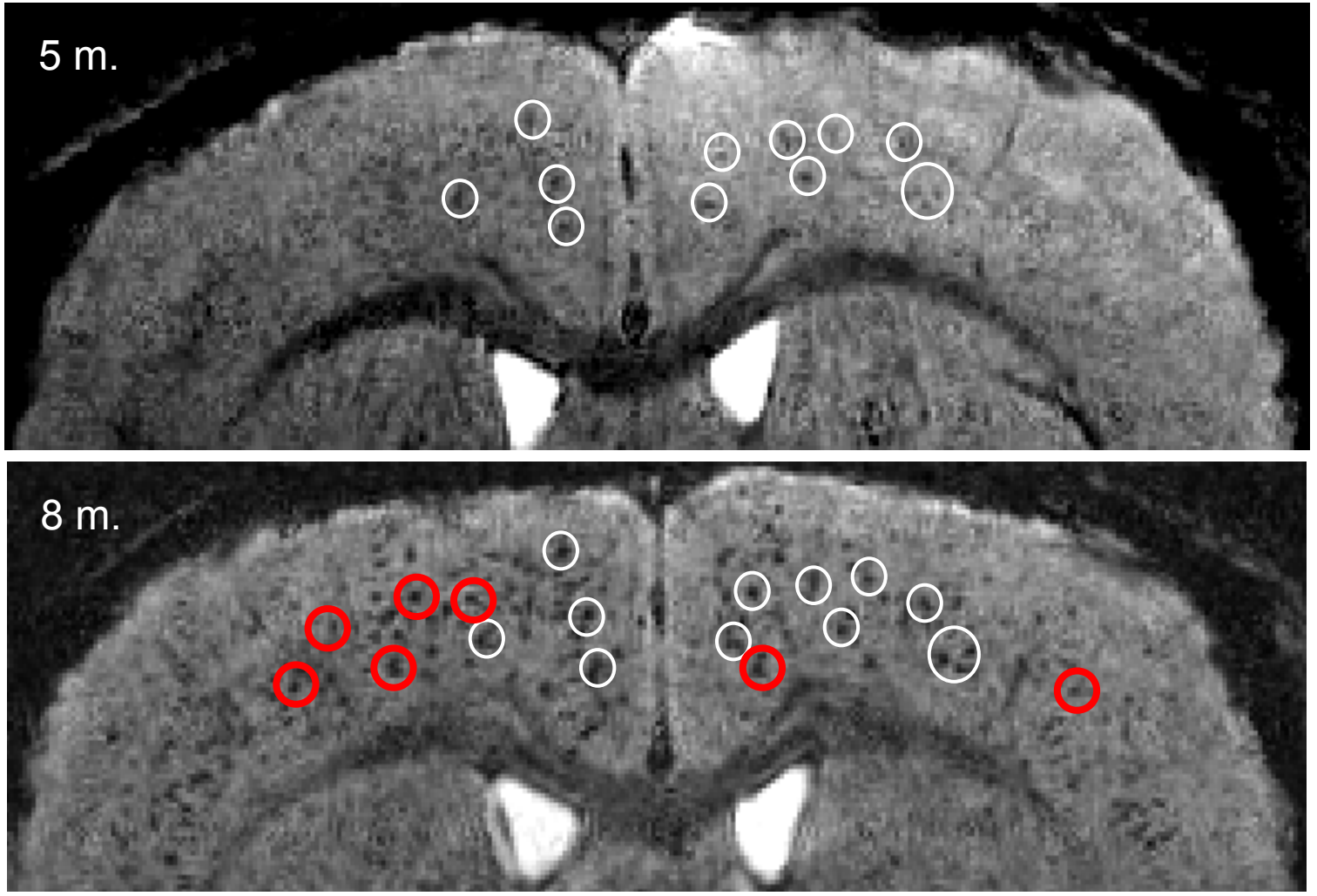
Detection of amyloid plaques by "*In-vivo* Gadolinium staining"

APP/PS1

Control

29*29*117 μm^3
Acq Time can be 32 min

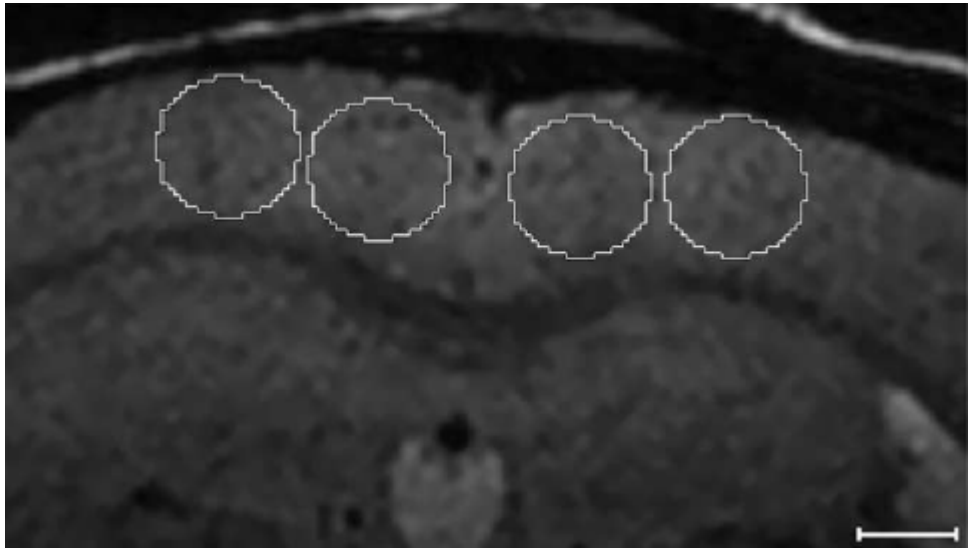
In-vivo longitudinal follow-up of amyloid plaques

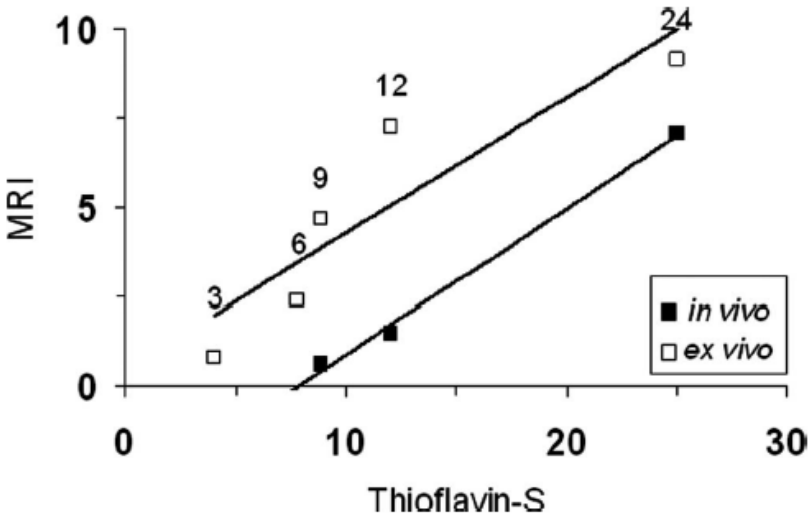


→ A tool for preclinical therapeutic evaluation

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

Quantification of amyloid plaques
Counting in regions of interest



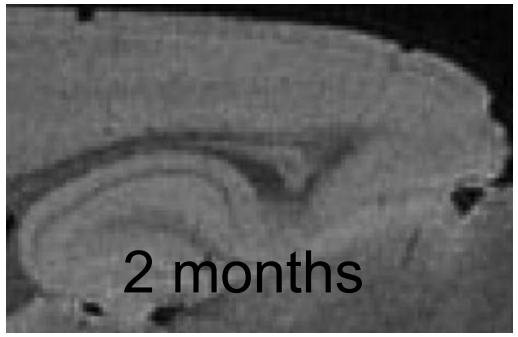


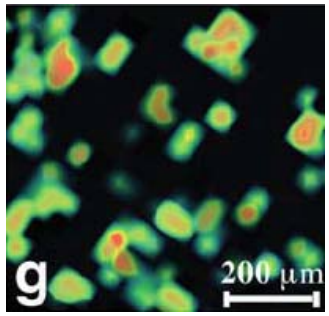
- Time consuming

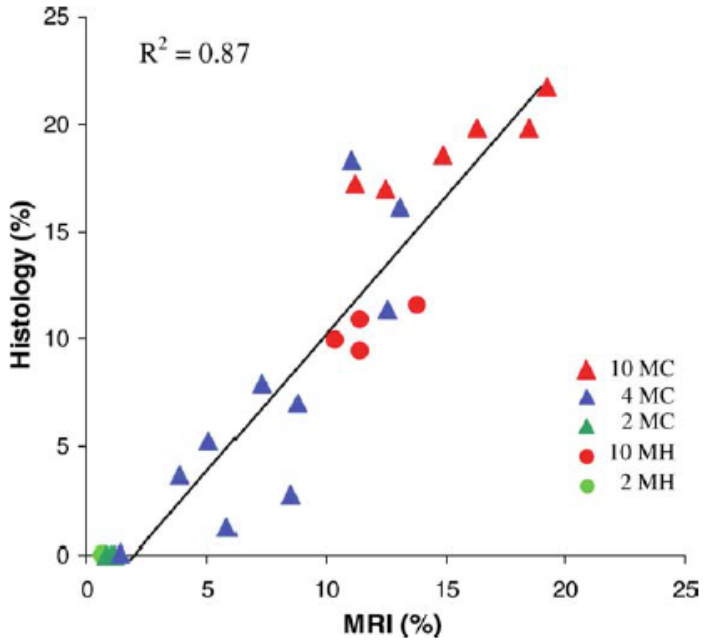
Jack CR Jr et al. J Neurosci 25, 10041-8; 2005

Quantification of amyloid plaques
Automatic segmentation

- Individual plaques in MR images are defined as regions with large intensity variation around local minima
  - Identification of plaques candidates: watershed method
  - Classification as plaque or non plaque: unsupervised learning method







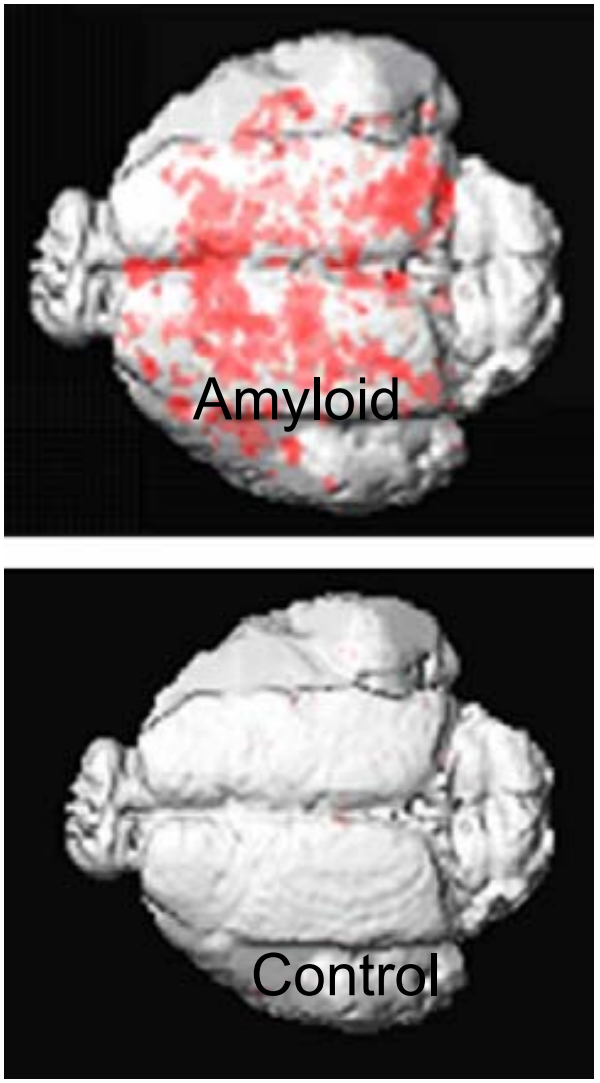
Iordanescu GM et al. Magn Reson Med. Ahead of Print.

Quantification of amyloid plaques

Group studied by voxel based analysis (VBA) methods

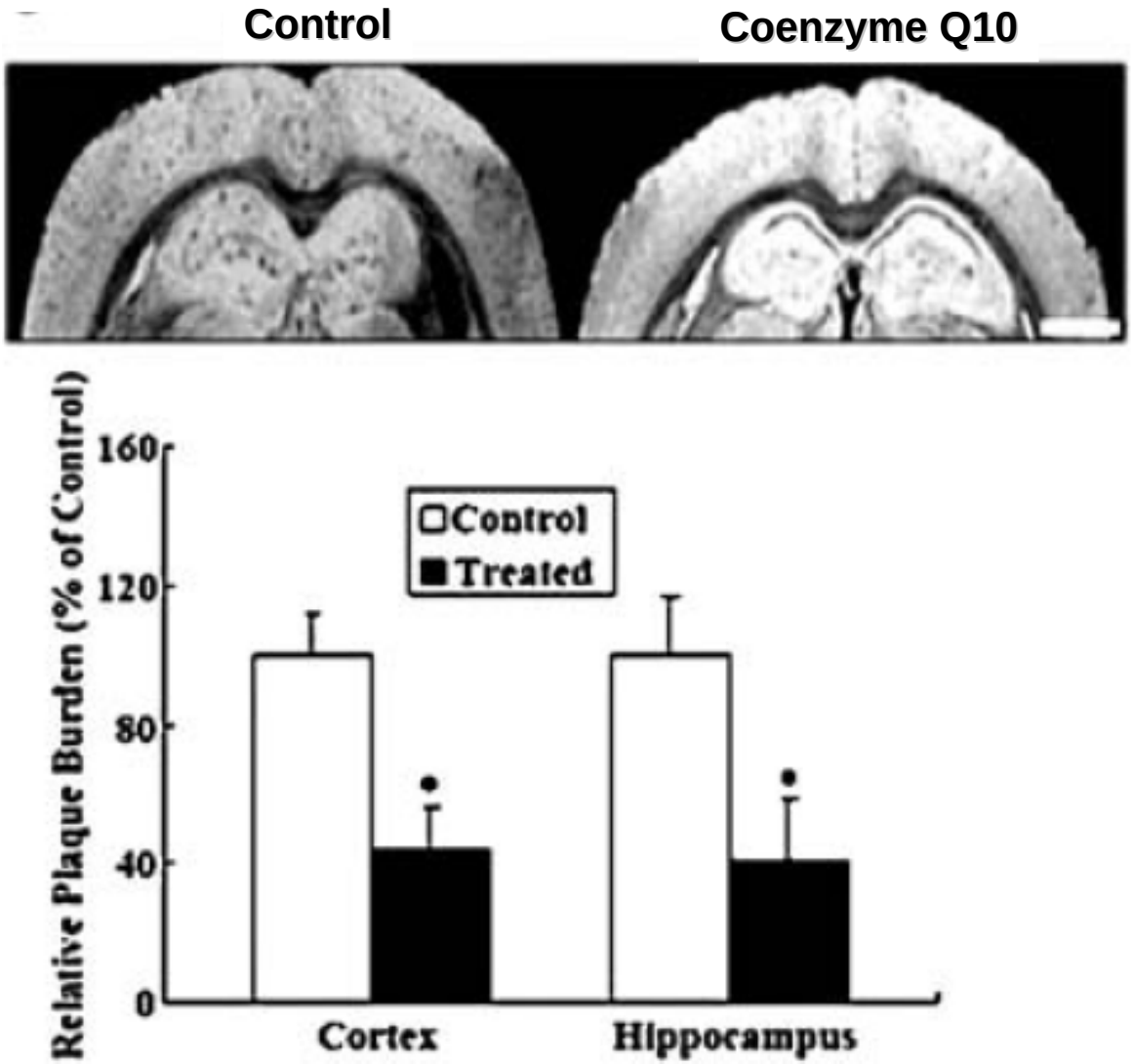
- Images recorded before and after administration of a contrast agent targeting amyloid plaques

- Group analysis by VBA



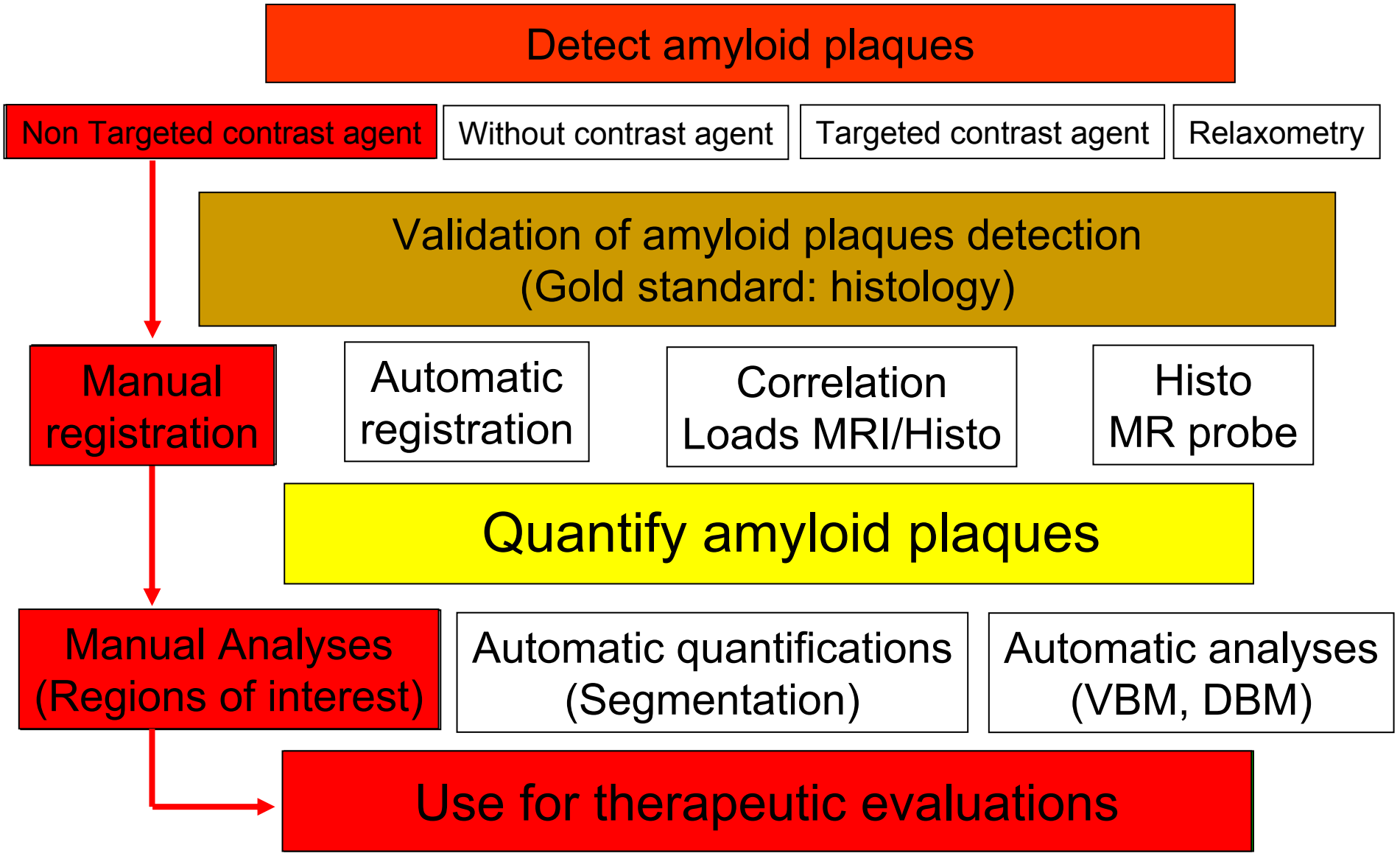
Sigurdsson EM et al. Neurobiology of Aging 29, 836-47, 2008

Use of MRI to quantify amyloid load in drug research

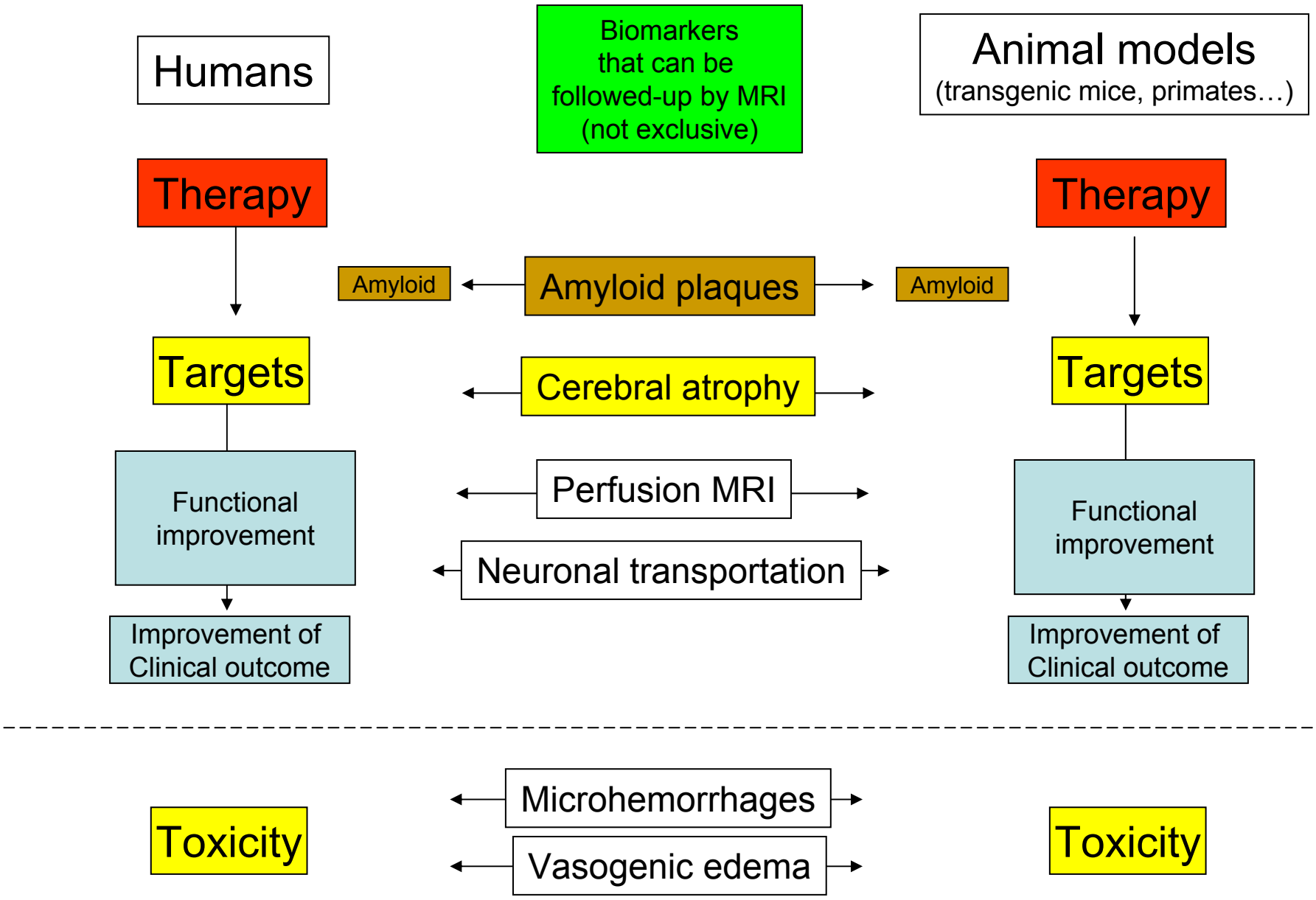


Yang X et al. J Mol Neurosci 41:110-113; 2011

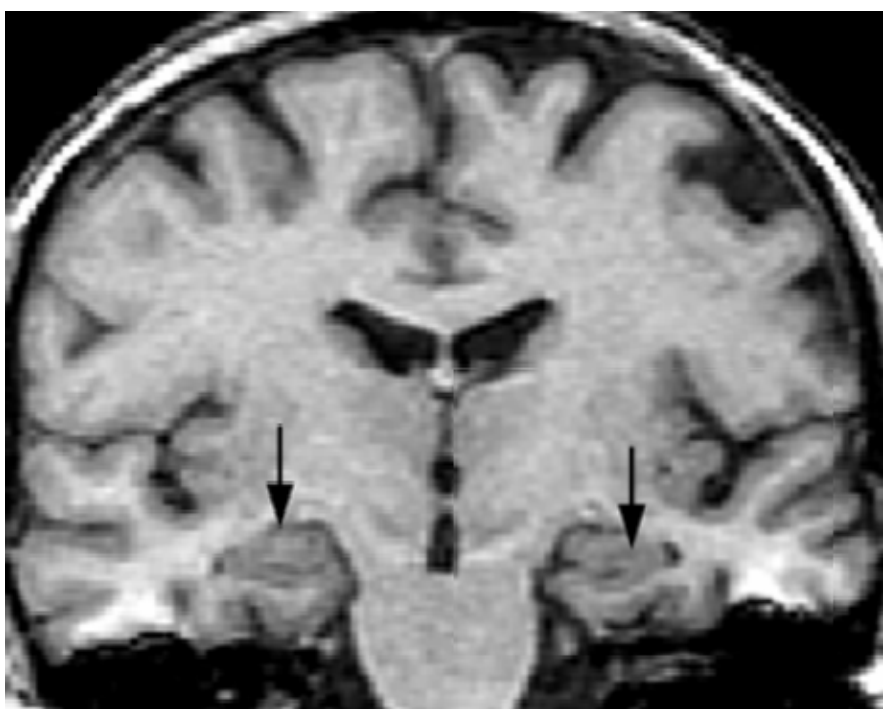
Detection of amyloid plaques by MRI: Summary



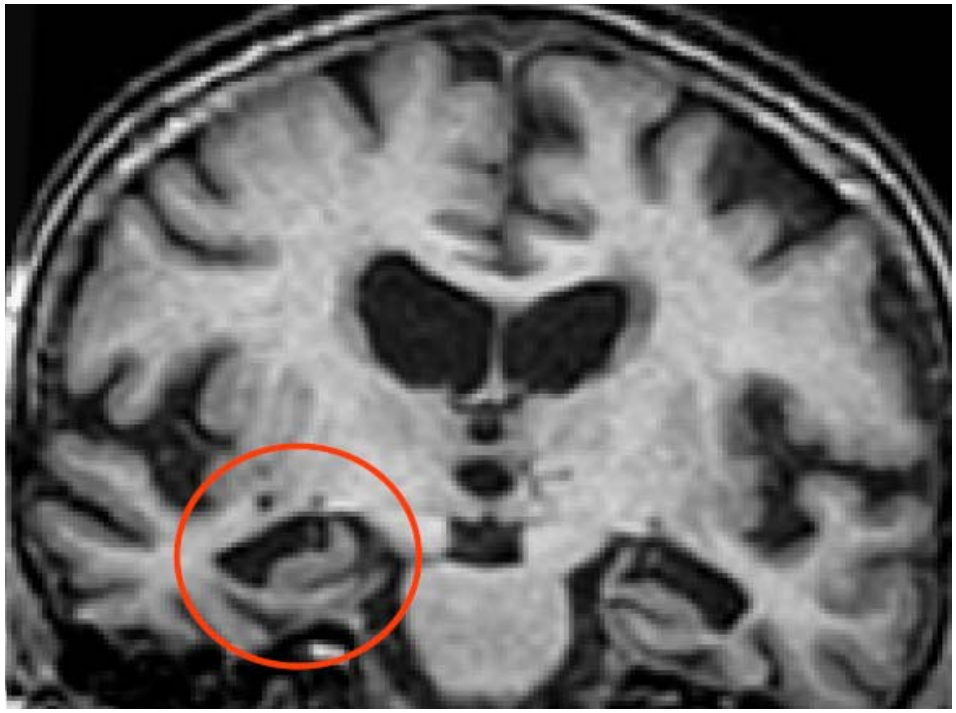
MRI biomarkers



Cerebral atrophy in humans with Alzheimer



Normal aging



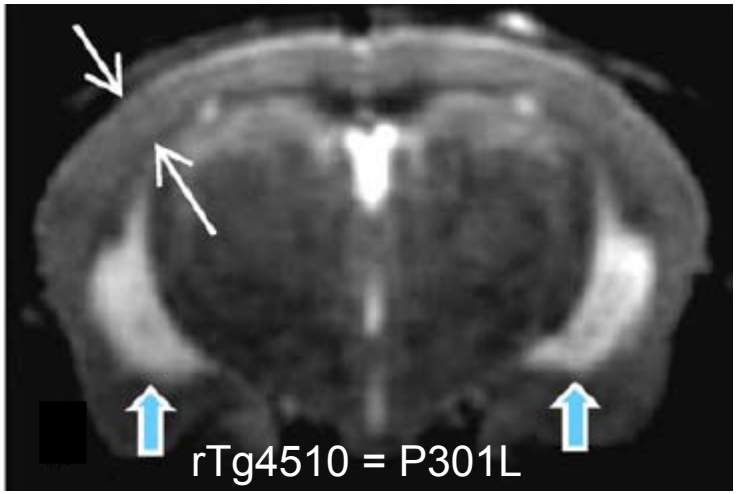
Alzheimer

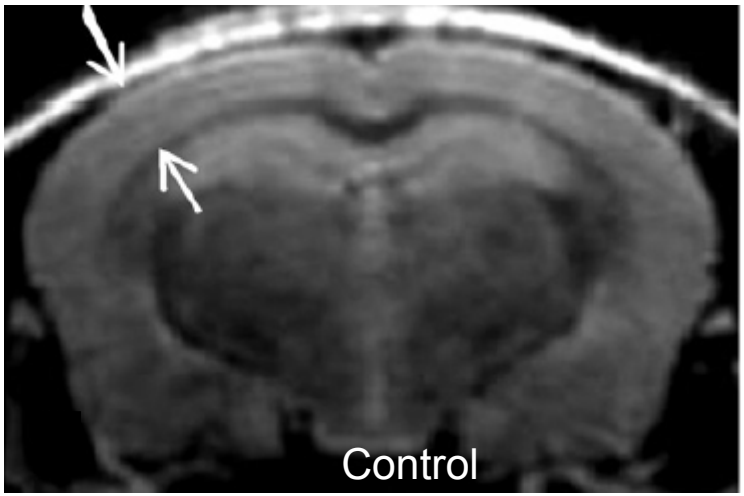
Starts in the hippocampus then spreads all over the brain

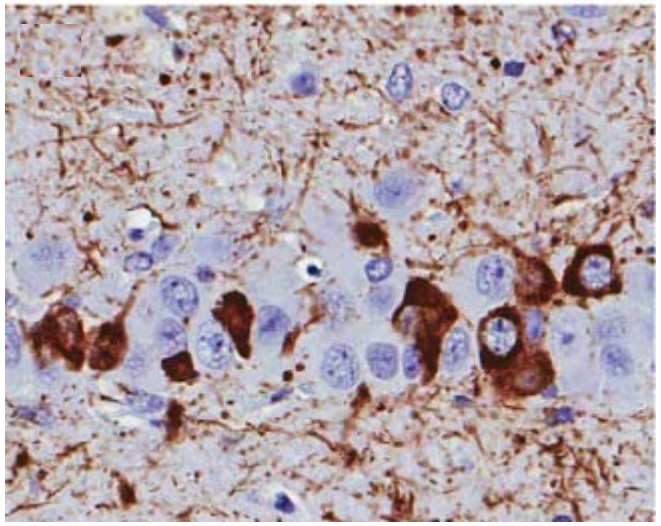
Evaluation of cerebral atrophy in animal models of AD

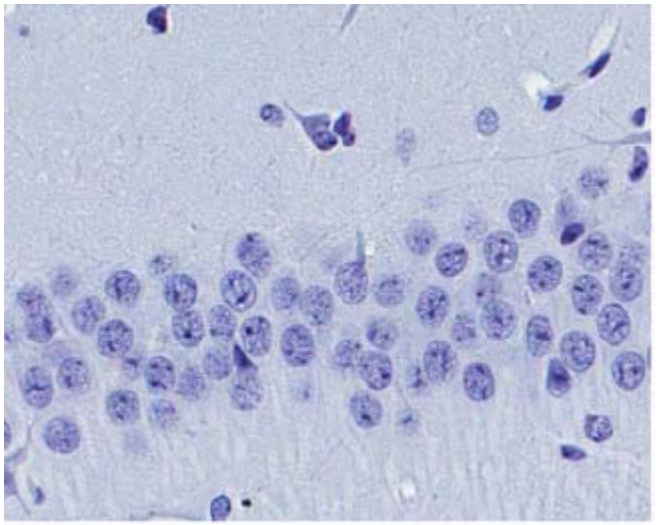
Images provided by Dr. S. Lehericy

Cerebral atrophy in Tau mice





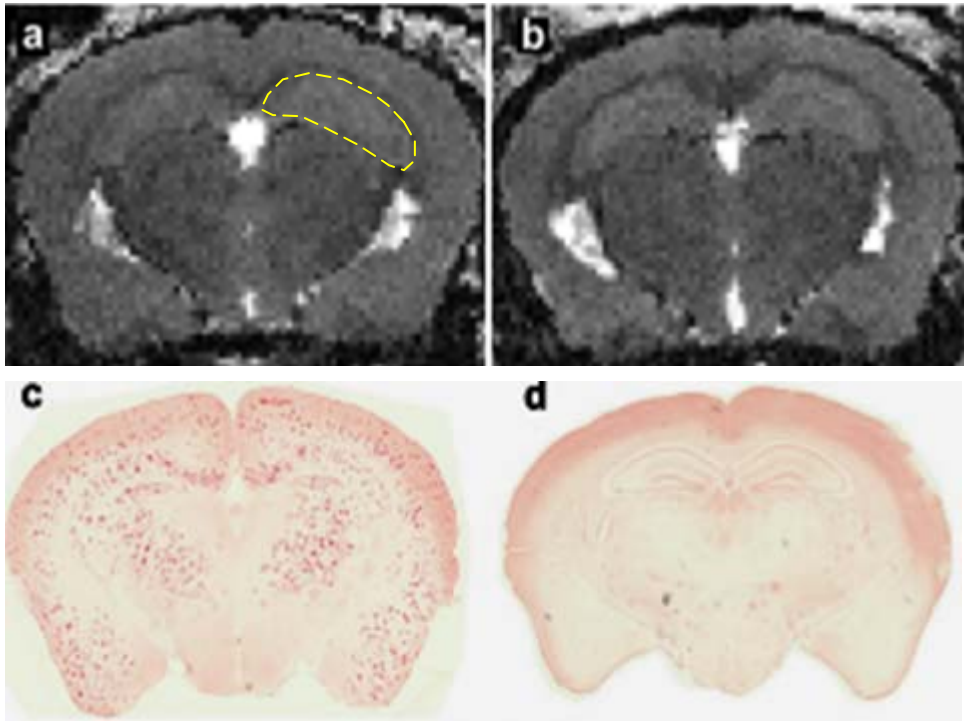


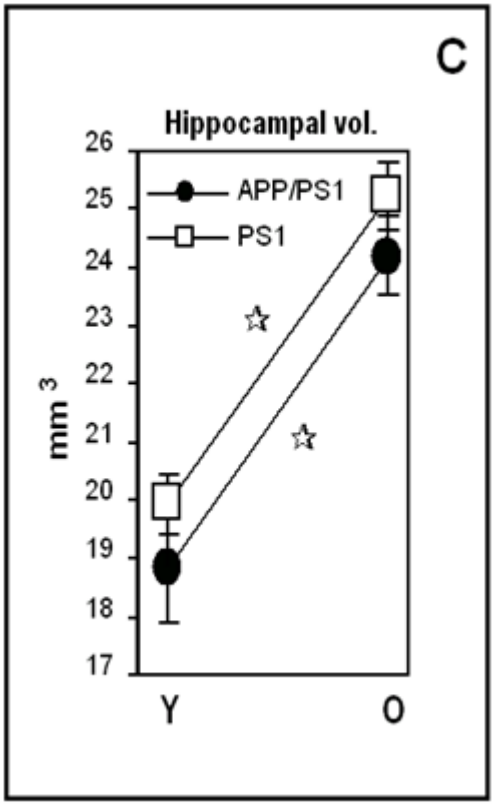


Suggests that atrophy is a marker of Tau pathology

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

Cerebral atrophy in transgenic mouse model of amyloidosis

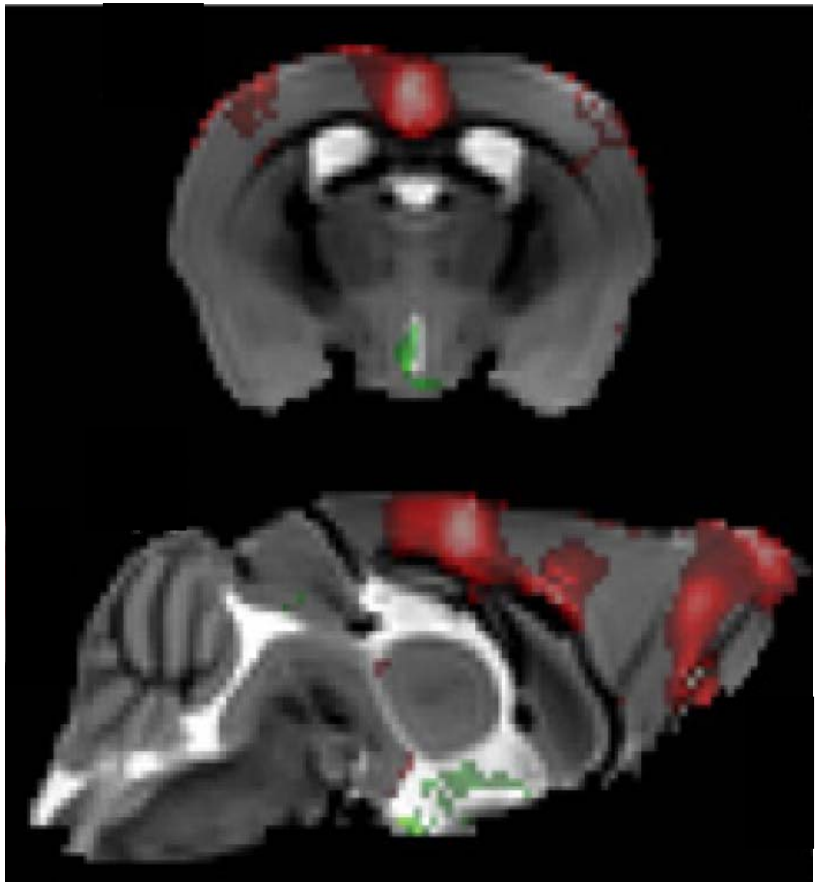




Brain and hippocampal growth
even in the presence of amyloid deposits…

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

Automatic procedures: Example of deformation-based morphometry



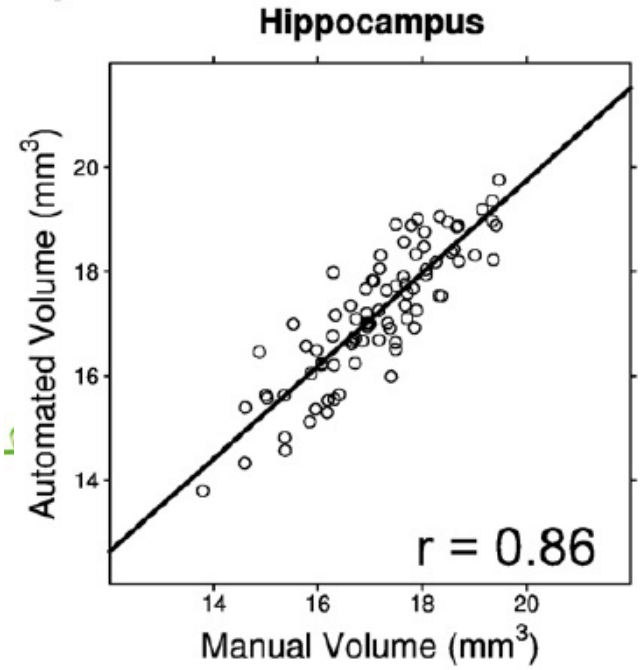
Control > APP/PS1

APPPS1 > Control

- Genotype effect detected
- Neurodevelopmental rather than degenerative process

Lau JC et al. Neuroimage, 42(1), 19-27, 2008.

Comparison of manual and automatic procedures



- Good correlation between manual and automatic procedures

	Manual (regions of interest)	Automatic analyses (VBM, DBM)
Technical level	Low	**High**
Time consuming	**Yes**	No
Intra-/inter-rater variability	**Yes**	No
Can detect atrophy in regions that can not be outlined	No	**Yes**
Group studies	Yes	Yes
Individual analyses	**Yes**	No

Lau JC et al. Neuroimage, 42(1), 19-27, 2008.

Detection of cerebral atrophy by MRI: Summary

Detection of cerebral atrophy

Manual method

Automatic method

Mouse model of Taupathy

Atrophy seems to be linked to Tau pathology

but few published studies so far

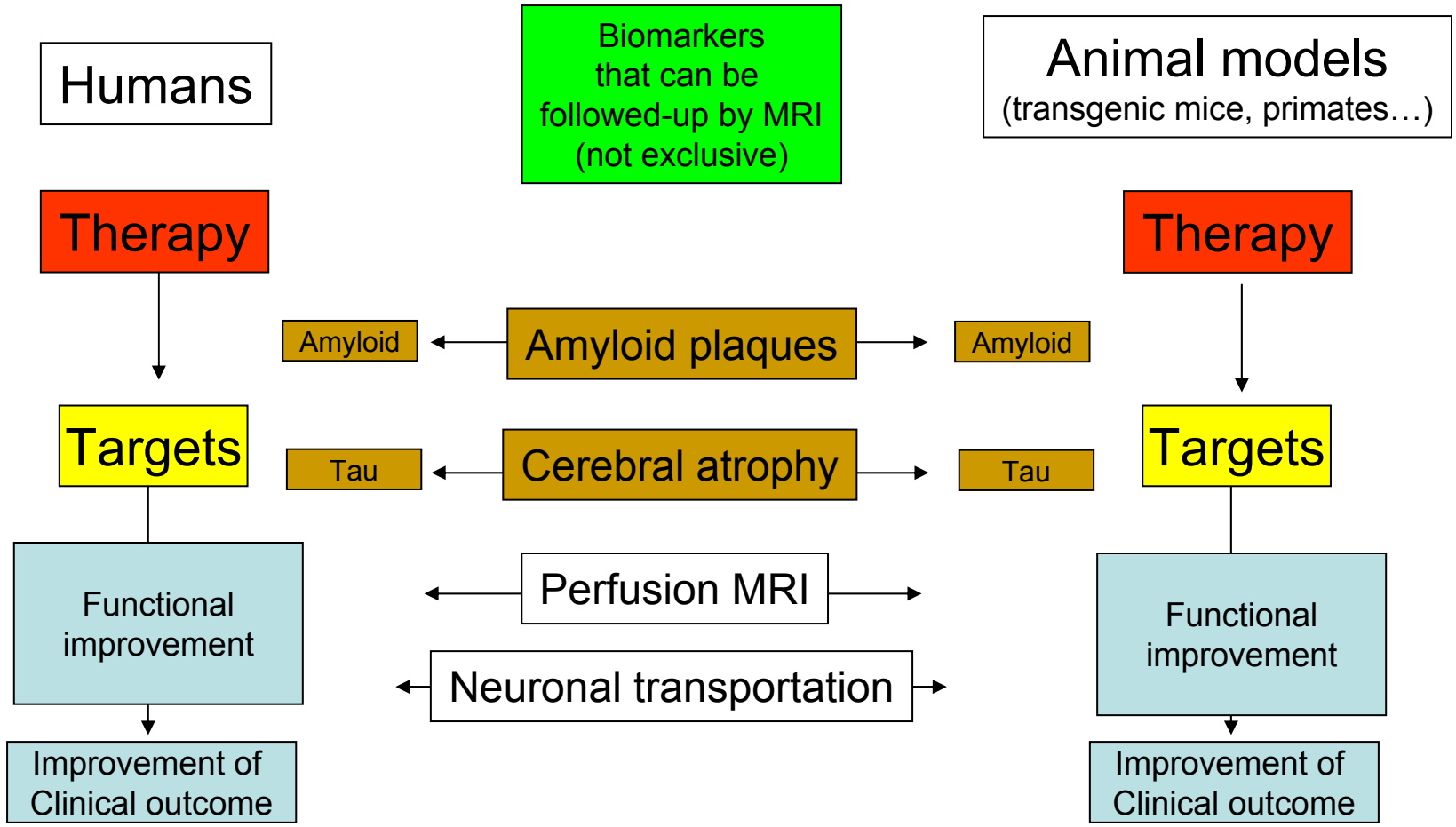
Mouse model of amyloidosis

Often linked to a neurodevelopmental

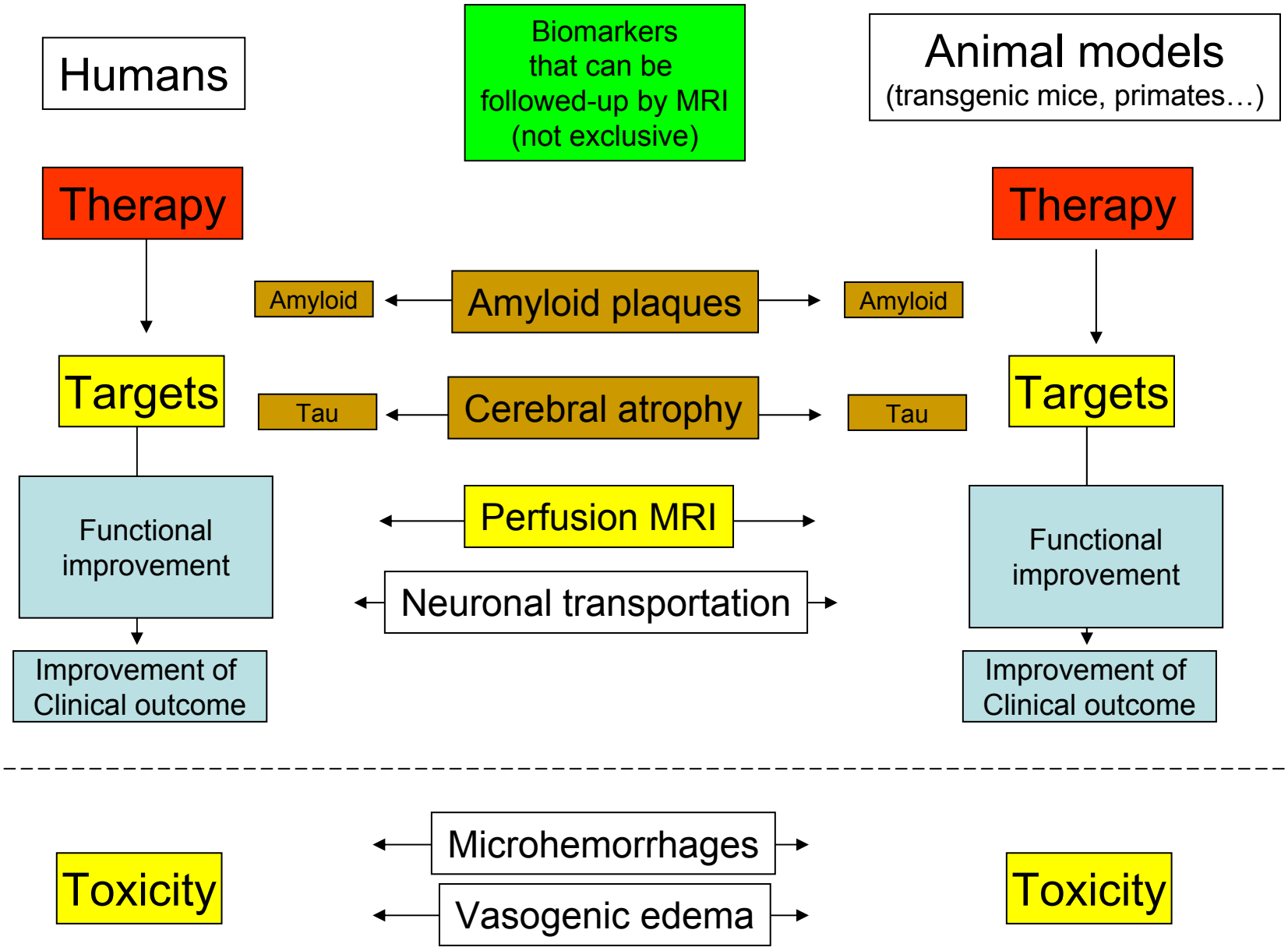
rather than degenerative process

Not use for therapeutic evaluations

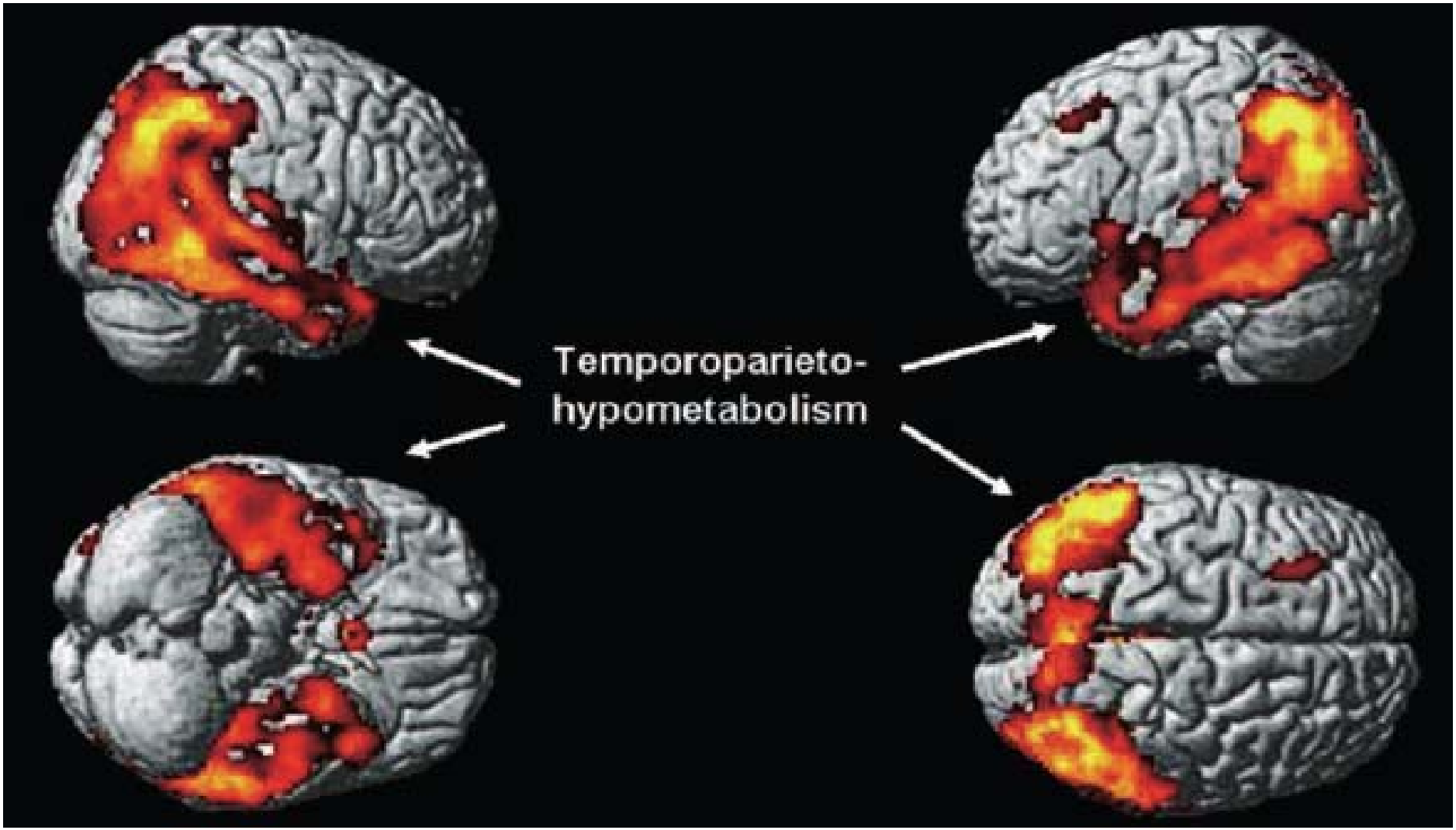
MRI biomarkers



MRI biomarkers



Alteration of glucose metabolism in AD

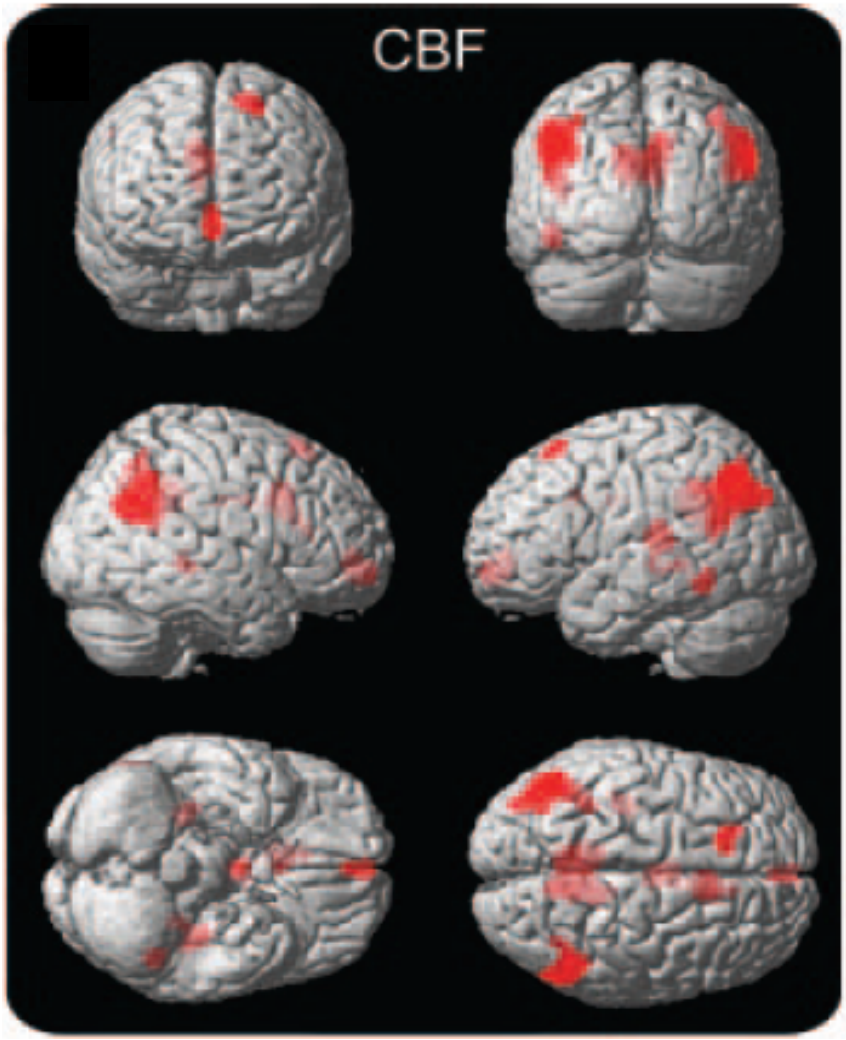


Fluorodeoxyglucose (FDG)-PET

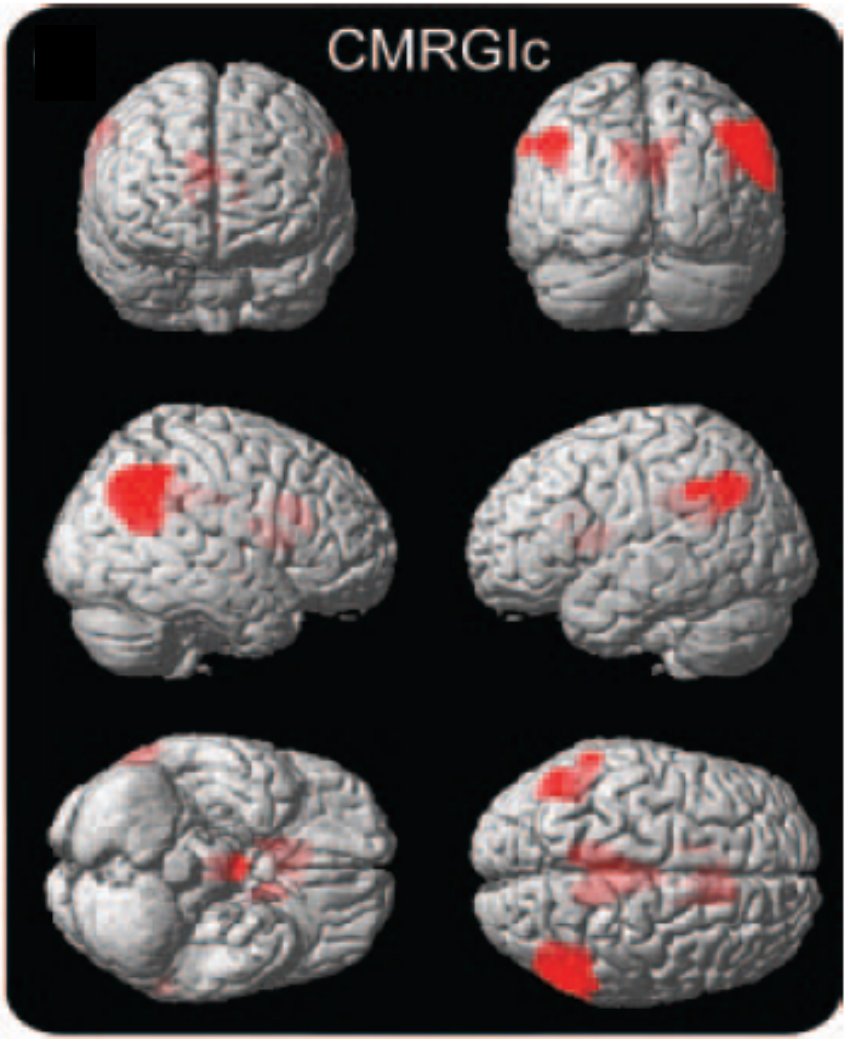
Edison P et al. Neurology. 68(7):501-8; 2007.

Perfusion measurements from MRI

ASL-MRI provides overlapping information with FDG-PET



ASL-MRI

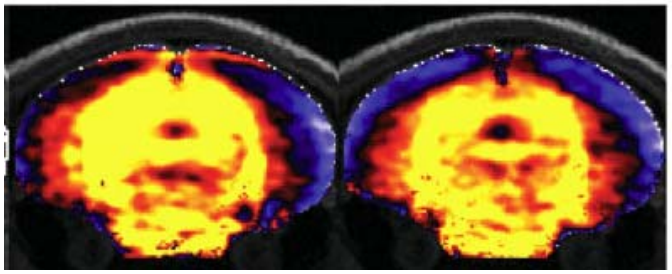


FDG-PET

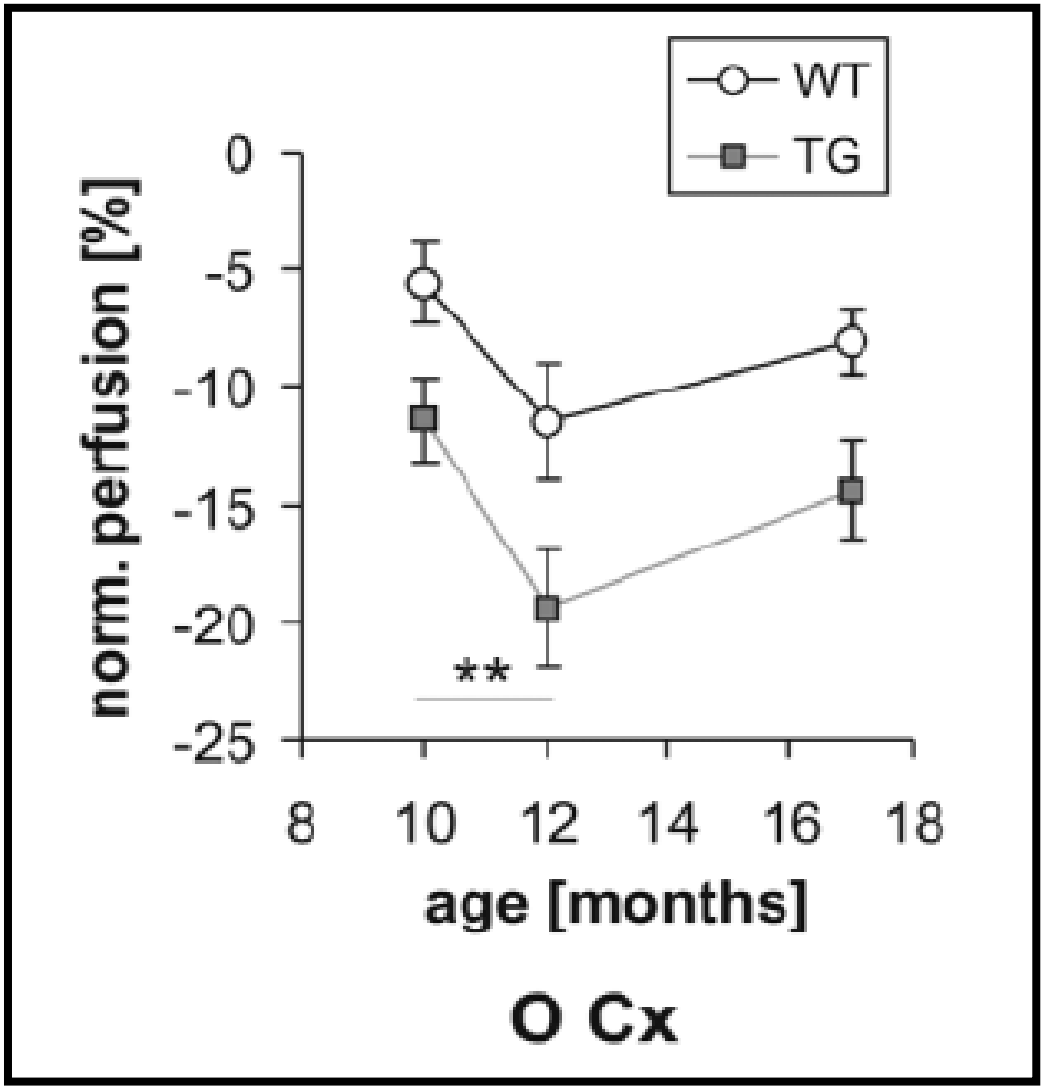
Chen Y et al. Neurology 77, 1977-85; 2011.

Alteration of perfusion response in mouse models of amyloidosis

Absolute perfusion

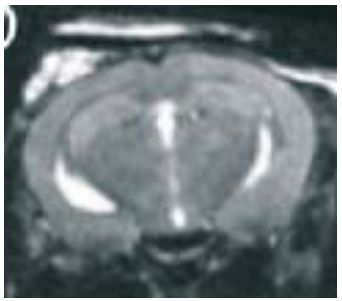


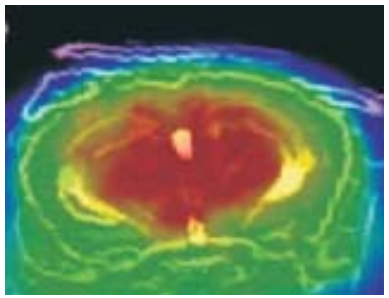
Wt Tg

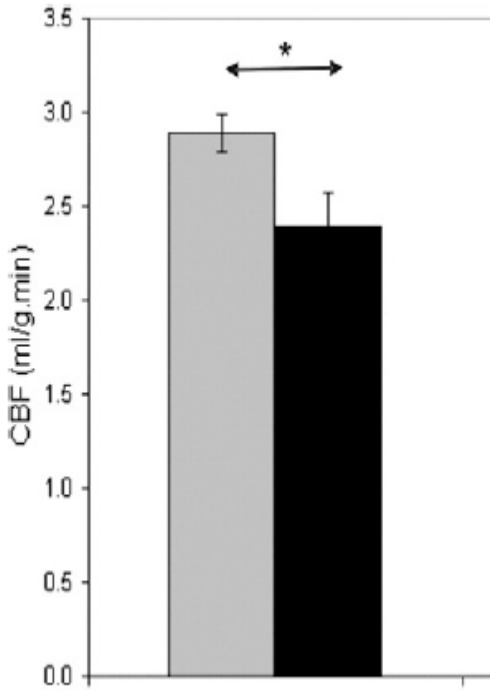


Weidensteiner C et al. Magn Reson Med 62, 35-45; 2009.

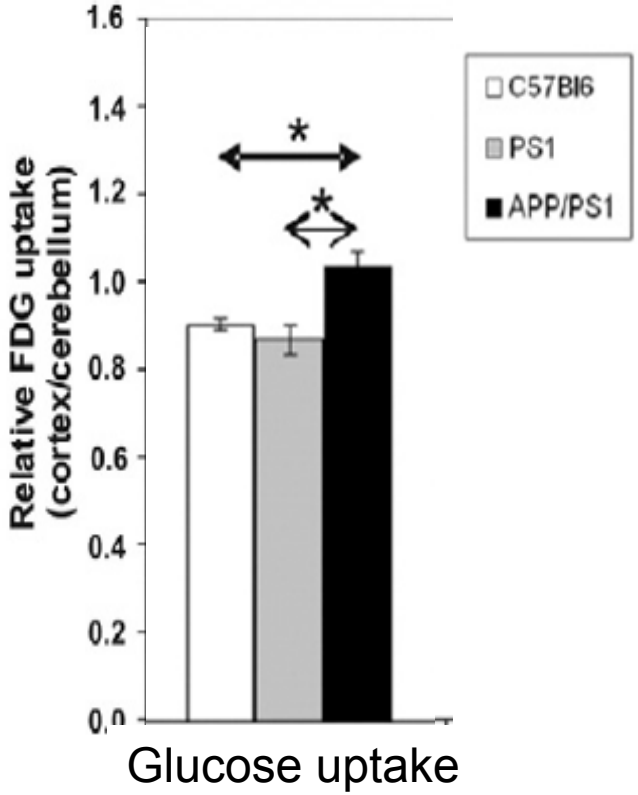
Dissociation between perfusion and glucose uptake in mouse models of amyloidosis







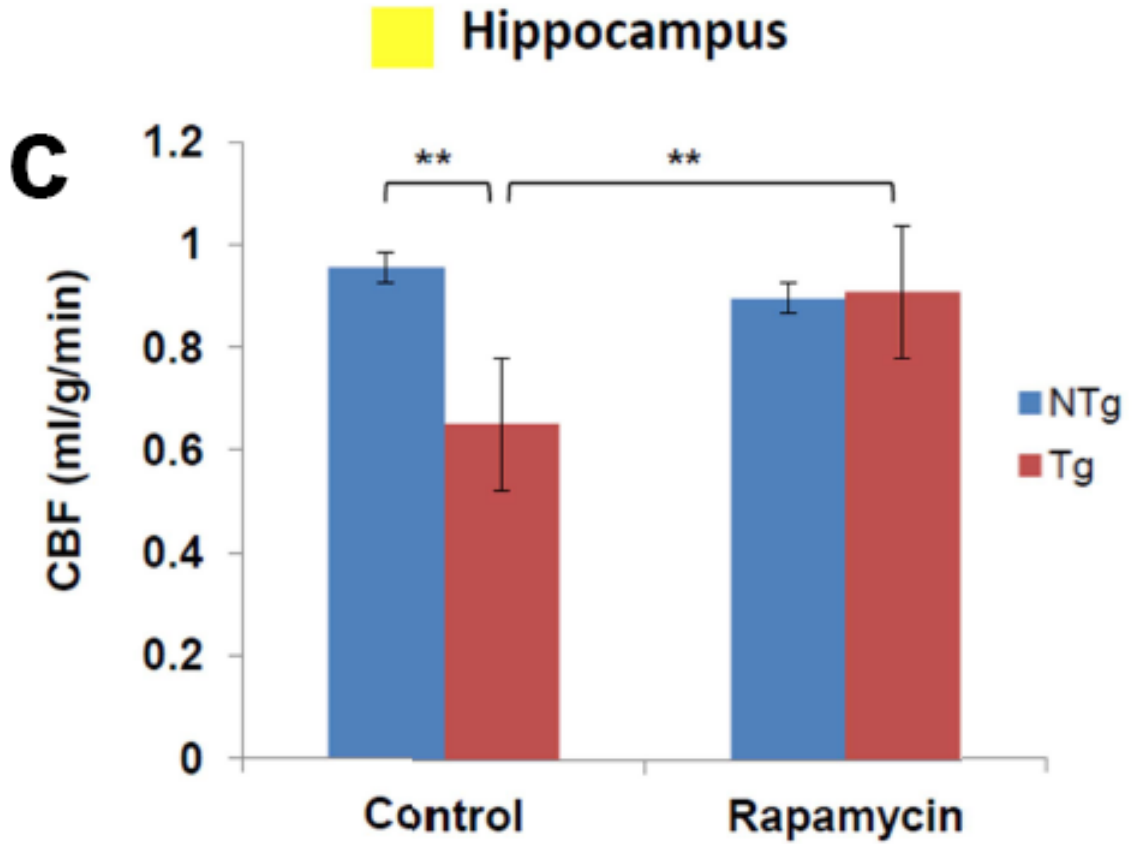
Perfusion



Glucose uptake

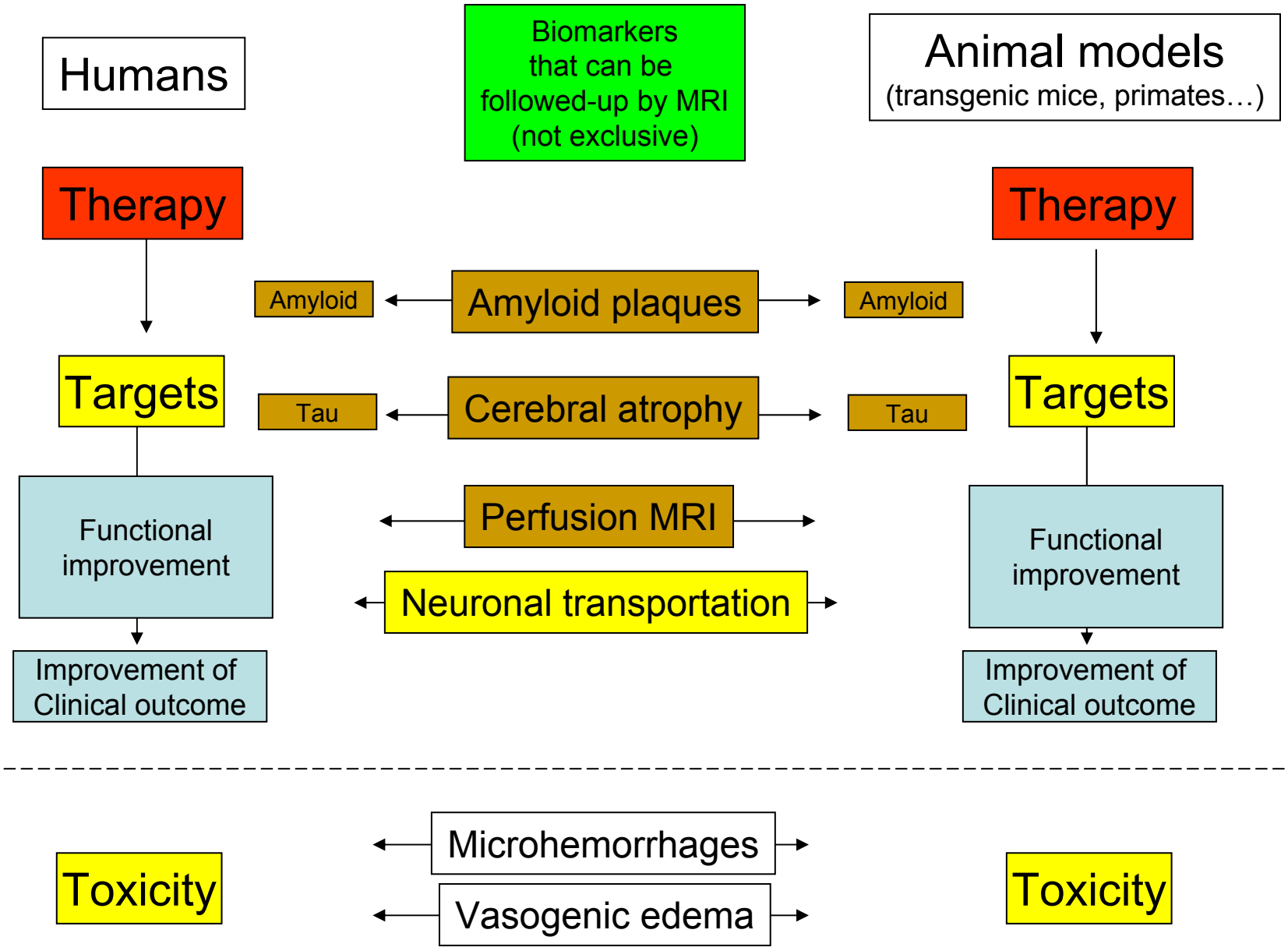
Poisnel G et al. Neurobiology of Aging. Ahead of Print.

Application for therapeutic evaluation

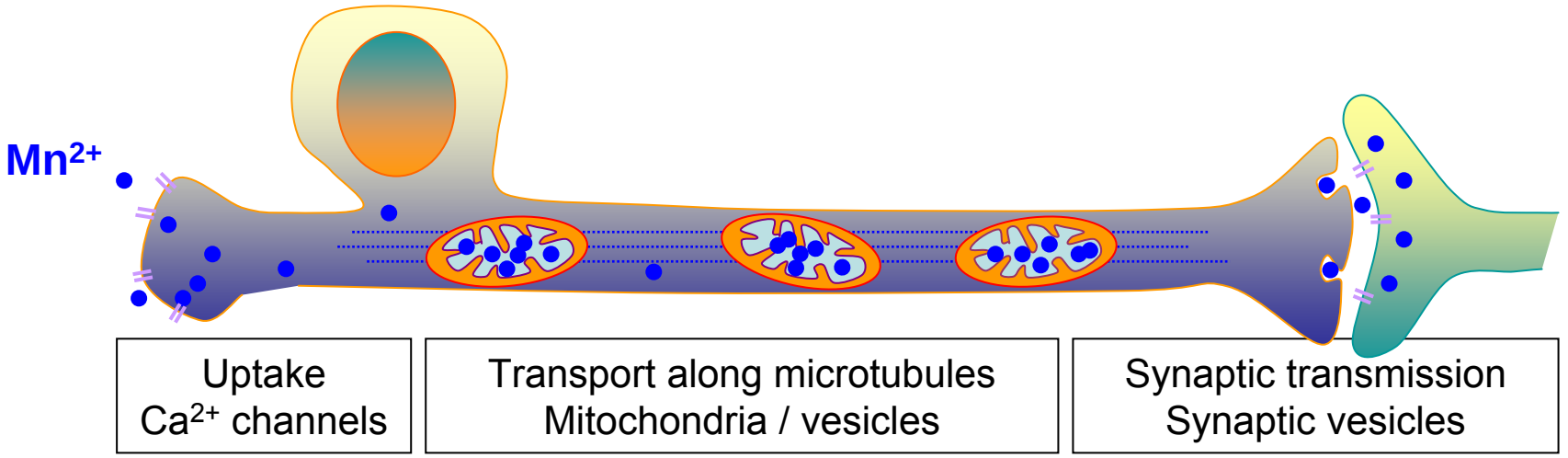


Ai-Ling Lin et al. ISMRM2012. 586.

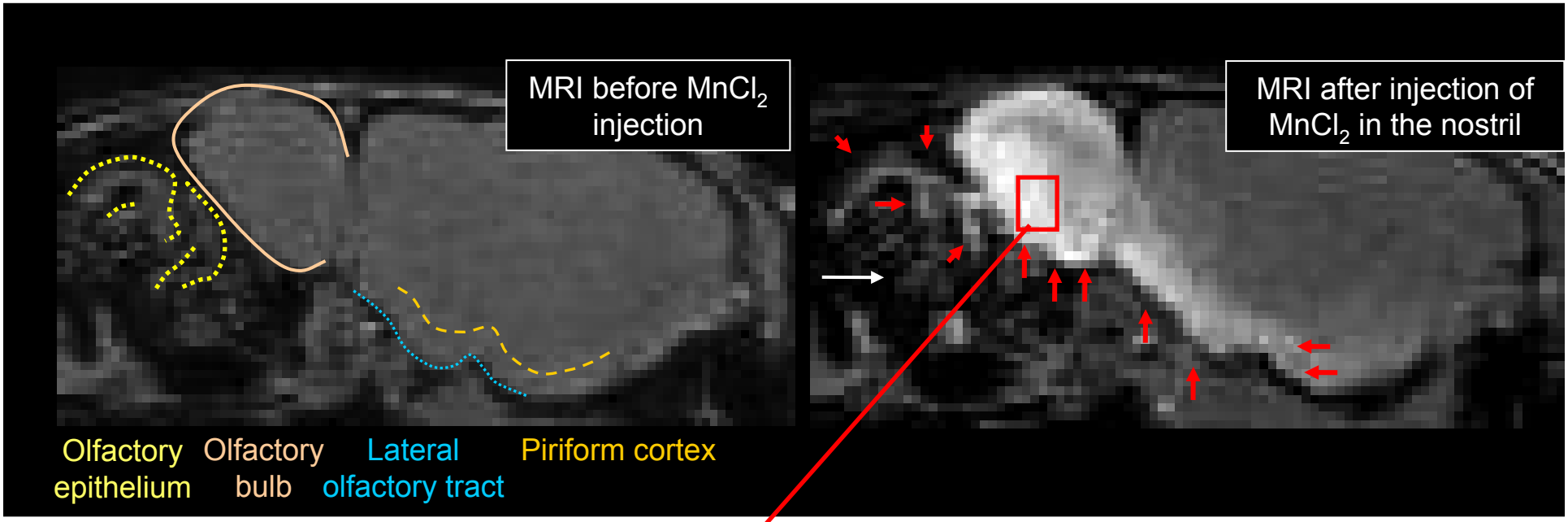
MRI biomarkers

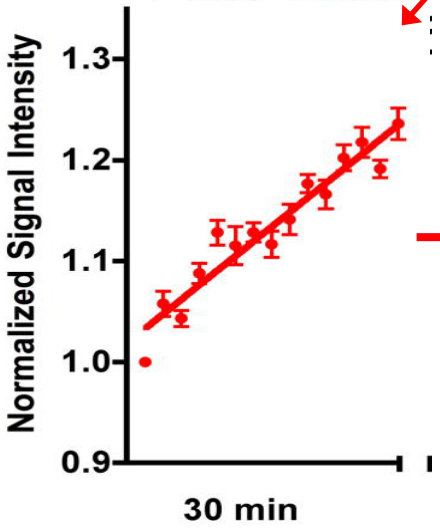


Manganese-enhanced MRI (MEMRI) & neuronal transport



MEMRI & neuronal transport



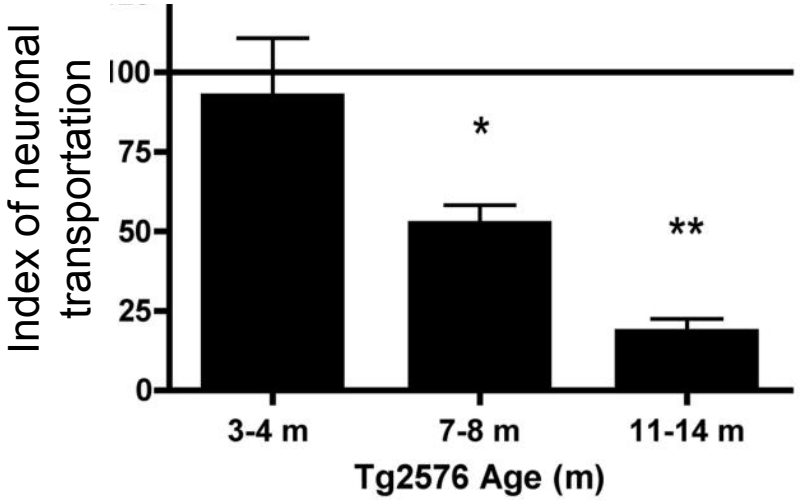


Index of the speed of neuronal transportation

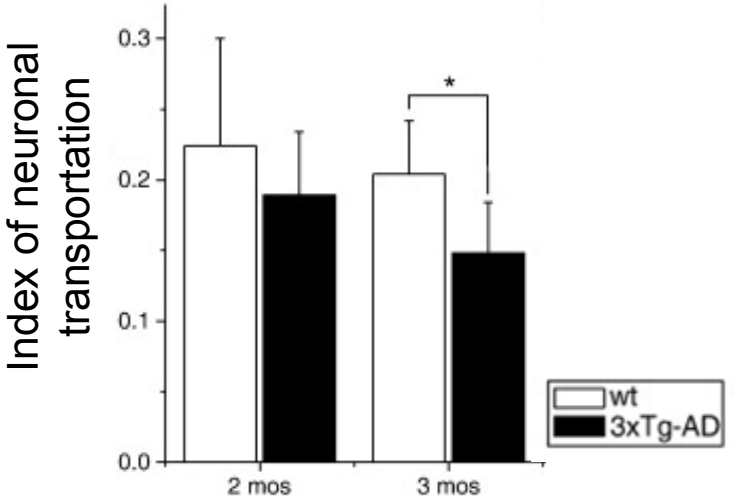
Smith KD et al.
Neuroimage. 2007

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

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

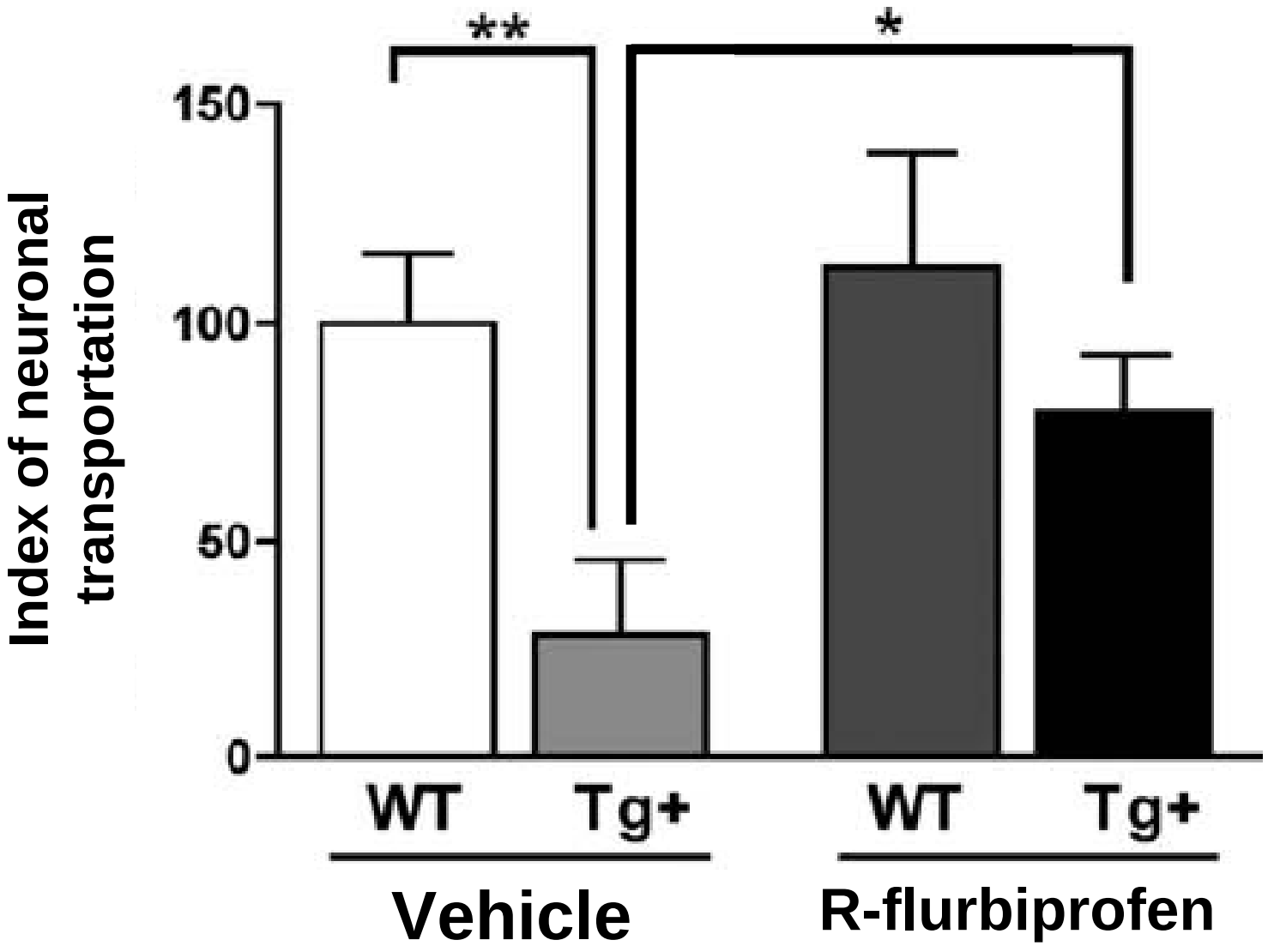


Smith KD et al. Neuroimage *2008*



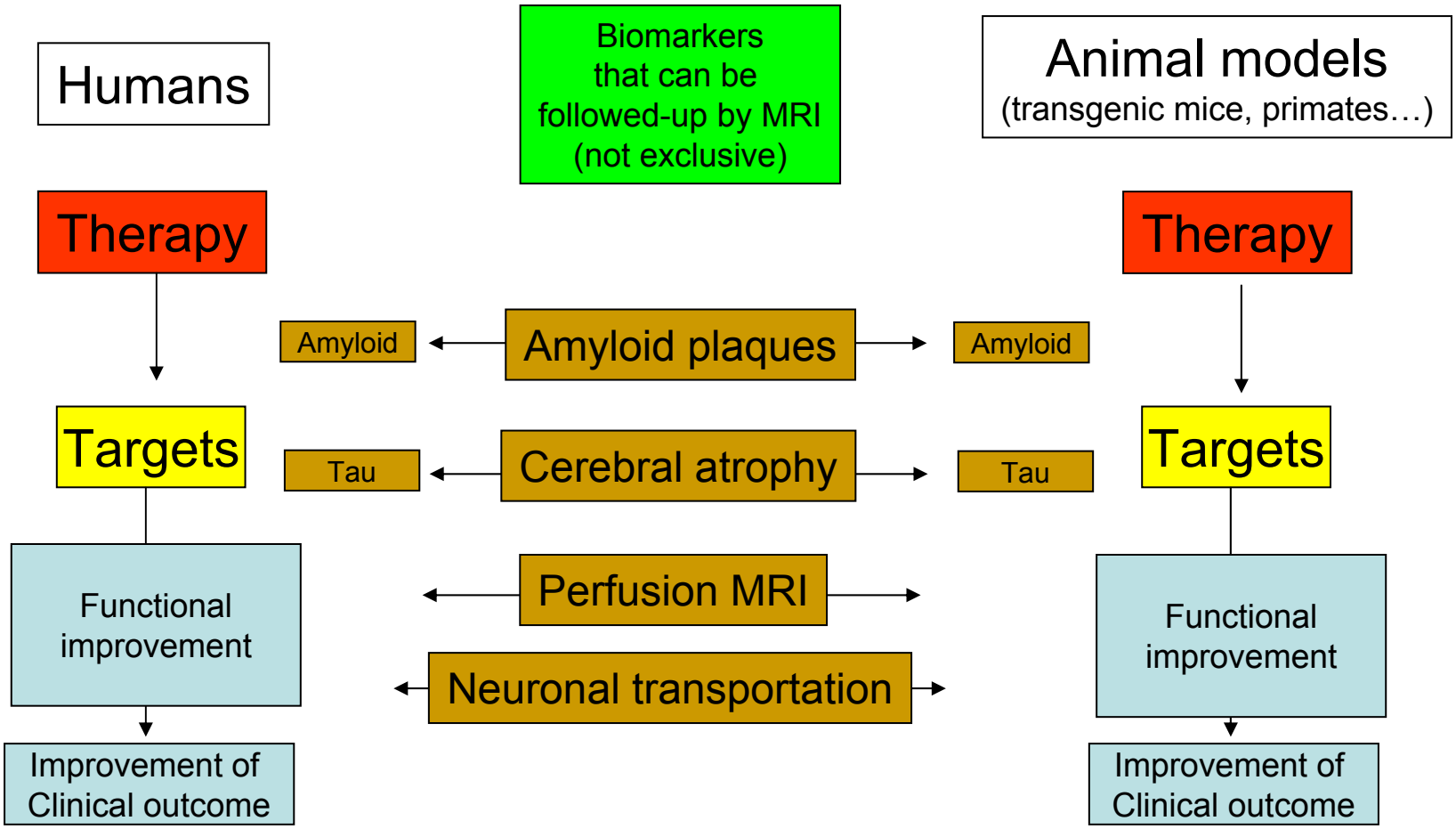
Kim J et al. Neuroimage 2011

MEMRI studies and therapeutic evaluations



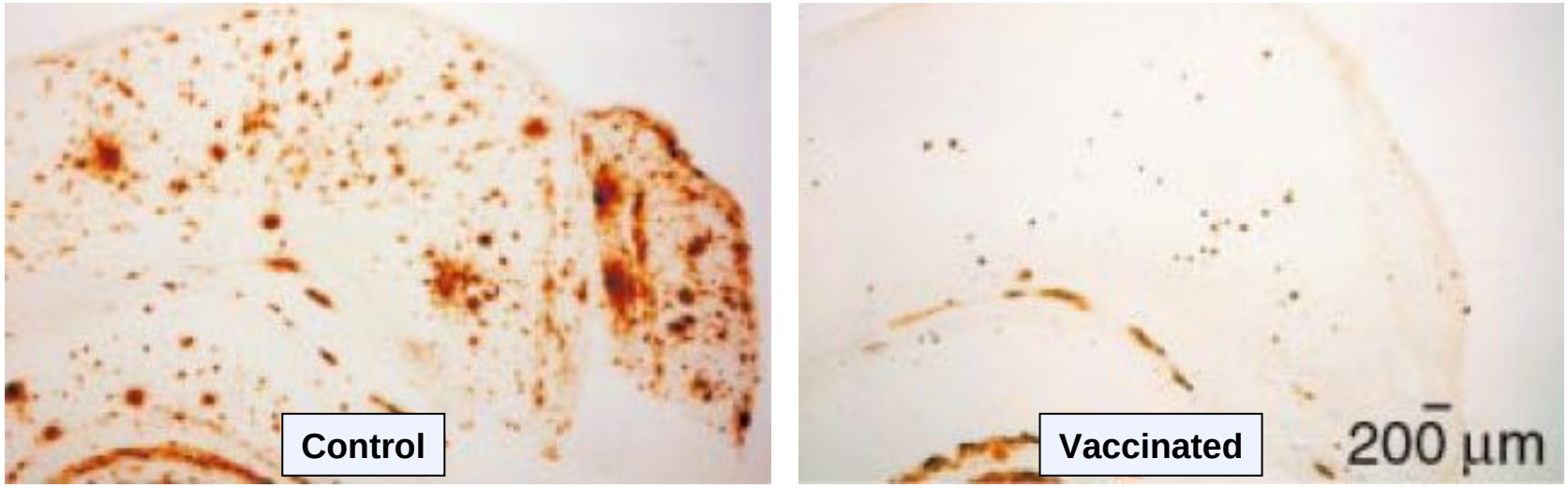
Smith KD et al. Magn Reson Med 65, 1423-9; 2011

MRI biomarkers



Anti-amyloid immunotherapy: a therapeutic strategy against AD

- Activation of anti-amyloid immune system by inoculating Aβ peptides or anti-amyloid monoclonal antibodies



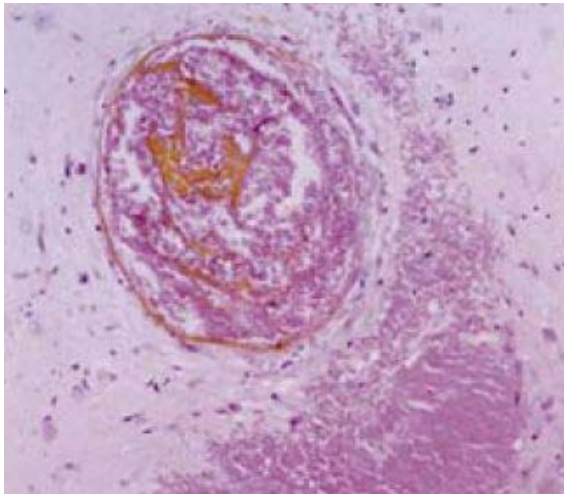
(Schenk et al, 1999)

- Reduction of the amyloid load in treated mice
- Most widely used experimental method to treat AD

Imaging biomarkers of Toxicity
Example of the immunotherapy

Severe side effects detected in human studies

Microhemorrhages



Ferrer I et al.
Brain Pathol, 2004

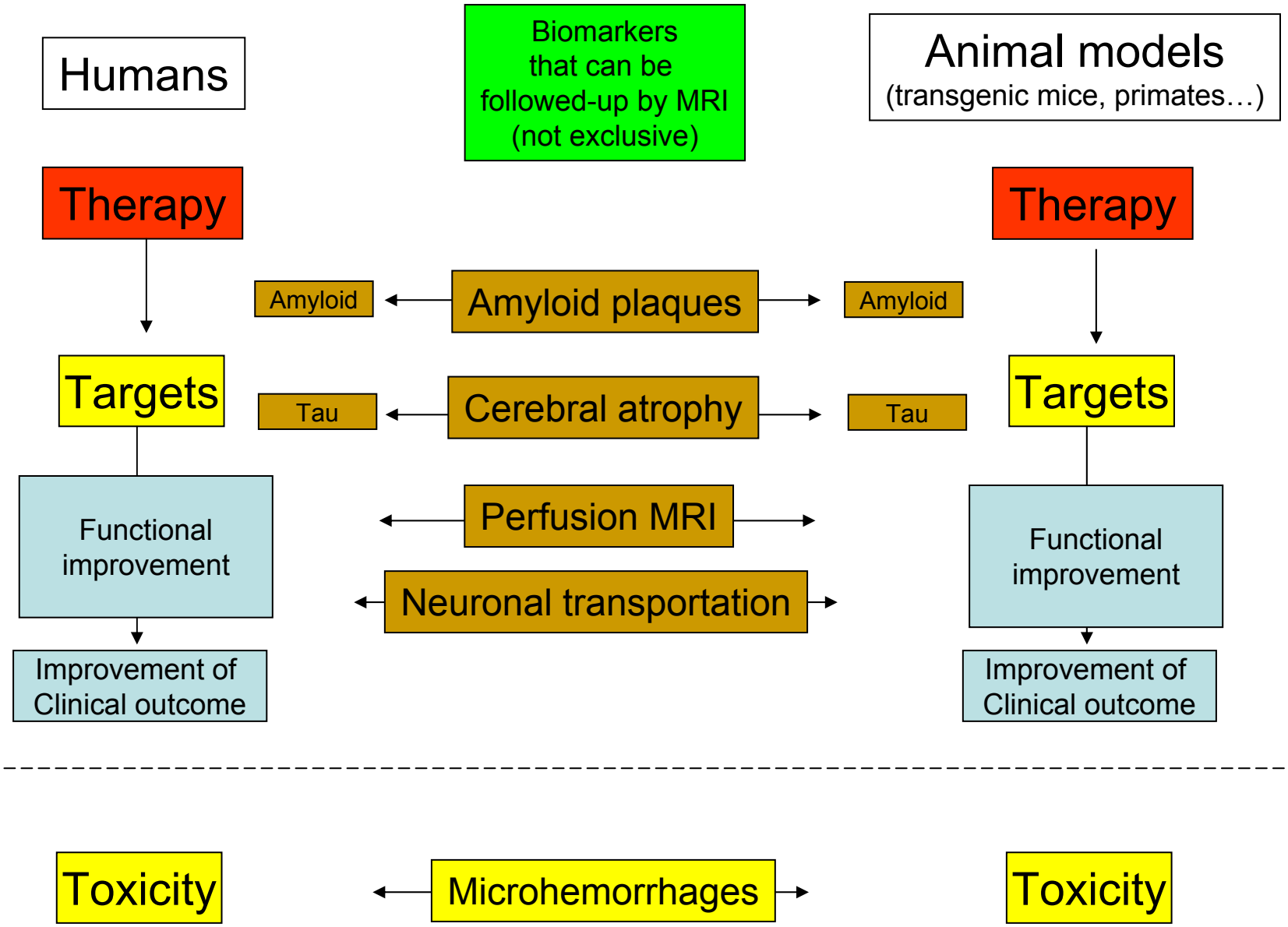
Meningoencephalitis

Orgogozo JM et al.
Neurology, 2003

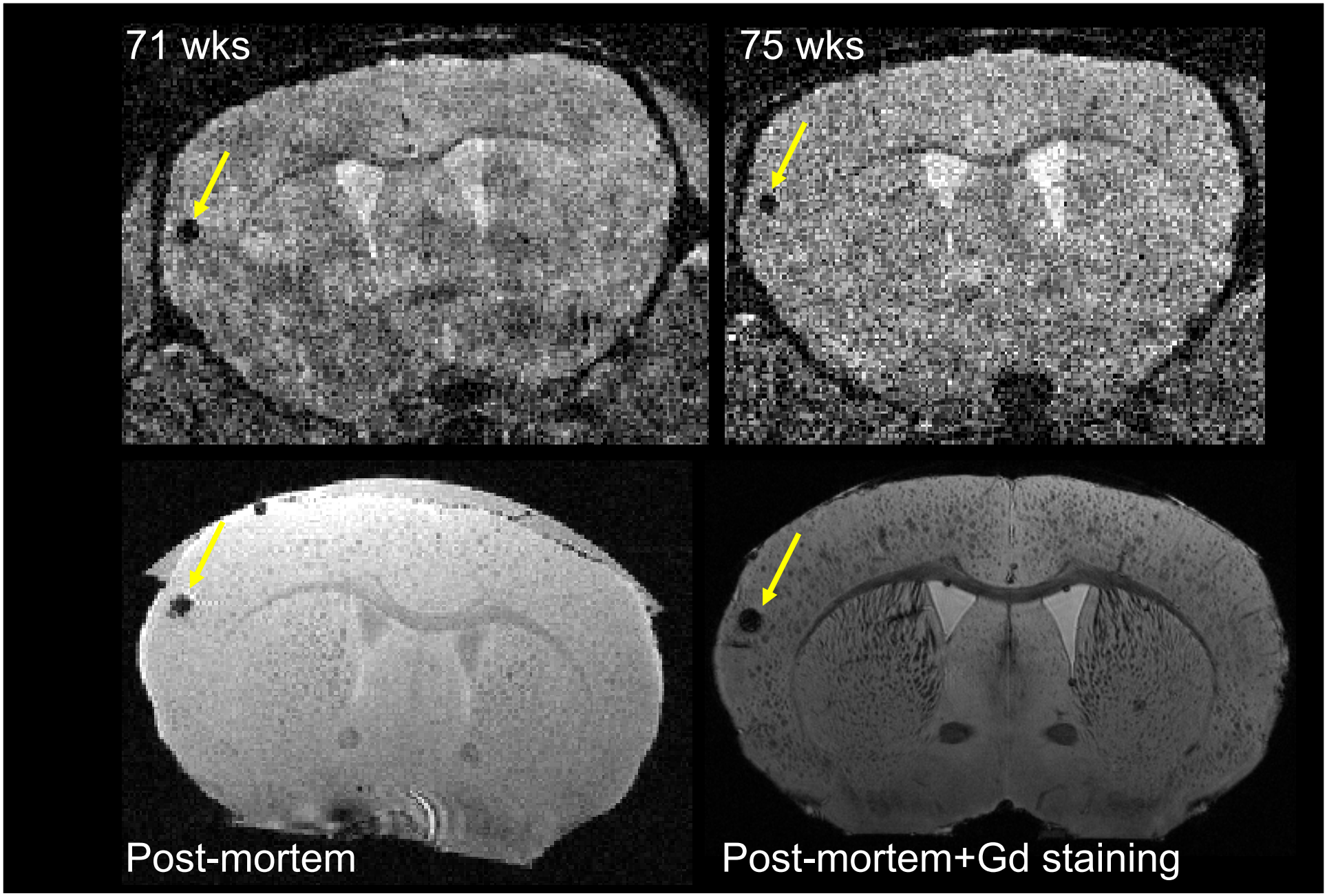
Vasogenic edema

Salloway S et al.
Neurology, 2009

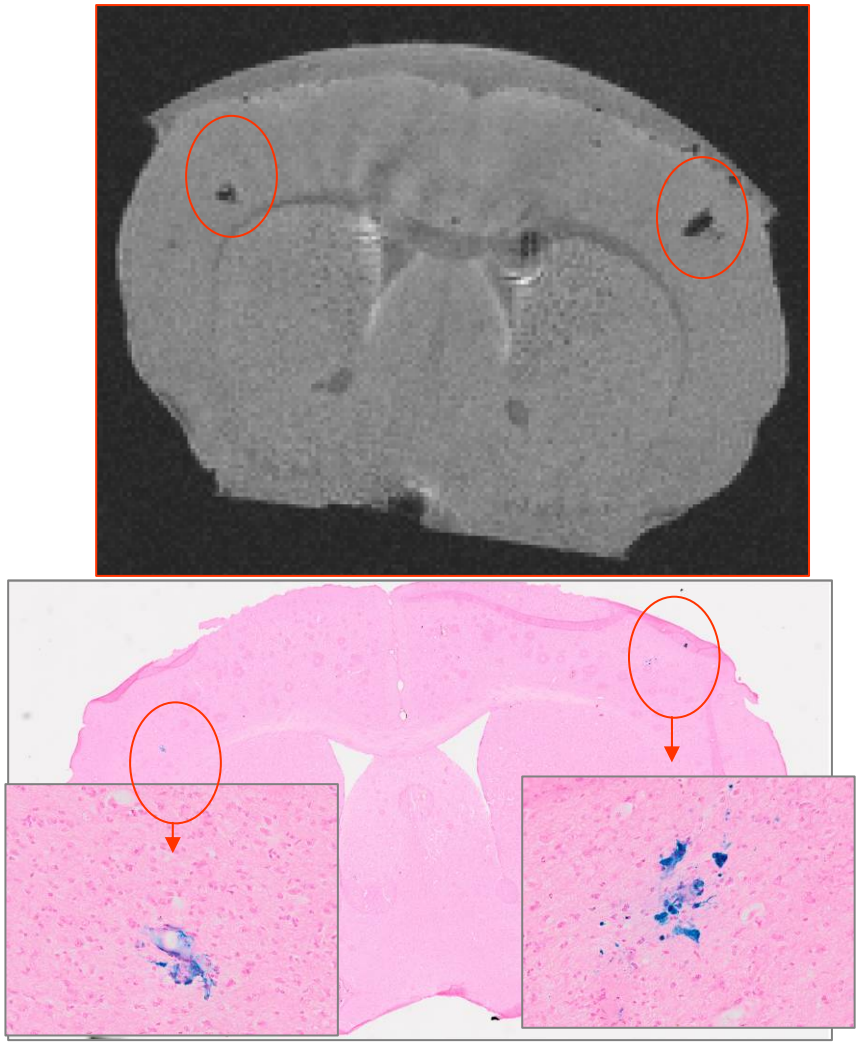
MRI biomarkers



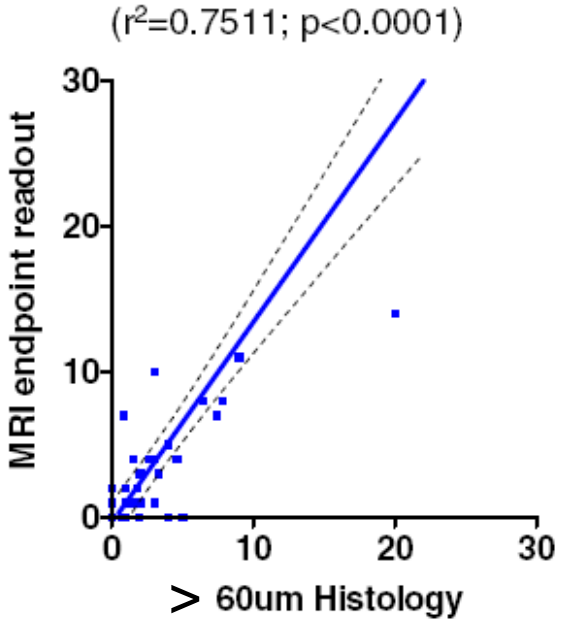
Detection of cerebral microhemorrhages by MRI



Validation of microhemorrhage detection



Registration between MRI and histological sections



Luo F et al. JPET, 2010

Comparison of counting in MRI and histological sections

Conclusions

- MRI is used to evaluate
  - Amyloid load
  - Cerebral atrophy (probably linked to Tau pathology)
  - Perfusion
  - Neuronal health
  - Microhemorrhages associated to immunotherapies
- Validation is based on the use of gold standard methods
  - Histology
  - Other methods (see next speaker)
- Quantification
  - Manual counting
    - Time consuming
    - Can not be applied during routine evaluation of drugs at a large scale
  - User-independent automatic methods
    - High throughput
- Several examples of the use of MRI to evaluate anti-Alzheimer therapies are already available
- **MRI evaluation in animals can be used to predict/interpret results from MRI studies in human clinical trials**

Thanks …

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- **Fondation de Coopération Scientifique Maladie d'Alzheimer et maladies apparentées**
- **France Berkeley**
- **Hoffman LaRoche**

One position currently available

Slides are available from:
http://marc.dhenain.free.fr/Diaps/ISMRM.pdf