Imageries précliniques pour la maladie d'Alzheimer

-

Recherche et utilisation de biomarqueurs pertinents

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URA CEA CNRS 2210 – MIRCen - Fontenay aux Roses
Eq. Maladie d'Alzheimer : Modélisation, Biomarqueurs, Imageries Précliniques, Evaluations Thérapeutiques

http://marc.dhenain.free.fr/Diaps/Presents.html

Plan

- Maladie d'Alzheimer
  - Généralités
  - Modèles animaux
  - Concepts de biomarqueurs
  - Quels biomarqueurs ?
    - Marqueurs cognitifs
    - Marqueurs de l'atrophie cérébrale
    - Marqueurs de l'amyloïdose
      - Liquide biologiques
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    - Marqueurs fonctionnels
    - Autres marqueurs
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- Exemples d'autres biomarqueurs pour d'autres pathologies

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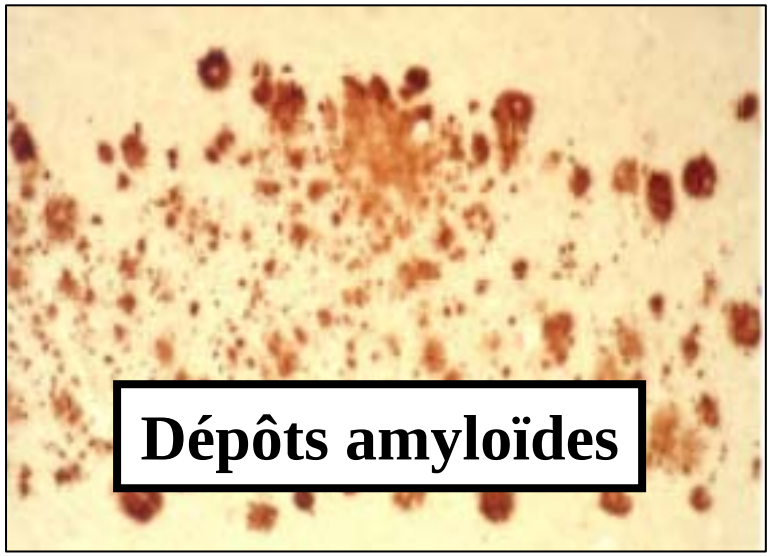
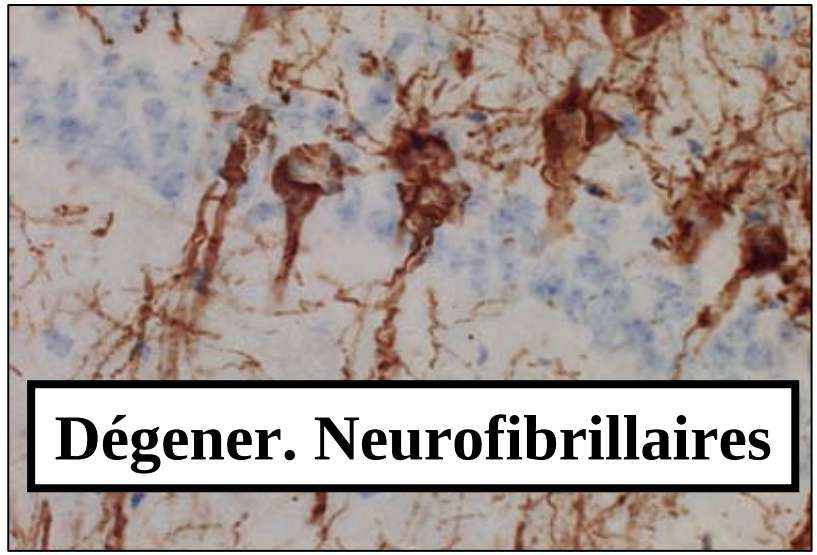
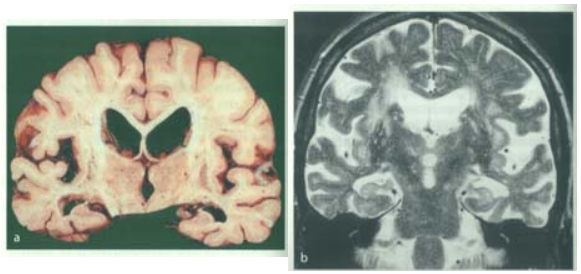
Maladie d'Alzheimer

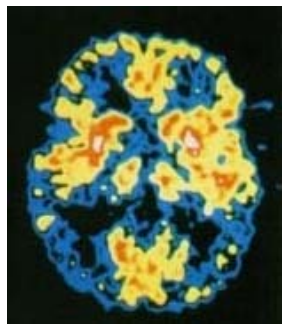




Atrophie cérébrale



Altérations fonctionnelles



Altérations cognitives Démence

Critères de diagnostique de la MA

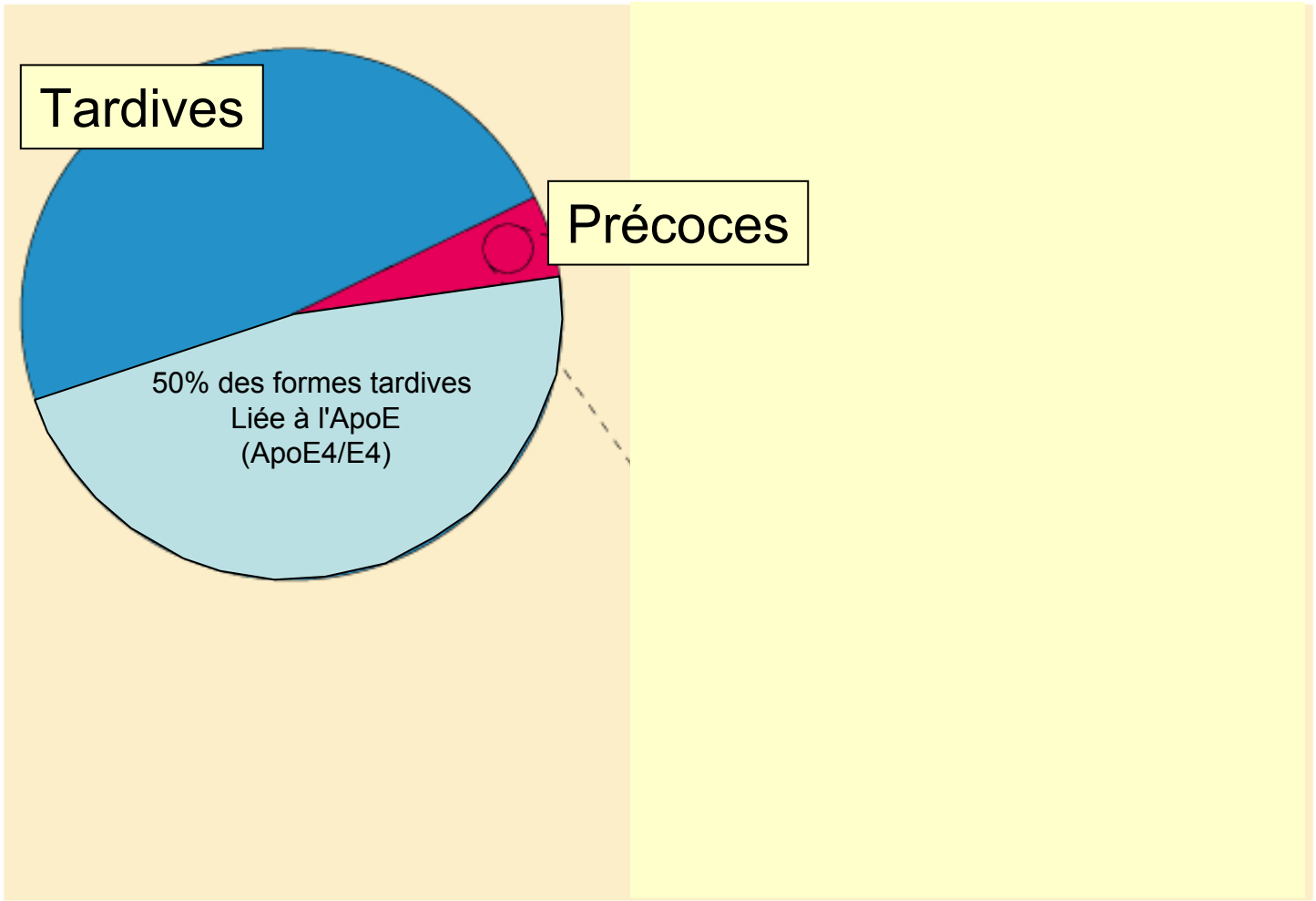
- Episodic memory impairments

- Supportive features
  - Medial temporal atrophy
  - Alteration of the CSF
  - Alterations of the PET
    - Reduced glucose metabolism in bilateral temporal-parietal regions
    - Amyloid detection by PET (PIB-FDDNP…)

Dubois, B. et al.-2007
Lancet Neurol **6**(8): 734-46.

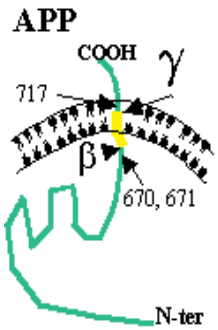
Quelques rares causes génétiques

Relative frequency of early and late-onset Alzheimer's and the proportion of early-onset cases attributed to mutations in specific genes such as APP, PS1, PS2 or others



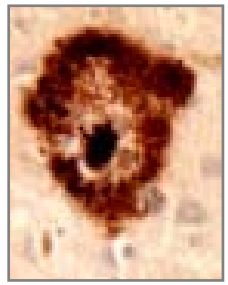
From, Piecing Together Alzheimer's by Peter H St George-Hyslop.

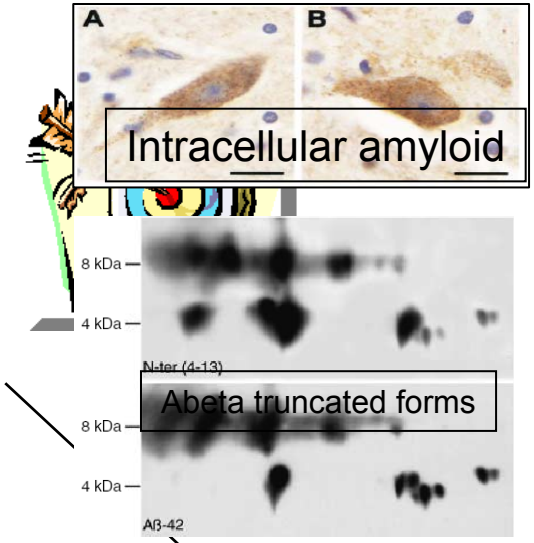
Amyloid cascade hypothesis (simplified)



Beta Amyloid

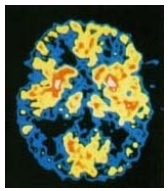
Mutations: APP + PS1



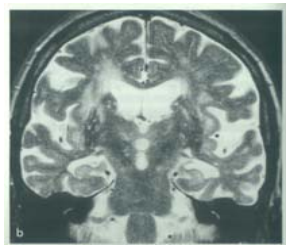


CAA

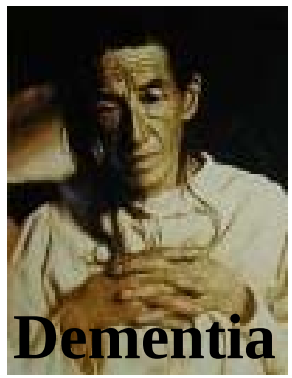
NFT



Functional alterations



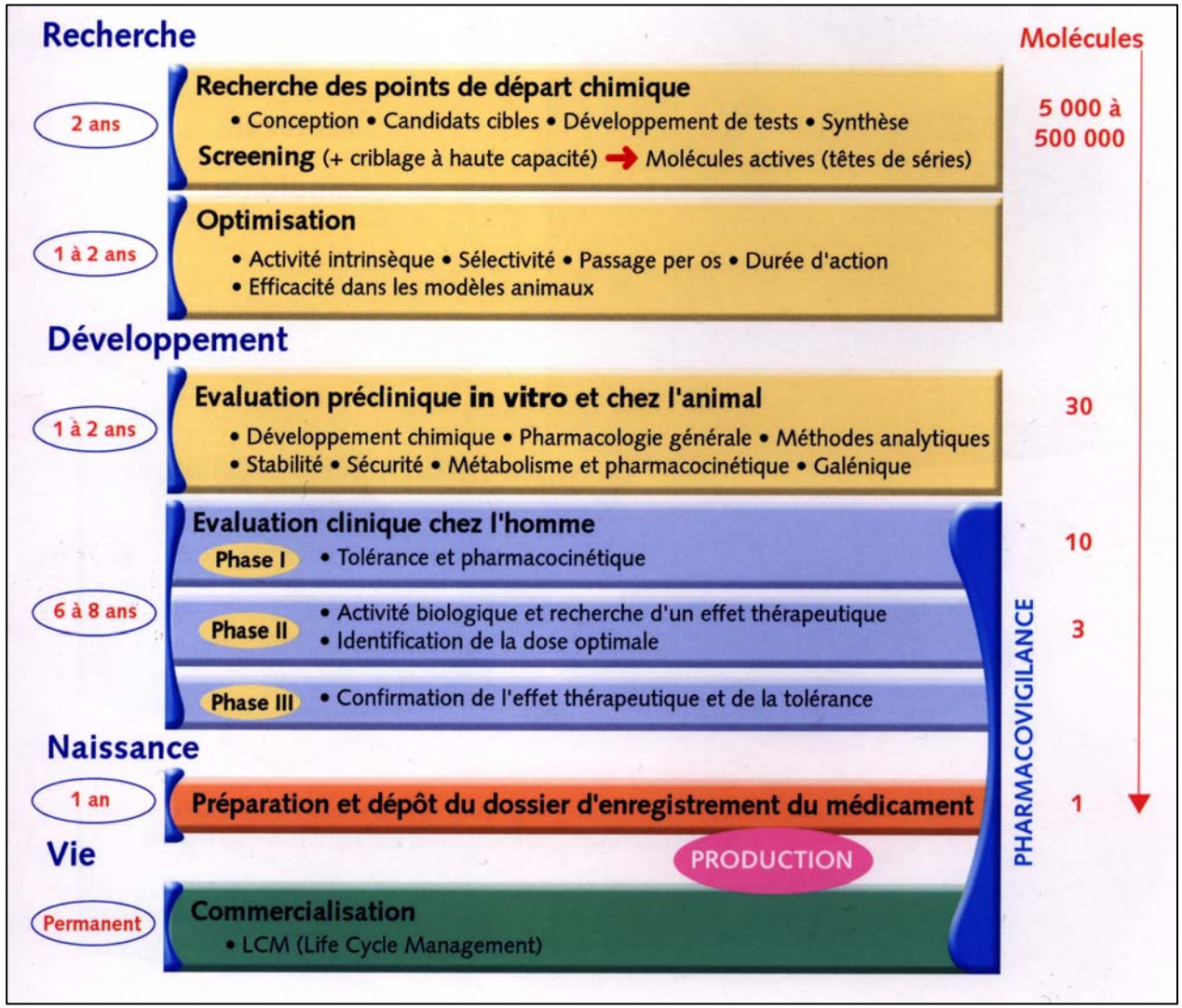
Atrophy Hippoc…



Dementia

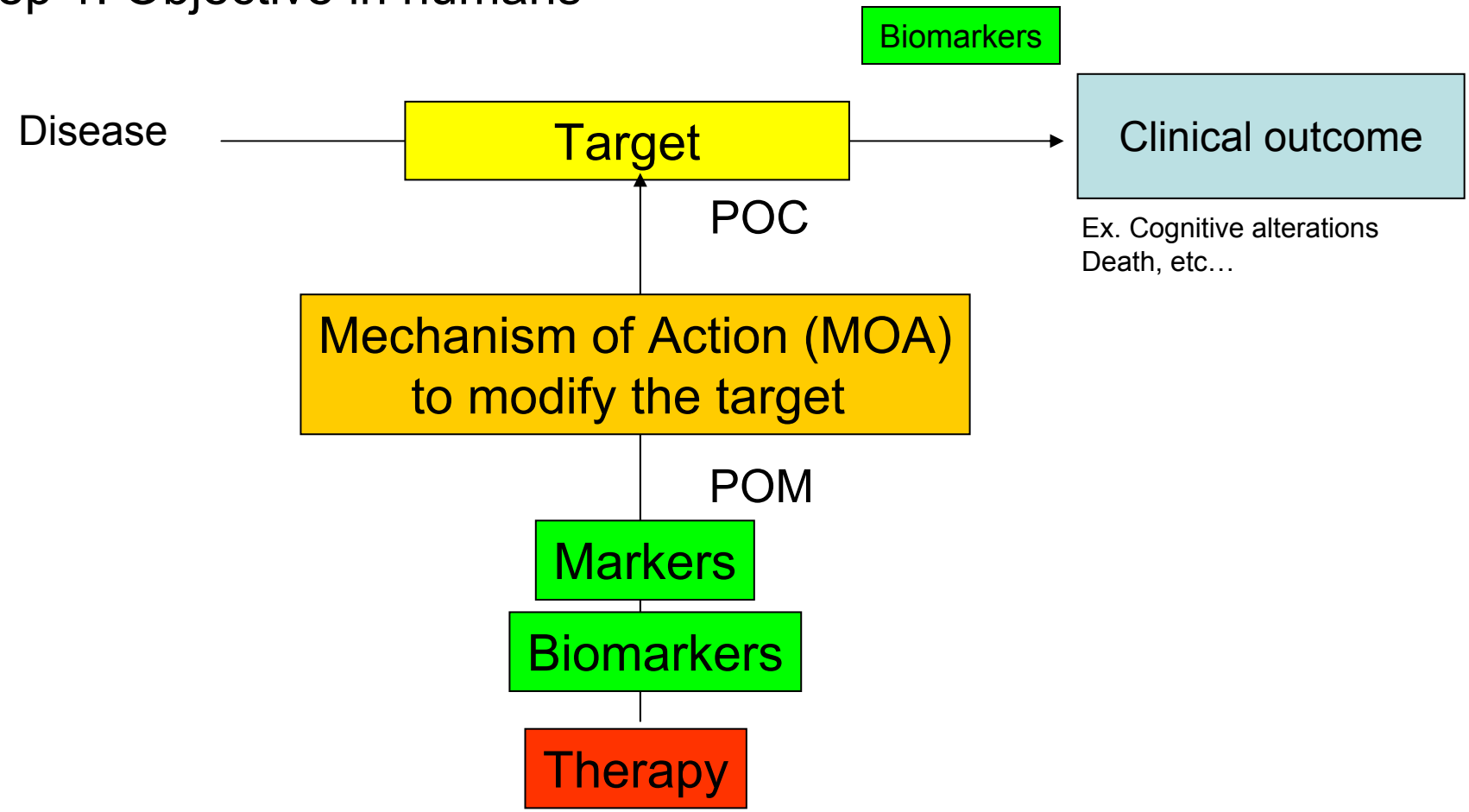
Vers de nouvelles thérapeutiques

Schéma de naissance d'un médicament



Basis of translational medicine

Step 1: Objective in humans



Proof of Concept (POC): If I modify the target, do I modify the disease ?

Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Basis of translational medicine

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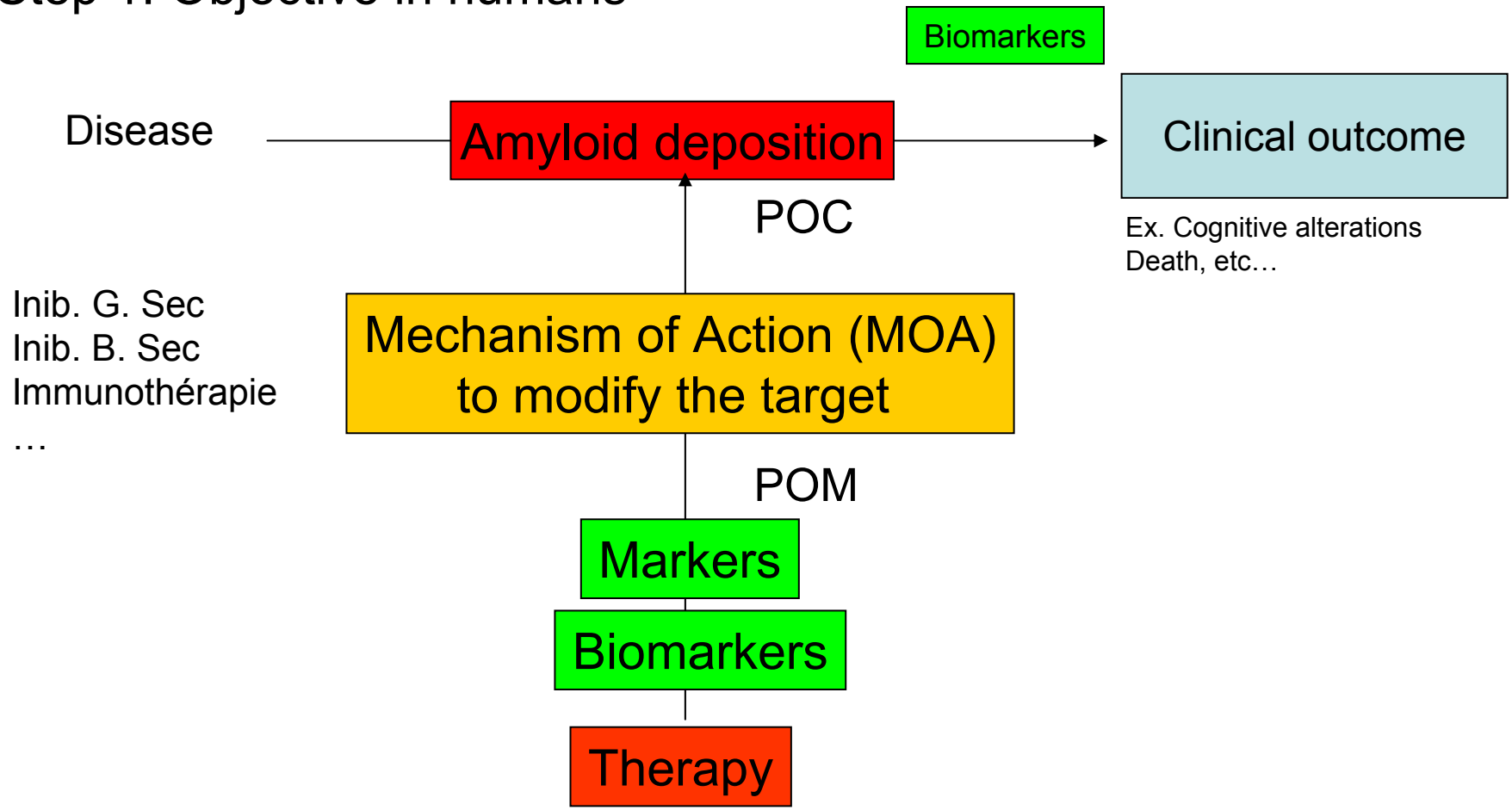

Proof of Concept (POC): If I modify the target, do I modify the disease ?

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Basis of translational medicine

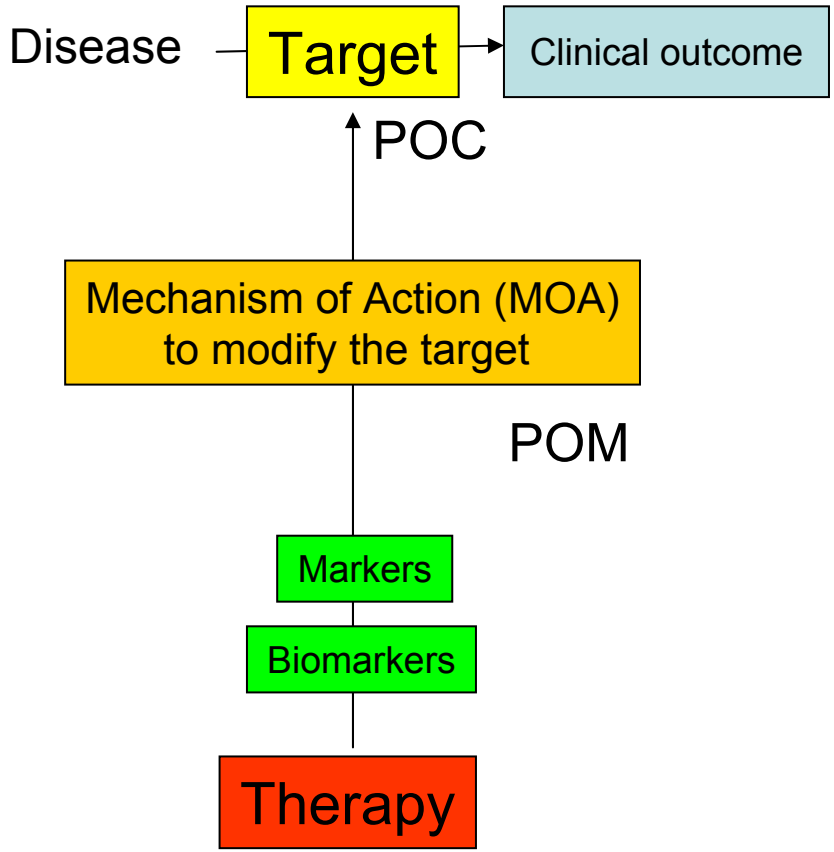
Step 2: Use of animals – Selection of a validated animal model

Choice of a good animal model ?

° Construct validity

° Face validity

° Prediction validity



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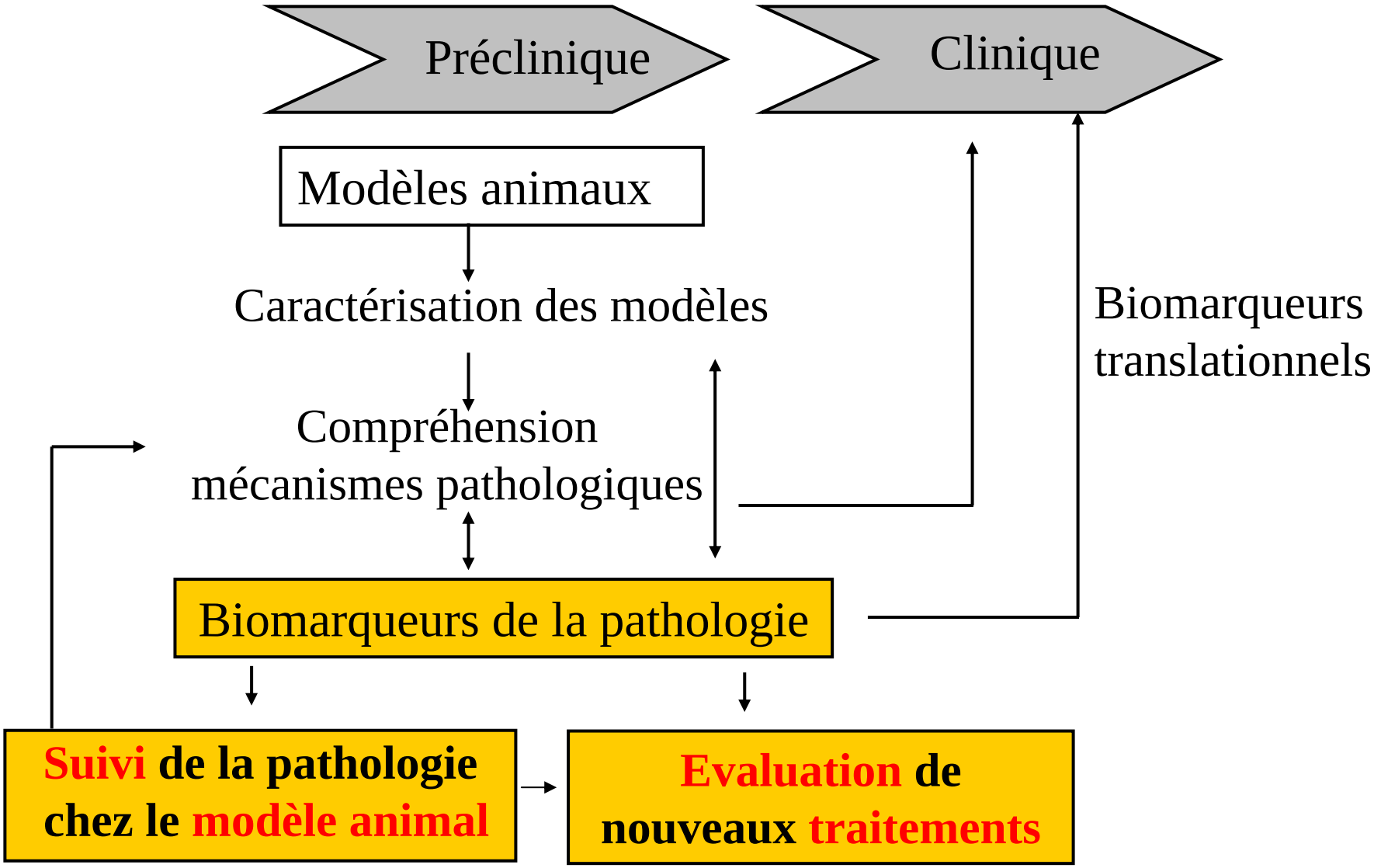
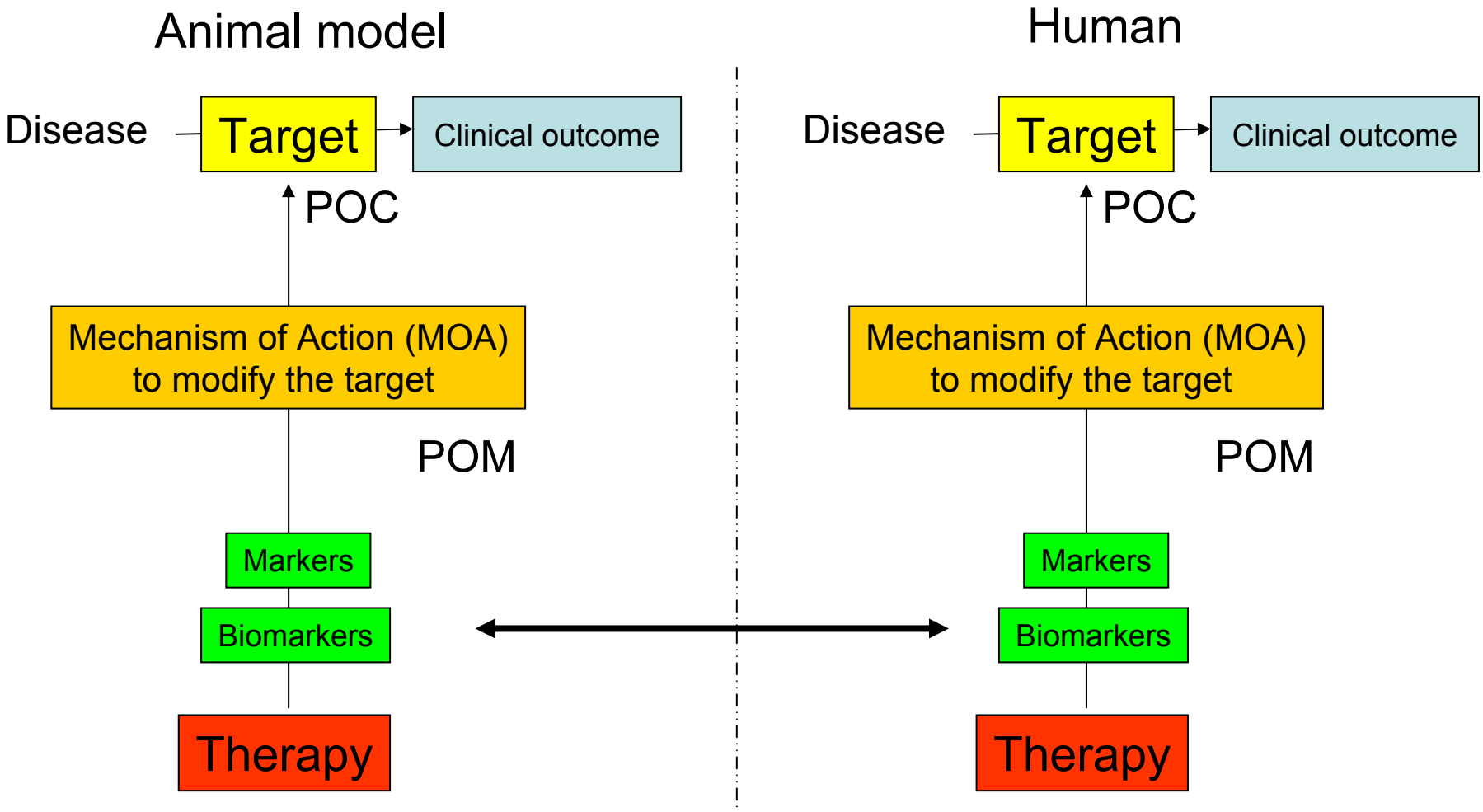


Basis of translational medicine

Step 3: Use of the validated animal model – Translational medicine



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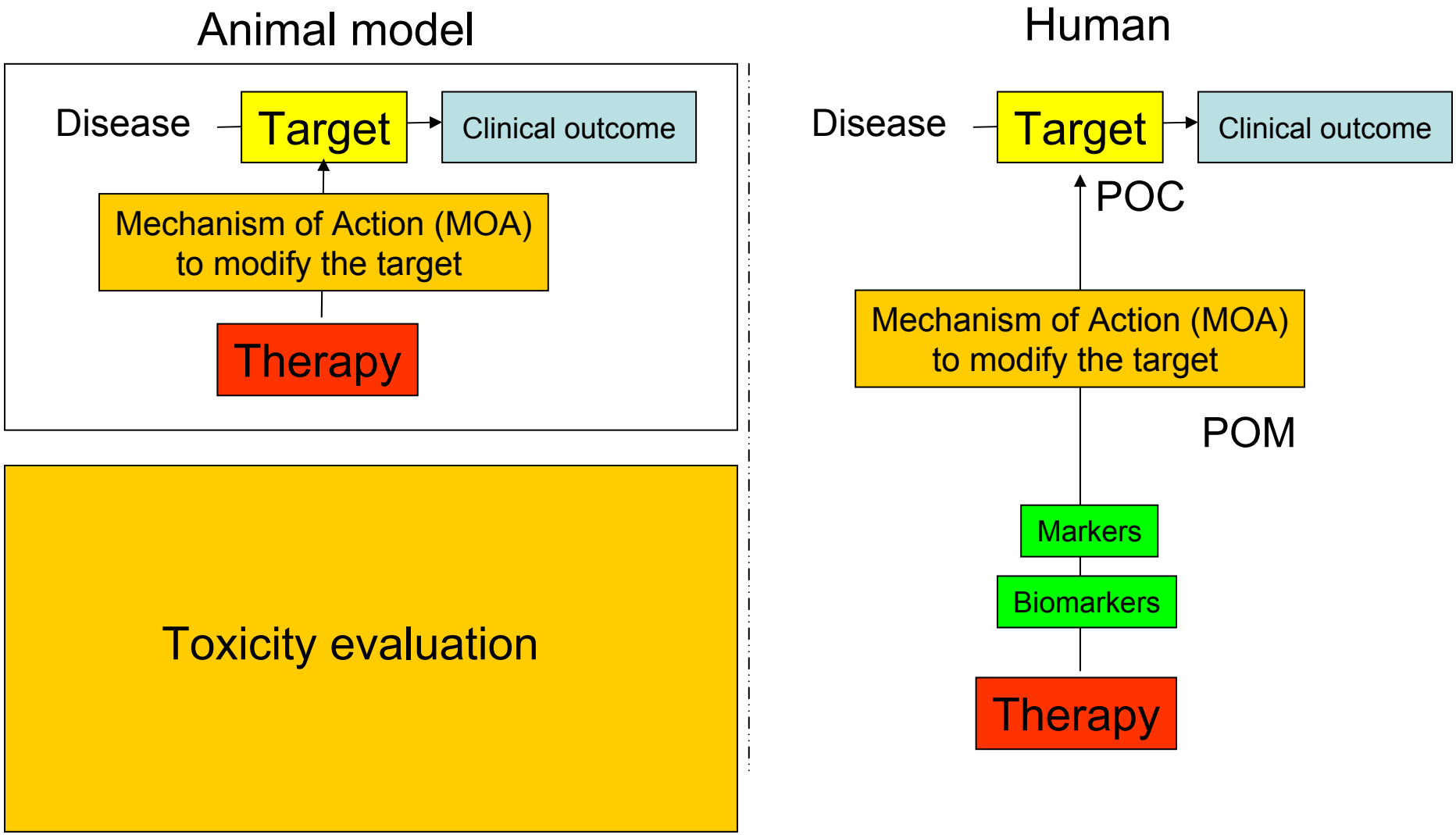
Basis of translational medicine

Step 3bis: Toxicity evaluation



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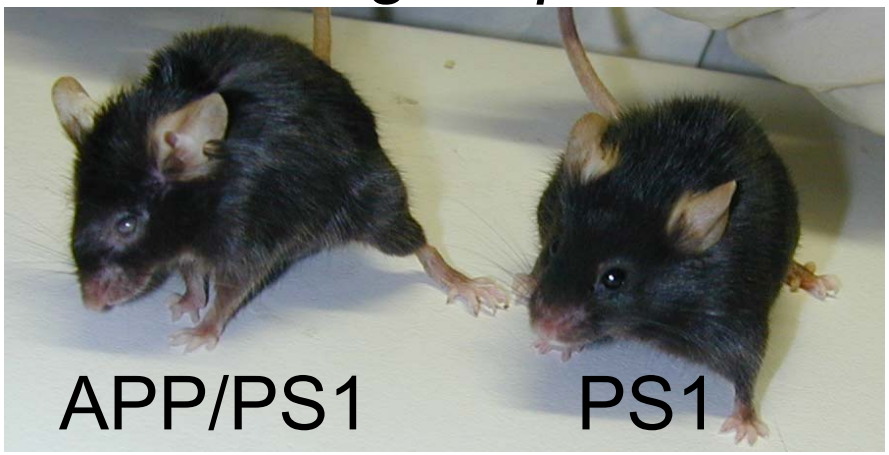
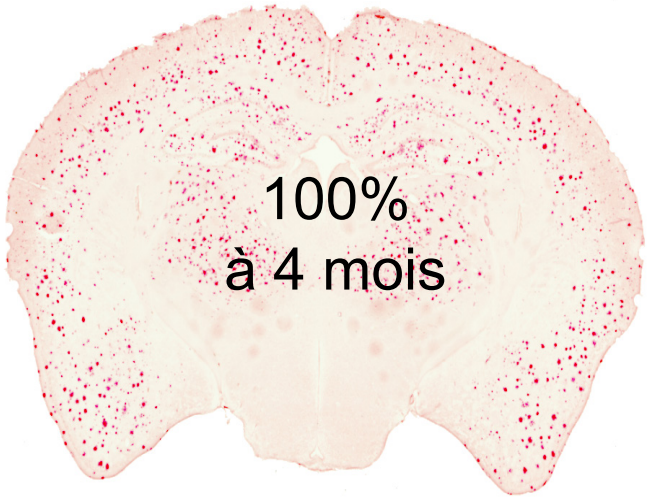
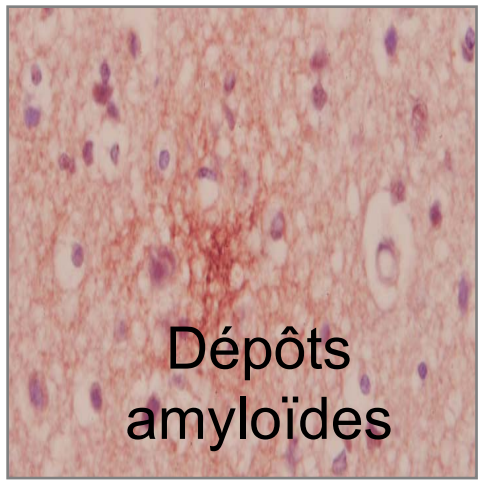
Maladie d'Alzheimer : Modèles animaux

Souris Transgeniques





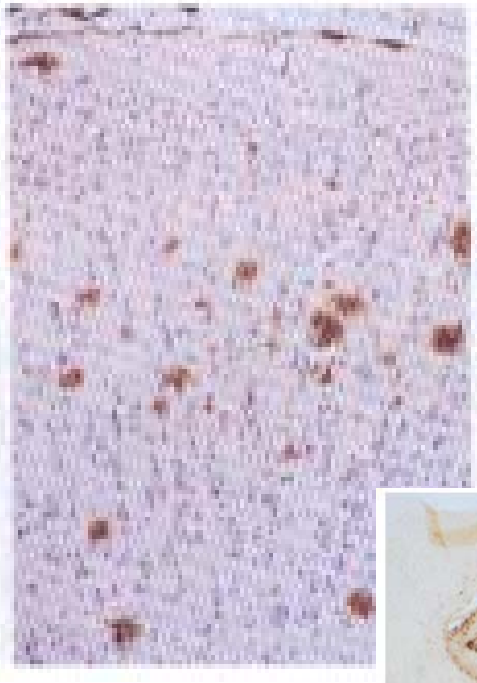
Primate Microcebus murinus



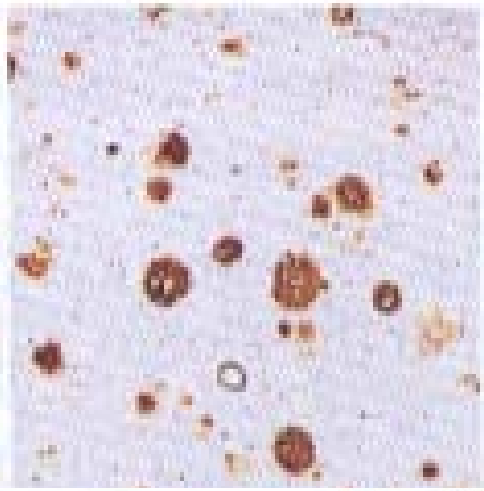
Modèles Primates Simiens

Chimpanzee

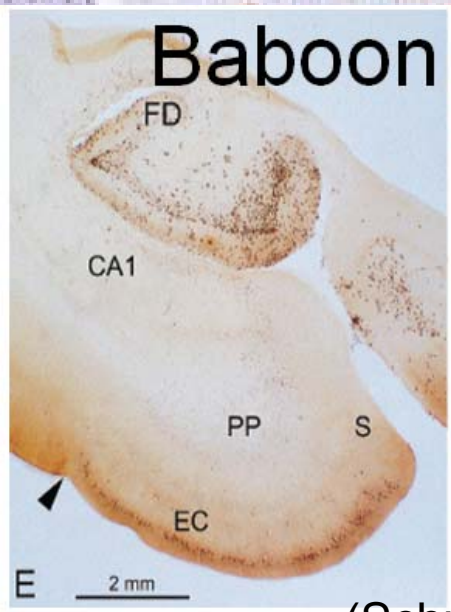
Rhesus

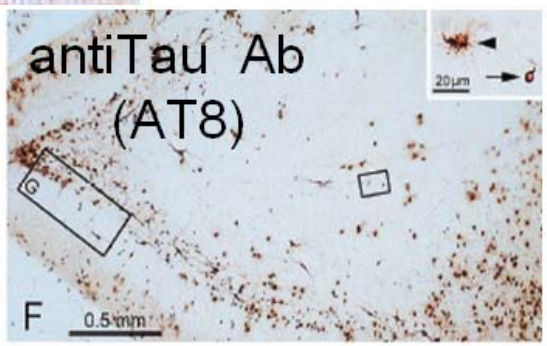


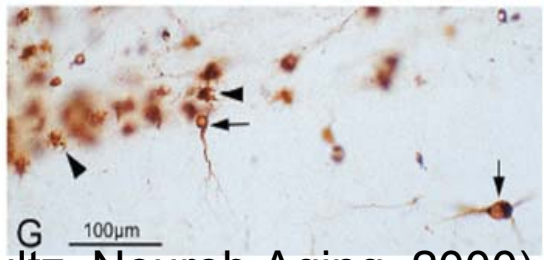
AD - Human



(Gearing et al, PNAS, 1994)







(Schultz, Neurob Aging, 2000)

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Biomarqueurs: Un concept faussement "simple"
Biomarker Definition Working group (2001)
http://ospp.od.nih.gov/biomarkers/

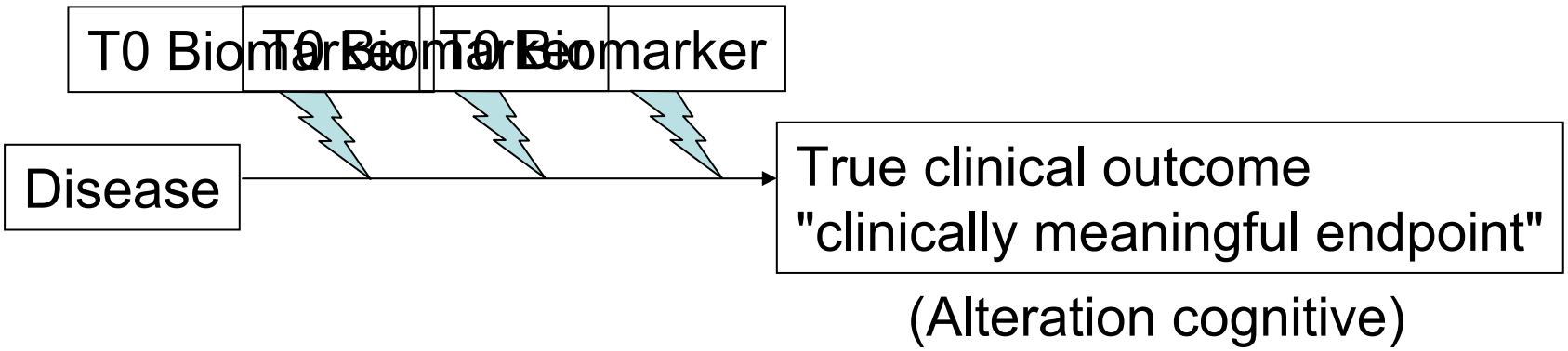
- CLINICAL ENDPOINT (critère ou marqueur clinique, ~symptôme?)
  - A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

- BIOLOGICAL MARKER (BIOMARKER)
  - A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
  - Replace a distal endpoint with a more proximal one, measured earlier
  - Can be measured more easily or frequently
  - Faster decision making

- 3 types of Biomarkers (Biomarker Def Working Grp, 2001)
  - Type 0 : **Reflects natural history of a disease**
  - Type I : **Reflects mechanism of action of an intervention**
  - Type II : **Predicts clinical benefit of a treatment (or toxicity)**

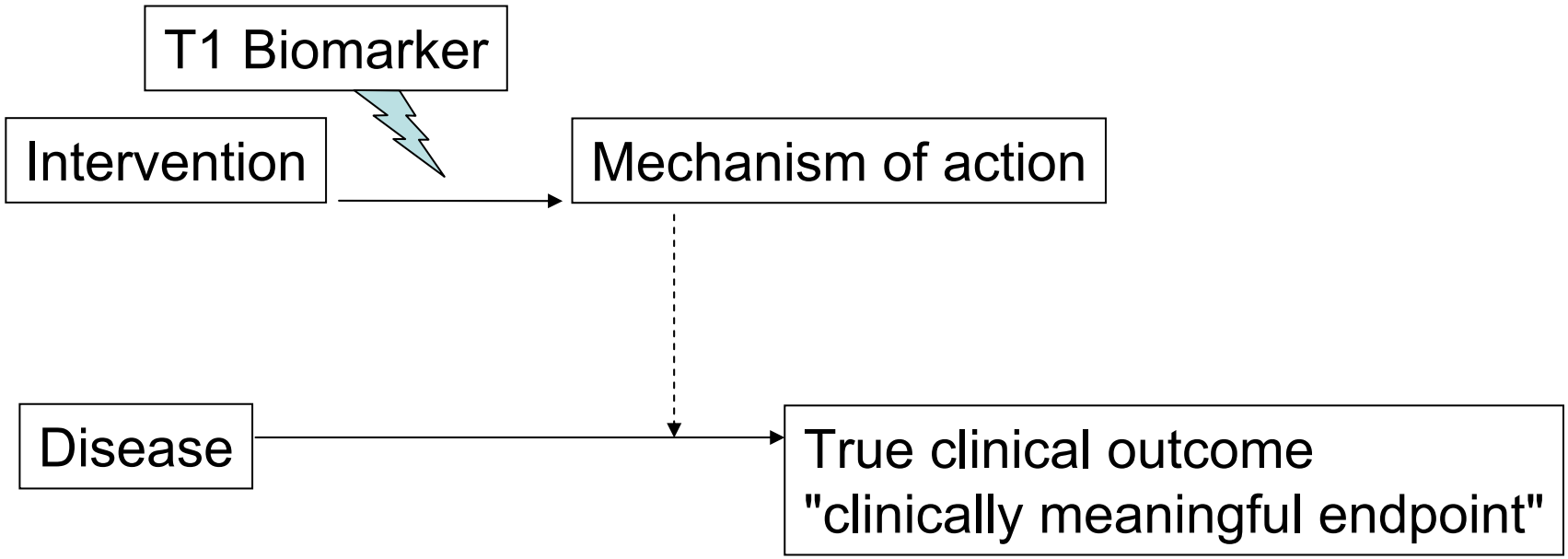
  (SURROGATE ENDPOINT (critère ou marqueur de substitution))

Type 0 Biomarker
Natural history of a disease

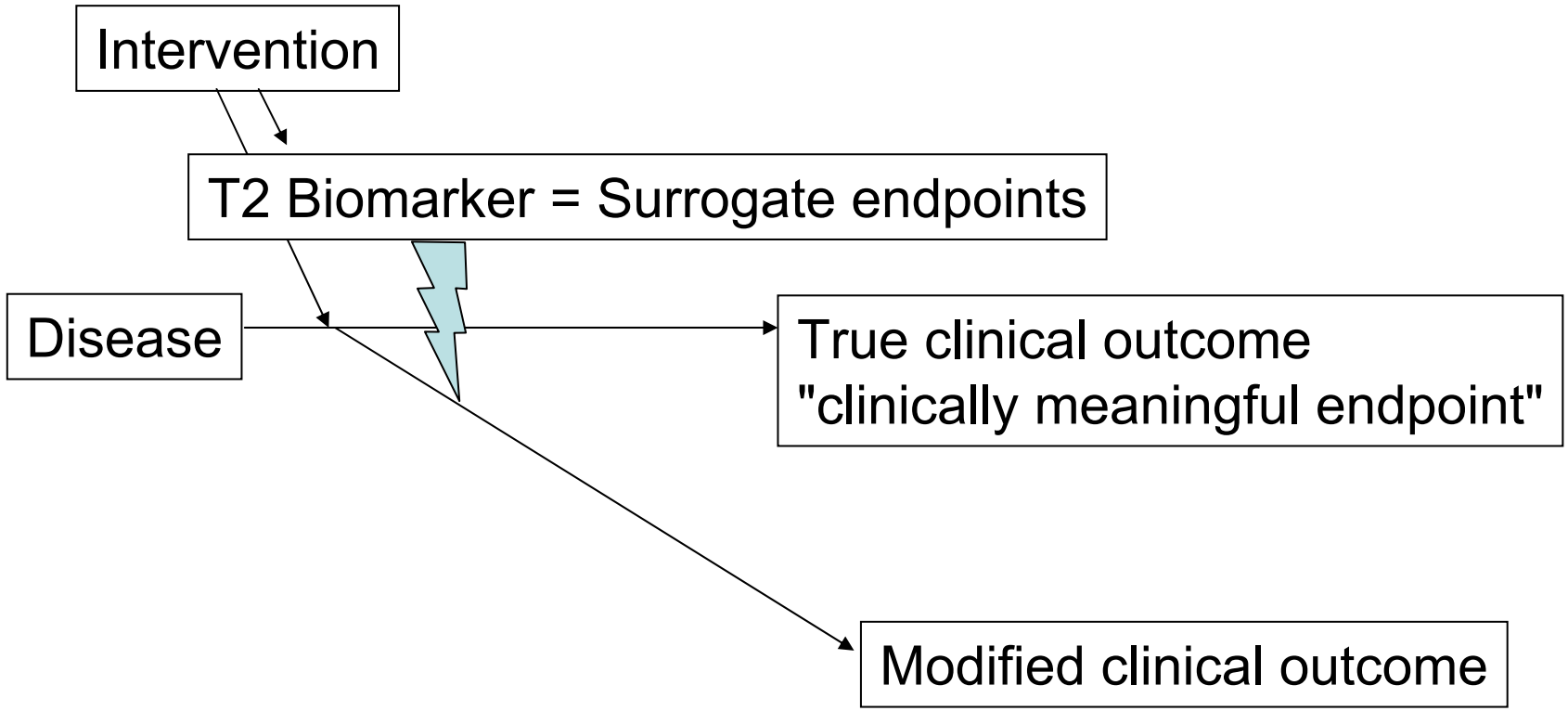


- Possible applications of T0 biomarkers
  - (Early) diagnosis
  - Clinical study enrichment

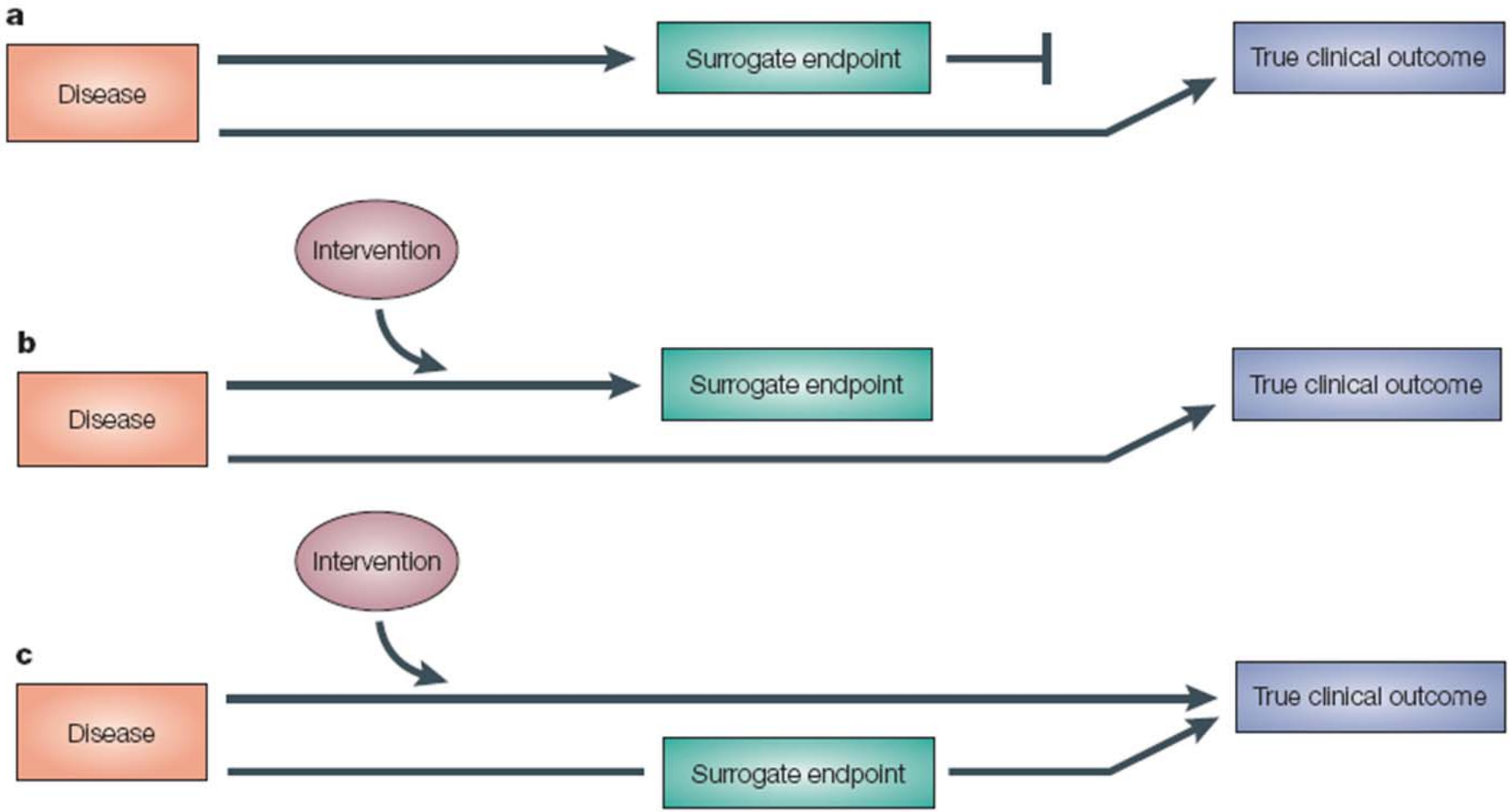
Type 1 Biomarker
Mechanism of action of an intervention



Type 2 Biomarker (surrogate endpoints)
(Critère ou marqueur de substitution)
Clinical benefits of an intervention



Many causes of surrogate biomarker failure



Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. Nat Rev Drug Discov. 2003 Jul;2(7):566-80.

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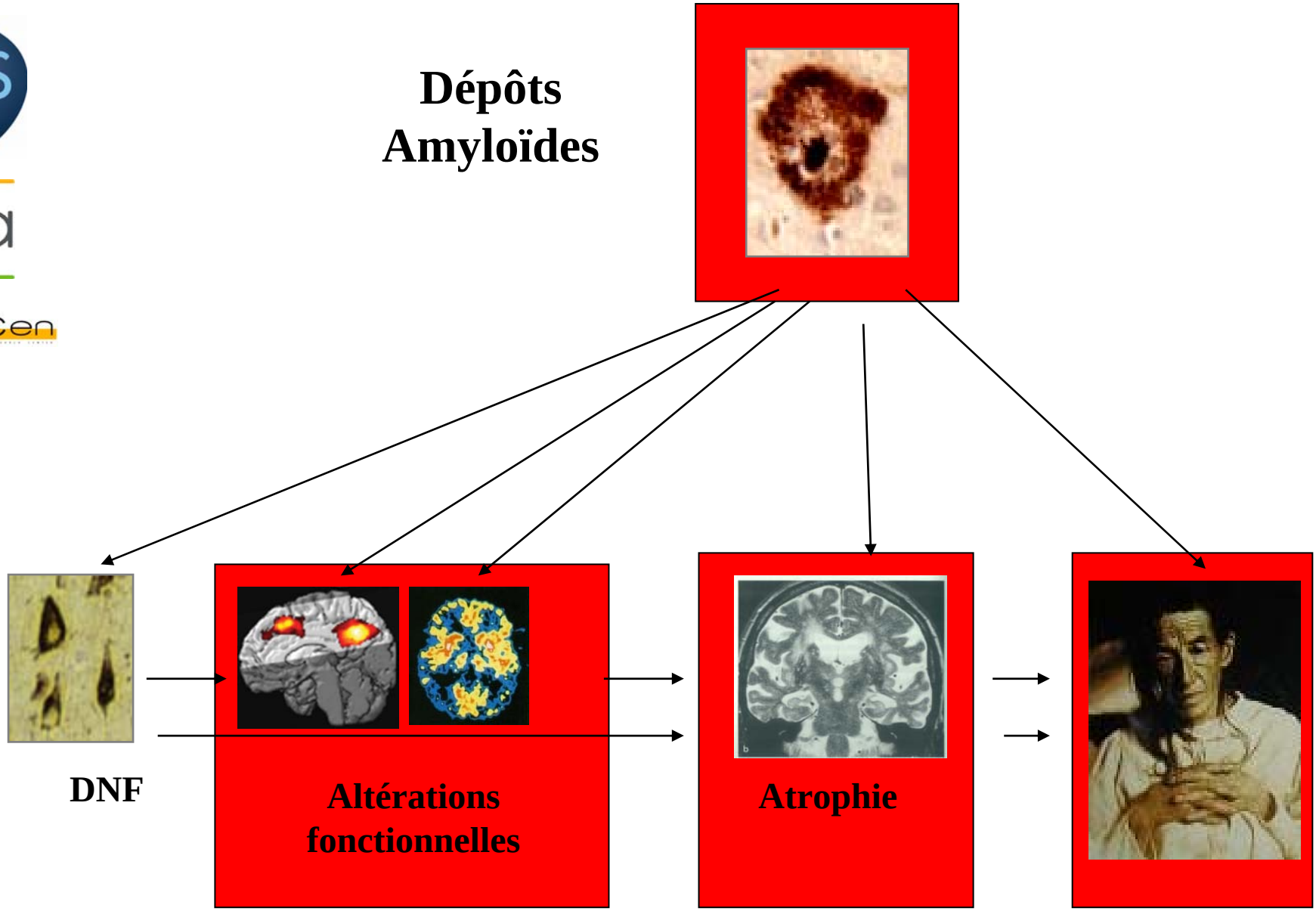
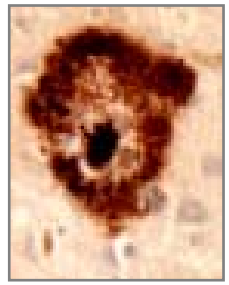
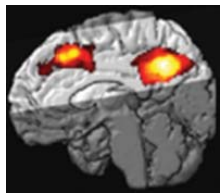
Maladie d'Alzheimer : Quels biomarqueurs ?

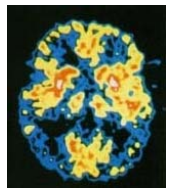


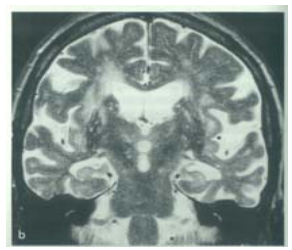
Maladie d'Alzheimer : Quels biomarqueurs ?

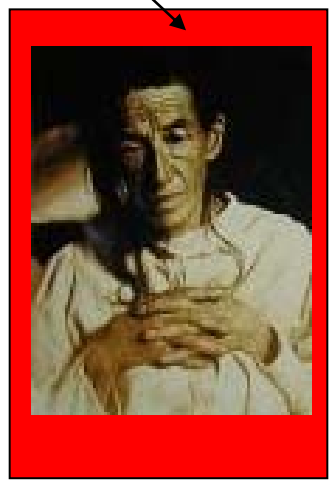
Dépôts Amyloïdes











DNF

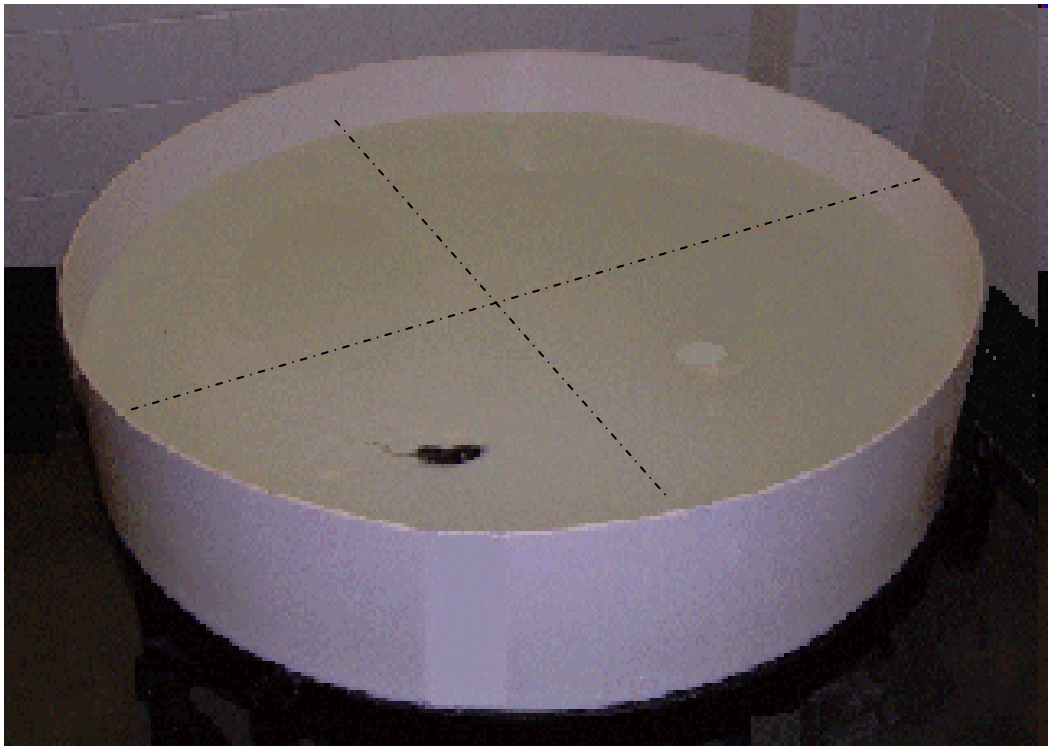
Altérations fonctionnelles

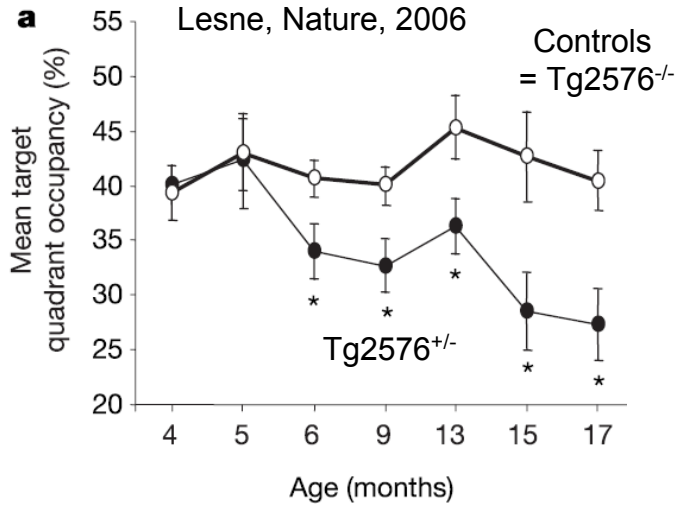
Atrophie

Altérations comportementales chez les rongeurs

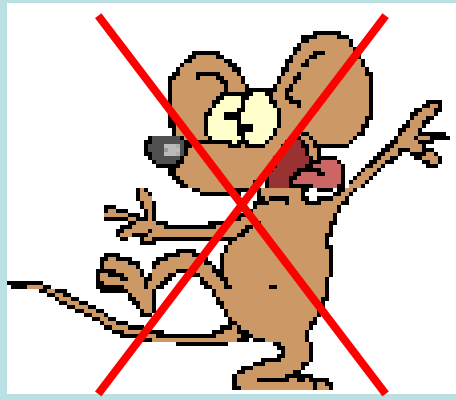
Ex. Piscine de Morris – Navigation Spatiale

- Mémoire spatiale de référence
- Intégrité de l'hippocampe
- Couramment utilisée

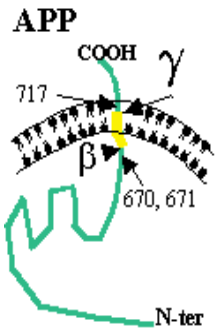




Altérations mnésiques
mais pas de "démence"

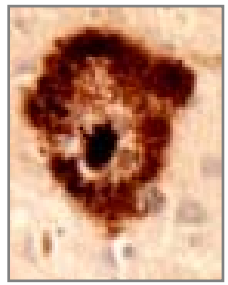


Origin of behavioral alterations: Oligomers

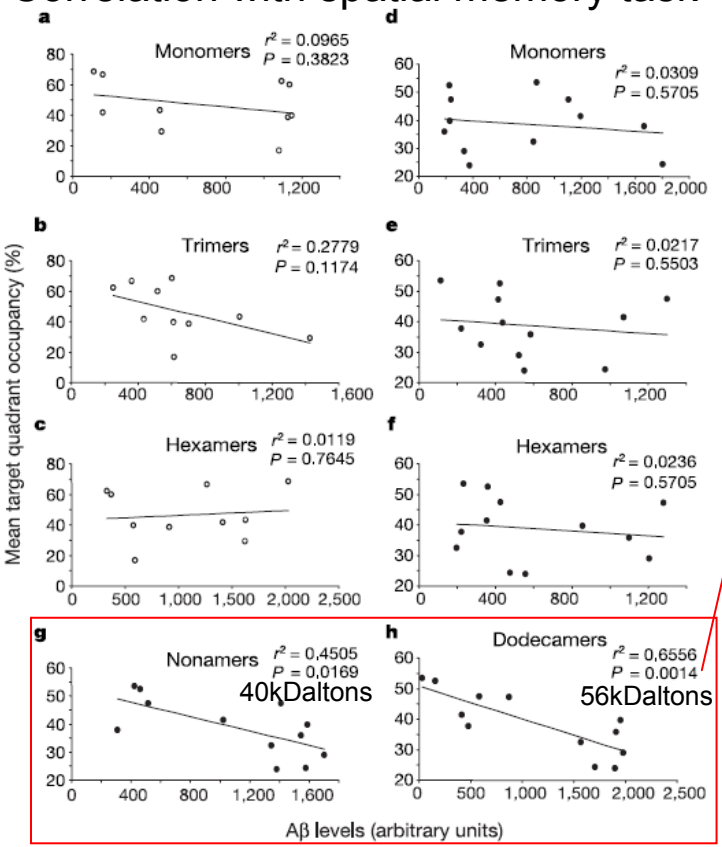


Beta Amyloid

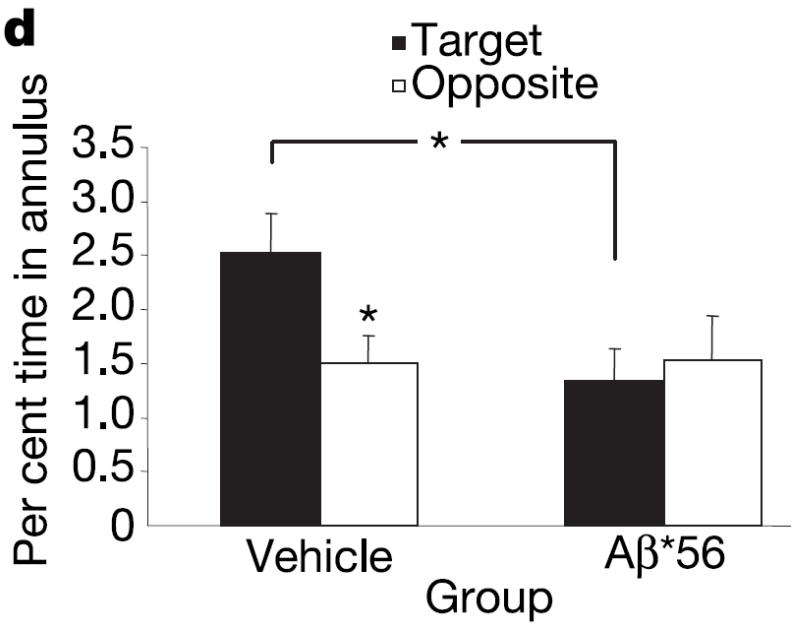
Monomers → Oligomers → Protofibrils → Fibrils



Correlation with spatial memory task



Injection of Aβ*56 in young rats



Lesne, Nature, 2006

Différence majeure cpt souris / Homme

Justification des études comportementales
La maladie d'Alzheimer est une démence…

Origine Troubles Comportementaux = DNF

Biais de raisonnement

Les troubles comportementaux des rongeurs n'ont pas la même origine que ceux de l'homme Alzheimer

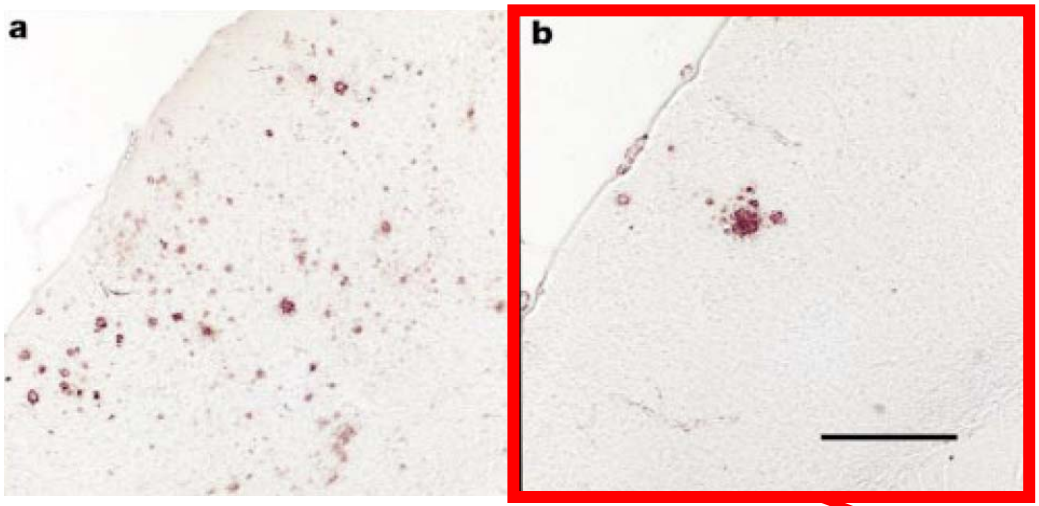
Troubles comportementaux modérés

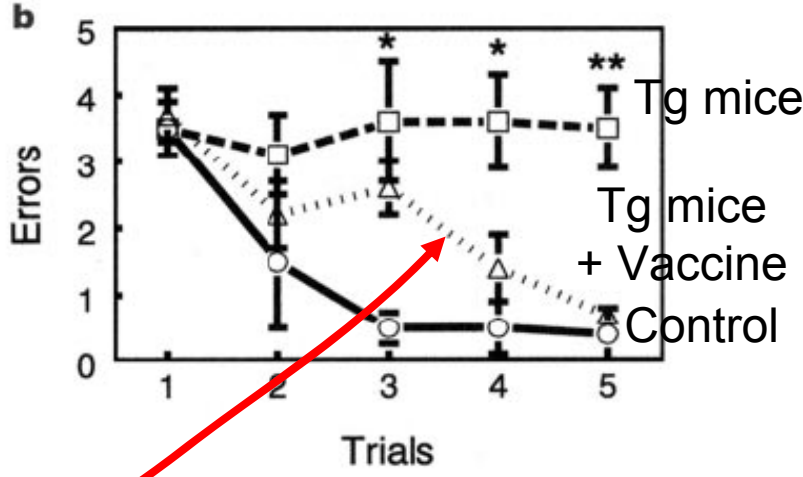
Origine Troubles Comportementaux = Oligomères

Predictivité des effets chez l'homme

- AN1792

Radial arm water maze





Morgan et al. (2000). Nature, 408(6815), 982-5.

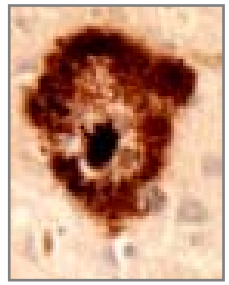
- In humans
  - Efficiency to reduce amyloid load
  - No effect on behavioral alterations

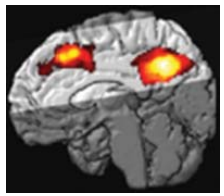
Conclusion comportement

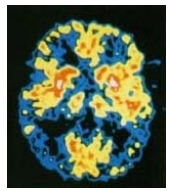
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Behavioral/cognitive evaluation	Yes	Yes	Yes	Yes

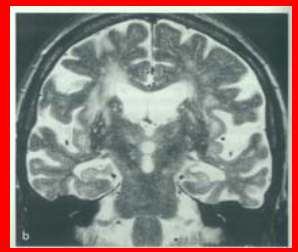
Maladie d'Alzheimer : Quels biomarqueurs ?

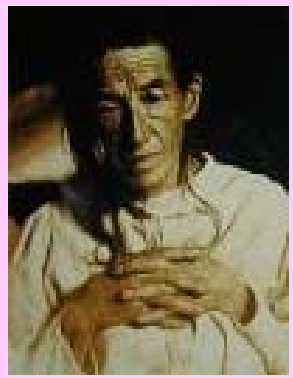
Dépôts Amyloïdes











DNF

Altérations fonctionnelles

Atrophie

Cerebral atrophy in humans with Alzheimer

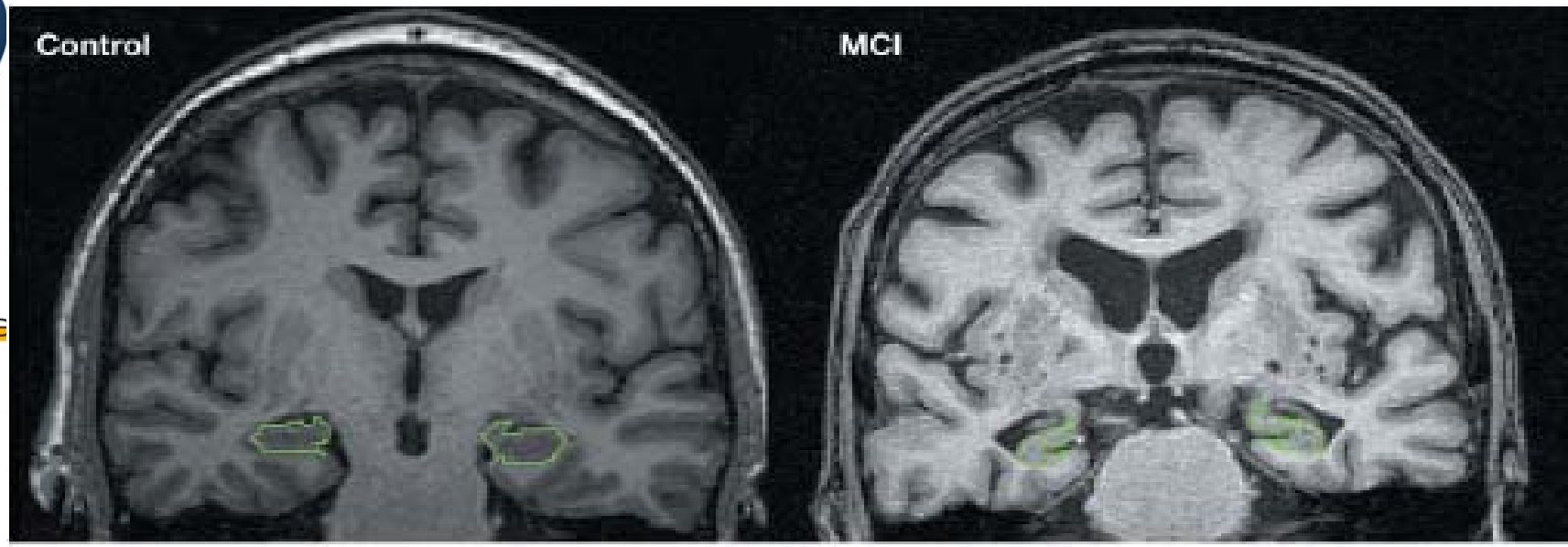
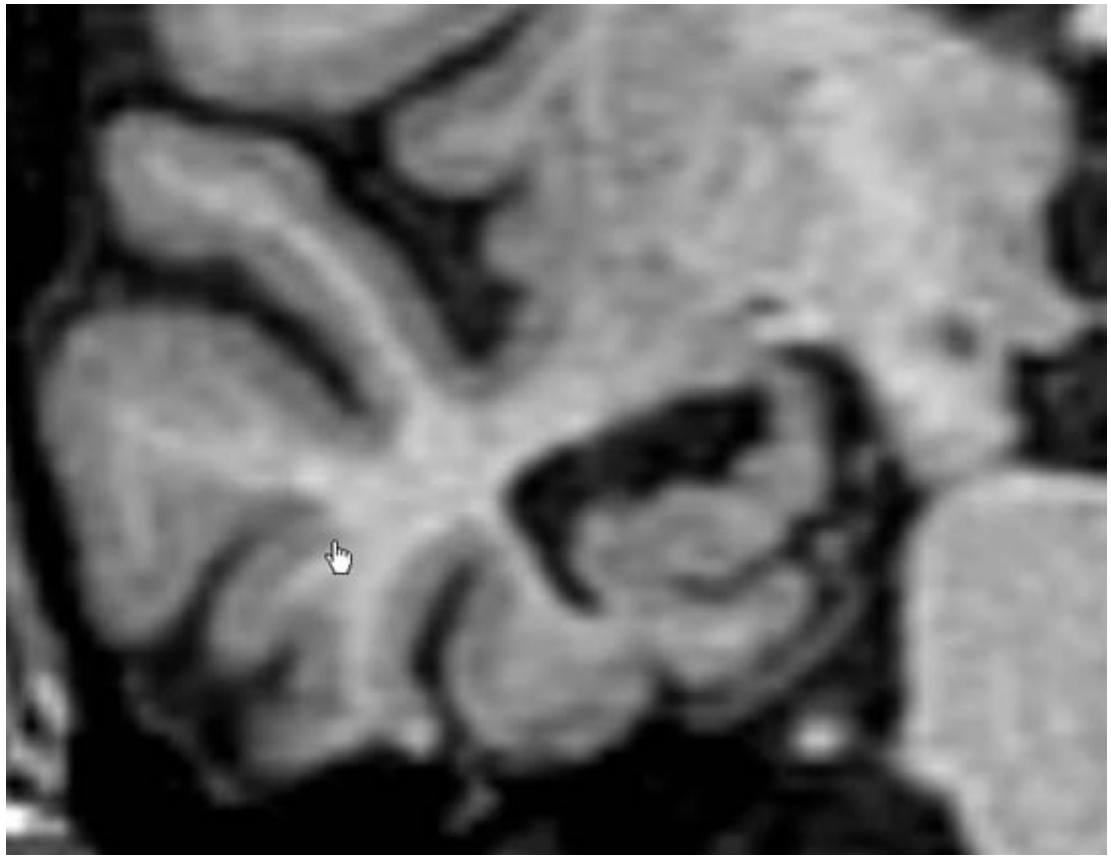


Figure 3 Comparable T1-weighted coronal MRI slices perpendicular to the long axis of the hippocampus showing a normal-sized hippocampus in a control person (total hippocampal volume uncorrected for head size 3,480 mm^3 right and 3,164 mm^3 left) and a smaller hippocampus in an MCI patient (total hippocampal volume uncorrected for head size 2,050 mm^3 right and 2,580 mm^3 left). Images courtesy of L. van der Pol, Alzheimer Center and Image Analysis Center, Vrije Universiteit Medical Center, Amsterdam, The Netherlands.

- Starts in the hippocampus then spread all over the brain

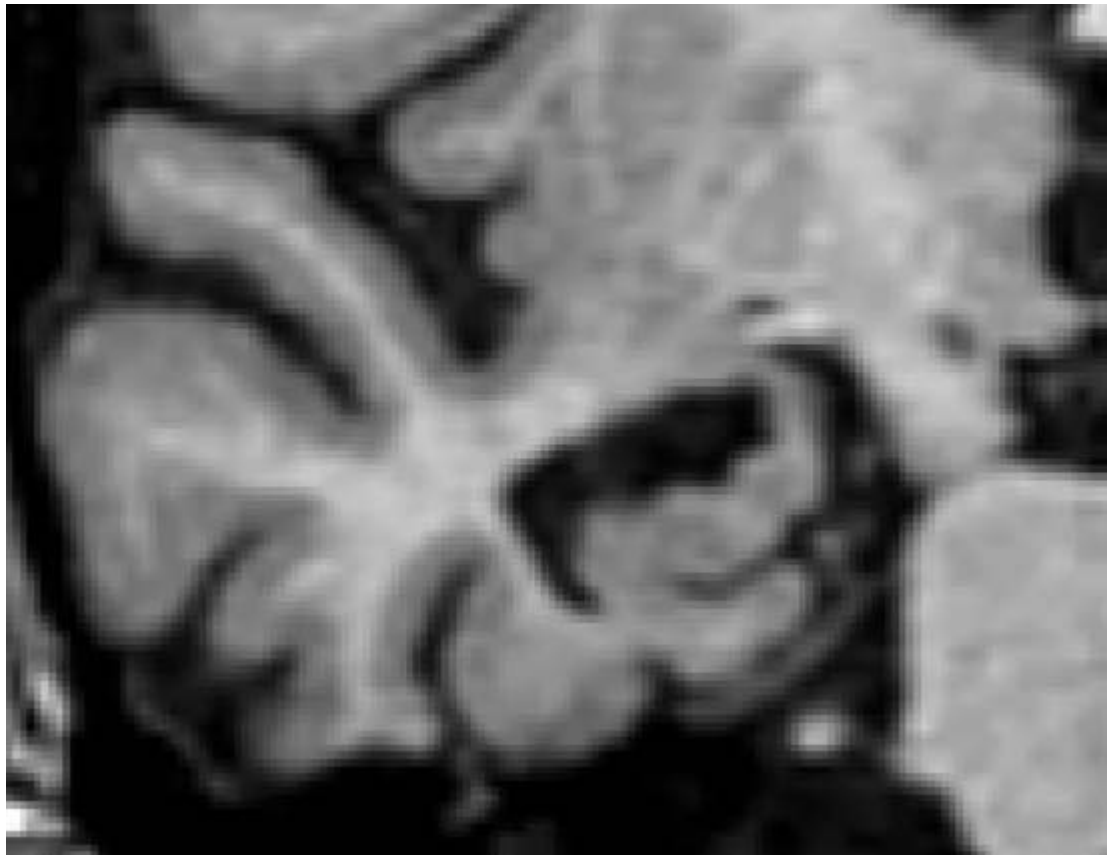
Cerebral atrophy in humans with Alzheimer

Progression from MCI to AD (10 years)



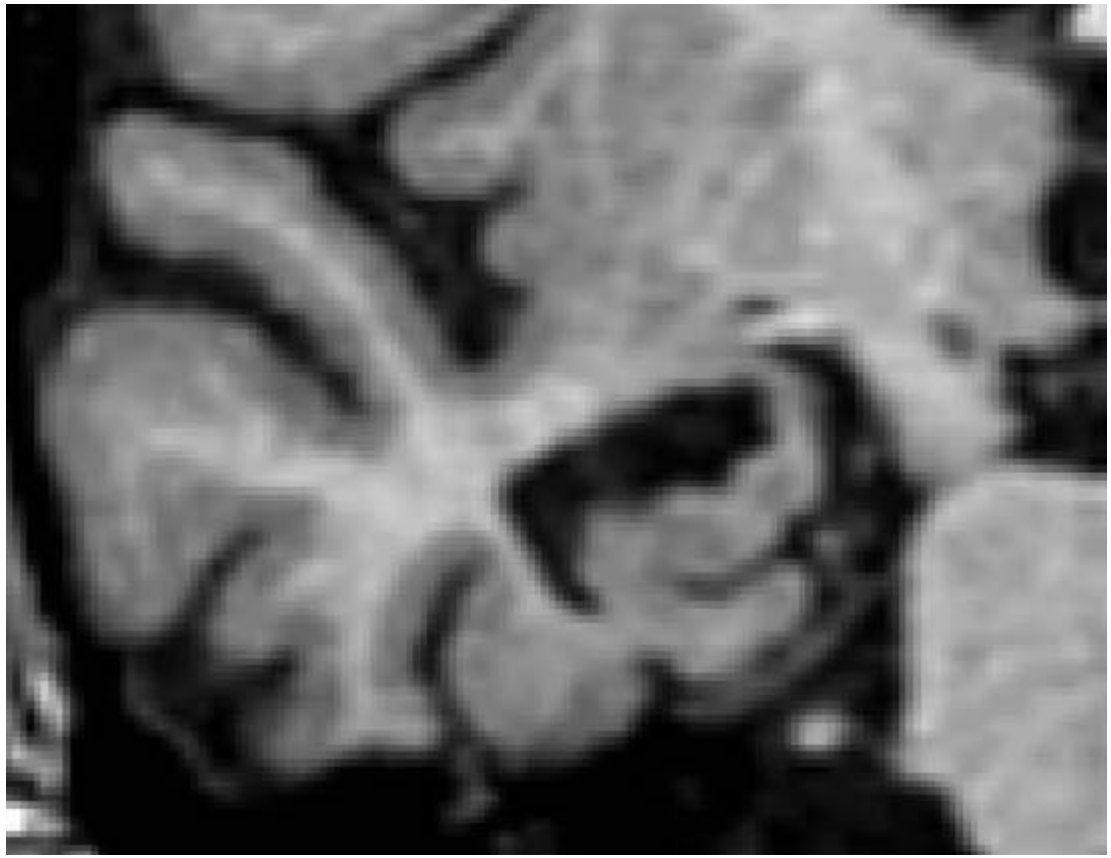
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



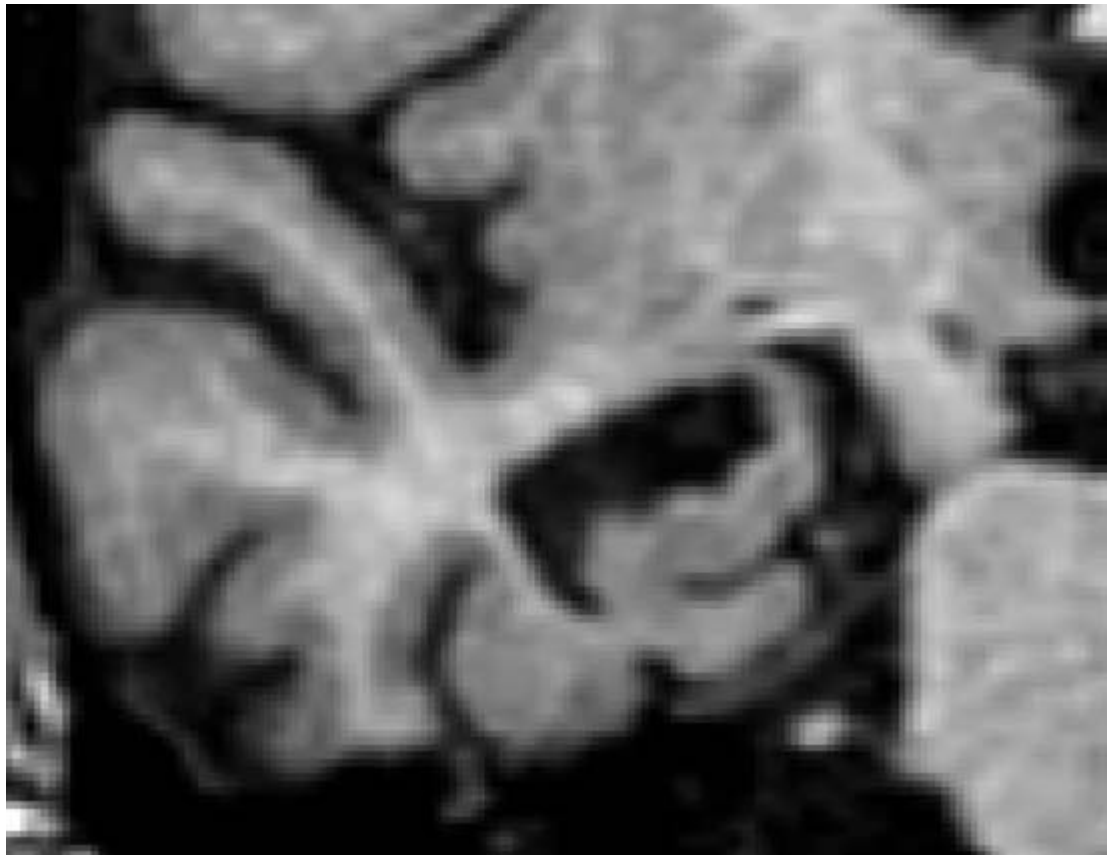
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



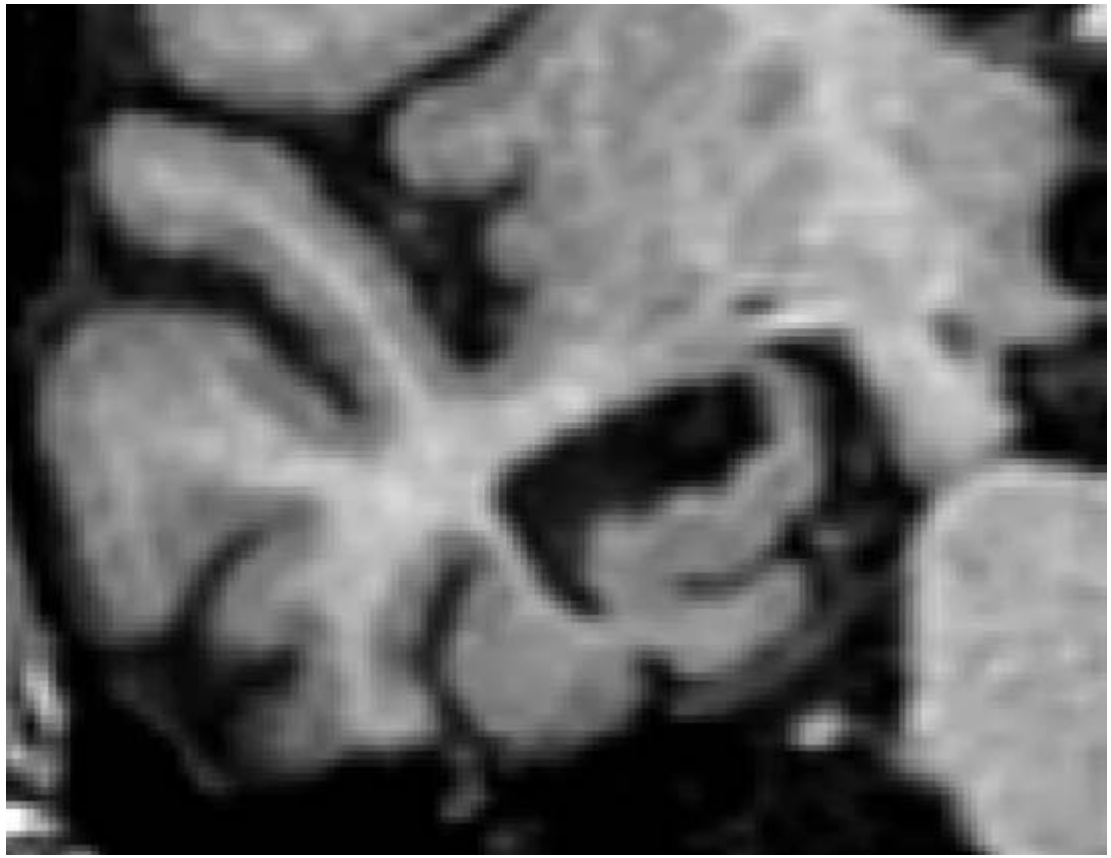
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



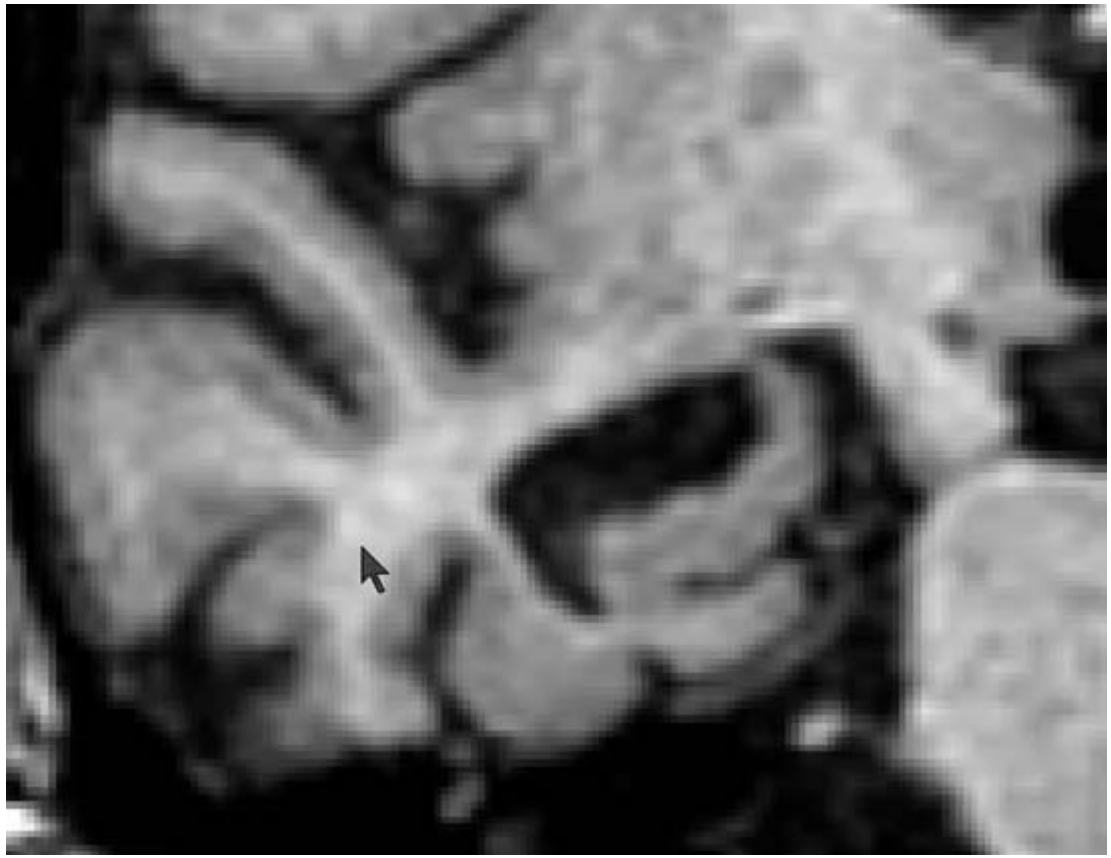
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



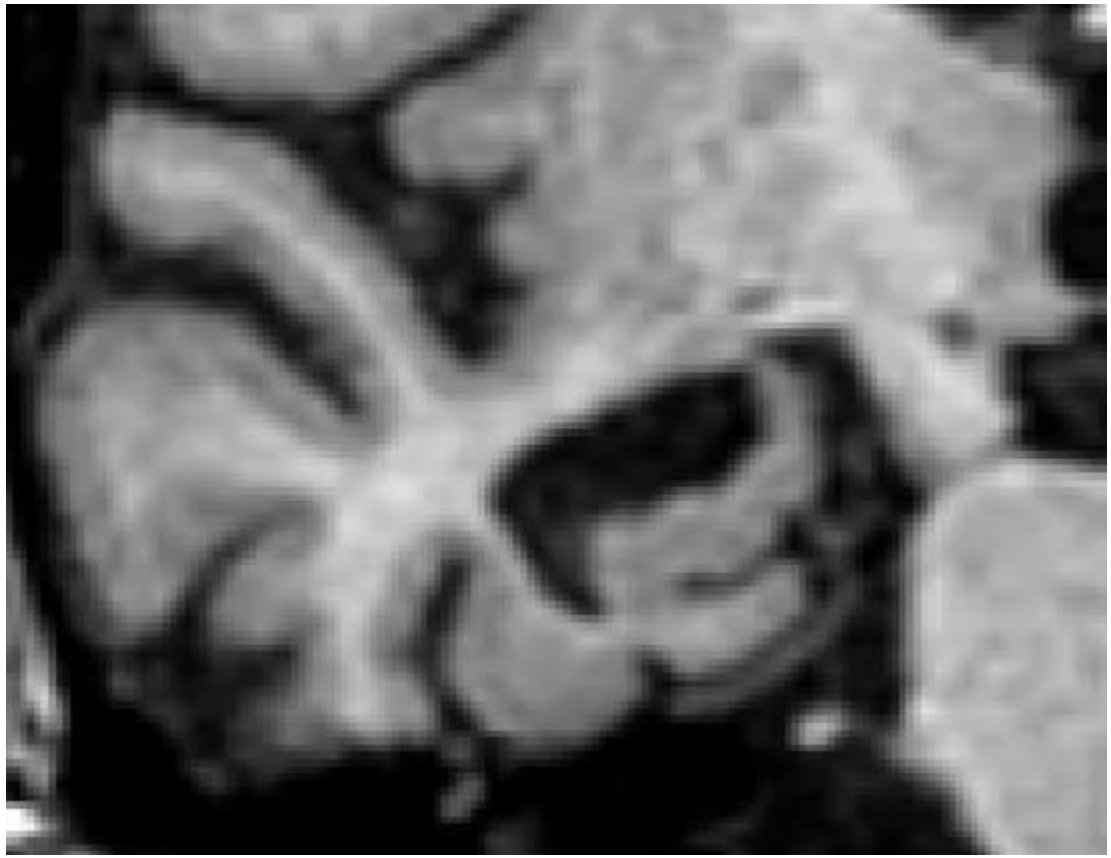
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



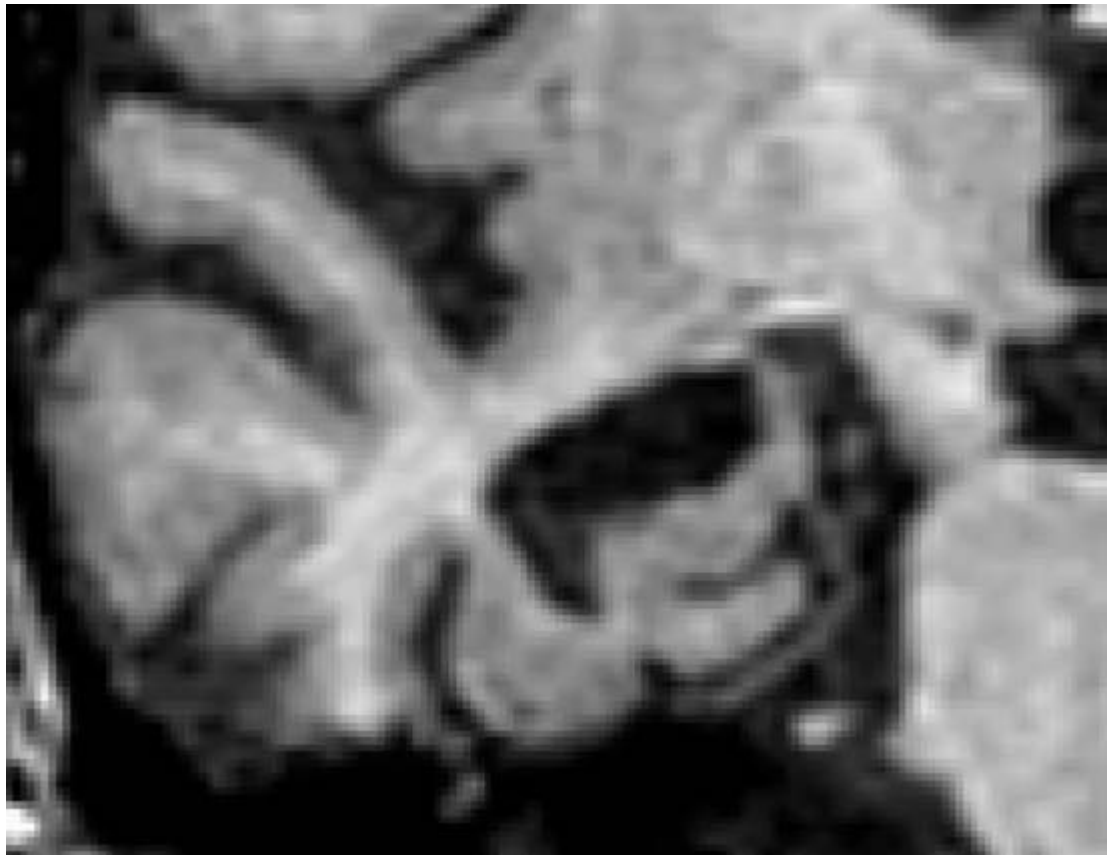
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



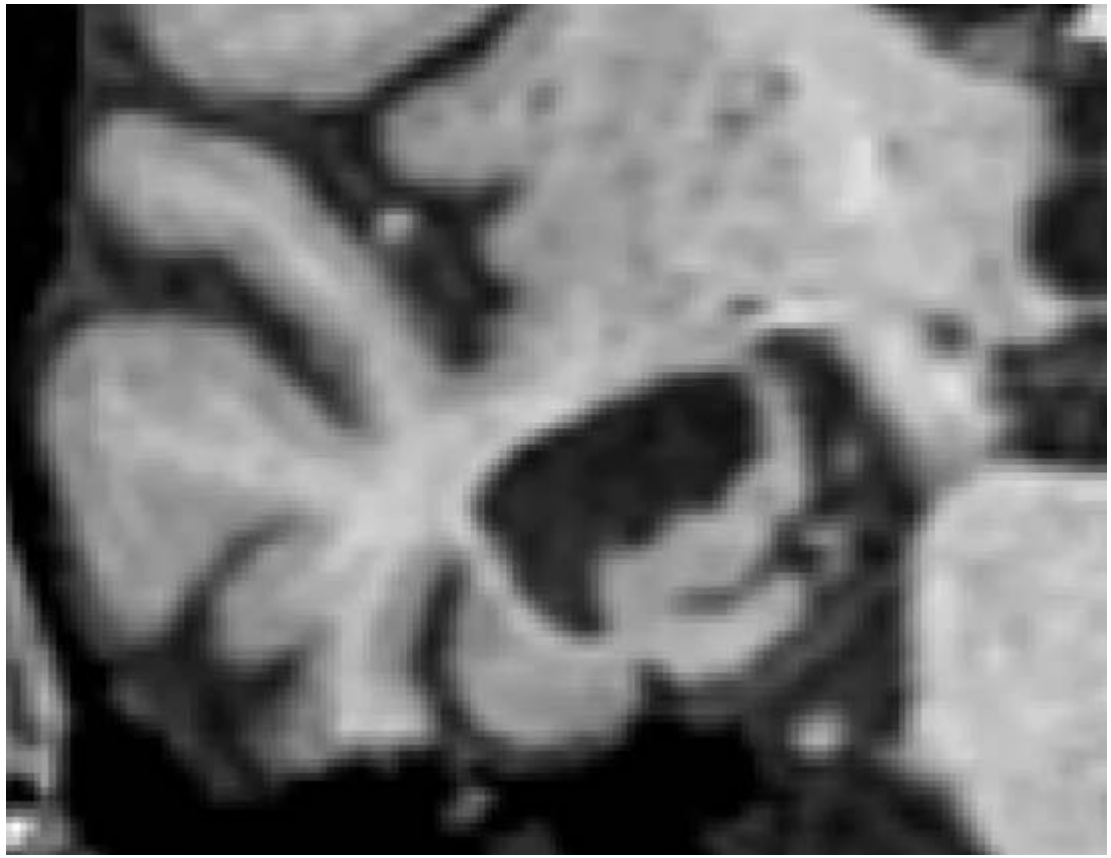
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



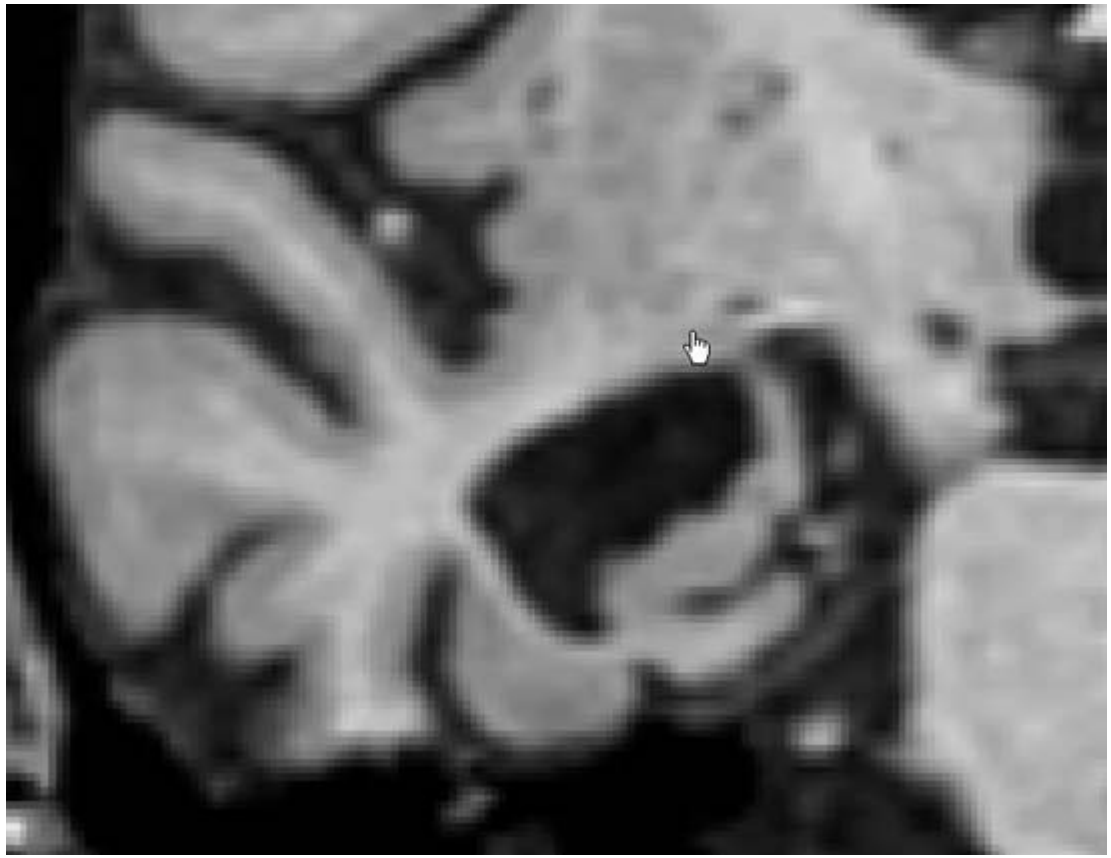
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



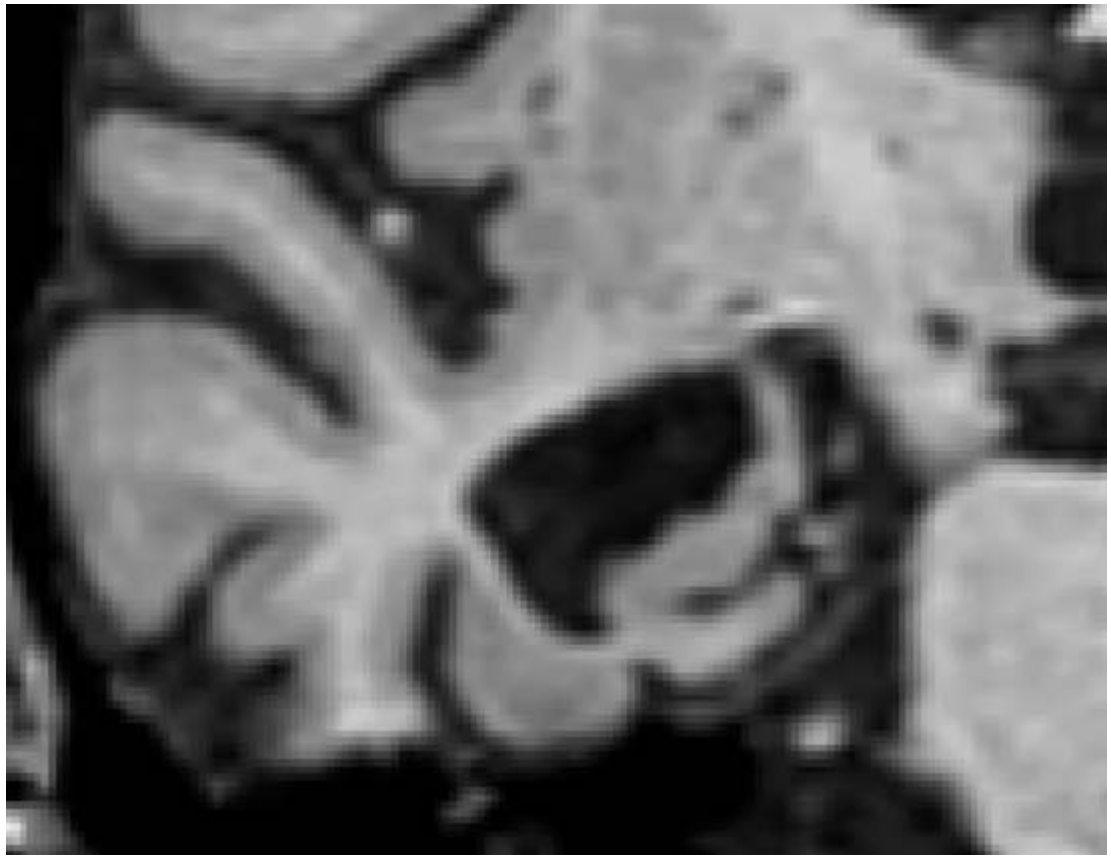
Clifford Jack, ISMRM, 2008

Progression from MCI to AD (10 years)



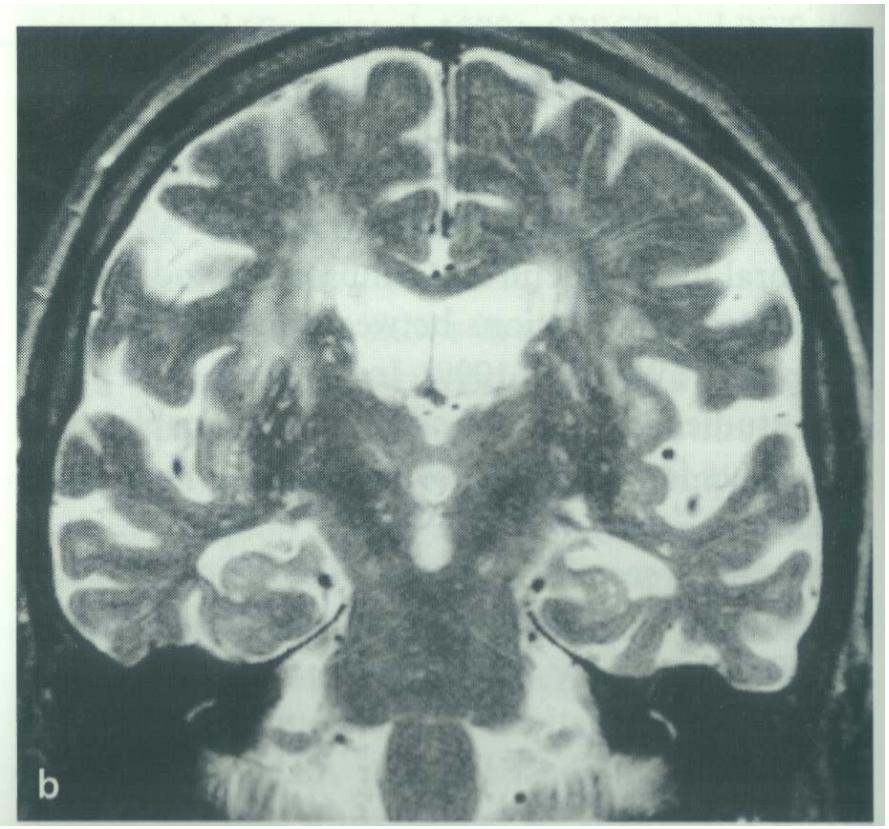
Clifford Jack, ISMRM, 2008

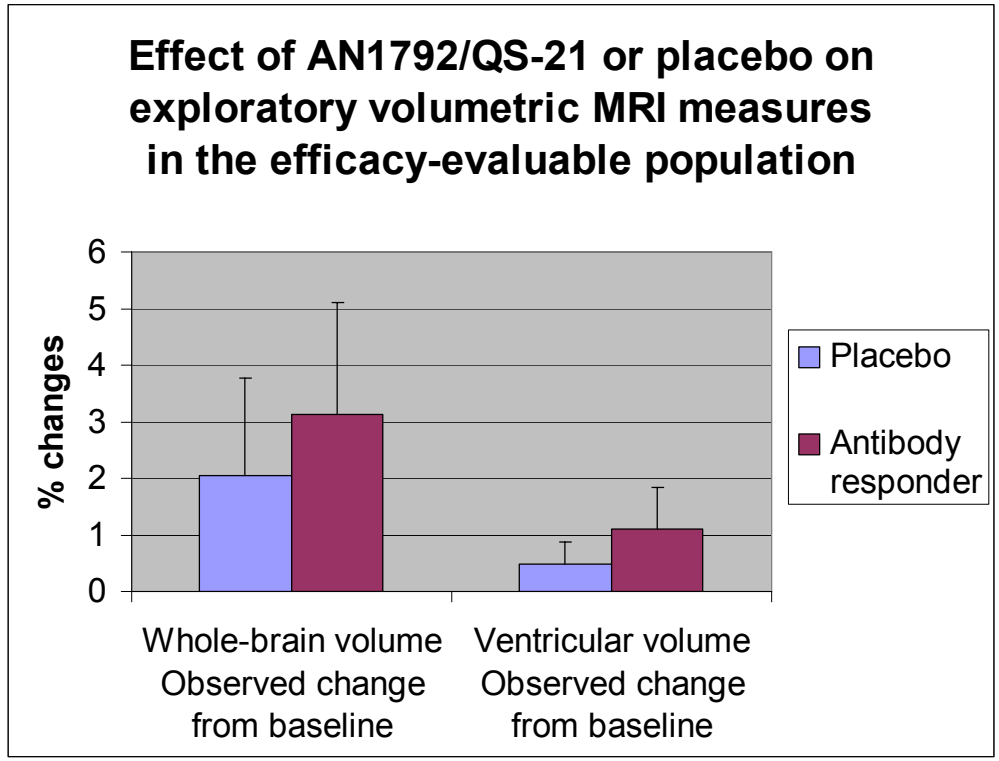
Progression from MCI to AD (10 years)



Clifford Jack, ISMRM, 2008

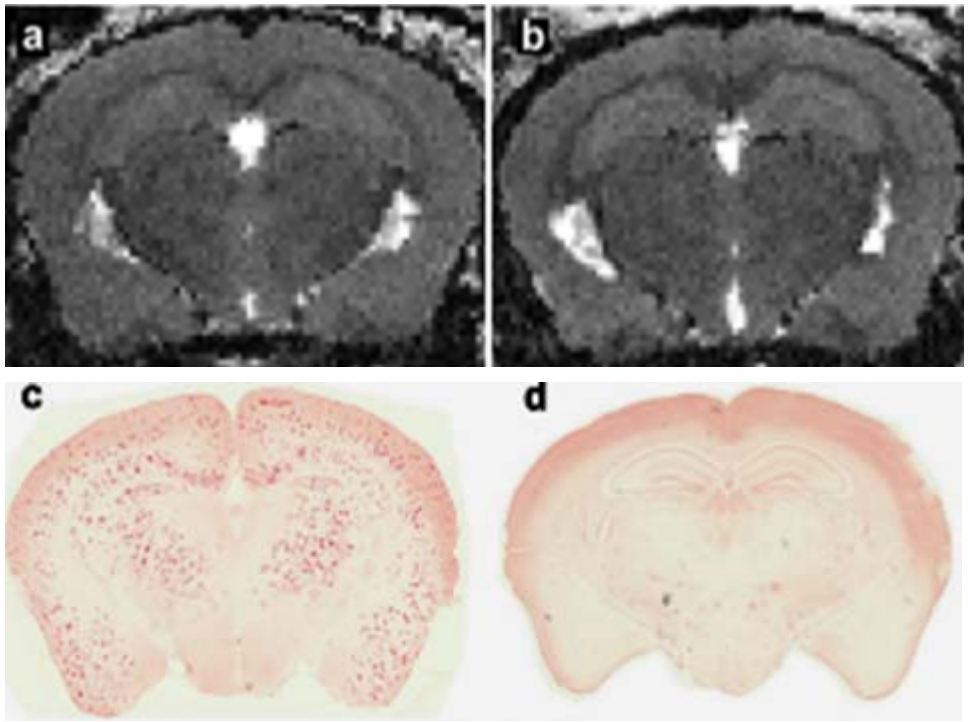
Cerebral (temporal) atrophy

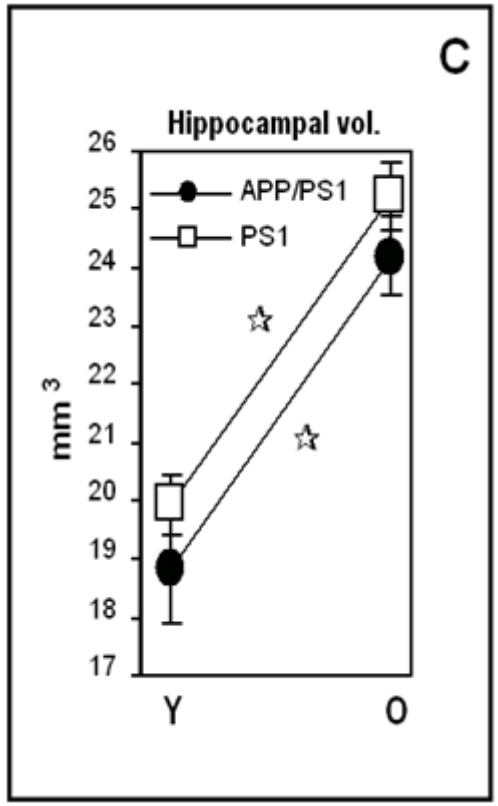




A good marker for the diagnosis (T0 biomarker)
can be questionable for therapeutic follow-up (T2 biomarker)

CSF and brain volumes in mice

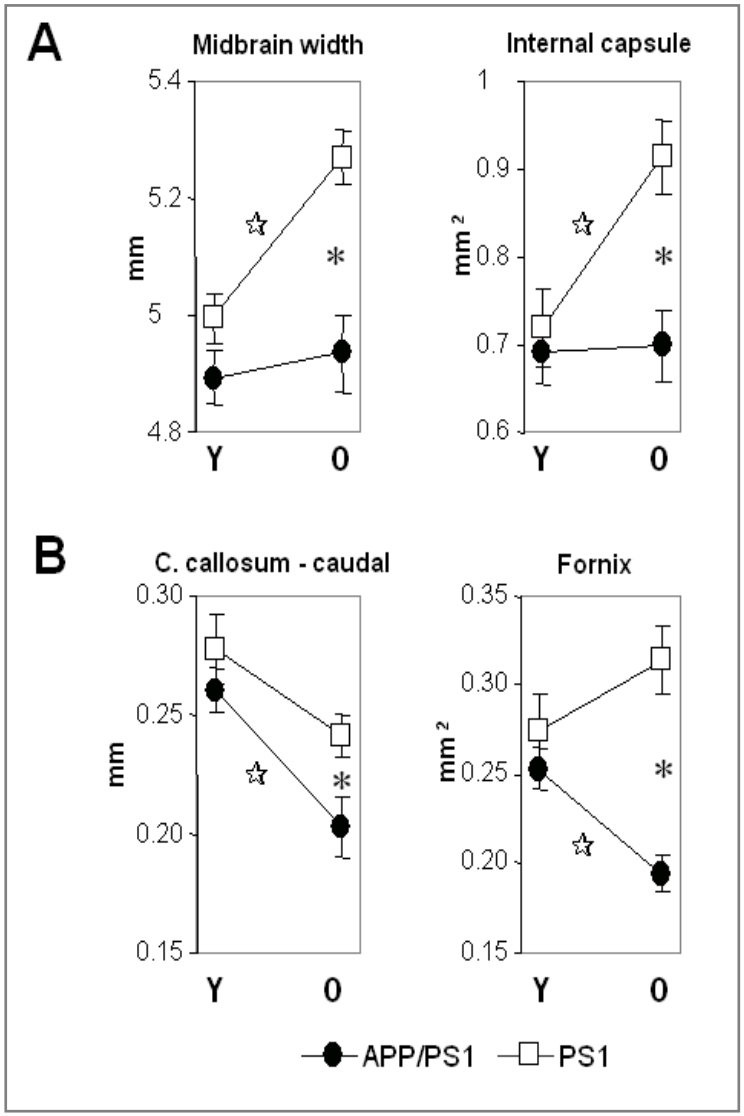




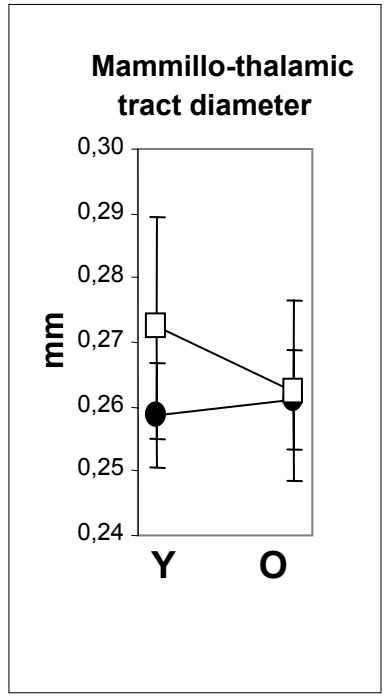
Brain and hippocampal growth
even in the presence of amyloid deposits…

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

Atrophy of white matter



White matter alterations



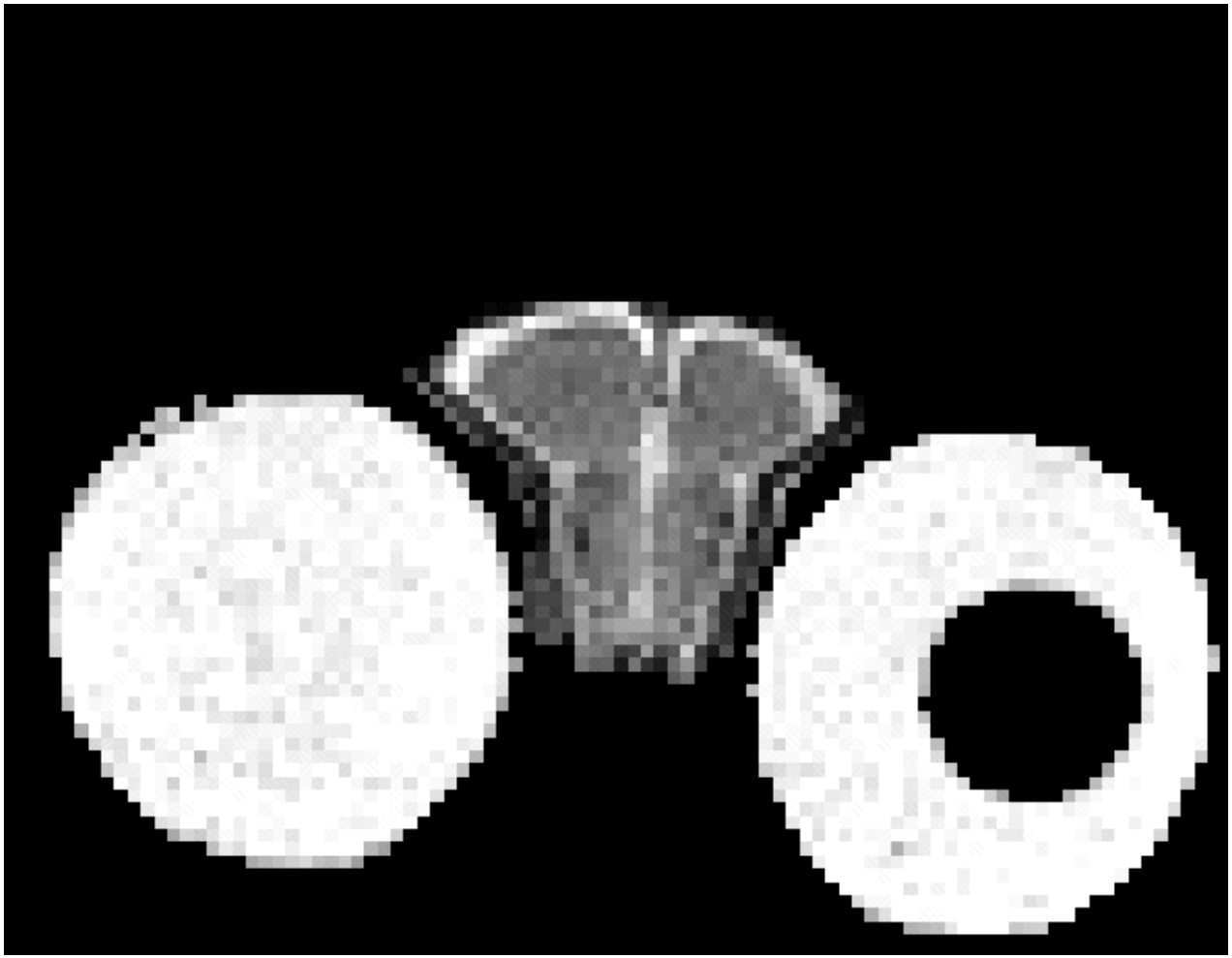
Delatour et al. (2006). Neurobiol Aging, 27(6), 835-847.

Conclusion atrophie souris

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Cerebral atrophy	No	No	Yes	No

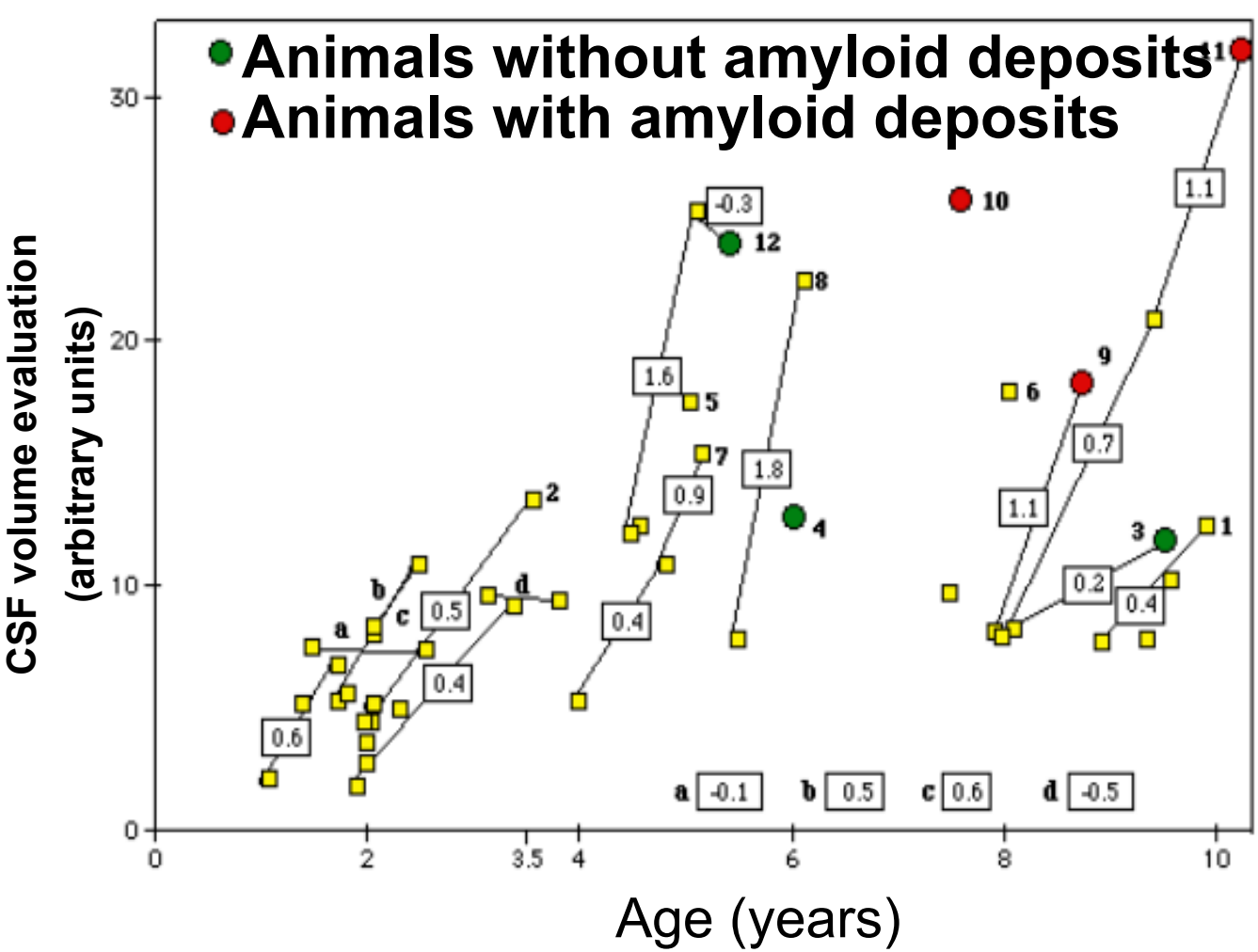
- Altération détectée : Atrophie substance blanche
- Biomarqueur de : ???
- Différence par rapport à la pathologie humaine
  - Mais voir : Villain, N., B. Desgranges, et al. (2008). "Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease." J Neurosci 28(24): 6174-81.

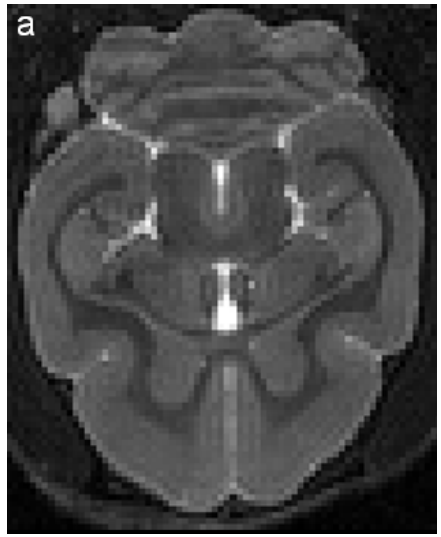
MRI evaluation of atrophy in mouse lemurs

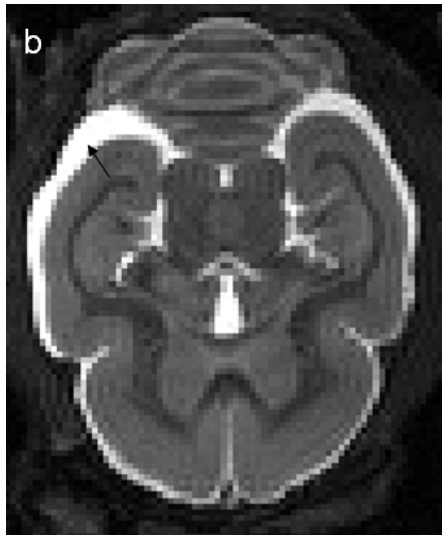


IR-RARE ; TR=2500 msec, TE=6 msec,
TEw=45 msec, TI=200 msec, Résol isotrope 234 µm

Longitudinal follow-up of temporo-parietal atrophy



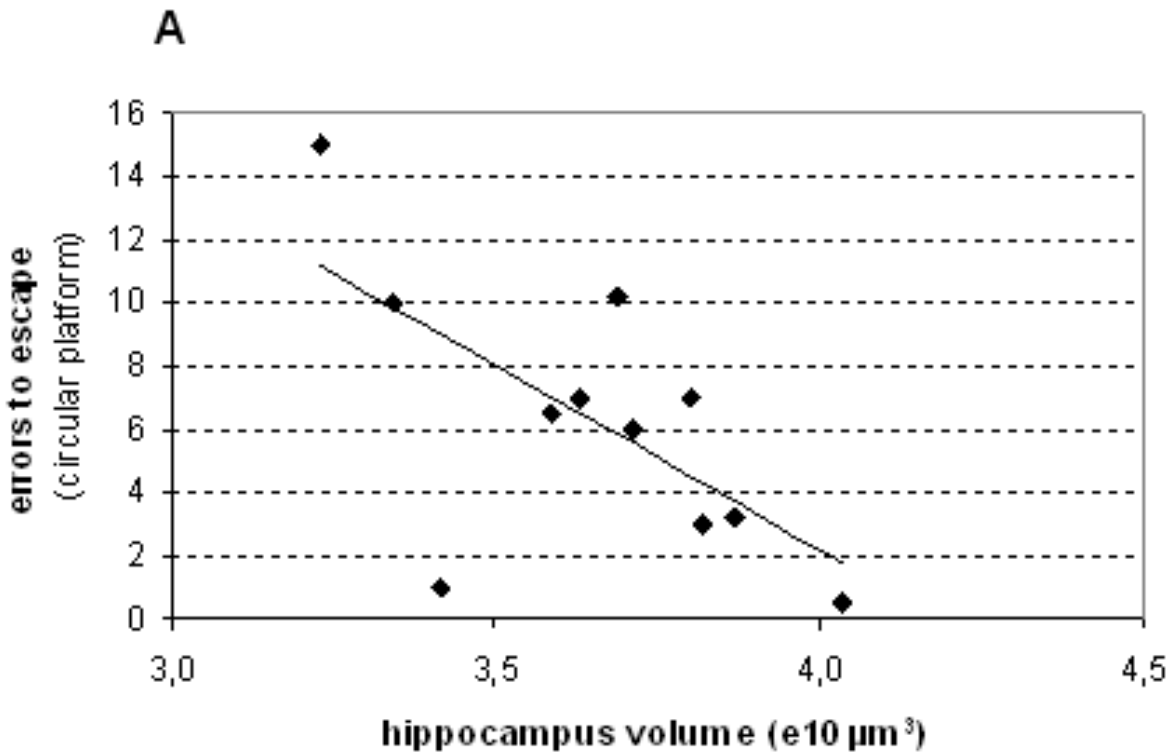




- Quick evolution once started

Dhenain et al. Neurobiol Aging. 2000;21(1):81-8.

Lien entre altérations comportementales et atrophie chez les animaux âgés



→Le microcèbe est le seul primate (non-humain) chez qui une corrélation entre atrophie cérébrale macroscopique et les altérations cognitives a été mise en évidence

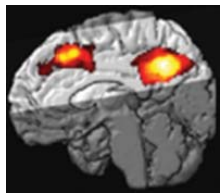
Picq et al. Neurobiol Aging. In Press

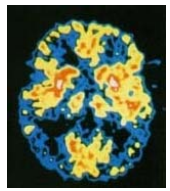
Conclusion atrophie Lemurs

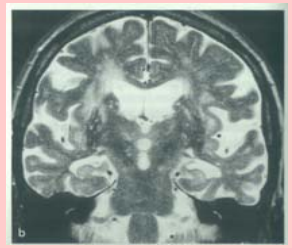
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Cerebral atrophy	Yes	No	Yes	No

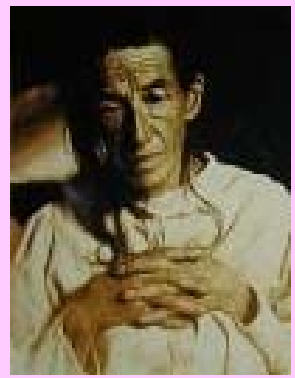
Maladie d'Alzheimer : Quels biomarqueurs ?

Dépôts Amyloïdes







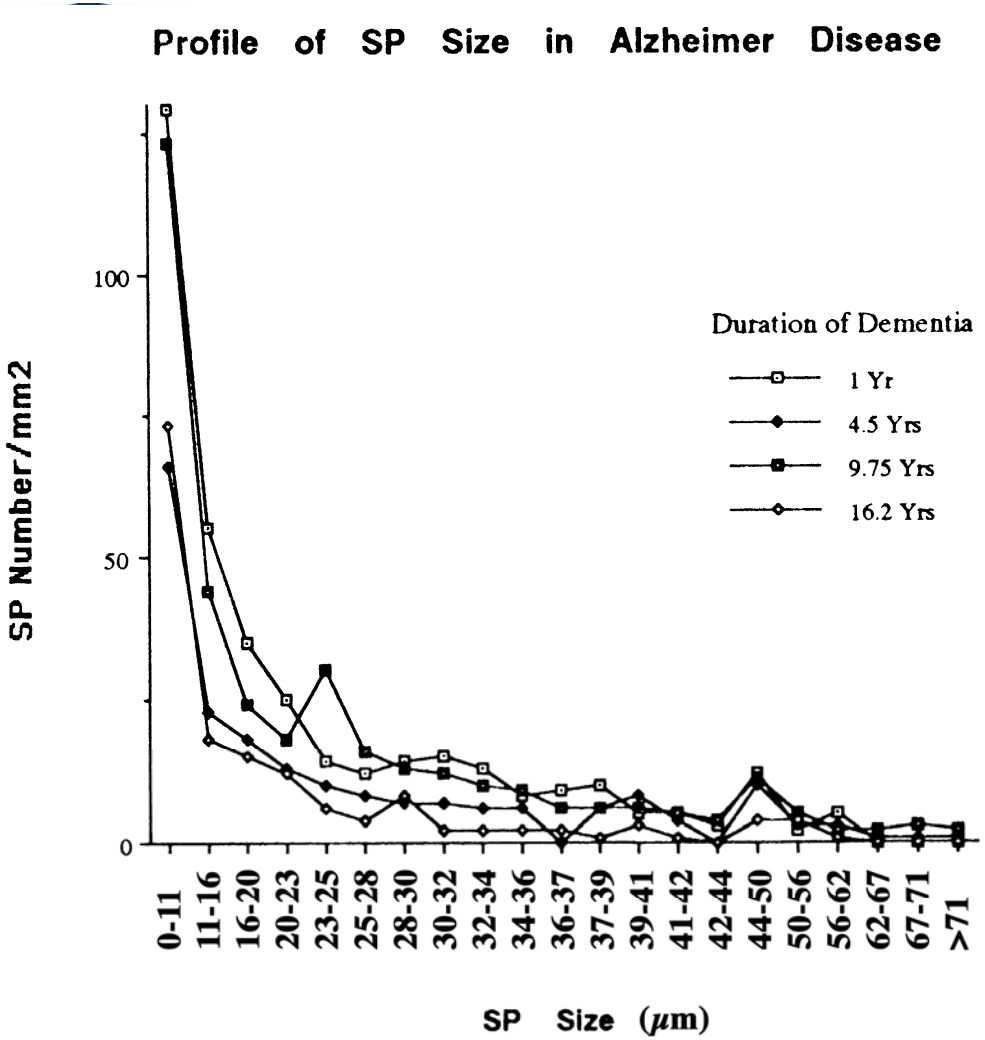


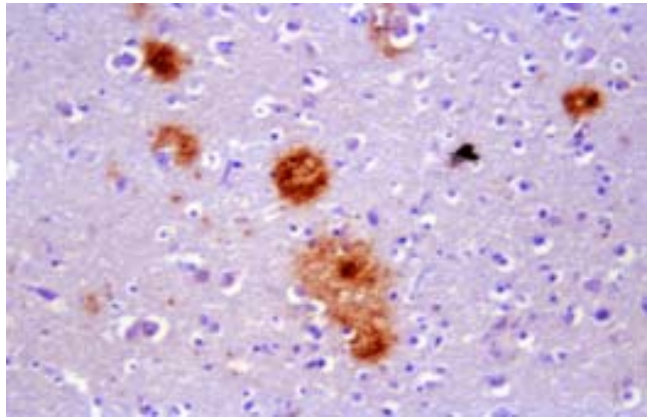
DNF

Altérations fonctionnelles

Atrophie

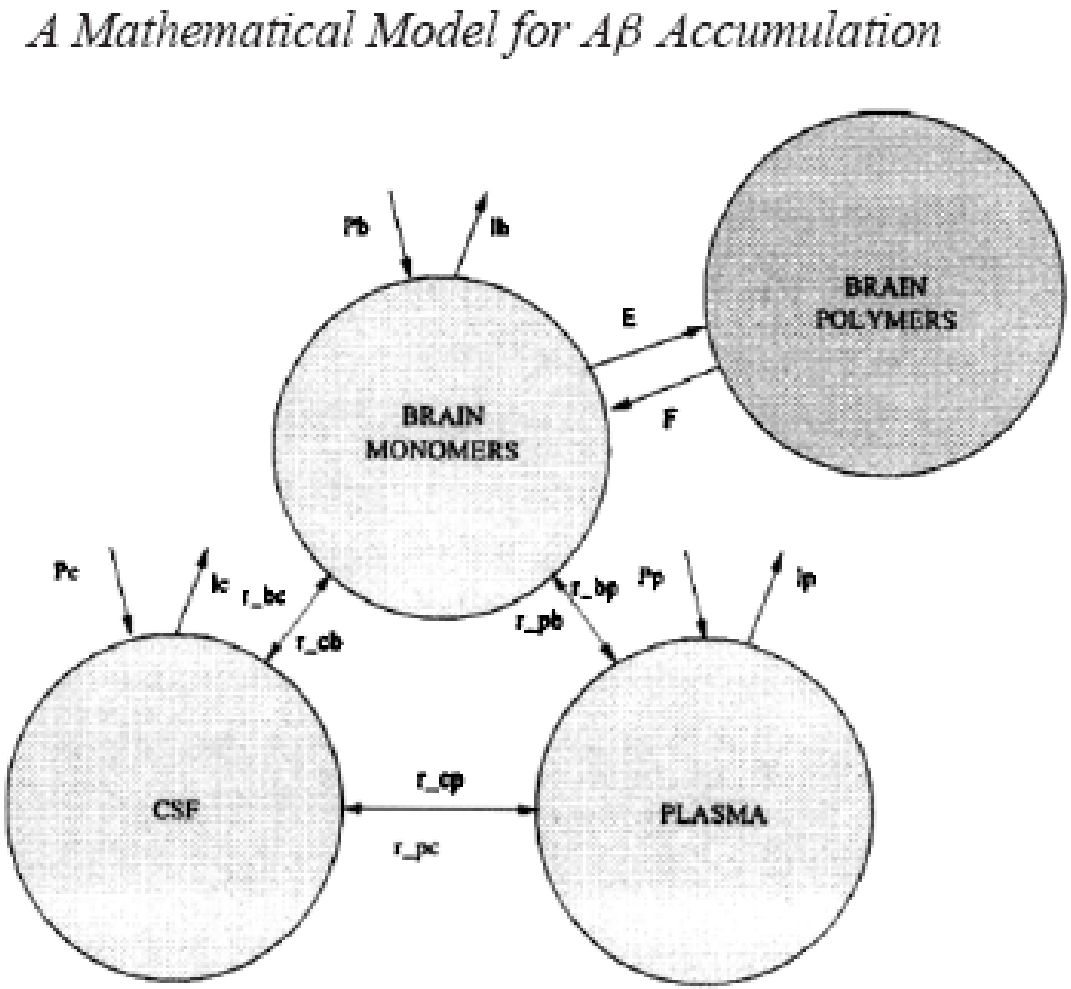
Les plaques amyloïdes





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

Autres formes d'amyloïde

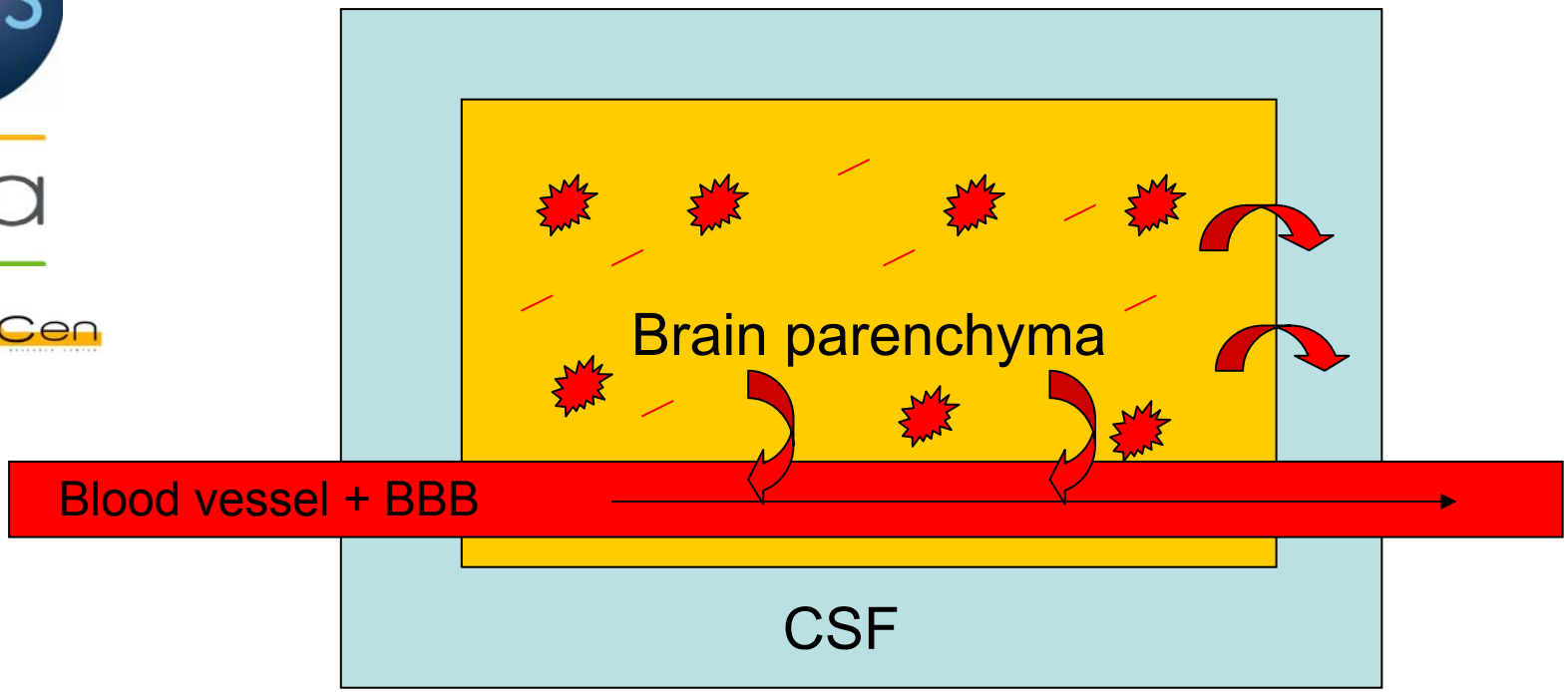


Craft, D. L., Wein L. M., Selkoe, D. J.. (2002). Bull Math Biol **64**(5): 1011-31.

Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

Evaluation of amyloid in CSF and plasma in humans



In Humans

- Decreased Abeta42 level in AD patients
- No change ?

Decreased amyloid42 level in Human CSF during AD

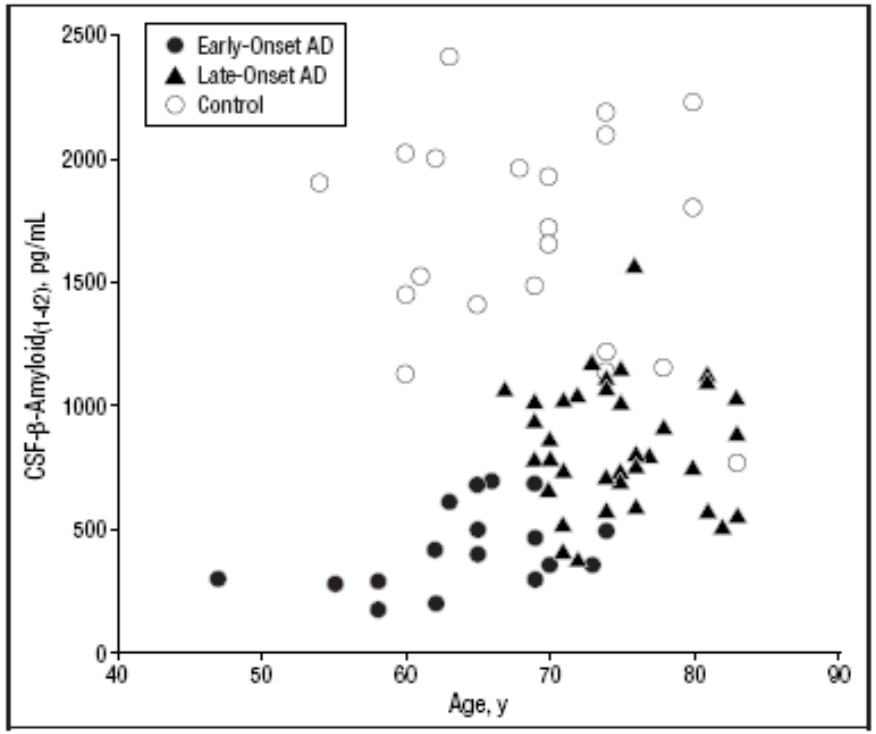


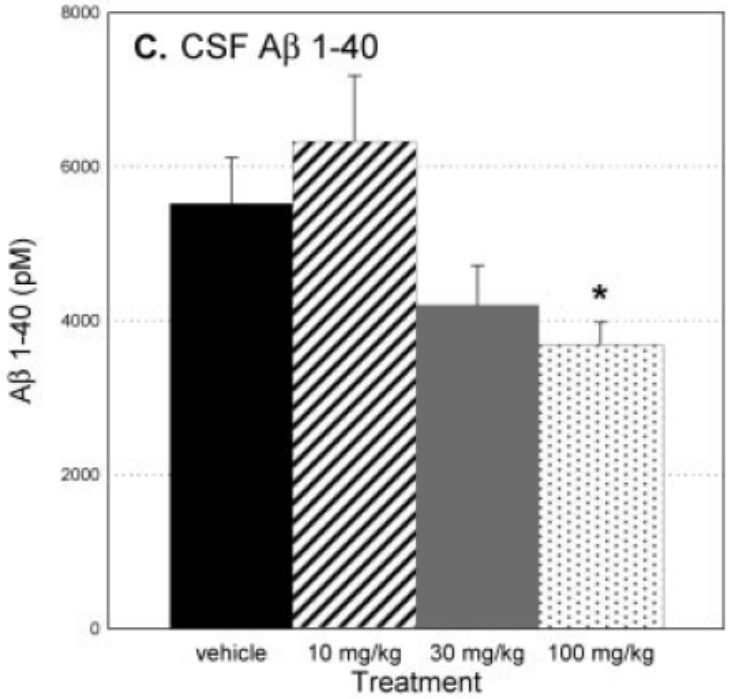
Figure 4. *Relation between age and cerebrospinal fluid (CSF) β-amyloid(1-42) level in patients with Alzheimer disease (AD) and healthy controls. Spearman r = 0.46 (P<.001) in the AD group and r = -0.15 (P = .30) in the control group.*

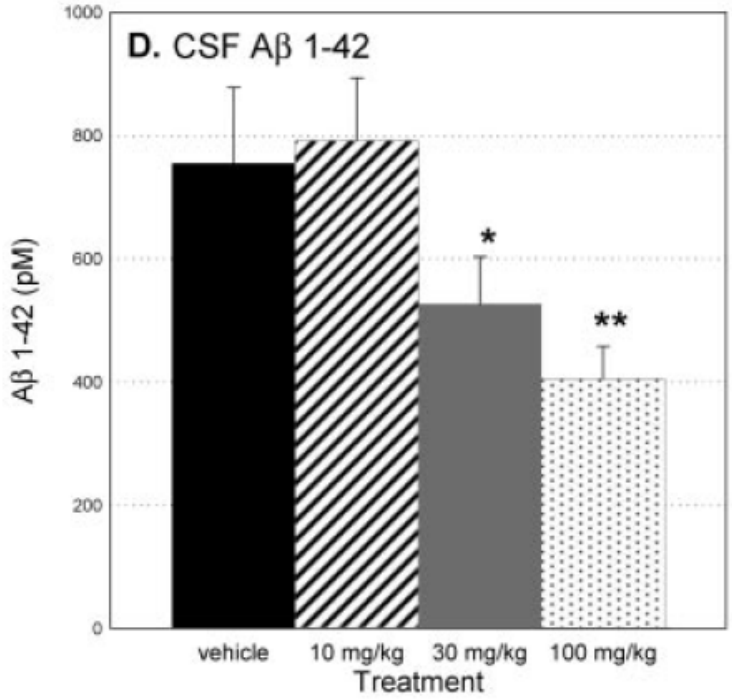
Andreasen, N., C. Hesse, et al. (1999). "Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease." Arch Neurol **56**(6): 673-80.

Evaluation of amyloid in CSF: Therapeutic evolution

Tg2576 – 17 months

Marker of soluble amyloid



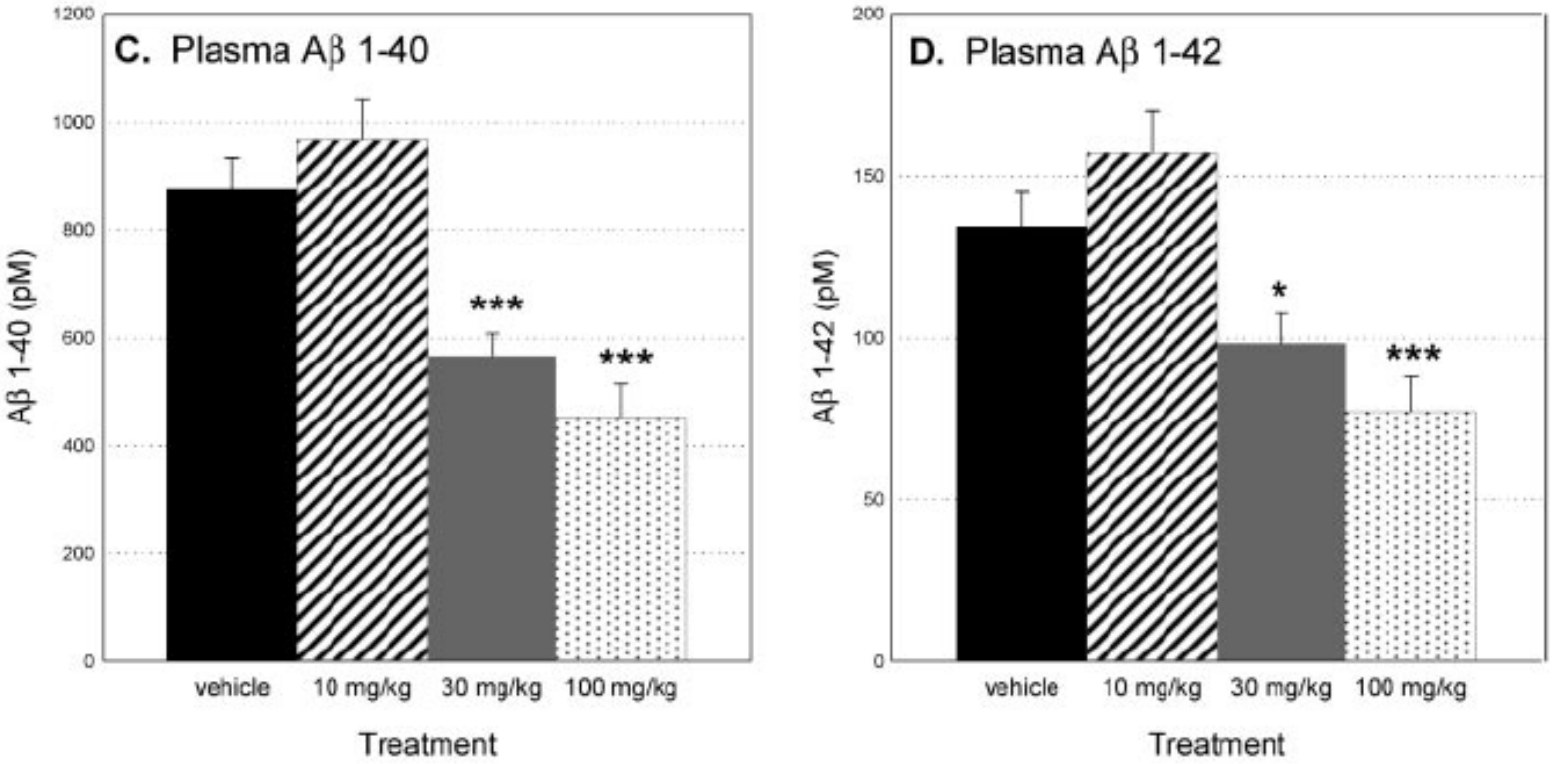


The γ-Secretase Inhibitor *N*-[*N*-(3,5-Difluorophenacetyl)-L-alanyl]-*S*-phenylglycine *t*-butyl Ester Reduces Aβ Levels in Vivo in Plasma and Cerebrospinal Fluid in Young (Plaque-Free) and Aged (Plaque-Bearing) Tg2576 Mice

Lanz, T. A, et al. (2003). J Pharmacol Exp Ther **305**(3): 864-71 (Pfizer).

Evaluation of amyloid in Plasma: Therapeutic evaluation

Tg2576 – 6 months



The γ-Secretase Inhibitor *N*-[*N*-(3,5-Difluorophenacetyl)-L-alanyl]-*S*-phenylglycine *t*-butyl Ester Reduces Aβ Levels in Vivo in Plasma and Cerebrospinal Fluid in Young (Plaque-Free) and Aged (Plaque-Bearing) Tg2576 Mice

Lanz, T. A, et al. (2003). J Pharmacol Exp Ther **305**(3): 864-71 (Pfizer).

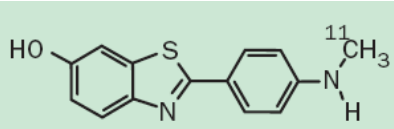
Evaluation of amyloid in CSF

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Amyloid in CSF (comes from soluble amyloid)	Yes	Yes	Yes	No
Amyloid in Plasma (comes from soluble amyloid)	Yes	Yes	No	No

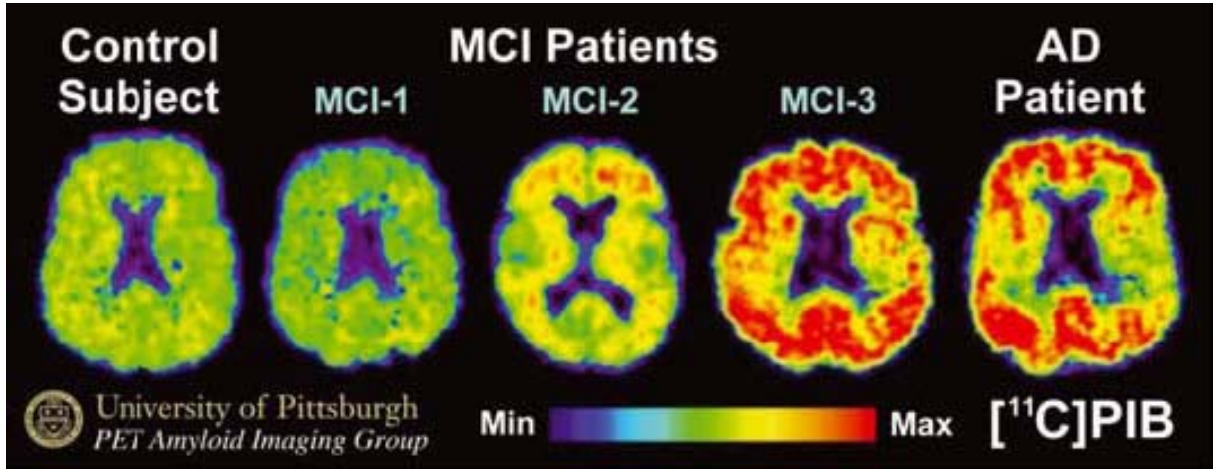
Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

Amyloid imaging in humans (by PET)



N-methyl-^{11}C-PIB



10598 • The Journal of Neuroscience, November 16, 2005 • 25(46):10598–10606

Cellular/Molecular

Binding of the Positron Emission Tomography Tracer Pittsburgh Compound-B Reflects the Amount of Amyloid-β in Alzheimer's Disease Brain But Not in Transgenic Mouse Brain

William E. Klunk,[1] Brian J. Lopresti,[2] Milos D. Ikonomovic,[3] Iliya M. Lefterov,[4] Radosveta P. Koldamova,[5] Eric E. Abrahamson,[3] Manik L. Debnath,[1] Daniel P. Holt,[2] Guo-feng Huang,[2] Li Shao,[1] Steven T. DeKosky,[3] Julie C. Price,[2] and Chester A. Mathis[2]

Departments of [1]Psychiatry, [2]Radiology, [3]Neurology, [4]Environmental and Occupational Health, and [5]Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

European Journal of Nuclear Medicine and Molecular Imaging

10.1007/s00259-005-1780-5

Molecular Imaging

PET imaging of brain with the β-amyloid probe, [^{11}C]6-OH-BTA-1, in a transgenic mouse model of Alzheimer's disease

Hiroshi Toyama[1, 2], Daniel Ye[3], Masanori Ichise[2], Jeih-San Liow[2], Lisheng Cai[2], David Jacobowitz[4], John L. Musachio[2], Jinsoo Hong[2], Mathew Crescenzo[2], Dnyanesh Tipre[2], Jian-Qiang Lu[2], Sami Zoghbi[2], Douglass C. Vines[2], Jurgen Seidel[5], Kazuhiro Katada[1], Michael V. Green[5], Victor W. Pike[2], Robert M. Cohen[3] and Robert B. Innis[2]

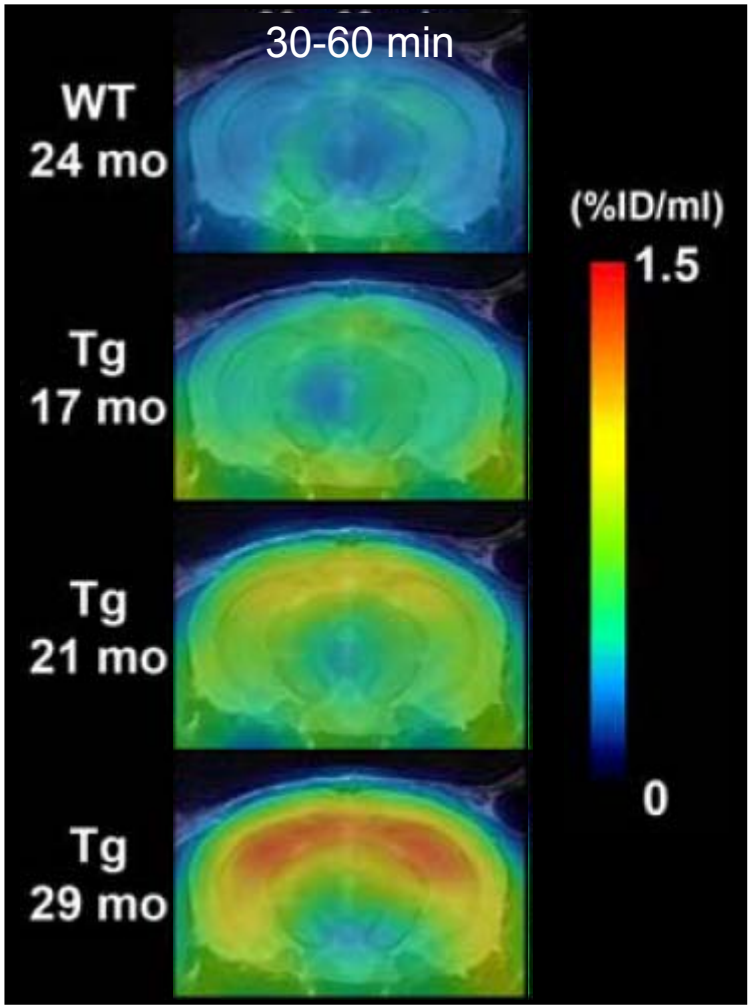
Critères de diagnostique de la MA

- Episodic memory impairments

- Supportive features
  - Medial temporal atrophy
  - Alteration of the CSF
  - Alterations of the PET
    - Reduced glucose metabolism in bilateral temporal-parietal regions
    - **Amyloid detection by PET (PIB-FDDNP…)**

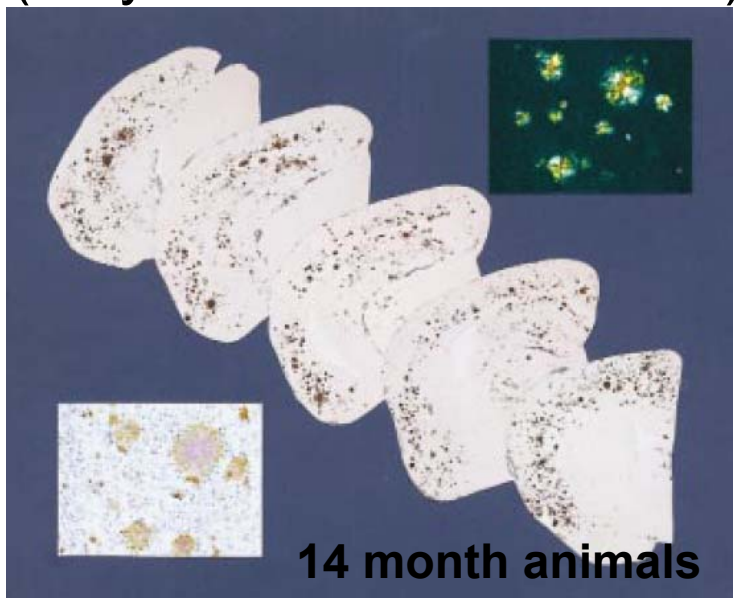
Dubois, B. et al.-2007
Lancet Neurol **6**(8): 734-46.

PIB Mice – Very late marker (if marker)



Maeda, J., B. Ji, et al. (2007).
J Neurosci **27**(41): 10957-68.

APP 23 mice
(Amyloid starts at 6 months)

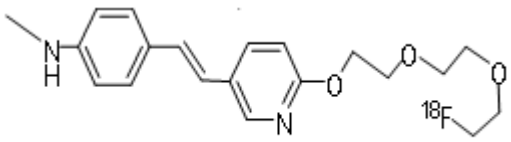


Binding of the Positron Emission Tomography Tracer Pittsburgh Compound-B Reflects the Amount of Amyloid-β in Alzheimer's Disease Brain But Not in Transgenic Mouse Brain

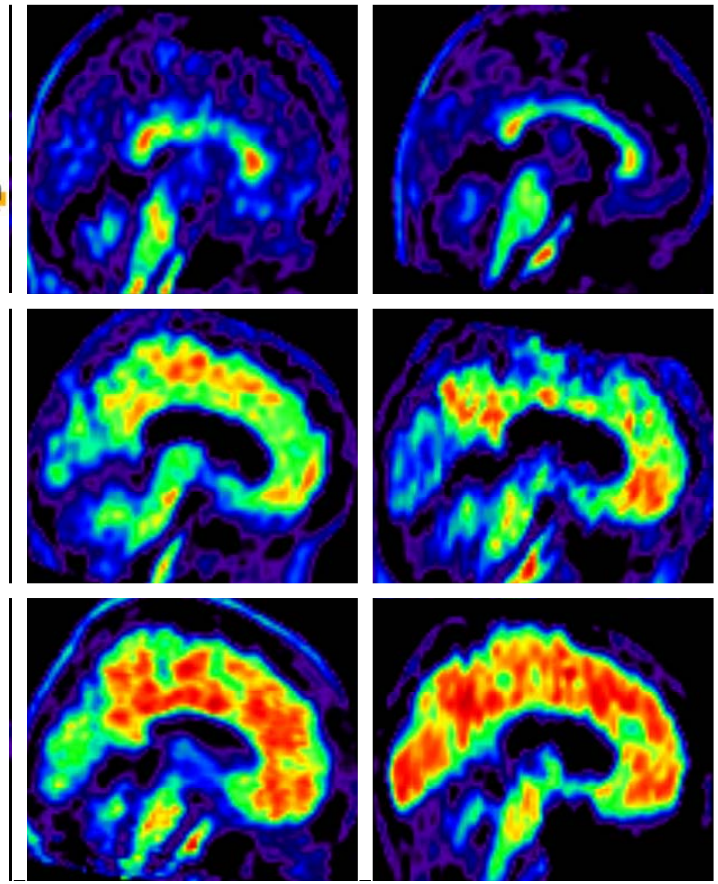
William E. Klunk,[1] Brian J. Lopresti,[2] Milos D. Ikonomovic,[3] Iliya M. Lefterov,[4] Radosveta P. Koldamova,[5] Eric E. Abrahamson,[3] Manik L. Debnath,[1] Daniel P. Holt,[2] Guo-feng Huang,[2] Li Shao,[1] Steven T. DeKosky,[3] Julie C. Price,[2] and Chester A. Mathis[2]
Departments of [1]Psychiatry, [2]Radiology, [3]Neurology, [4]Environmental and Occupational Health, and [5]Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

Klunk, W. E., B. J. Lopresti, et al. (2005).
J Neurosci **25**(46): 10598-606.

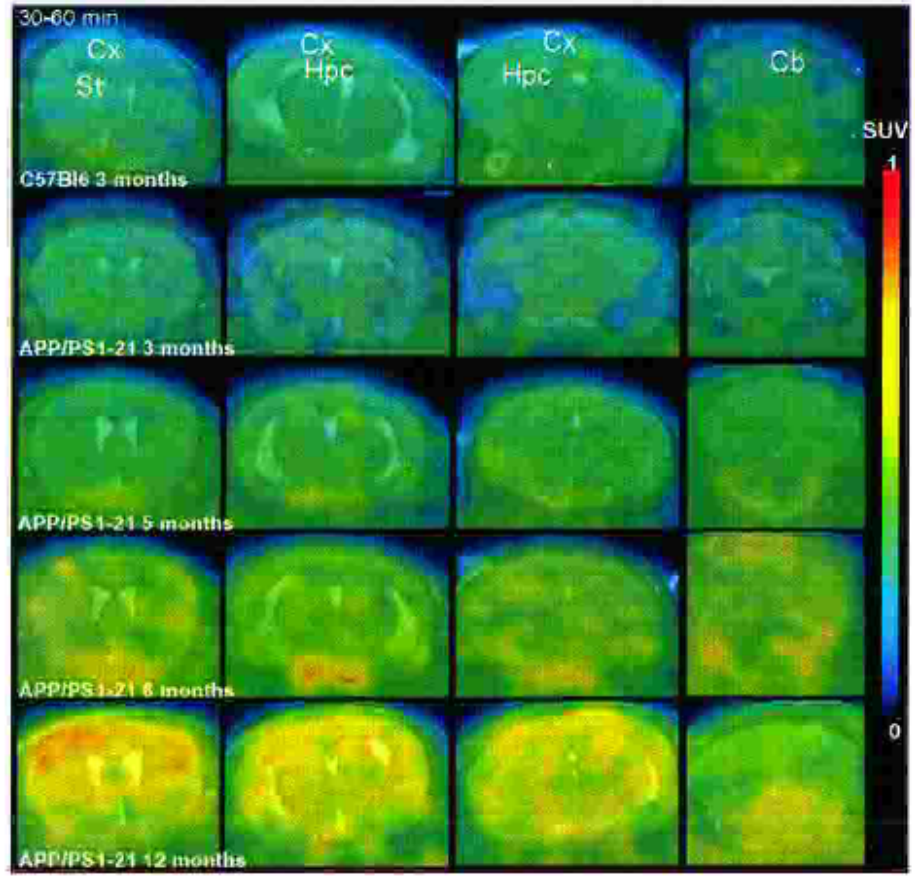
AV45 – a new marker for AD



^{18}F-AV-45



Visualization of amyloid plaques in APP/PS1-21 mice by [^{18}F]-AV-45 microPET



Poisnel & Barre, ICAD, 2011

Conclusion: amyloid detection - PET

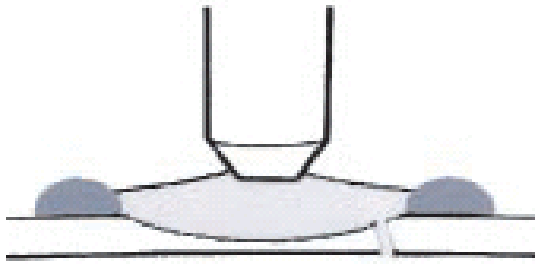
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Amyloid (Aggregated - PET + PIB)	Yes	No	Yes	No
Futur contrast agents (AV45) ?	Yes	Yes ?	Yes	No

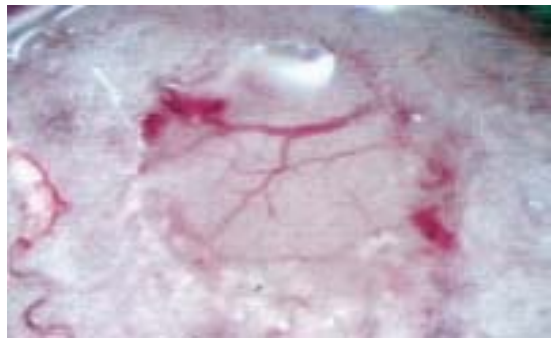
Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
    - Multiphoton microscopy
    - Near Infra red imaging
  - IRM
- Les yeux

Multiphoton microscopy

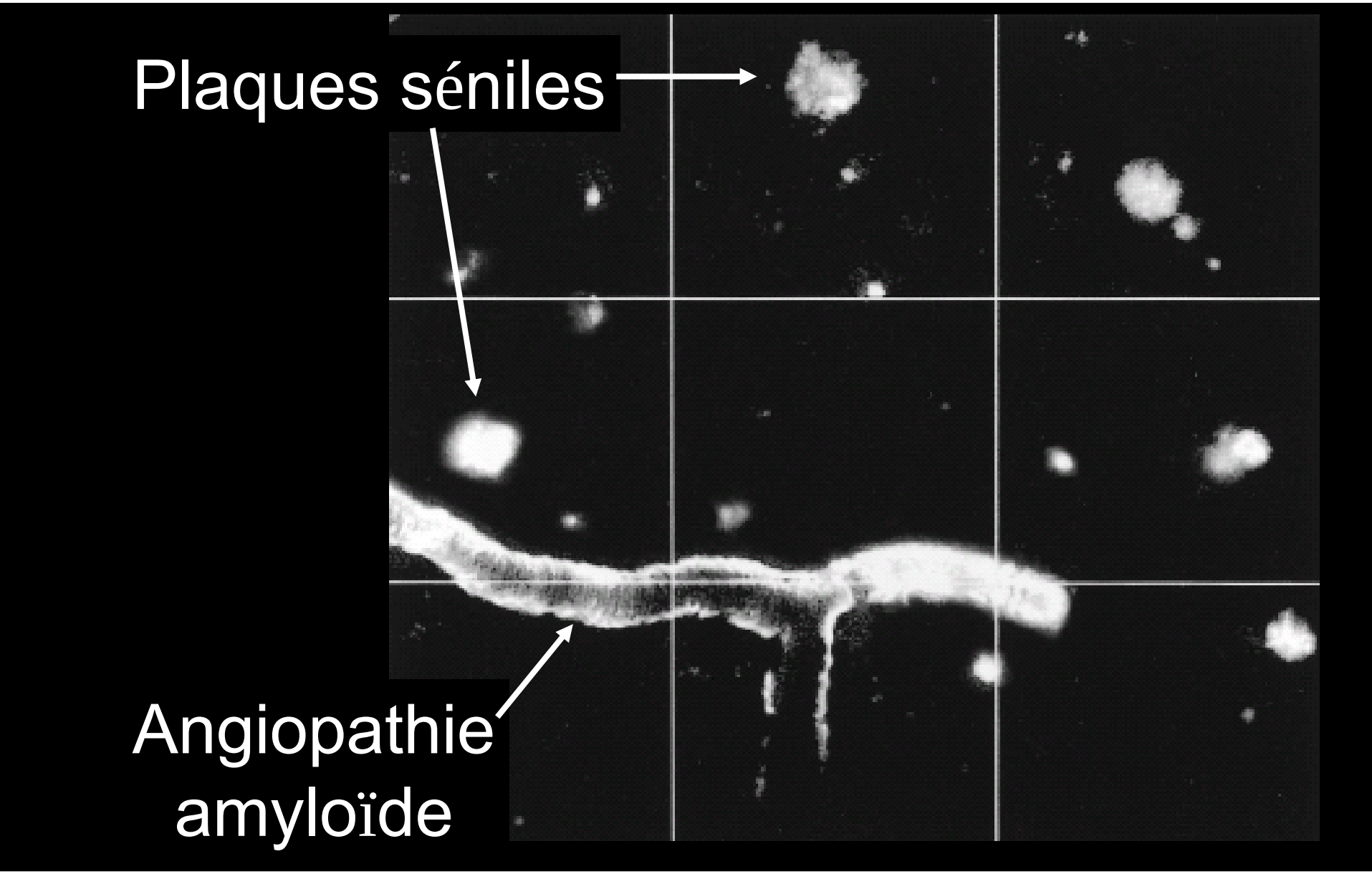
- Fenêtre sur le cerveau





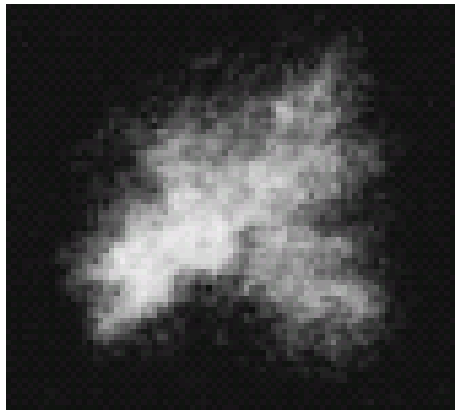
- Marquage par un fluorophore
  - Thioflavine S (par exemple)
- Résolution = 1 µm
- Profondeur = 150 µm

Multiphoton microscopy

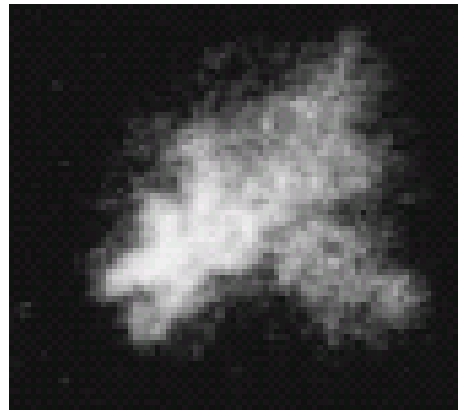


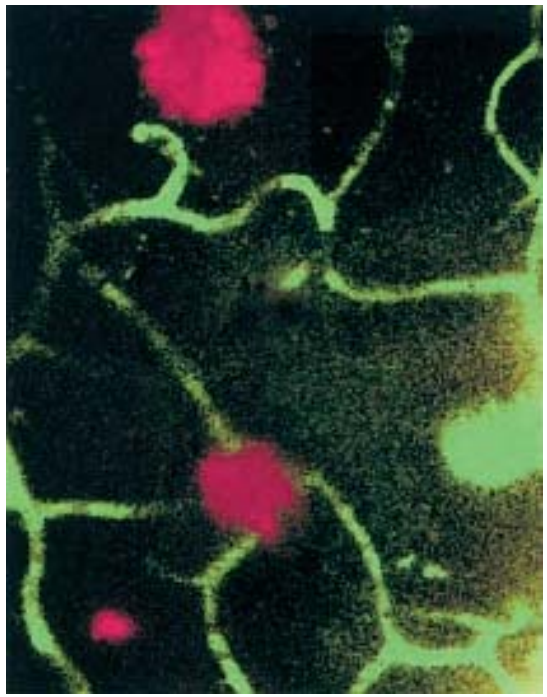
Christie R. H. et al., The Journal of Neuroscience, 21(3), 858-864, 2001

Multiphoton microscopy: Longitudinal follow up of plaque turn over

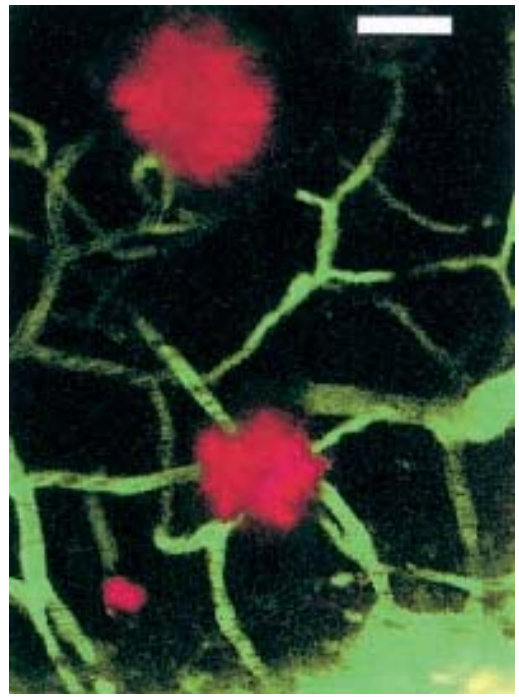


+ 2 jours





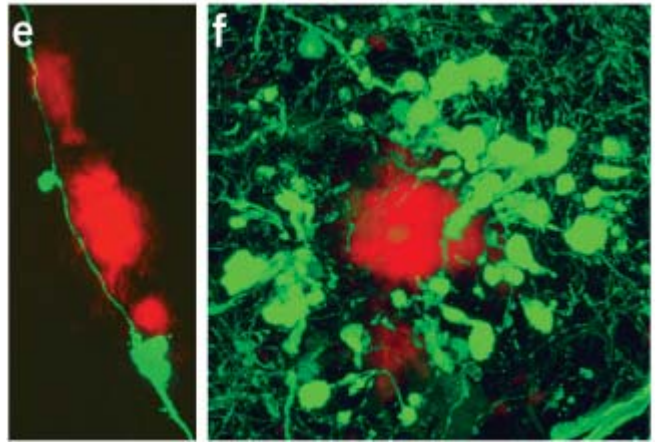
+ 104 jours



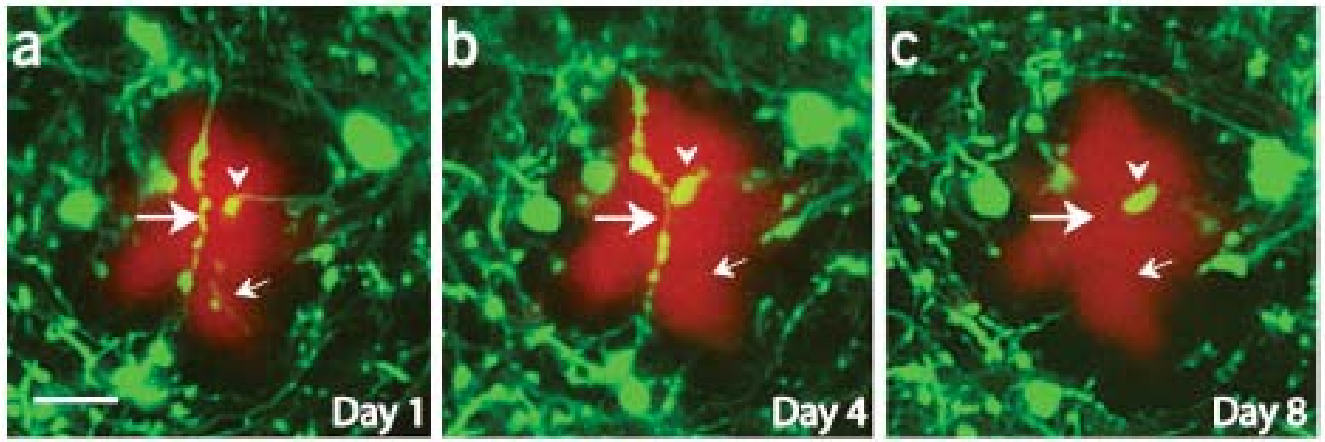
Christie R. H. et al., The Journal of Neuroscience, 21(3), 858-864, 2001

Multiphoton microscopy: Longitudinal follow up of plaque toxicity

- Neuronal varicosities associated to amyloid plaques



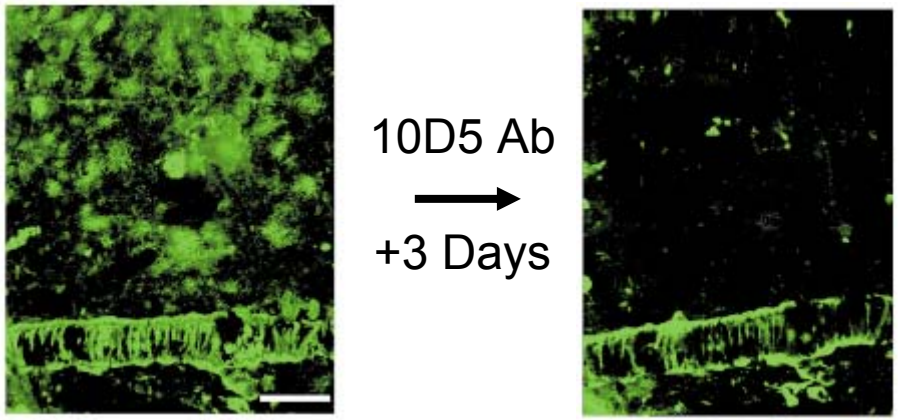
- Neurite breakage close to amyloid plaques



Tsai, J., J. Grutzendler, et al. (2004). Nat Neurosci 7(11): 1181-3.

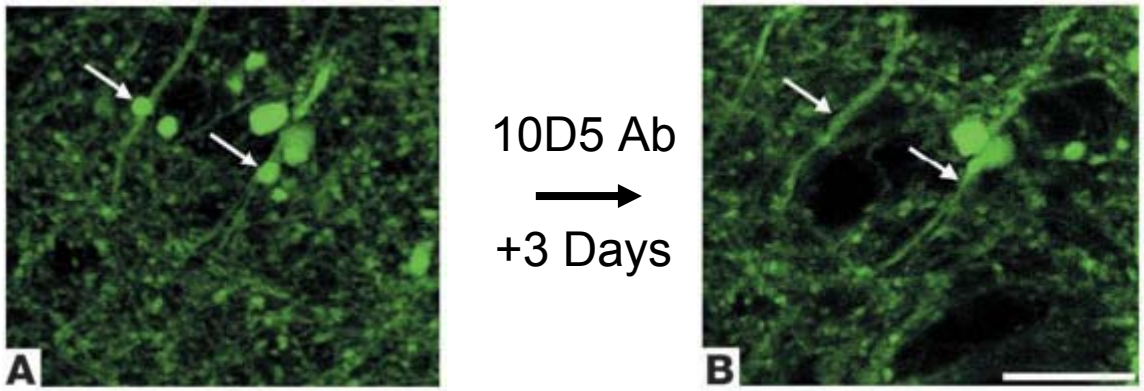
Multiphoton microscopy: Use to evaluate experimental therapies

- Détection of amyloid clearance following immunotherapy



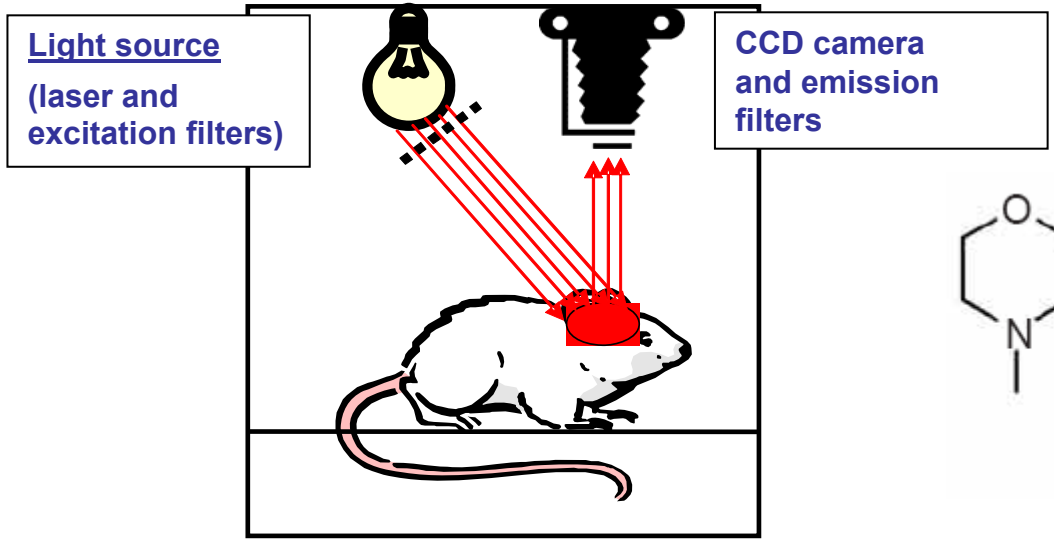
Bacskai, B. J., et al. (2001). Nat Med 7(3): 369-72.

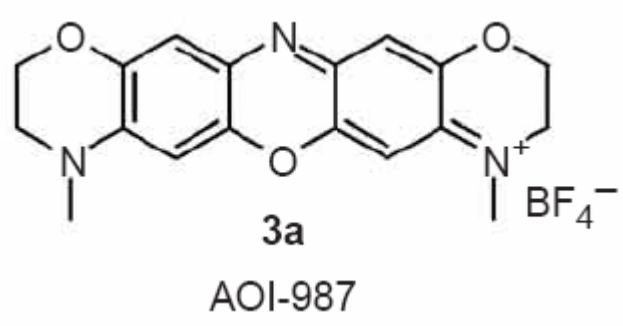
- Détection of effects of treatments on amyloid-associated neuronal modifications



Brendza, R. P., (2005). J Clin Invest **115**(2): 428-33.

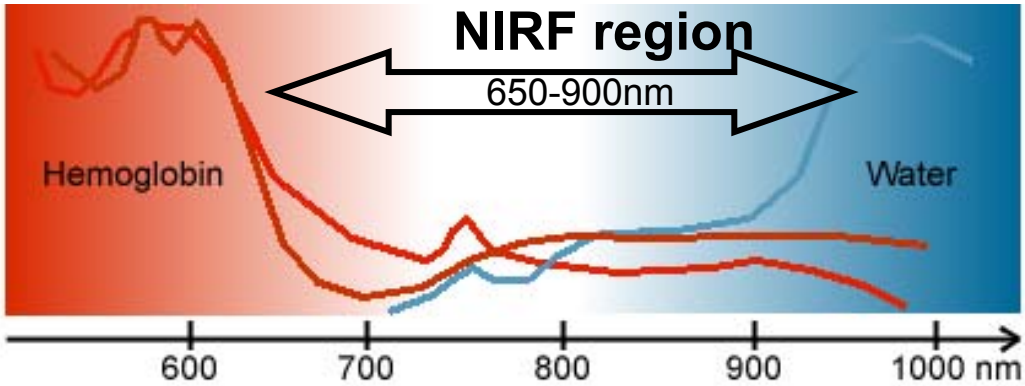
Near Infrared imaging : Longitudinal follow up of plaque toxicity





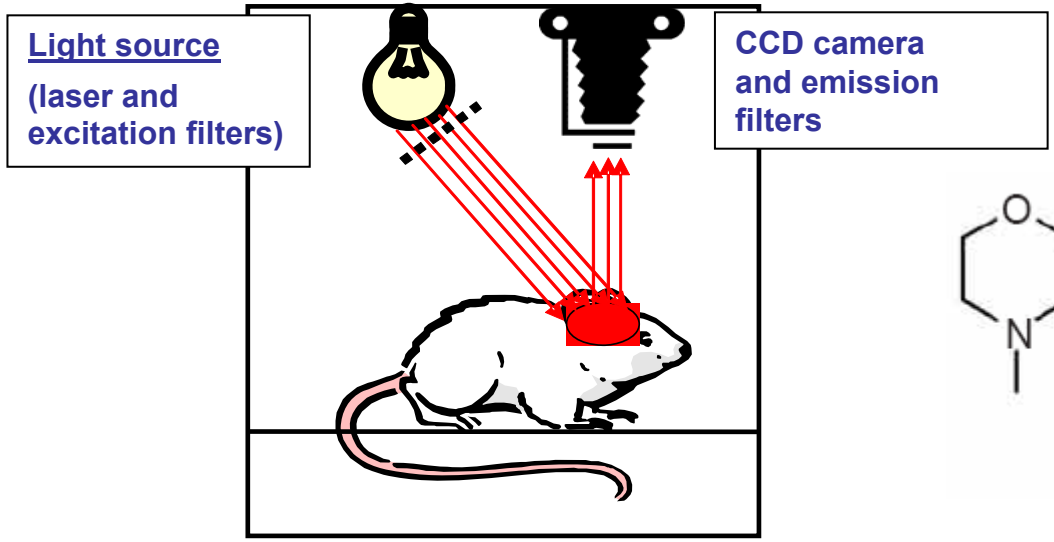
3a

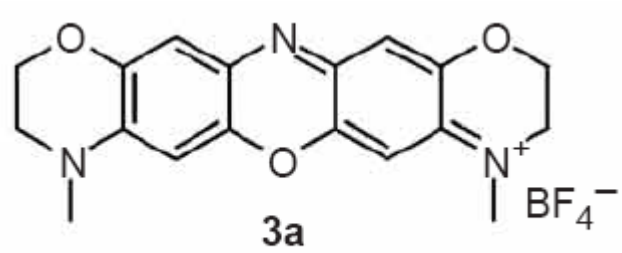
AOI-987



Hintersteiner, M., et al. (Novartis)(2005). " Nat Biotechnol **23**(5): 577-83.

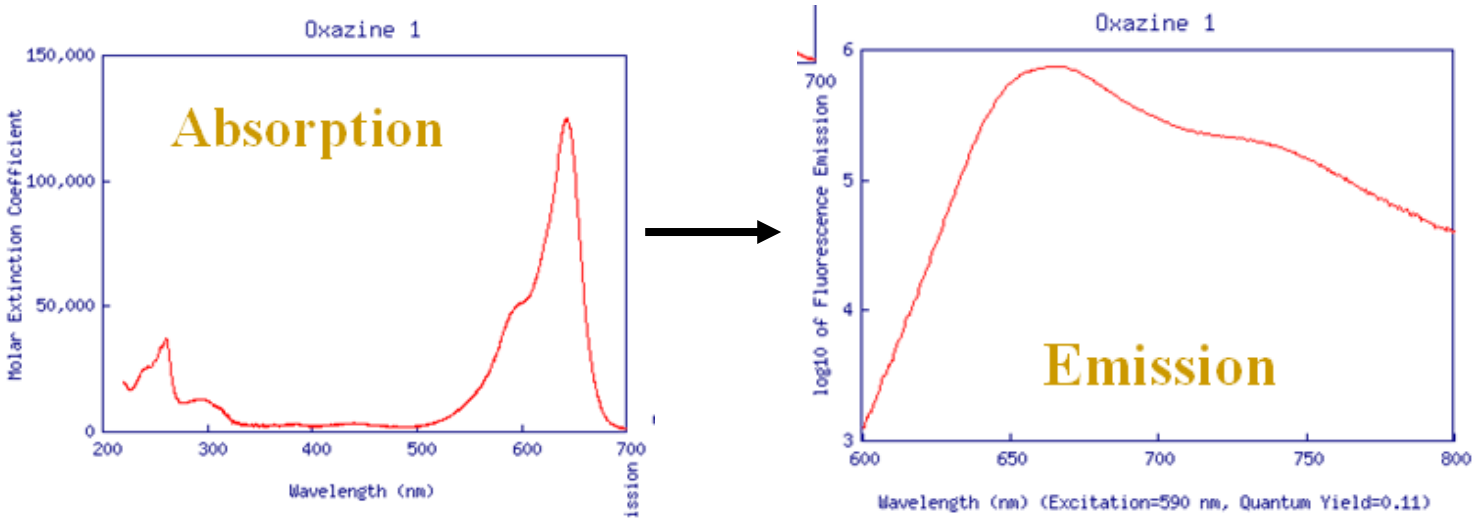
Near Infrared imaging : Longitudinal follow up of plaque toxicity





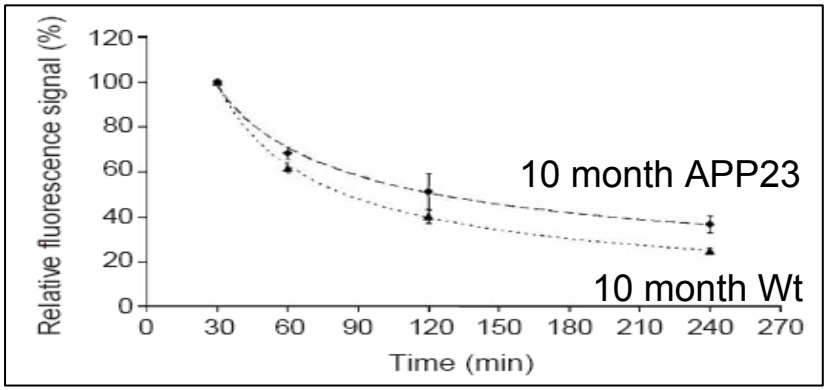
3a

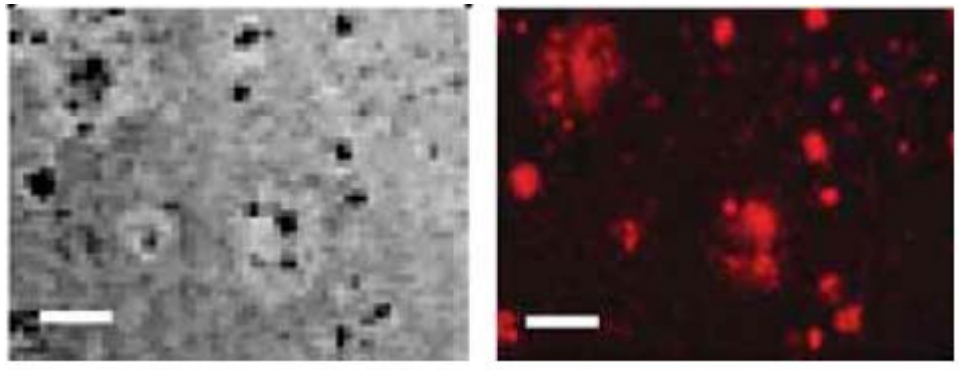
AOI-987



Hintersteiner, M., A. Enz, et al. (2005). " Nat Biotechnol **23**(5): 577-83.

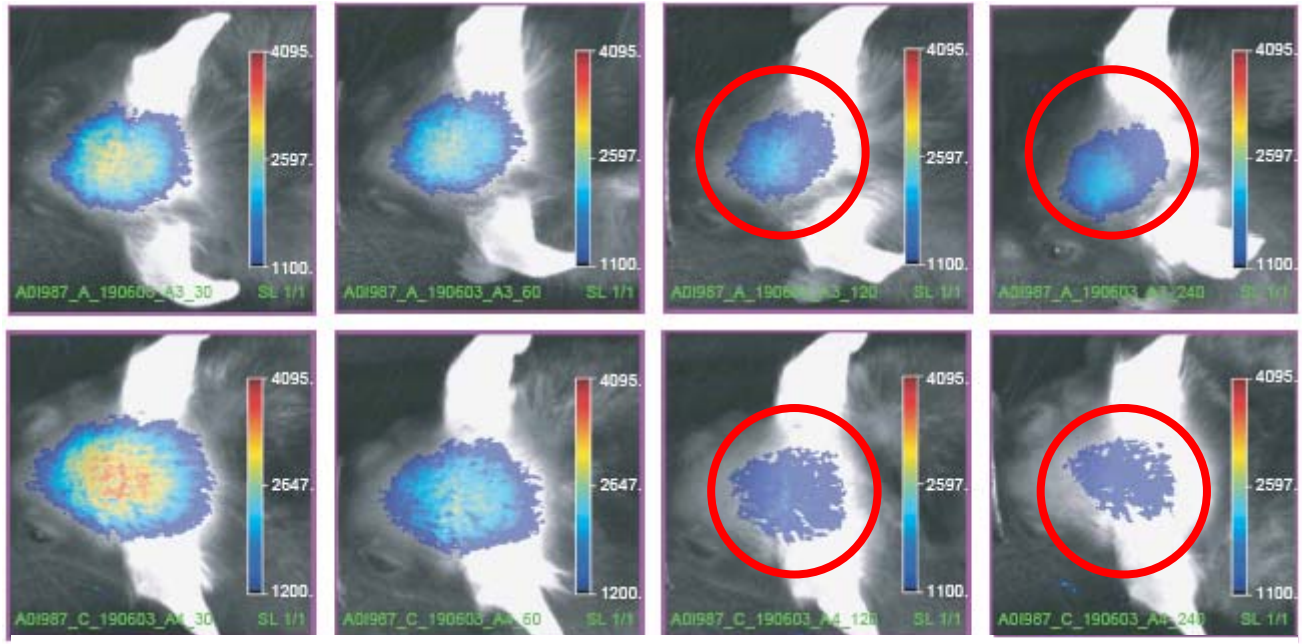
Near Infrared imaging : Longitudinal follow up of plaque toxicity





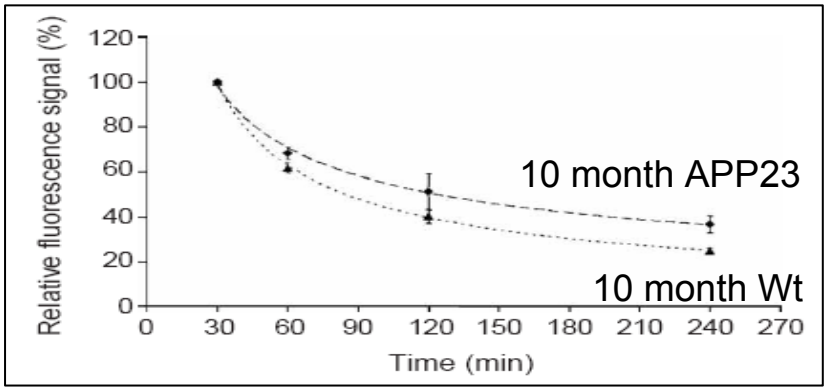
APP23 (17 months)

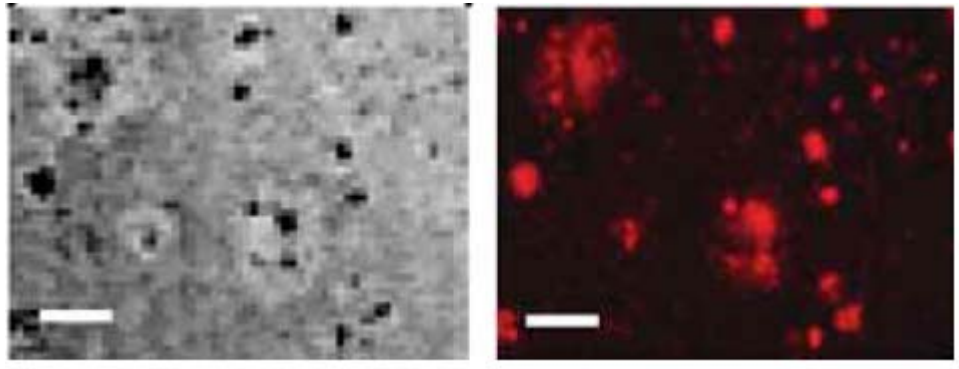
Wt=Control (17 months)

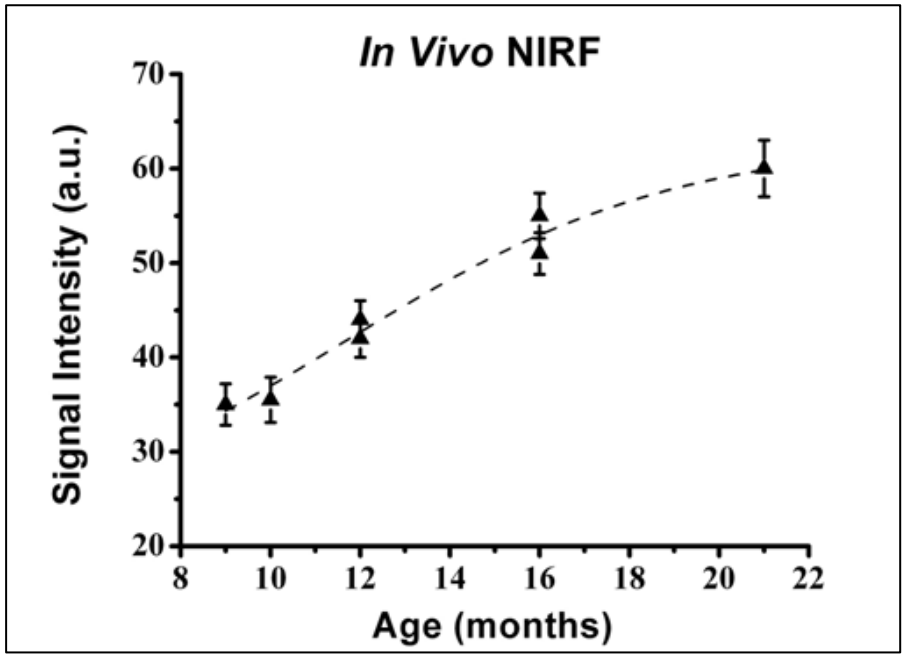


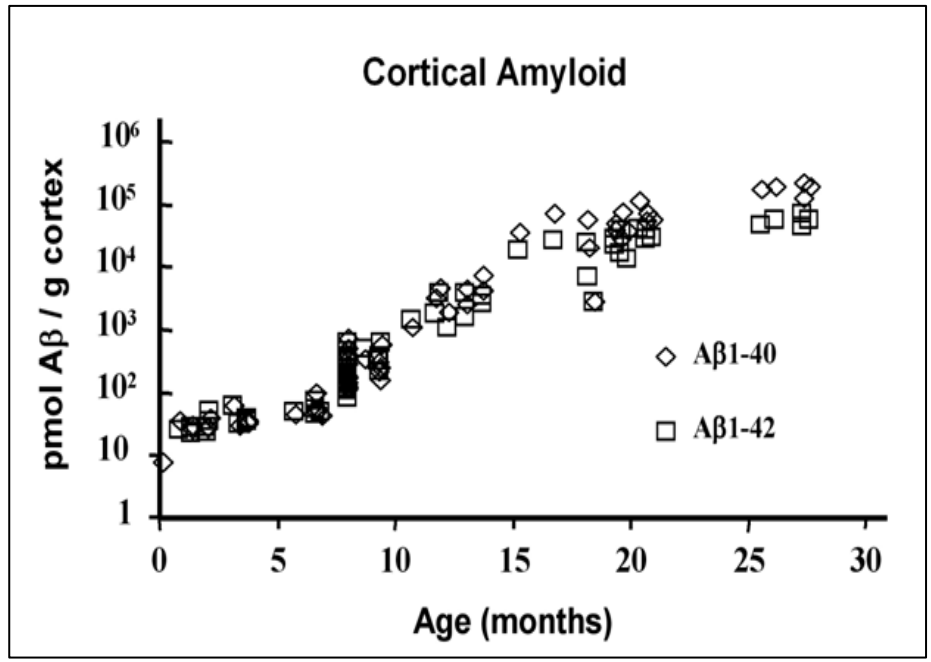
Hintersteiner, M., A. Enz, et al. (2005). " Nat Biotechnol **23**(5): 577-83.

Near Infrared imaging : Longitudinal follow up of plaque toxicity









Hintersteiner, M., et al. (Novartis) (2005). " Nat Biotechnol **23**(5): 577-83.

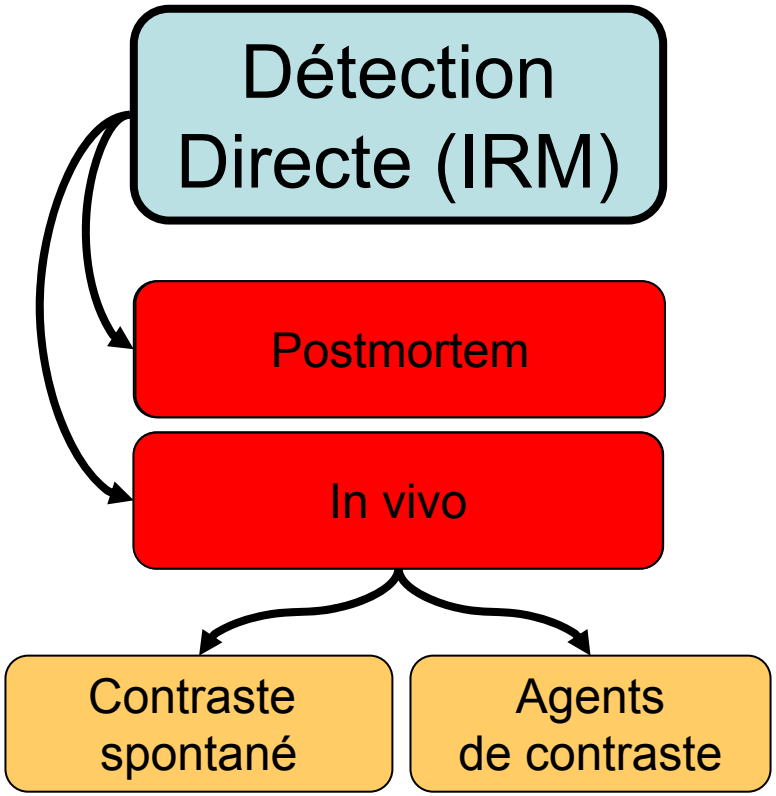
Conclusion: amyloid detection – Multiphoton and NIR

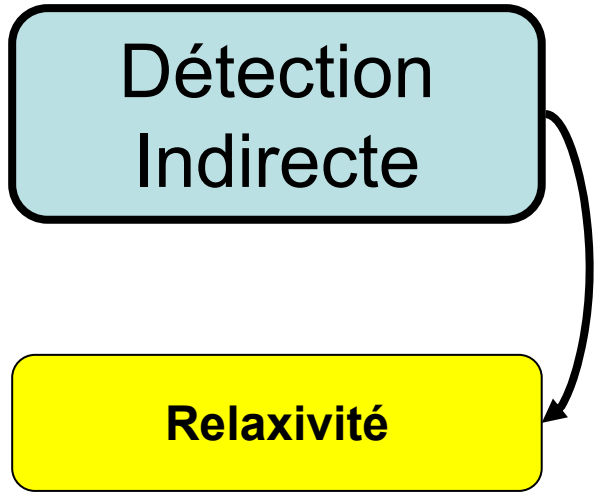
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Multiphoton	Yes	Yes	No	No
NIR	Yes	Yes	No	No

Où chercher l'Amyloïde béta

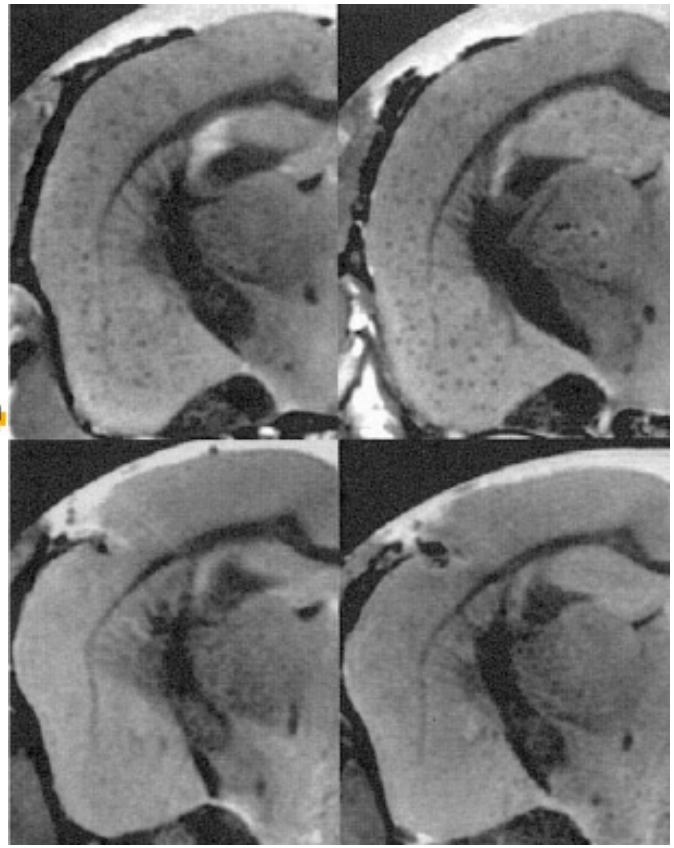
- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

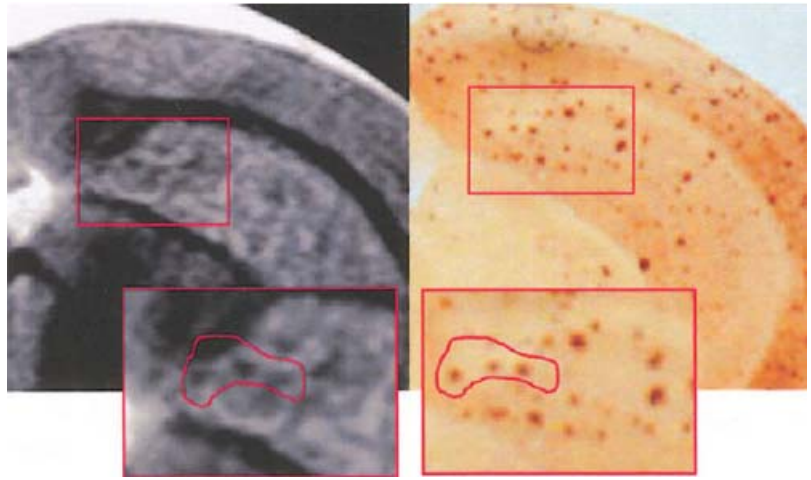
Imagerie des plaques en IRM





Post-mortem detection of amyloid plaques

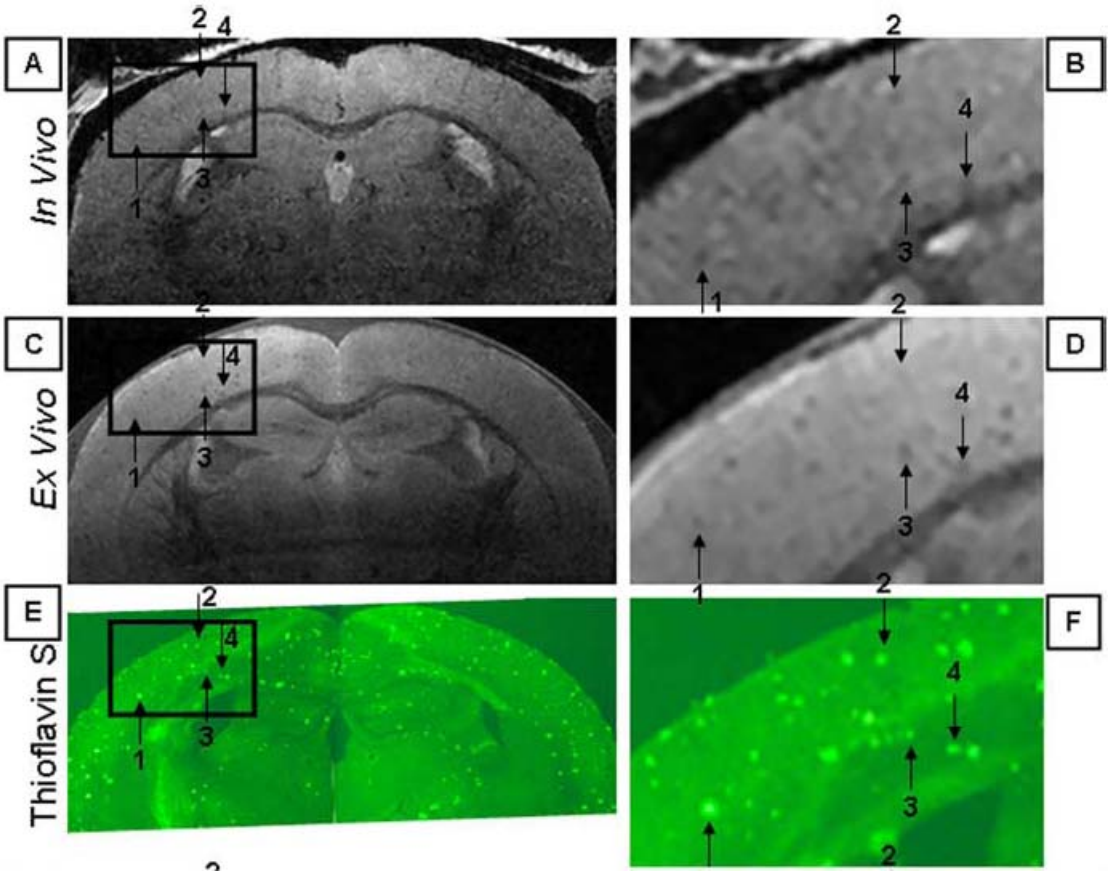




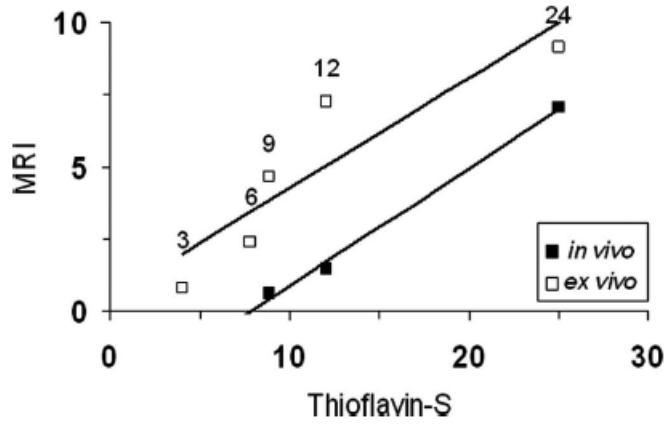
- Tg2576 (APP)/PS1
- 17-19 months
- T2-w images @ 7 Tesla
- 2 hours

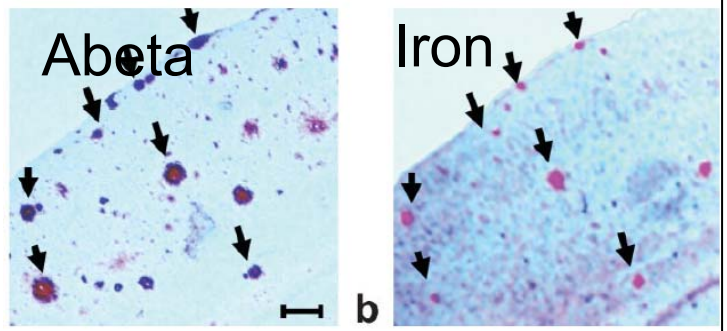
Lee, S. P., M. F. Falangola, et al. (2004).
Magnetic Resonance in Medicine **52**: 538-544.

In-vivo plaques imaging without contrast agent



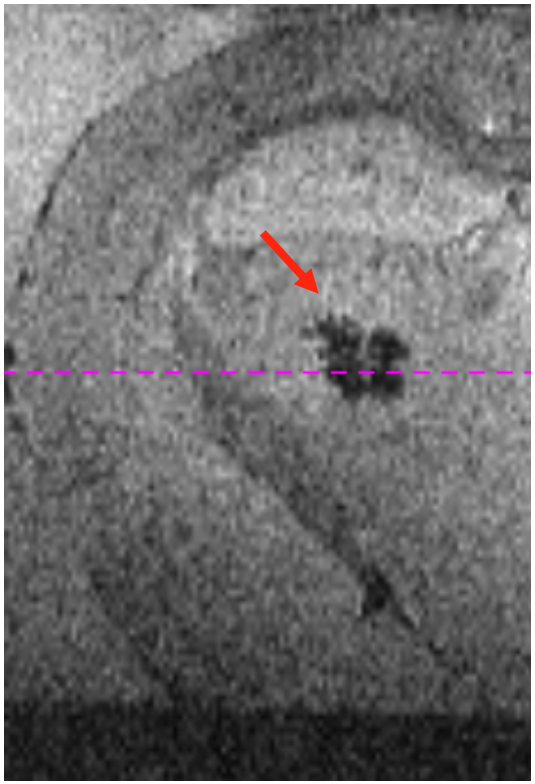
Jack, J Neurosc, 2005



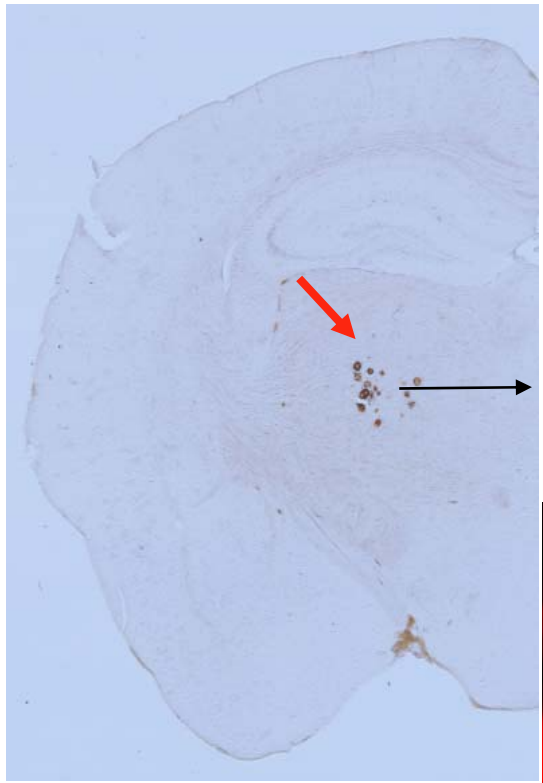


Braakman, JMRI, 2006

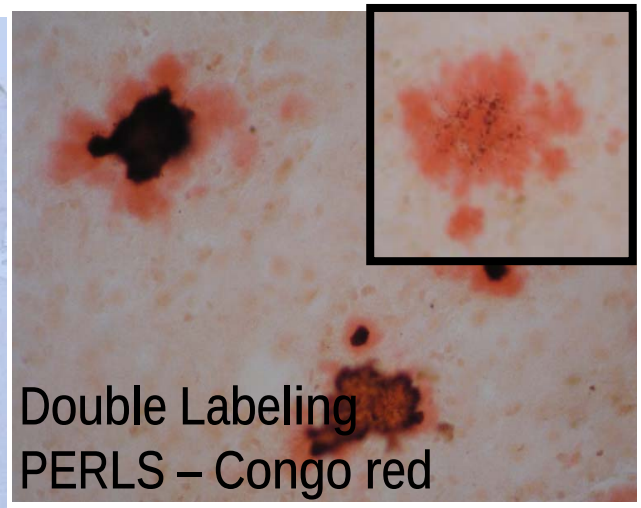
Detection of thalamic plaques by MRI

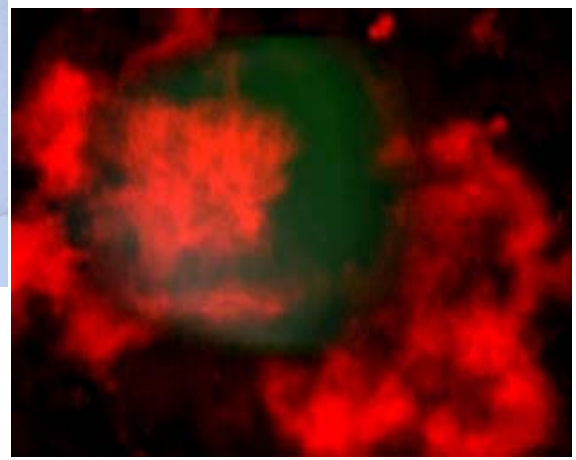


APP/PS1
MRI



Iron staining
(PERLS DAB)
Same mouse

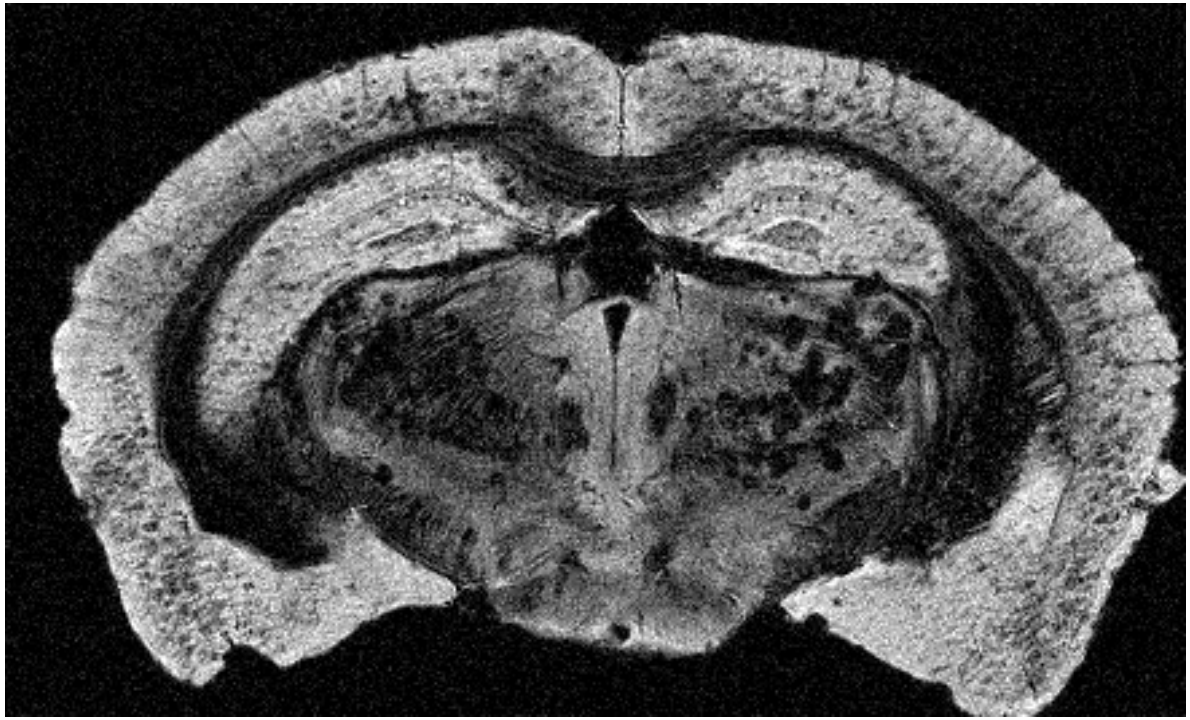




→ In APP/PS1 mice, thalamic spots are linked to the presence of iron/calcium agregates in the senile plaques

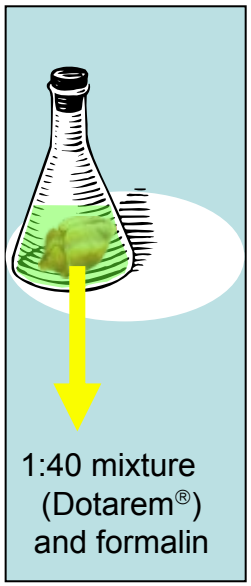
Dhenain et al. Neurobiol Aging. 2009 January.

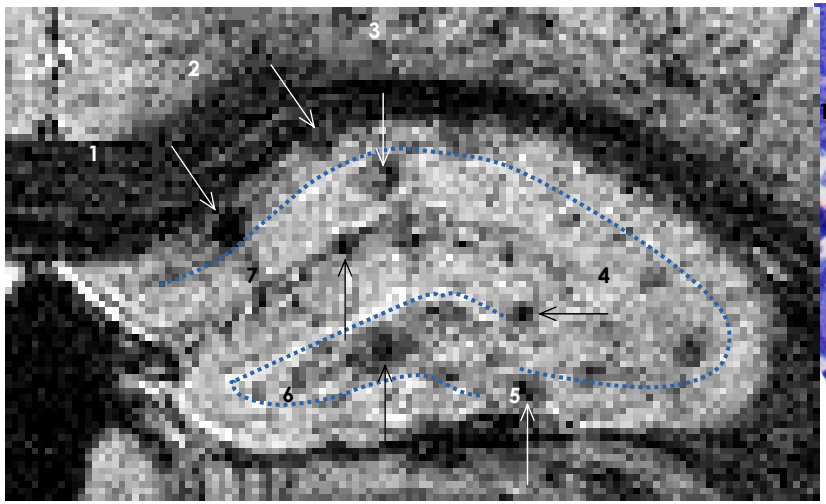
Optimisation of plaque imaging thanks to contrast agents

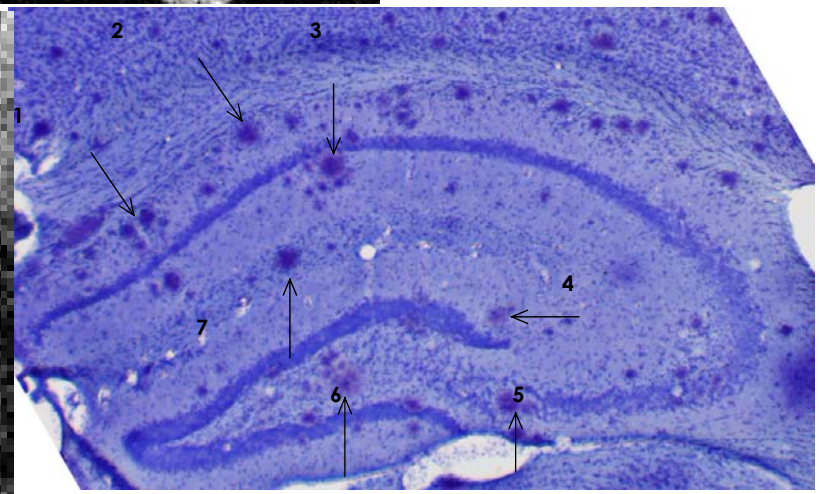


7T Clinical Scanner
Siemens
23.4 x 23.4 x 90 μm^3
Tacq = 13 hours 50 min
Sequence: GRE

Alexandra Petiet
Anne Bertrand
Chris Wiggins

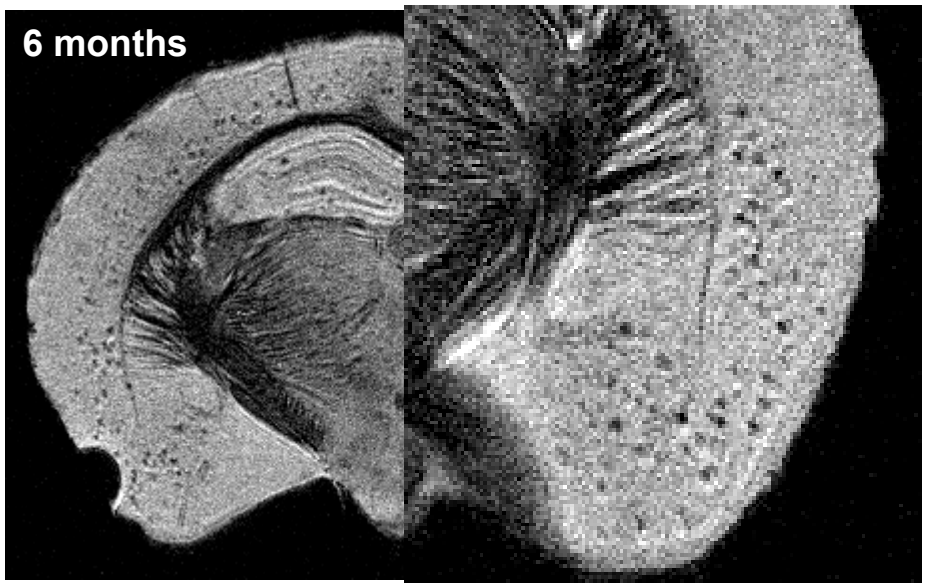


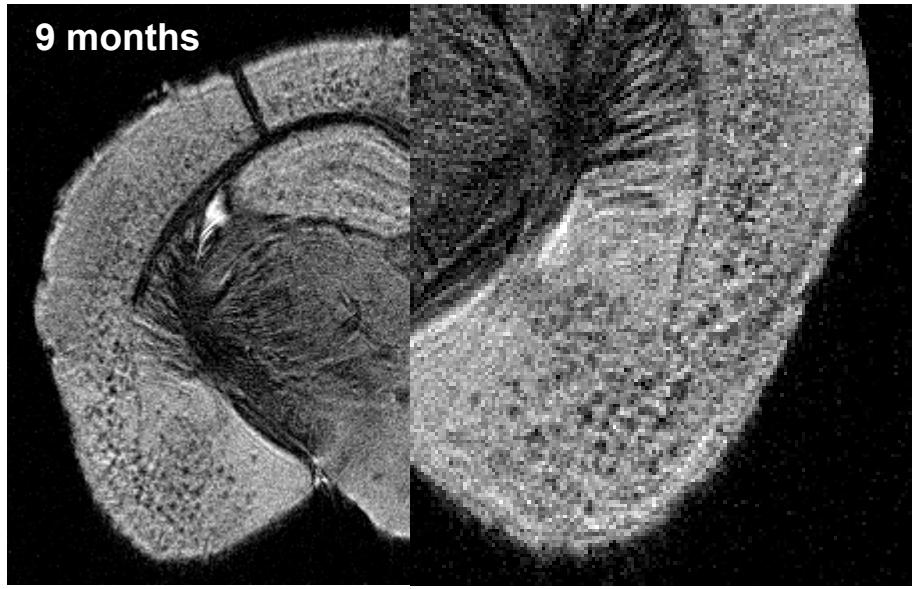


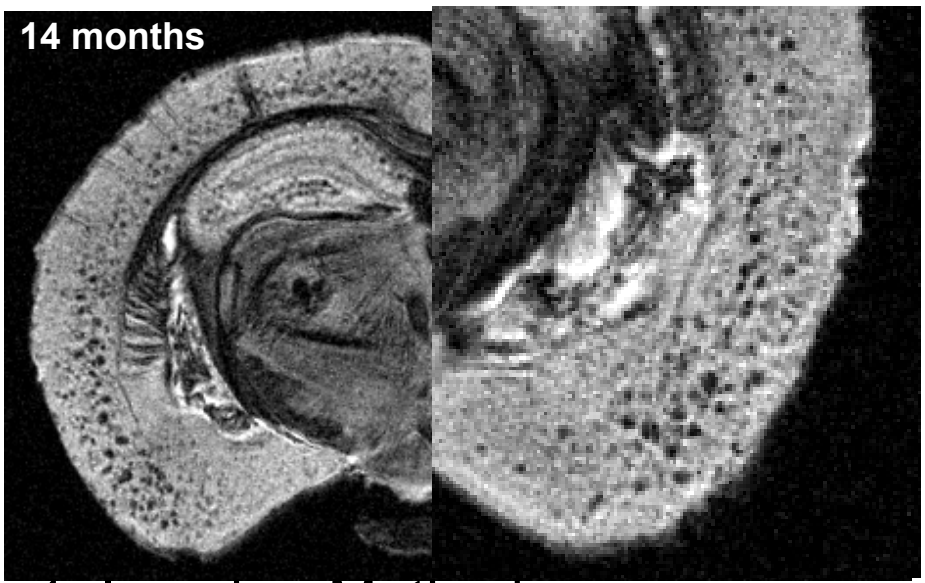


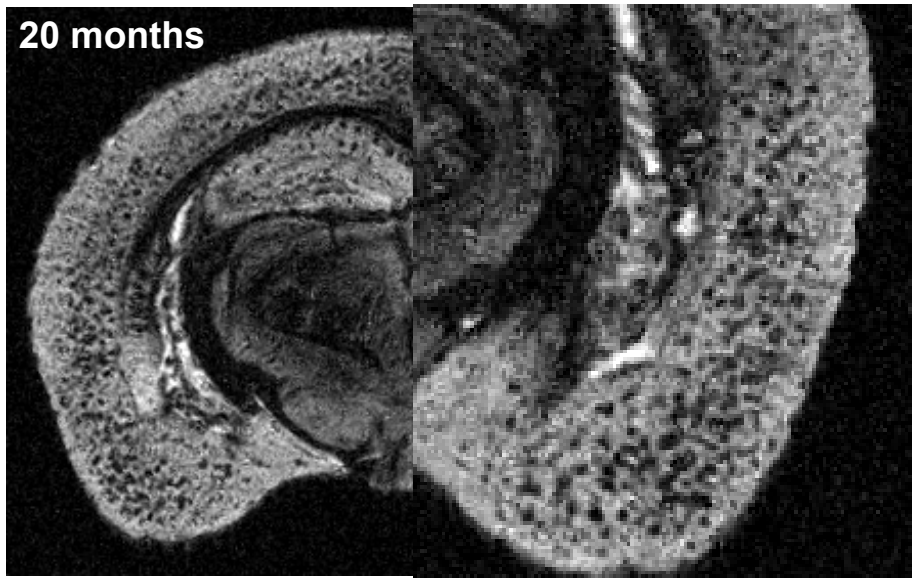
Dhenain M, et al. MRM. 55. 687-693. 2006.

Gd-staining: Follow-up of amyloid plaques by MRI









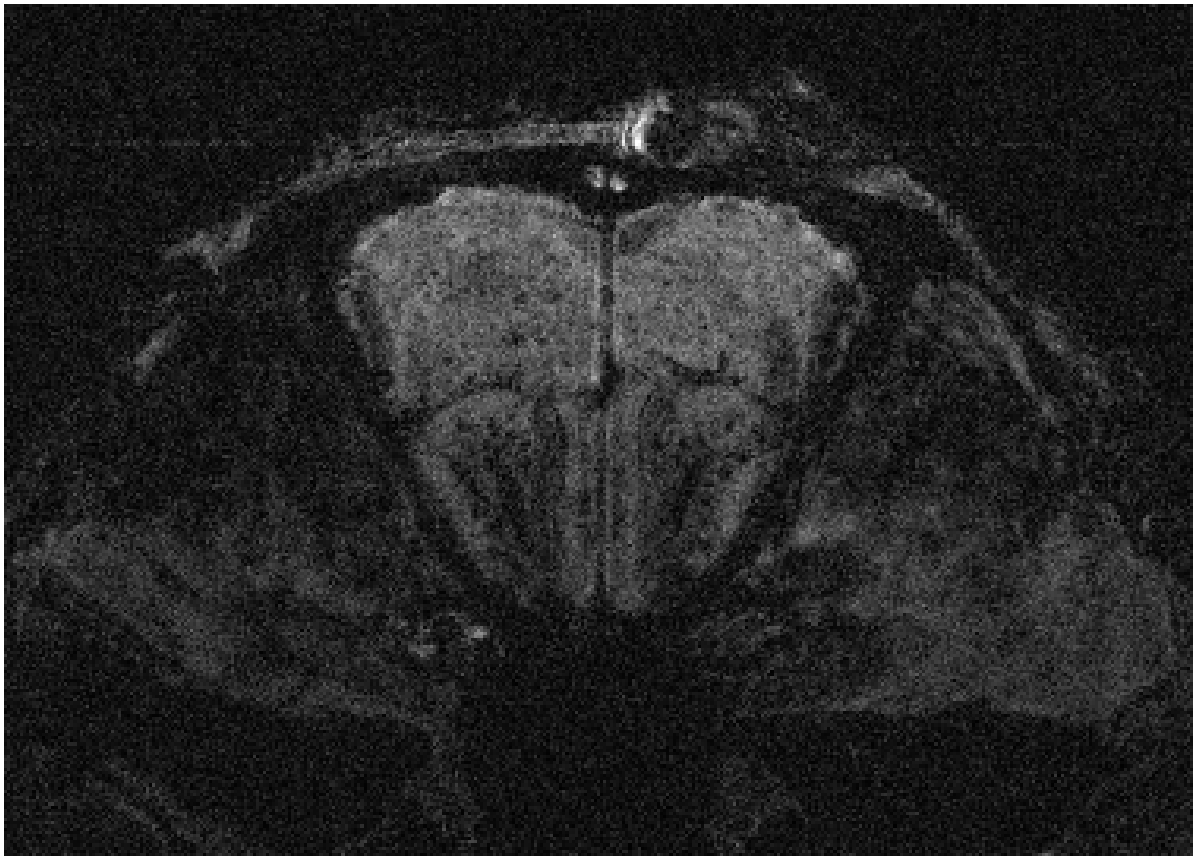
1. Imaging-Methodo

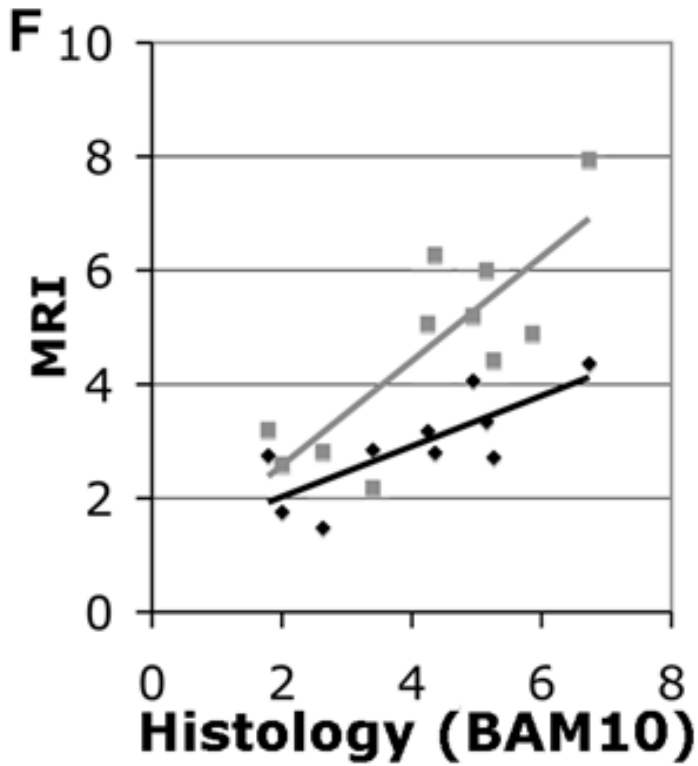
Resolution: 23 x 23 x 90 µm^3 - **Acquisition time:** 13h49min

A. Petiet (Transal), C Wiggins

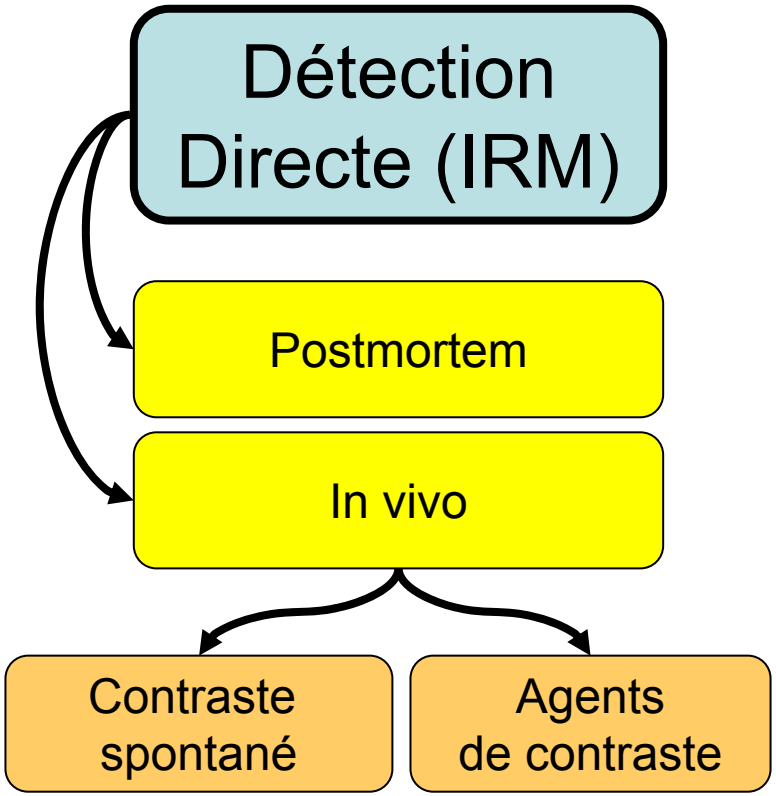
Etat de l'art

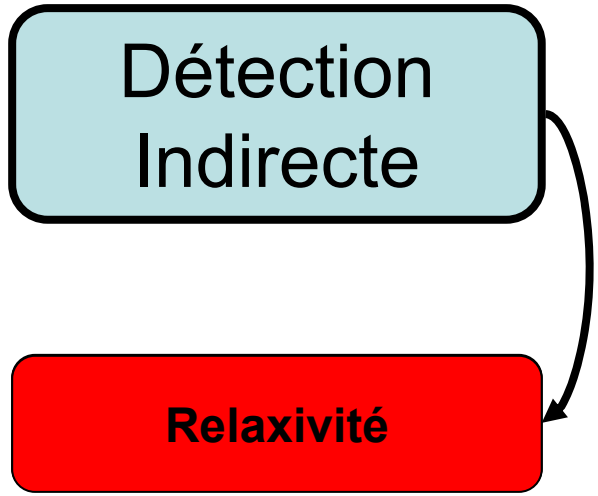
Détection - In vivo / 3D (Gd-staining (GdSt))



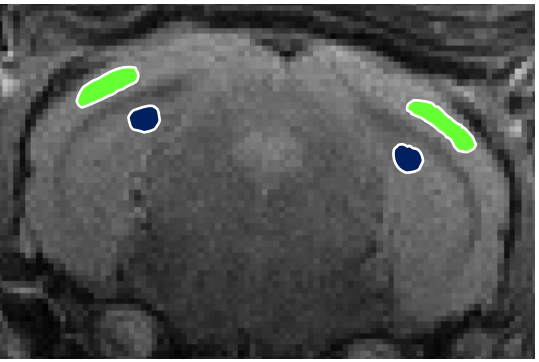


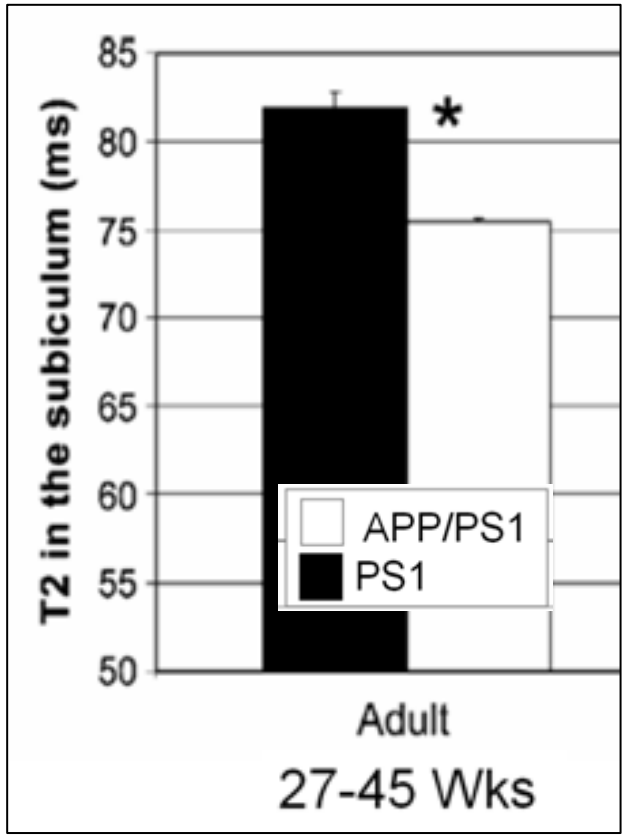
Imagerie des plaques en IRM

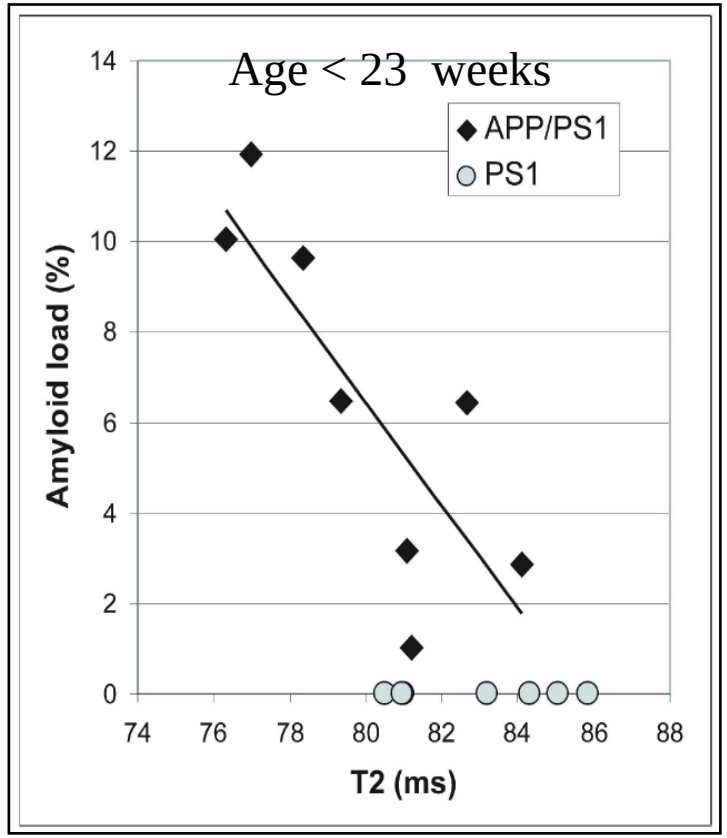




T2 decrease in the subiculum







- Caused by iron accumulation within the plaques

El Tannir El Tayara N. Neurobiol Dis. 2006 Apr;22(1):199-208.

- Caused by amyloid plaques per se

El Tannir El Tayara N. Magn Reson Med. 2007 Jul;58(1):179-84.

Conclusion: amyloid detection - MRI

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Amyloid (PET + contrast agent)	Yes	No	Yes	No
Amyloid (MRI without contrast agent)	Yes	Yes	No	No
Amyloid (MRI + contrast agent)	Yes	No	No	No
Amyloid load (MRI + Relaxometry)	Yes	No	No	No

Dhenain, MR Insights, 2008 (http://www.la-press.com/)

Où chercher l'Amyloïde béta

- Liquides périphériques
  - LCR
  - Sang
- Le cerveau
  - PET
  - Imagerie optique
  - IRM
- Les yeux

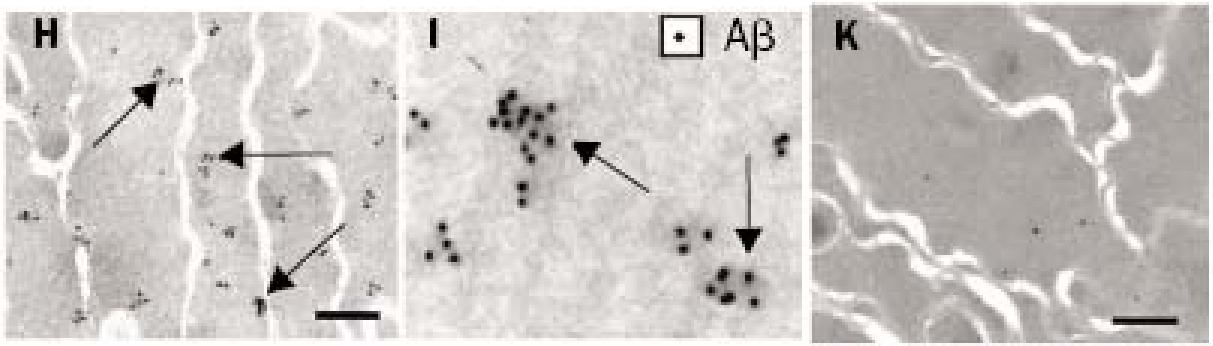
Evaluation of amyloid in the eyes

FIGURE 1. The screening system developed by Neuroptix combines quasi-elastic light scanning and fluorescent ligand scanning on a single platform.

Evaluation of amyloid in the eyes

Anti-Aβ immunogold electron photomicrograph of the lens

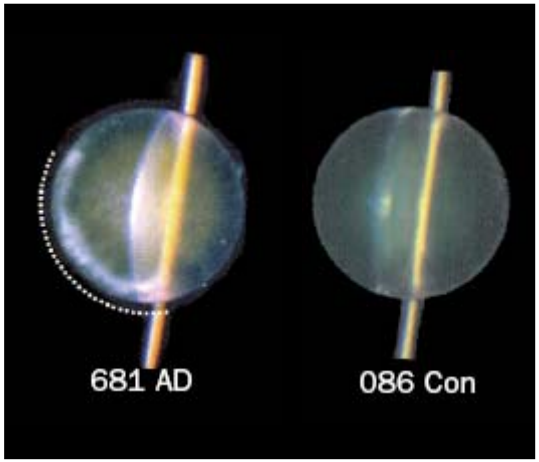
← Alzheimer →← Control →



Goldstein, L. E., et al. (2003)." Lancet **361**(9365): 1258-65.

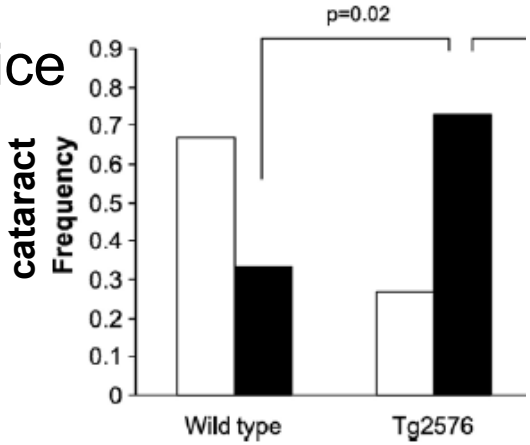
→ AD related cataract in humans and animals

Human



Goldstein, L. E

Tg mice



Melov, 2005

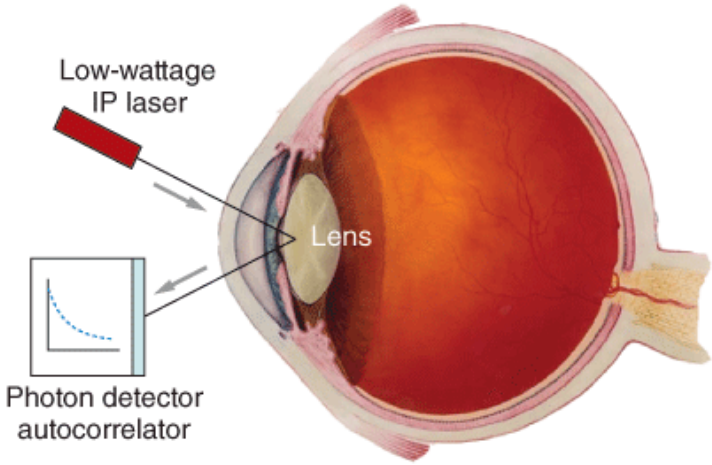
Infrared quasi-elastic light scattering (QLS) technology + Fluorescent Ligand Scanning (FLS)

QLS technology

- Low-power infrared laser light into the eye
- Measure of the backscattered light.

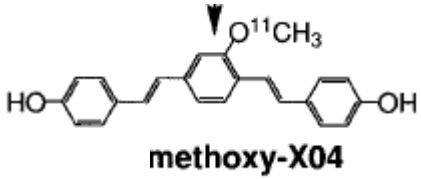
→ Index of the amyloid pathology in transgenic animals

Moncaster, J. A., (2008). Alzheimer's & Dementia -The journal of the Alzheimer's Association -**4**(4-Suppl2): T330.

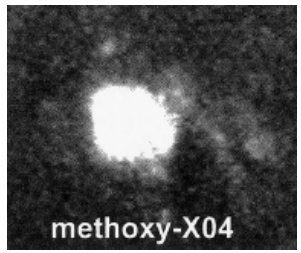


FLS technology = Use of a specific contrast agent

- QLS technology can be associated to the use of fluorescent ligands (ex. Methoxy-X04) that improve its ability to detect the amyloid load (Moncaster et al 2008).



methoxy-X04



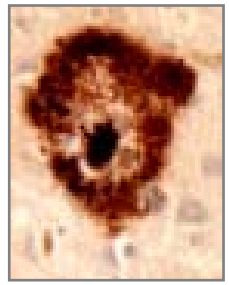
Neuroptix Corporation (European Patent 1 913 866 A1).
$1 million milestone payment in collaboration with merck & Co., inc., for early detection and monitoring of Alzheimer's disease process

Conclusion amyloid plaque imaging

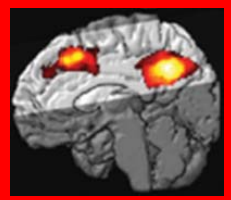
Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
QLS + FLS	Yes ?	Yes ?	Yes	No

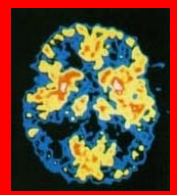
Maladie d'Alzheimer : Quels biomarqueurs ?

Dépôts Amyloïdes

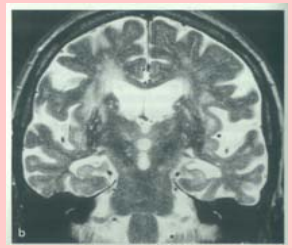


DNF

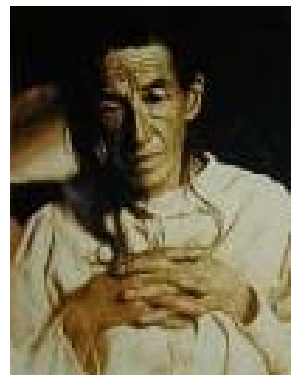




Altérations fonctionnelles



Atrophie



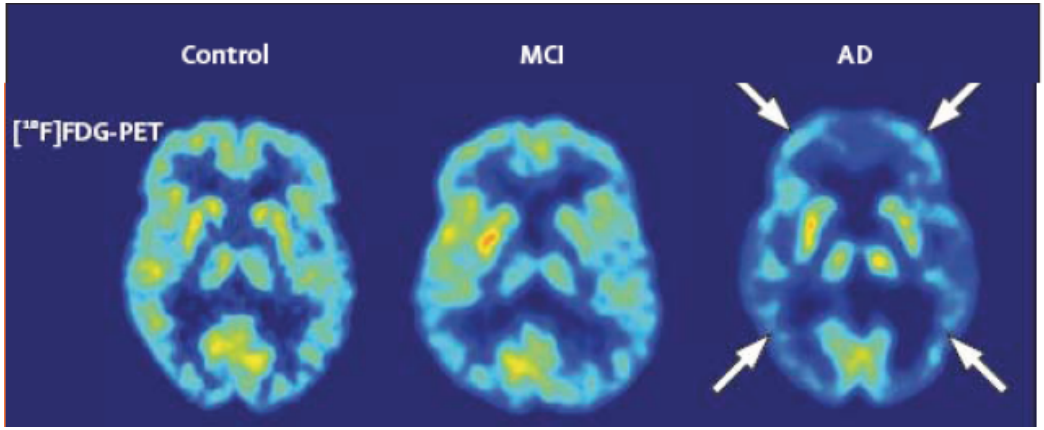
Altérations fonctionnelles associées à la MA

- Métabolisme cérébral
- Perfusion cérébrale
- Transport neuronal

Altérations fonctionnelles associées à la MA

- Métabolisme cérébral
- Perfusion cérébrale
- Transport neuronal

Imagerie du métabolisme cérébral

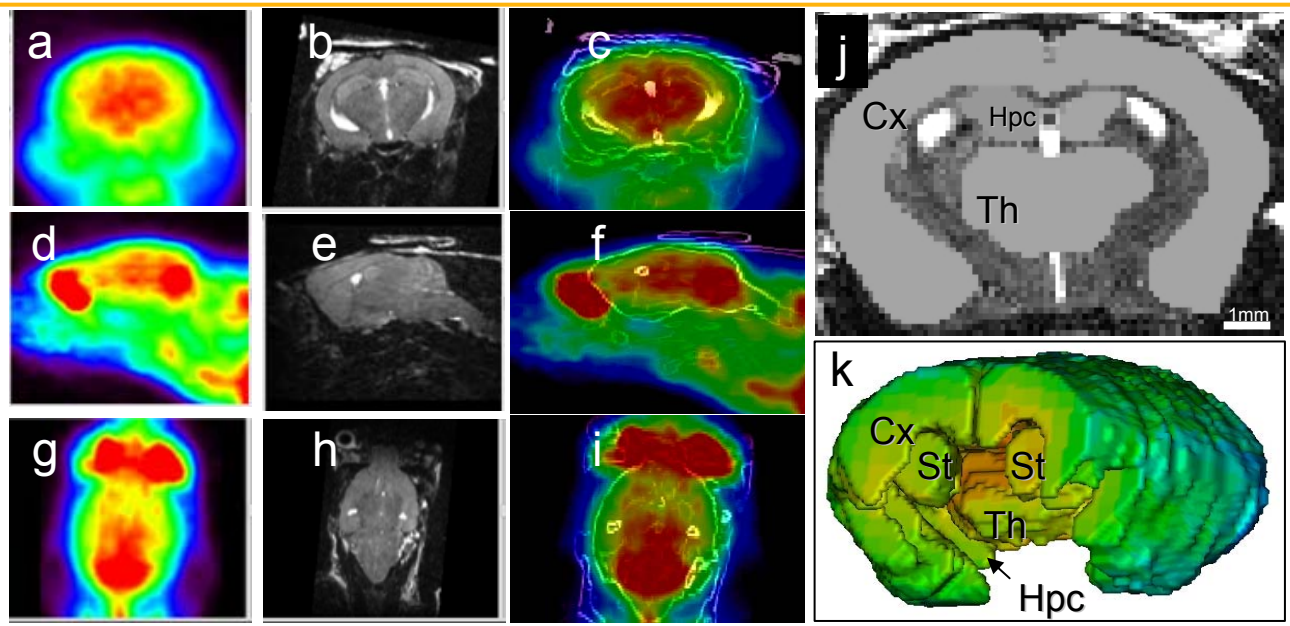


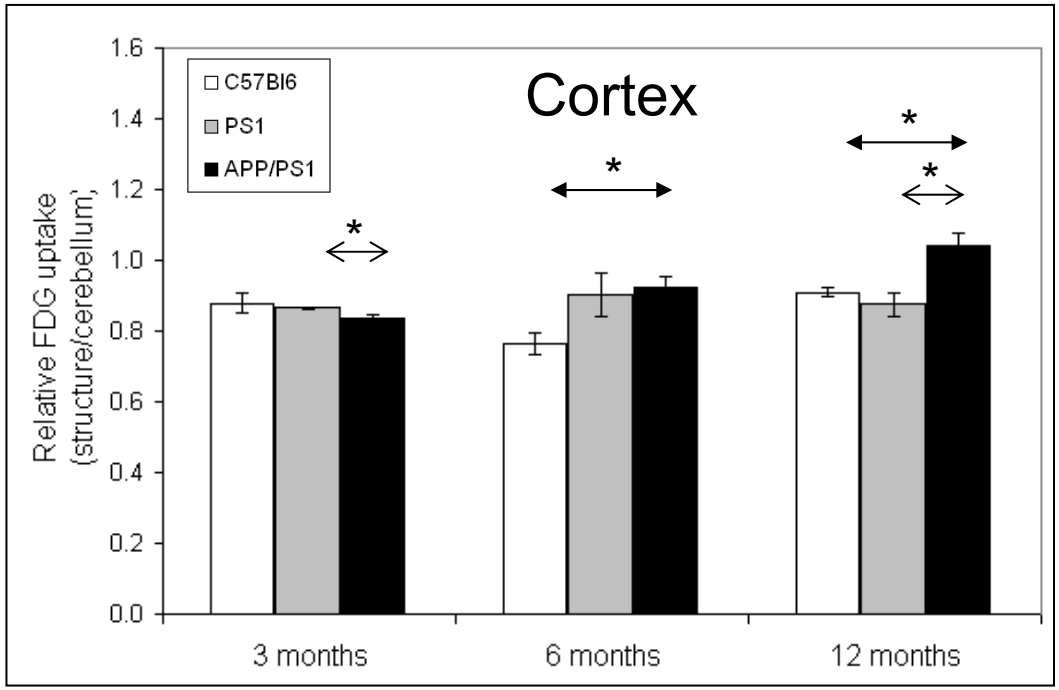
Images [^{18}F]-FDG-TEP de cerveaux présentant des altérations cognitives.
Kepe et al., 2006

µPET Focus 220

Amyloid is associated to an increased glucose uptake in Tg mice

FDG-PET study

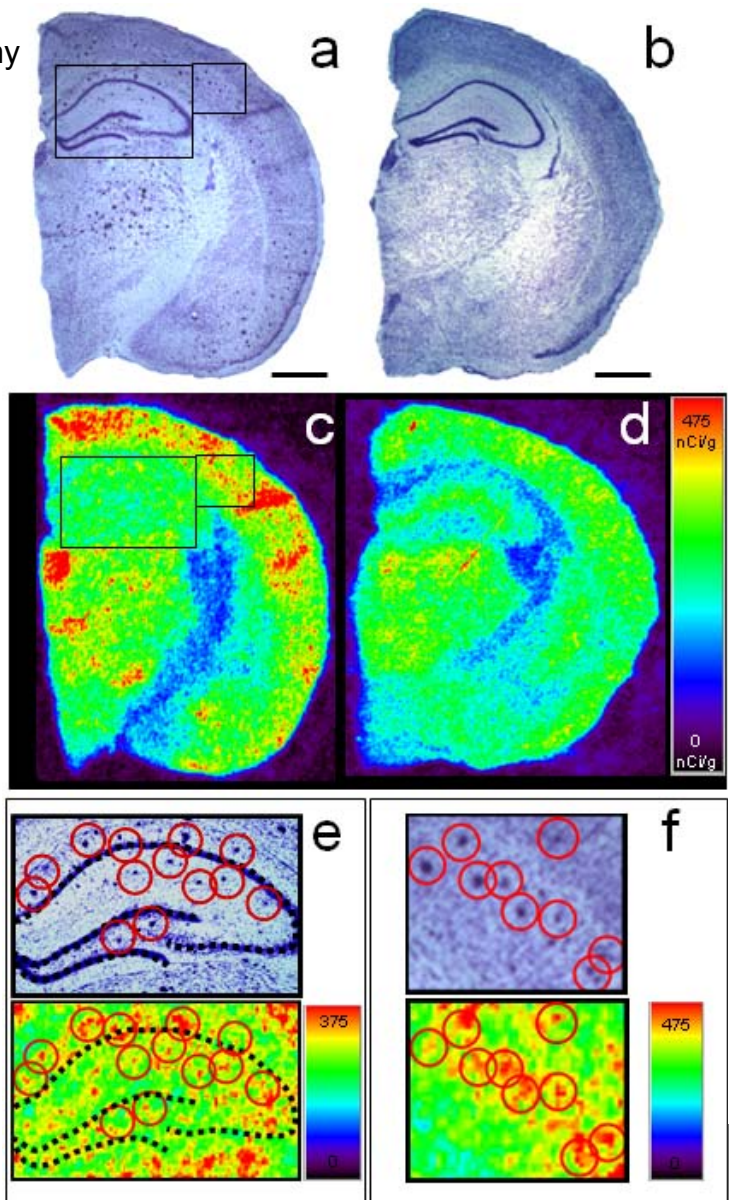


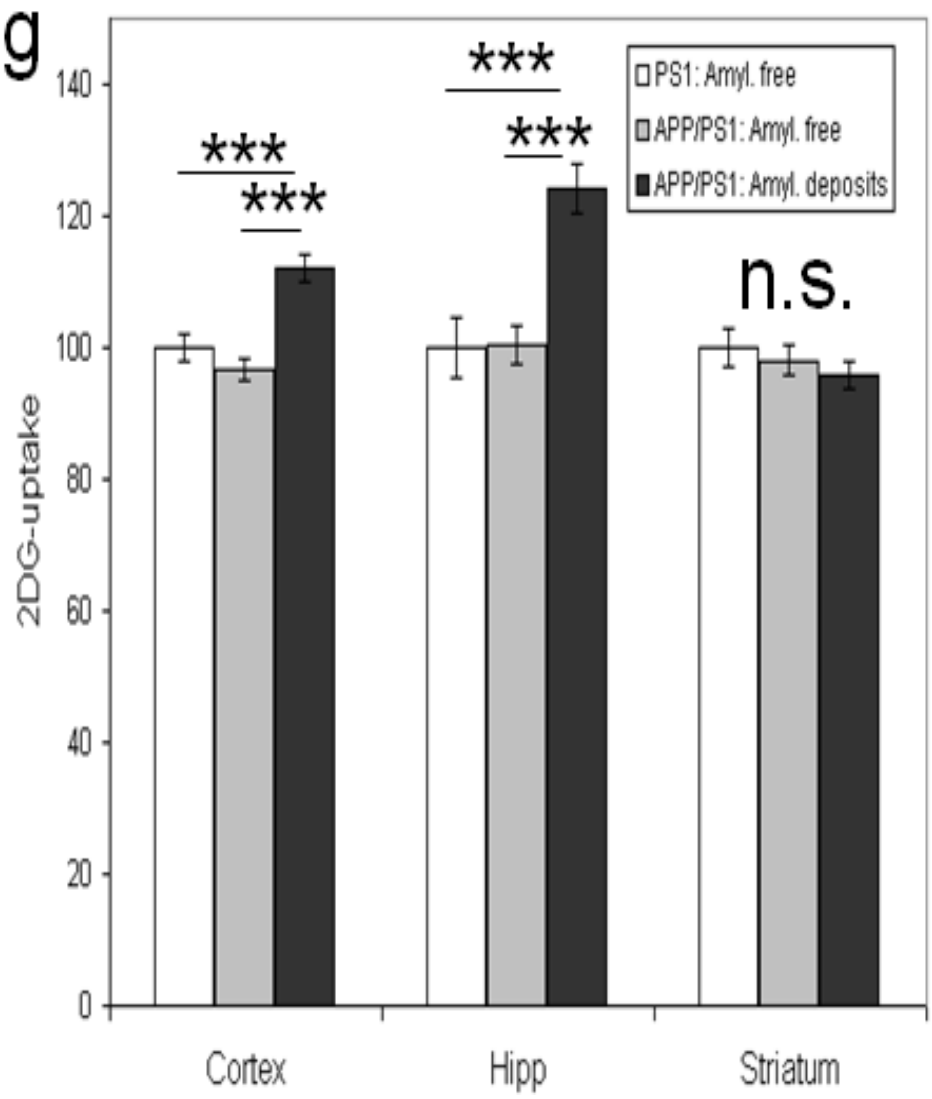


G. Poisnel et al,
Neurobiology of Aging, In press

Amyloid plaques are associated to an increased glucose uptake

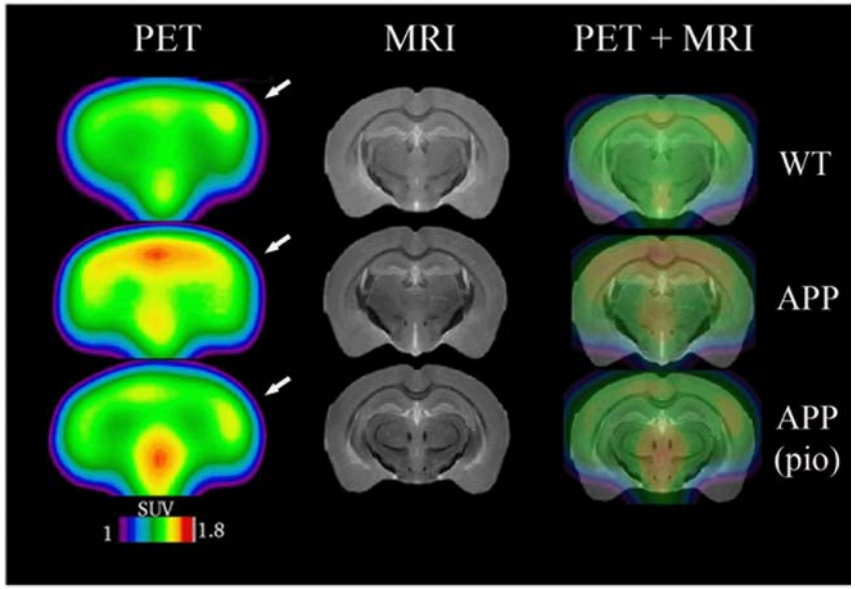
2DG autoradiography

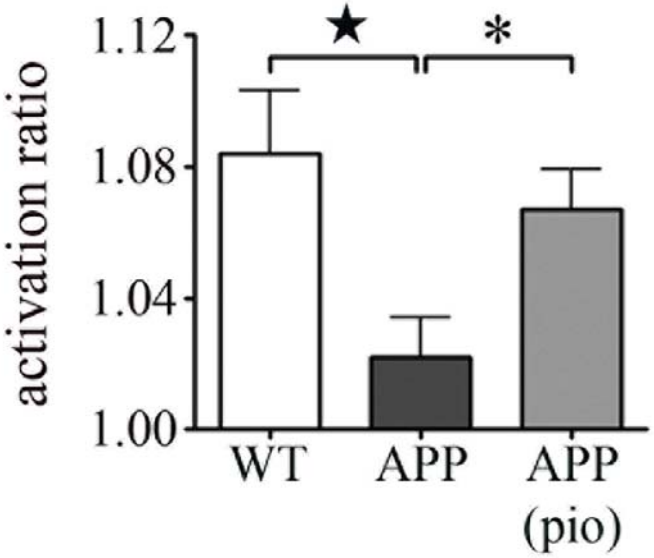




G. Poisnel et al, Neurobiology of Aging, In press

[18F]-FDG et µTEP
Hypométabolisme chez les Souris Alzheimer sous stimulation





18F]-FDG - µTEP - souris APP de 16 mois
(Nicolakakis et al., 2008, J Neurosci 28(37): 9287-96.)

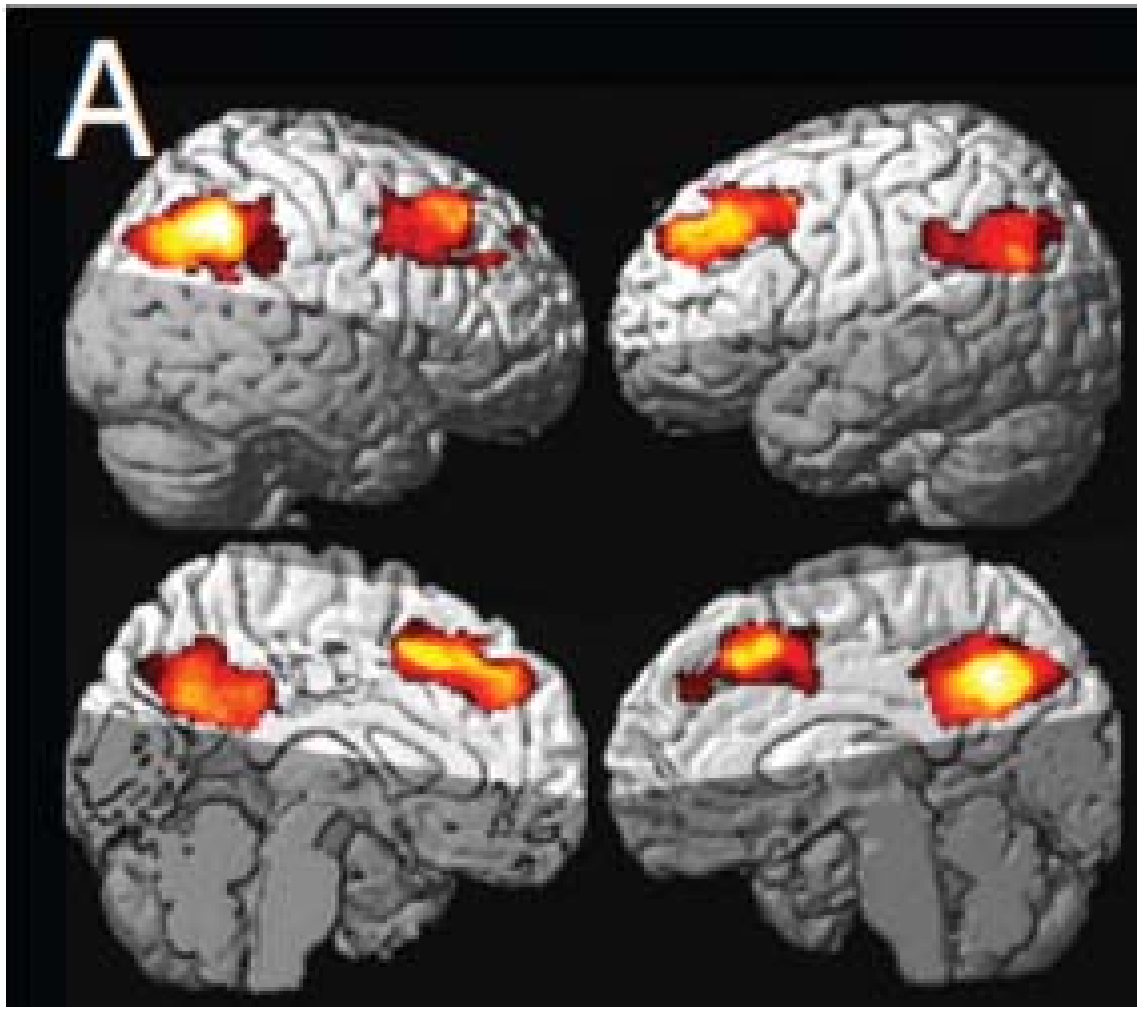
- Zones cérébrales non stimulées=↑ rétention de [18F]-FDG

- Stimulation des moustaches= ↓ rétention du [18F]-FDG dans cortex sensorimoteur

Altérations fonctionnelles associées à la MA

- Métabolisme cérébral
- Perfusion cérébrale
- Transport neuronal

Hypoperfusion in AD patients



Johnson et al., Radiology, 2005

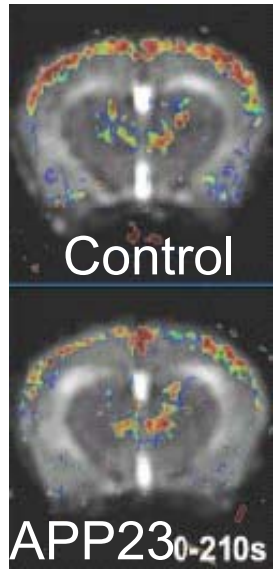
Stimulation pharmacologique

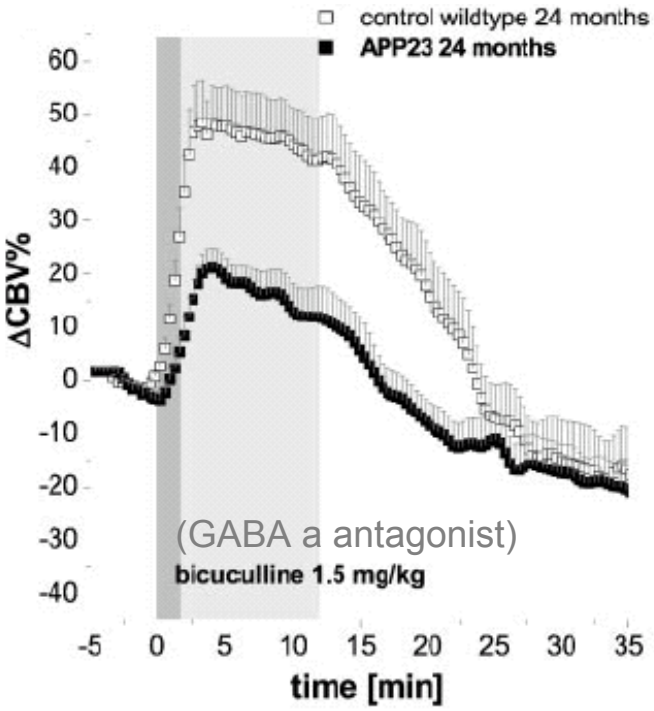
MRI 1

Pharmacological Treatment

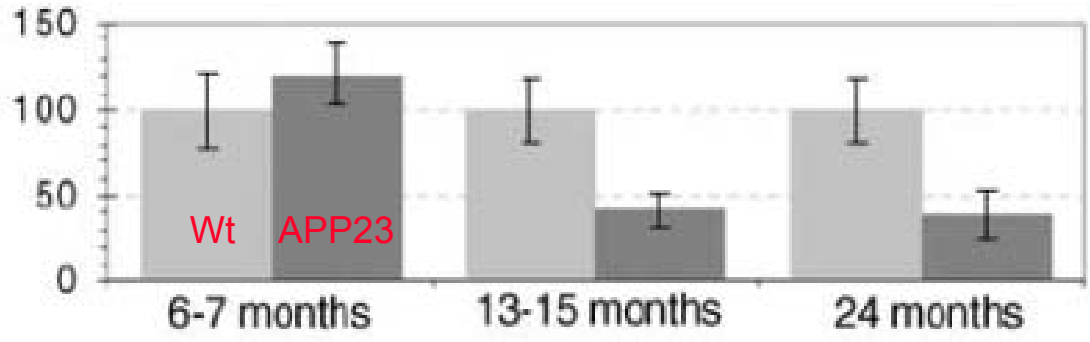
MRI 2

Pre-treatment endorem



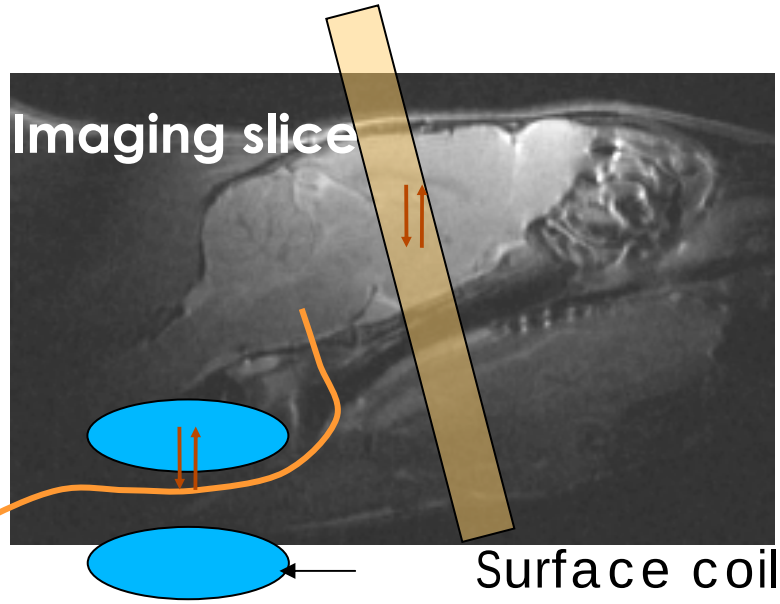


GABAa antagonist : Neuronal dis-inhibitor

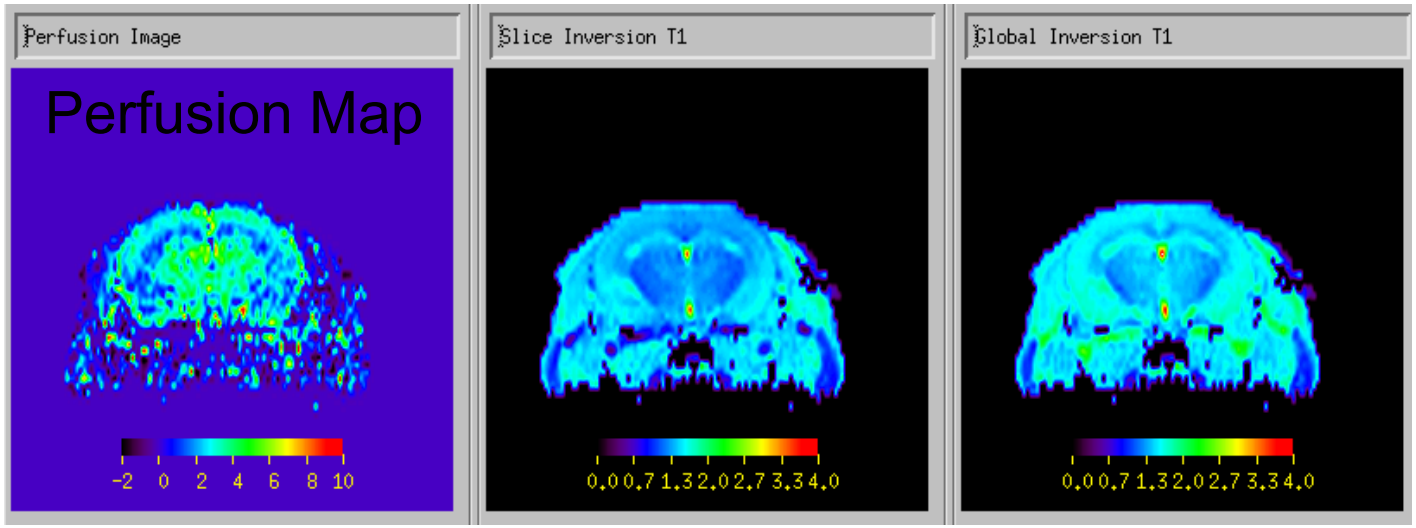


Mueggler (Novartis), J. Neurosc., 2002

Perfusion evaluation by MRI: Principle

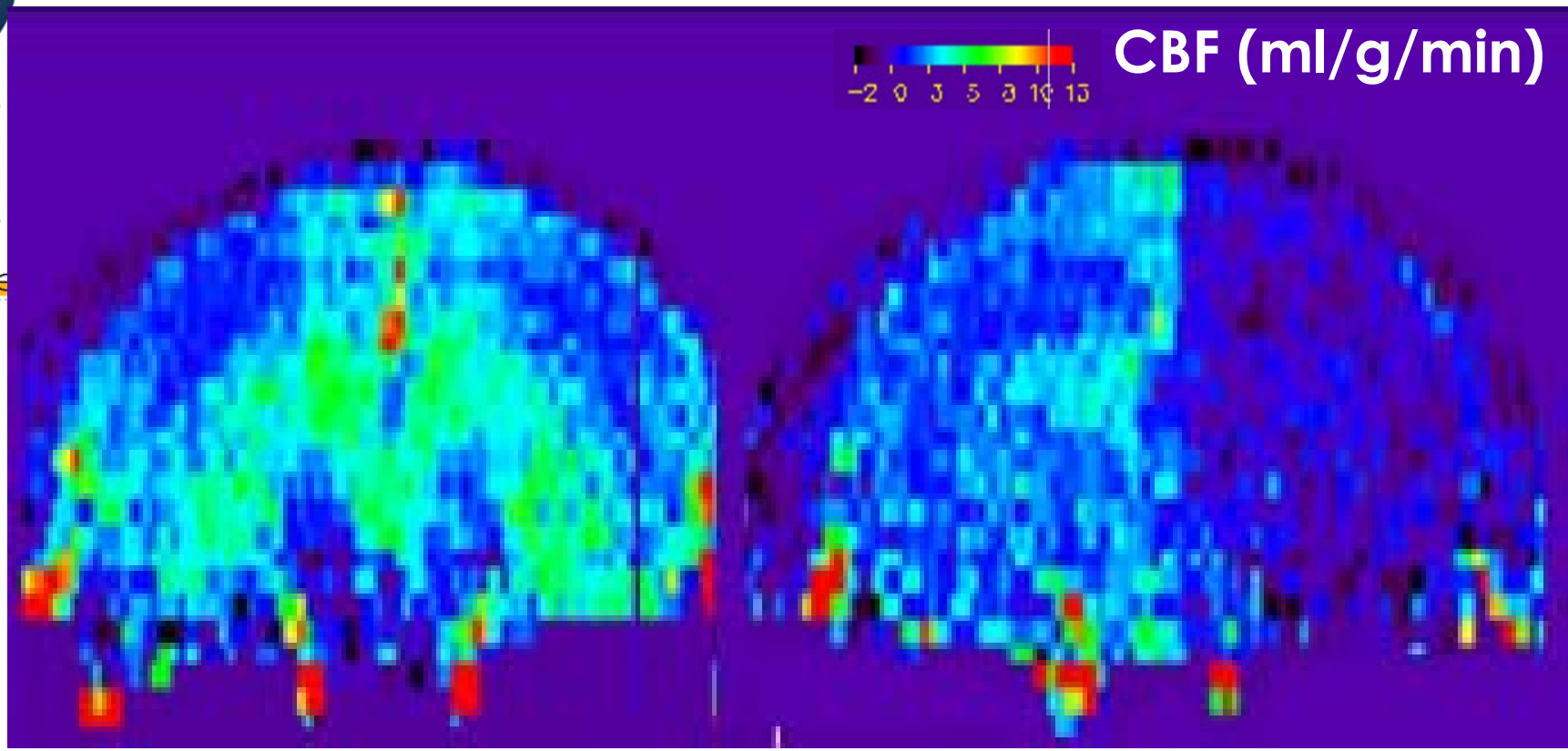


Comparaison of the contrast between « spin tagging » and « controle conditions »



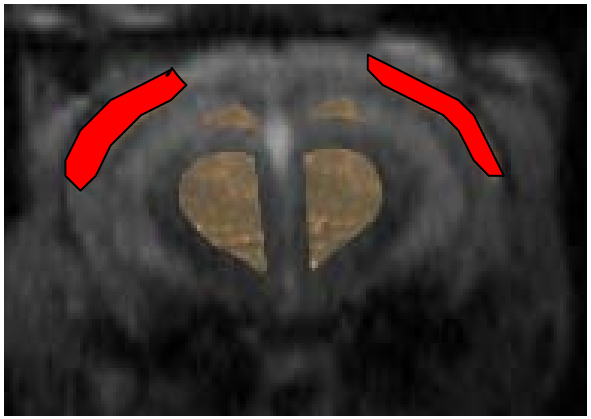
Frank Kober CRMBM

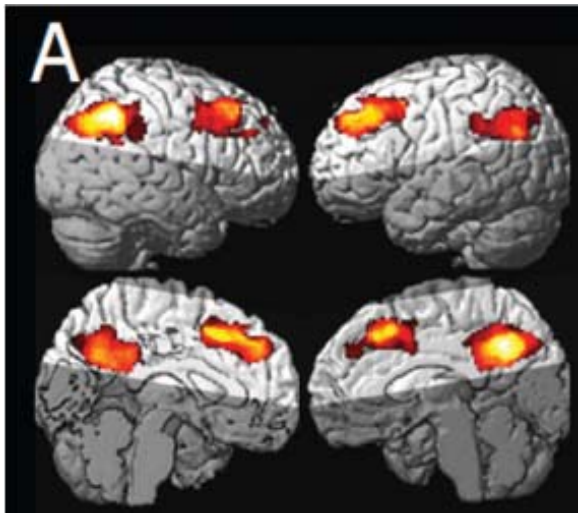
Cartes de perfusion dans un modèle d'ischémie cérébrale (MCAO)

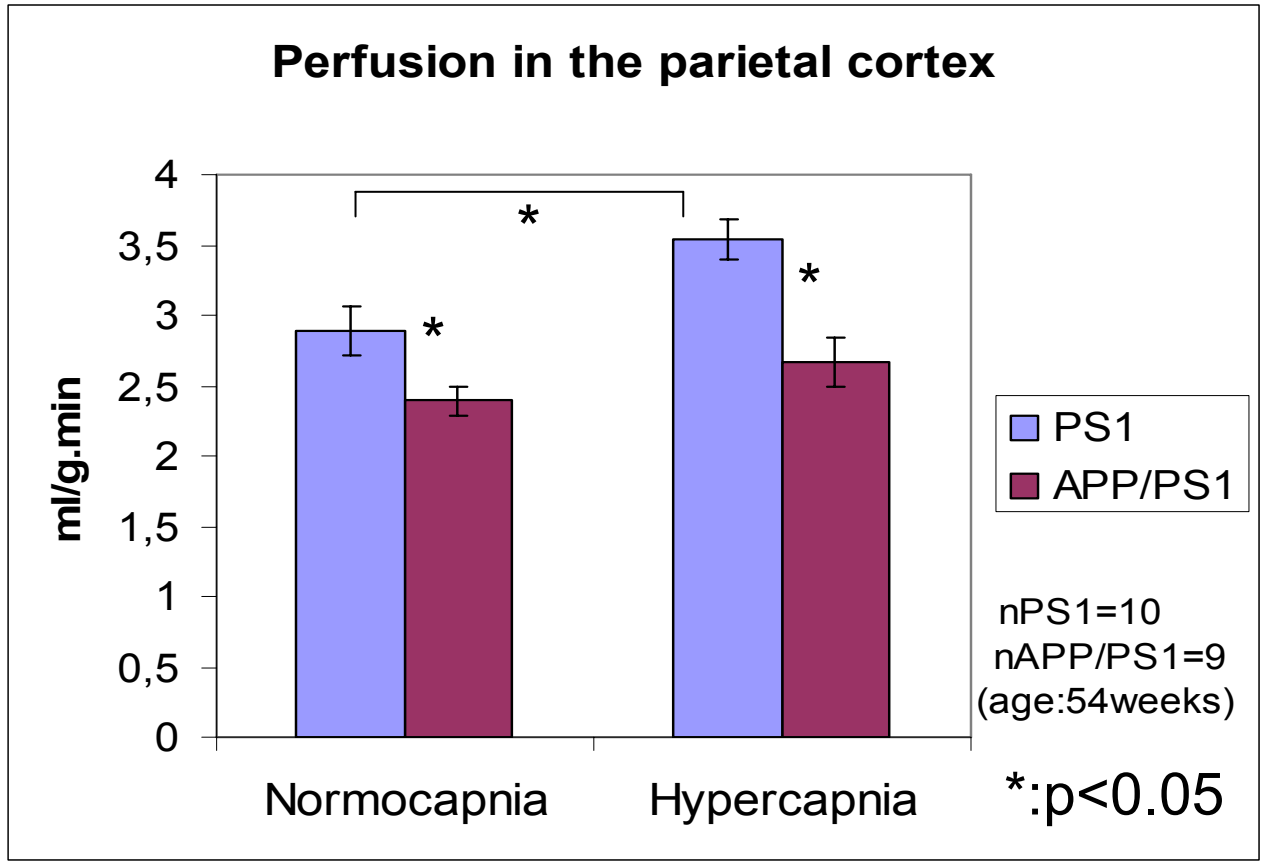


C. Laigle, A. Viola, CRMBM

Cortical hypoperfusion in Tg mice







Perfusion alterations are also detected in AD patients

* Johnson et al., Radiology, 2005

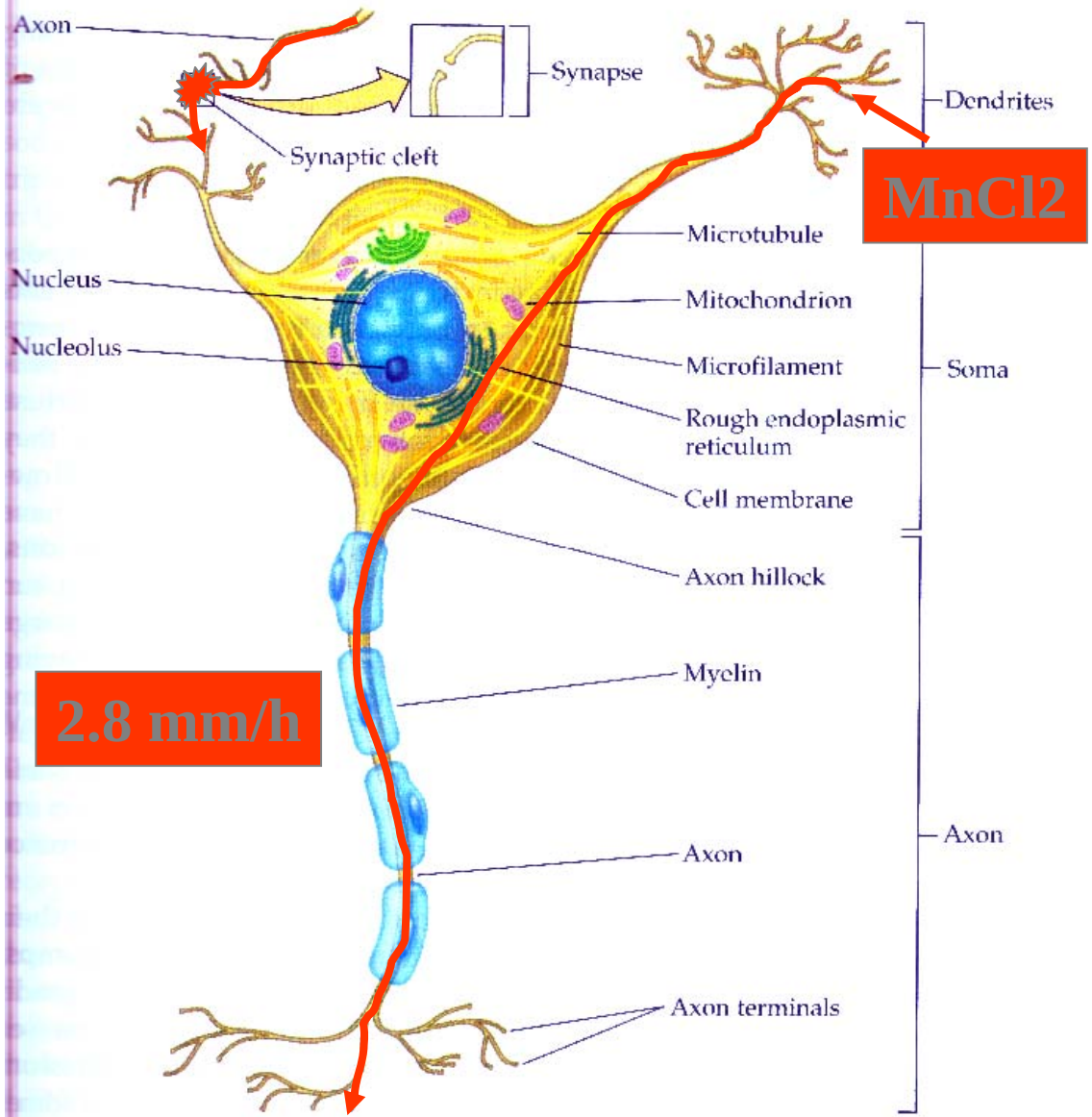
Nadine El Tannir El Tayara
Faure et al, Neurobiology of aging, 2010
Poisnel et al, Neurobiology of Aging, In press

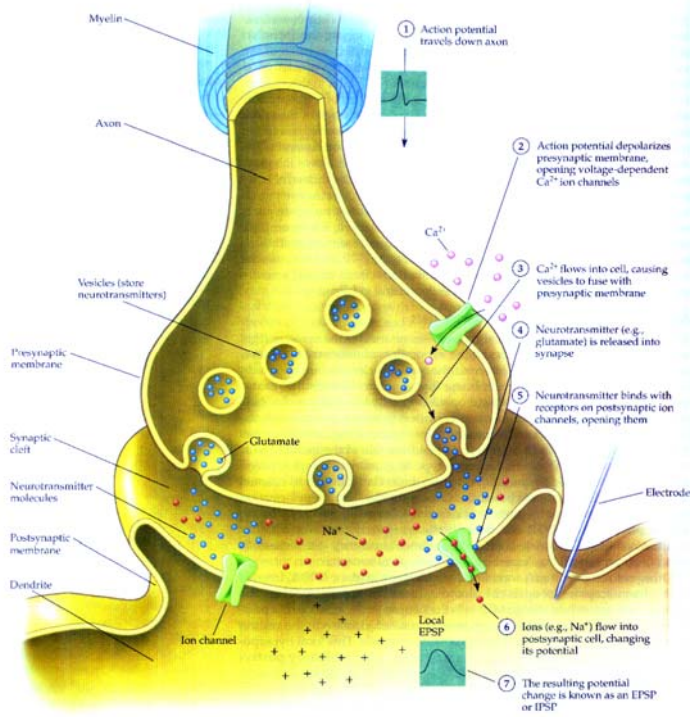
Method developped in collaboration with F. Kober, CRMBM, Marseille

Altérations fonctionnelles associées à la MA

- Métabolisme cérébral
- Perfusion cérébrale
- Transport neuronal : MEMRI (Manganese enhanced MRI)
  - Manganese : Traçage axonal
  - Manganese : Activité neuronale
  - Manganese : Transport neuronal

Evaluation of neuronal transportation by MEMRI





Traçage des voies nerveuses (MnCl2)

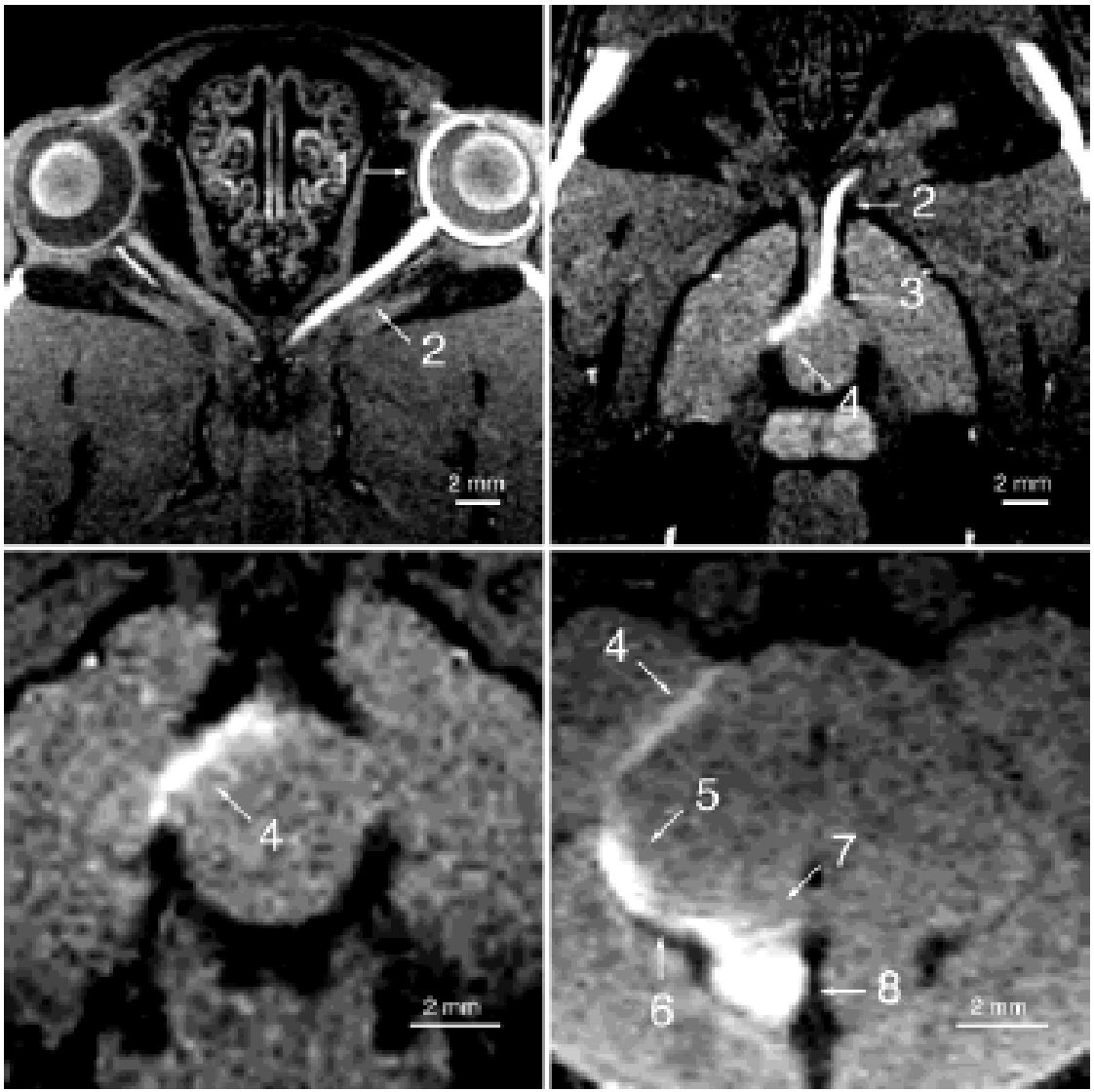
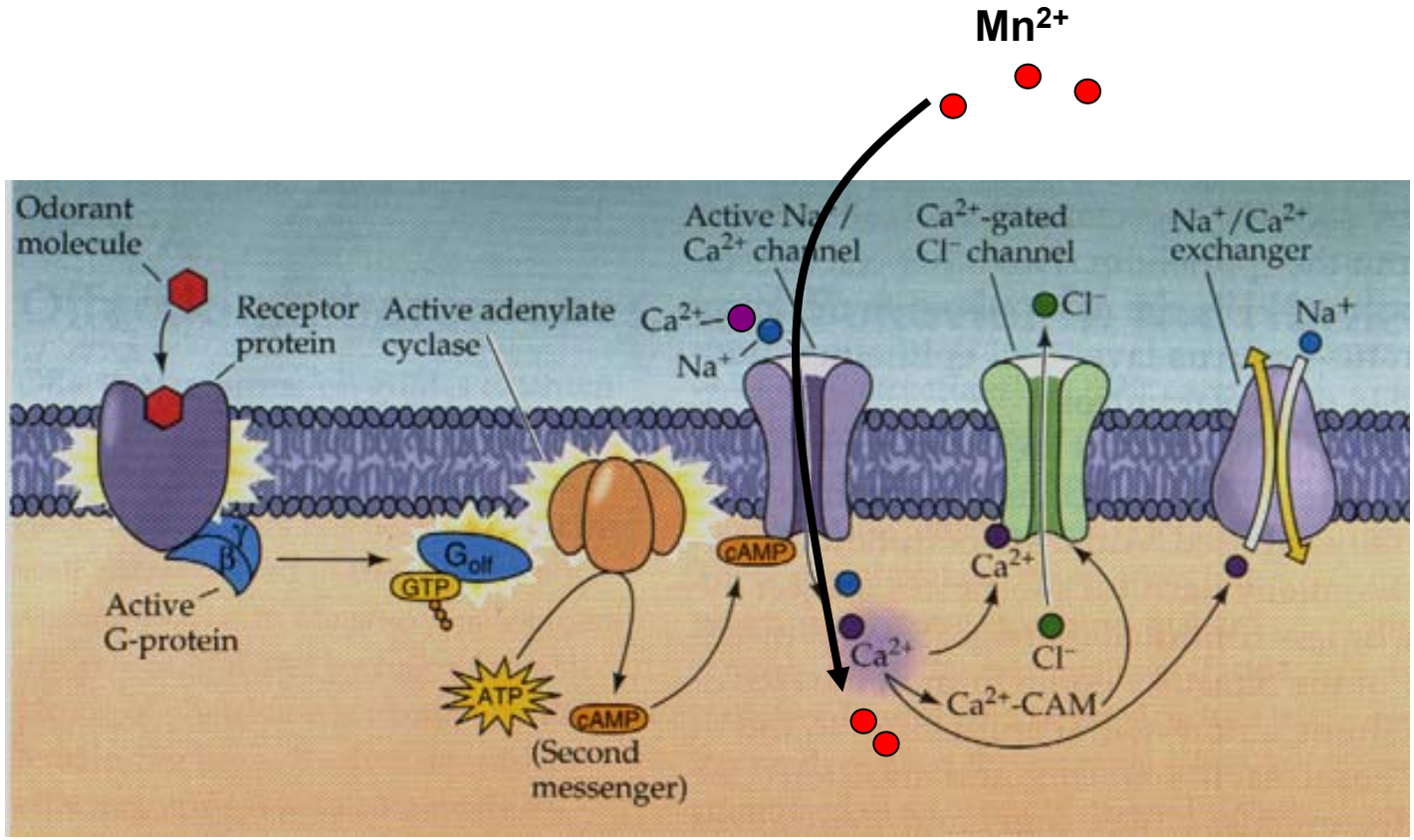


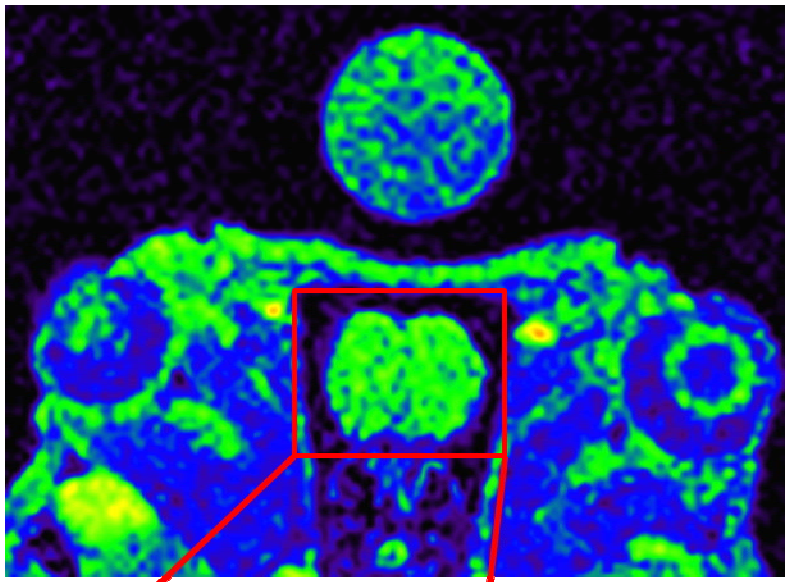
FIG. 2. Signal enhancement of the rat visual pathway (24 h after Mn^{2+}-injection into the left eye) in oblique sections −35° (top left), −10° (top right), +5° (bottom left), and +37.5° (bottom right) relative to the transverse reference plane shown in Fig. 1 (sections indicated in Fig. 1). Enhanced structures are: (1) left retina, (2) left optic nerve, (3) optic chiasm, (4) right optic tract, (5) right lateral geniculate nucleus, (6) right brachium of the superior colliculus, (7) right pretectal region, and (8) right superior colliculus.

Watanabe, MRM, 2001

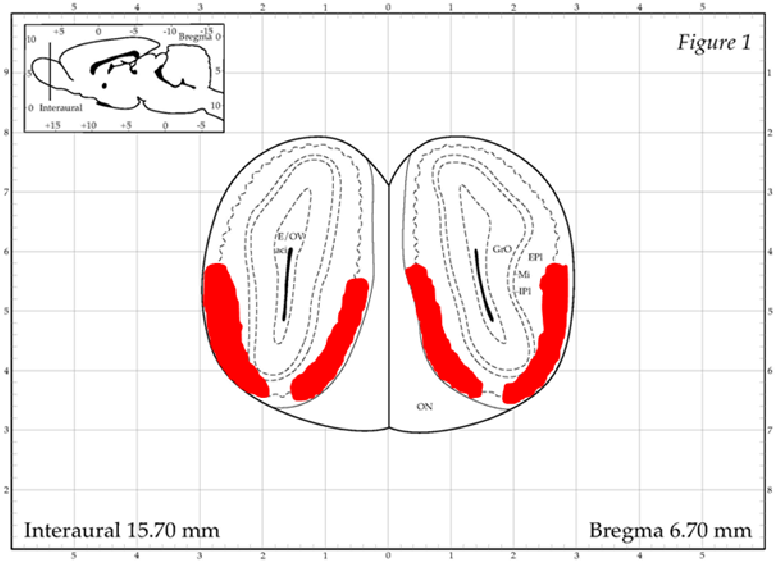
Functional imaging (MEMRI)



Méthodologie IRM

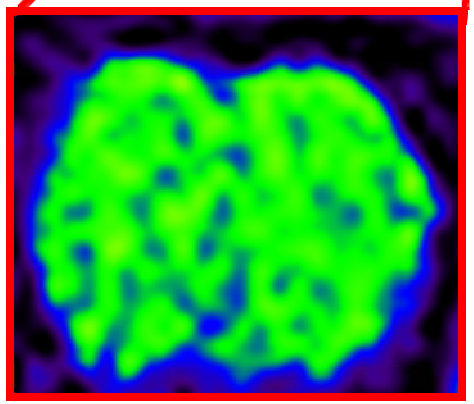


From Paxinos and Watson atlas

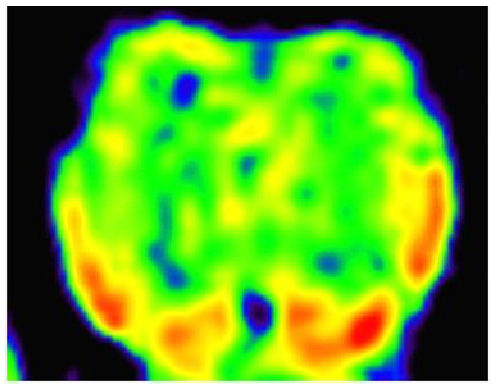


SI
+
−

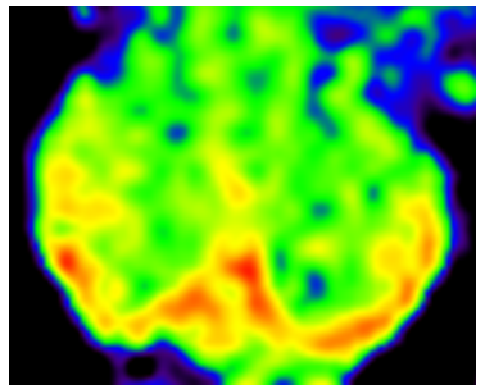
Before manganese



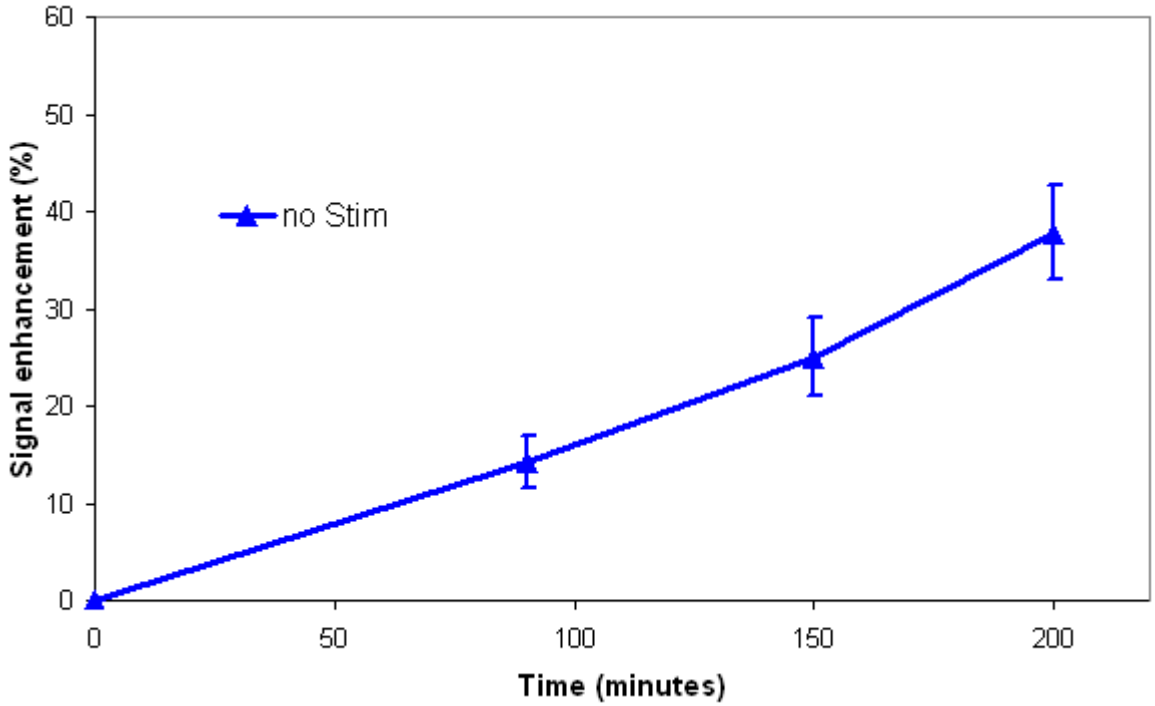
Odor-stimulated rat



Quinolinate-injected rat

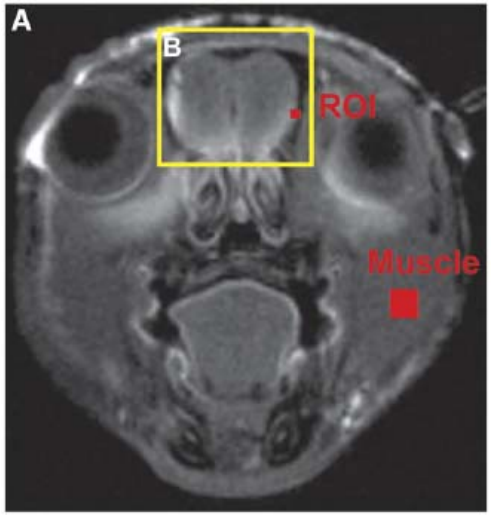


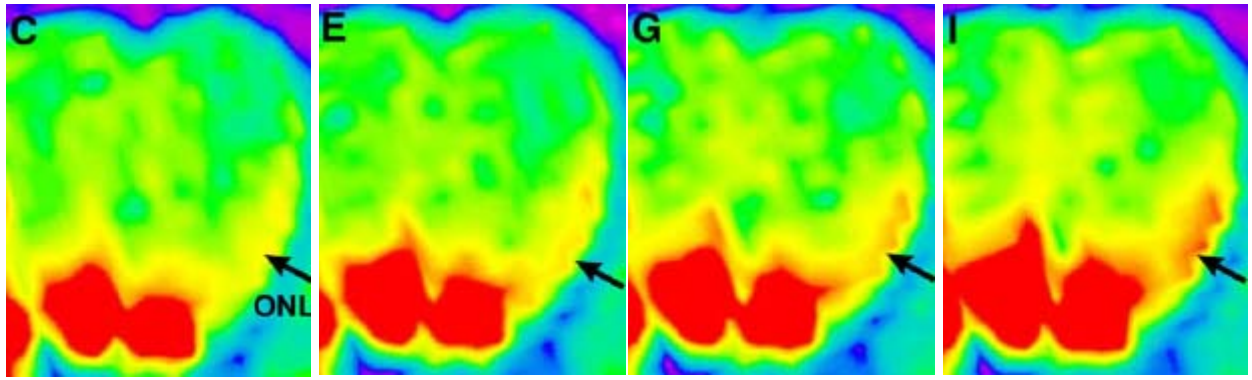
Evolution du signal MEMRI



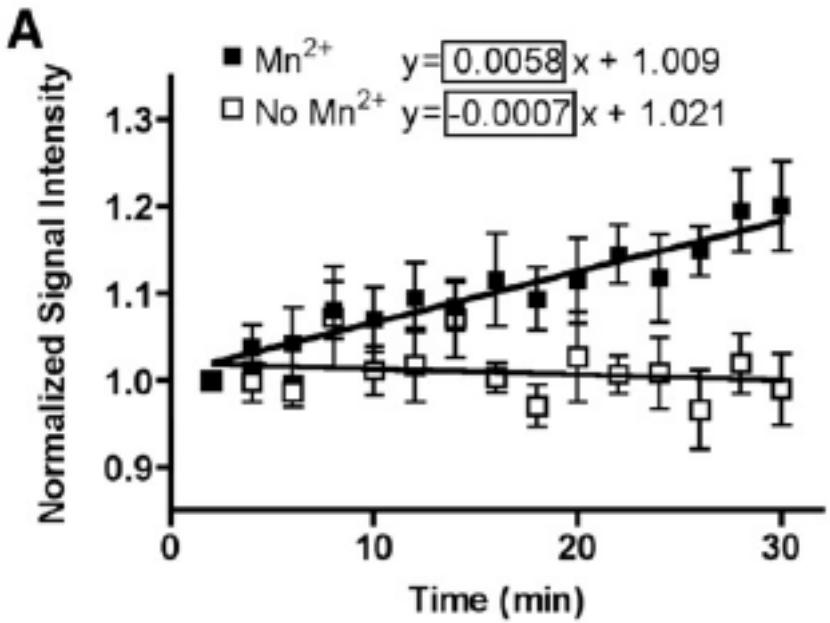
Gobbo O et al, Magnetic Resonance in Medicine, sous presse

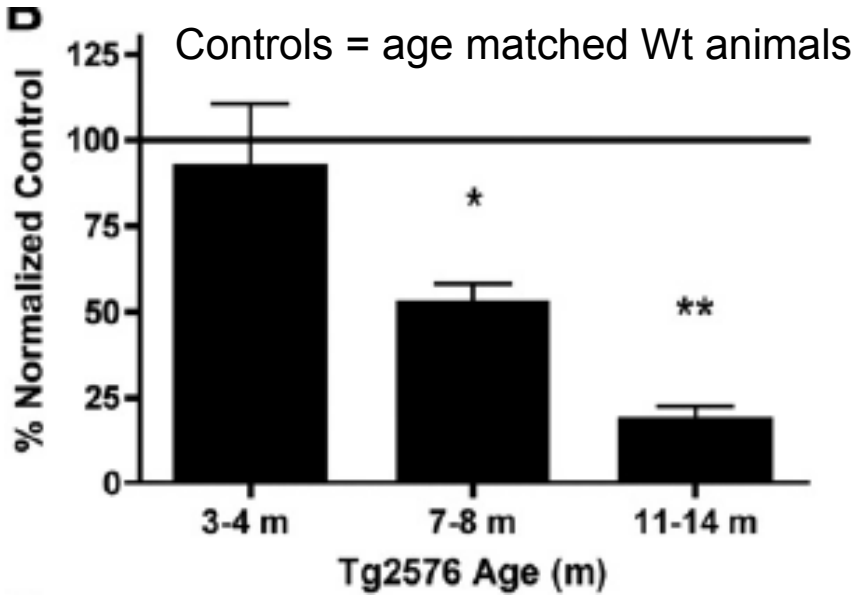
MEMRI – Neuronal conduction





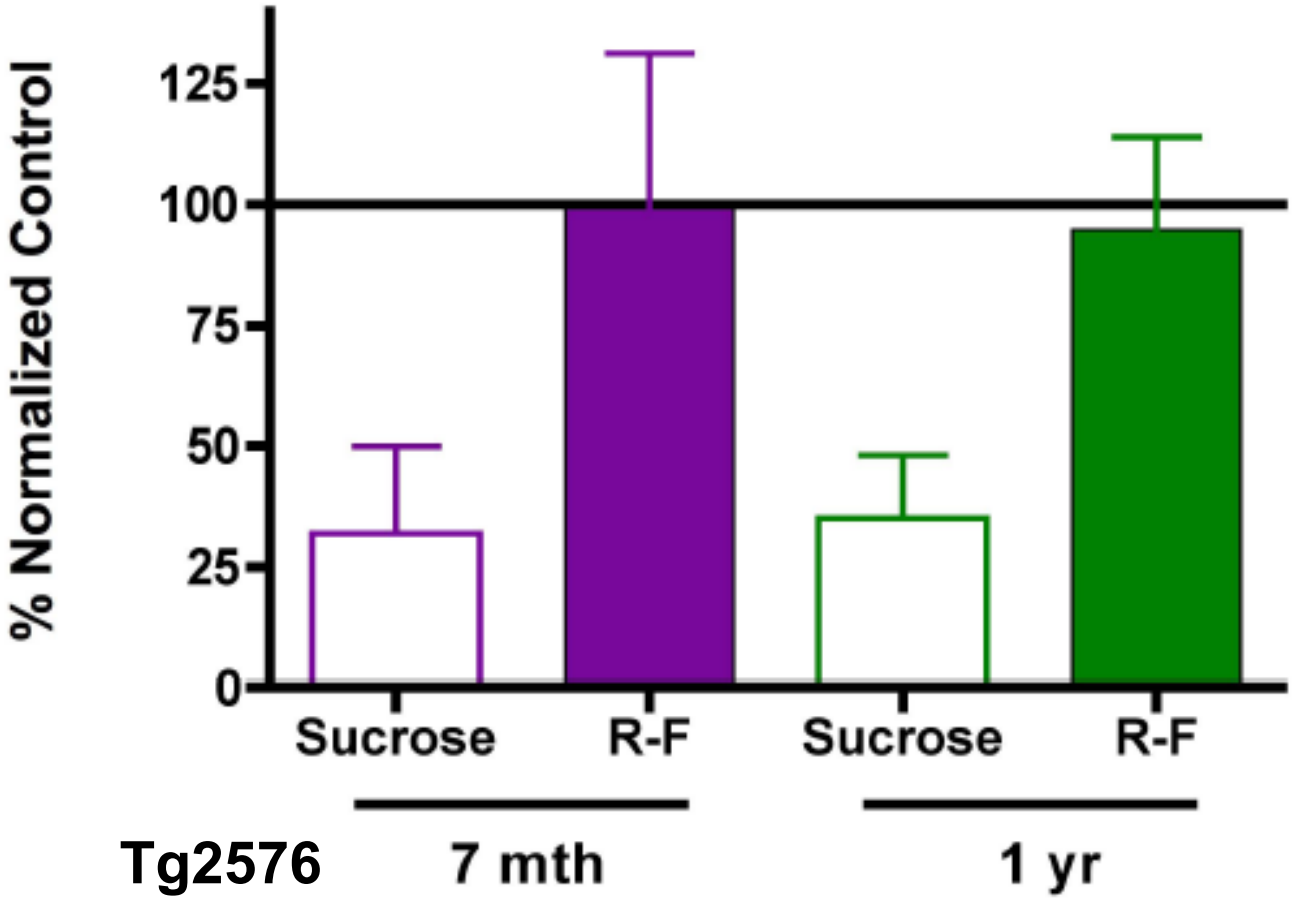
2 min 12 min 22 min 32 min





Smith, K. D., V. Kallhoff, et al. (2007). Neuroimage **35**(4): 1401-8.

Effect of an Aβ1-42 lowering drug (R-Flurbiprofen) on neuronal conduction



Smith-Pautler-ISMRM-2008

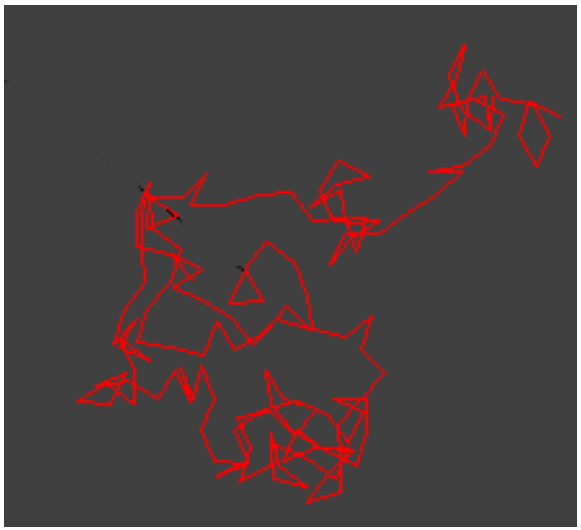
Conclusion: Functional biomarkers

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Cerebral Metabolism (PET + FDG)	Yes ?	No	Yes	No
Perfusion	Yes	No	Yes	No
Axonal transportation (MEMRI)	Yes	Yes	No	No

Plan

- Maladie d'Alzheimer
  - Généralités
  - Modèles animaux
  - Concepts de biomarqueurs
  - Quels biomarqueurs ?
    - Marqueurs cognitifs
    - Marqueurs de l'atrophie cérébrale
    - Marqueurs de l'amyloïdose
      - Liquide biologiques
      - Imagerie
    - Marqueurs fonctionnels
    - Autres marqueurs
      - Diffusion
      - Spectroscopie
    - Marqueurs toxicologiques
- Exemples d'autres biomarqueurs pour d'autres pathologies

Mesure de la diffusion : Mouvement brownien de l'eau



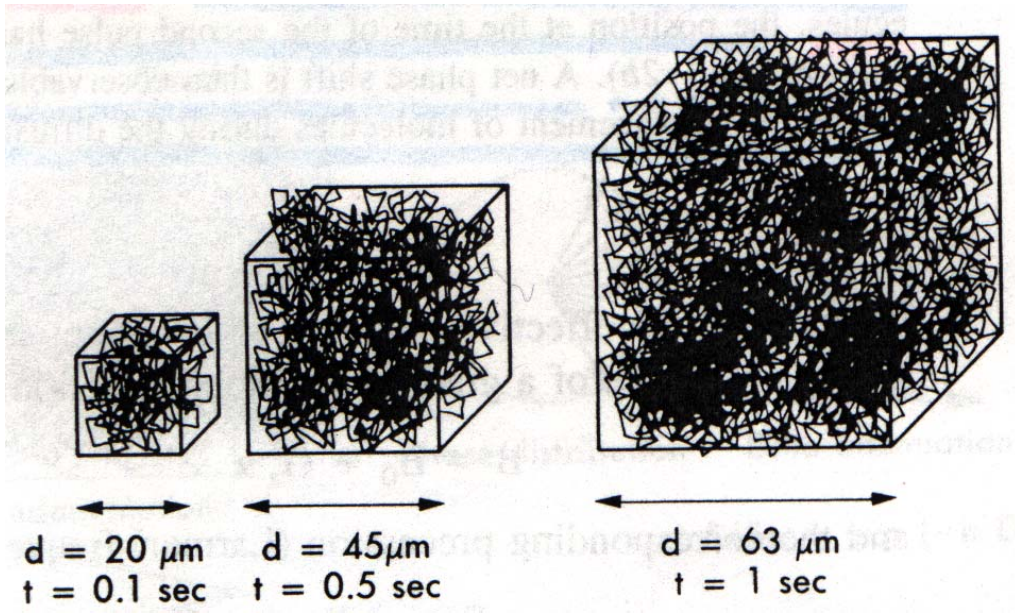
$r^2 = 6\ D\ t$ (Equation d'Einstein)

r = distance parcourue (en 3D)

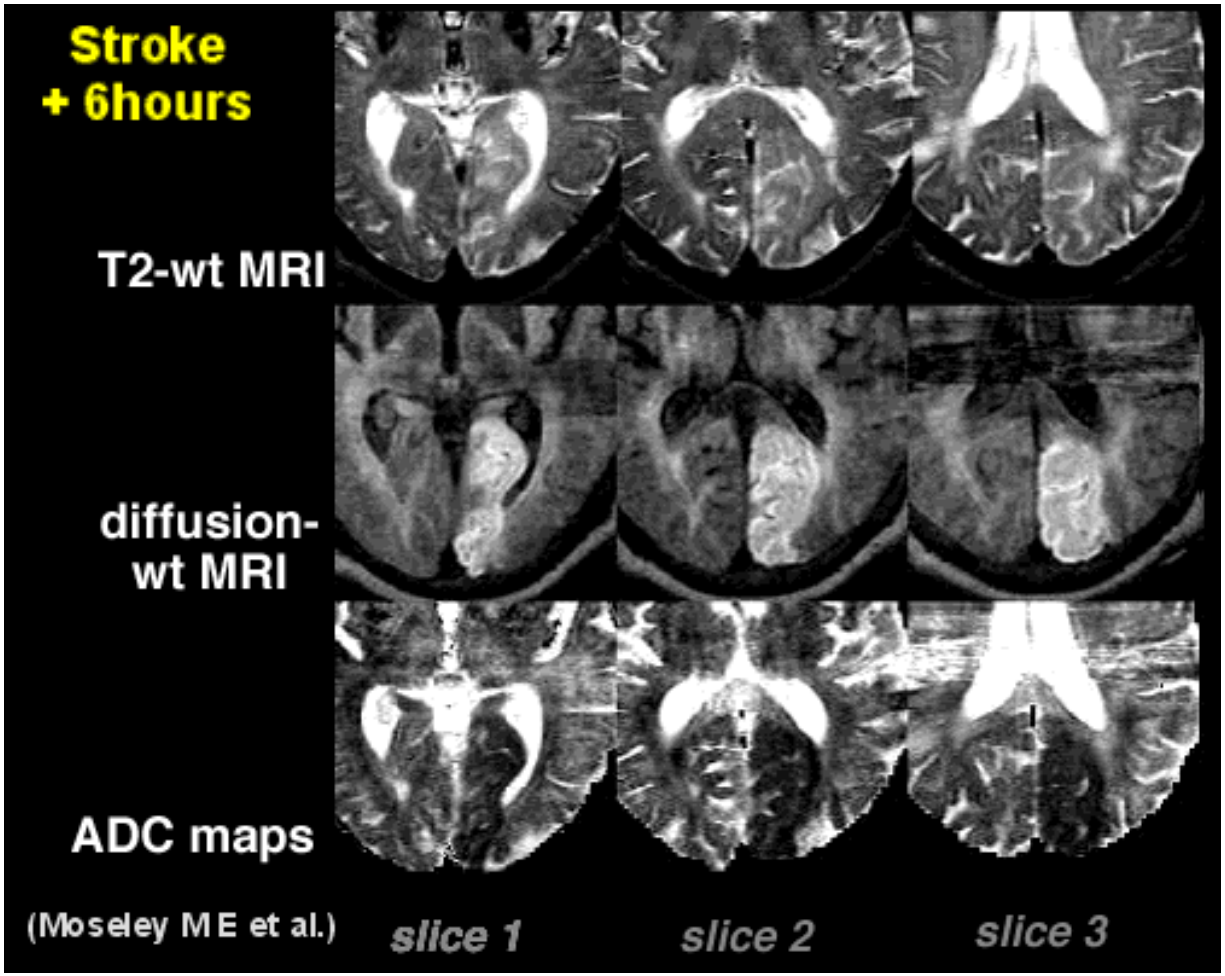
D = coefficient de diffusion

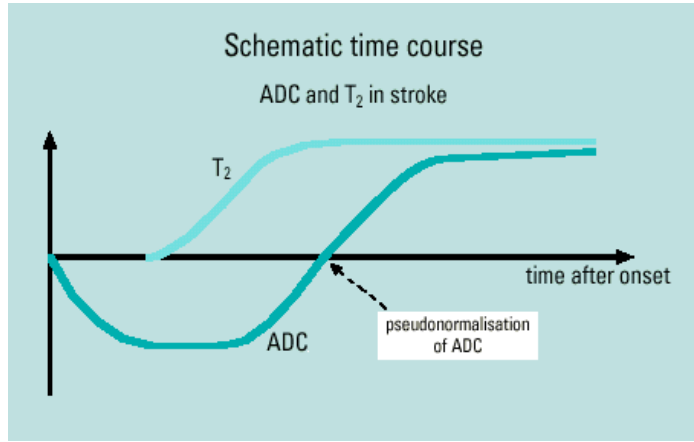
= 2.2x10-3 mm2/sec pour H20 (à 25 °c)

t = temps

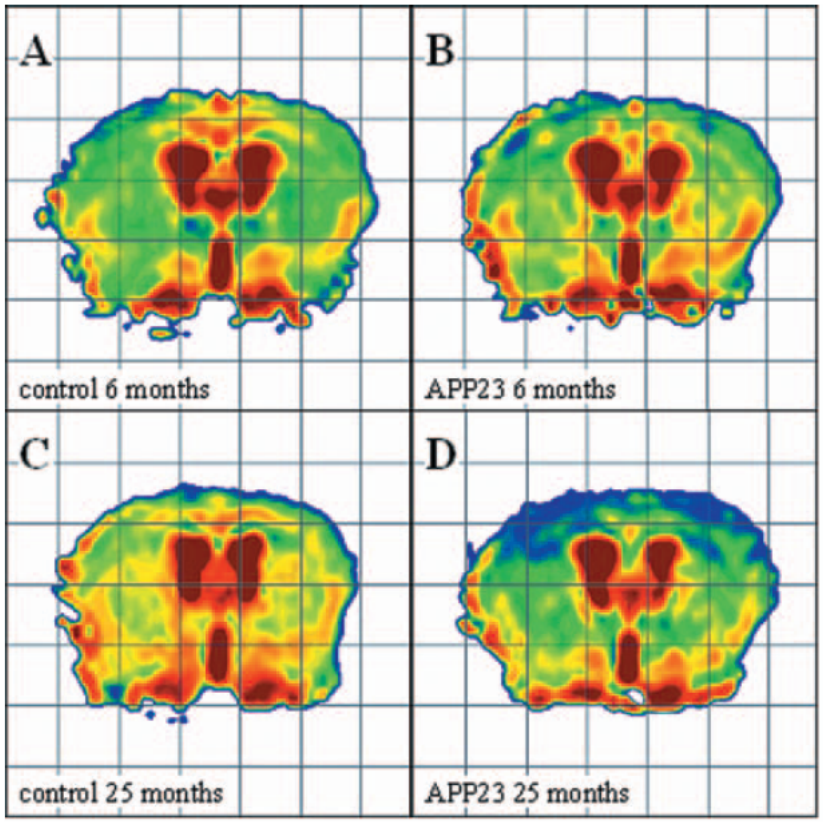


Modification précoce lors d'ischémie aiguë

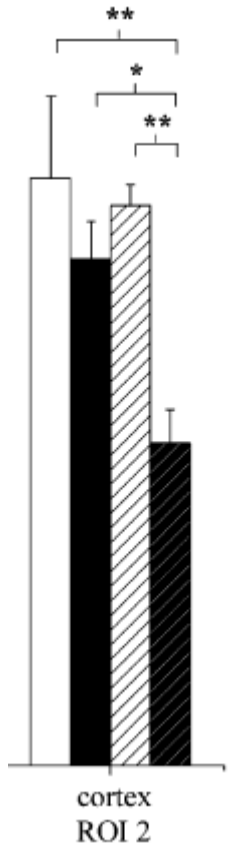




Mesure de la diffusion chez des souris Alzheimer



Coefficient apparent de diffusion

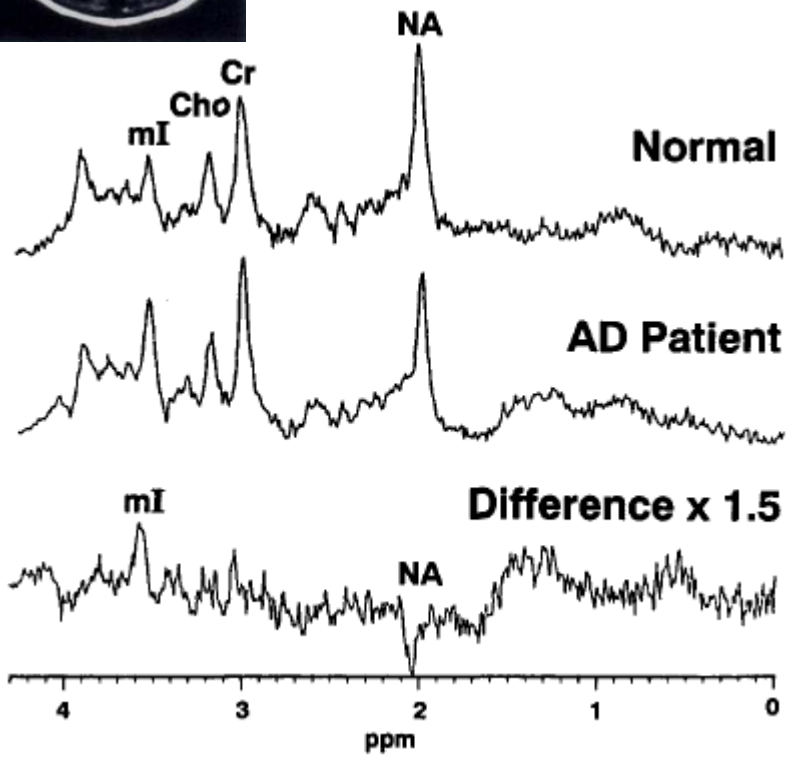


Diminution chez veilles souris APP23

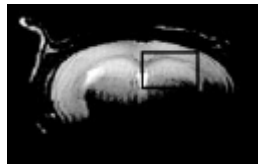
Mueggler, T., (2004). Eur J Neurosci **20**(3) 811-7.

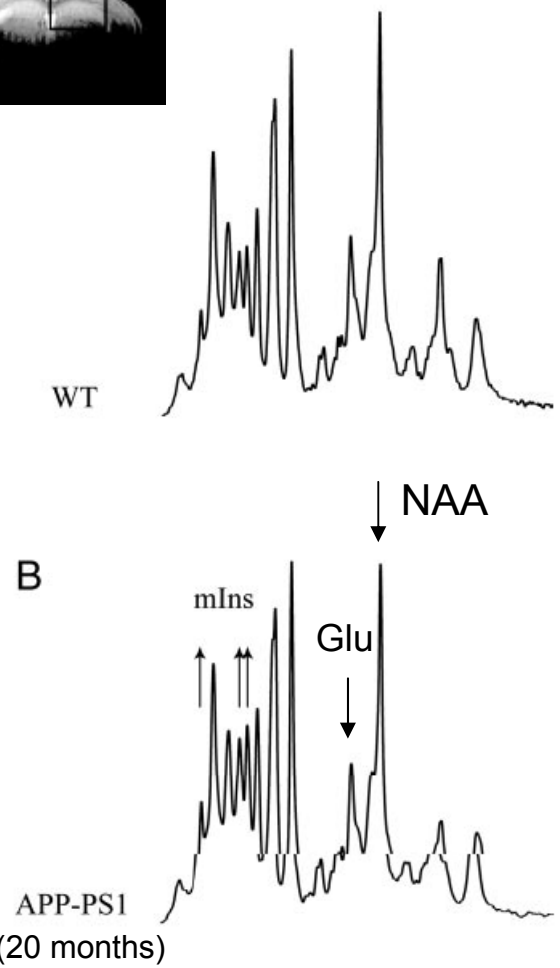
- Marqueur tardif
- Pas reproduit par toutes les études

MR spectroscopie



Moats, R. A., et al. (1994).
Magnetic Resonance in Medicine
32: 110-115.





Marjanska, M., et al. (2005).
Proc Natl Acad Sci U S A
102(33):11906-10.

Conclusion: Autres biomarqueurs

Biomarker	Use in animals		Use in humans	
	Detection of AD-like pathology	Preclinical evaluation of drugs	Clinical diagnostic	Clinical endpoint True benefits of a drug
Diffusion MRI	In developpment	No	No	No
Spectroscopy	In developpment	No	Yes	No

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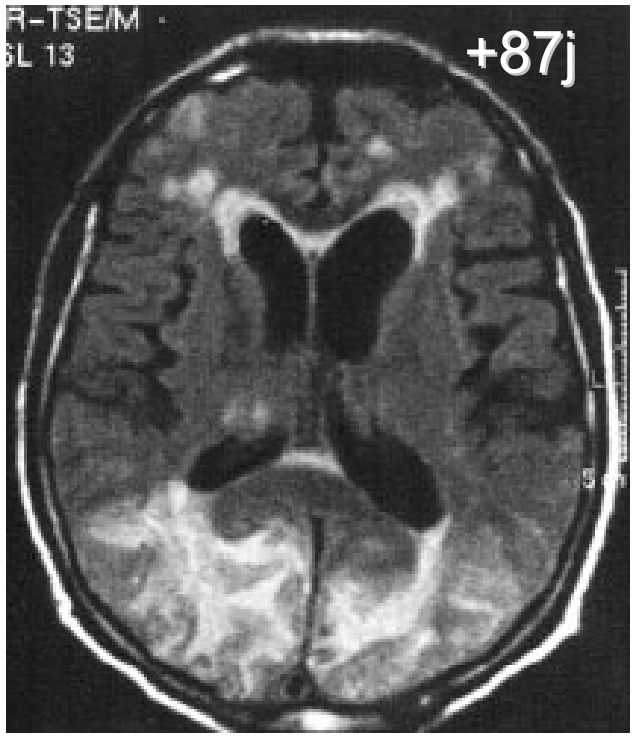
- Exemples d'autres biomarqueurs pour d'autres pathologies

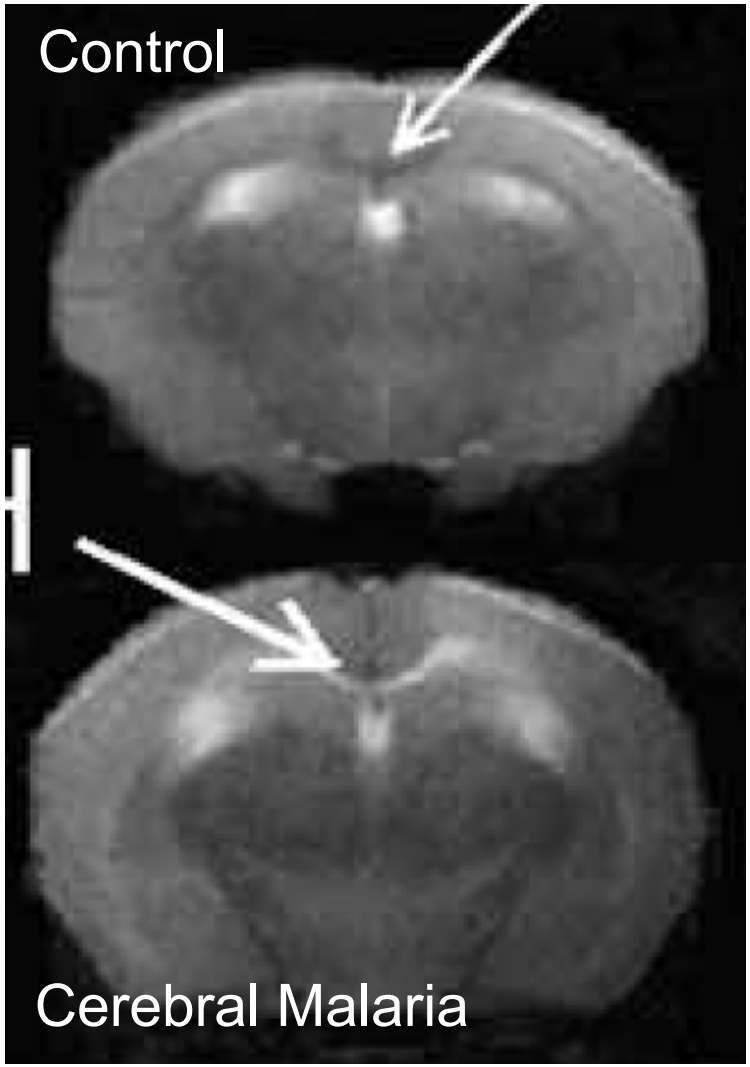
Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization

J.-M. Orgogozo, MD; S. Gilman, MD, FRCP; J.-F. Dartigues, MD, PhD; B. Laurent, MD; M. Puel, MD; L.C. Kirby, MD; P. Jouanny, MD, PhD; B. Dubois, MD; L. Eisner, MD; S. Flitman, MD; B.F. Michel, MD; M. Boada, MD; A. Frank, MD, PhD; and C. Hock, MD



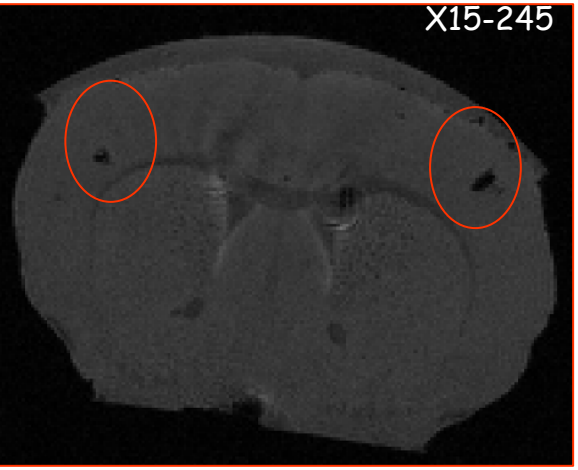
Neurology, 2003

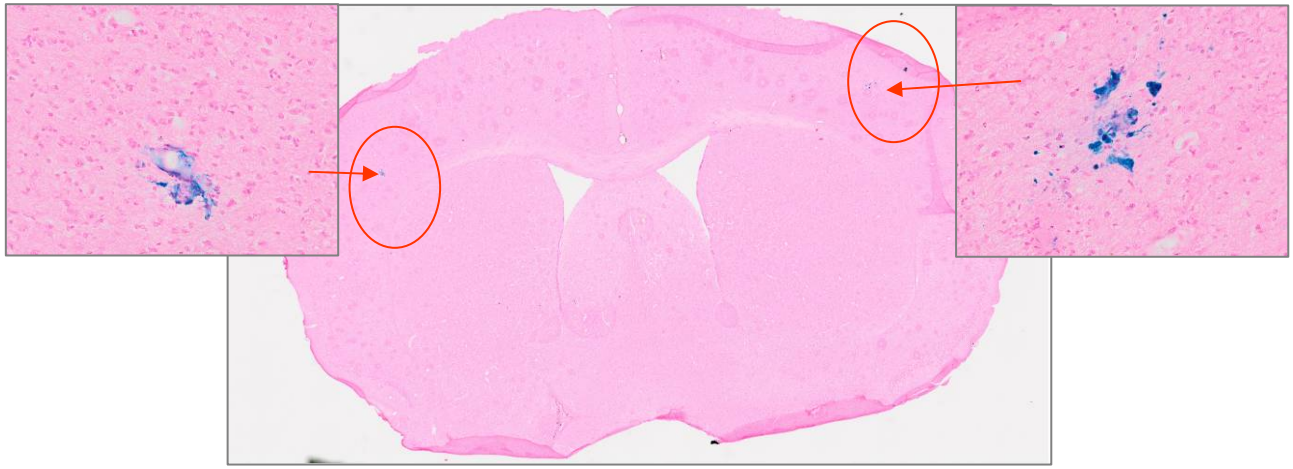
Marqueurs toxicologiques chez l'animal
Neuroinflammation

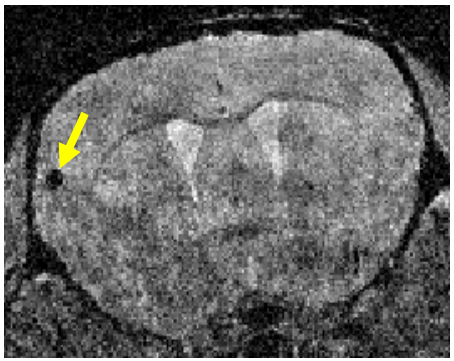


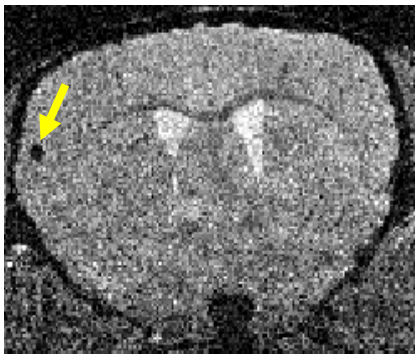
Penet, M. F.. (2005).
J Neurosci **25**(32): 7352-8.

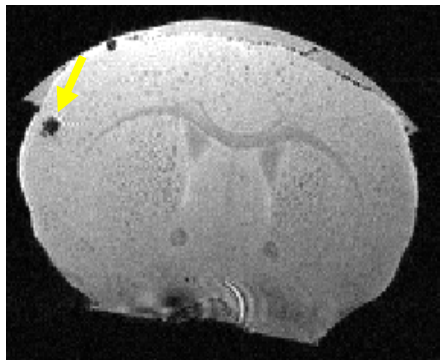
Marqueurs toxicologiques chez l'animal
Microhémorragies cérébrales

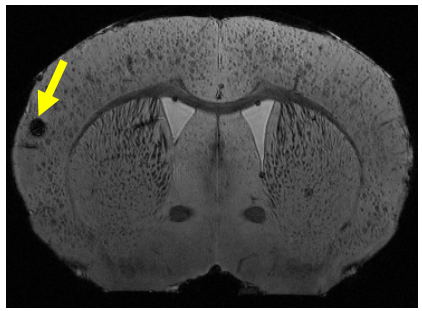










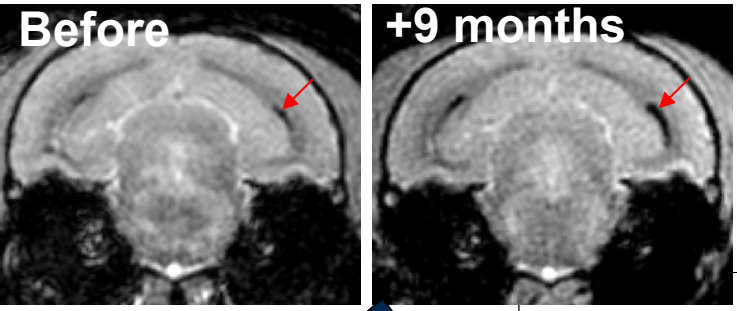


71 wks

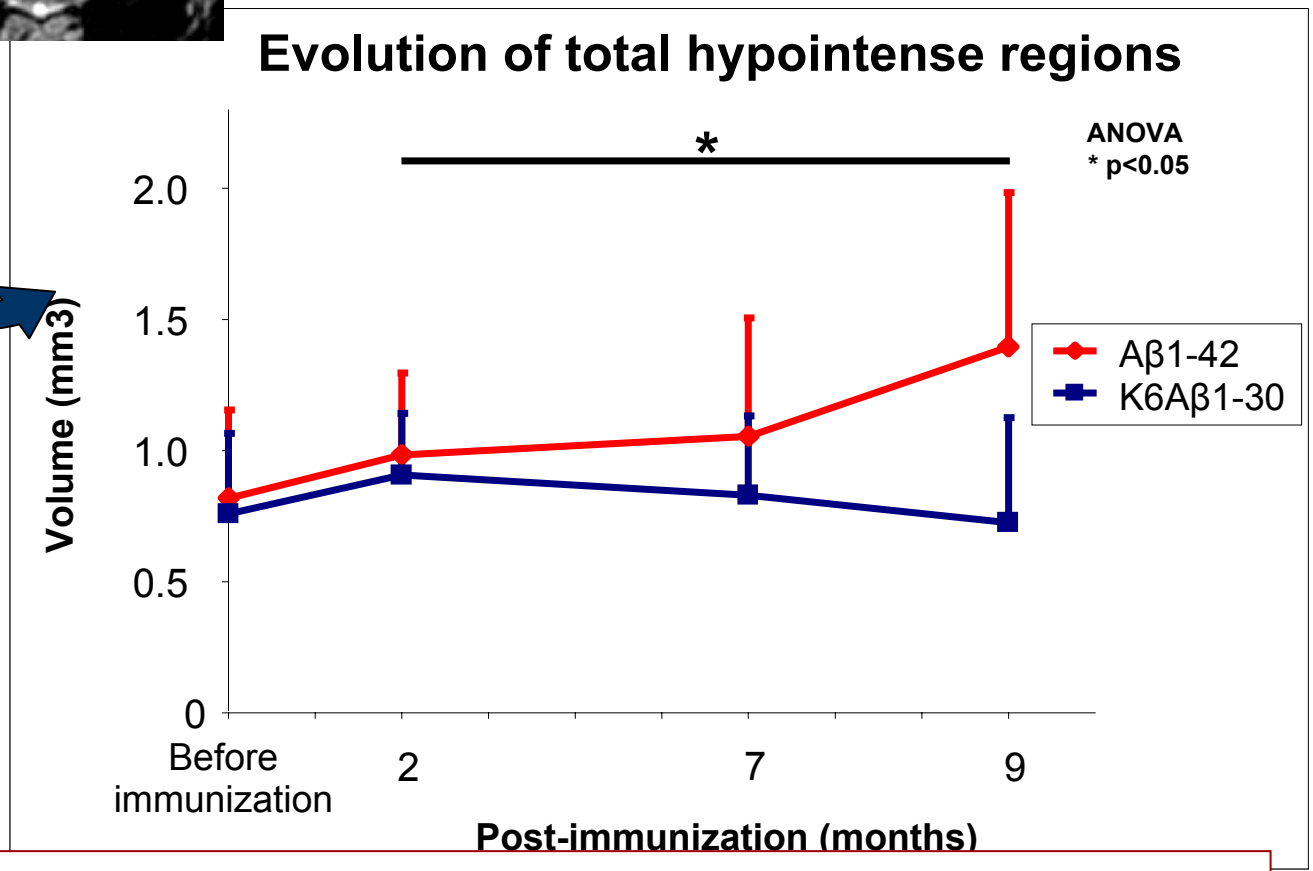
75 wks

Post-mortem

Follow-up of iron deposits in the choroid plexus during immunotherapy

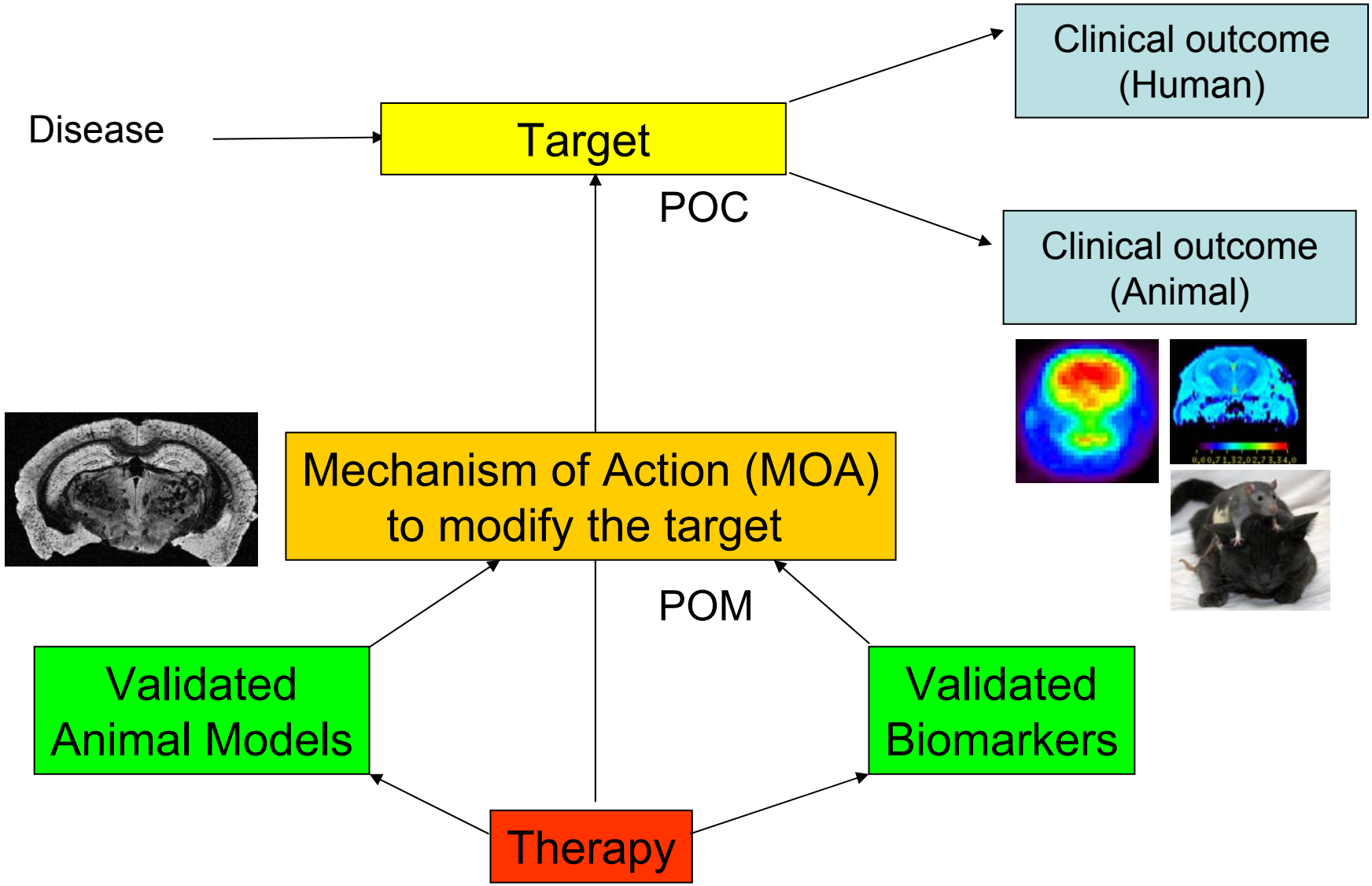


Segmentation of the hypointense regions



A lower increase of iron accumulation in choroid plexus in animals treated with K6Aβ1-30

Exemple de l'immunothérapie anti-amyloïde



Proof of Concept (POC): If I modify the target, do I modify the disease ?
Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Exemple de l'immunothérapie anti-amyloïde

From bench to bed in AD (Aβ antibody)

Bench (TG mice)

- Safety
  - Brain Microhemorrhages: Histology, next MRI-FLAIR
- Efficacy
  - Aβ: Biochem/Histology, next CSF and imaging
  - Neuroinflammation: RNA markers
  - Cognition: Cognitive tests
  - Neuroprotection: Histology

Bed (AD patients)

- Safety
  - Brain Microhemorraghes, MRI (Phase I, AD)
- Efficacy/POM
  - Aβ: PET scanning and CSF Aβ, others? (Phase II)
  - Neuroinflammation: PBR PET (Phase II)
- Clinical efficacy
  - Clinical evaluation: ADAS-Cog and others (Phase III)
  - Brain atrophy: MRI (Phase III)
  - CSF Tau markers (PhaseII/III)

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Concl : Intérêt des approches multimodales