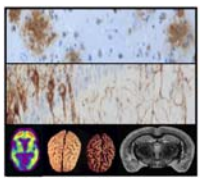
In-vivo imaging of amyloid plaques by MRI



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and

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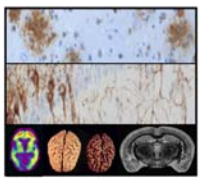
Available from: http://mamobipet.free.fr/Teaching/130413-Dhenain-Conf-J-Monod.pdf

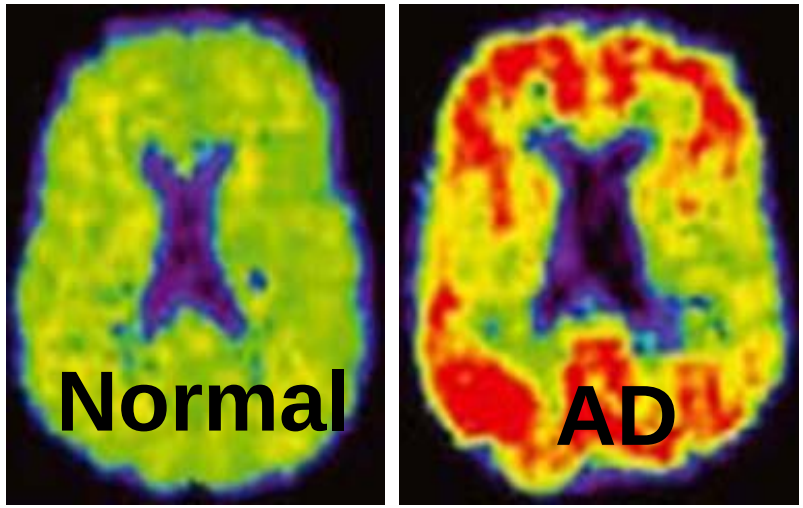
Imaging amyloid plaques



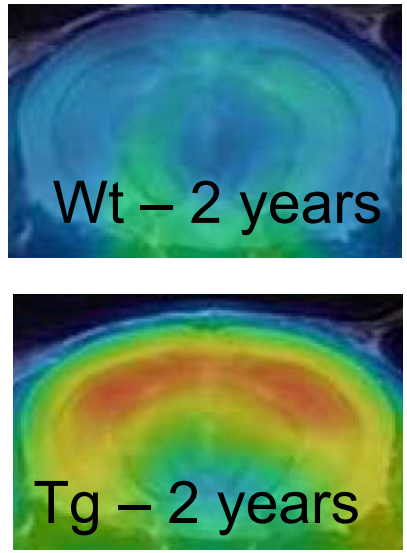
- In humans
  - Early diagnosis
  - Understand the natural history of the disease
  - Follow-up therapy efficacy
- In animals
  - Follow-up therapy efficacy
  - Develop new methods and concepts to image amyloid plaques in humans

Imaging amyloid plaques: PET

- In humans
  - PIB, AV45, …
    Klunk WE et al. Ann Neurol, 2004
  - Radioactivity
  - Not enough PET available

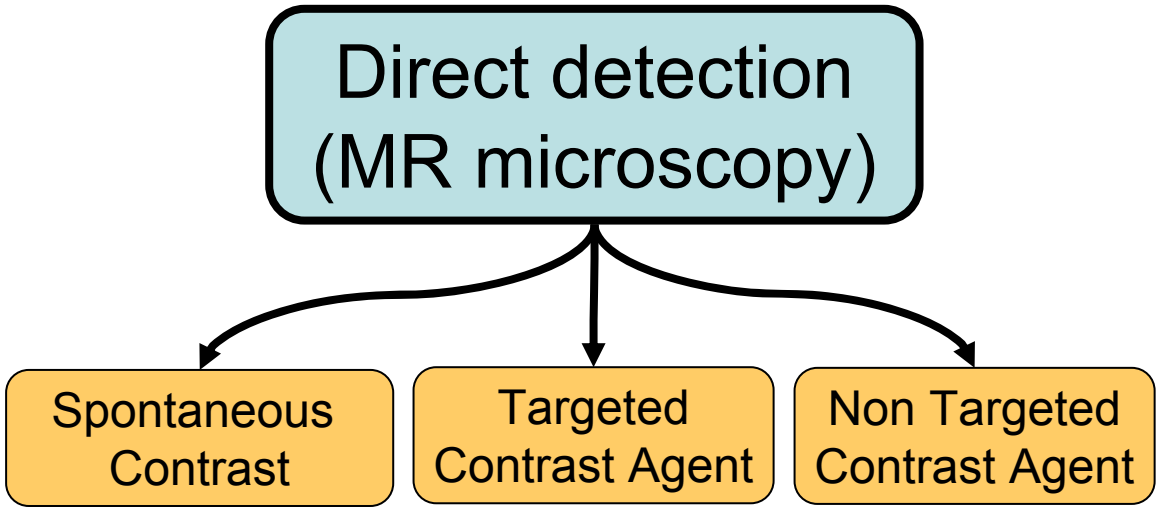


- In animals
  - PIB: not very efficient
  - Low resolution of PET: 1 to 1.5 mm
    - 30 to 50 pixels per brain slice
    - Partial volume effects

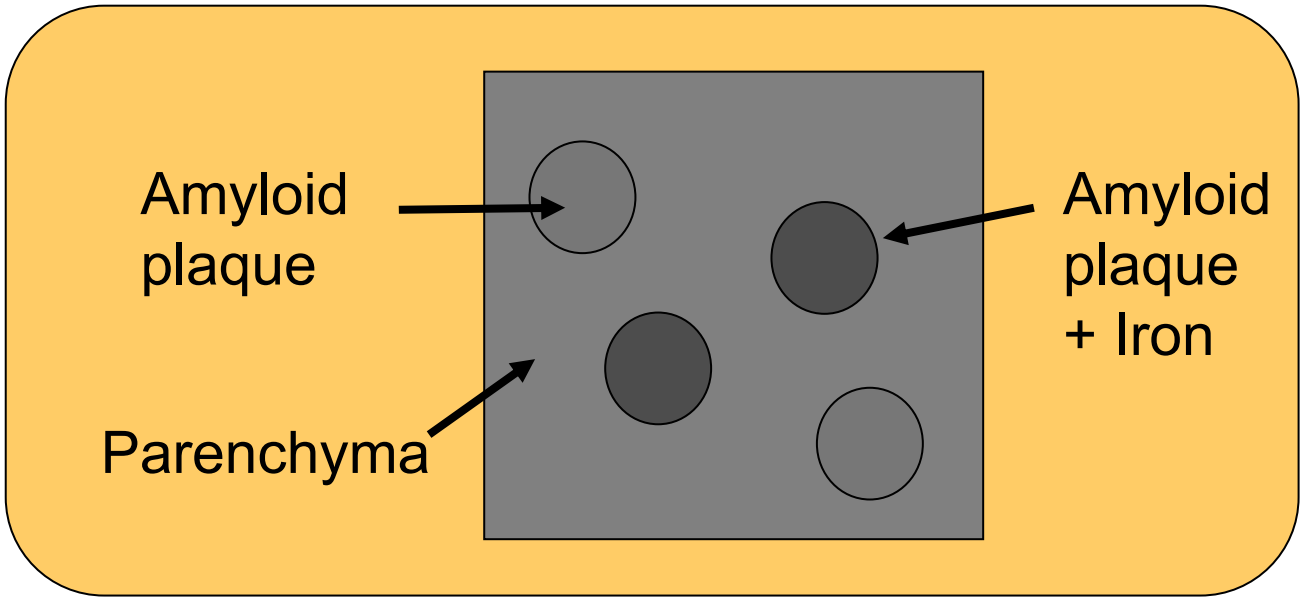


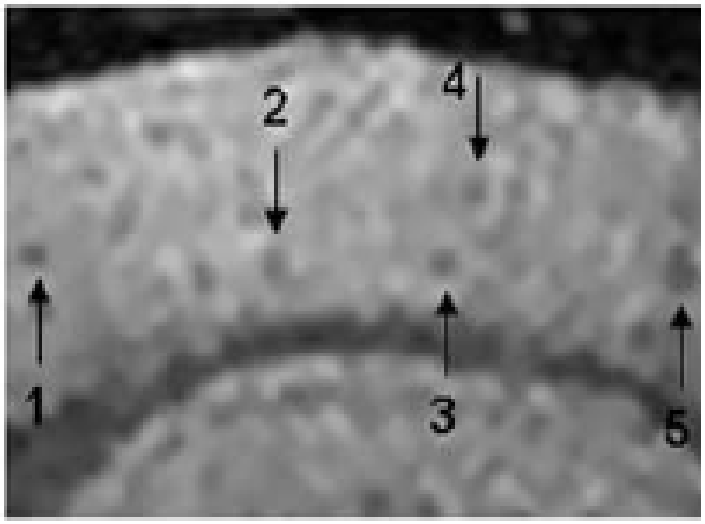
Poisnel et al., NBA, 2012

Imaging amyloid plaques by MRI in animals



Detection of amyloid plaques thanks to spontaneous contrast

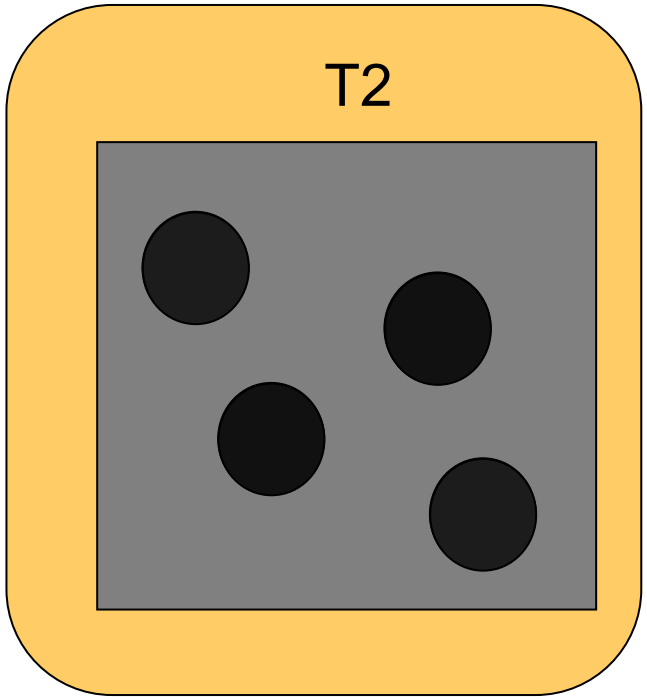


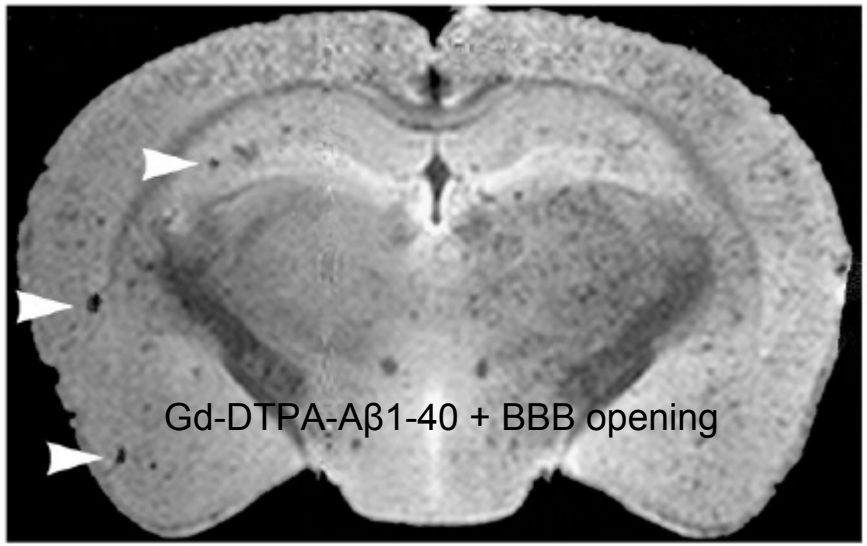


Jack C. R. et al. J Neurosc, 2005

60x60x120µm^3

Detection of amyloid plaques thanks to targeted contrast agents





Zaim Wadghiri Y. et al.
Magnetic Res in Medicine, 2003

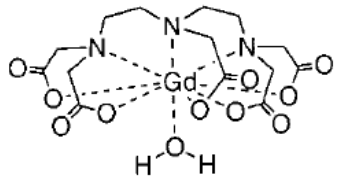
$59x59x250\mu m^3$

Detection of amyloid plaques thanks to non targeted contrast agents

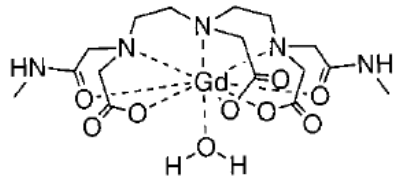
- Increase the signal in the brain
  - Allow to record images with a better resolution or faster
- Increase the contrast between amyloid plaques and the parenchyma

Use of clinically approved MR contrast agents

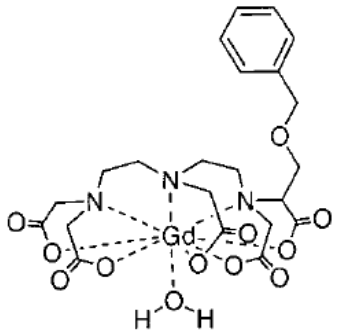
10 millions MRI exams with contrast agents each year in the USA



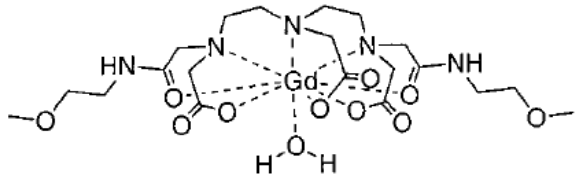
$[Gd(DTPA)(H_2O)]^{2-}$ (Magnevist™)



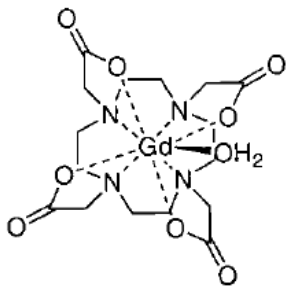
$[Gd(DTPA\text{-}BMA)(H_2O)]$ (Omniscan™)



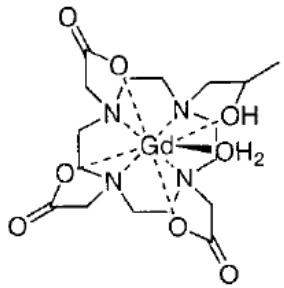
$[Gd(BOPTA)(H_2O)]^{2-}$ (MultiHance™)



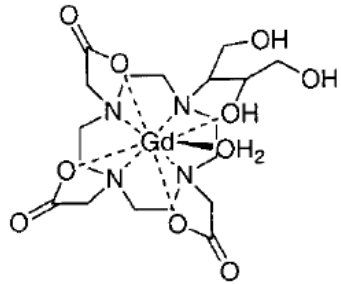
$[Gd(DTPA\text{-}BMEA)(H_2O)]$ (OptiMARK™)



$[Gd(DOTA)(H_2O)]^-$ (Dotarem™)



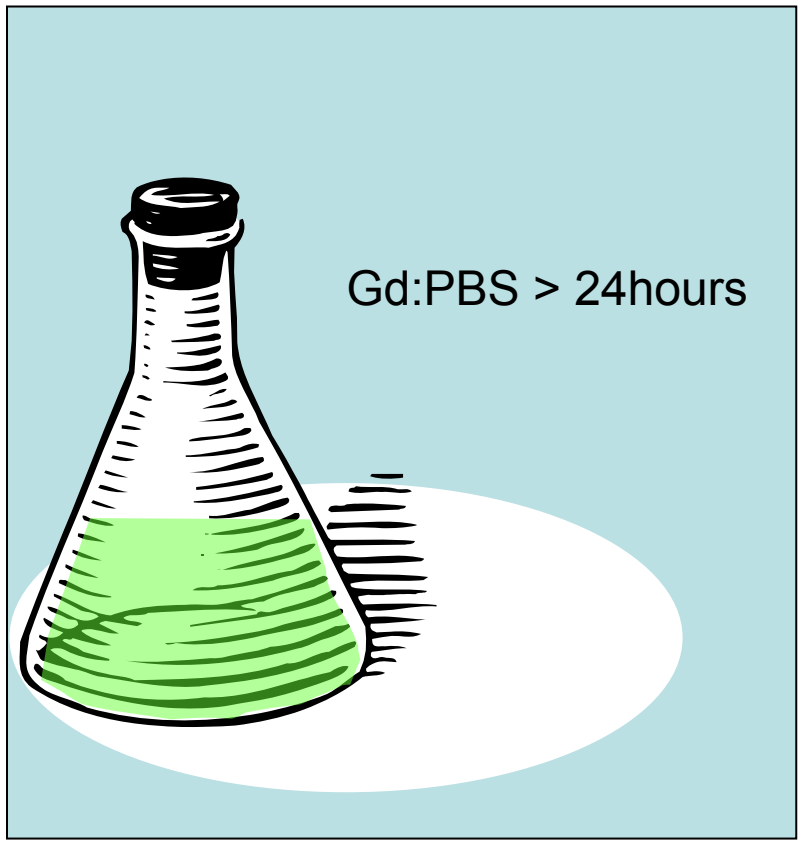
$[Gd(HP\text{-}DO3A)(H_2O)]$ (ProHance™)



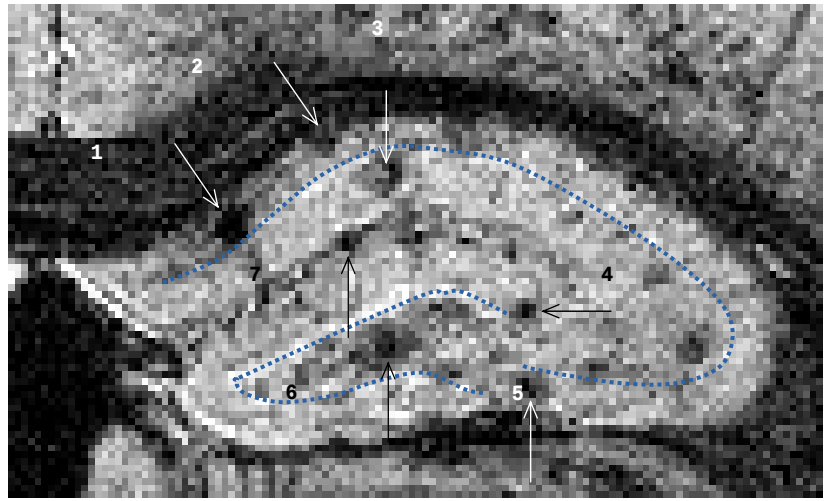
$[Gd(DO3A\text{-}butrol)(H_2O)]$ (Gadovist™)

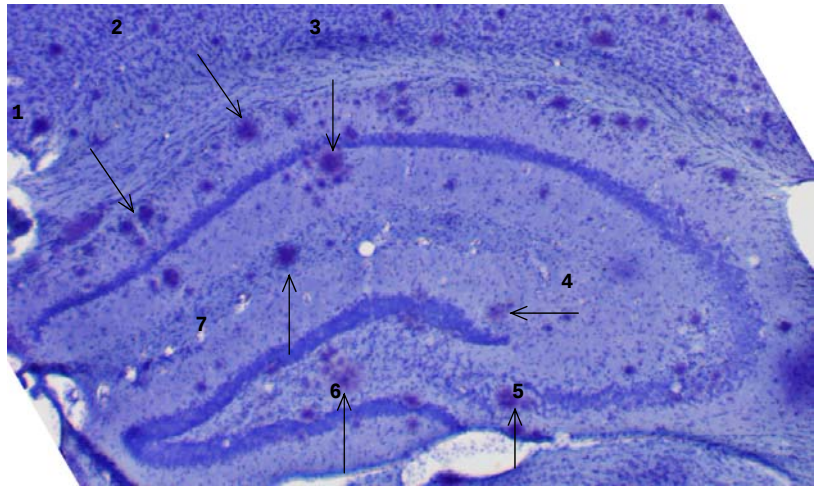
Caravan P. et al. *Chem Rev* **1999**, *99*, 2293-352.

Passive Gadolinium Staining method



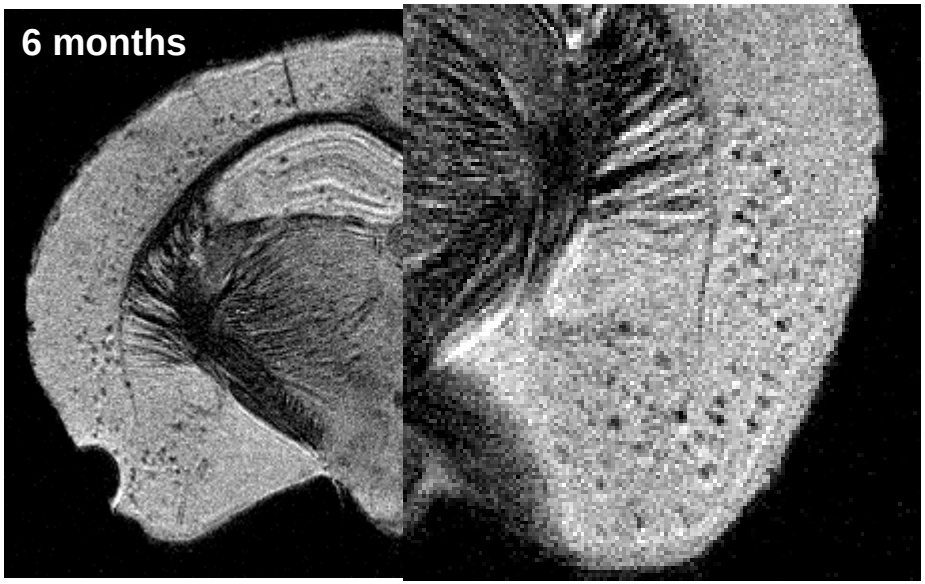
Alzheimer's mice
Detection of amyloid plaques

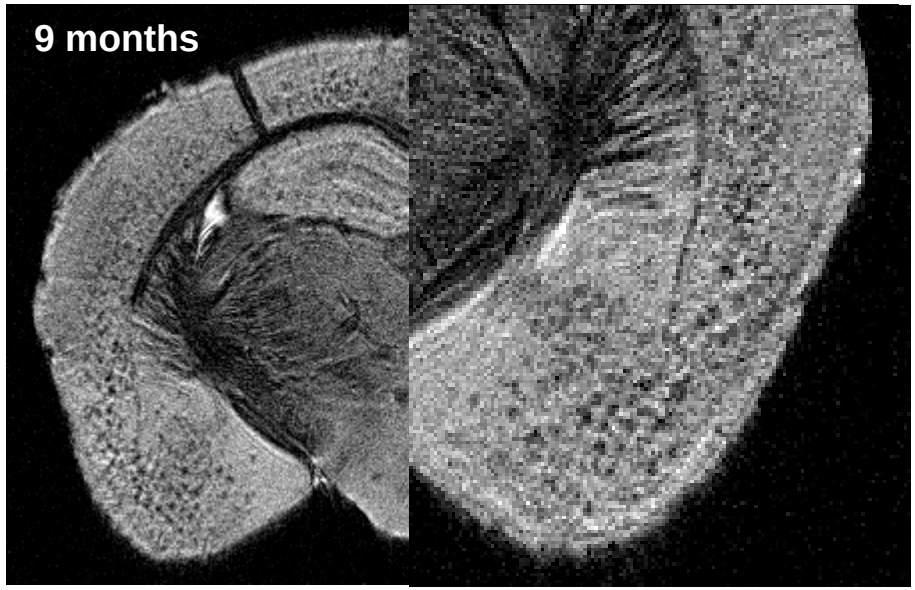


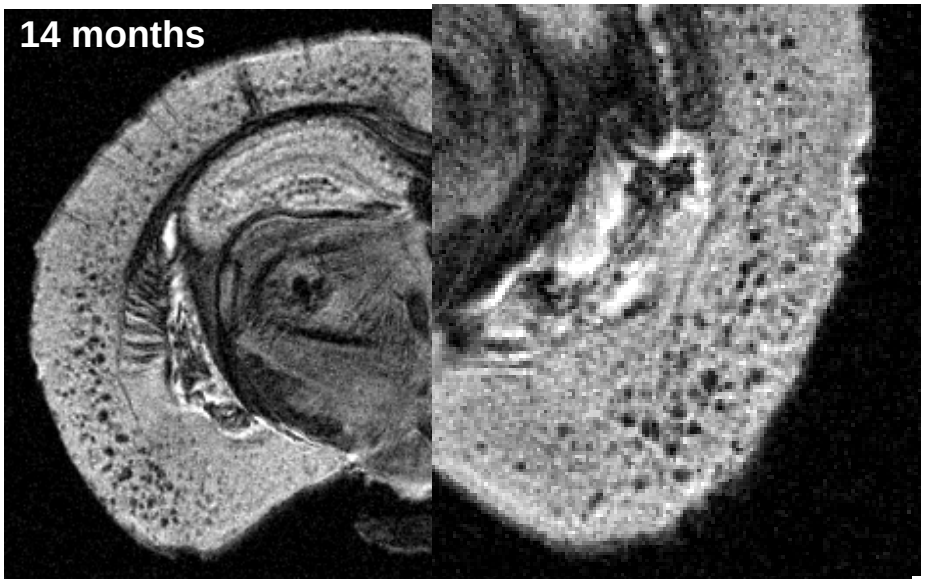


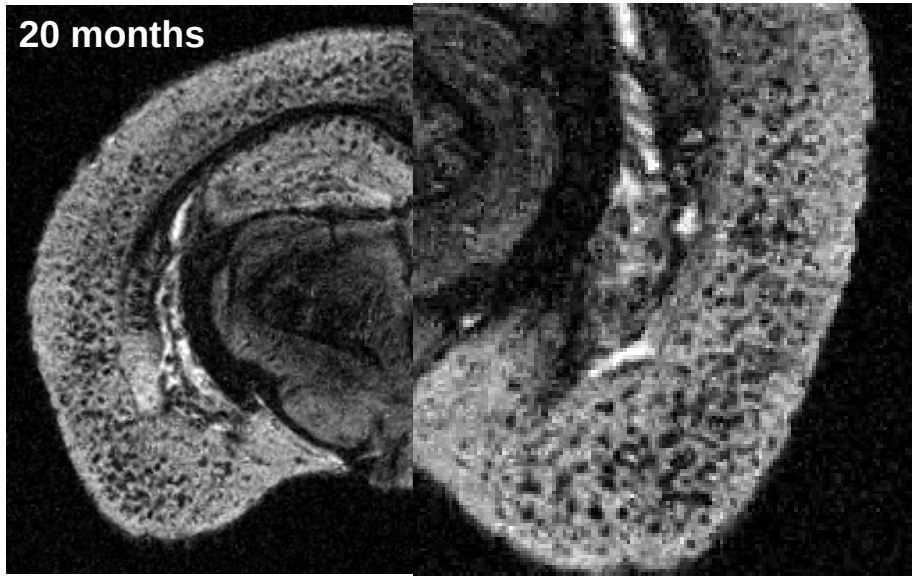
Dhenain M. et al. Magnetic Resonance in Medicine, 2006; 55 - 687-695.

Detection of amyloid plaques by Passive staining





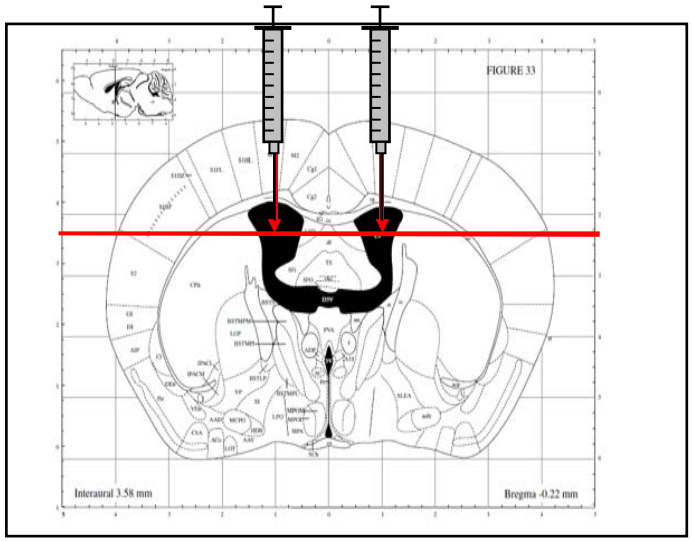




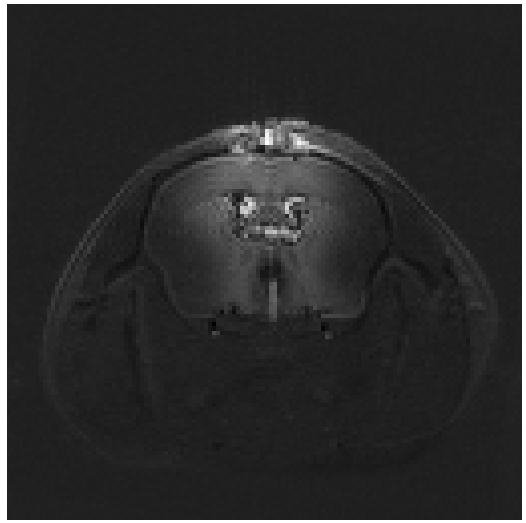
Petiet A. et al. Neurobiology of Aging, 2012, 33 - 1533-1544

In vivo application of Passive-Staining method
How to by-pass the blood brain barrier ?

- Intra-cerebro-ventricular (ICV) administration
  - Commonly used procedure in experimental research



Movie
30 min to 2 hours
After Gd injection



→ Diffusion of the contrast agent in the brain

"*In-vivo* Gadolinium staining"

In-vivo follow-up of amyloid load

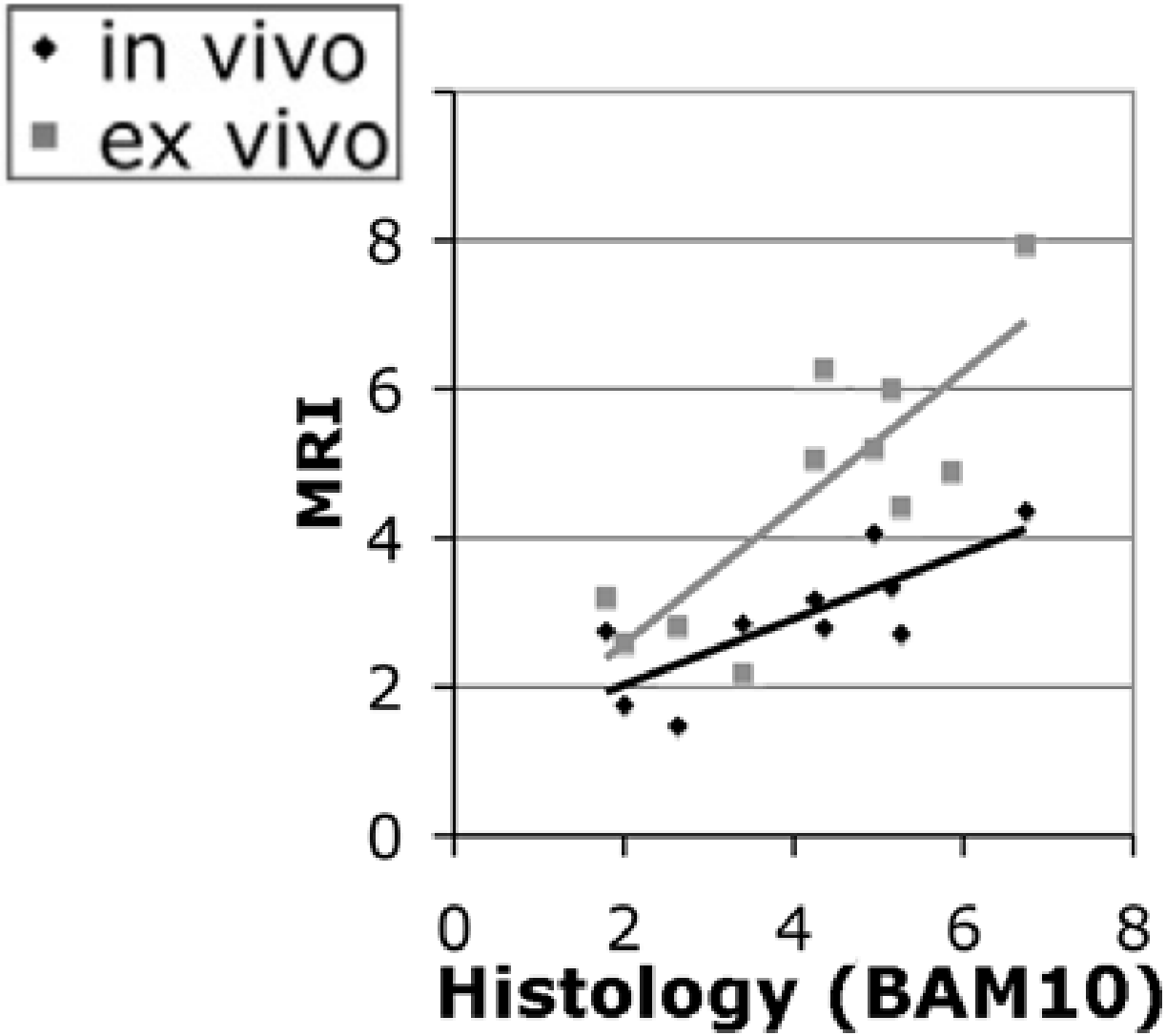
Detection of amyloid plaques by "*In-vivo* Gadolinium-Staining"

$APP_{SL}/PS1_{M146L}$

Control (amyloid free)

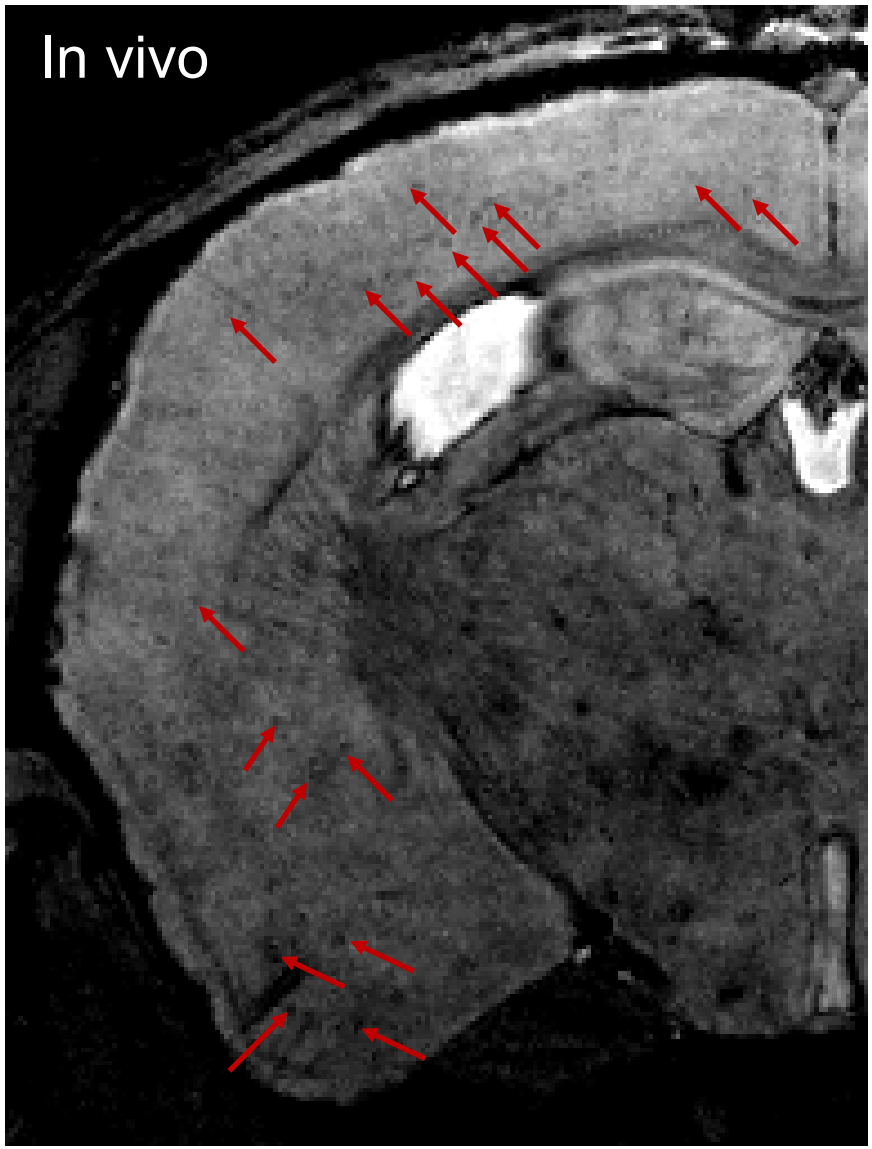
29*29*117 μm^3

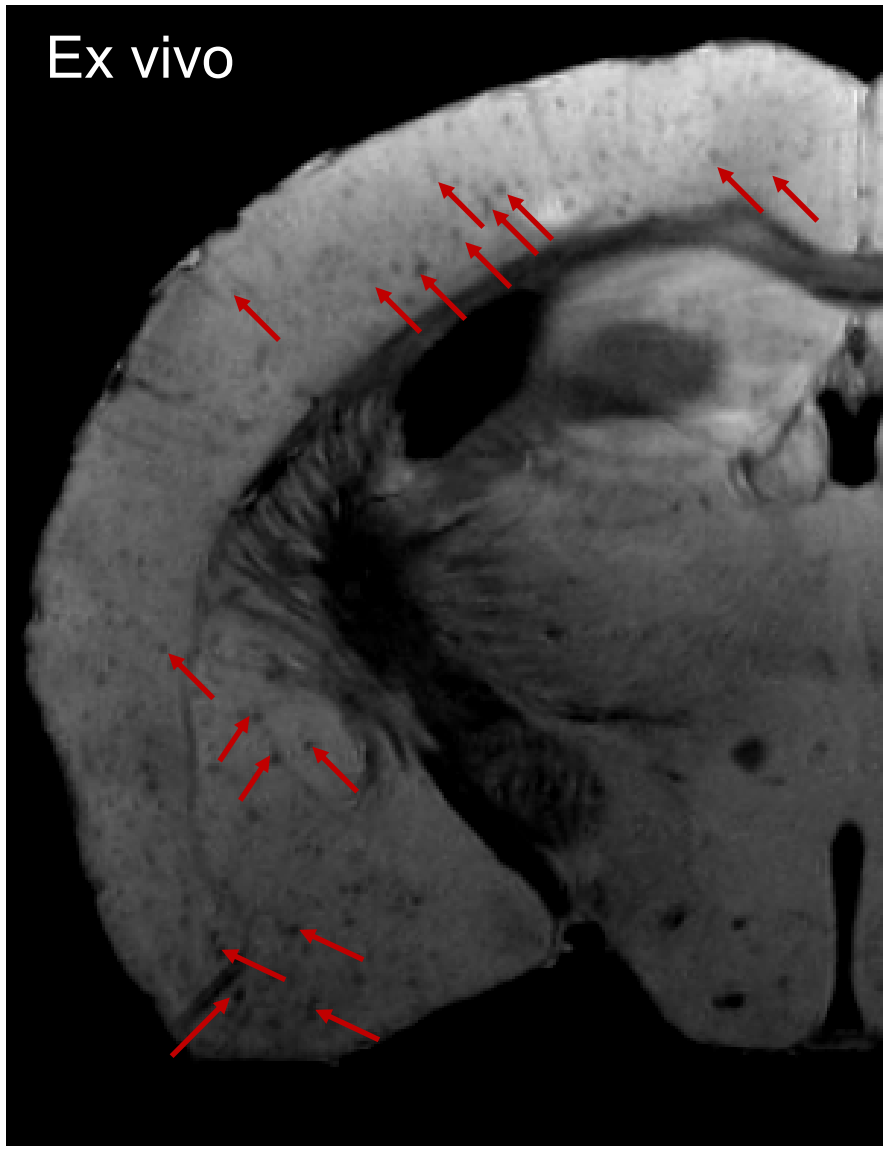
Correlation with histology



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

Imaging in other mouse strains



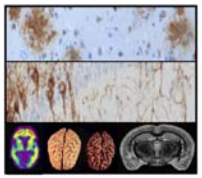


APP/PS1dE9 (76 weeks), tested also in APP_{SDI}, TripleTg, primate models

Bertrand A et al., 2013, PlosOne 8(2)

In vivo application of Passive-Staining method
How to by-pass the blood brain barrier after IV injection?

- Opening of the blood brain barrier thanks to ultrasounds and microbubbles
  - *Hynynen K. et al. Noninvasive MR imaging-guided focal opening of the blood-brain barrier in rabbits. Radiology 2001, 220, 640-6.*

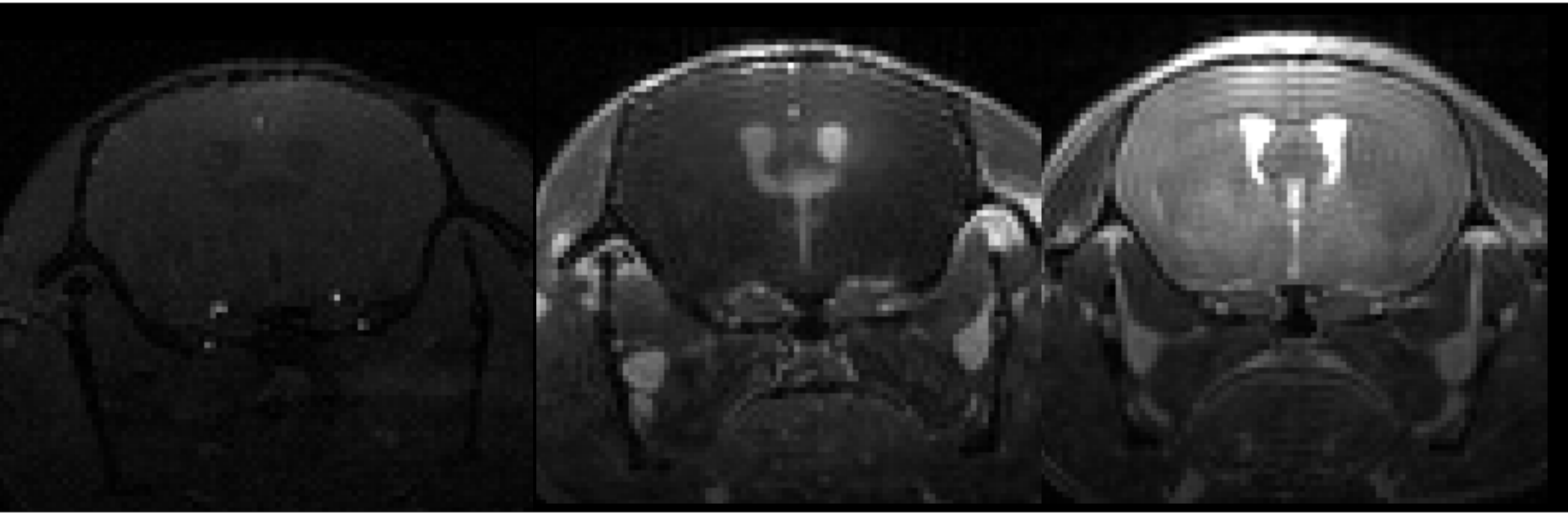


Penetration of the Gd in the brain

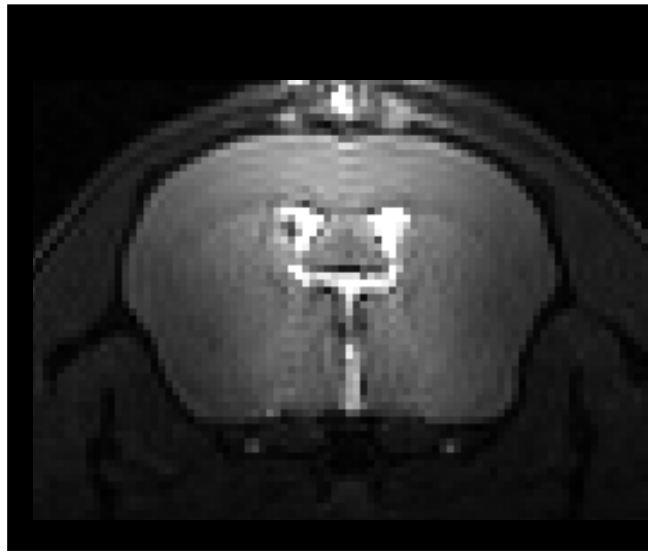
Control

Gadolinium – Intra-Venous

US-Gd-Staining

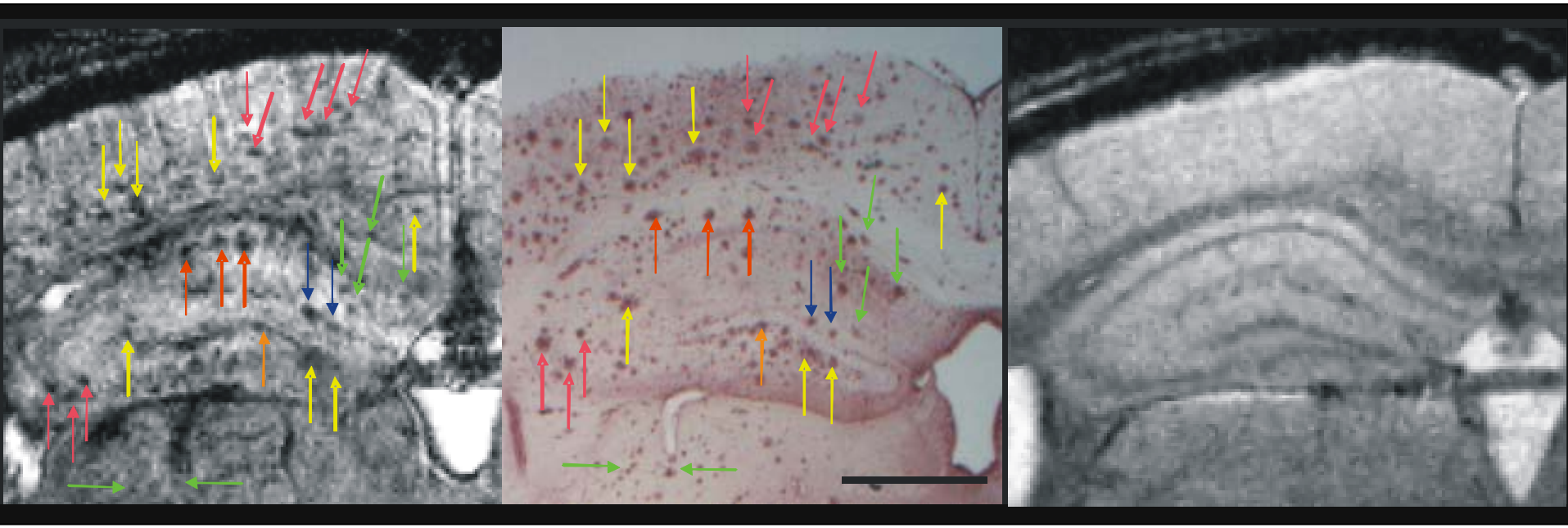


ICV-Gd-Staining



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

US-Gd-staining: amyloid plaques detection



$APP_{SL}/PS1_{M146L}$

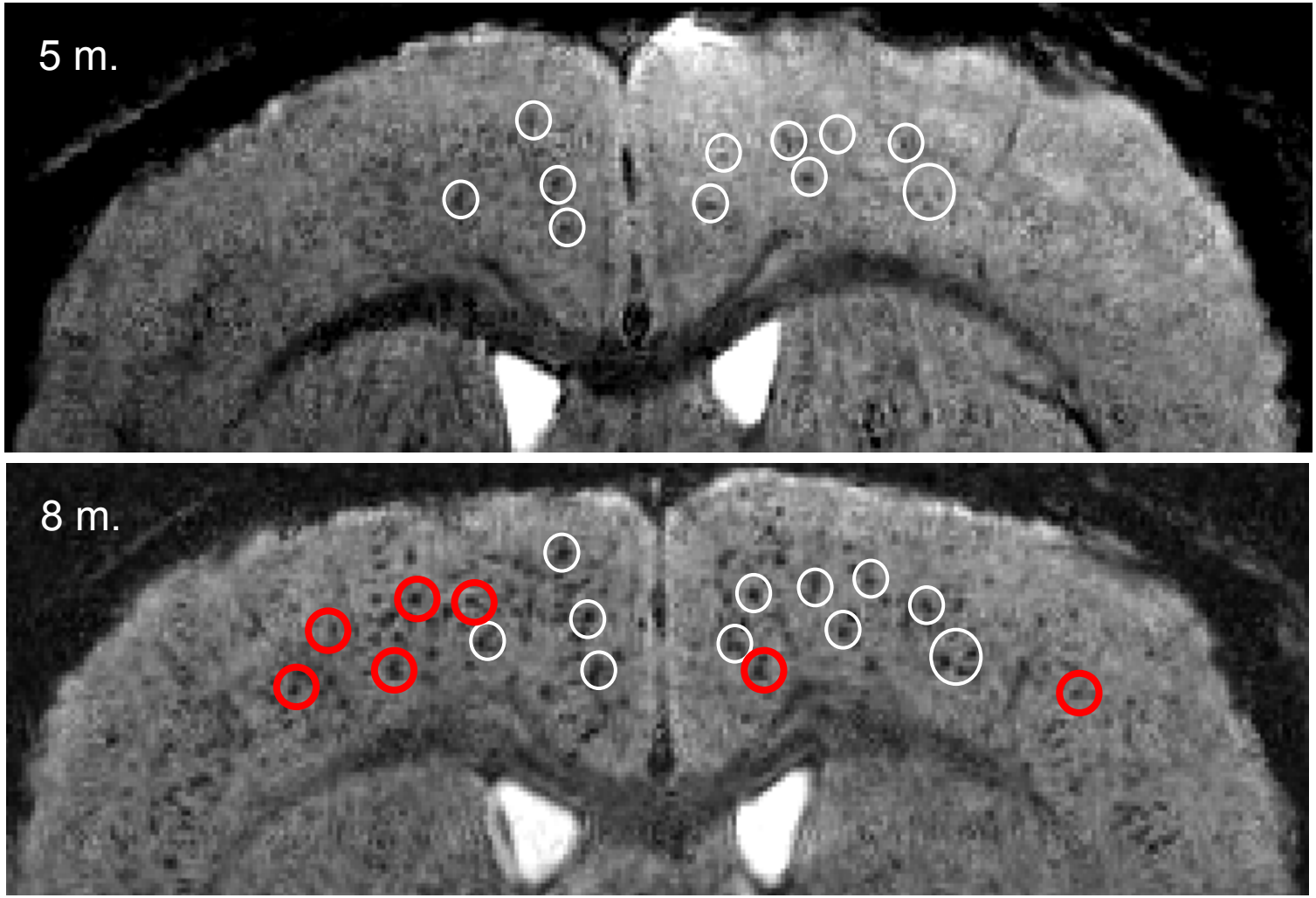
$PS1_{M146L}$

$29*29*117\ \mu m^3$

FA=20°, TR=30ms, TE=15ms, SW=25kHz, Nex=1

Acquisition time: 32 min

In-vivo longitudinal follow-up of amyloid plaques

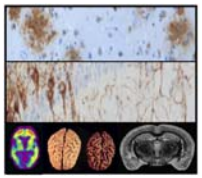


→ A tool for preclinical therapeutic evaluation

Conclusion

- Imaging of amyloid plaques
  - Peripheric administration of the contrast agent
  - Quick MRI method (32 min)
  - High in vivo resolution (in-plane resolution: 29 µm)

- Applications of the method
  - Therapeutic evaluation in animals
  - Longitudinal follow-up of the plaques
  - Gold standard to compare with new contrast agents



  - Proof of concept of the ability to detect amyloid plaques with a non targeted contrast agent after IV administration

Thanks …

- MIRCen, CEA-CNRS URA 2210 MAMOBIPET
  - Marc.Dhenain@cea.fr
  - Matthias Vandesquille
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  - Cecile Cardoso
  - Geraldine Poisnel
- NEUROSPIN
  - Christopher Wiggins
  - Denis Lebihan
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- CEA/IMETI/SEPIA/L4PA
  - Emmanuel Comoy
- Sanofi-Aventis Neurodegenerative Disease Group

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- NIH
- Programme longévité du CNRS 2009
- Fondation de Coopération Scientifique Maladie d'Alzheimer et maladies apparentées
- France Berkeley
- Hoffman LaRoche
- Alliance Biosecure

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