Models in Primates

Progress in Imaging Techniques

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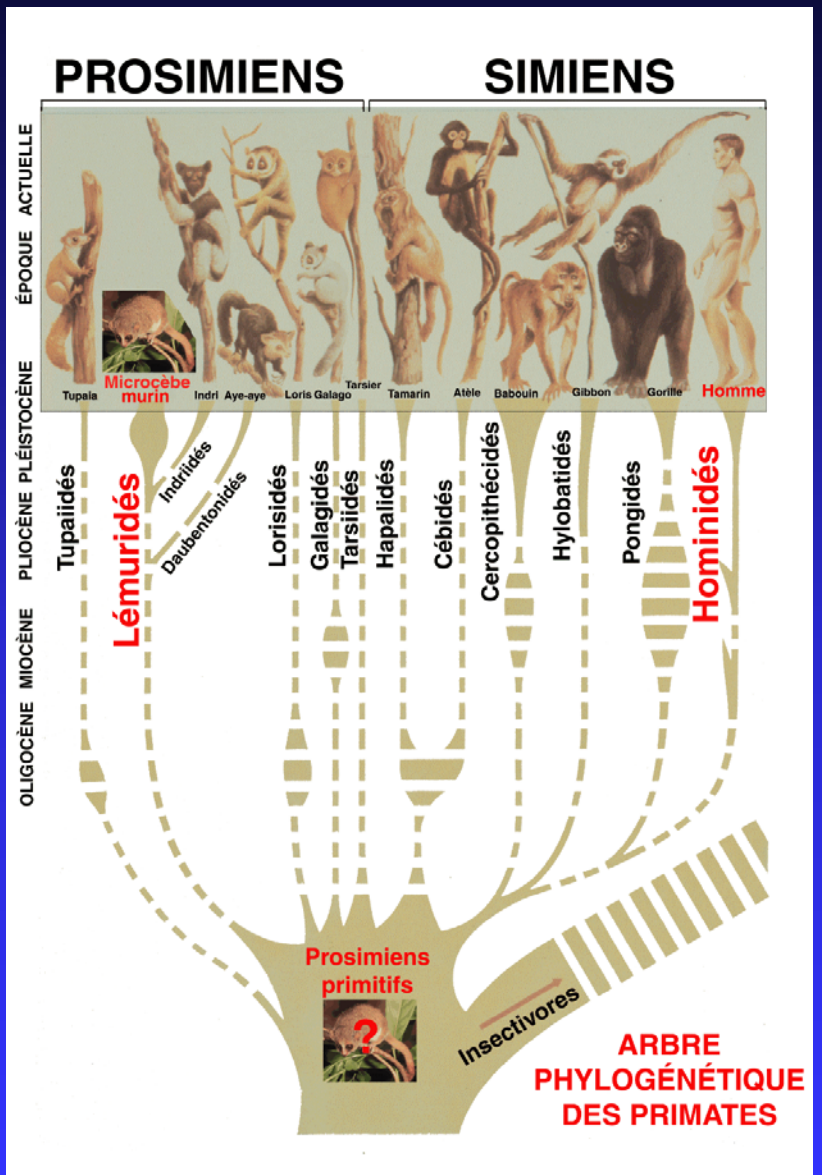
SECTION RECHERCHE

Models in Primates

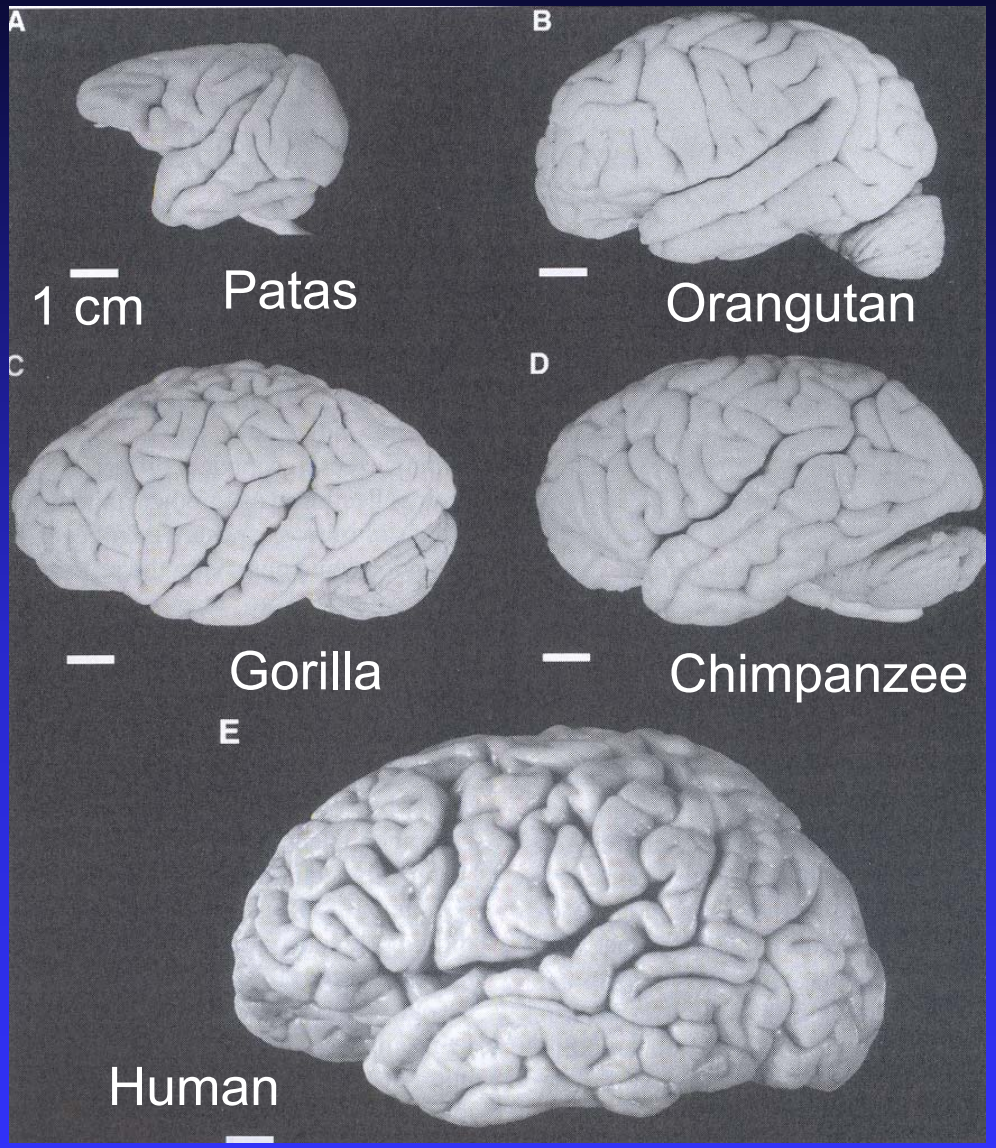
Example of spontaneous and heterogeneous models

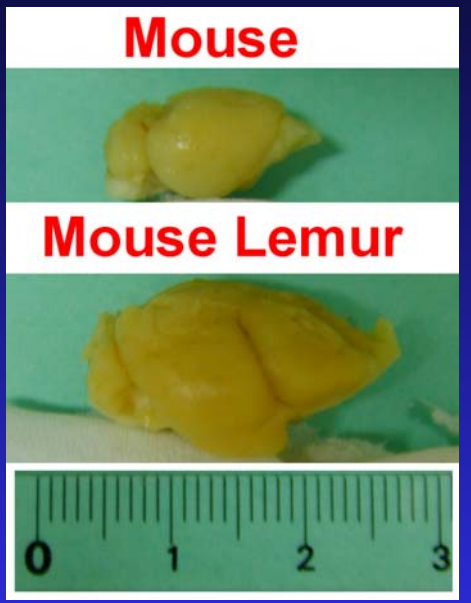
Primate heterogeneity



Species	Maximum life span (years)
Primates	
Human	122
Chimpanzee	59
Rhesus monkey	40
Squirrel monkey	27
Mouse lemur	12
Tree shrew	12
Polar bear	34
Sheep, goat	20
Dogs	
Small size (Pekinese)	20
Middle size (Beagle)	16
Large size (Saint Bernard)	14
Cat	~30
Guinea pig	8
Rodents	
Mouse	3.5
Rat	4

Brain heterogeneity in Primates



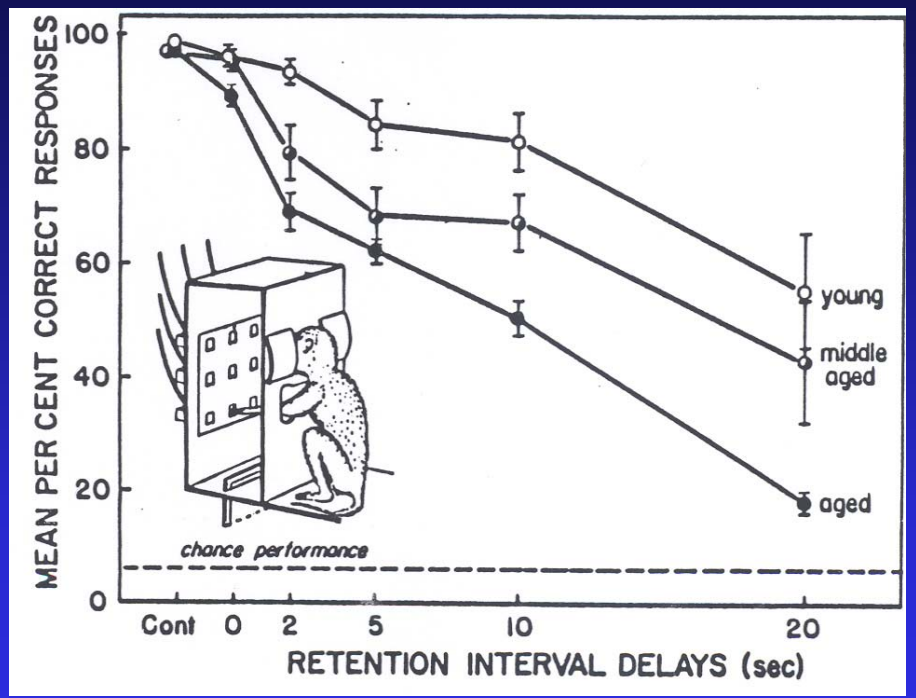


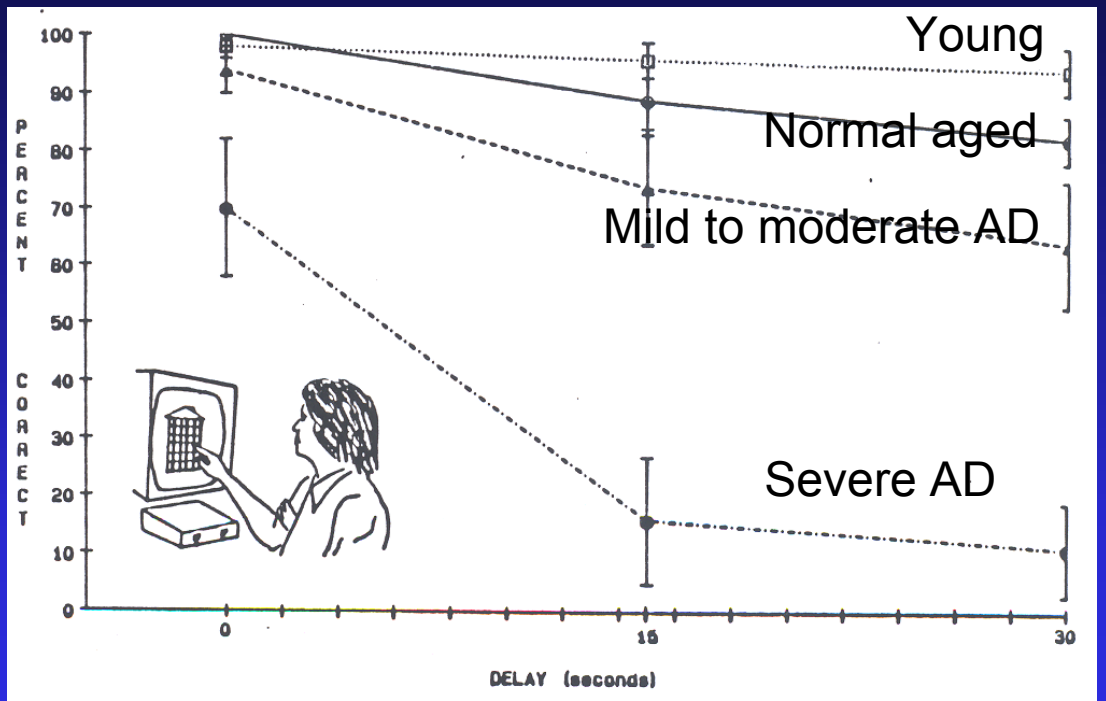
What are age related alterations in primates ?

Do they reproduce human alterations ?

How many animals are involved ?

Age related cognitive alterations





Delayed Response

(Bartus and Dean. Normal Aging, Alzheimer's disease and senile dementia, Aspects on Etiology, Pathogenesis, Diagnosis and Treatment, 1985)

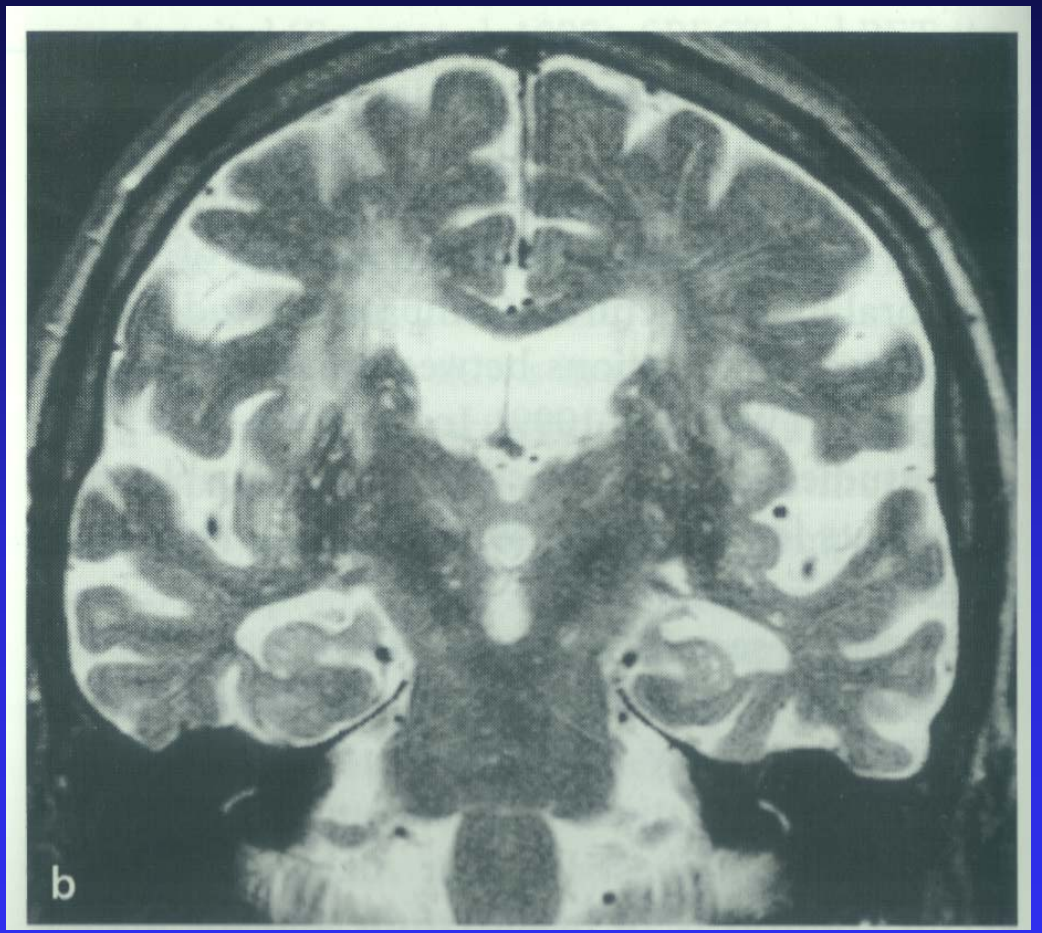
Age related cognitive alterations

- Prefrontal impairments, perseveration
  - ~ 15-20 years in Rhesus monkeys
  - Very constant in different animals
- Tasks depending on medial temporal areas
  - ~25-30 years in Rhesus monkeys
  - (But) Interindividual variations

What is responsible for these alterations ?

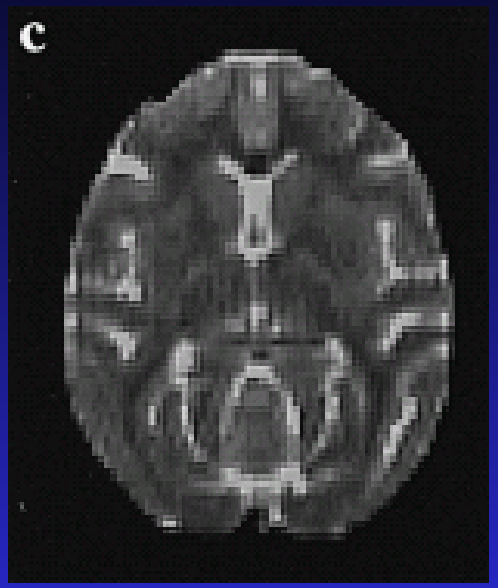
Macroscopic alterations

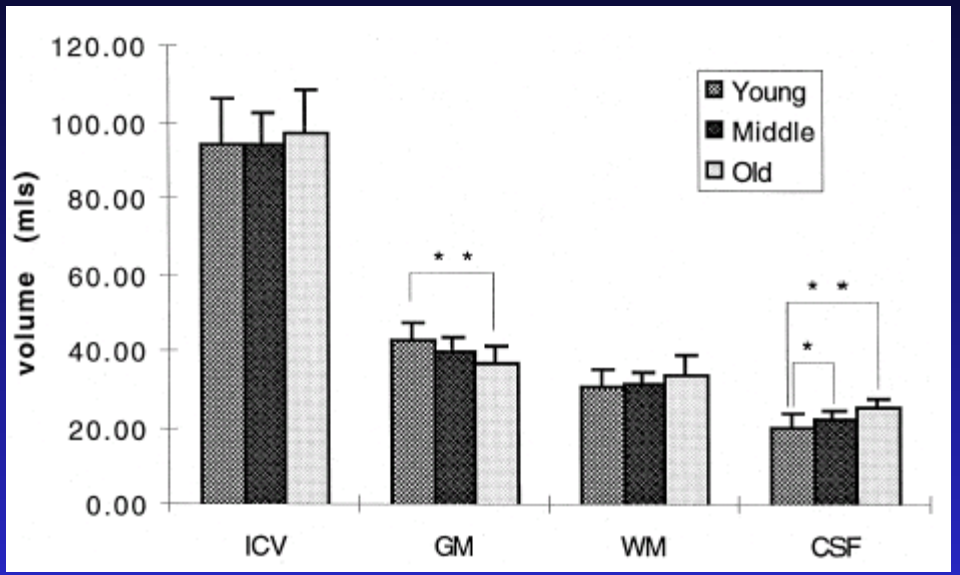
Cerebral atrophy

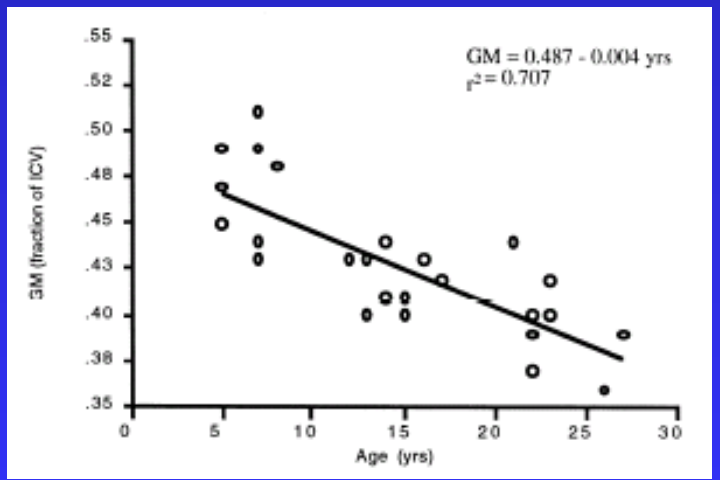


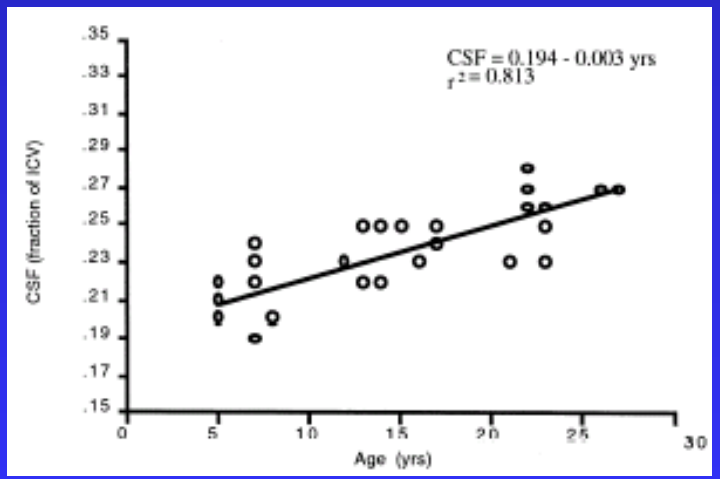
Cerebral atrophy in human

Cerebral atrophy in Rhesus monkey



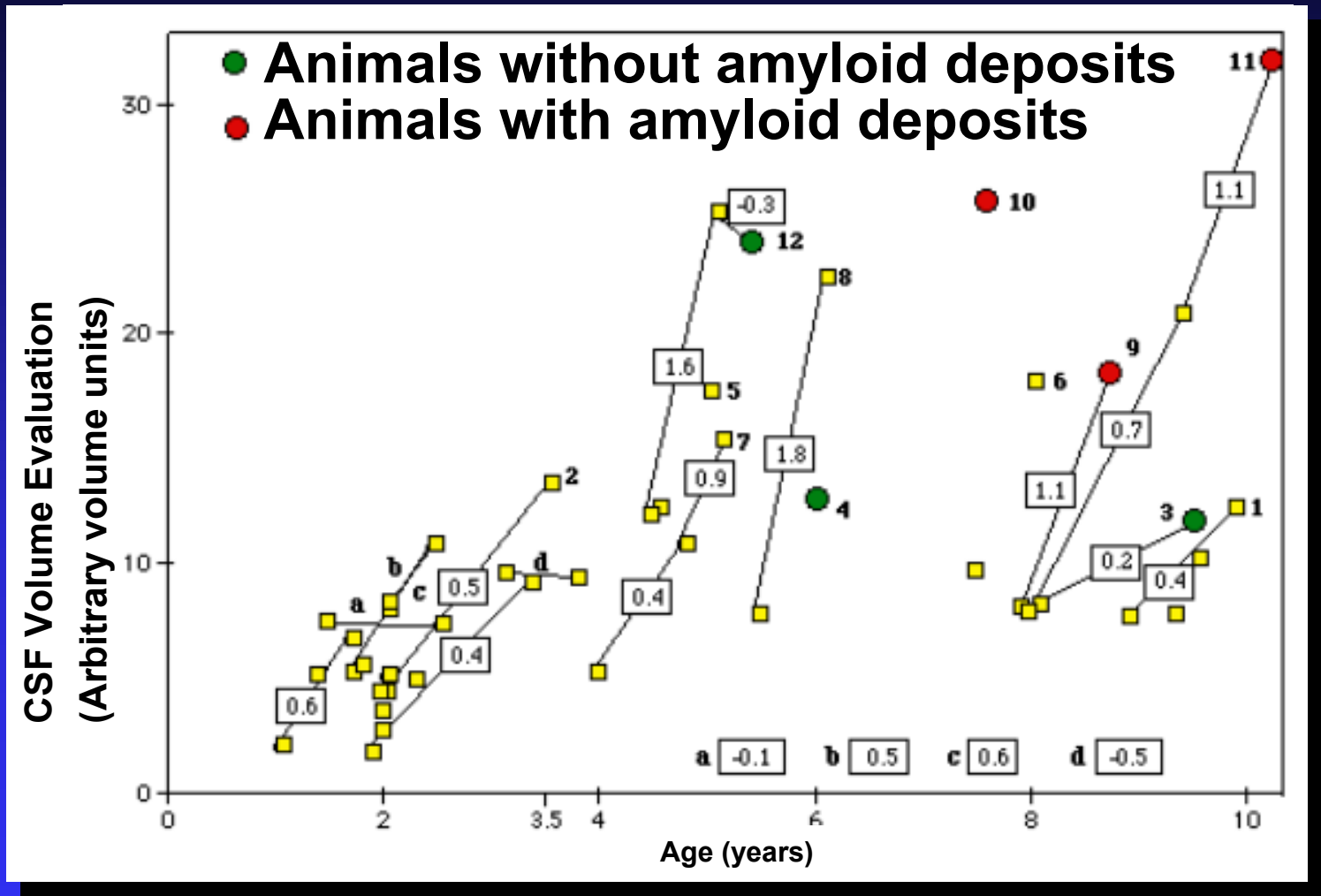


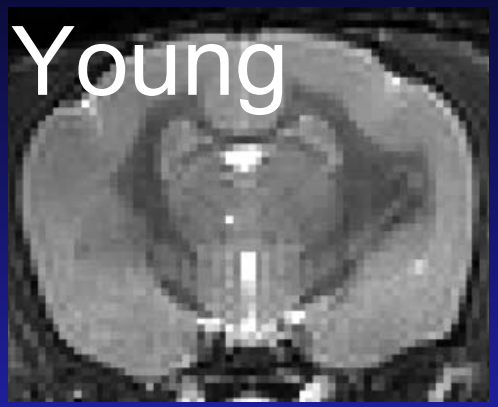


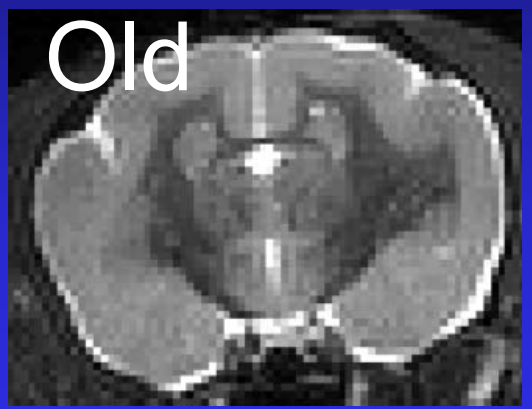


(Andersen et al., Brain Research, 1999)

Temporo-parietal atrophy in mouse lemurs



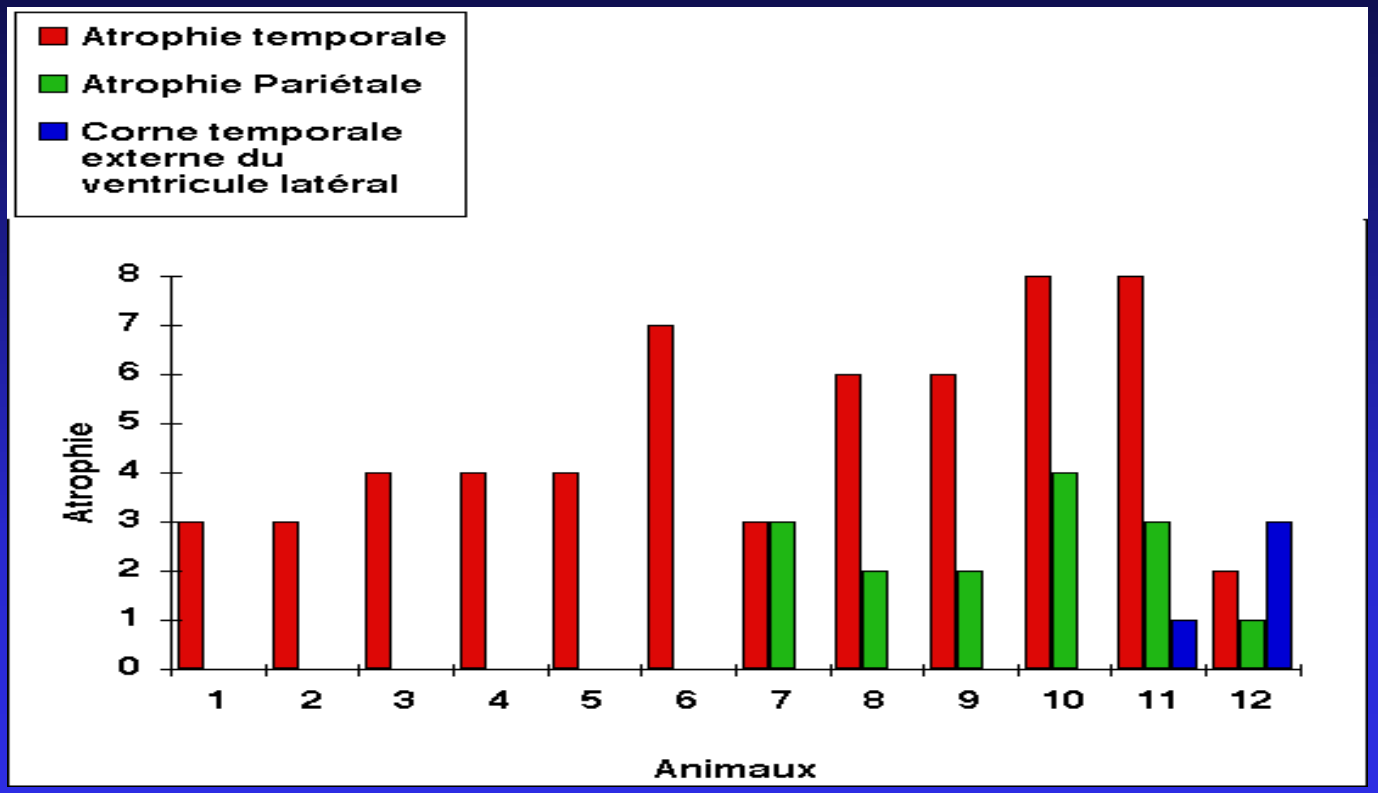




(Dhenain et al., Neurob. Aging, 2000)

- Fast evolution when the process is started

Regional atrophy evaluation
Several types of brain atrophies



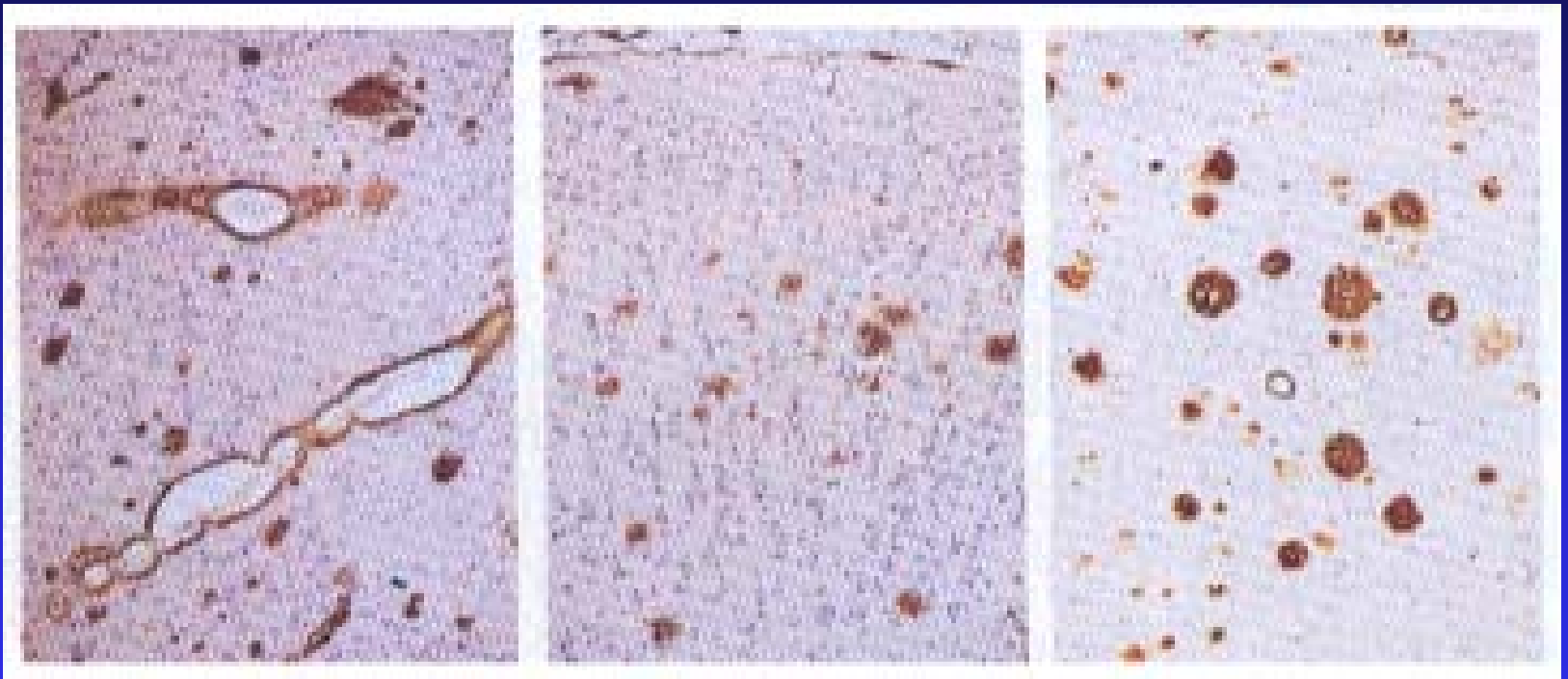
Dhenain et al., Neurob. Aging, 2000

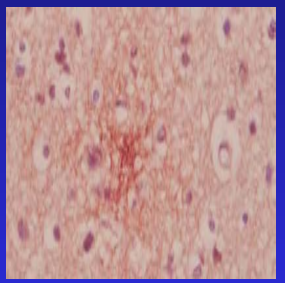
- Various clinical entities in spontaneous animal models ?
- Human like disease or Primate specific disease ?

Microscopic alterations

Amyloid deposits

Chimpanzee | Rhesus | AD - Human





Mouse lemur

(Gearing et al, PNAS, 1994)

Microscopic alterations

Amyloid deposits

Animal species	Maximum amyloid deposits density	References
AD brain	256 /mm²	Hyman, 1993
Rhesus monkeys	8 /mm²	Walker, 1987
New world monkeys Squirrel monkeys	4-5 /mm²	Walker, 1987
Lemurian primates Mouse lemurs	16 /mm²	Bons, 1993
Tree Shrews	0 /mm²	Pawlik, 1999
Polar Bears	8-10 /mm²	Cork, 1988
Dogs	Similar or exceeding severe cases of AD	Cummings, 1996

(Dhenain, Handbook of Neuropsychology (2nd ed, 2001)

Sequence homologies

APP – beta amyloid

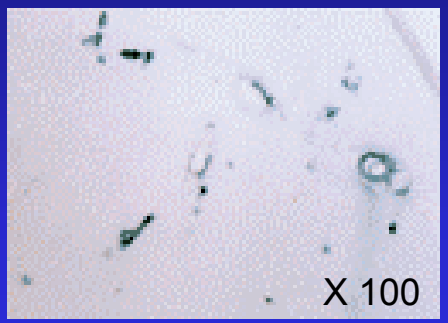
Animal species	β-APP	A β Sequence	Mutations
Cynomolgus monkeys	Homology 100%	Homology 100%	Not reported
New world monkeys Squirrel monkeys	Difference 3 amino acids	Homology 100%	Not reported
Lemurian primates Mouse lemurs	??	Homology 100%	Not reported
Tree Shrews	Difference 3 amino acids	Homology 100%	Not reported

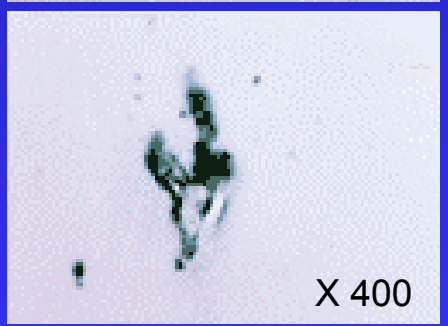
(Dhenain, Handbook of Neuropsychology (2nd ed, 2001)

Microscopic alterations

Amyloid angiopathy

- Amyloid angiopathy in most of the primates
- Squirrel monkey : model of amyloid angiopathy



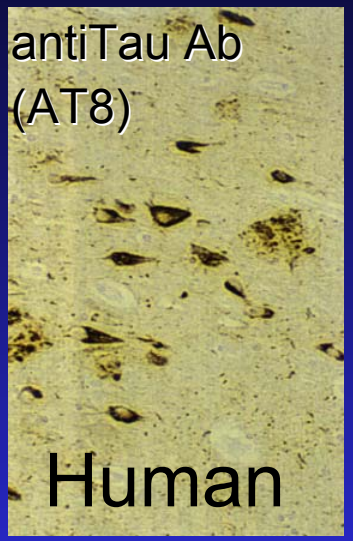


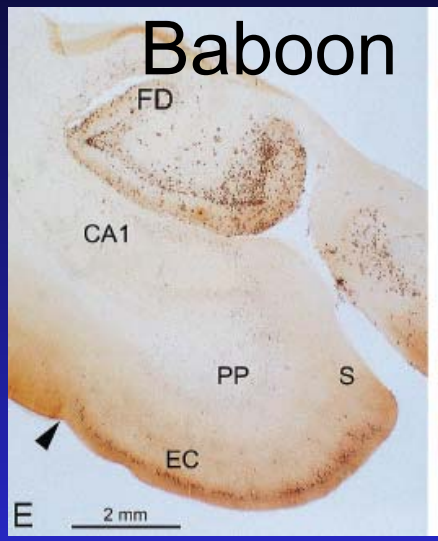
monoclonal anti–Aß antibody (4G8)

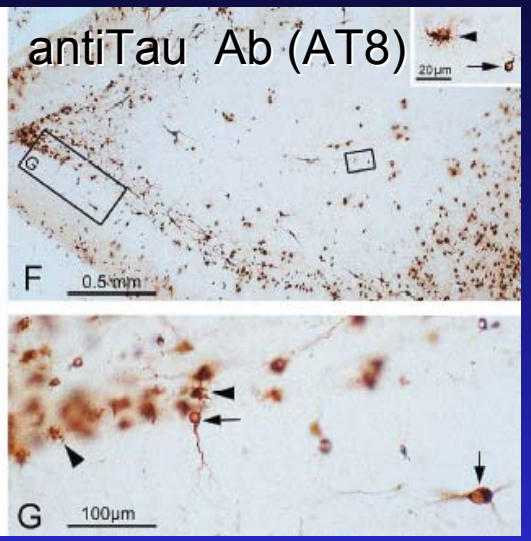
- Mutation similar to that of Icelandic patients with hereditary cerebral hemorrhage with amyloidosis (HCHWA-I) or cystatin C amyloid angiopathy (Wei et al. Stroke, 1996)

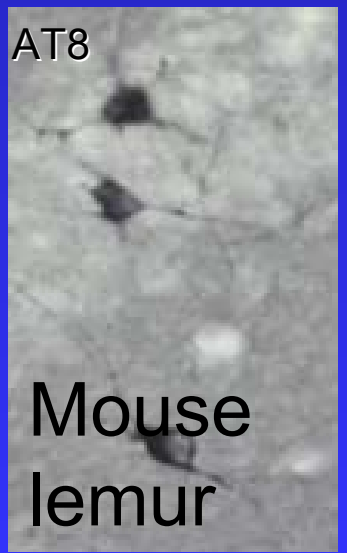
Microscopic alterations

Neurofibrillary alterations

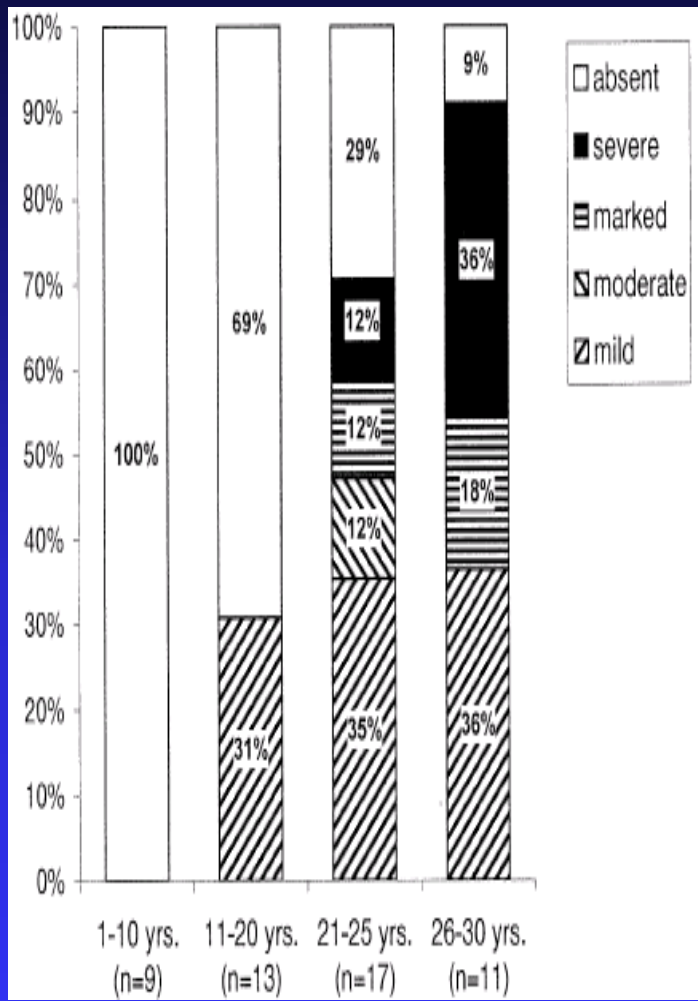








Hartig



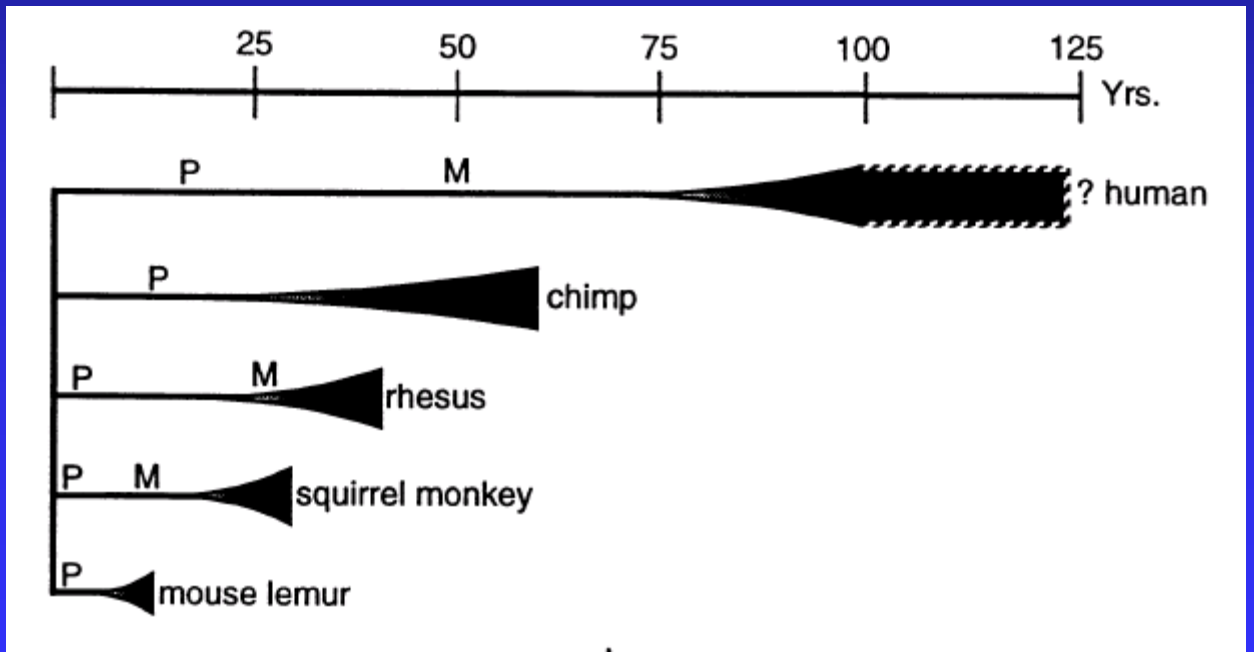
(Schultz, Neurob Aging, 2000)

Functional consequences of neuropathological alterations

- No correlation between amyloid deposits and behavioral alterations
- No study concerning neurofibrillary / behavioral alterations (especially in baboons)

Apolipoprotein E

- In Human : ApoE4 is a risk factor for AD
- In Human : ApoE3 and E2, protection for AD
- ApoE4-like forms in primates
- ApoE3 and E2 forms seem to be ‘favorable mutations’ that occurred in the course of evolution.



Finch et al, Neurobiology of Aging, 1999

Alteration of the neurotransmission

- Acetylcholine
- Monoaminergic
  - Serotonin
  - Noradrenaline
- Somatostatin
- …

- Correlation between occurrence of neurotransmission alterations and behavioral alterations

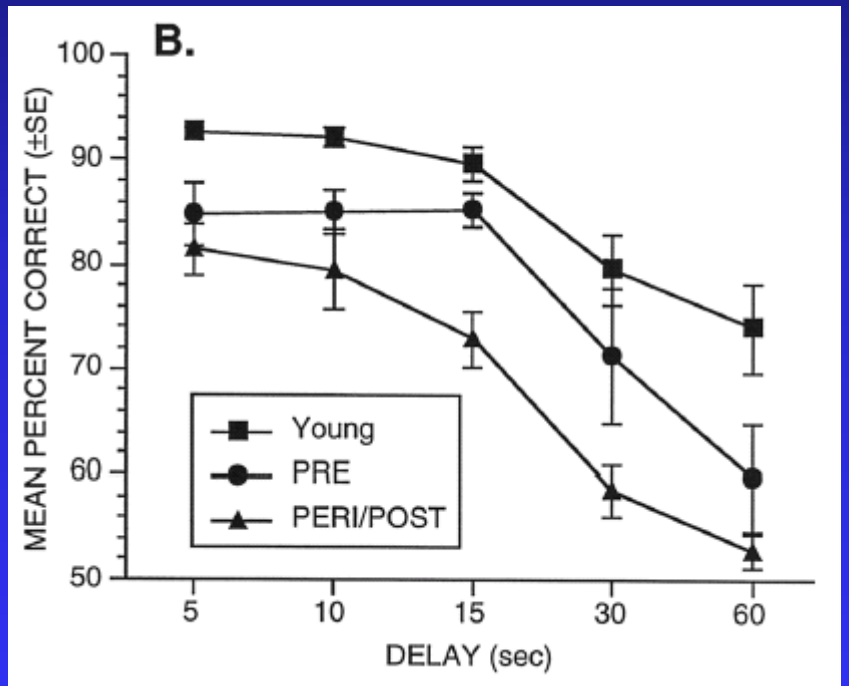
- First evaluation of treatments modulating the neurotransmission

Traitement	Classe	Amélioration Primates âgés	Date étude
Physostigmine	Anticholinestérase	Oui	Bartus, 1979
Tetrahydroaminoacridine	Anticholinestérase	Oui	Bartus, 1983
Arecoline	Agoniste muscarinique	Oui	Bartus, 1980
Oxotremorine	Agoniste muscarinique	Oui	Bartus, 1983
Choline	Cholinergique Precurseur de phospholipides	Non	Bartus, 1980
Apomorphine	Agoniste dopaminergique	Non	Bartus, 1983
Muscimol	Agoniste GABA	Non	Bartus, 1983
Clonidine	Agoniste α agoniste	Non	Bartus, 1983

- More recently
  - Neurotrophic Factors
  - Neurotransmitters
  - Genic Therapy

Neuroendocrinologic proximity of the primates ? Example of estrogenic alteration

- Menopauses in superior primates
  - Associated behavioral alterations



Roberts, Neuroreport, 1997

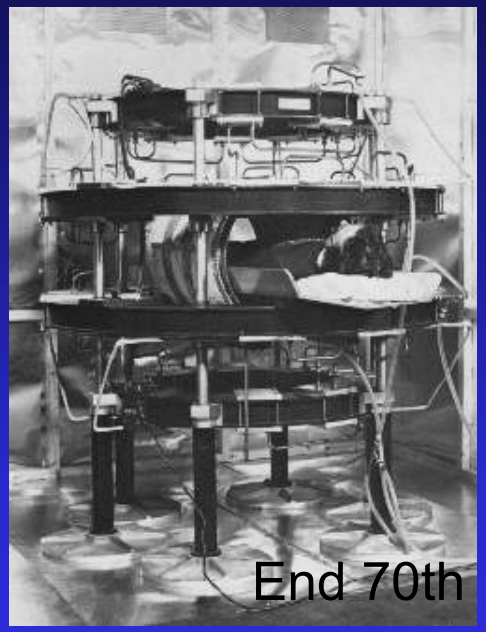
Conclusion Primates

- No case of AD in primates = Models for normal aging
  - No mutation reported for AD-like lesions
  - Few animals evaluated
- Evaluation of the factors that are responsible for inter-individual differences
  - Clinical approach in animals with well known historical records
- Factors modulating cognitive aging
  - Neuroendocrinologic factors, Biological rhythms,…

Progress in Magnetic Resonance Imaging Techniques

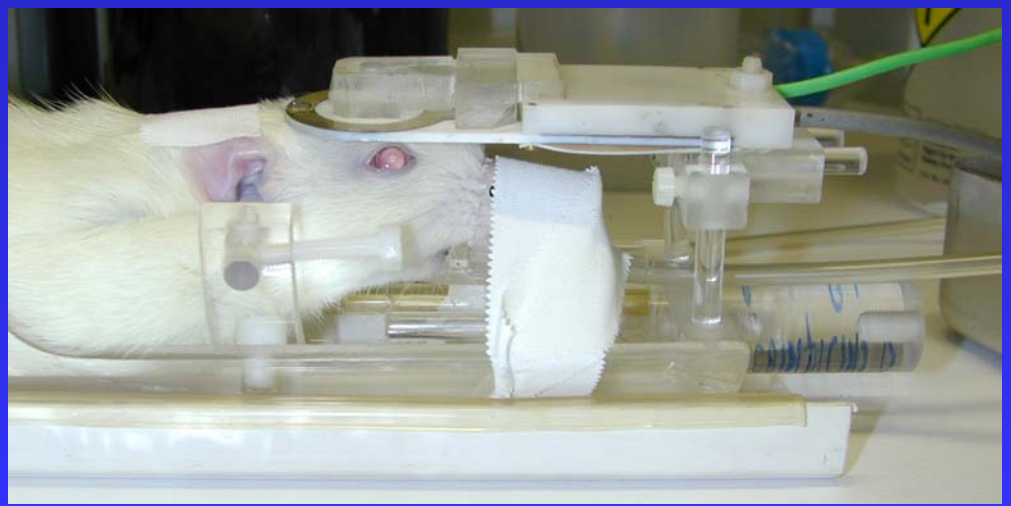
Animal models and imaging (MRI)

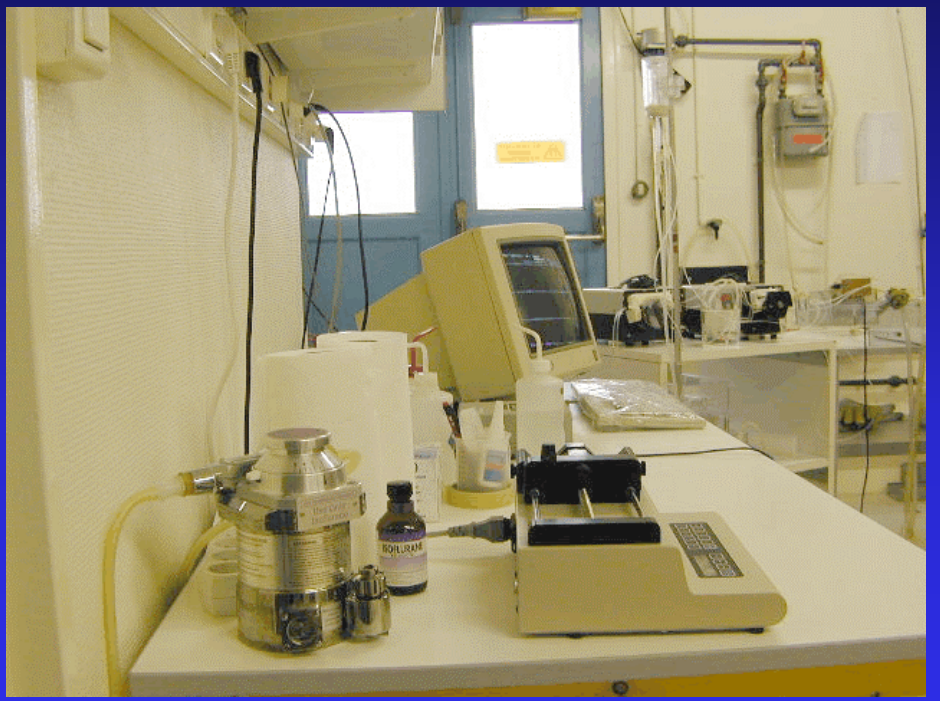
- Methodological progress in imagery performed in human



- Progress in small animal imaging
  - Animal model Phenotyping
  - Longitudinal follow-up of pathologies and treatments
    - Non invasive / Rapid transfer in humans

MRI in small animals





In-vivo imaging – Mouse brain

Resolution = 234x117x117 μm3

Imaging time = 51 minutes

Post mortem imaging

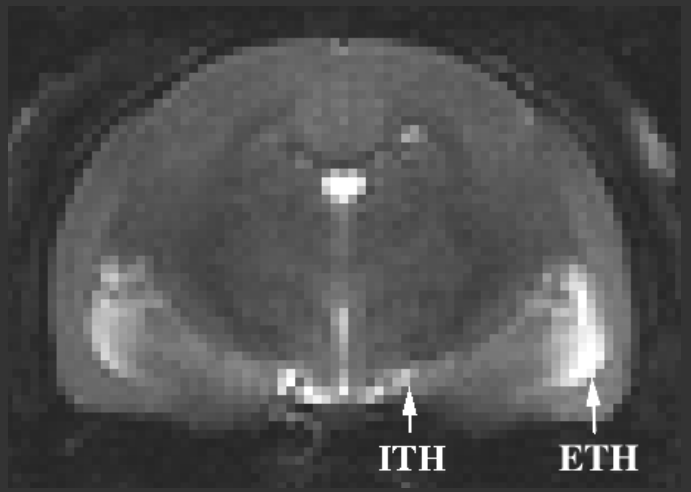
Resolution = 117x58x58 µm3

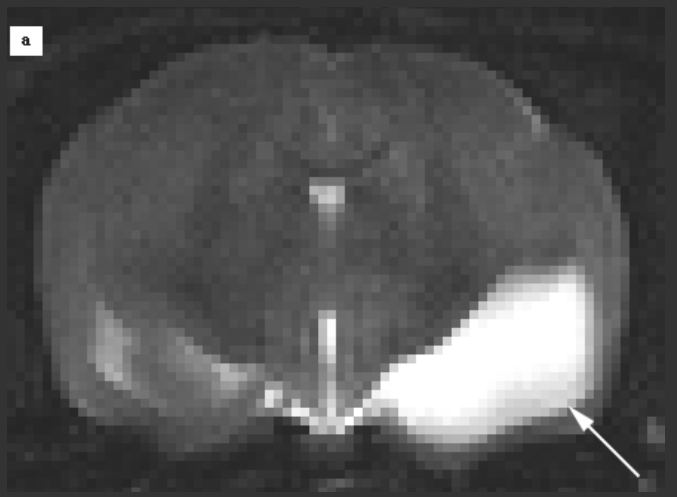
Imaging time = 7 hours 36 min

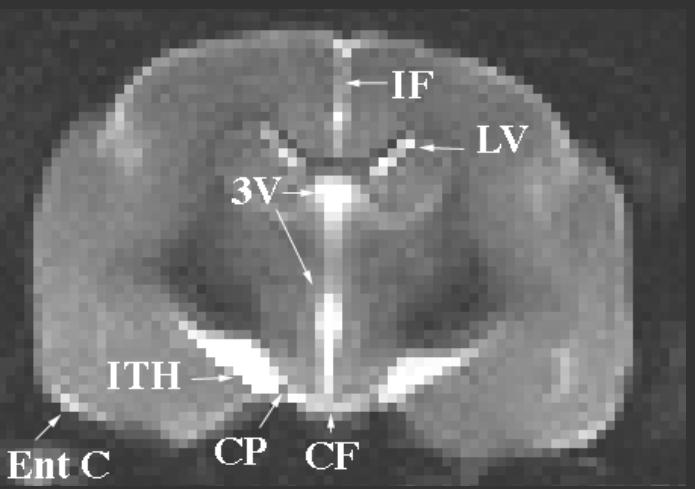
Many parameters accessible

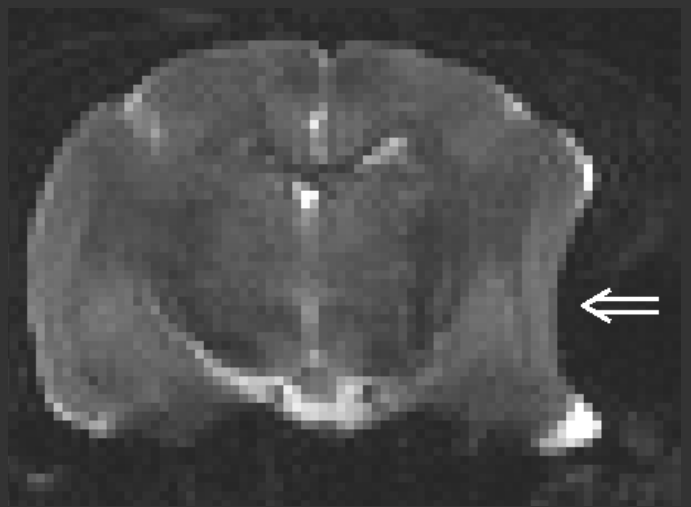
- Examples of NMR parameters
  - Anatomy
  - Perfusion / Functional imaging
  - Spectroscopy
  - Molecular/cellular imaging (amyloid plaque imaging)

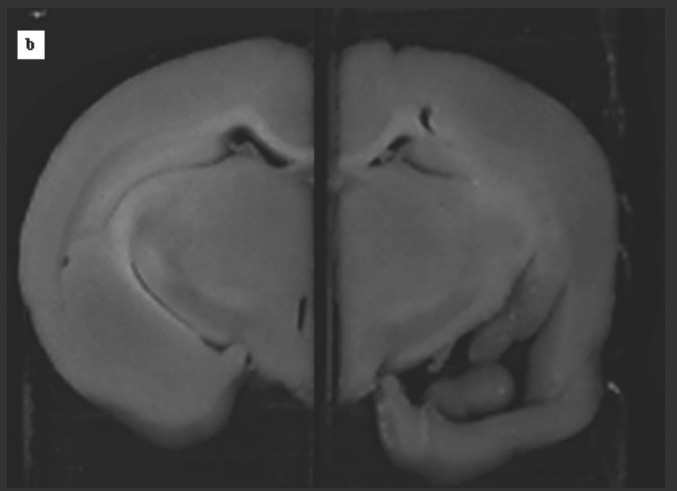
Cerebral atrophy in mouse lemurs



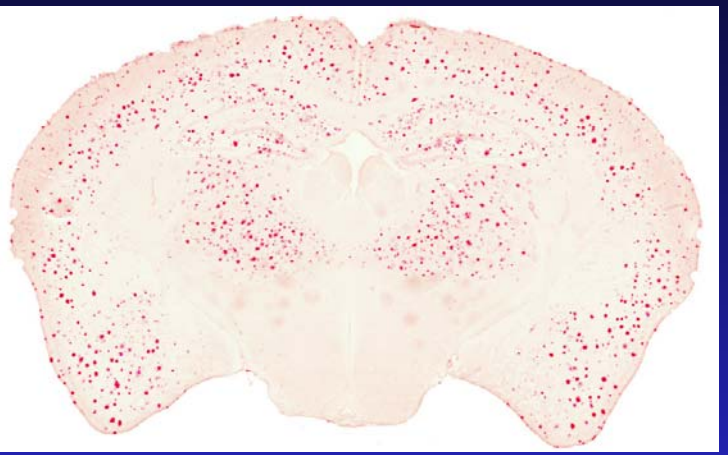


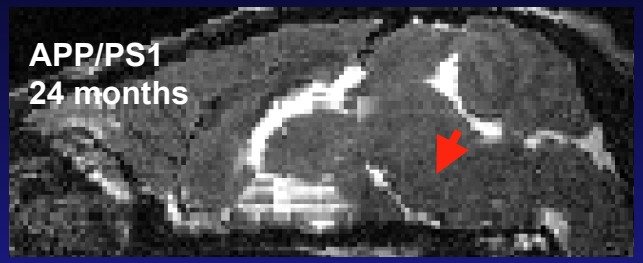


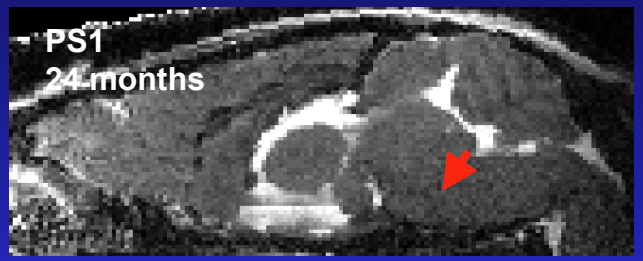




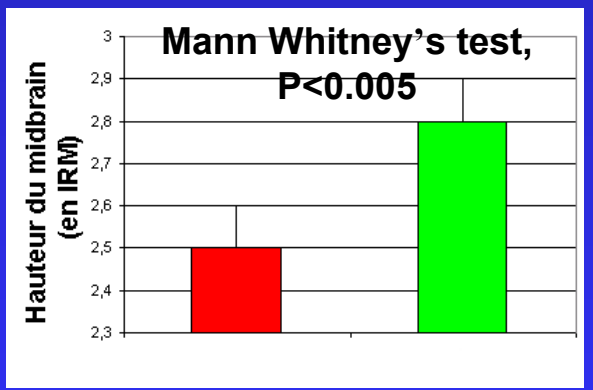
Cerebral atrophy in APP/PS1 mice





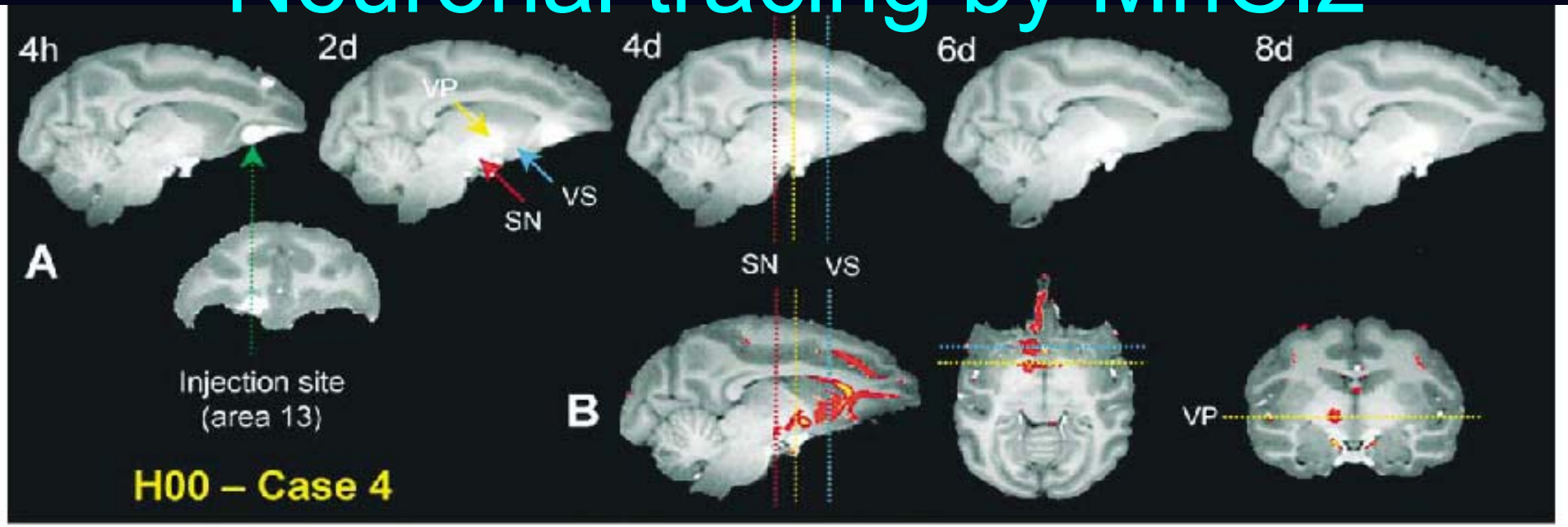


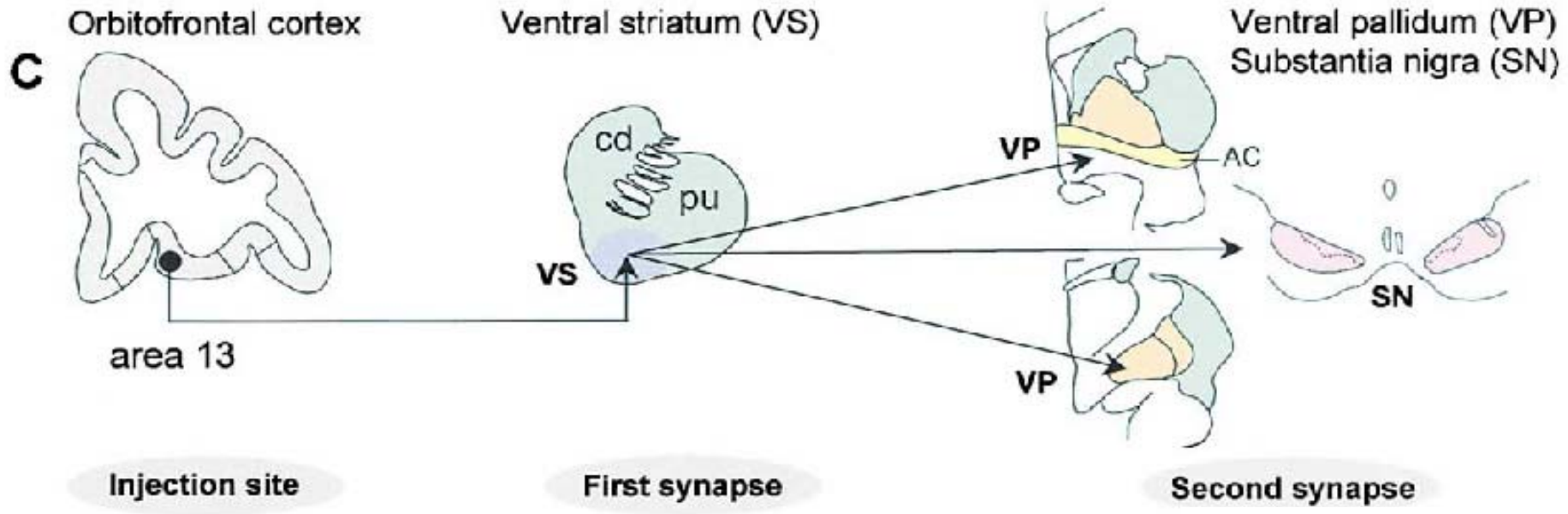
- Midbrain atrophy
- No cortical atrophy
- No hippocampal atrophy



Collaboration Benoît Delatour (NAMC)
Collaboration AventisPharma

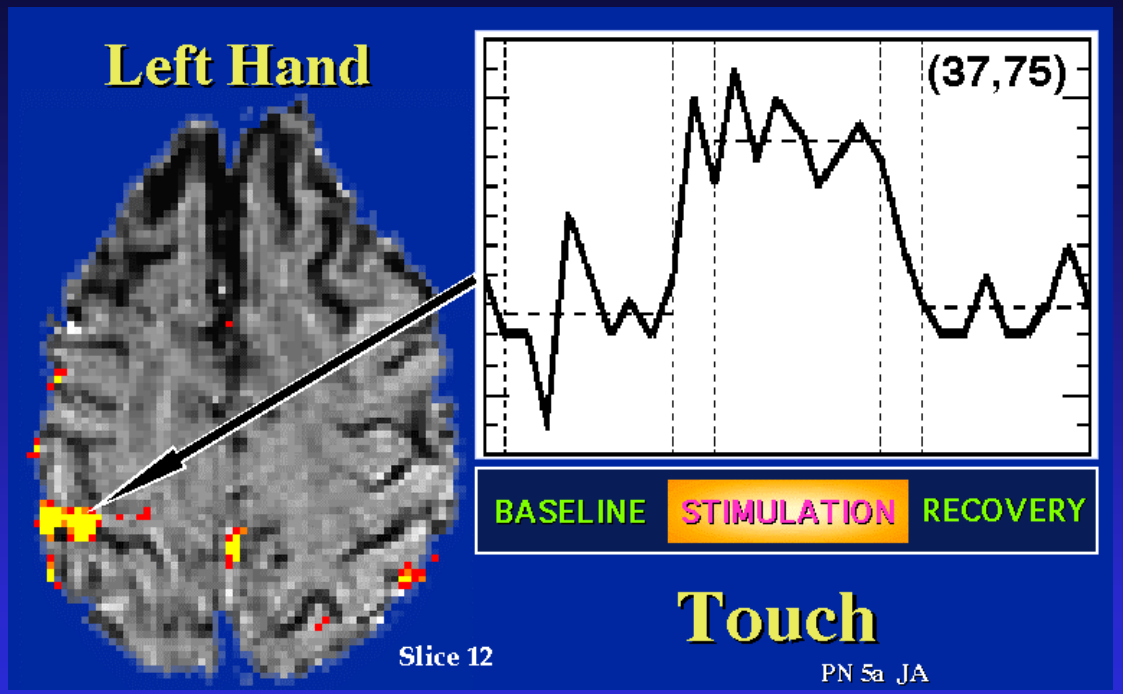
Neuronal tracing by MnCl2





Saleem et coll., 2002

Functional imaging



In human

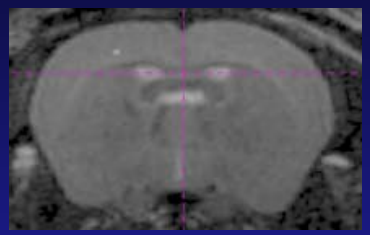
- More difficult to perform in animals (anesthetized during the MR exam)

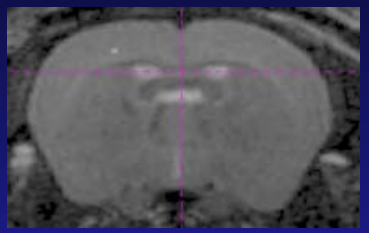
Hemodynamic response imaging in small animal

MRI 1

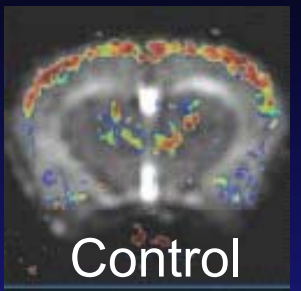
Pharmacological Treatment

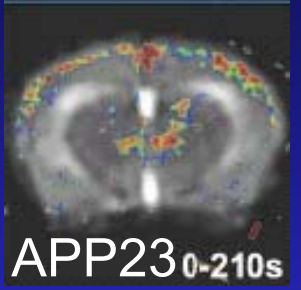
MRI 2

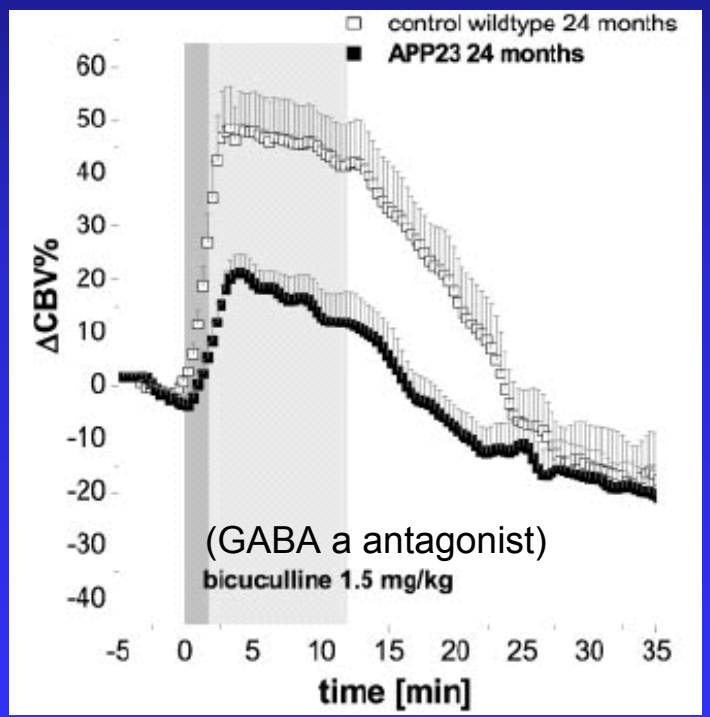




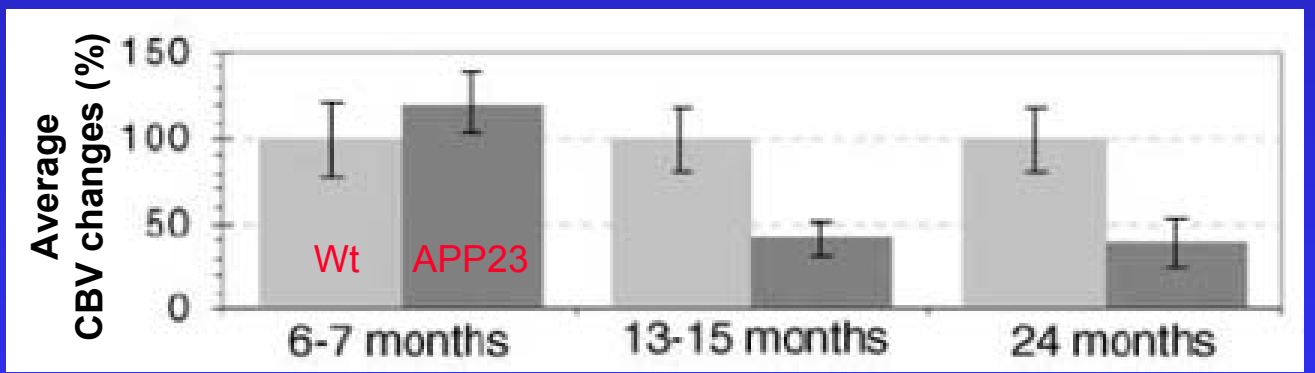
Pre-treatment endorem







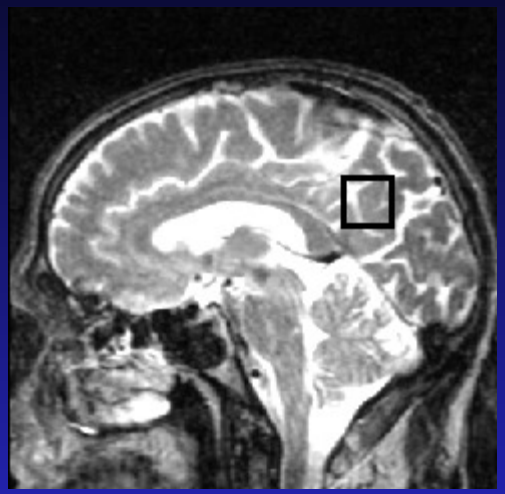
GABAa antagonist : Neuronal dis-inhibitor

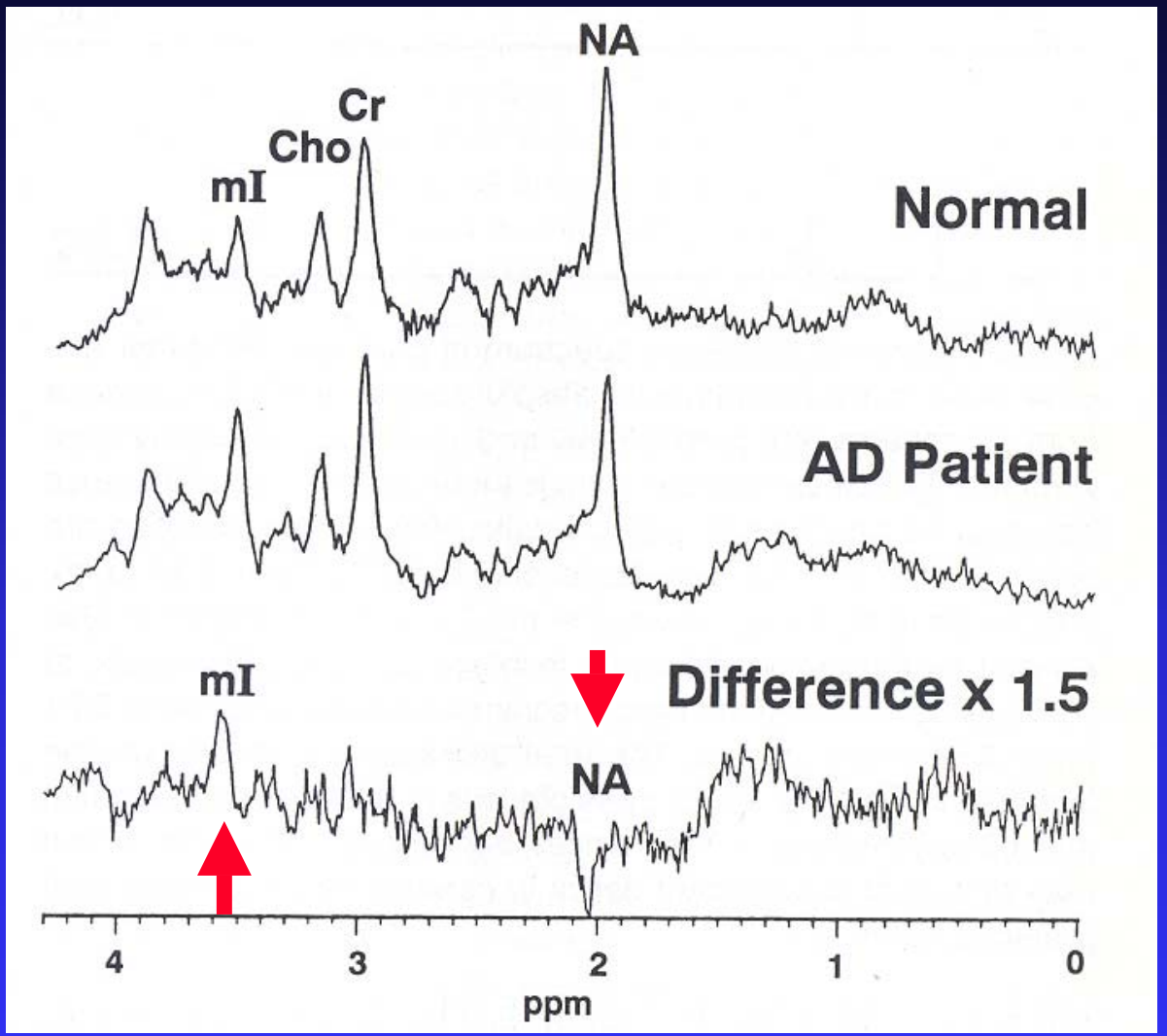


Alterations caused by amyloid angiopathy ?

Mueggler, J. Neurosc., 2002

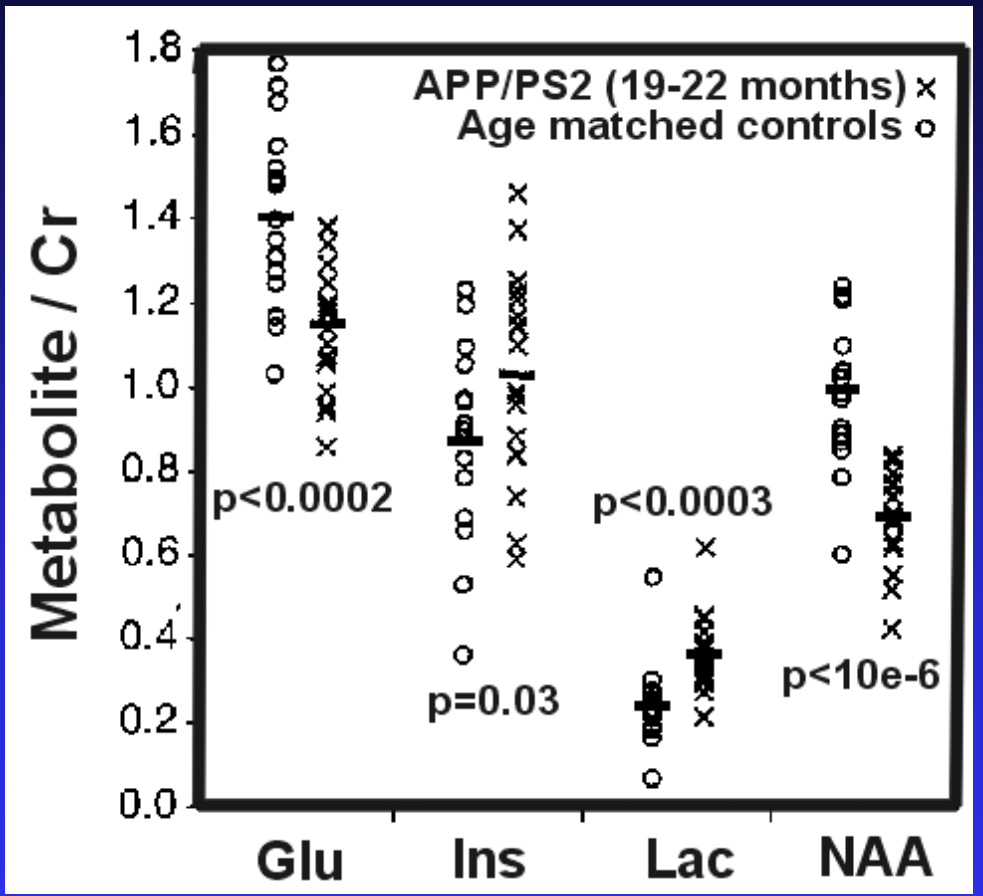
Spectroscopy





Moats et al, 1994, MRM

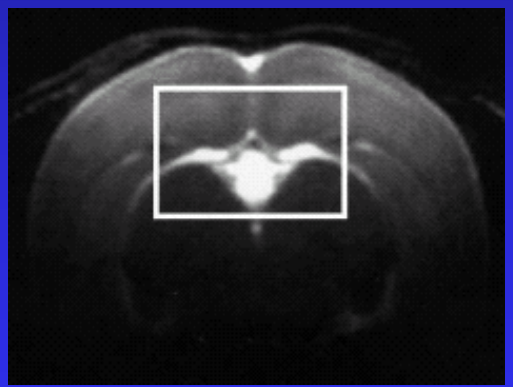
Spectroscopy – Mouse models of Alzheimer's disease

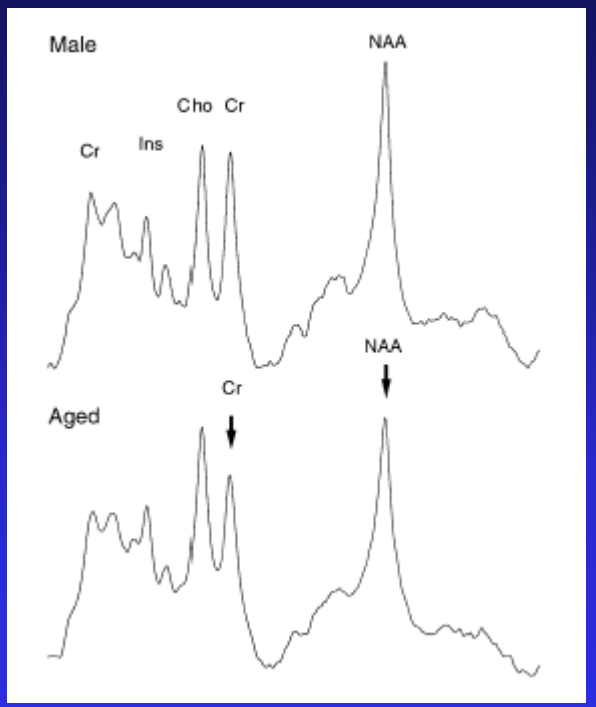


No difference in younger animals

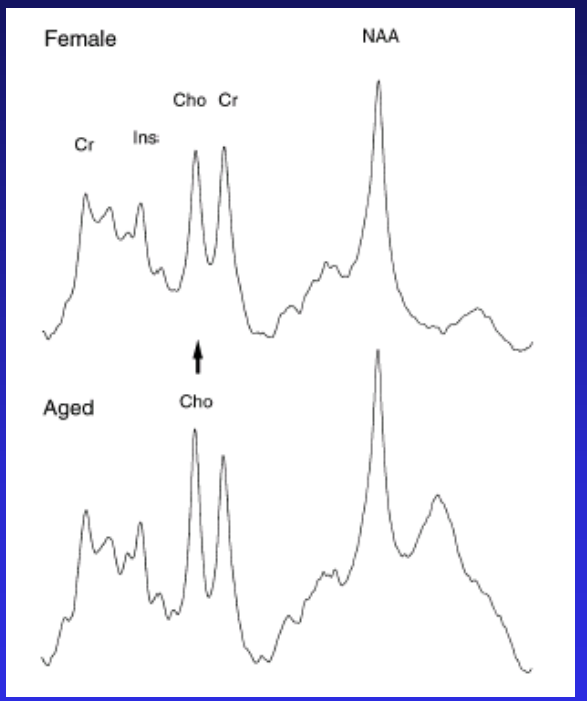
Von Kienlin, ISMRM, 2002

Spectroscopy





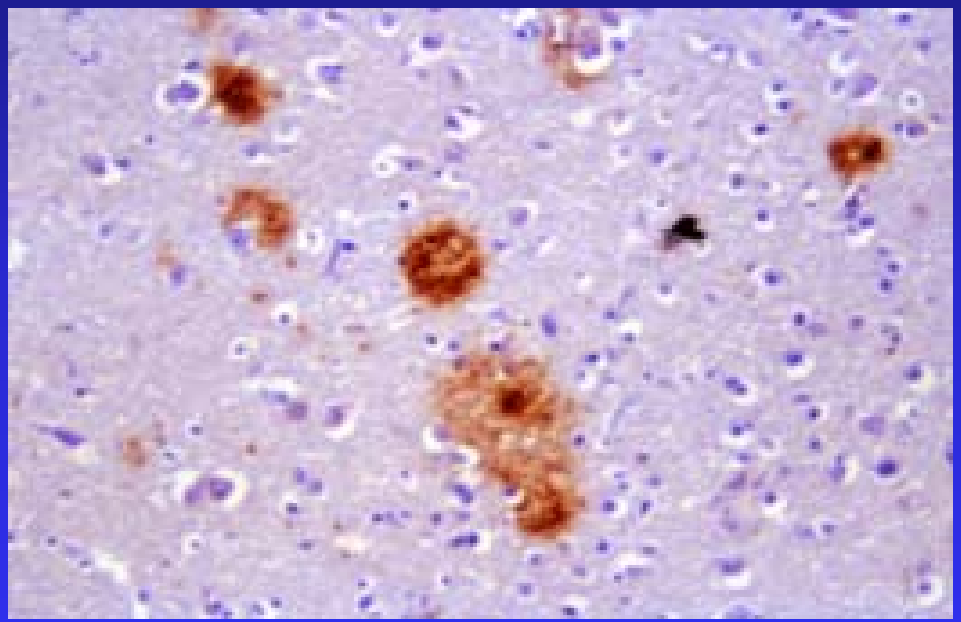
Neuronal loss ?



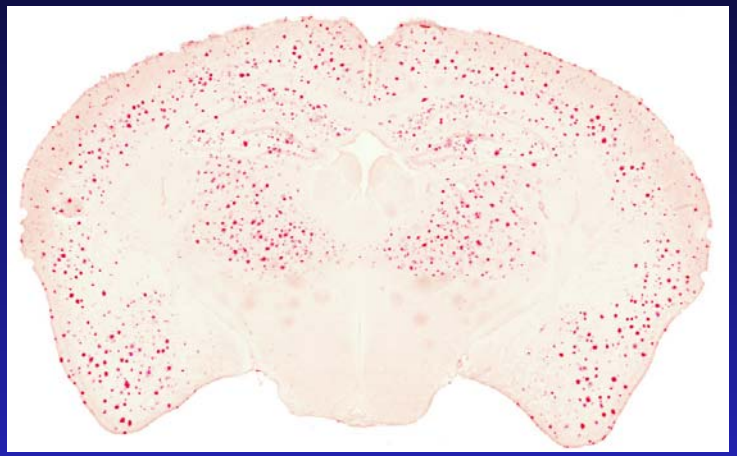
Glial proliferation ?

Michaelis et al. J. Psychiatric Research, 2001

Toward amyloid deposits detection by MRI ?

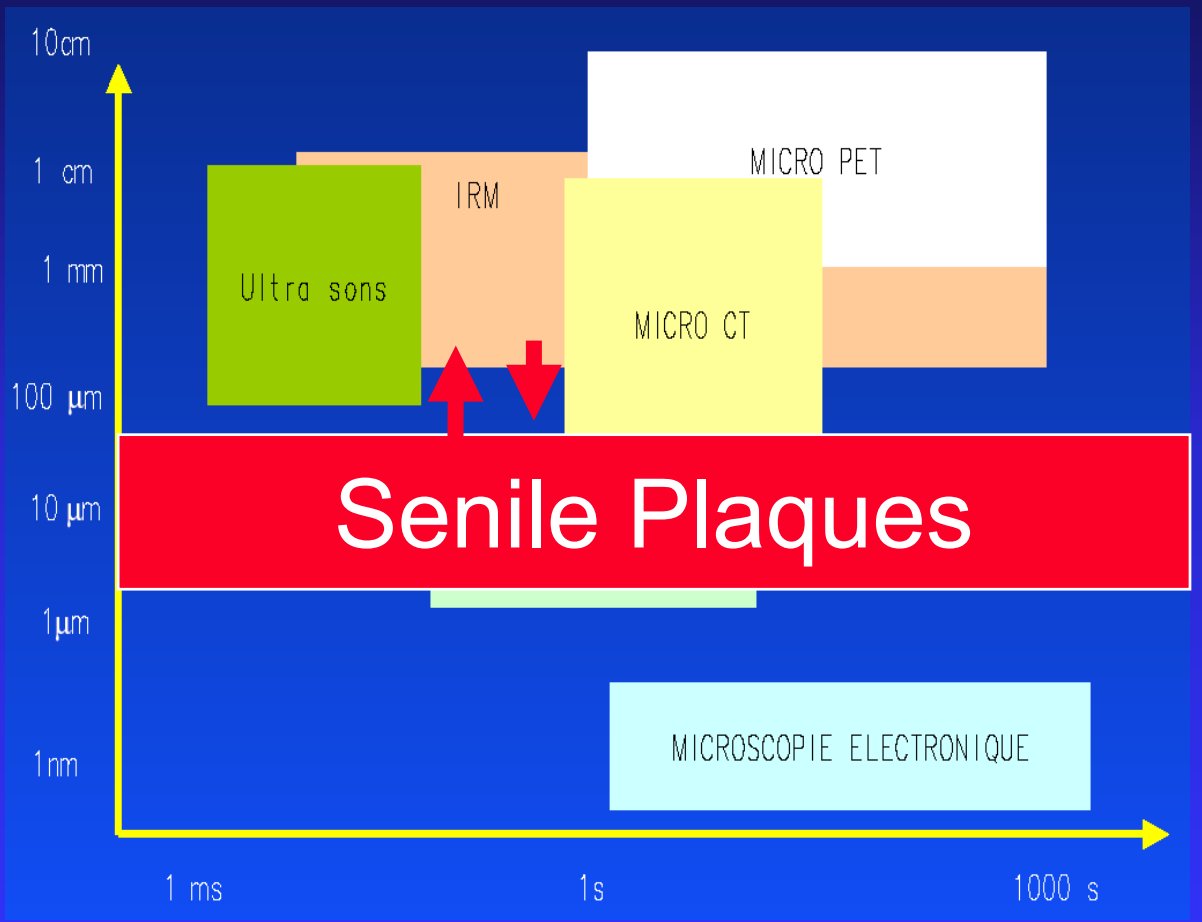


Amyloid imaging in mice



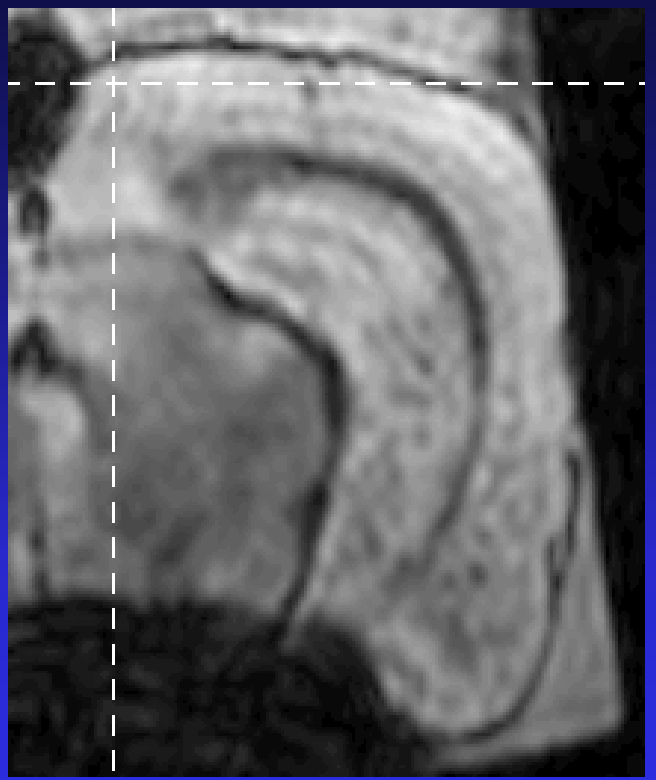
° Large deposits

° Good resolution possible



Post mortem detection

Resolution = 62x47x59 μm^3



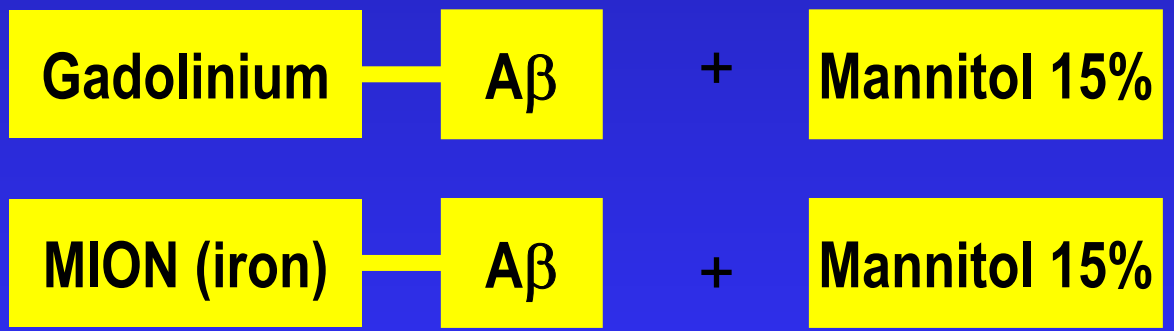
Resolution = 234x117x117 μm^3

APP/PS1 mice

Dhenain, Delatour, Volk et al.
Collaboration AventisPharma

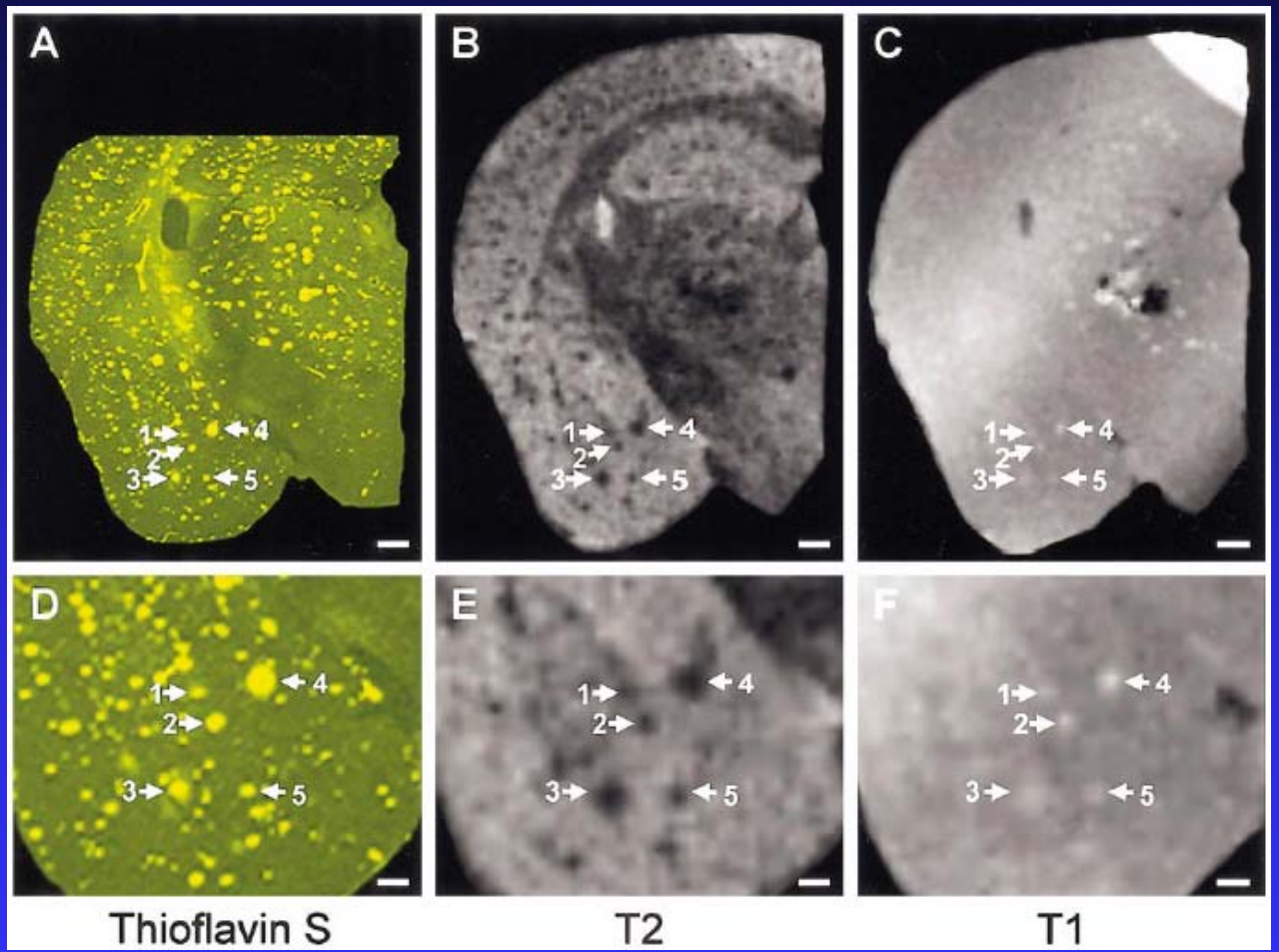
Toward in-vivo detection Amyloid deposit vectorization by contrast agents

Poduslo J F et coll., Neurobiology of disease, 11, 315-329, 2002



Zaim Wadghiri Y et coll., MRM, 50, 293-302, 2003

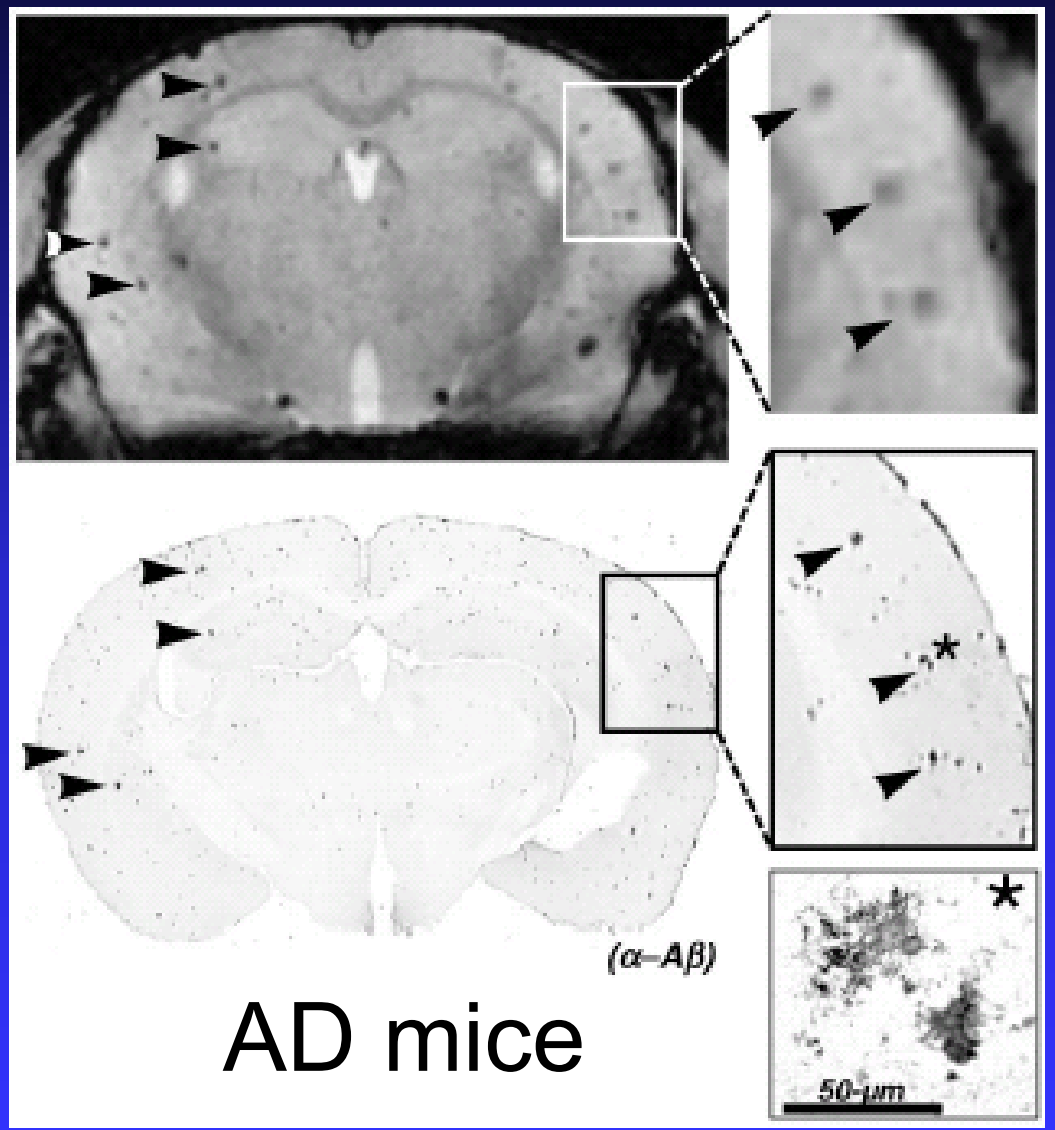
Gadolinium — **Putrescine** — **Aβ**



Poduslo J F et coll., Neurobiology of disease, 11, 315-329, 2002

Ex Vivo

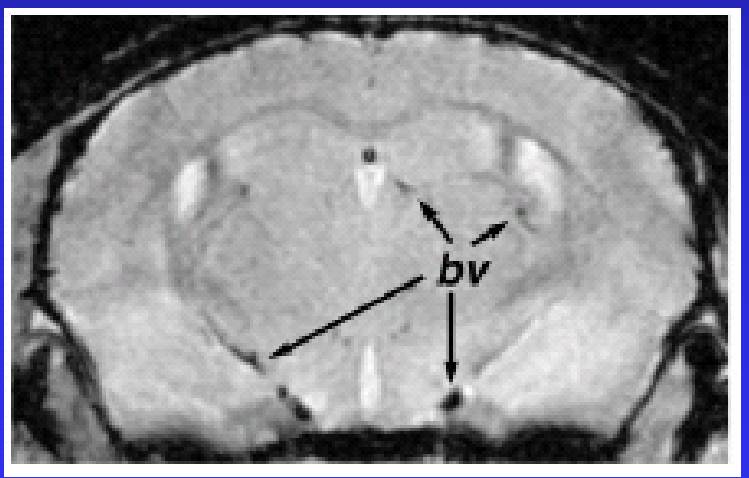
Gadolinium — **Aβ** + **Mannitol 15%**



AD mice

In Vivo

Zaim Wadghiri Y et coll.,
MRM, 50, 293-302, 2003



Control

Conclusion - small animal imaging

- Many parameters
  - Anatomy
  - Perfusion
  - Spectroscopy
  - Cellular imaging

- Evaluation of the parameters that are the most relevant to the diseases/models

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