UE3 Modèles Animaux
UE3 Animal Models

Preclinical Models of neurodegenerative diseases

Exemple of Alzheimer's disease

Marc DHENAIN
Marc.Dhenain@cea.fr

URA CEA CNRS 2210, MIRCen

Master 2 Biothérapies Tissulaires, Cellulaires et géniques

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

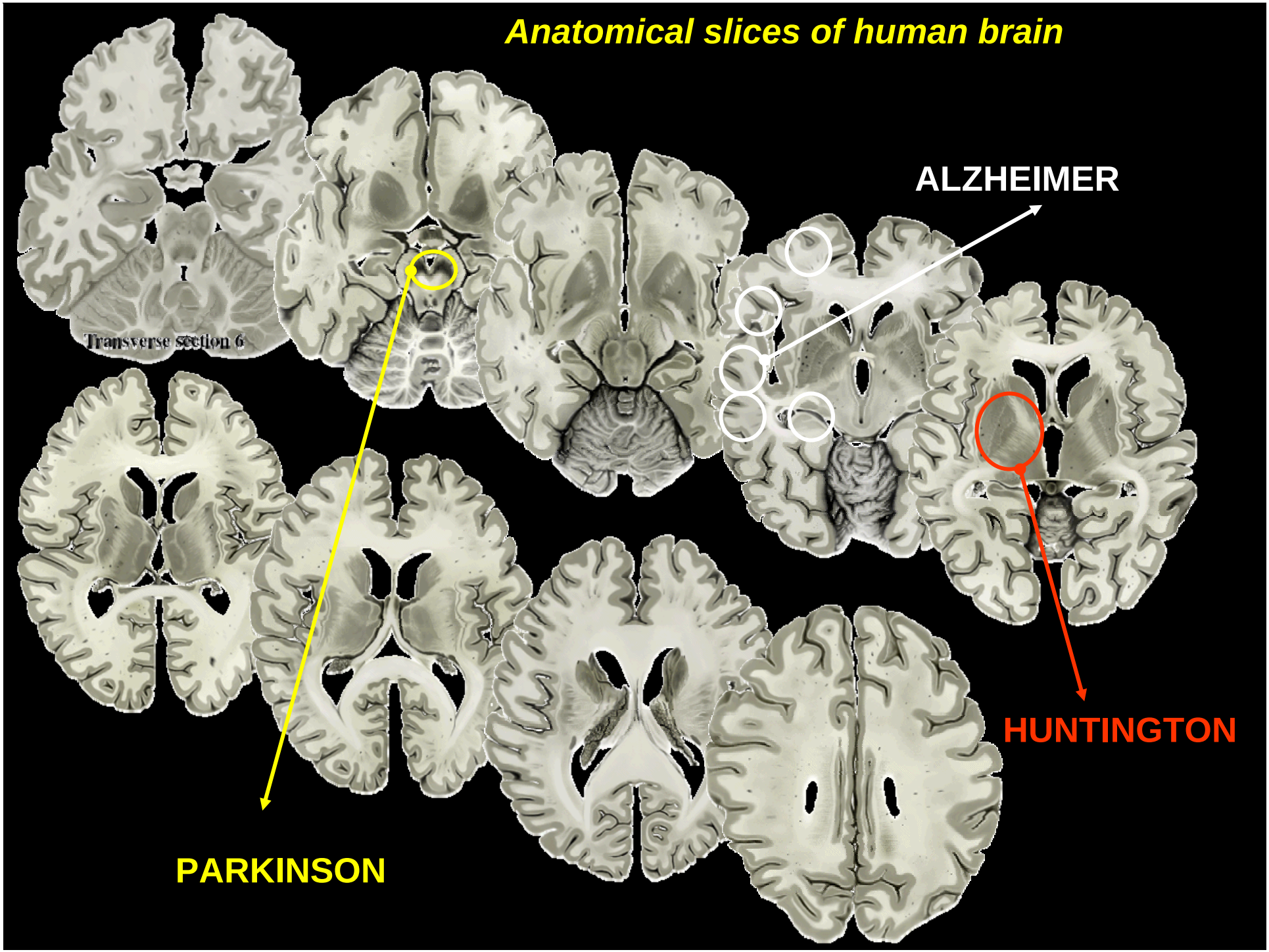
NEURODEGENERATIVE DISEASES

- **<u>Definition</u> :**

- **Diseases of the nervous system caused by a loss or incapacitation of neurons.**

- **<u>Examples</u> :**

- **Multiple sclerosis (Sclérose en plaques) (Myelin loss)**
- **Alzheimer's disease (loss of cholinergic neurons)**
- **Parkinson's disease (loss of dopaminergic neurons)**
- **Huntington's disease (loss of GABAergic neurons)**


Anatomical slices of human brain
ALZHEIMER
Transverse section 6
HUNTINGTON
PARKINSON

Neurodegenerative diseases

Disease	*Anatomy*	*Patients (Fr)*
Alzheimer	cortex	860 000
Parkinson	subst. nigra	80 000
Huntington	striatum	6 000
Spino-cereb. ataxia	cerebellum	<5 000
Amyotrophic Lat. Scler.	cortex, medulla	<5 000
Multiple Sclerosis	cortex, stem, medulla	60 000

Neurodegenerative disease : General problems

- **Neurological symptoms**
  - **Cellular loss**
    - **Risk factors**
      (aging, genes, environment)
      - **Incurable diseases**
        - **Unknown etiology**

Mechanisms?

Therapies?

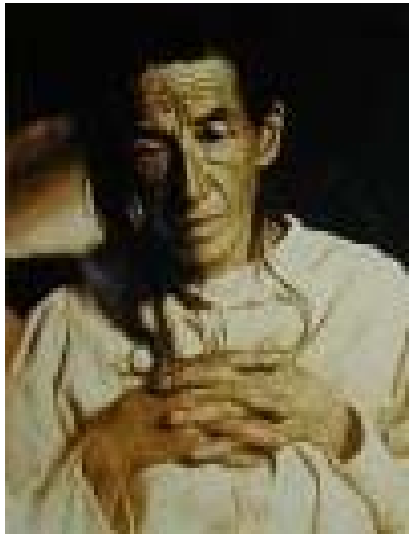
Overview

- Alzheimer's disease
  - Disease in humans
  - Modelization in animals
- Huntington's disease
  - Disease in humans
  - Modelization in animals

Alzheimer's disease

Symptoms

Dementia

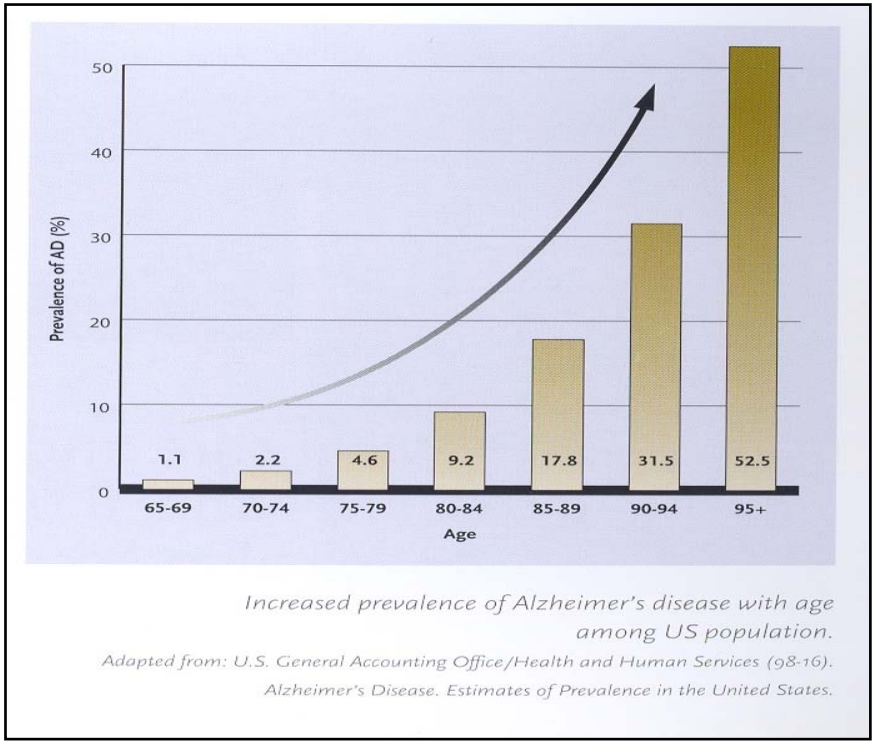


- spatio-temporal disorientation

- Alteration of short term memory (episodic)

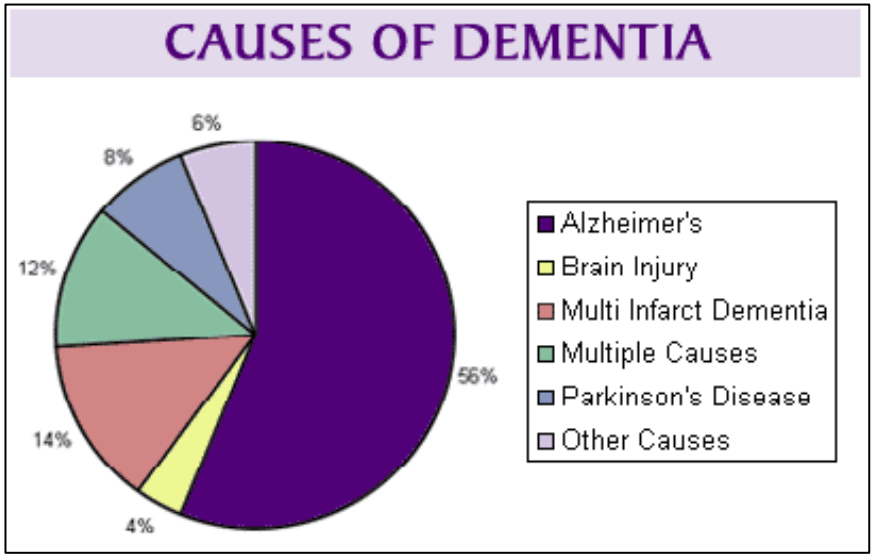
- language, visual recognition

Alzheimer's disease



Increased prevalence of Alzheimer's disease with age among US population.

Adapted from: U.S. General Accounting Office/Health and Human Services (98-16). Alzheimer's Disease. Estimates of Prevalence in the United States.



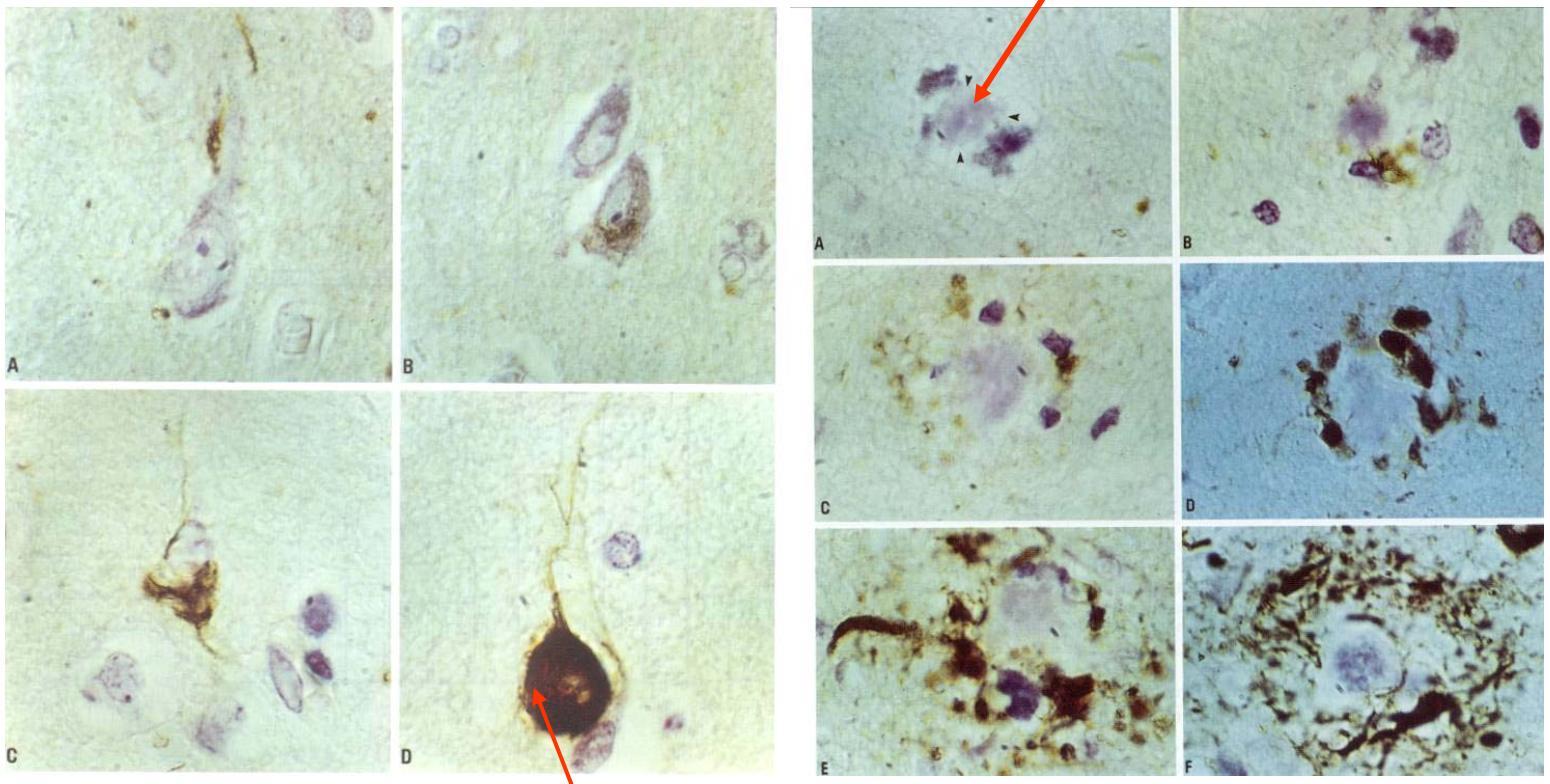
Risk factors (Alzheimer)

- Age
- Education level
- Familial History
- Positive genotype Apolipoprotein E 4/4
- Arterial hypertension
- Hyperinsulinemia

Alzheimer's disease

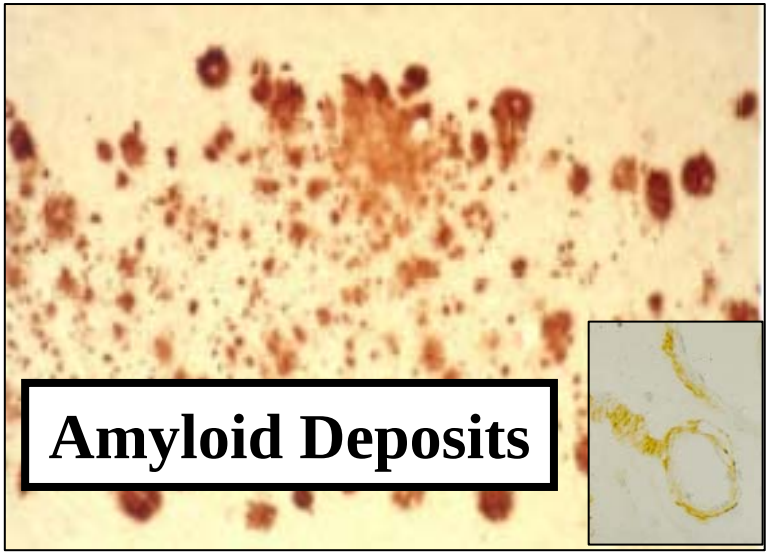
Certitude Diagnosis

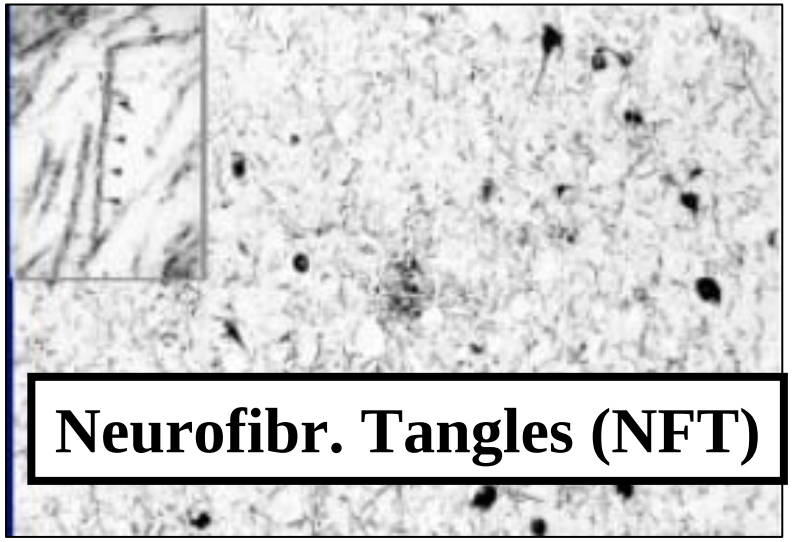
Amyloid deposits (beta-A4)



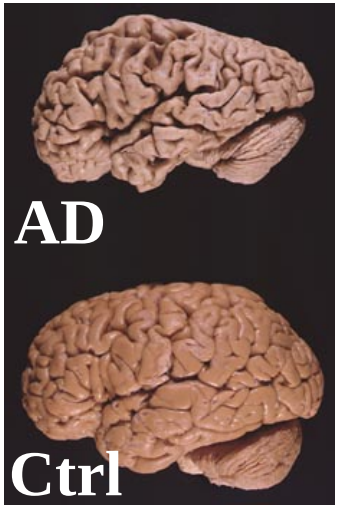
Neurofibrillary tangles (Phosphorylated Tau)

Alzheimer's disease

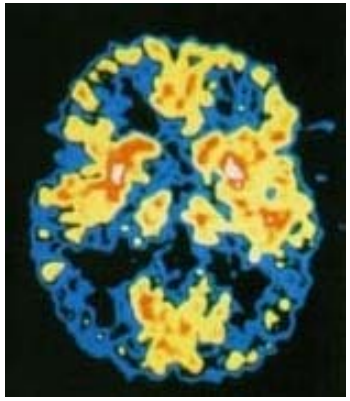




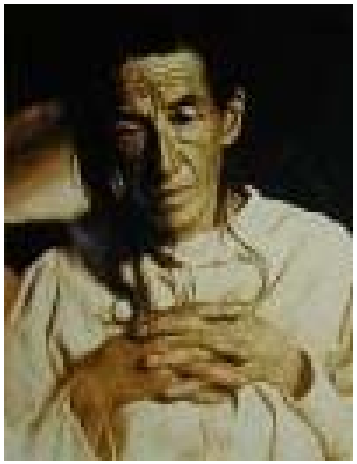
Cerebral atrophy



Functional alterations

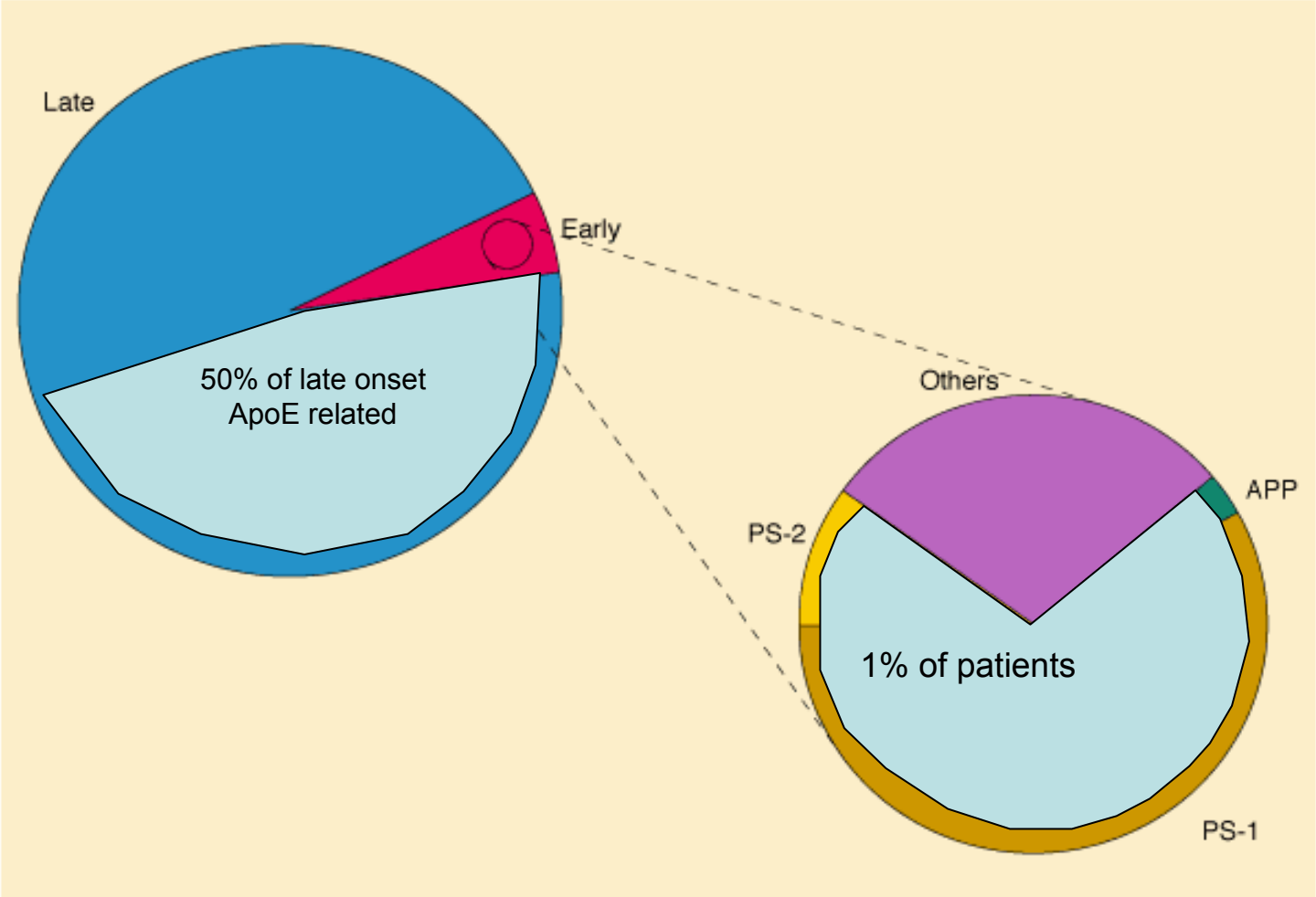


Cognitive alterations



Alzheimer's disease : Few genetic causes

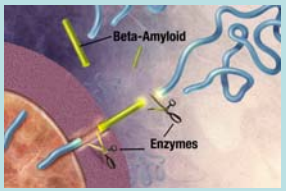
Relative frequency of early and late-onset Alzheimer's and the proportion of early-onset cases attributed to mutations in specific genes such as APP, PS1, PS2 or others



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

Amyloid cascade hypothesis

Amyloid Pathology



Monomeres → Oligomeres →

Plaques

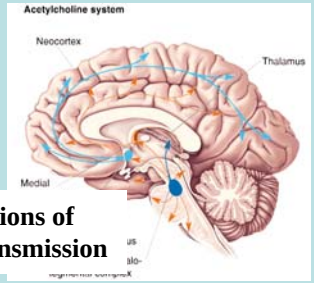
Agregated amyloid

Inflammation

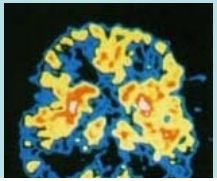
Tau Pathology

Neurofib. Tangles

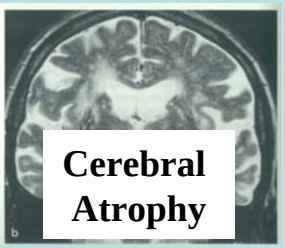
Neurodegenerescence



Alterations of Neurotransmission



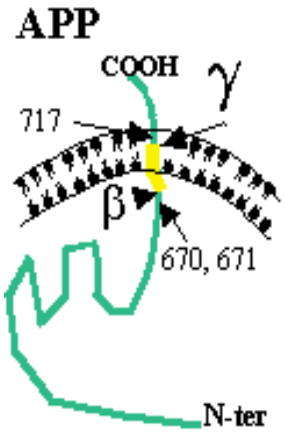
Hypometabolism



Cerebral Atrophy

Dementia

Amyloid cascade hypothesis



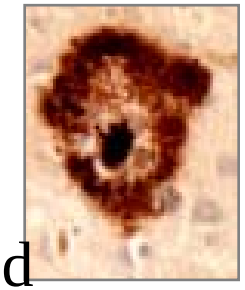
Amyloid beta

Monomer

Oligomer

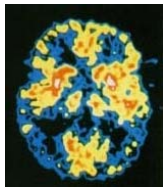
Plaque

Aggregated

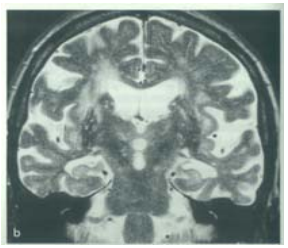


Amyloid cascade hypothesis

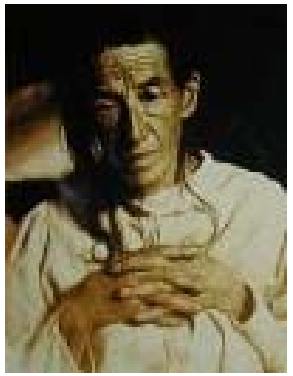
NFT tau



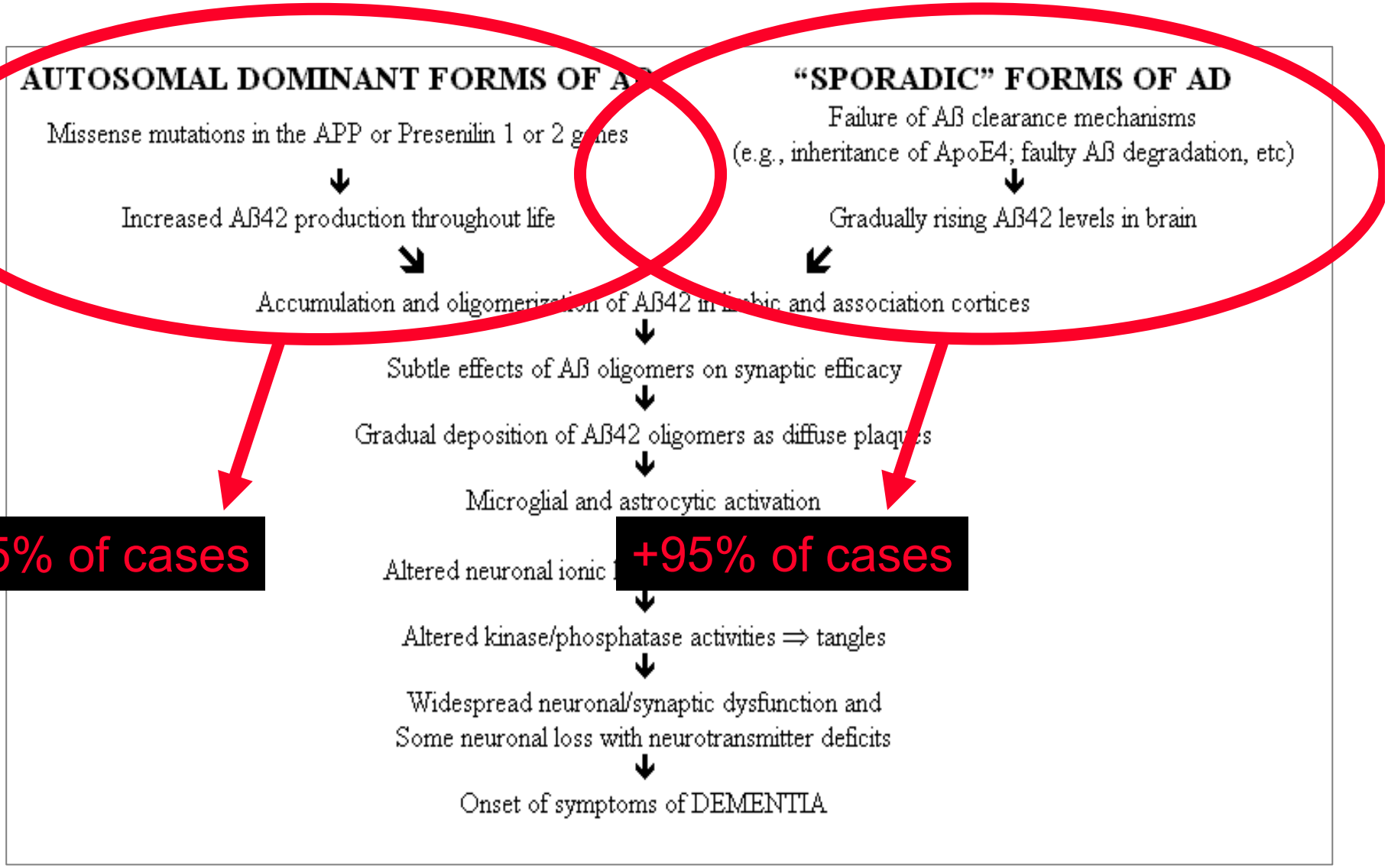
Functional alterations



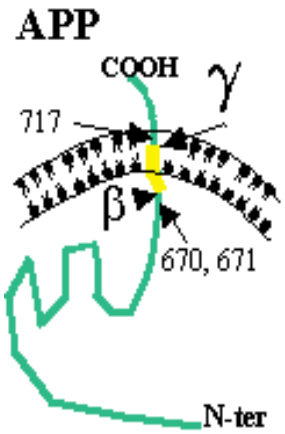
Atrophy Hippoc…



Two forms of Alzheimer's disease : genetic versus sporadic forms

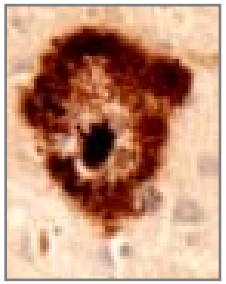


Causes for amyloid accumulation



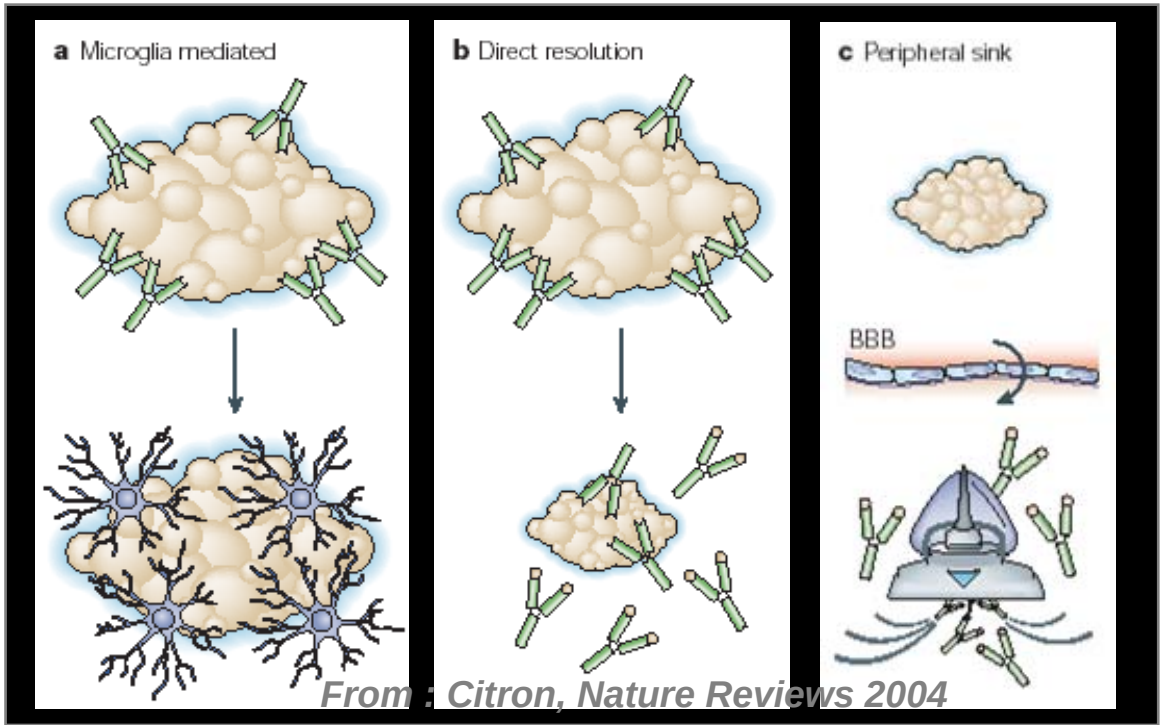
Amyloid beta

Plaque



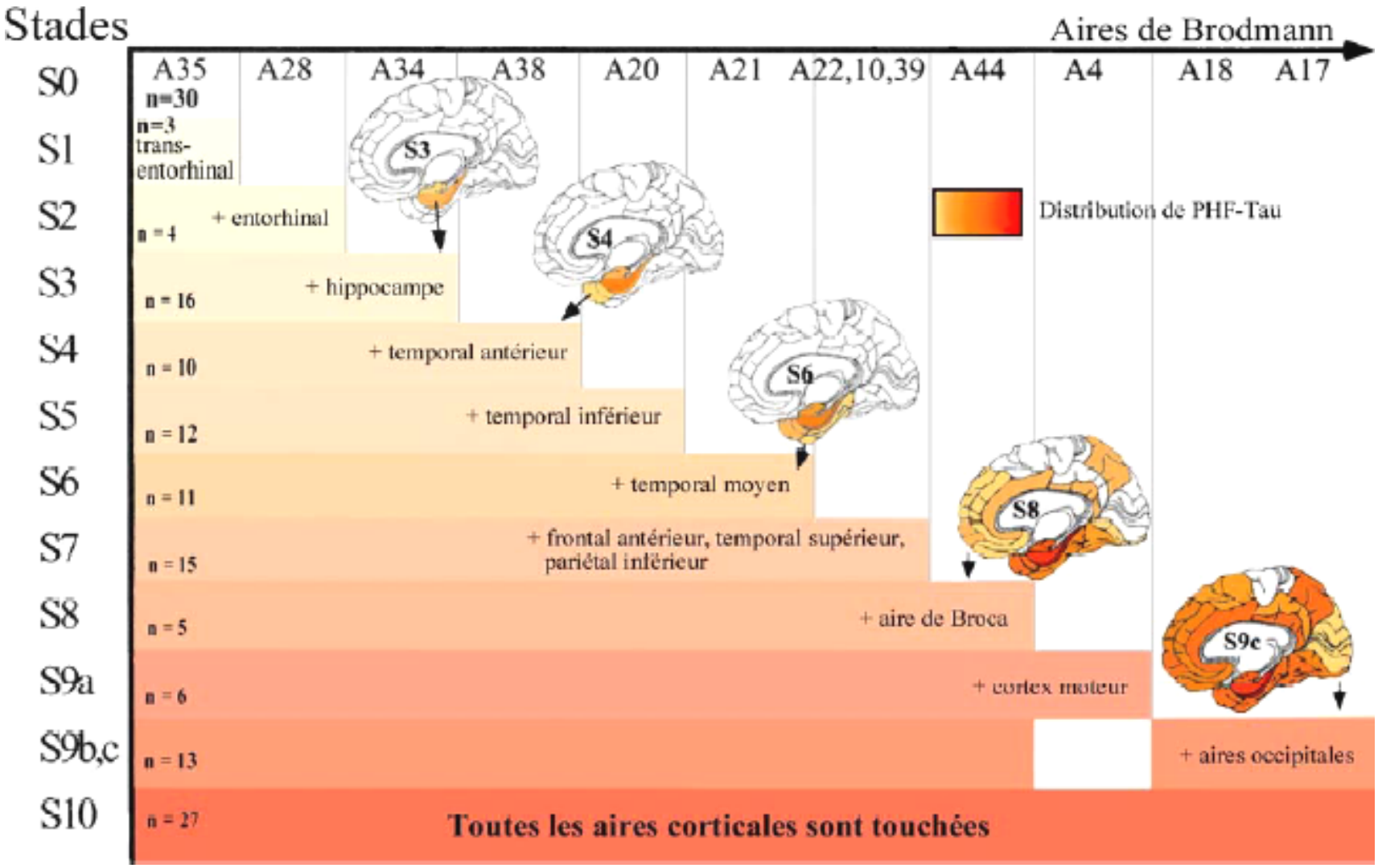
Clearance failure

Overproduction
Mutations: APP – PS1 –PS2

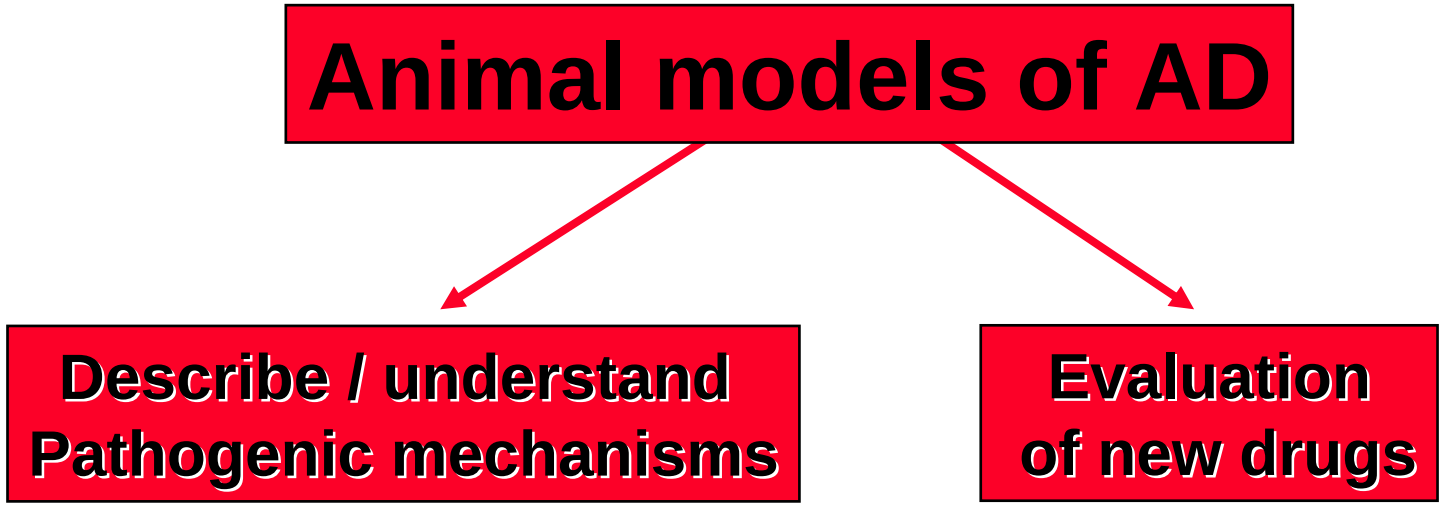


From : Citron, Nature Reviews 2004

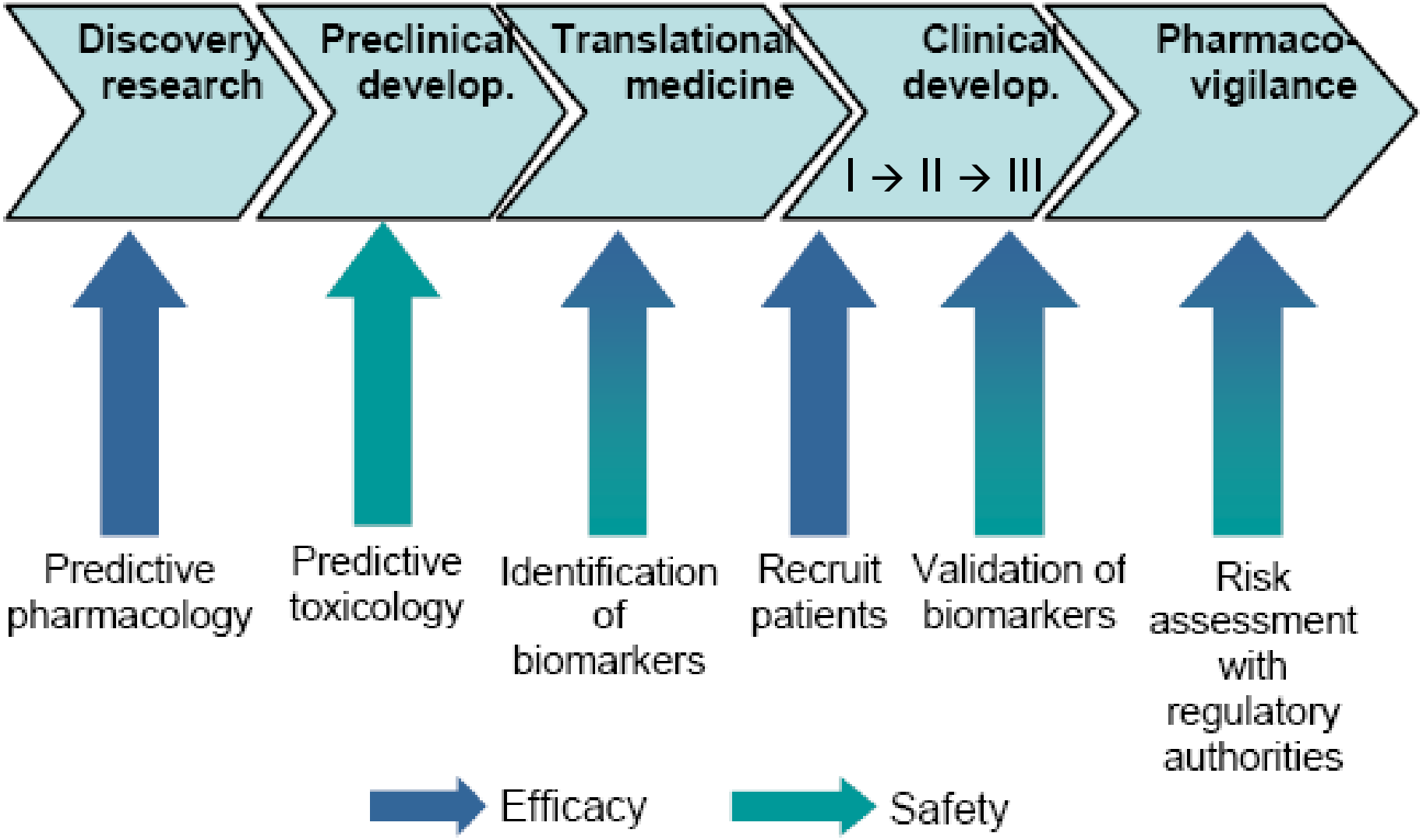
Neurofibrillary Tangles



How/why to evaluate animal models of AD

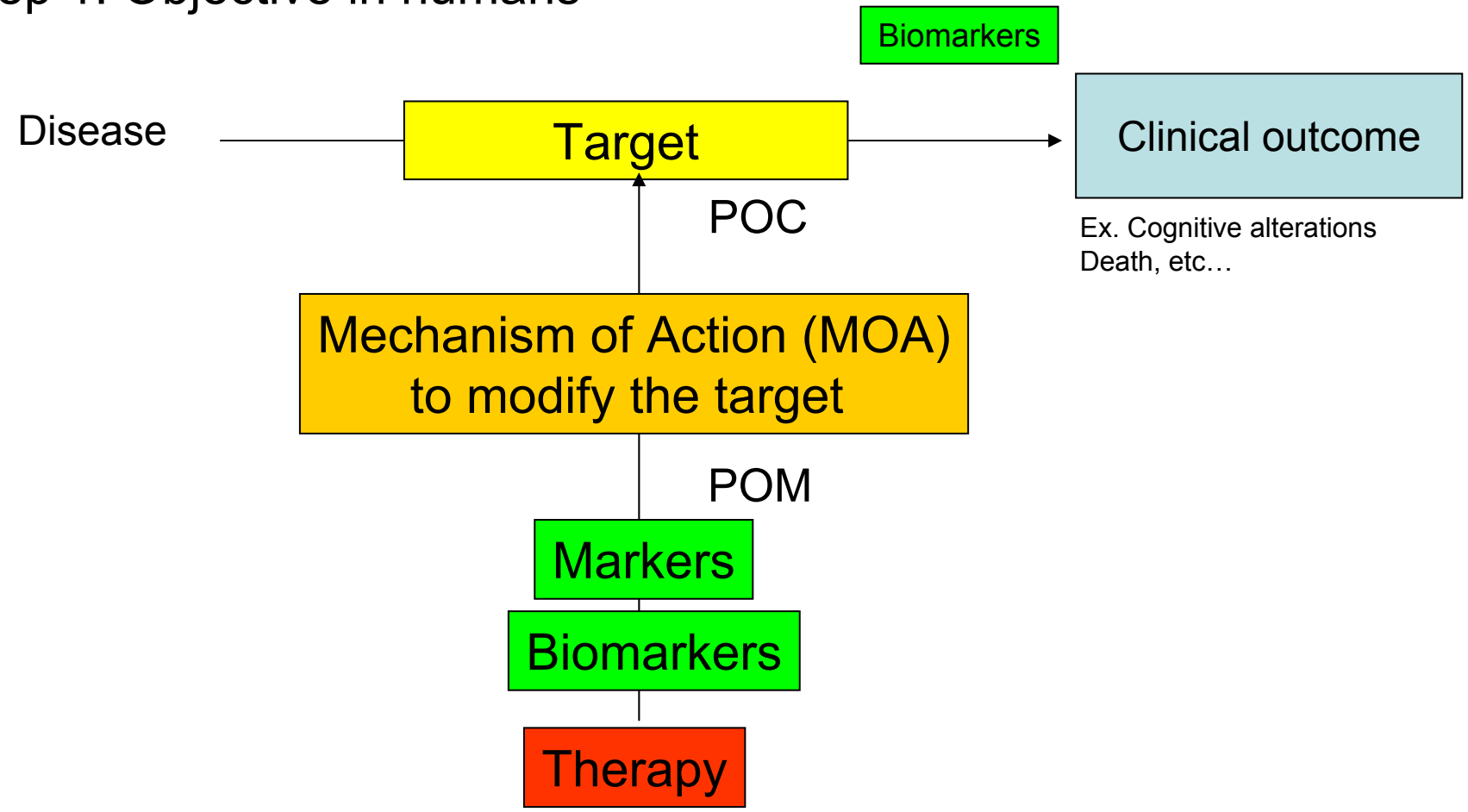


Pharmaceutical R&D process and key bottlenecks



Basis of translational medicine

Step 1: Objective in humans

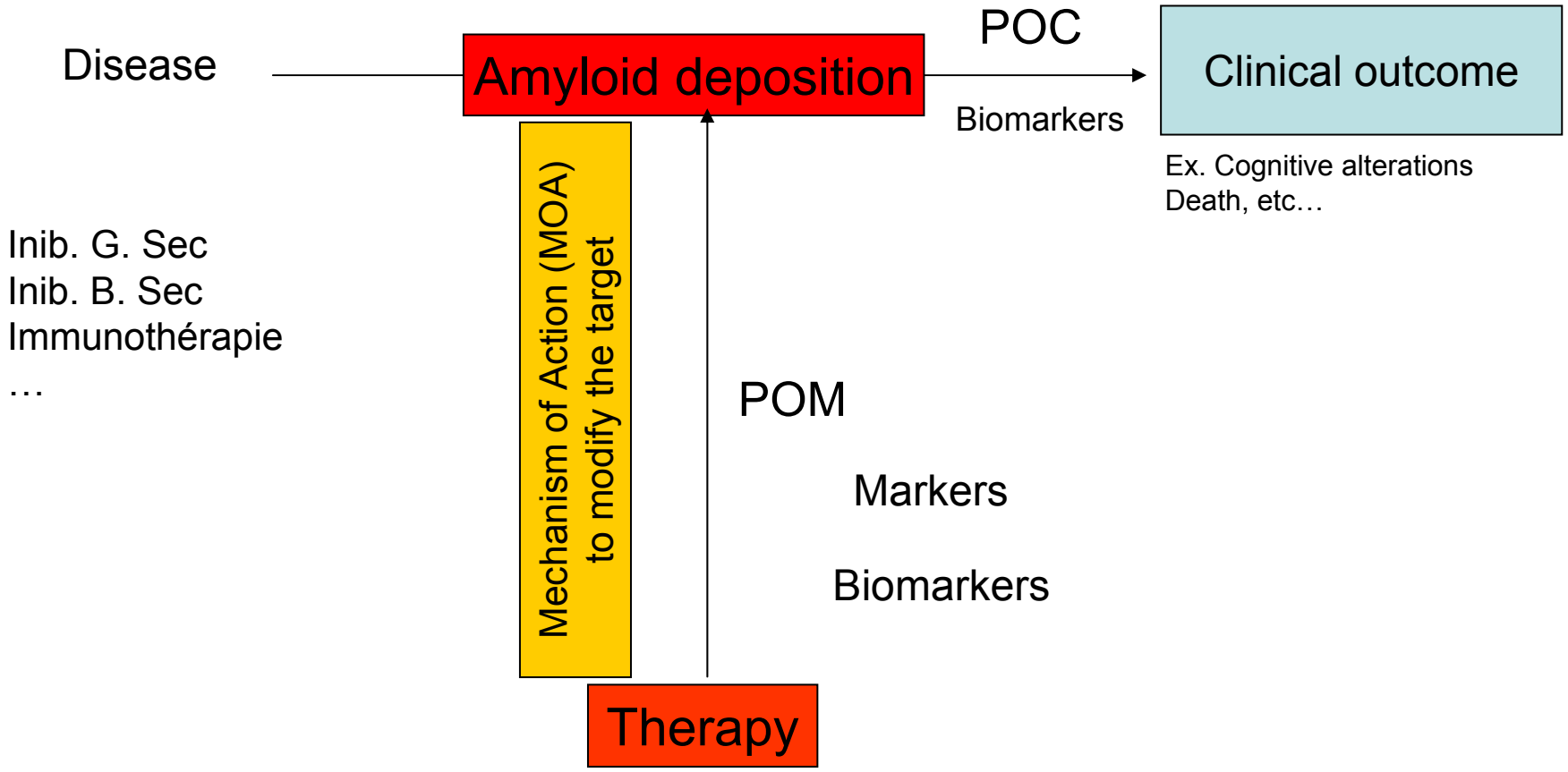


Proof of Concept (POC): If I modify the target, do I modify the disease ?

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

Basis of translational medicine

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

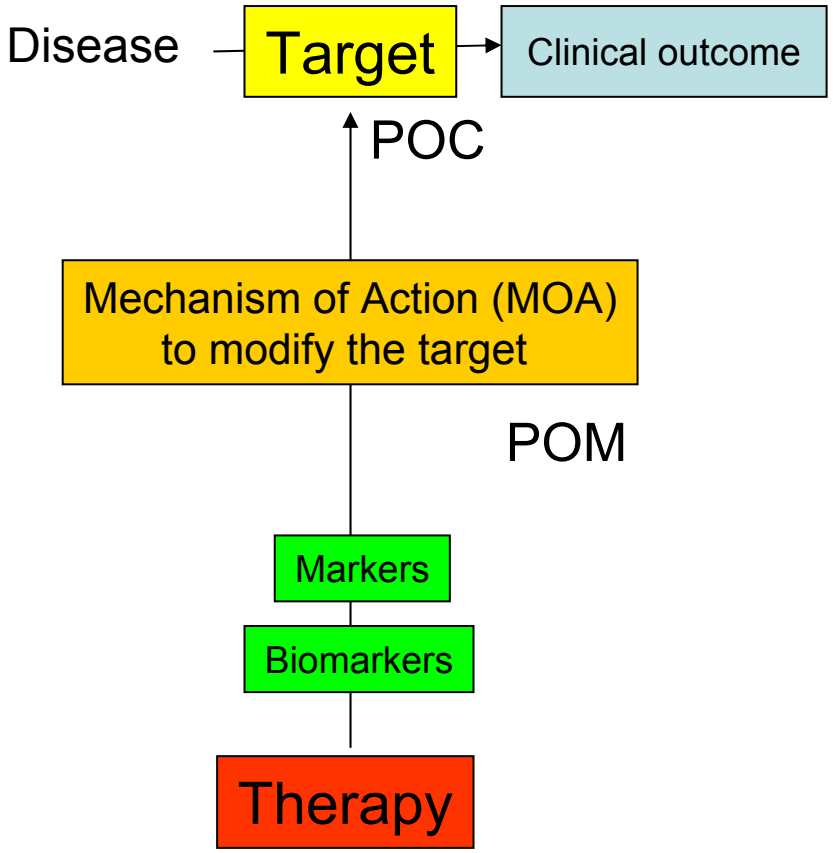
Step 2: Use of animals – Selection of a validated animal model

Choice of a good animal model ?

° Construct validity

° Face validity

° Prediction validity

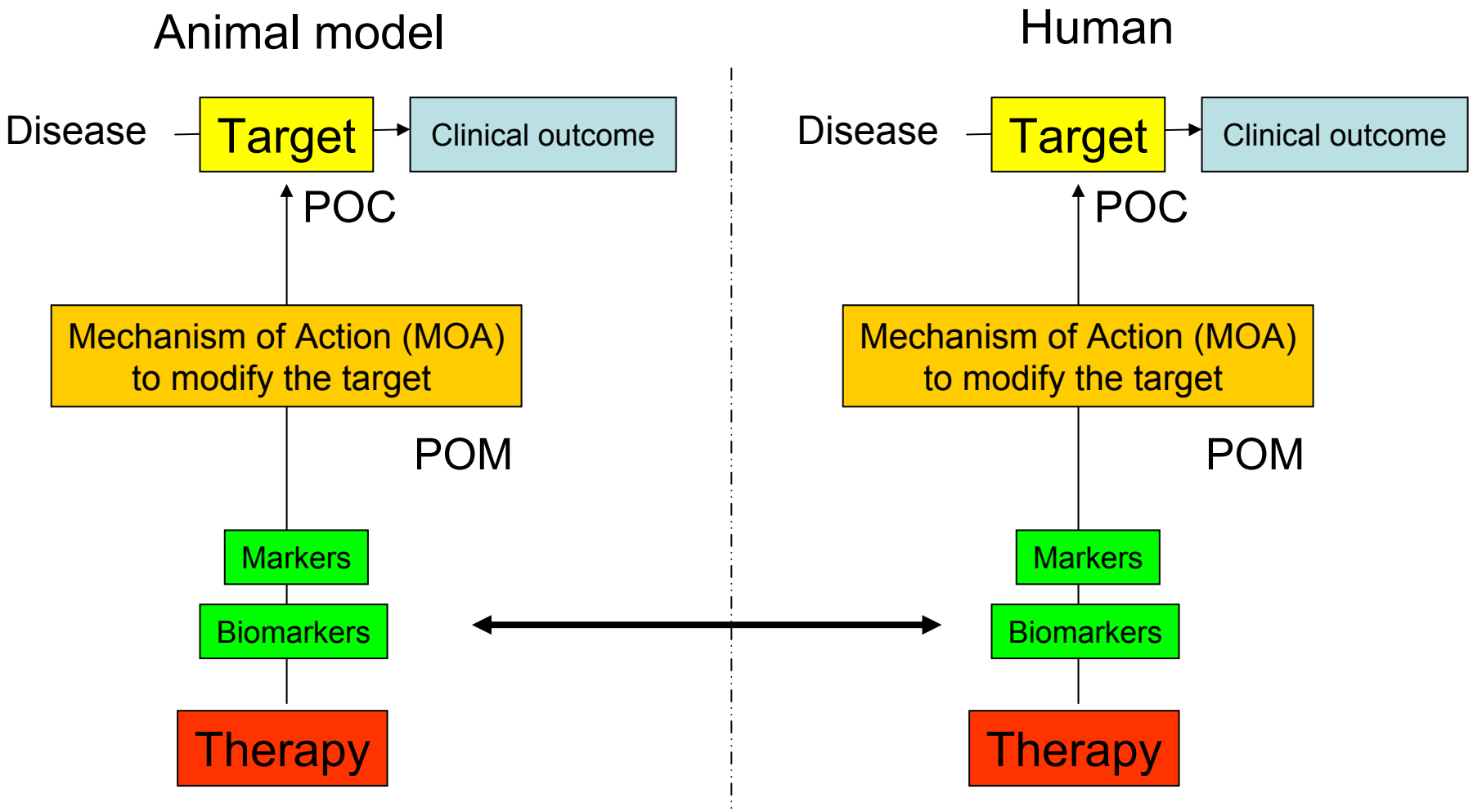


Proof of Concept (POC): If I modify the target, do I modify the disease ?

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

Basis of translational medicine

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

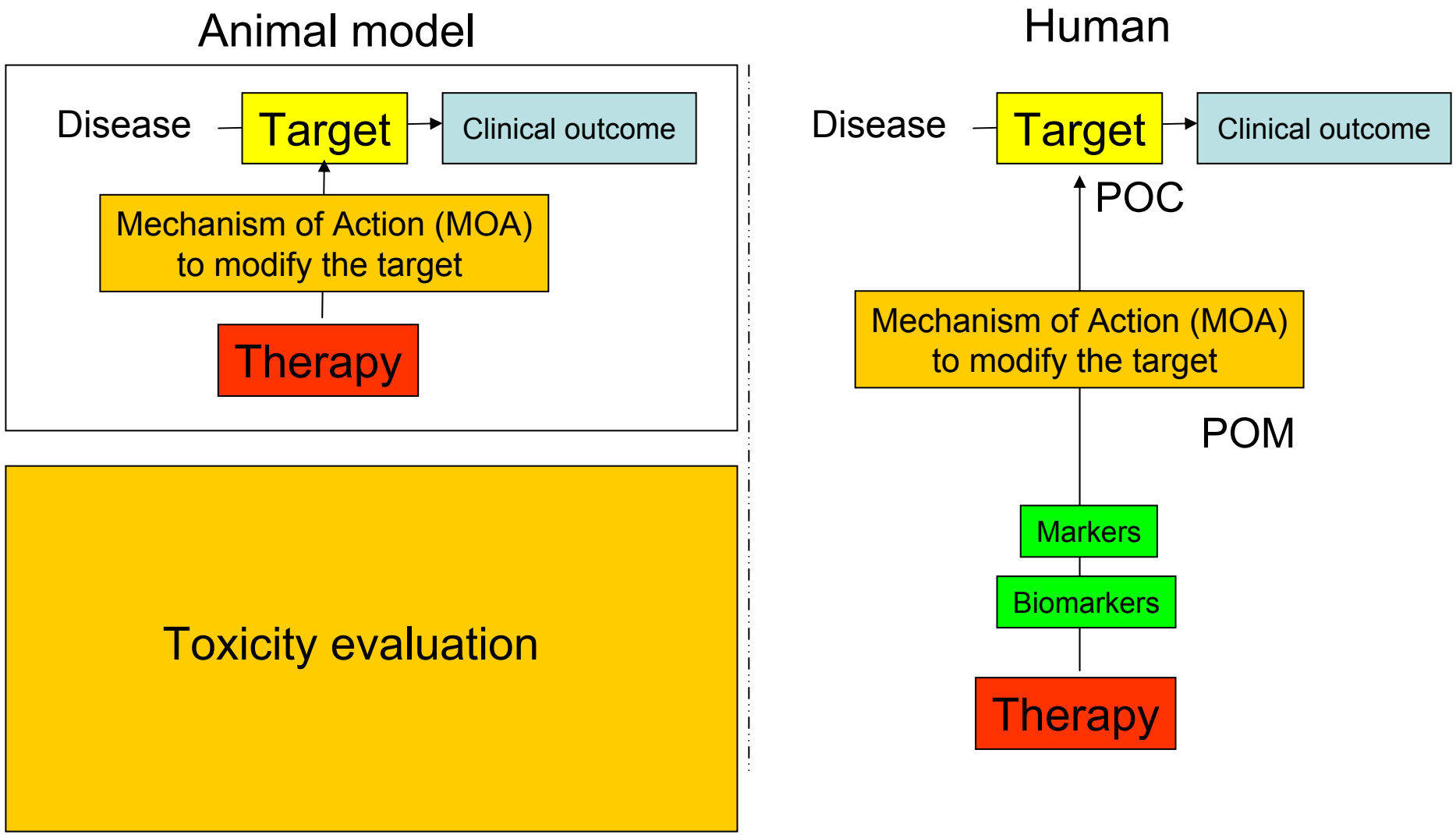


Proof of Concept (POC): If I modify the target, do I modify the disease ?

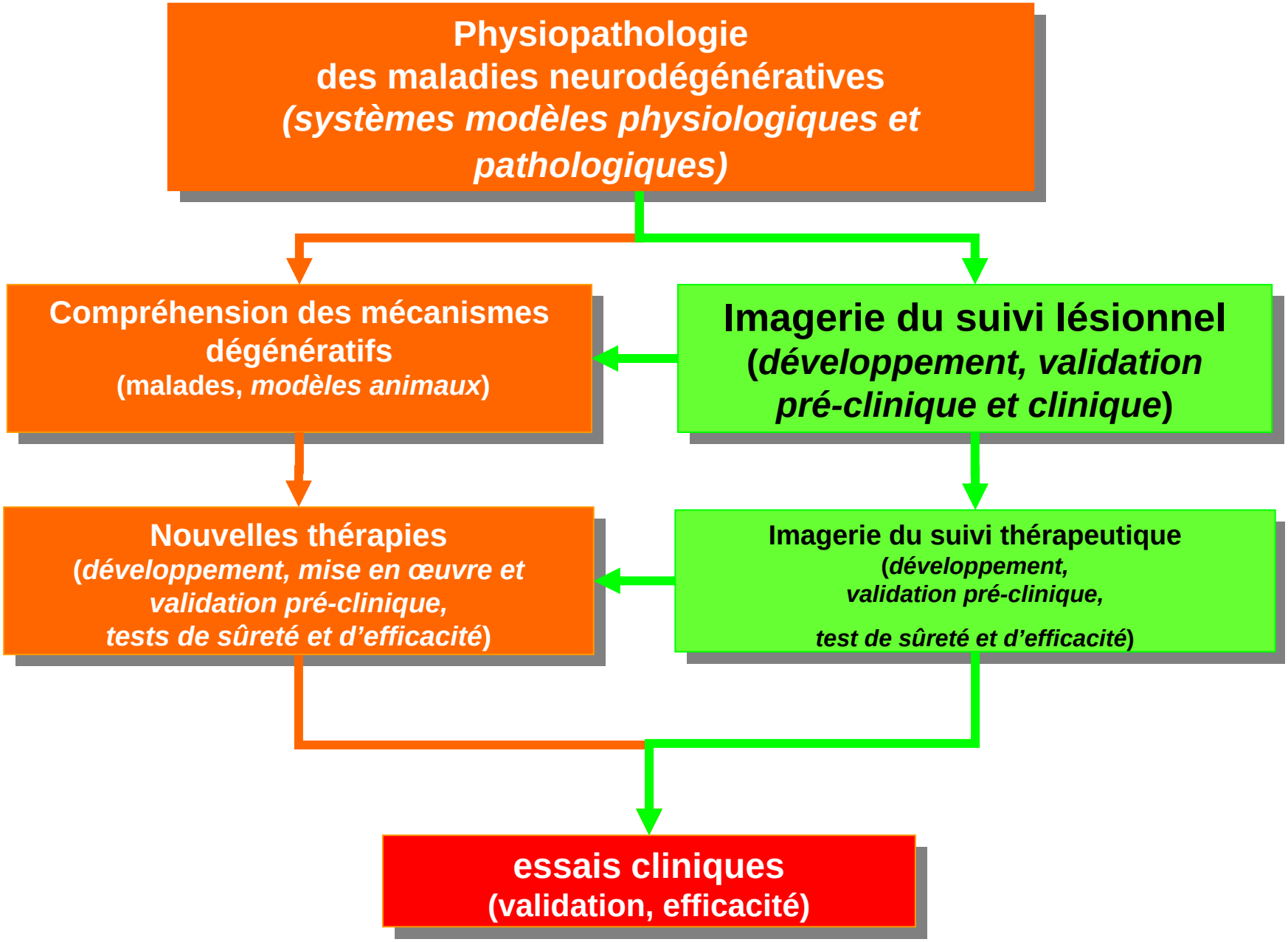
Proof of Mechanism (POM): Is my drug really active on the supposed mechanism ?

Basis of translational medicine

Step 3bis: Toxicity evaluation



Stratégie générale



Animal models of AD

Reproduction, Easy acces

→ Genetic

Non-transgenic → SAMP8 mice, rats

Transgenic mice → 90', familial forms of AD

- genetic, mecanistic

- Therapeutic evaluations but limit of the models = genetic distance to humans

→ Therapeutic evaluation

Life span

2-3 months

2-3 years

30 years

Duyckaerts C. et al., Acta Neuropathol 2008 ; Woodruff-Pak S.D., J Alzheimers Dis 2008 ; Philipson O. *et al.,* FEBS Journal 2010

Animal models of AD

Reproduction, facilité d'accès

Débit

→ Genetic

The choice of the model depend on the question :

Genetic studies ?

Mecanistic studies ?

Therapeutic evaluations ?

One question
=
One animal model

→ Therapeutic evaluation

Life span

2-3 months

2-3 years

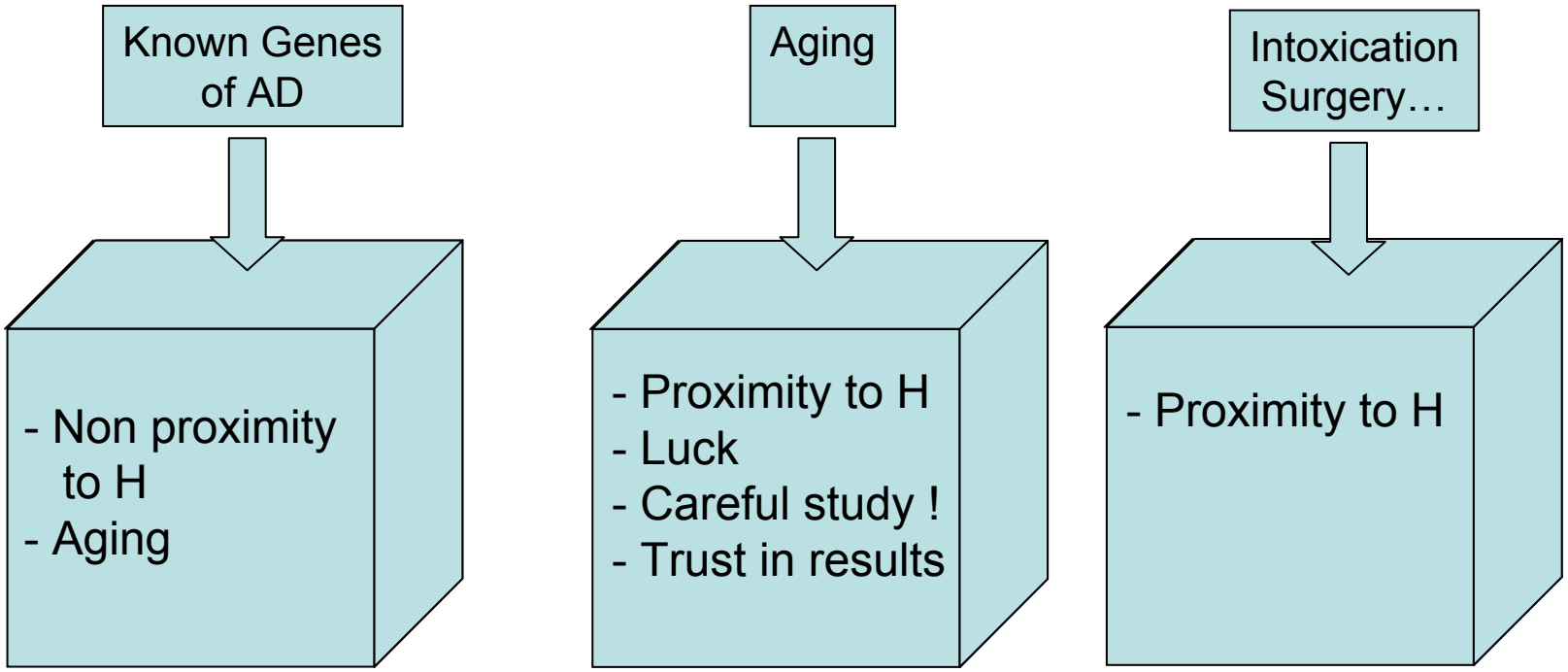
30 years

Duyckaerts C. et al., Acta Neuropathol 2008 ; Woodruff-Pak S.D., J Alzheimers Dis 2008 ; Philipson O. *et al.,* FEBS Journal 2010

Validity criteria of experimental disease models

- Construction validity: Causes of human pathology
- Face validity: Comparison to human pathology
- Prediction validity
  - Validity for a fundamental research question
  - Validity for POM (from therapy to target)
  - Validity for Mechanism of Action
  - Validity for Toxicity evaluation
  - Validity for POC (from target to disease outcome modification)

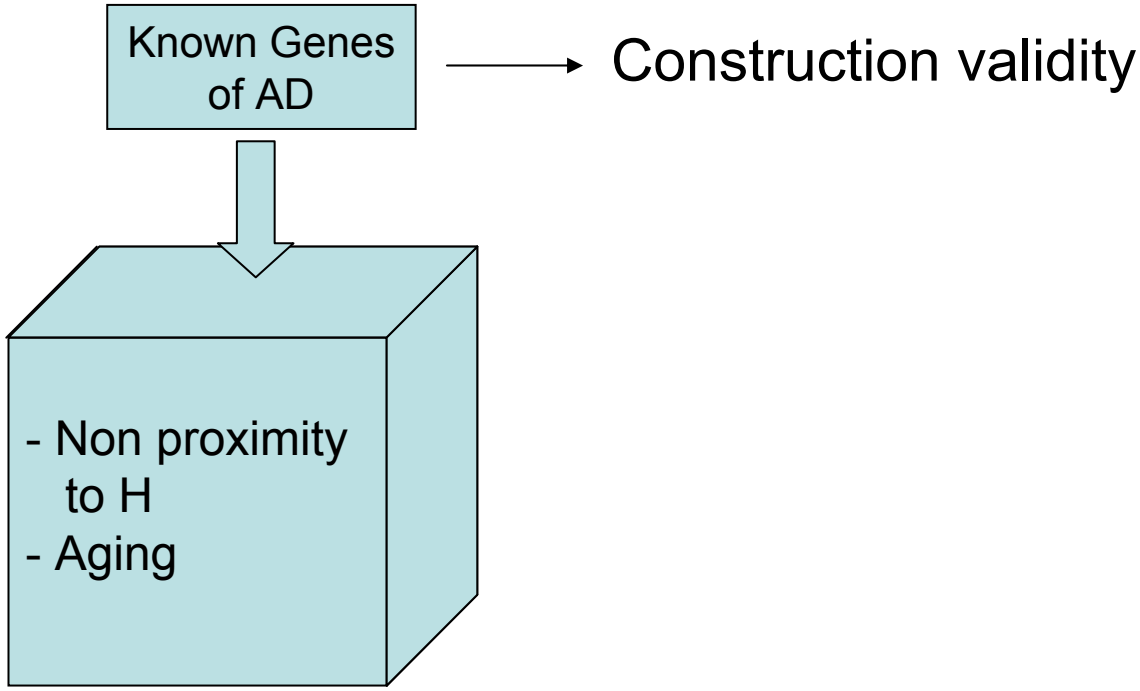
Specificity of the disease for humans ?



Ex.
- APP, APP/PS1 mice
- Tau mice
- Triple Tg

Ex.
- Primates
- Dogs

Models in transgenic Animals (Rodents)



What about face validity ?
What about prediction validity ?

A long list of mouse models of AD…

RESEARCH MODELS

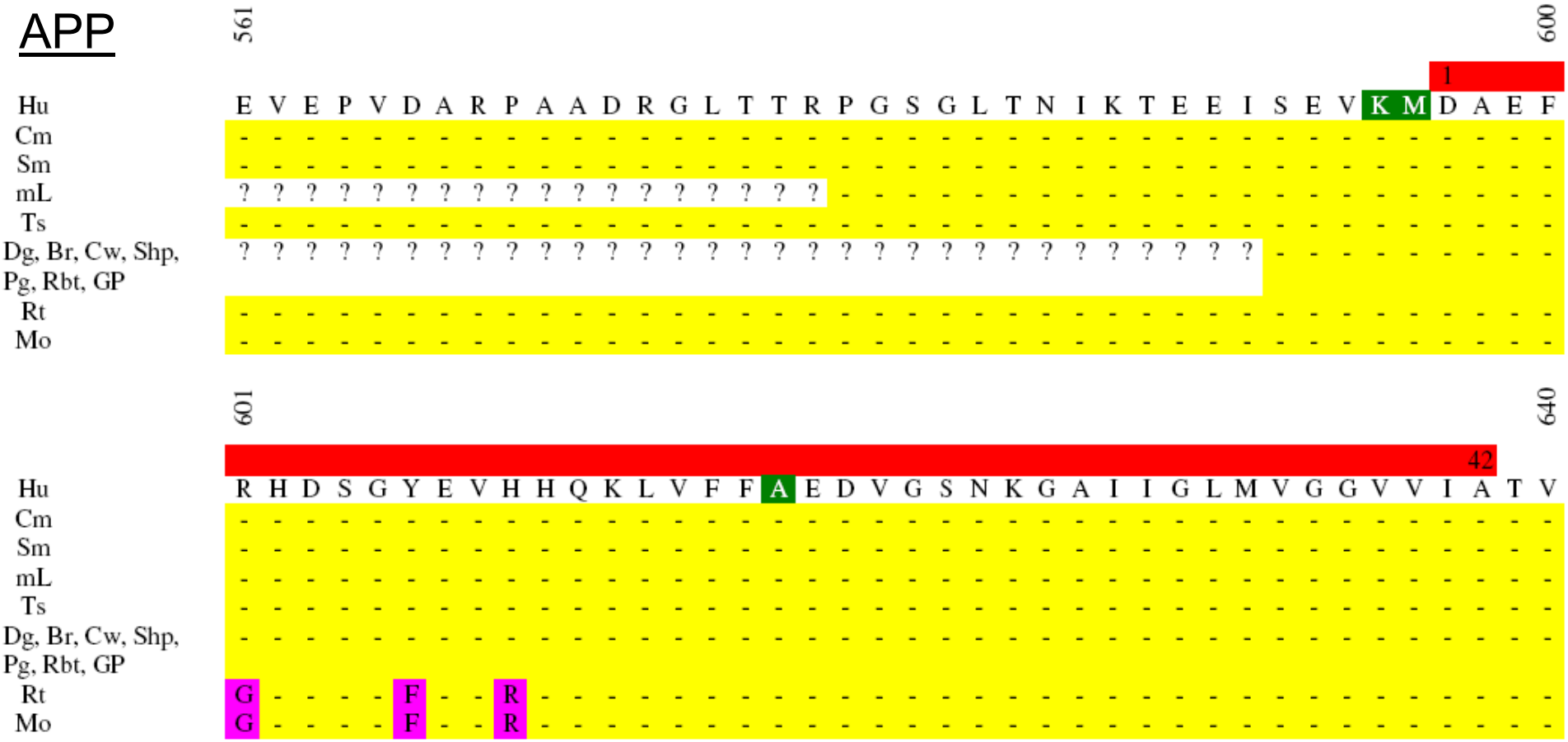
Mice expressing pathogenic mutations of human genes have become a critical tool for biomedical research and drug discovery, and nowhere more so than in the Alzheimer field. The generation of research models that develop some of the pathologic hallmarks of Alzheimer's has given a sizable boost to drug discovery efforts, and has also raised many intriguing questions about the underlying disease process. Identical mutations result in surprisingly divergent phenotypes in different mouse strains. Why? No model perfectly mimics the human disease. Why?

To support investigators' efforts, we are compiling this list of research models that are relevant to understanding Alzheimer disease.

- APP → 38
- ApoE → 18
- Alpha-Synuclein → 6
- Cox-2 → 5
- PS1 → 17
- PS2 → 5
- Tau → 26
- Other → 46
- Double-Cross → 25
- Triple-Cross → 4

As March 26, 2007

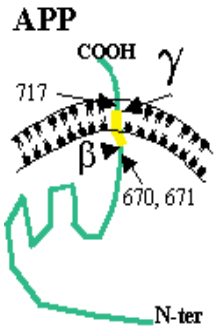
No spontaneous amyloid aggregation in rodents



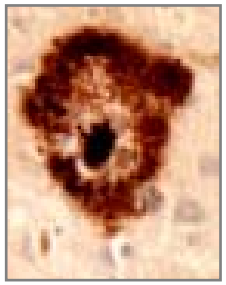
(Dhenain, Handbook of Neuropsychology (2nd ed, 2001))

Related to a different structure of the Abeta protein in rodents

Amyloid cascade hypothesis (simplified)



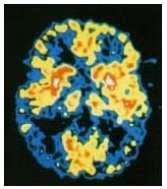
Beta Amyloid



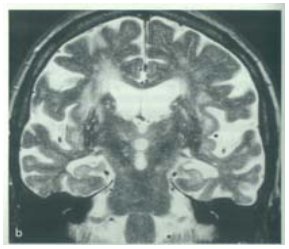
Mutations: APP + PS1

CAA

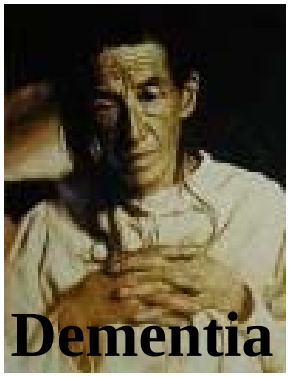
NFT



Functional alterations



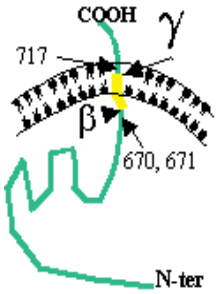
Atrophy Hippoc…



Dementia

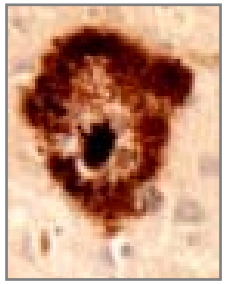
Mouse models of Alzheimer's disease

APP



Beta Amyloid

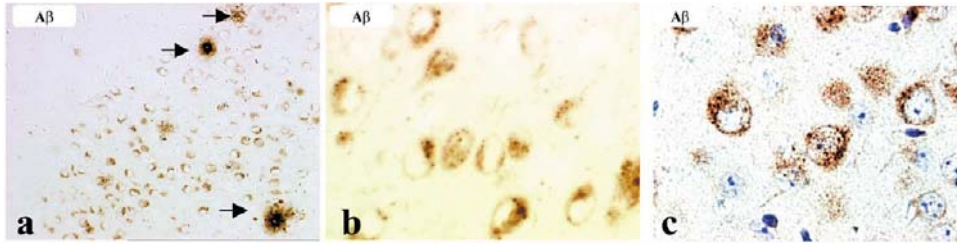
Plaque



Mutations:
APP_{751SL} + $PS1_{M146L}$

APP/PS1

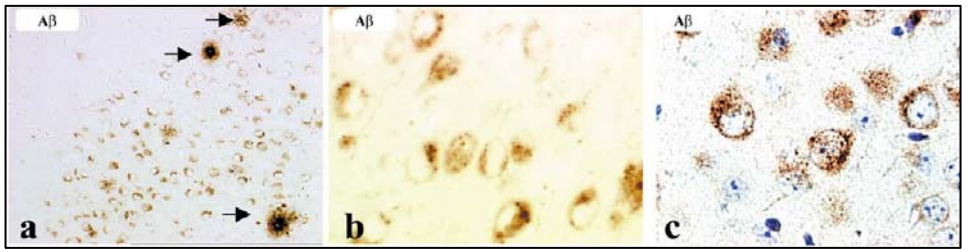
No Tau Pathology …



Intracellular Aß deposits

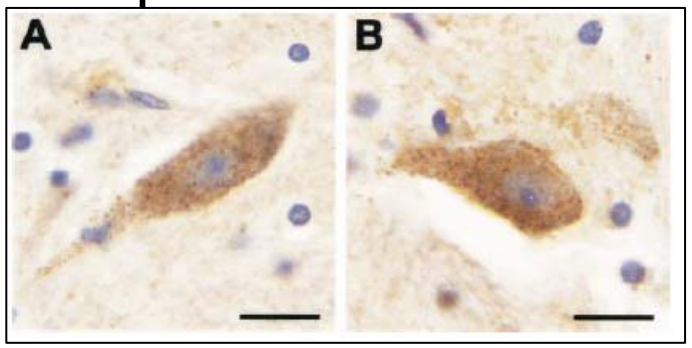
Intracellular Aß deposits: New finding from Tg models

- Intracellular Aß deposits in Tg mice

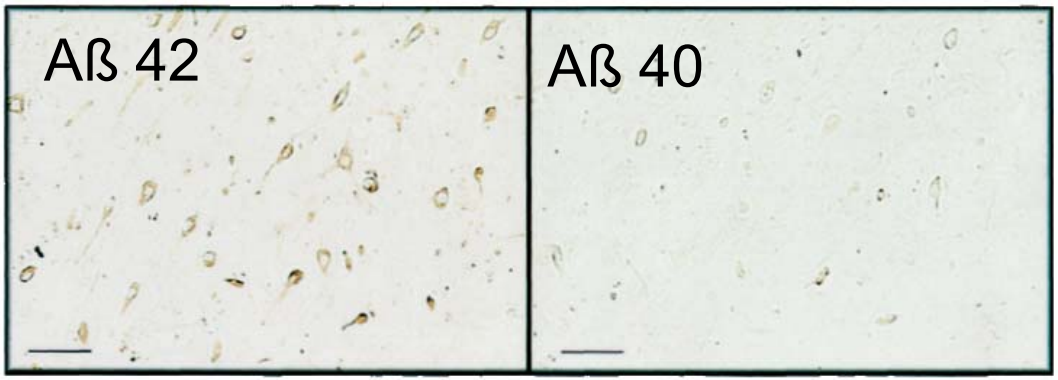


Blanchard,
Exp Neurol, 2003

- Intracellular Aß deposits in Humans

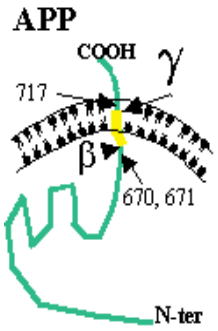


Gyure
Arch Pathol Med, 2001

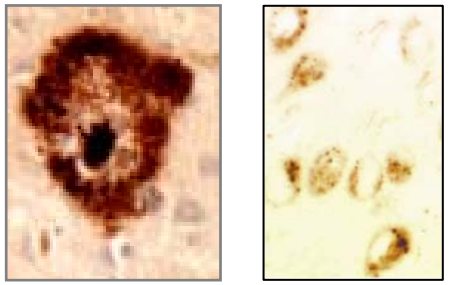


Gouras
Am J Pathol, 2000

Amyloid cascade hypothesis (simplified)



Beta Amyloid

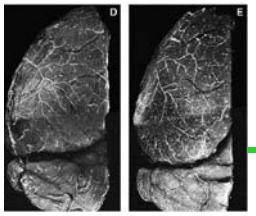


Mutations: APP + PS1

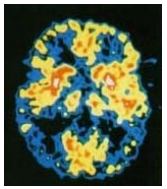
X

?

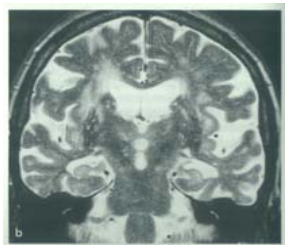
CAA



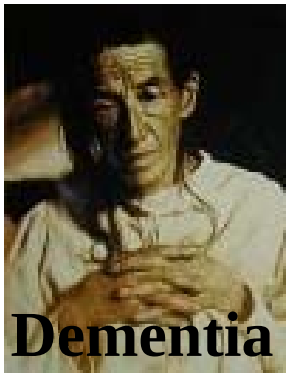
NFT



Functional alterations

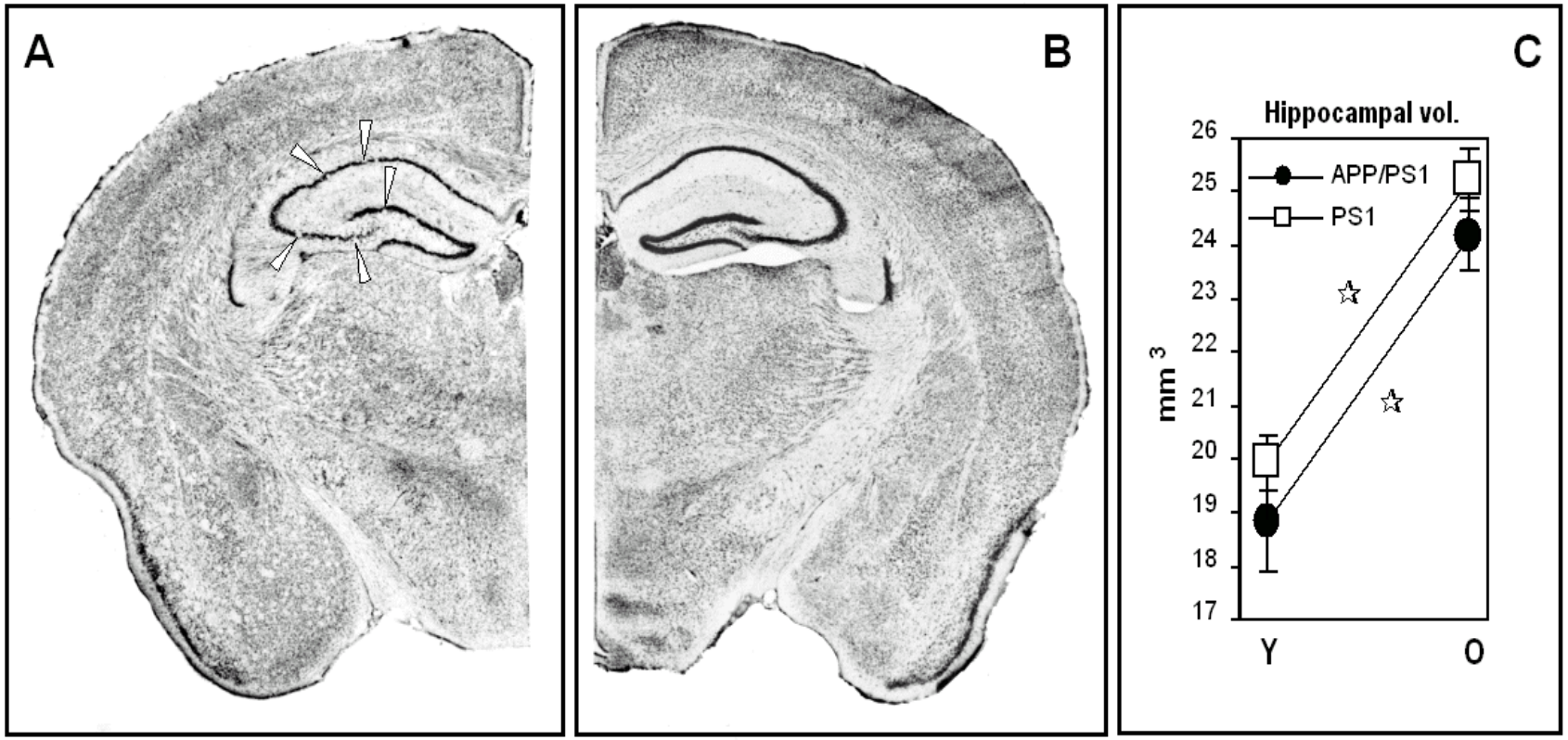


Atrophy Hippoc…



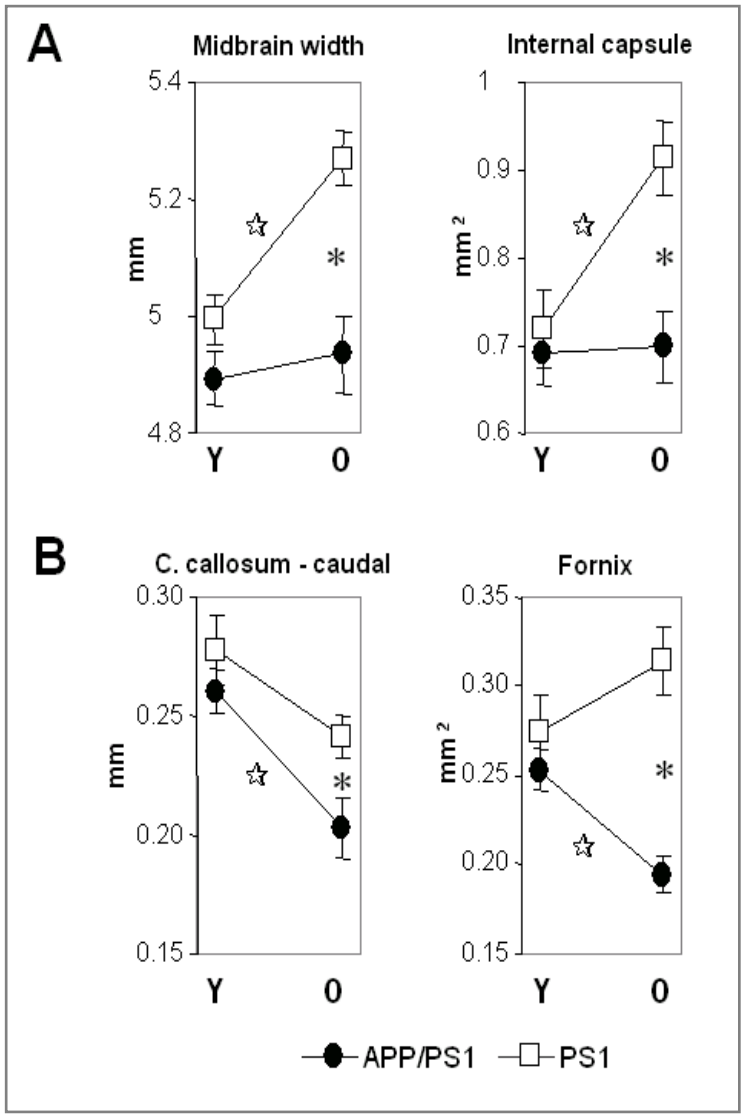
Dementia

Hippocampal growth

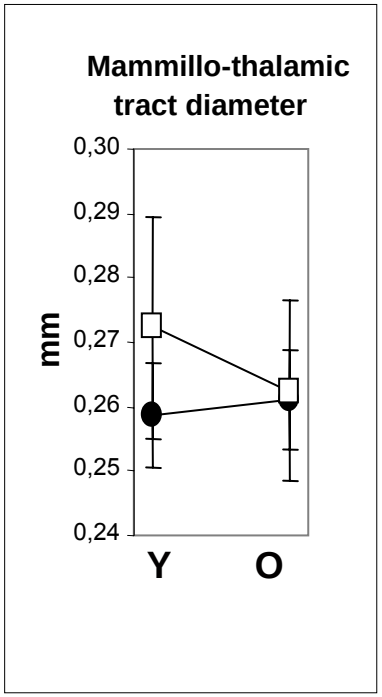


Even in the presence of amyloid deposits…

Atrophy of white matter tracts

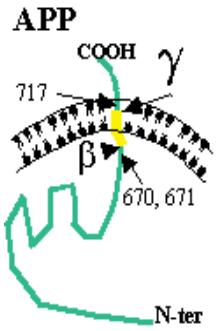


White matter alterations

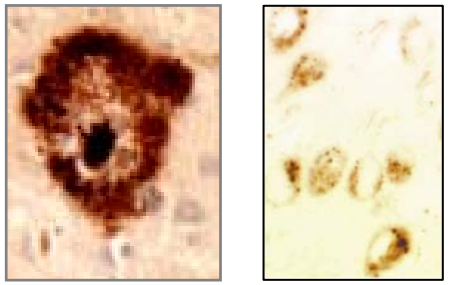


Delatour et al,
Neurob Aging, 2006

Amyloid cascade hypothesis (simplified)



Beta Amyloid



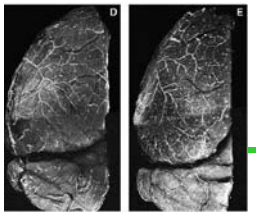
Mutations: APP + PS1

X

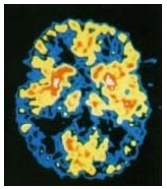
X

?

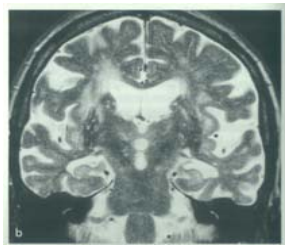
CAA



NFT

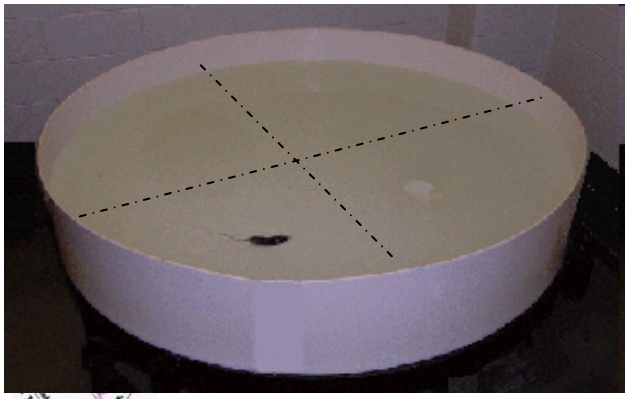


Functional alterations



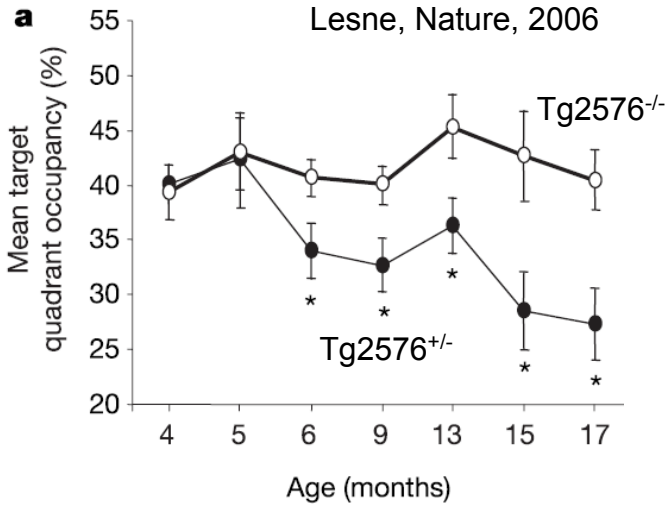
Atrophy Hippoc…

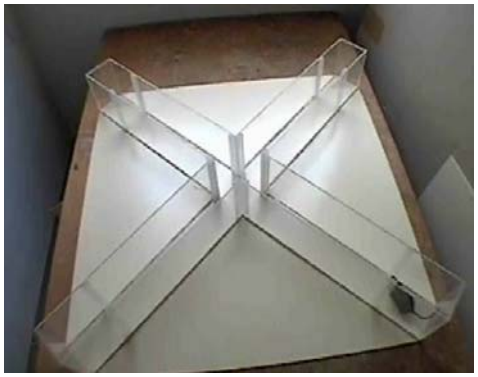
Behavioral tests



SPATIAL NAVIGATION

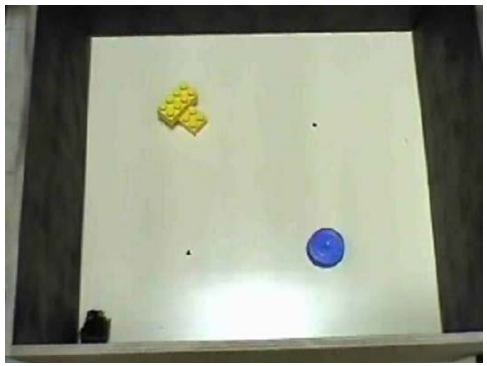
- Spatial reference memory
- Hippocampal integrity
- Very used





SPATIAL ALTERNATION

- Spatial working memory
-Require the integrity of the hippocampus and of frontal cortex



OBJECT RECOGNITION

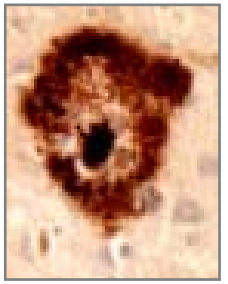
- Short term visual memory
- Require integrity of rhinal cortex (and hippocampus)
- Very used

Alterations of memory
But no dementia

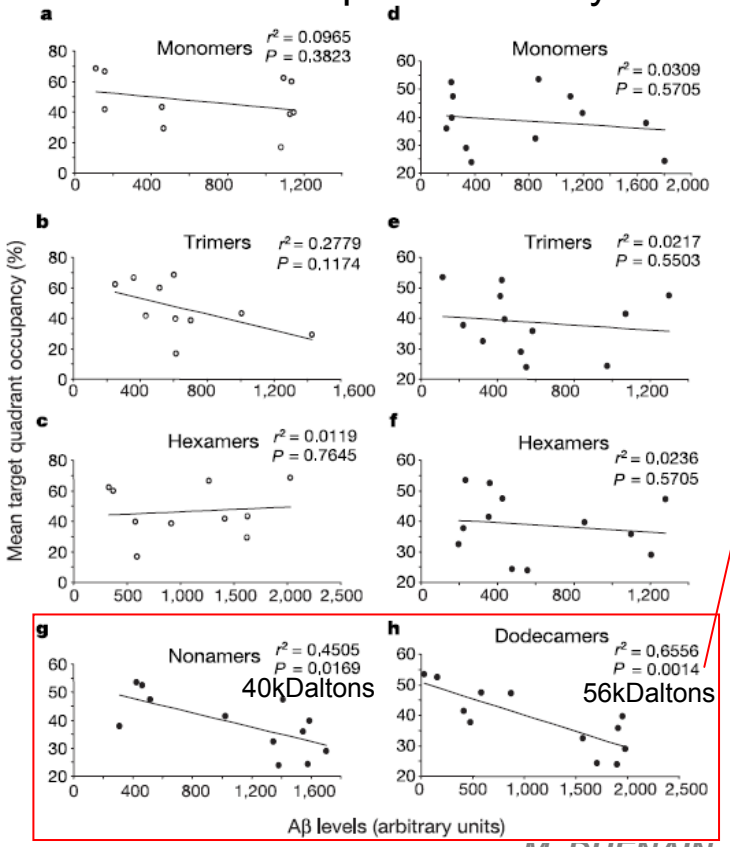
Origin of behavioral alterations: Oligomers

Beta Amyloid

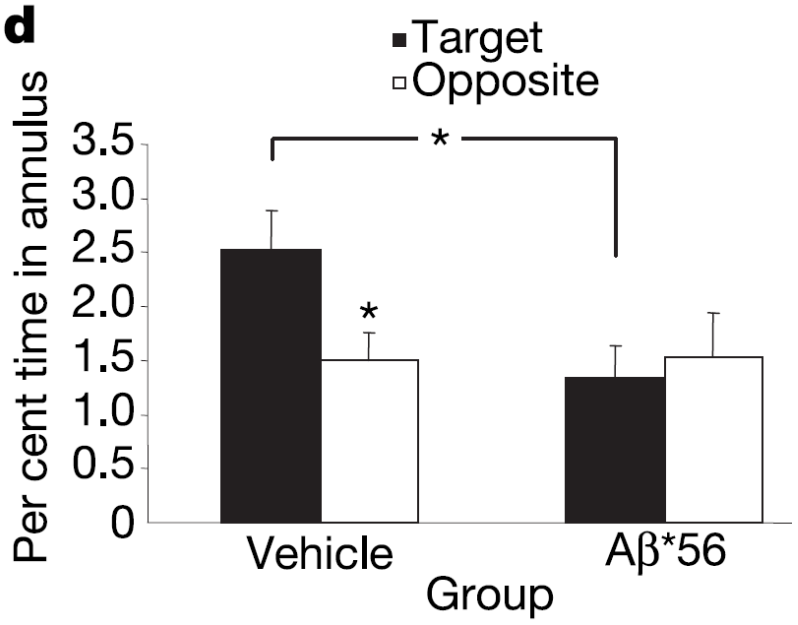
Monomers → Oligomers → Protofibrils → Fibrils



Correlation with spatial memory task



Injection of Aβ*56 in young rats



Lesne, Nature, 2006

Oligomers target synapses

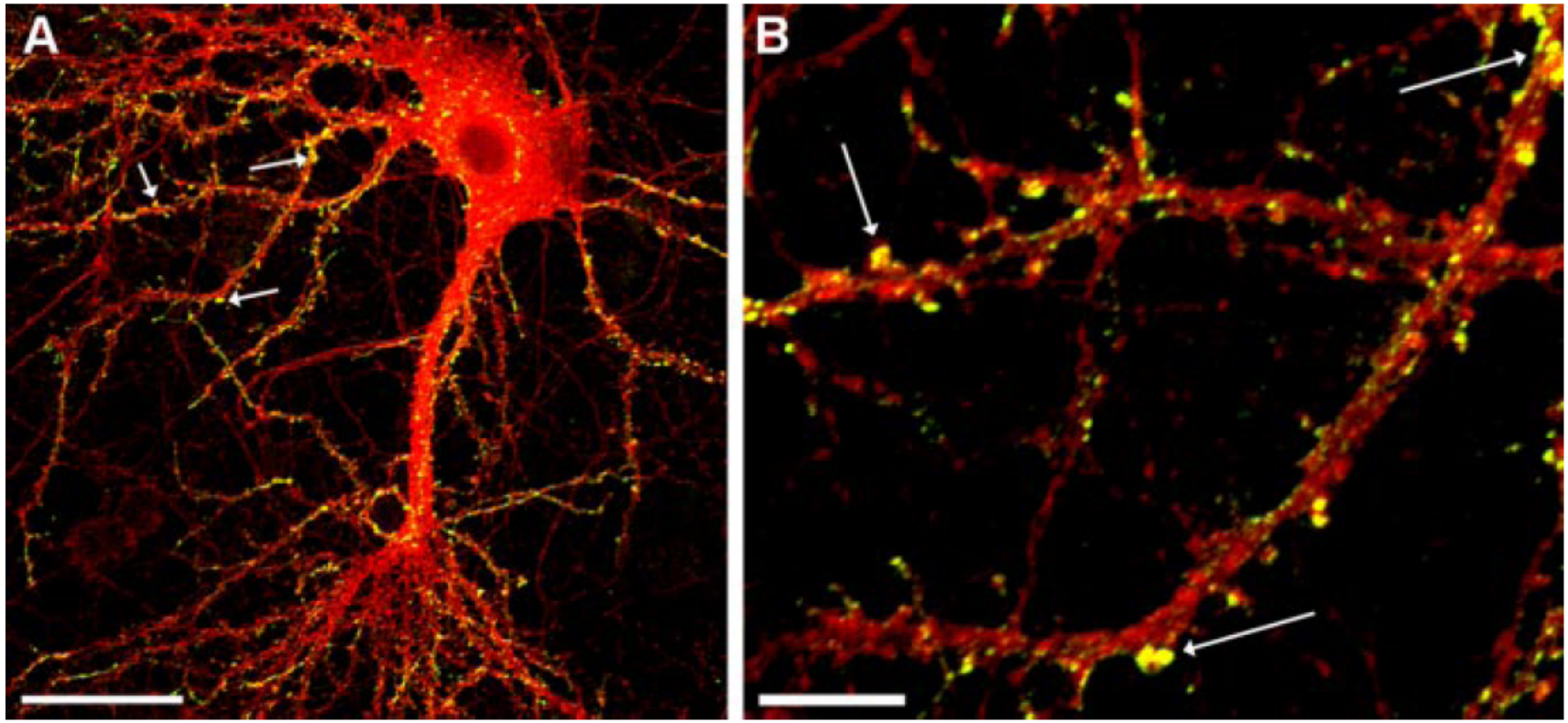
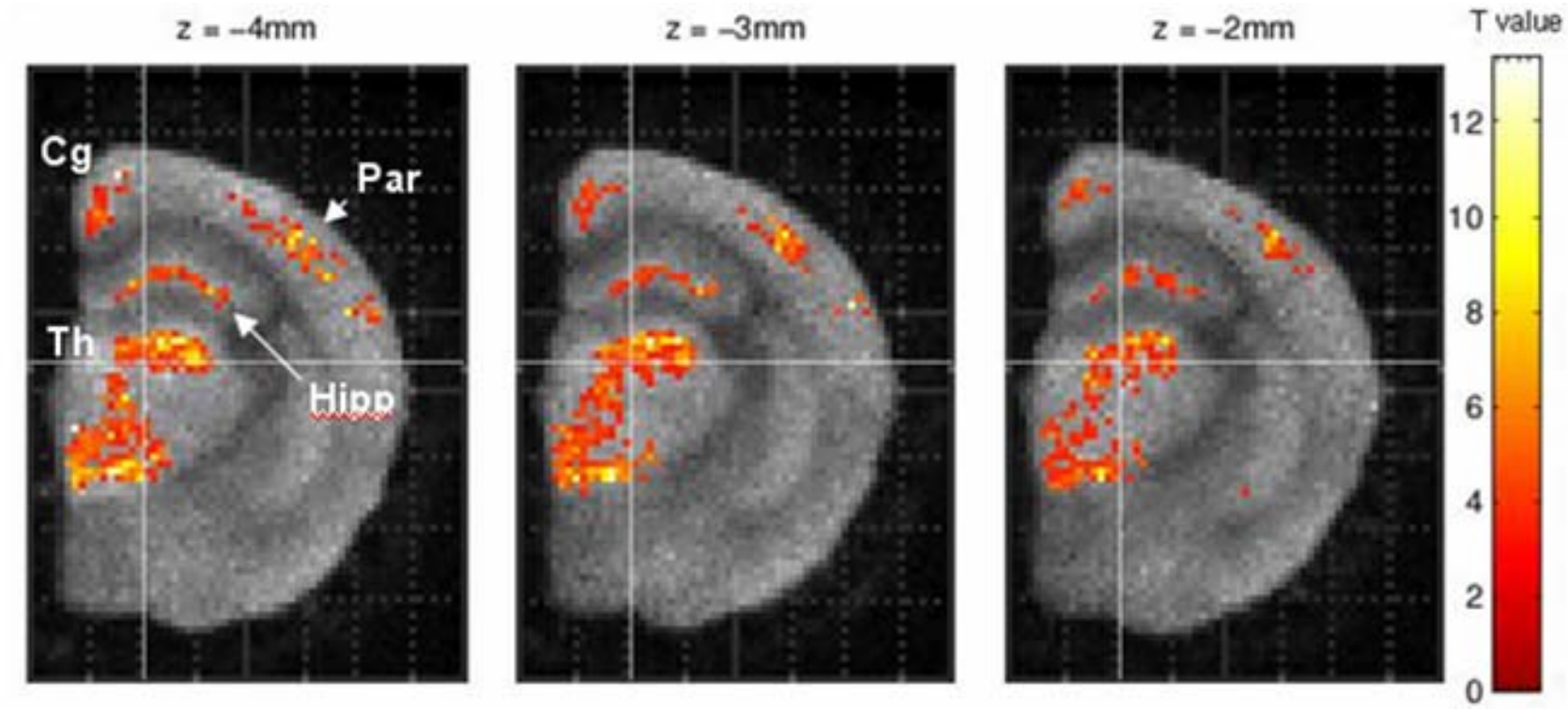


Figure 6. Localization of ADDL binding sites to dendritic spines.

Synaptic binding → Ectopic induction of Arc (synaptic immediate-early gene) → dysfunctional learning

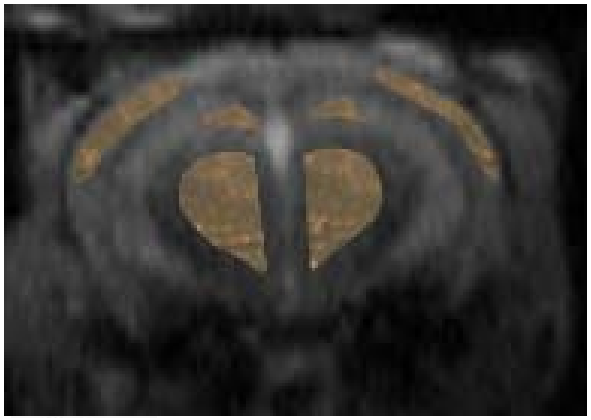
Lacor, J Neurosc, 2004

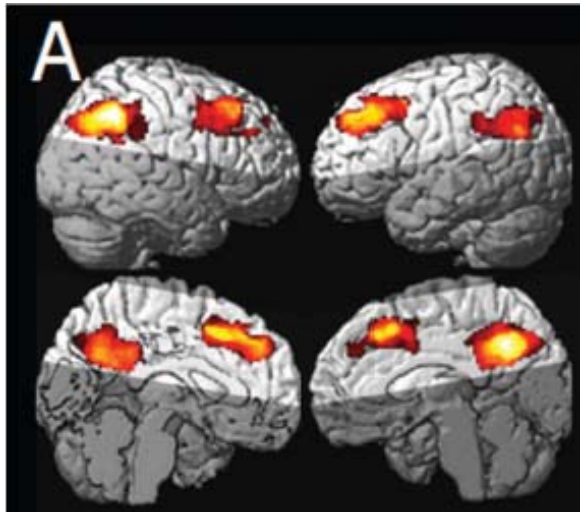
Hypometabolism in Tg mice

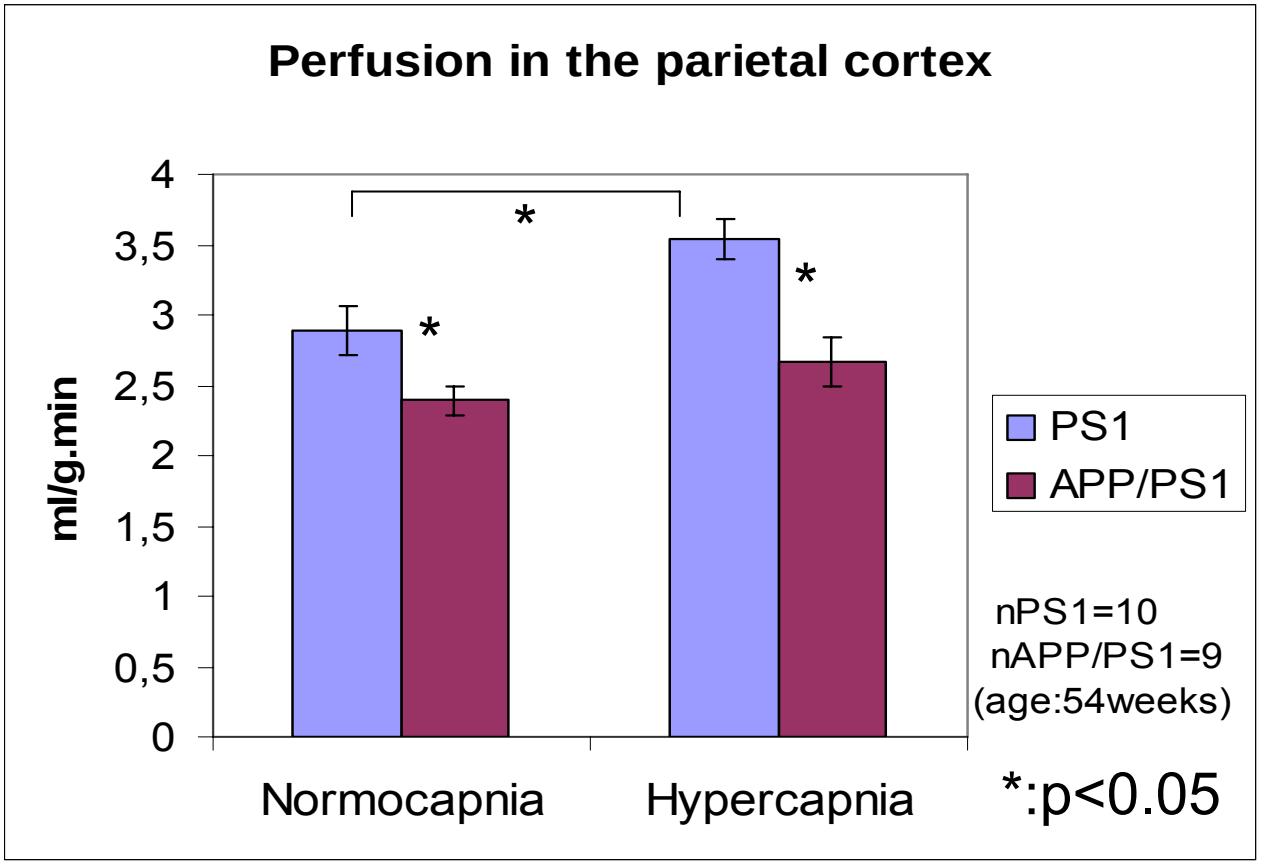


Hypometabolic areas in APP/PS1 mice as compared to control animals

Cortical hypoperfusion in Tg mice



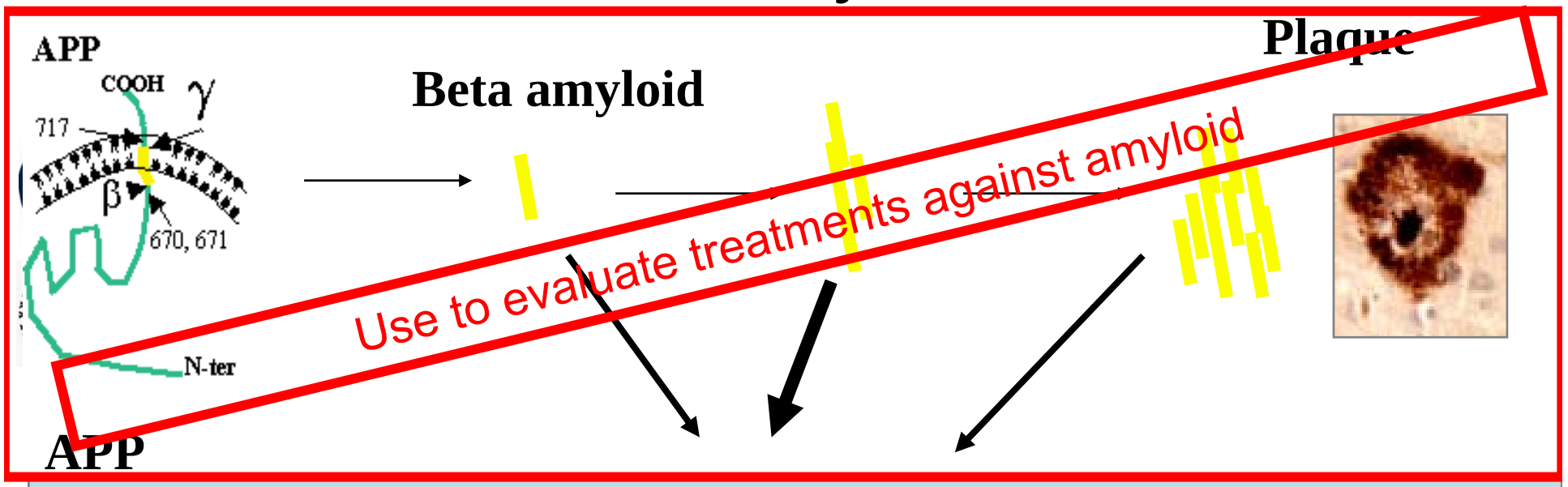




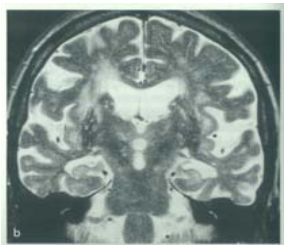
Perfusion alterations are also detected in AD patients

* Johnson et al., Radiology, 2005

« murine » amyloid cascade

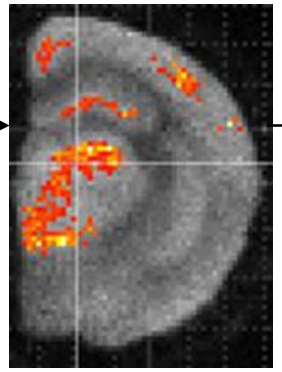


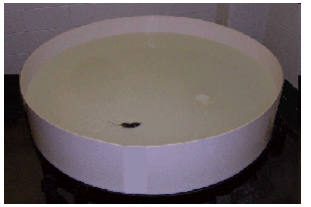
Amyloid cascade hypothesis



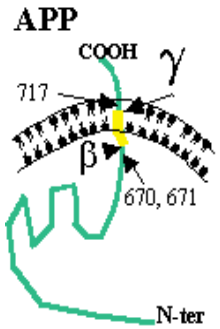
Synaptic alterations

Alterations of LTP

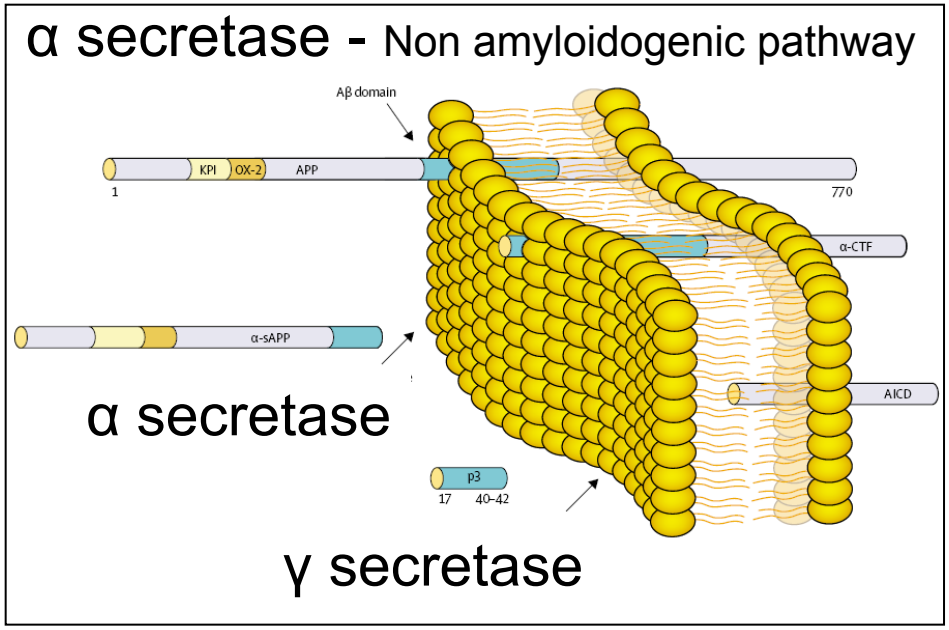


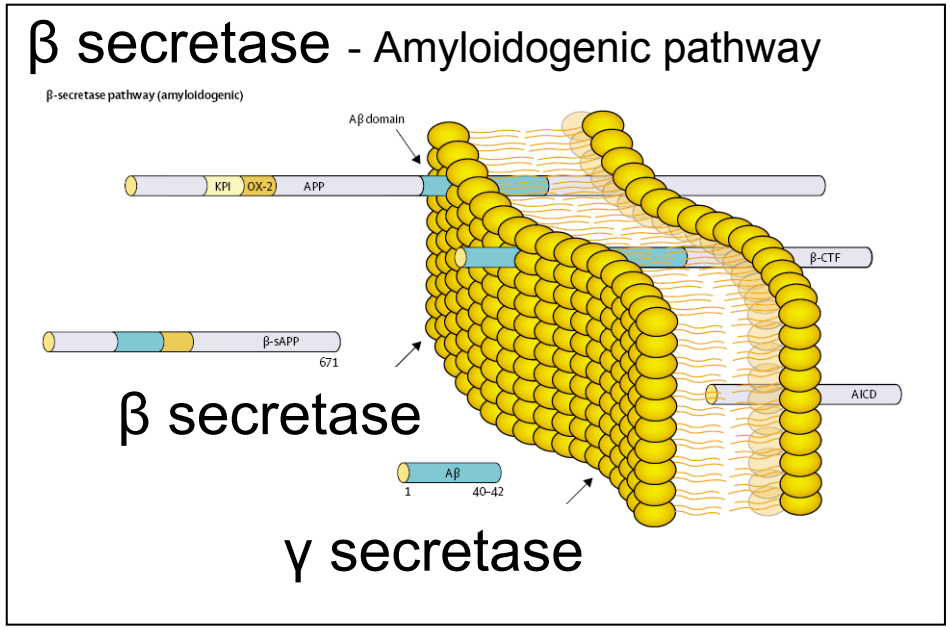


Potential treatments against amyloid pathology in AD



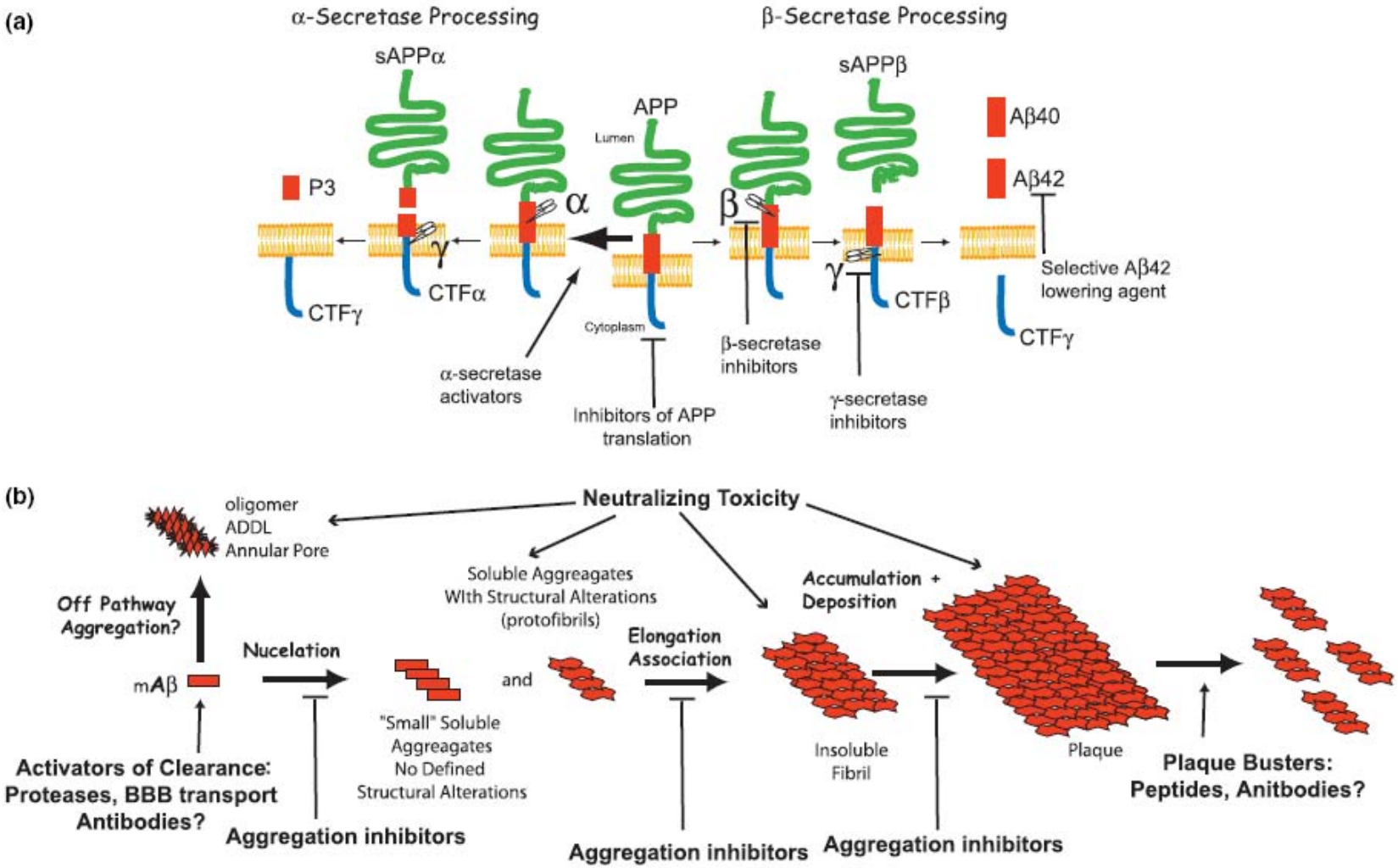
Monomers





From Blennow K et al., Lancet, 2006

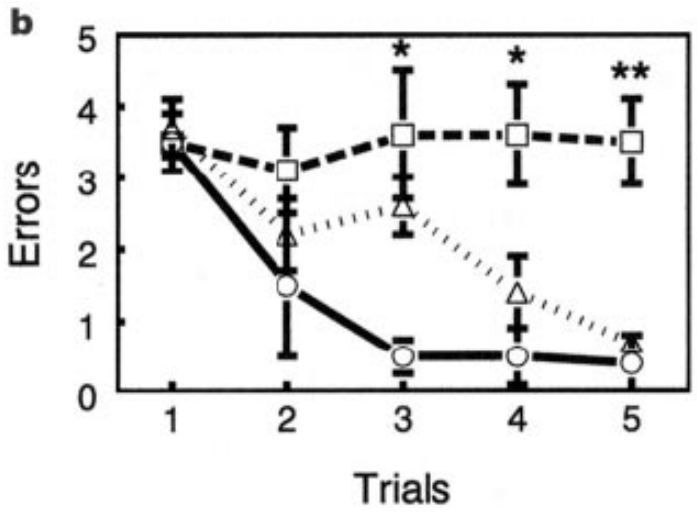
Potential treatments against amyloid pathology in AD



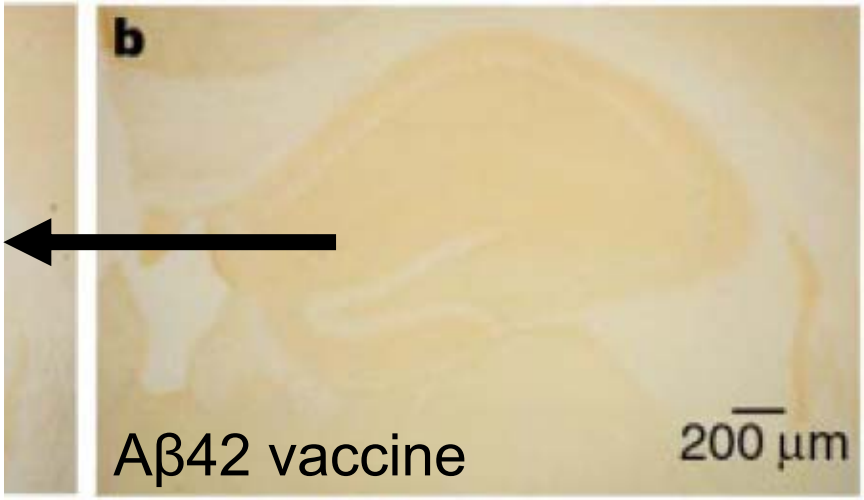
T Golde, J Neurochem, 2006

Use of Tg mice for treatment evaluation

- Ex Immunotherapy in mice



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

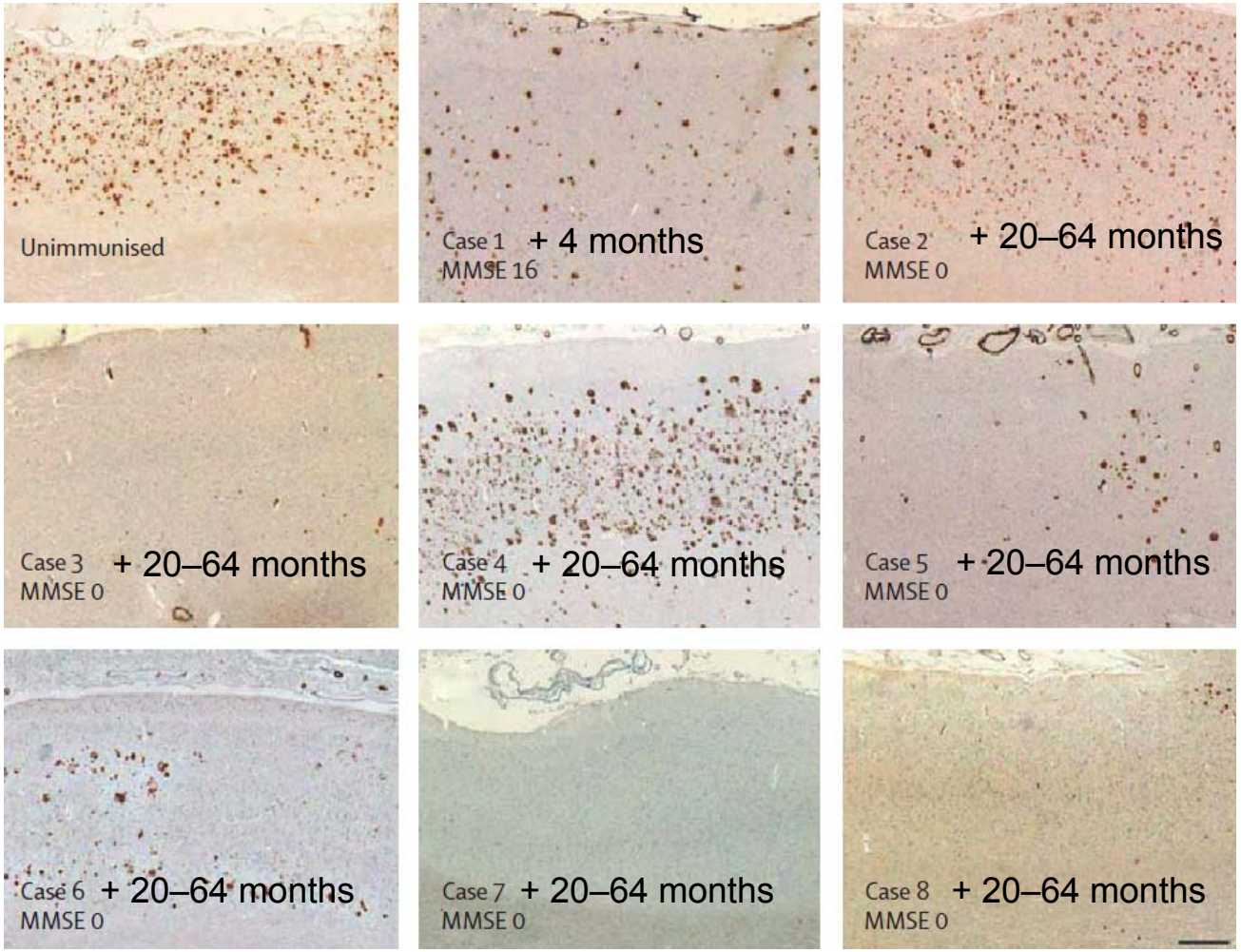


Schenk, D., Nature 1999

- Mice are a very useful first way to test new treatments against amyloidosis

- What is the benefit for the patient ?

Immunotherapy suppress amyloid in some patients



Holmes 2008, Lancet

… But immunotherapy does not suppress evolution of cognitive impairments

Future Treatments of the disease

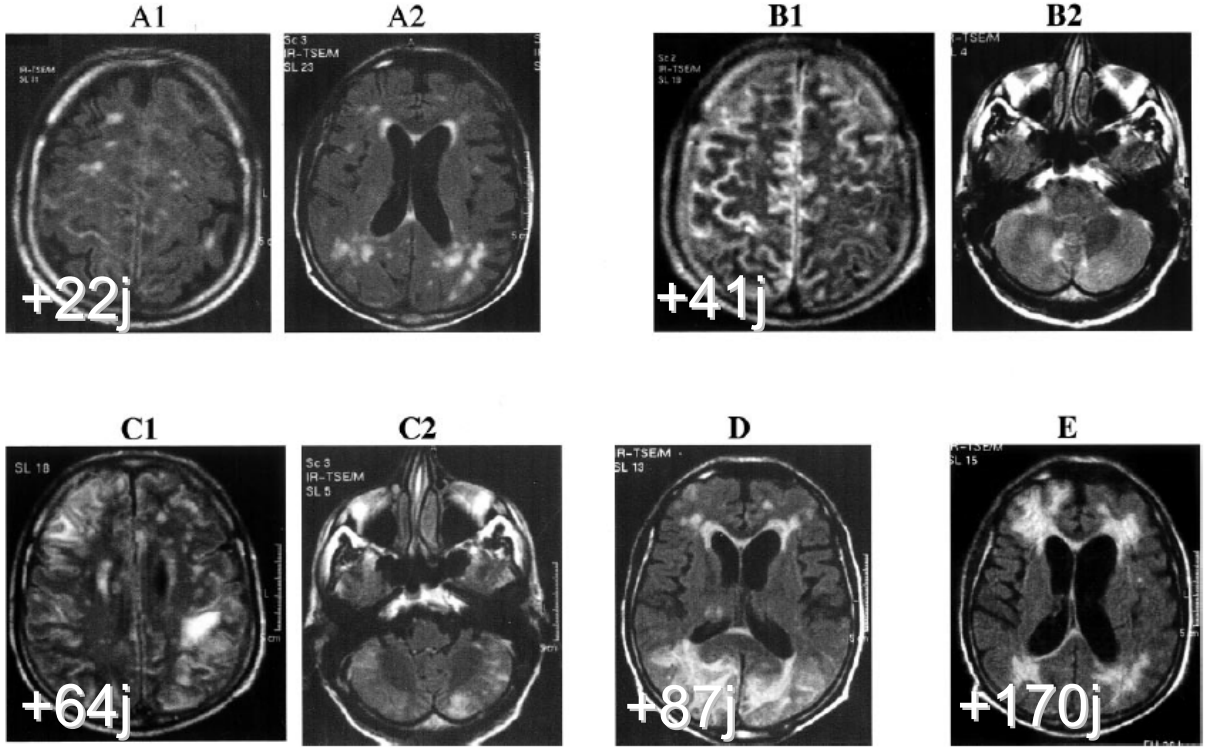
	Treatment	Mechanism of action	Mouse model
Secretase modulation	[OM00-3]DR9	β-secretase inhibitor	Tg2576
	DAPT	γ-secretase inhibitor	PDAPP
	Bryostatin	PKC activator, α-secretase stimulator	$APP_{V717I}/PS1_{A246E}$
Aβ immunotherapy	Pre-aggregated Aβ1-42+adjuvant	Active immunisation	PDAPP
	Anti-Aβ antibodies	Passive immunisation	PDAPP
Anti-aggregation	iAβ5p peptide	β-sheet breaker peptide	$APP_{V717I}/PS1_{A246E}$
	Aβ12-28P peptide	ApoE-Aβ binding blocker	$APP_{Swe}/PS1_{M146L}$
	Neprilysin gene transfer	Increased Aβ degradation	PDAPP
Lipid/carbohydrate metabolism modulation	BM15.766	Cholesterol lowering	Tg2576
	High cholesterol diet	Cholesterol challenge	APP_{Swe}
	Caloric restriction	Reduced insulin levels	$APP_{Swe/Ind}$
	High saturated fat/low carbohydrate diet	Unkown. Ketogenic diet?	APP_{V717I}
	CP-113,818	ACAT inhibitor	APP_{Swe} and APP_{V717I}
	Omega-3 fatty acid	Altered APP processing? Anti-oxidative?	Tg2576
	T0901317	Liver X receptor ligand	APP23
Kinase modulation	Wortmannin	Phosphatidyl-inositol kinase inhibitor	Tg2576
	Lithium	GSK3β inhibition	PDAPP
	Valproic acid	GSK3β inhibition	PDAPP
Anti-inflammatory/anti-oxidative	NSAIDs (8 FDA-approved drugs)	Anti-inflammatory	Tg2576
	NCX-2216	Anti-inflammatory, anti-oxidative, NO-release	$APP_{Swe}/PS1_{M146L}$
	Pioglitazone	PPARγ-agonist, anti-inflammatory	APP_{V717I}
	Lipopolysaccharide	Activation of the innate immune system	Tg2576
	Curcumin (curry spice)	Anti-inflammatory, anti-oxidative	Tg2576
	Vitamin E	Anti-oxidative	Tg2576
	N-acetyl cysteine	Anti-oxidative	TgCRND8

From Blennow K et al., Lancet, 2006

Poor models of toxicity ?

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



At the time of this report, 12 months after the initial onset of symptoms, he remains hospitalized and totally dependent, although his level of consciousness and language continue to improve slowly.

Neurology, 2003

Validity criteria of APP/PS1 transgenic models

- **Construction validity: mutations in familial forms of AD**

- **Face validity: Comparison to human pathology**
  - Amyloid plaques: Yes
  - Neurofibrillary tangles: No
  - Neuroinflammation: Yes
  - Neuronal loss: No
  - Cholinergic alterations: No

  - Cerebral atrophy: No
  - Metabolic alterations: Yes?

  - Cognitive alterations: Yes
  - Dementia: No

- **Prediction validity (for anti-amyloid drugs)**
  - Validity for a fundamental research question: Yes if question on amyloid
  - Validity for POM (from therapy to target): Yes if therapy on amyloid
  - Validity for Mechanism of Action: Yes
  - Validity for Toxicity evaluation: Not obvious
  - Validity for POC (from target to disease outcome modification in humans): No

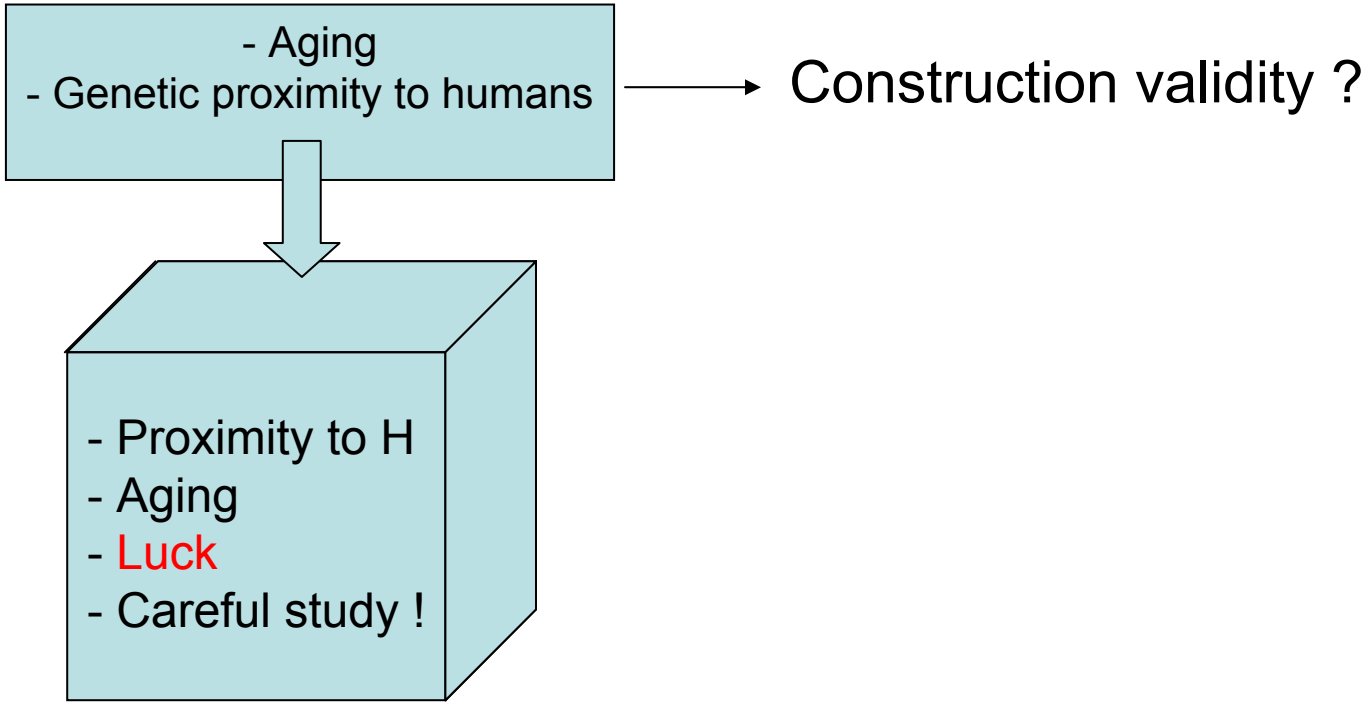
Tg mice are used to evaluate future treatments of the disease

	Treatment	Mechanism of action	Mouse model
Neurotransmitter modulation	Nicotine	Cholinergic stimulation	Tg2576
	AF267B	Selective M1 muscarinic agonist	3×Tg AD mice
	PEC	Butyrylcholinesterase inhibitor	$APP_{Swe}/PS1_{A246E}$
	Paroxetine	Serotonin re-uptake inhibitor	TgCRND8
Hormone modulation	17α-oestradiol and 17β-oestradiol	Hormone replacement	Tg2576
	Leuprorelin	Gonadotropin-releasing hormone agonist	Tg2576
	Melatonin	Unknown. Multiple potential mechanisms	Tg2576
Environmental exposure	Environmental enrichment	Unknown	$APP_{Swe}/PS1_{\Delta E9}$
	Experimental acute brain trauma	Unknown. Aβ clearance by microglia?	PDAPP
Heavy metal modulation	Dietary copper	Copper supplementation	APP23
	Clioquinol	Copper/zinc chelator	Tg2576
	DP-109	Heavy metal chelator	Tg2576
Miscellaneous	Cerebrolysin (porcine brain peptide mix)	Neurotrophic	mThy1-hAPP751
	Enoxaparin (low MW heparin)	Unknown.	APP23
	RAGE	Blockage of Aβ transport to the brain?	APP_{Swe}/APP_{V717F}
	Insulin-like growth factor I (IGF-I)	Increased Aβ elimination from brain?	APP/PS2
	Epigallocatechin-3-gallate (green tea)	Unknown. α-secretase stimulation?	Tg2576
	Erythromycin	Macrolide antibiotic	TgCRND8
	Soluble Nogo-66 receptor fragment	Unknown. Multiple potential mechanisms.	$APP_{Swe}/PS1_{\Delta E9}$
	Rosiglitazone	Increased insulin sensitivity? Cortisol lowering?	Tg2576
	Propentofylline	Unknown. Multiple potential mechanisms	Tg2576

From Blennow K et al., Lancet, 2006

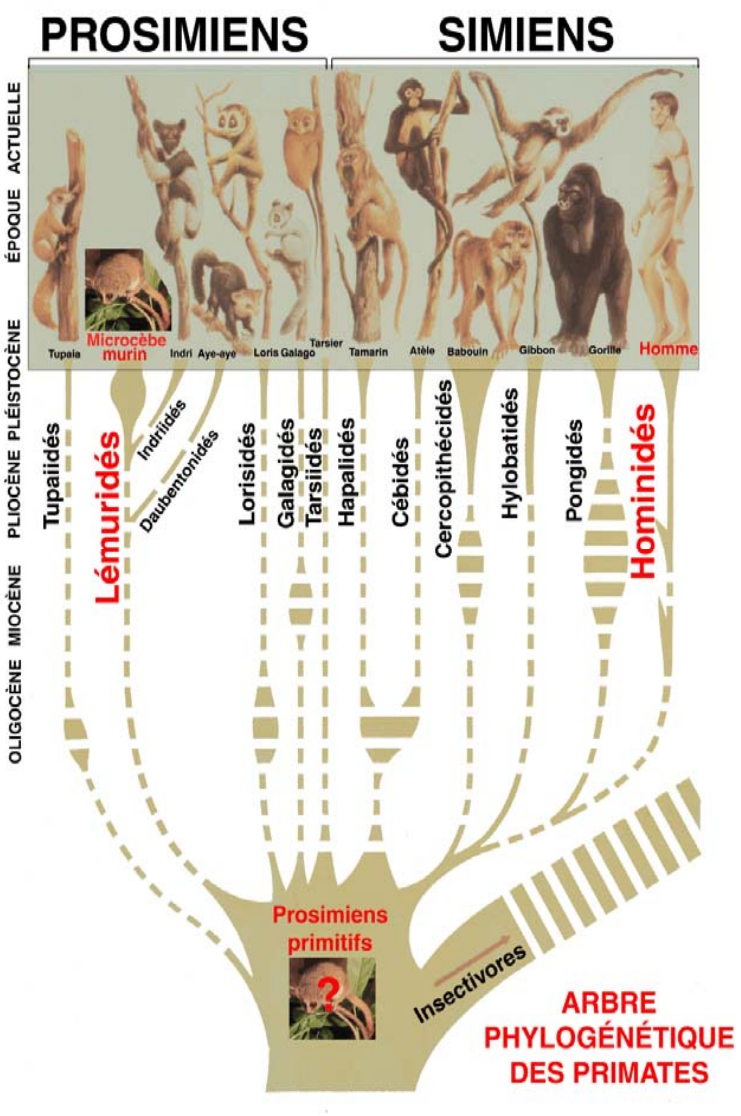
- Other models of AD such as Tau mice not discussed here

Spontaneous models. Ex. of the primates



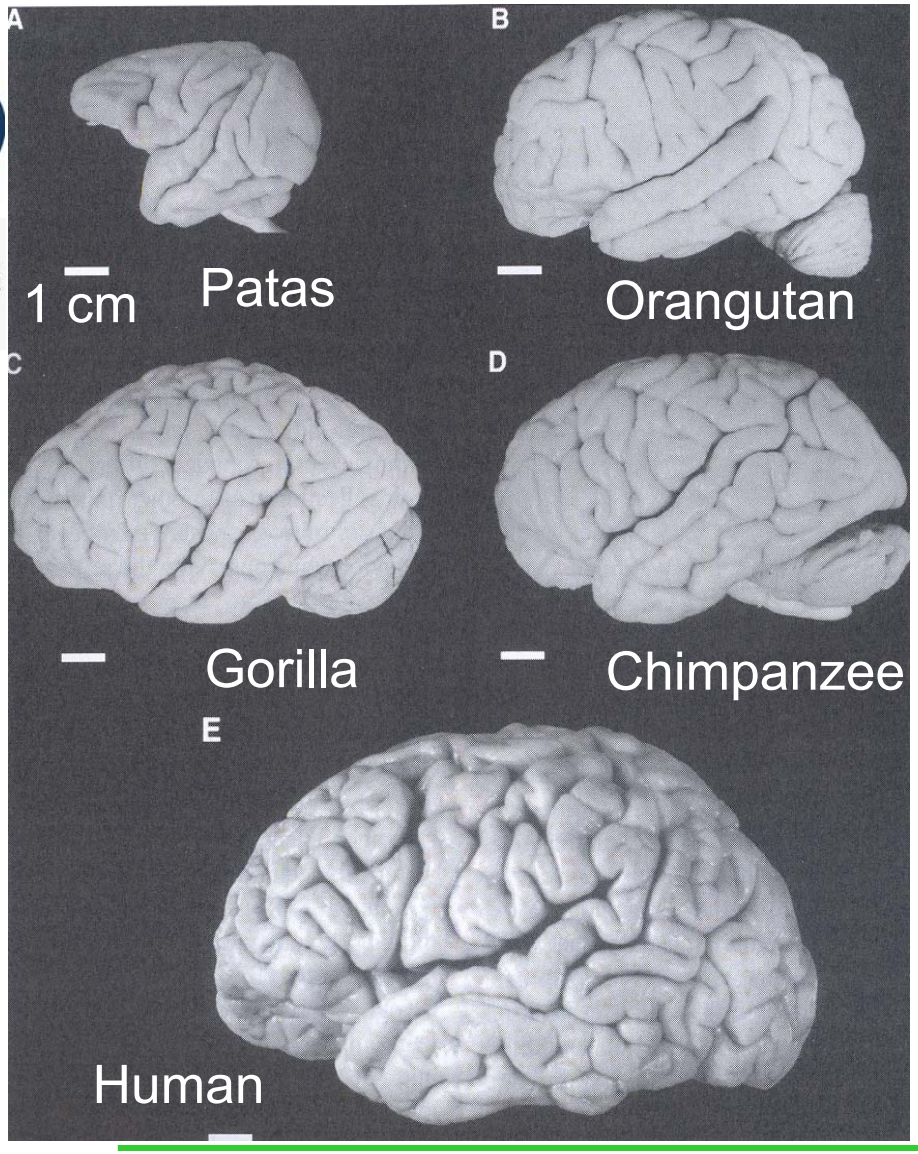
What about face validity ?
What about prediction validity ?

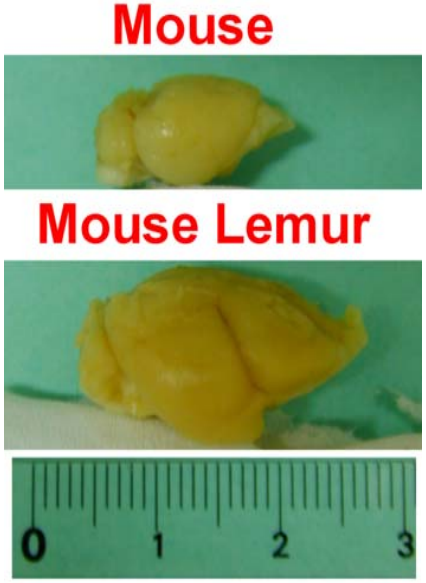
Primate heterogeneity



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



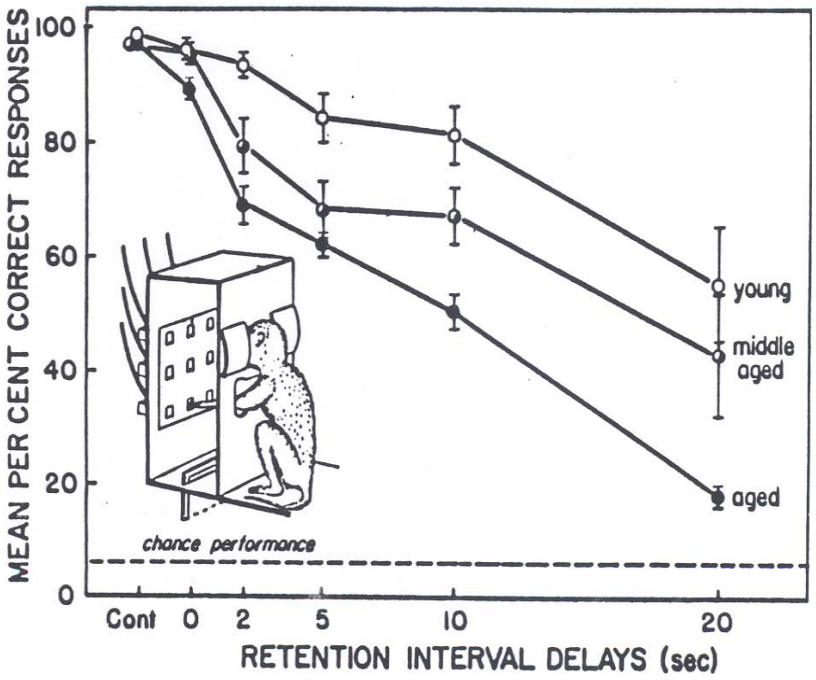


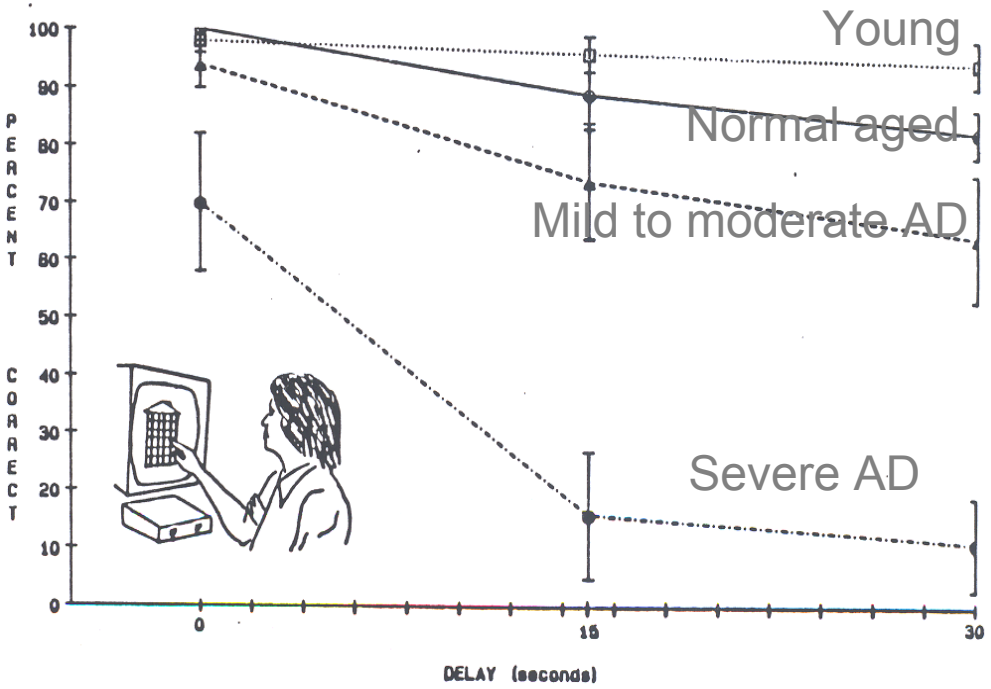
What are age related alterations in primates ?

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)

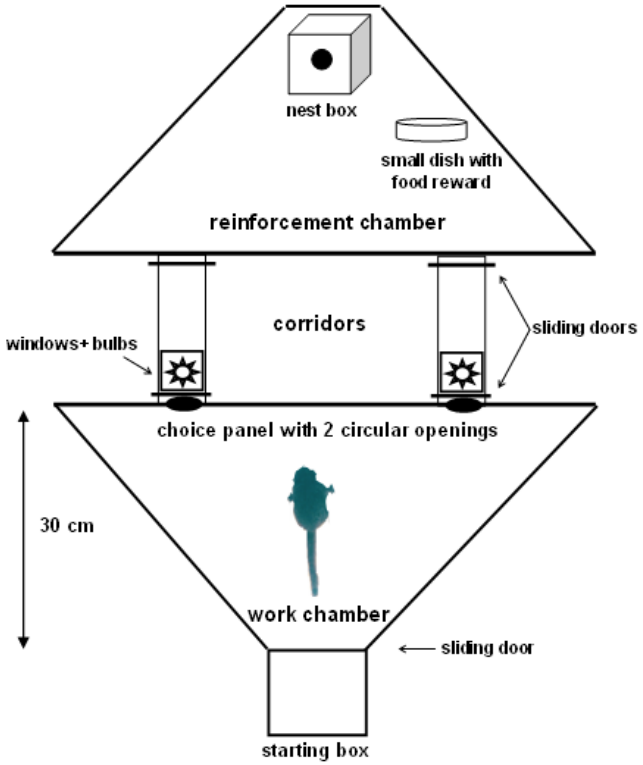
Age related cognitive alterations

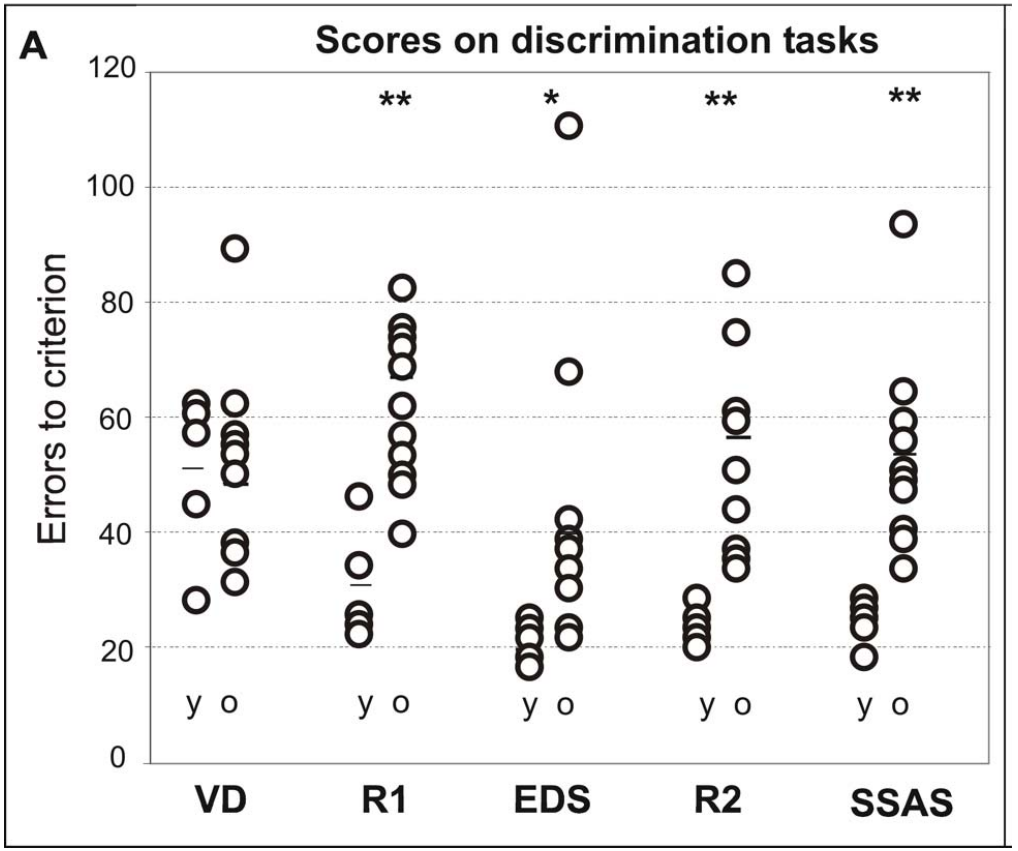
- Prefrontal impairments, perseveration
  - ~ 15-20 years in Rhesus monkeys
  - Very constant in different animals

- Tasks depending on medial temporal areas
  - ~25-30 years in Rhesus monkeys
  - (But) Interindividual variations

What is responsible for these alterations ?

Behavioral alterations in aged lemurs: Shift tasks





VD:  = 

EDS: Right corridor = 

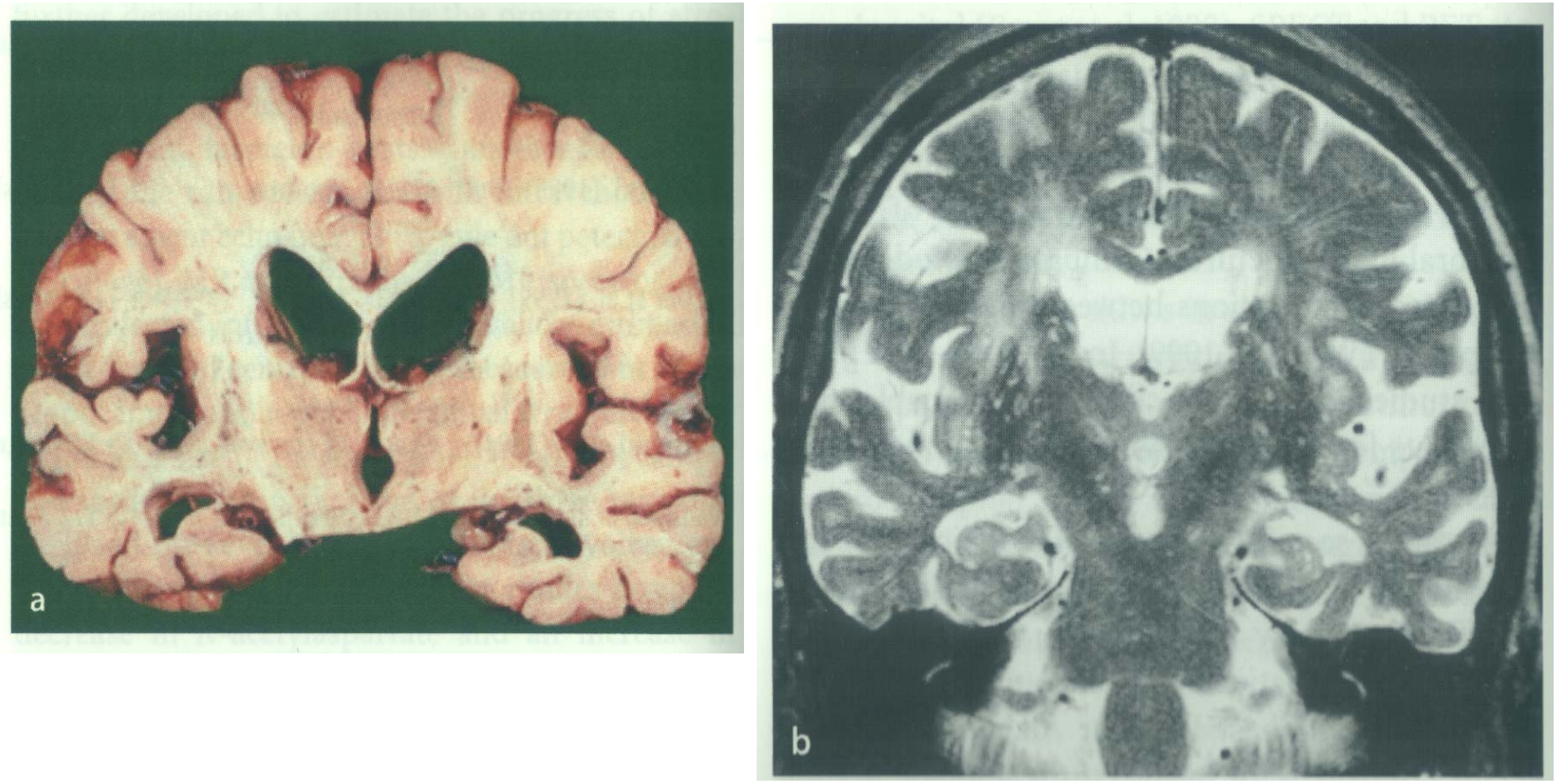
R1:  = 

R2: Left corridor = 

Picq et al. Neurobiology of Aging, In press

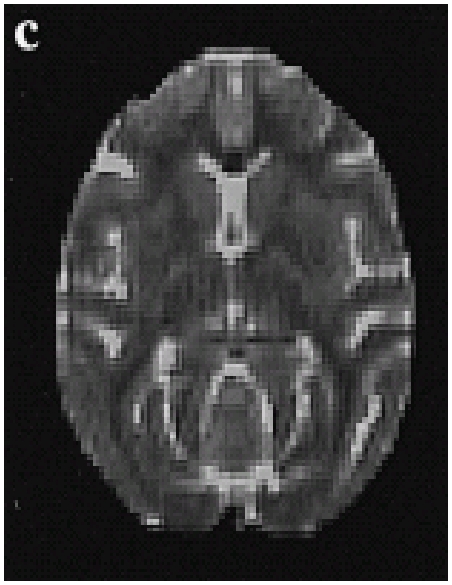
Macroscopic alterations

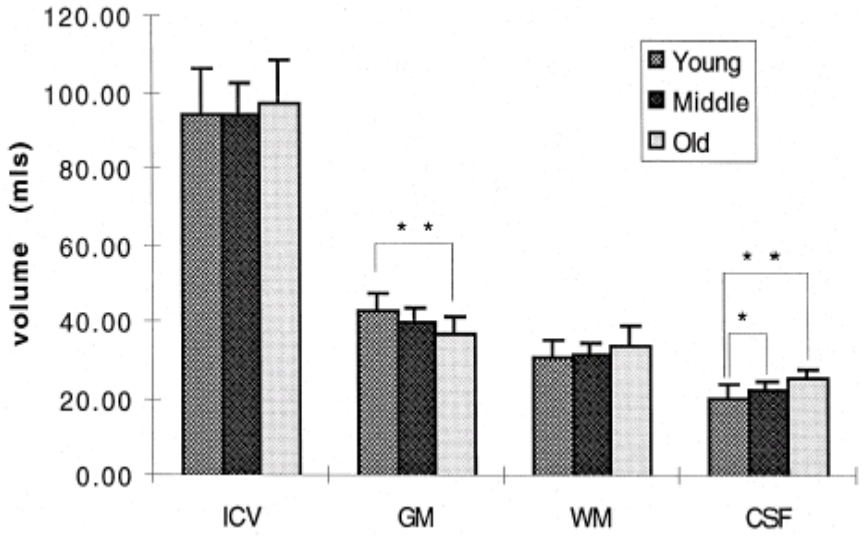
Cerebral atrophy

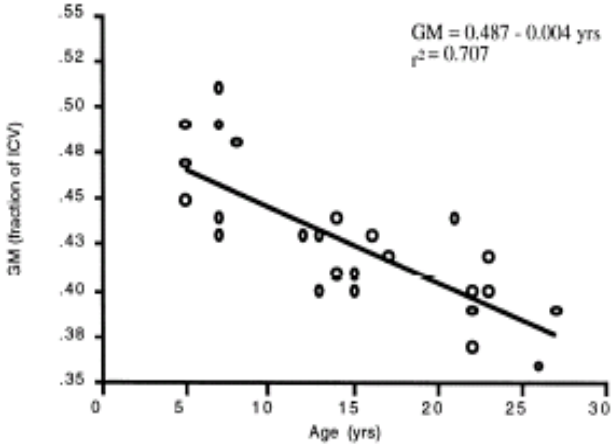


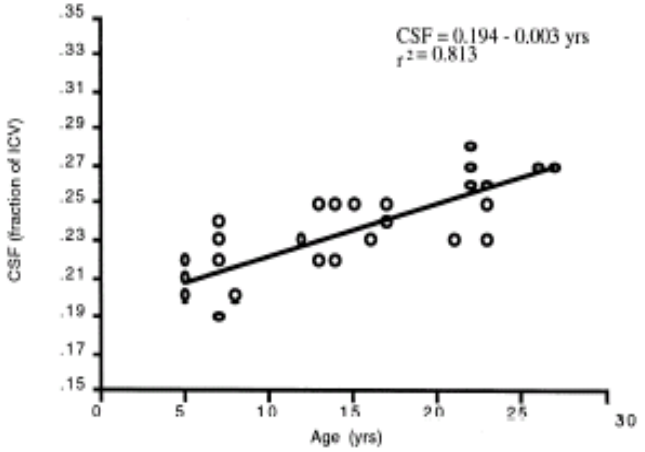
Cerebral atrophy in human

Cerebral atrophy in Rhesus monkey



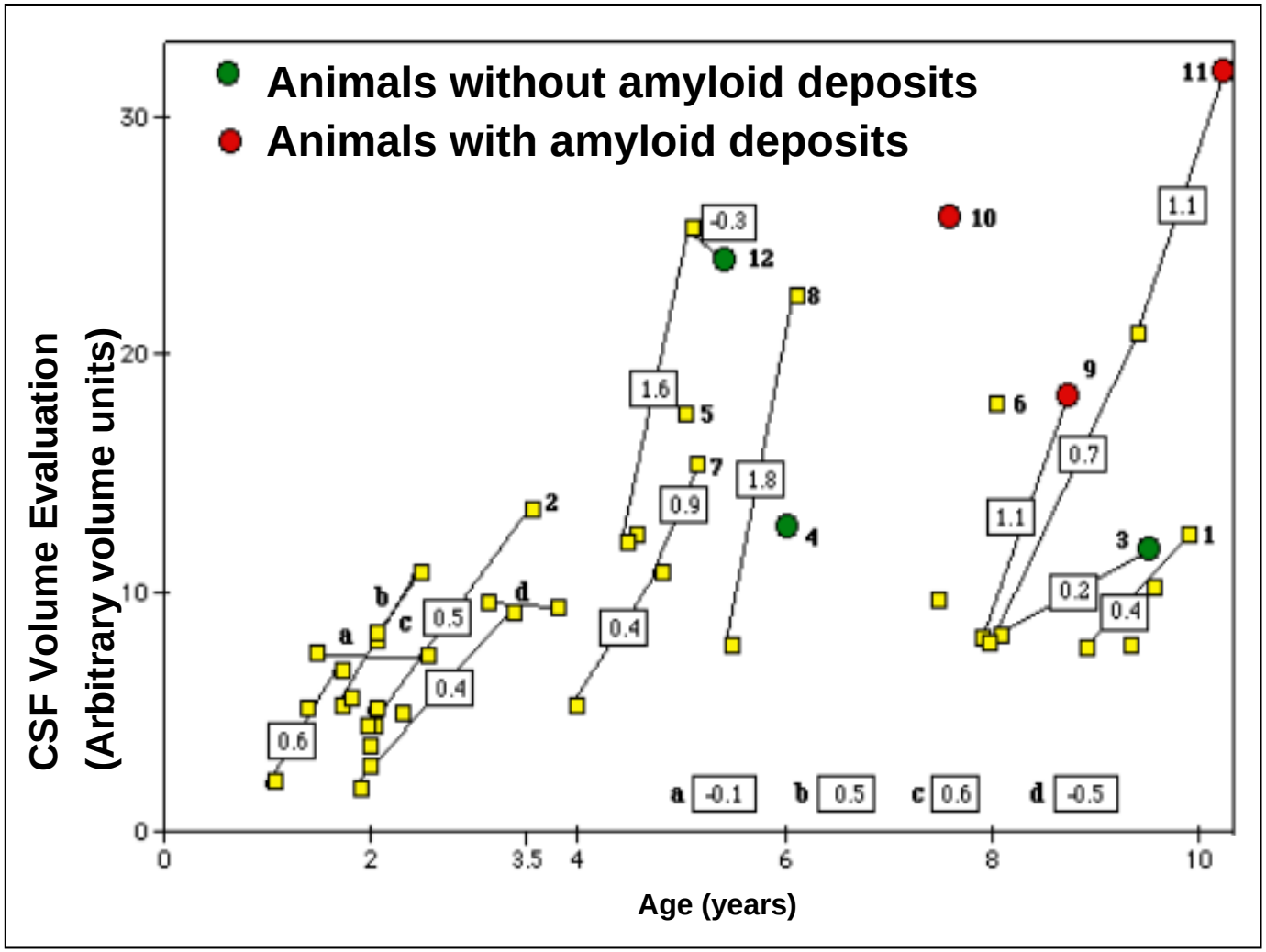


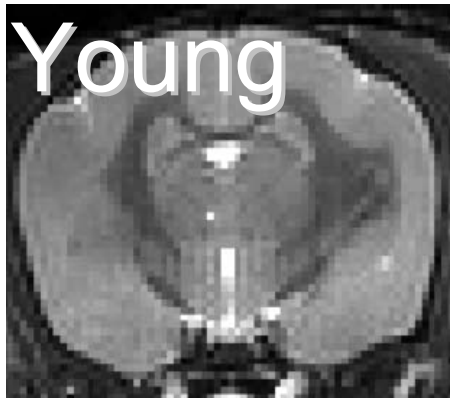


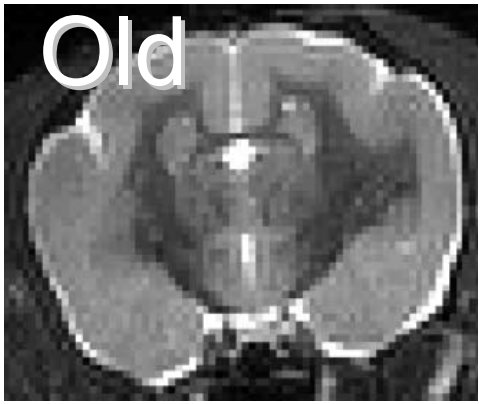


(Andersen et al., Brain Research, 1999)

Temporo-parietal atrophy in mouse lemurs



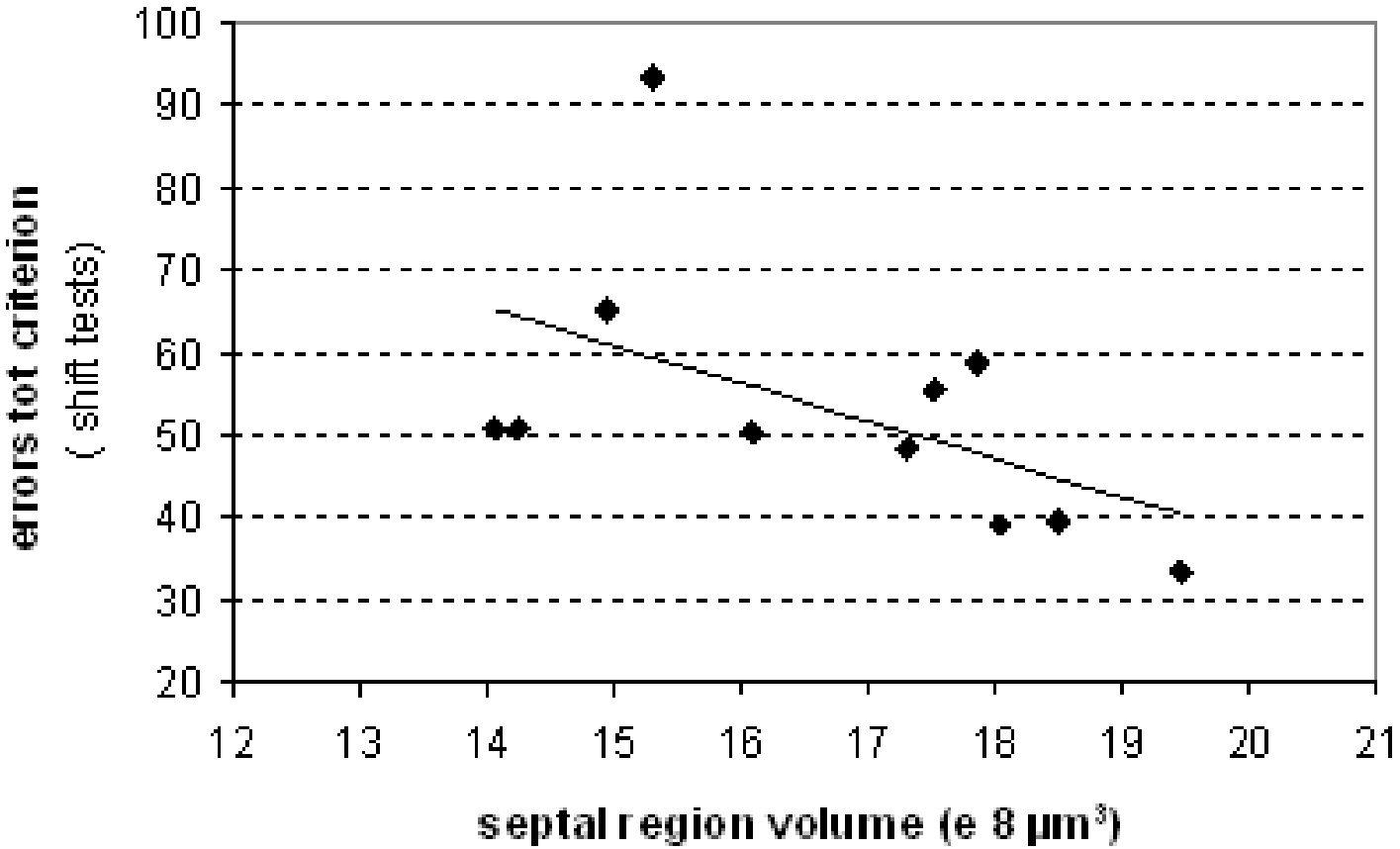




(Dhenain et al., Neurob. Aging, 2000)

- Fast evolution when the process is started

Link between behavioral alterations and atrophy in aged animals



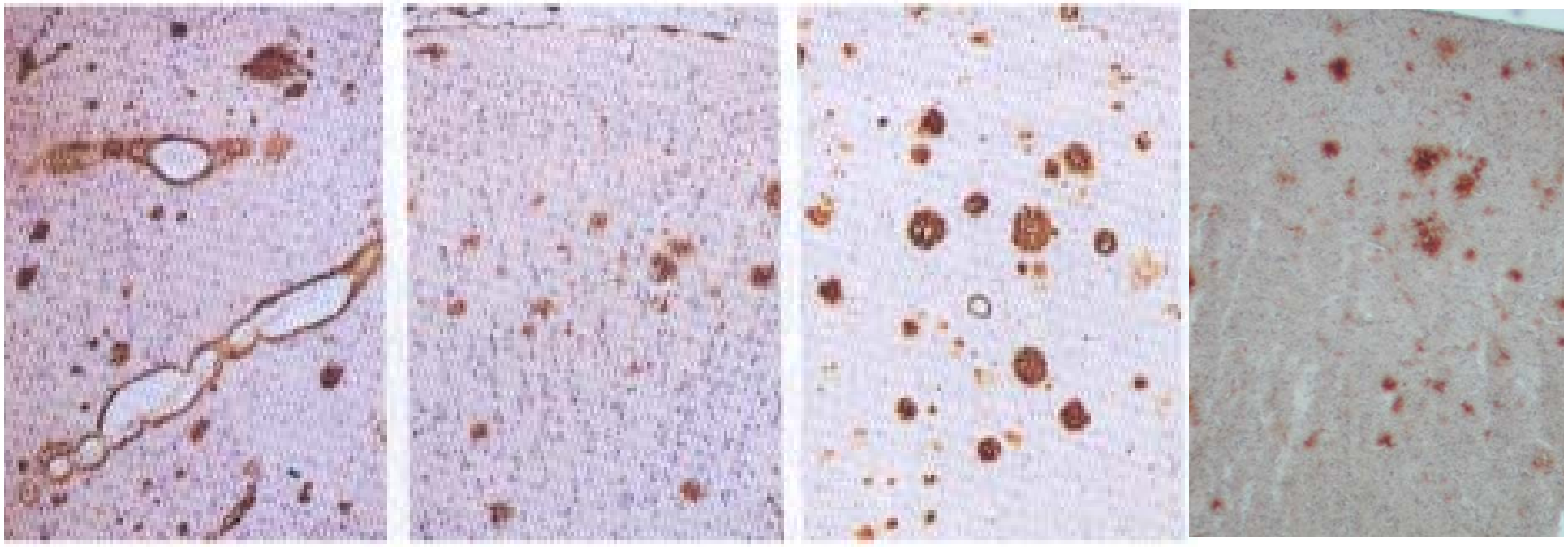
Only primate showing a correlation between macroscopic brain atrophy and age-related cognitive alterations

Picq et al. Neurobiology of Aging, In press

Microscopic alterations

Amyloid deposits

Chimpanzee | Rhesus | AD - Human | Mouse lemur



Gearing et al, PNAS, 1994

http://m.lemur.free.fr

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

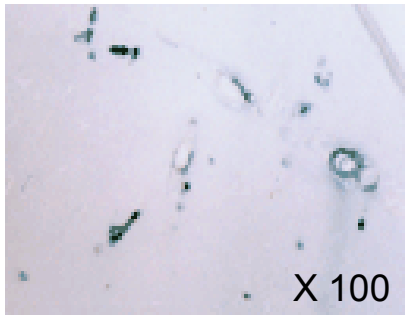
Animal species	β-APP	A β Sequence	Mutations
Cynomolgus monkeys	Homology 100%	Homology 100%	Not reported
New world monkeys Squirrel monkeys	Difference 3 amino acids	Homology 100%	Not reported
Lemurian primates Mouse lemurs	??	Homology 100%	Not reported
Tree Shrews	Difference 3 amino acids	Homology 100%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

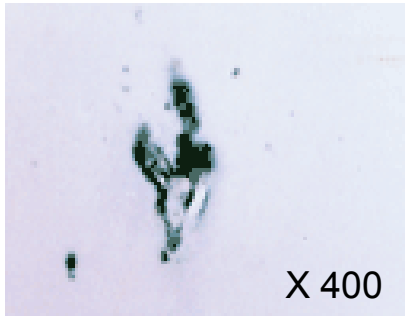
(Dhenain, Handbook of Neuropsychology (2nd ed, 2001)

Microscopic alterations

Amyloid angiopathy

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



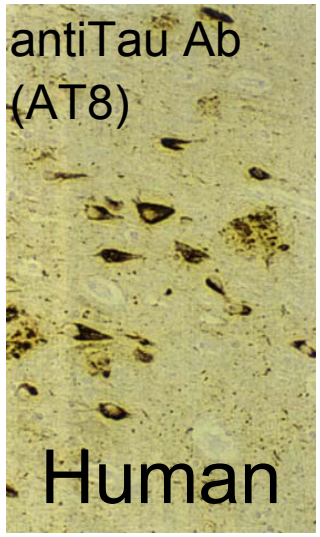


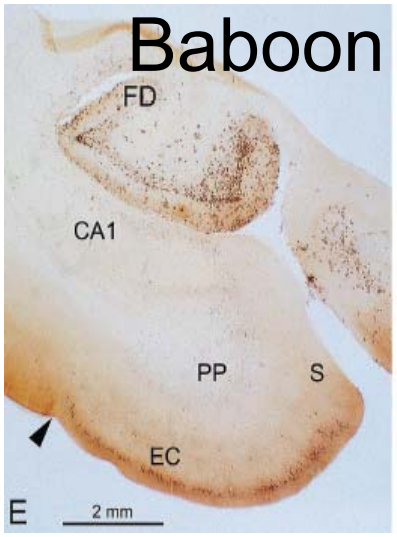
monoclonal anti–Aß antibody (4G8)

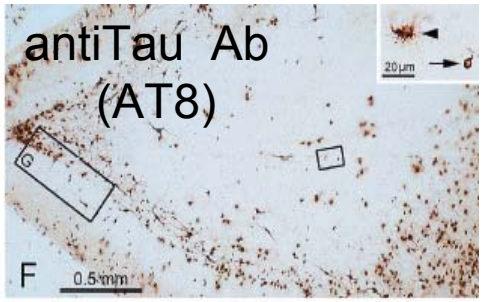
- Mutation similar to that of Icelandic patients with hereditary cerebral hemorrhage with amyloidosis (HCHWA-I) or cystatin C amyloid angiopathy (Wei et al. Stroke, 1996)

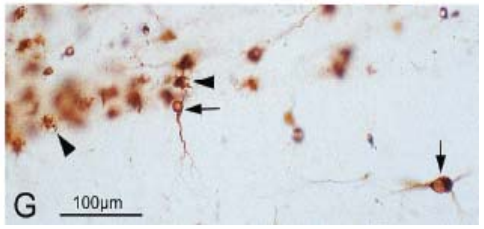
Microscopic alterations

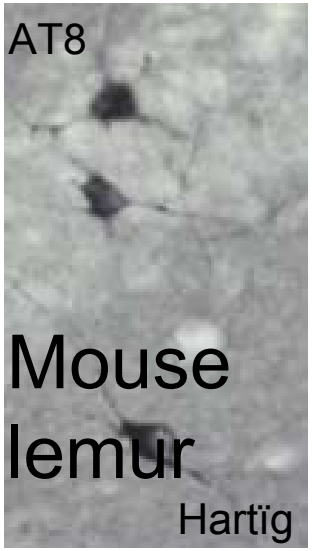
Neurofibrillary alterations

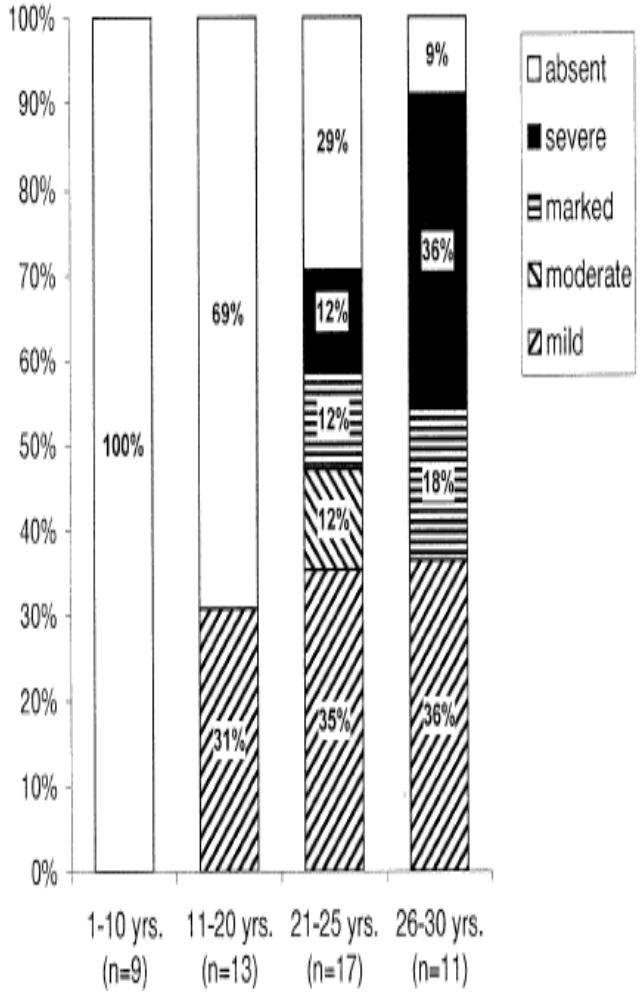












(Schultz, Neurob Aging, 2000)

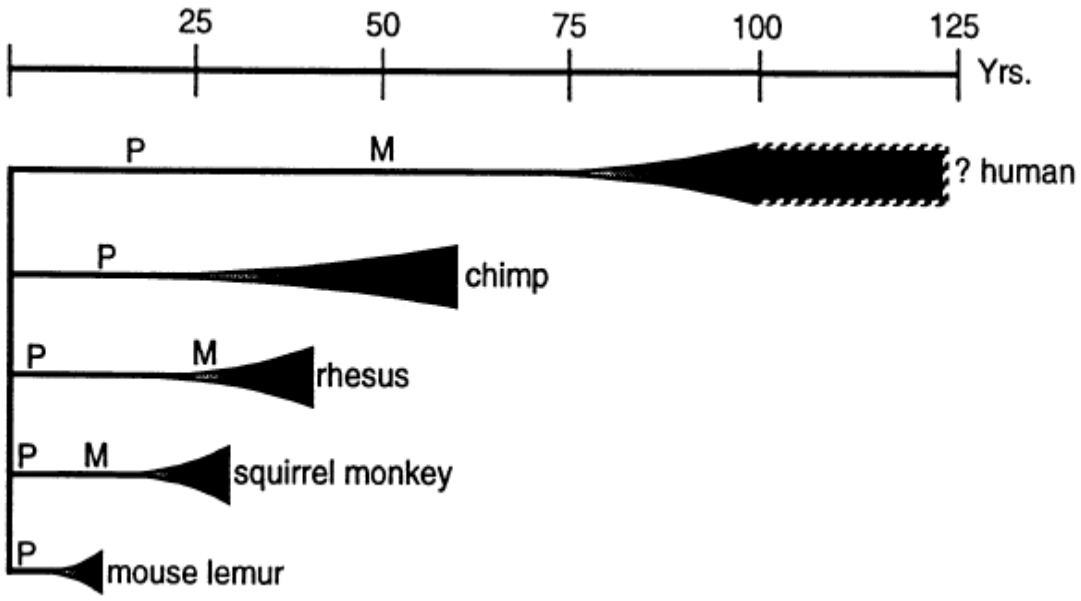
Functional consequences of neuropathological alterations

- 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

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
  - Gene Therapy

Validity criteria of Primate models

- **Construction validity: Aging / Genetic proximity to humans**

- **Face validity: Comparison to human pathology**
  - Amyloid plaques: Yes in some case
  - Neurofibrillary tangles: Rare
  - Neuroinflammation: Yes
  - Neuronal loss: Rare
  - Cholinergic alterations: Yes

  - Cerebral atrophy: Yes
  - Metabolic alterations: Yes

  - Cognitive alterations: Yes
  - Dementia: No

- **Prediction validity**

(for anti-acetylcholinesterase drugs, Neurotrophic Factors)
  - Validity for a fundamental research question: ?
  - Validity for POM (from therapy to target): Yes for some drugs
  - Validity for Mechanism of Action: Yes
  - Validity for Toxicity evaluation: Yes
  - Validity for POC (from target to disease outcome modification in humans): Yes for non specific drugs

Current treatments of the disease

	Donepezil	Galantamine	Rivastigmine	Memantine
Indication	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Moderate to severe AD
Mode of action	Selective AChE inhibition	Selective AChE inhibition and allosteric nicotine receptor modulation	Slowly reversible AChE and BuChE inhibition	Non-competitive NMDA-receptor antagonist
CYP450 metabolism	Yes (CYP2D6 and CYP3A4)	Yes (CYP2D6 and CYP3A4)	No, hydrolysed by esterases	No
Half-life	Long (70 h)	Short (7–8 h)	Very short (1 h)	Long (60–100 h)
Doses per day	One	Two (tablets) One (prolonged release capsule)	Two	Two (first week once a day)
Given with food	Irrelevant	Recommended	Yes (increased bio-availability)	Irrelevant
Initial dose	5 mg/day	8 mg/day	3 mg/day (1·5 mg×2)	5 mg/day
Dose escalation	4–6 weeks	Every 4 weeks, up to recommended or tolerated dose	Every 2 weeks, up to recommended or tolerated dose	Every week, up to recommended or tolerated dose
Recommended clinically efficient dose	10 mg/day	16–24 mg/day	6–12 mg/day	20 mg/day

AD=Alzheimer's disease. AChE=acetylcholinesterase. BuChE=buturylcholinesterase. CYP450=cytochrome P450. NMDA=N-methyl-D-aspartate.

Table 1: **Characteristics of drugs for symptomatic treatment of Alzheimer's disease**

From Blennow K et al., Lancet, 2006

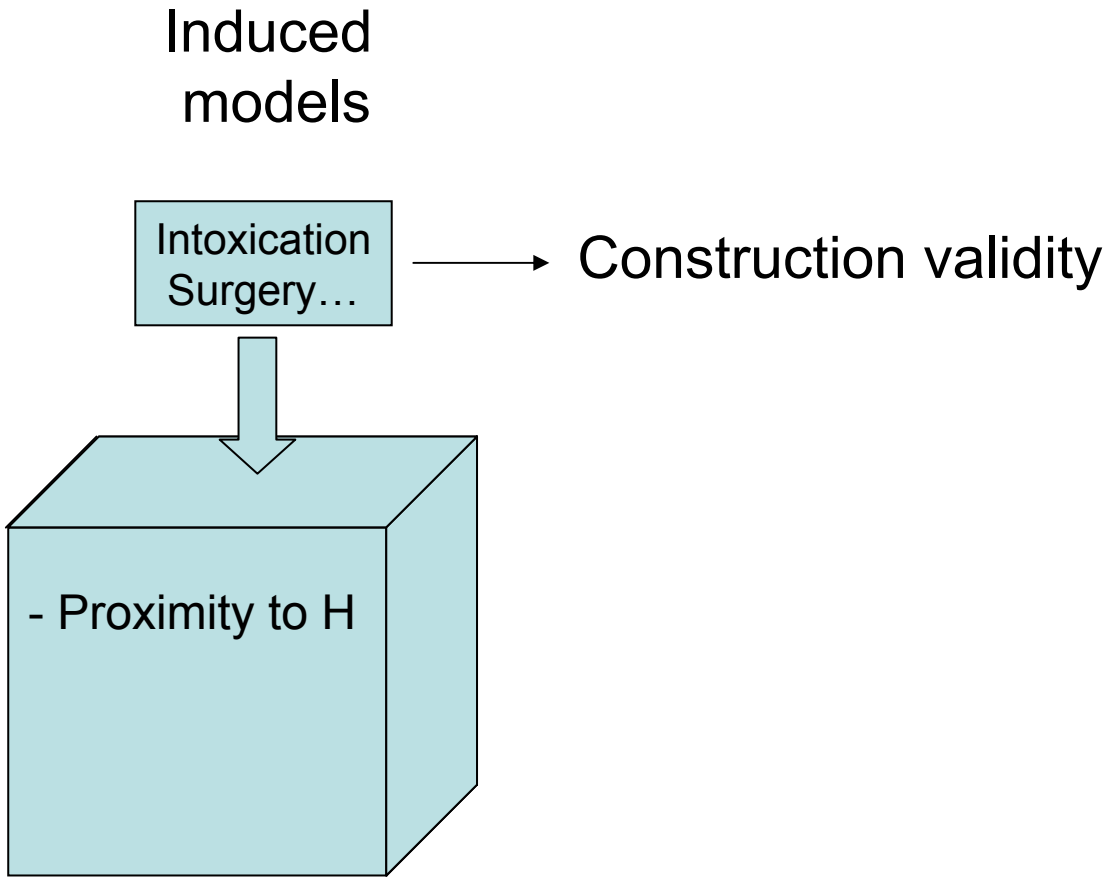
Conclusion Primates

- 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,…

Induced models



What about face validity ?
What about prediction validity ?

Atrophy in Humans and Macaques

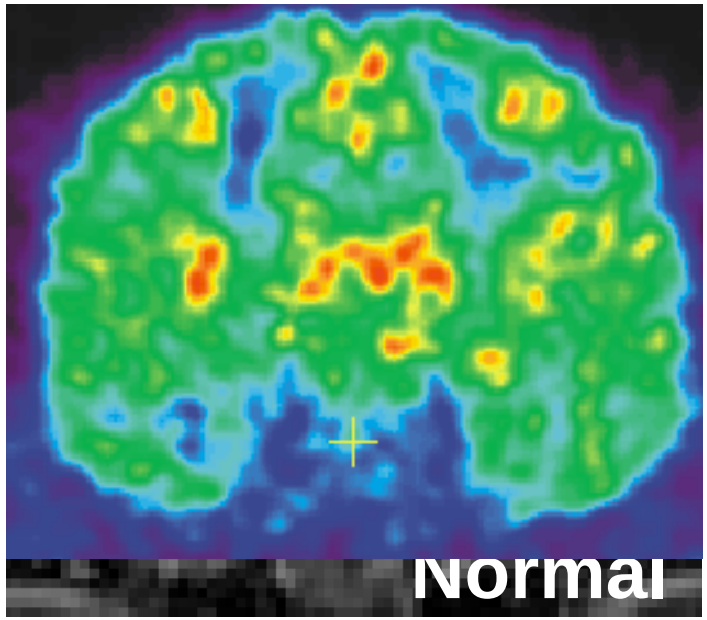
Jack, Neurology, 1999

+ 4 years

Normal

Alzheimer

Macaques



+ 4 months