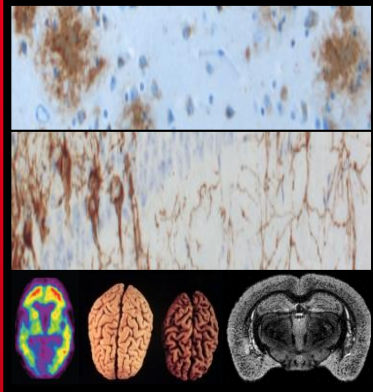


# Nouvelles pistes pour comprendre et traiter la maladie d'Alzheimer



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Académie Vétérinaire de France  
Académie Nationale de Médecine

Maladie d'Alzheimer : Modélisation – Biomarqueurs  
Imageries Précliniques – Evaluations Thérapeutiques

MIRCent, CEA-CNRS UMR 9199,  
Fontenay aux Roses, France



# MALADIE D'ALZHEIMER: HISTORIQUE

## TRADUCTION DE L'ARTICLE ORIGINAL DE Alois ALZHEIMER :

Au total, il s'agit apparemment, selon nous, d'un processus pathologique particulier. Au cours des dernières années, de tels processus pathologiques particuliers ont été observés en nombre croissant. Cette observation nous

Une femme âgée de 51 ans présenta comme premiers symptômes des idées de jalousie envers son mari. Peu après, apparurent des troubles de la mémoire de progression rapide. Elle n'arrivait plus à s'orienter dans sa

examen par le Directeur SIOLI.

à délimiter plus précisément sa propre clinique.

(Communication personnelle).  
Munich 1907.

Le tableau clinique faisait tellement exception à la règle qu'il n'était pas possible de le ranger parmi les maladies connues, le tableau anatomique donnait un résultat différent des processus pathologiques connus jusqu'à présent.

Une femme âgée de 51 ans présenta comme premiers symptômes des idées de jalousie envers son mari. Peu après, apparurent des troubles de la mémoire de progression rapide. Elle n'arrivait plus à s'orienter dans sa maison, elle laissait traîner les choses çà et là, les cachait parfois ; elle croyait qu'on voulait la tuer et se mettait à pousser des cris.

A l'asile, tout son comportement était marqué par une perplexité complète. Elle présentait une désorientation temporo-spatiale totale. Quelquefois elle faisait remarquer qu'elle ne comprenait rien et ne s'y retrouvait pas. Quelquefois, elle saluait le médecin comme s'il était un visiteur en s'excusant de n'avoir pas fini son ménage, tantôt elle se mettait à crier qu'il



En raison de son incapacité à comprendre la situation, elle se mettait à crier fort dès qu'on voulait s'approcher pour l'examiner. On n'arrivait à

crier fort dès qu'on voulait s'approcher pour l'examiner. On n'arrivait à obtenir quelques informations qu'après de multiples efforts répétés. La mémoire était sévèrement touchée. Quand on lui montrait des objets, elle arrivait le plus souvent à les nommer correctement, mais tout de suite après, elle avait tout oublié. En lisant, elle passe d'une ligne à l'autre, elle lit en épelant, d'une façon monotone. En écrivant, elle recommence la même



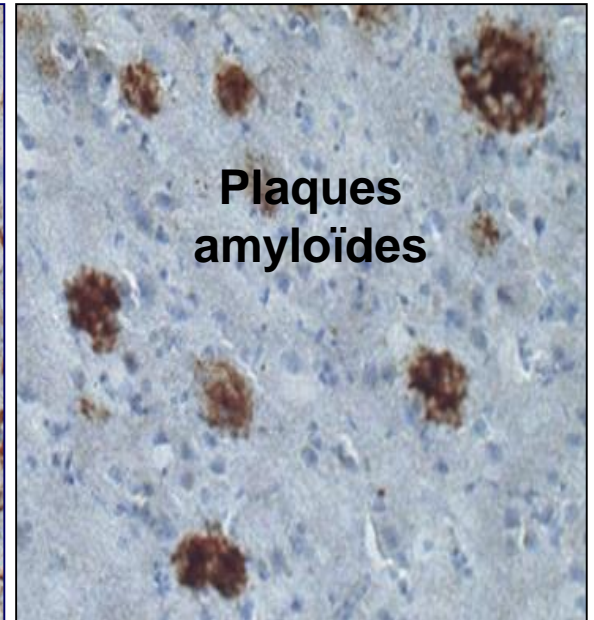
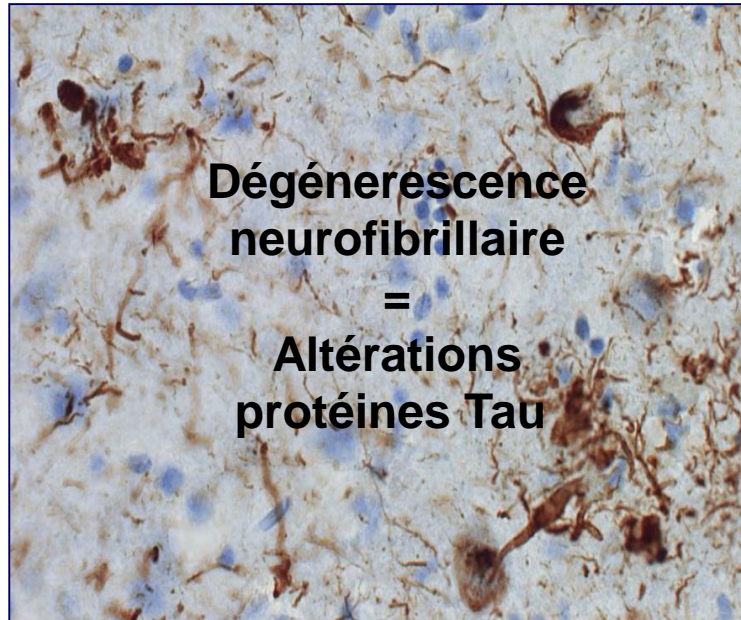
Auguste Deter

# MALADIE D'ALZHEIMER : HISTORIQUE



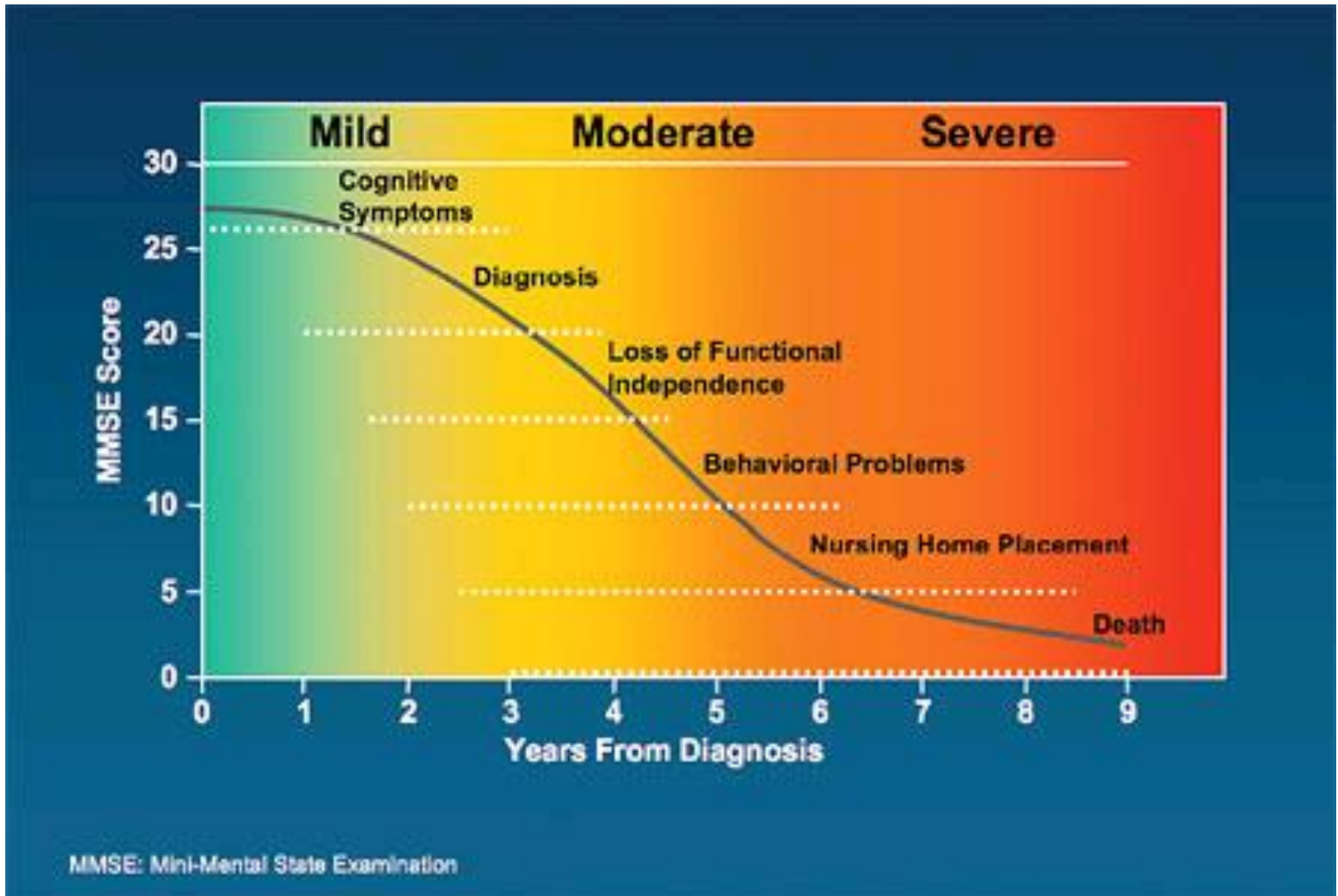
Mort en 8 avril 1906 à 55 ans (suite de septicémie/ulcères de décubitus)

Description des lésions

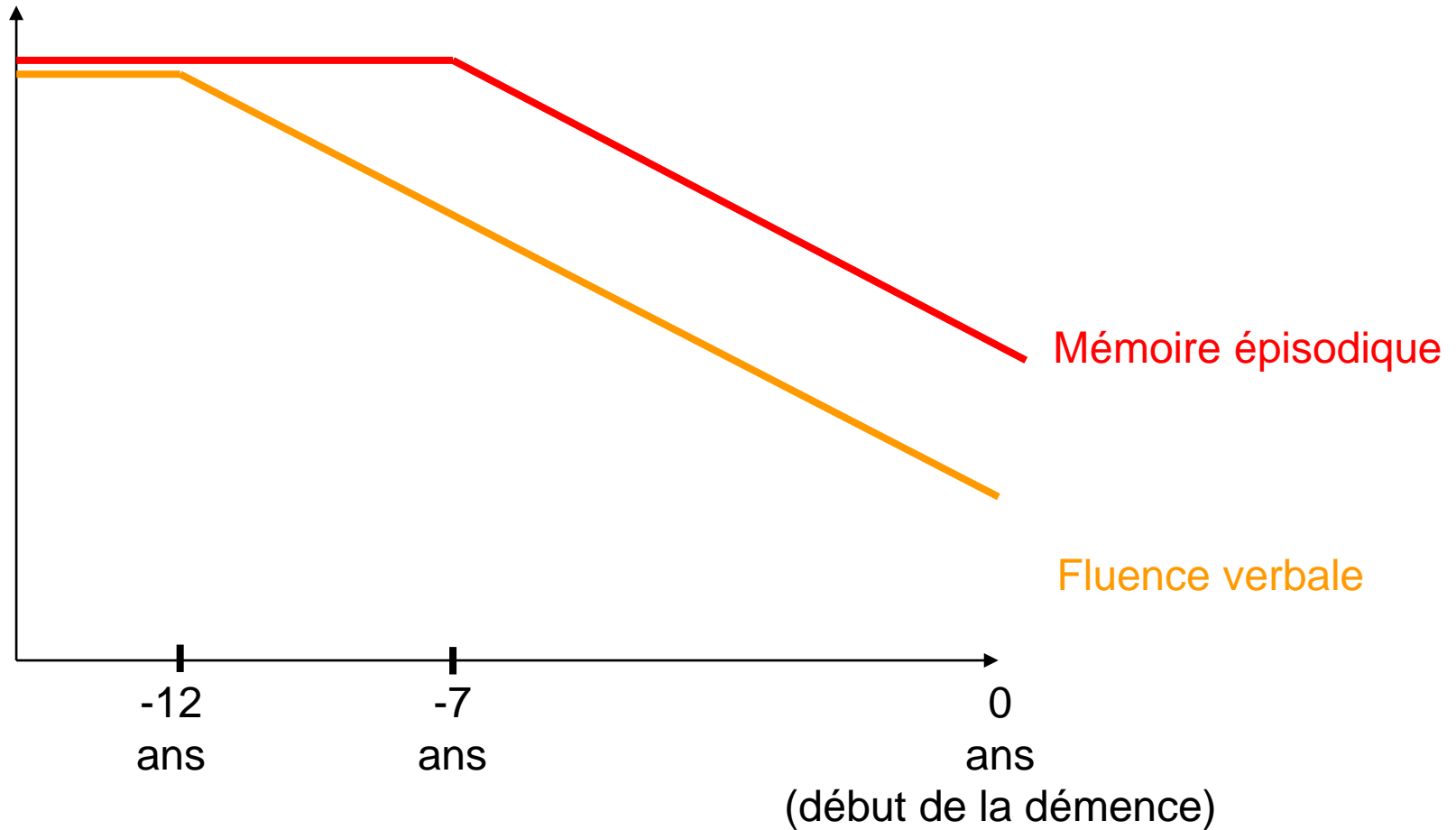


Auguste Deter

# LA MALADIE D'ALZHEIMER DURE 10 ANS APRÈS LES PREMIERS SYMPTÔMES



# LA MALADIE D'ALZHEIMER DÉBUTE PLUS DE 10 ANS AVANT LES PREMIERS SYMPTÔMES

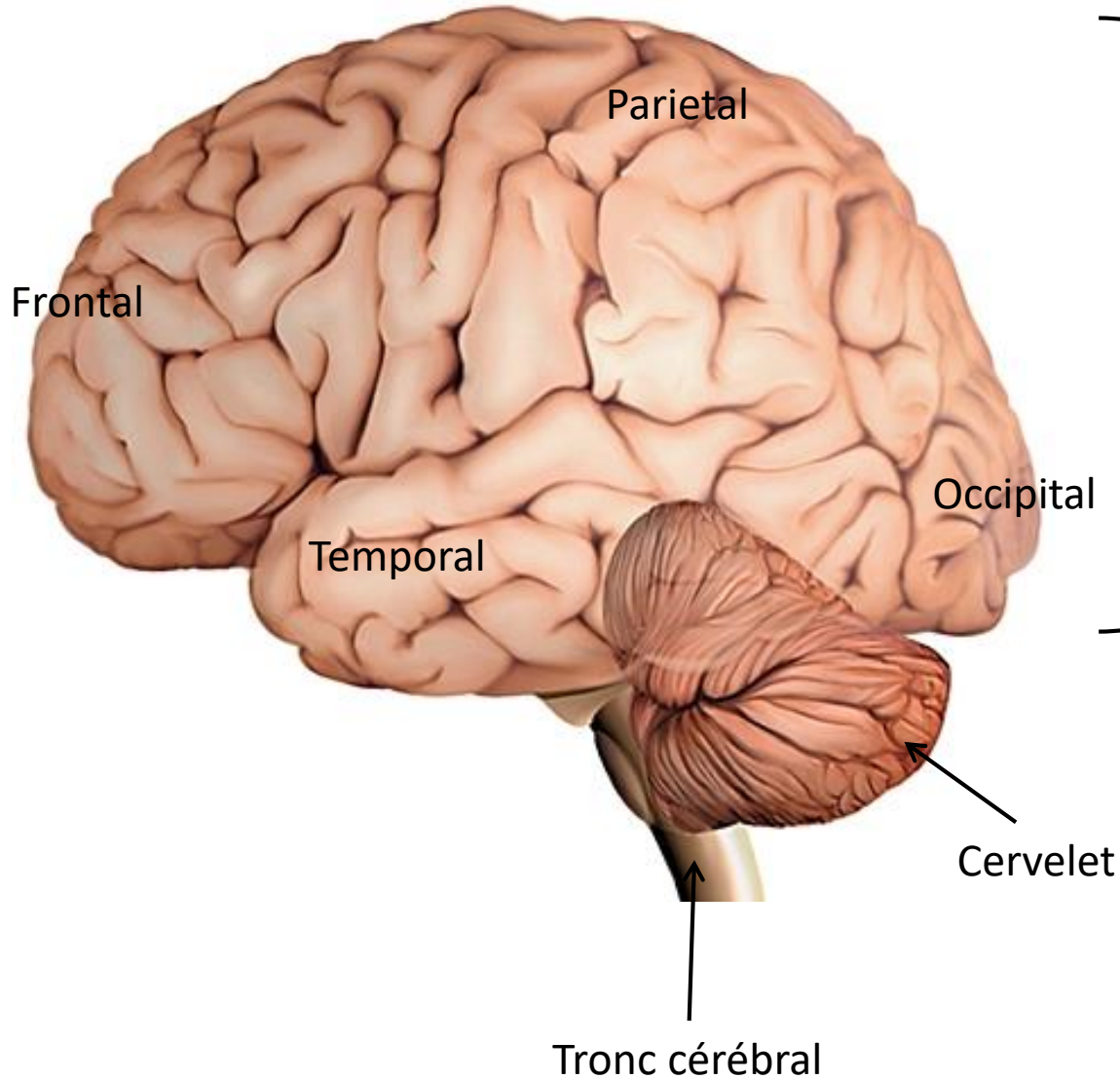




# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Les différents acteurs**

# LE CERVEAU HUMAIN



## Cerveau

- Substance grise
- Substance blanche

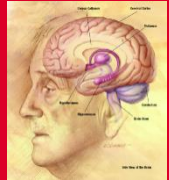
~1.5 kg

2% du poids total du corps

25% de la consommation de glucose

20% de la consommation d'oxygène

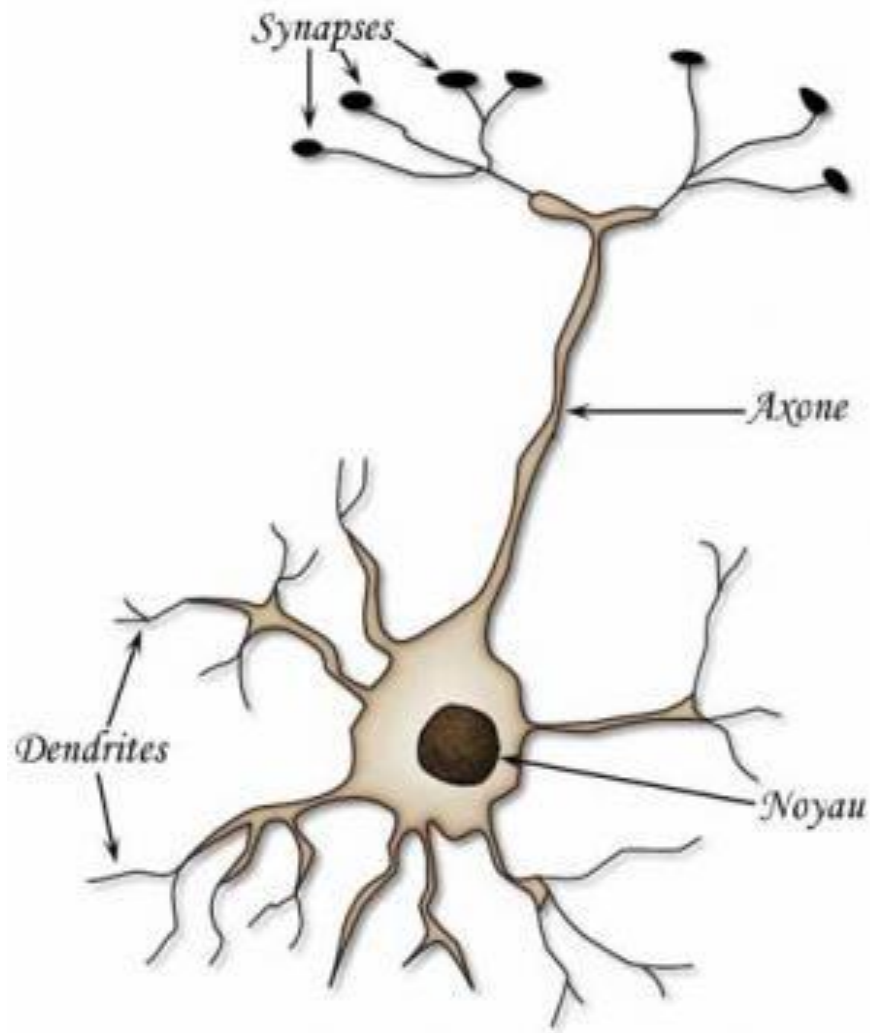




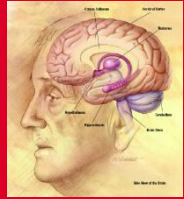
# LE CERVEAU HUMAIN

## LES NEURONES

° 86 milliards de neurones

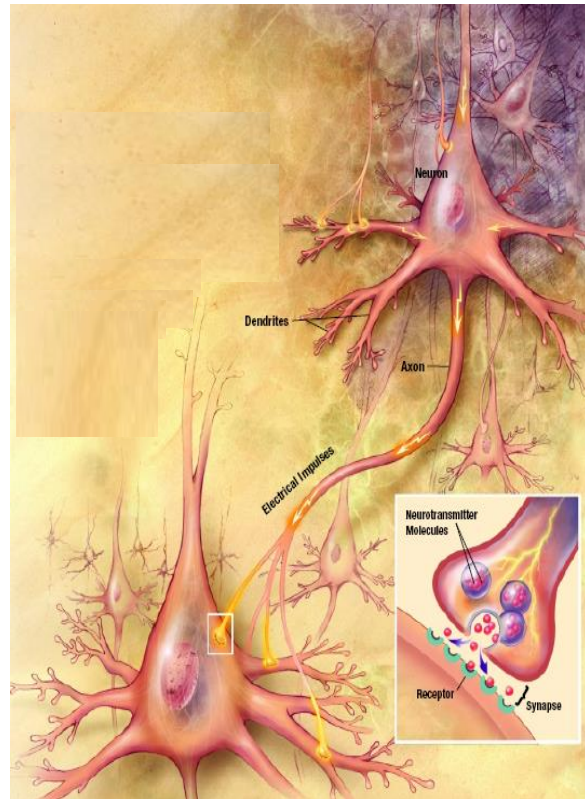


Synthèse → → → → → Transport → → → → → Utilisation

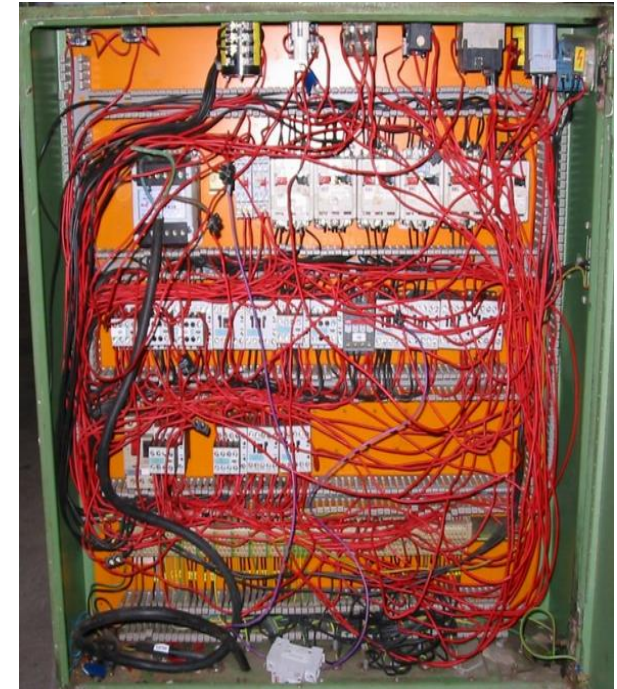
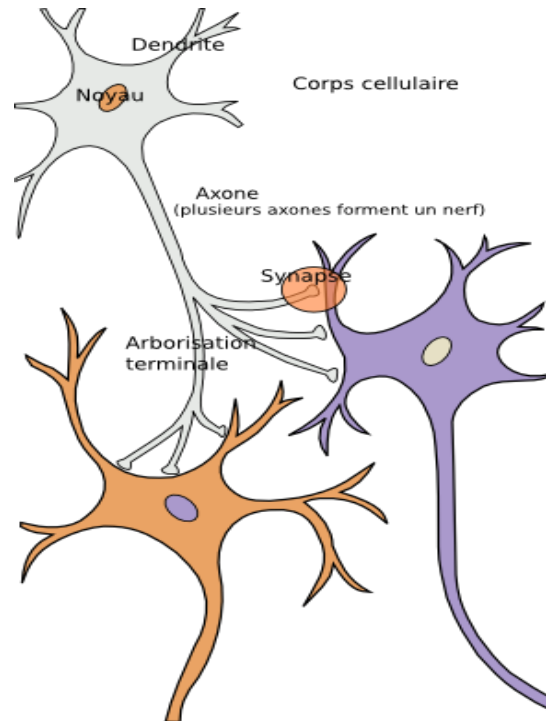


# LE CERVEAU HUMAIN

## Les neurones sont interconnectés



◦ 86 milliards de neurones



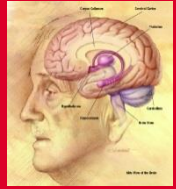
◦ 100 000 milliards de connexions entre les neurones

→ Transmission d'informations

→ Les messages transitent selon deux formes différentes:

>> Electrique à l'intérieur du neurone

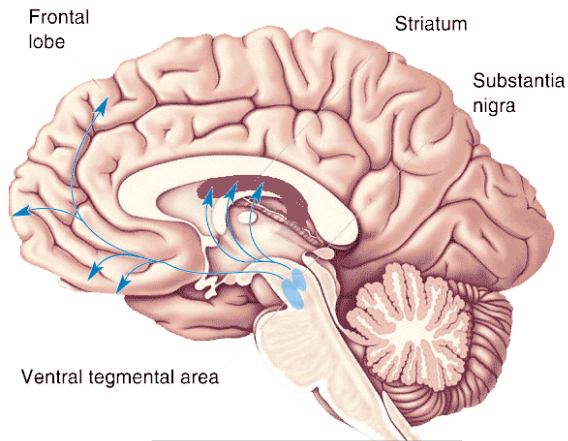
>> Chimique pour passer d'un neurone à l'autre



# LE CERVEAU HUMAIN

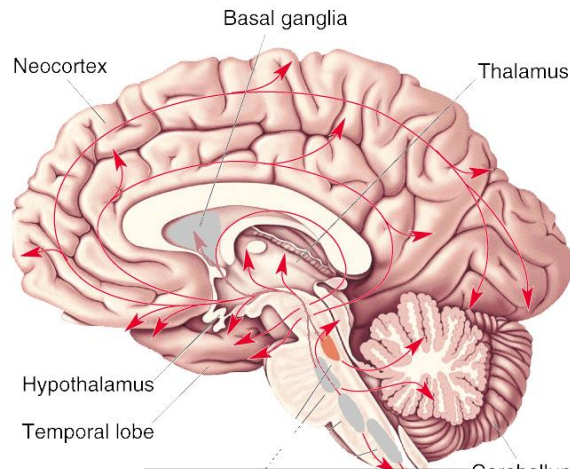
## LES NEUROTRANSMETTEURS

**Dopamine system**



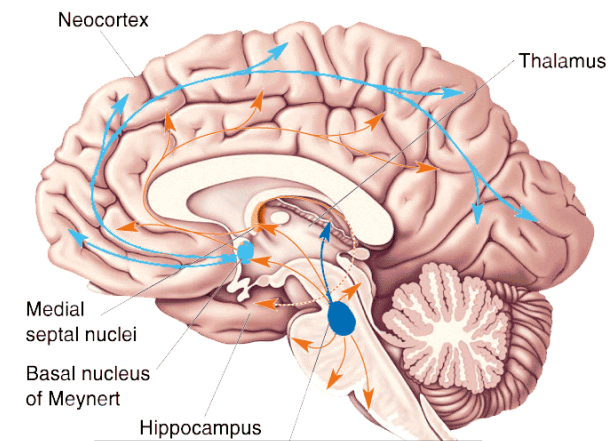
Dopamine

**Serotonin system**

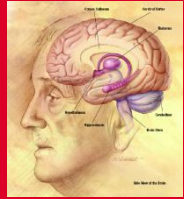


Serotonine

**Acetylcholine system**

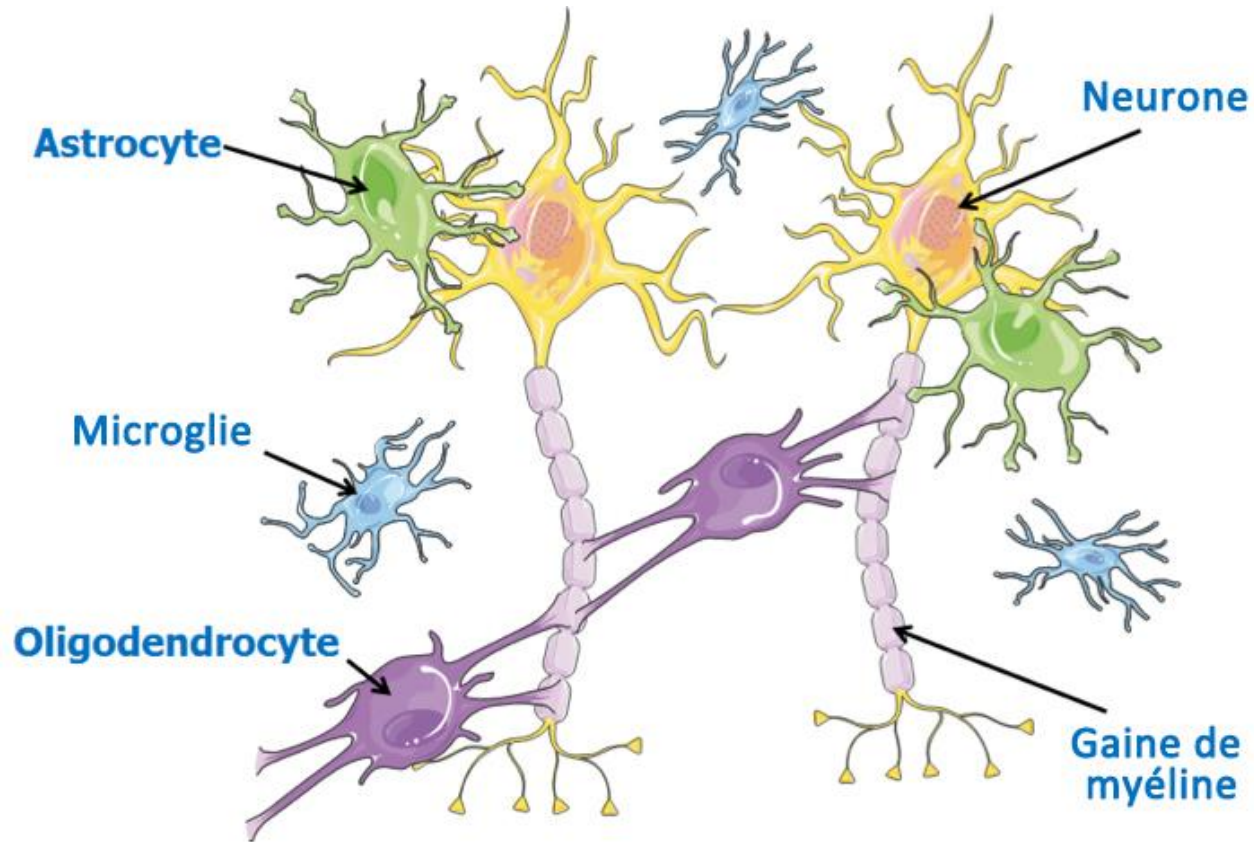


Acetylcholine

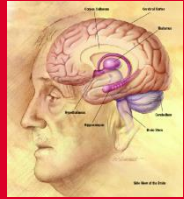


# LES VOISINS DES NEURONES

## Les cellules gliales

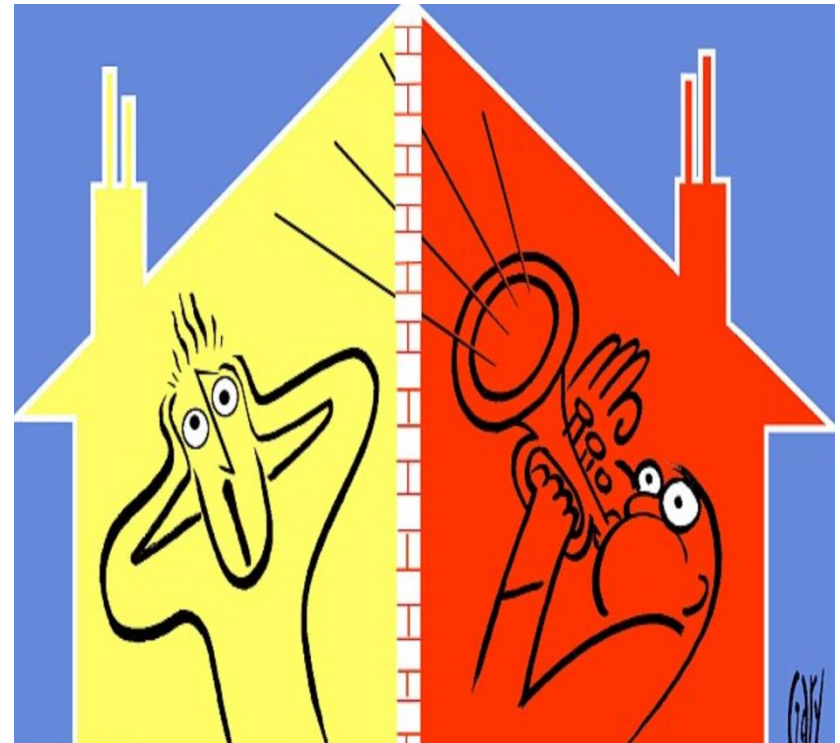


- ° Autant de cellules gliales que de neurones
- Aide au fonctionnement
- protections



# LES VOISINS DES NEURONES

## Des voisins sympathiques ou pas...





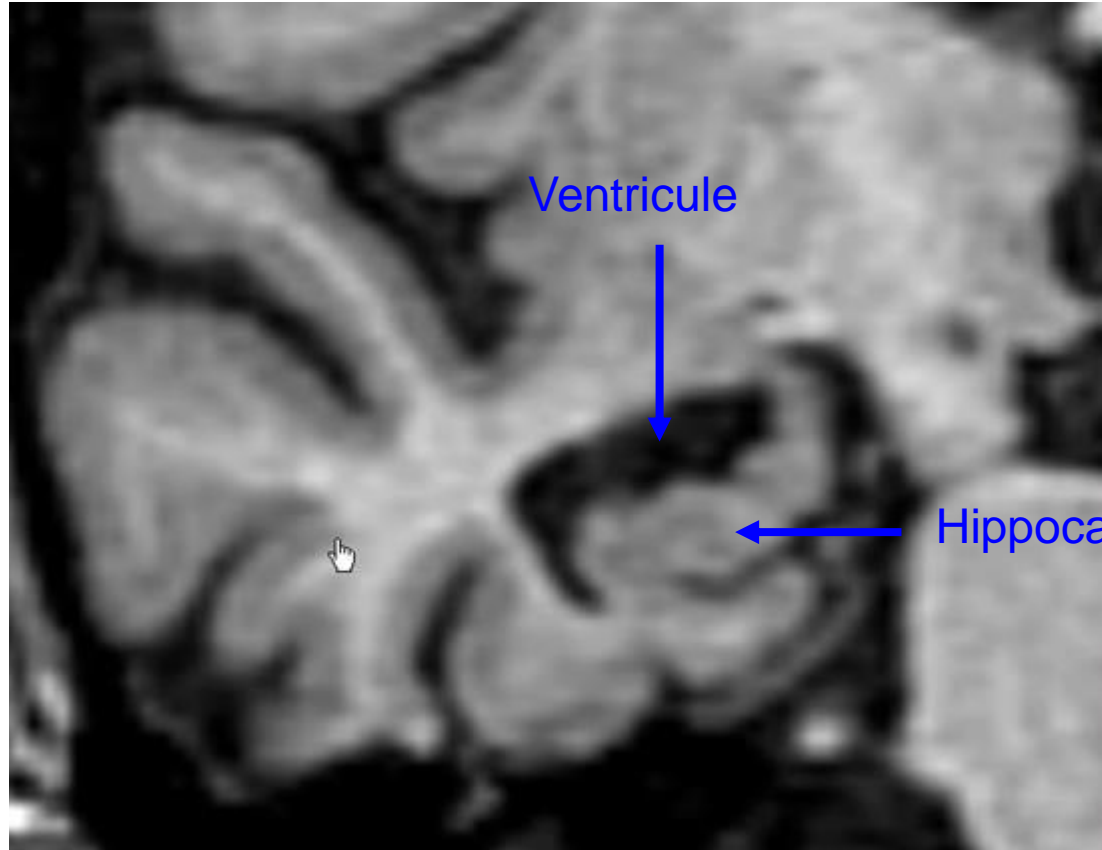
# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Atrophie cérébrale**

# DÉGÉNÉRESCENCE CÉRÉBRALE

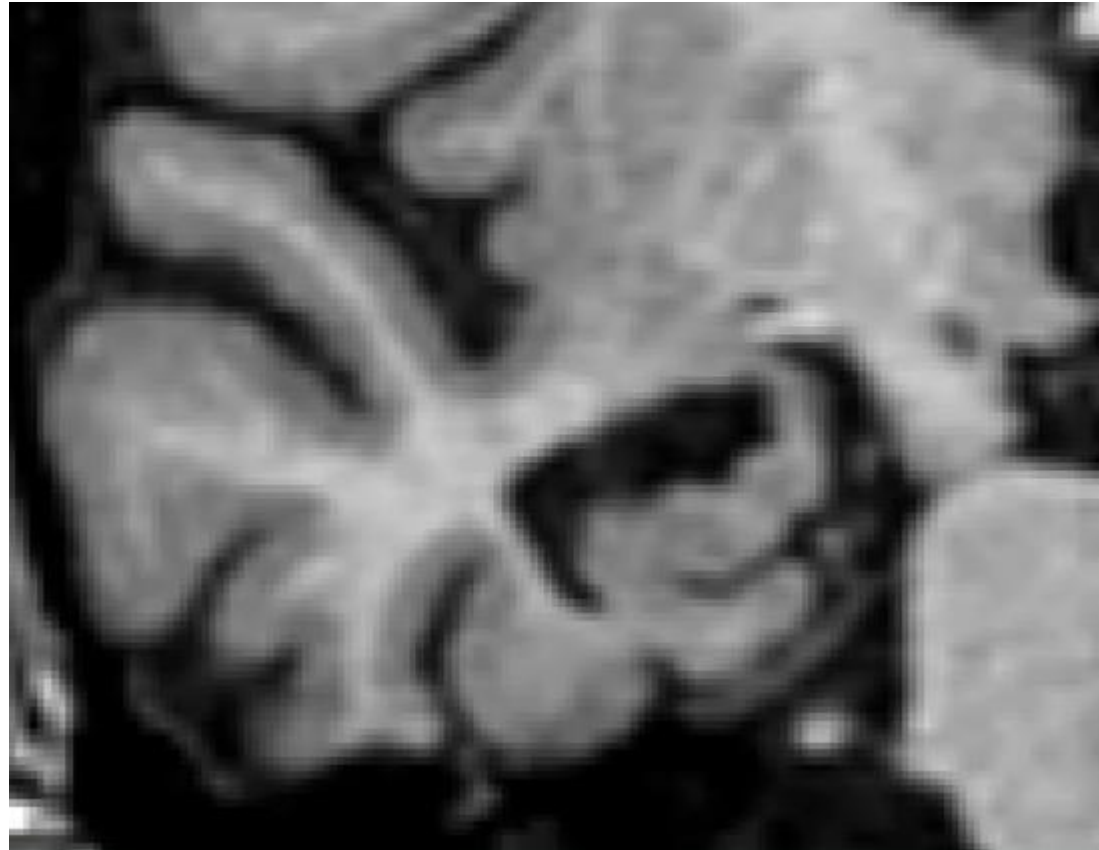


# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS

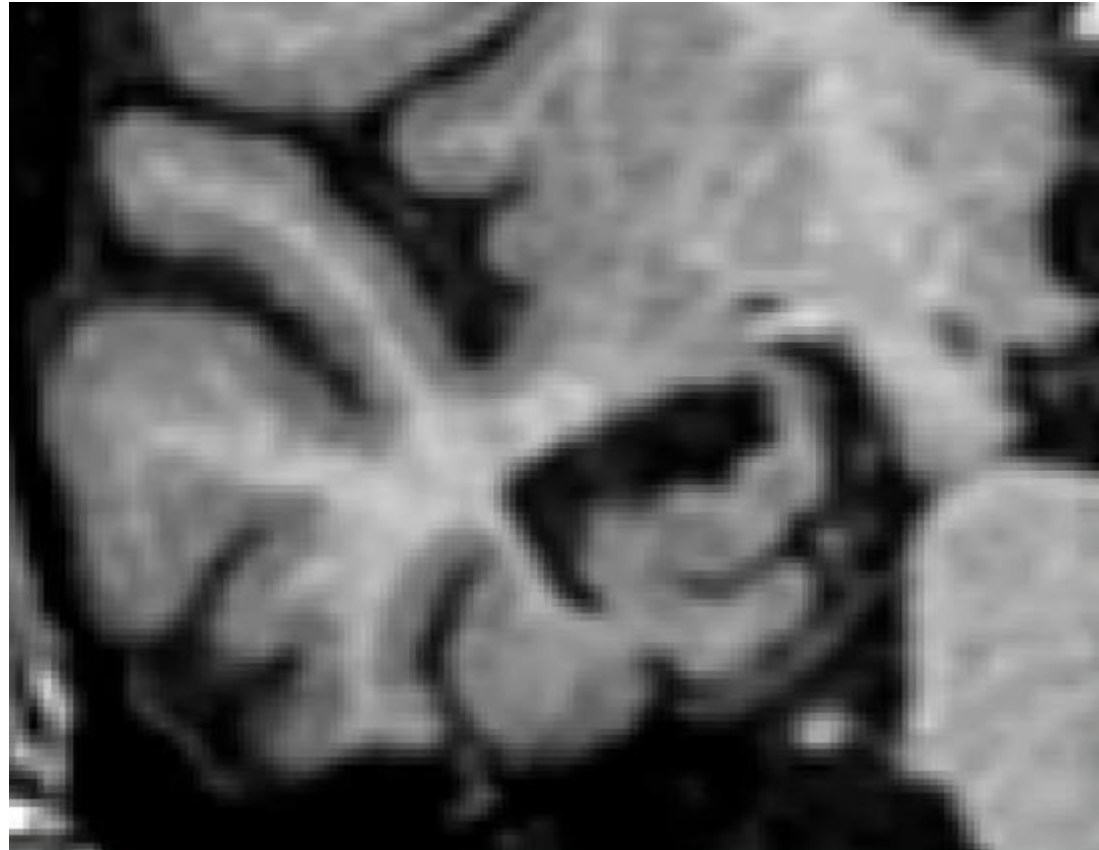




# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



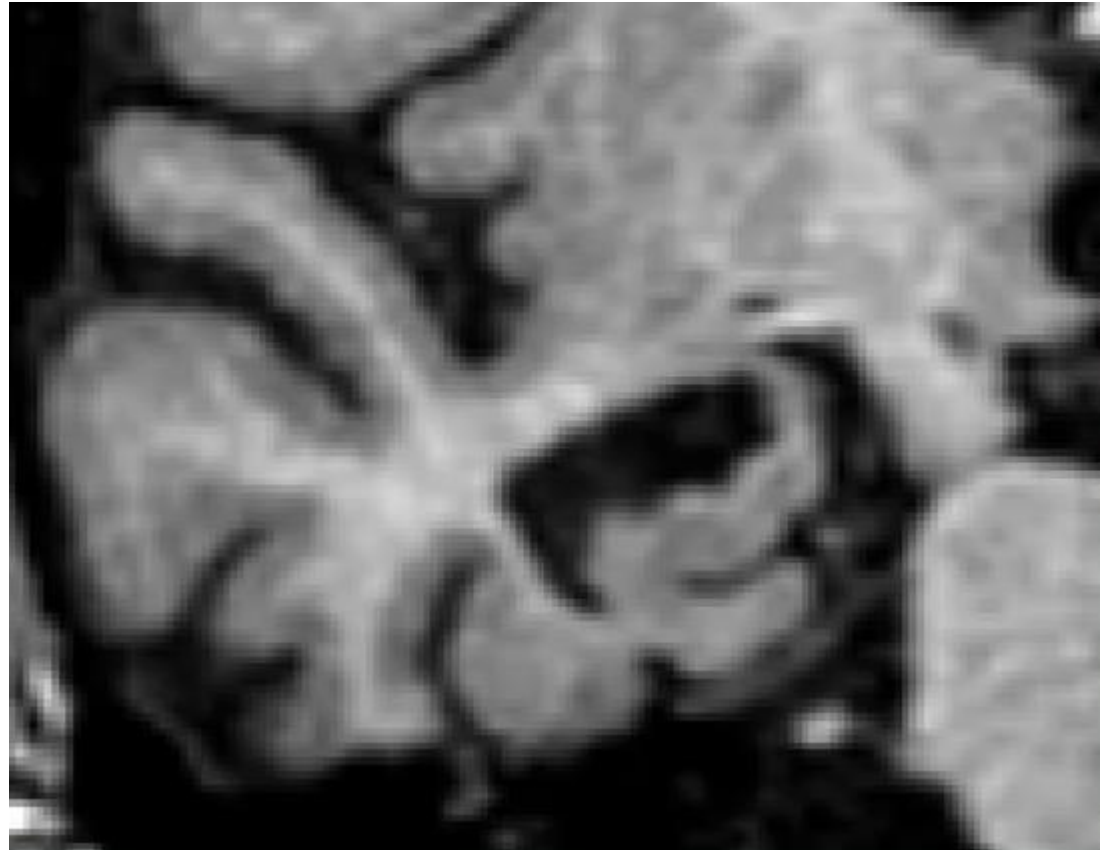
# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



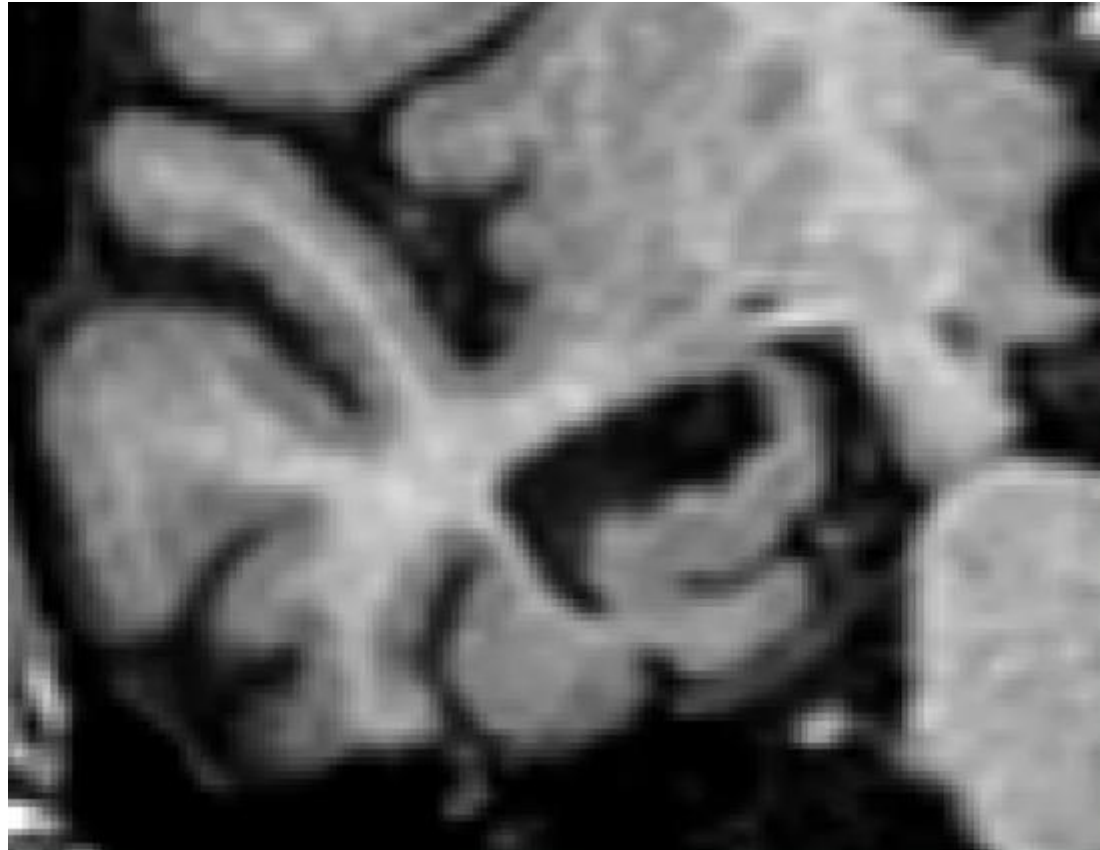
DE LA RECHERCHE À L'INDUSTRIE



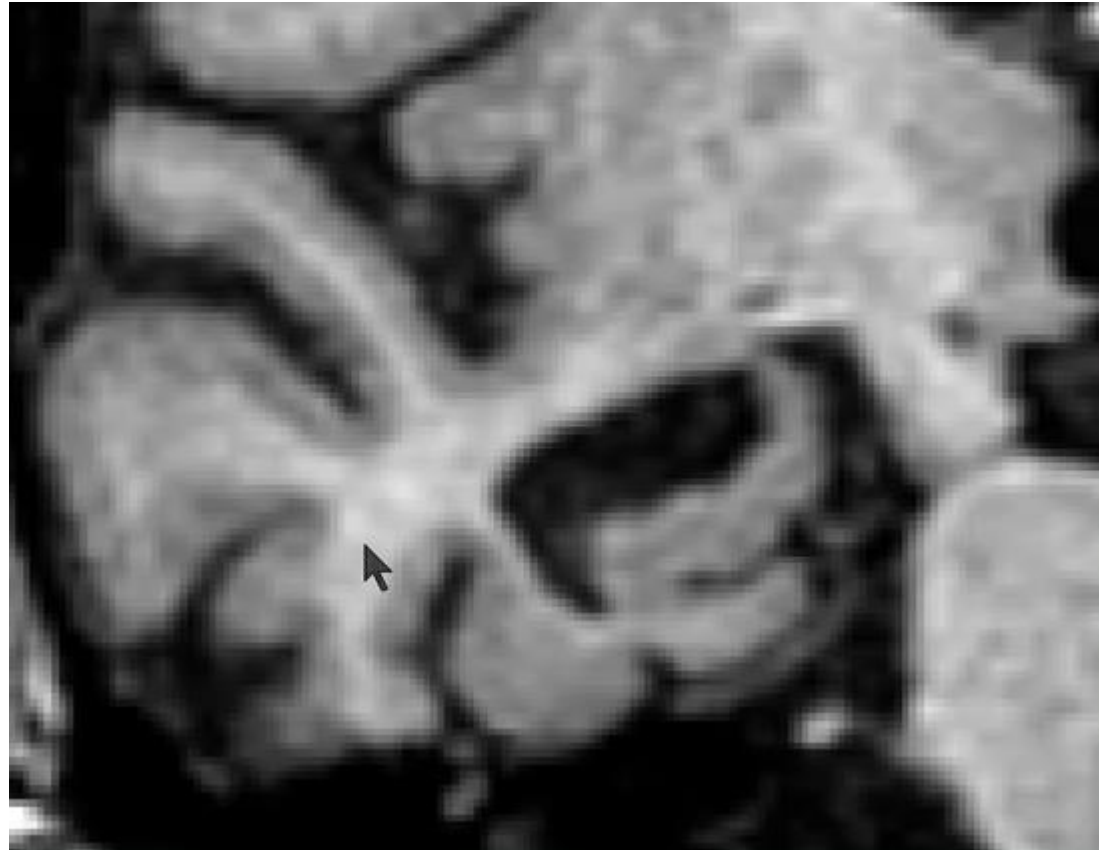
# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



DE LA RECHERCHE À L'INDUSTRIE



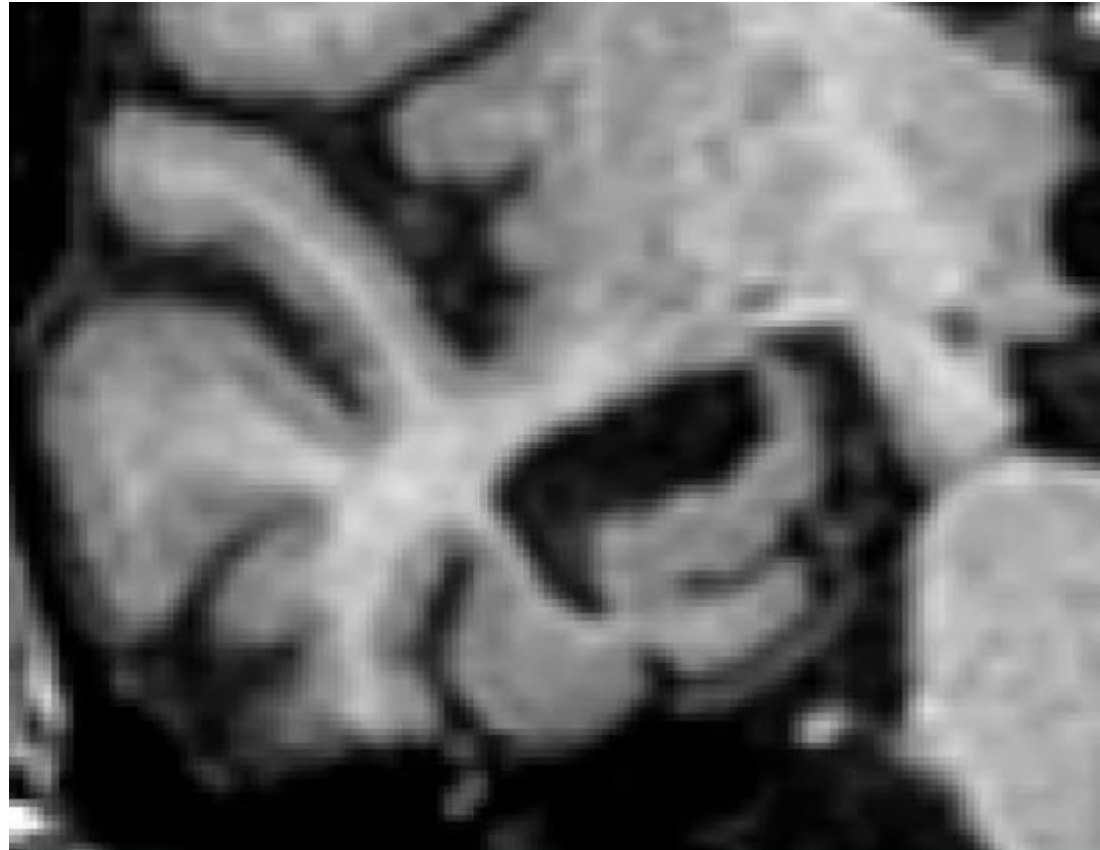
# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



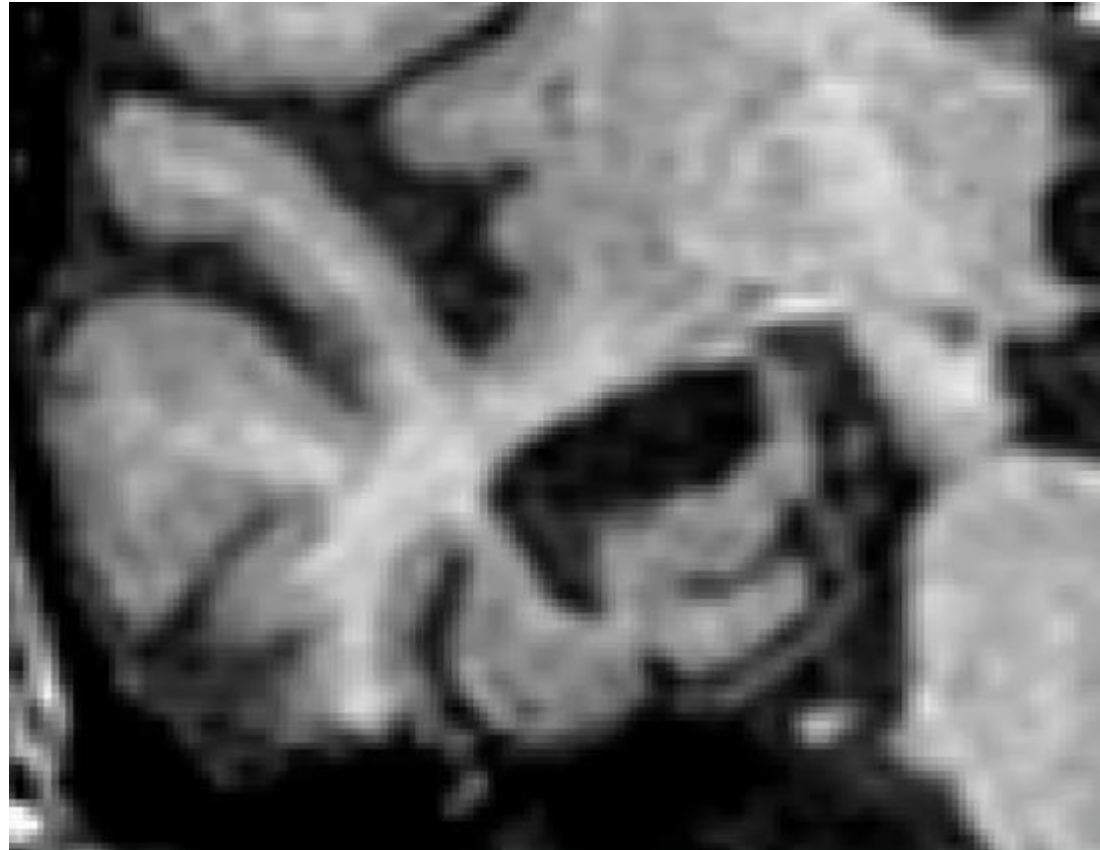
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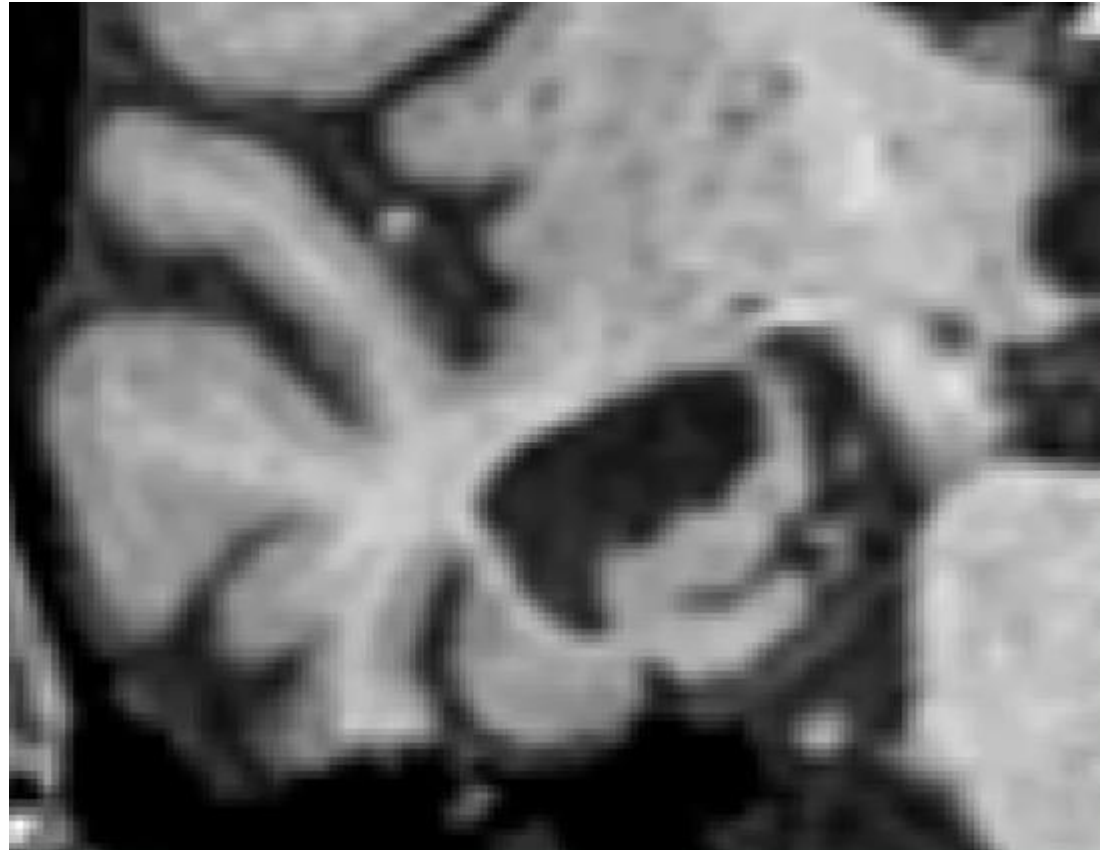
DE LA RECHERCHE À L'INDUSTRIE



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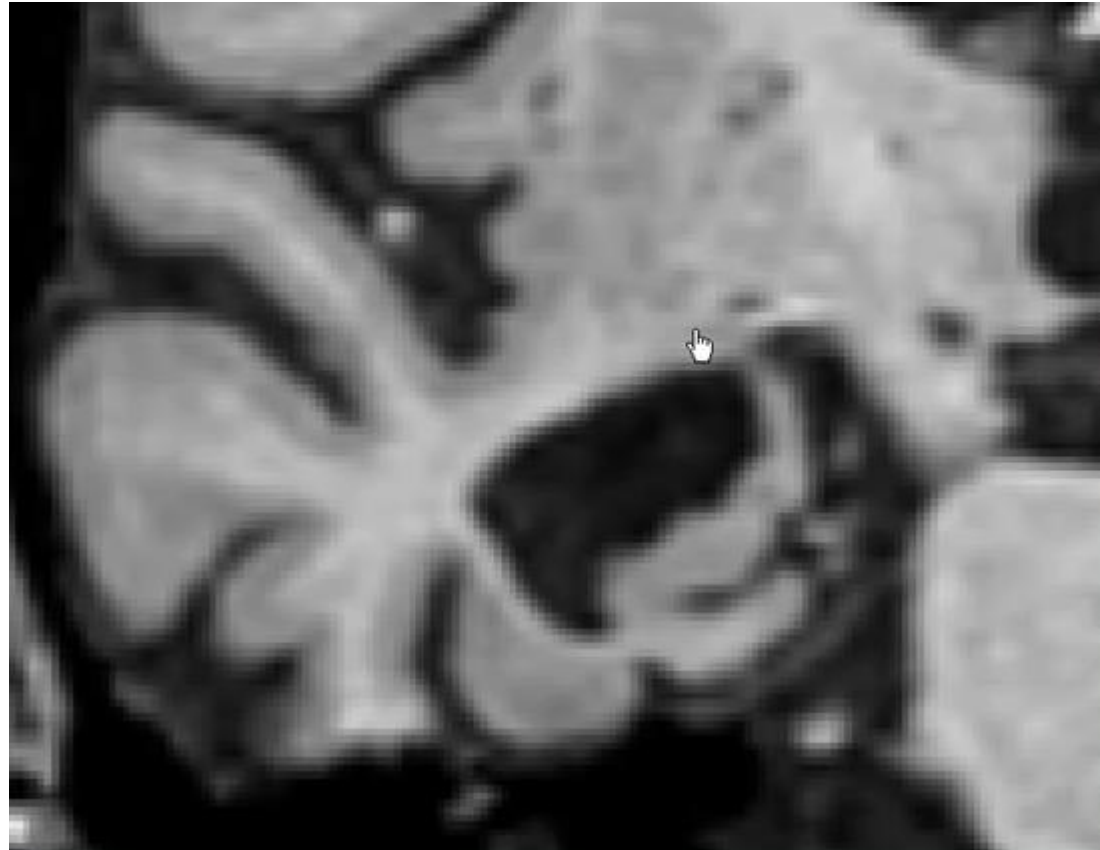


# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS





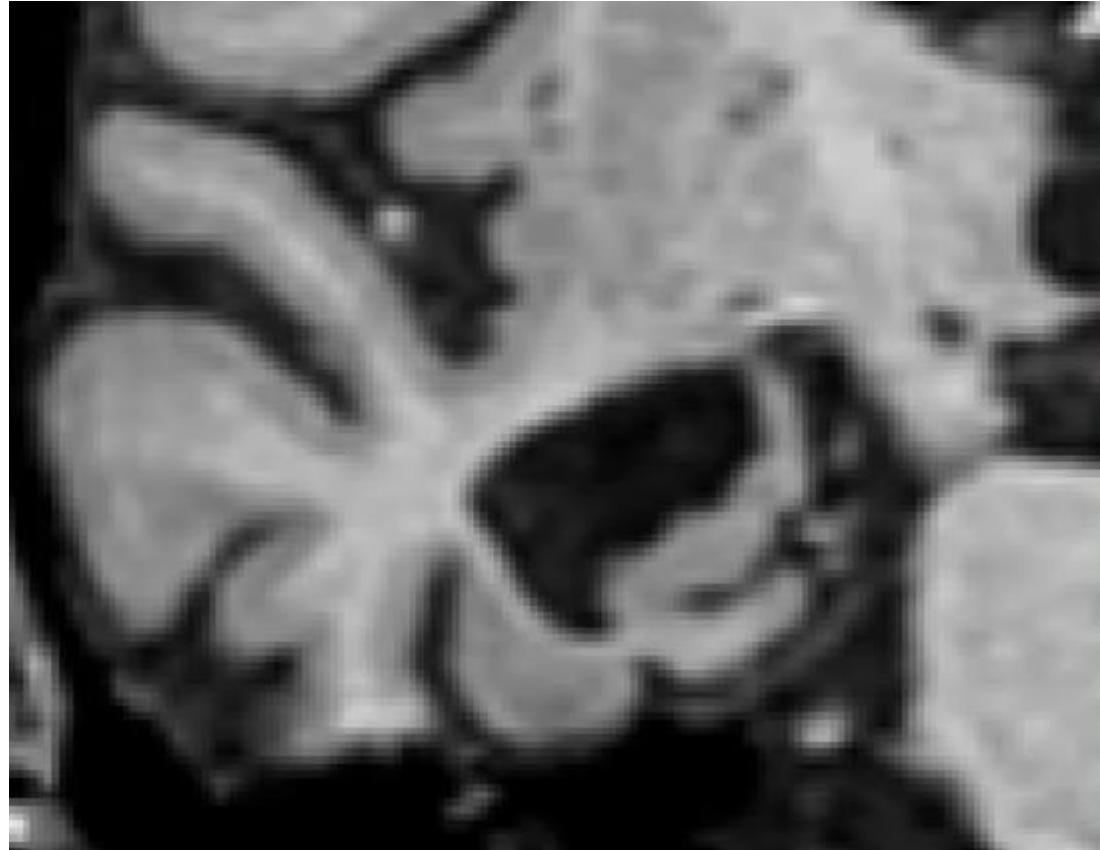
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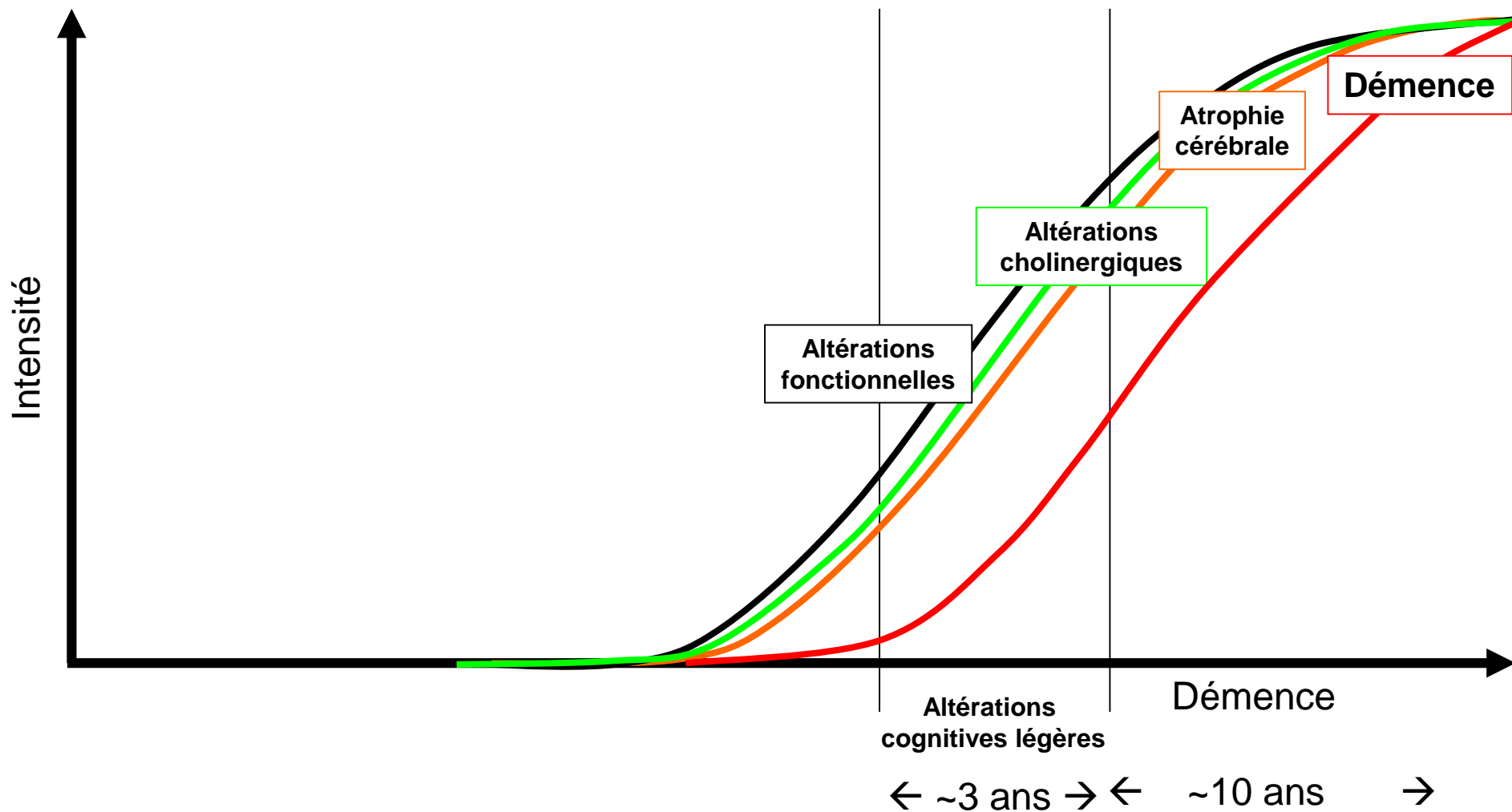
# PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



DE LA RECHERCHE À L'INDUSTRIE



# HISTOIRE NATURELLE DE LA MALADIE





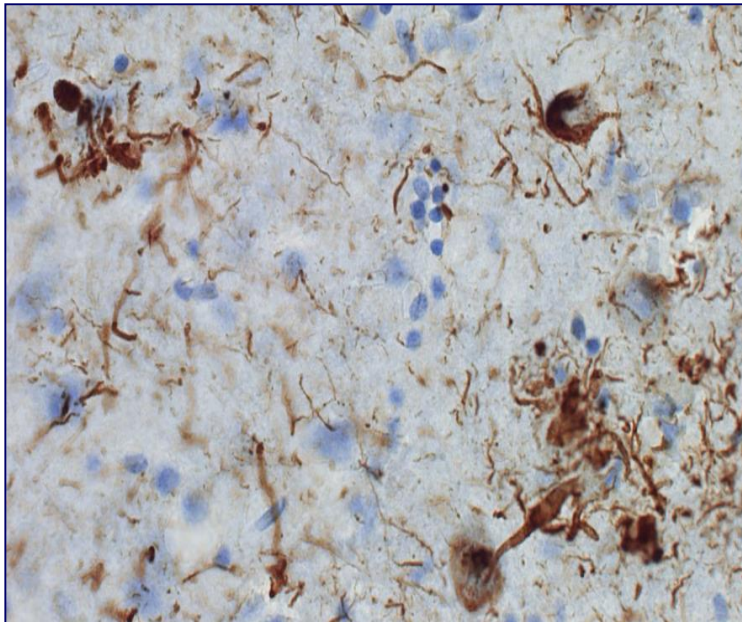
# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Dégénérescences neurofibrillaires – Lésions Tau**

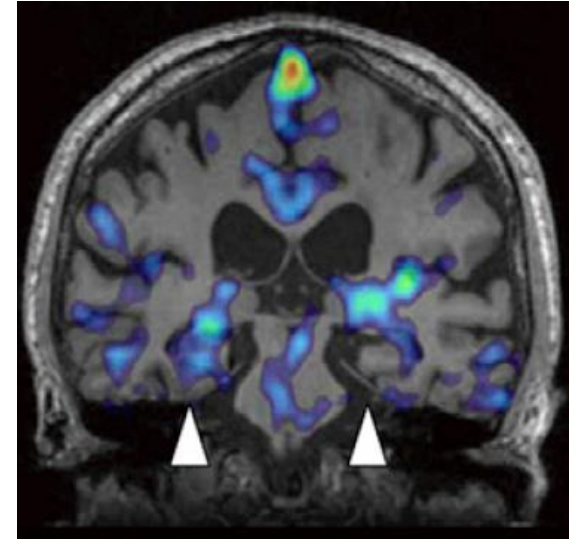
# IMAGERIE DE TAU CHEZ L'HOMME (TEP)



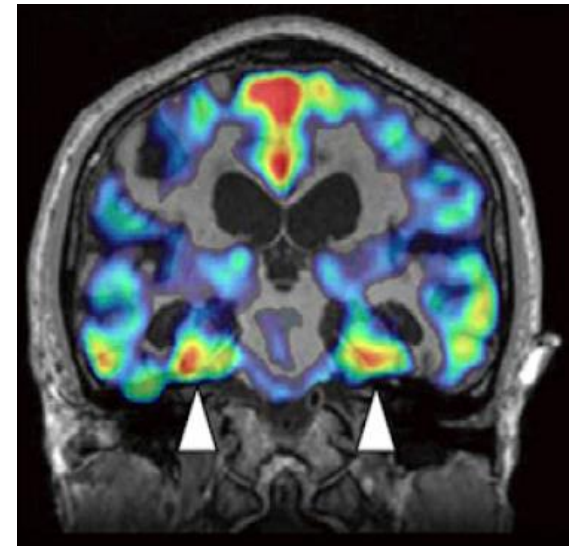
DE LA RECHERCHE À L'INDUSTRIE



Tau (TEP)



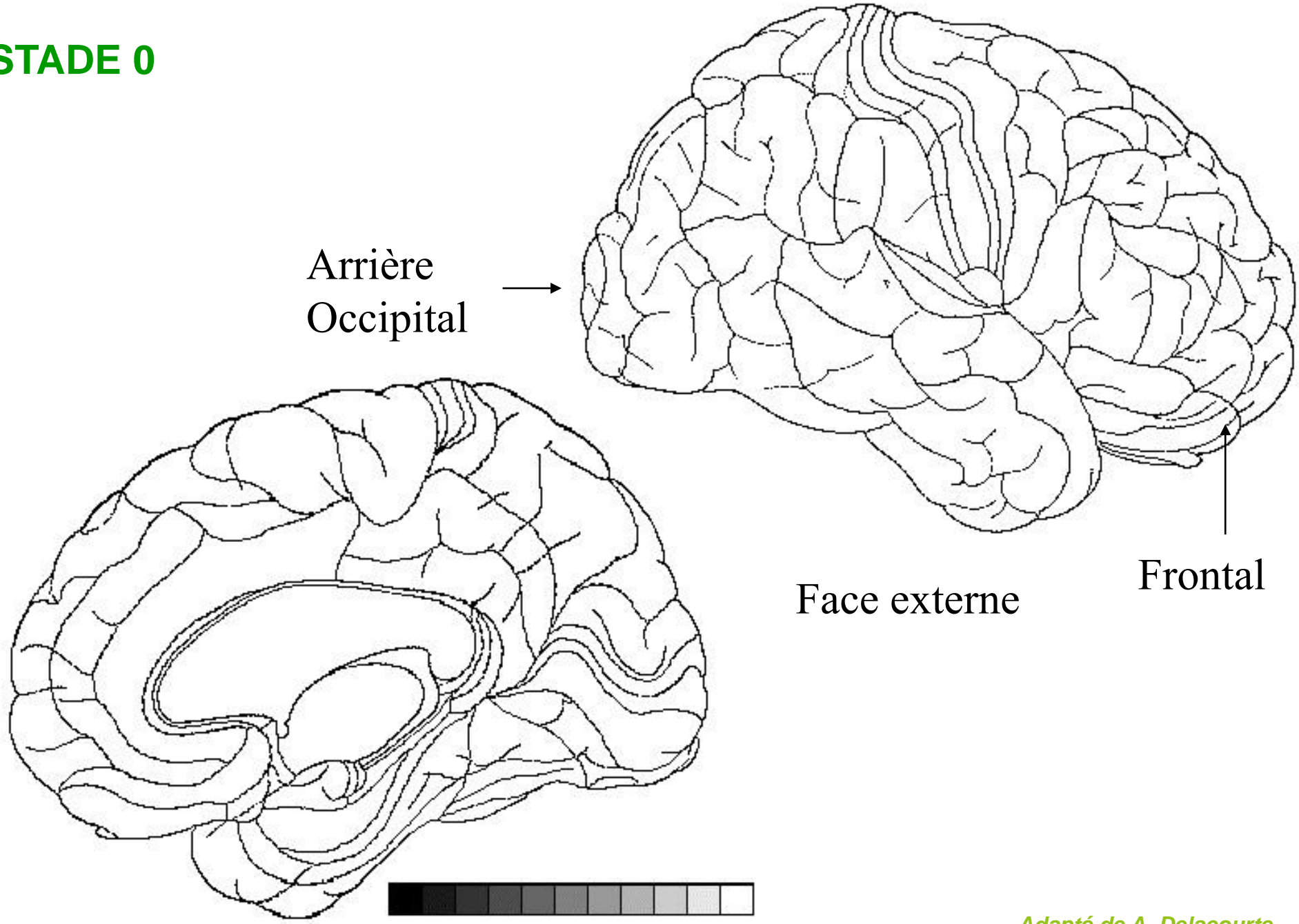
Normal



Alzheimer

Maruyama, 2013

# STADE 0



Arrière  
Occipital



Face externe

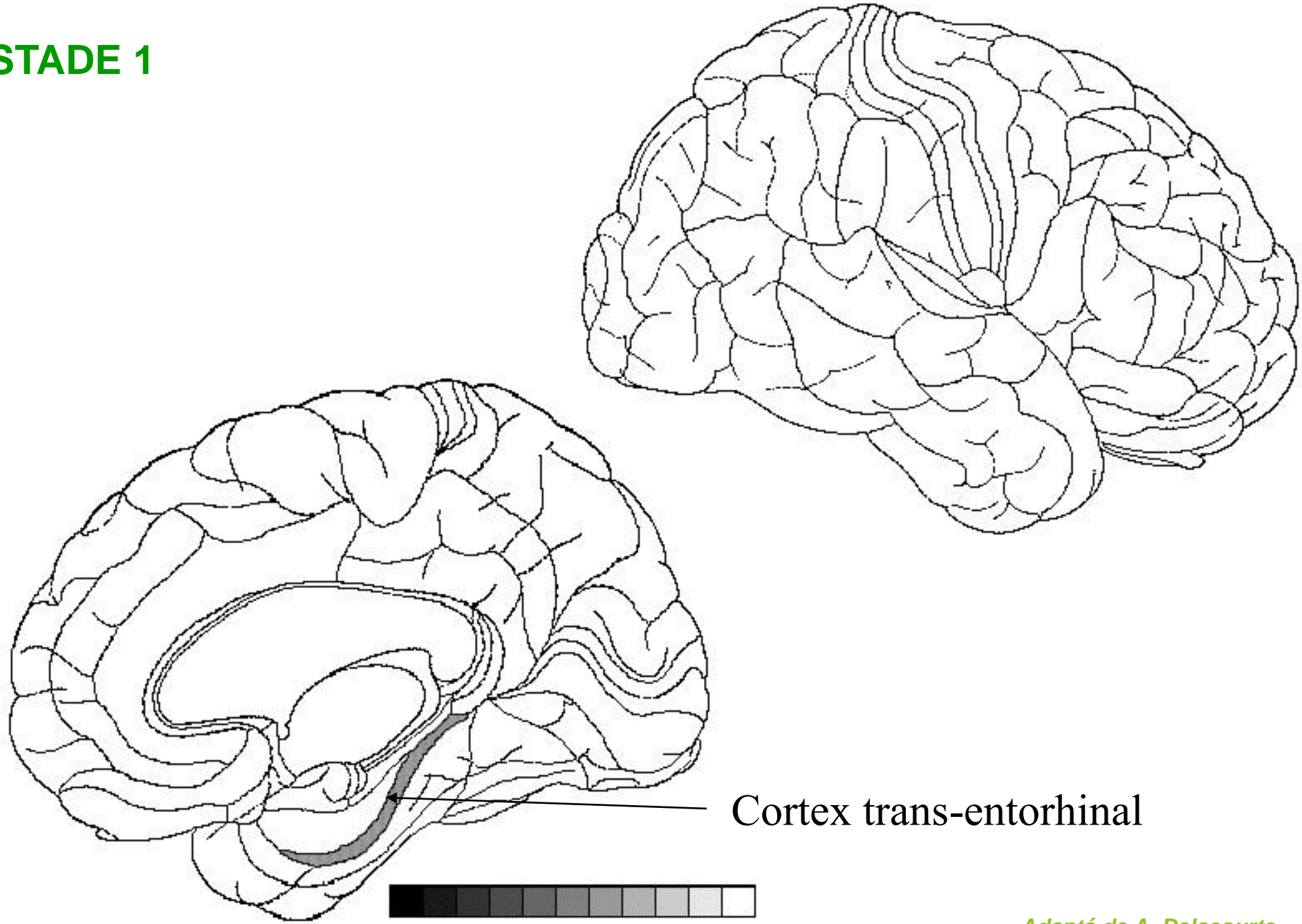
Frontal

Face interne



*Adapté de A. Delacourte*

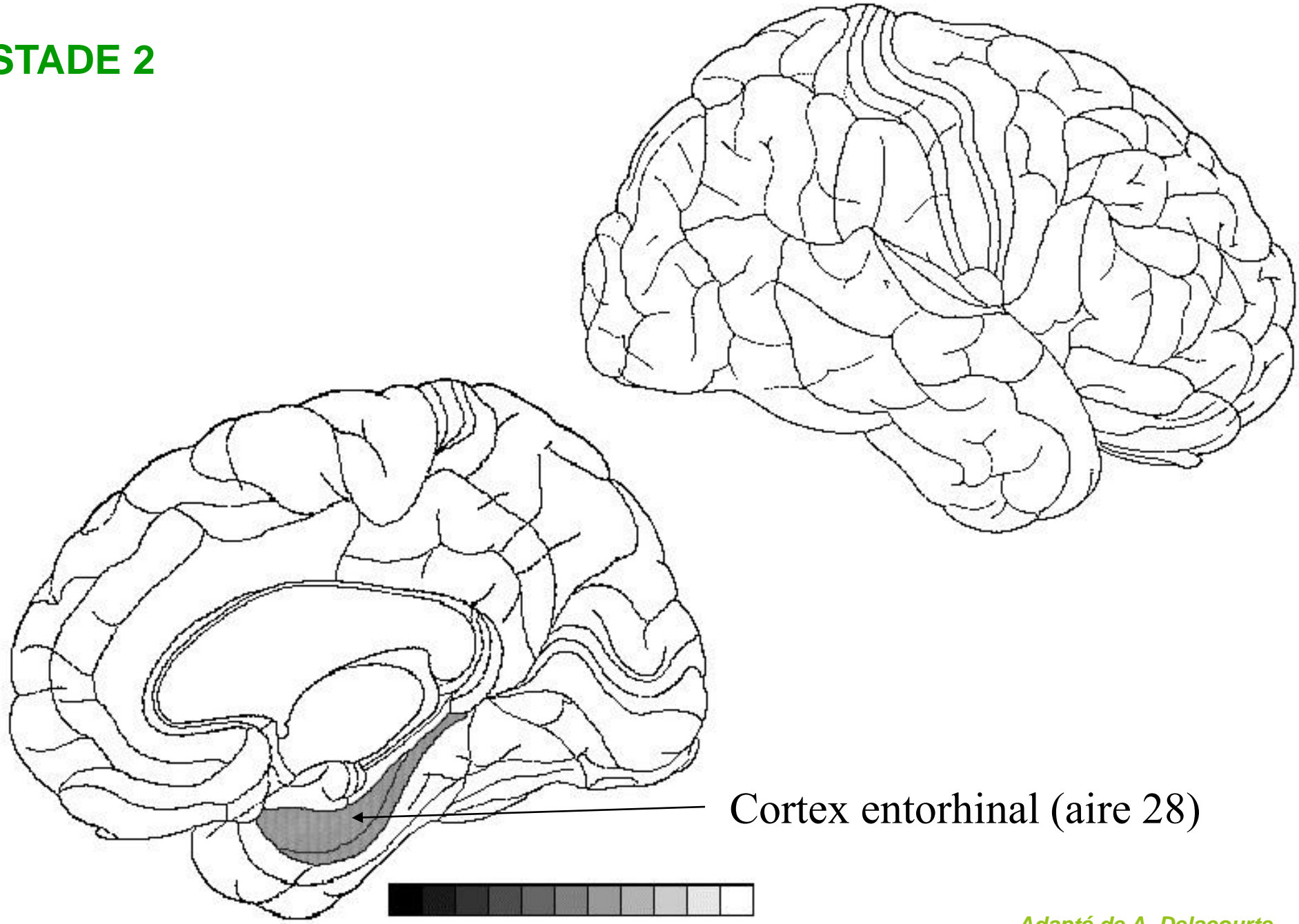
# STADE 1



Cortex trans-entorhinal

*Adapté de A. Delacourte*

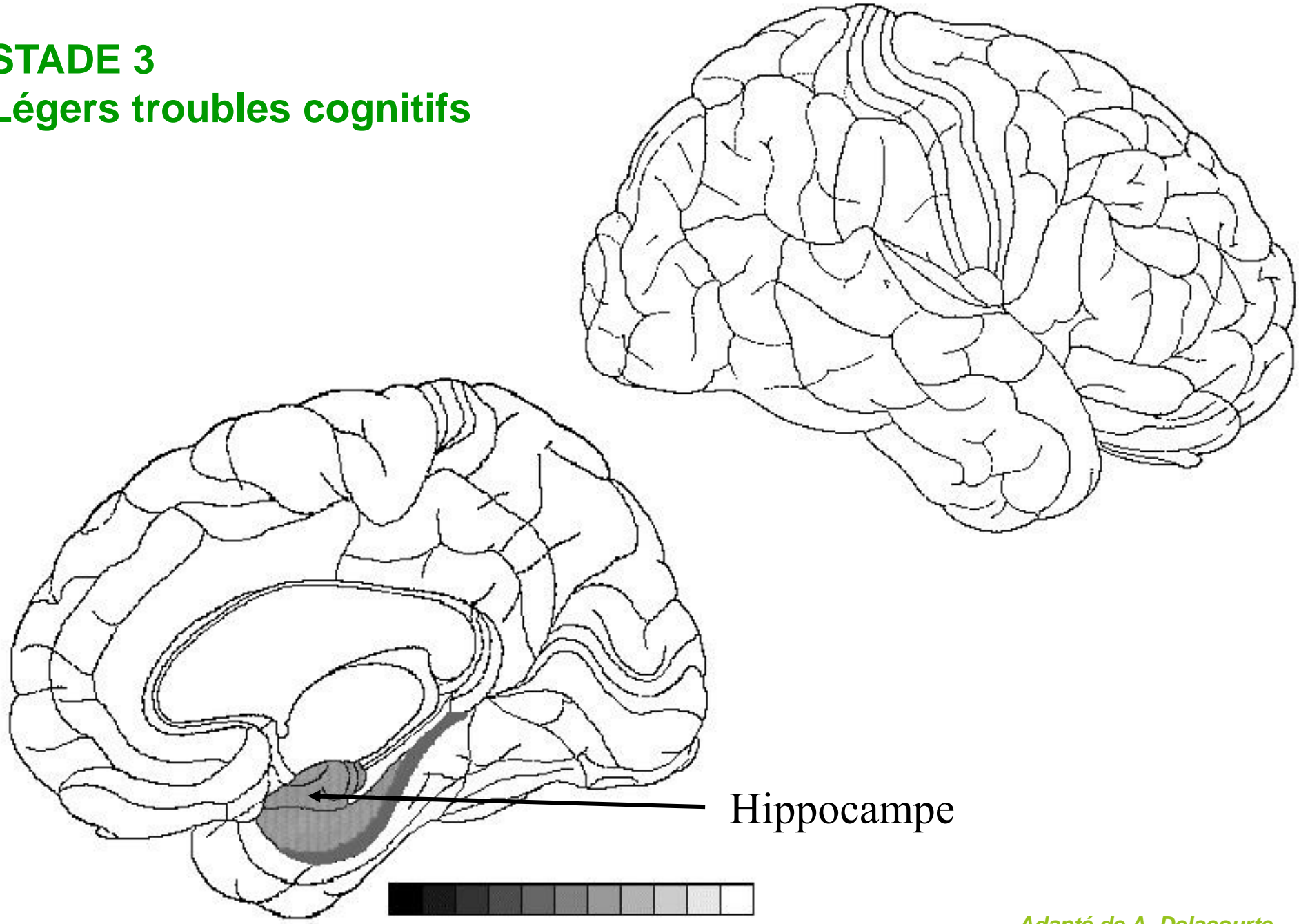
# STADE 2



Cortex entorhinal (aire 28)



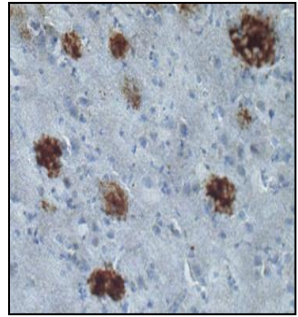
**STADE 3**  
**Légers troubles cognitifs**



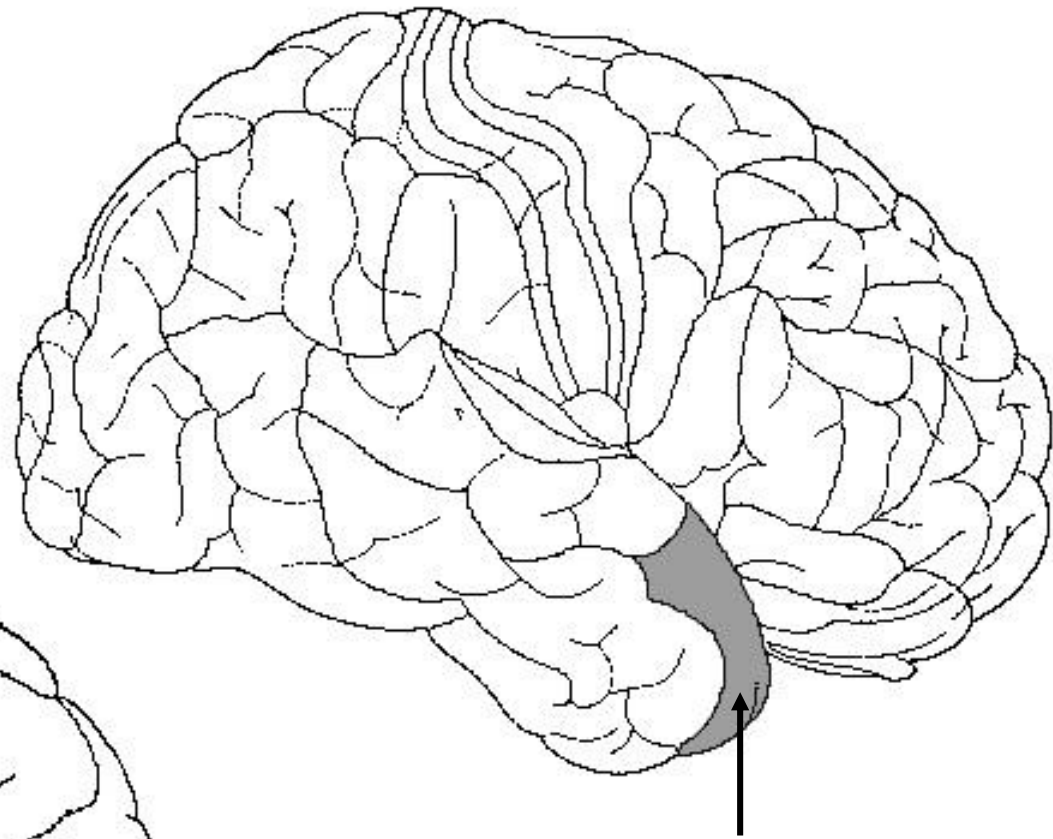
Hippocampe

# STADE 4

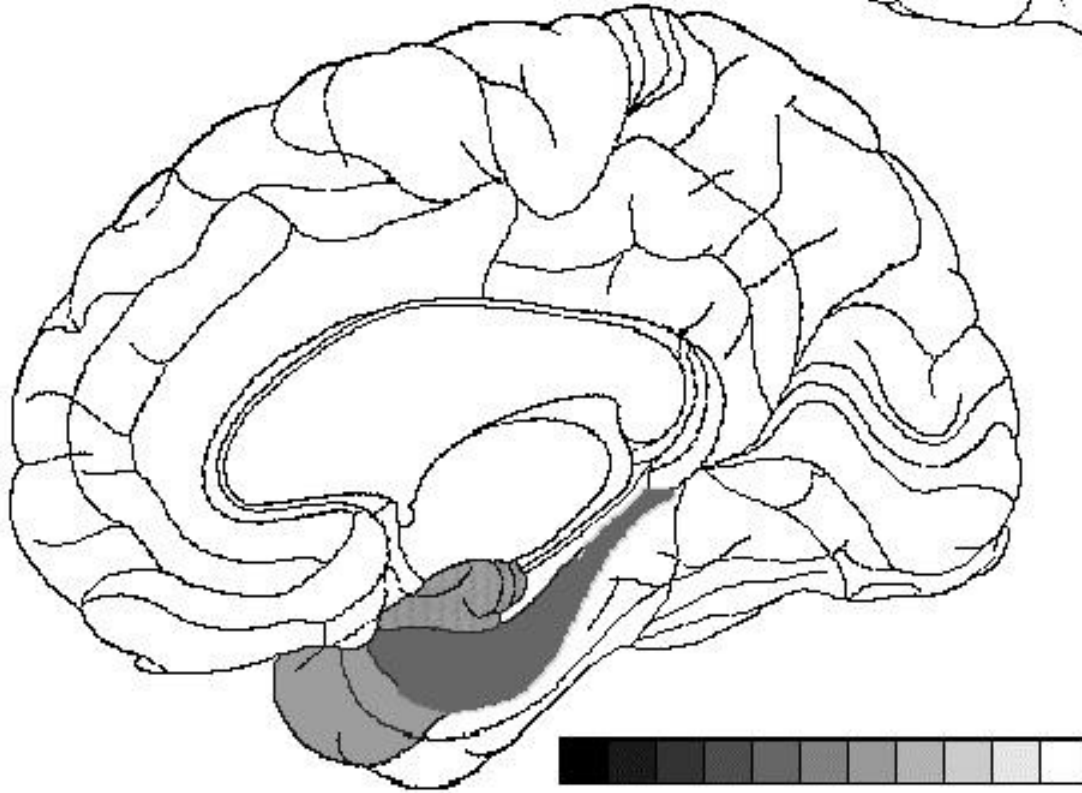
## Légers troubles cognitifs



Dépôts discrets  
(diffus ?) de  
substance  
amyloïde



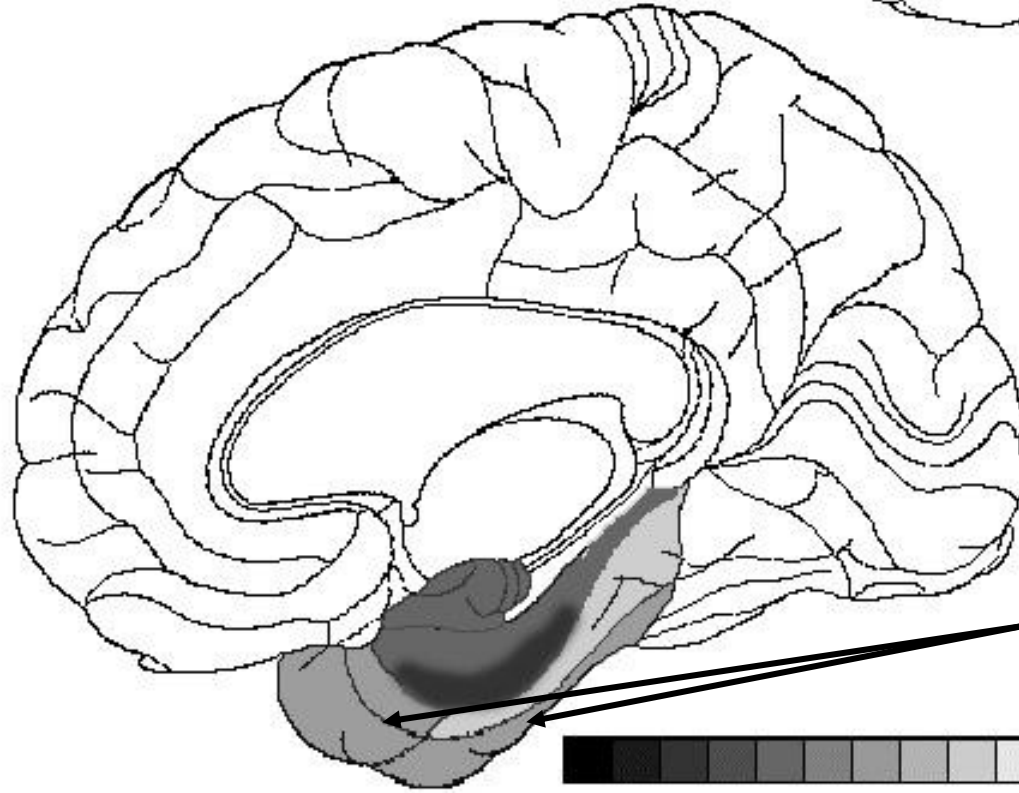
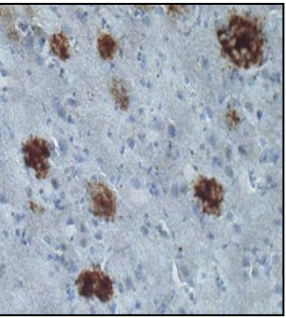
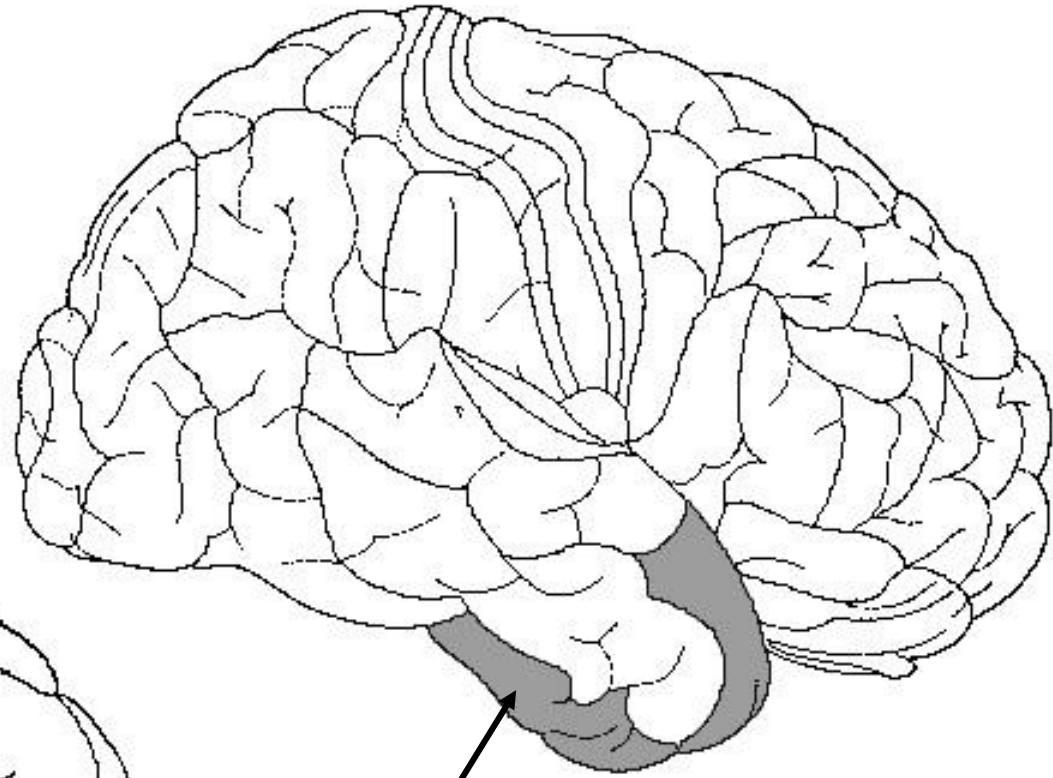
Cortex temporal antérieur



# STADE 5

## Troubles cognitifs aggravés

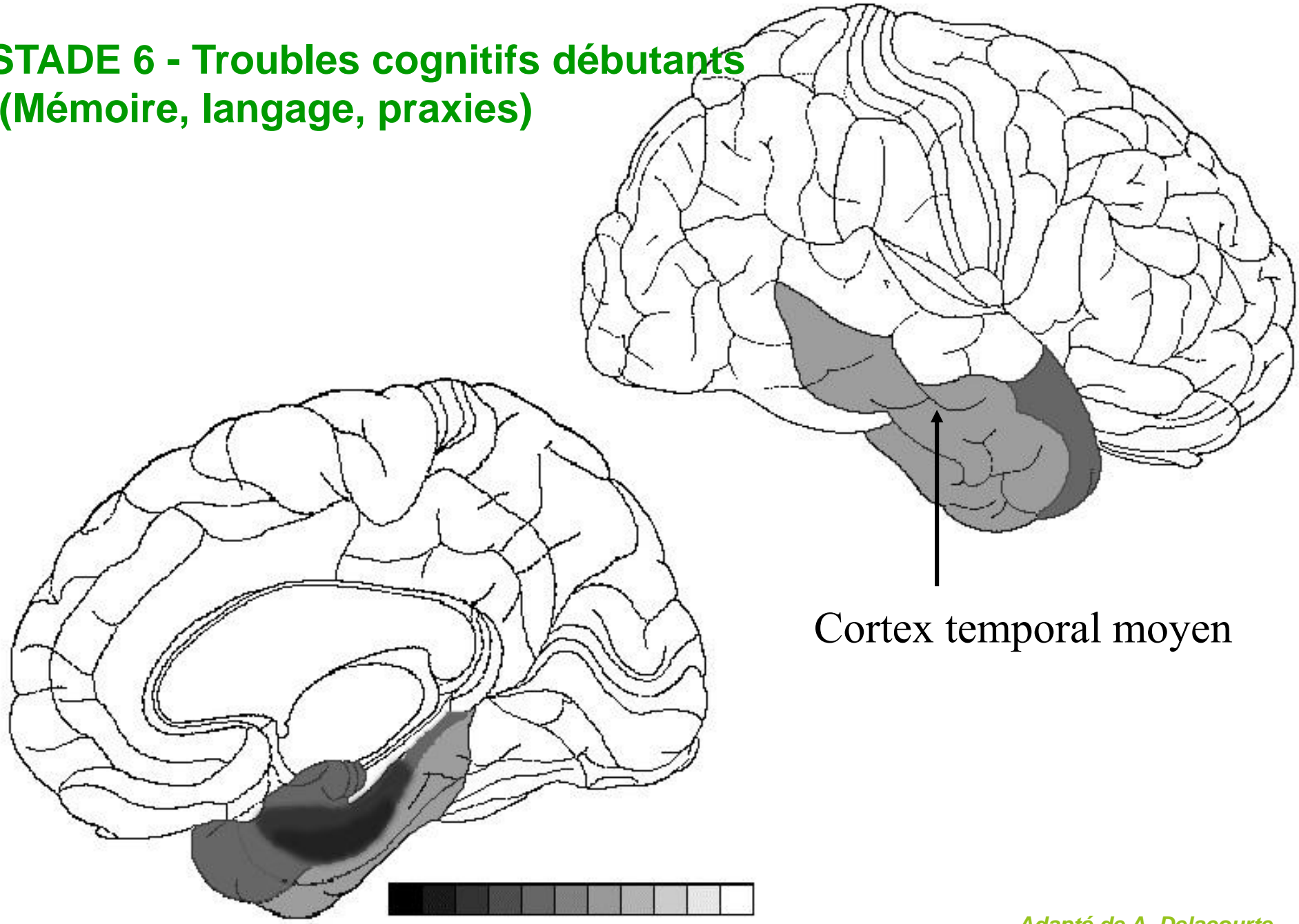
Agrégation du peptide Abeta 42



Cortex temporal inférieur



# STADE 6 - Troubles cognitifs débutants (Mémoire, langage, praxies)

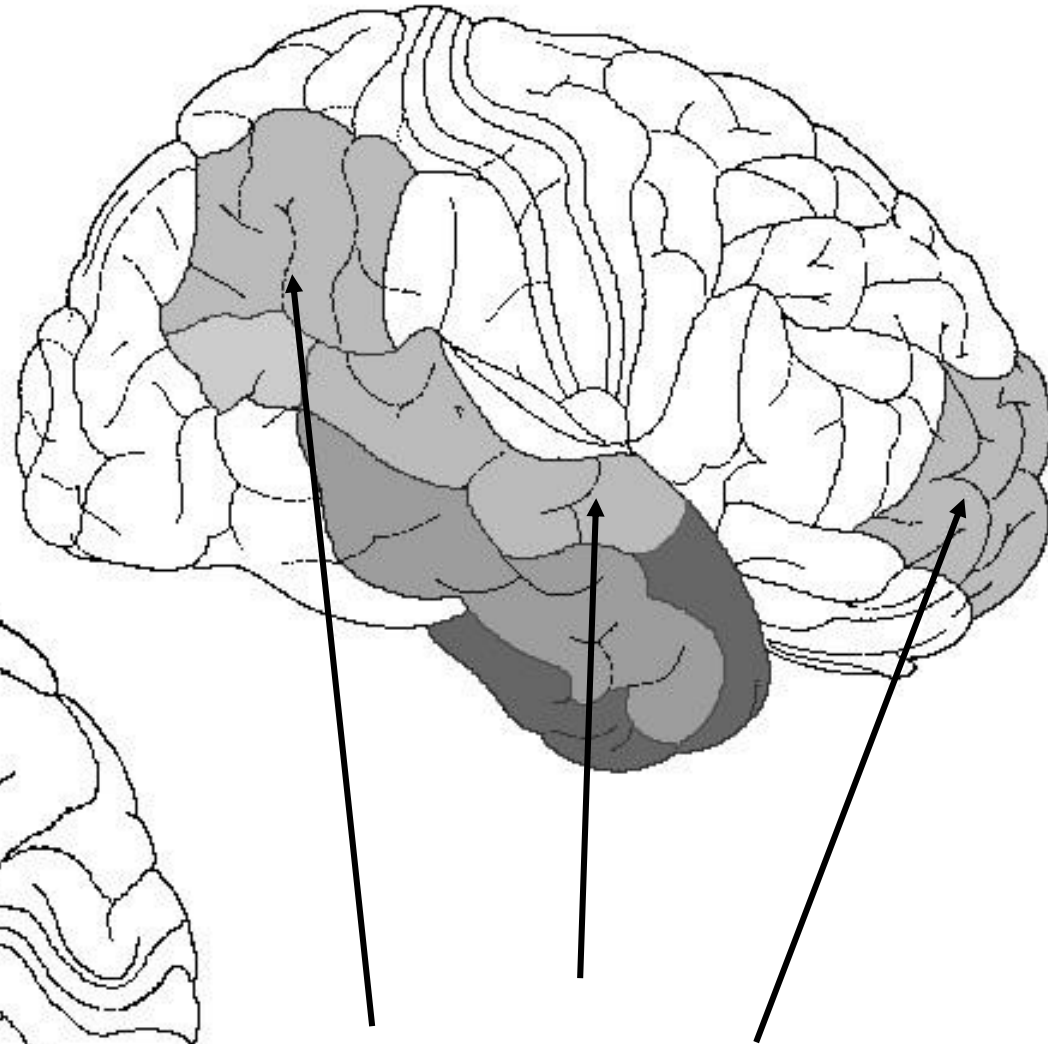
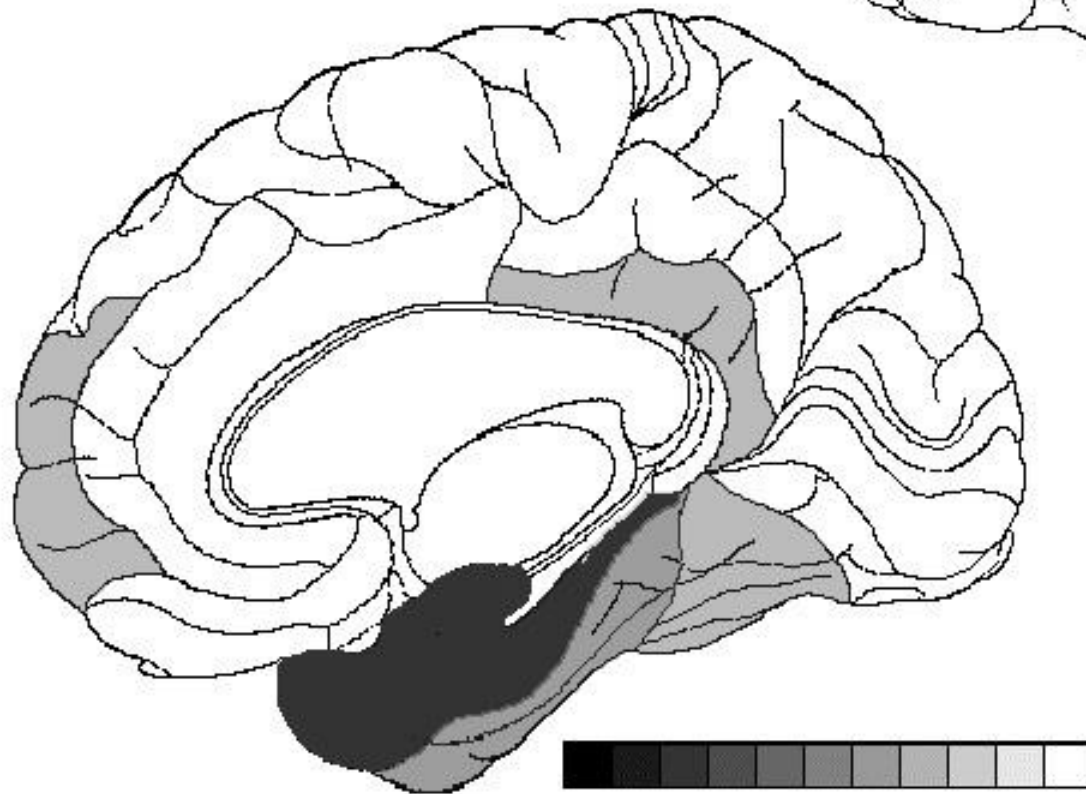


Cortex temporal moyen

# STADE 7

Démence débutante  
(Mémoire, langage, praxies)

Aires associatives

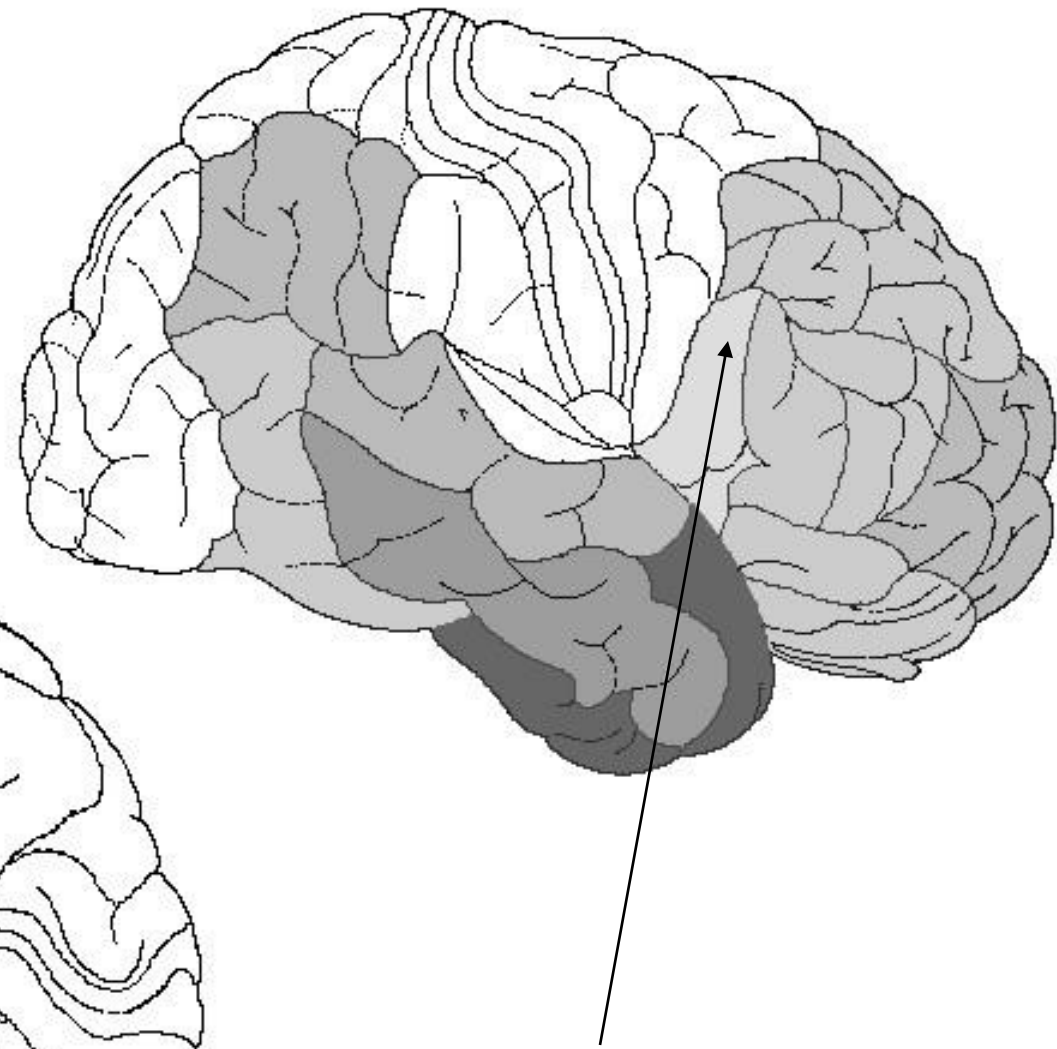
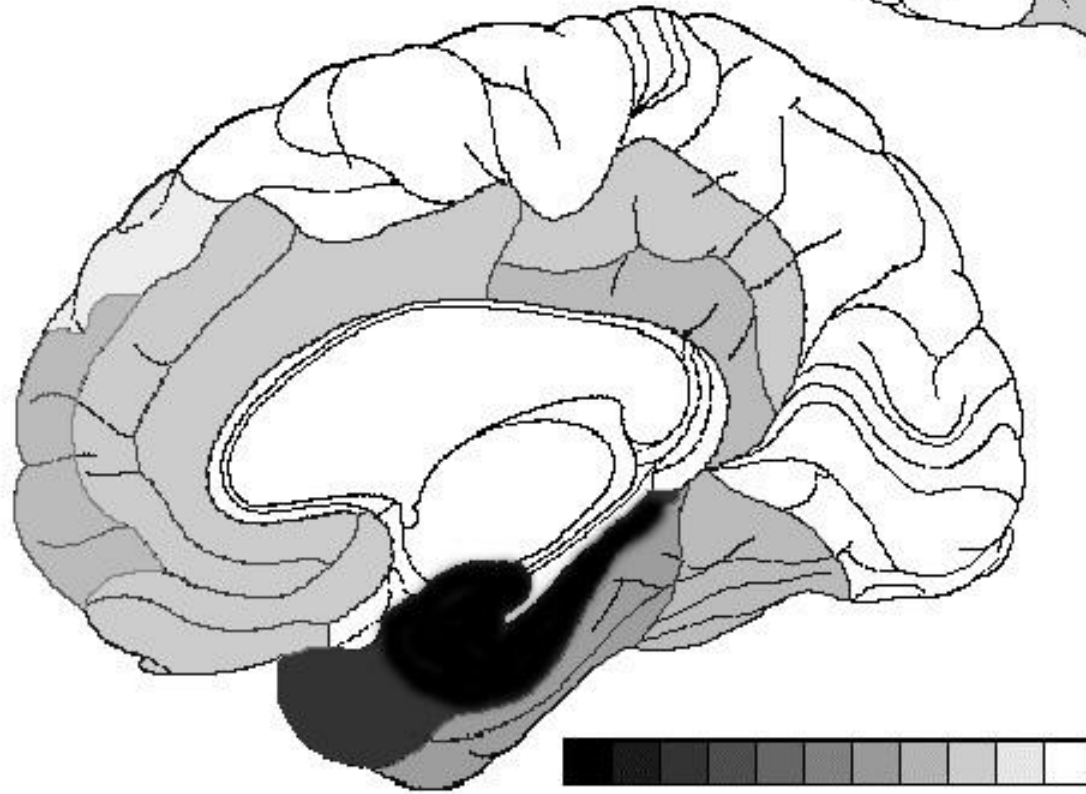


Cortex polymodal associatif

## STADE 8

### Démence légère à modérée

Cortex secondaire sensitif  
ou moteur



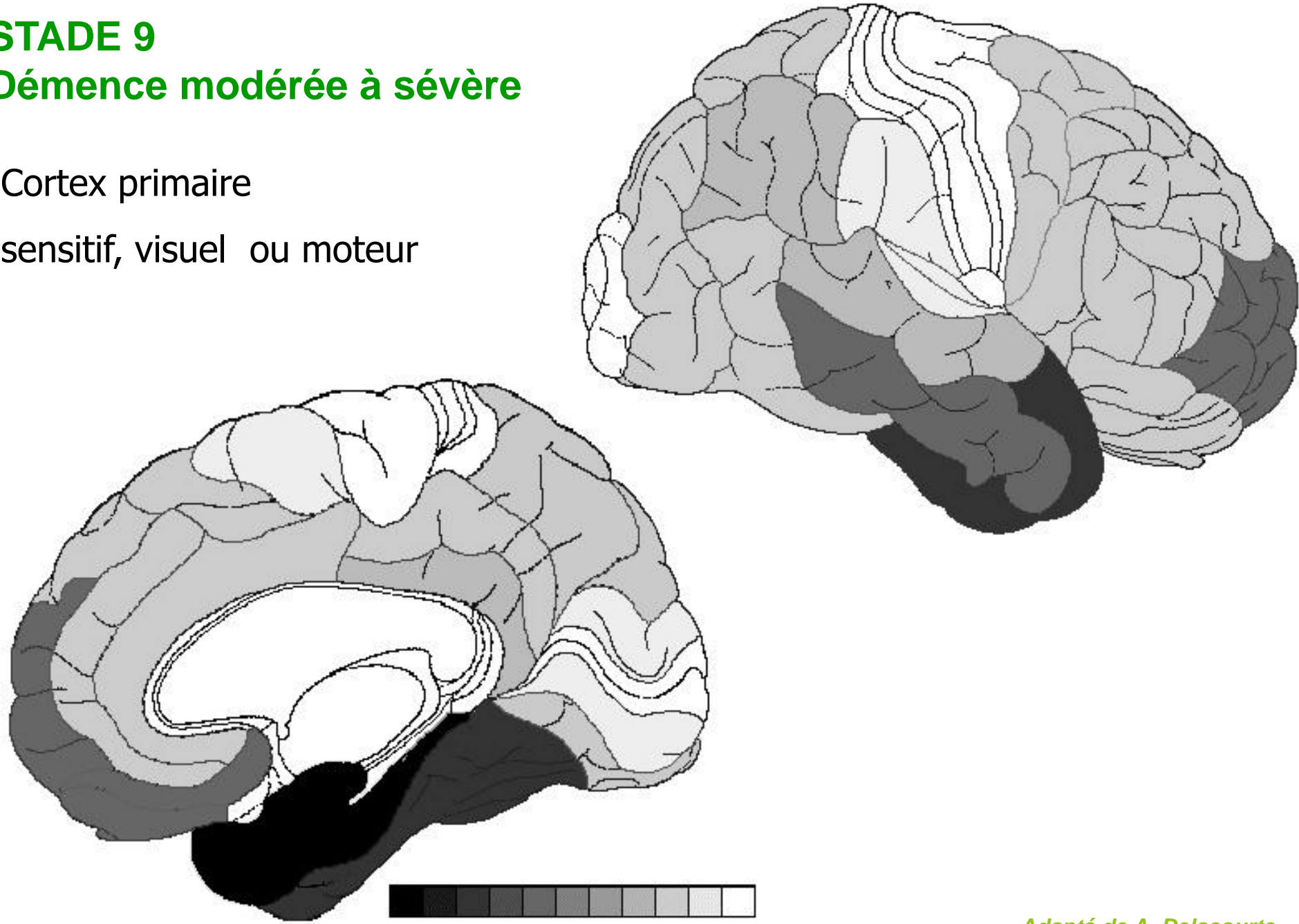
Aire de Broca

## STADE 9

### Démence modérée à sévère

Cortex primaire

sensitif, visuel ou moteur



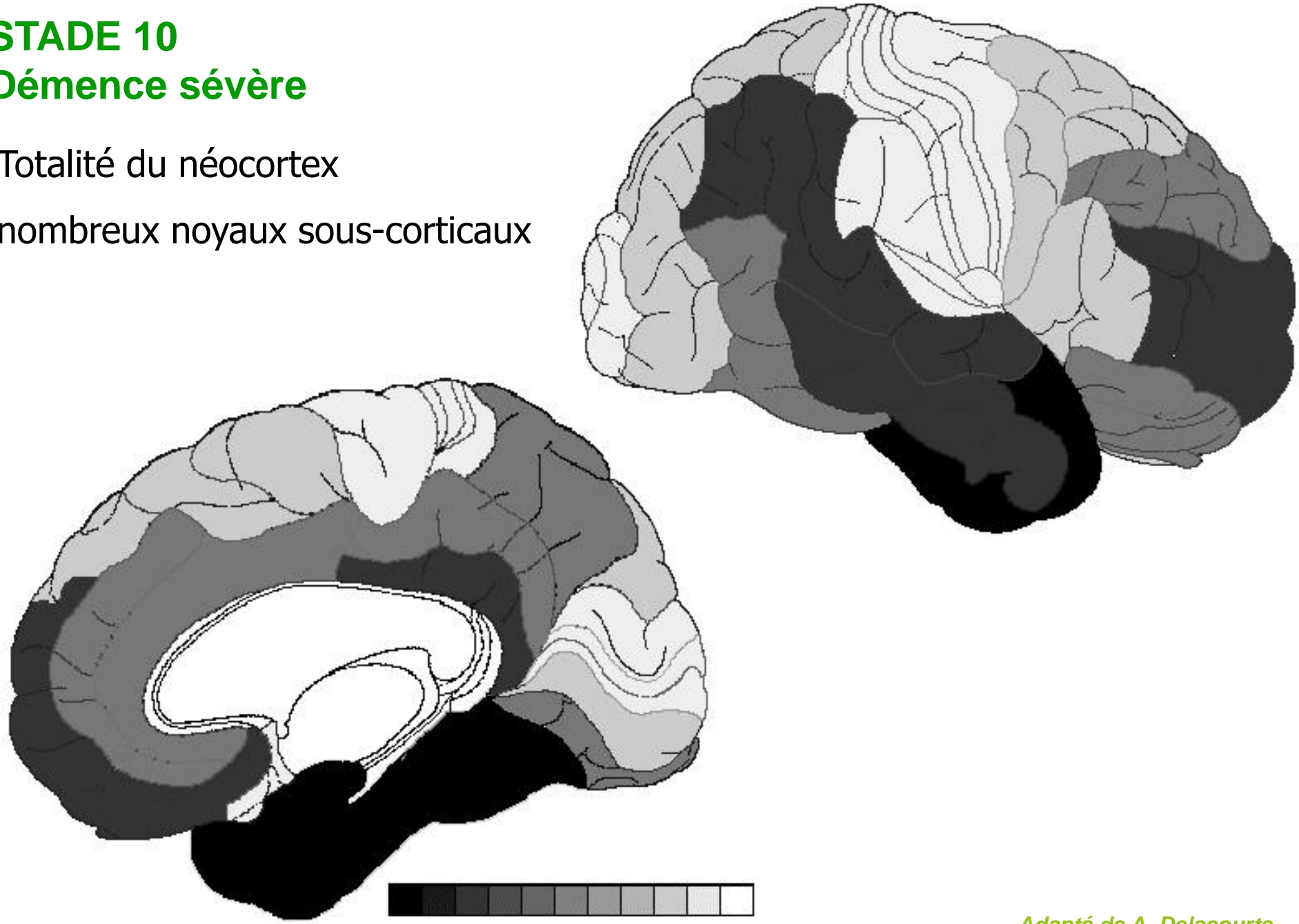
*Adapté de A. Delacourte*

# STADE 10

## Démence sévère

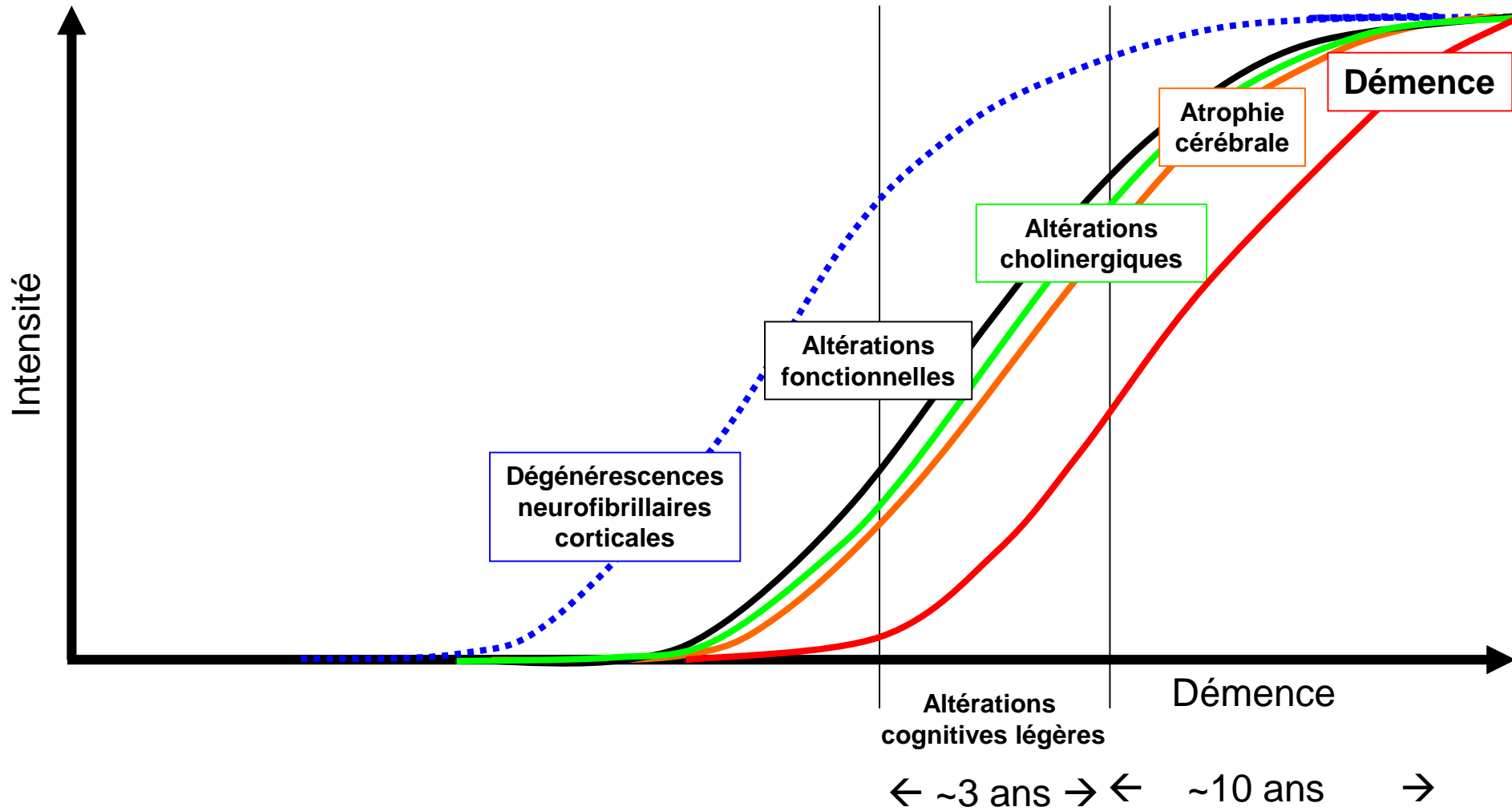
Totalité du néocortex

nombreux noyaux sous-corticaux





# HISTOIRE NATURELLE DE LA MALADIE

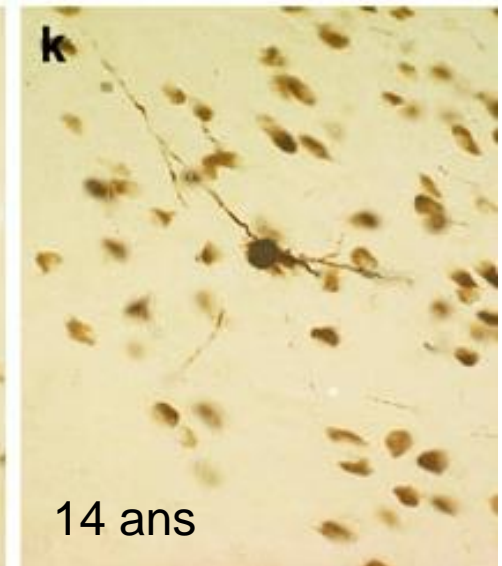
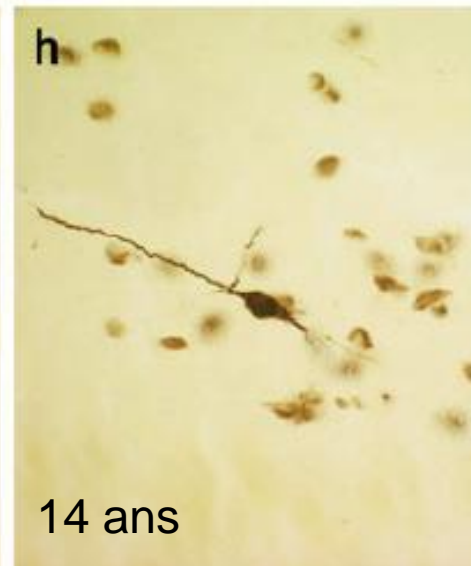
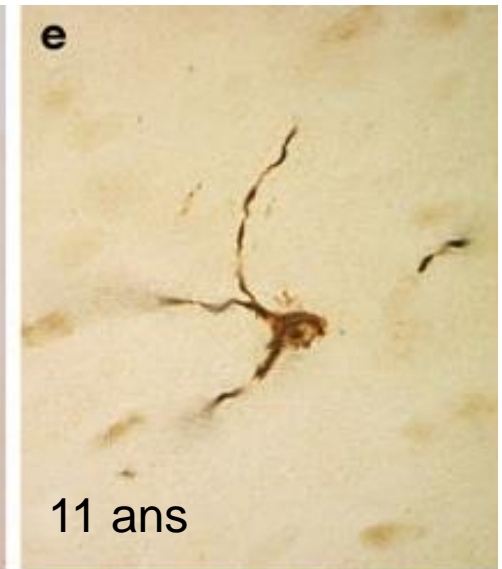
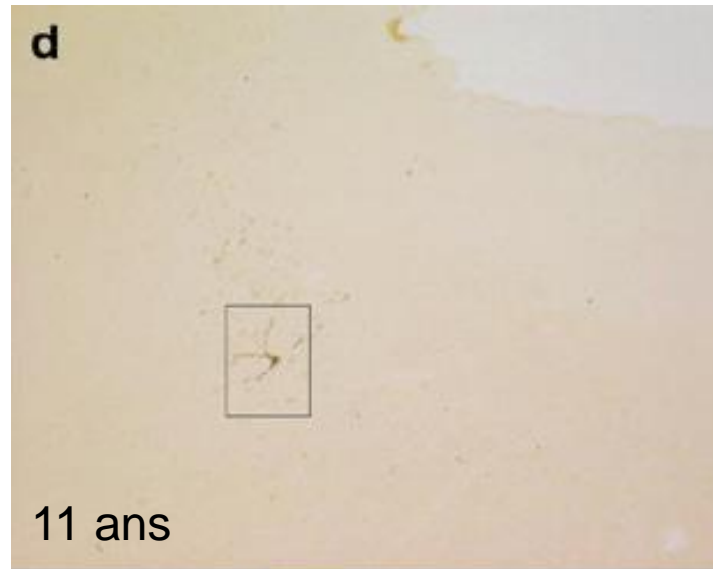
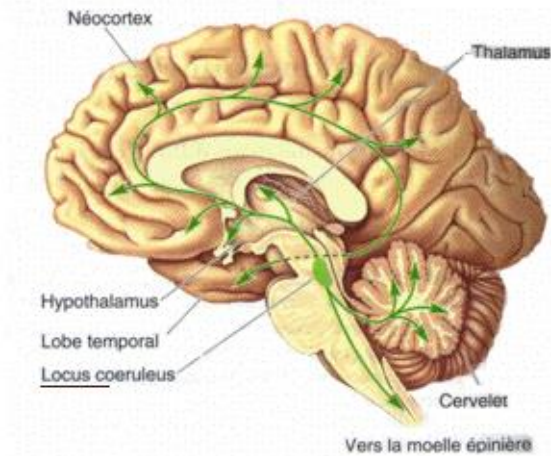
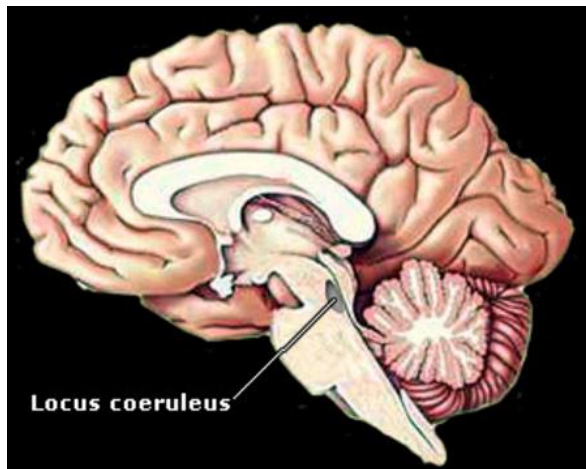




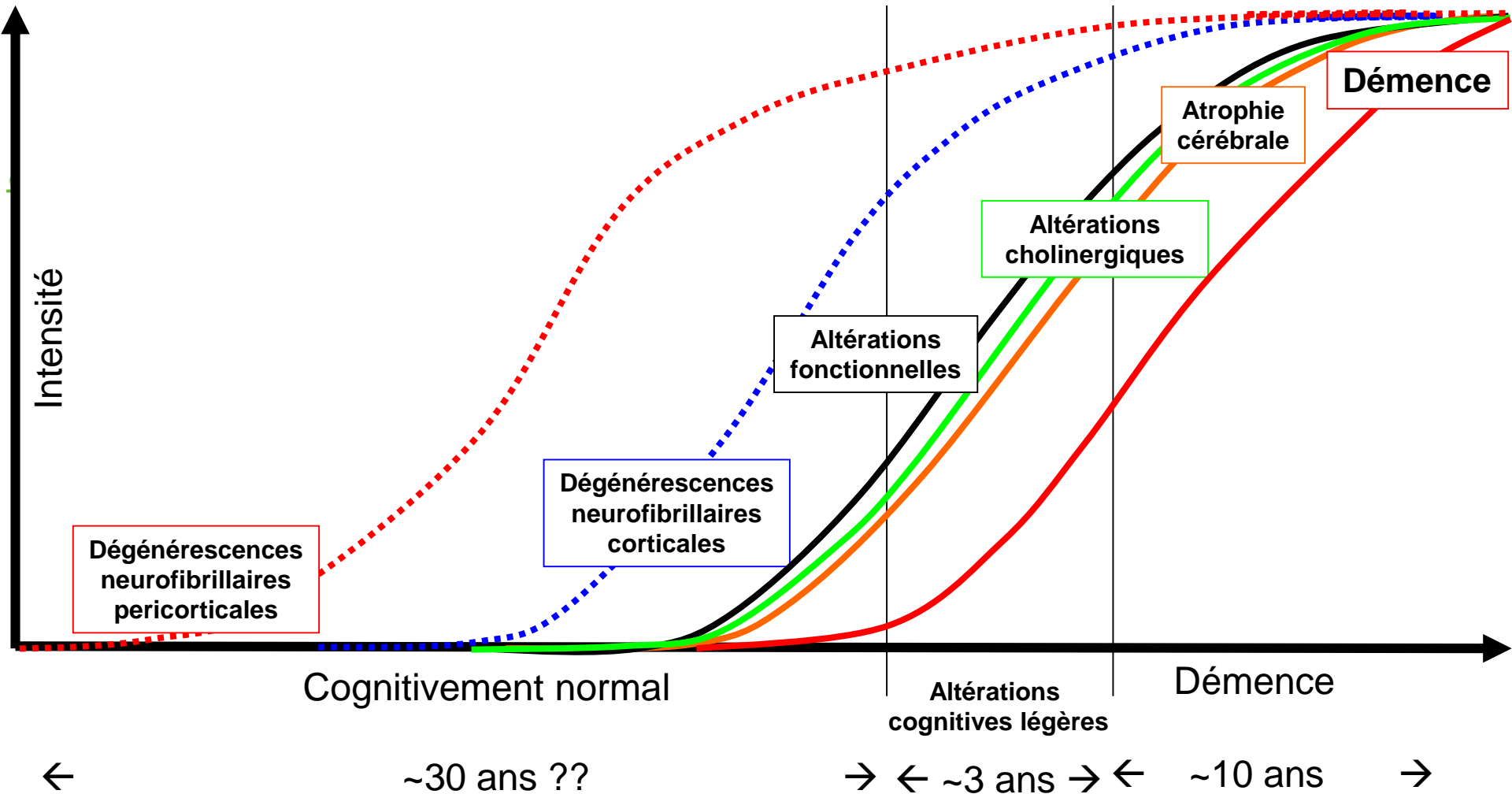
# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Quelles sont les toutes premières lésions ?**

# LES TOUTES PREMIÈRES LÉSIONS DE LA MALADIE ?



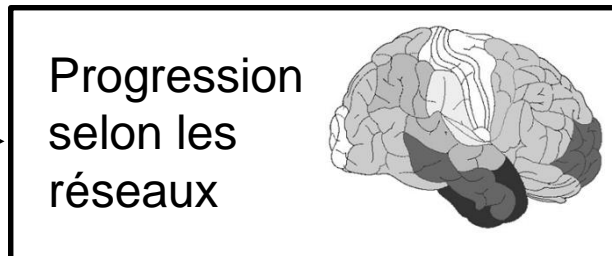
# HISTOIRE NATURELLE DE LA MALADIE



# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

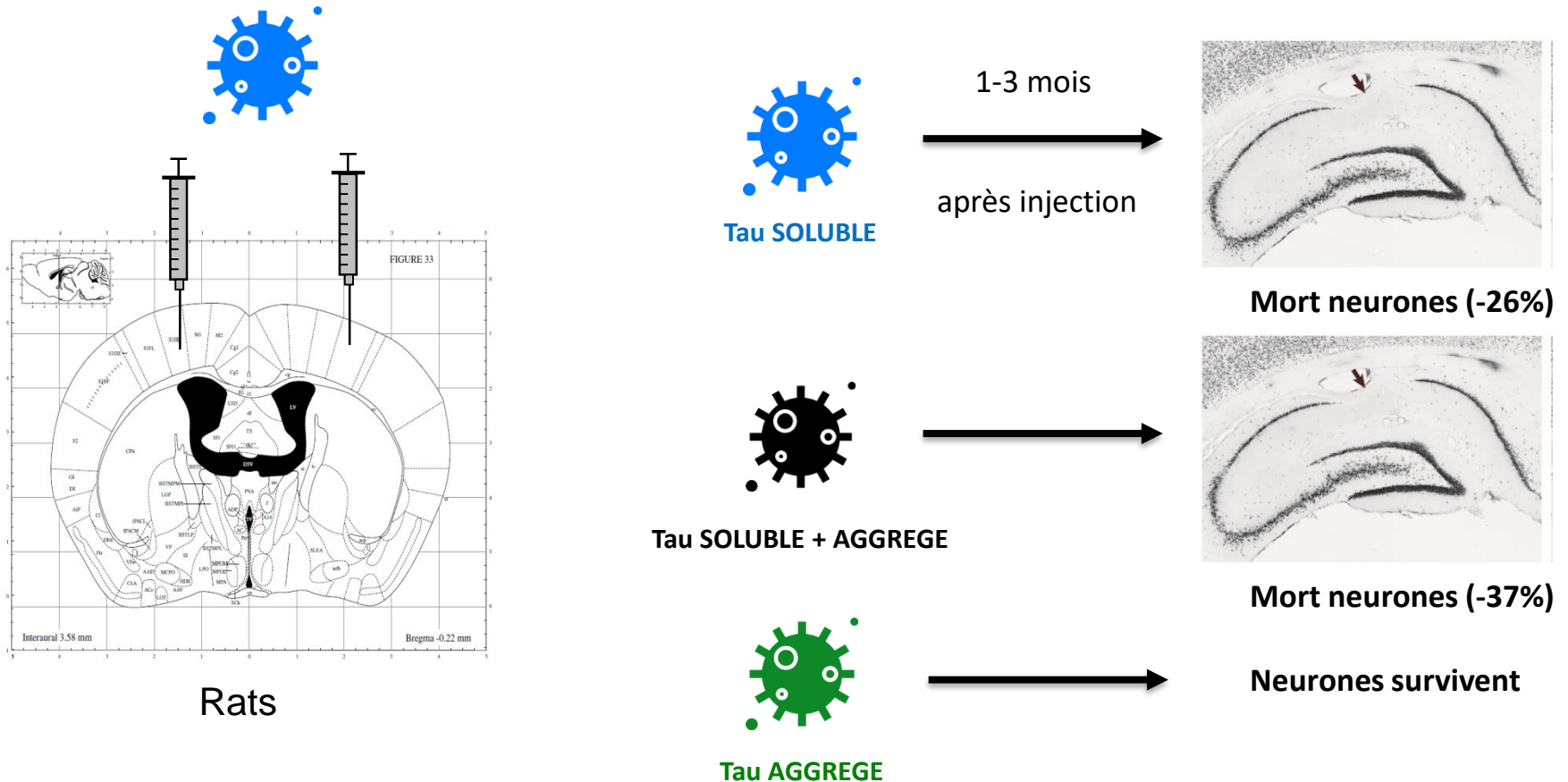
## Hypothèse explicative

Origine  
de Tau ?



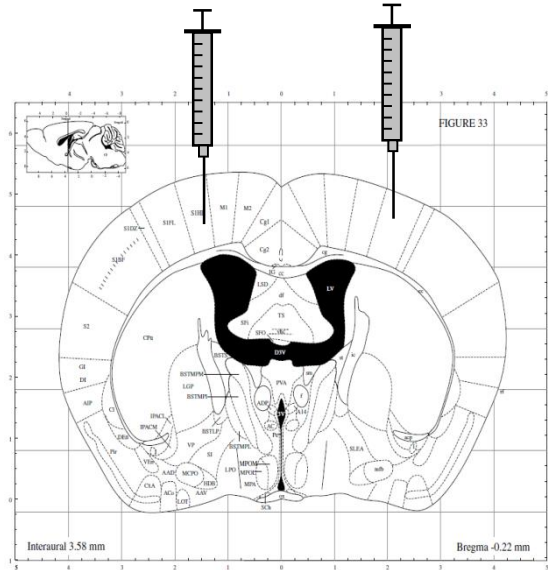
# LES FORMES LES PLUS TOXIQUES DE TAU SONT INVISIBLES

Tranfert du gène de la protéine tau gene (Adeno-associated virus AAV2/8)

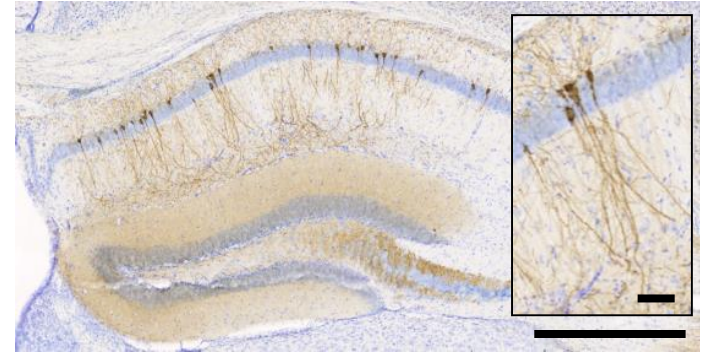


# INDUCTION ET DIFFUSION DE LA PATHOLOGIE TAU

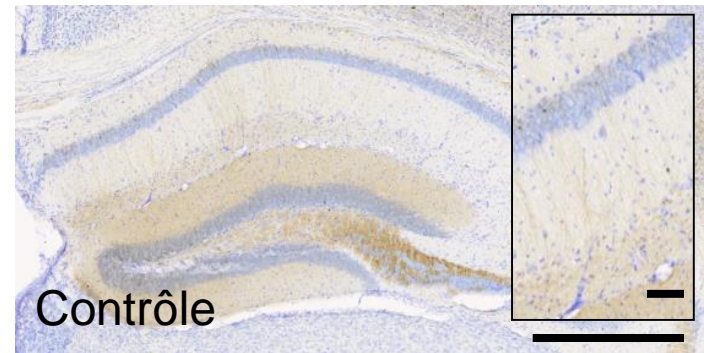
Tissu riche en Tau



Souris  
jeune



Lesions

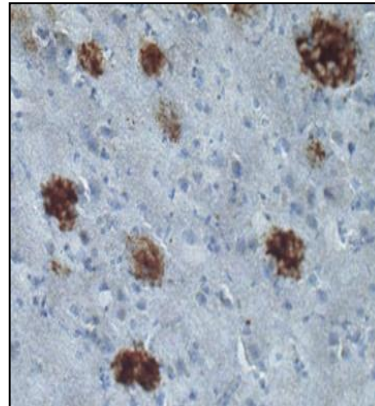


Contrôle



# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

## Plaques amyloïdes





# IMAGERIE DE L'AMYLOÏDE CHEZ L'HOMME (TEP)

**Control  
Subject**

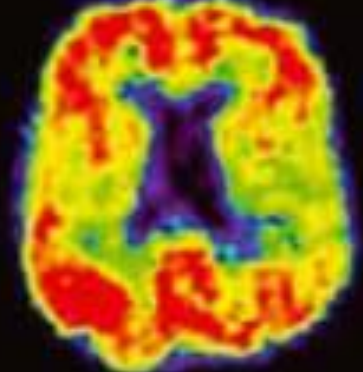
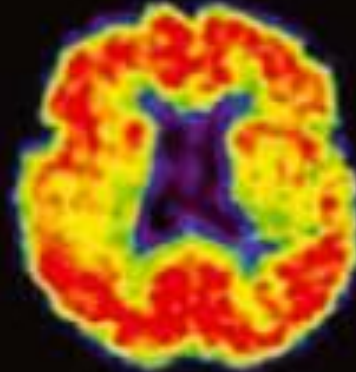
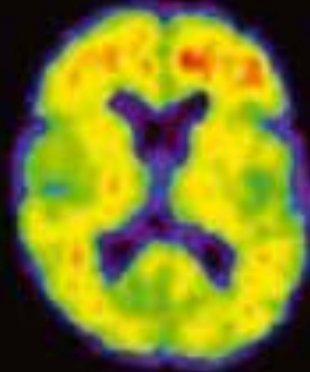
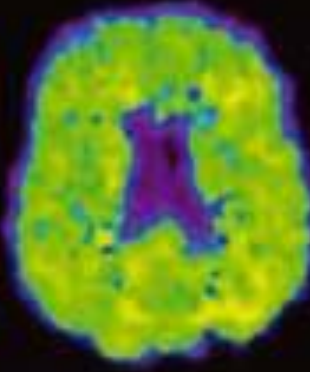
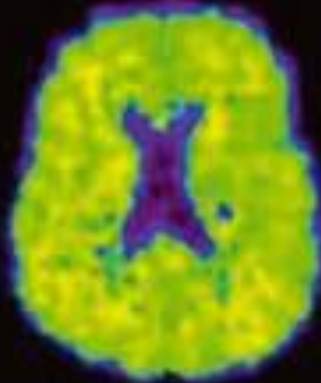
**MCI-1**

**MCI Patients**

**MCI-2**

**MCI-3**

**AD  
Patient**



University of Pittsburgh  
*PET Amyloid Imaging Group*

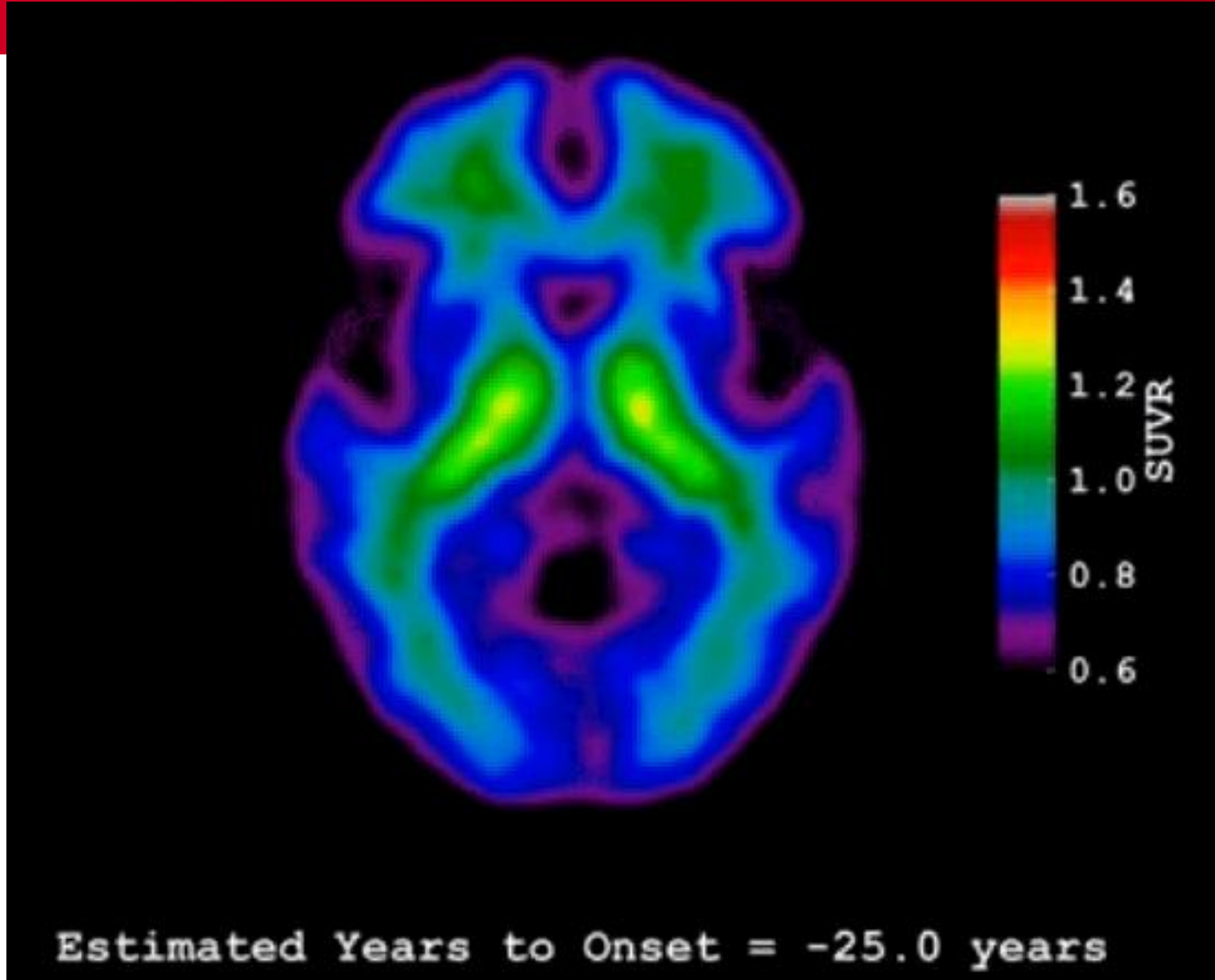
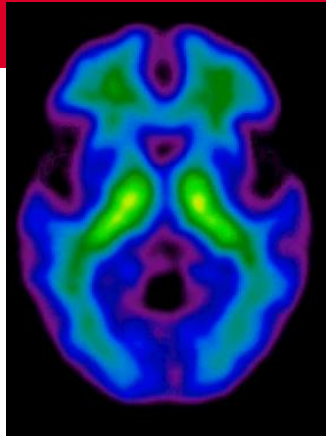
Min

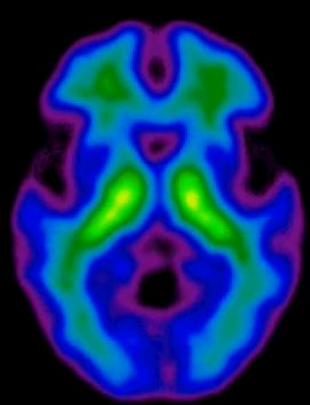


Max

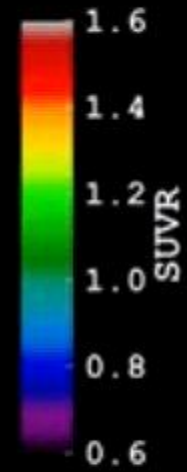
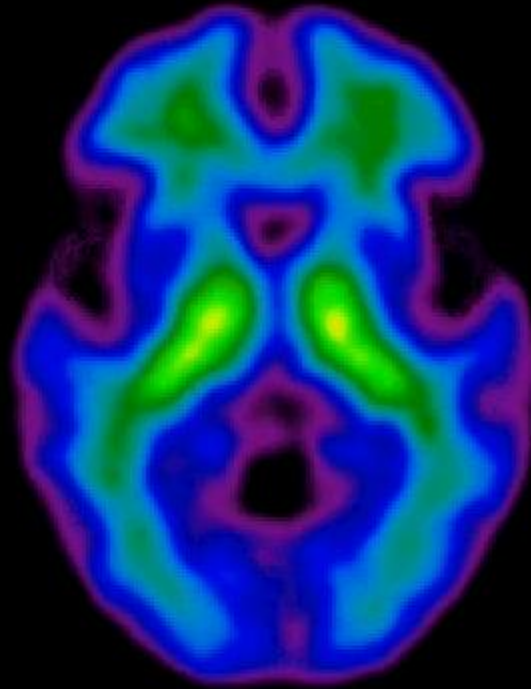
**[<sup>11</sup>C]PIB**

# IMAGERIE DE L'AMYLOÏDE CHEZ L'HOMME (TEP)

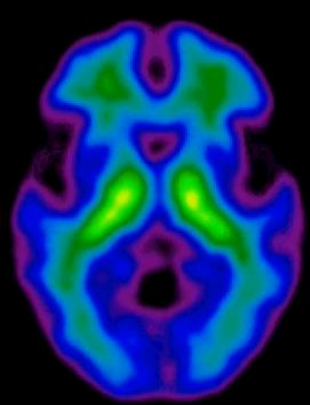




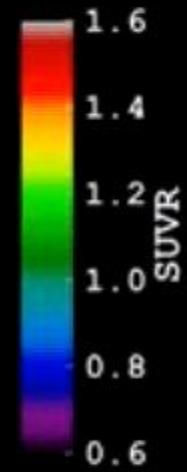
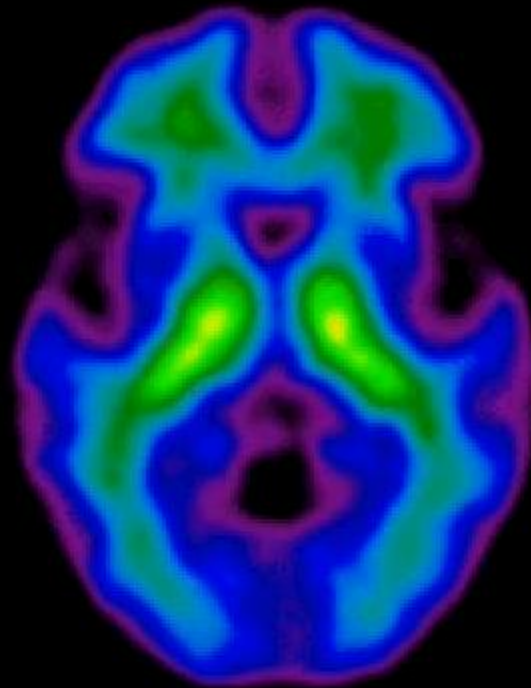
-25.0 years



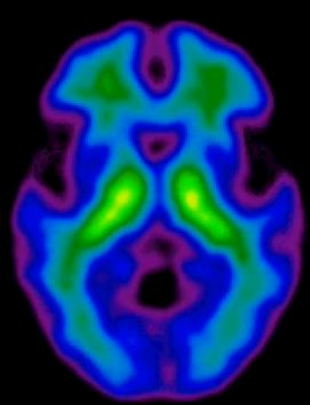
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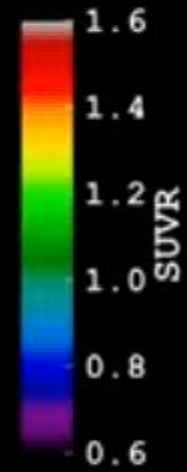
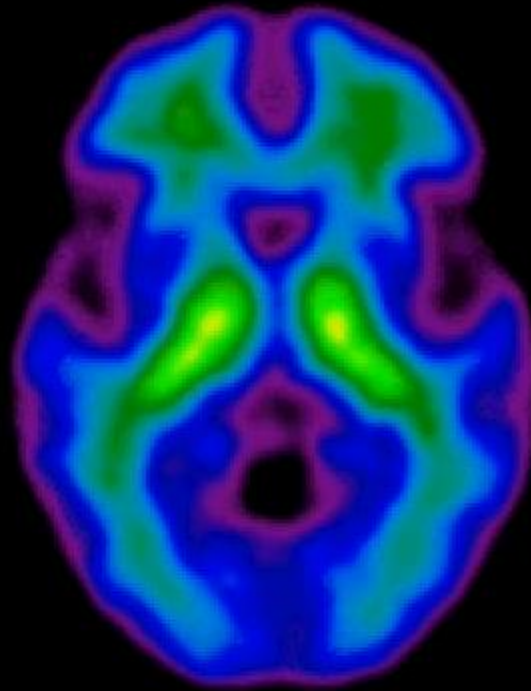
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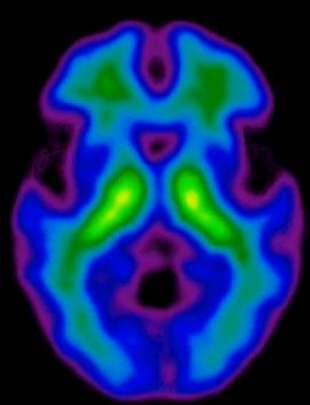
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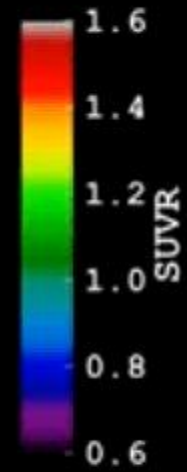
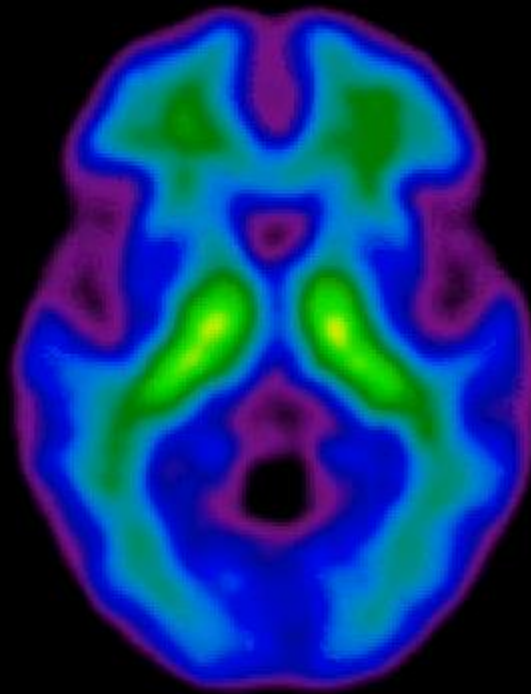
-25.0 years



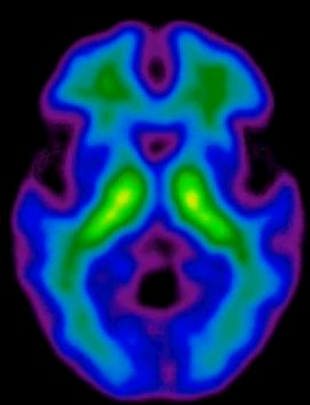
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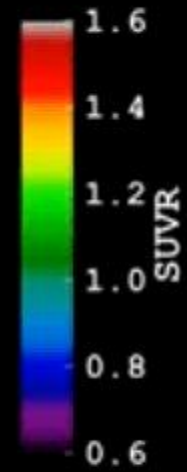
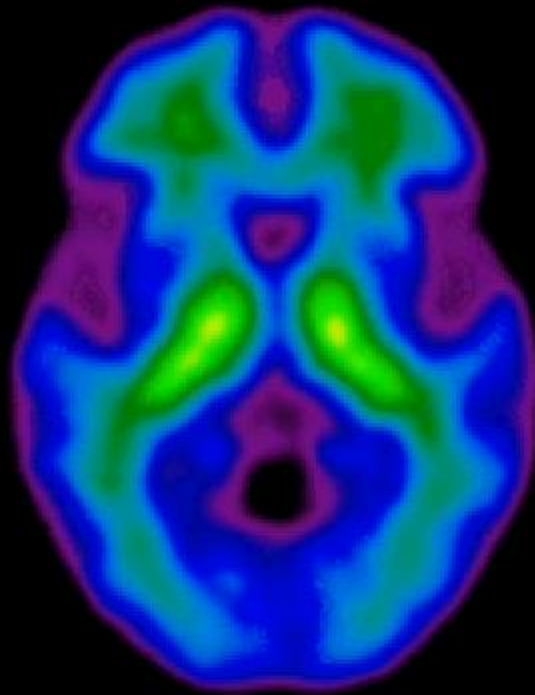
-25.0 years



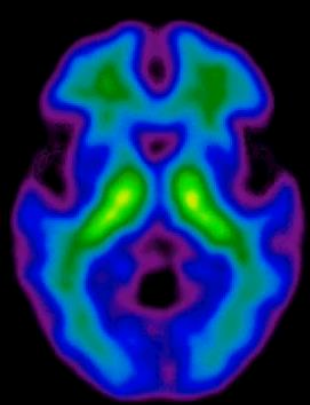
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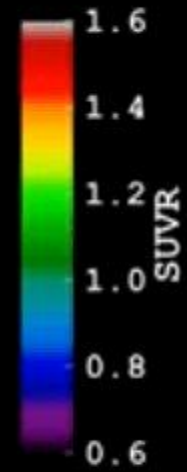
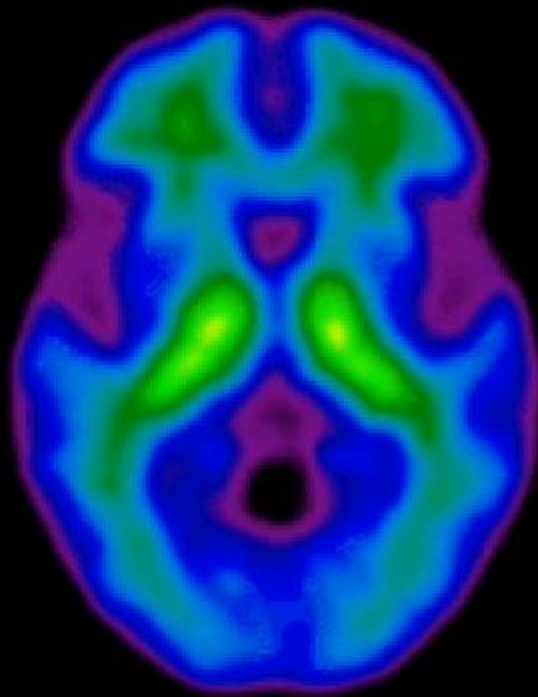
-25.0 years



Estimated Years to Onset = -21.0 years

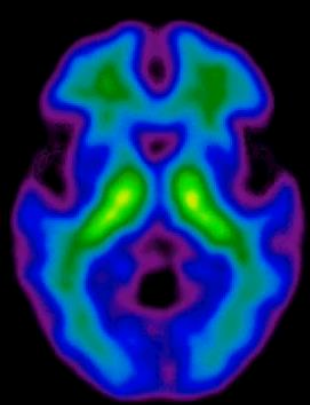


-25.0 years

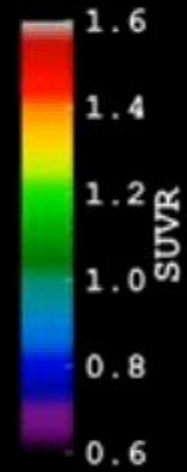
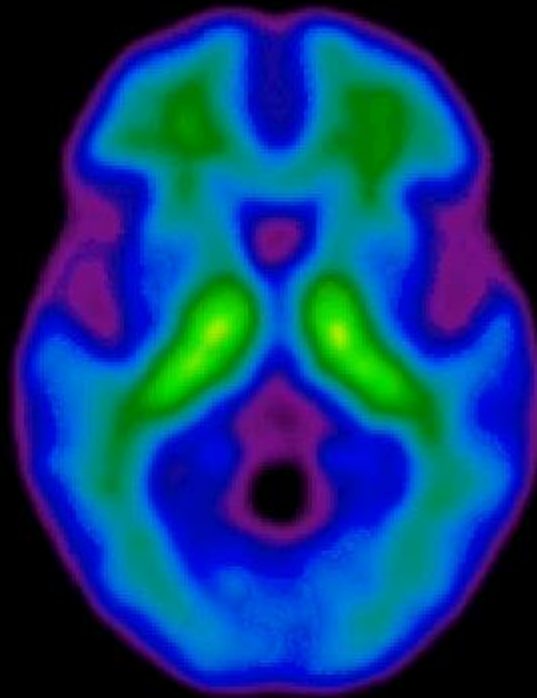


Estimated Years to Onset = -20.0 years

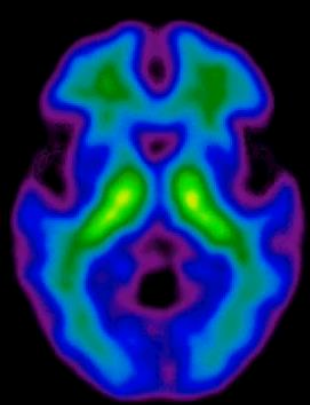




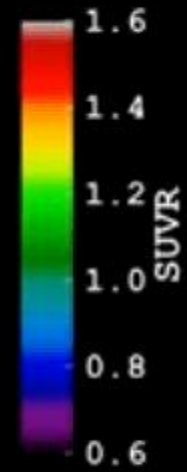
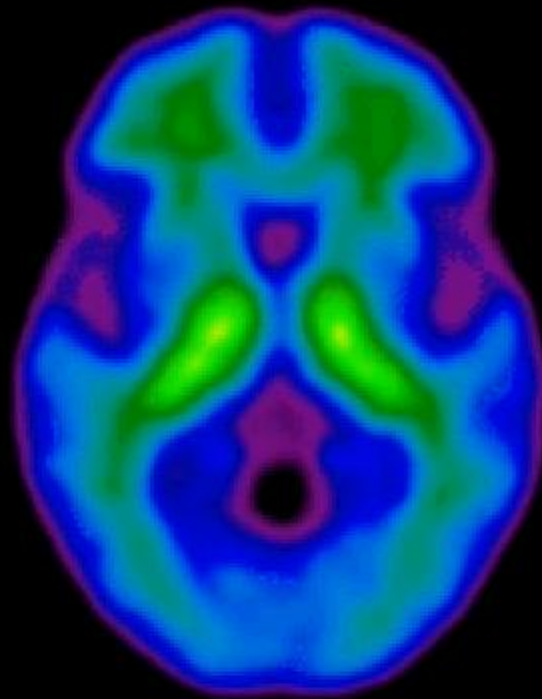
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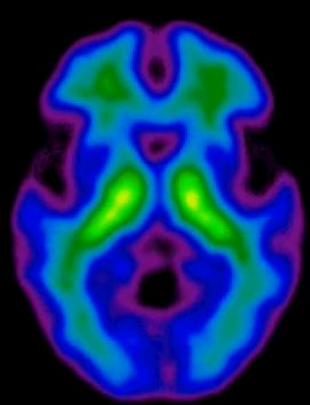
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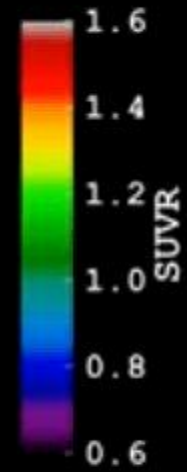
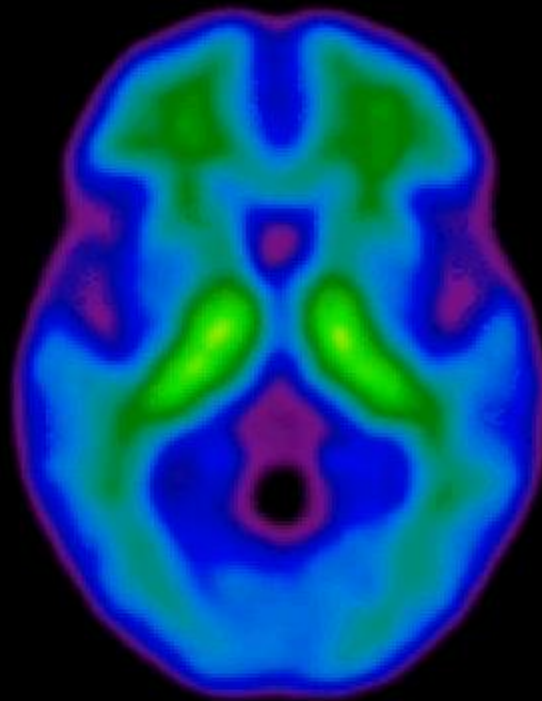
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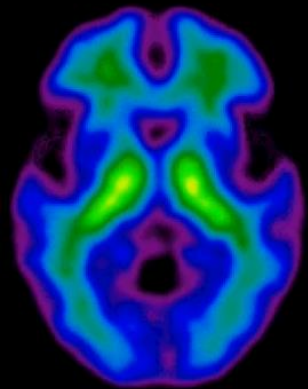
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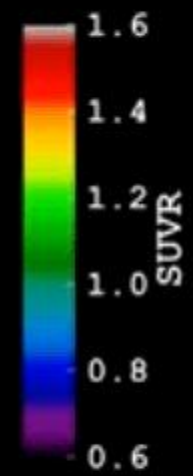
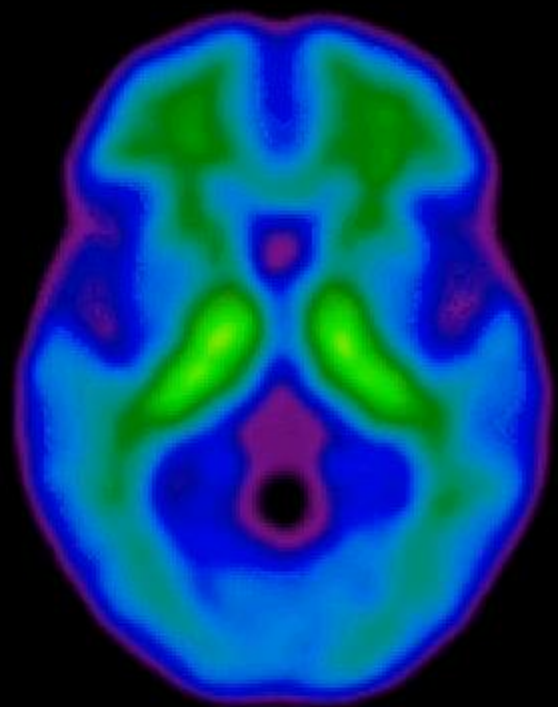
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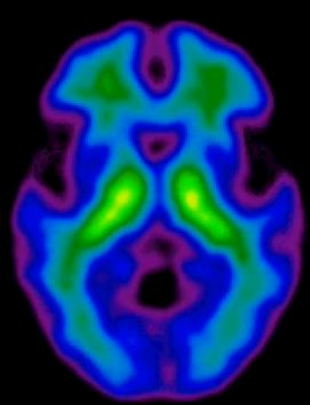
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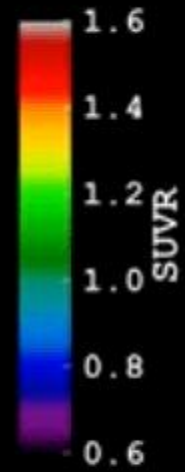
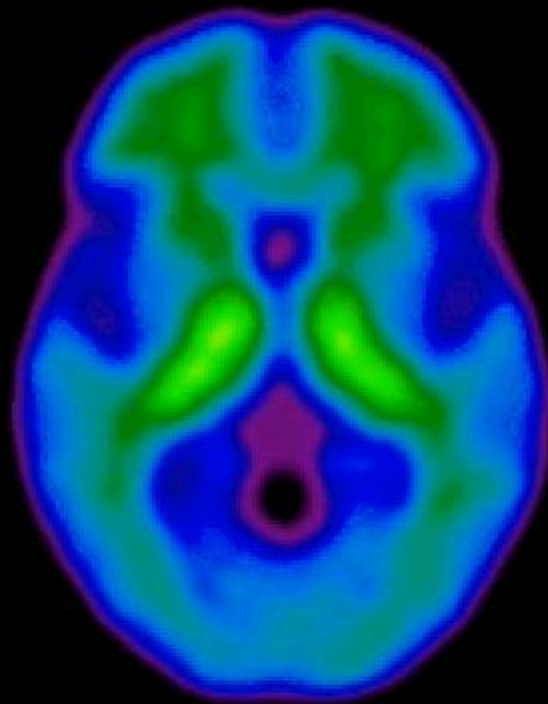
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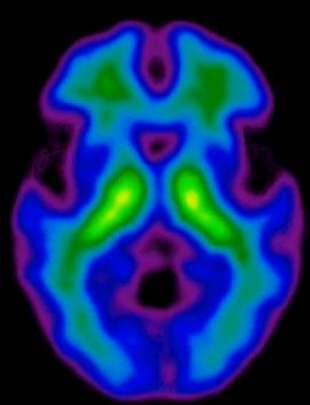
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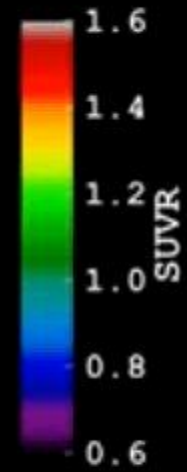
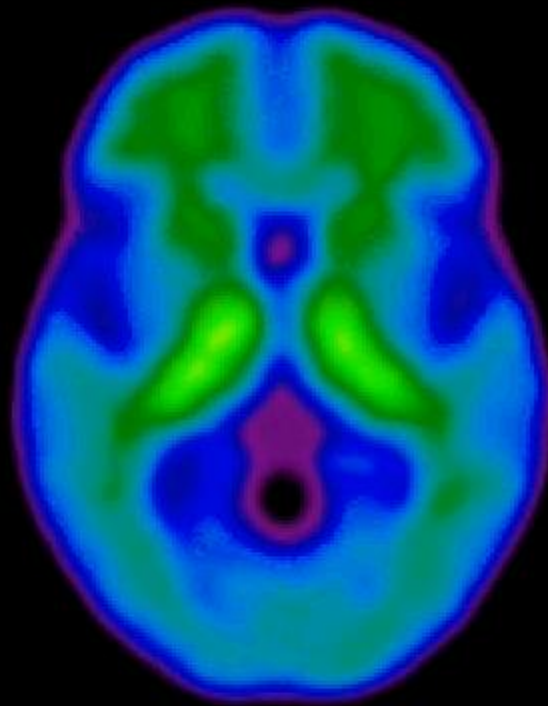
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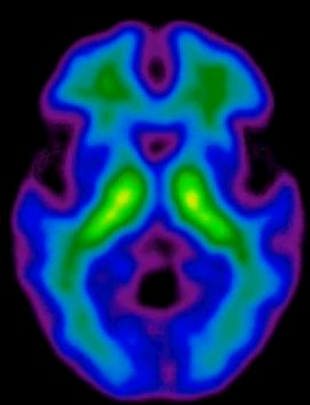
Estimated Years to Onset = -15.0 years



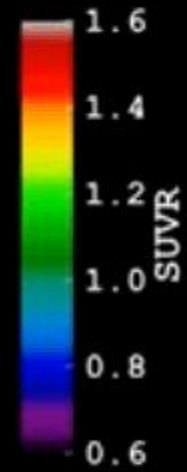
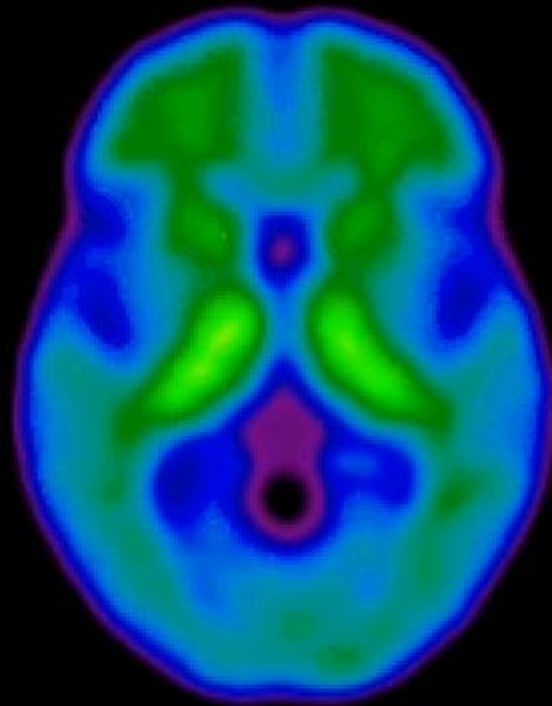
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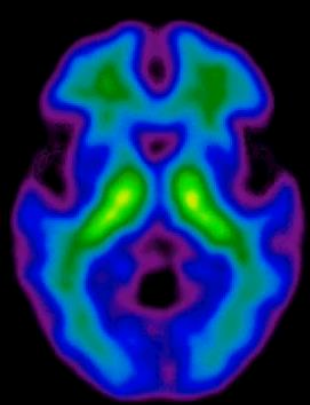
Estimated Years to Onset = -14.0 years



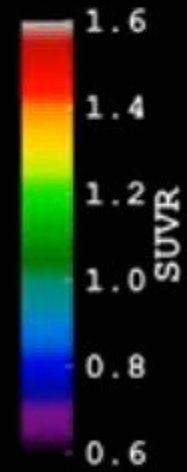
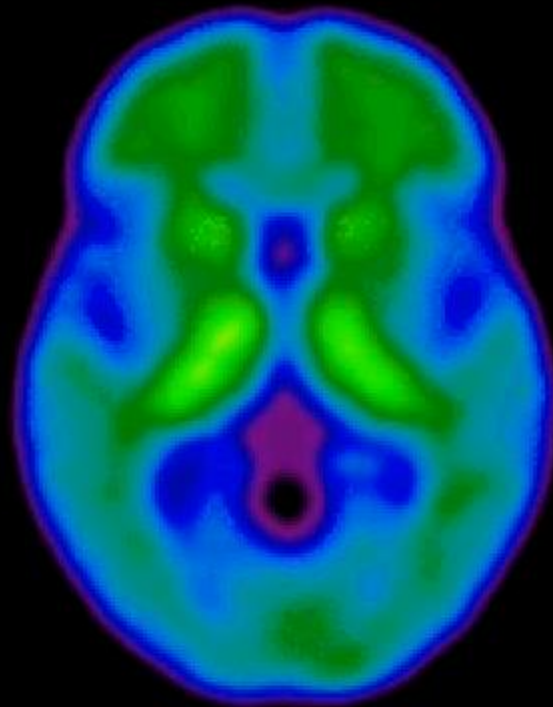
-25.0 years



Estimated Years to Onset = -13.0 years

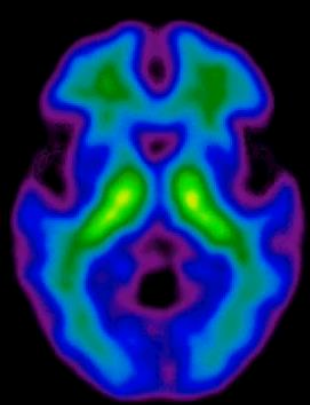


-25.0 years

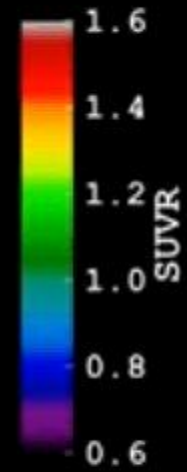
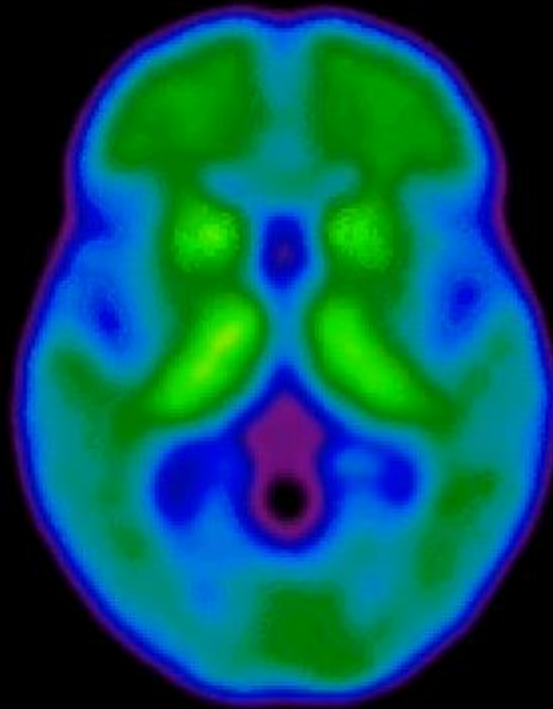


Estimated Years to Onset = -12.0 years

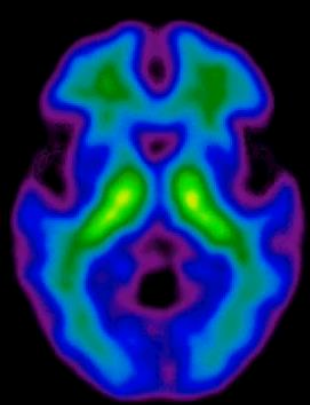




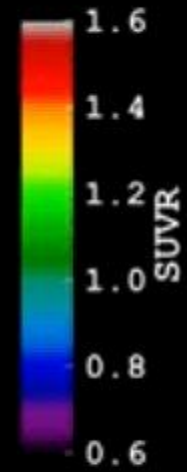
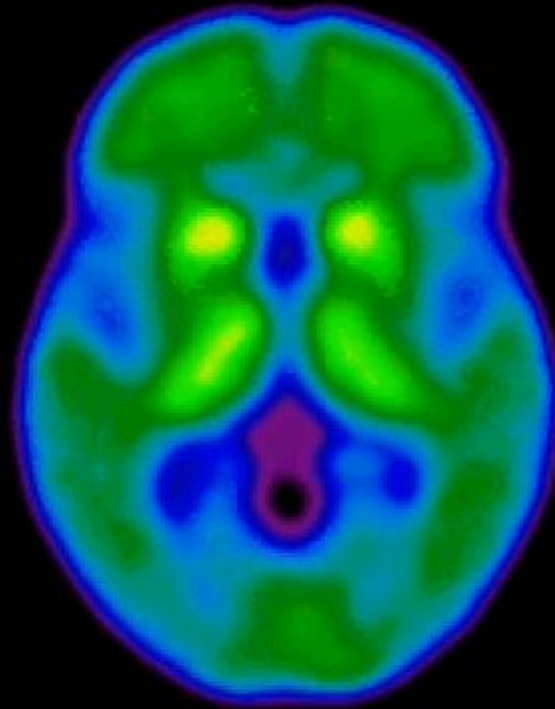
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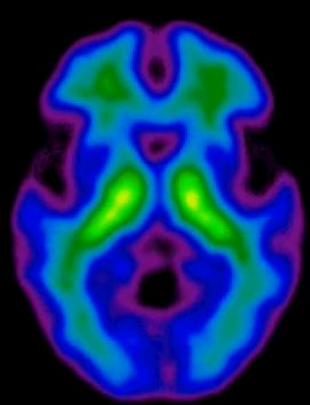
Estimated Years to Onset = -11.0 years



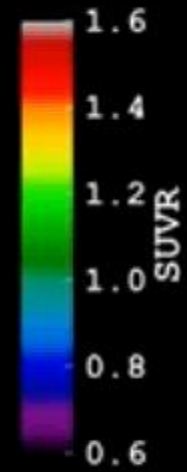
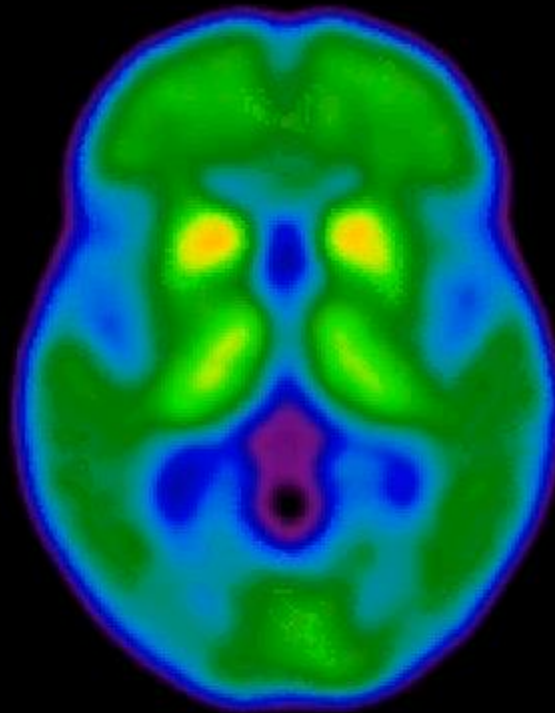
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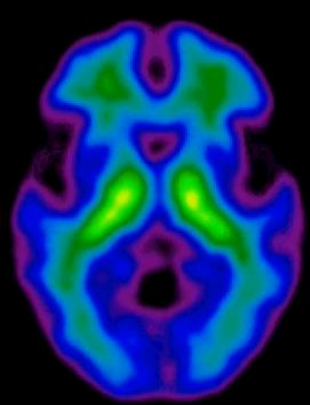
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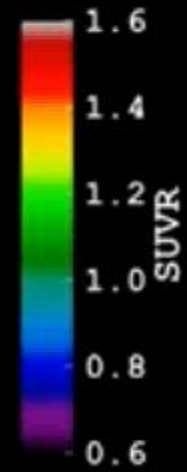
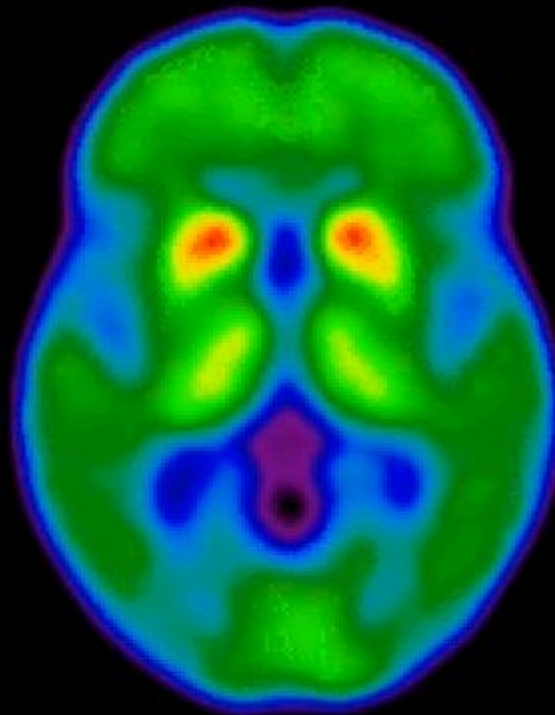
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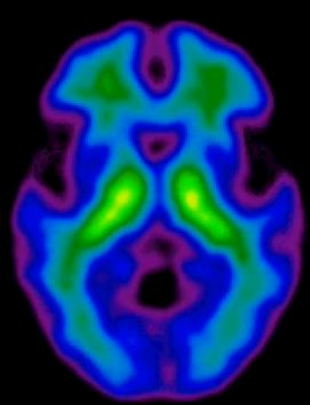
Estimated Years to Onset = -9.0 years



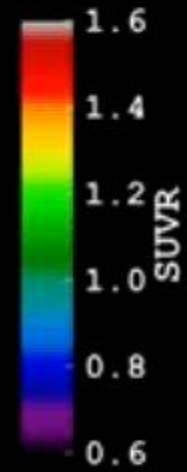
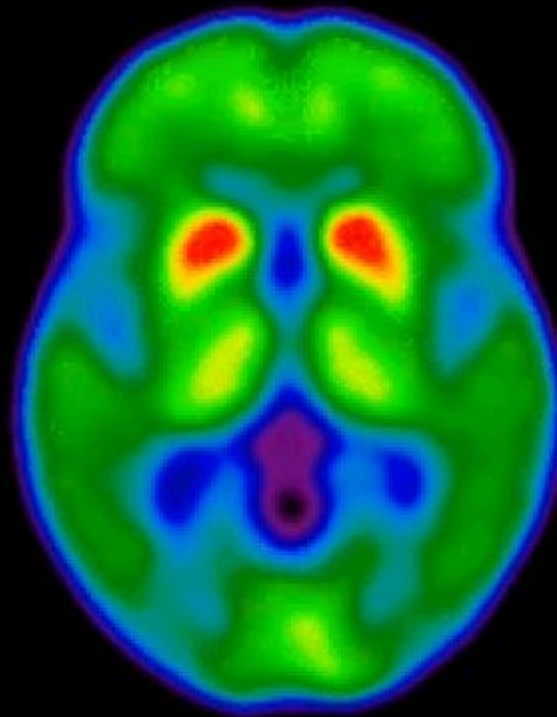
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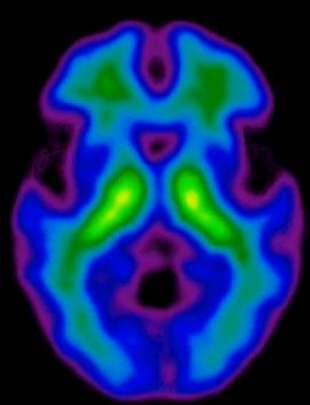
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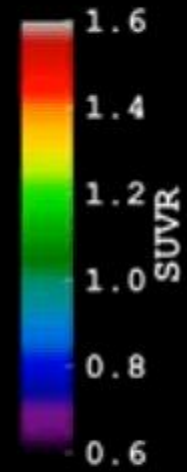
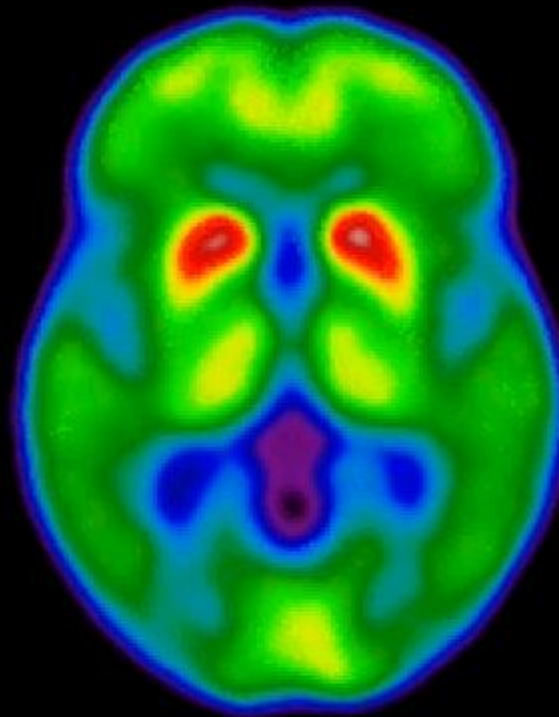
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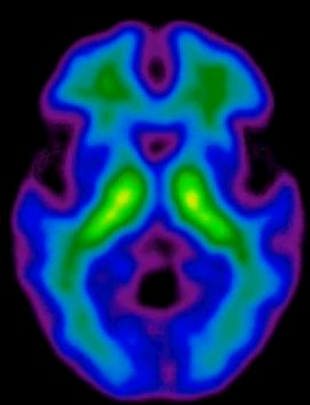
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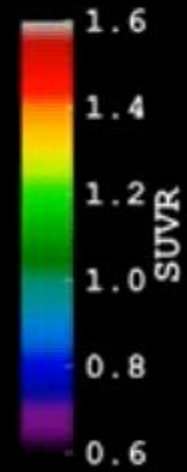
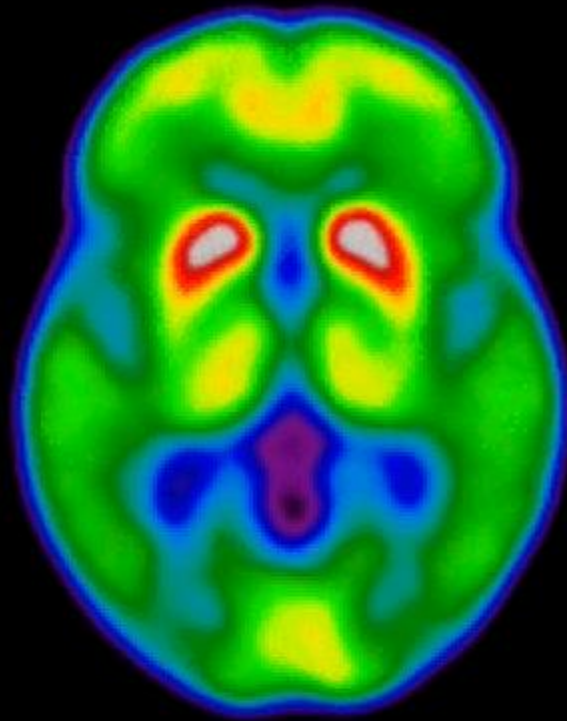
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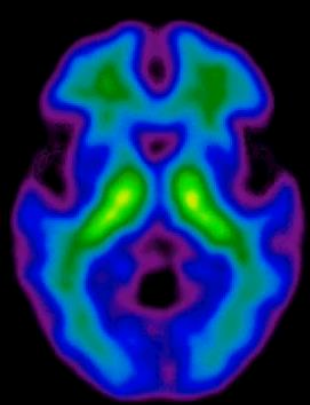
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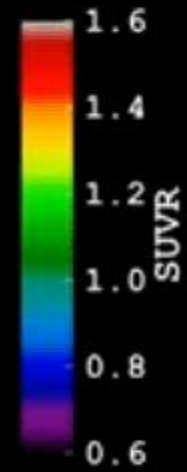
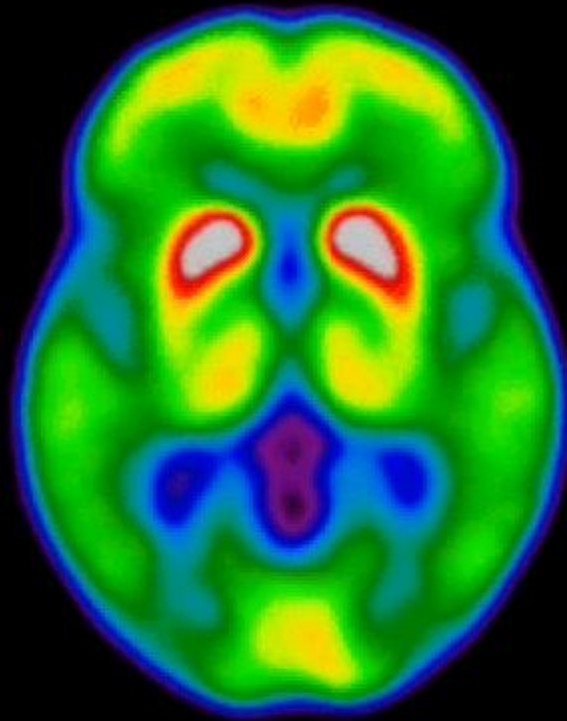
-25.0 years



Estimated Years to Onset = -5.0 years

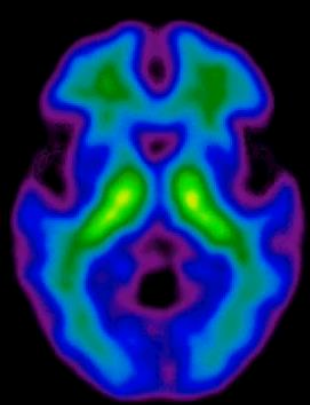


-25.0 years

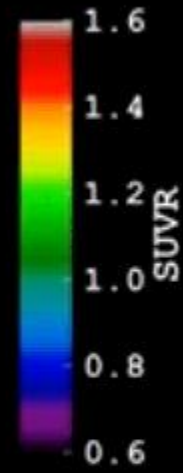
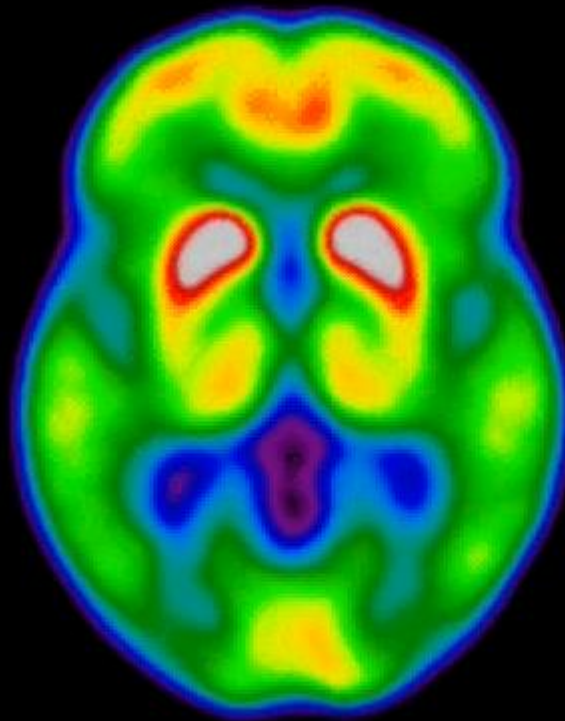


Estimated Years to Onset = -4.0 years

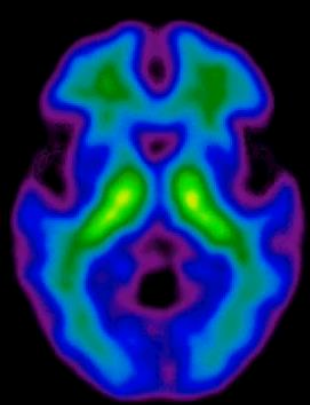




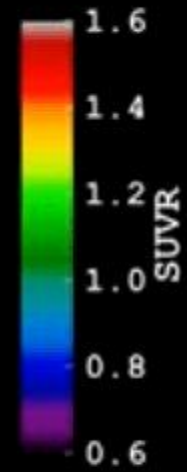
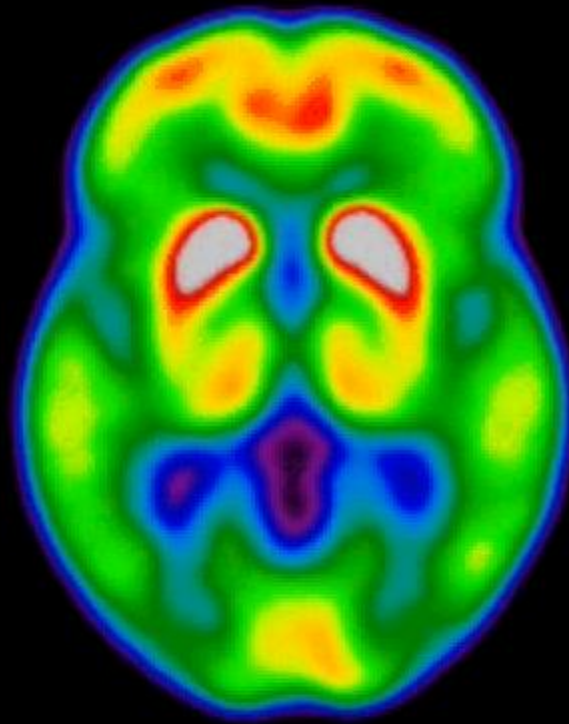
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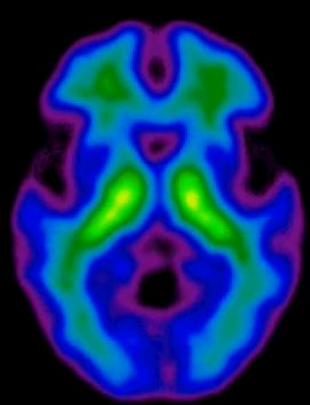
Estimated Years to Onset = -3.0 years



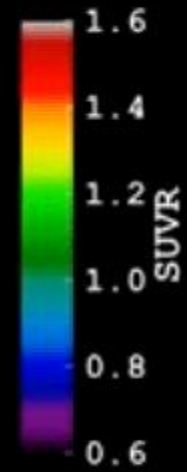
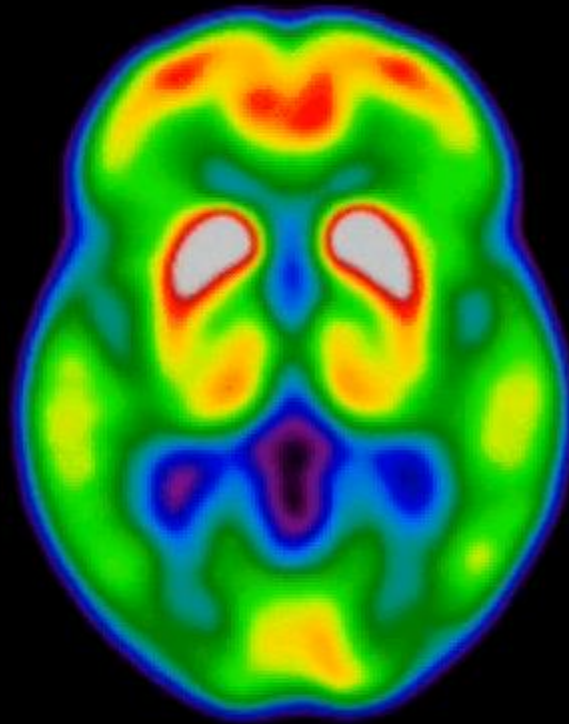
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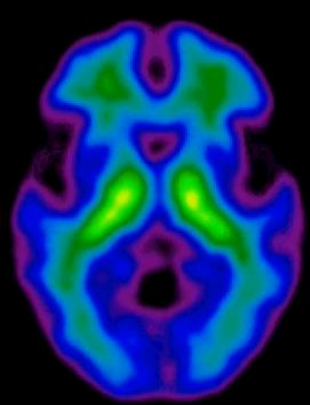
Estimated Years to Onset = -2.0 years



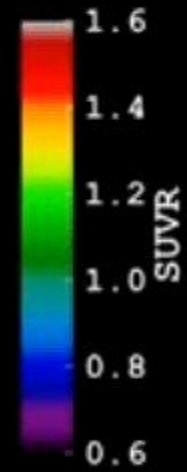
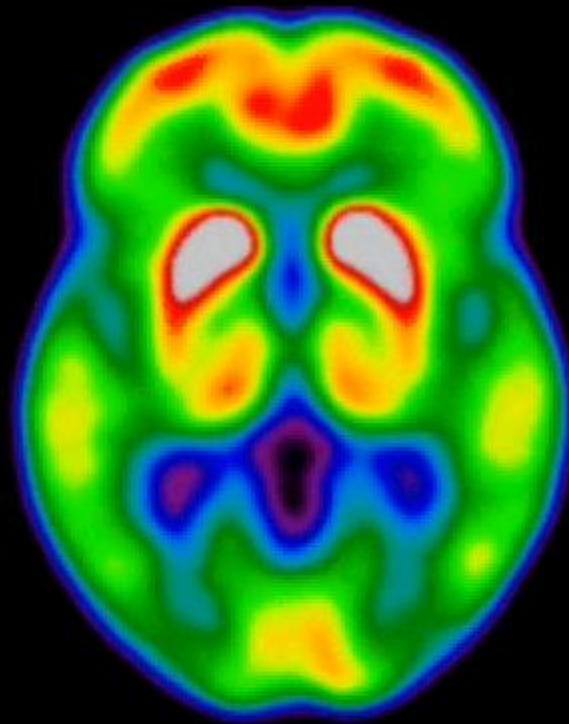
-25.0 years



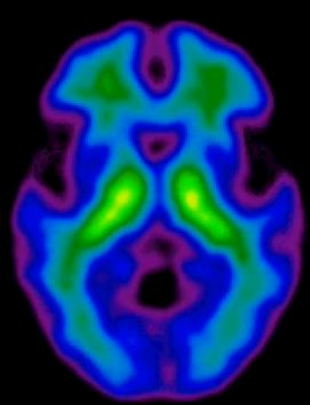
Estimated Years to Onset = -1.0 years



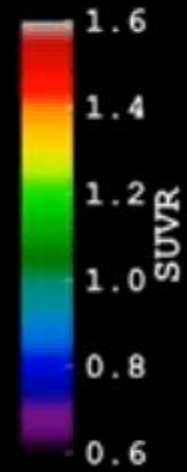
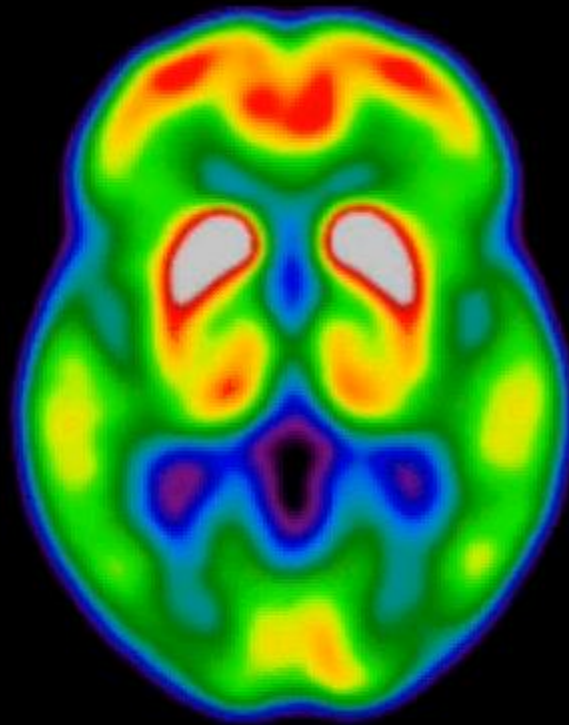
-25.0 years



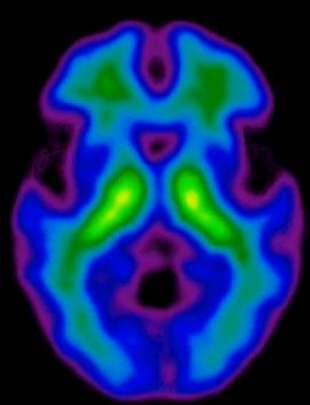
Estimated Years to Onset = -0.0 years



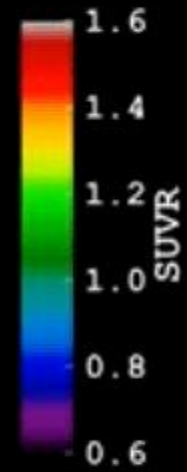
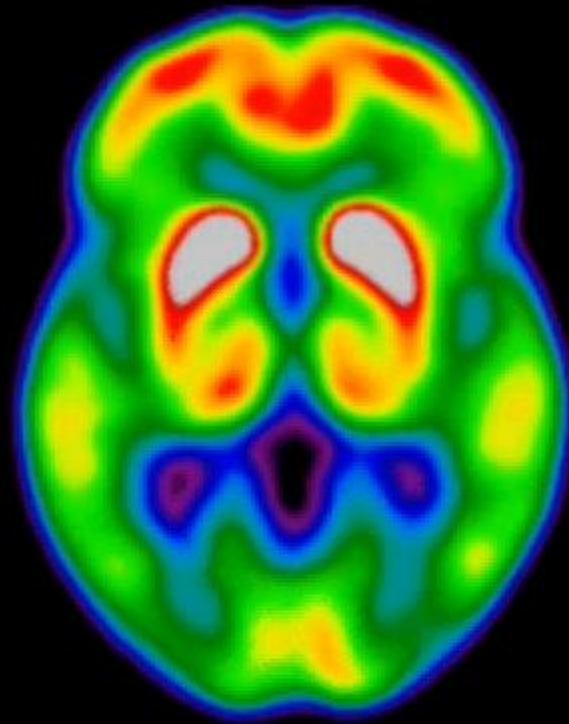
-25.0 years



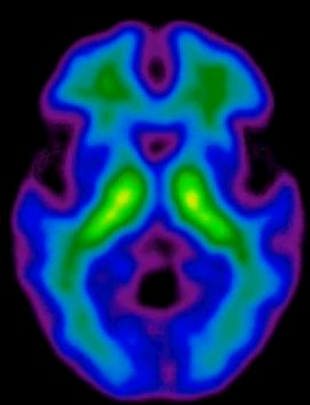
Estimated Years to Onset = +1.0 years



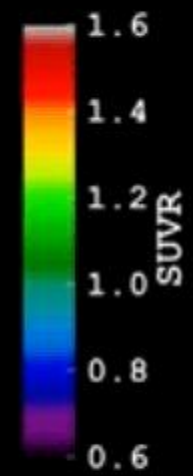
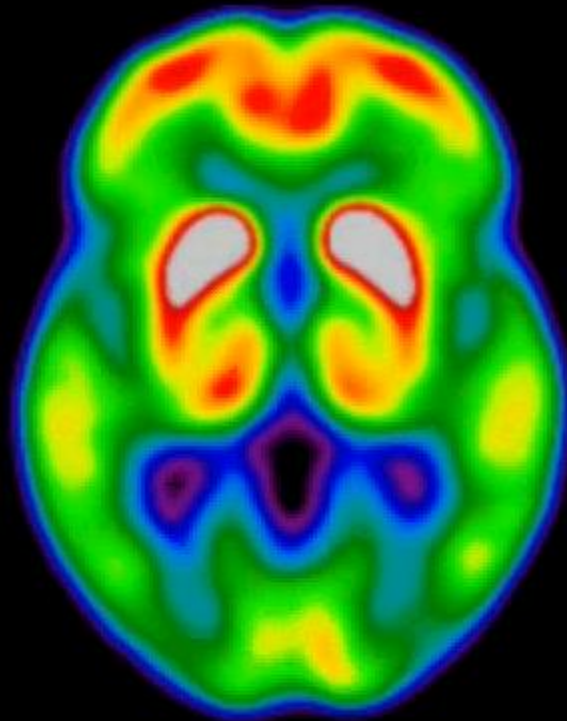
-25.0 years



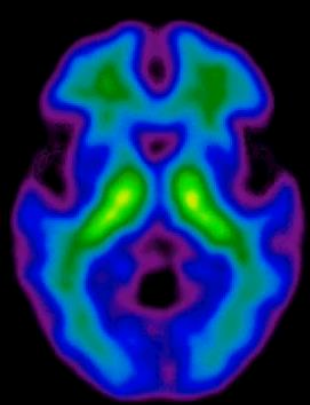
Estimated Years to Onset = +2.0 years



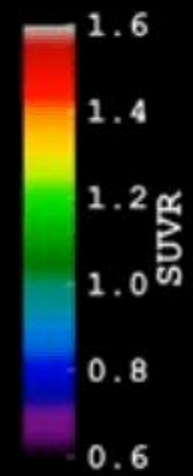
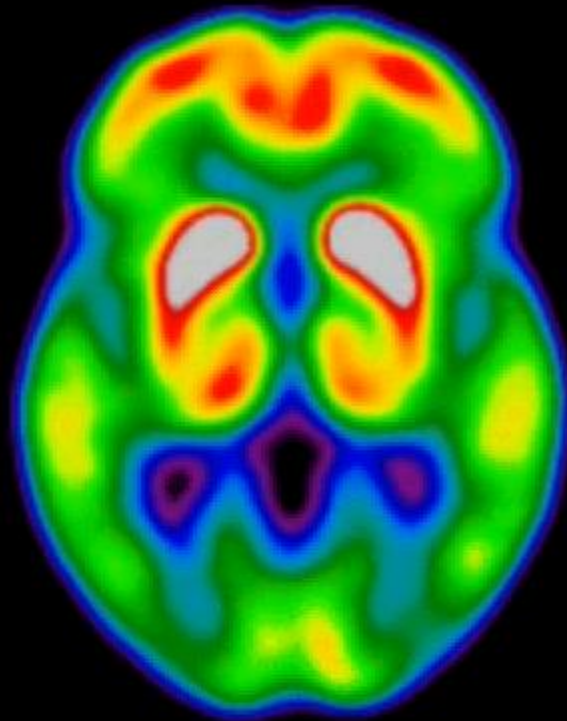
-25.0 years



Estimated Years to Onset = +3.0 years

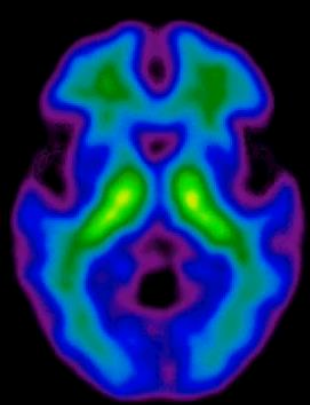


-25.0 years

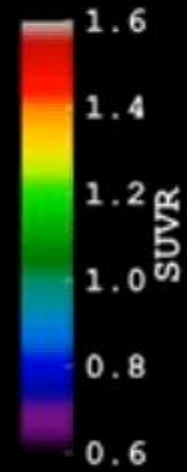
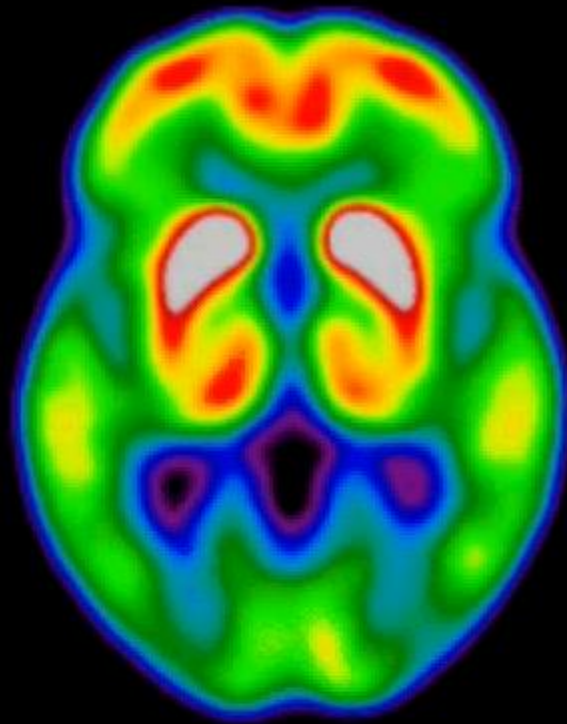


Estimated Years to Onset = +4.0 years

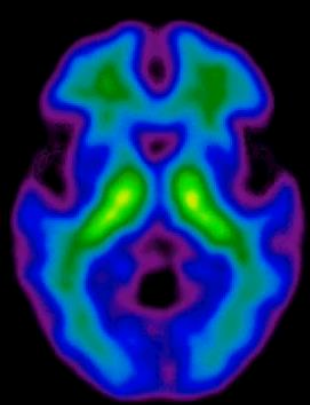




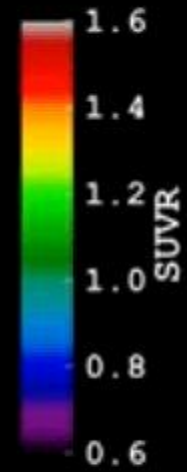
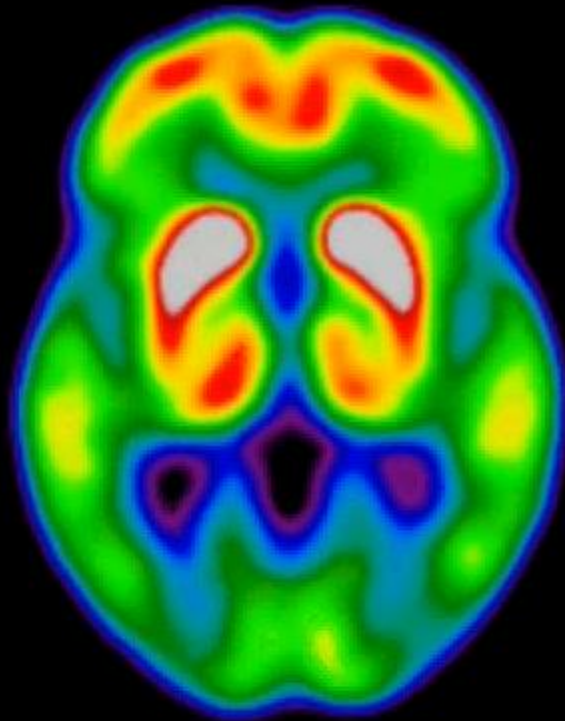
-25.0 years



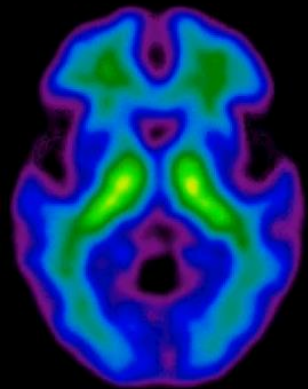
Estimated Years to Onset = +5.0 years



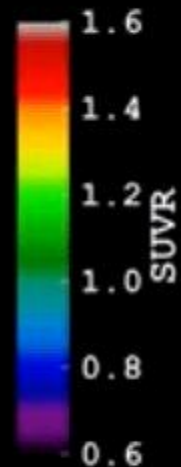
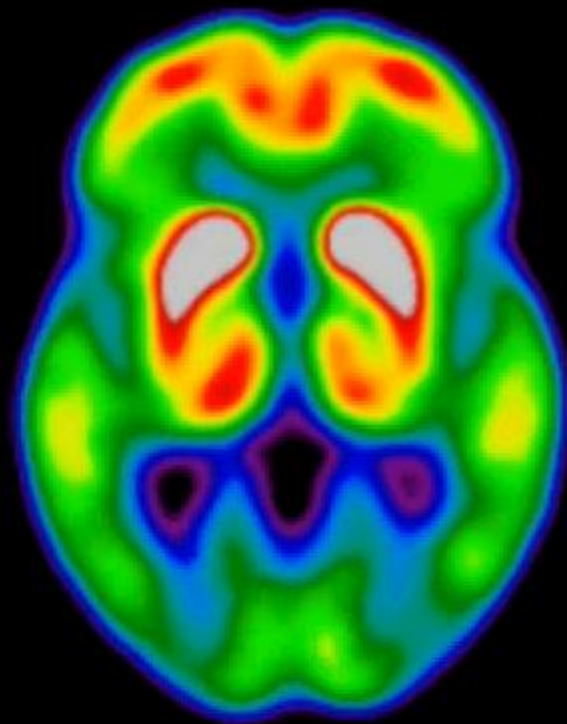
-25.0 years



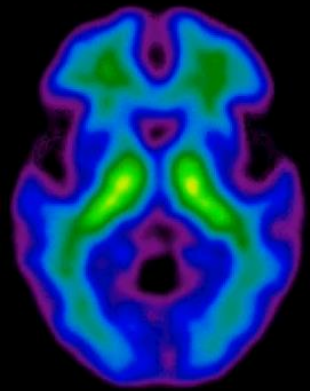
Estimated Years to Onset = +6.0 years



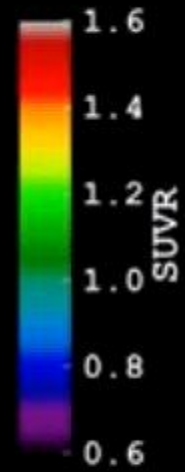
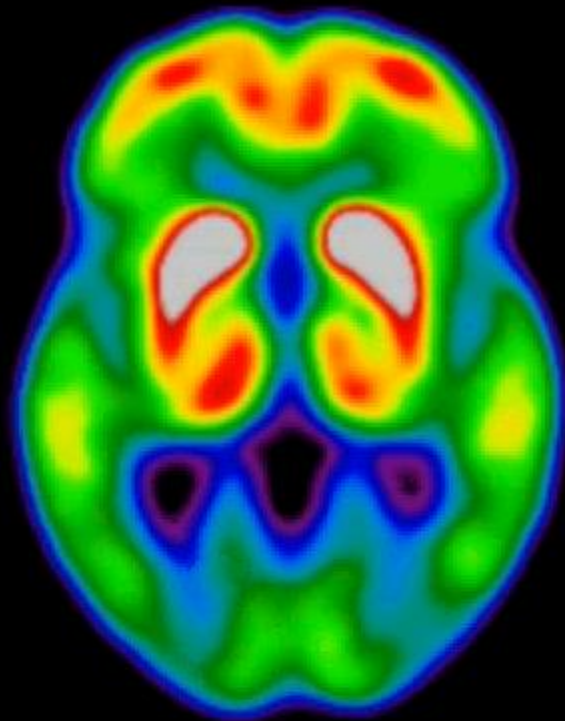
-25.0 years



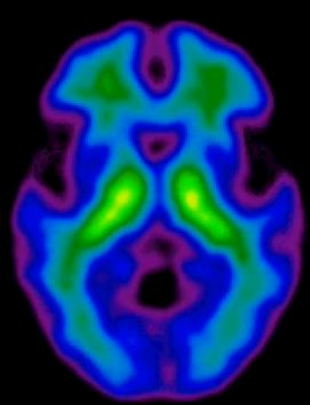
Estimated Years to Onset = +7.0 years



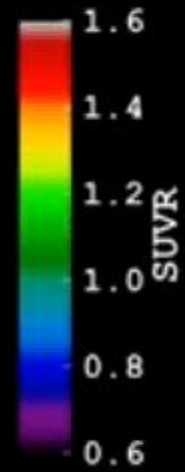
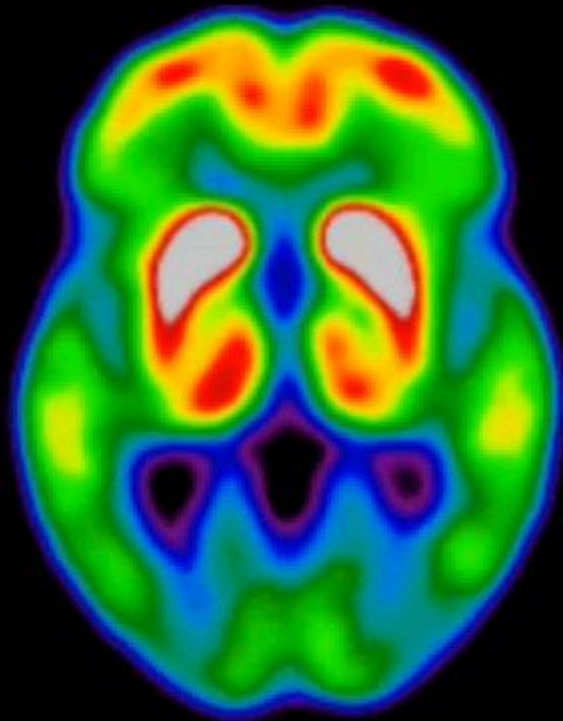
-25.0 years



Estimated Years to Onset = +8.0 years

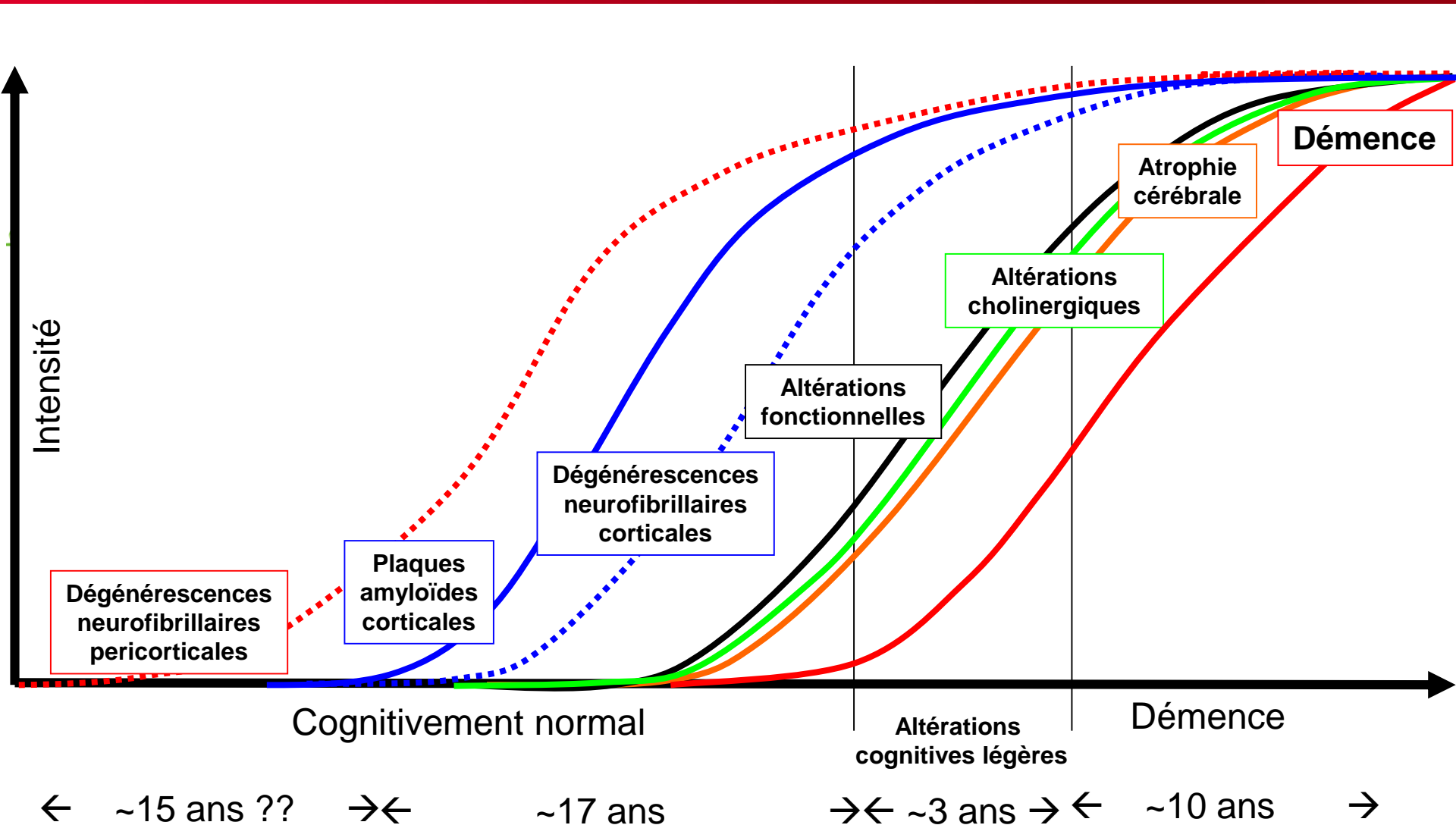


-25.0 years

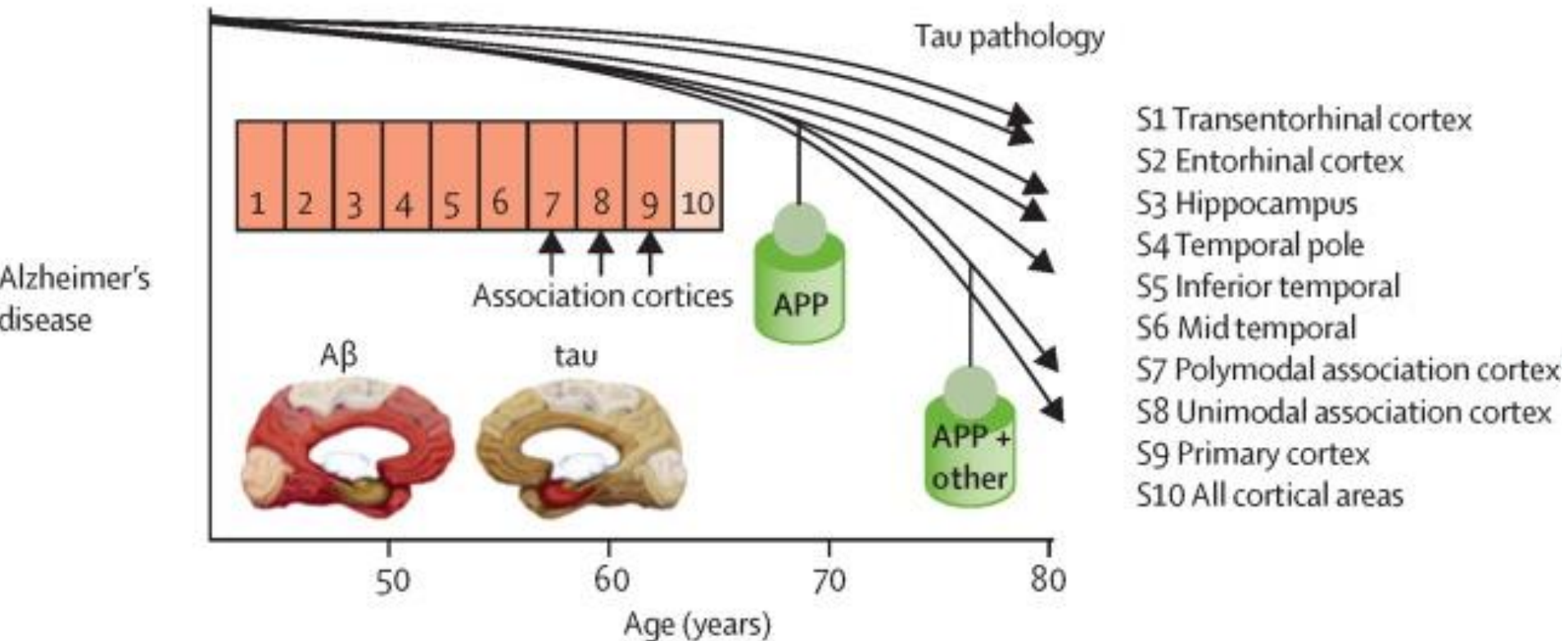


Estimated Years to Onset = +9.0 years

# HISTOIRE NATURELLE DE LA MALADIE



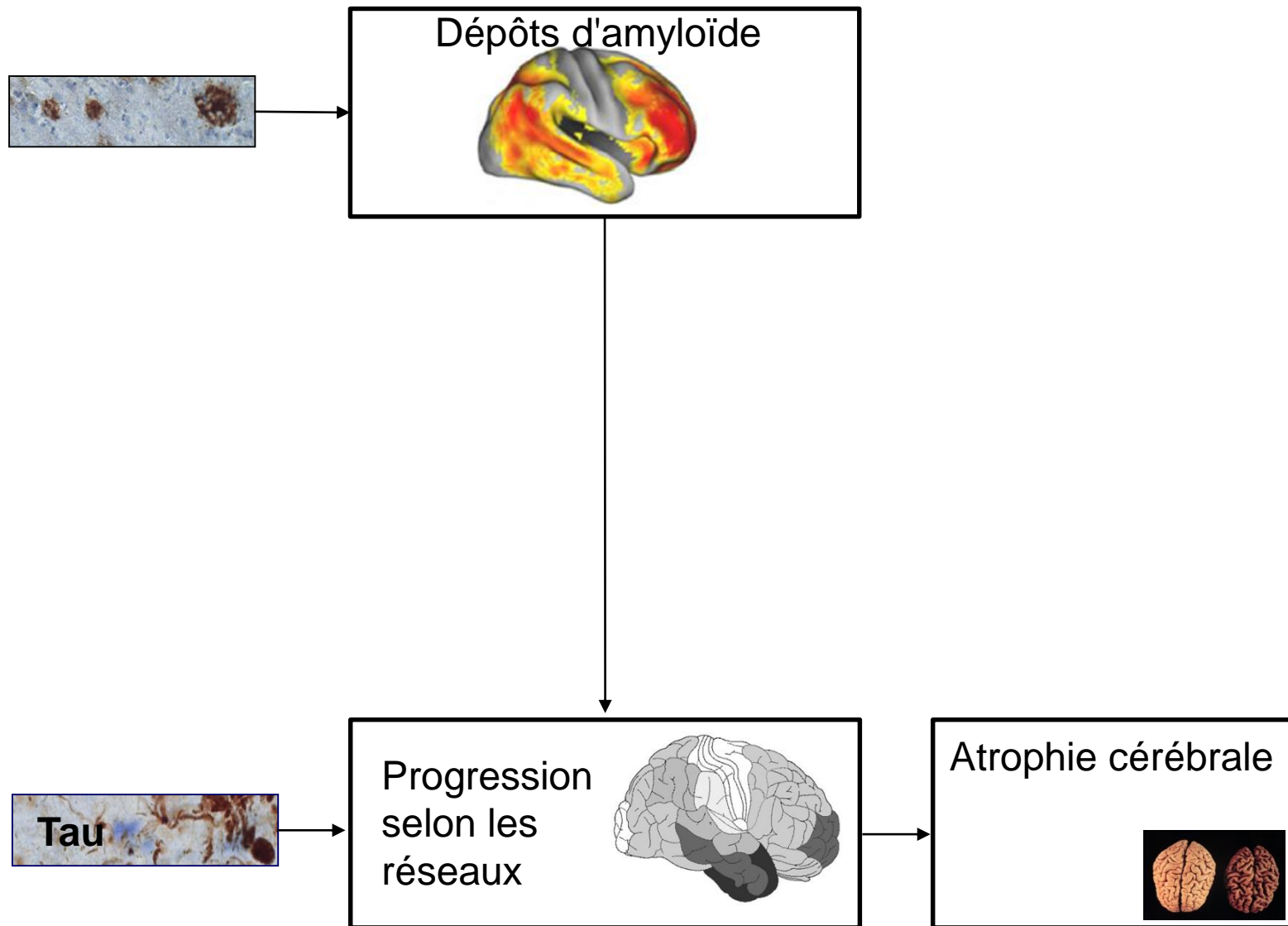
# VISION INTEGREEE DE LA MALADIE D'ALZHEIMER



Villemagne, V. L. (2015). Lancet Neurology **14(1)**: 114-124.  
Concept initially proposed by A. Delacourte

# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

## Hypothèse explicative



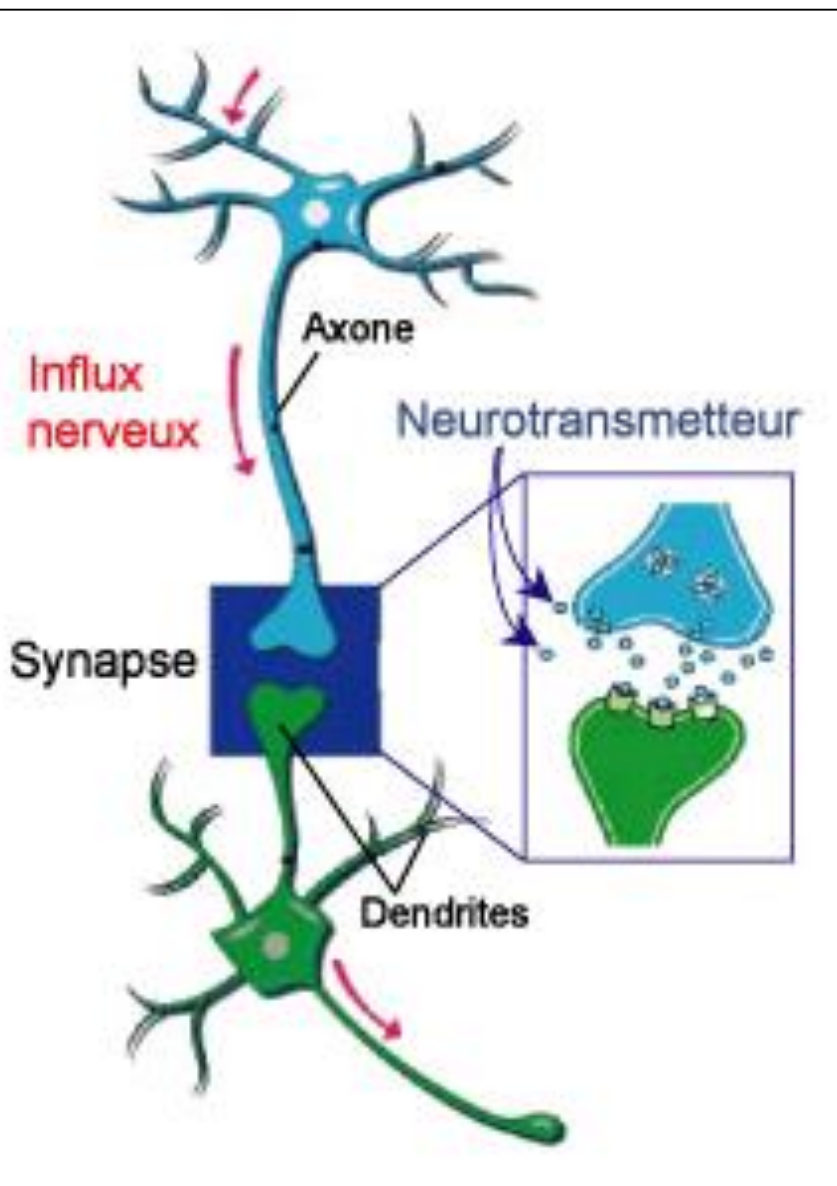




# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Atteintes synaptiques**  
**Atteinte des neurotransmetteurs**

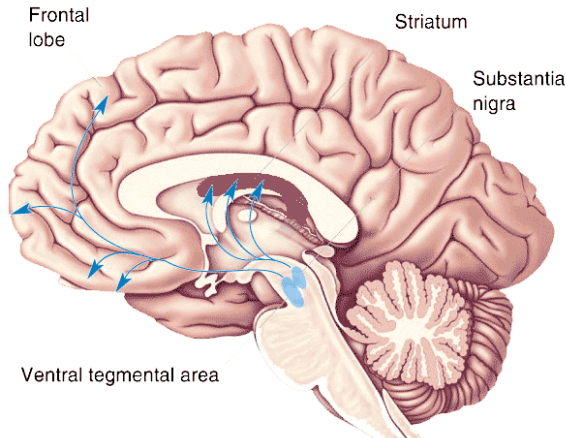
# ATTEINTE DES NEUROTRANSMETTEURS



- Substances chimiques libérées dans la jonction synaptique
- Permettent à l'influx nerveux de passer d'un neurone à l'autre

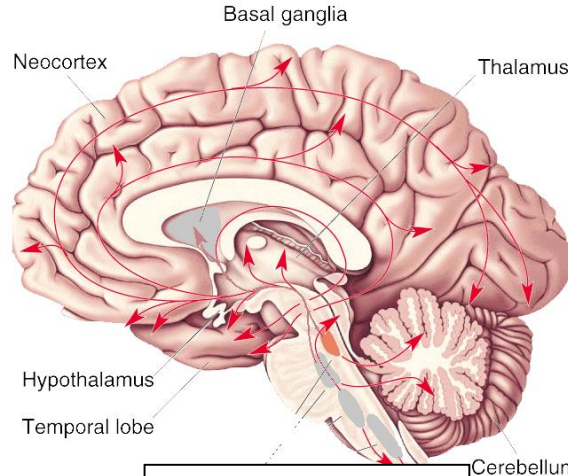
# ATTEINTE DES NEUROTRANSMETTEURS

Dopamine system



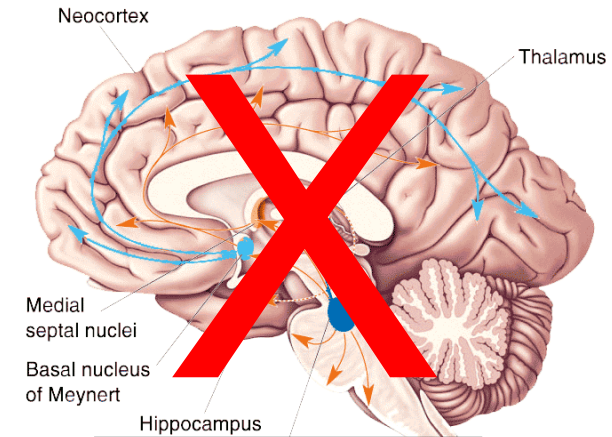
Dopamine

Serotonin system



Serotonine

Acetylcholine system



Acetylcholine

Atteinte prioritaire des neurones à acétylcholine (cholinergiques)

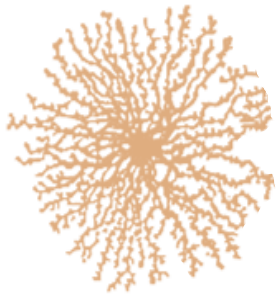


# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**N'oublions pas les voisins...**

# INDUCTION ET DIFFUSION DE LA PATHOLOGIE TAU

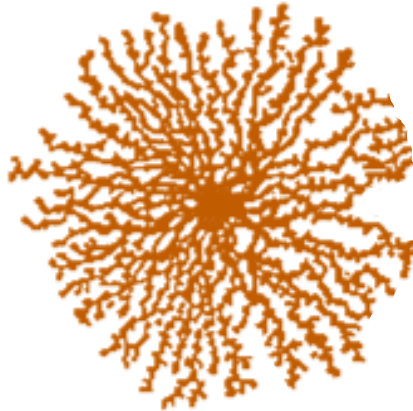
Astrocyte normal



Alzheimer



Astrocyte réactif

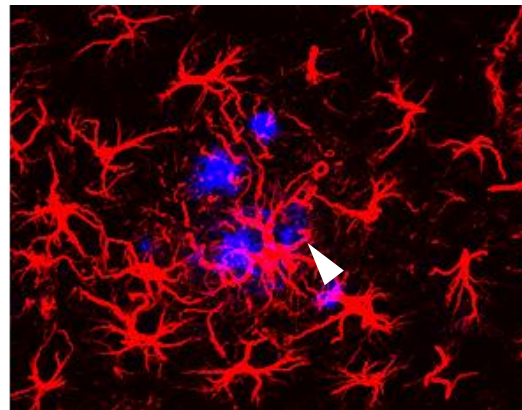
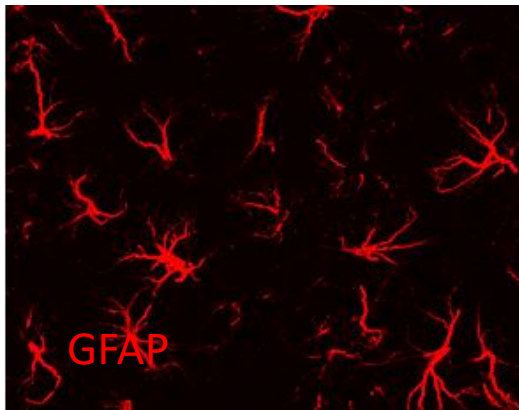


**Réduction de la réactivité astrocytaire**

Module le dépôt de plaques amyloïdes  
Améliore des troubles cognitifs  
Restore les déficits synaptiques

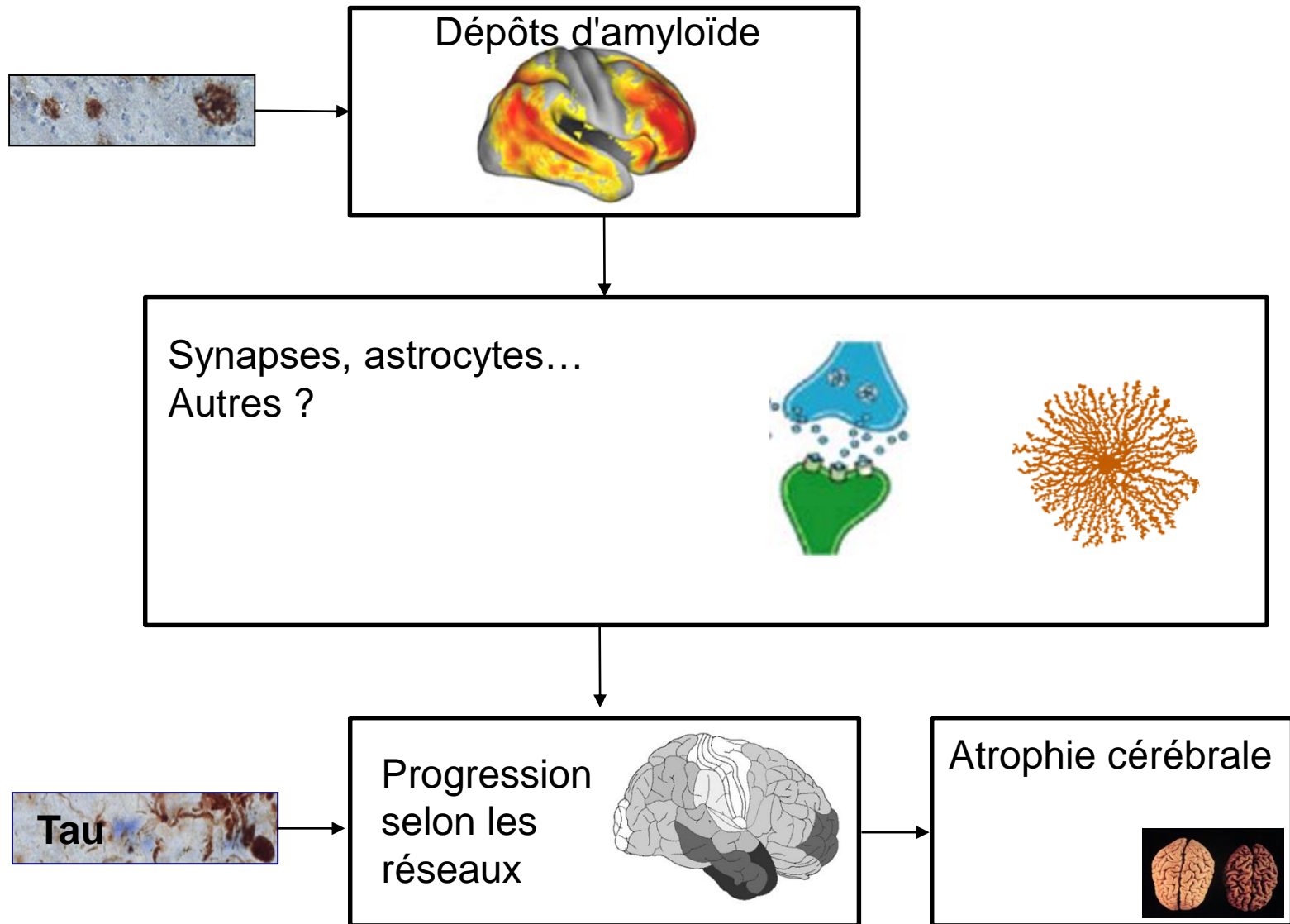
Contrôle

Alzheimer



# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

## Hypothèse explicative

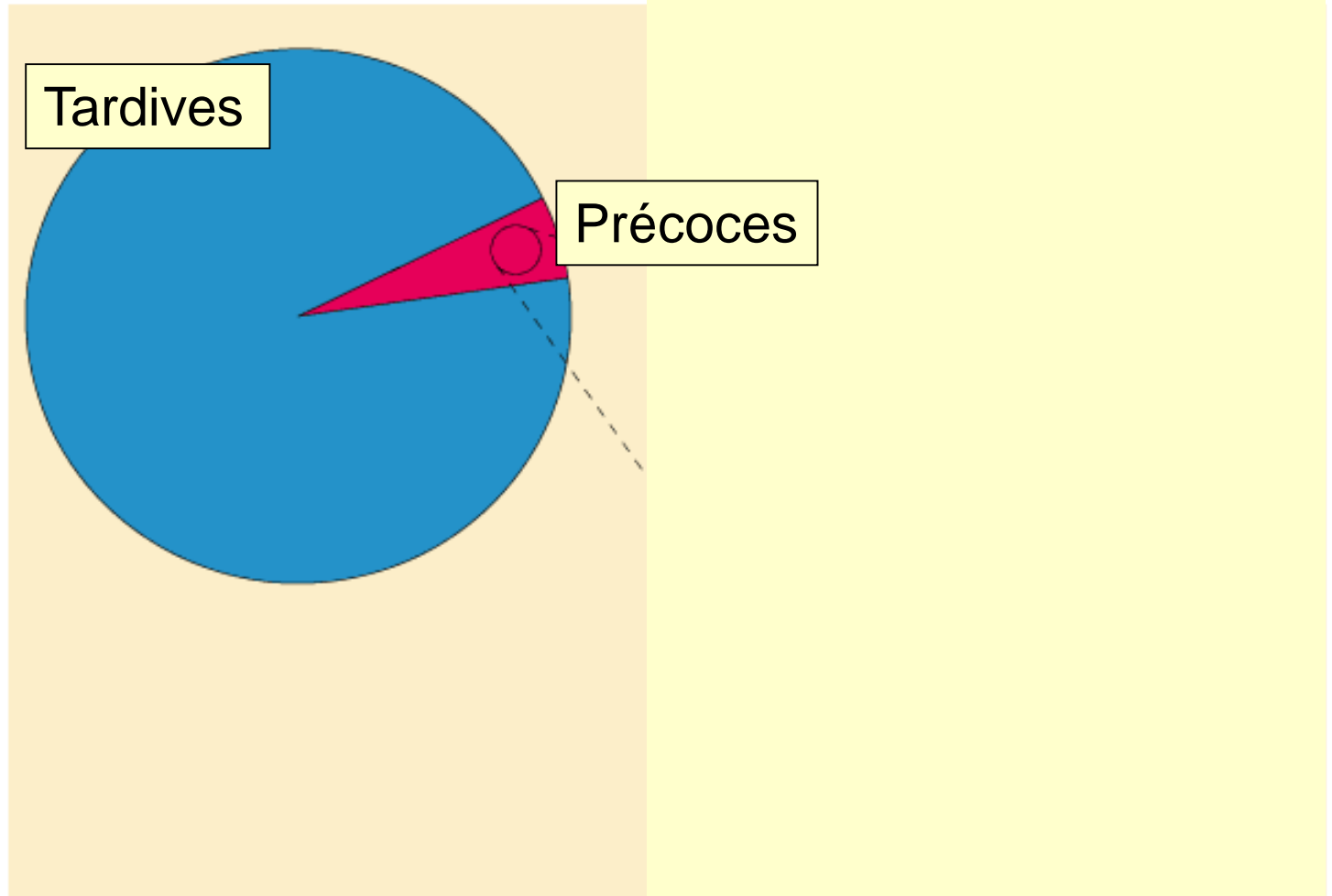




# LES CAUSES DE LA MALADIE D'ALZHEIMER?

**Quelques causes avérées**  
**Beaucoup de facteurs de risque**  
**Et encore plus d'éléments qu'on ne comprend pas**

# DE RARES FACTEURS GÉNÉTIQUES DÉTERMINANTS



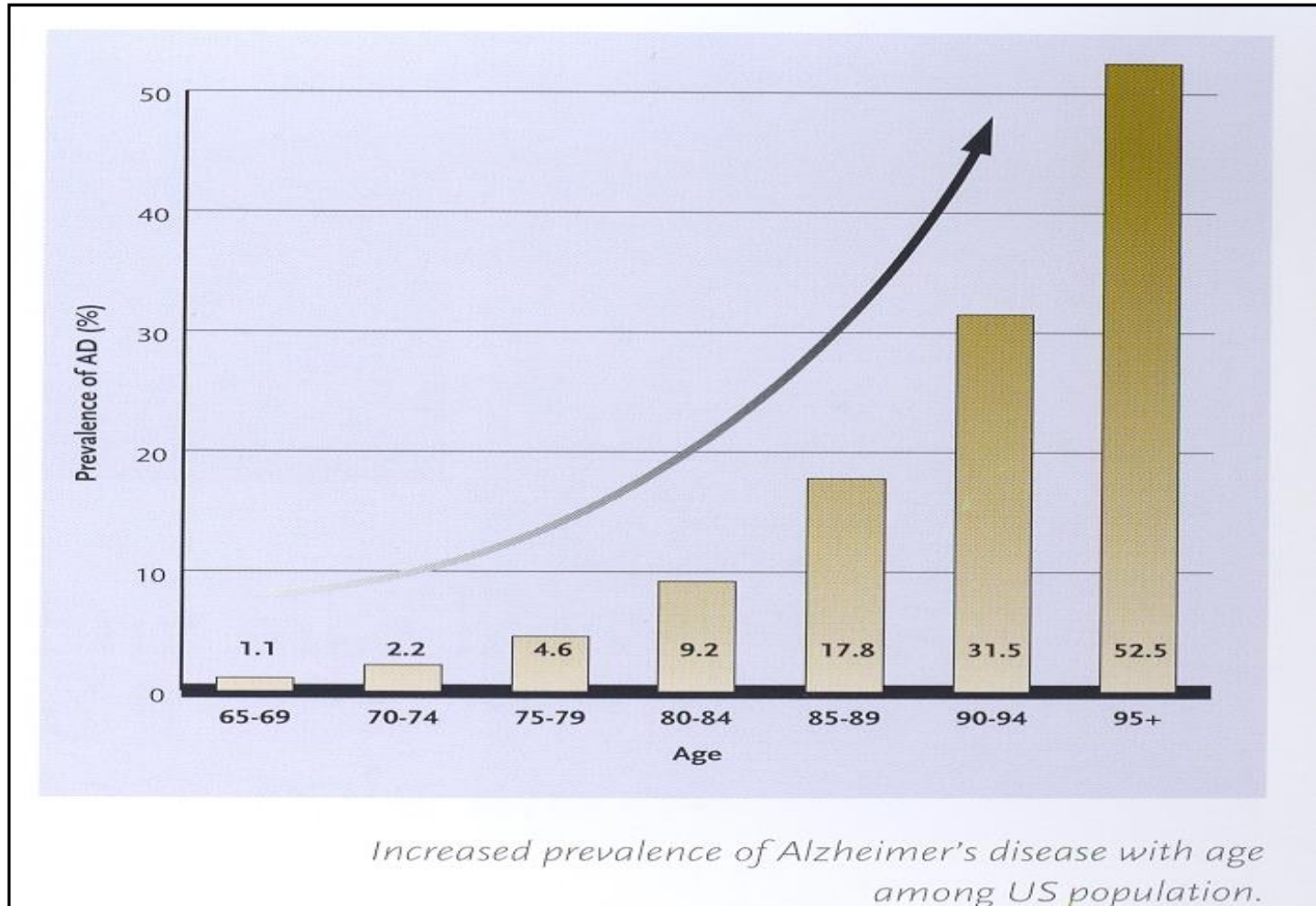
→ Rôle important de la pathologie amyloïde dans la maladie



# DE NOMBREUX FACTEURS DE RISQUE



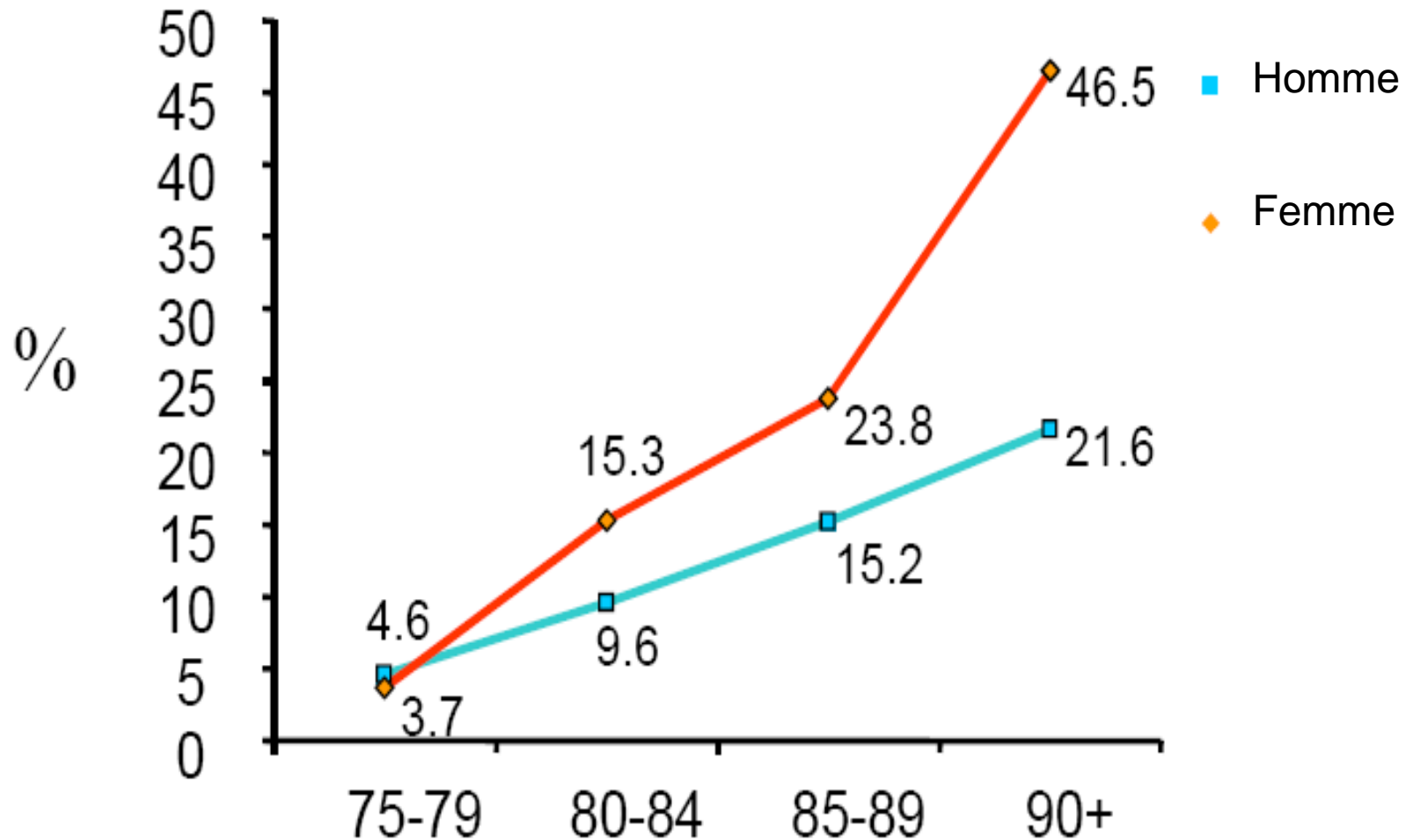
## 1er Facteur de risque : l'âge



# DE NOMBREUX FACTEURS DE RISQUE



## Sexe



# FACTEURS DE RISQUES ÉVITABLES



Dépression : x1.90



Inactivité physique : x1.82



Hypertension à âge intermédiaire : x1.61

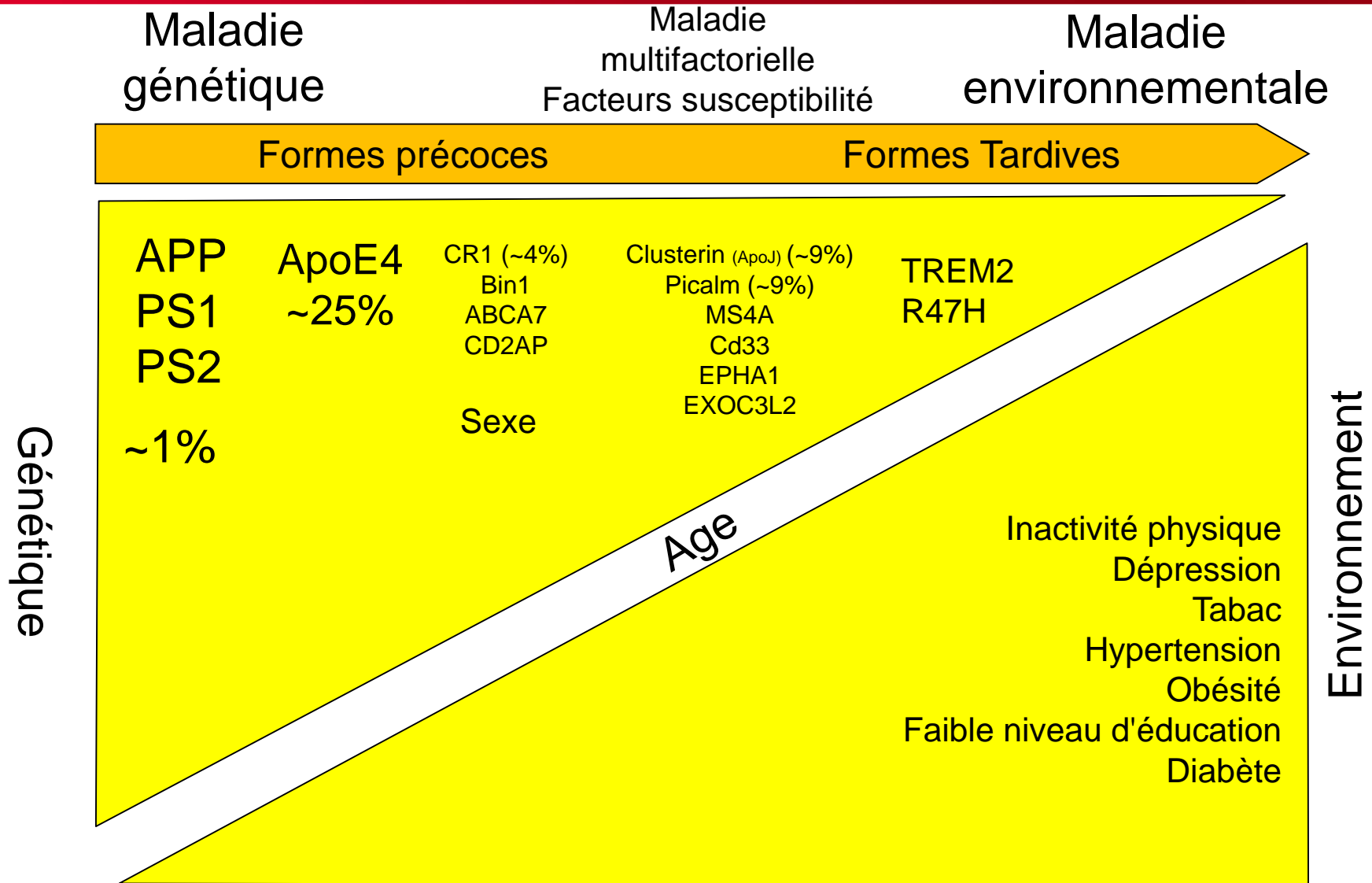
Obésité à âge intermédiaire : x1.60

Tabagisme : x1.59

Faible éducation : x1.59

Diabète : x1.39

# FACTEURS DE RISQUES ET DE SUSCEPTIBILITÉ



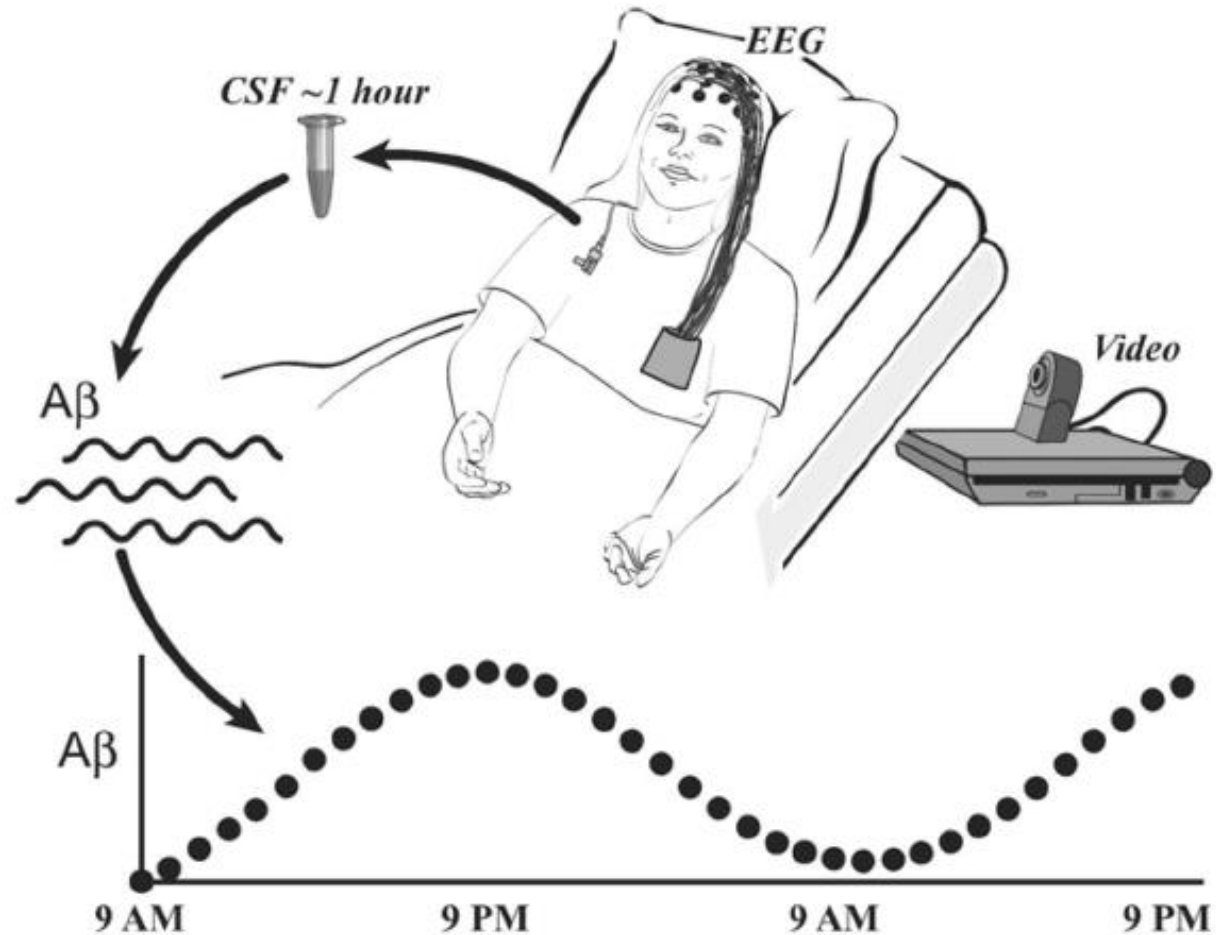


# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Modulateurs de la synthèse d'amyloïde**

# SÉCRÉTION D'AMYLOÏDE

## Variations journalières

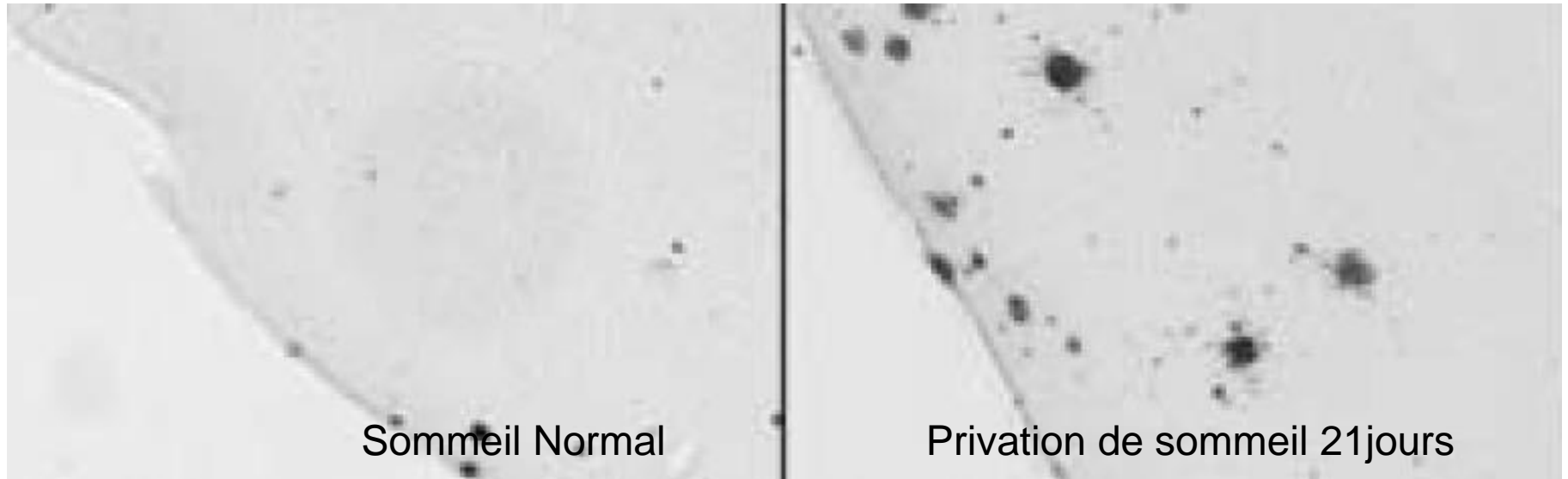


Huang, 2012

La sécrétion d'amyloïde fluctue dans la journée

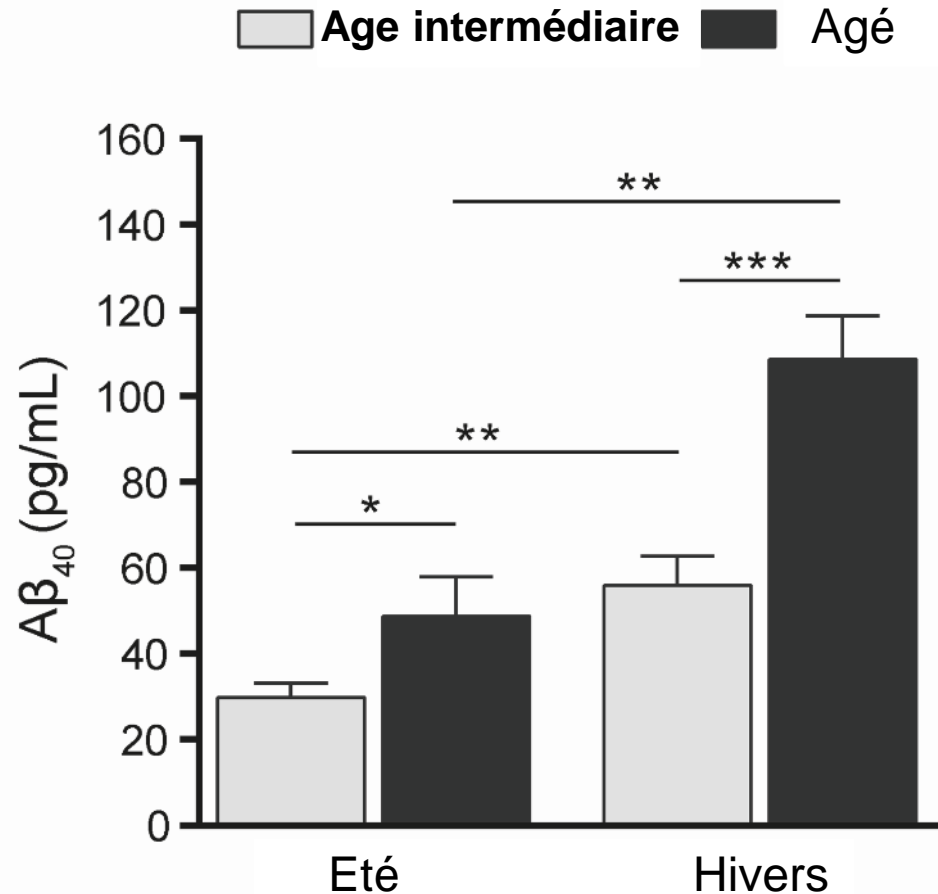
- Monte le jour
- Baisse la nuit

# DÉPÔT D'AMYLOÏDE AUGMENTE QUAND PRIVATION DE SOMMEIL



# SÉCRÉTION D'AMYLOÏDE

## Variations saisonnières



La sécrétion d'amyloïde fluctue au cours des saisons





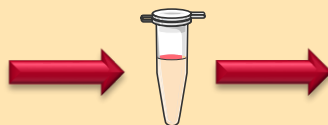
# HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

**Transmissibilité ?**

# Inoculation intracérébrale d'extraits de cerveaux Alzheimer



Cerveau Alzheimer

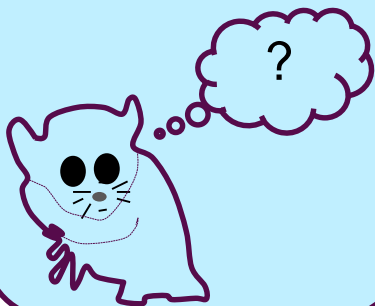


Homogénat



Modèle

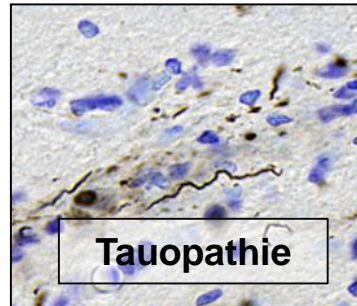
## Pertes de mémoire



## Lésions microscopiques typiques de la maladie d'Alzheimer



Amylose



Tauopathie

## Pertes neuronales Atrophie du cerveau



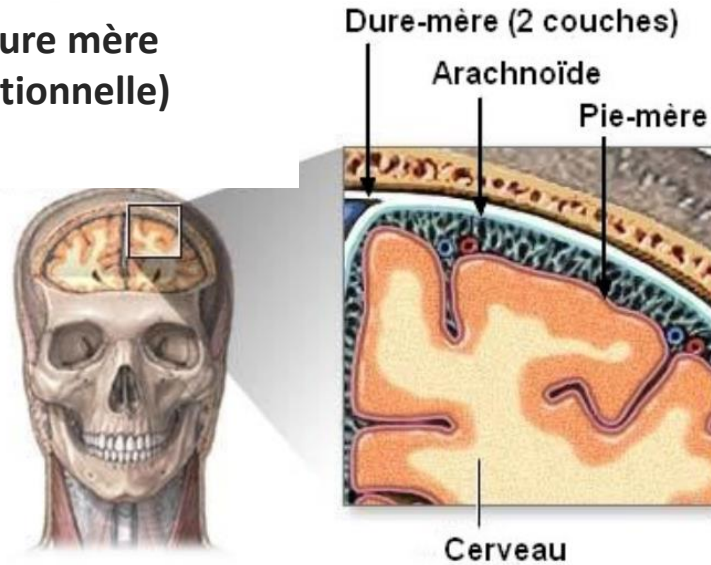
Perte communication entre neurones

= Induction d'une maladie neurodégénérative

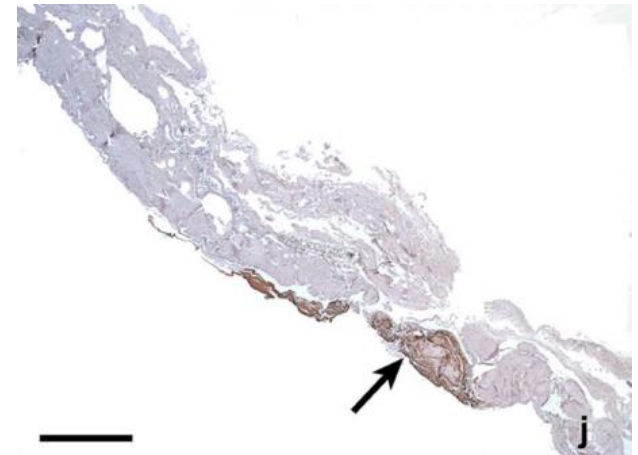
# REALITÉ DE LA TRANSMISSION DES LESIONS DE LA MALADIE D'ALZHEIMER

Exemple des greffes de dure mère (réalisées de façon exceptionnelle)

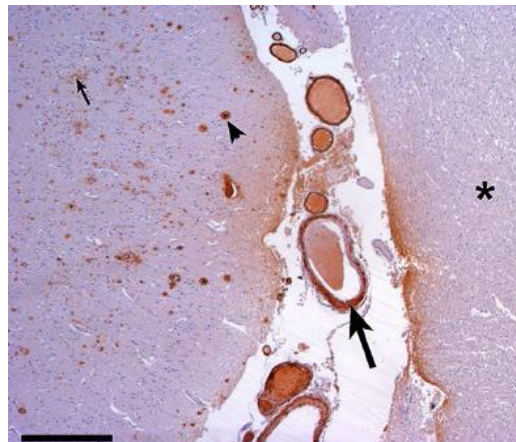
Greffe à l'âge de 2 ans  
Mort à 46 ans  
Hémorragies cérébrales répétées



Amyloïde au niveau de la greffe



Amyloïde vasculaire



		1	5	10	15	20	25	30	35	40	45	50	55
Patient 1	#1												
Patient 2	#2												
Patient 3	#3												
Patient 4	#4												
Ehling et al [15]	#5												
Purrucker et al [39]	#6												
Purrucker et al [39]	#7												
Nakayama et al [36]	#8												

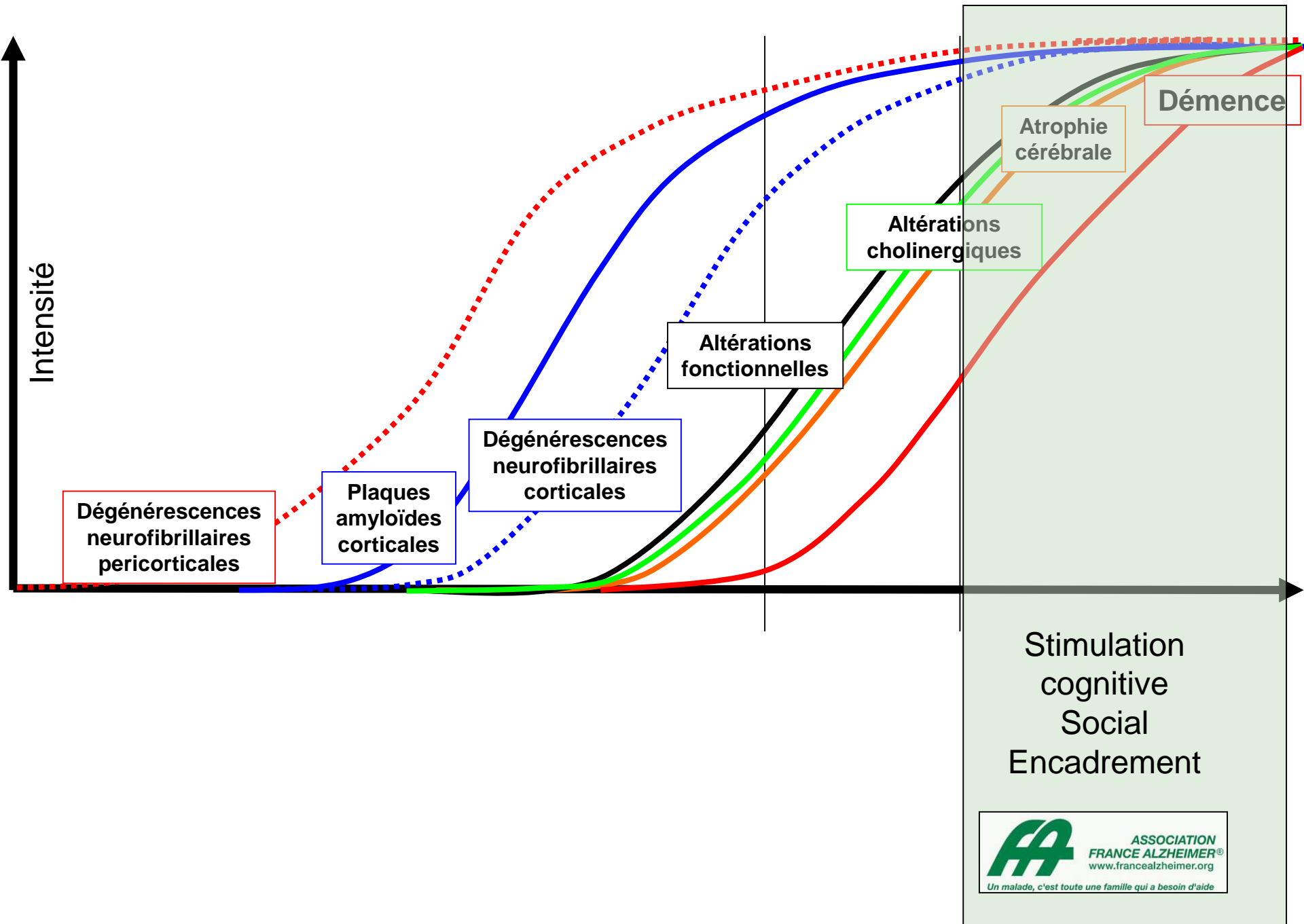
~10 patients décrits

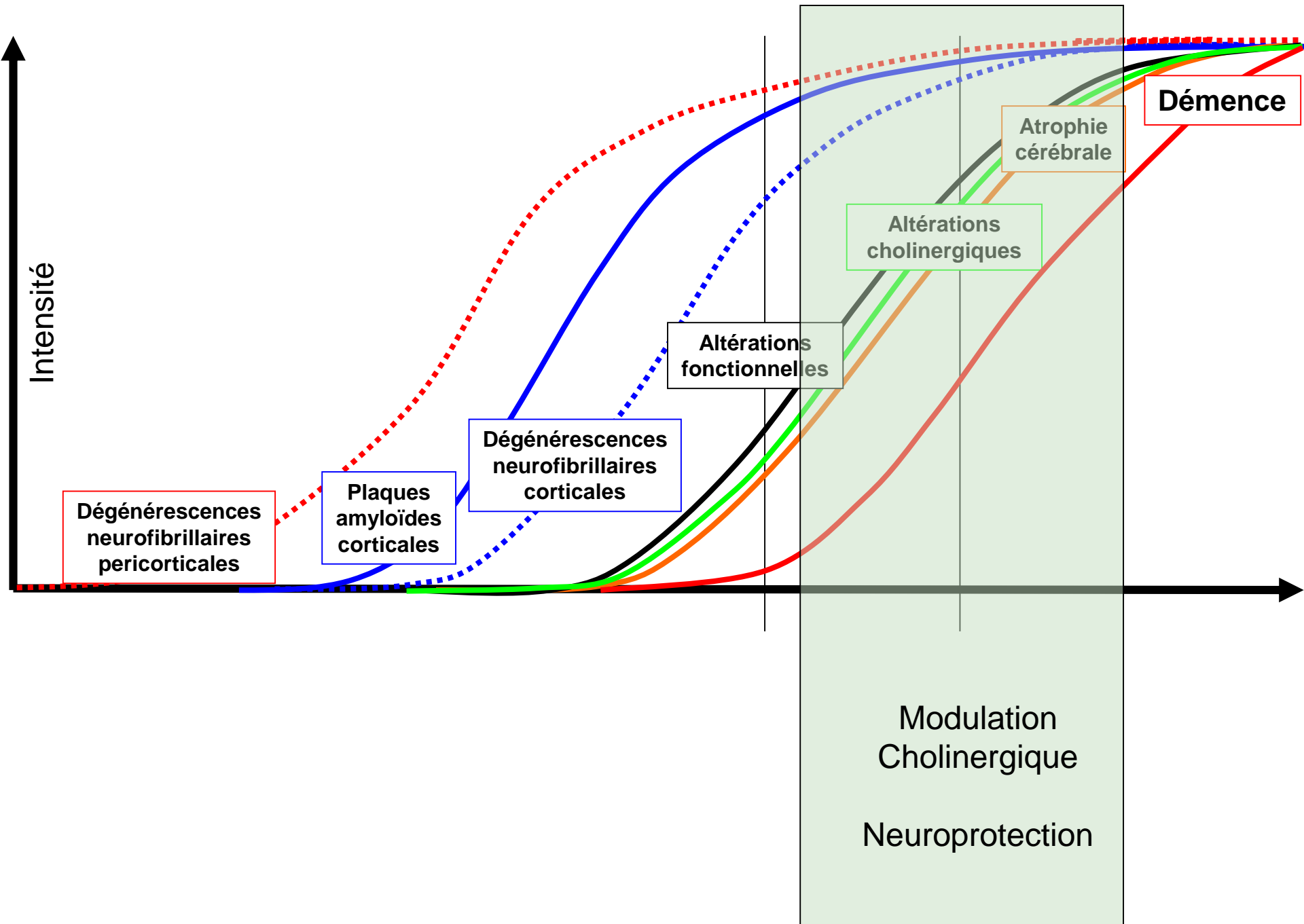
Versus 50 millions de patients Alzheimers dans le monde



# THÉRAPIES CONTRE LA MALADIE

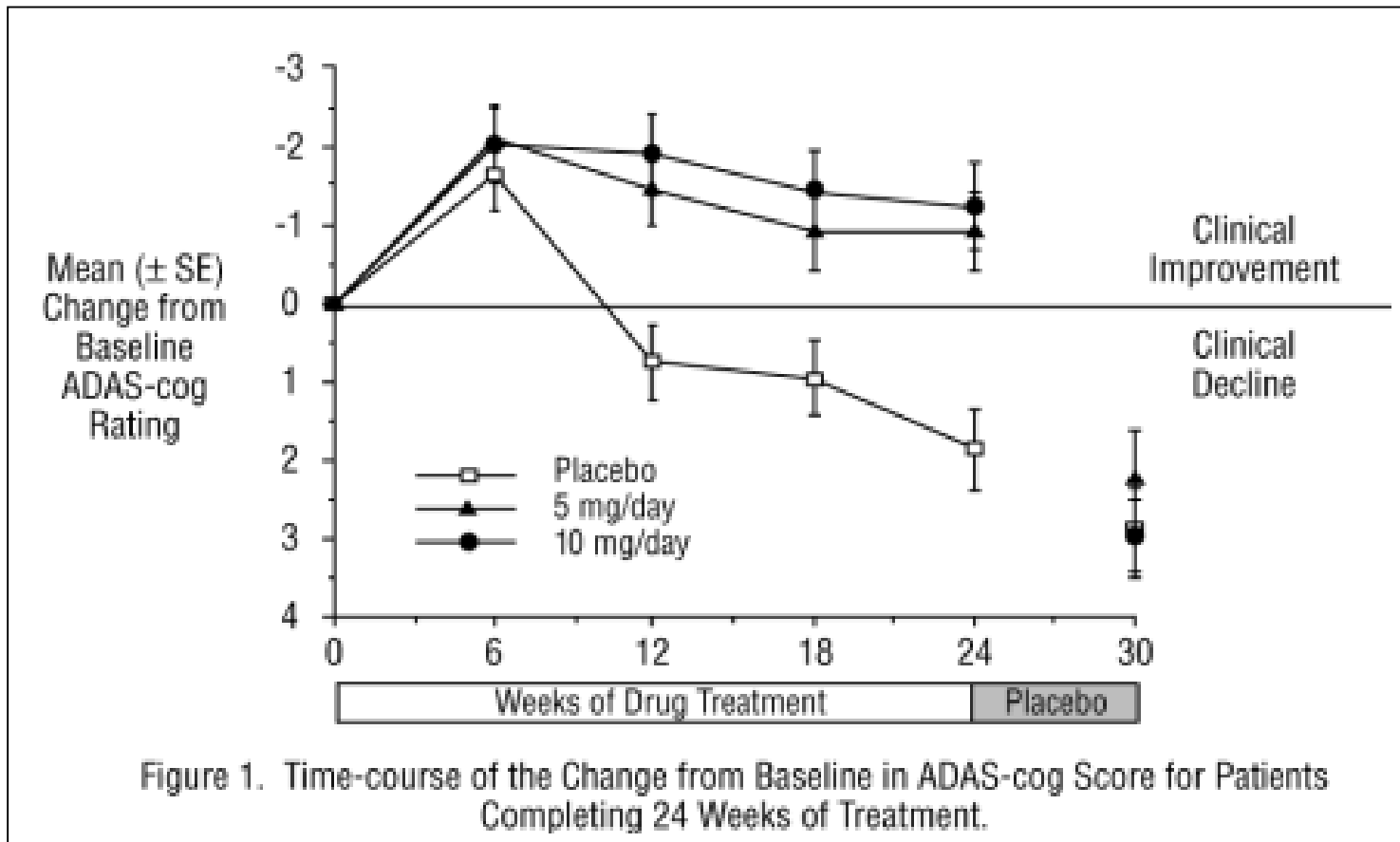
Dépend du stade de la maladie





# TRAITEMENTS ACTUELS DE LA MALADIE

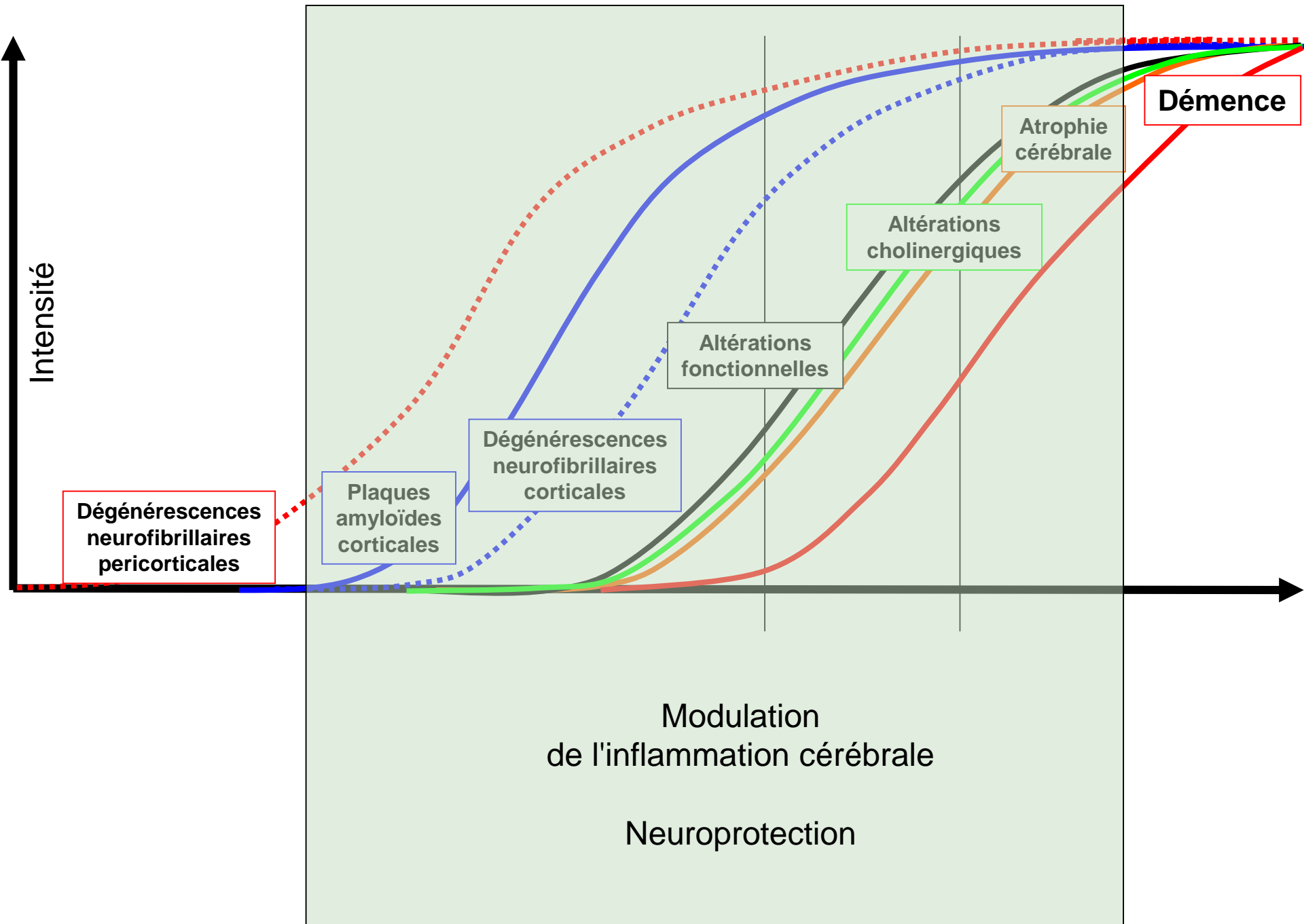
Effet typique du traitement sur les capacités mnésiques  
Exemple de Donepezil (Aricept)



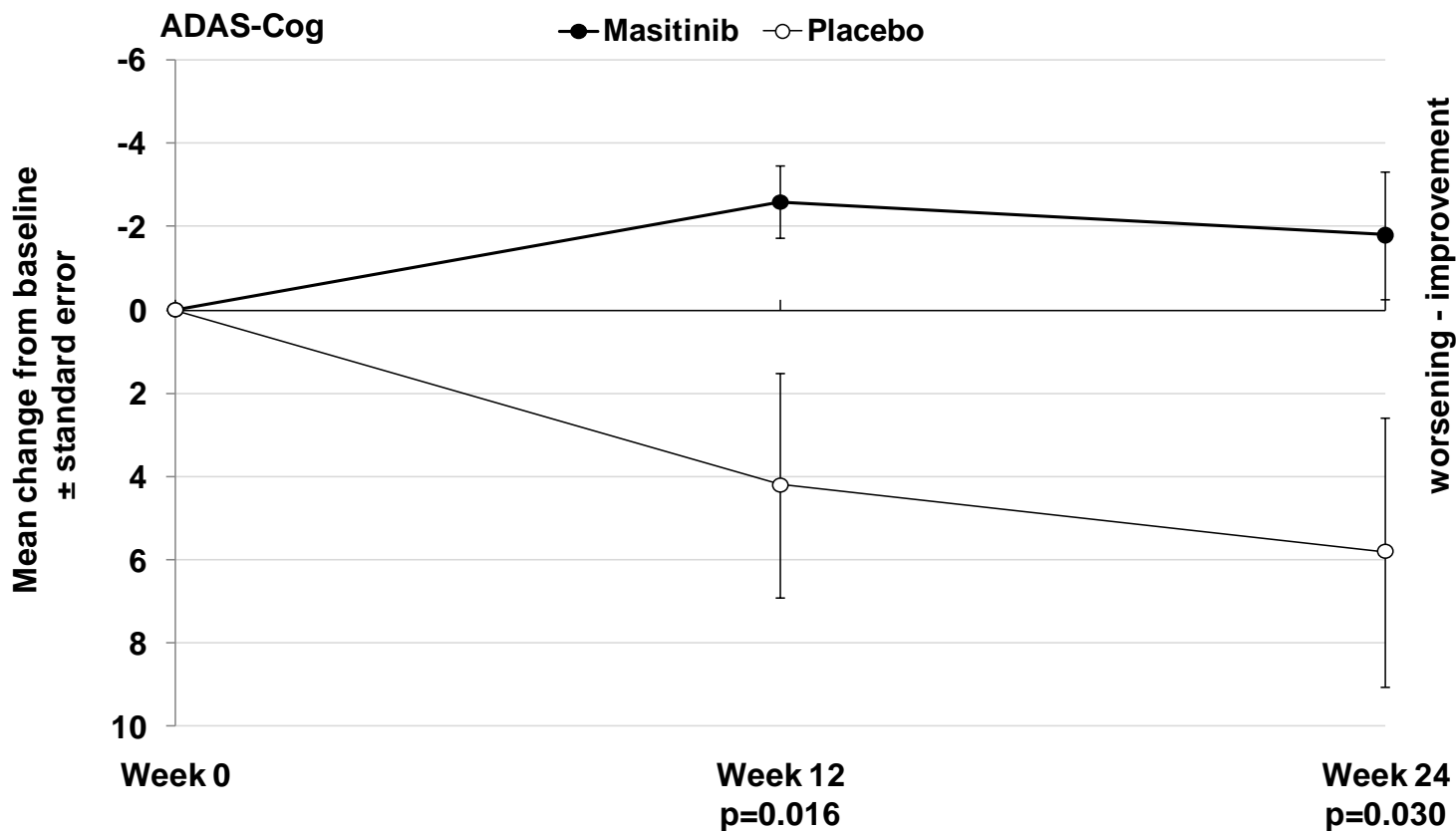
# TRAITEMENTS ACTUELS DE LA MALADIE

- Anticholinestérasiques
  - Donépézil ( [Aricept®](#)),
  - Galantamine ( [Reminyl®](#))
  - Rivastigmine ( [Exelon®](#)).
  
- Effets indésirables fréquents au niveau digestif (nausées, perte d'appétit, diarrhées).
  
- Antiglutamates
  - Mémantine ( [ebixa®](#)).
  - Patients plus avancés (stades modérément sévère à sévère)
  
- Réévaluation des médicaments HAS décembre 2011 :
  - un "faible intérêt" médical
  - [http://www.has-sante.fr/portail/jcms/c\\_1108356/medicaments-de-la-maladie-dalzheimer-la-has-revele-les-resultats-de-sa-reevaluation](http://www.has-sante.fr/portail/jcms/c_1108356/medicaments-de-la-maladie-dalzheimer-la-has-revele-les-resultats-de-sa-reevaluation)
  - Arrêt du remboursement en 2018

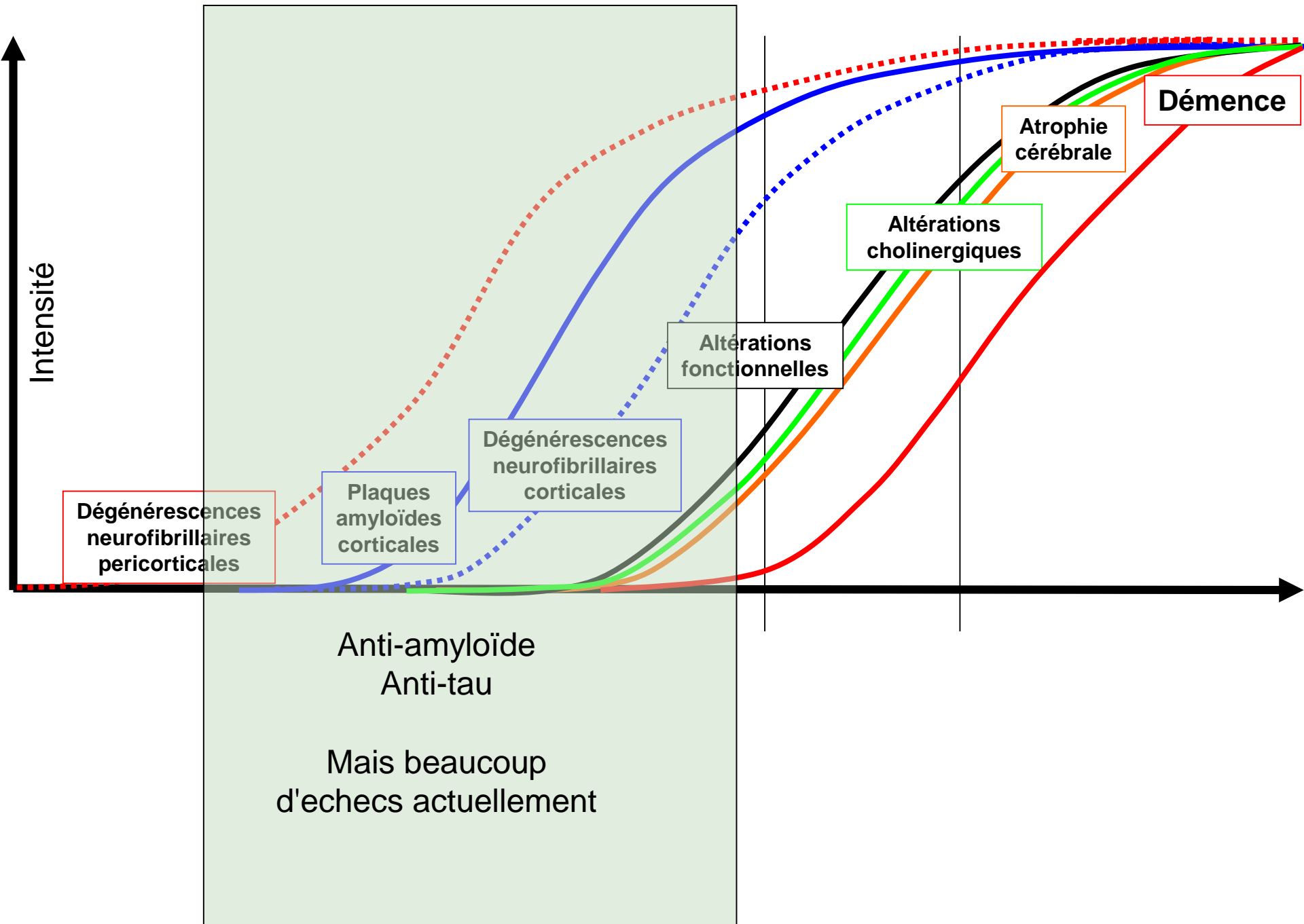


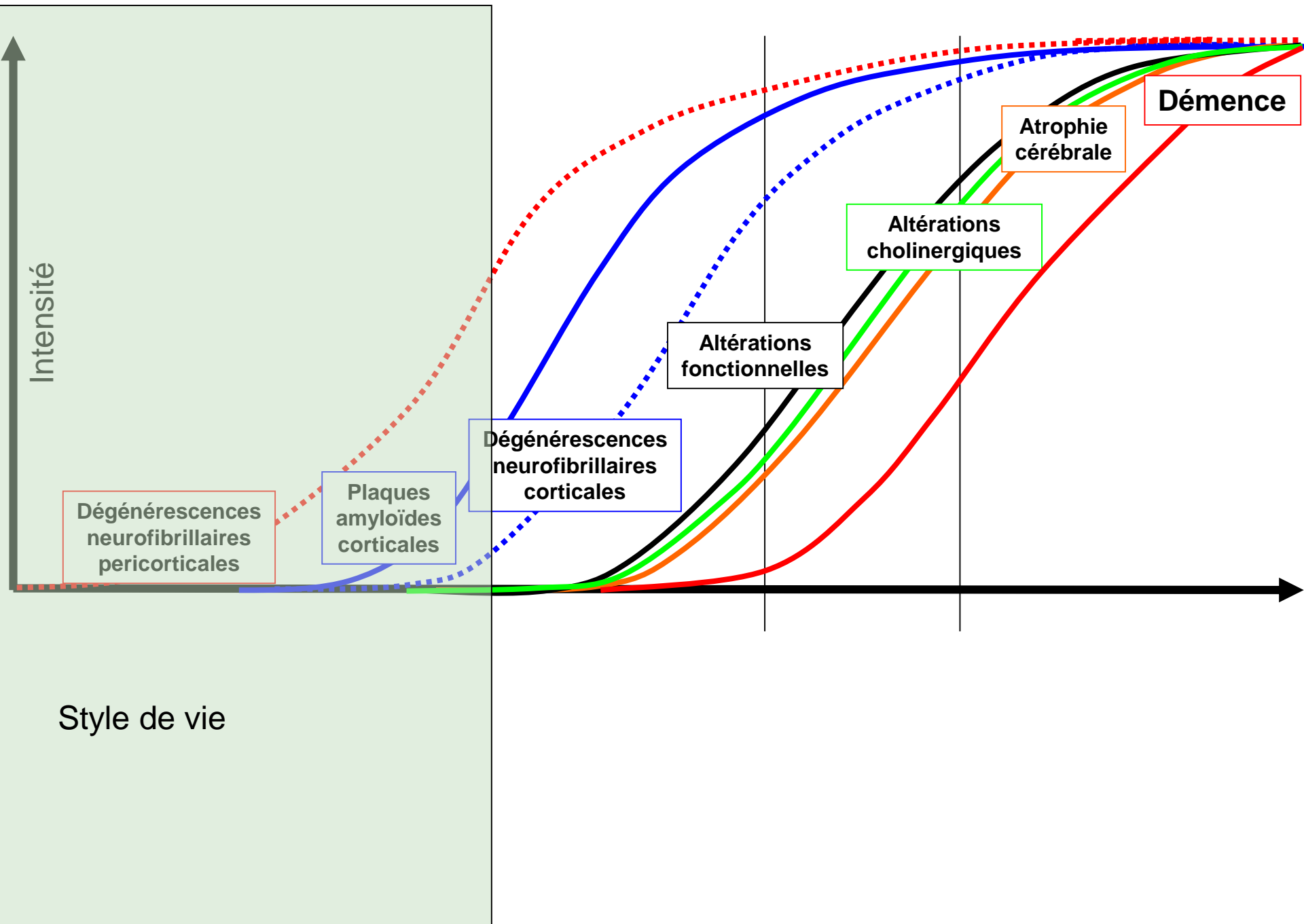


# THÉRAPIE PAR MODULATEUR DES MASTOCYTES

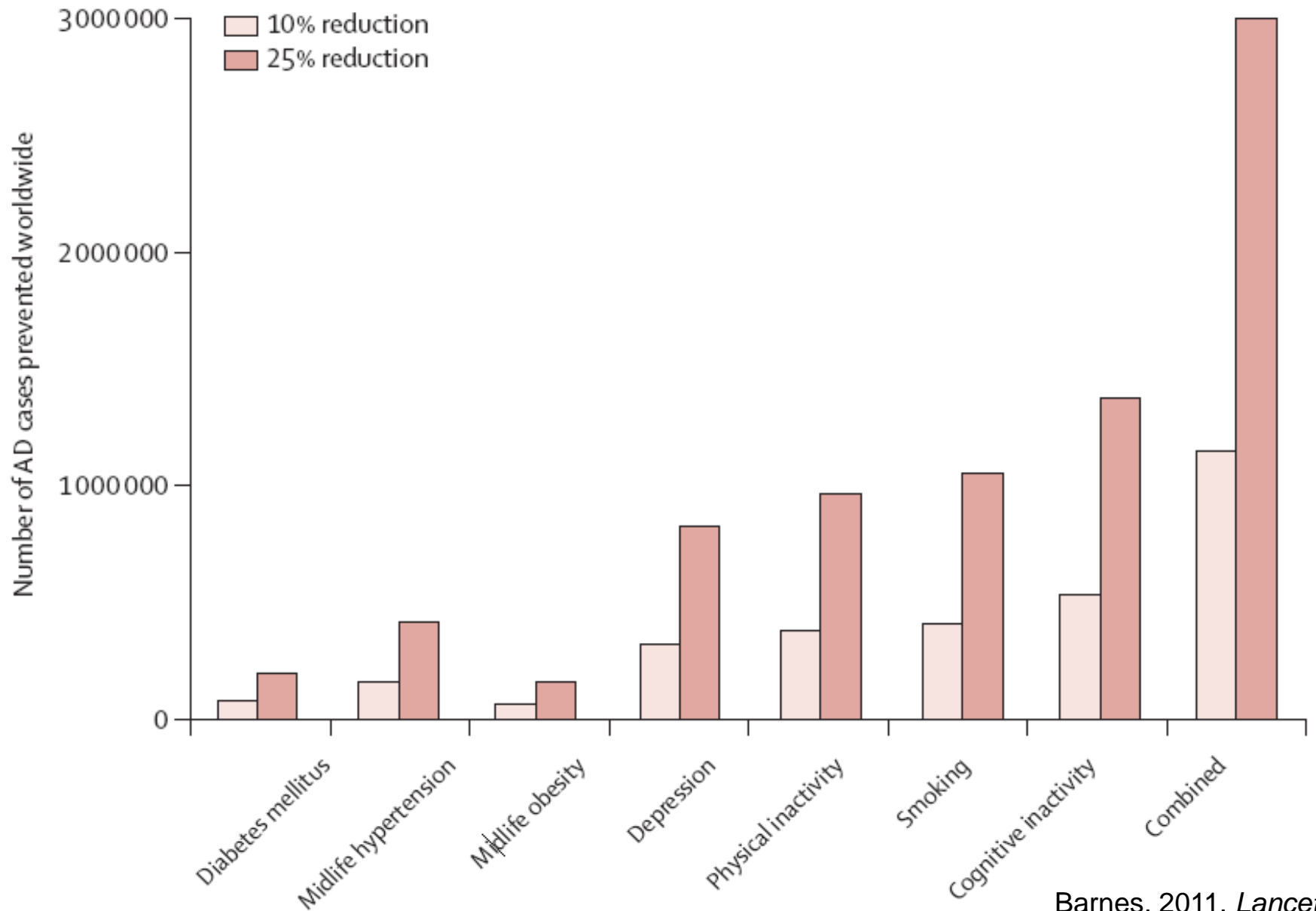


Phase 3 en cours

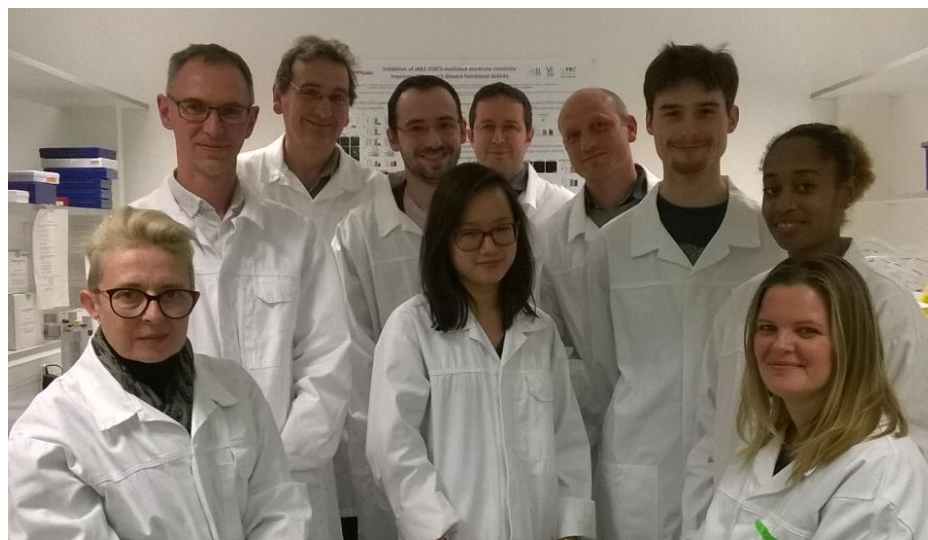
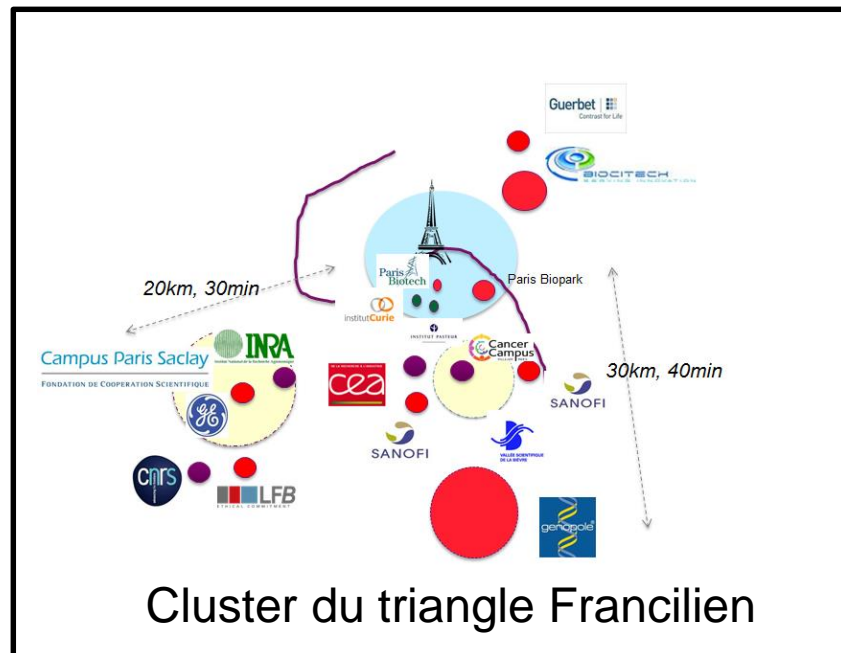
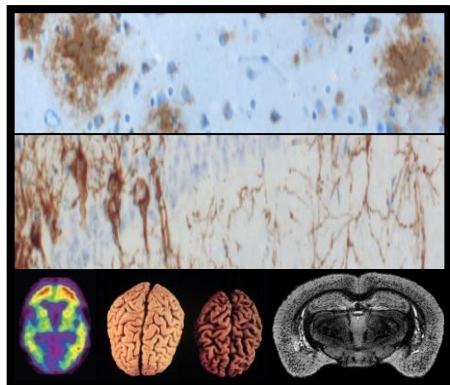




# THÉRAPIE PAR MODULATION DE FACTEURS DE RISQUES



# MERCI



Et les autres...

Marc.Dhenain@cea.fr