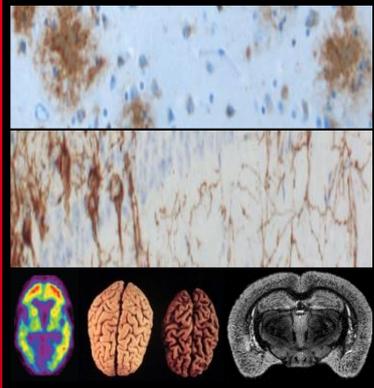


Nouvelles pistes pour comprendre et traiter la maladie d'Alzheimer



Marc Dhenain

Directeur de Recherche
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



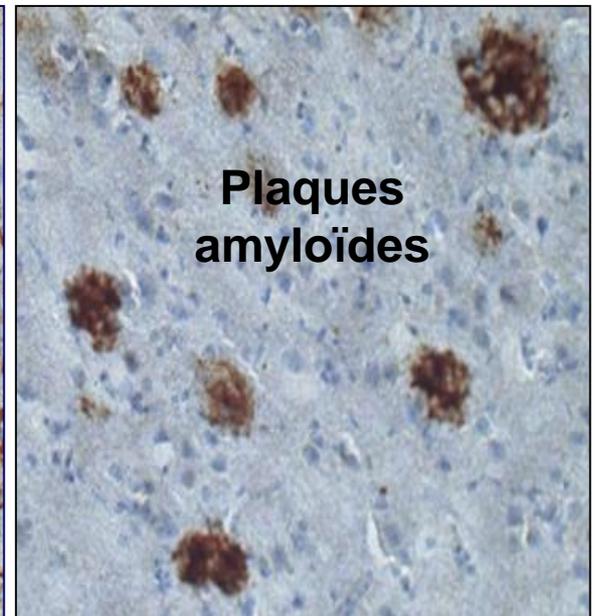
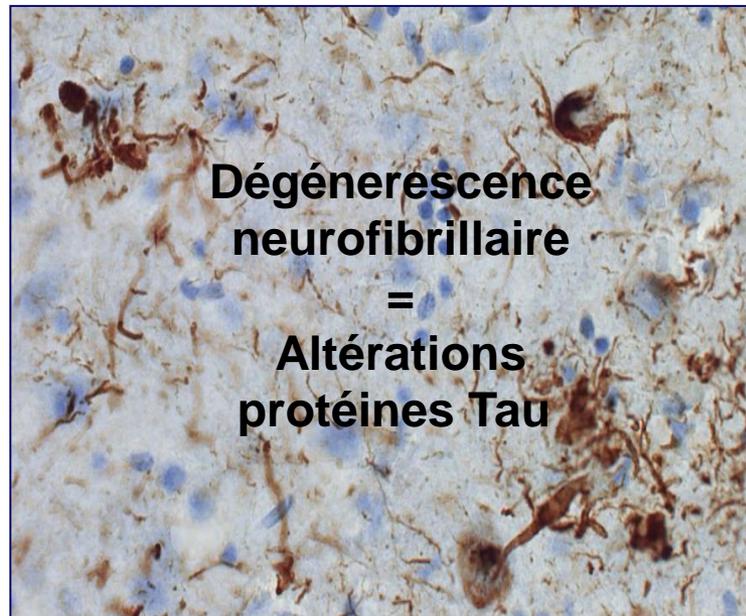
Auguste Deter

MALADIE D'ALZHEIMER : HISTORIQUE



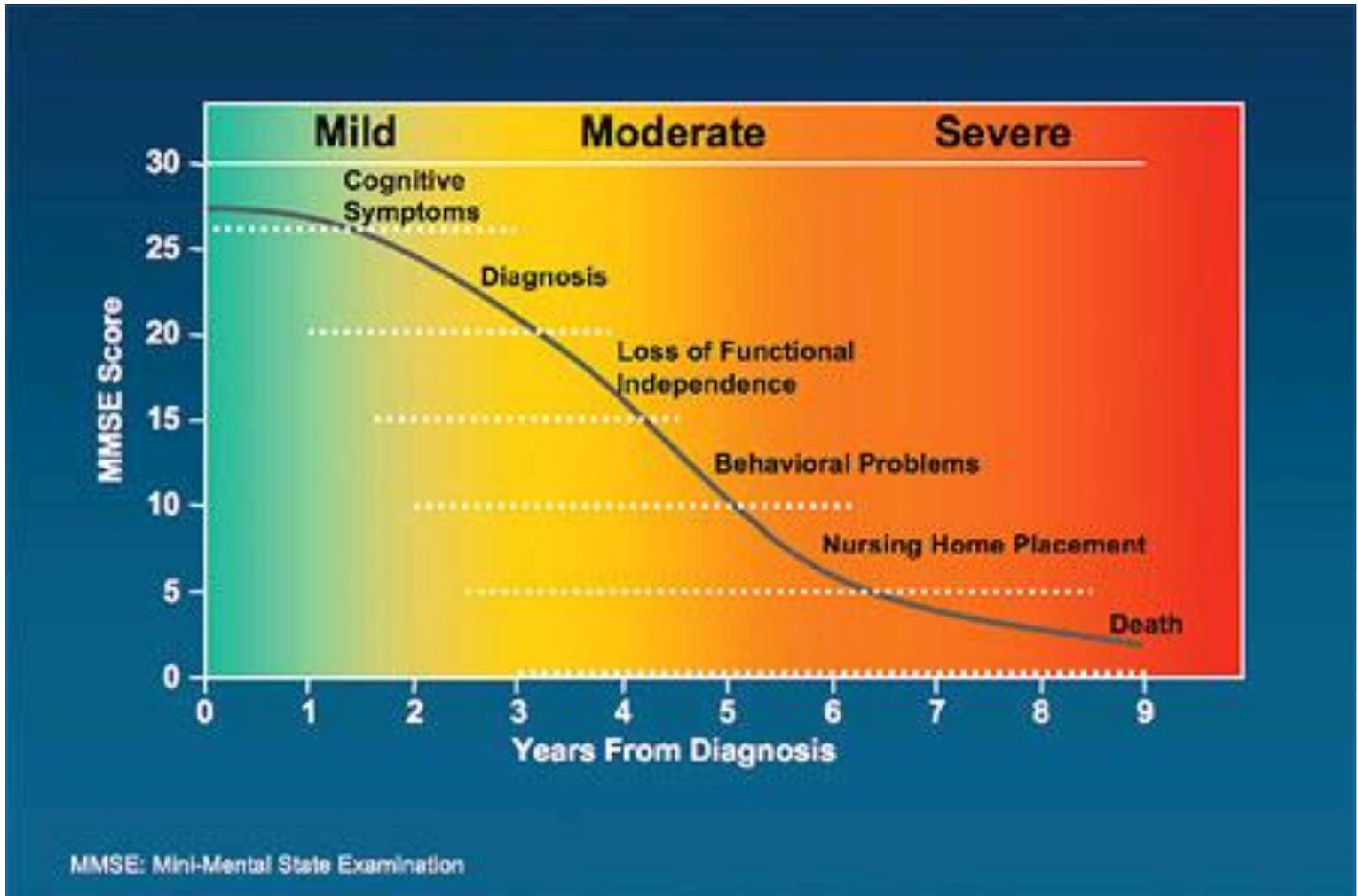
Mort en 8 avril 1906 à 55 ans (suite de septicémie/ulcères de décubitus)

Description des lésions

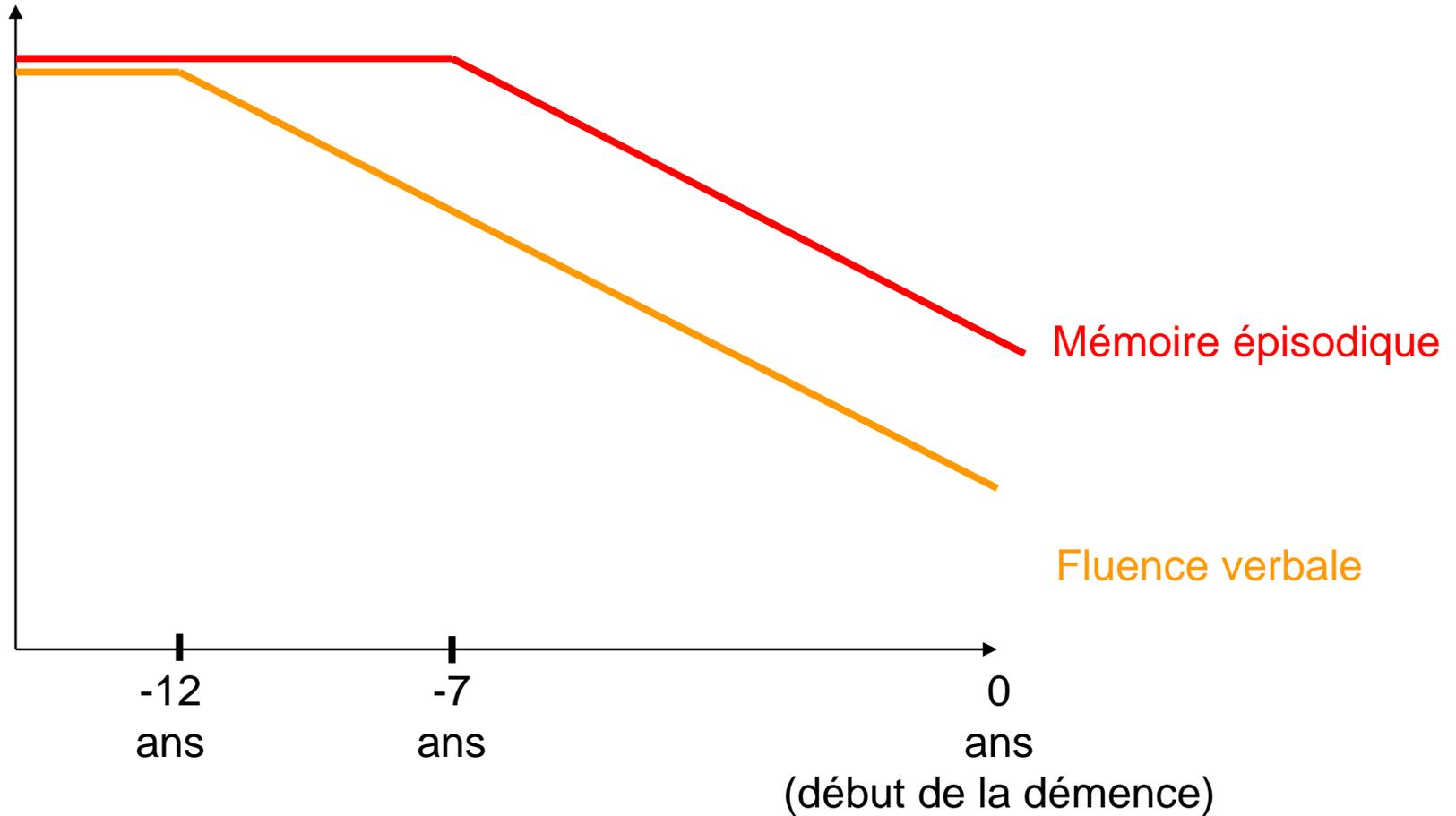


Auguste Deter

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



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

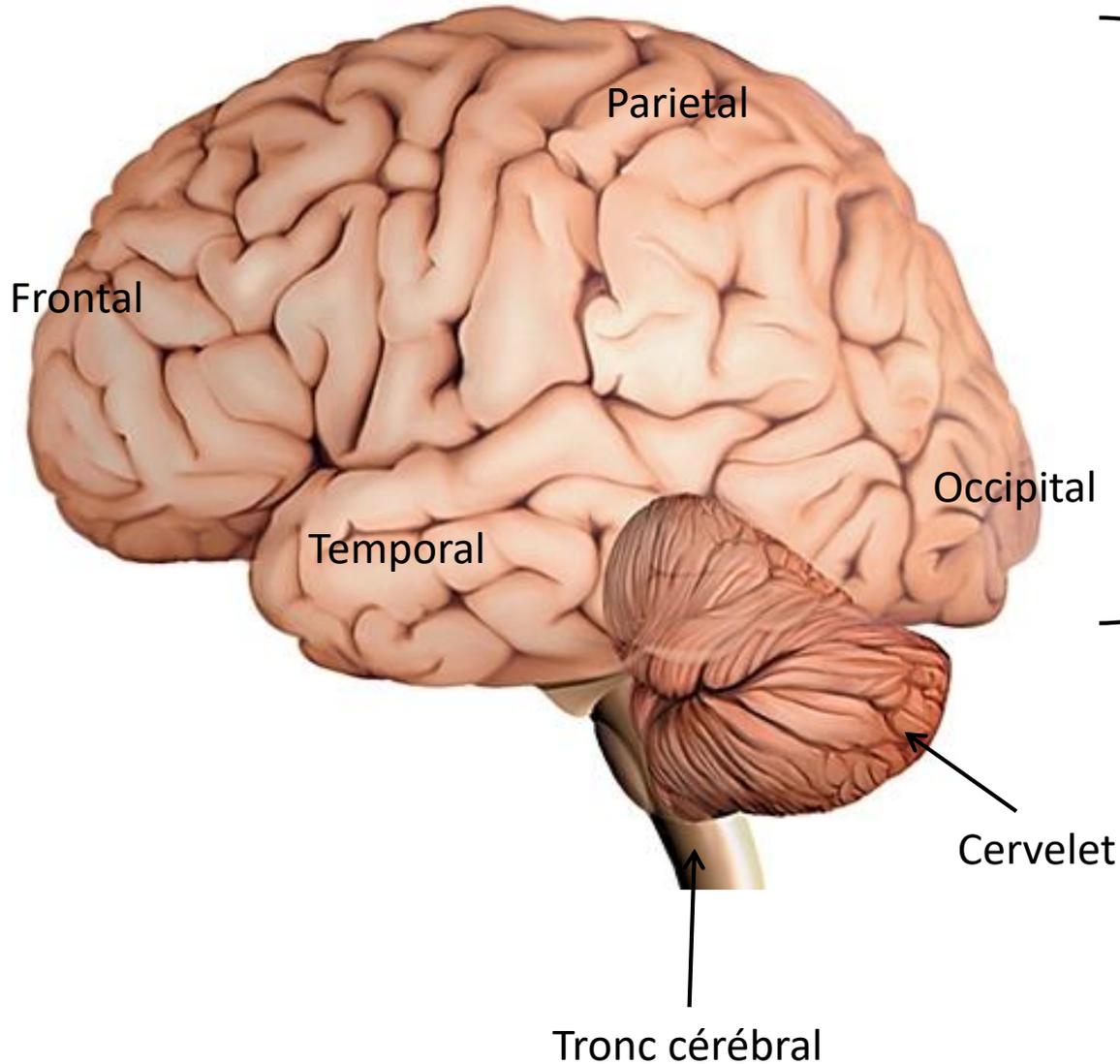




HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Les différents acteurs

LE CERVEAU HUMAIN



Cerveau

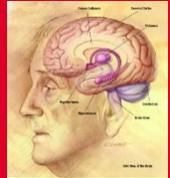
- Substance grise
- Substance blanche

~1.5 kg

2% du poids total du corps

25% de la consommation de glucose

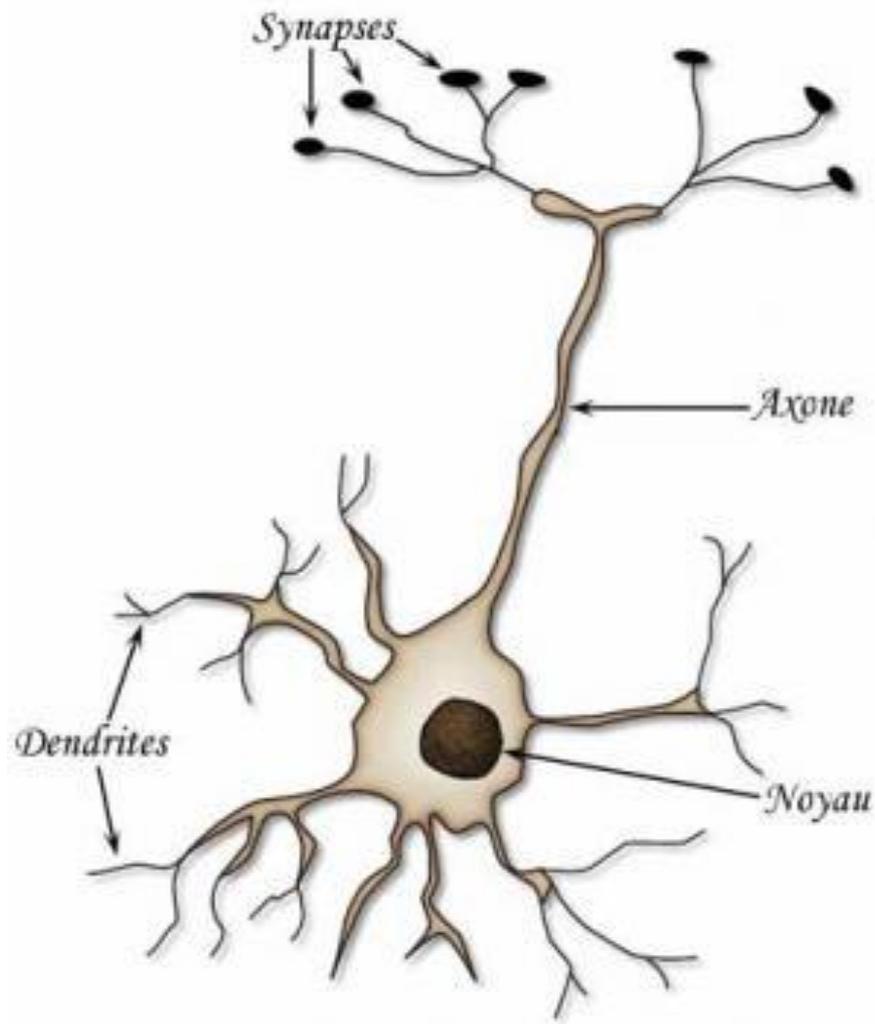
20% de la consommation d'oxygène



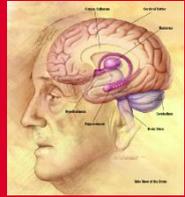
LE CERVEAU HUMAIN

LES NEURONES

° 86 milliards de neurones

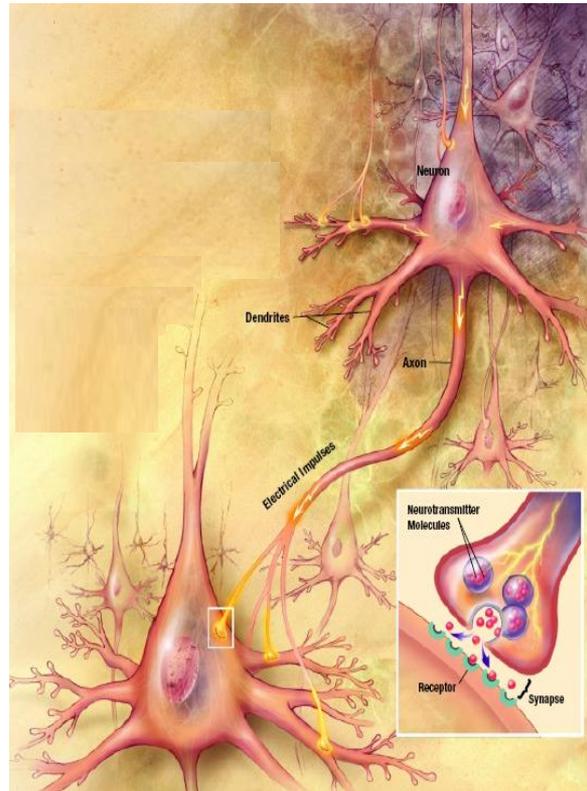


Synthèse → → → → → Transport → → → → → Utilisation

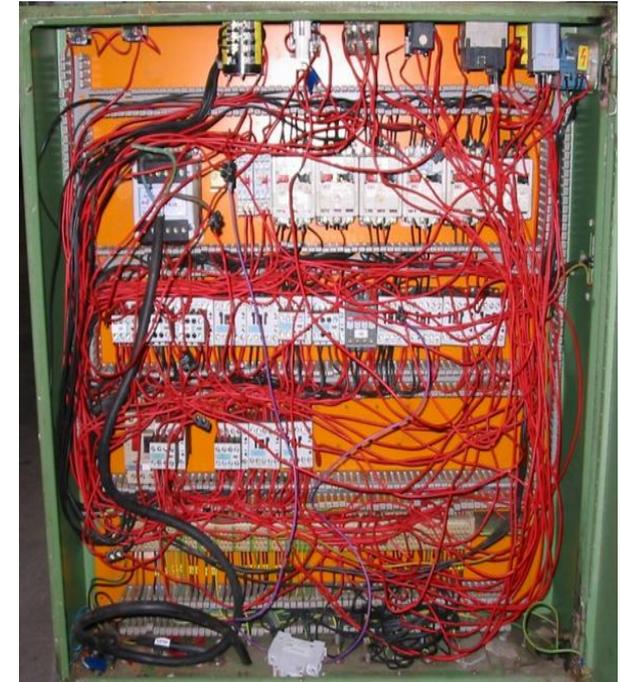
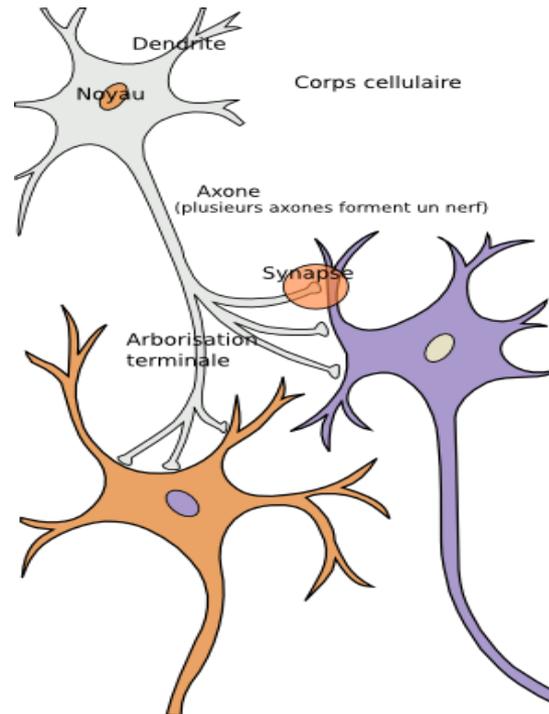


LE CERVEAU HUMAIN

Les neurones sont interconnectés



◦ 86 milliards de neurones



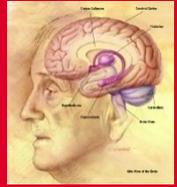
◦ 100 000 milliards de connexions entre les neurones

→ Transmission d'informations

→ Les messages transitent selon deux formes différentes:

>> Electrique à l'intérieur du neurone

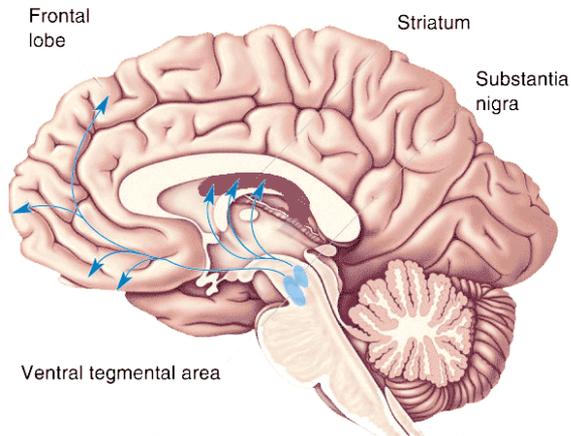
>> Chimique pour passer d'un neurone à l'autre



LE CERVEAU HUMAIN

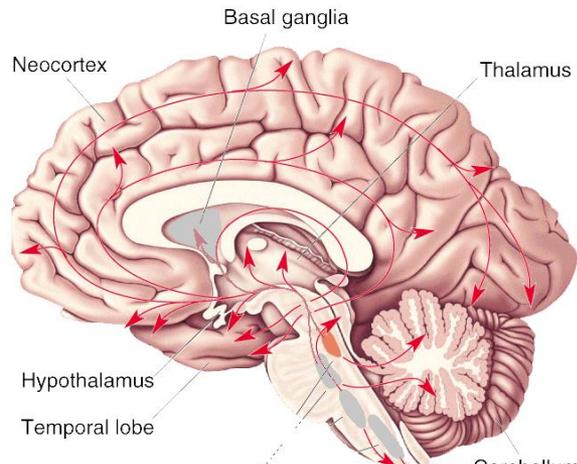
LES NEUROTRANSMETTEURS

Dopamine system



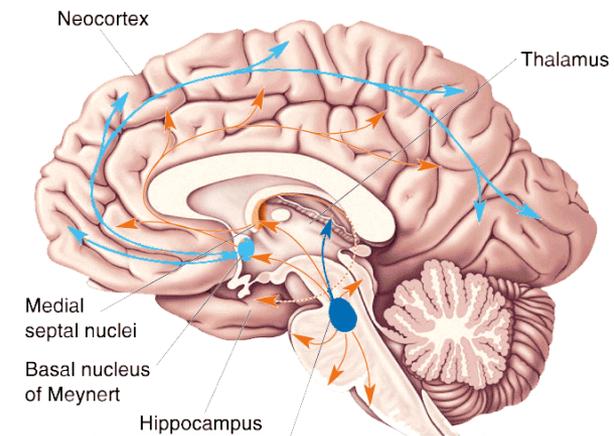
Dopamine

Serotonin system

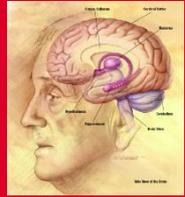


Serotonine

Acetylcholine system

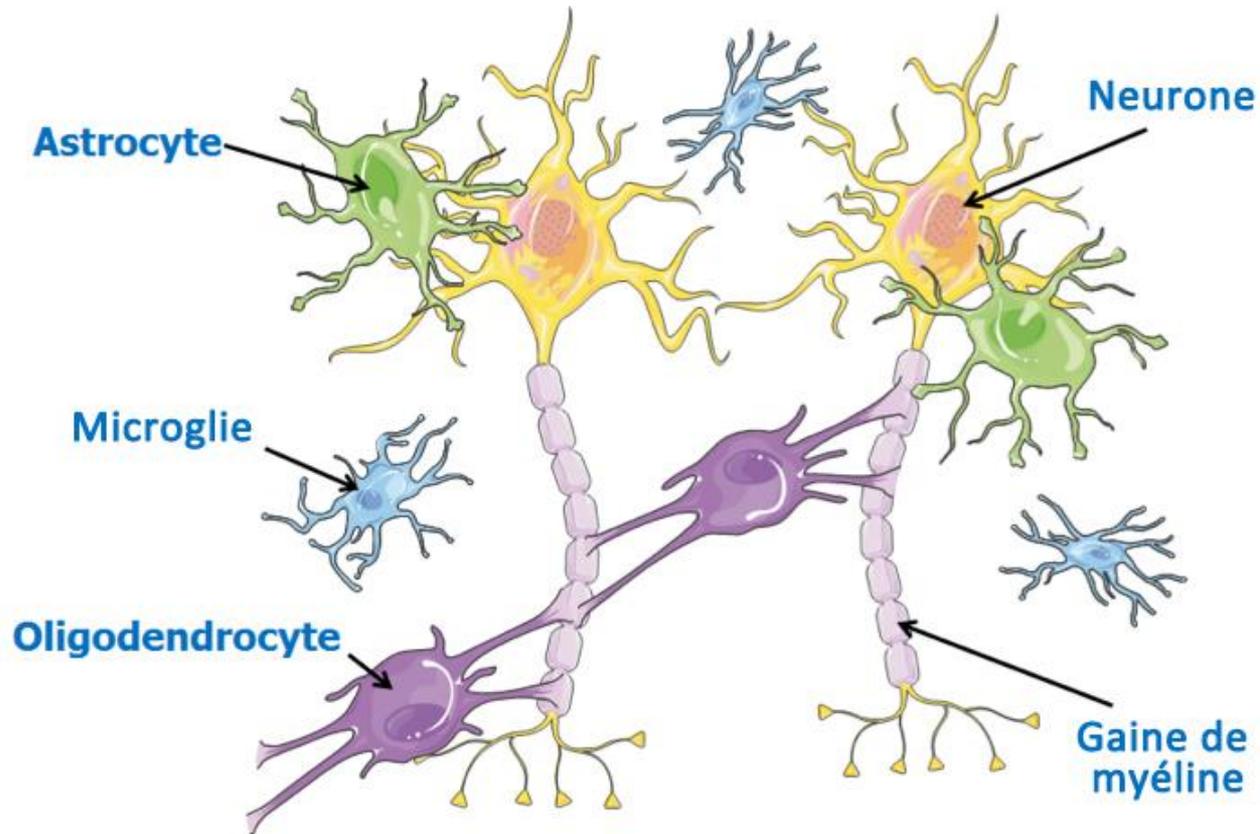


Acetylcholine

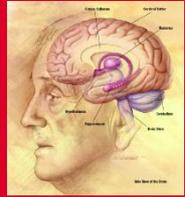


LES VOISINS DES NEURONES

Les cellules gliales

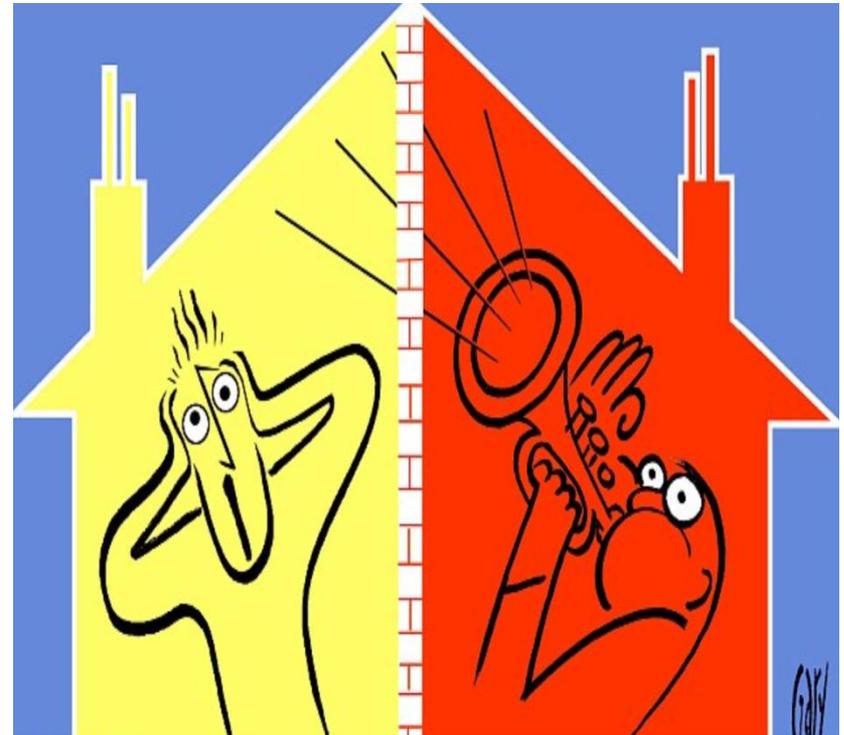


- ° Autant de cellules gliales que de neurones
- Aide au fonctionnement
- protections



LES VOISINS DES NEURONES

Des voisins sympathiques ou pas...





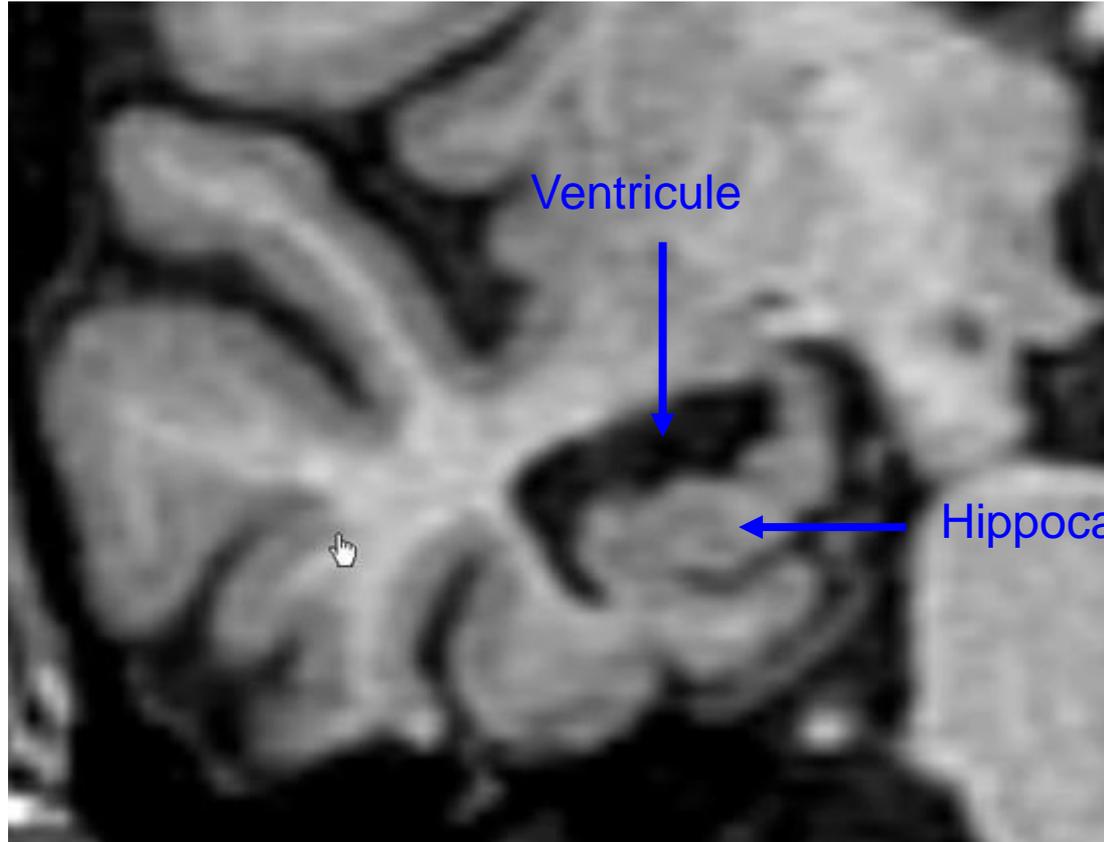
HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Atrophie cérébrale

DÉGÉNÉRESCENCE CÉRÉBRALE



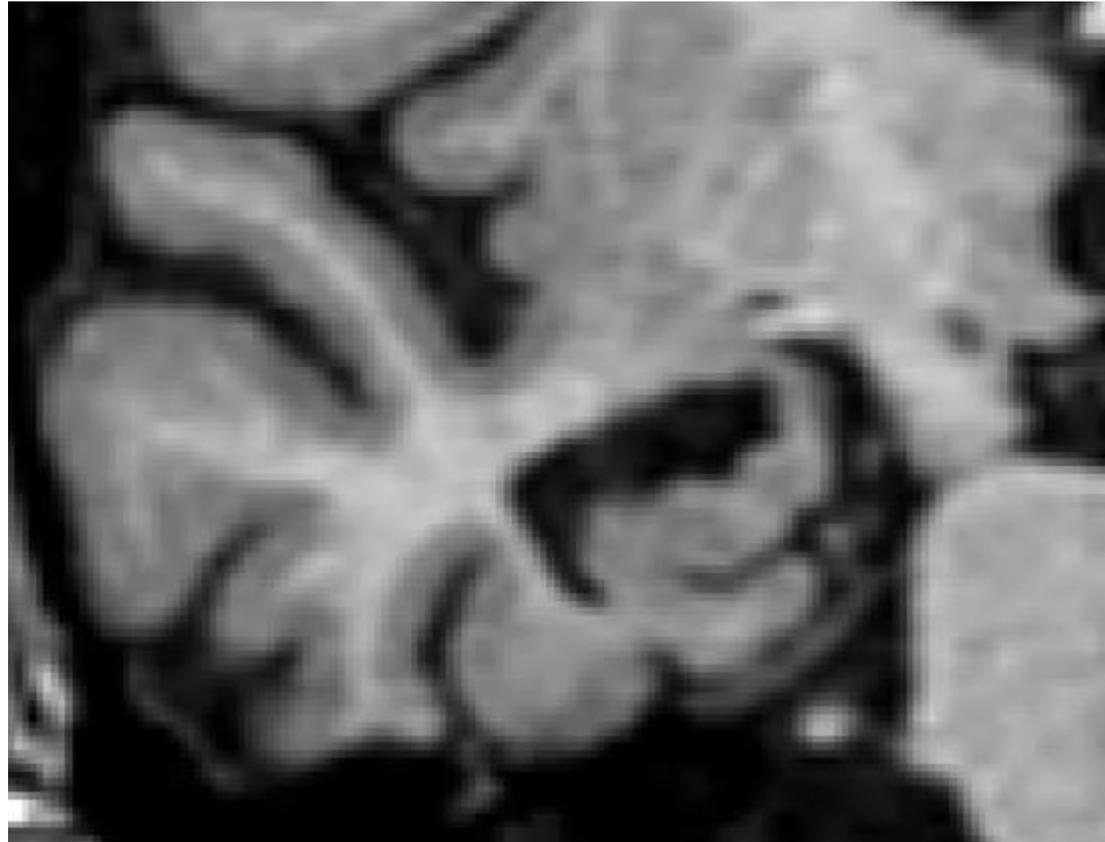
PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



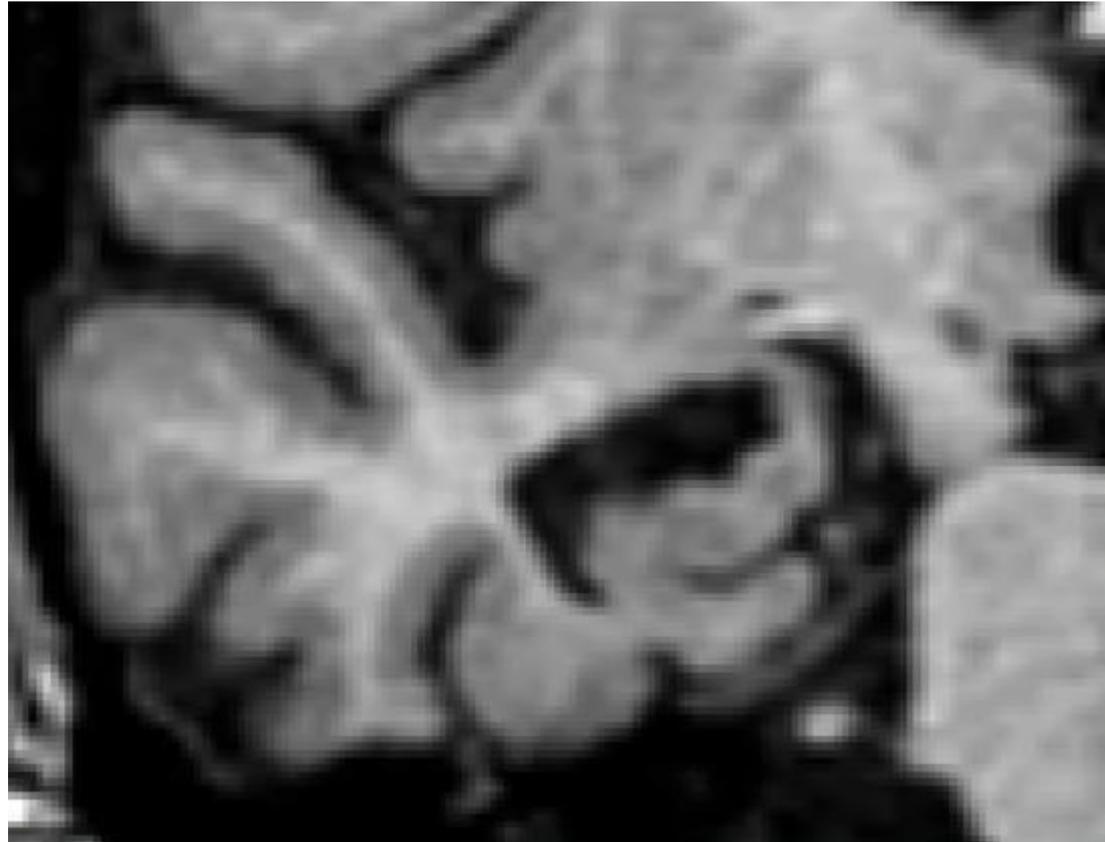
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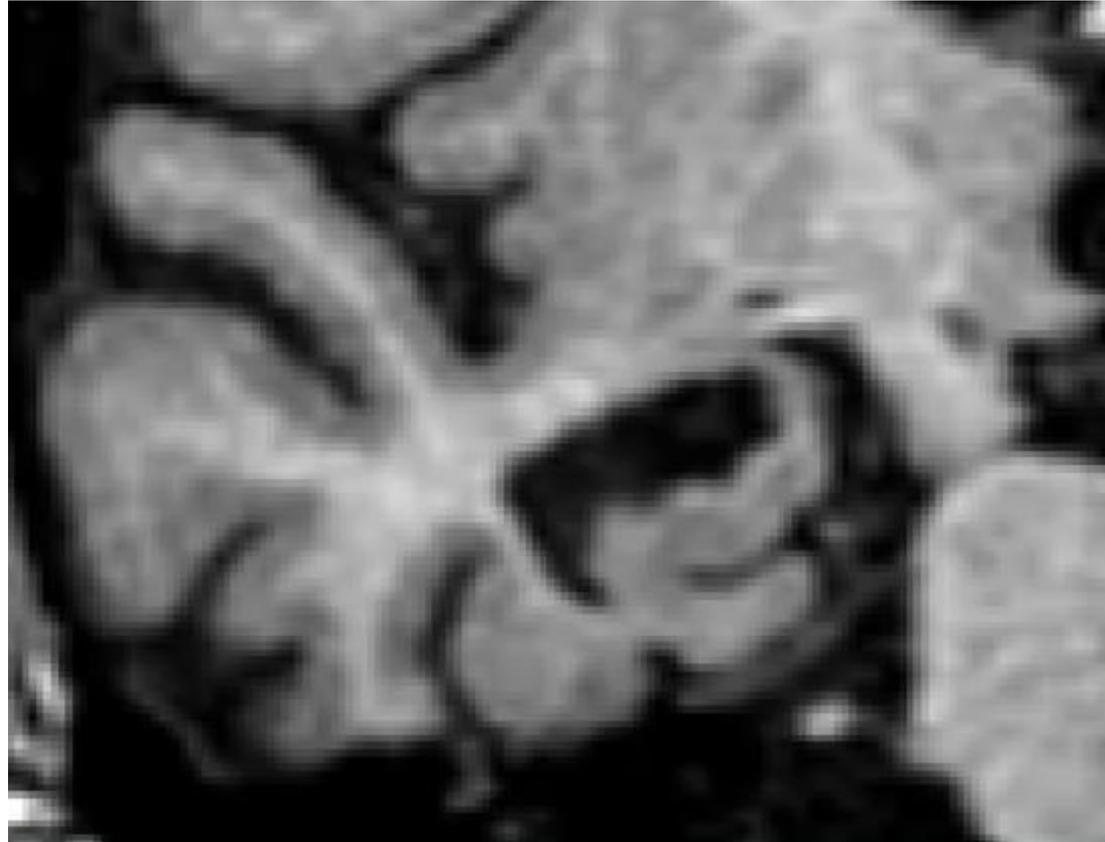
DE LA RECHERCHE À L'INDUSTRIE



PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



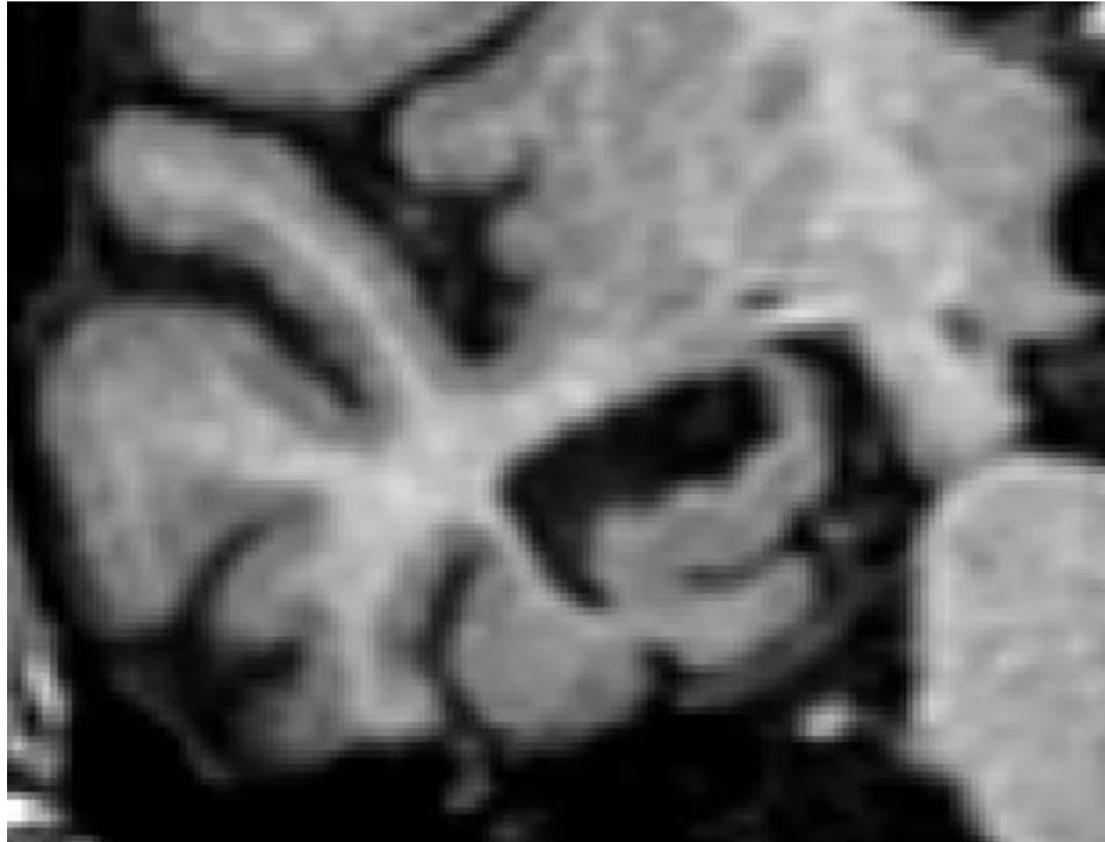
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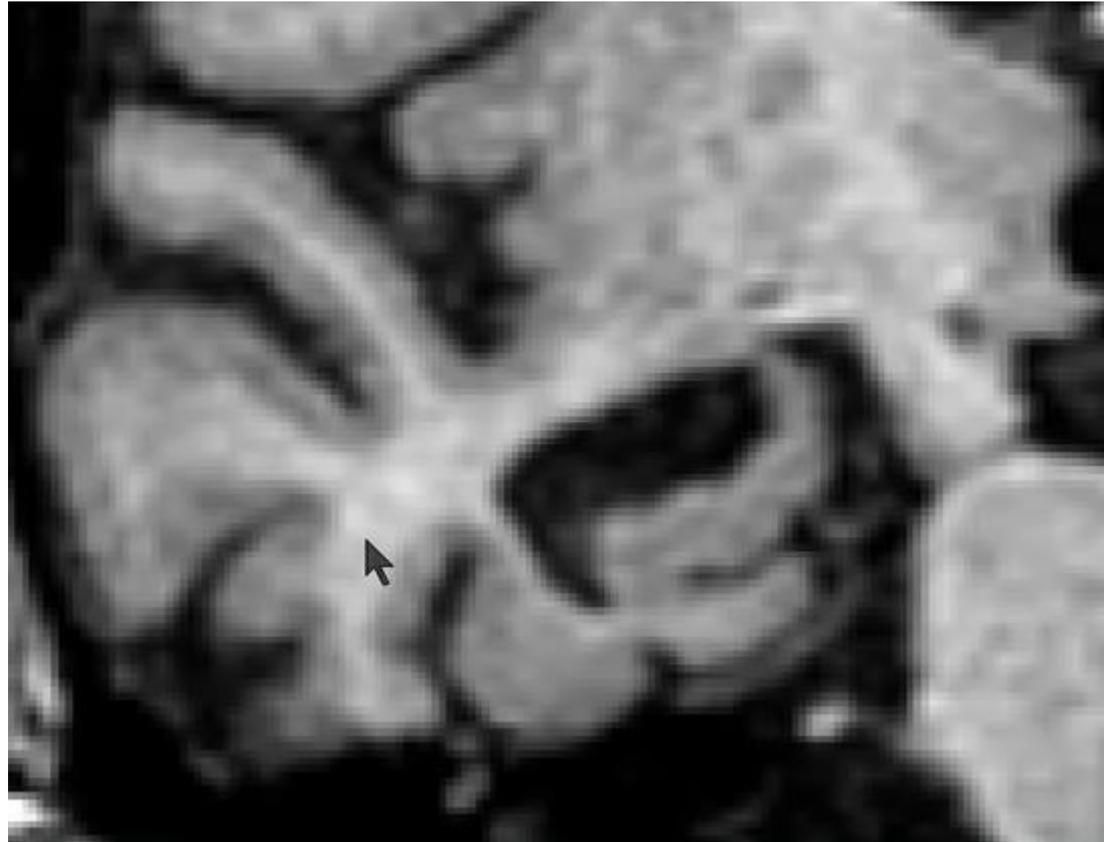
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DE LA RECHERCHE À L'INDUSTRIE



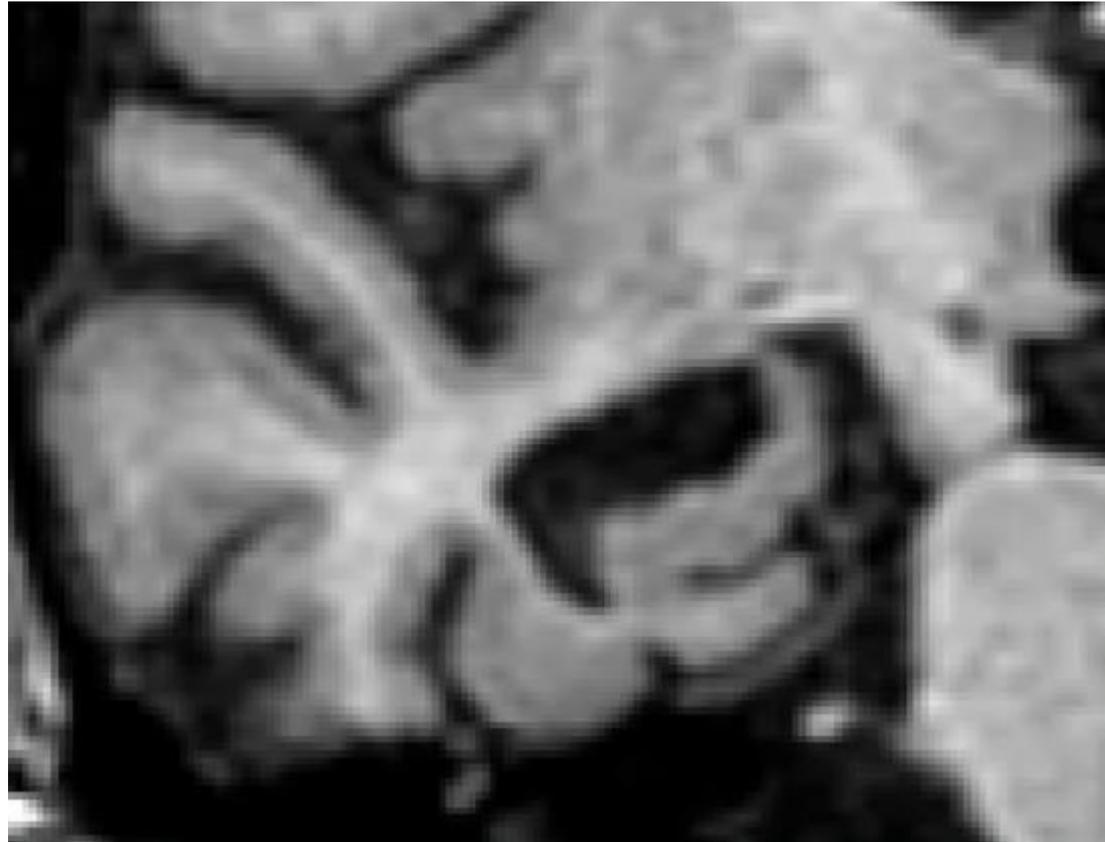
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PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



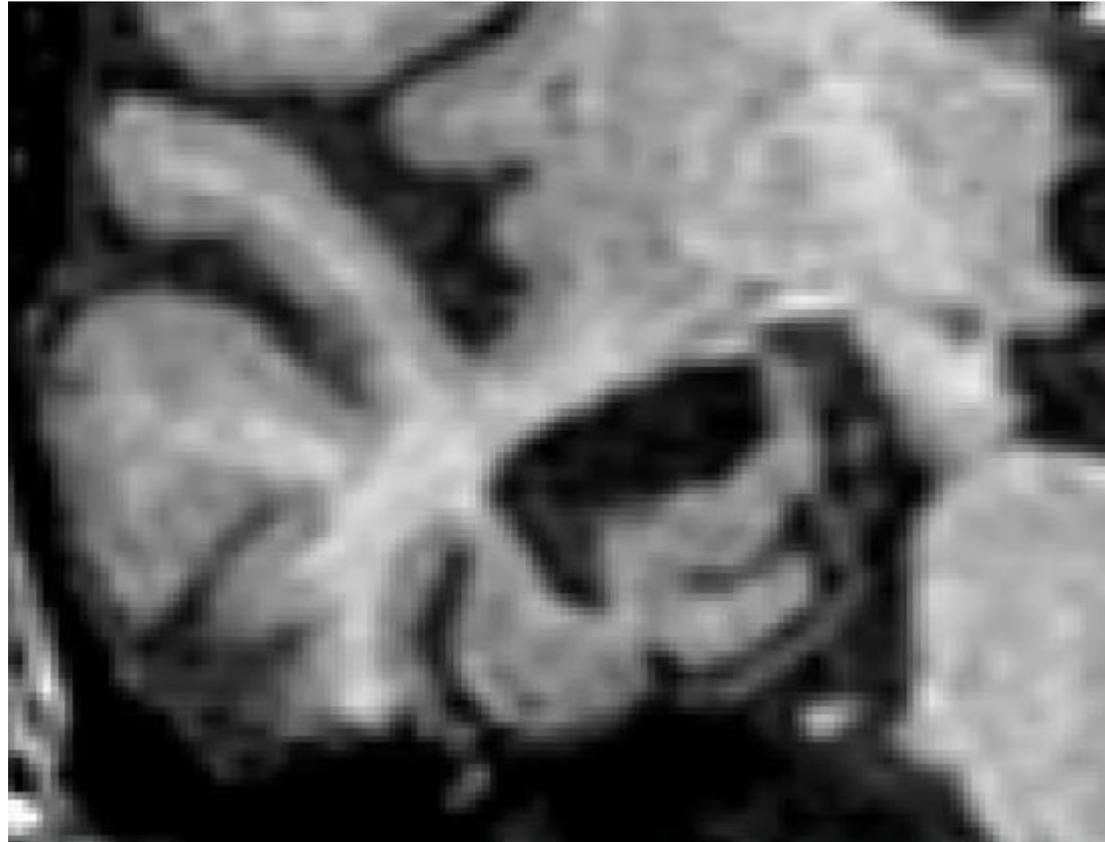
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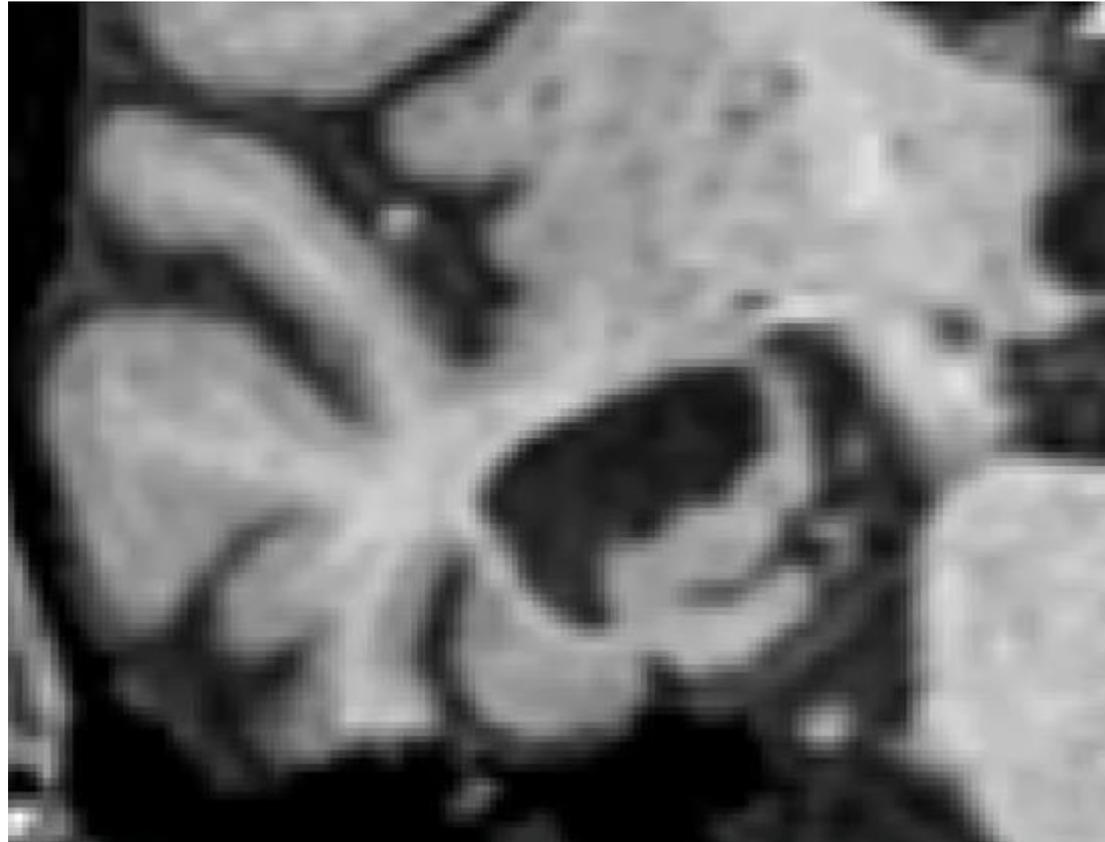
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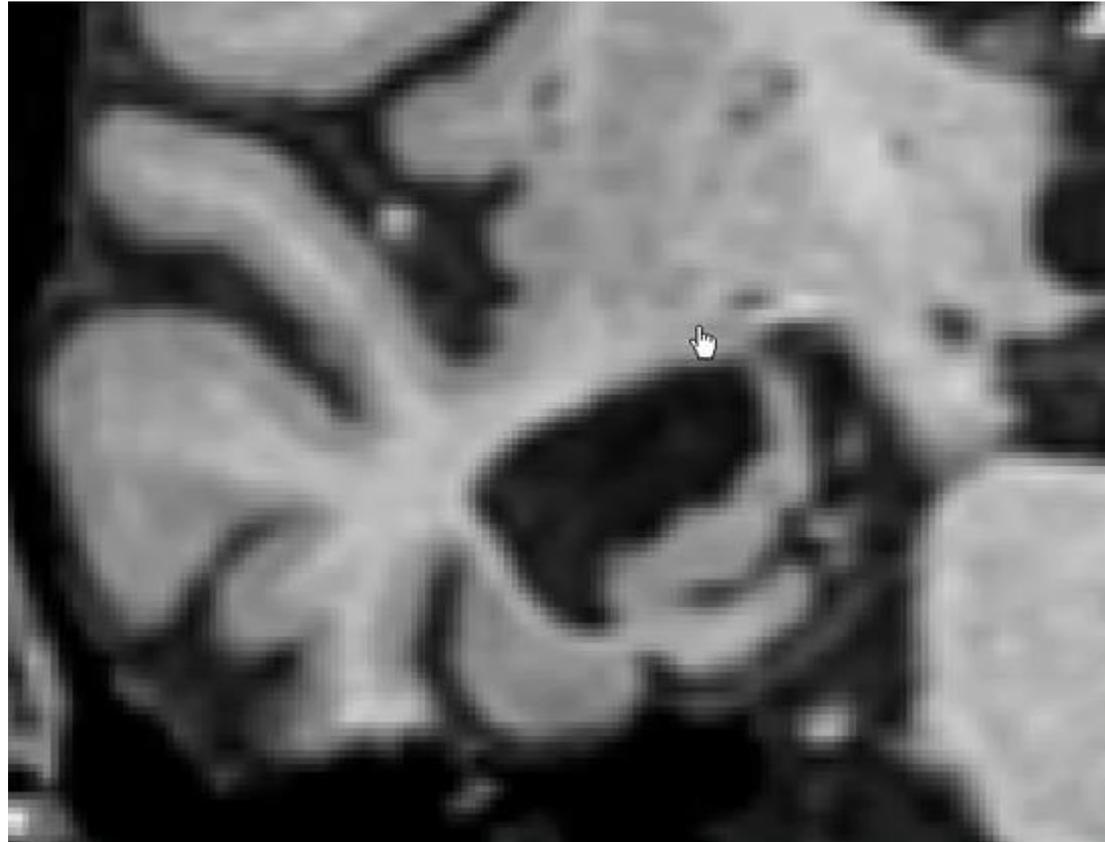
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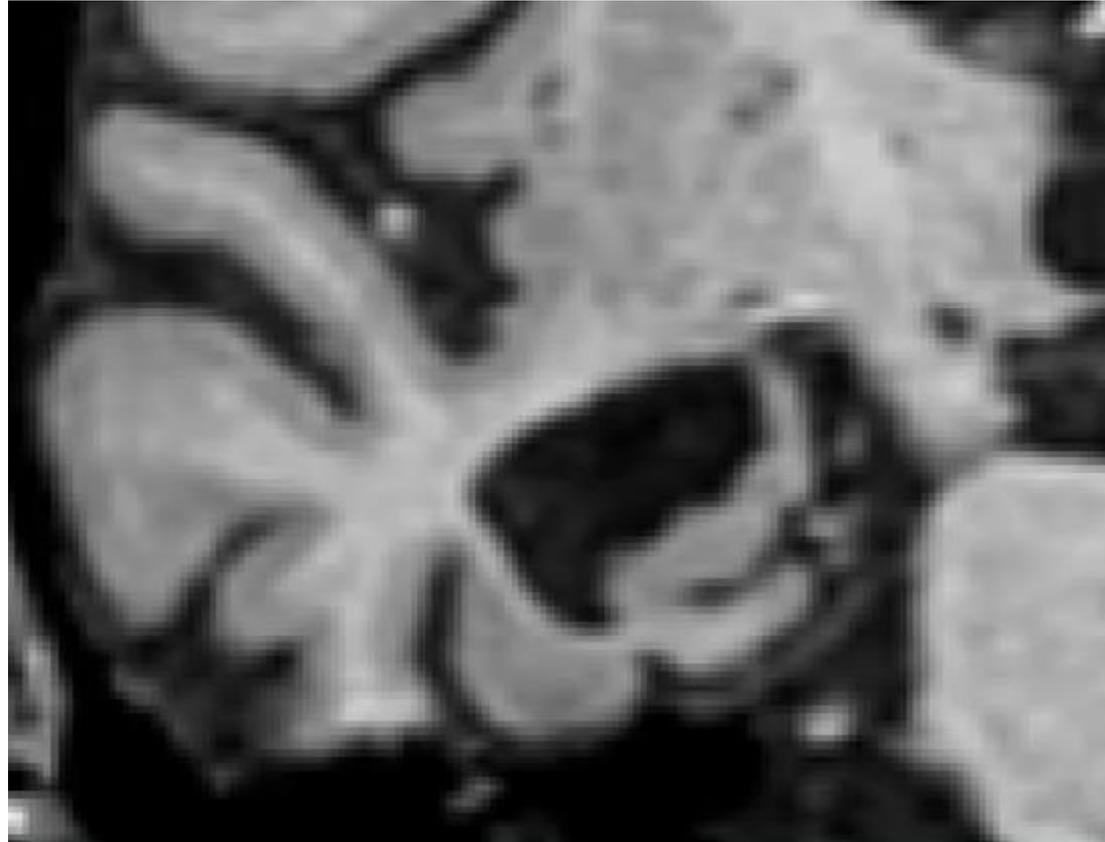
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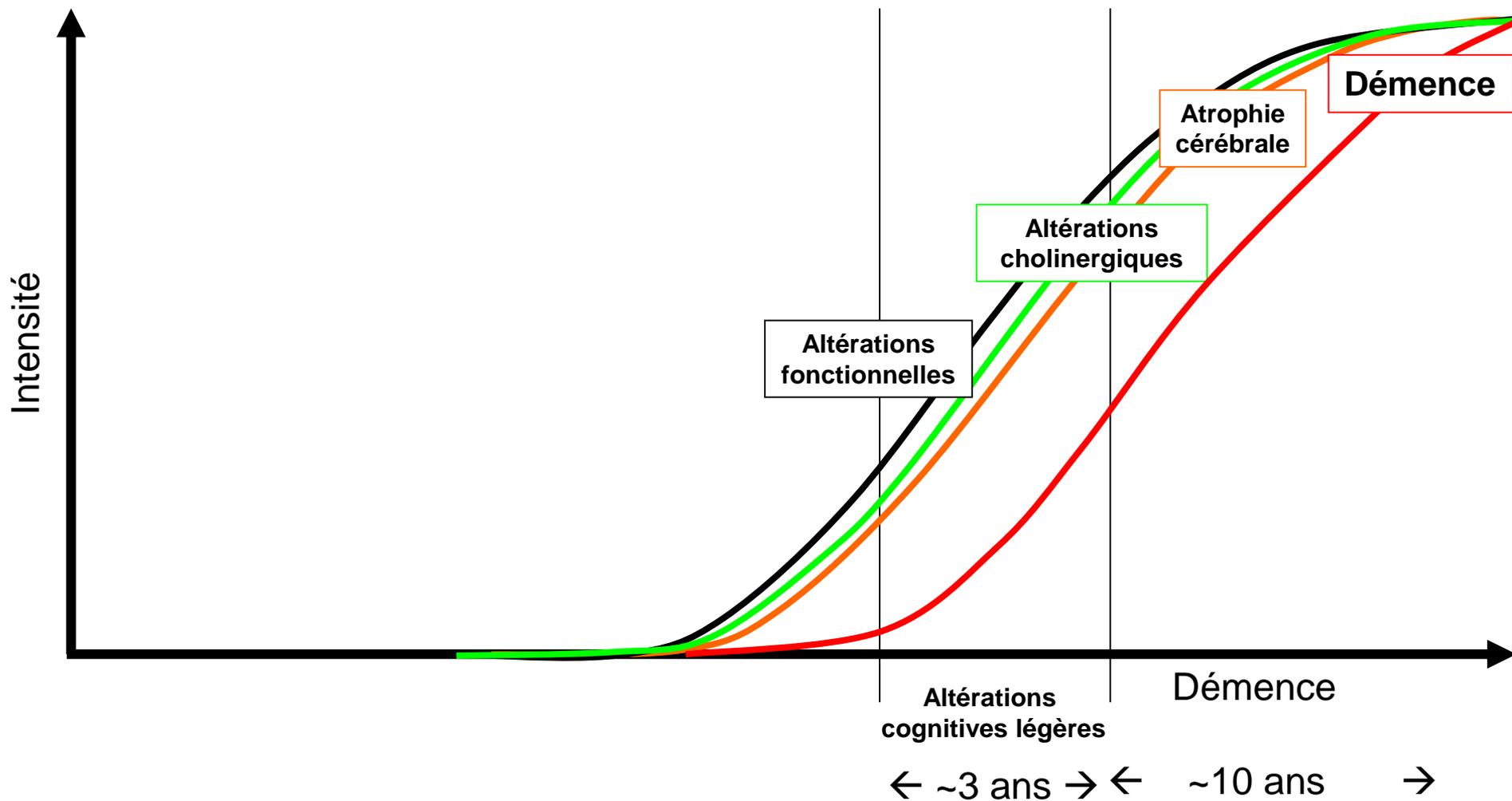
PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



PROGRESSION DE L'ATROPHIE CÉRÉBRALE PENDANT 10 ANS



HISTOIRE NATURELLE DE LA MALADIE





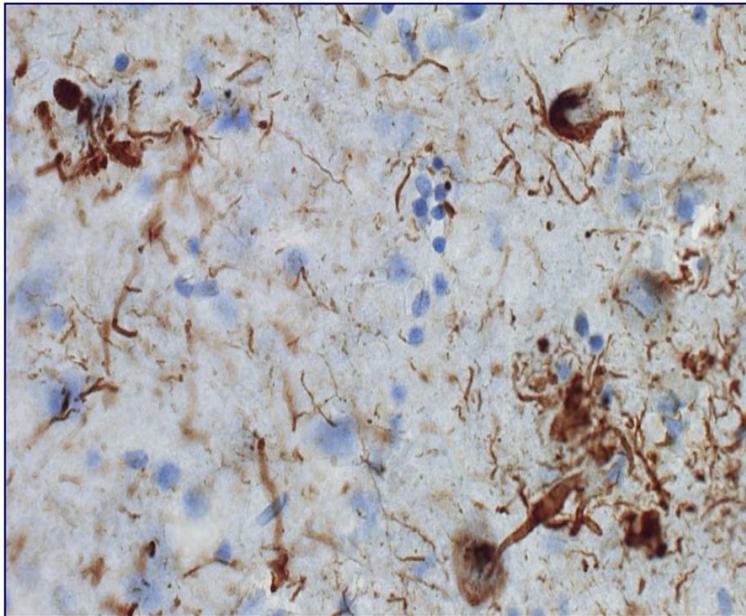
HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Dégénérescences neurofibrillaires – Lésions Tau

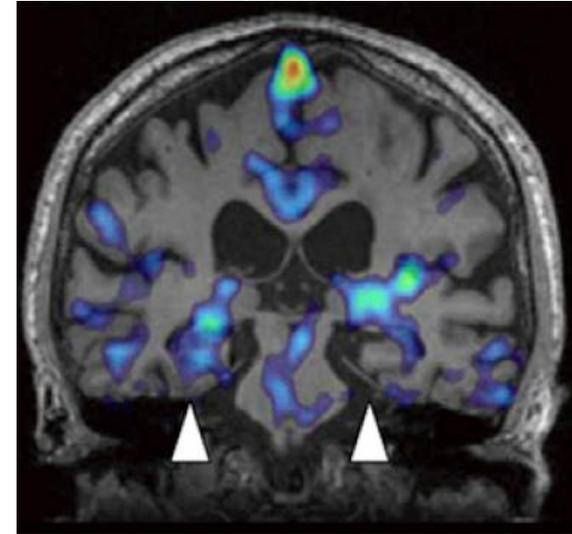
IMAGERIE DE TAU CHEZ L'HOMME (TEP)



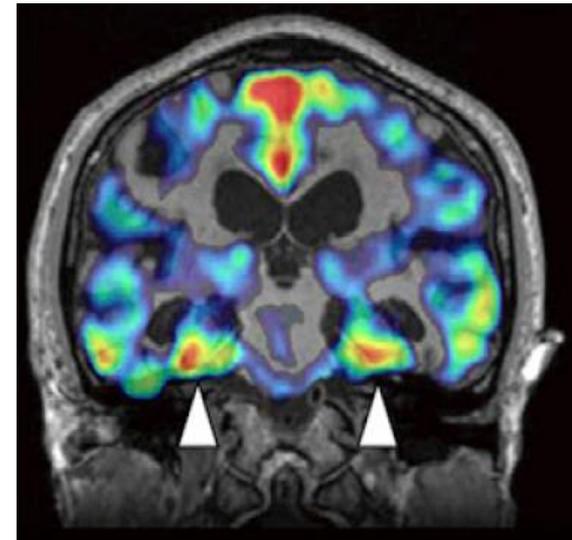
DE LA RECHERCHE À L'INDUSTRIE



Tau (TEP)



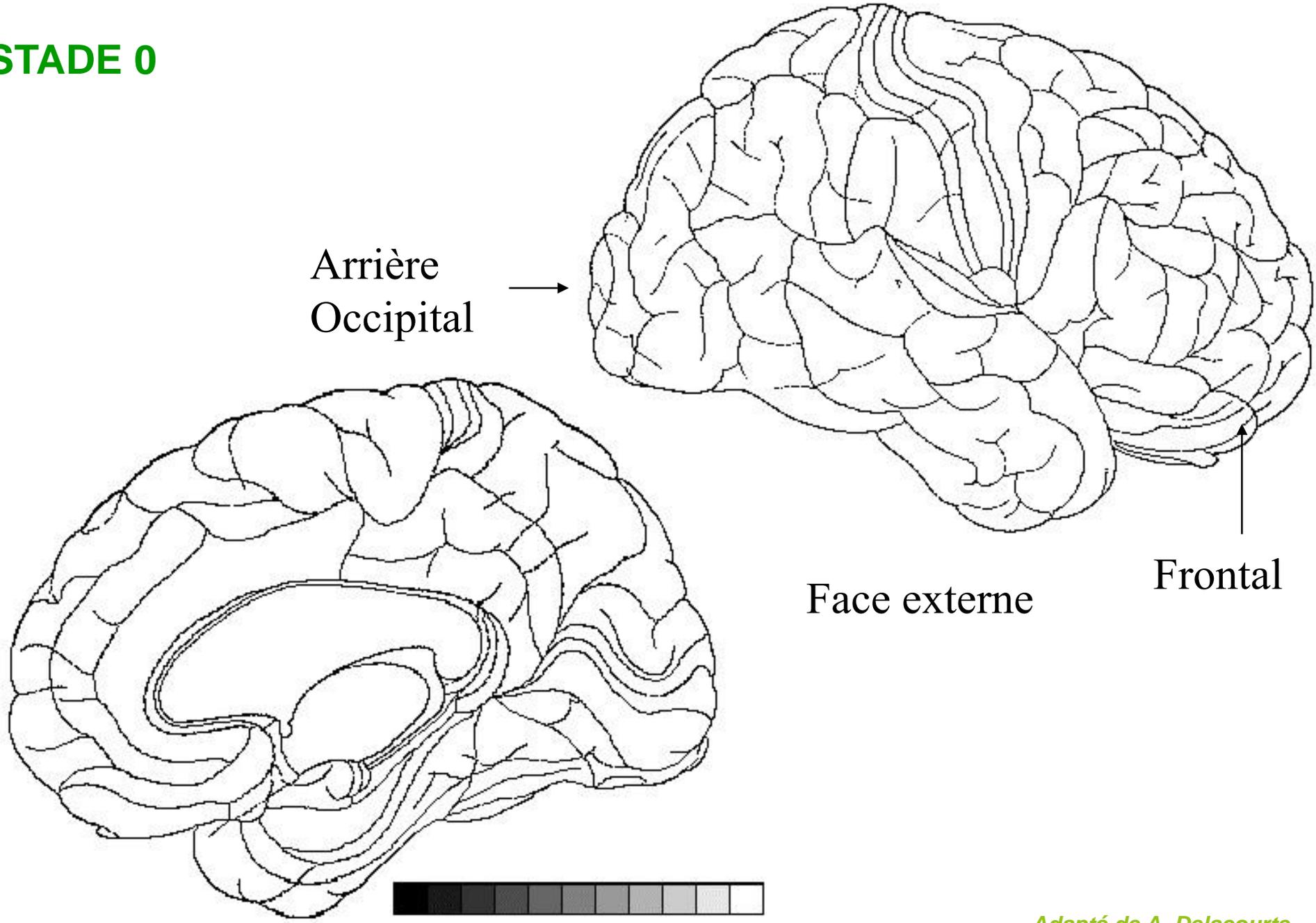
Normal



Alzheimer

Maruyama, 2013

STADE 0



Arrière
Occipital



Face externe

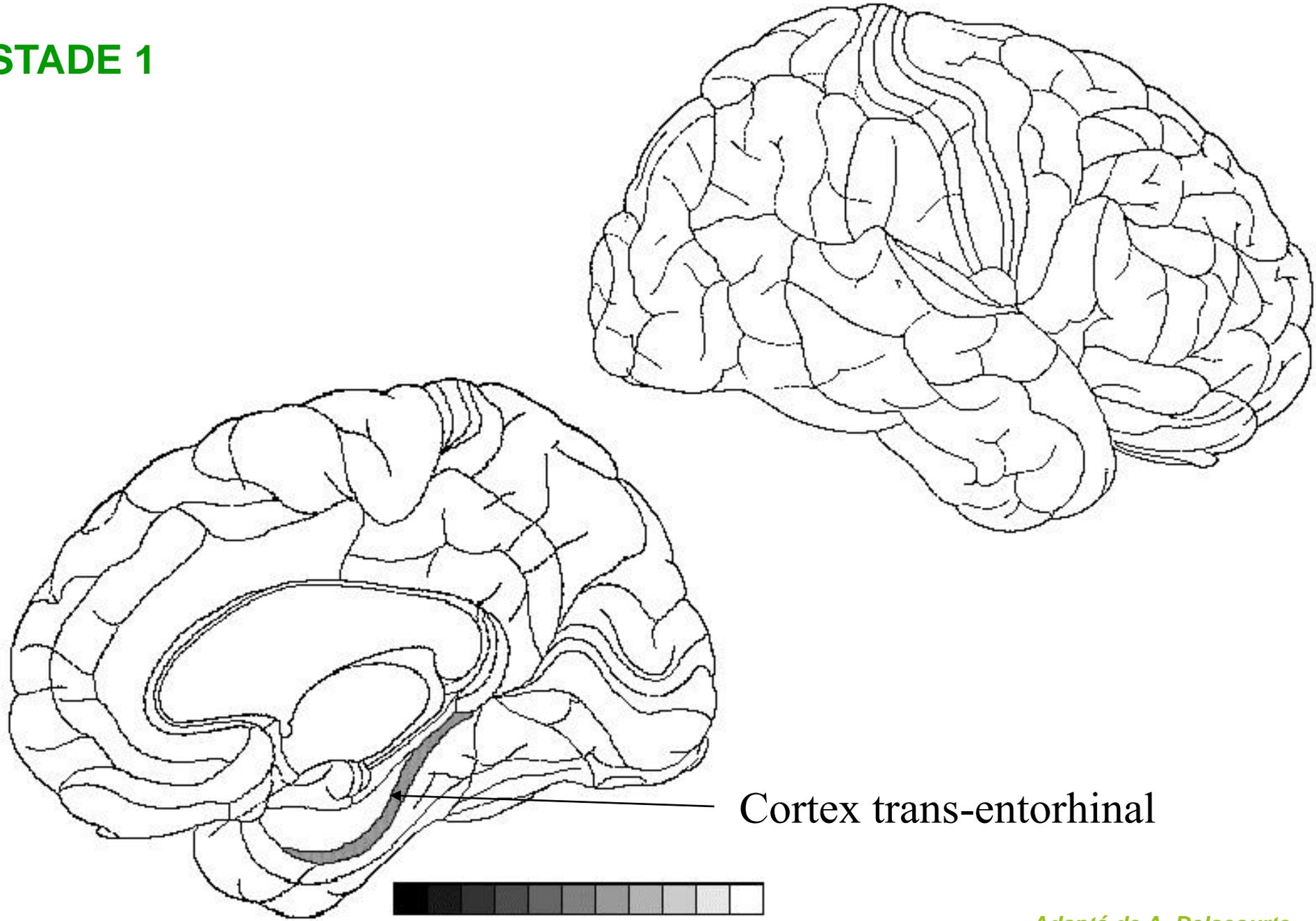
Frontal

Face interne



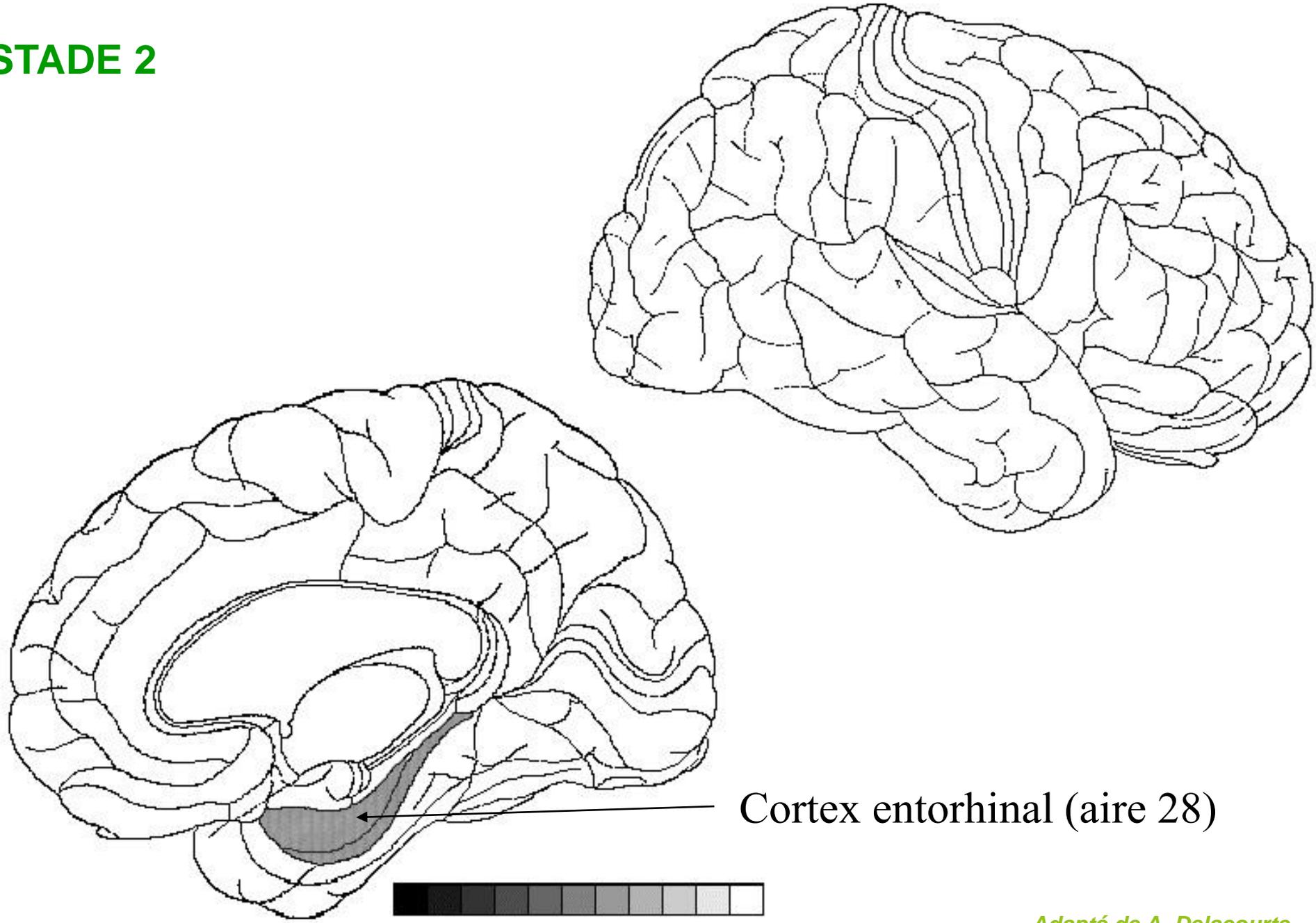
Adapté de A. Delacourte

STADE 1



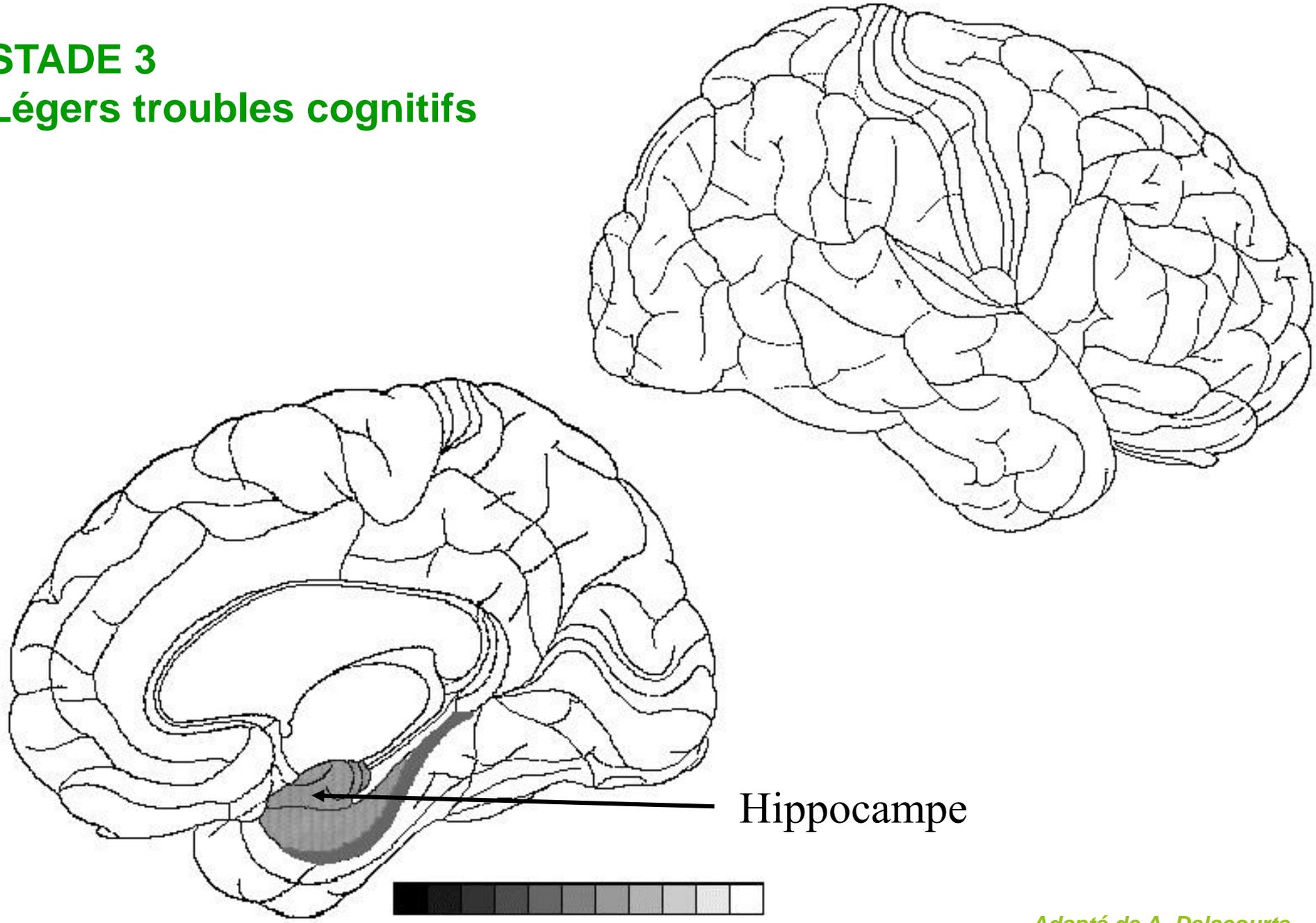
Cortex trans-entorhinal

STADE 2



Cortex entorhinal (aire 28)

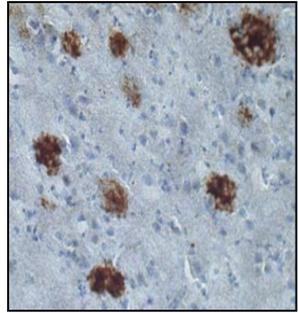
STADE 3
Légers troubles cognitifs



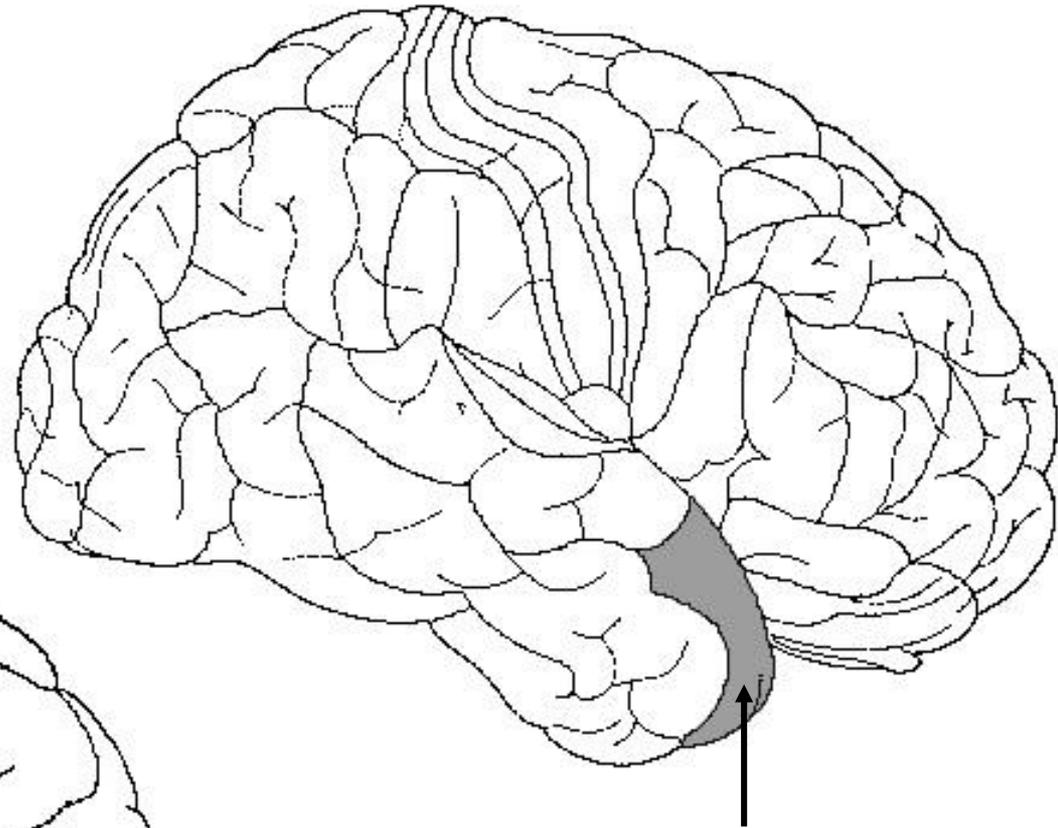
Hippocampe

STADE 4

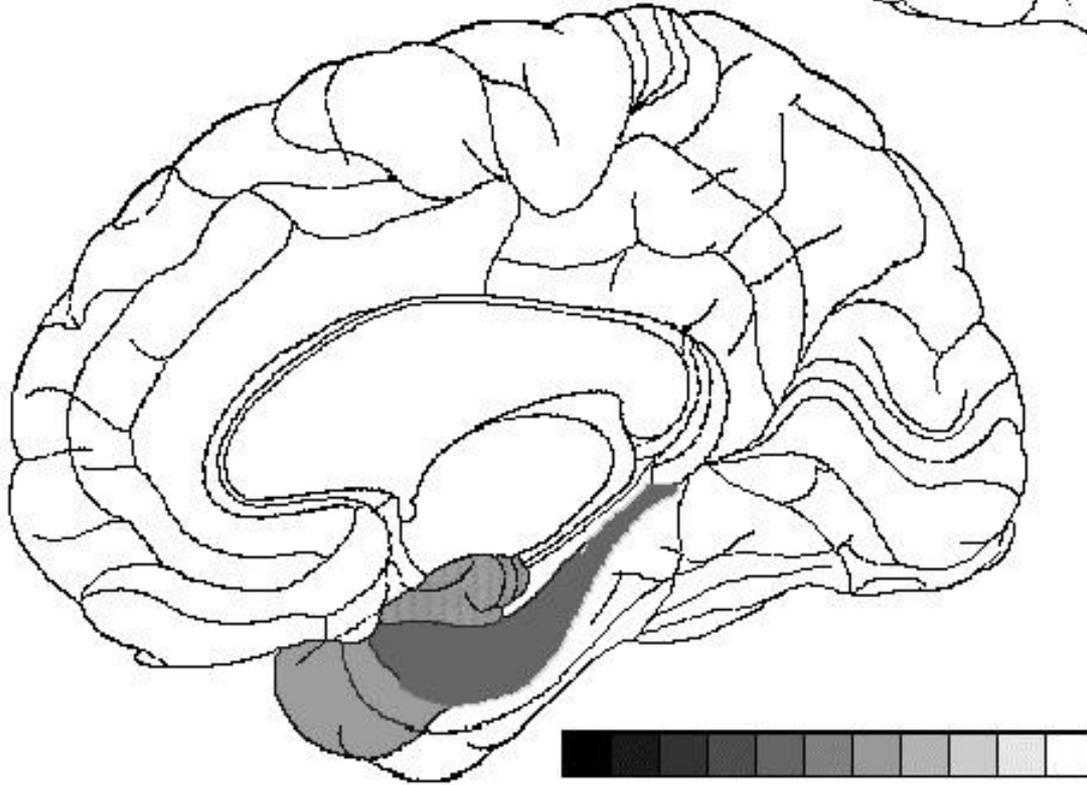
Légers troubles cognitifs



Dépôts discrets
(diffus ?) de
substance
amyloïde

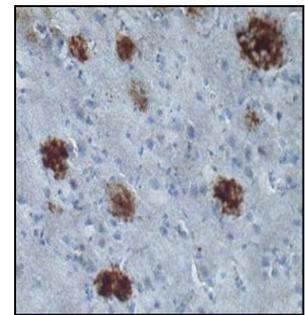


Cortex temporal antérieur

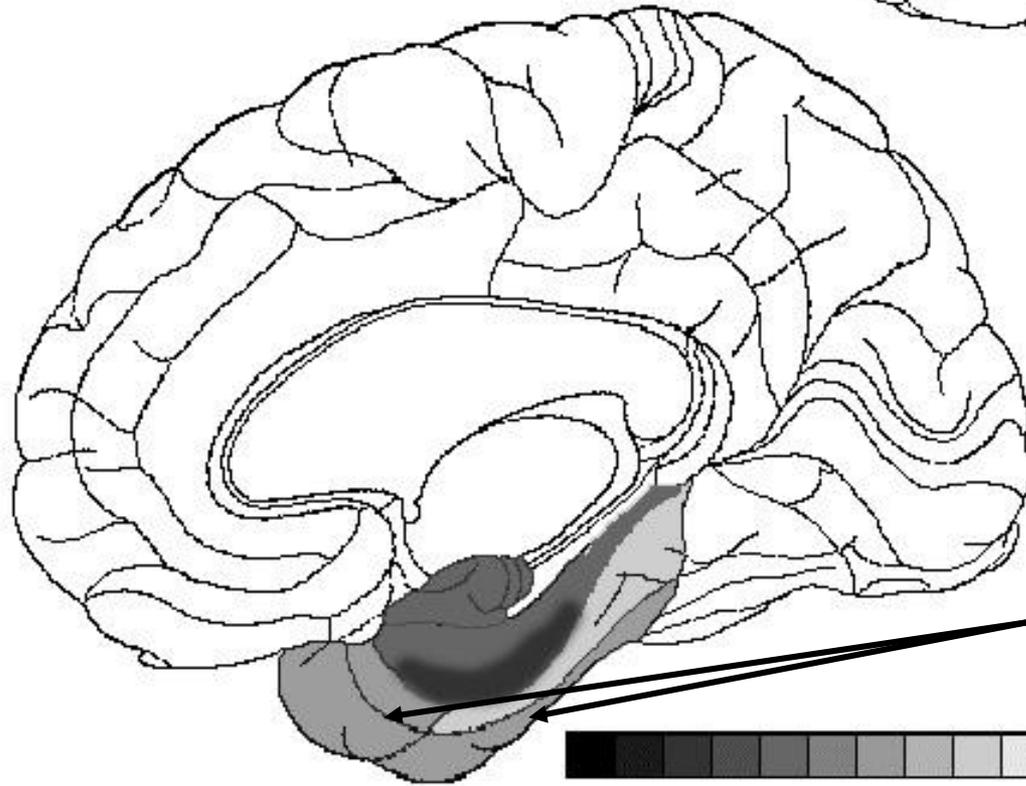
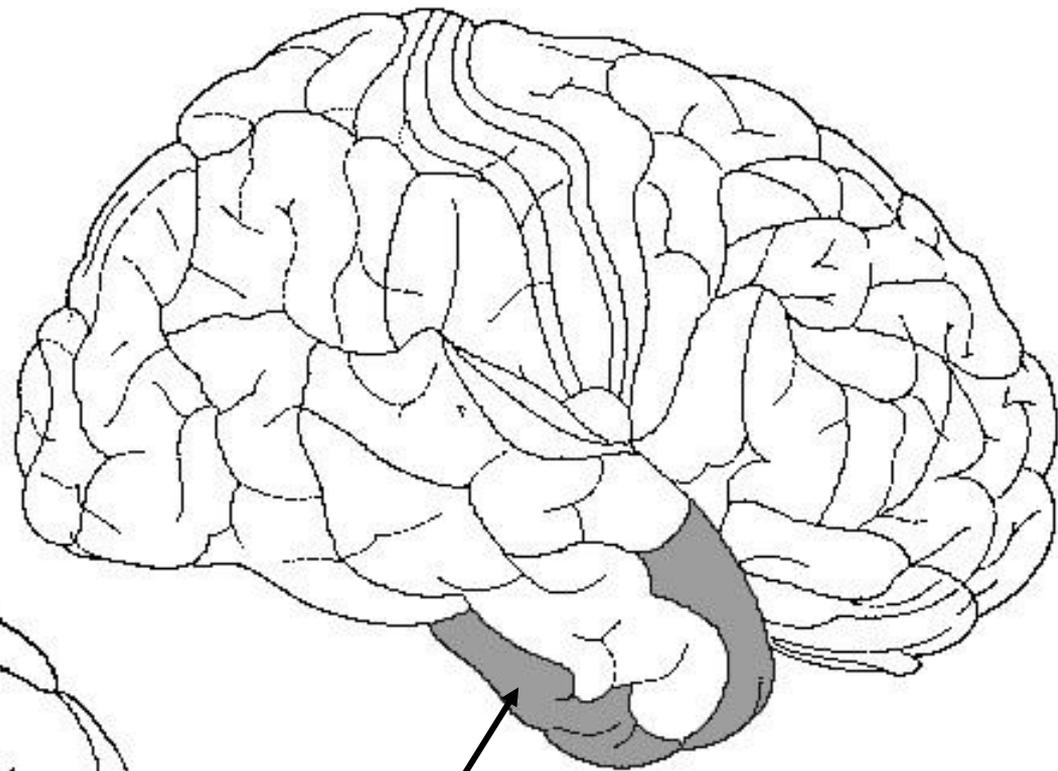


STADE 5

Troubles cognitifs aggravés



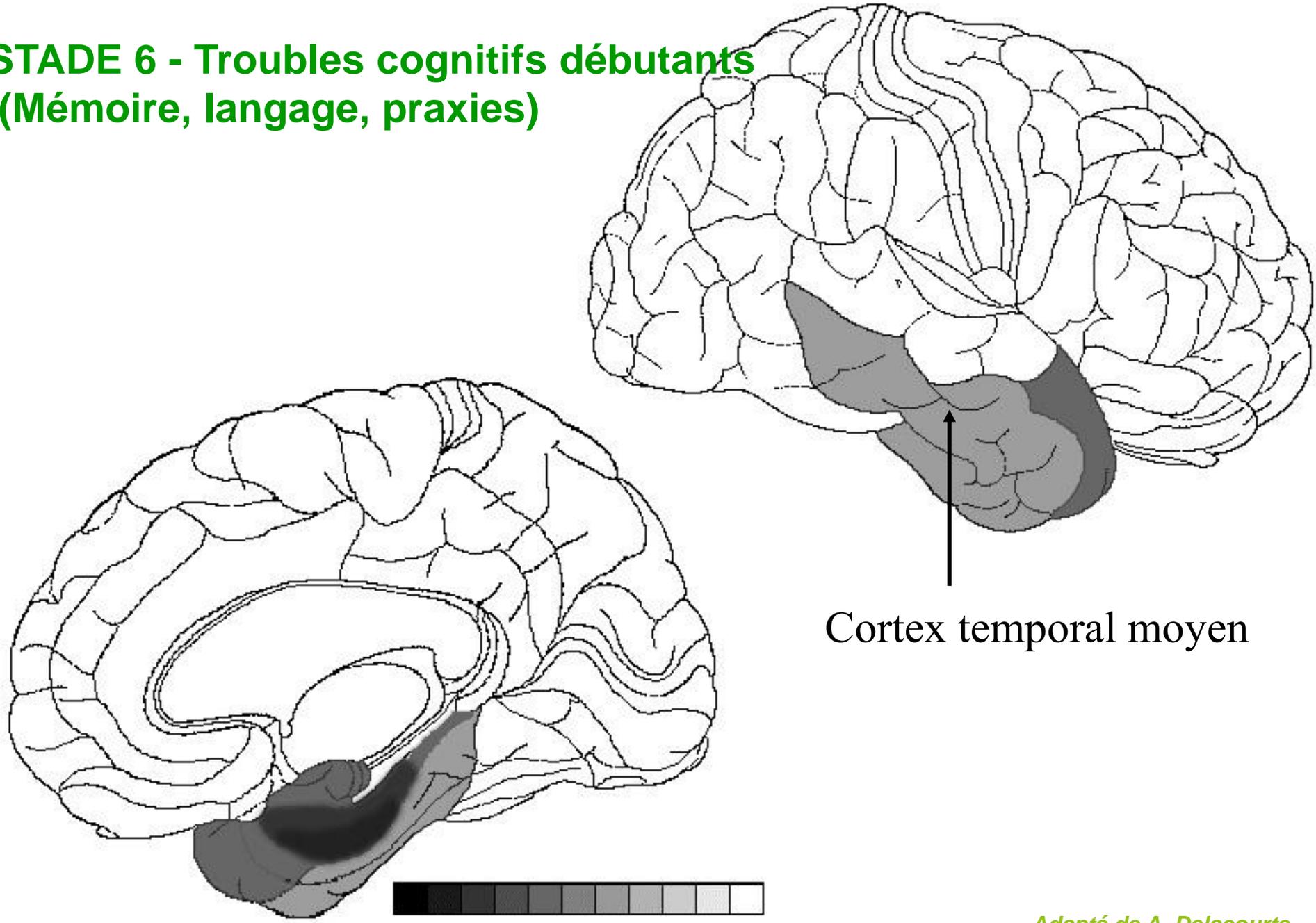
Agrégation du peptide Abeta 42



Cortex temporal inférieur



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

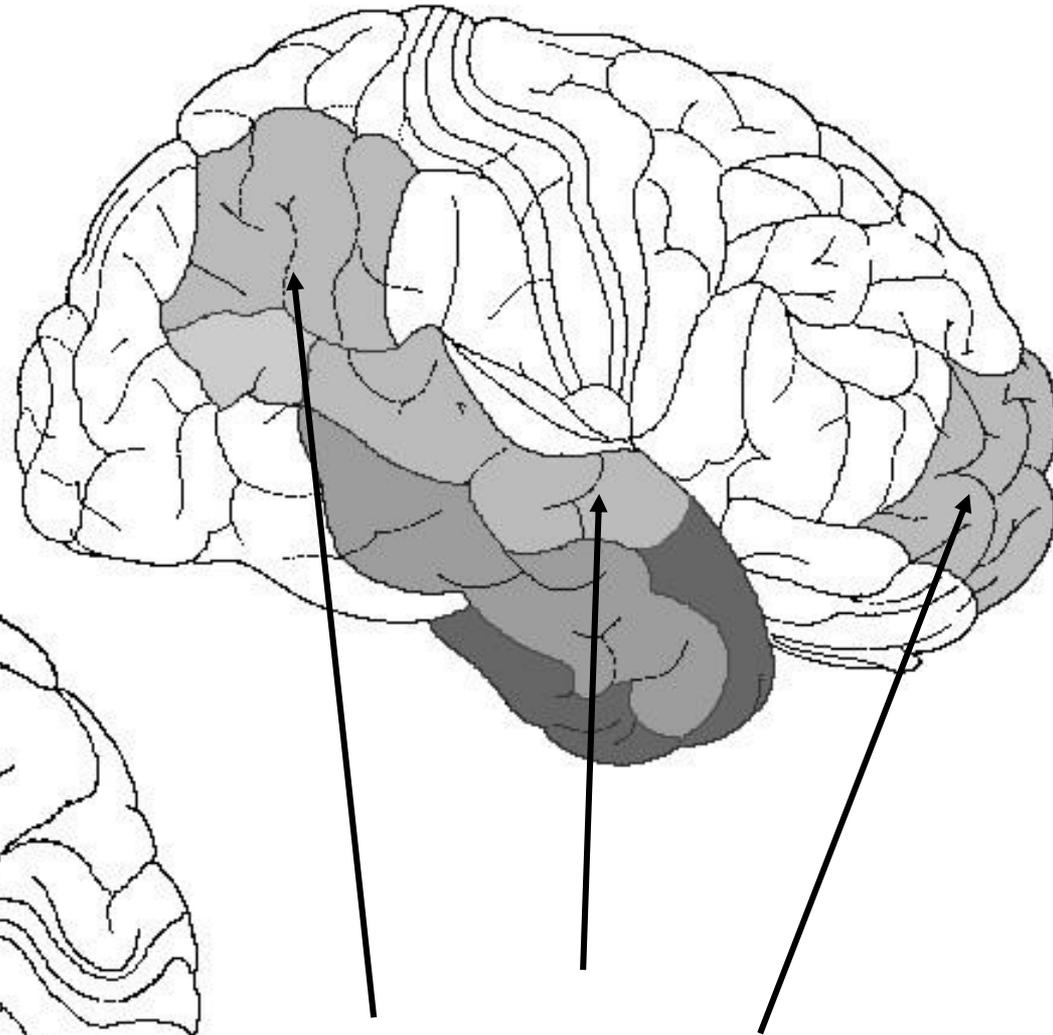
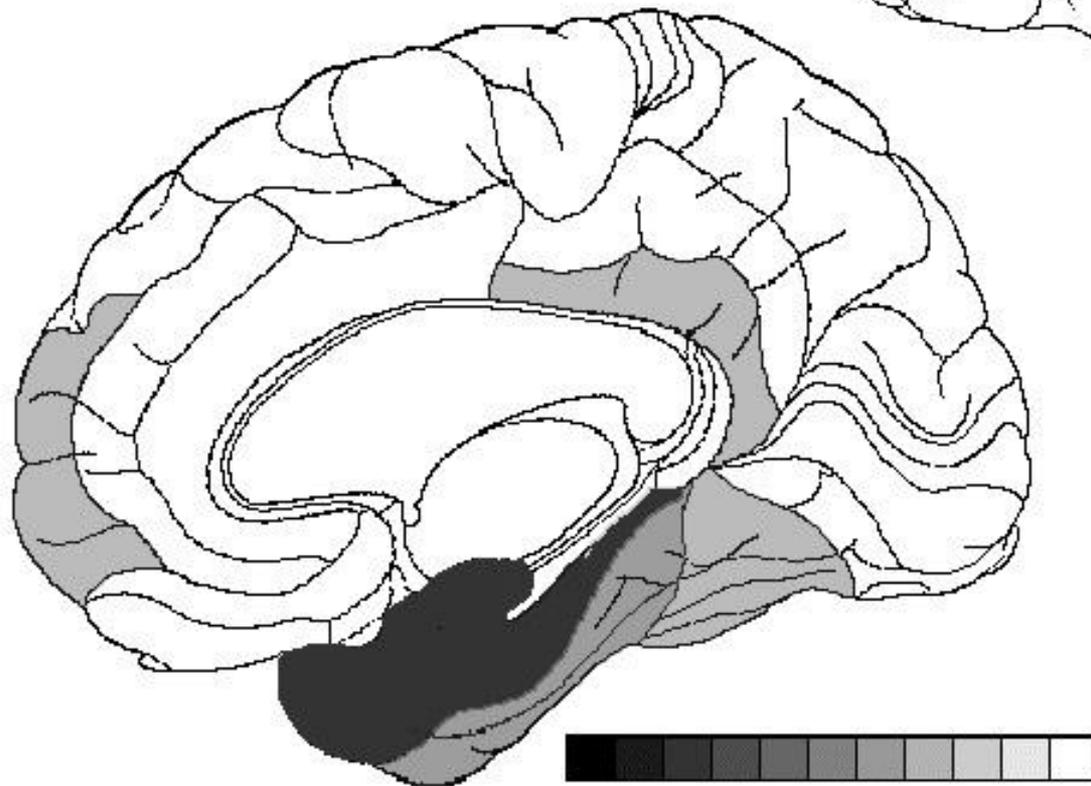


Cortex temporal moyen

STADE 7

Démence débutante
(Mémoire, langage, praxies)

Aires associatives

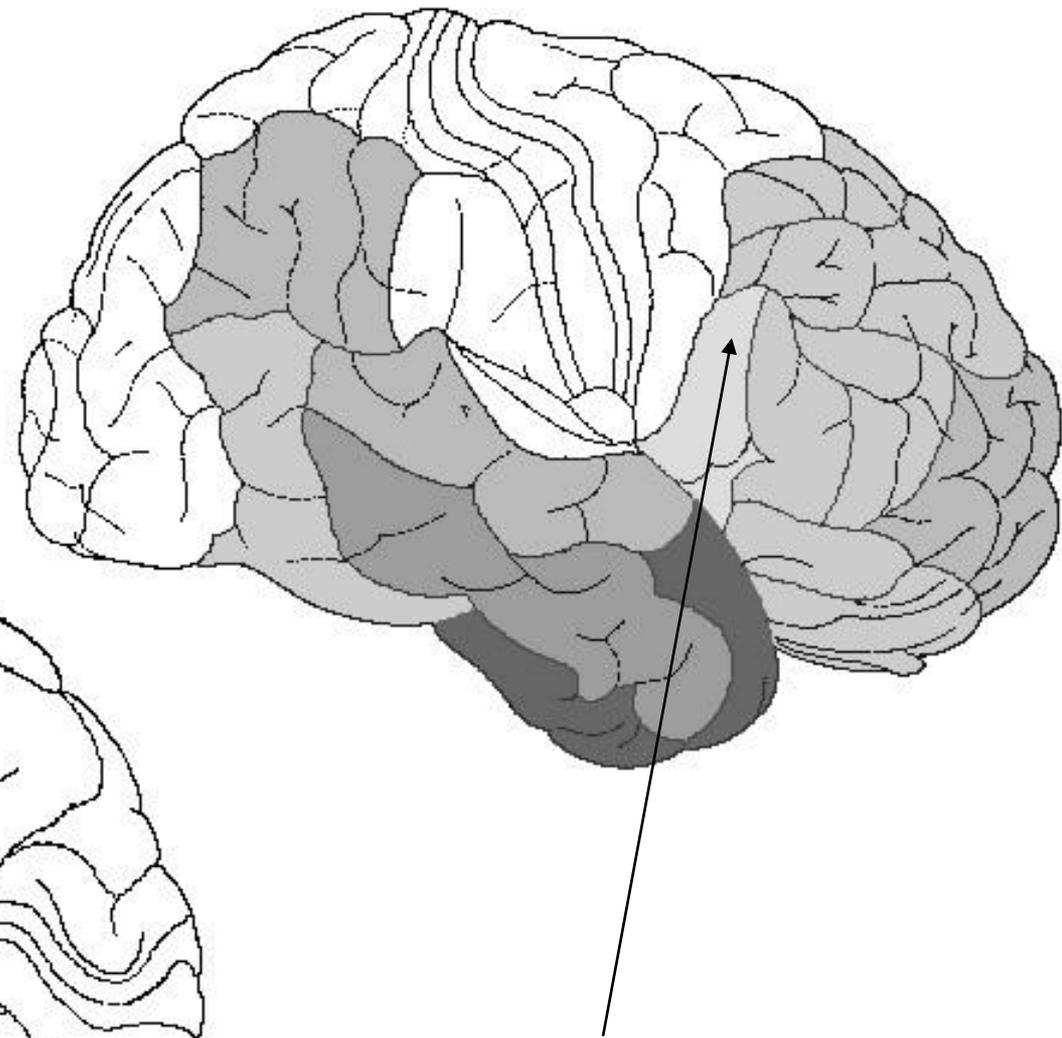
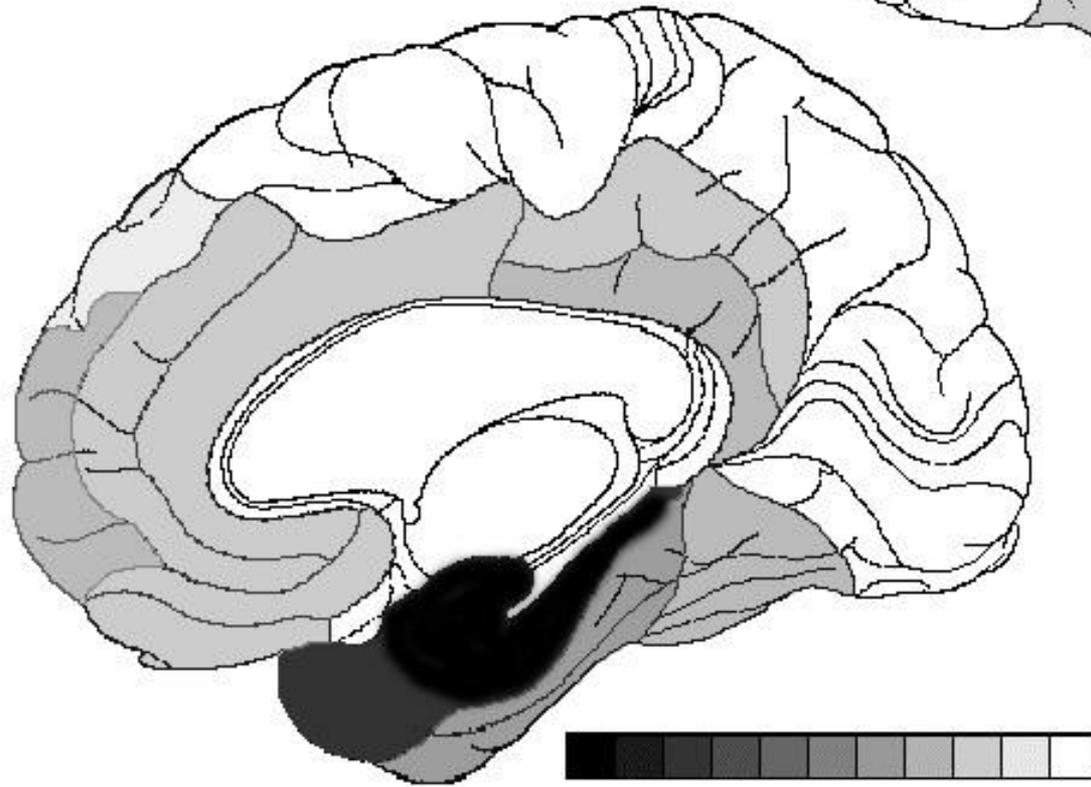


Cortex polymodal associatif

STADE 8

Démence légère à modérée

Cortex secondaire sensitif
ou moteur



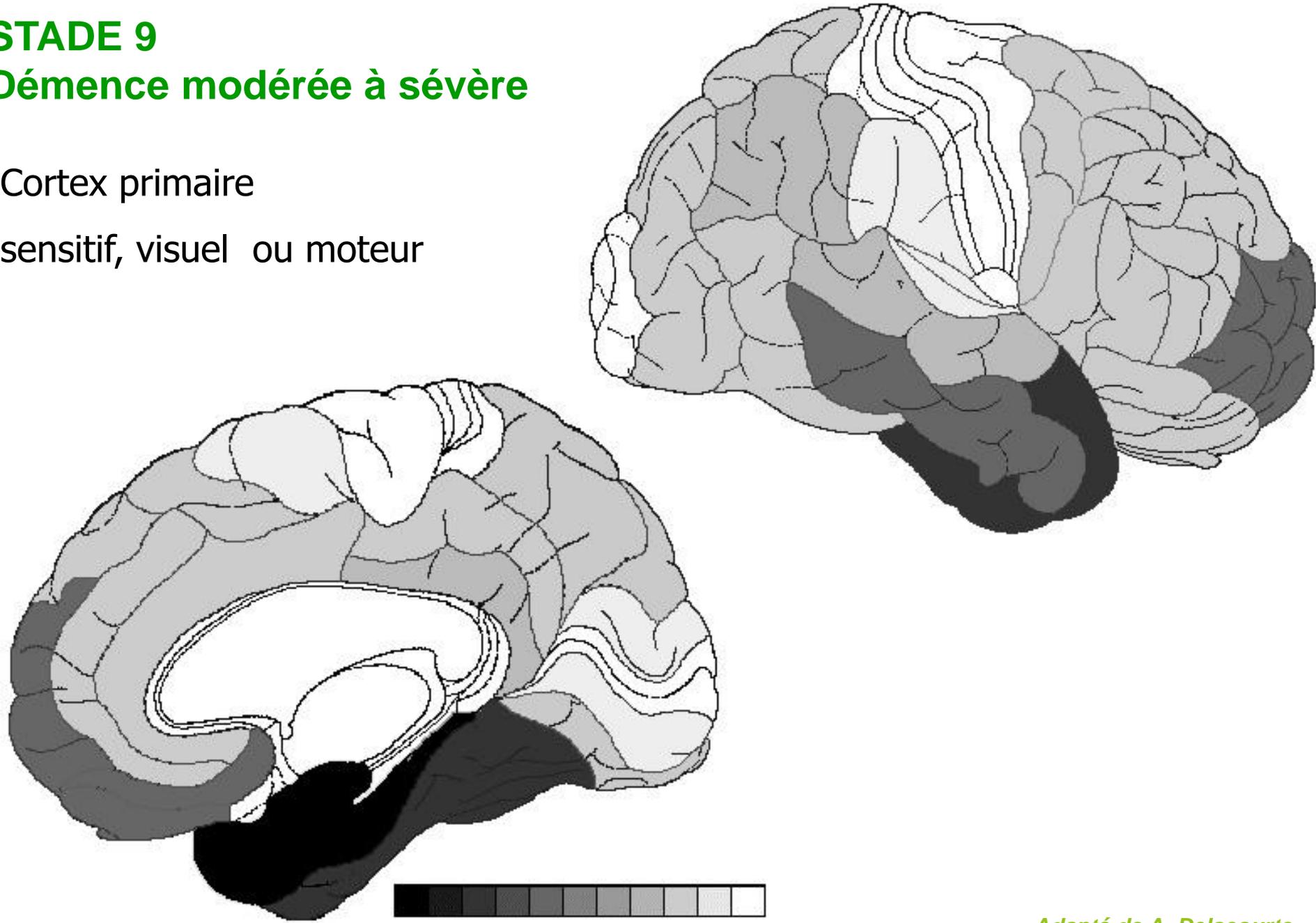
Aire de Broca

STADE 9

Démence modérée à sévère

Cortex primaire

sensitif, visuel ou moteur

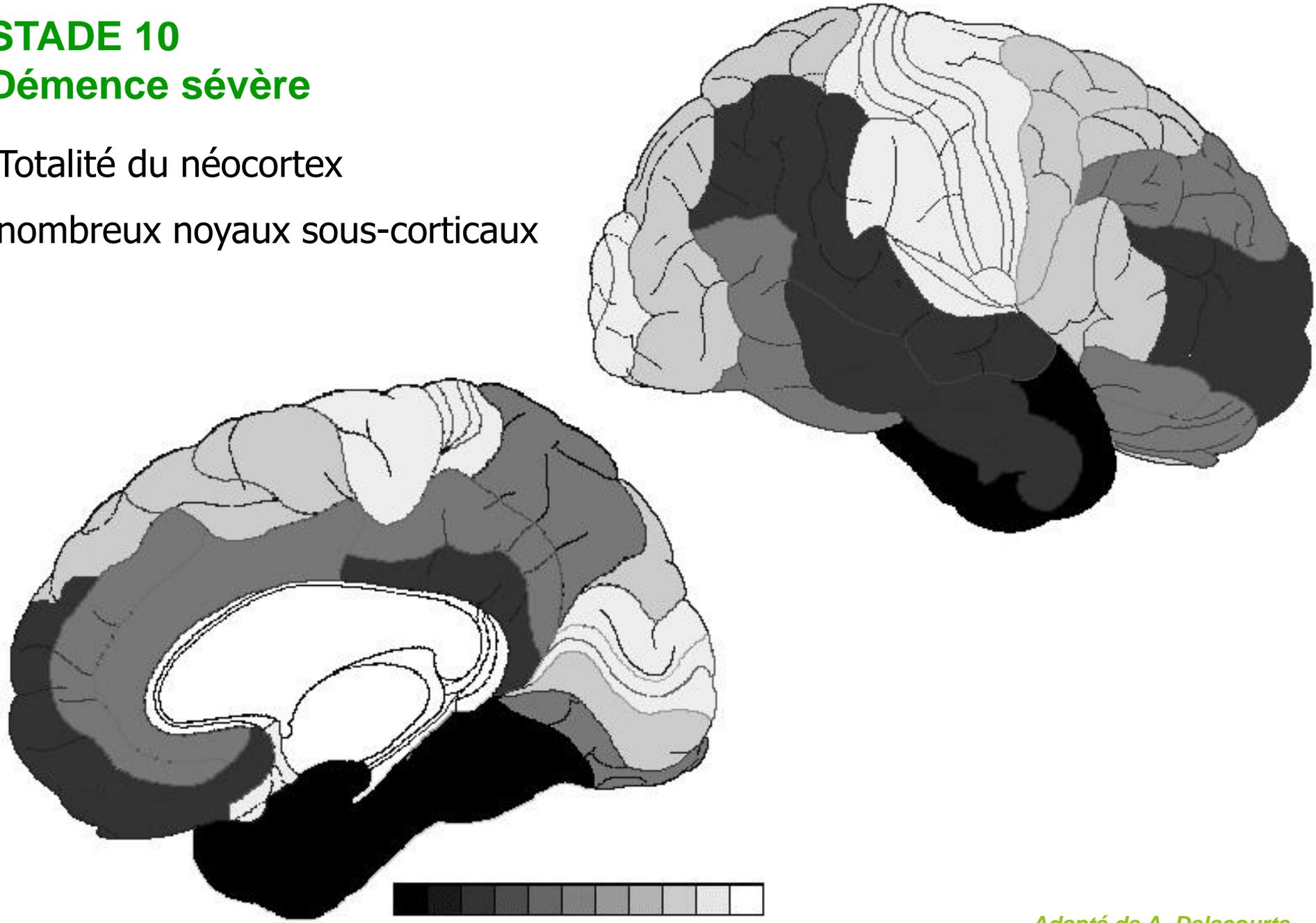


STADE 10

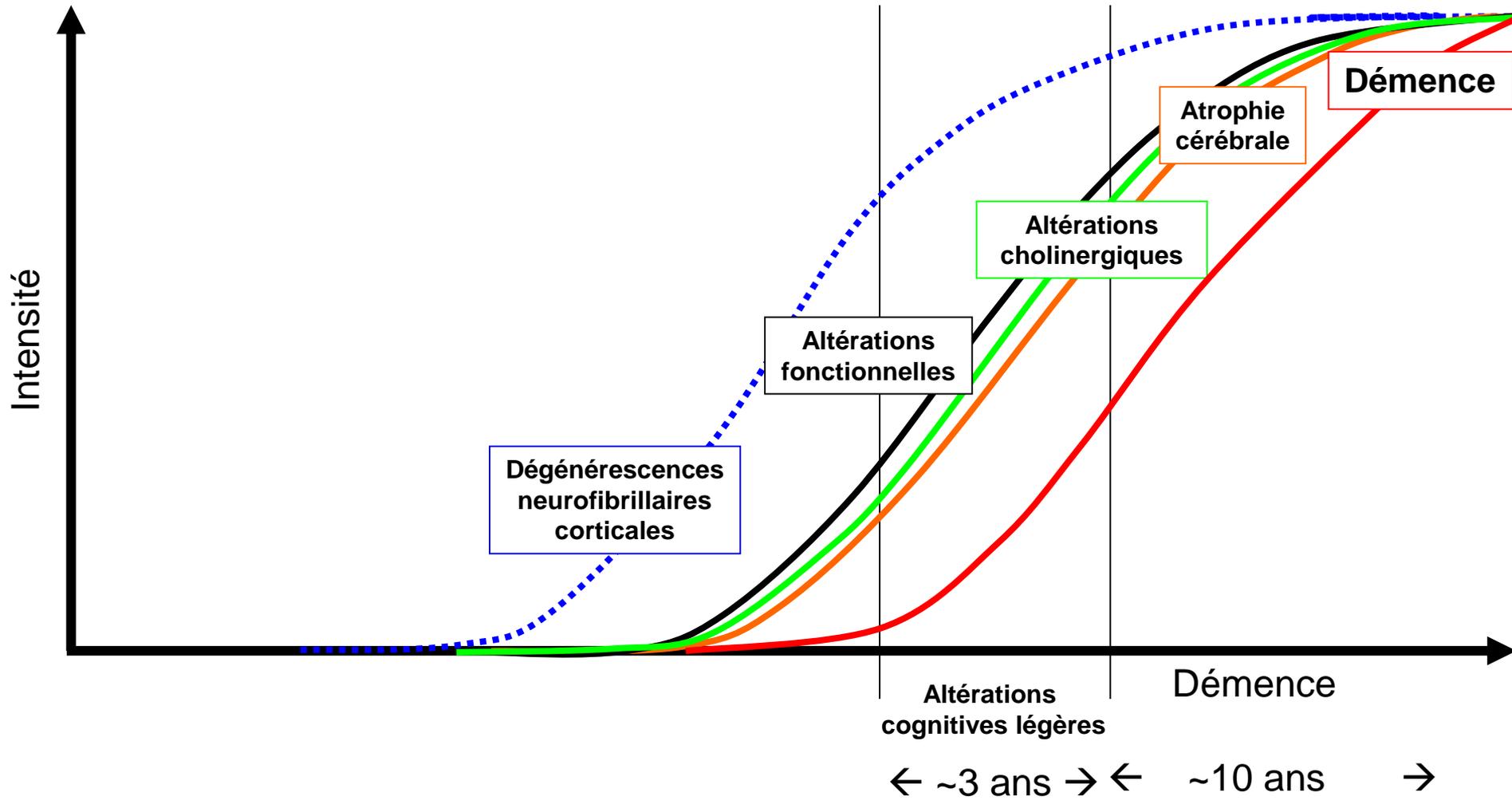
Démence sévère

Totalité du néocortex

nombreux noyaux sous-corticaux



HISTOIRE NATURELLE DE LA MALADIE

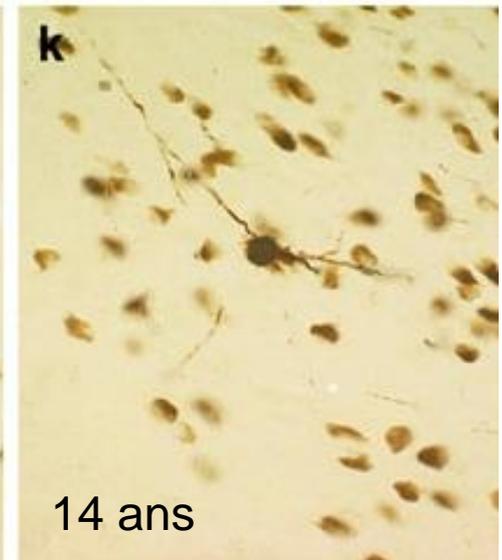
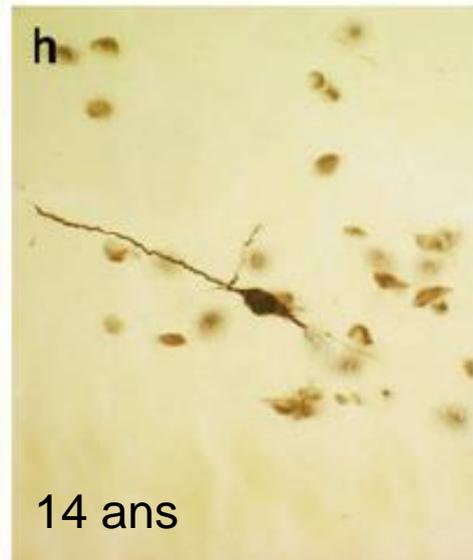
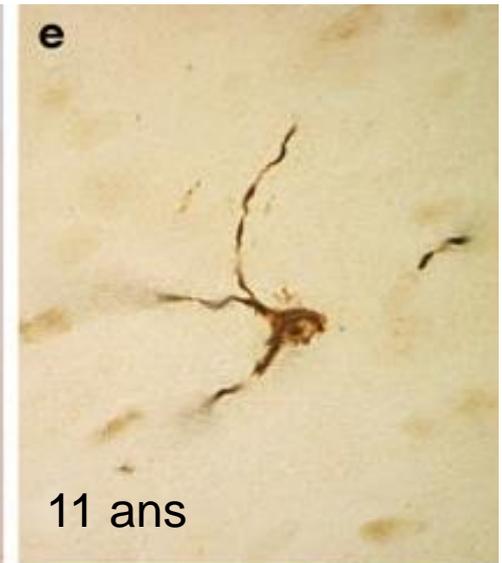
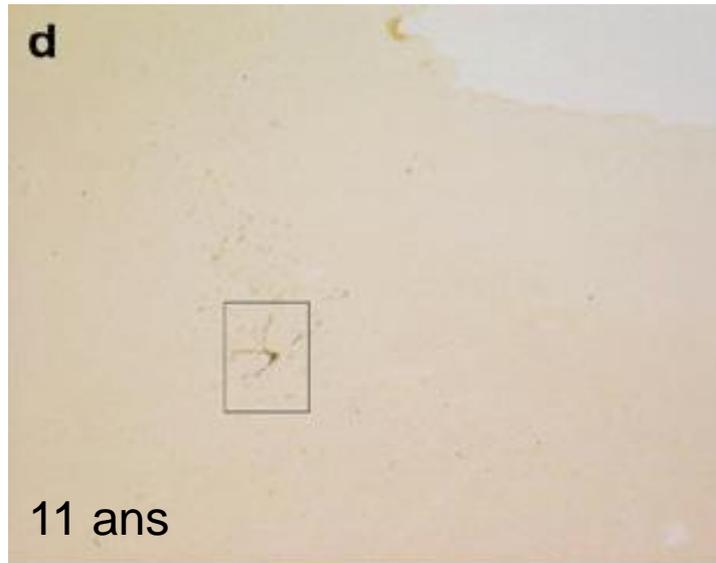
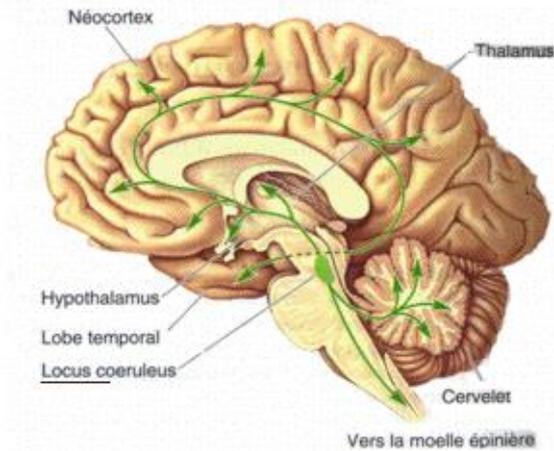
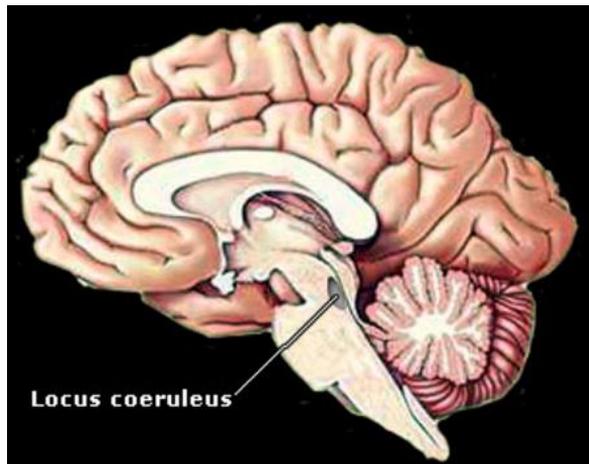




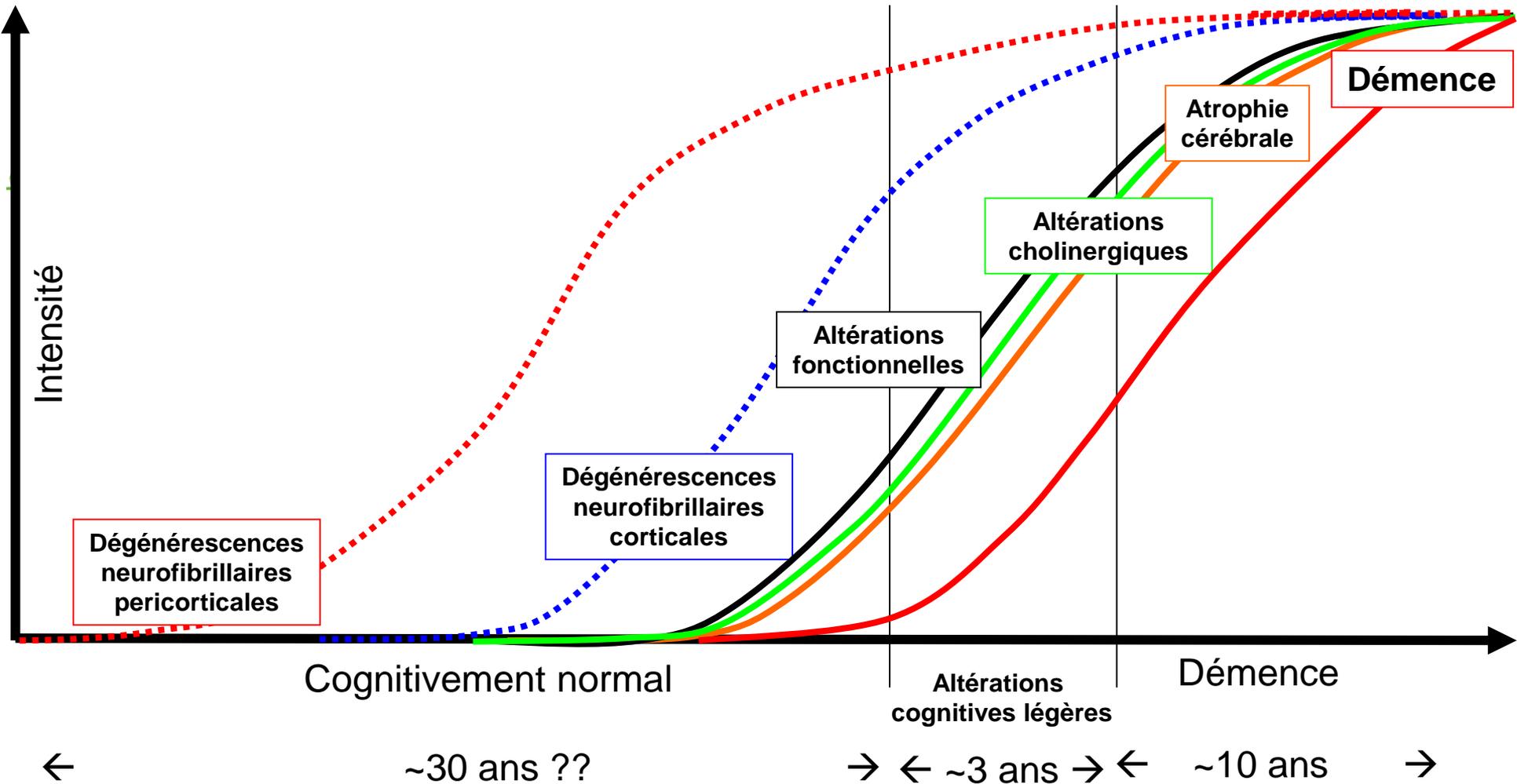
HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Quelles sont les toutes premières lésions ?

LES TOUTES PREMIÈRES LÉSIONS DE LA MALADIE ?



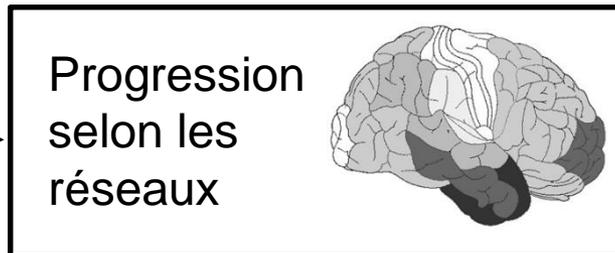
HISTOIRE NATURELLE DE LA MALADIE



HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Hypothèse explicative

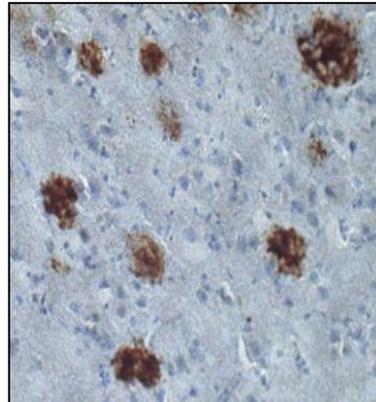
Origine
de Tau ?





HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Plaques amyloïdes



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

**Control
Subject**

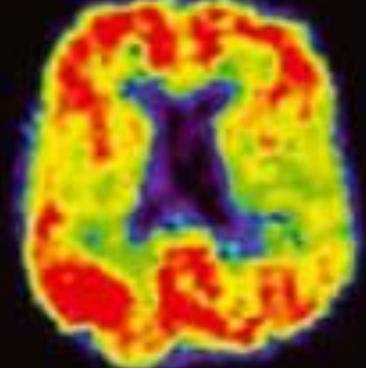
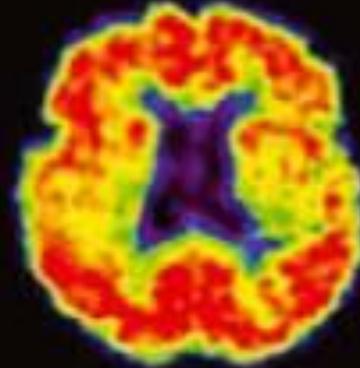
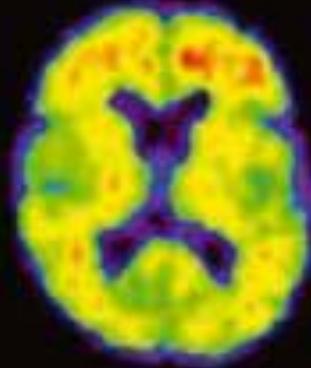
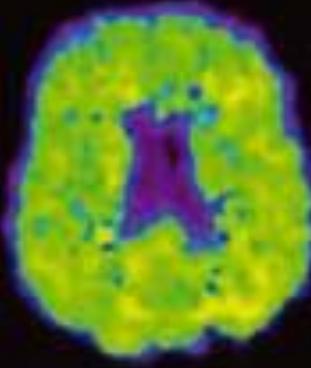
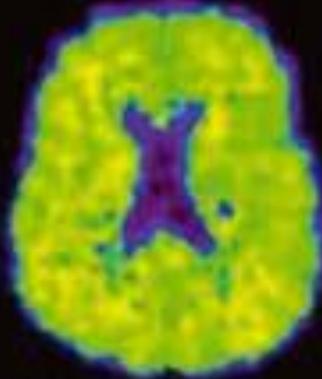
MCI-1

MCI Patients

MCI-2

MCI-3

**AD
Patient**



University of Pittsburgh
PET Amyloid Imaging Group

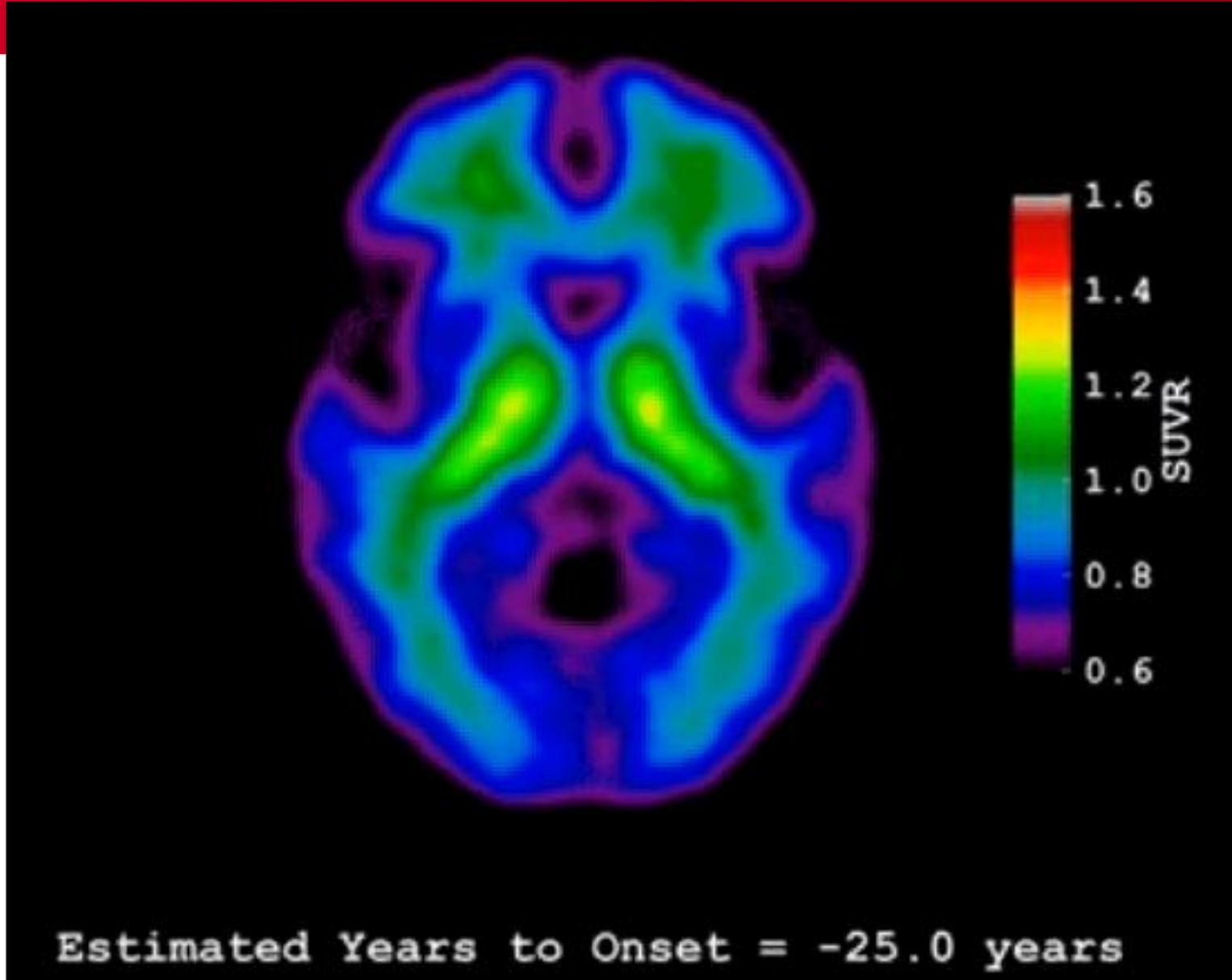
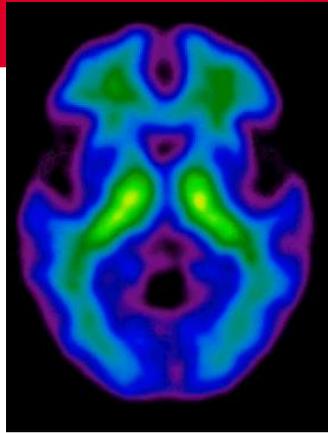
Min

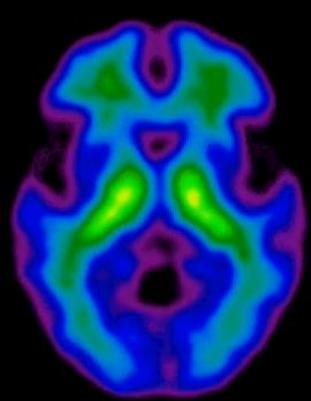


Max

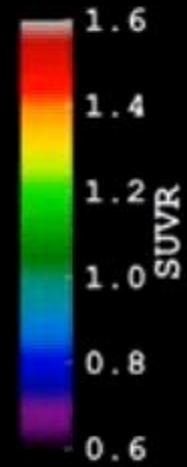
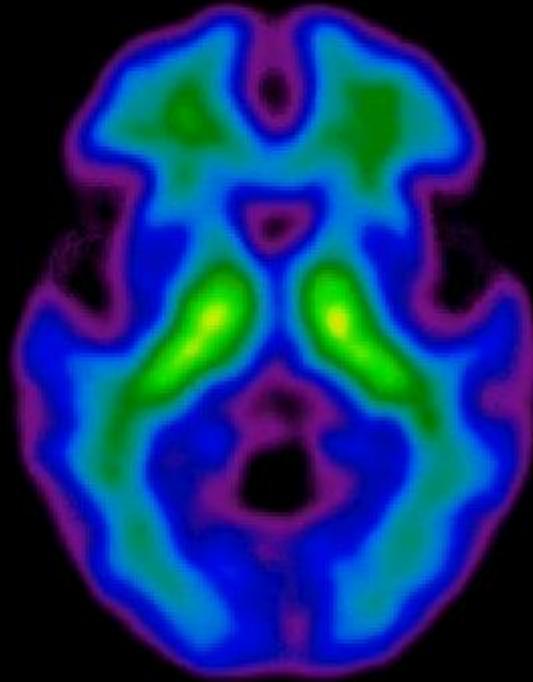
[¹¹C]PIB

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

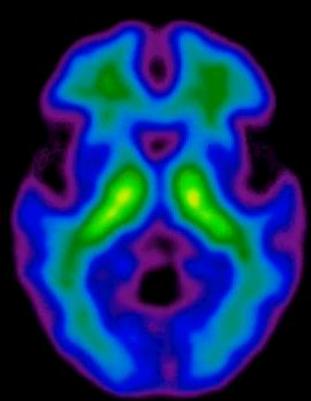




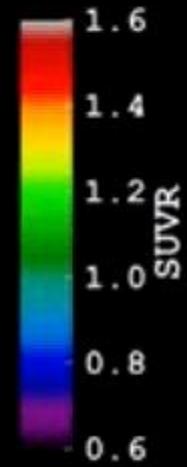
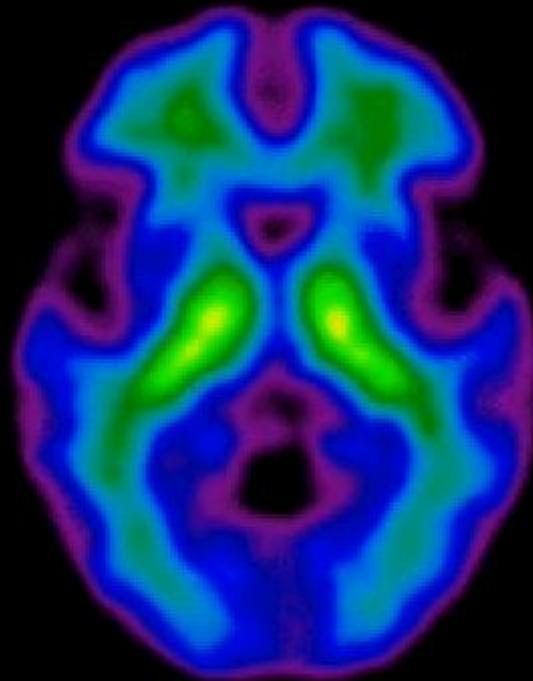
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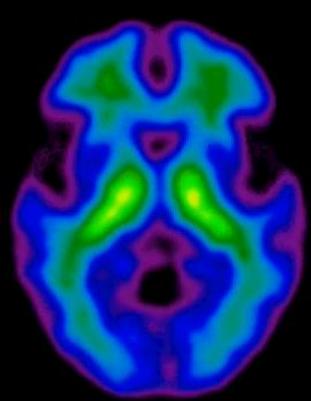
Estimated Years to Onset = -25.0 years



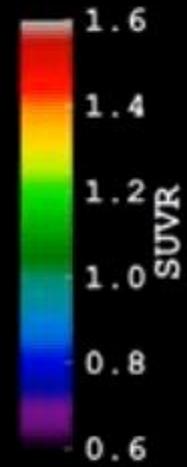
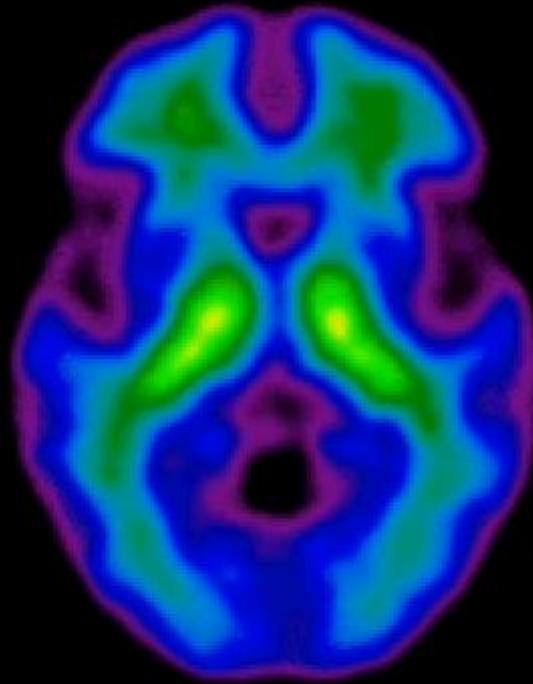
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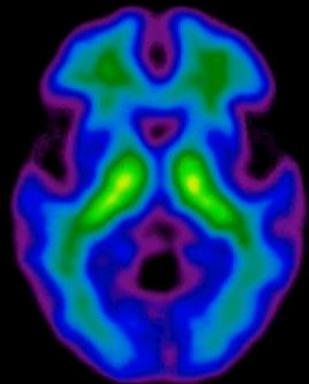
Estimated Years to Onset = -24.0 years



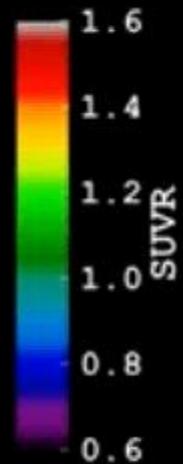
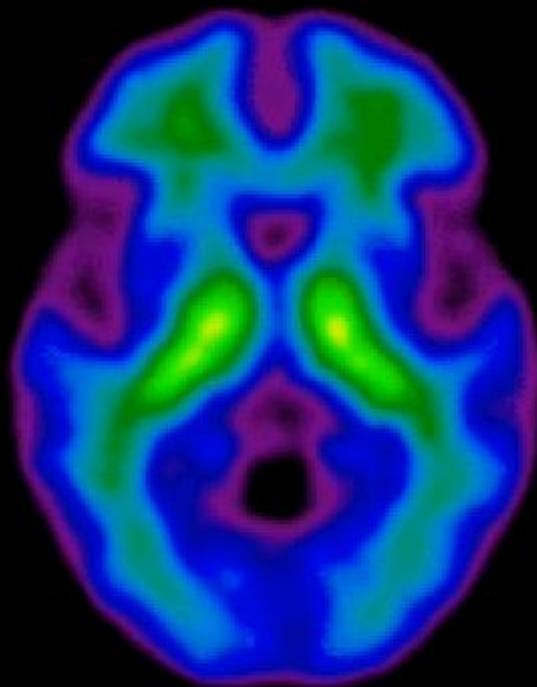
-25.0 years



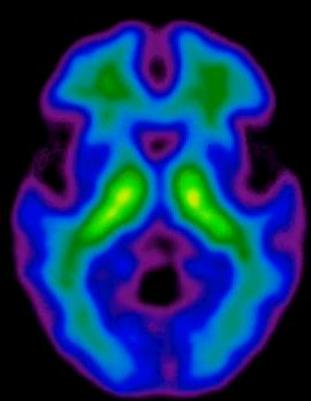
Estimated Years to Onset = -23.0 years



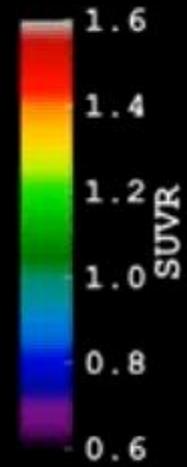
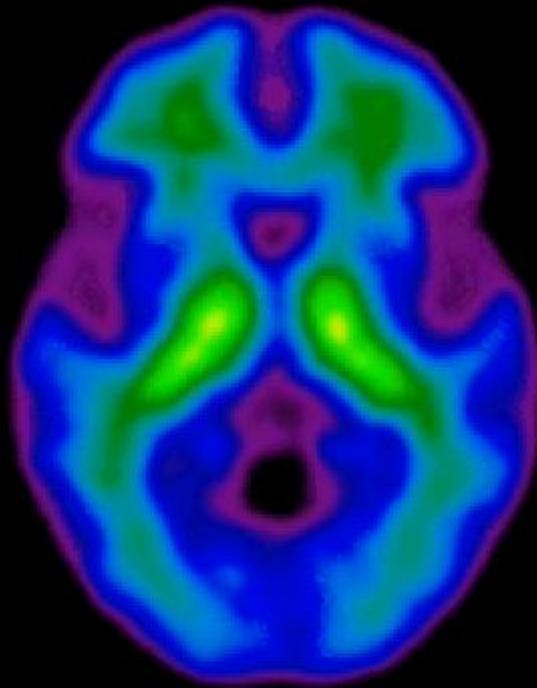
-25.0 years



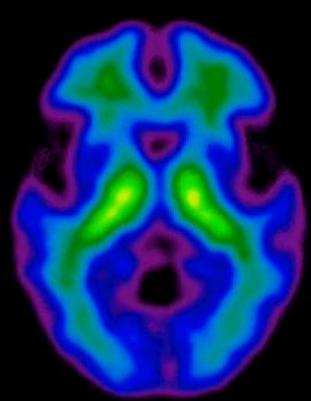
Estimated Years to Onset = -22.0 years



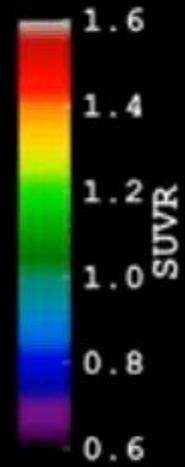
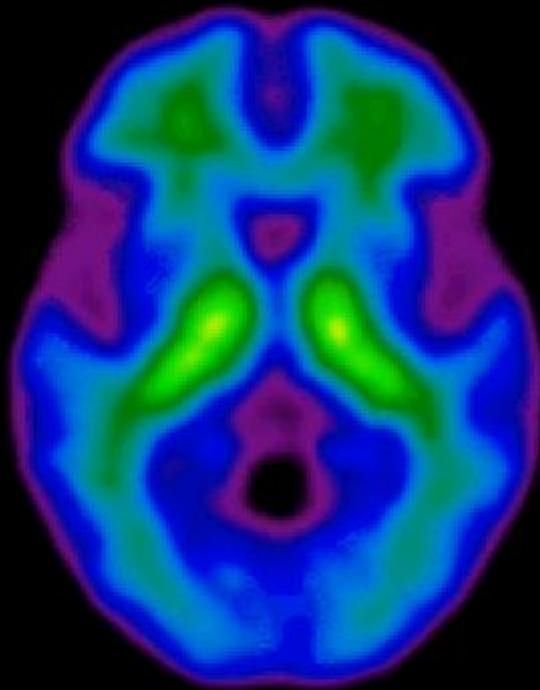
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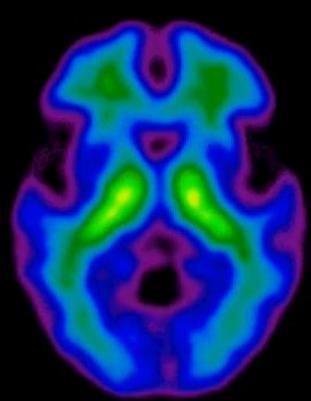
Estimated Years to Onset = -21.0 years



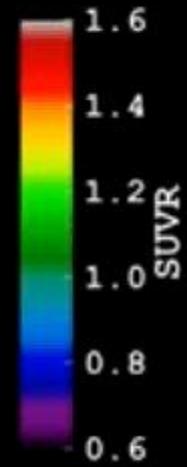
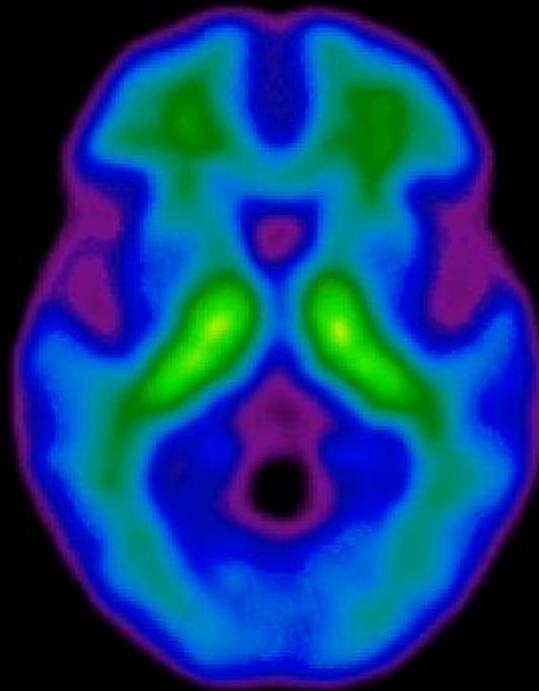
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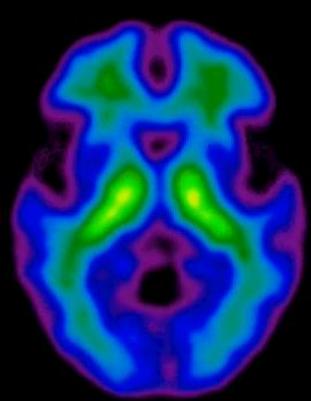
Estimated Years to Onset = -20.0 years



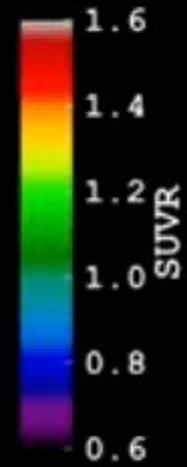
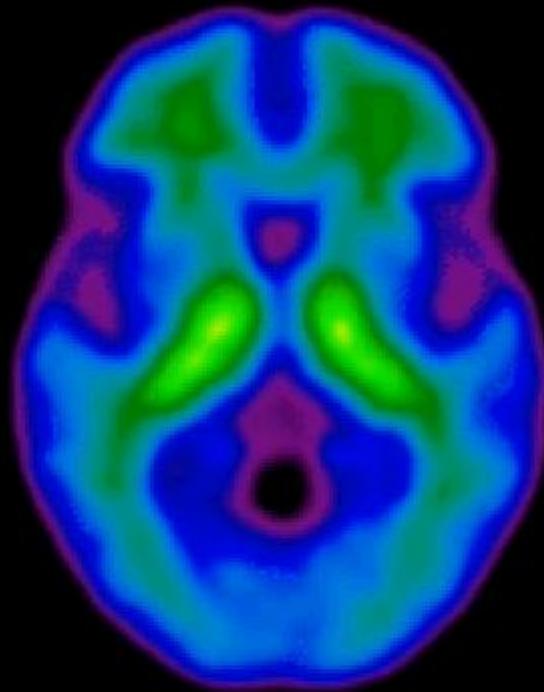
-25.0 years



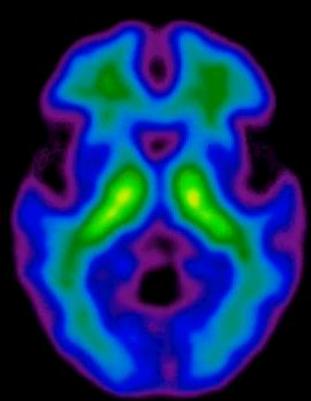
Estimated Years to Onset = -19.0 years



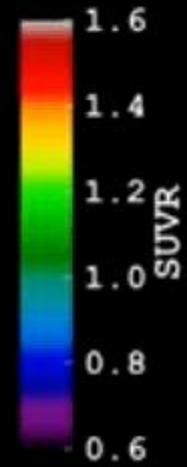
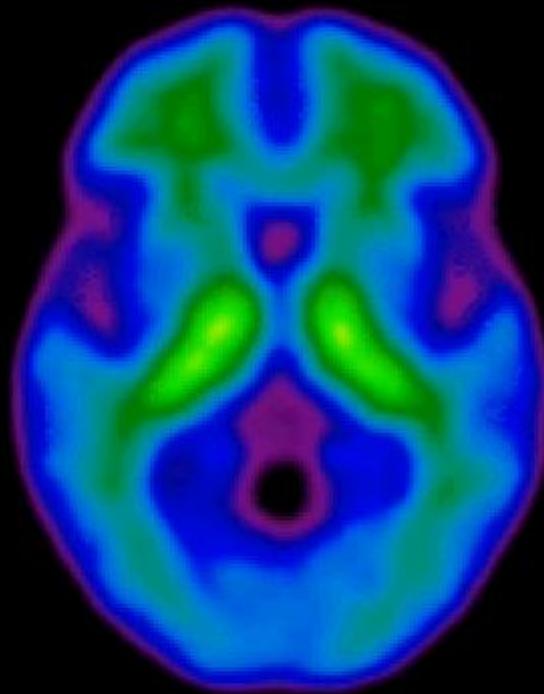
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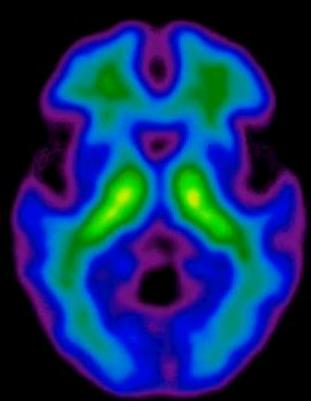
Estimated Years to Onset = -18.0 years



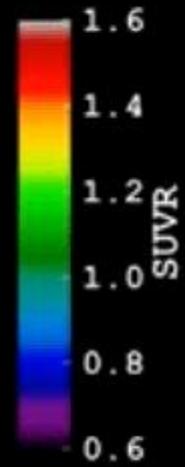
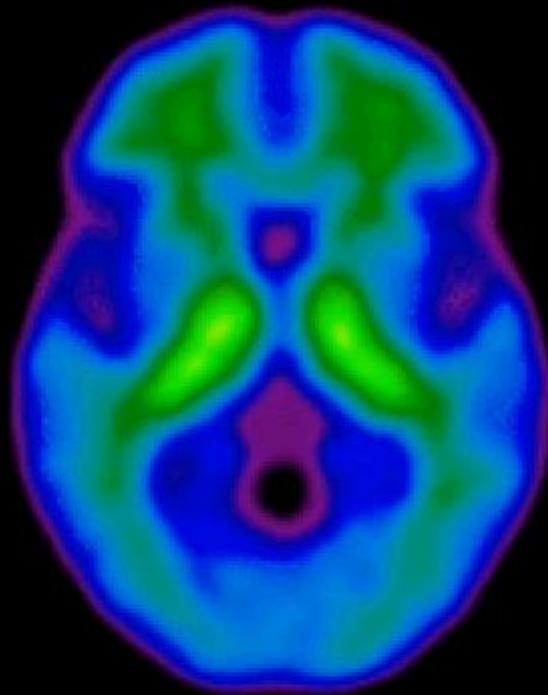
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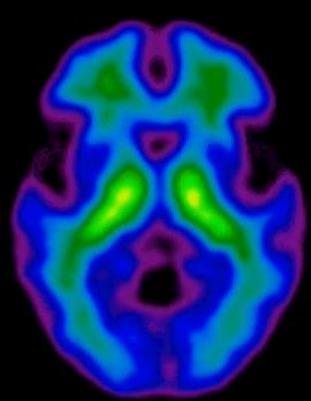
Estimated Years to Onset = -17.0 years



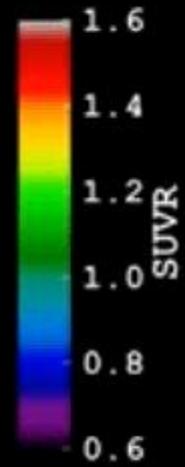
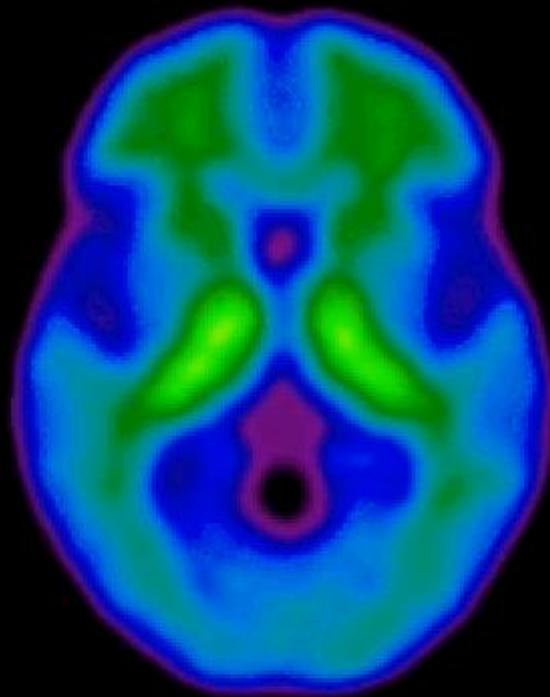
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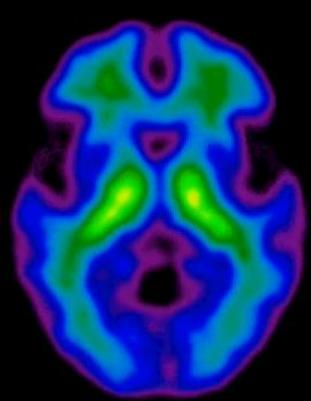
Estimated Years to Onset = -16.0 years



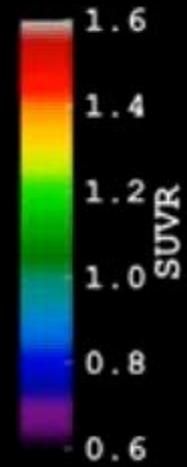
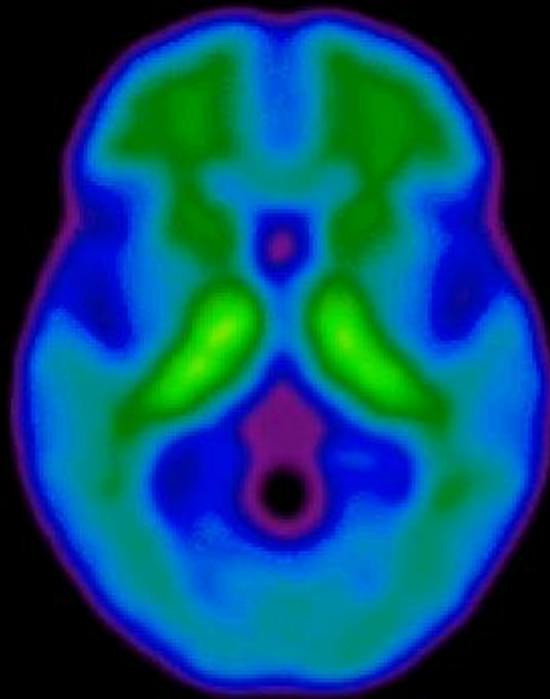
-25.0 years



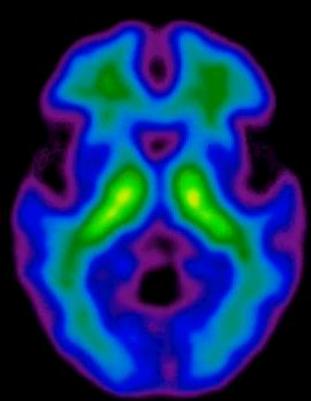
Estimated Years to Onset = -15.0 years



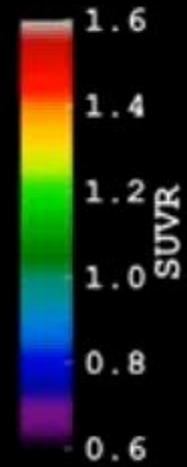
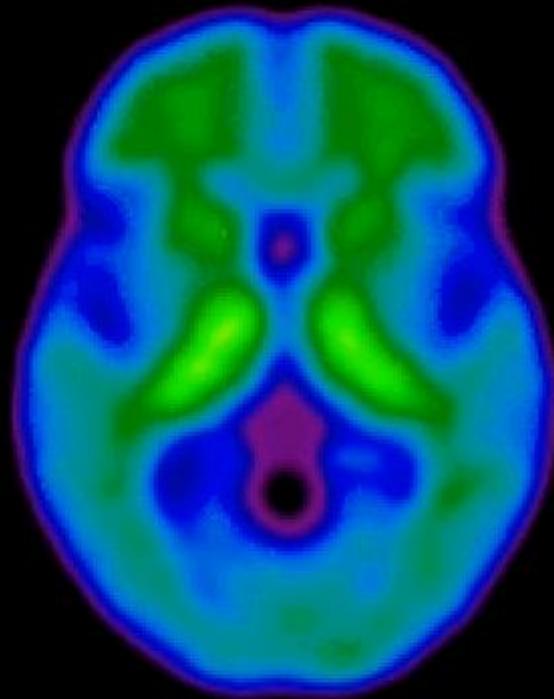
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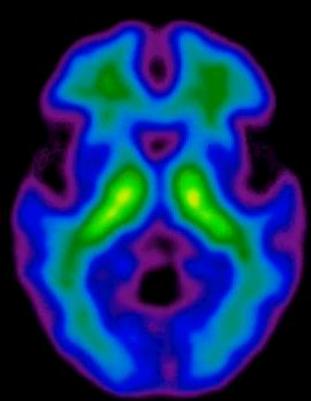
Estimated Years to Onset = -14.0 years



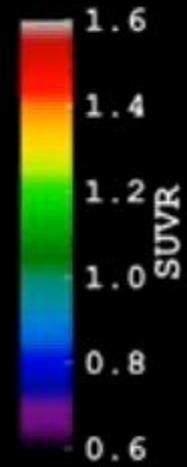
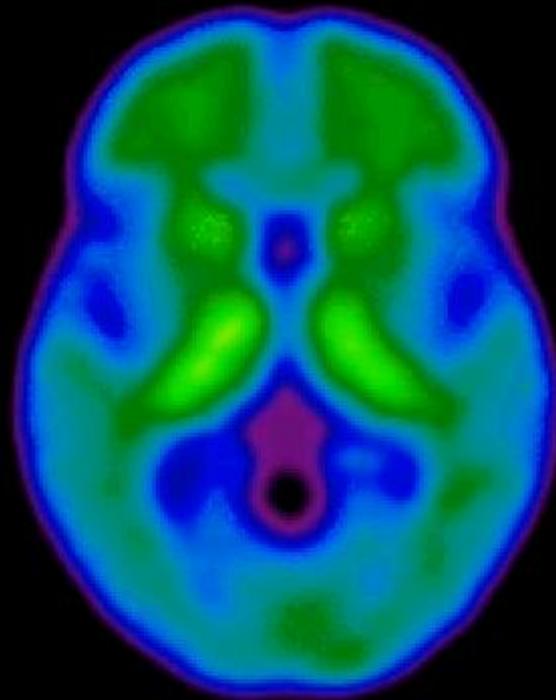
-25.0 years



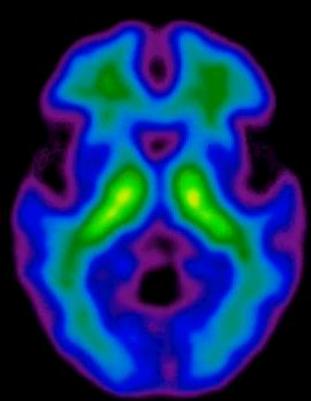
Estimated Years to Onset = -13.0 years



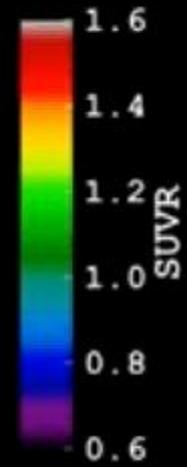
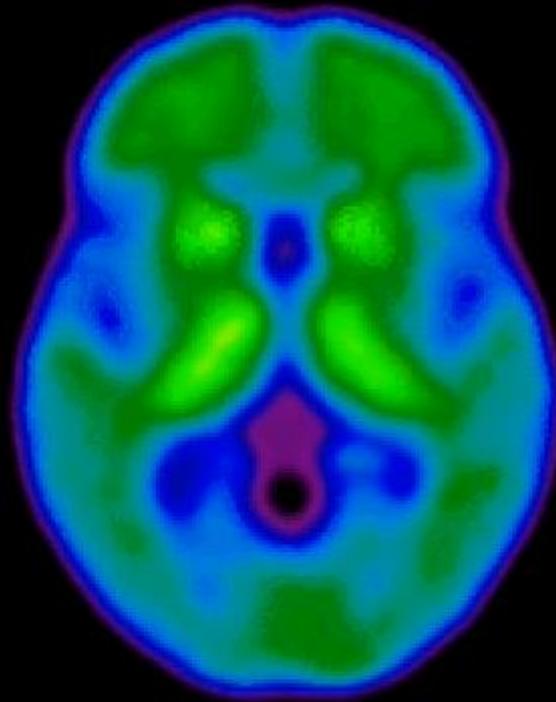
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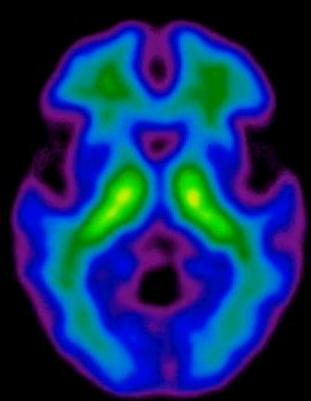
Estimated Years to Onset = -12.0 years



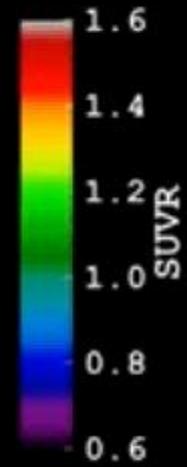
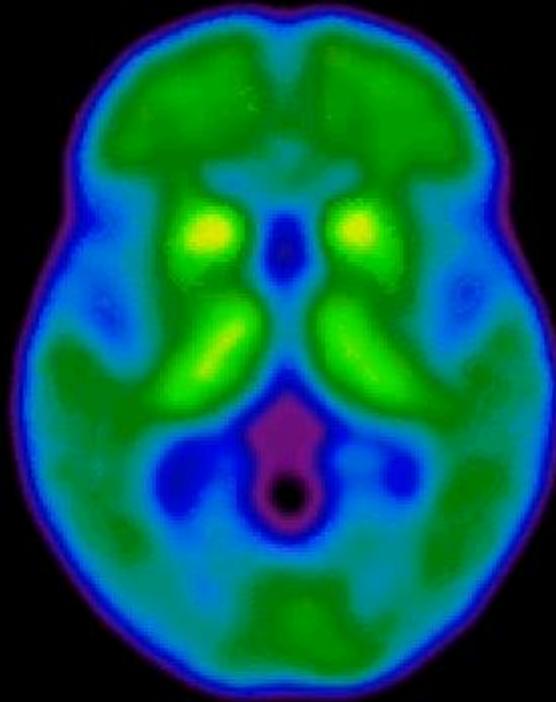
-25.0 years



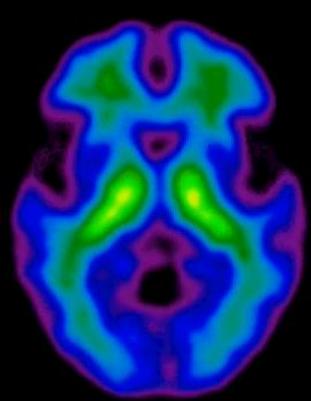
Estimated Years to Onset = -11.0 years



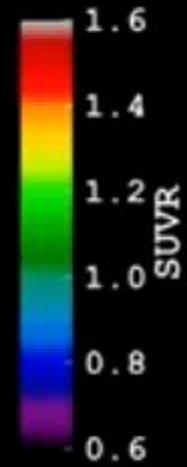
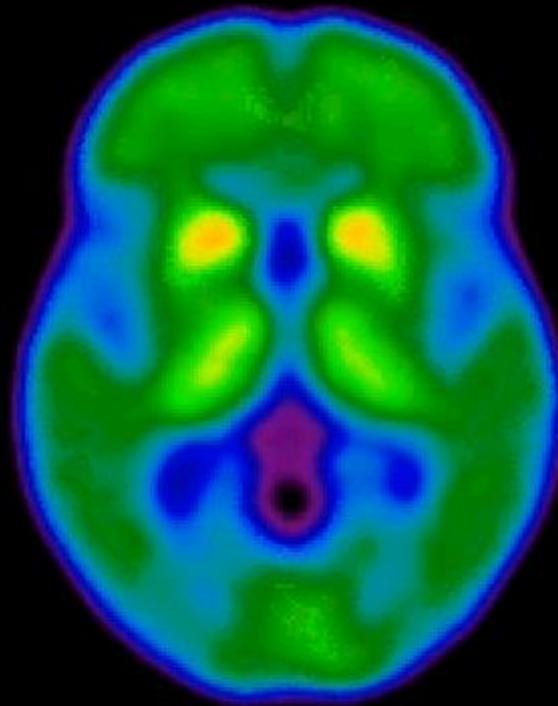
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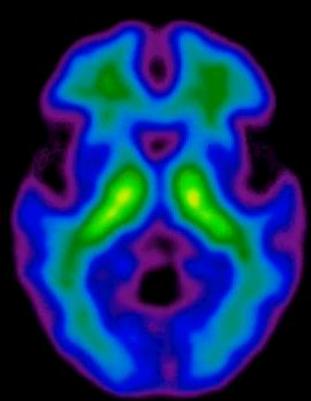
Estimated Years to Onset = -10.0 years



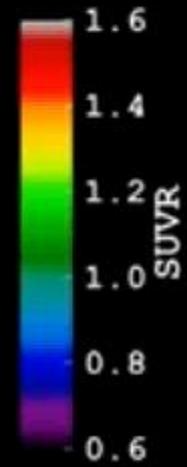
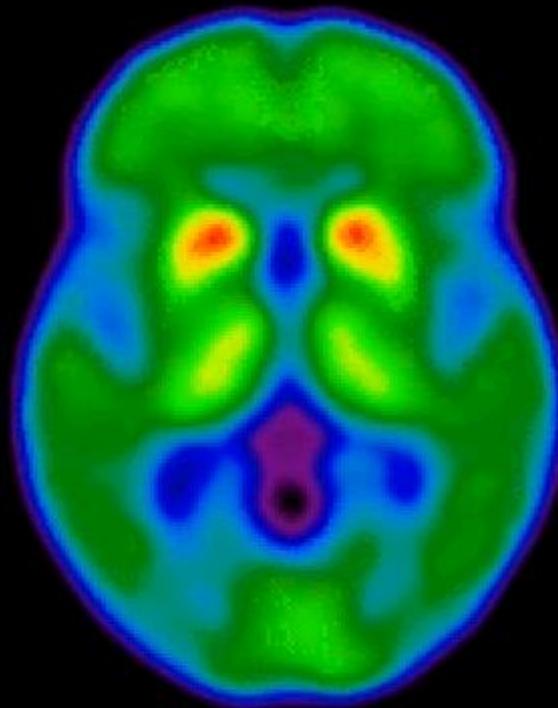
-25.0 years



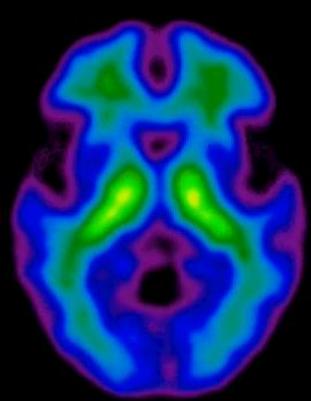
Estimated Years to Onset = -9.0 years



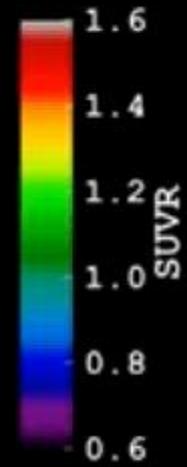
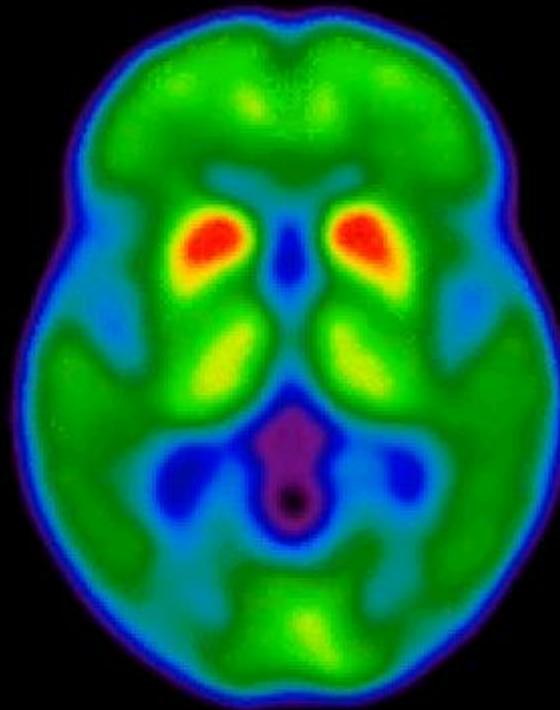
-25.0 years



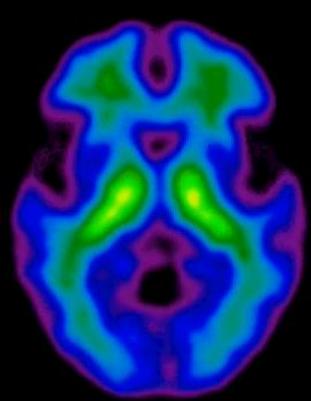
Estimated Years to Onset = -8.0 years



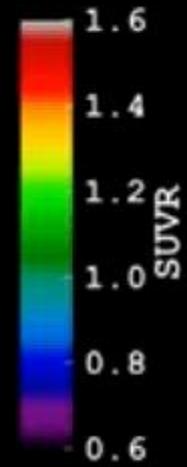
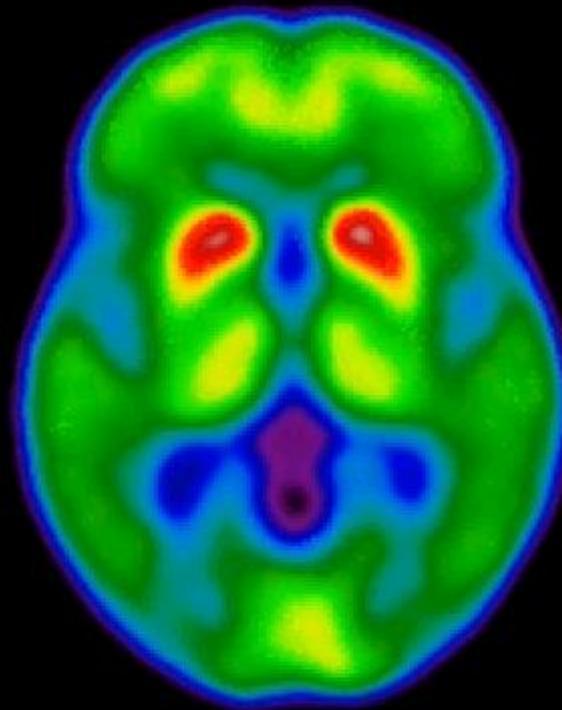
-25.0 years



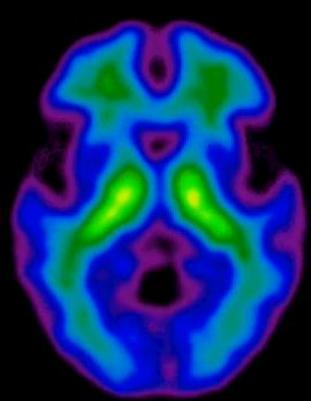
Estimated Years to Onset = -7.0 years



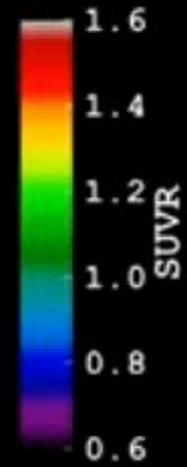
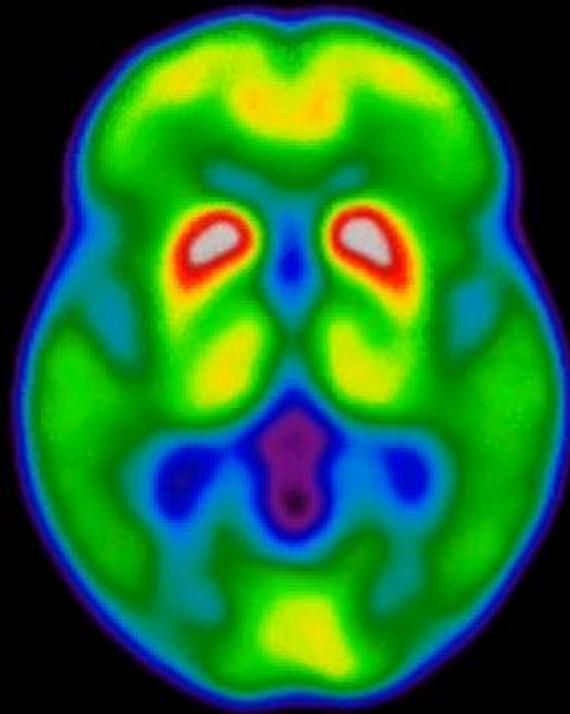
-25.0 years



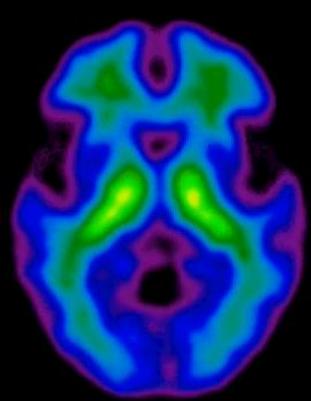
Estimated Years to Onset = -6.0 years



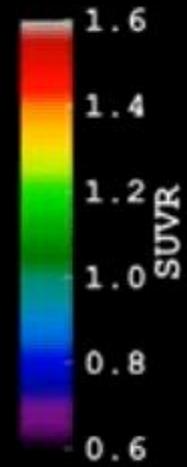
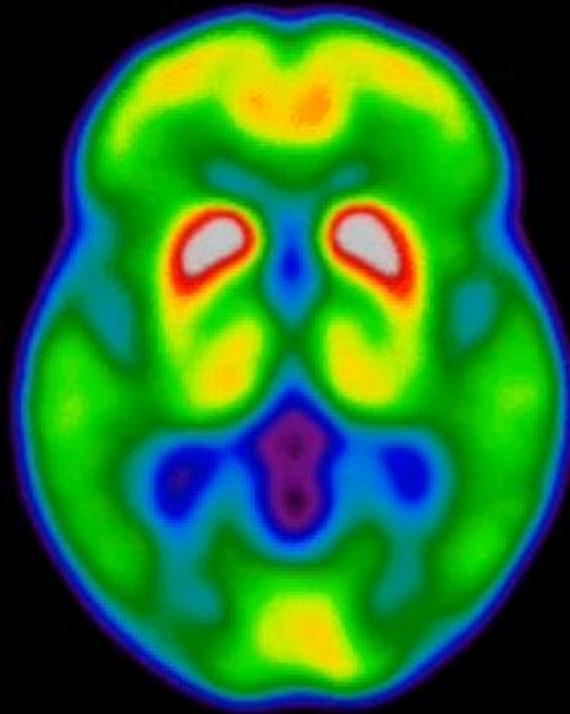
-25.0 years



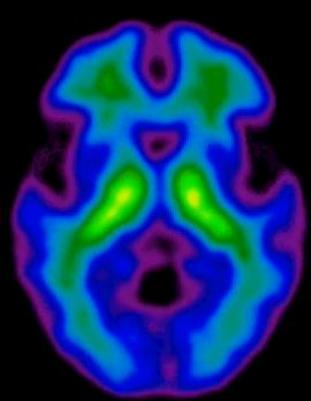
Estimated Years to Onset = -5.0 years



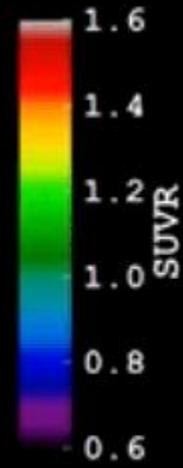
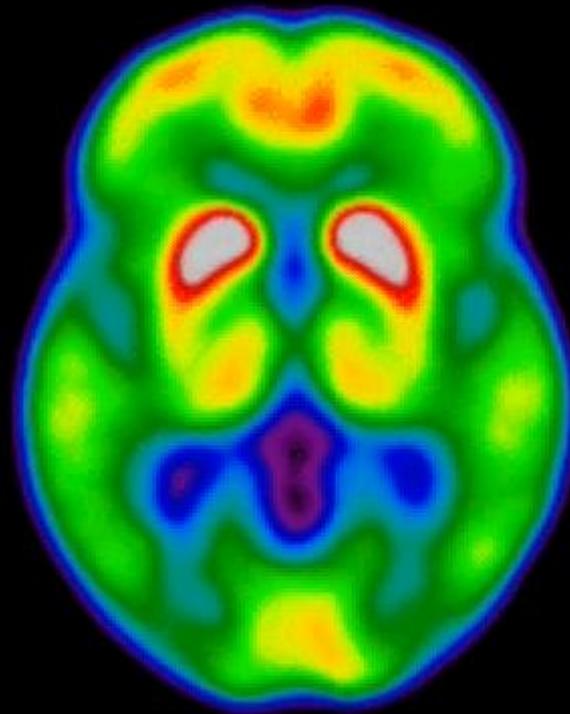
-25.0 years



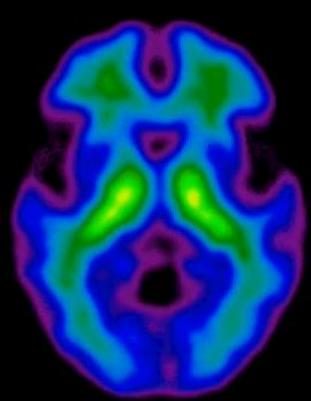
Estimated Years to Onset = -4.0 years



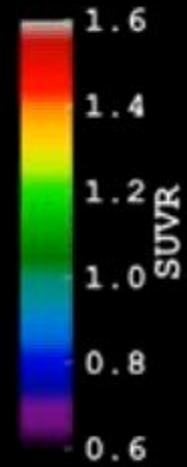
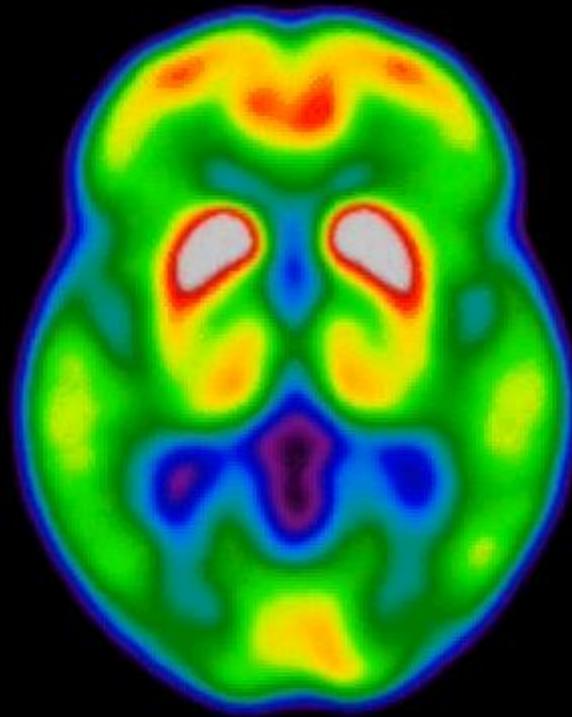
-25.0 years



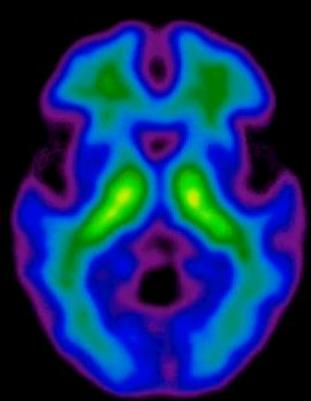
Estimated Years to Onset = -3.0 years



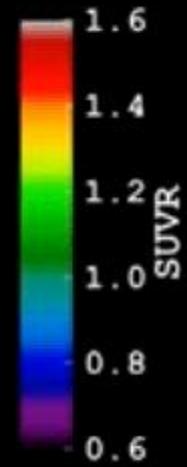
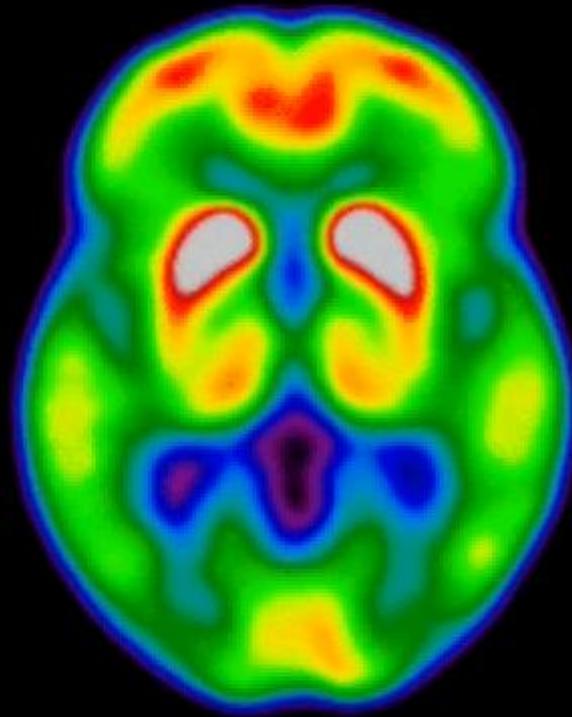
-25.0 years



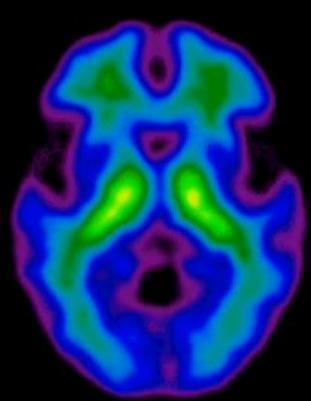
Estimated Years to Onset = -2.0 years



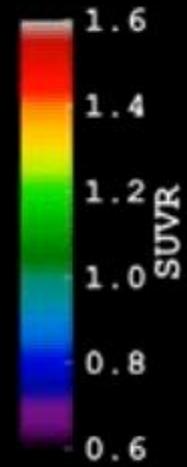
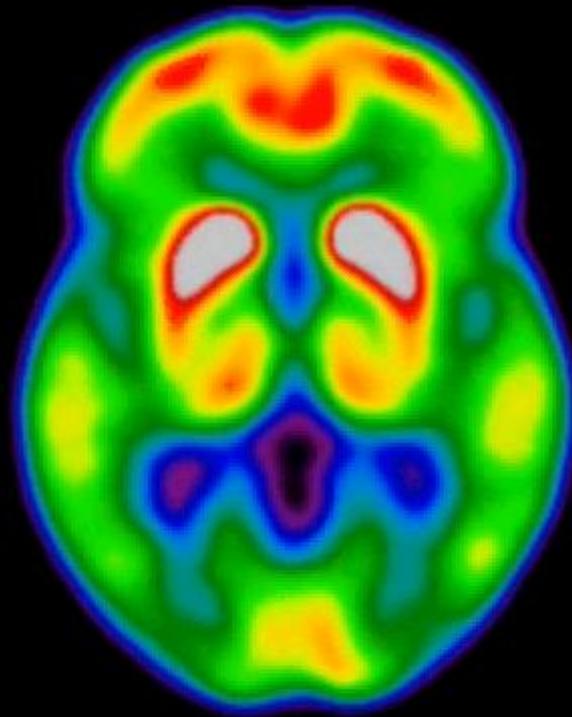
-25.0 years



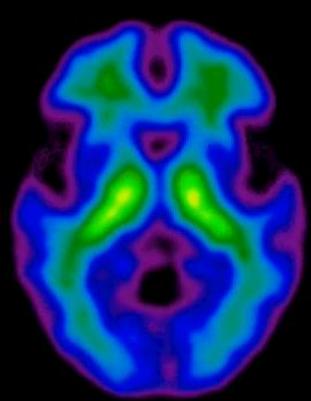
Estimated Years to Onset = -1.0 years



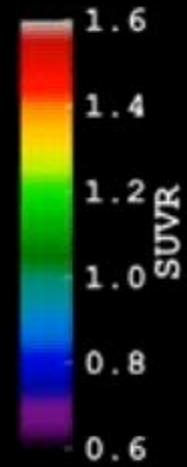
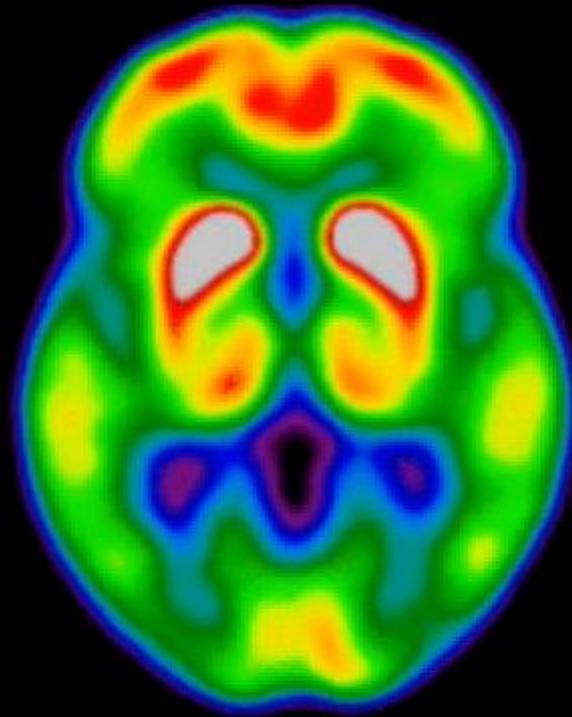
-25.0 years



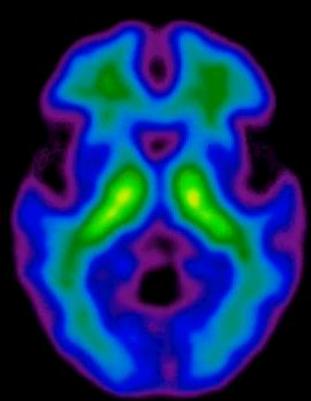
Estimated Years to Onset = -0.0 years



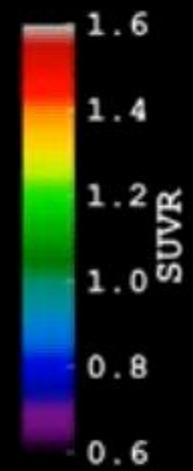
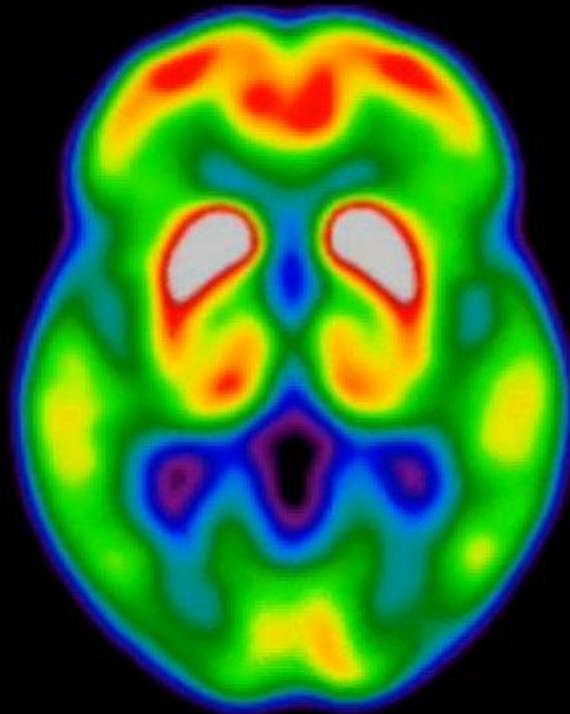
-25.0 years



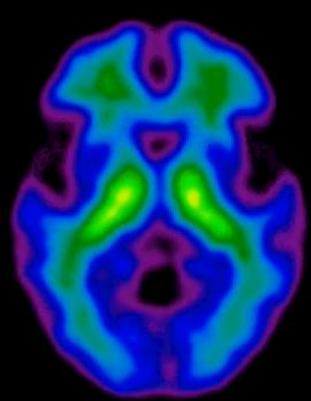
Estimated Years to Onset = +1.0 years



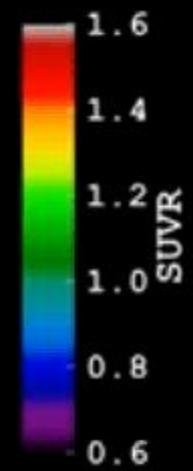
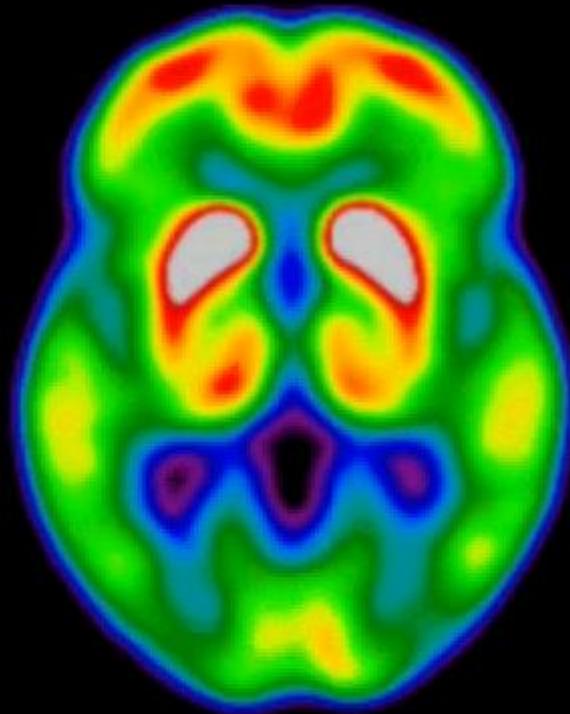
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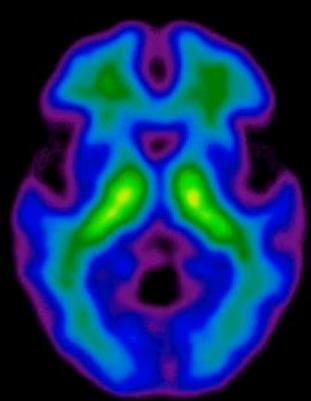
Estimated Years to Onset = +2.0 years



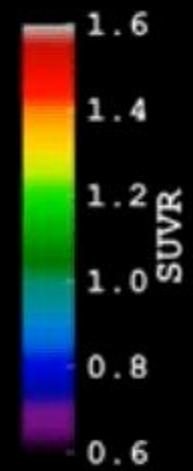
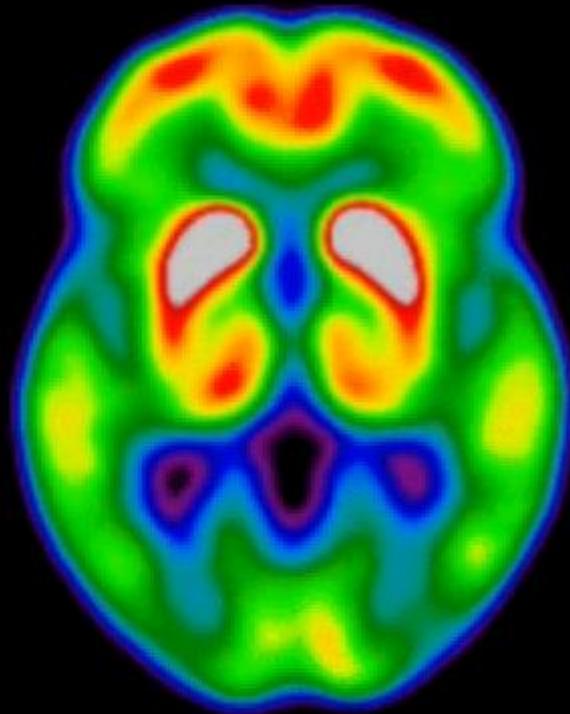
-25.0 years



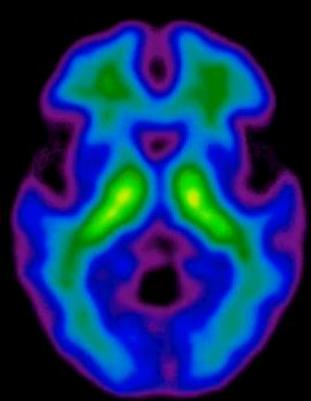
Estimated Years to Onset = +3.0 years



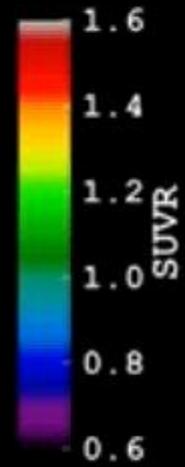
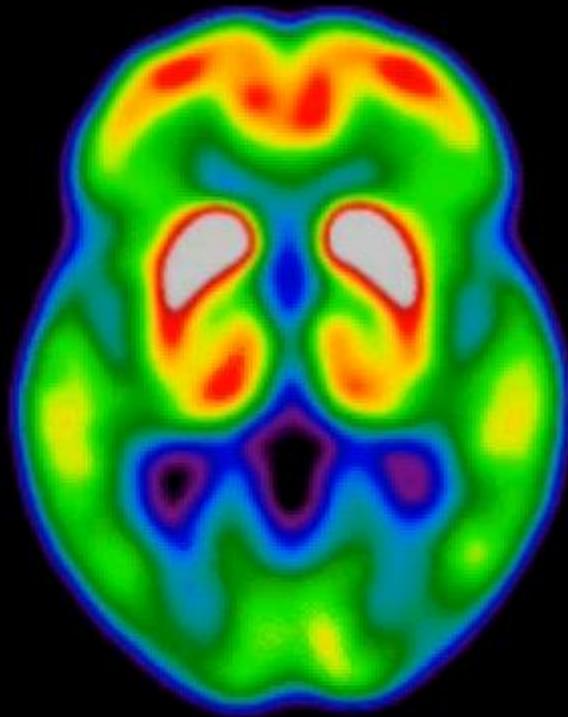
-25.0 years



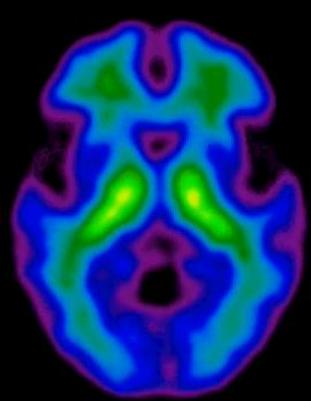
Estimated Years to Onset = +4.0 years



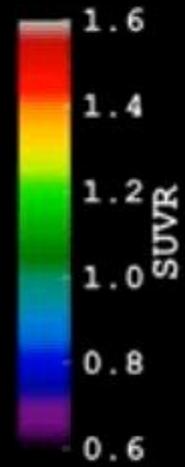
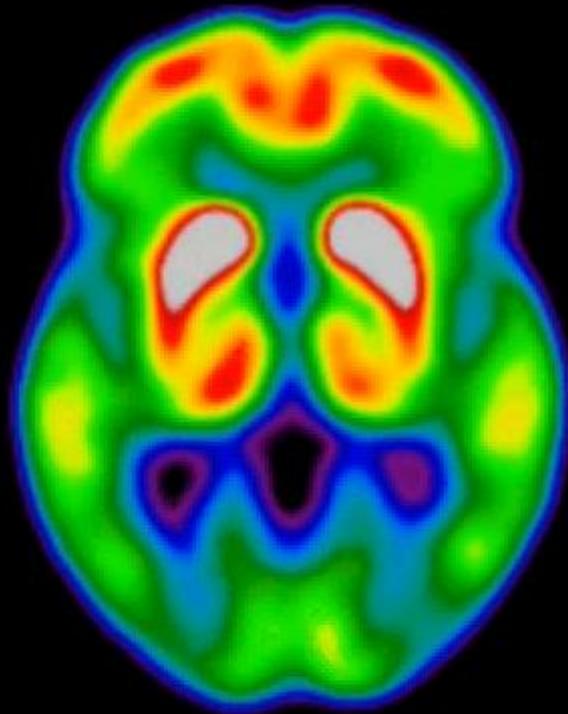
-25.0 years



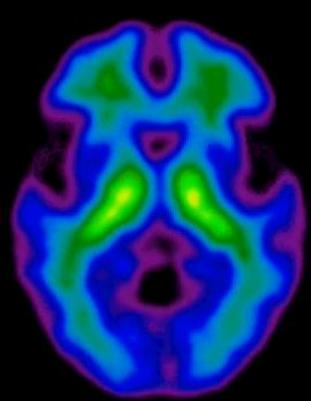
Estimated Years to Onset = +5.0 years



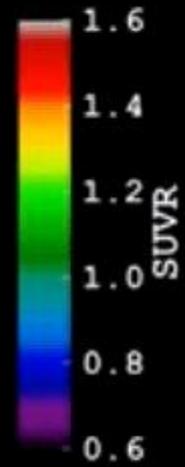
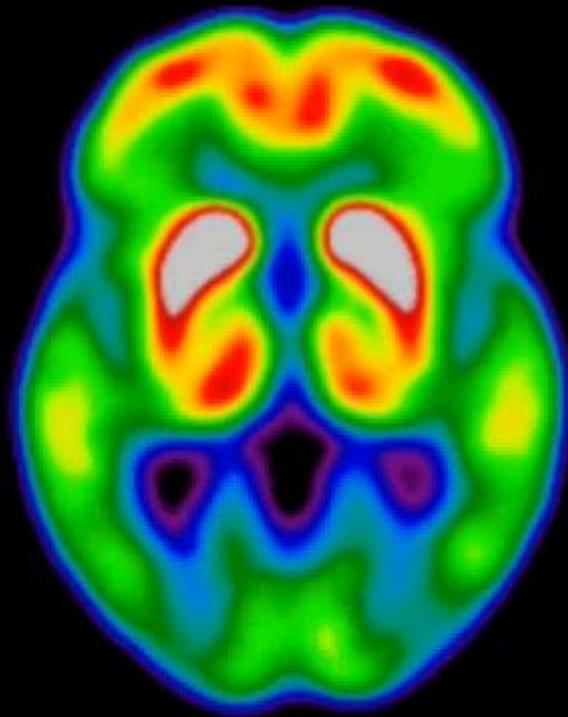
-25.0 years



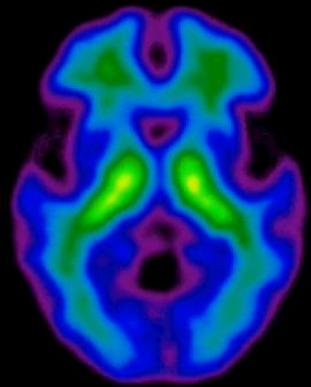
Estimated Years to Onset = +6.0 years



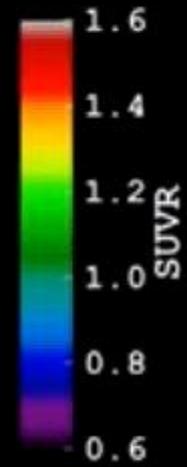
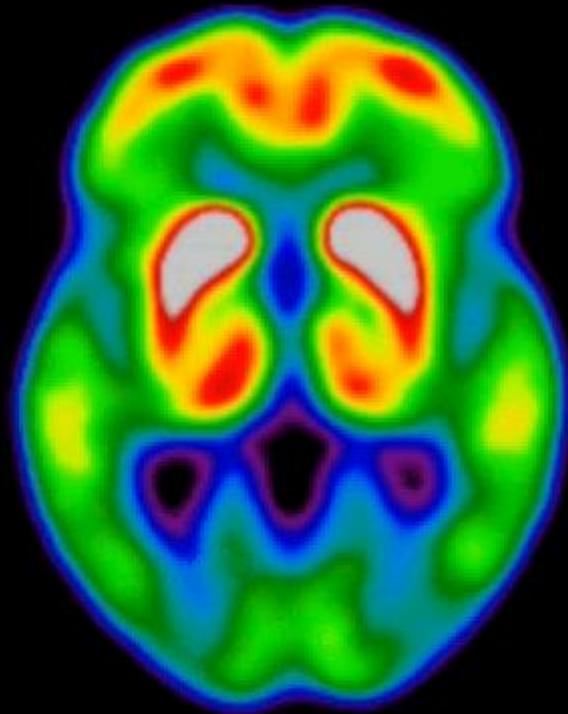
-25.0 years



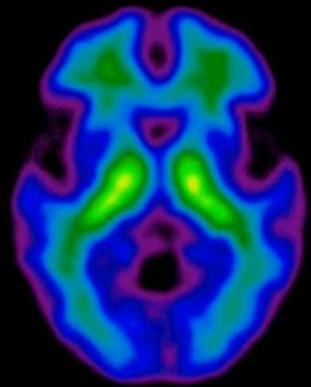
Estimated Years to Onset = +7.0 years



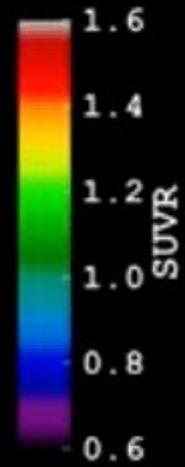
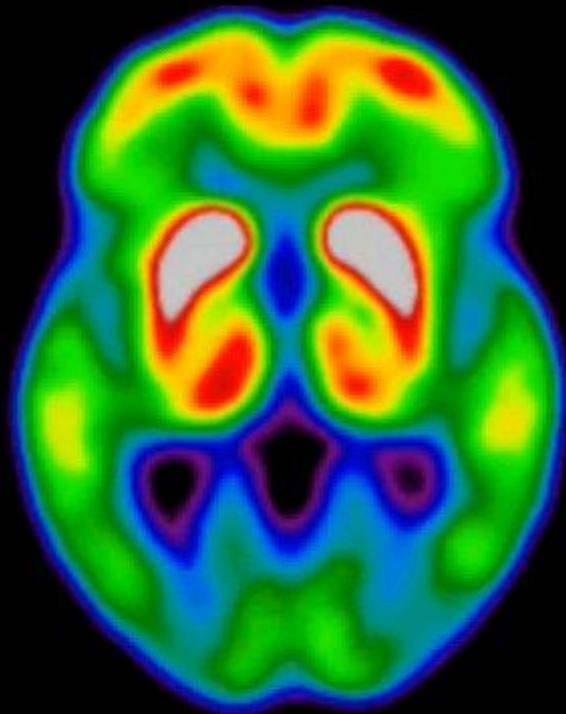
-25.0 years



Estimated Years to Onset = +8.0 years

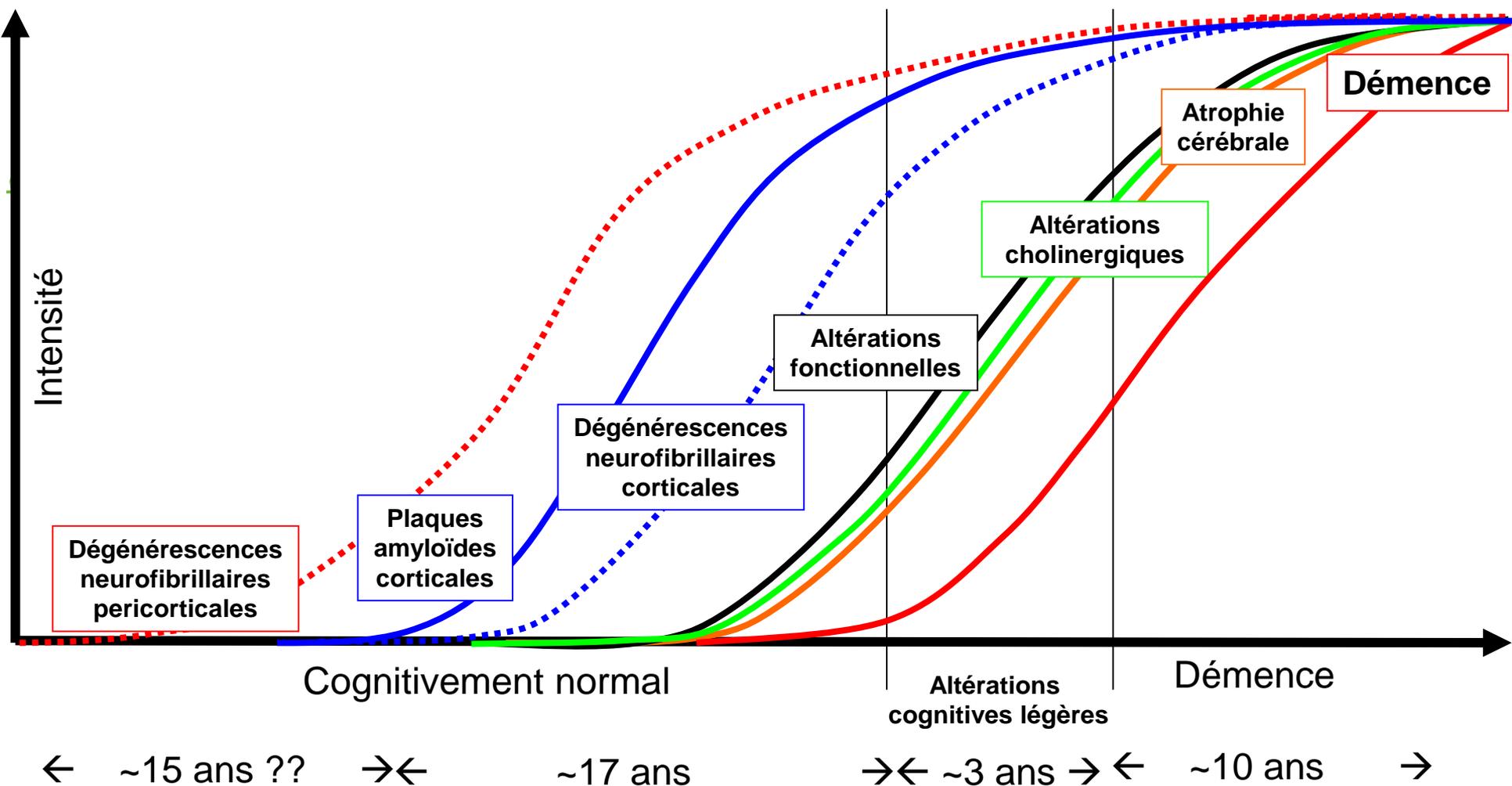


-25.0 years

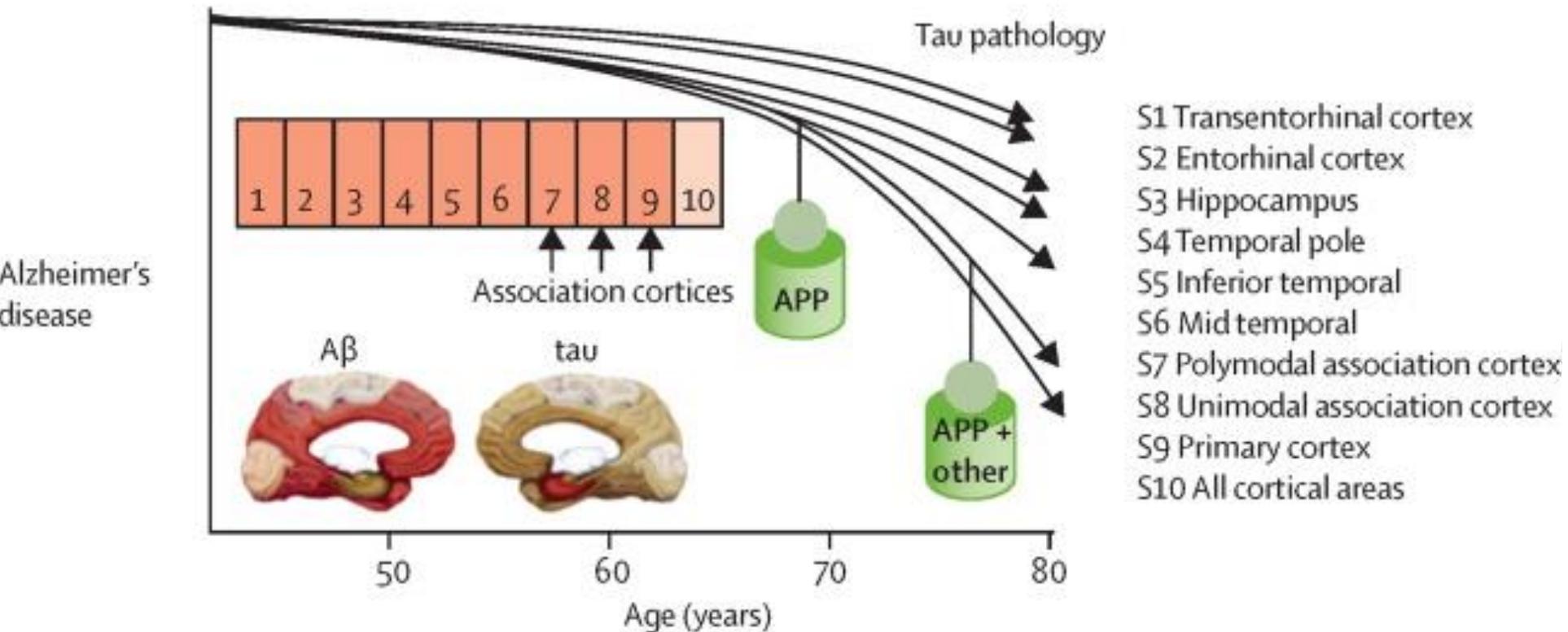


Estimated Years to Onset = +9.0 years

HISTOIRE NATURELLE DE LA MALADIE



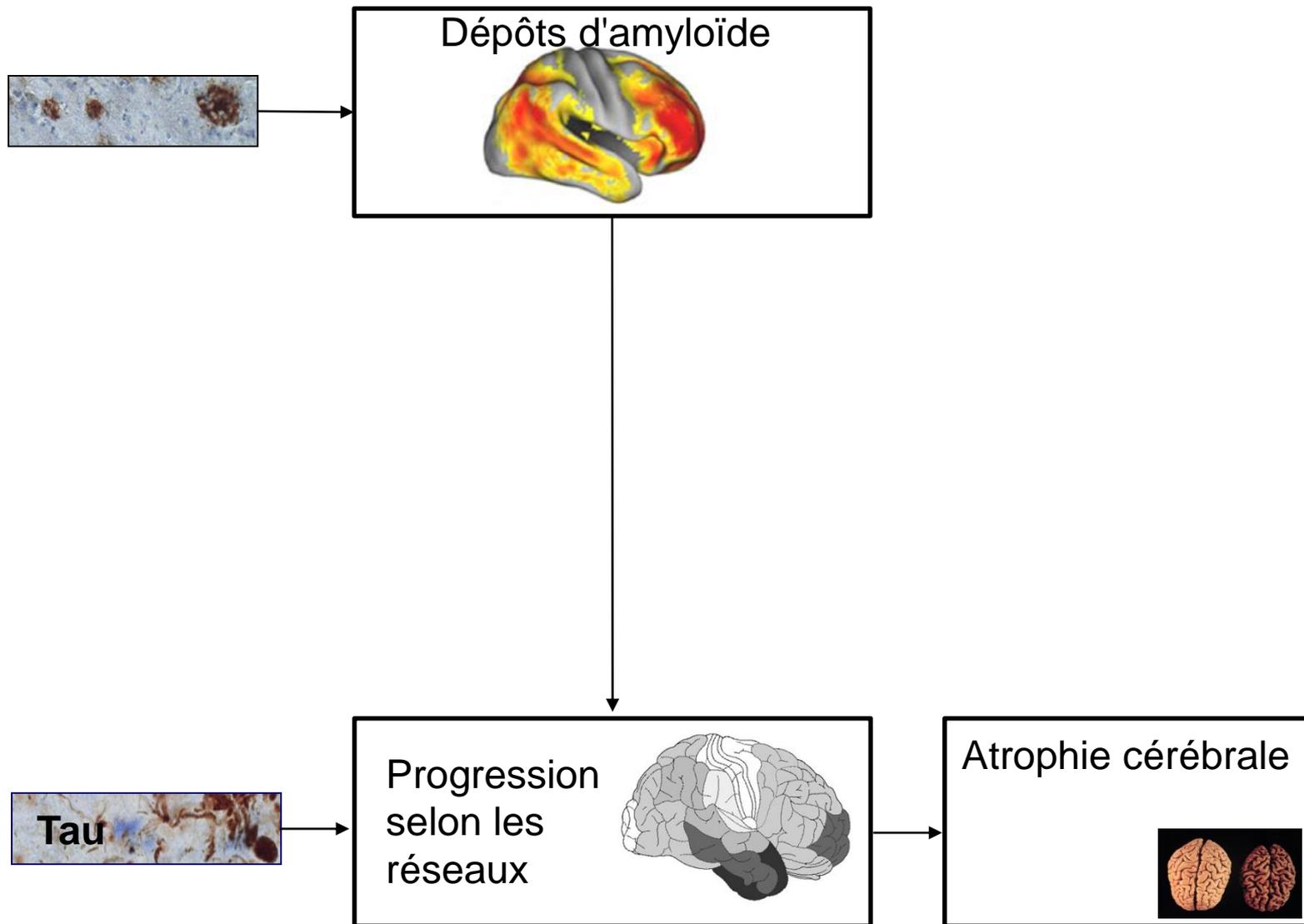
VISION INTEGREEE DE LA MALADIE D'ALZHEIMER



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

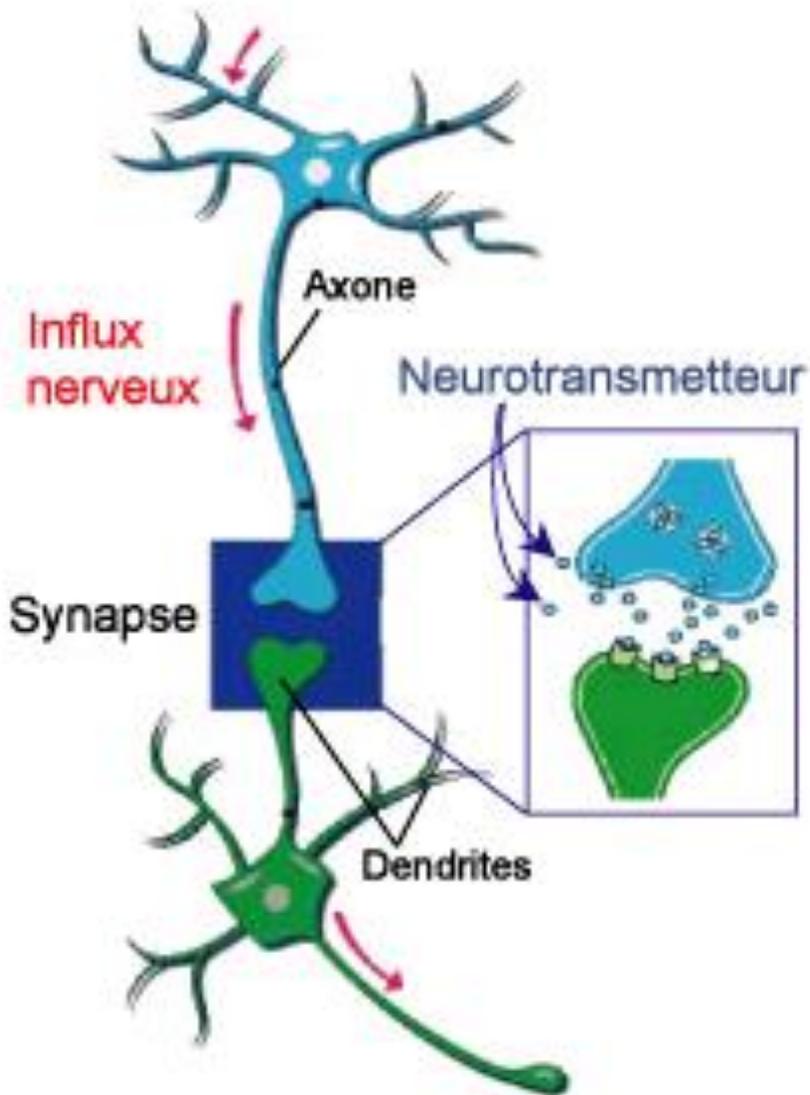




HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Atteintes synaptiques
Atteinte des neurotransmetteurs

ATTEINTE DES NEUROTRANSMETTEURS

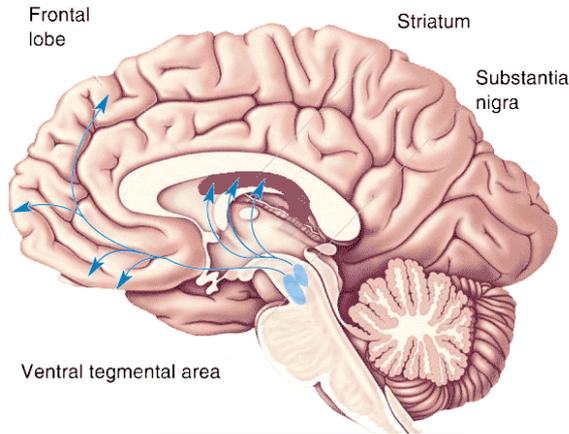


- Substances chimiques libérées dans la jonction synaptique

- Permettent à l'influx nerveux de passer d'un neurone à l'autre

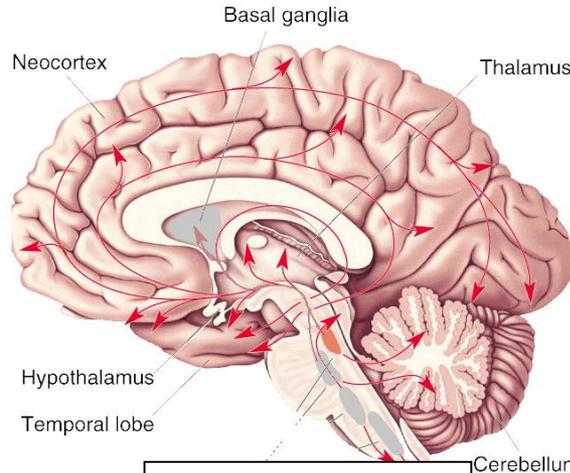
ATTEINTE DES NEUROTRANSMETTEURS

Dopamine system



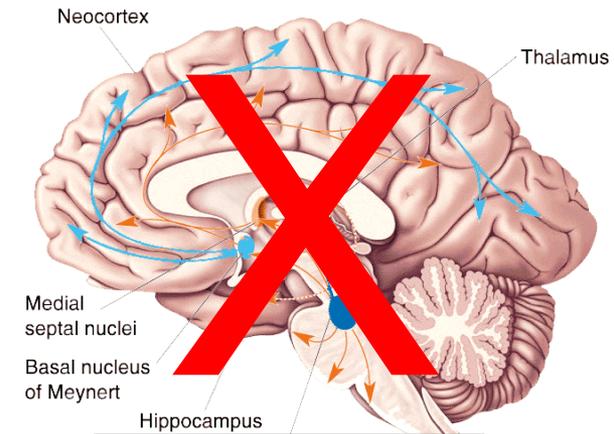
Dopamine

Serotonin system



Serotonine

Acetylcholine system



Acetylcholine

Atteinte prioritaire des neurones à acétylcholine (cholinergiques)

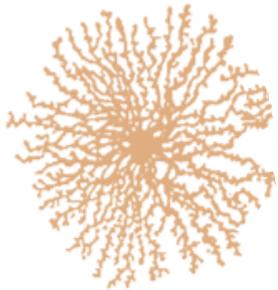


HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

N'oublions pas les voisins...

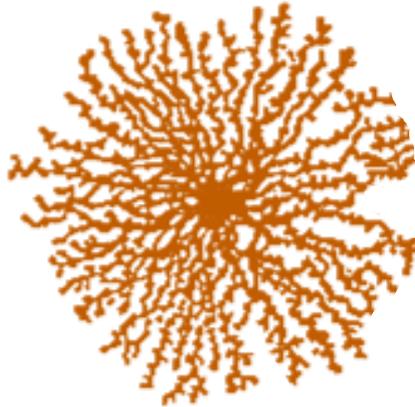
INDUCTION ET DIFFUSION DE LA PATHOLOGIE TAU

Astrocyte normal



Alzheimer
→

Astrocyte réactif

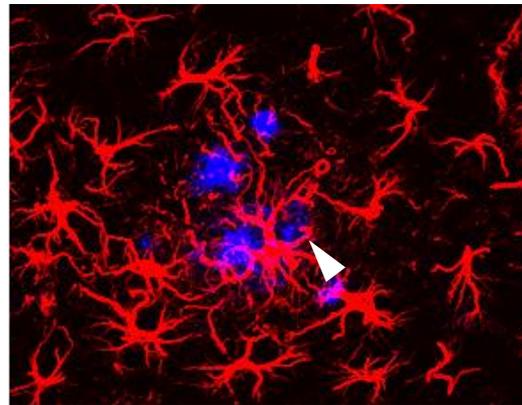
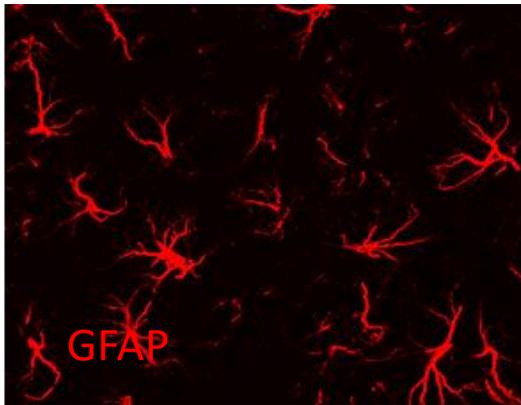


Réduction de la réactivité astrocytaire

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

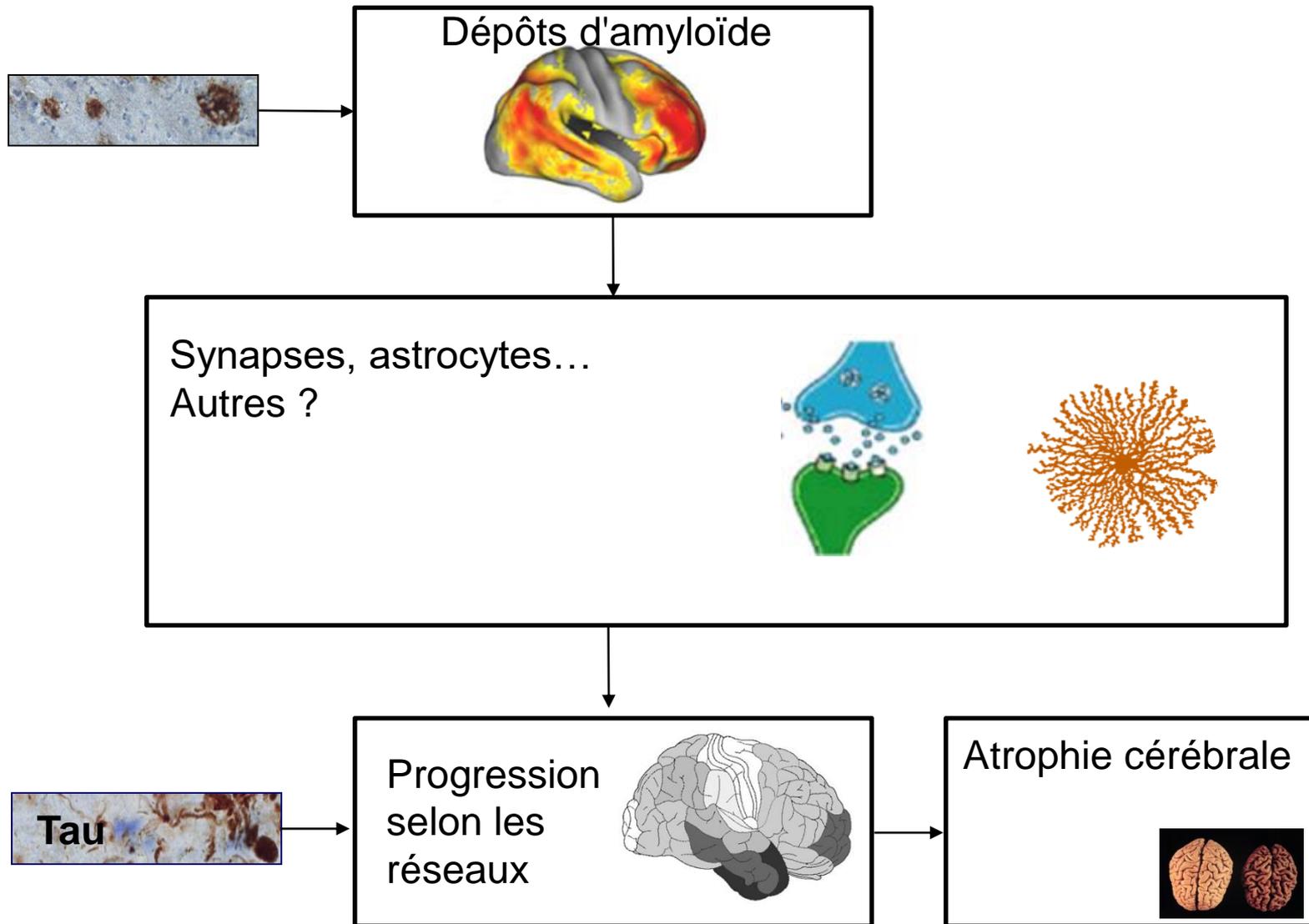
Contrôle

Alzheimer



HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Hypothèse explicative

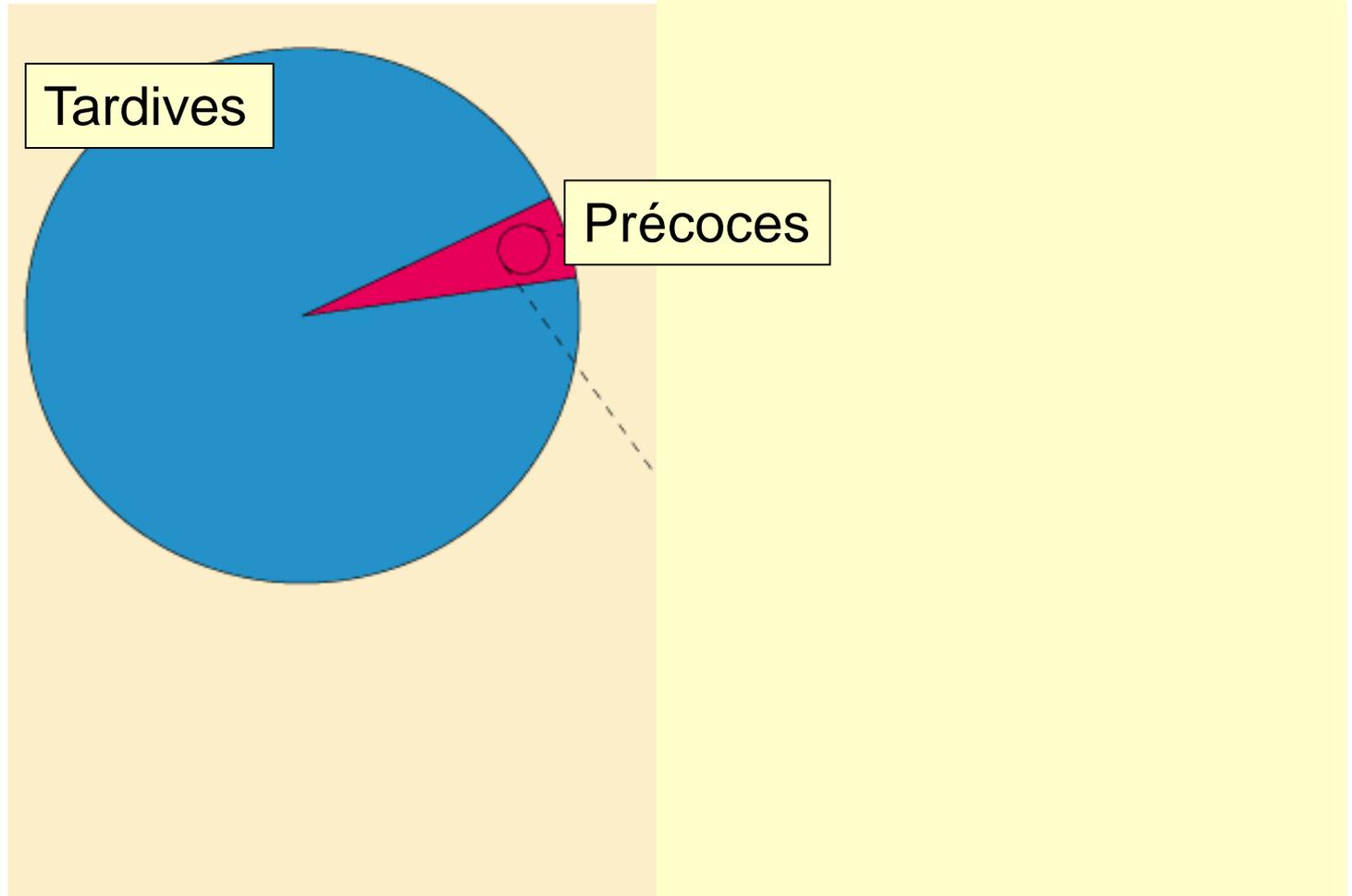




LES CAUSES DE LA MALADIE D'ALZHEIMER?

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

DE RARES FACTEURS GÉNÉTIQUES DÉTERMINANTS

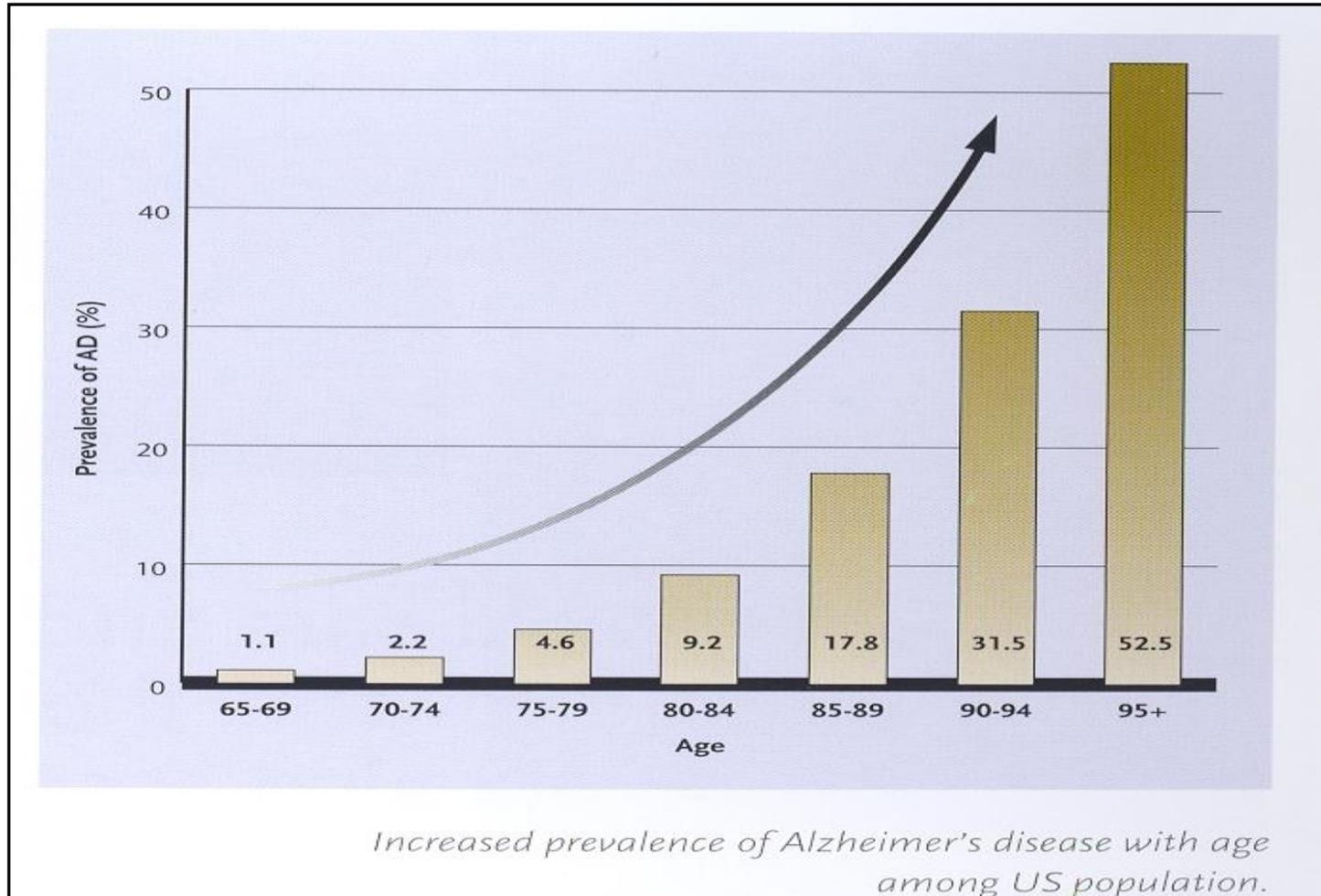


→ Rôle important de la pathologie amyloïde dans la maladie

DE NOMBREUX FACTEURS DE RISQUE



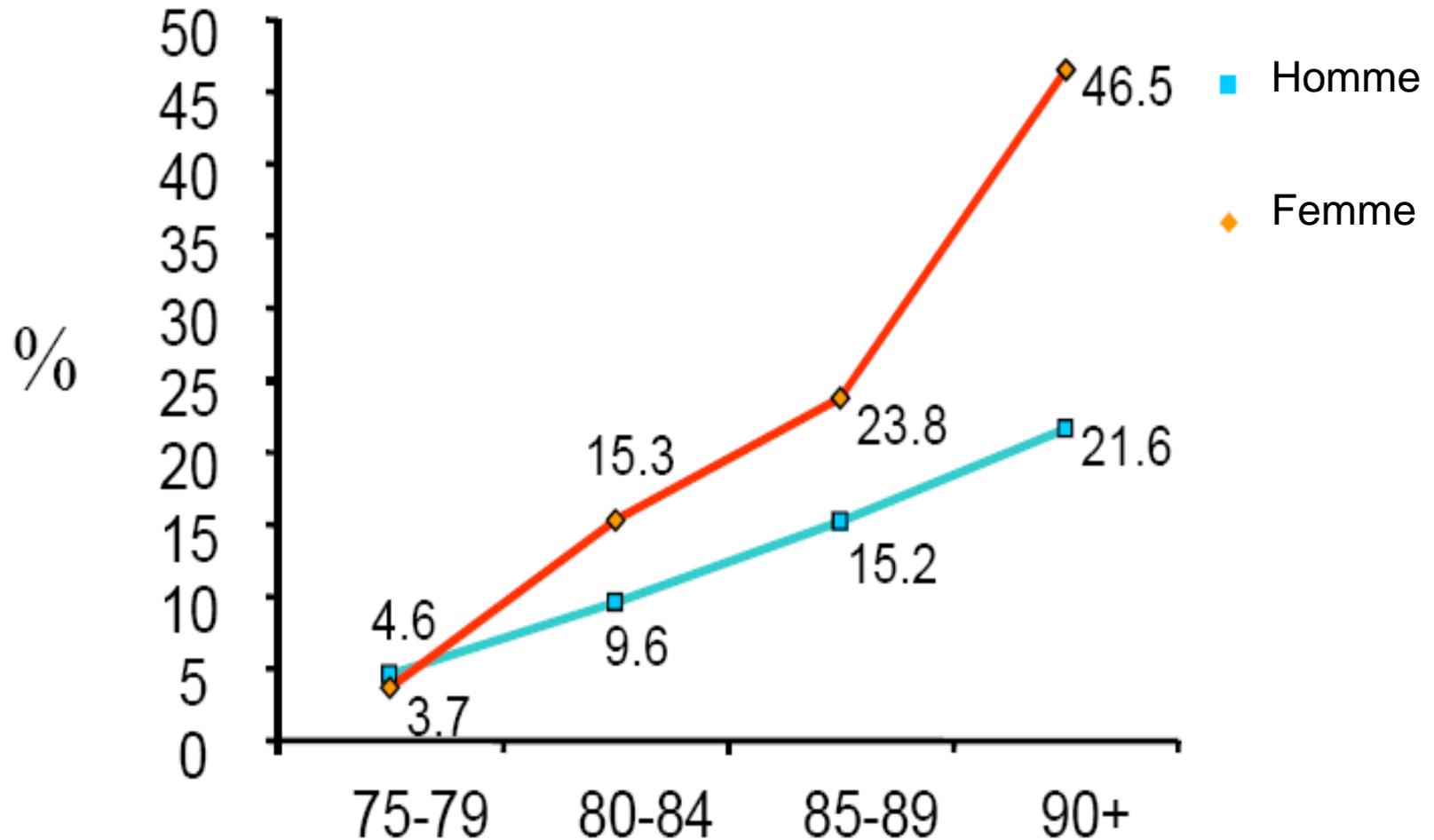
1er Facteur de risque : l'âge



DE NOMBREUX FACTEURS DE RISQUE



Sexe



FACTEURS DE RISQUES ÉVITABLES



Dépression : x1.90



Inactivité physique : x1.82



Hypertension à âge intermédiaire : x1.61

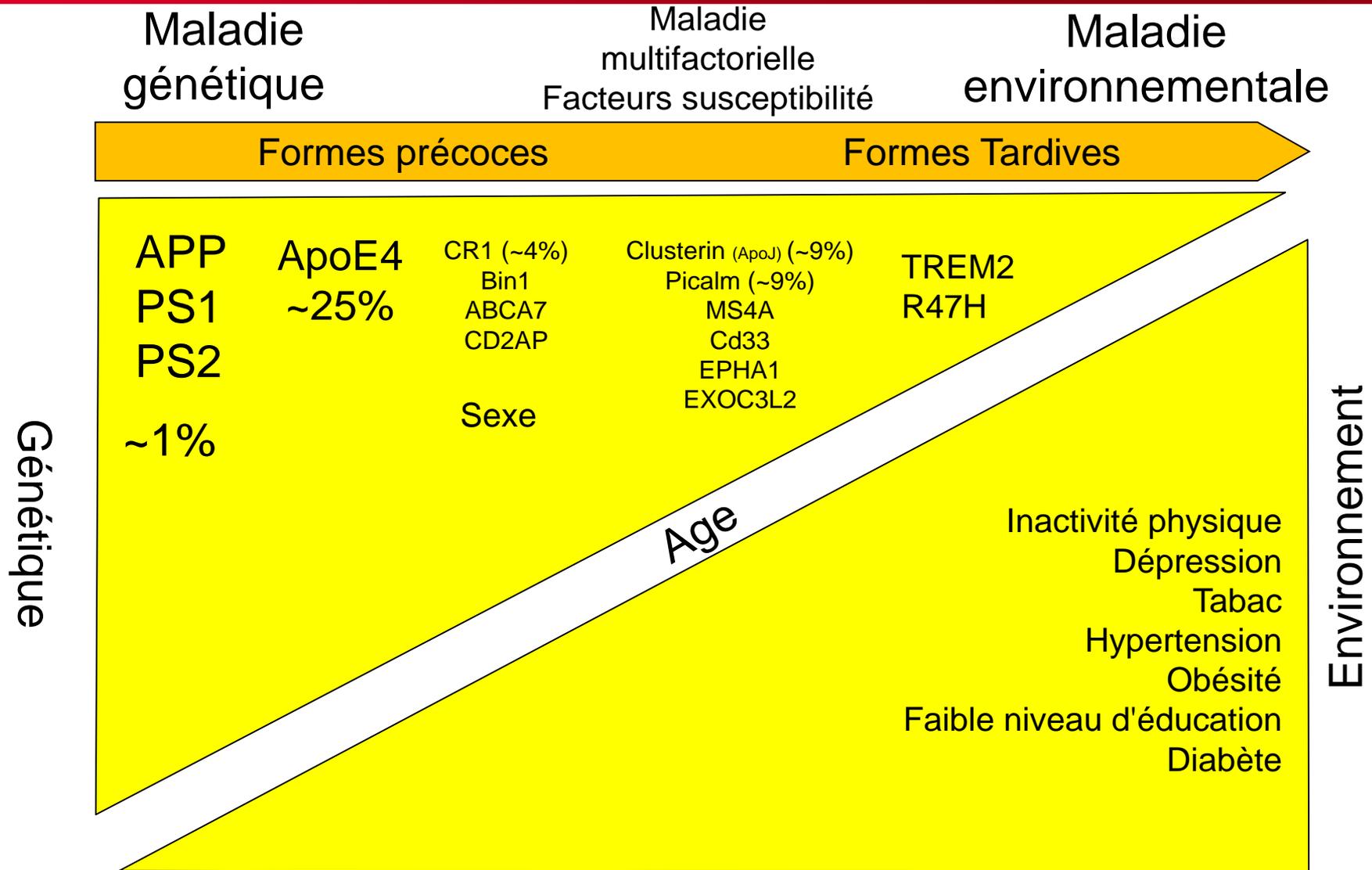
Obésité à âge intermédiaire : x1.60

Tabagisme : x1.59

Faible éducation : x1.59

Diabète : x1.39

FACTEURS DE RISQUES ET DE SUSCEPTIBILITÉ



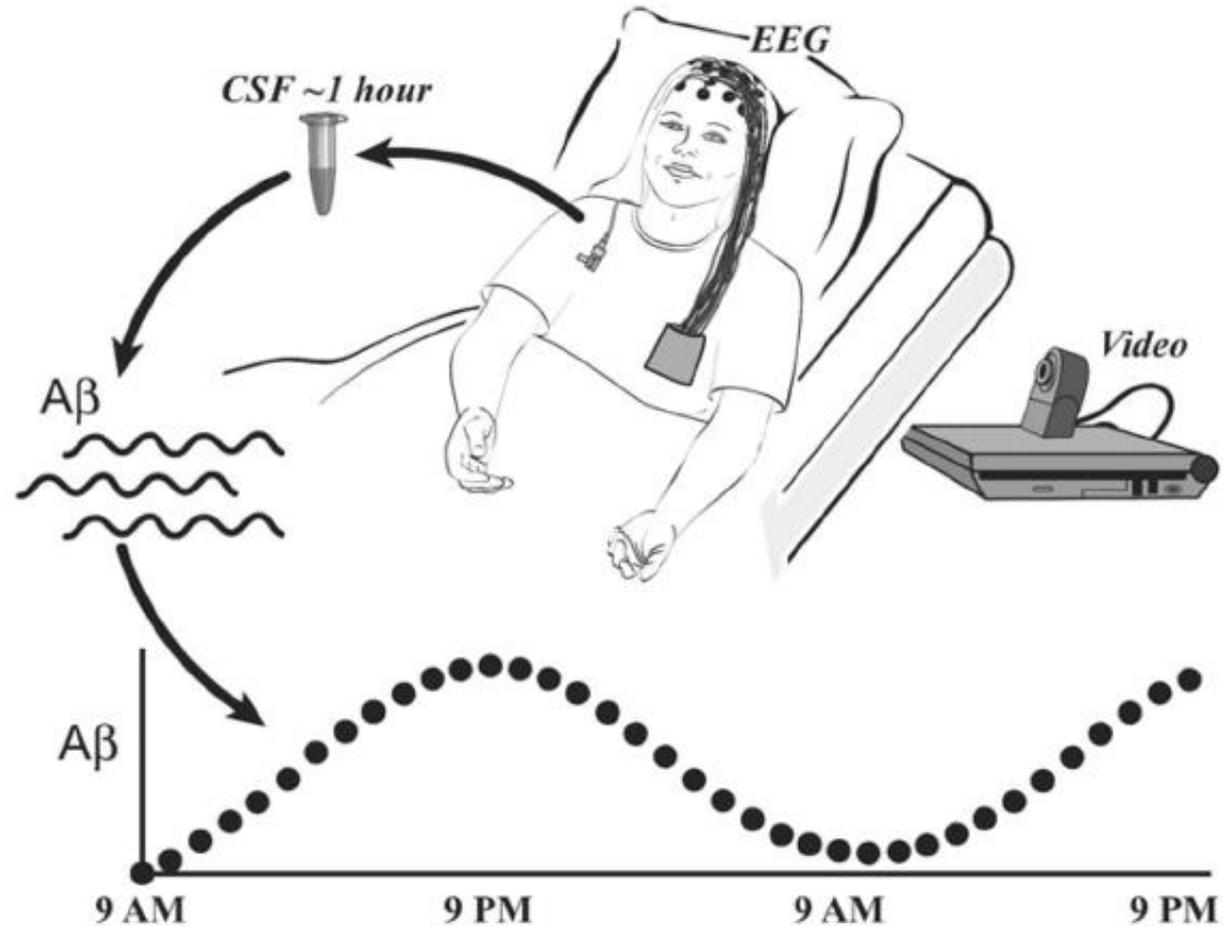


HISTOIRE NATURELLE DE LA MALADIE D'ALZHEIMER

Modulateurs de la synthèse d'amyloïde

SÉCRÉTION D'AMYLOÏDE

Variations journalières

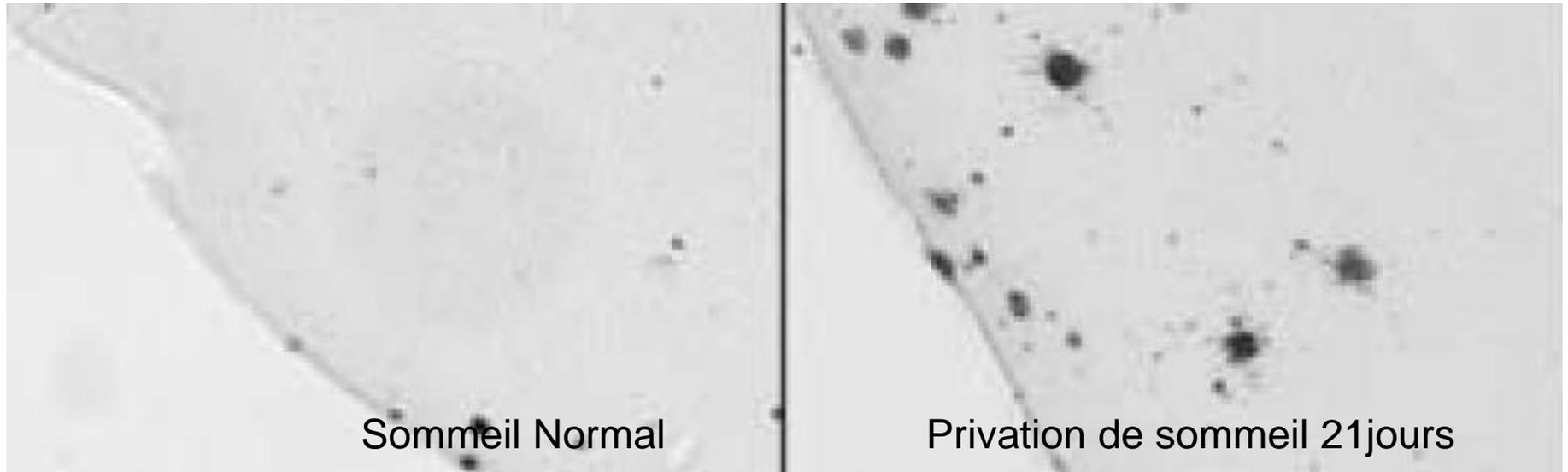


Huang, 2012

La sécrétion d'amyloïde fluctue dans la journée

- Monte le jour
- Baisse la nuit

DÉPÔT D'AMYLOÏDE AUGMENTE QUAND PRIVATION DE SOMMEIL

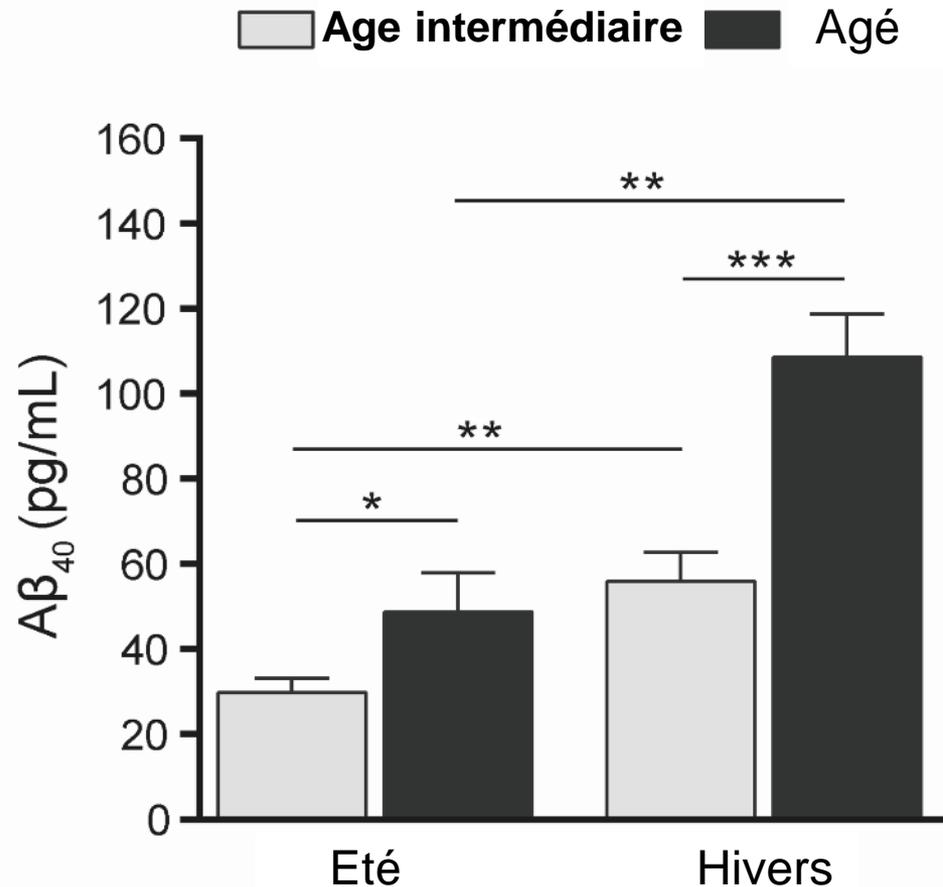


Sommeil Normal

Privation de sommeil 21 jours

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

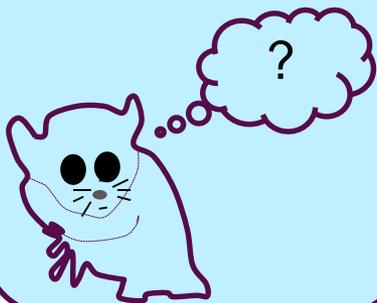


Homogénat

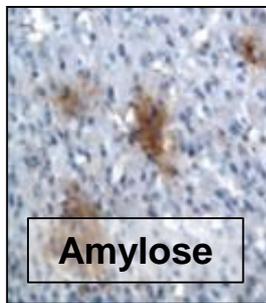


Modèle

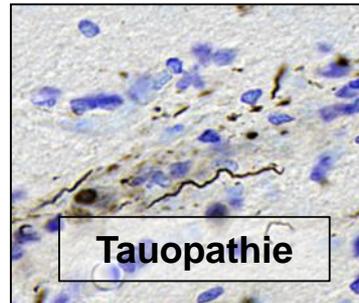
Pertes de mémoire



Lésions microscopiques typiques de la maladie d'Alzheimer



Amylose



Tauopathie

Pertes neuronales Atrophie du cerveau



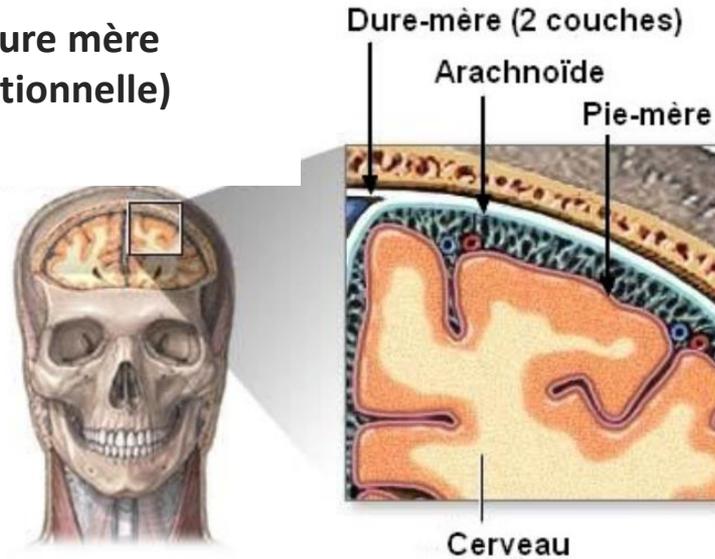
Perte communication entre neurones

= Induction d'une maladie neurodégénérative

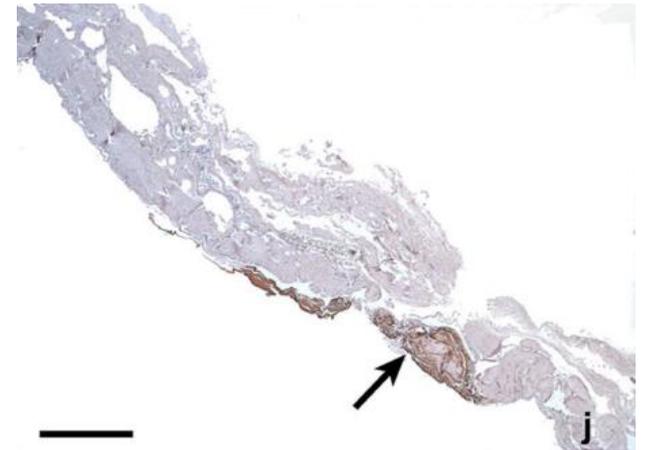
REALITÉ DE LA TRANSMISSION DES LESIONS DE LA MALADIE D'ALZHEIMER

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

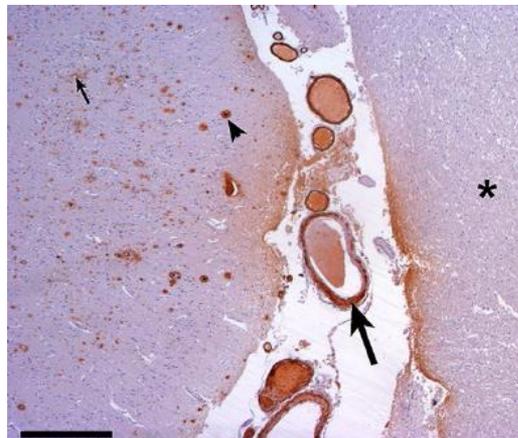
Greffe à l'âge de 2 ans
Mort à 46 ans
Hémorragies cérébrales répétées



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												

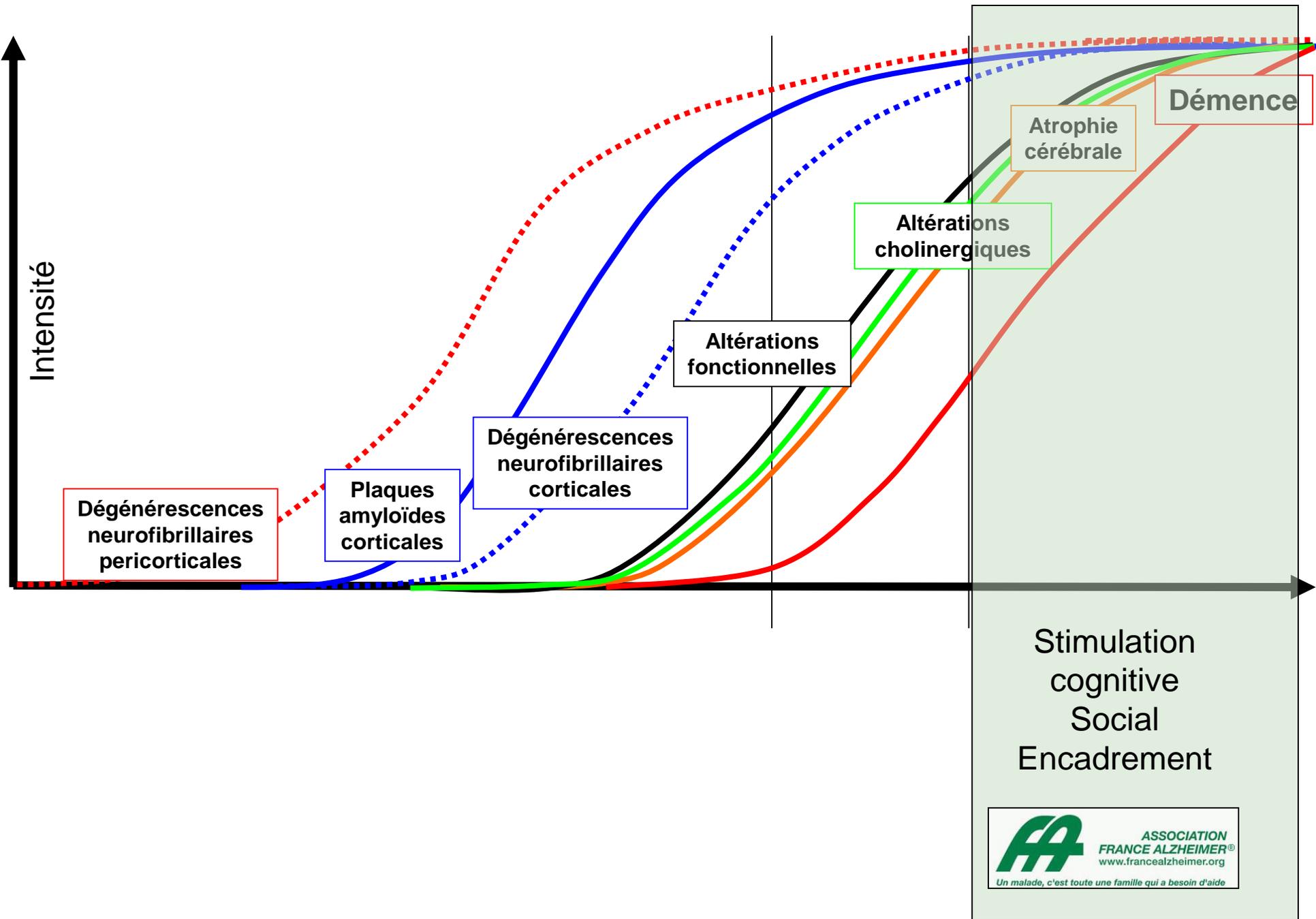
~10 patients décrits

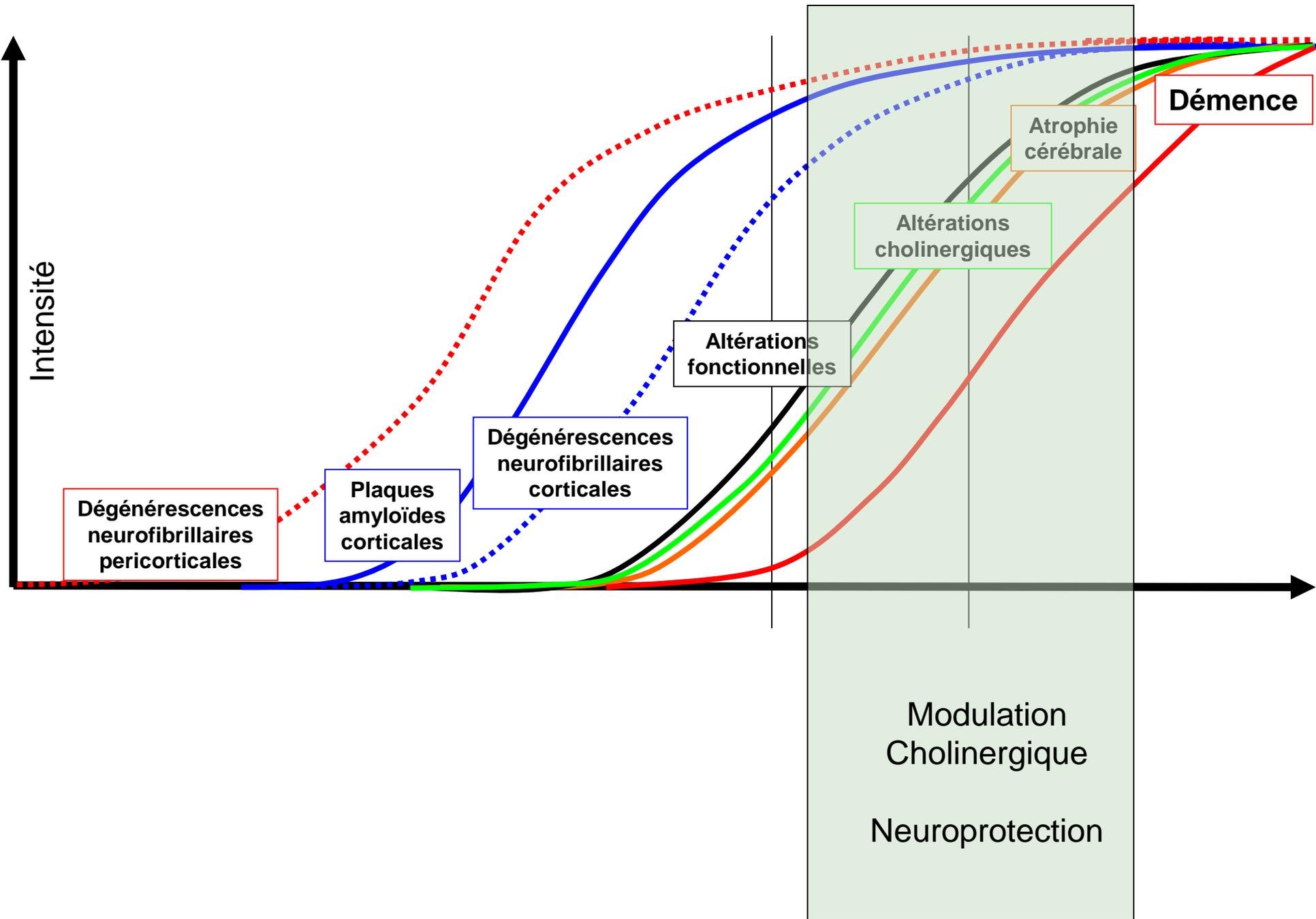
Versus 50 millions de patients Alzheimers dans le monde



THÉRAPIES CONTRE LA MALADIE

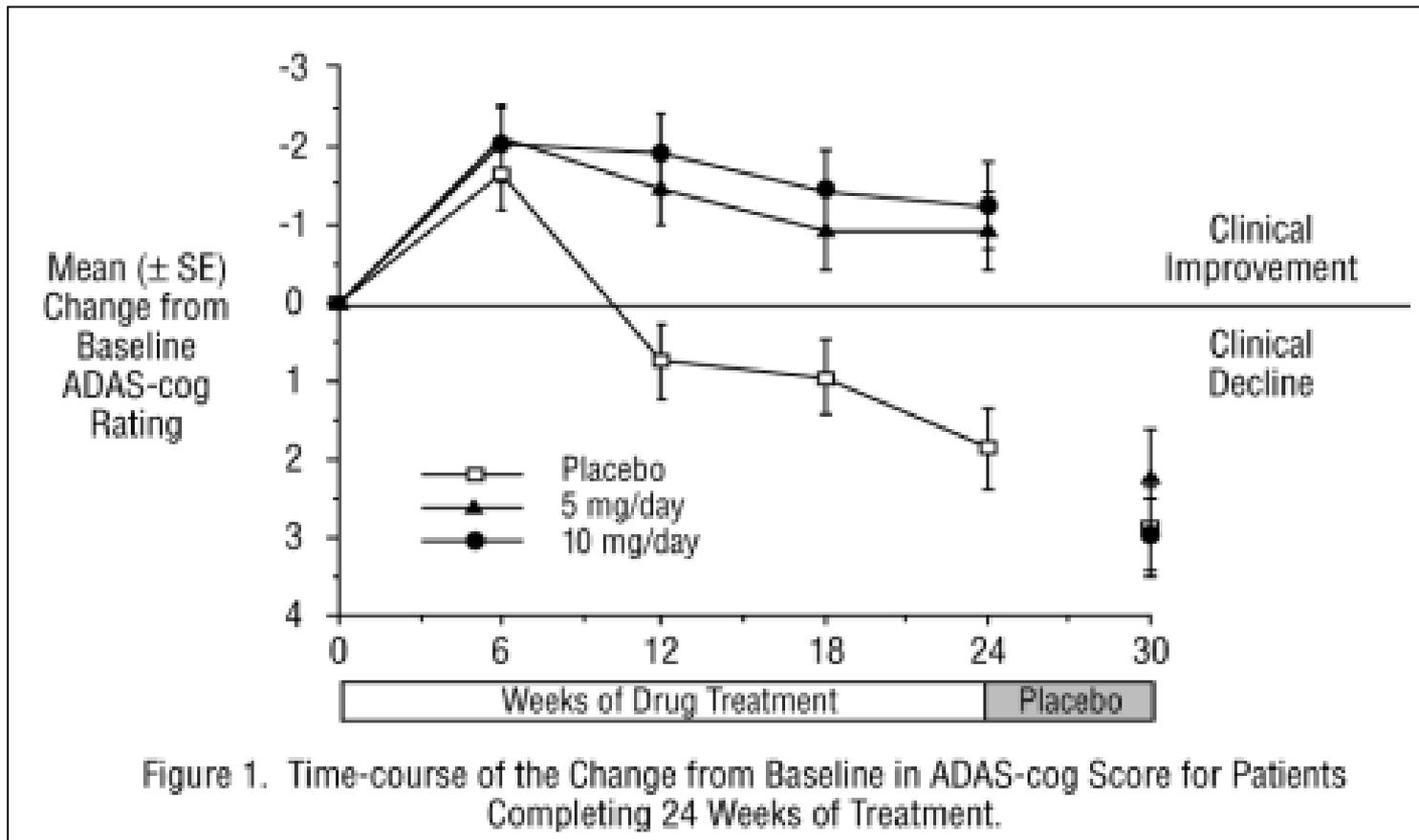
Dépend du stade de la maladie





TRAITEMENTS ACTUELS DE LA MALADIE

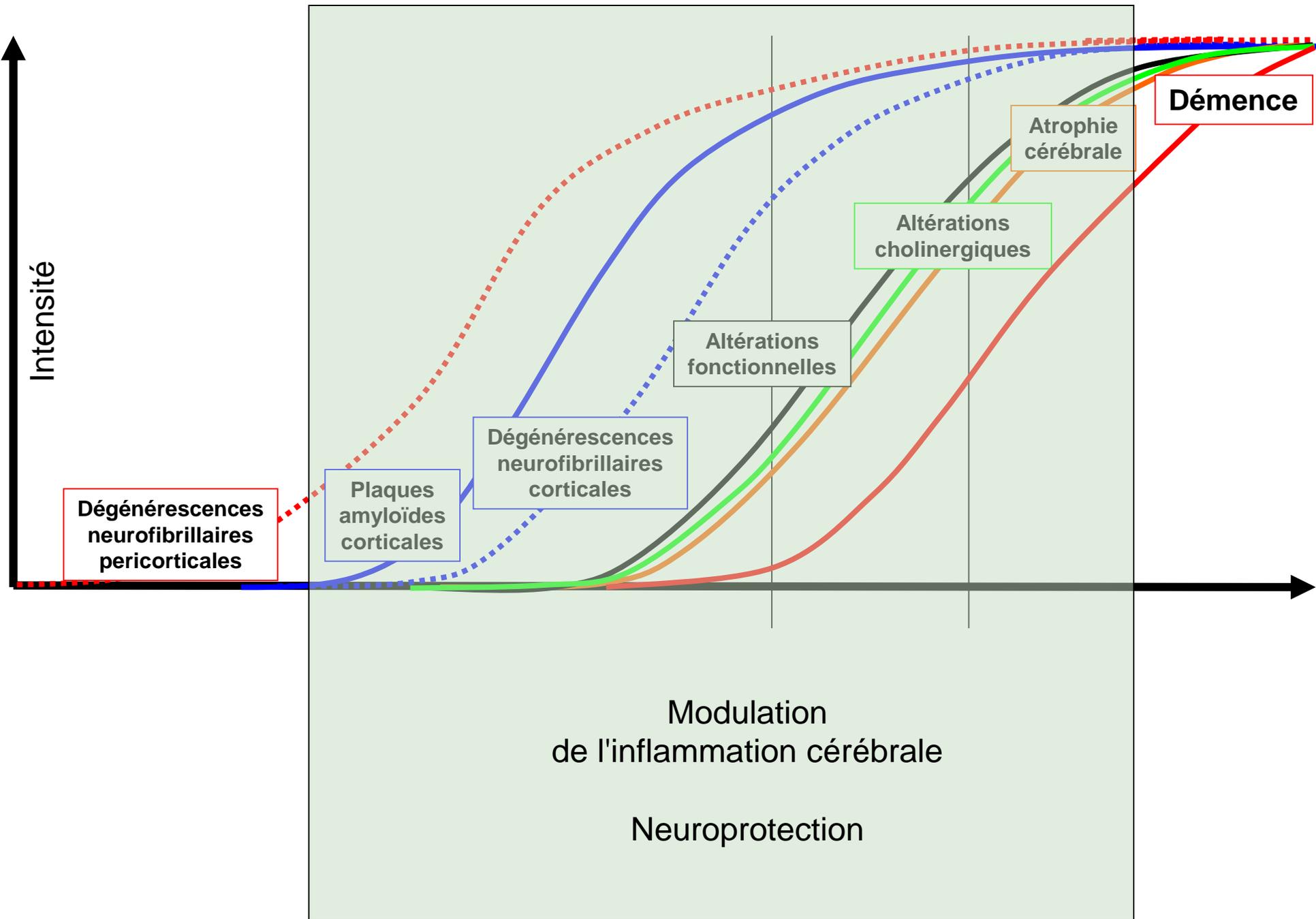
Effet typique du traitement sur les capacités mnésiques
Exemple de Donepezil (Aricept)



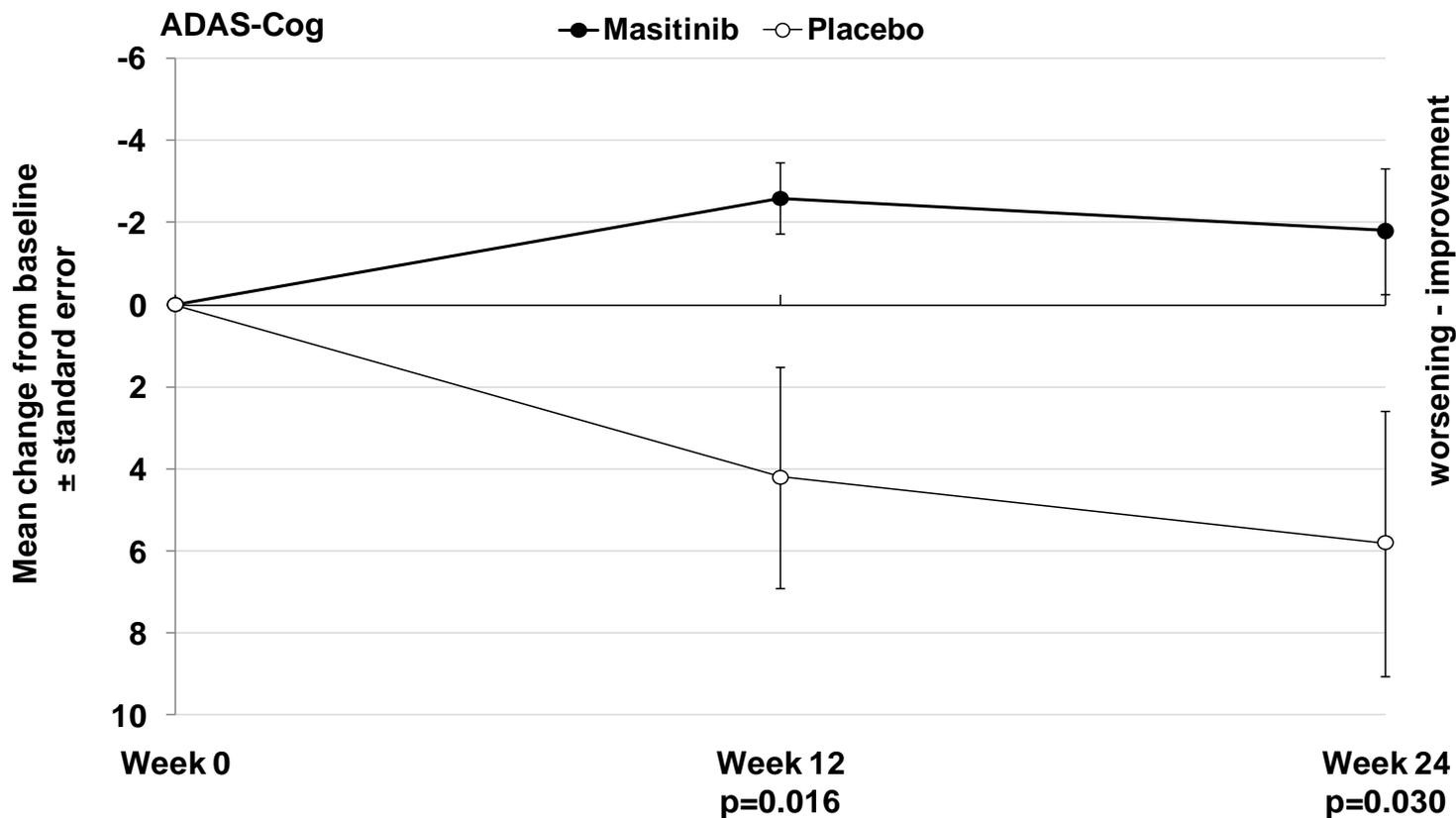
TRAITEMENTS ACTUELS DE LA MALADIE

- Anticholinestérasiques
 - Donépézil ([Aricept®](#)),
 - Galantamine ([Reminyl®](#))
 - Rivastigmine ([Exelon®](#)).

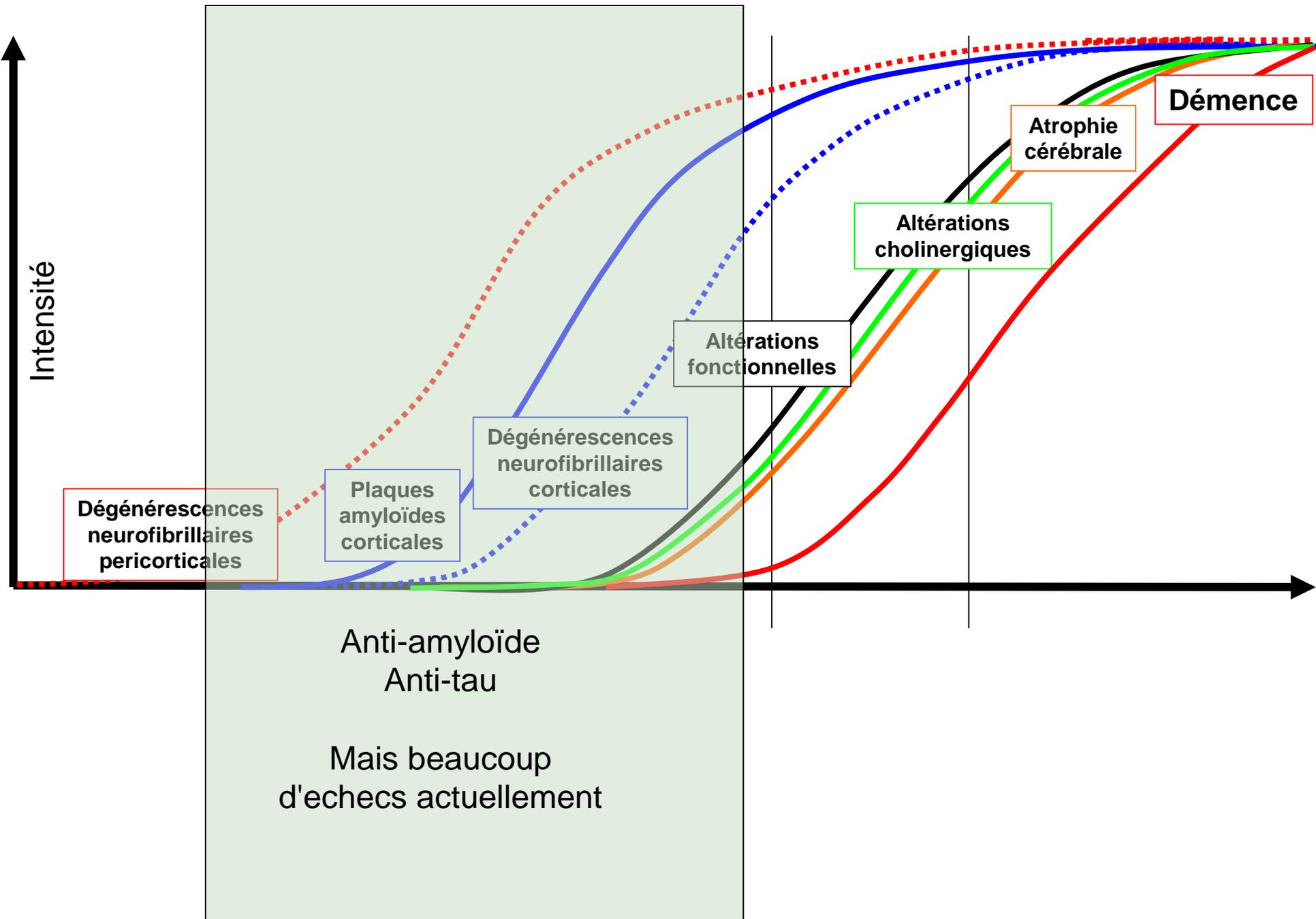
 - Effets indésirables fréquents au niveau digestif (nausées, perte d'appétit, diarrhées).
- Antiglutamates
 - Mémantine ([ebixa®](#)).
 - Patients plus avancés (stades modérément sévère à sévère)
- Réévaluation des médicaments HAS décembre 2011 :
 - un "faible intérêt" médical
 - http://www.has-sante.fr/portail/jcms/c_1108356/medicaments-de-la-maladie-dalzheimer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

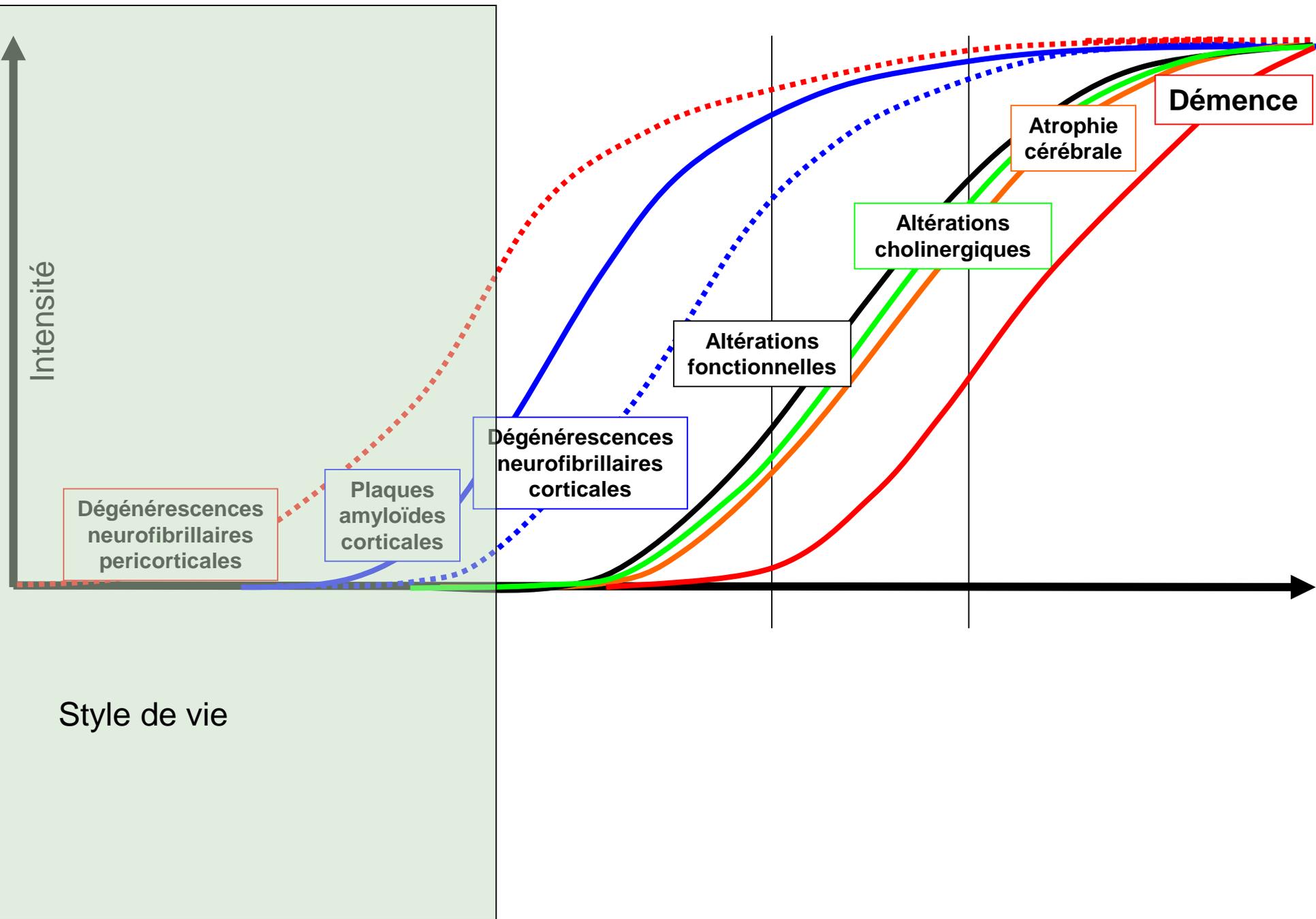


THÉRAPIE PAR MODULATEUR DES MASTOCYTES

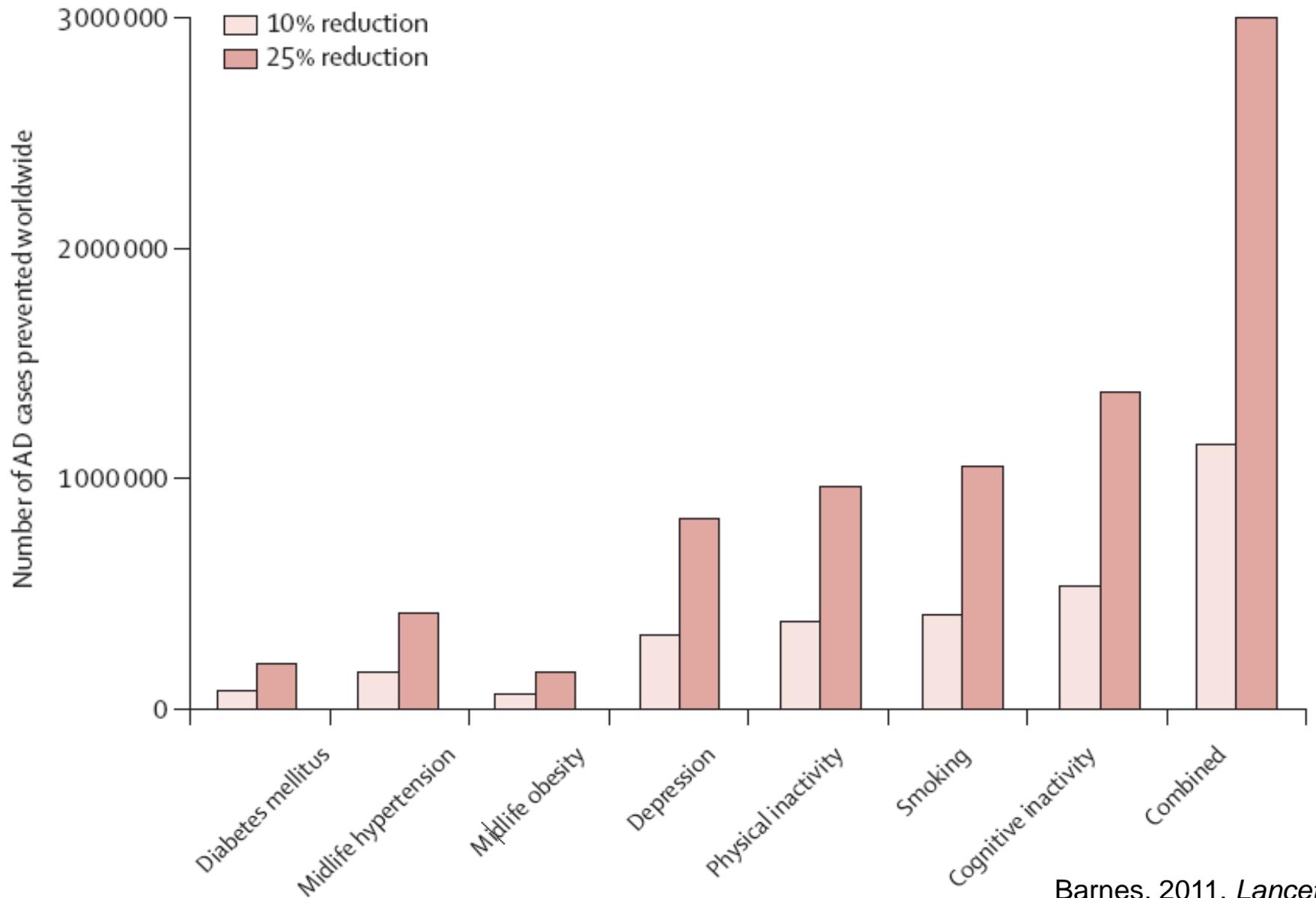


Phase 3 en cours

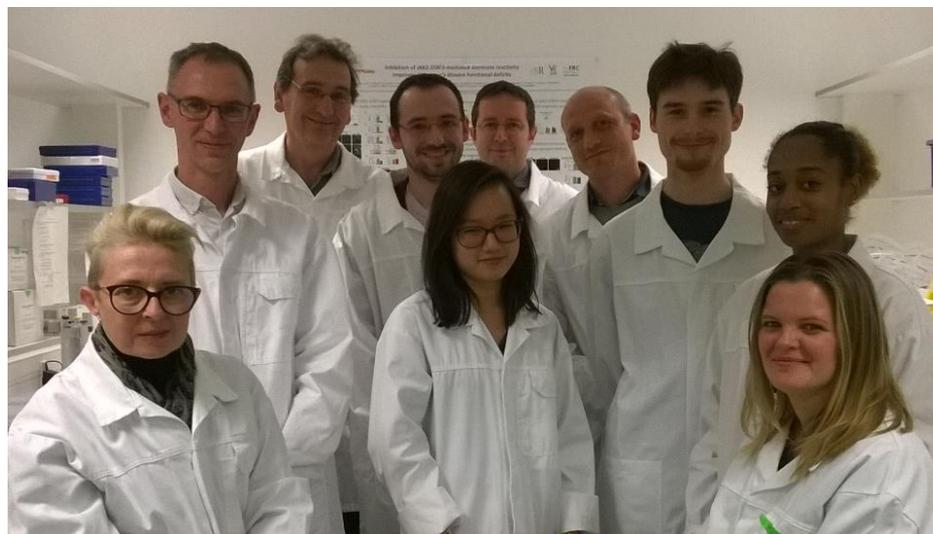
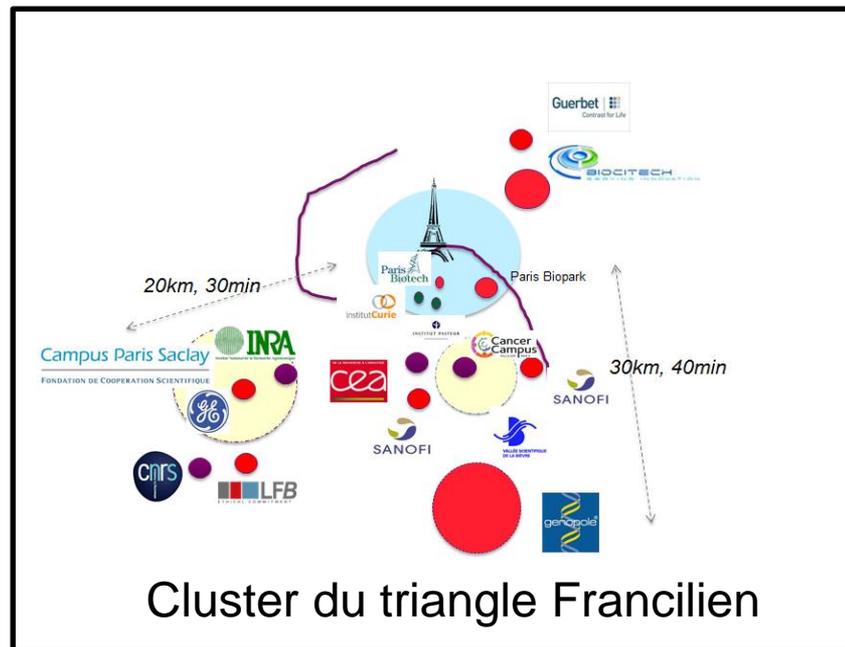
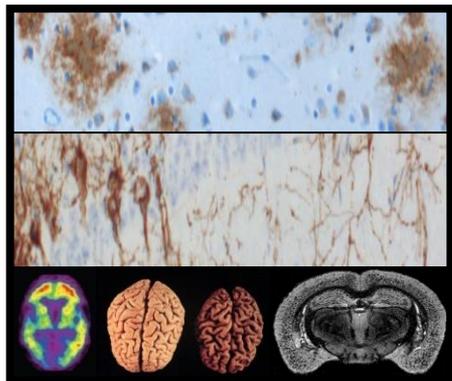




THÉRAPIE PAR MODULATION DE FACTEURS DE RISQUES



MERCI



Et les autres...

Marc.Dhenain@cea.fr