



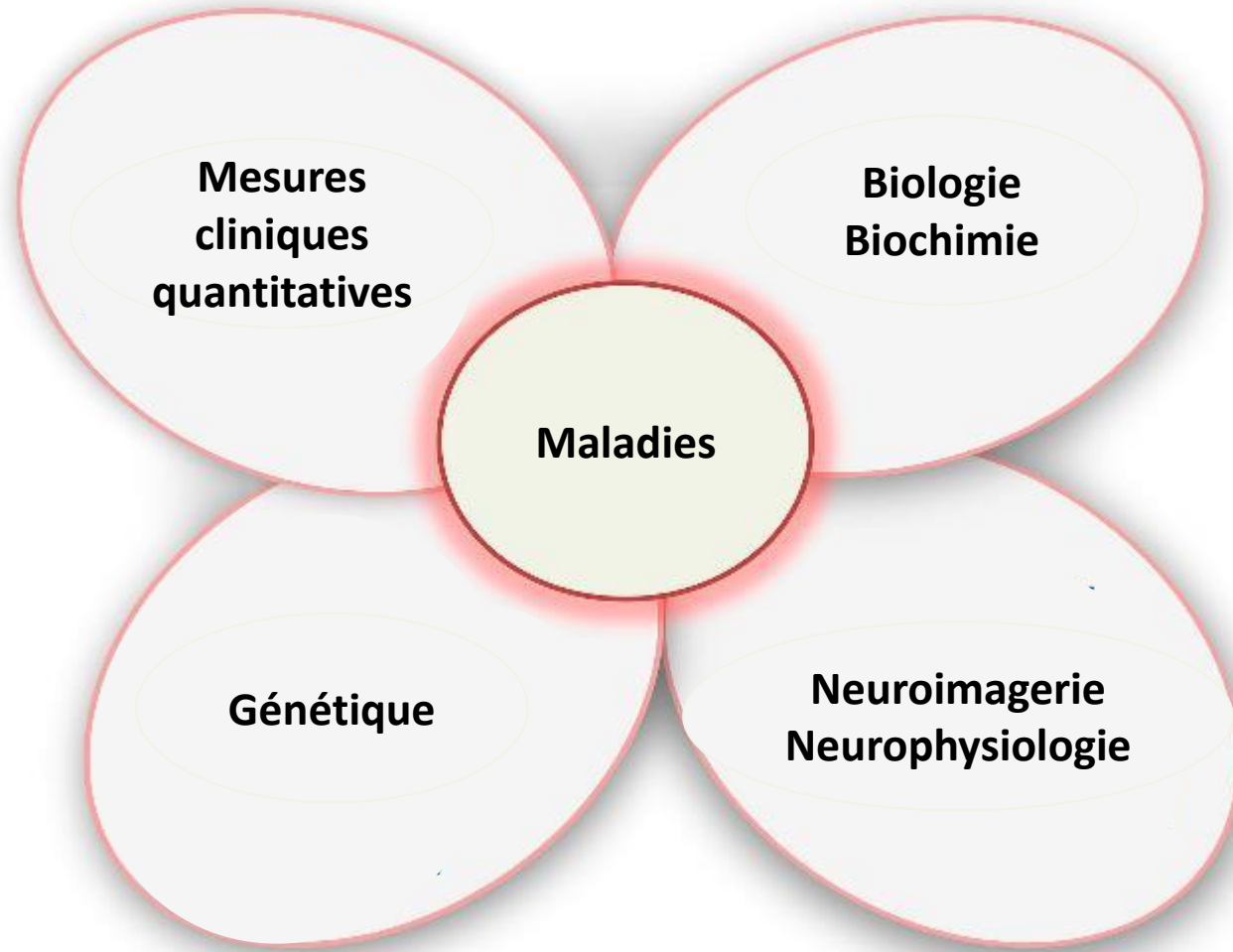
Nouveaux outils diagnostiques en neurologie

Gaëtan Garraux

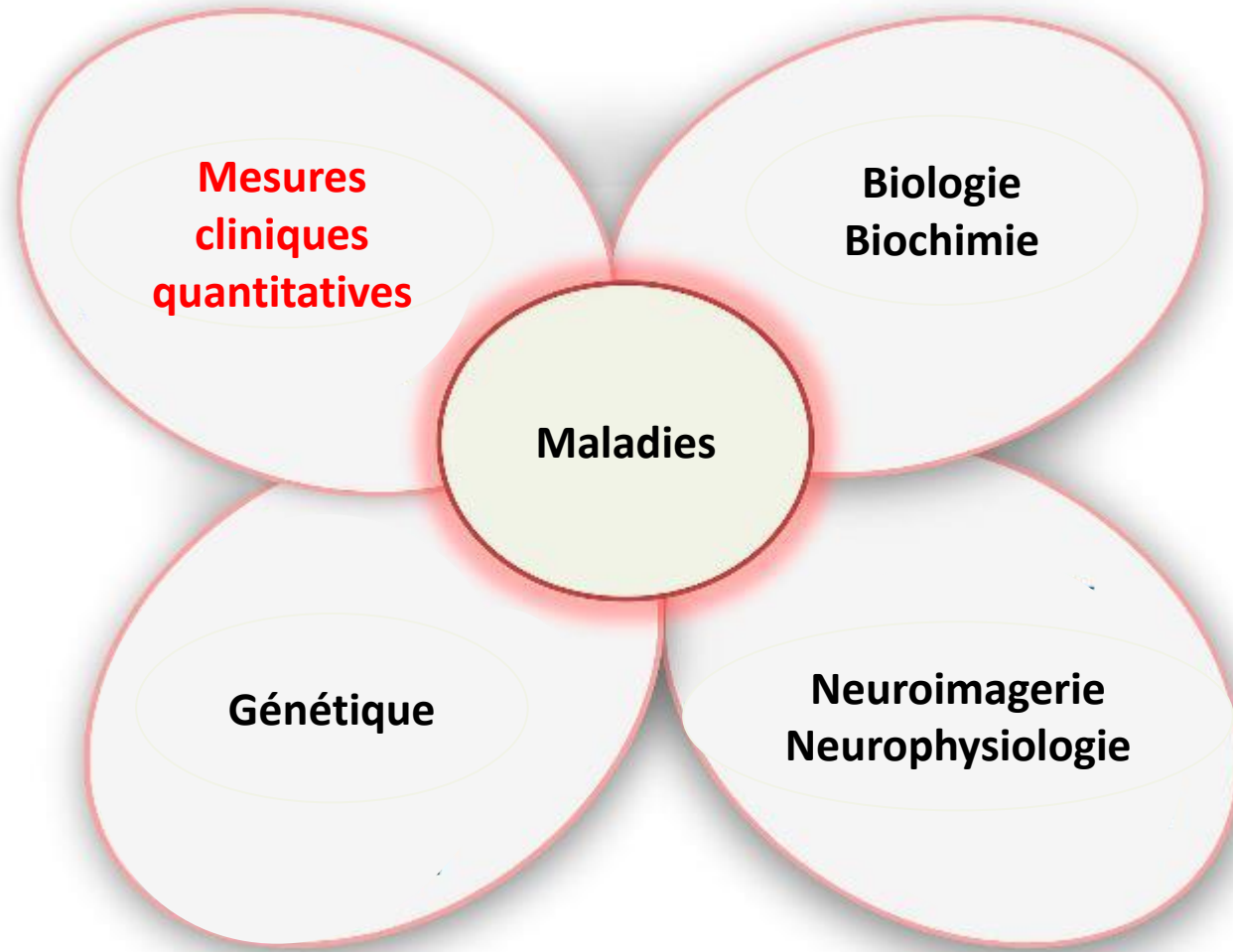
MoVeRe www.movere.org



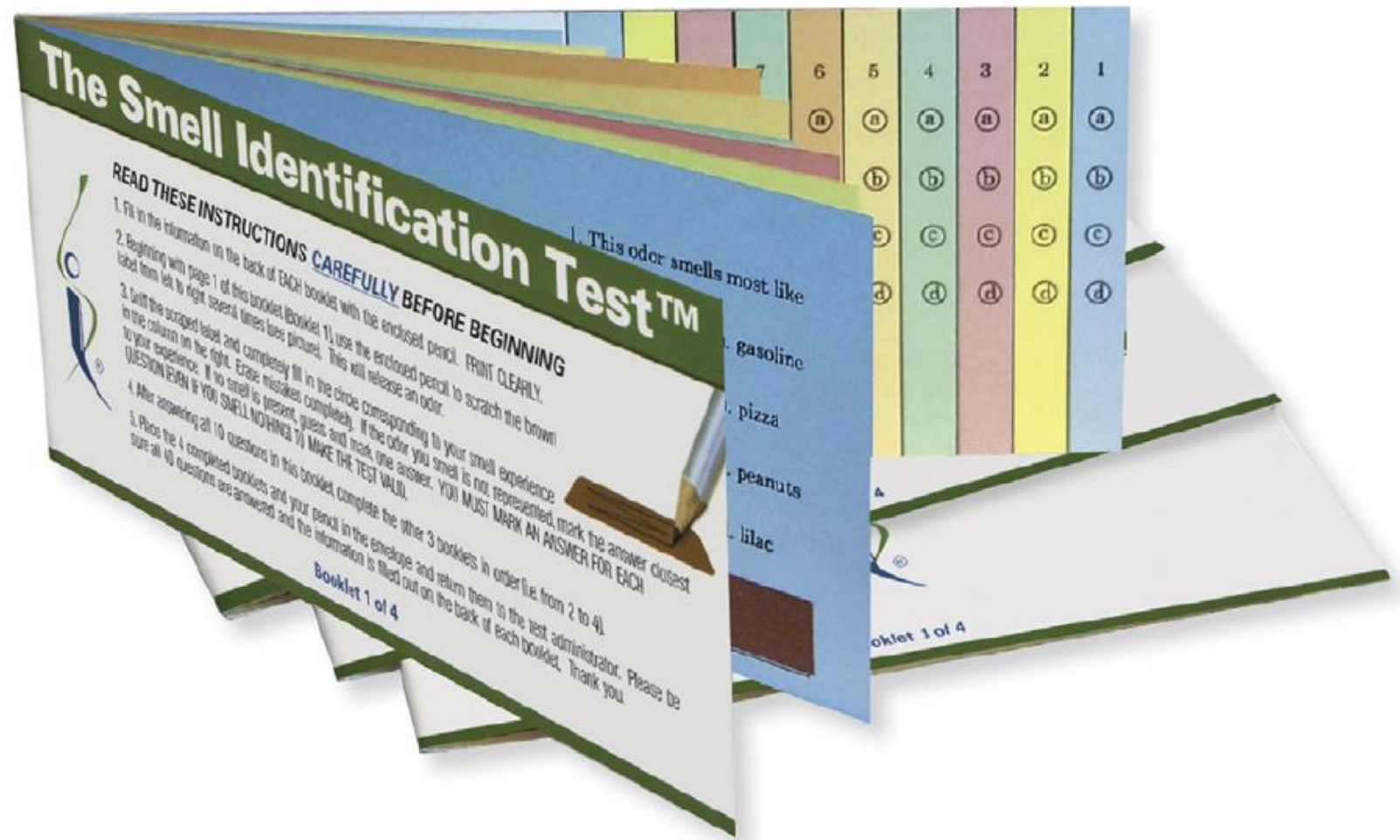
Nouveaux outils diagnostiques



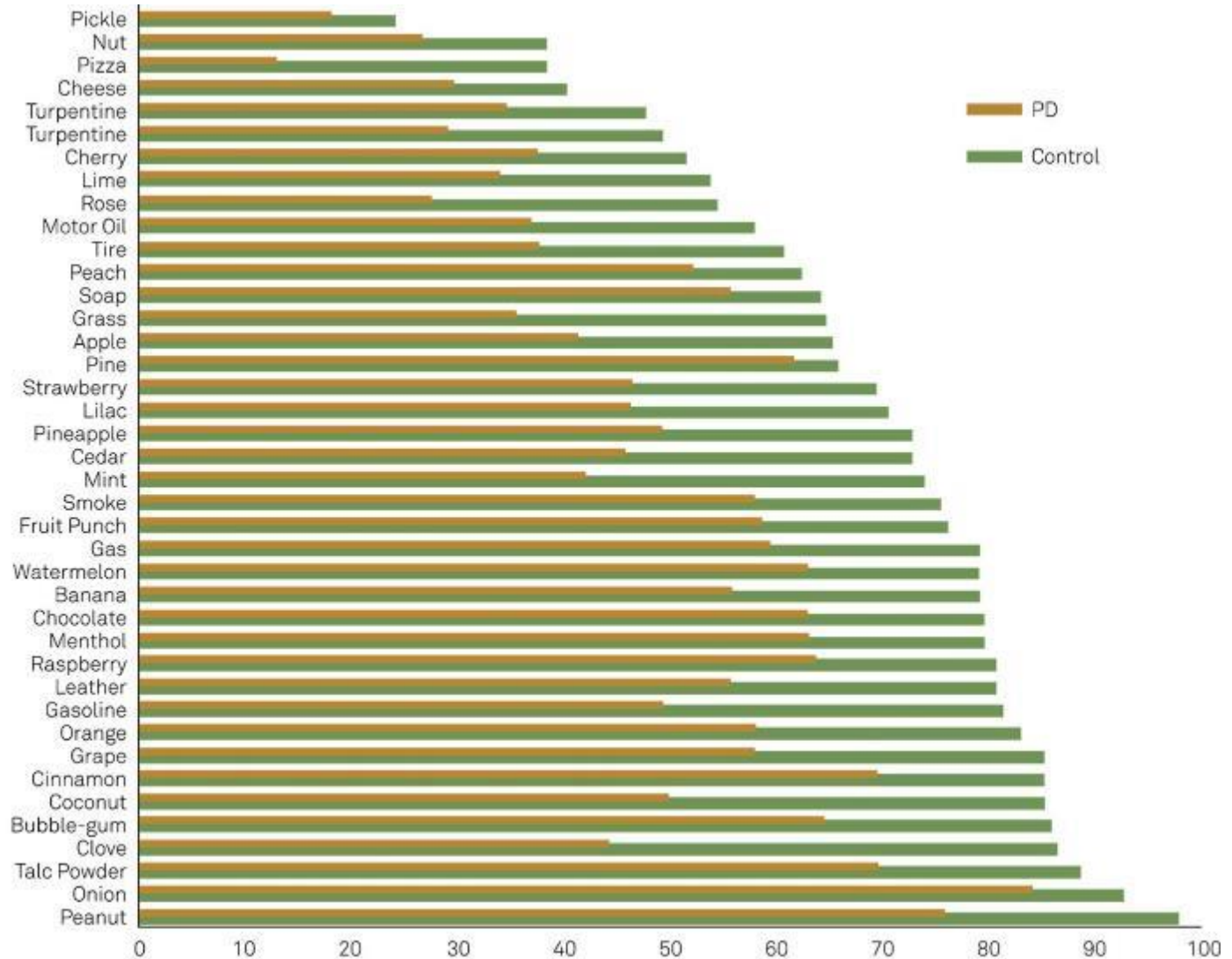
Nouvelles techniques diagnostiques



Ex: UPSIT (hyposmie)

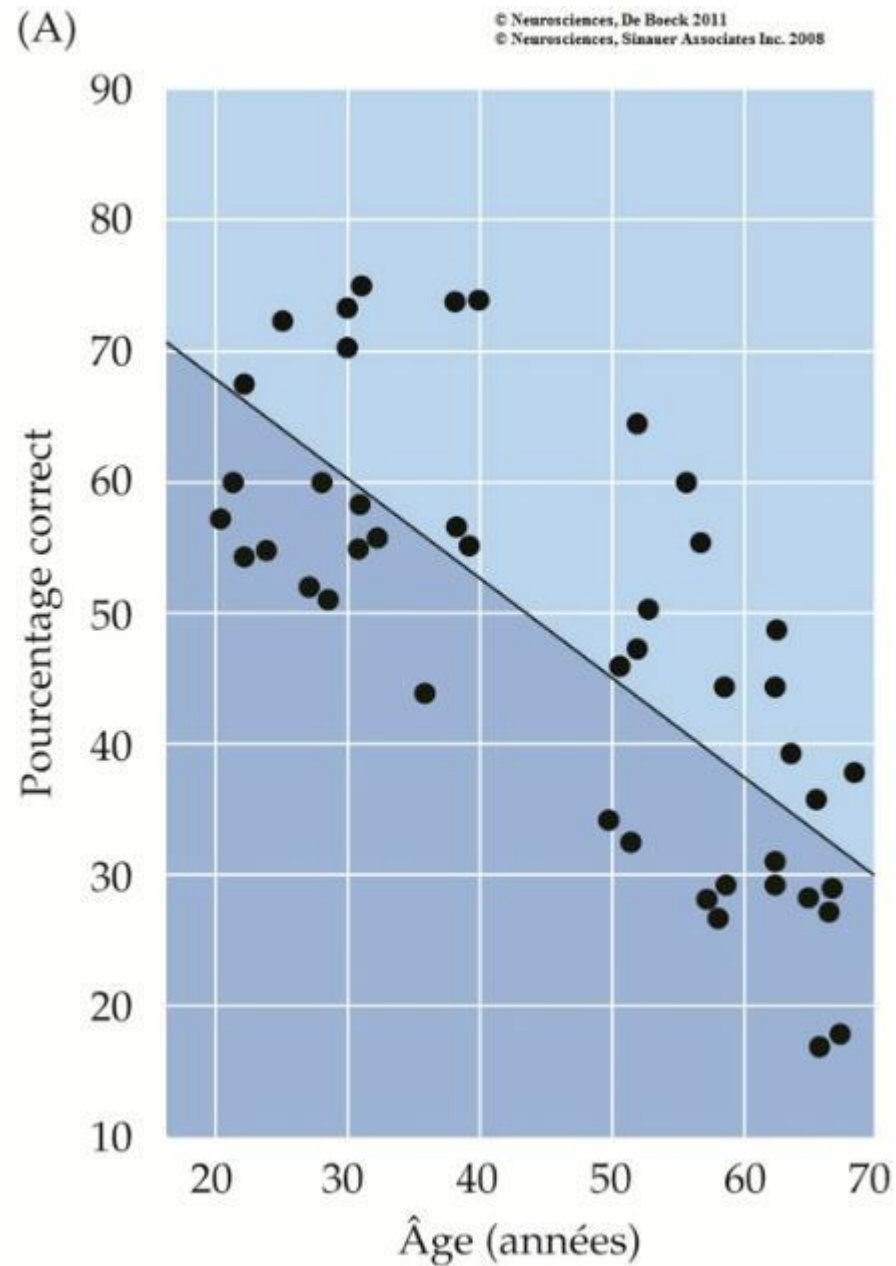


UPSIT: Parkinson vs N

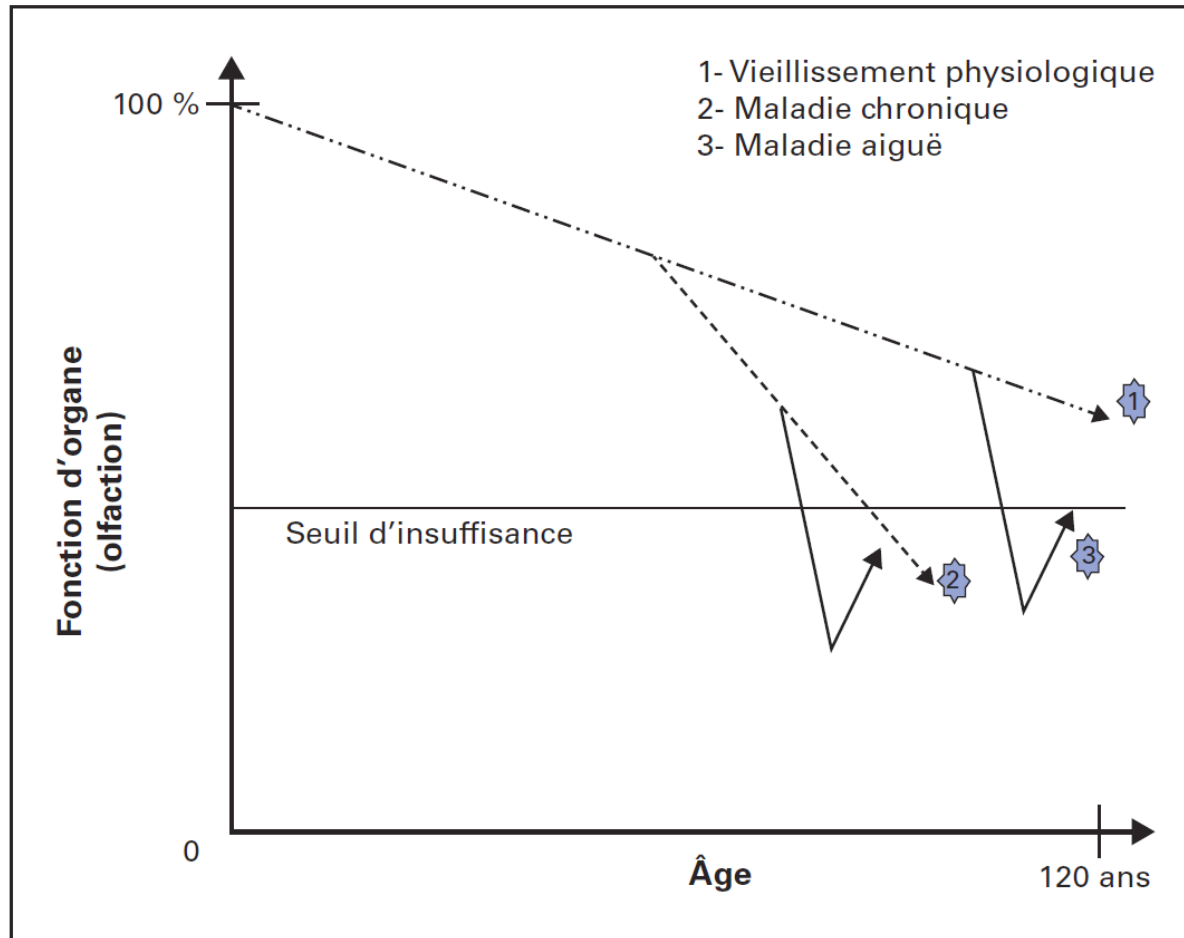


PD: Parkinson's disease; UPSIT: University of Pennsylvania Smell Identification Test.

Ontogénie de l'olfaction




Effets d'événements « aigus »



Choix du calcul du score le plus approprié

RESEARCH ARTICLE

Improved diagnosis of Parkinson's disease from a detailed olfactory phenotype

Richard C. Gerkin¹ , Charles H. Adler², Joseph G. Hentz², Holly A. Shill³, Erika Driver-Dunckley², Shyamal H. Mehta², Marwan N. Sabbagh³, John N. Caviness², Brittany N. Dugger^{4,5}, Geidy Serrano⁴, Christine Belden⁴, Brian H. Smith¹, Lucia Sue⁴, Kathryn J. Davis⁴, Edward Zamrini⁴ & Thomas G. Beach⁴

¹Arizona State University, School of Life Sciences, Tempe, Arizona

²Mayo Clinic College of Medicine, Scottsdale, Arizona

³Barrow Neurological Institute, Phoenix, Arizona

⁴Banner Sun Health Research Institute, Phoenix, Arizona

⁵University of California, San Francisco, California

Quantification de l'hyposmie

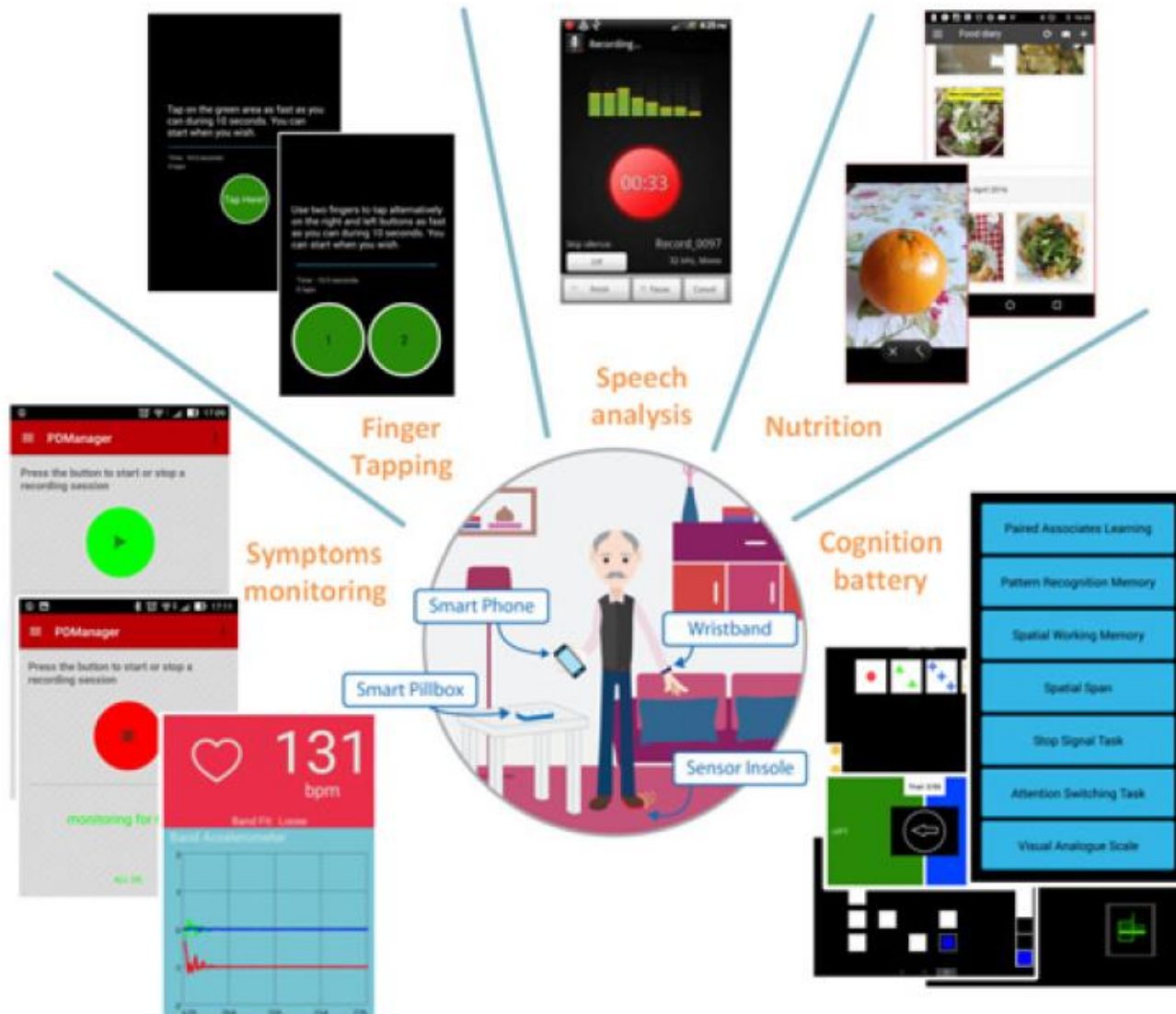
Sensibilité ?

- Interview: 1/3 patients hyposmiques en sont anosognosiques (Hawkes et al. 1997)
- Batterie: identification vs seuil de détection, distinction des odeurs, mémoire olfactive? (Potagas 1998)
- Aspects techniques: différences culturelles, vigueur de l'inspiration (Sobel et al. 2001)

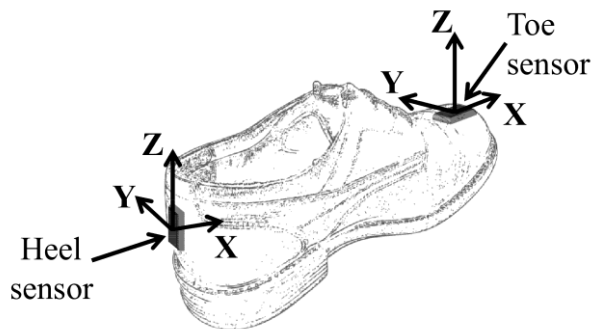
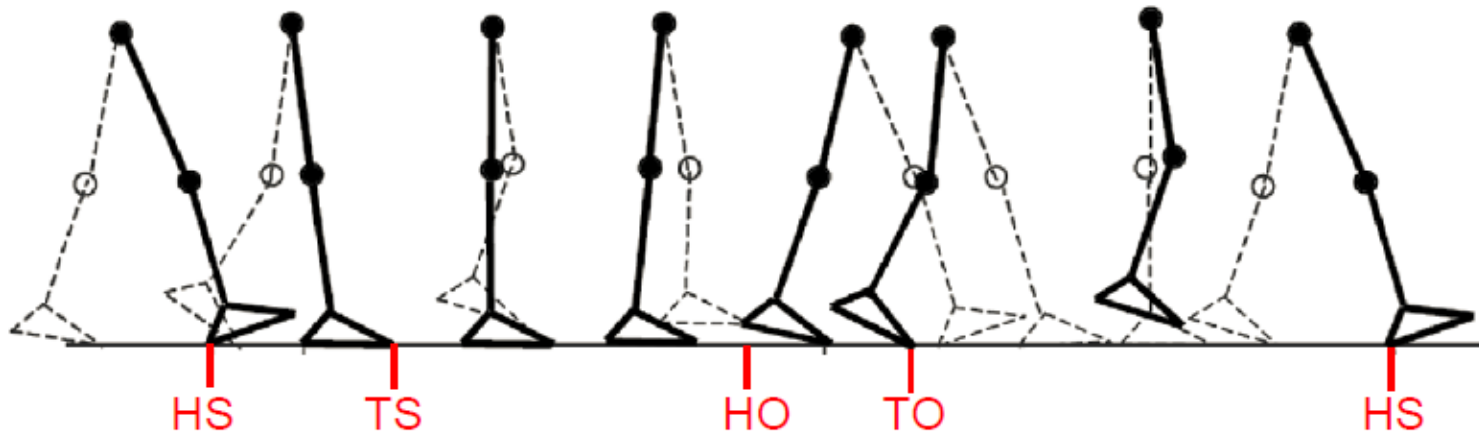
Spécificité ?

- Hyposmie démontrée dans Alzheimer, démence à corps de Lewy, atrophie multisystémique, maladie de Huntington, dystonie-parkinsonisme (Hawkes et al. 2003)
- Pathologies ORL (infect. virales, fractures), tabagisme,...

Internet of things (IOT)



Capteurs de mouvements de la marche



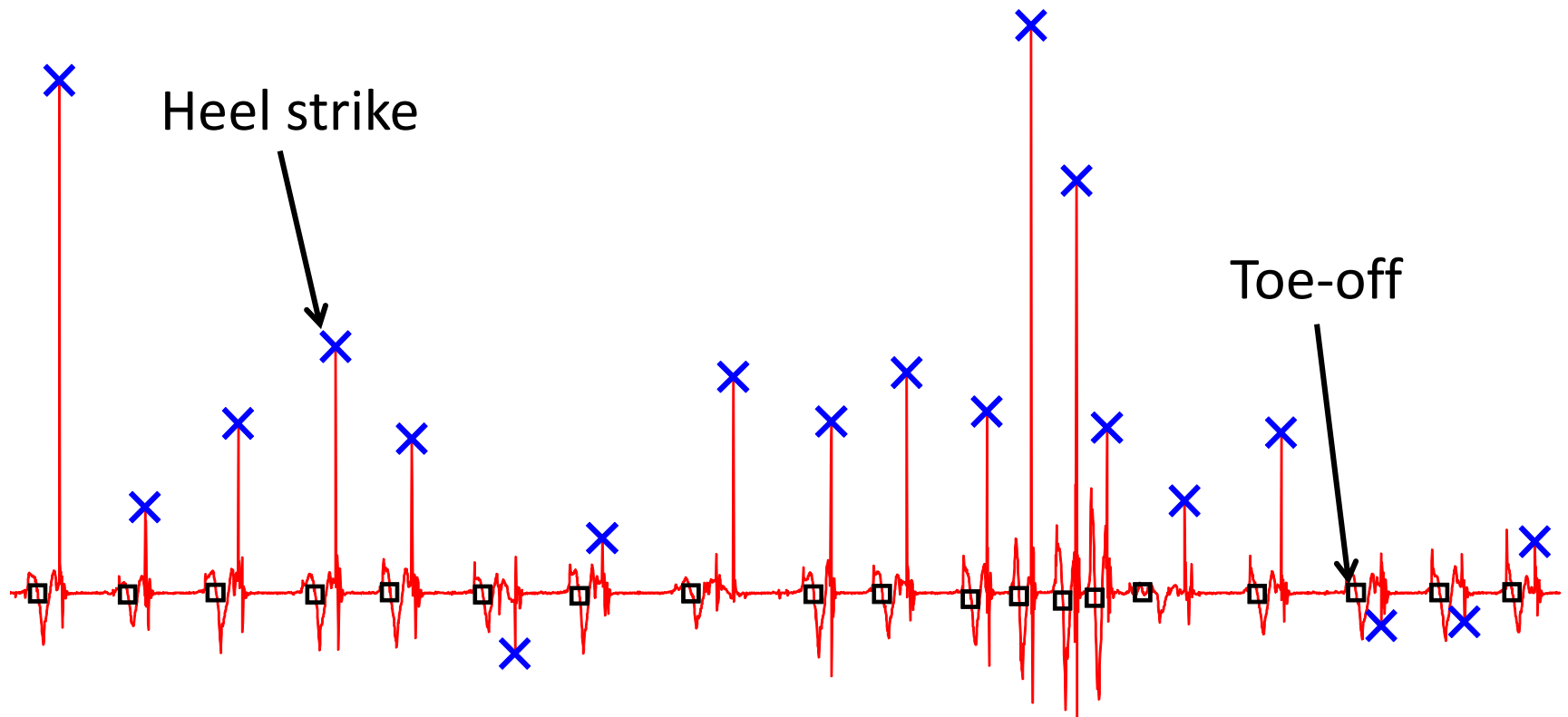
HS: Heel-strike

TO: Toe-off

Enregistrement ambulatoire de la marche



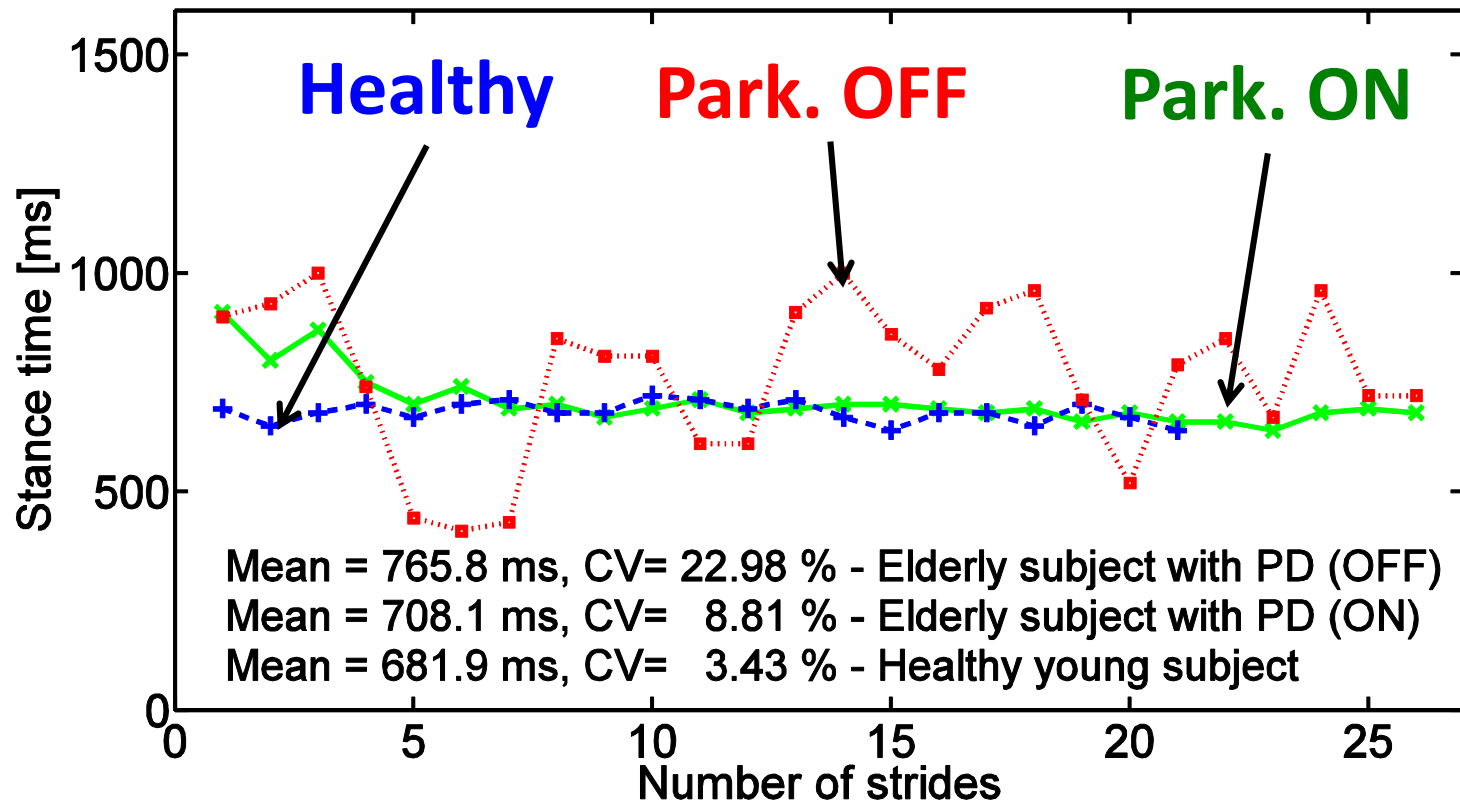
Enregistrement ambulatoire de la marche



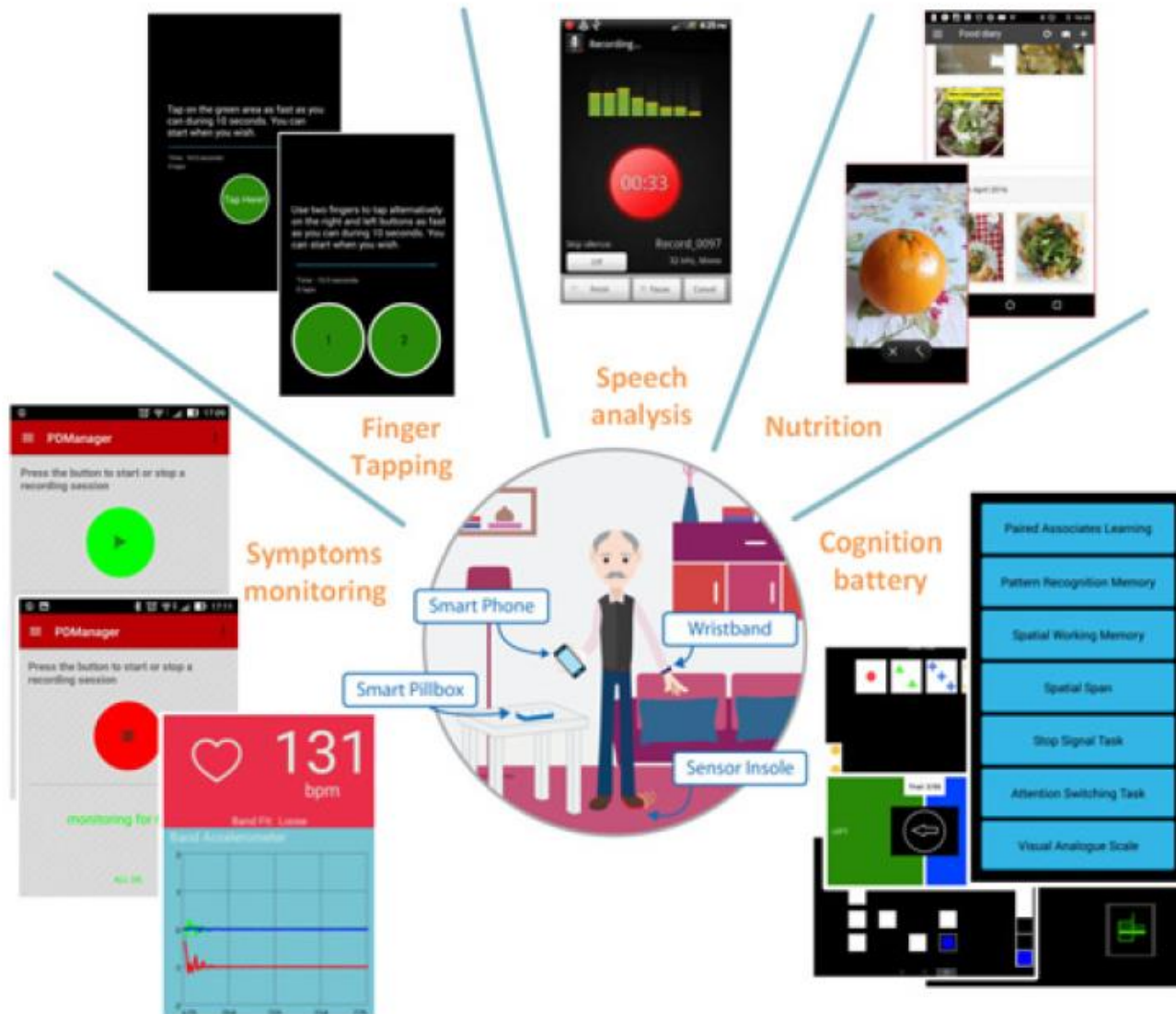
Enregistrement ambulatoire de la marche

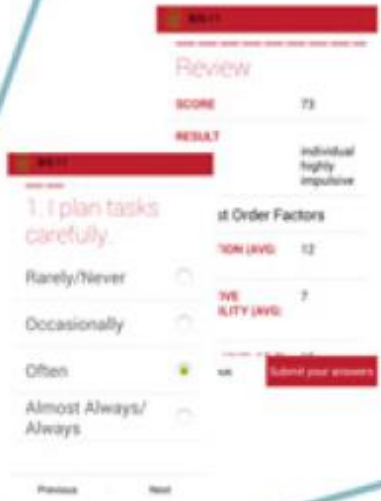


Ex: variabilité de la durée de la phase d'appui



Internet of things (IOT)





Medication

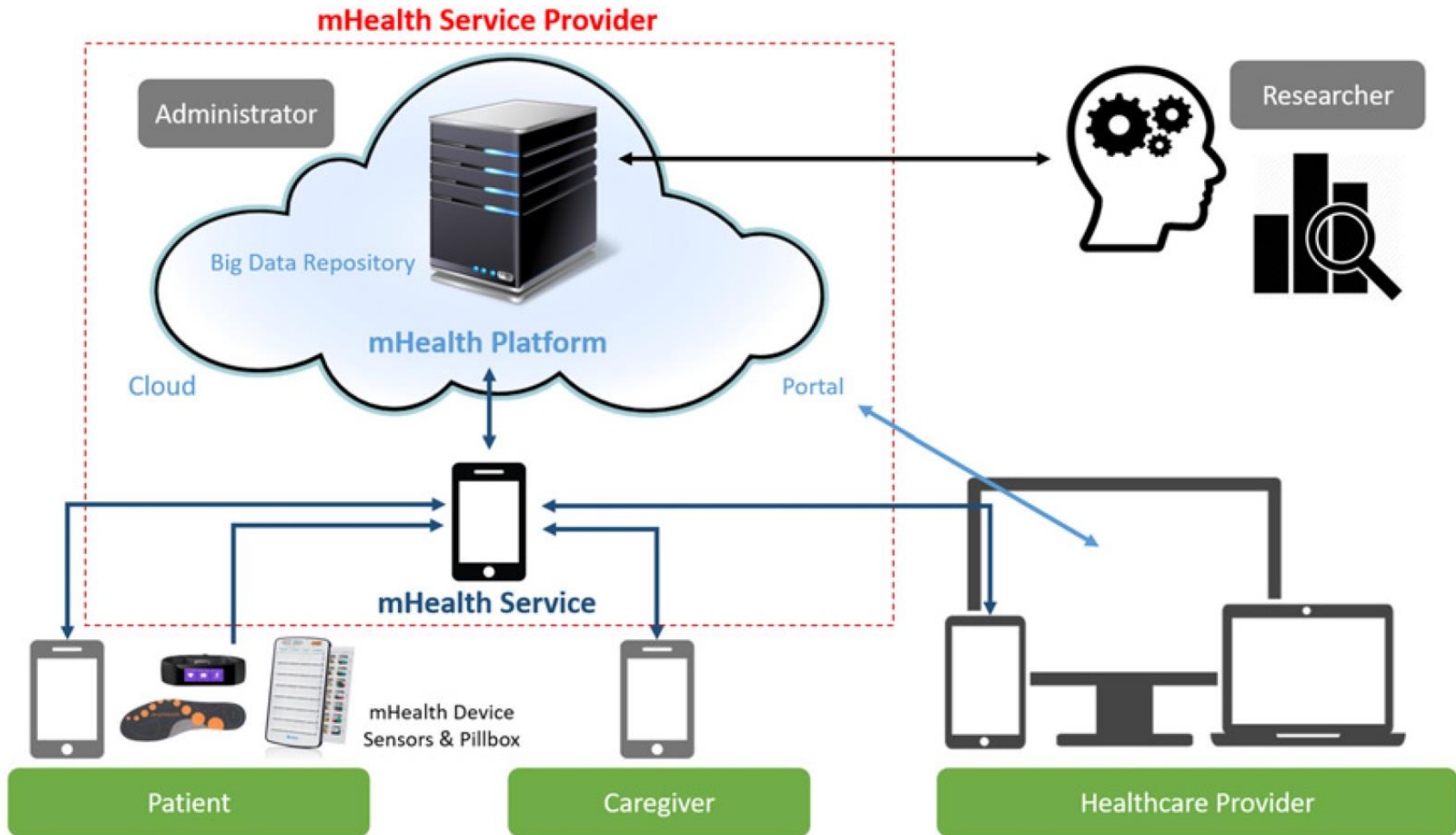
Assessment

Tests

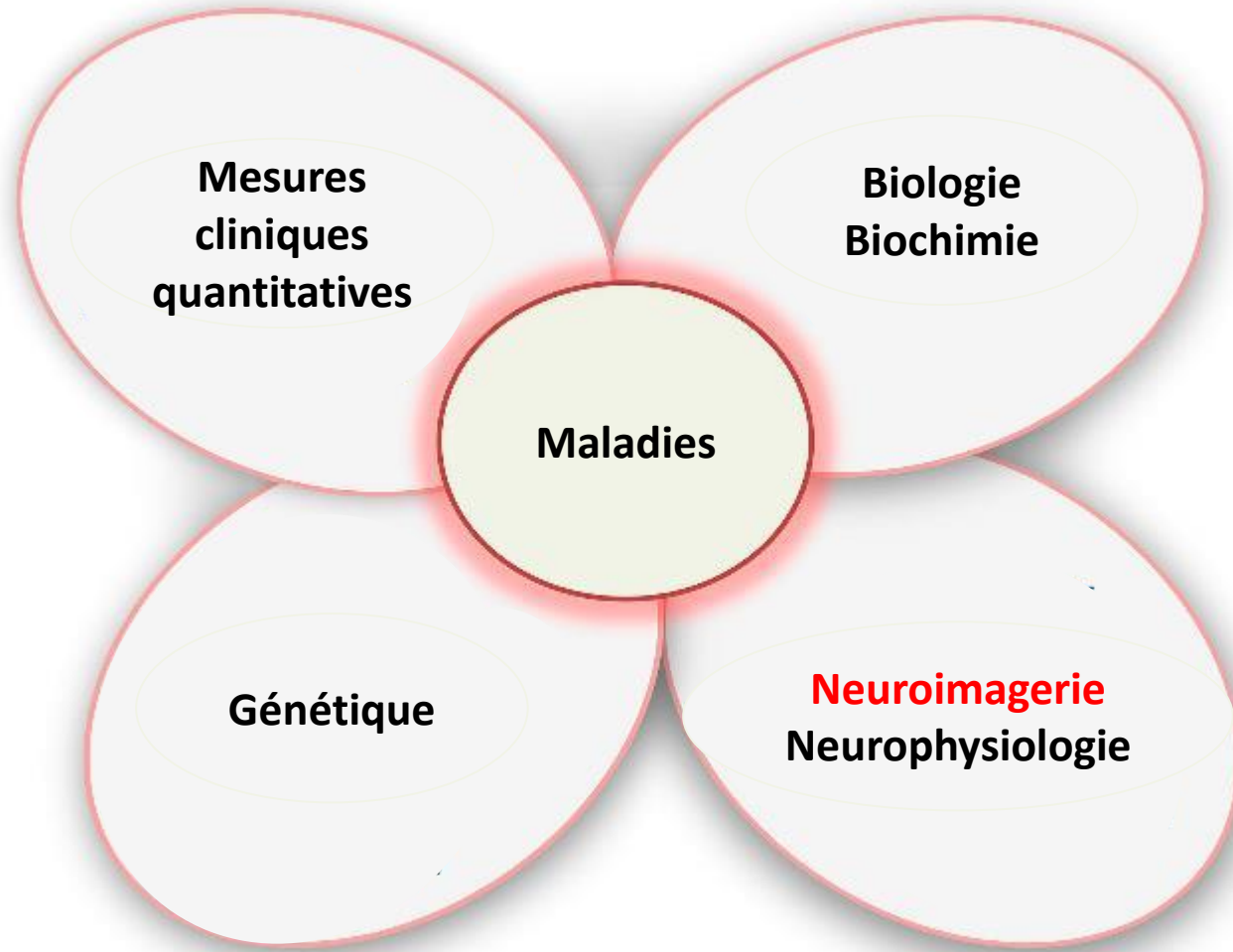
Calendar

Clinical record & Charting

IOT → profilage & « Big » data



Nouvelles techniques diagnostiques



Tomographie par émission de positons



TEP FDG: Principe général

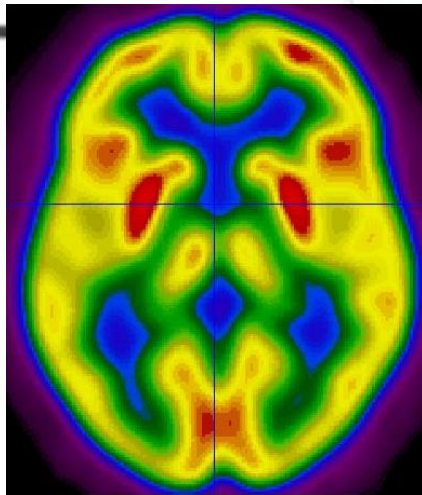
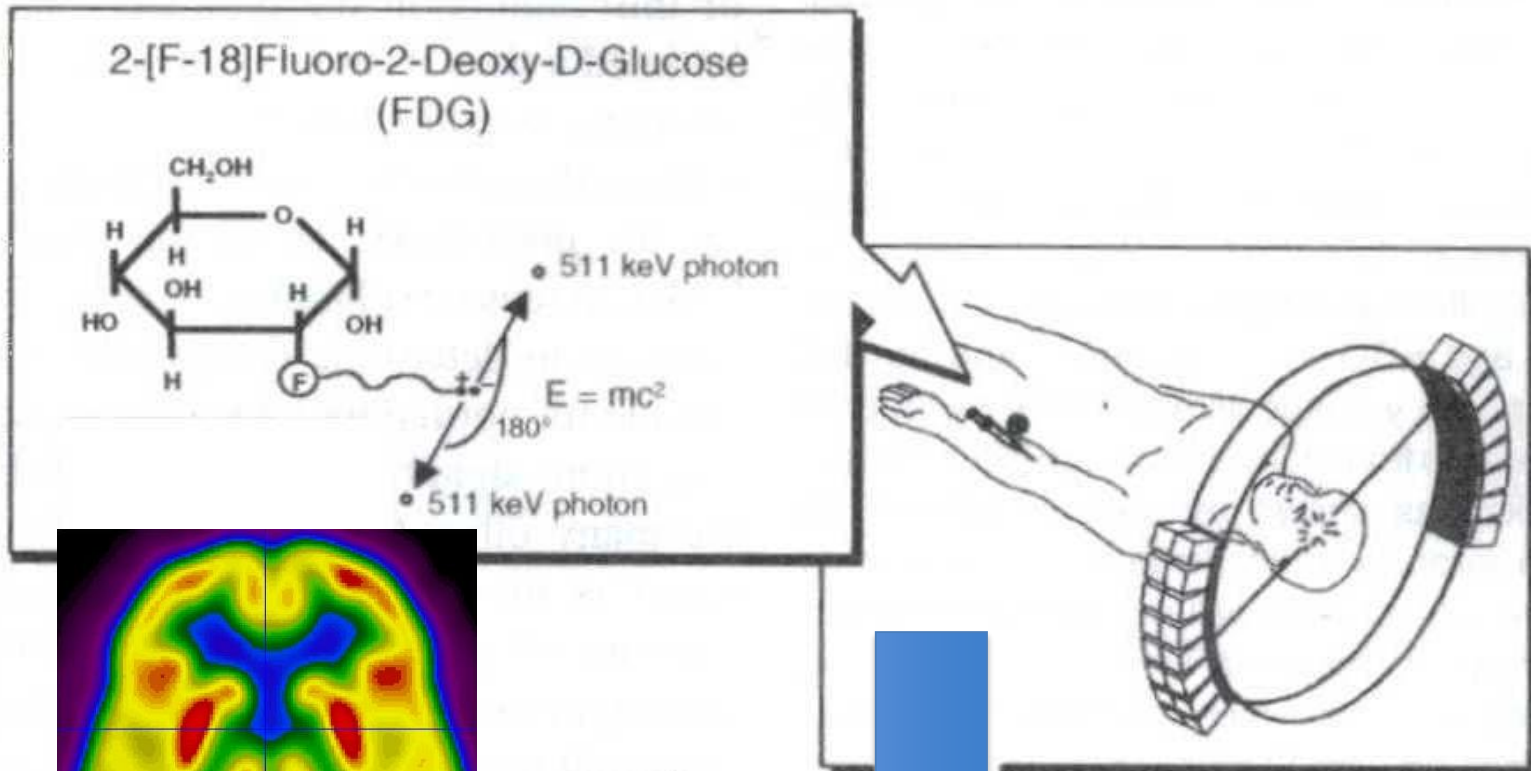


Image de la distribution cérébrale du ^{18}F FDG

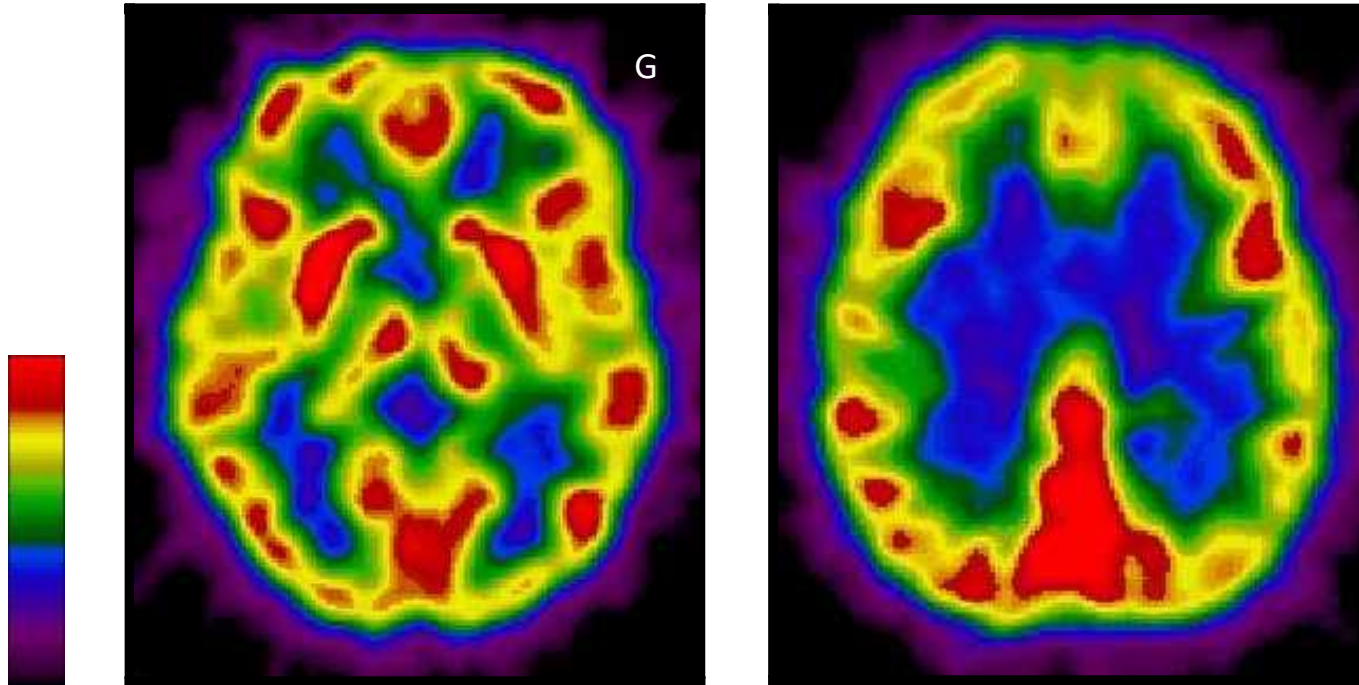
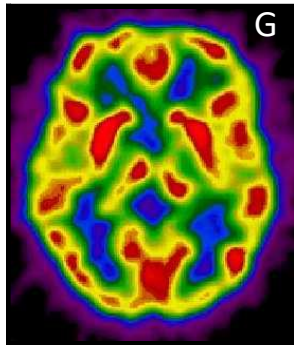
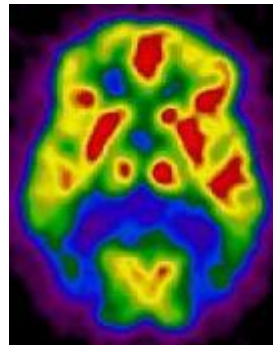


Image de la distribution cérébrale du ^{18}F FDG

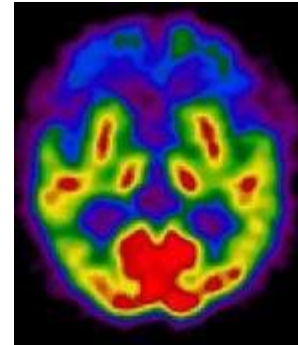
Sujet
sain



Démence
de type
Alzheimer



Démence
fronto-
temporale



Paralysie
supranucléaire
progressive

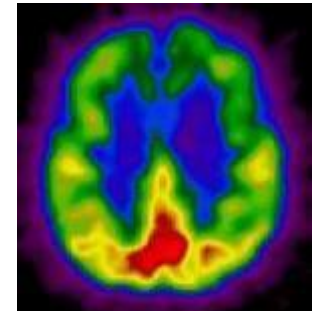
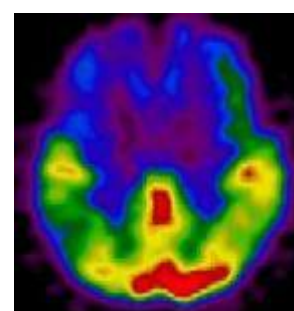
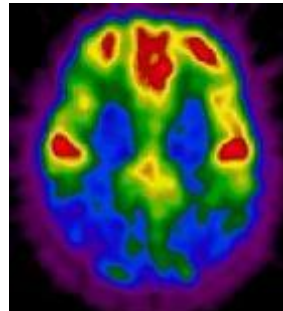
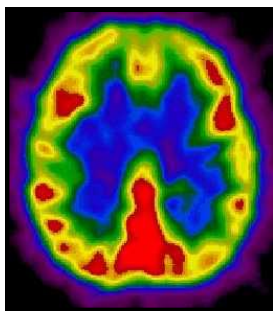
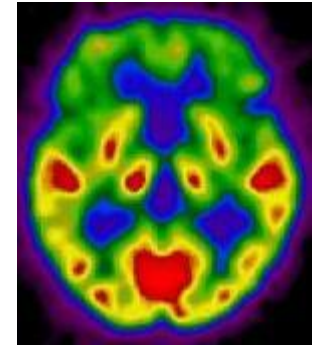
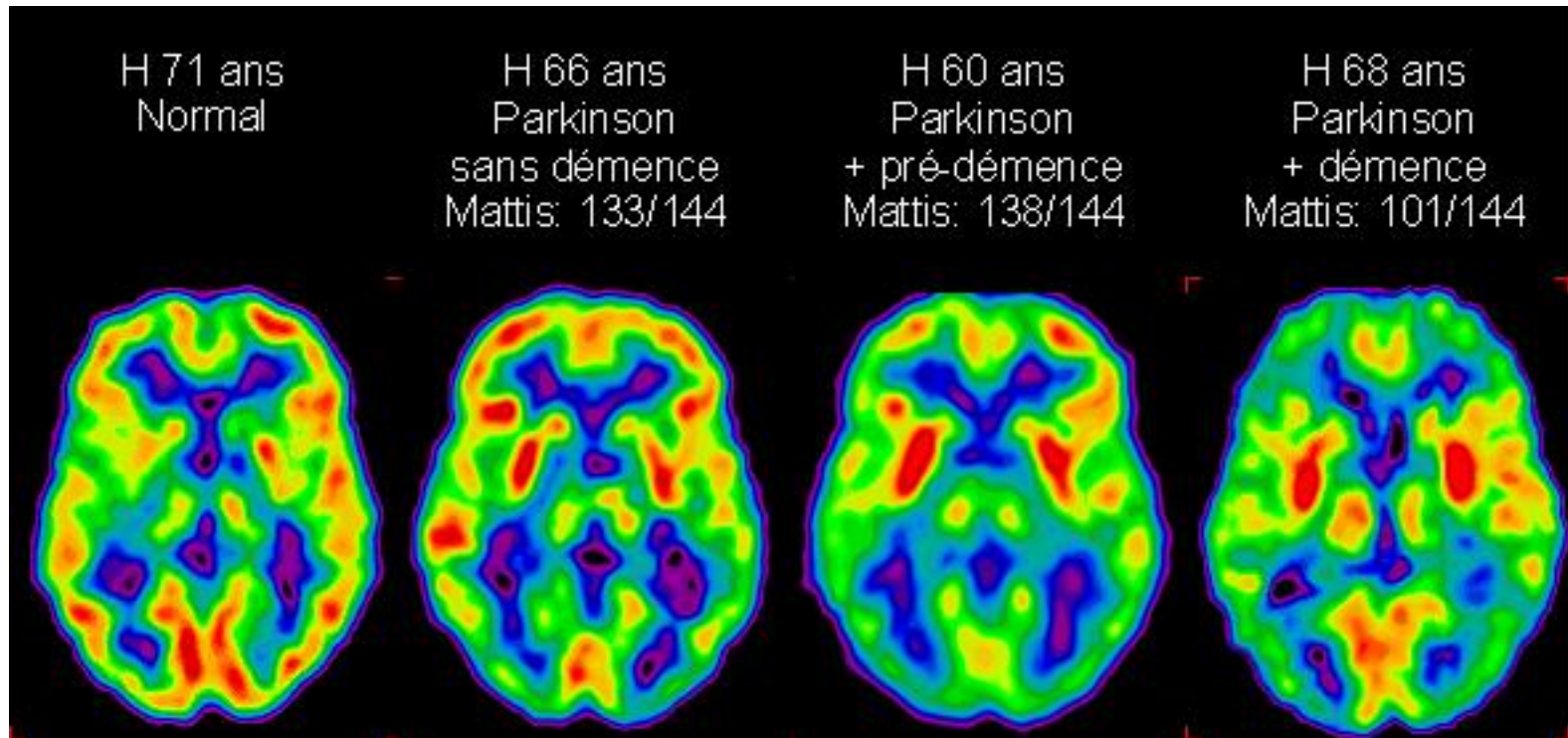
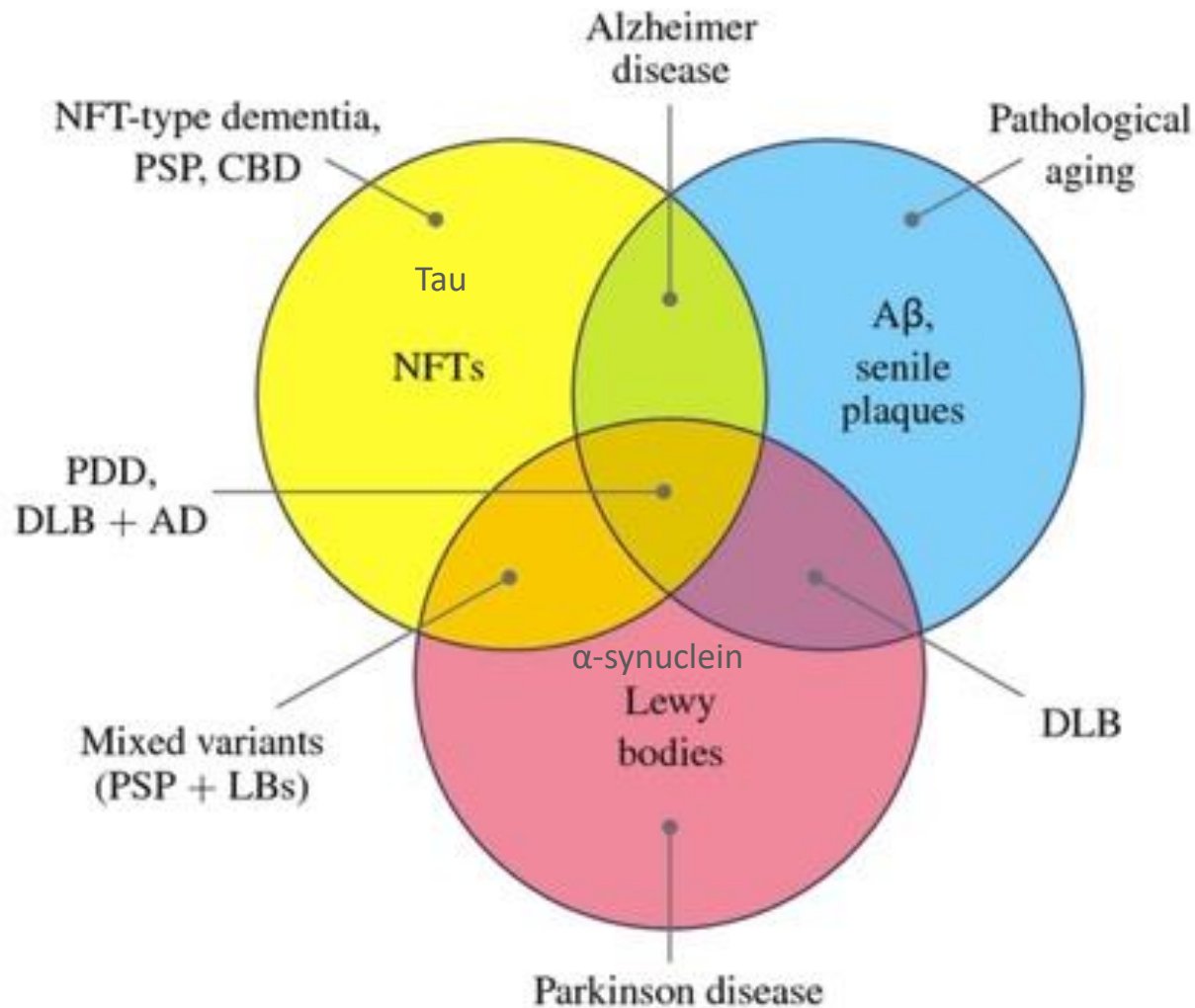


Image de la distribution cérébrale du ^{18}F FDG dans la MP

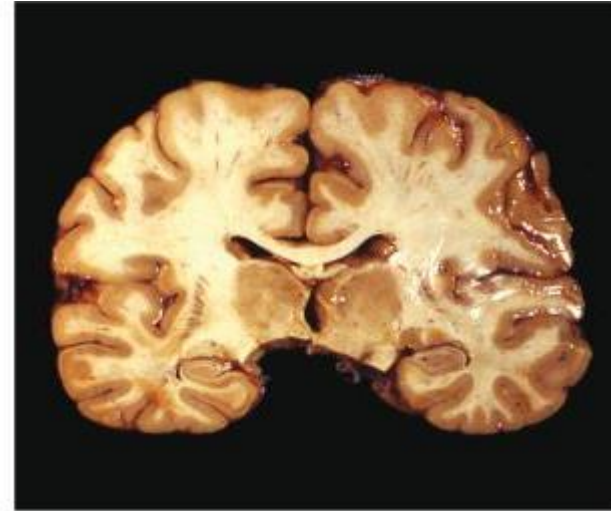
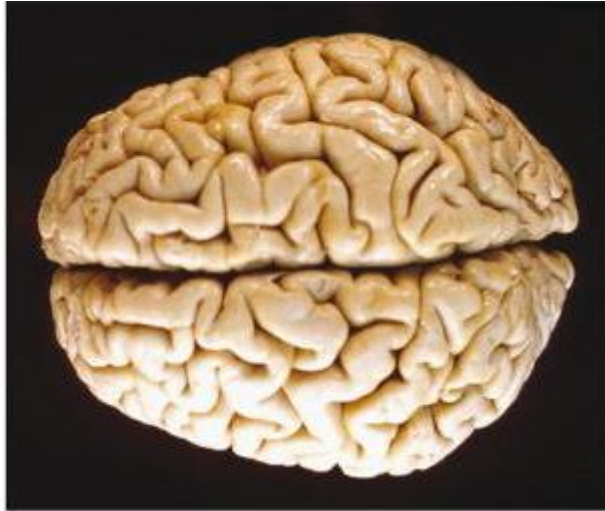


Protéinopathies des maladies neurodégénératives

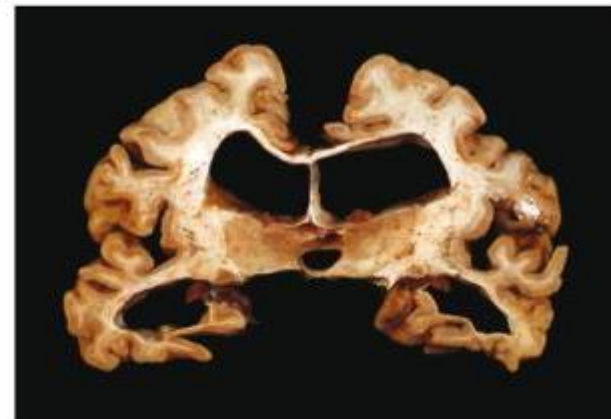
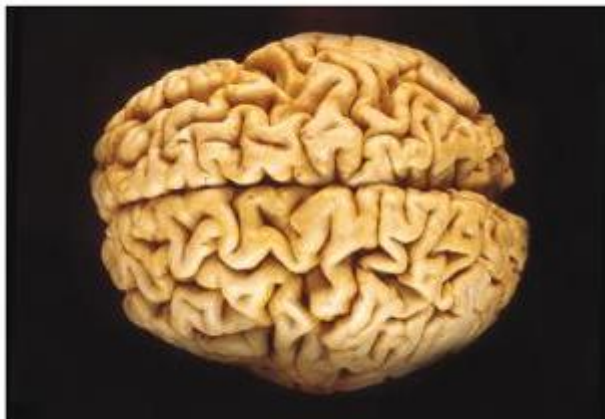


Atteinte étendue des aires associatives dans l'Alzheimer

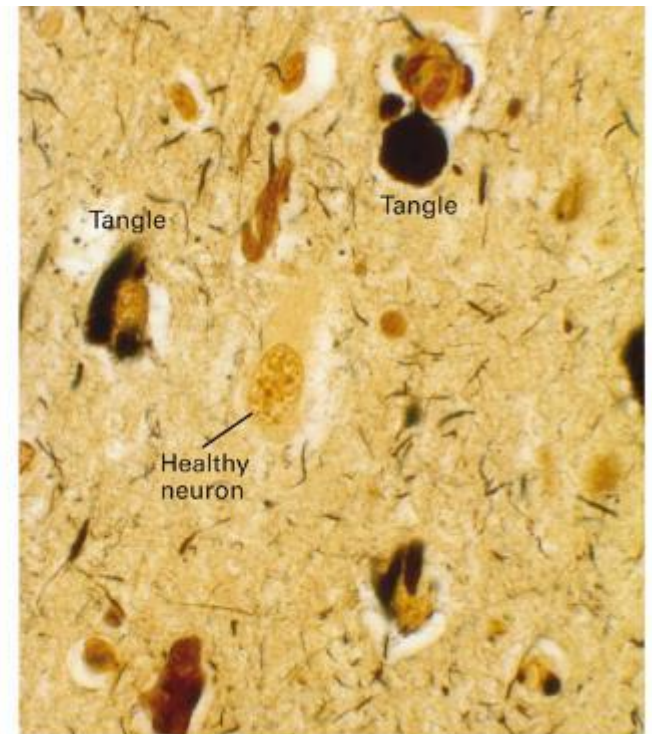
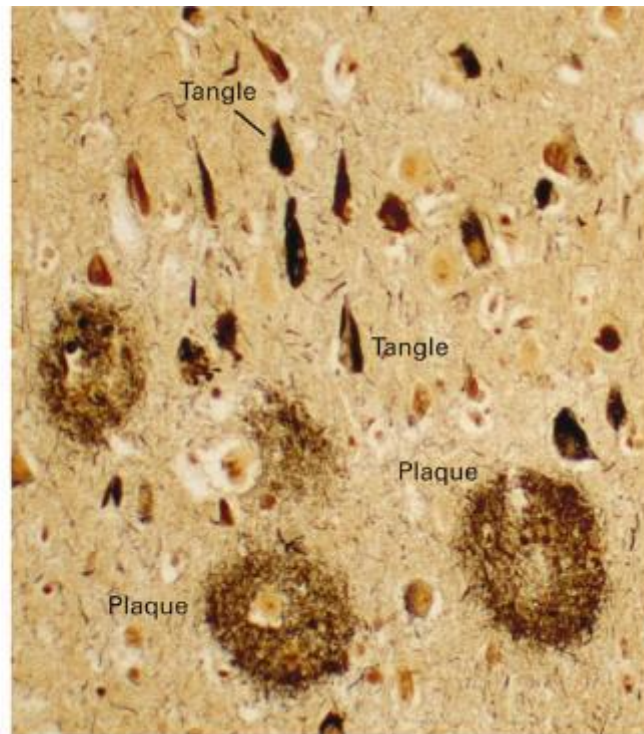
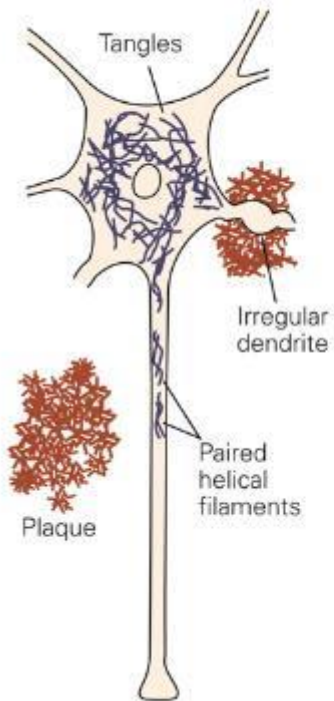
Normal



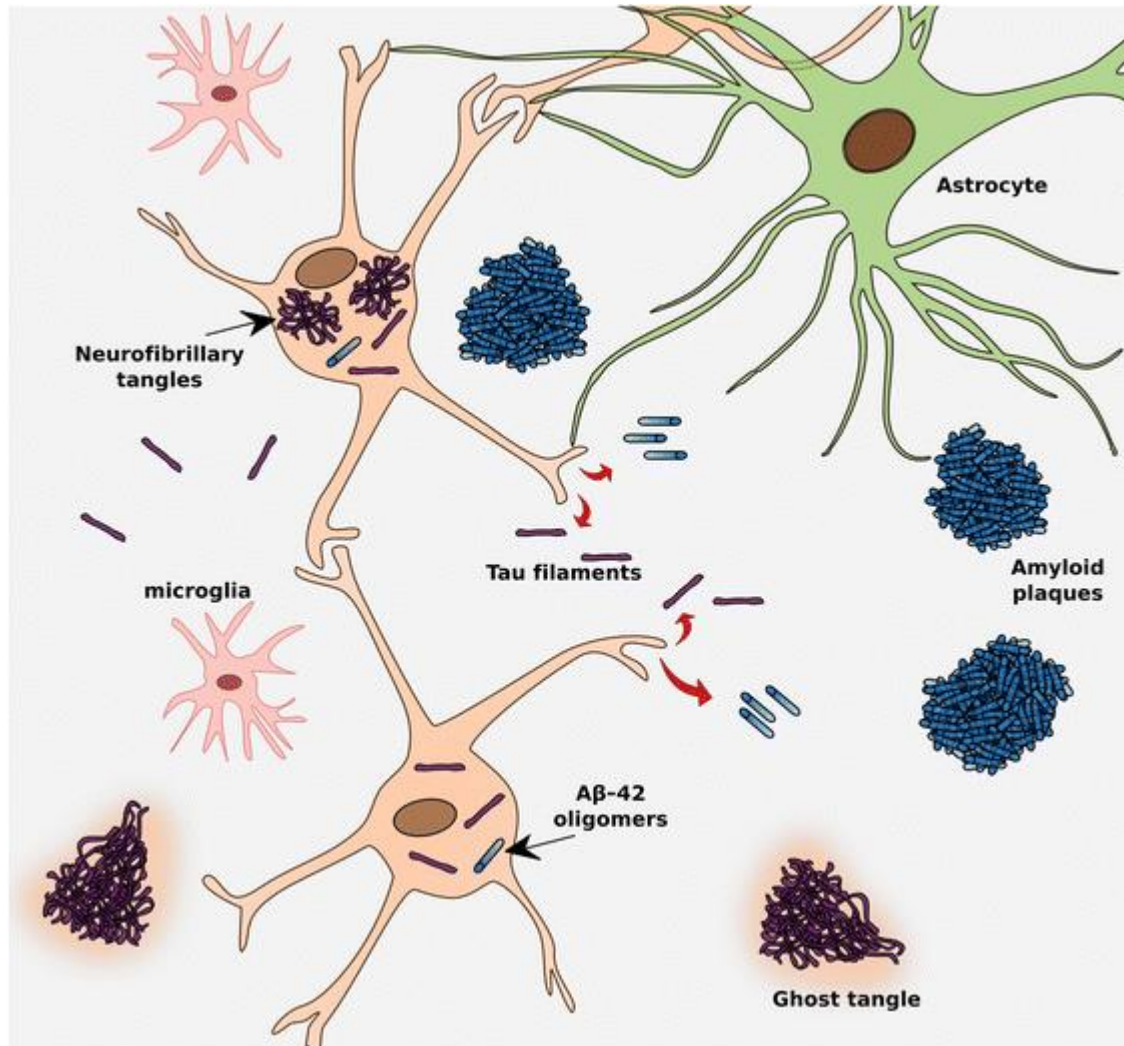
Alzheimer disease



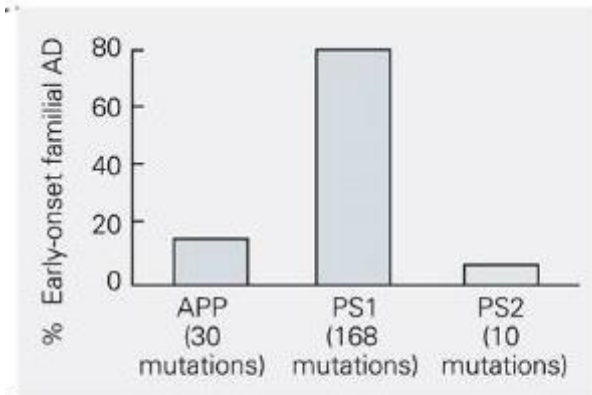
2 grands types d'inclusions neuropathologiques de la MA: plaque sénile (amyloïde) et dégénérescence neurofibrillaire (tangle)



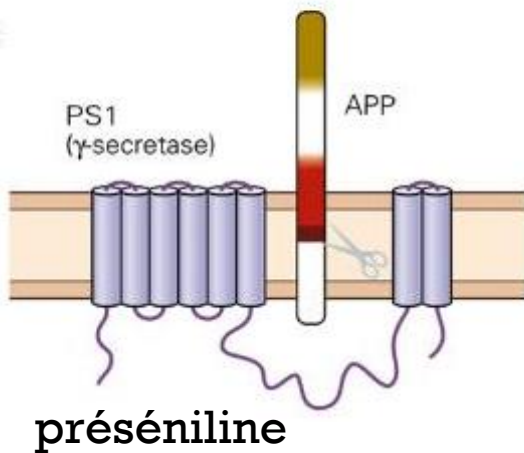
Plaques amyloïdes et tangles (protéine tau)



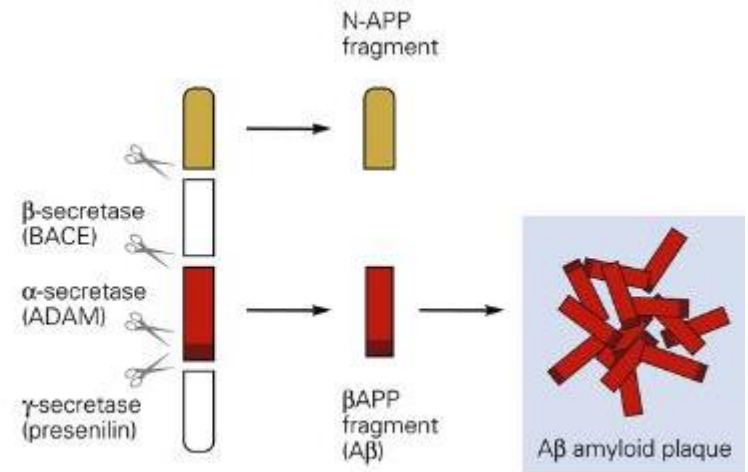
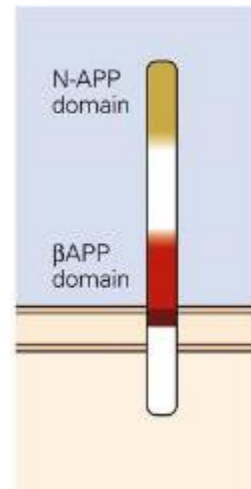
+ Les plaques séniles sont riches en protéines amyloïdes $A\beta$ (<APP)



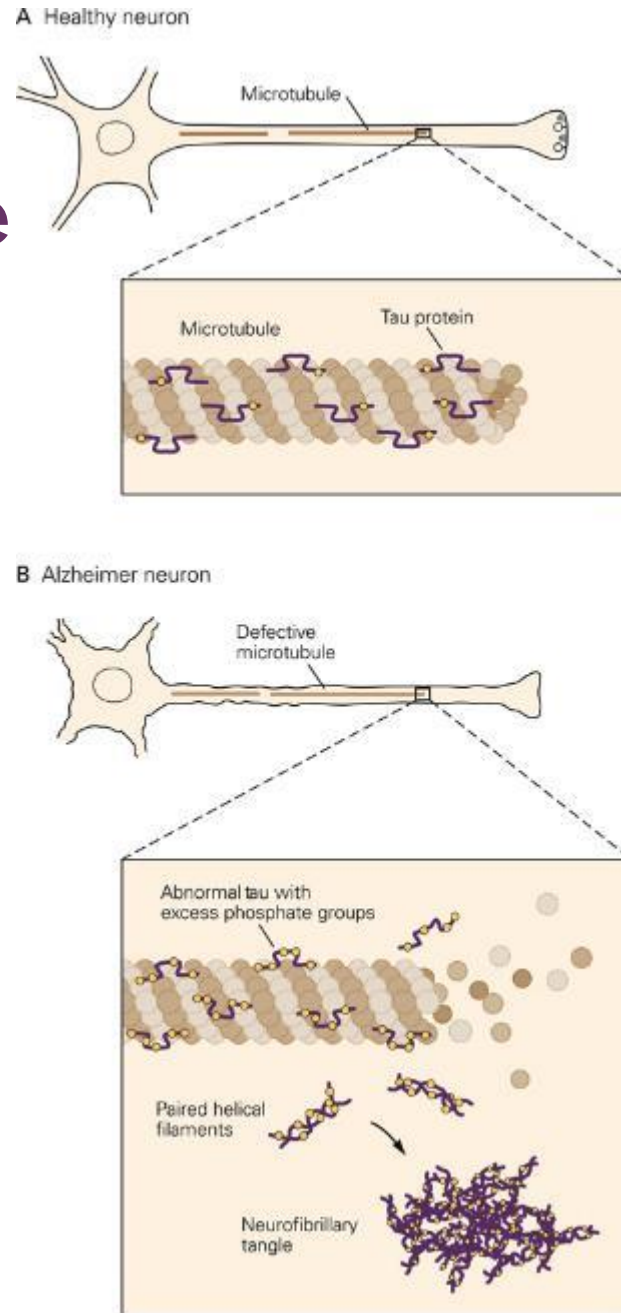
C



Amyloid precursor protein

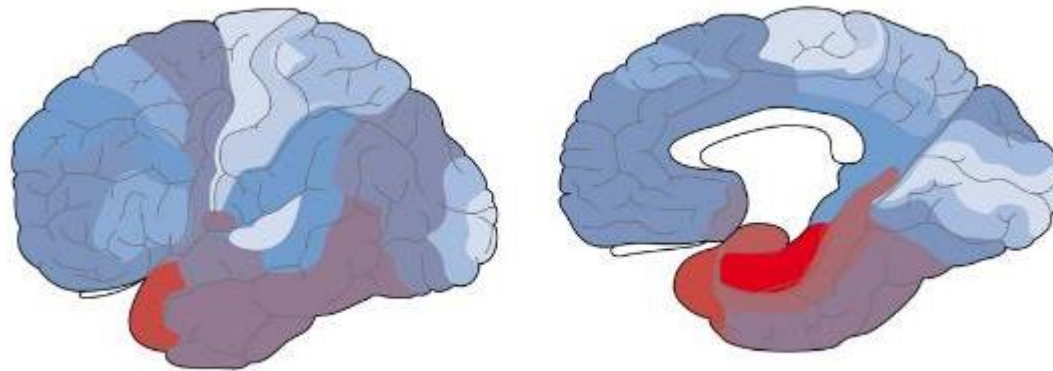


+ Les lésions de dégénérescence neurofibrillaire riches en protéines Tau anormales

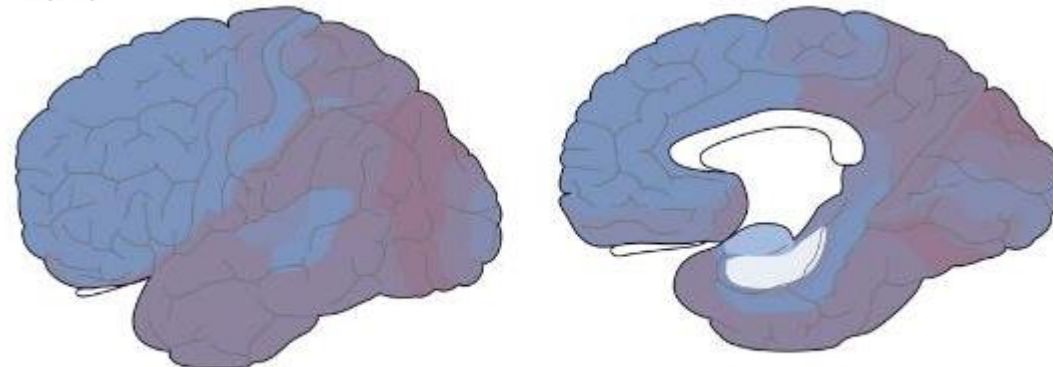


Distribution cérébrale des inclusions neuropathologiques dans la MA

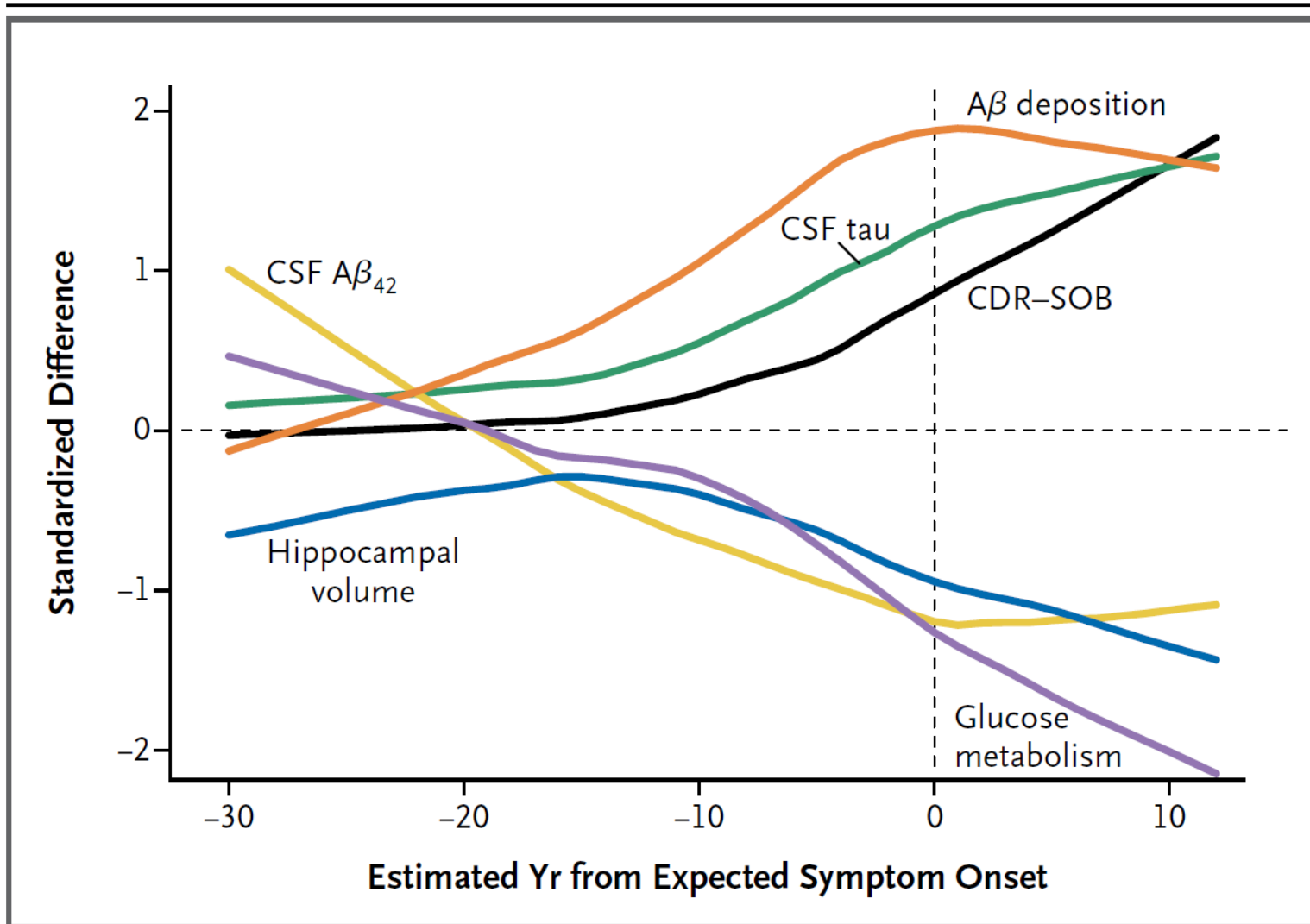
Neurofibrillary tangles



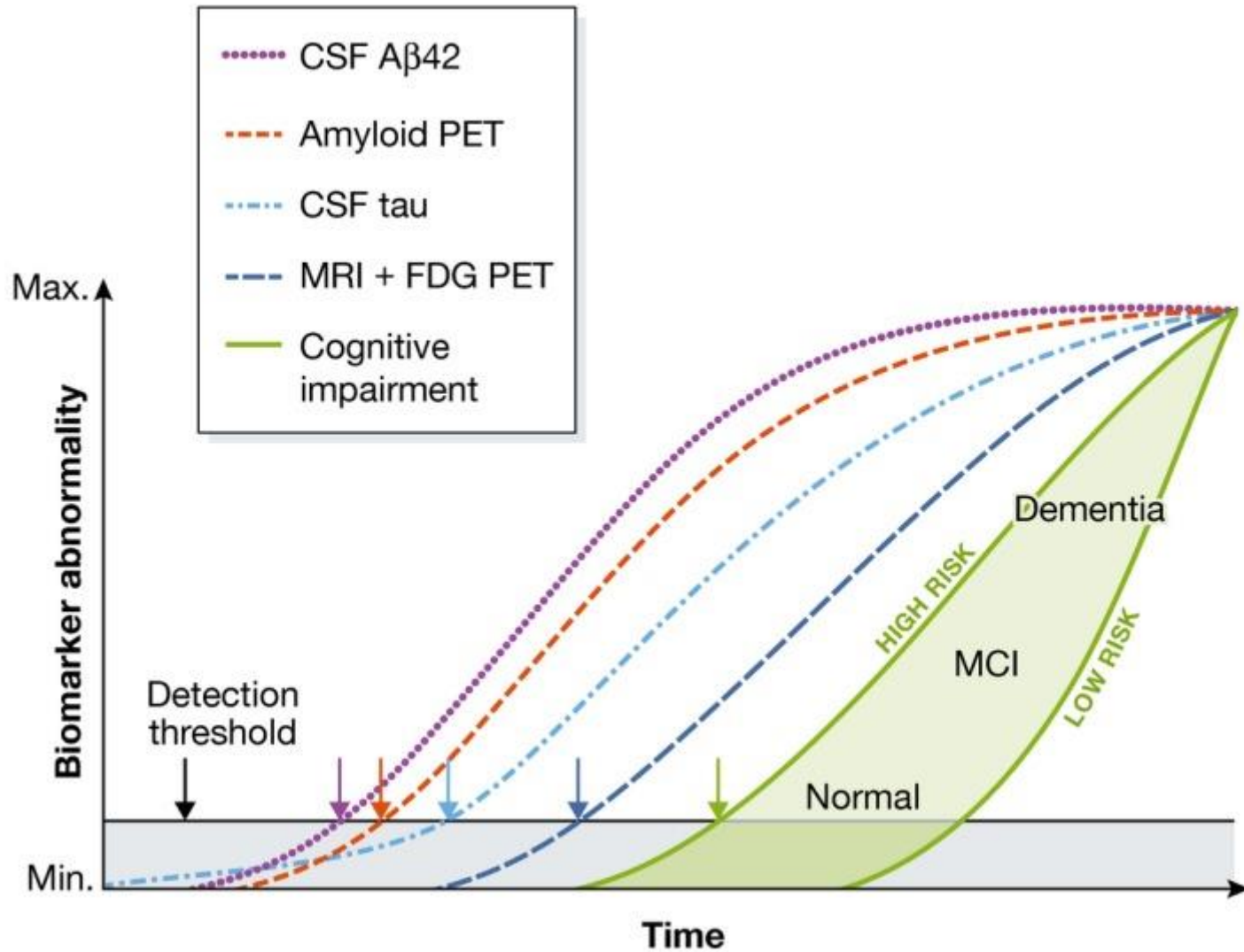
Senile plaques



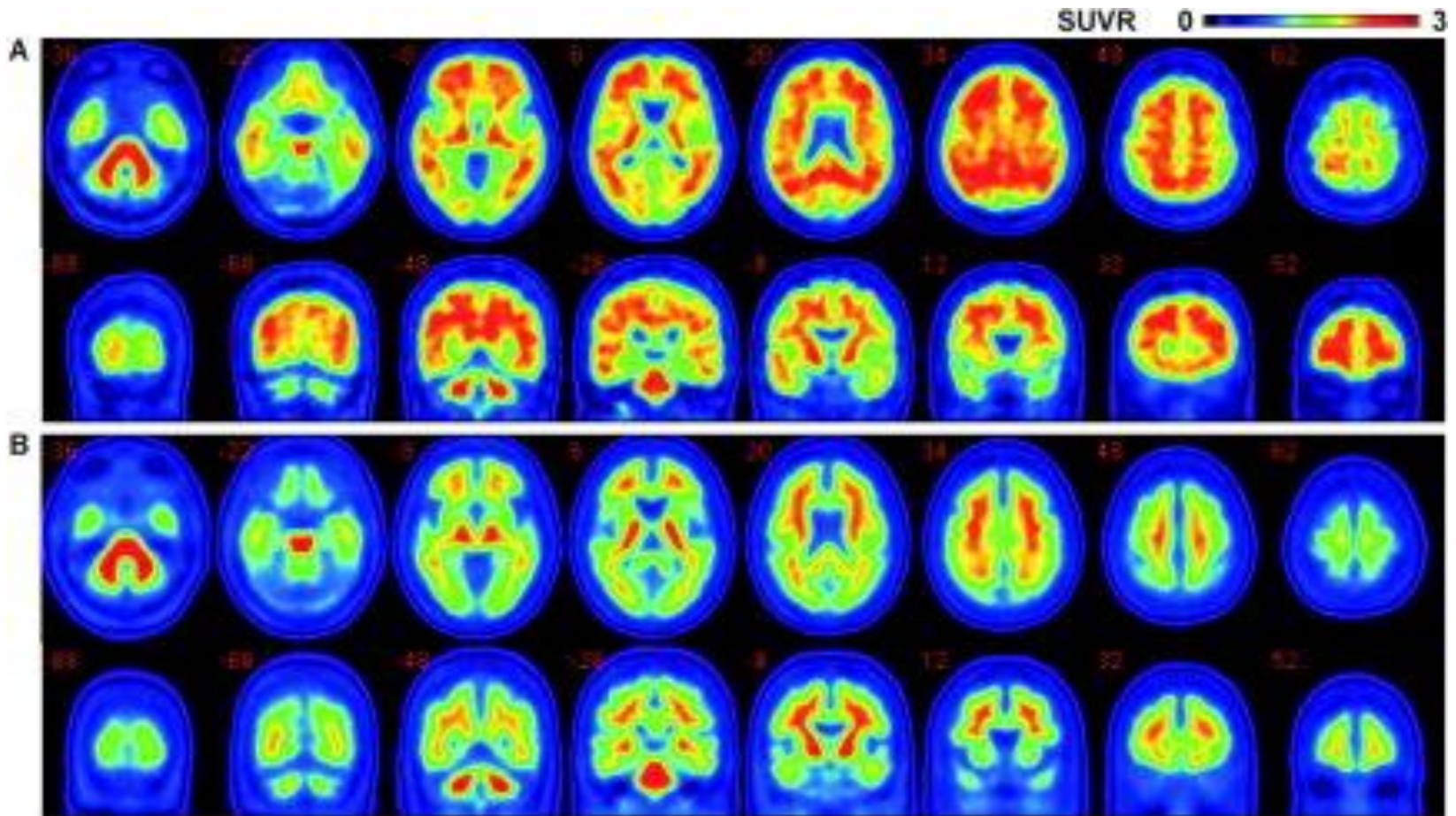
Les inclusions apparaissent précocement



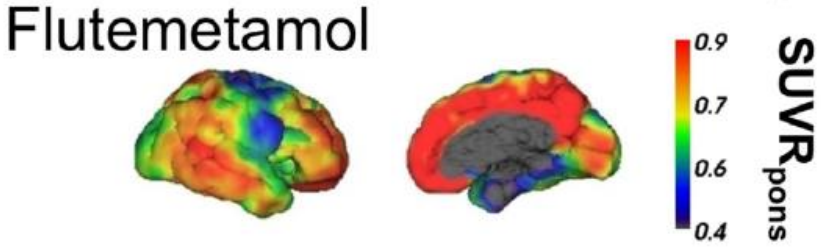
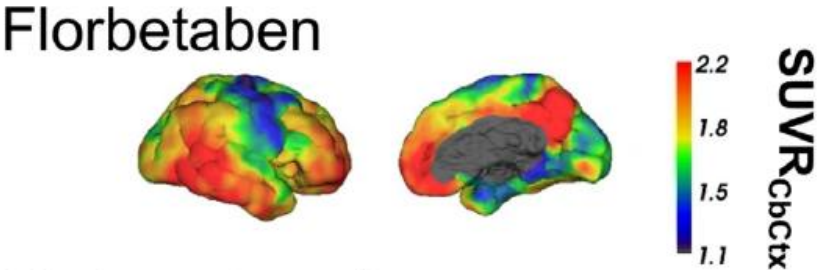
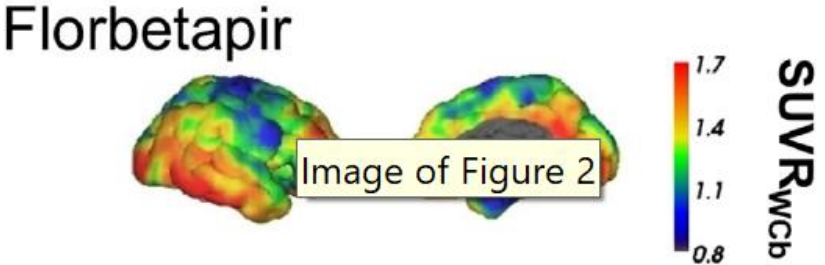
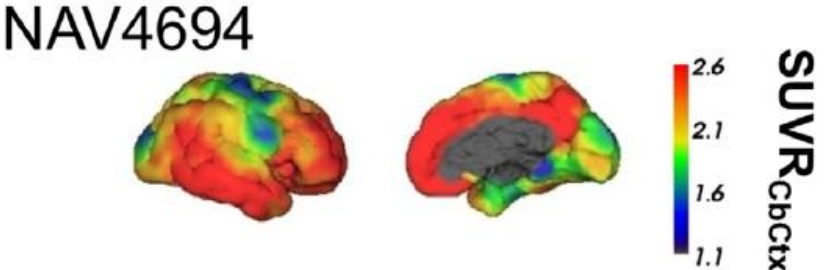
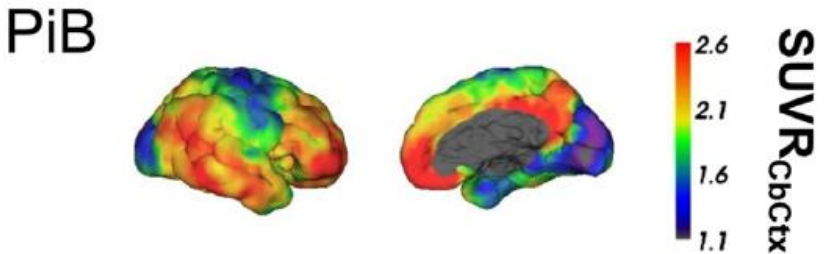
Sensibilité des biomarqueurs



+ Visualisation des dépôts amyloïdes (PET scan au ^{18}F -Flutemetamol)



Plusieurs marqueurs TEP des plaques amyloïdes



Traceurs TEP de la protéine Tau

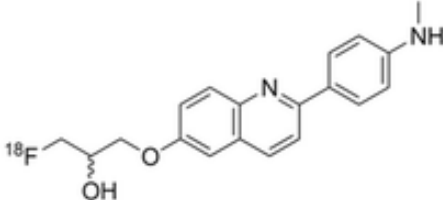
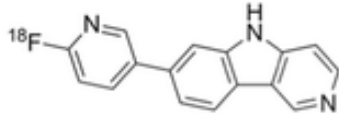
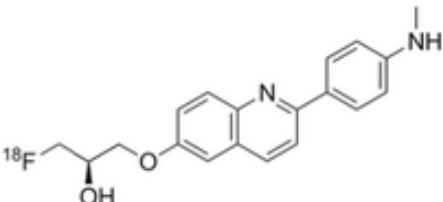
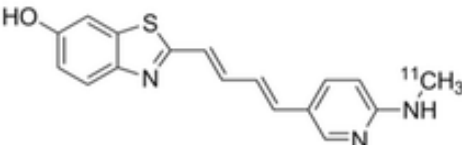
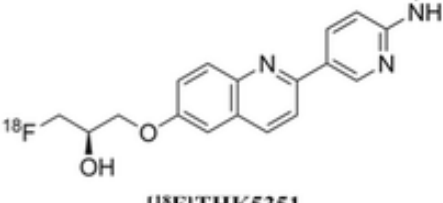
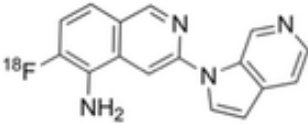
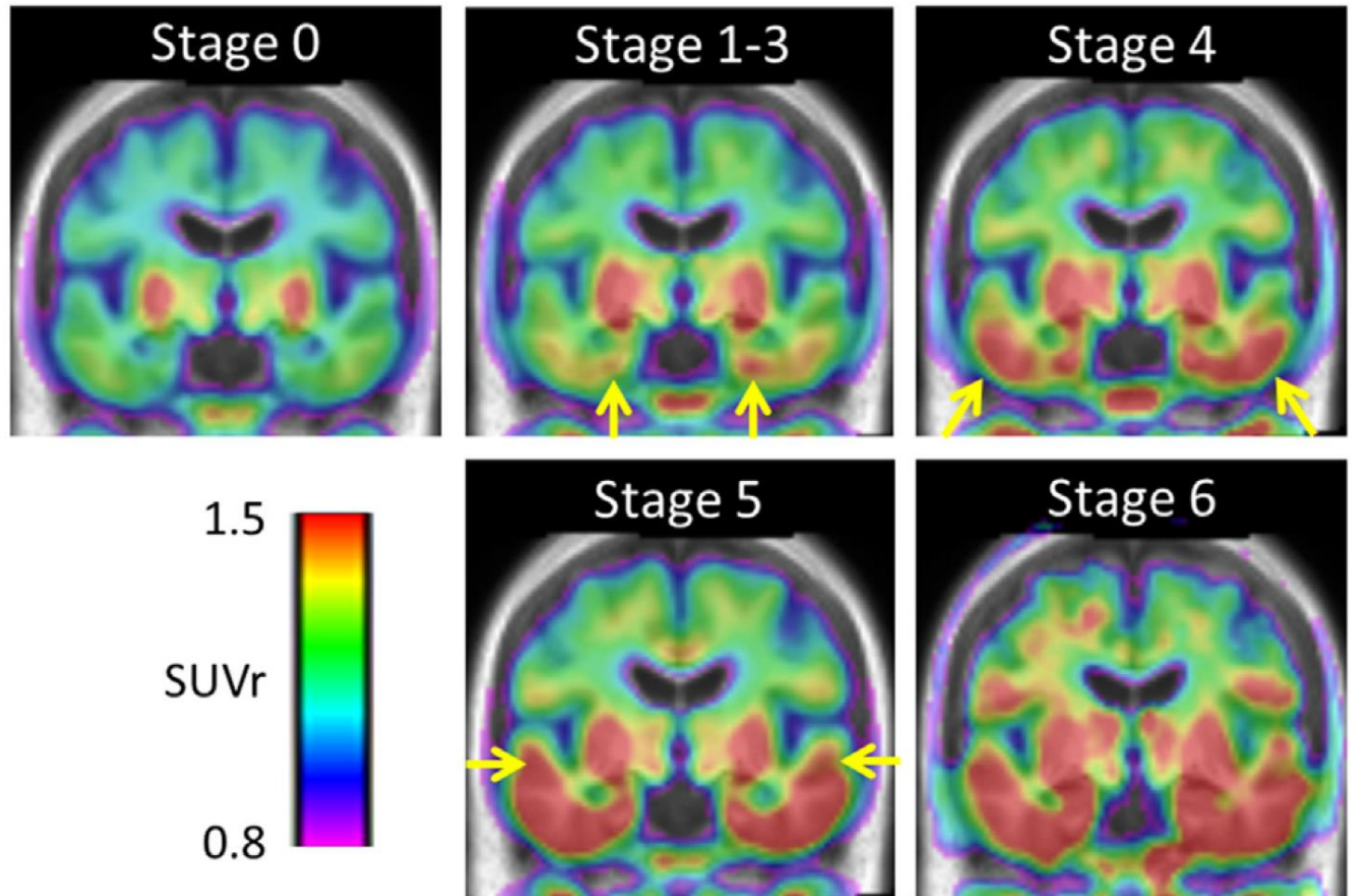
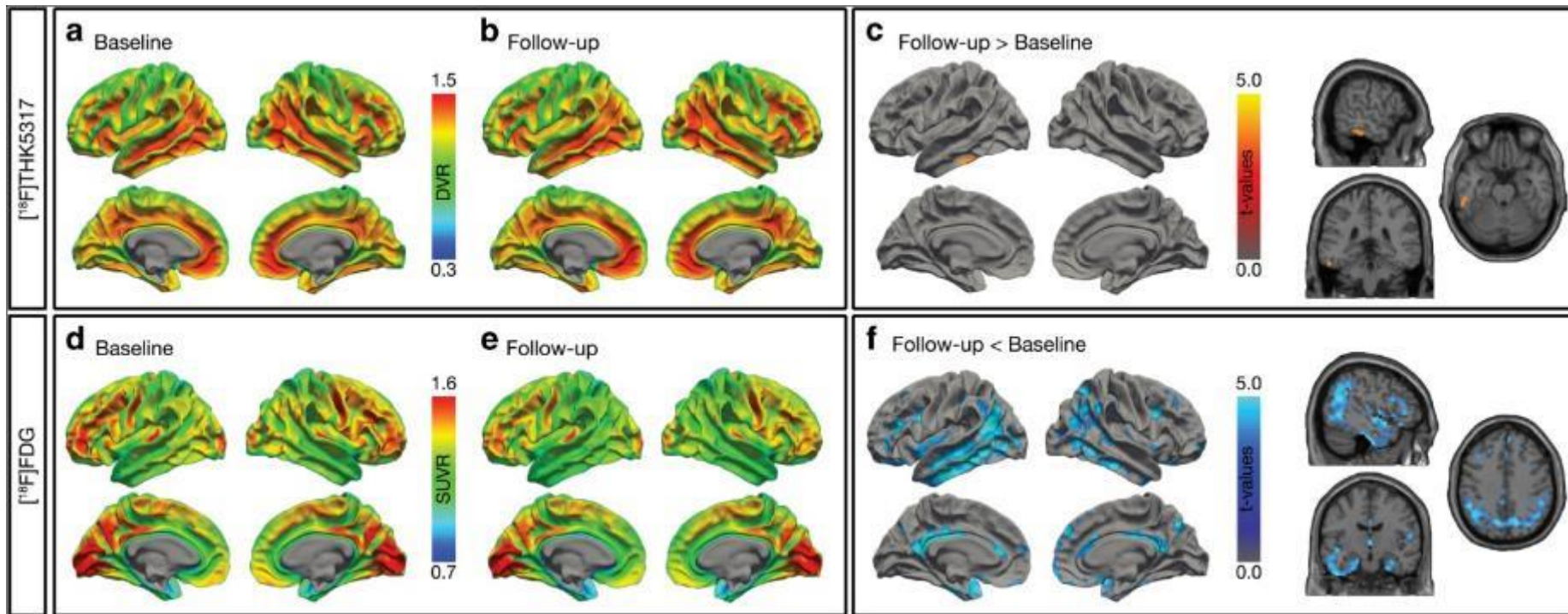
Quinoline derivatives	Pyrido-indole derivatives
 <p data-bbox="668 576 834 605">[¹⁸F]THK5117</p>	 <p data-bbox="1166 539 1321 596">[¹⁸F]AV-1451 (or [¹⁸F]T807)</p>
 <p data-bbox="645 885 877 942">[¹⁸F]THK5317 (or (<i>S</i>)-[¹⁸F]THK5117)</p>	<p data-bbox="1039 645 1526 702">Phenyl/pyridinyl-butadienyl-benzothiazole/benzothiazolium derivatives</p>  <p data-bbox="1224 913 1340 942">[¹¹C]PBB3</p>
 <p data-bbox="668 1205 834 1233">[¹⁸F]THK5351</p>	<p data-bbox="1128 1008 1437 1065">Pyridine isoquinolin-amine derivatives</p>  <p data-bbox="1224 1253 1379 1282">[¹⁸F]MK-6240</p>

Image de captation de ^{18}F -flortaucipir



A Schwartz et al 2017

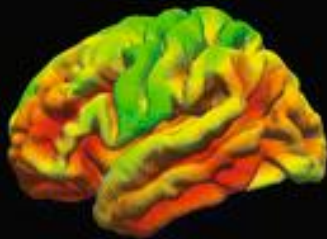
Etude TEP longitudinale Tau FDG



Comparaison de 3 traceurs TEP

Patient with prodromal Alzheimer's disease
74 y, male, MMSE: 27

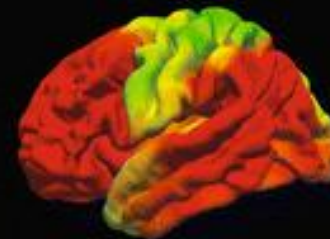
[¹⁸F]THK5317



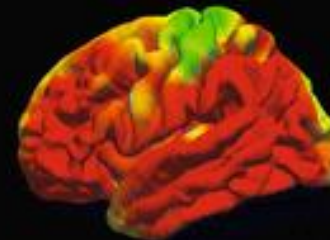
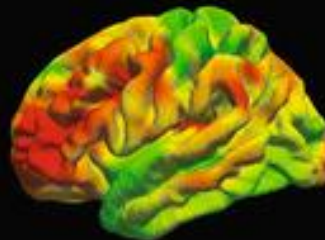
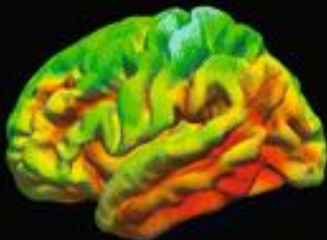
[¹⁸F]FDG



[¹¹C]PIB



Patient with Alzheimer's disease dementia
74 y, female, MMSE: 23



0.10  DVR 1.60

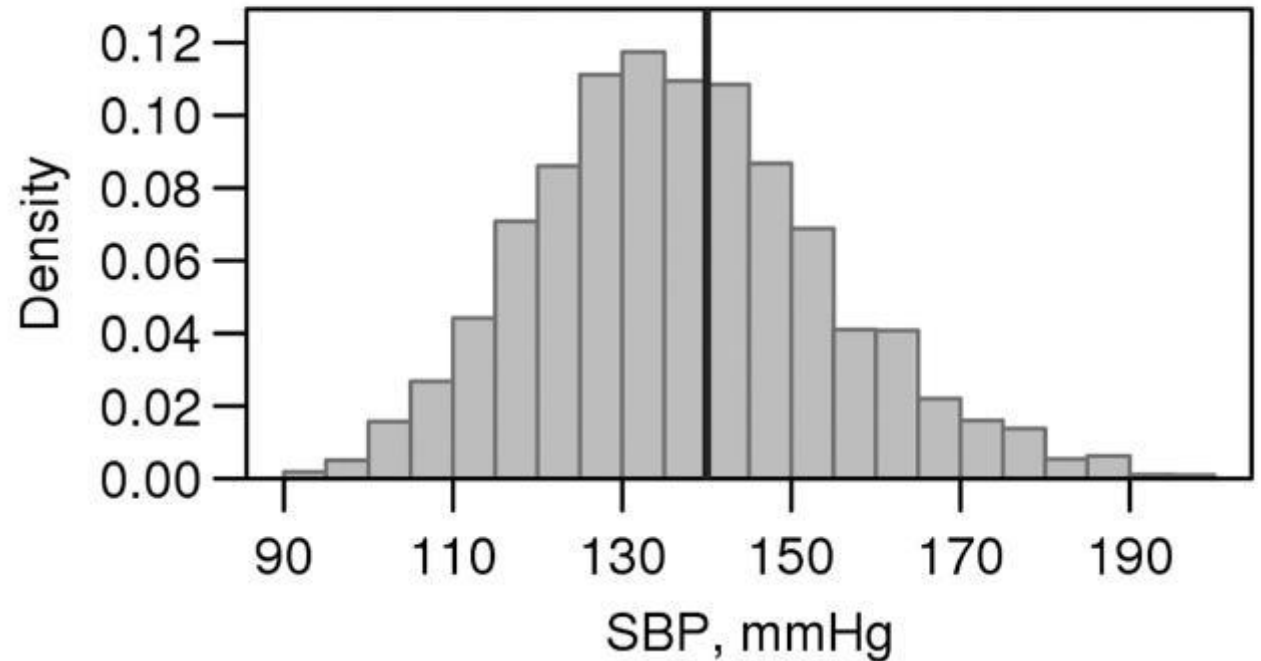
0.10  SUVR 1.80

0.10  SUVR 2.00

Définition d'un seuil (cut-off) diagnostique

E

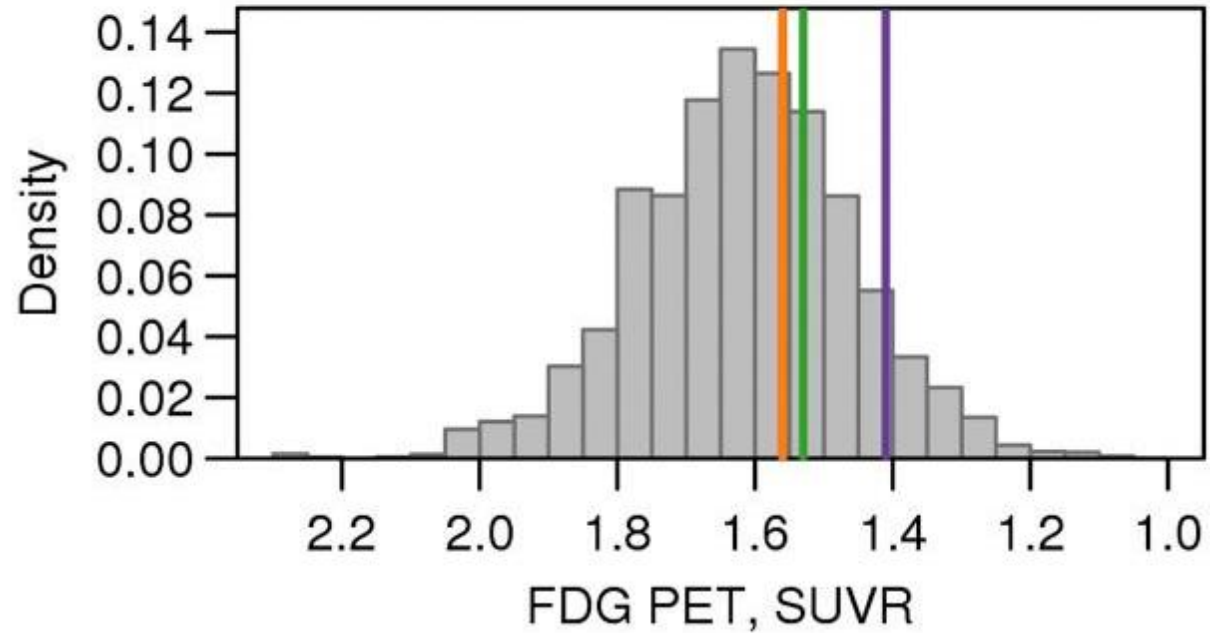
Cut-point
— 140



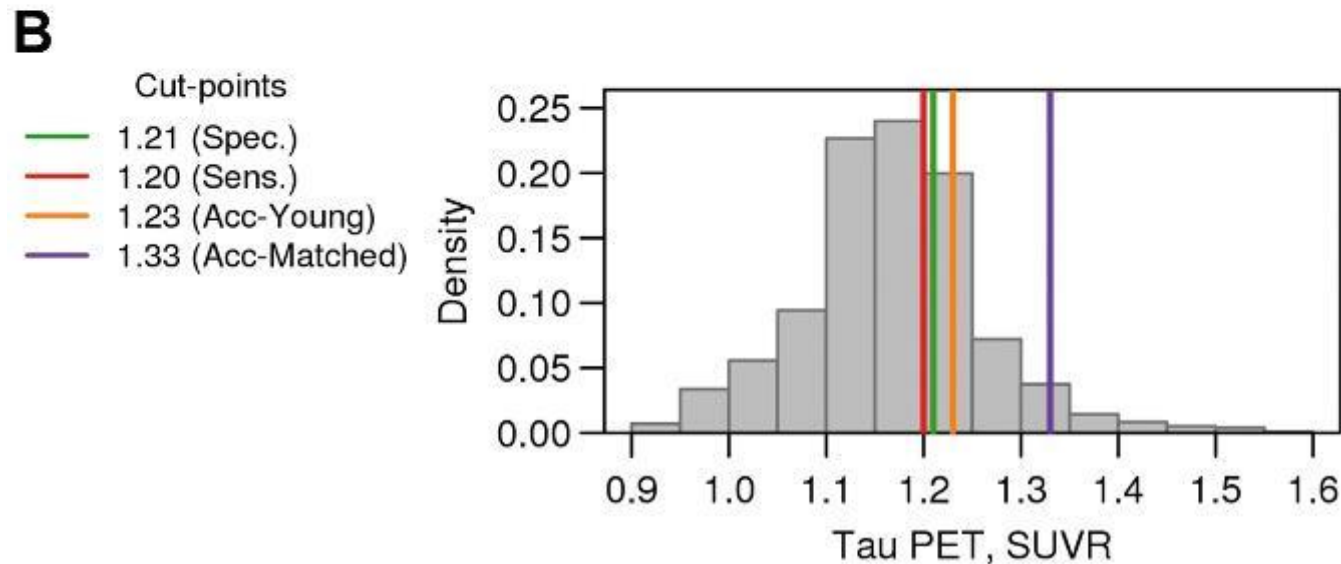
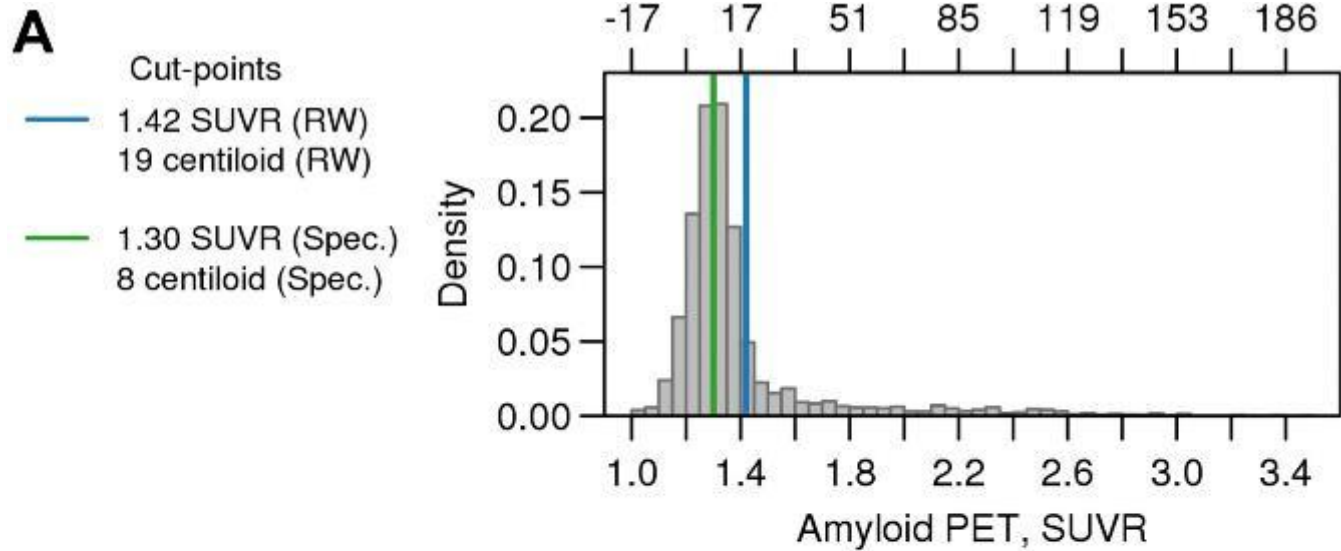
Seuils FDG (SUVR)

C

- Cut-points
- 1.53 (Spec.)
 - 1.56 (Sens.)
 - 1.56 (Acc-Young)
 - 1.41 (Acc-Matched)

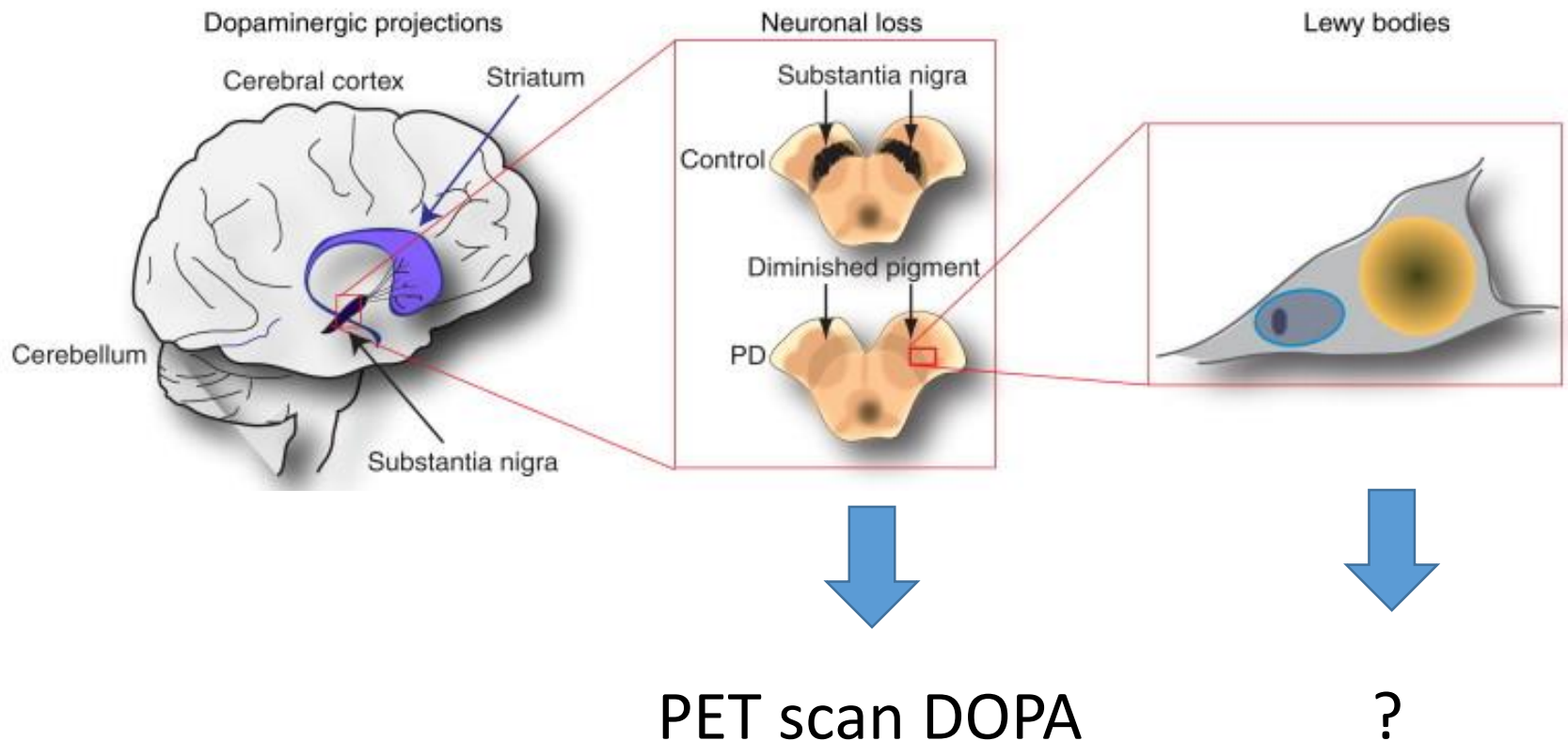


Seuil des traceurs amyloïdes & Tau (SUVR)

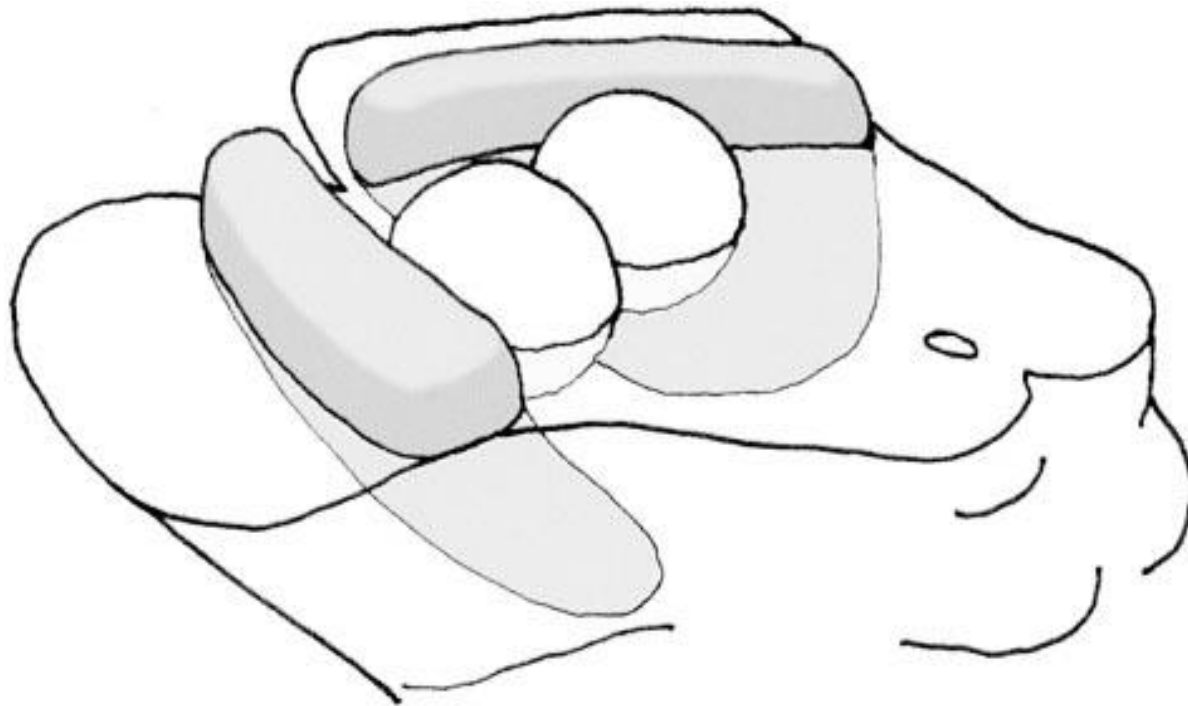


Parkinson → 2 anomalies cérébrales

- 1) Disparition des neurones pigmentés du locus niger
- 2) Inclusions de protéines anormales (alpha-synucléine)



Locus niger



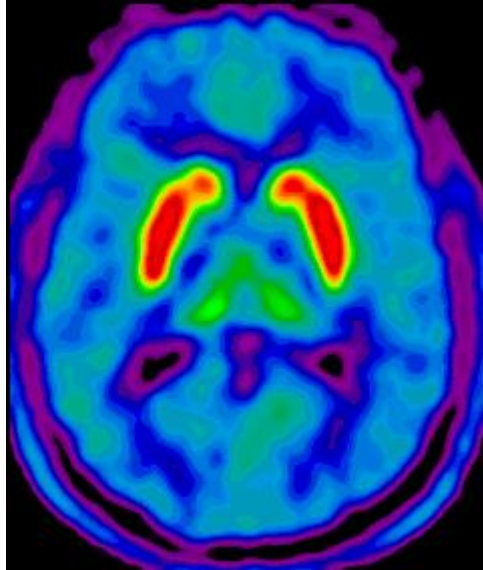
volume



coupe transverse



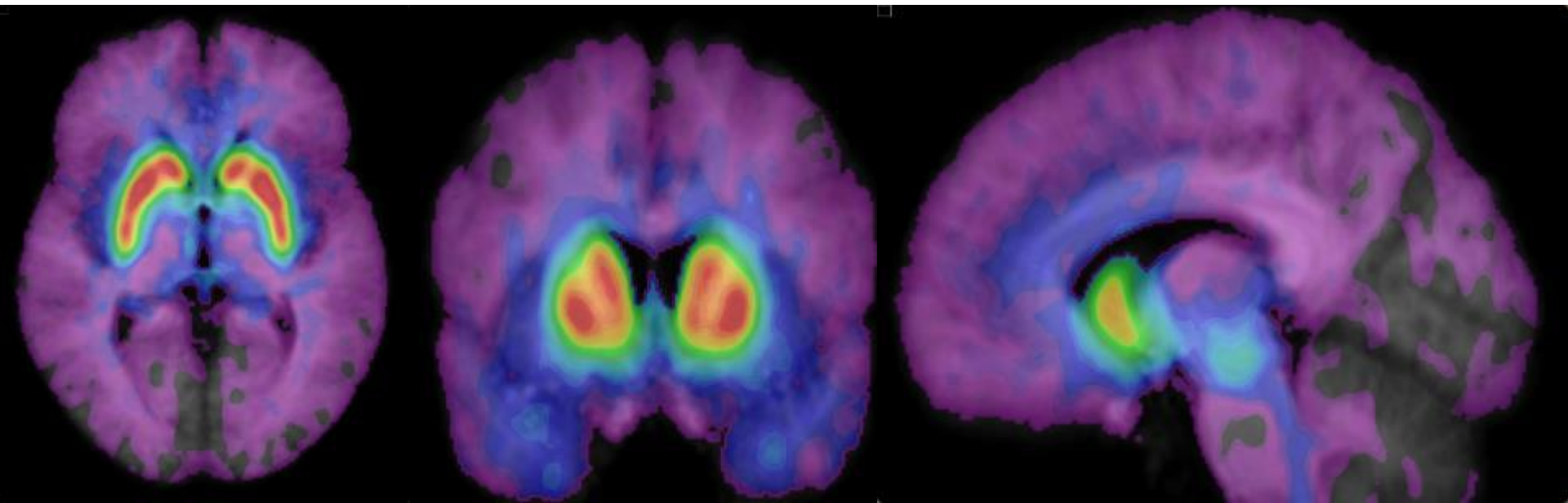
TEP (« PET scan ») à la ^{18}F -DOPA



-Sujet normal

-Patient avec tremblement
essentiel,...

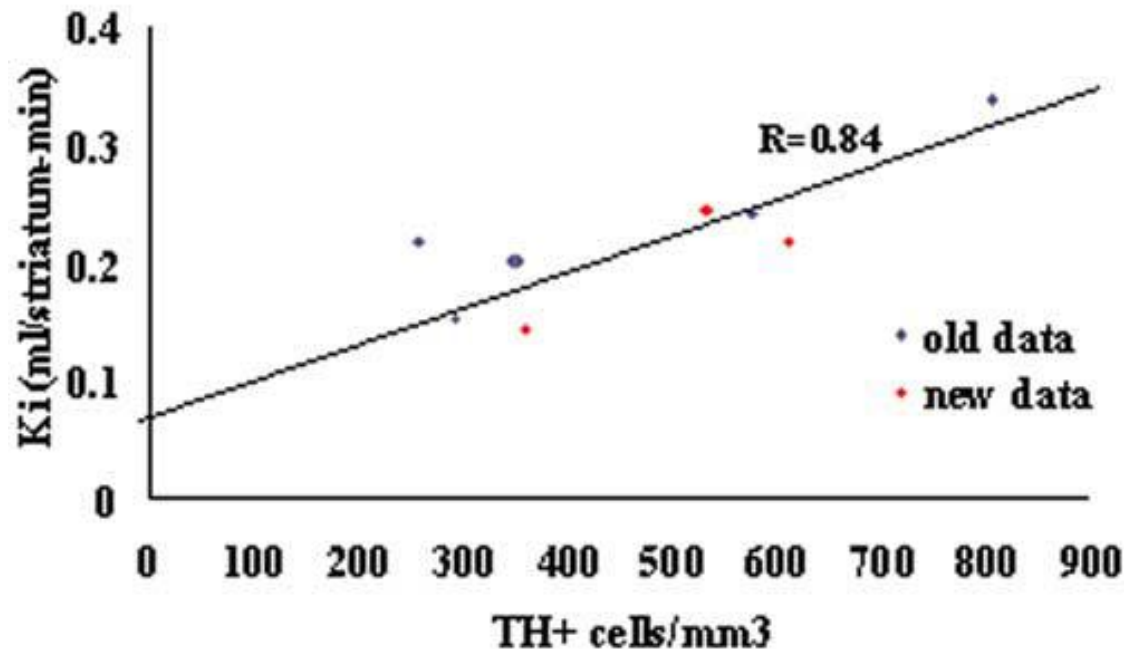
^{18}F -DOPA PET (K_i^{occ}); N=16



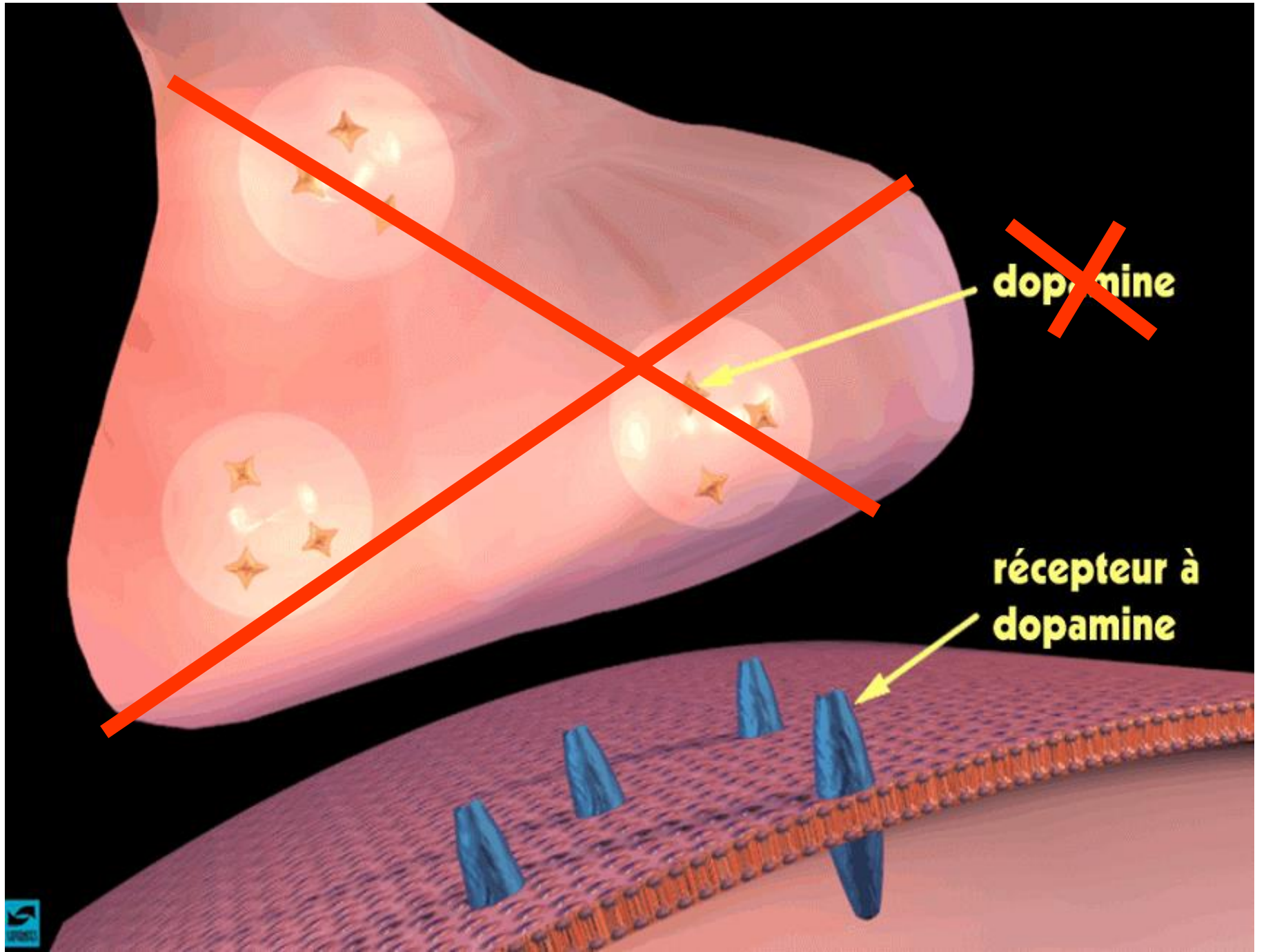
G. Garraux (unpublished data)

Validation de la TEP à la ^{18}F -DOPA

Fluorodopa Uptake Constant vs.
Nigral DA Cell Density (Human)



Brooks (2003)
Ann N Y Acad Sci.
991:22-35.

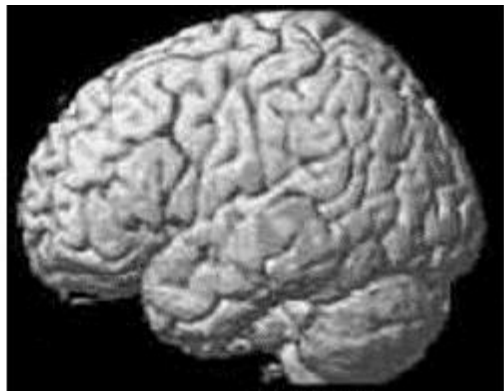


~~dopamine~~

récepteur à
dopamine



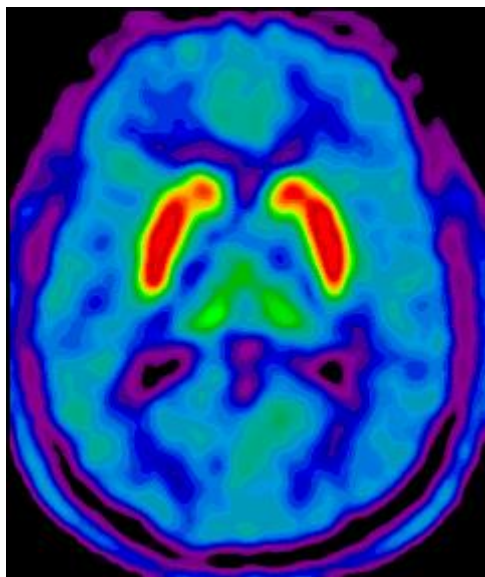
volume



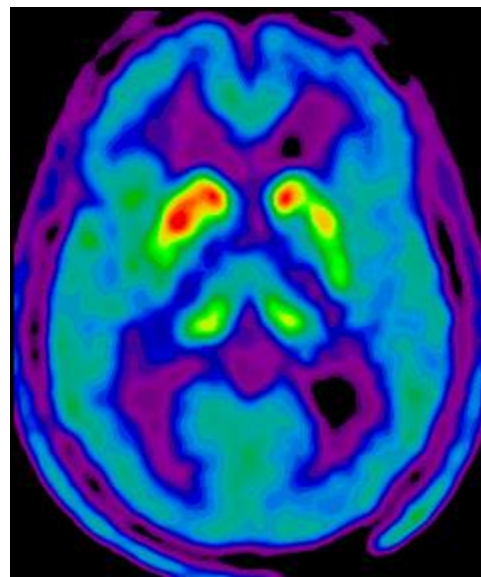
coupe transverse



TEP (« PET scan ») à la ^{18}F -DOPA

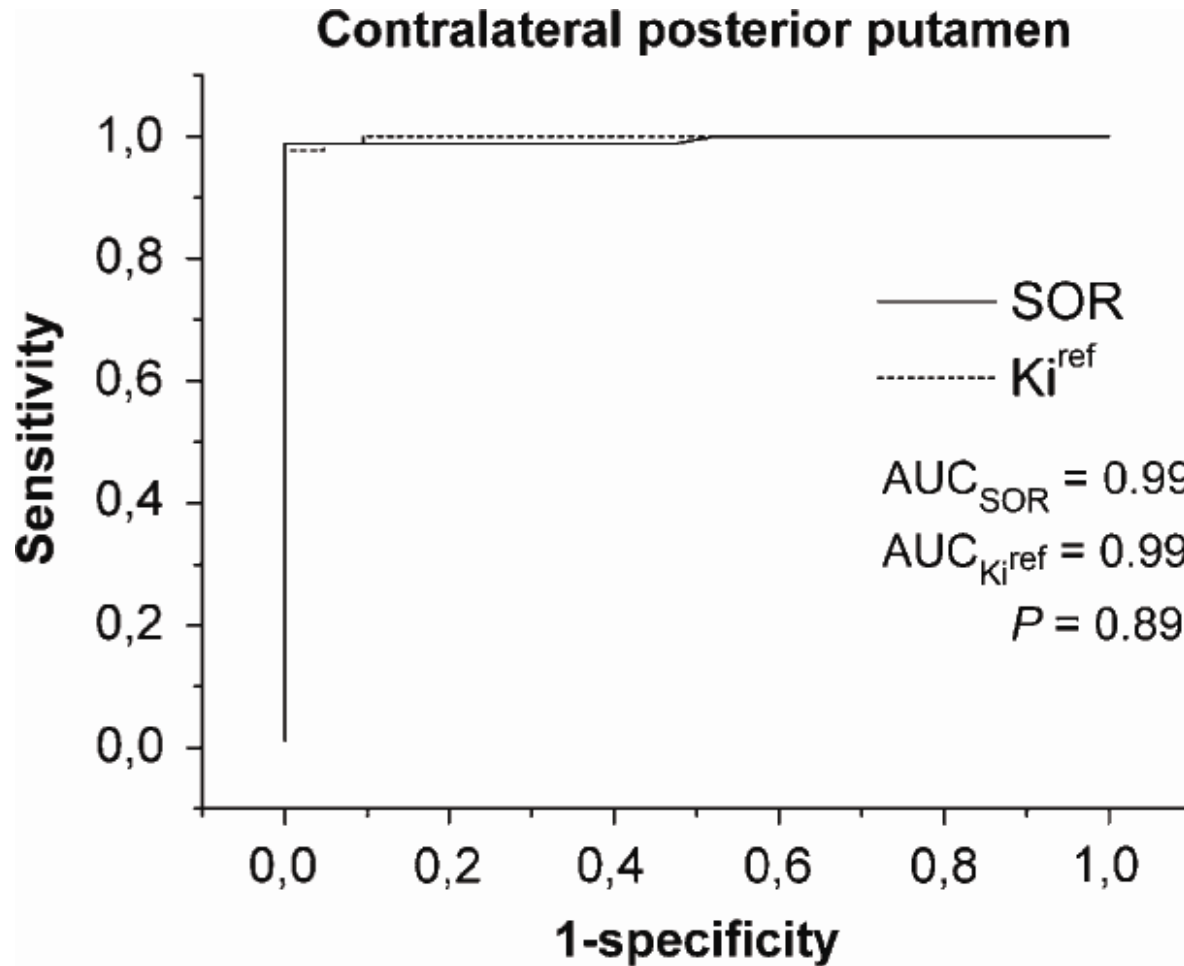


N, TE, ...

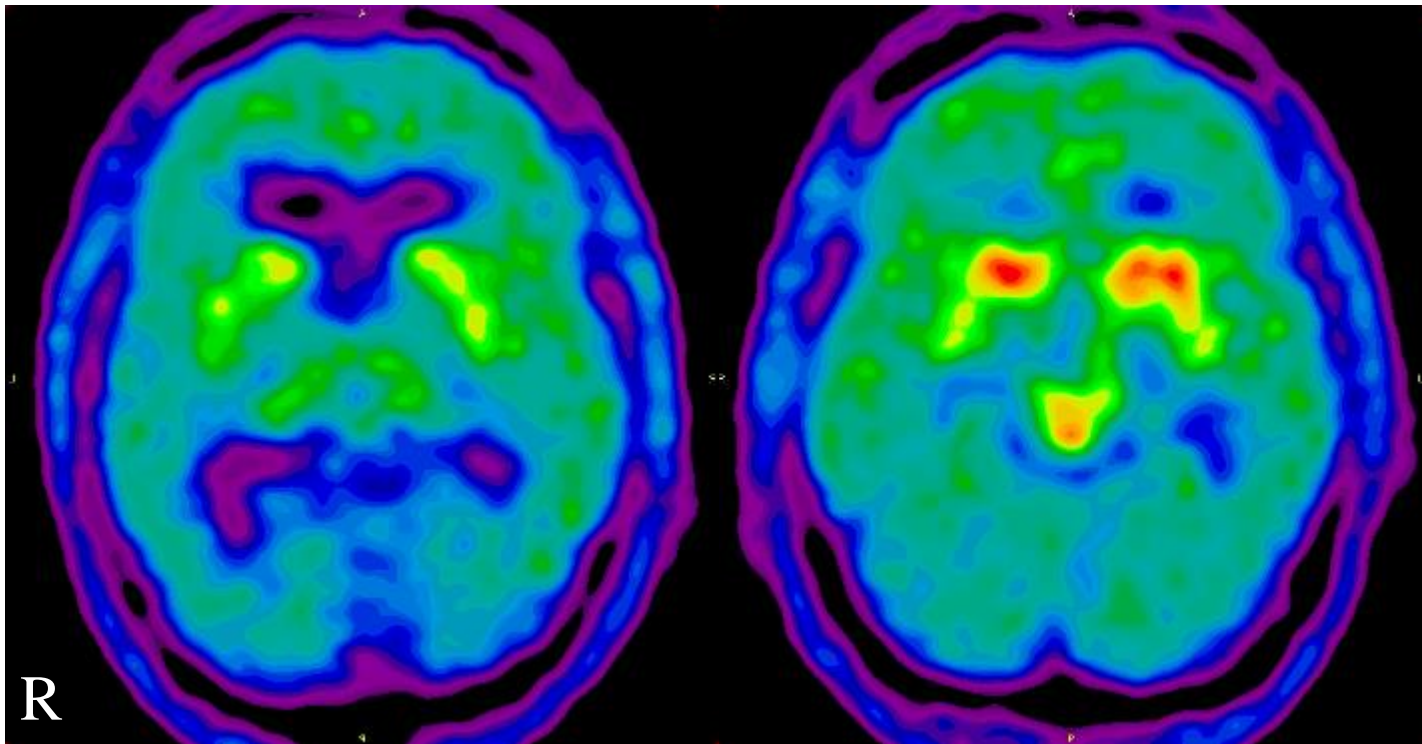


Maladie de Parkinson

TEP à la ^{18}F -DOPA: parkinson vs. N



F (1970) – raideur main gauche à 31 ans



Garraux et al. 2012

F (1970) – raideur main gauche

Parkinson & Movement Disorders

MoVeRe

Science Alliance



Trisomie partielle 4q

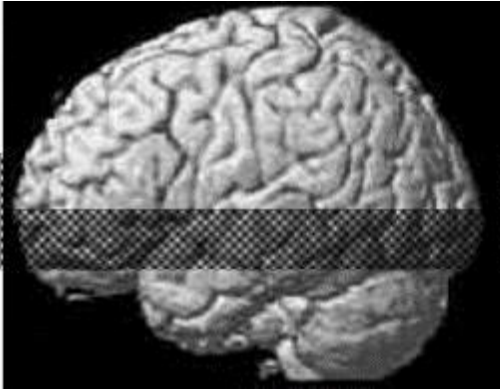
Duplication hétérozygote d'un segment du chromosome 4 où se situe le locus du gène SNCA (α -synucléine)

Taille de la région dupliquée: 41.2MB (4q21.23 to 4q28.1)

volume

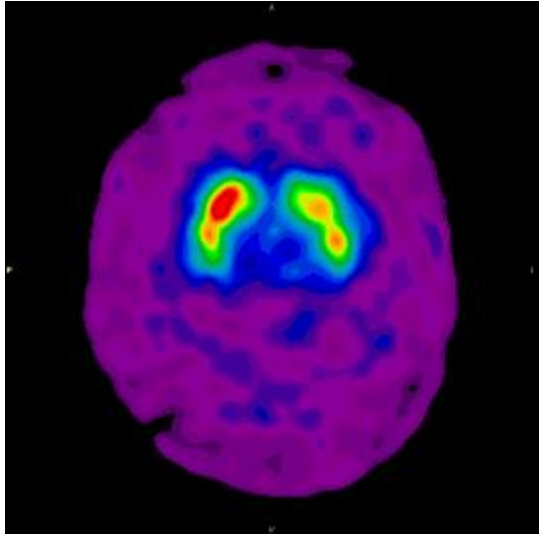
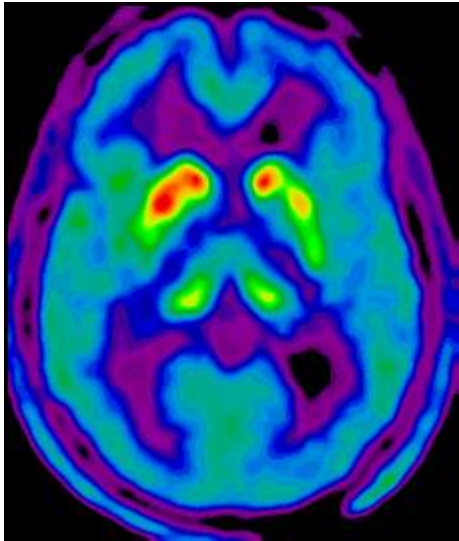


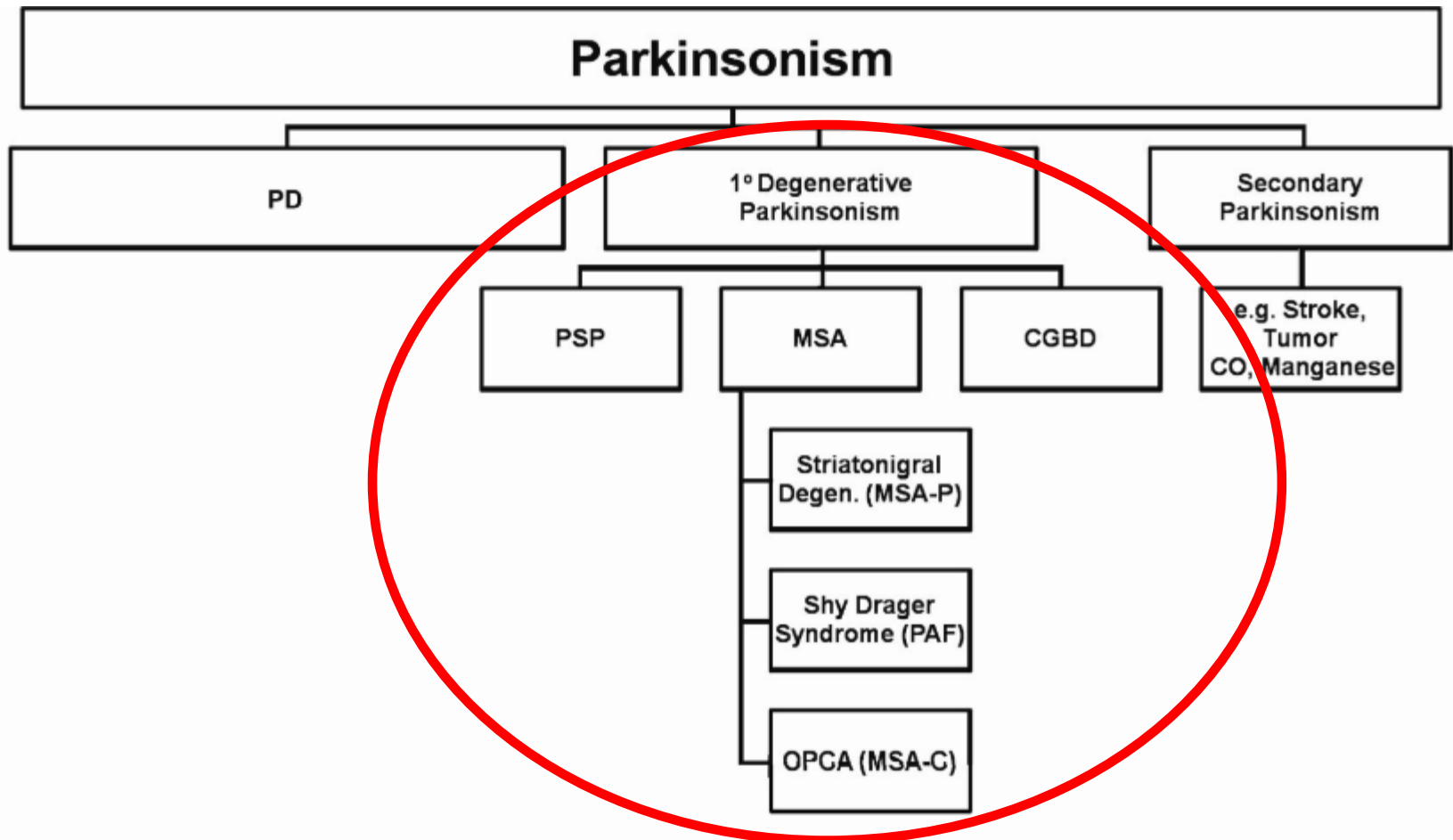
coupe transverse



PET scan

DAT scan





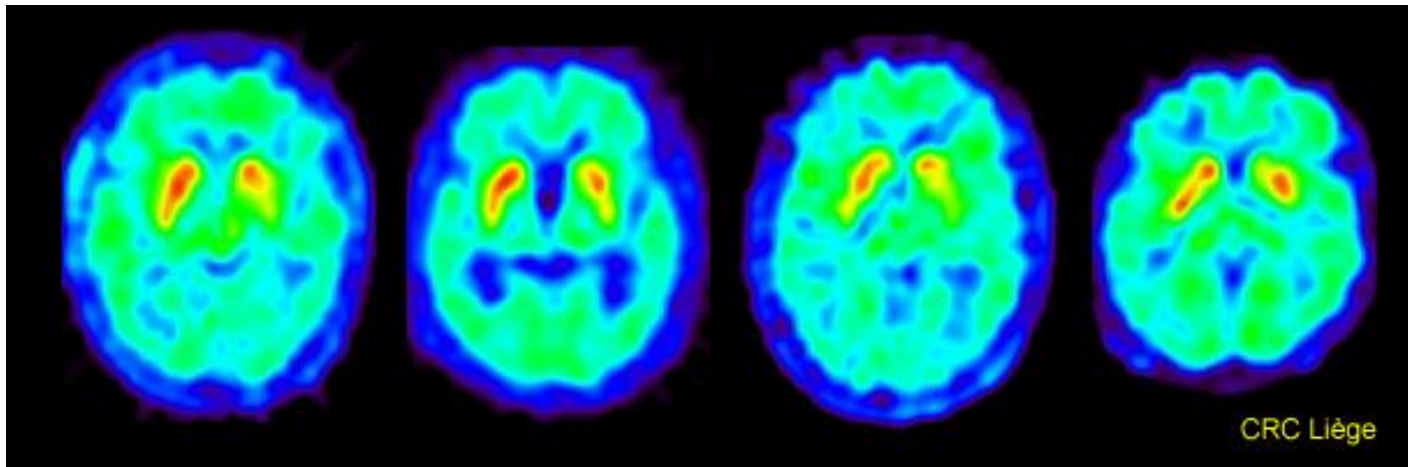
PD = Parkinson disease; MSA-P = multiple system atrophy-parkinsonian; MSA-C = multiple system atrophy-parkinsonian cerebellar.

TEP à la ^{18}F -DOPA - parkinsonisme

Parkinson & Movement Disorders

MoVeRe

Science Alliance

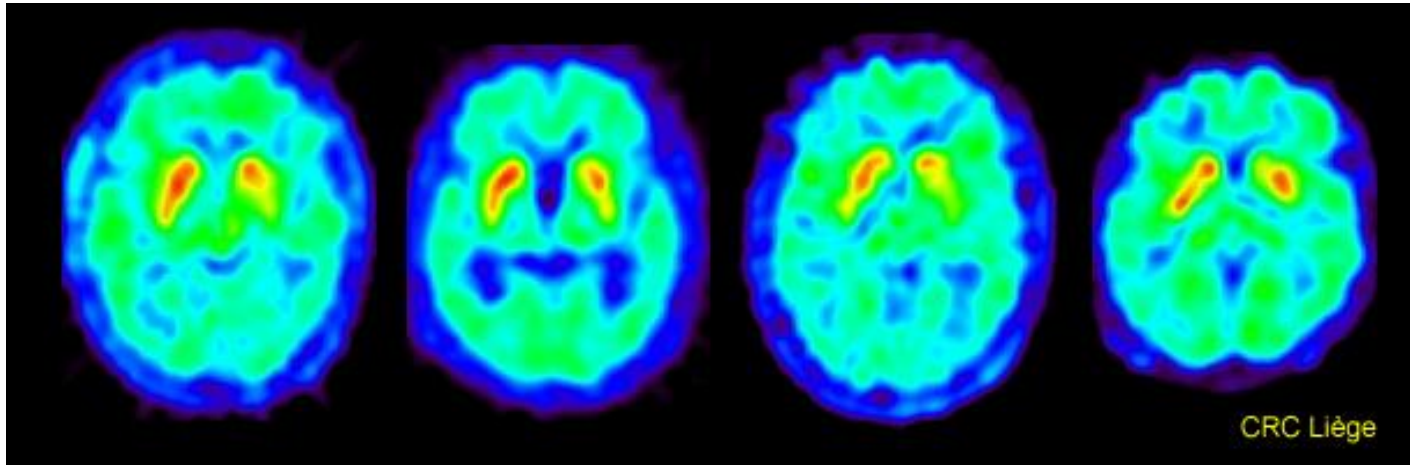


TEP à la ^{18}F -DOPA - parkinsonisme

Parkinson & Movement Disorders

MoVeRe

Science Alliance

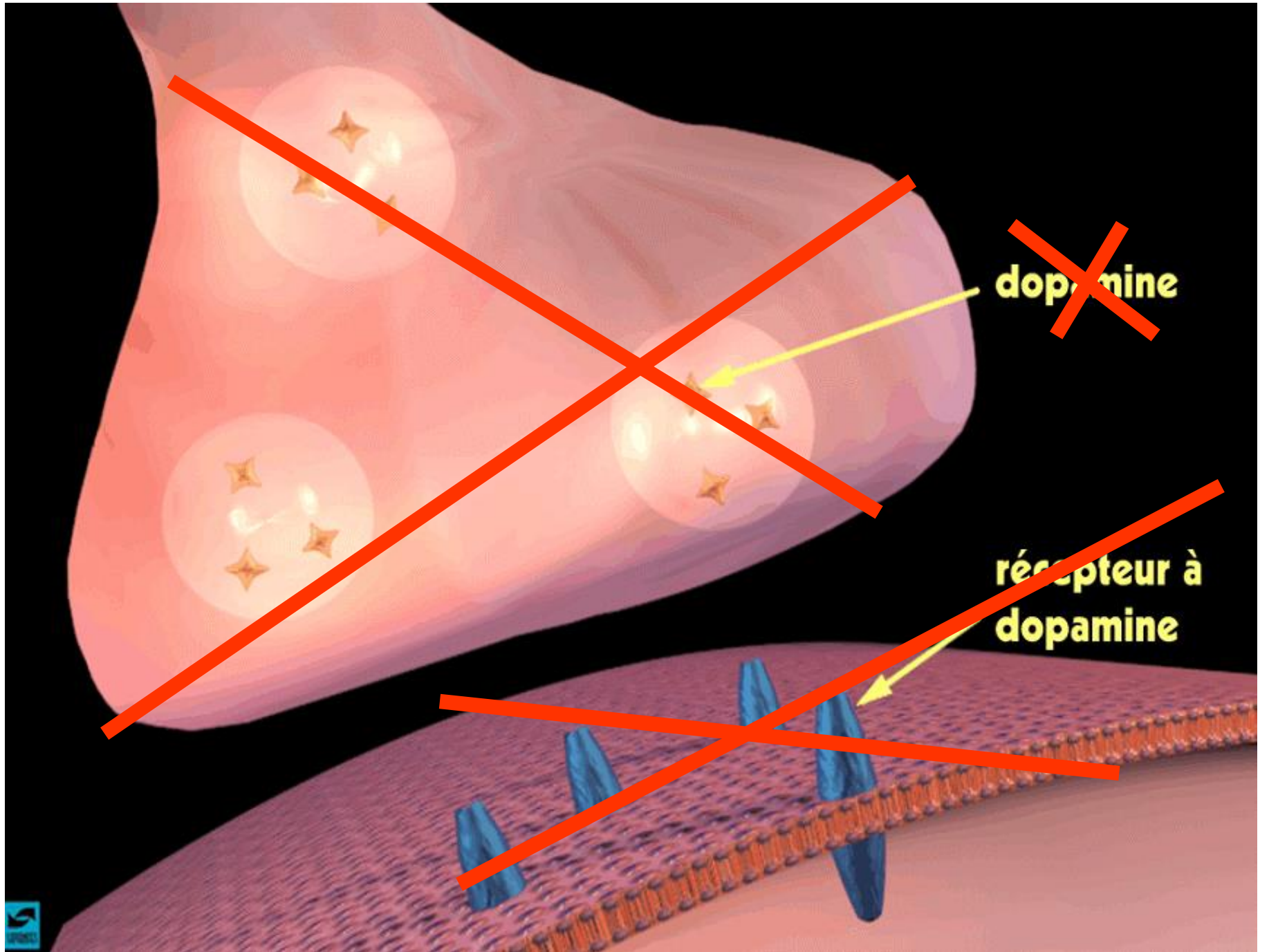


CBD

MSA

PD

CBD



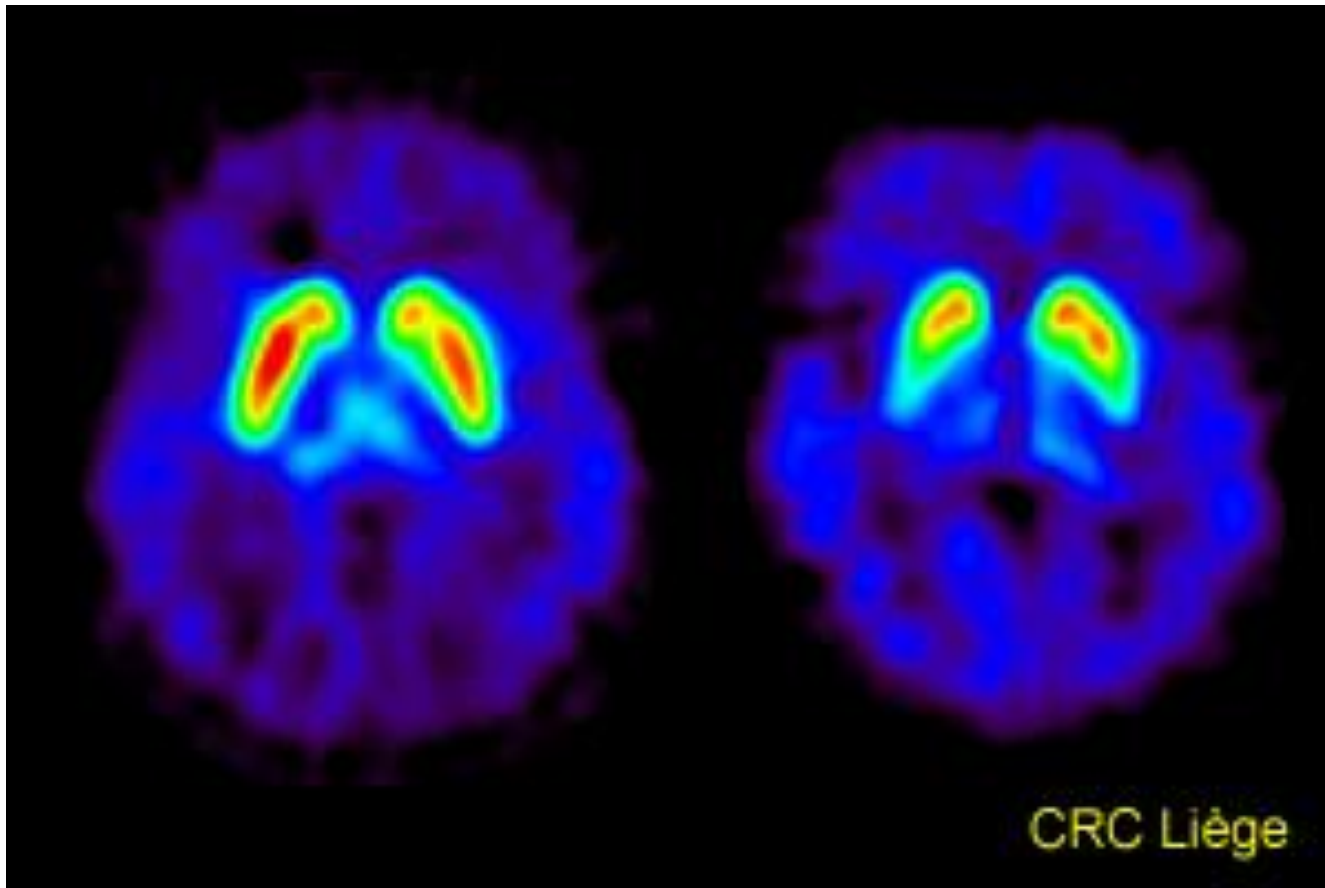
dopamine

récepteur à
dopamine

TEP au ^{18}F -tropapride

MP

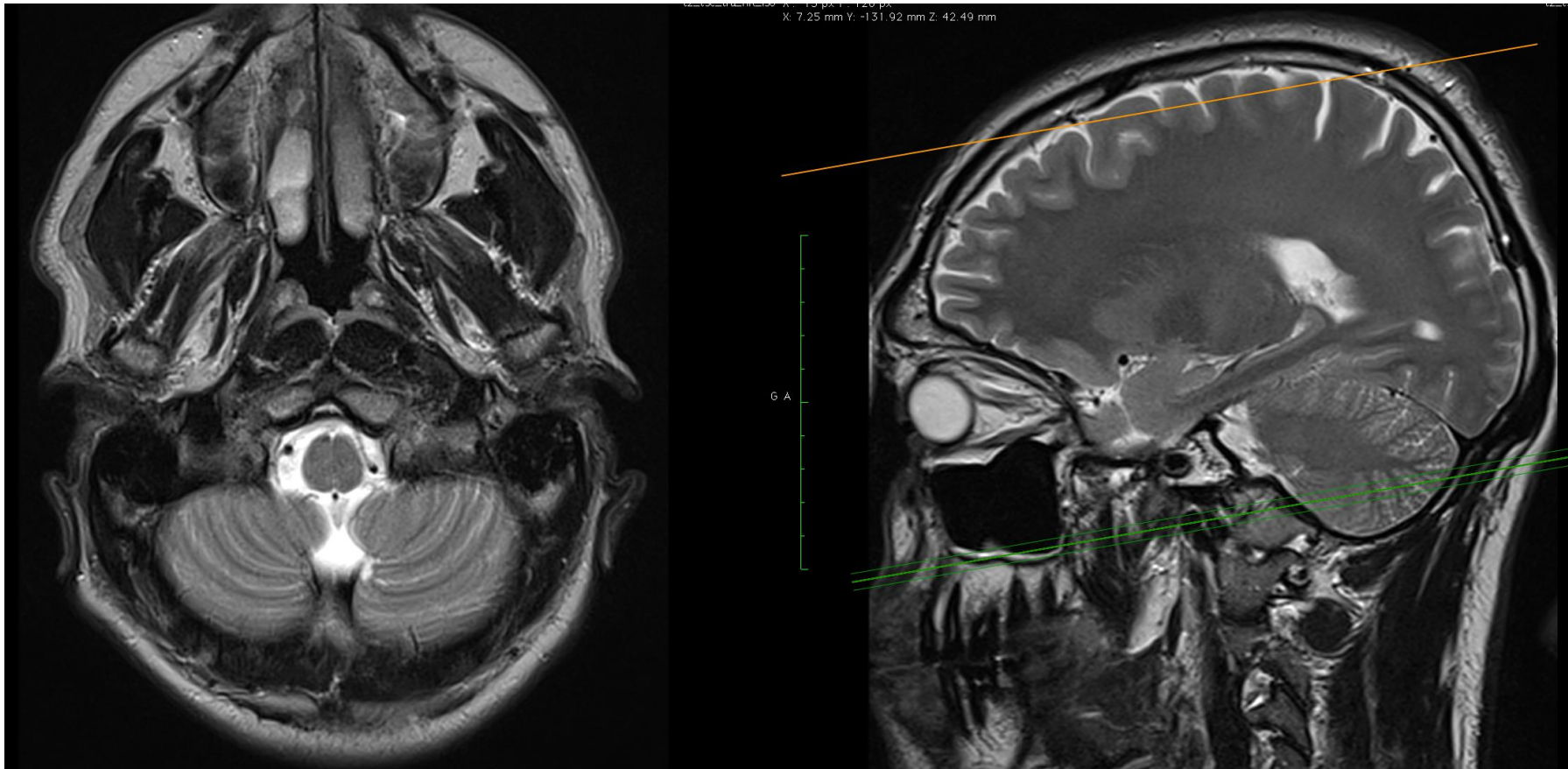
MSA-P



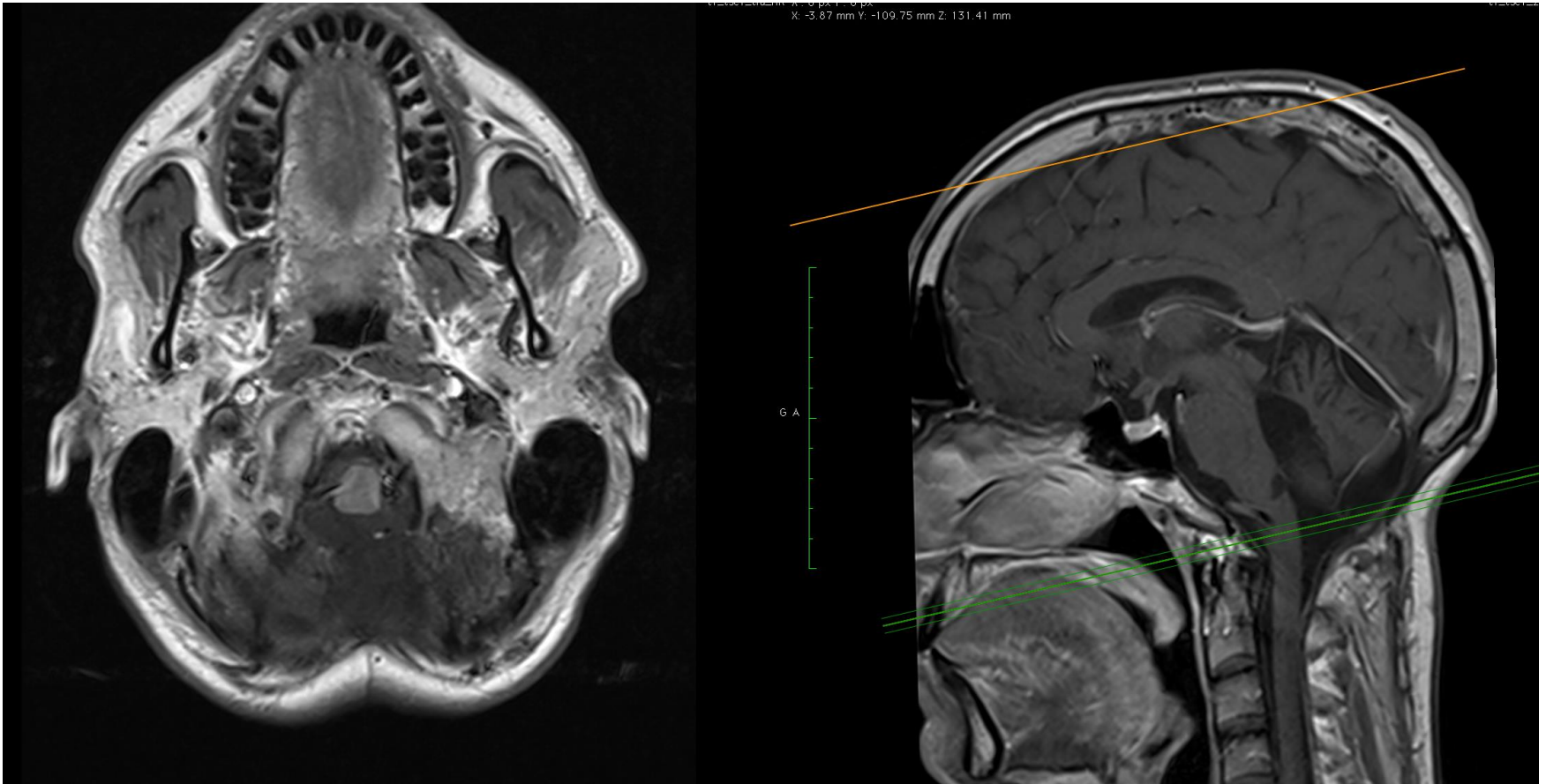
Imagerie par résonance magnétique (IRM)



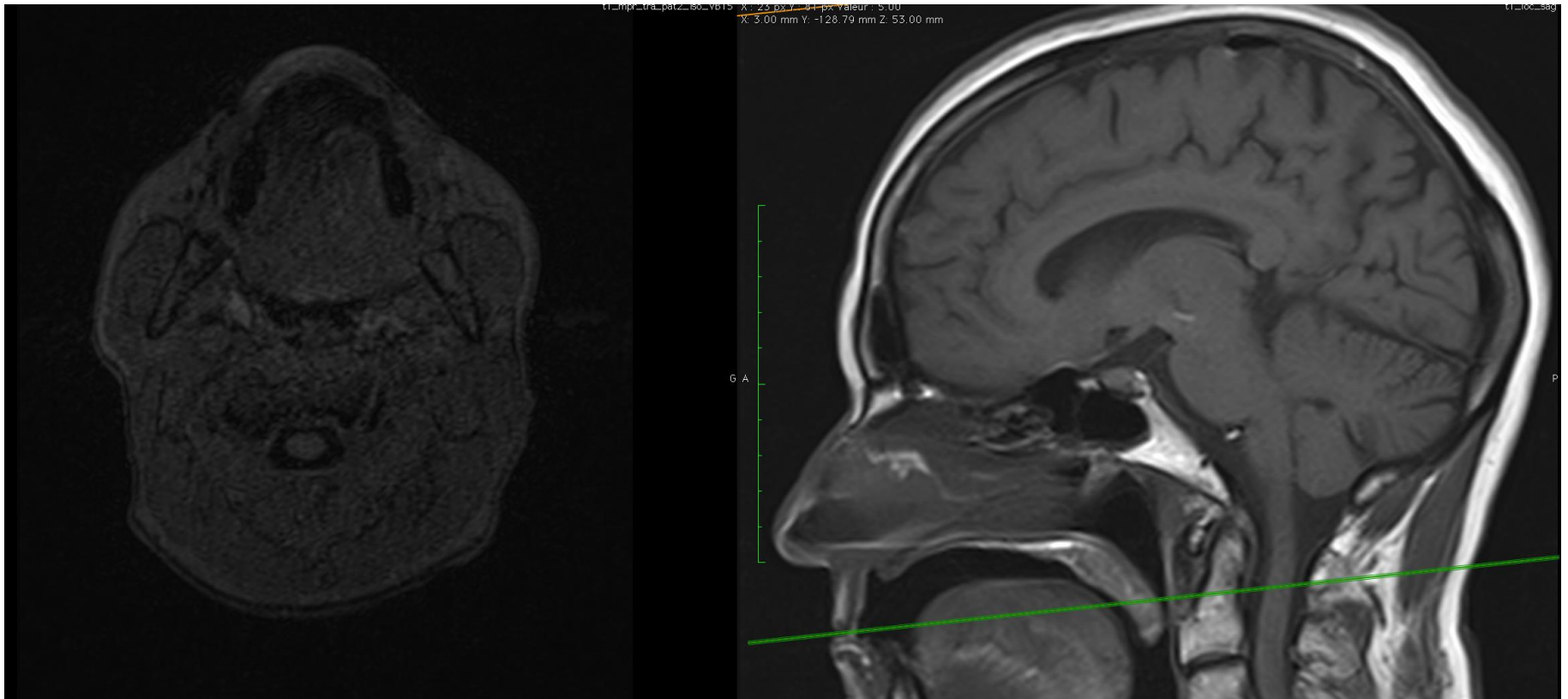
Coupes IRM (en pondération T2)



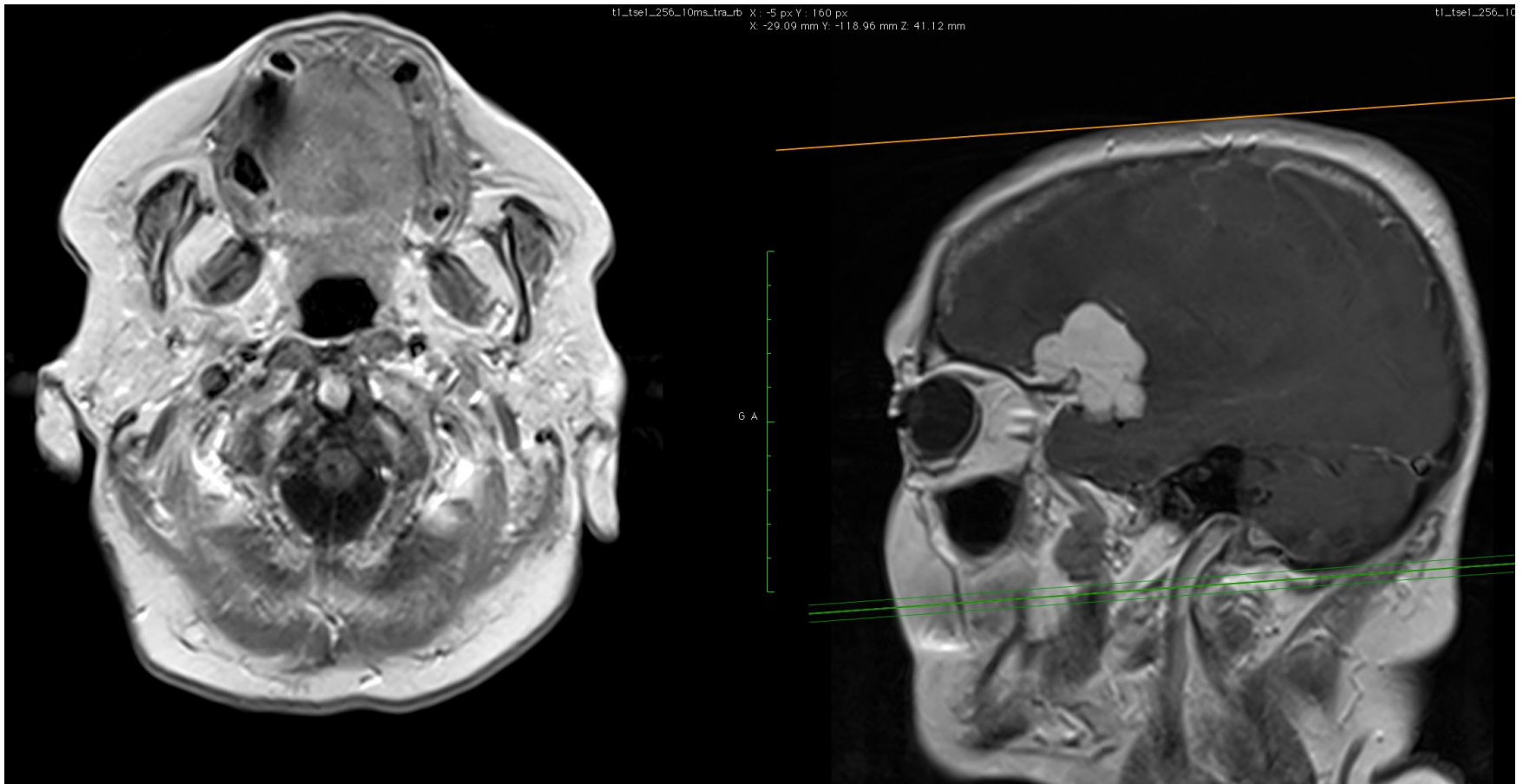
Coupes IRM (en pondération T1)



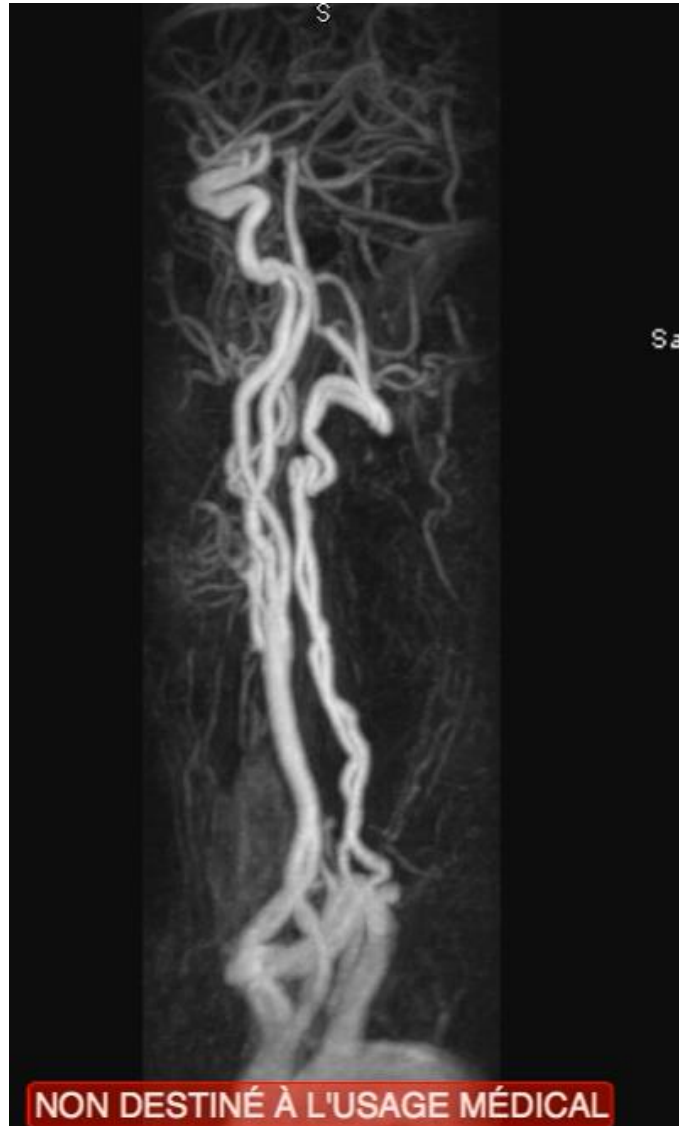
Coupes IRM (en pondération T1 à haute résolution)



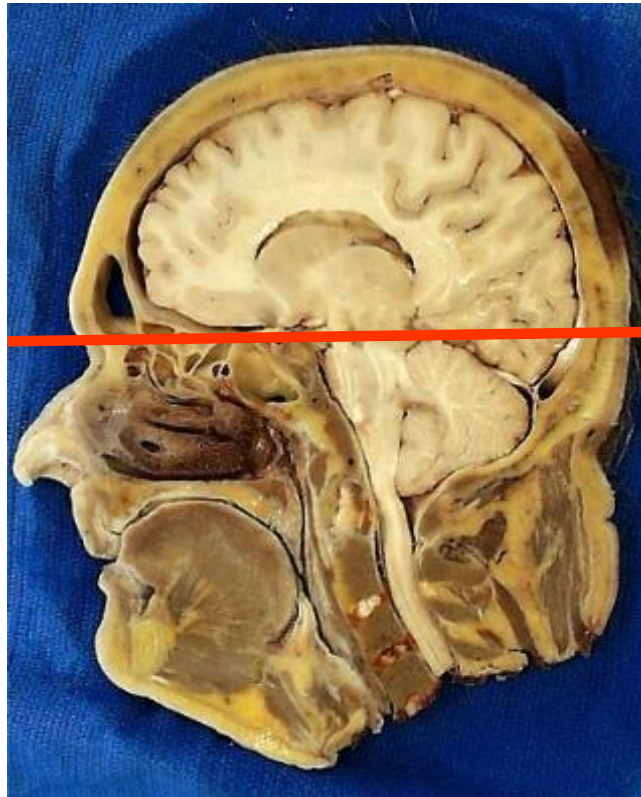
Coupes IRM (en pondération T1 après injection d'un produit de contraste)



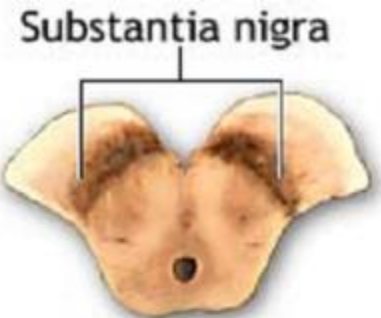
Reconstruction IRM 3D des troncs artériels



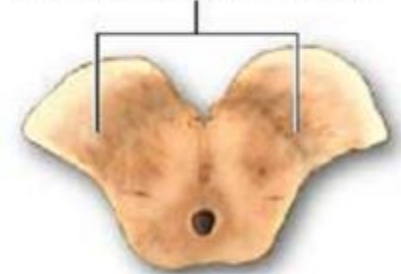
Perte de neurones pigmentés (locus niger)



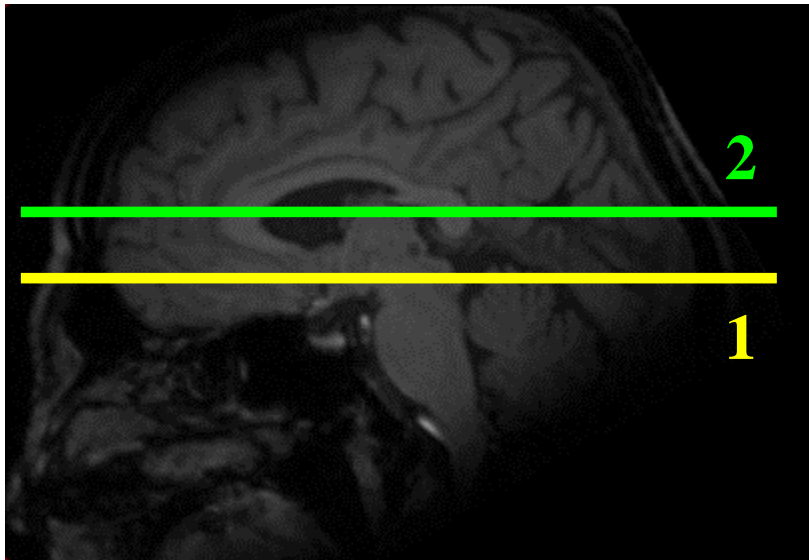
Cut section
of the midbrain
where a portion
of the substantia
nigra is visible



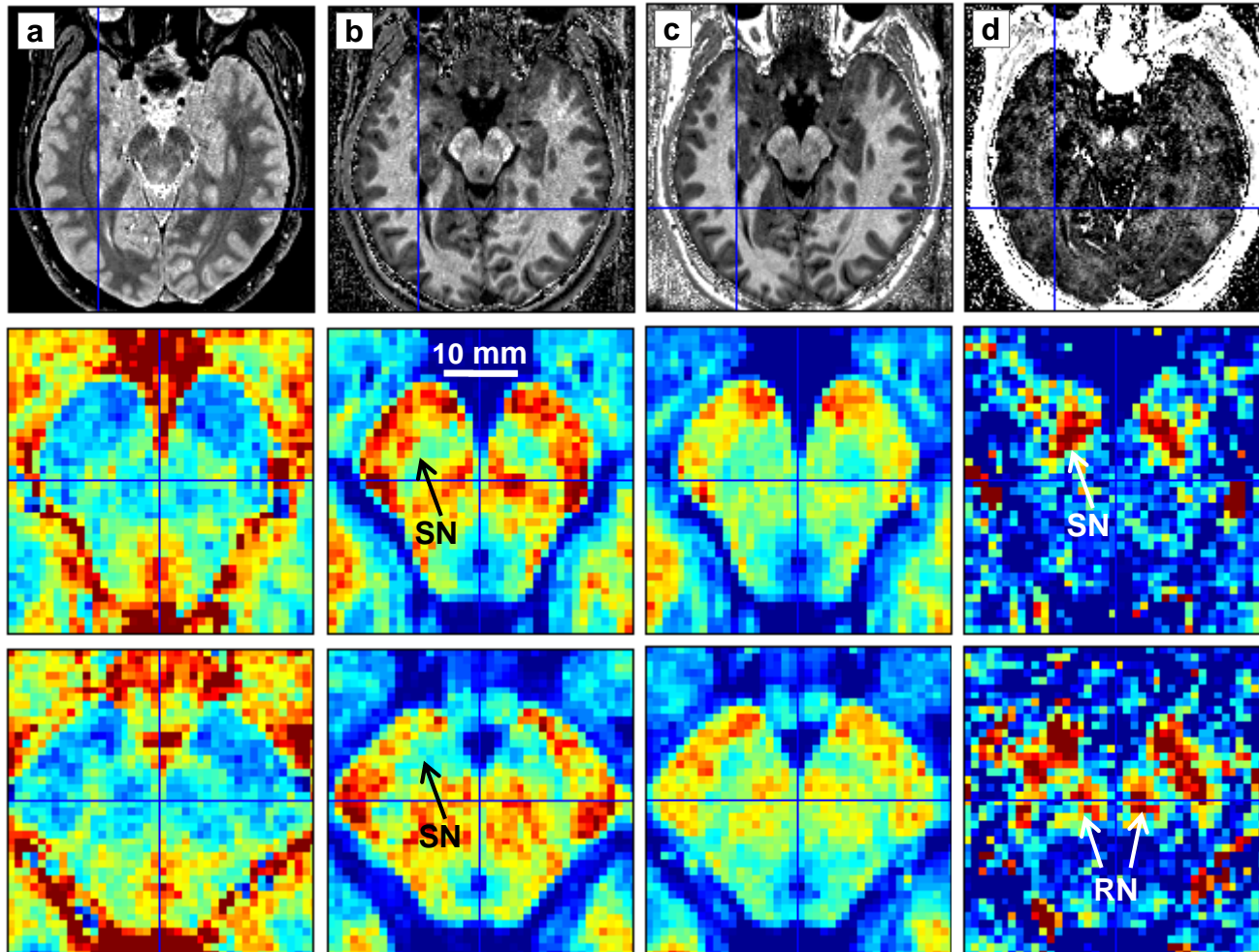
Diminished substantia
nigra as seen in
Parkinson's disease



IRM conventionnelle MP: normale

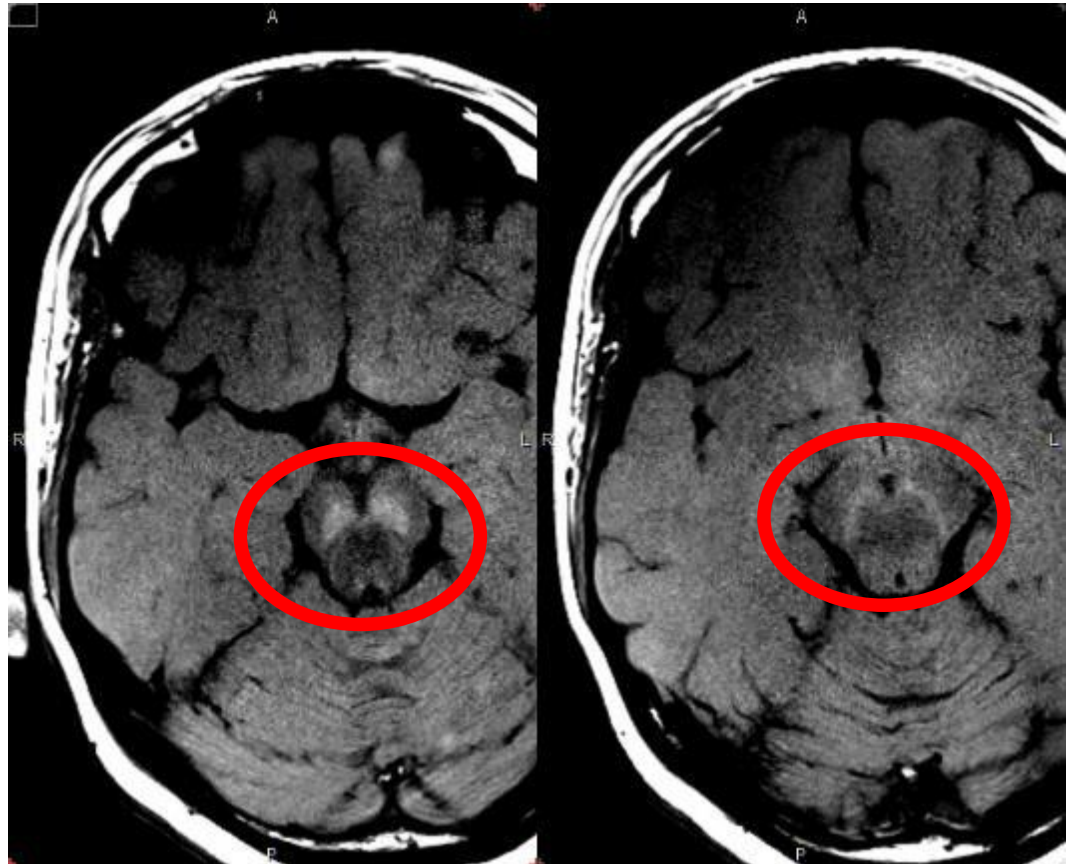
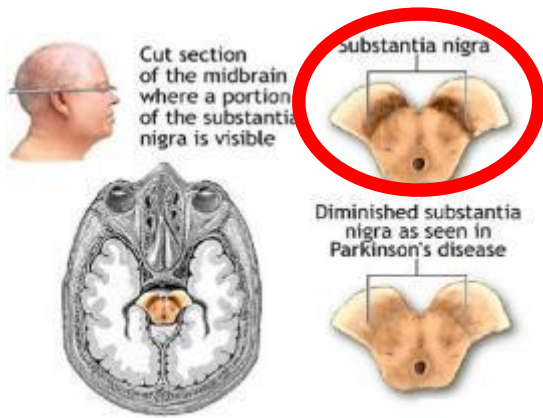


IRM anatomique haute résolution

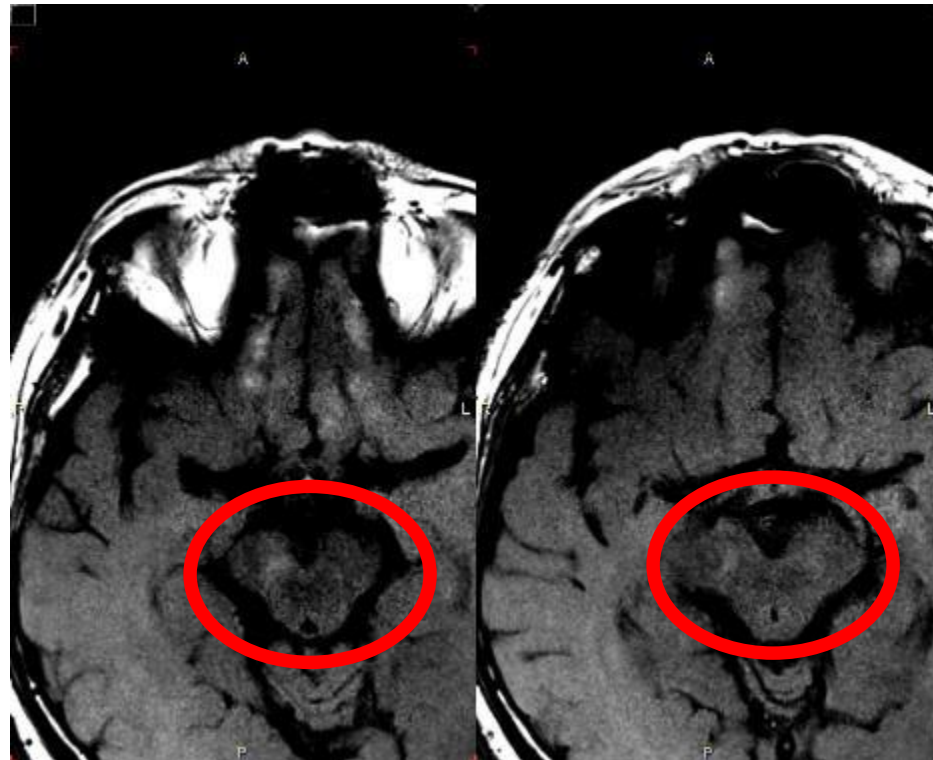
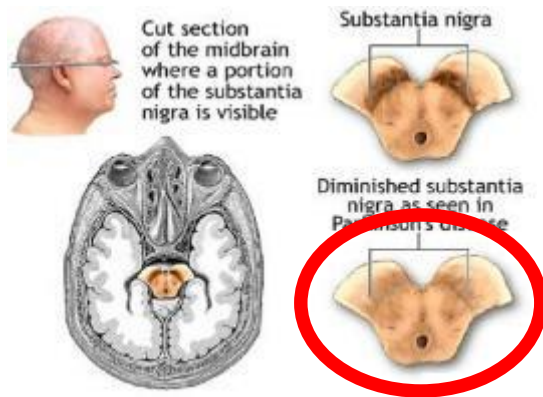


E. Balteau. CRC ULiège, unpublished

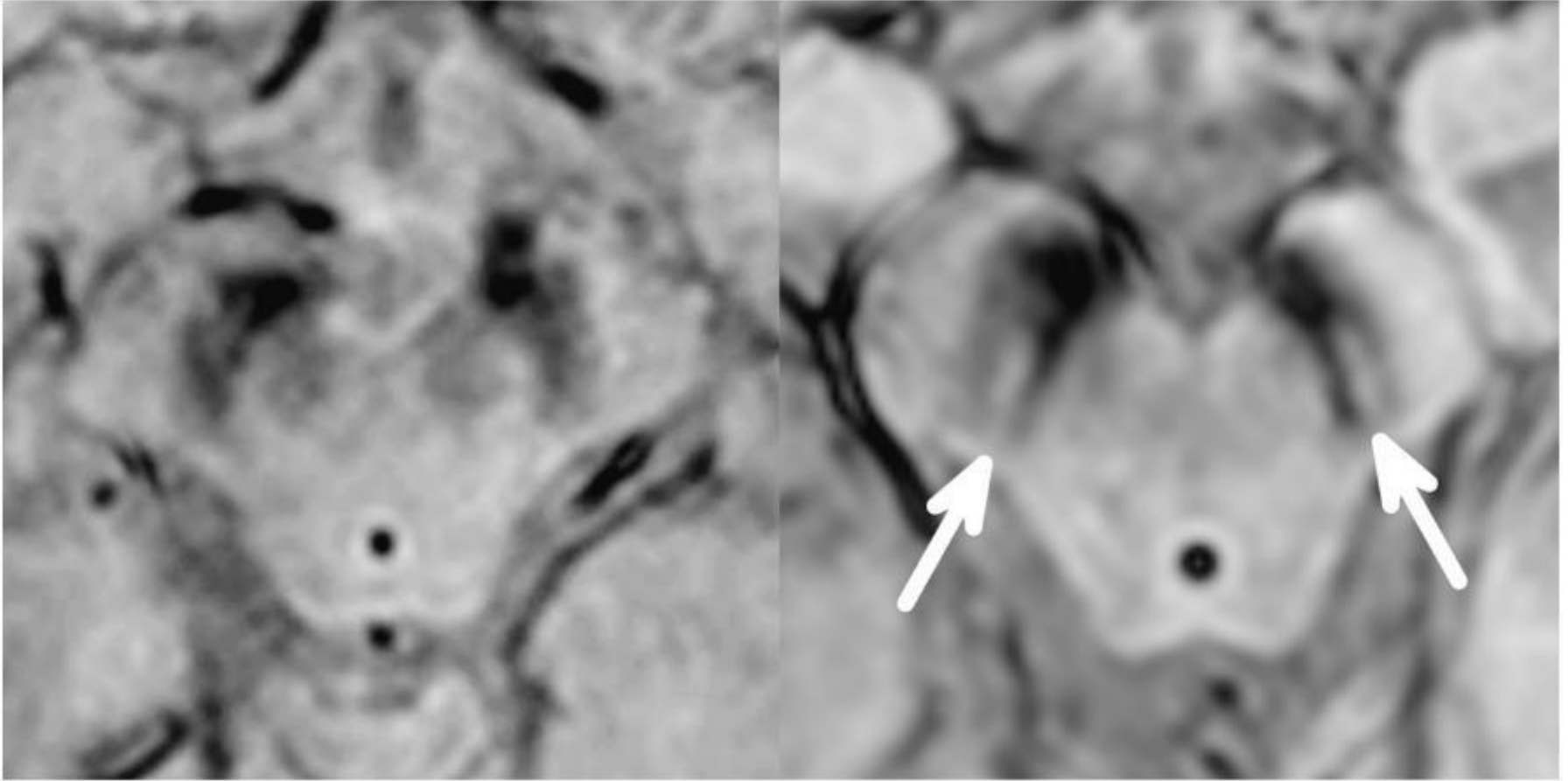
IRM "neuromélanine": individu N



IRM "neuromélanine": H (1937) tbt main droite

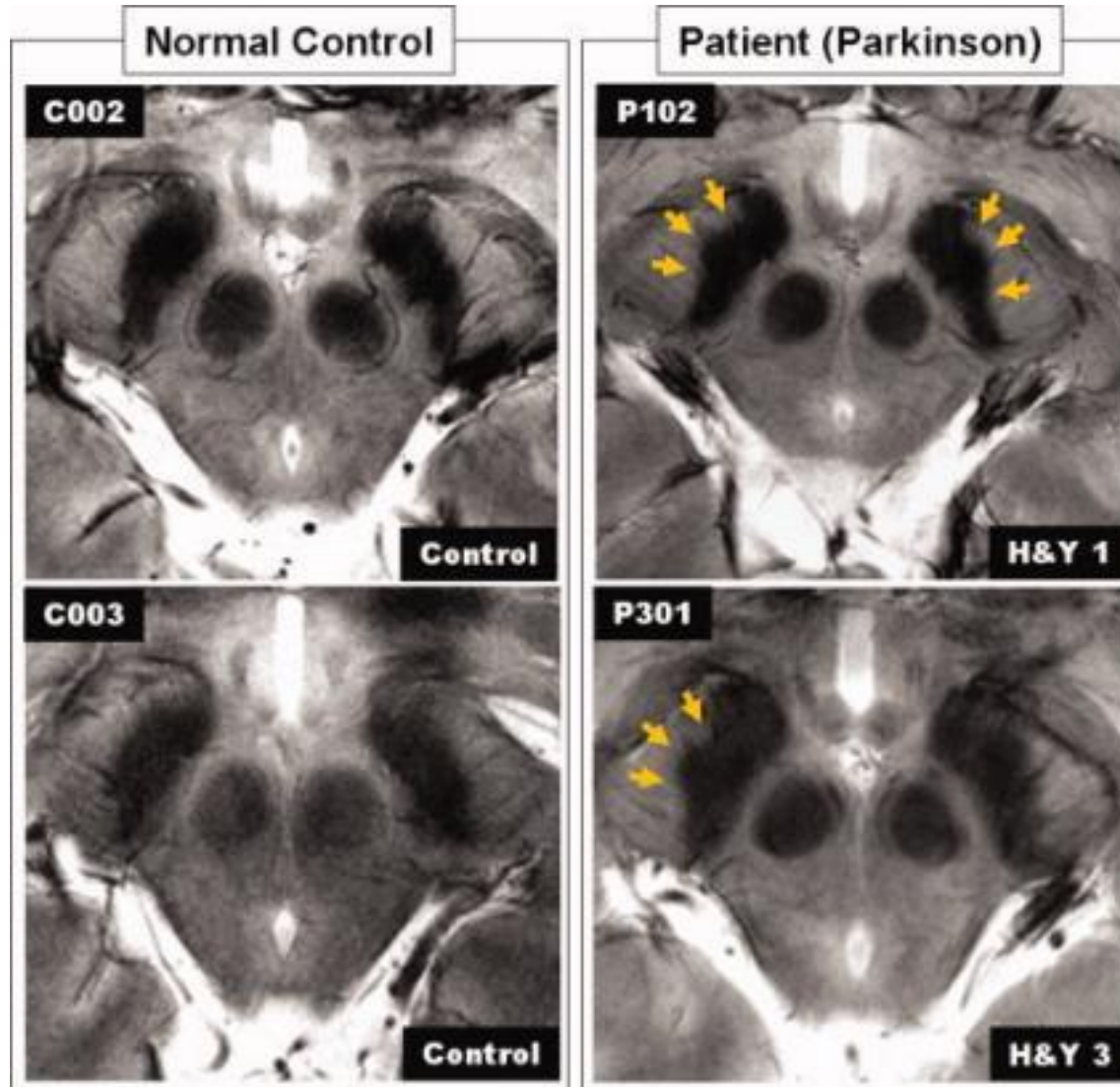


IRM en pondération de susceptibilité (SWI)

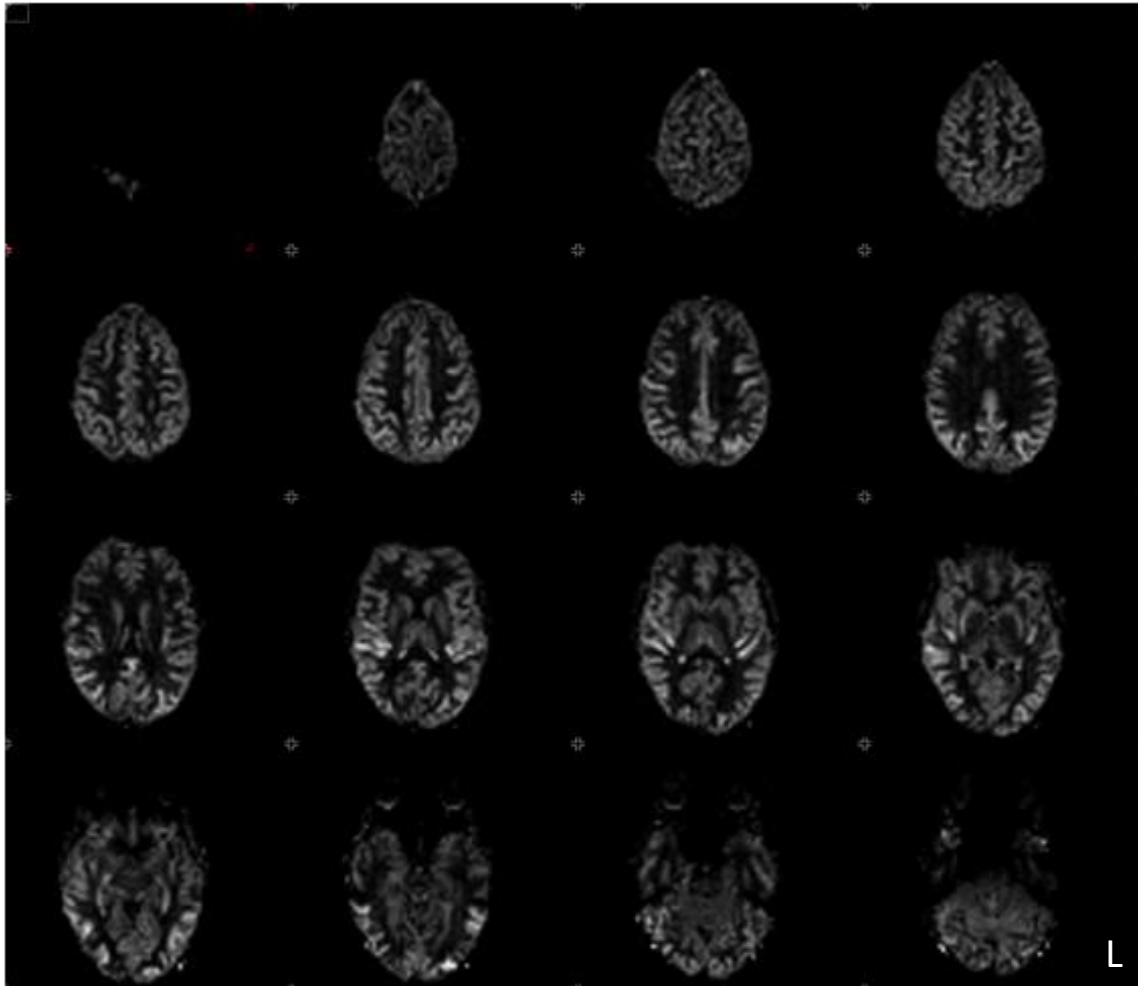


NI Clinical

Locus niger en IRM à 7 Tesla



Images de la perfusion cérébrale au repos par IRMf ASL

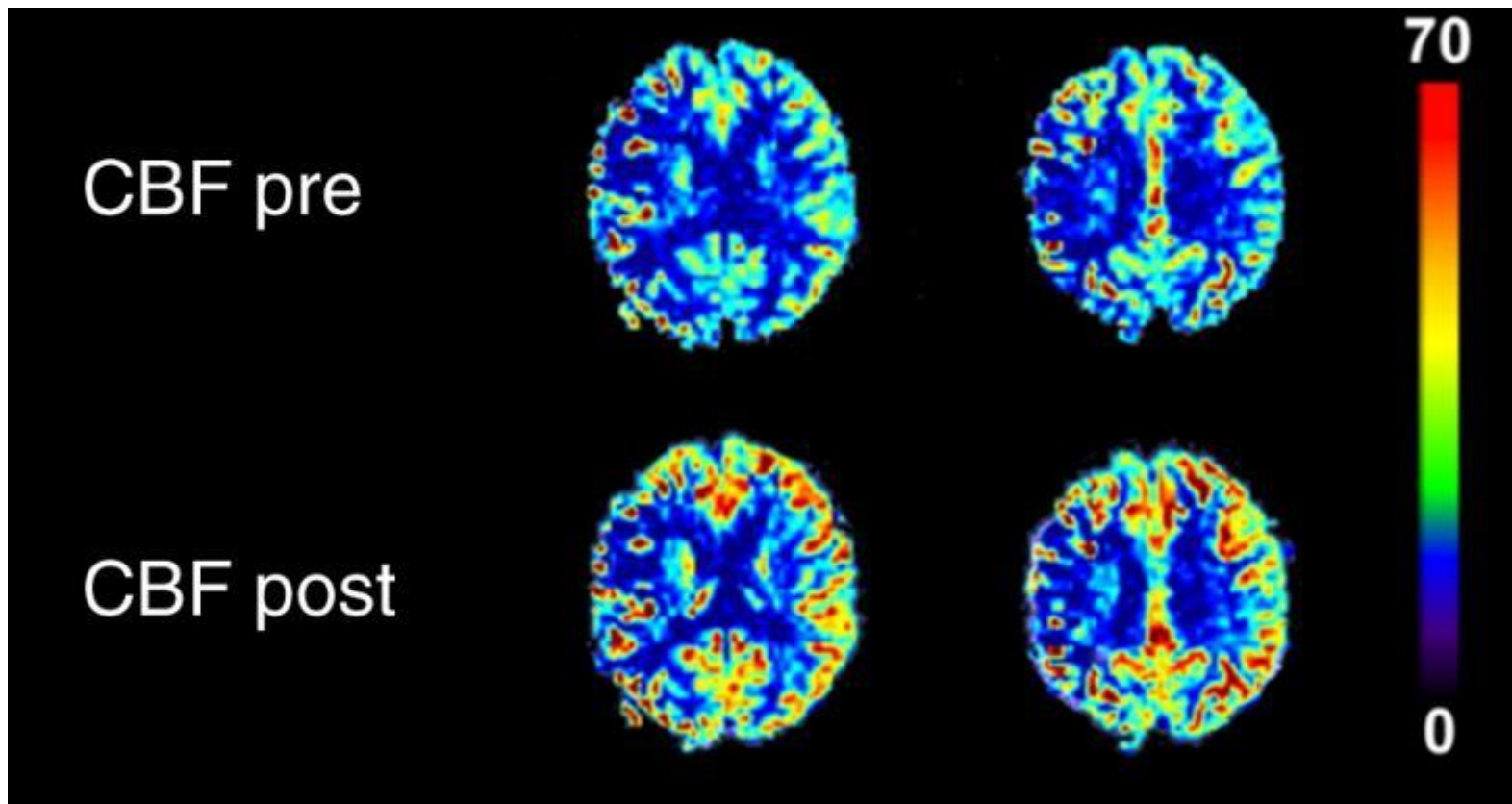


DSC global:
50 ml/100g tissu/min

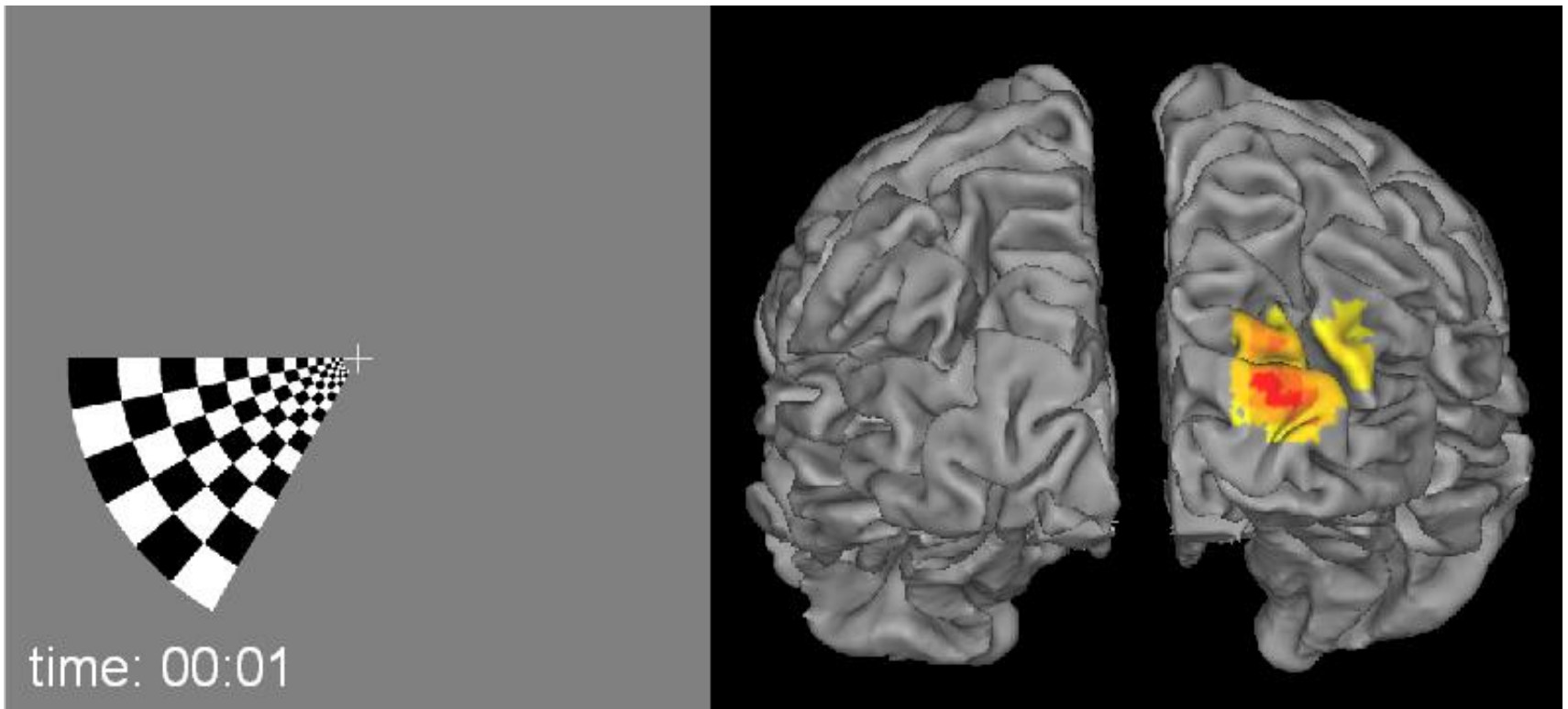
DSC m. grise
80 ml/100g tissu/min

DSC m. blanche
20 ml/100g tissu/min

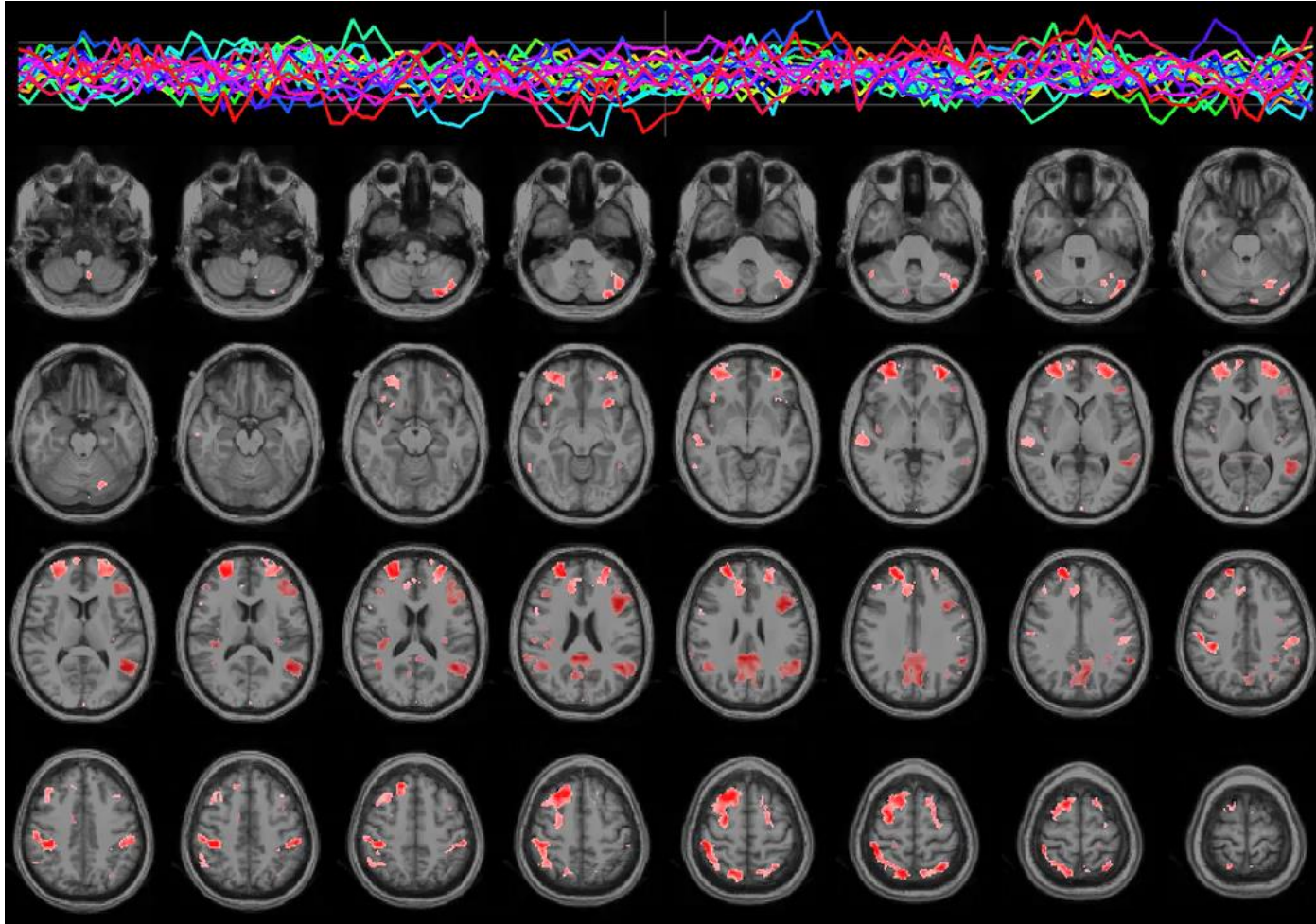
Exploration de la réserve vasculaire cérébrale (test à l'acétalozamide)



+ Mesure de l'activité sensorielle (visuelle) par IRMf BOLD

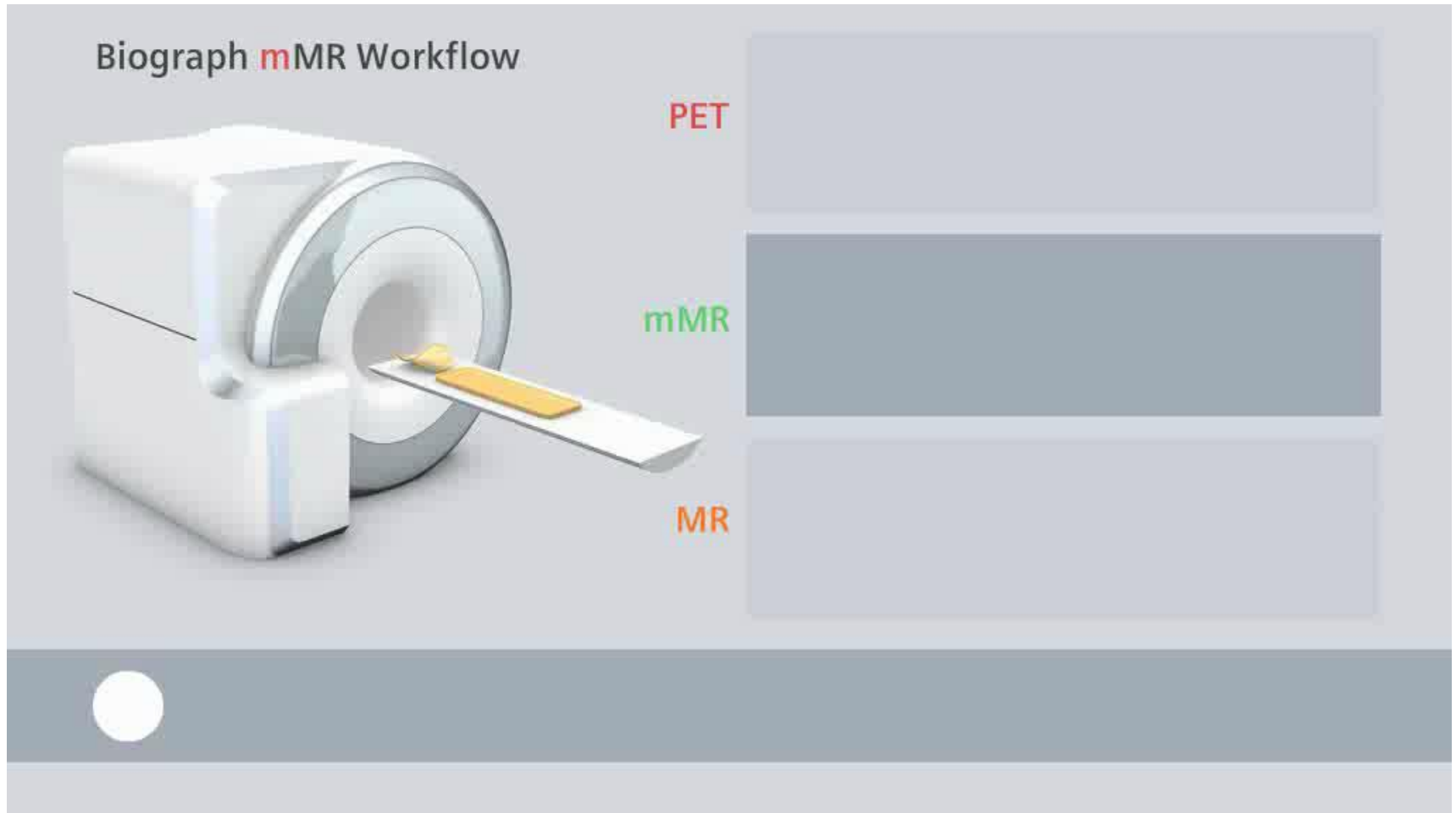


+ Etude dynamique des connexions cérébrales



Technologie de pointe (2017)

2 appareils combinés: IRM & PET scan

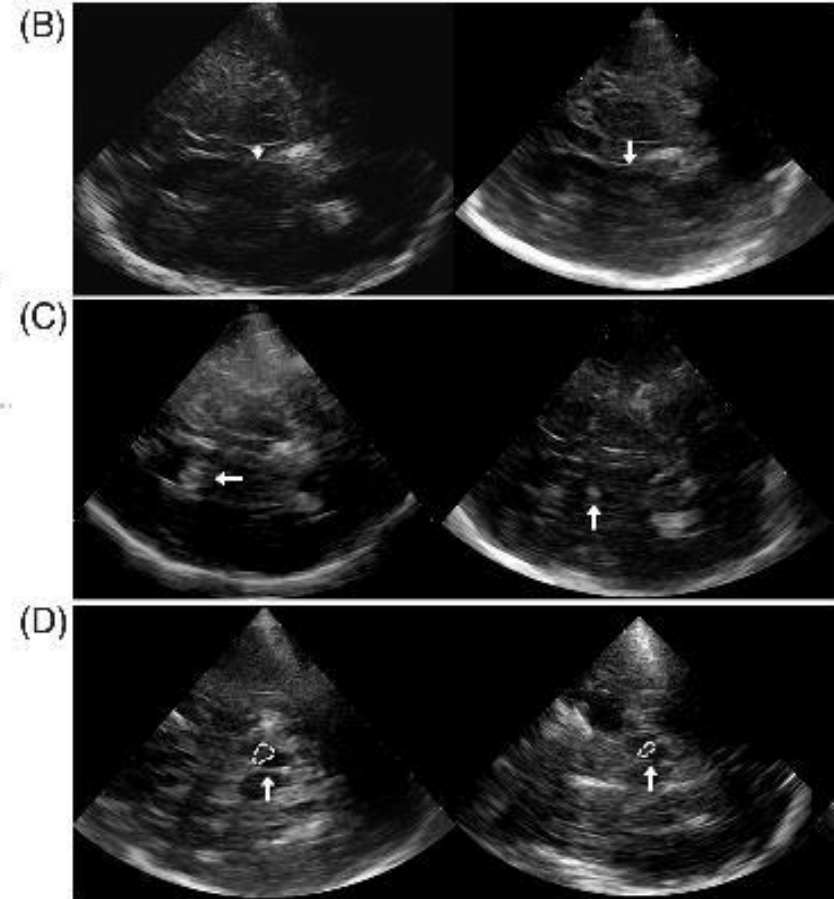
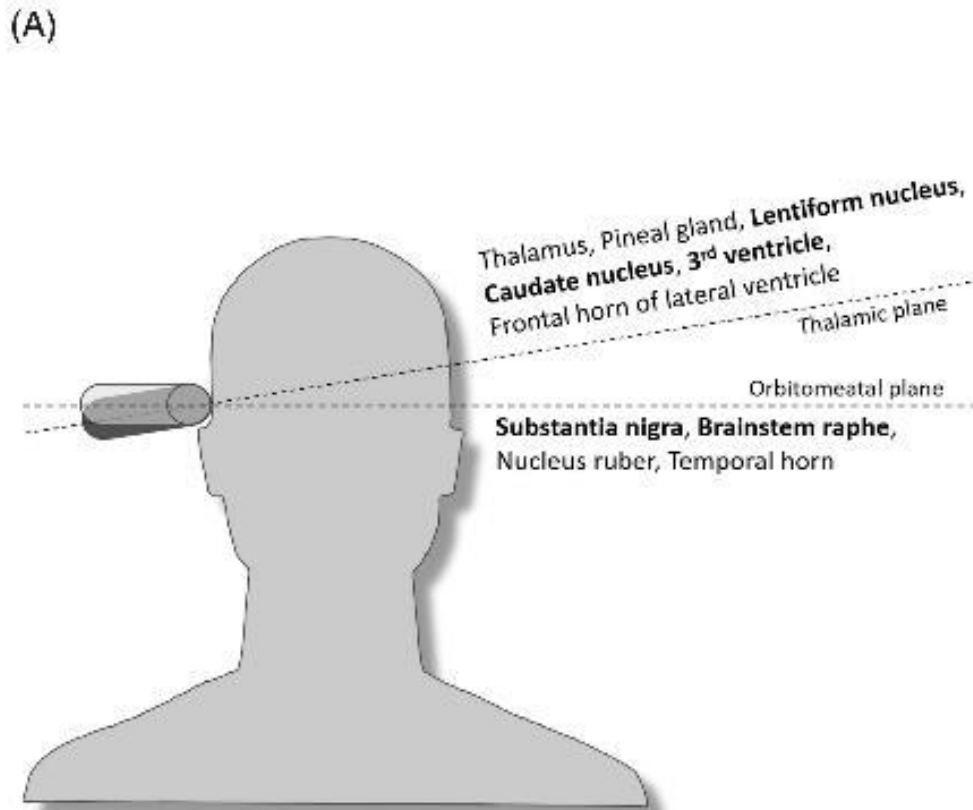


Echographie transcrânienne

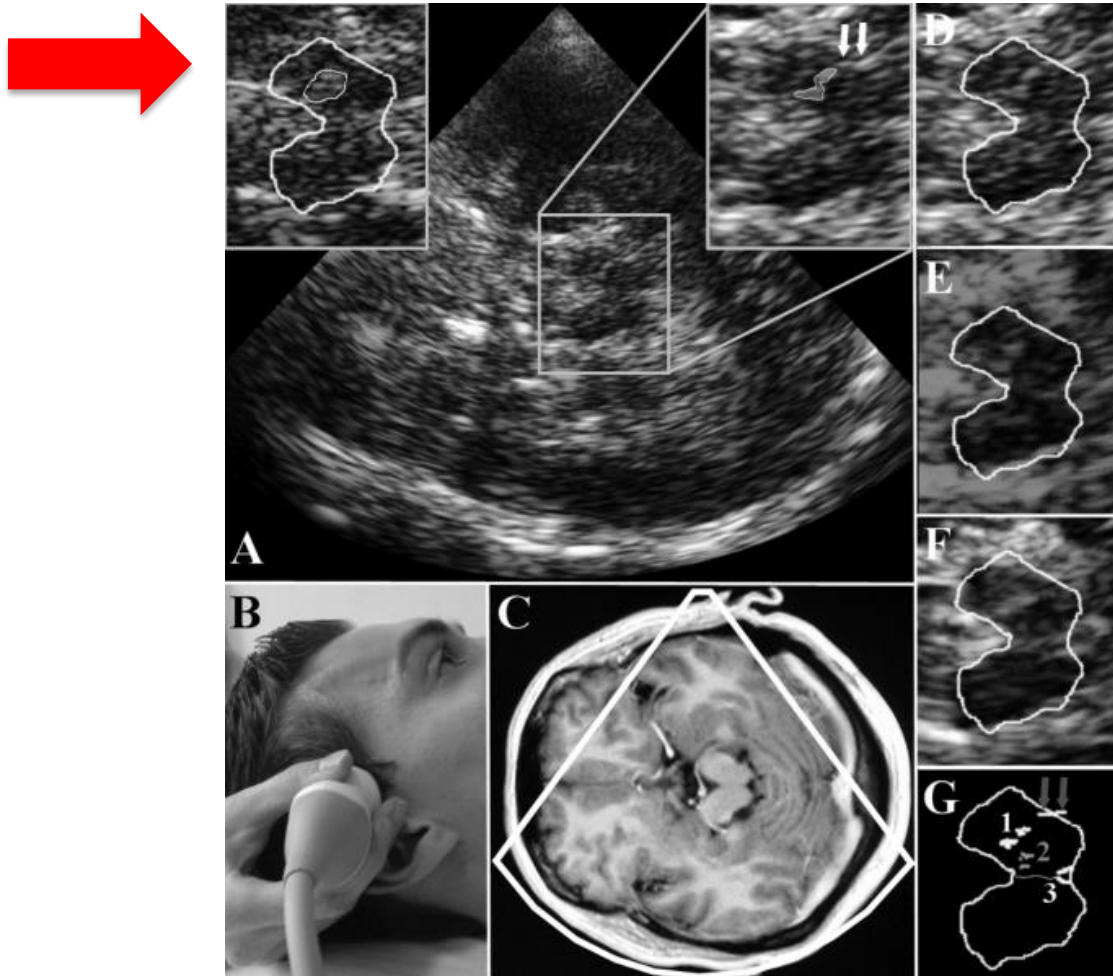


Echographie transcrânienne

→ structures cérébrales profondes



Elargissement de l'hyperéchogénéité du locus niger dans la maladie de Parkinson

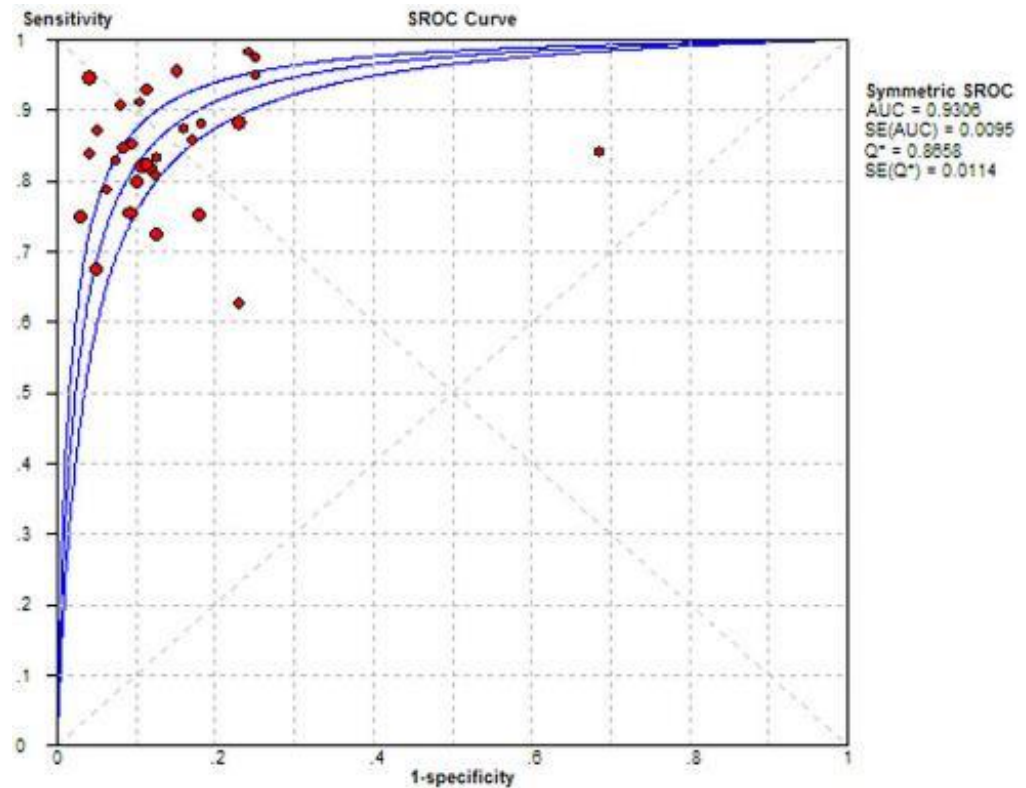


Hyperéchogénéicité de la substance noire dans la maladie de Parkinson

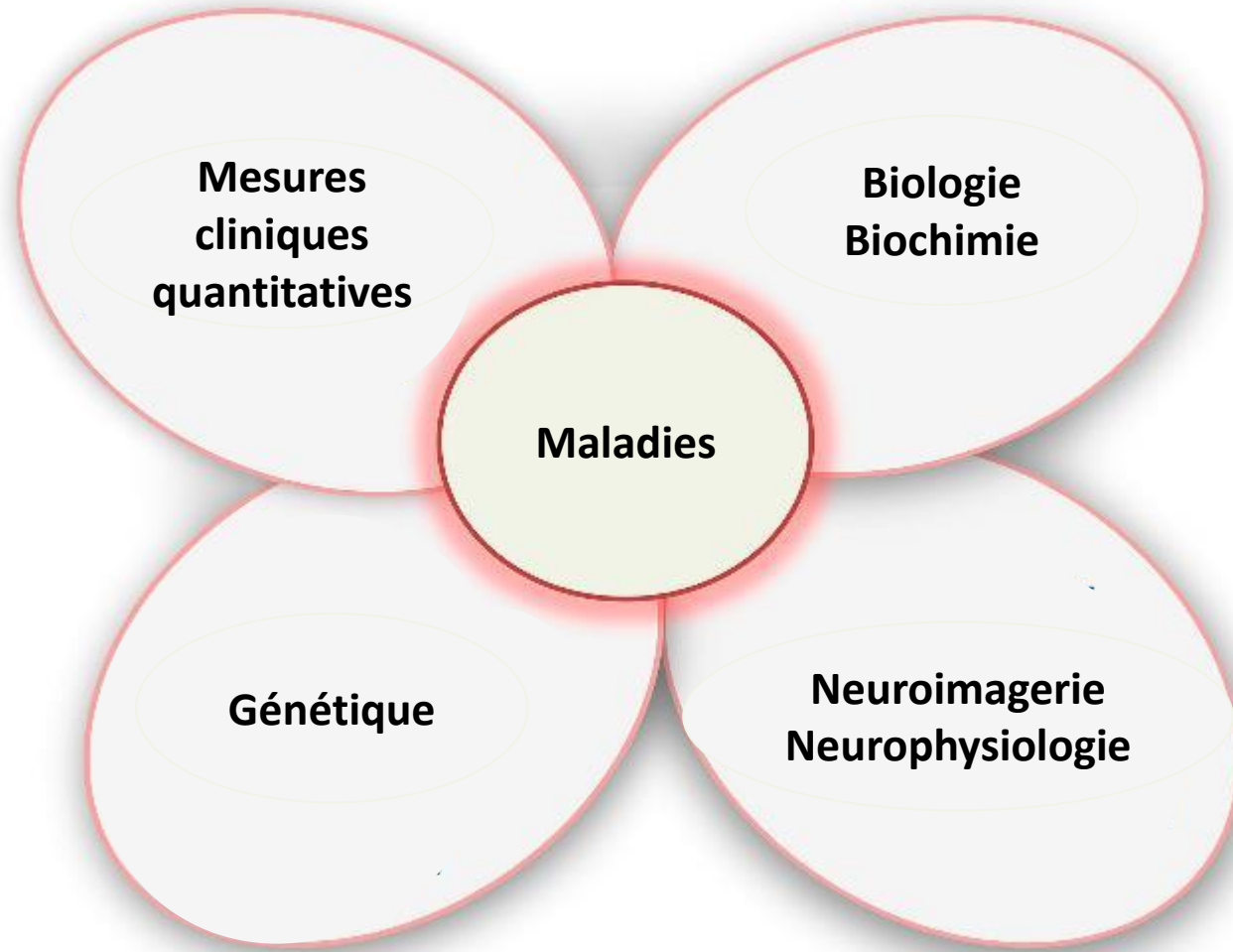
Sensibilité: 83%
Spécificité: 87%

Anomalies comparables
chez les porteurs
asymptomatiques
de mutations LRRK2

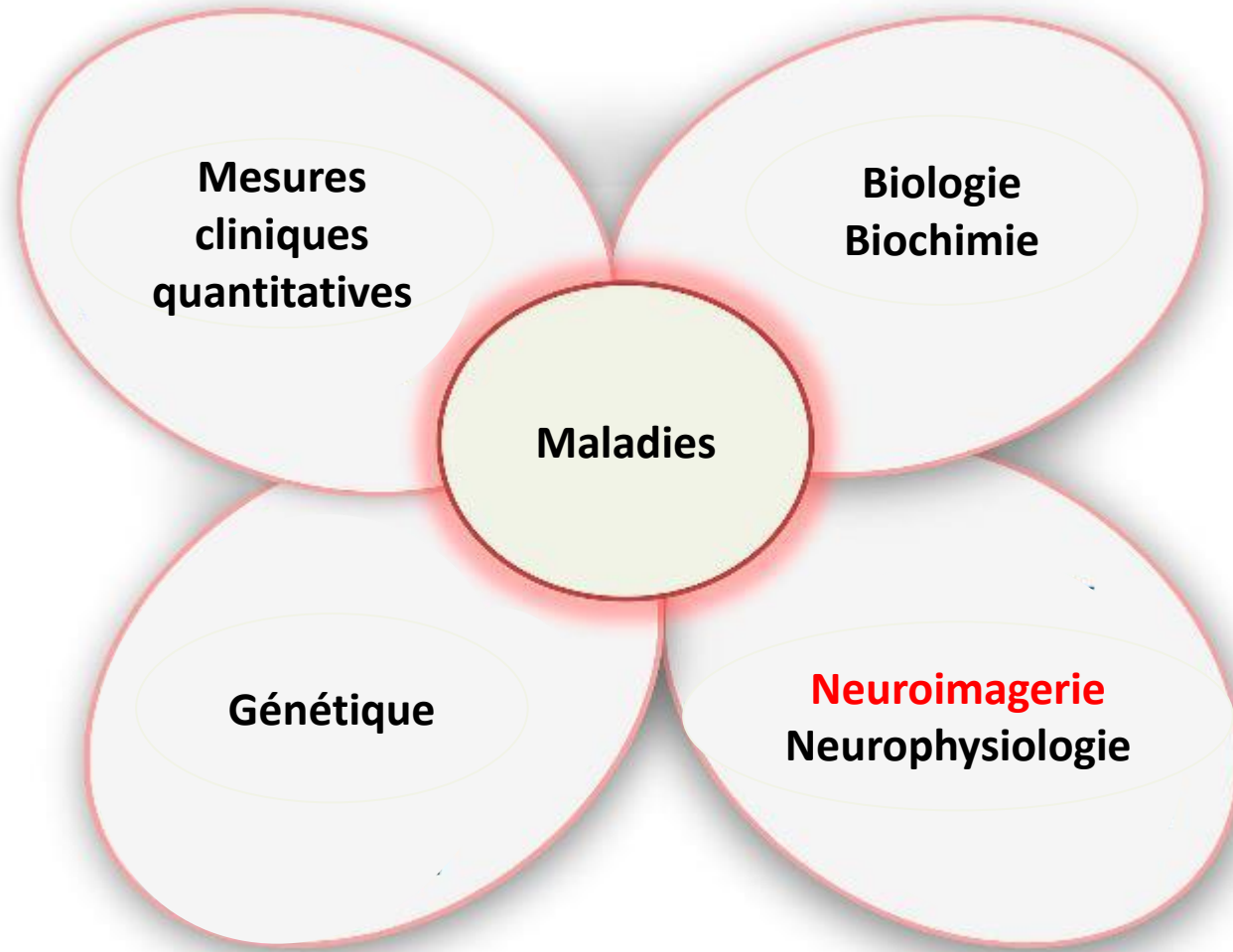
Fenêtre osseuse
insuffisante chez 4-15% de
la population caucasienne



Nouvelles méthodes d'analyse

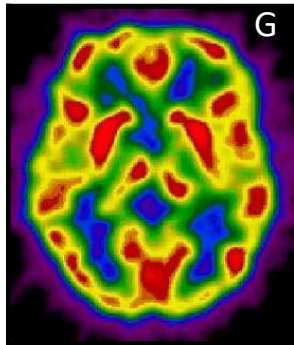


Nouvelles méthodes d'analyse

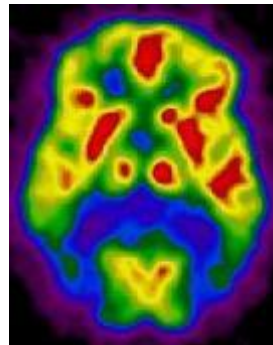


Analyse visuelle des images TEP

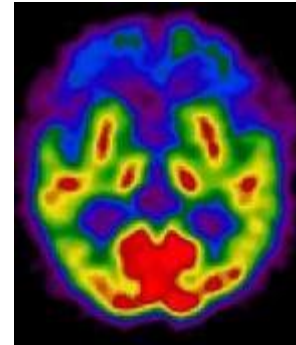
Sujet
sain



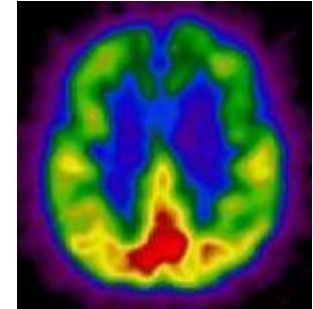
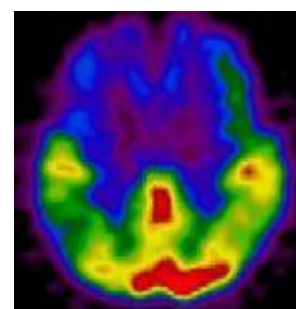
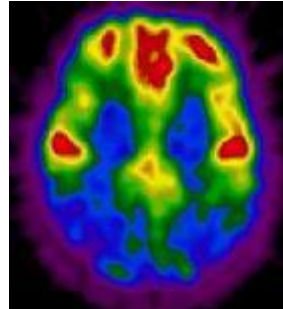
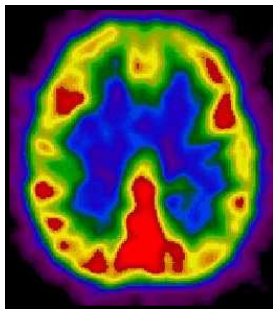
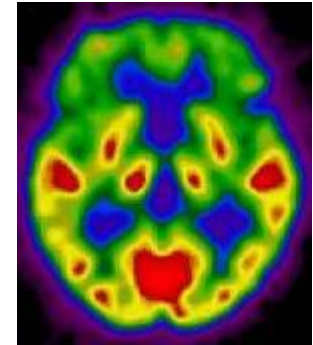
Démence
de type
Alzheimer



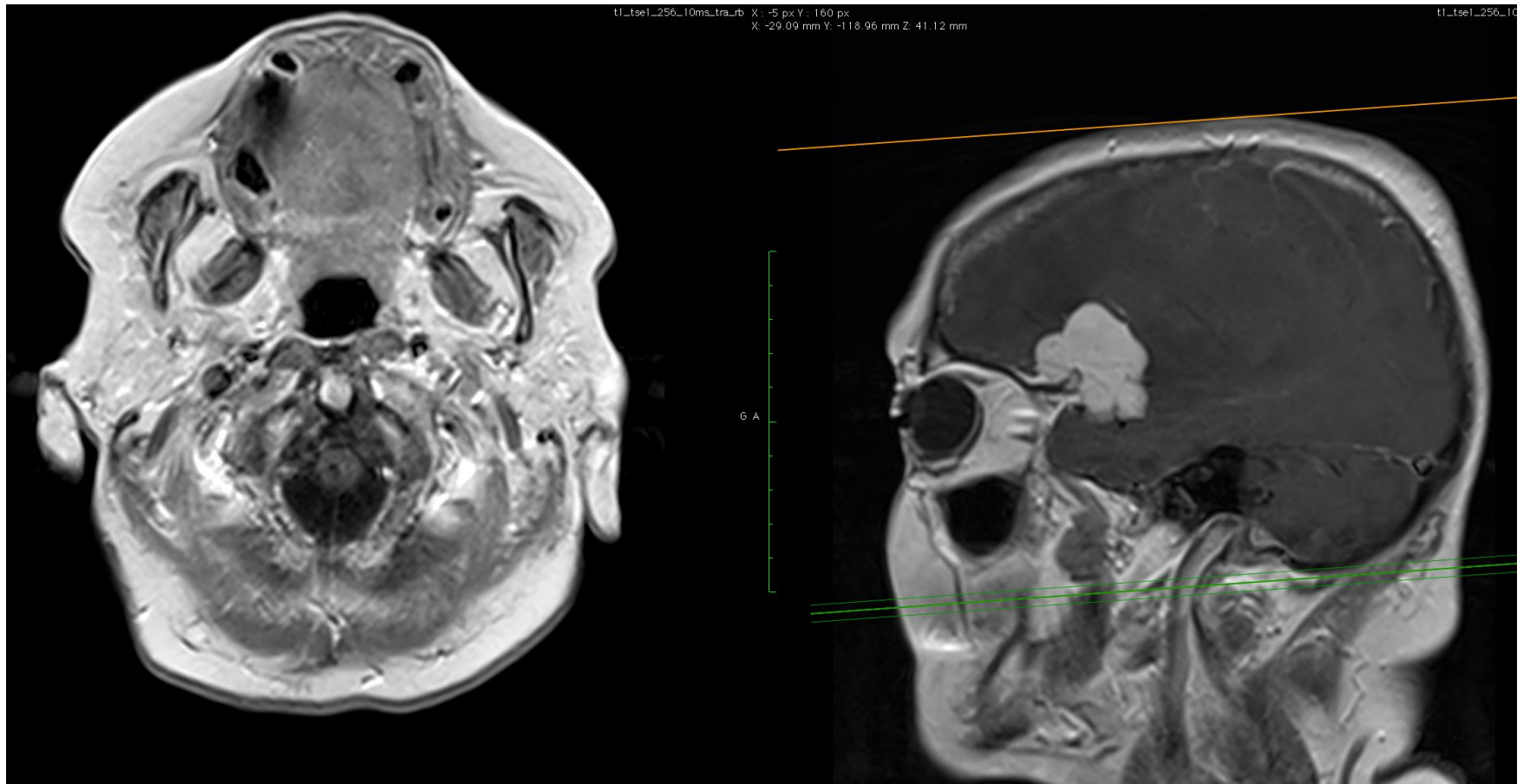
Démence
fronto-
temporale



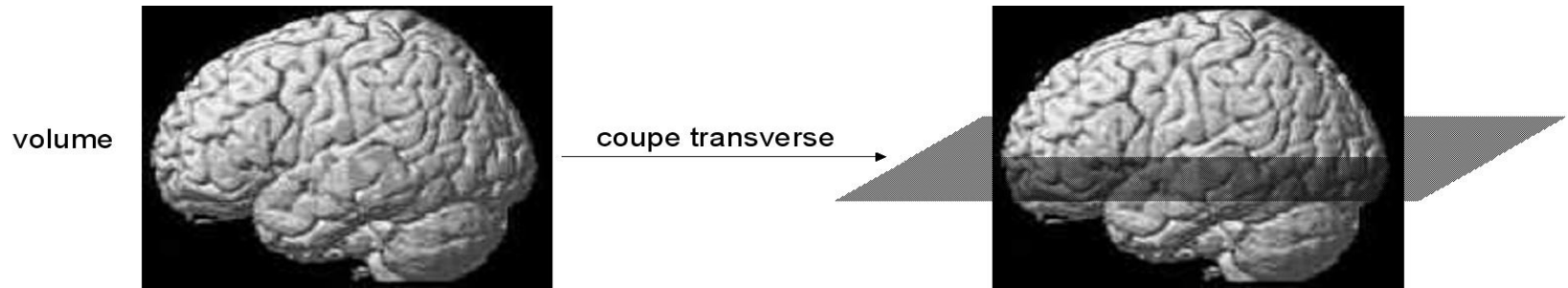
Paralysie
supranucléaire
progressive



Analyse visuelle des images IRM

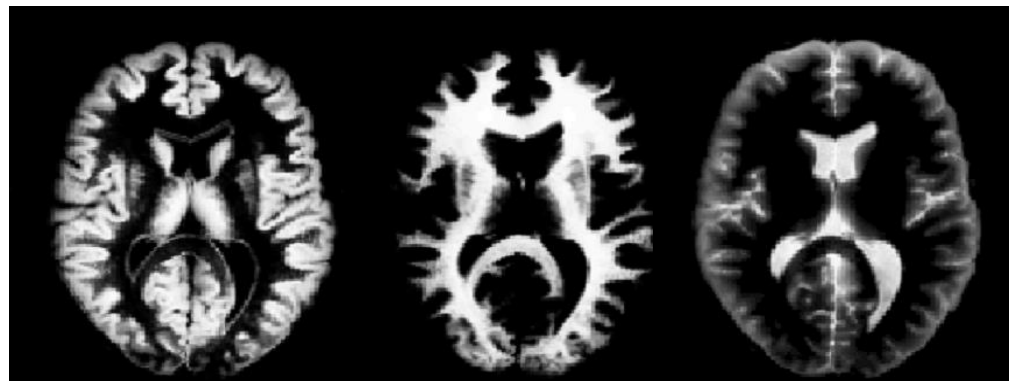


Ex: segmentation automatique des images en tissus de représentation de MG, MB et LCR



arrière

gauche

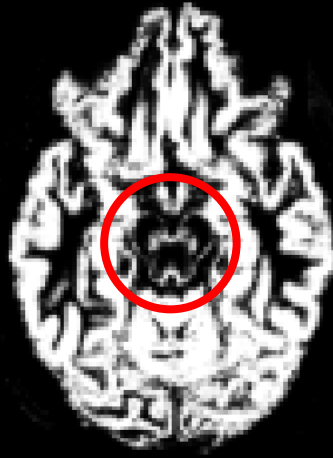


Segmentation automatique du locus niger

Sans transfert de
magnétisation



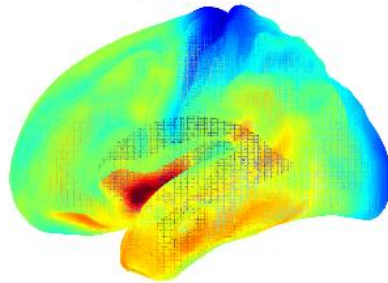
Avec transfert de
magnétisation



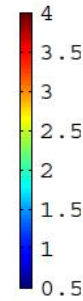
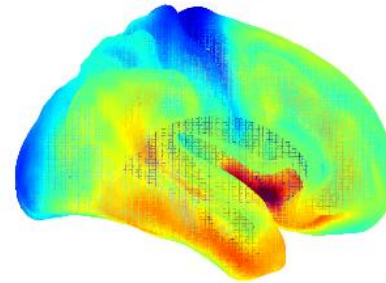
Calcul automatique de l'épaisseur du manteau cortical



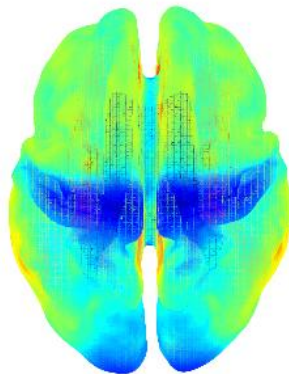
Left lateral



Right lateral

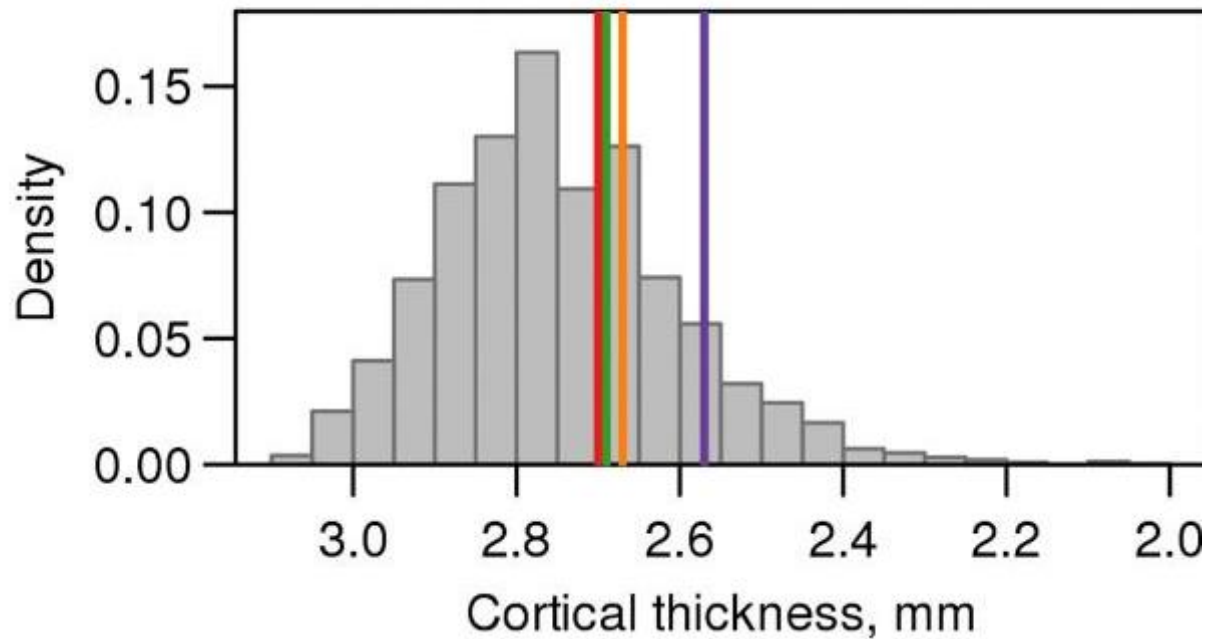
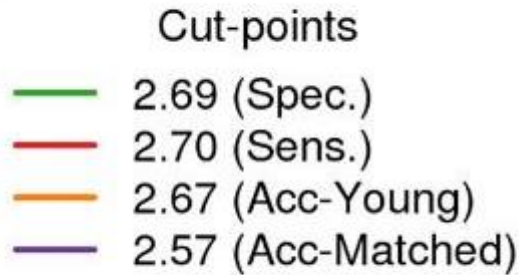


Dorsal

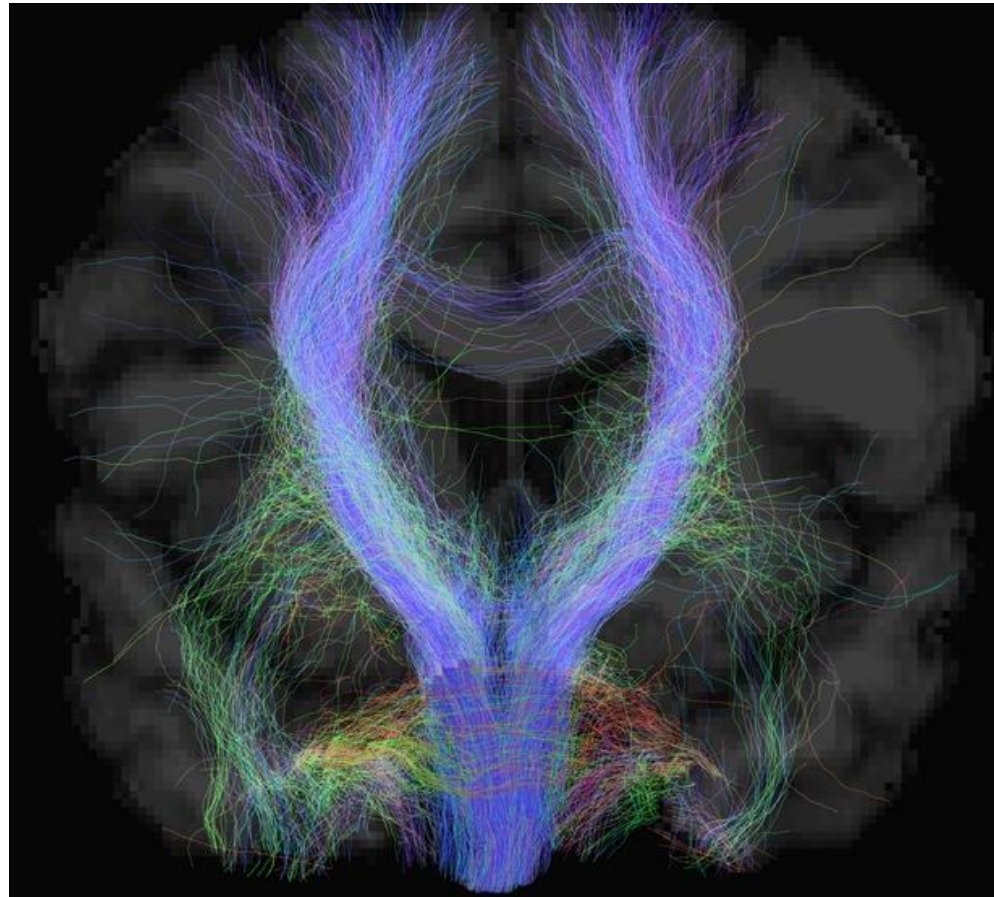
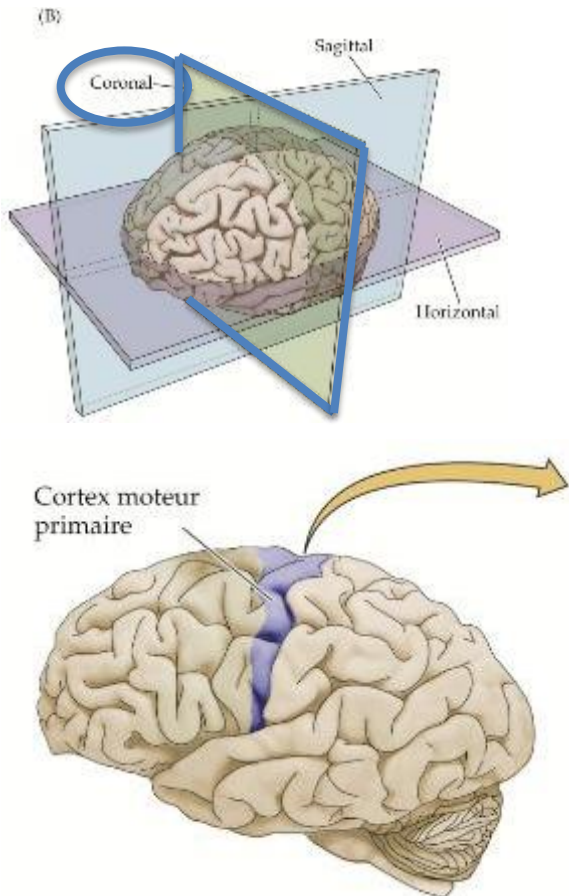


Seuil d'épaisseur du manteau cortical de la région parahippocampique dans la MA

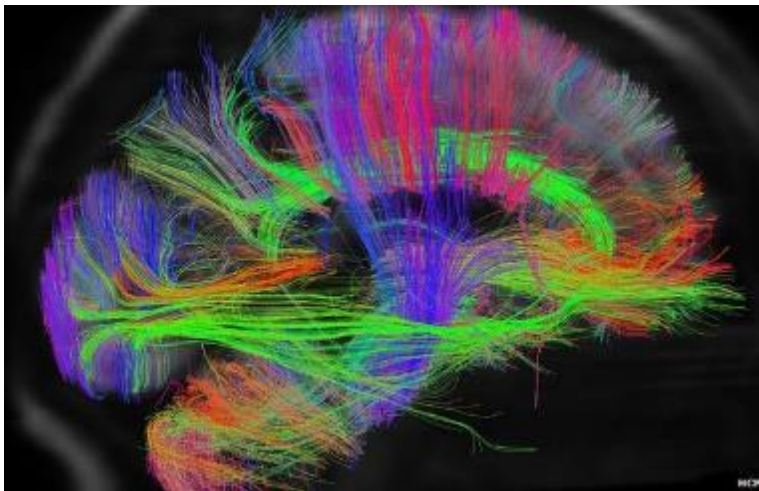
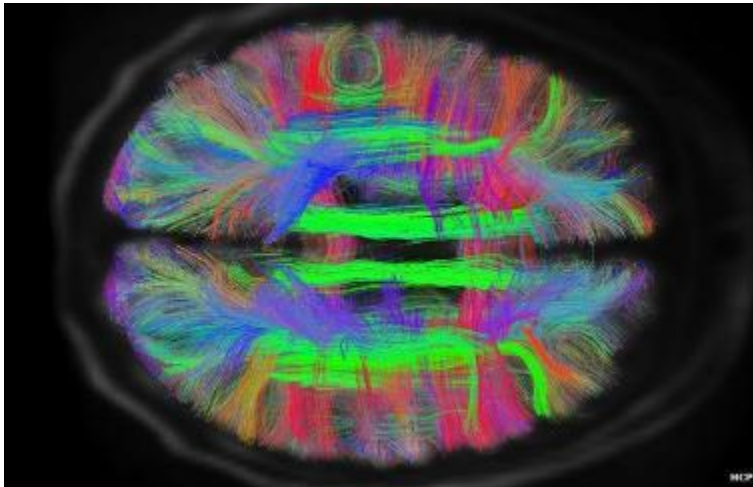
D



IRM en pondération de diffusion → trajet des fibres de matière blanche

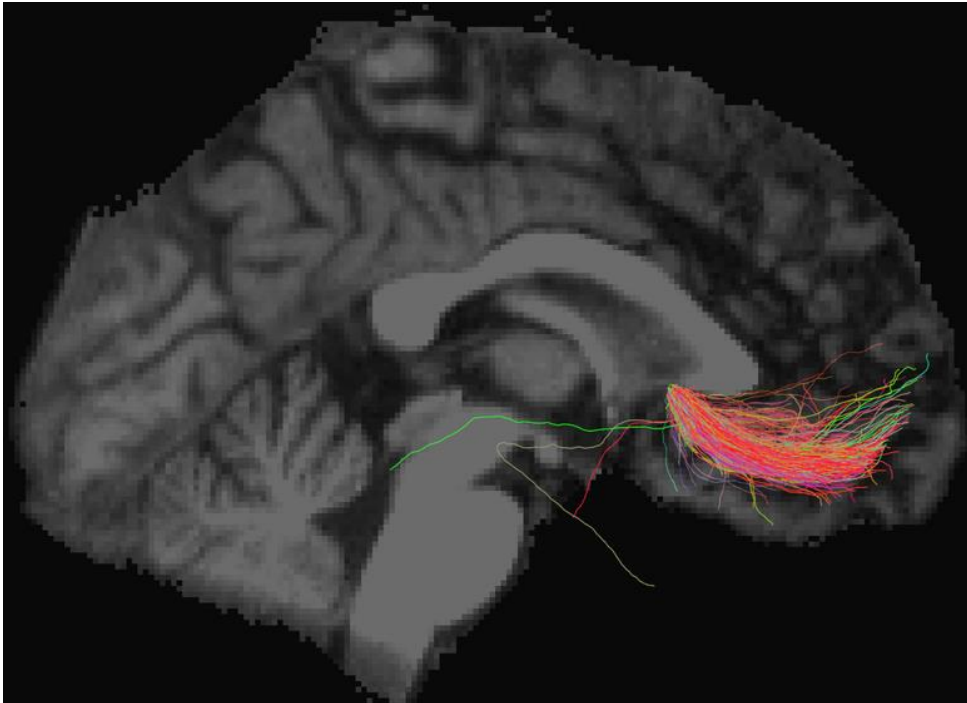


IRM en pondération de diffusion
→ trajet des fibres de matière blanche

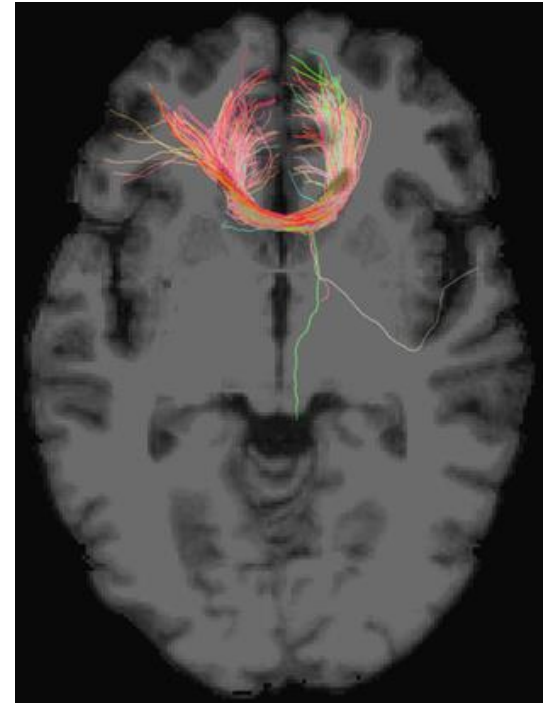


IRM en diffusion → reconstruction du trajet des fibres de matière blanche entre les 2 hémisphères cérébraux

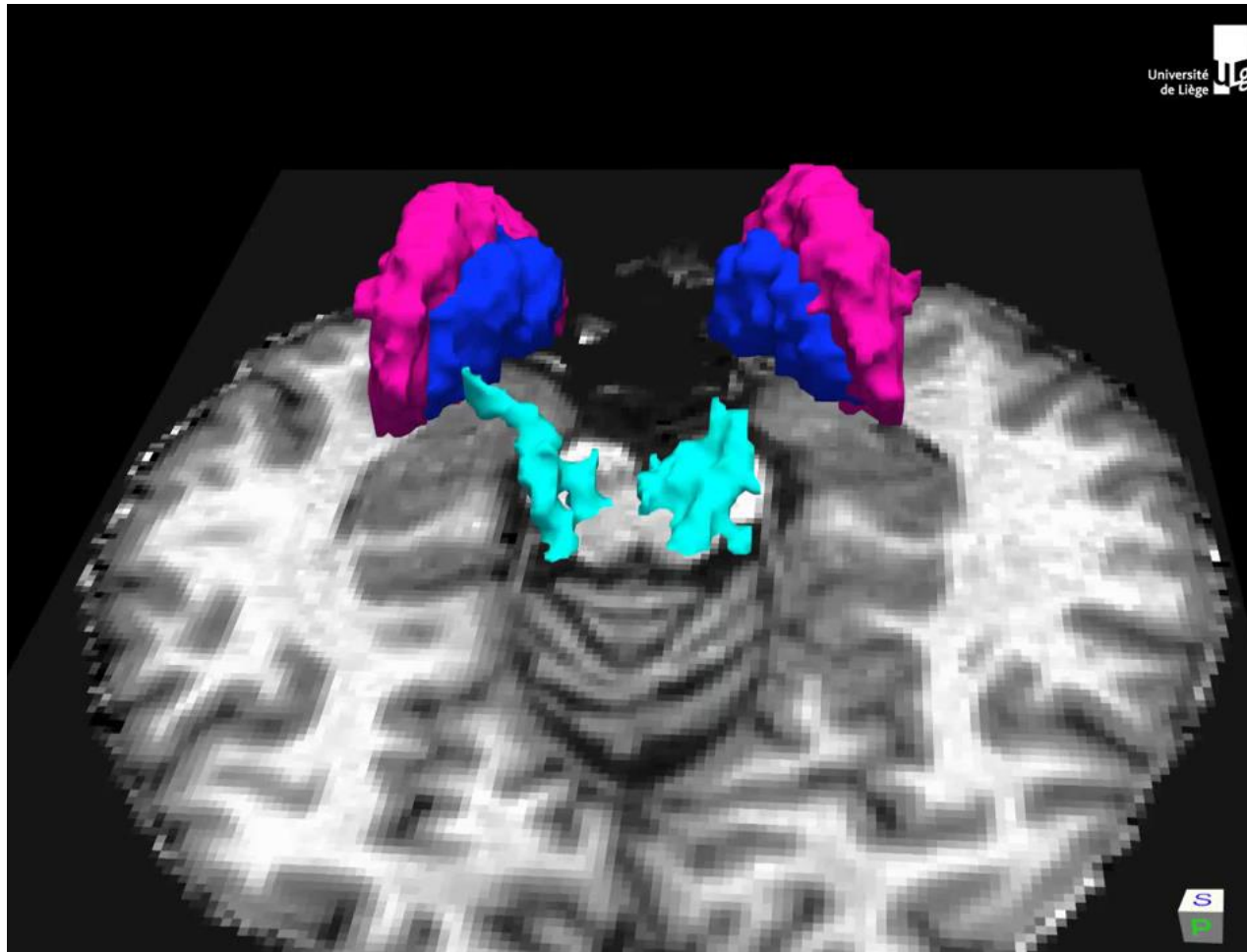
Coupe sagittale

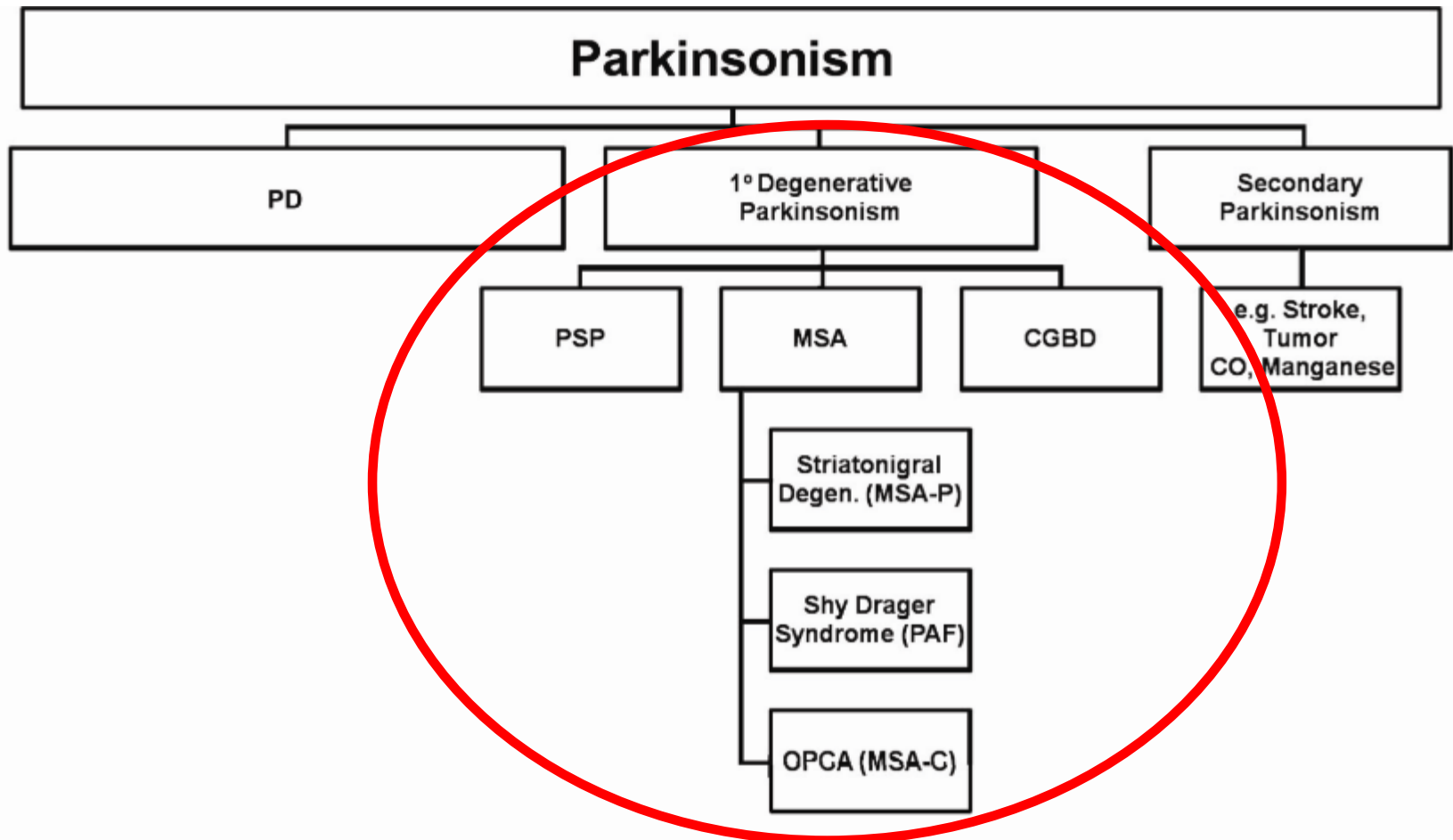


Coupe horizontale (axiale)



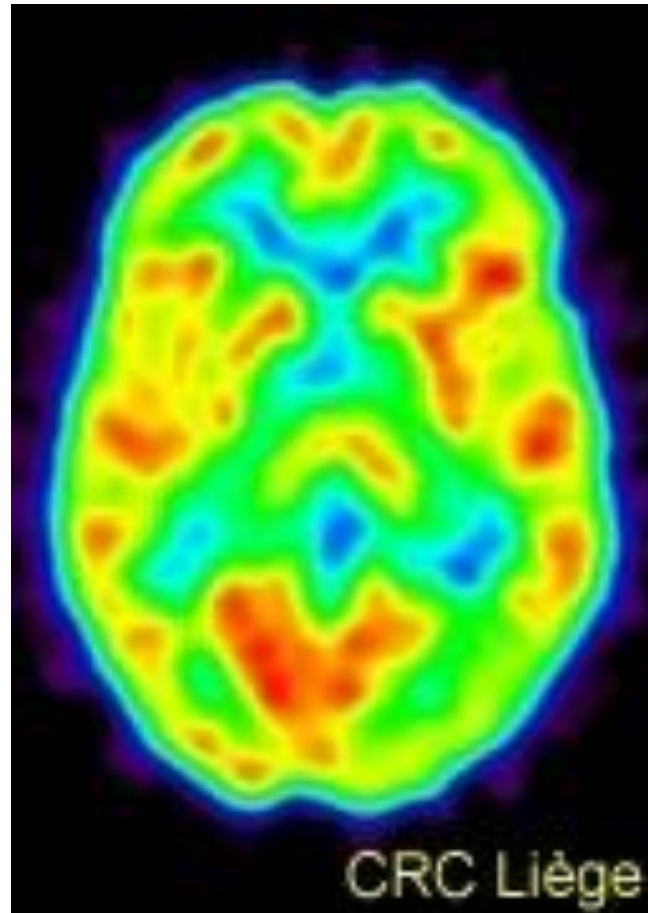
Visualisation de l'atteinte des fibres nerveuses du locus niger dans la MP



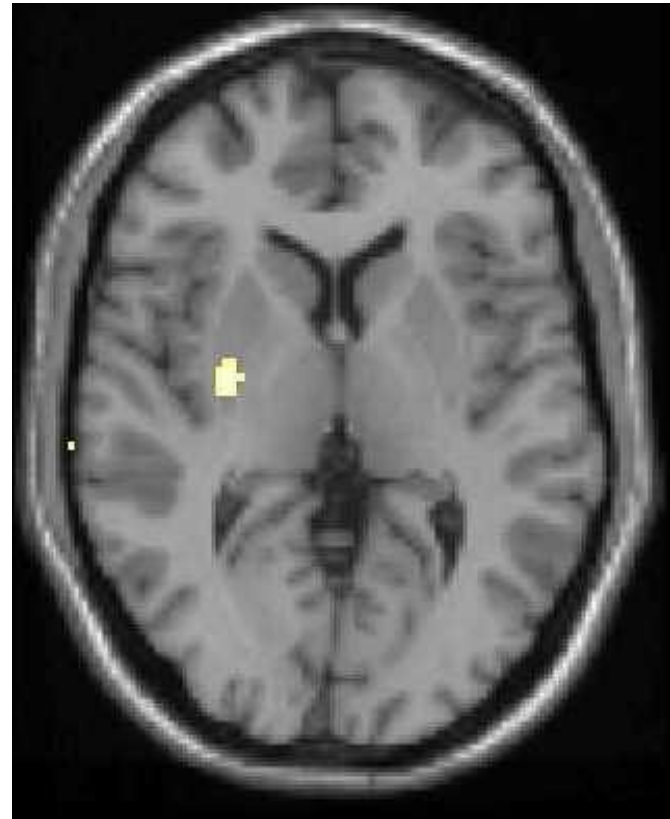
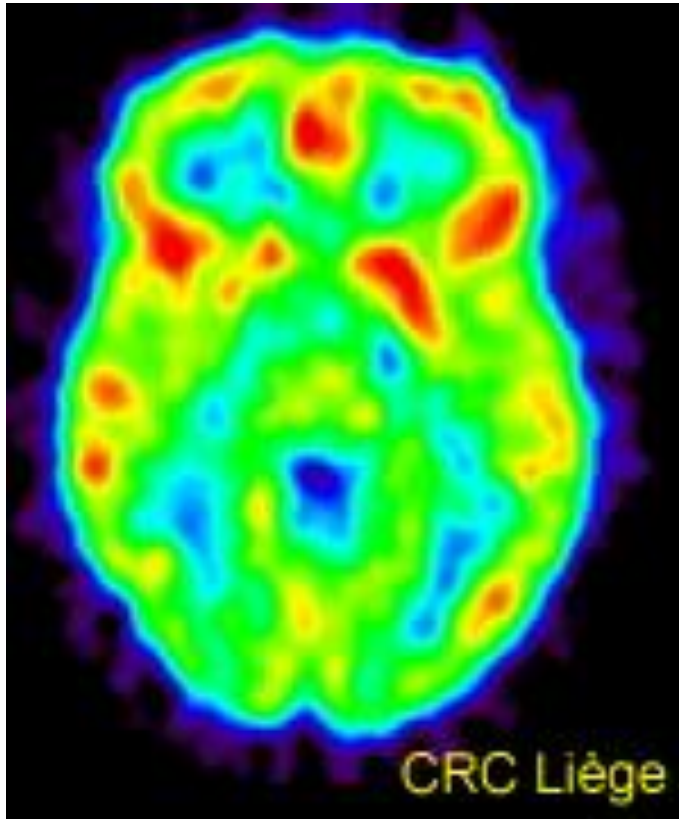


PD = Parkinson disease; MSA-P = multiple system atrophy-parkinsonian; MSA-C = multiple system atrophy-parkinsonian cerebellar.

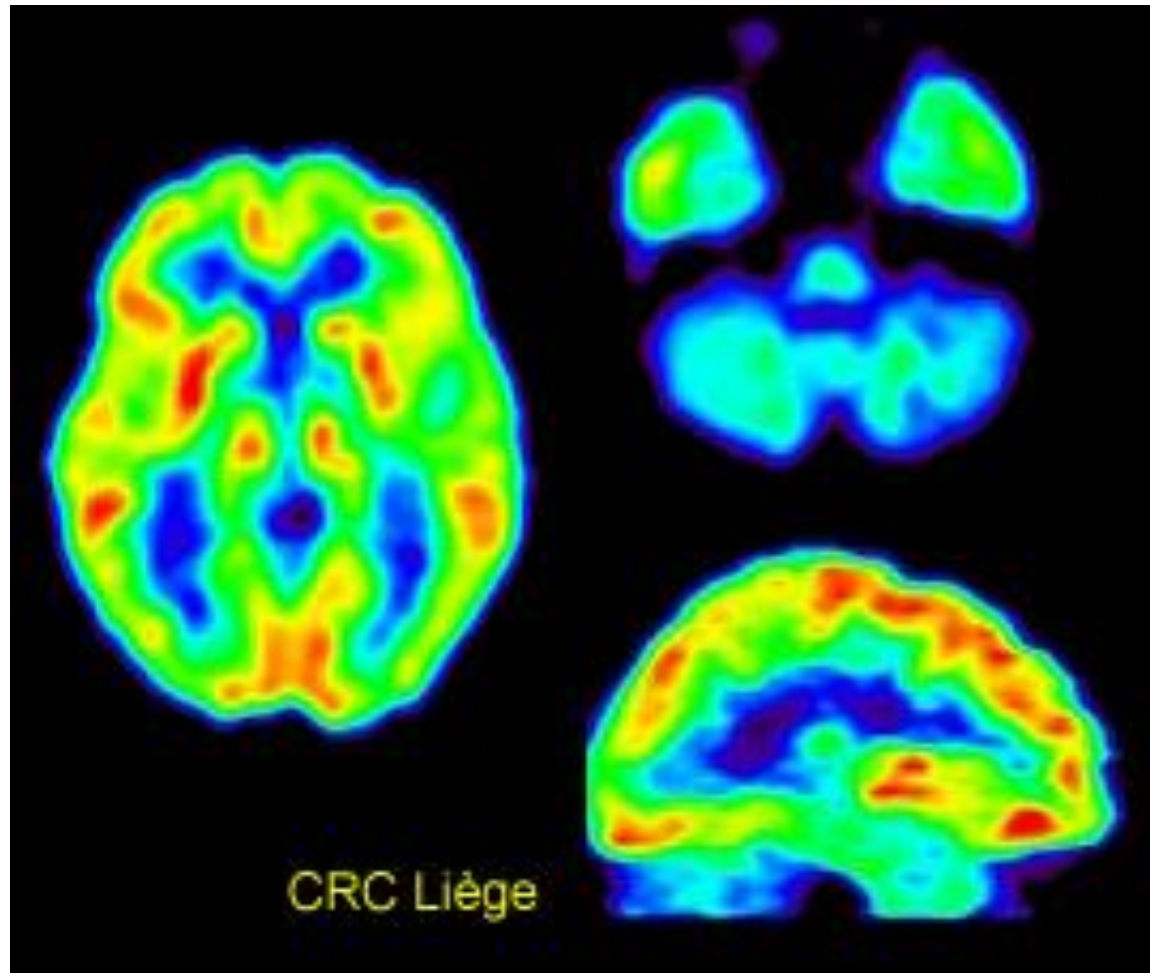
TEP au ^{18}F FDG chez un patient atteint de MP



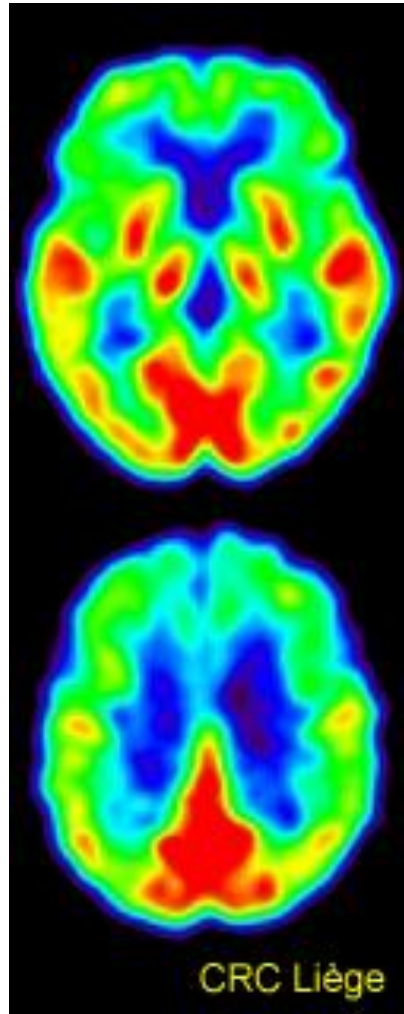
TEP au ^{18}F FDG chez un patient atteint de MSA-P



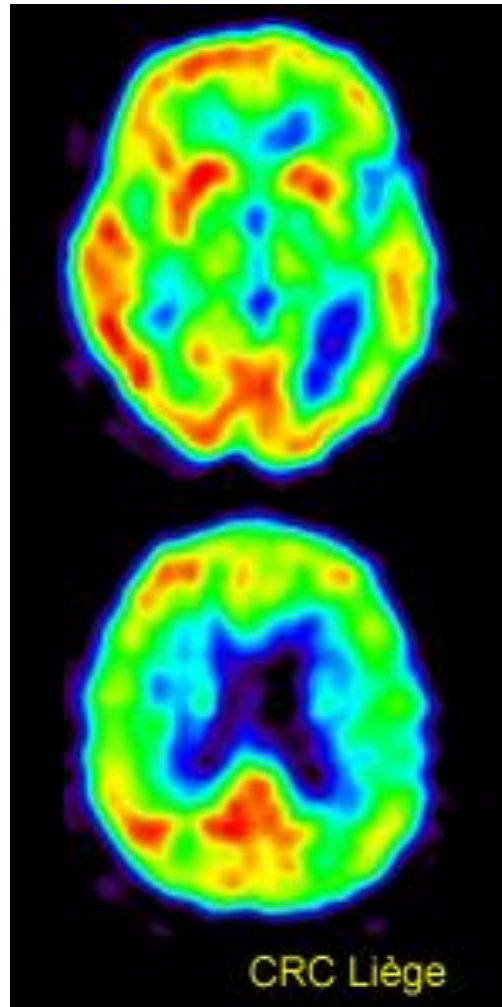
TEP au ^{18}F FDG chez un patient atteint de MSA-C



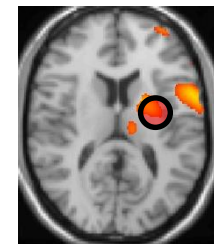
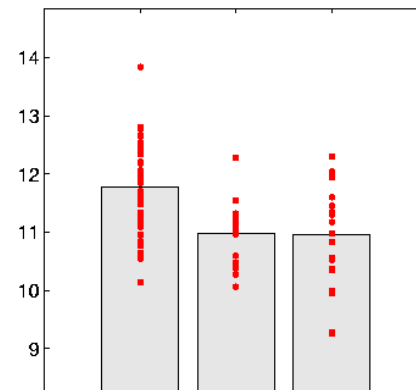
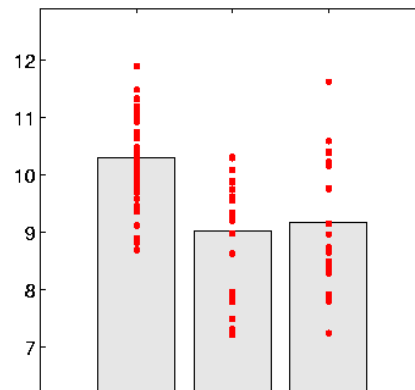
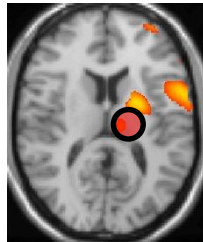
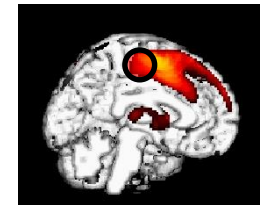
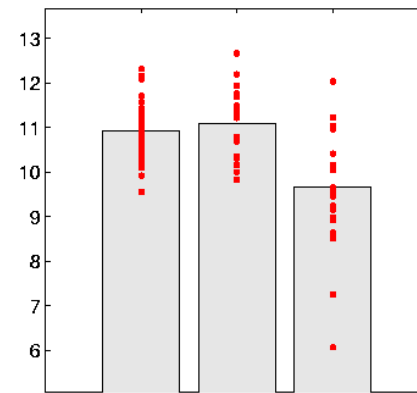
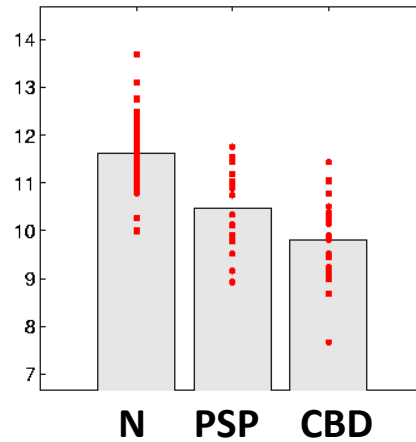
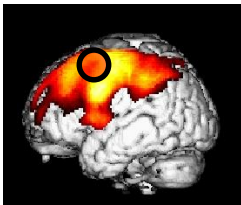
TEP au ^{18}F FDG chez un patient atteint de PSP



TEP au ^{18}F FDG chez un patient atteint de SCB



Chevauchement des valeurs individuelles de captation du ^{18}F FDG



Classification automatique de PET scans par une méthode d'intelligence artificielle (IA)

But: Tester une méthode d'analyse multivariée de reconnaissance automatique de motifs sur 120 PET scans réalisés en moyenne 3,5 ans après l'apparition des premiers symptômes chez des patients parkinsoniens pour lesquels il existait un doute diagnostique

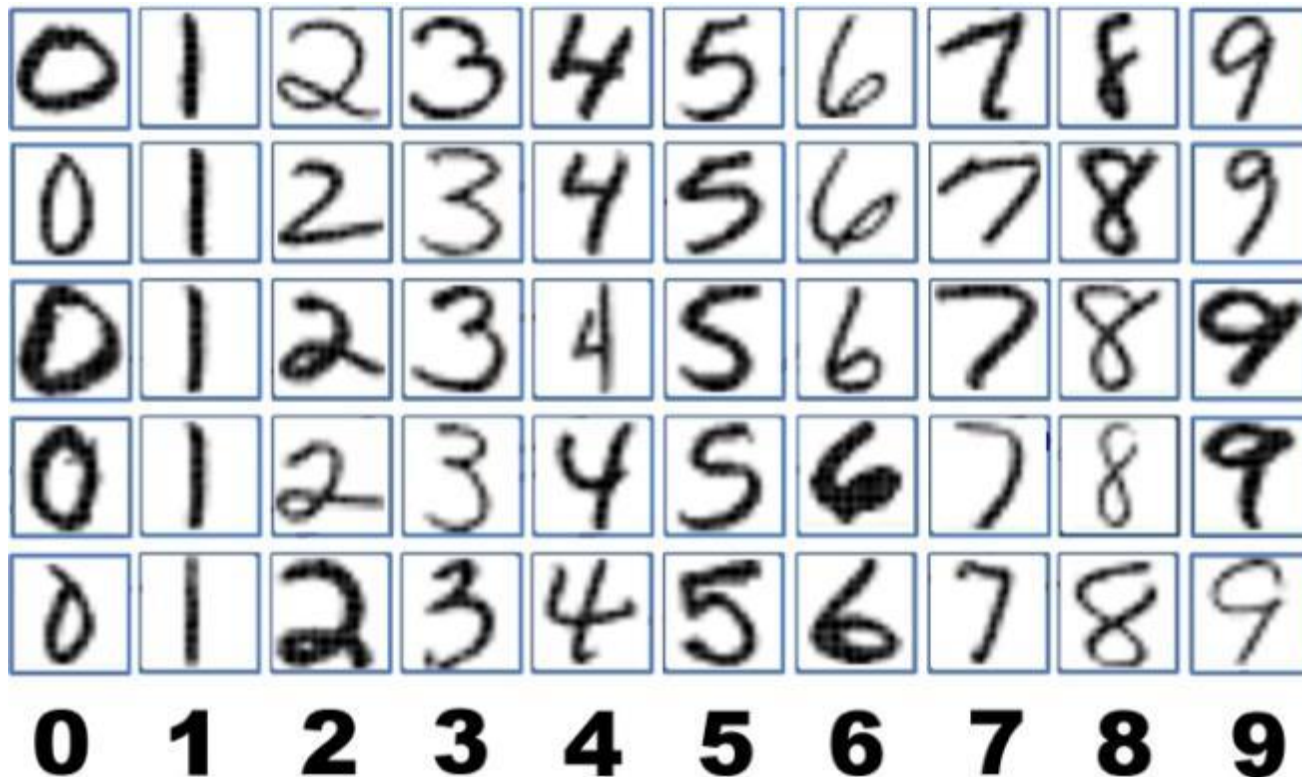
Classification binaire: maladie de Parkinson (PK)
ou syndrome parkinsonien atypique (PK+)

Comparaison avec le diagnostic clinique final ('gold standard')
respectivement ~8 et ~2,8 ans après la réalisation du PET scan

120 PET scans (95 Cyclotron ULiège/25 CHU Liège)

	N	Genre (F/M)	Age lors du PET scan	Durée de la maladie lors du PET scan	Durée du follow up après PET	
	PK	42	17/25	56.9 ± 10.3	3.6 ± 3.1	11.6 ± 5.1
PK+	MSA	31	18/13	66.0 ± 8.8	3.4 ± 2.9	6.4 ± 3.9
	PSP	26	9/17	69.4 ± 7.3	3.1 ± 2.4	5.9 ± 4
	CBS	21	15/6	67.8 ± 7	3.3 ± 2	5.9 ± 2.9
	All classes	120	59/61	63.9 ± 10.2	3.4 ± 2.7	8.0 ± 5.0

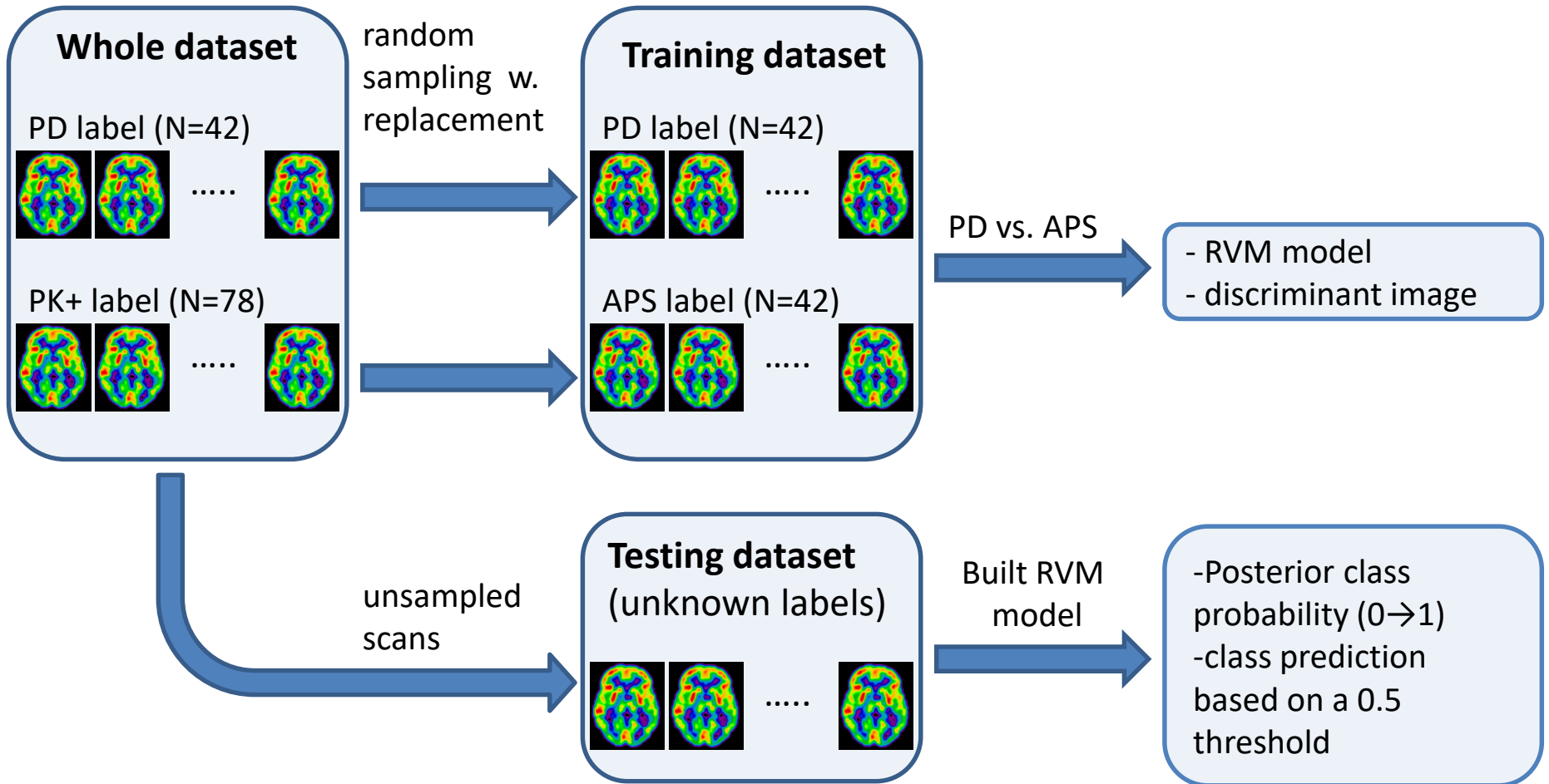
Méthode: reconnaissance de motifs



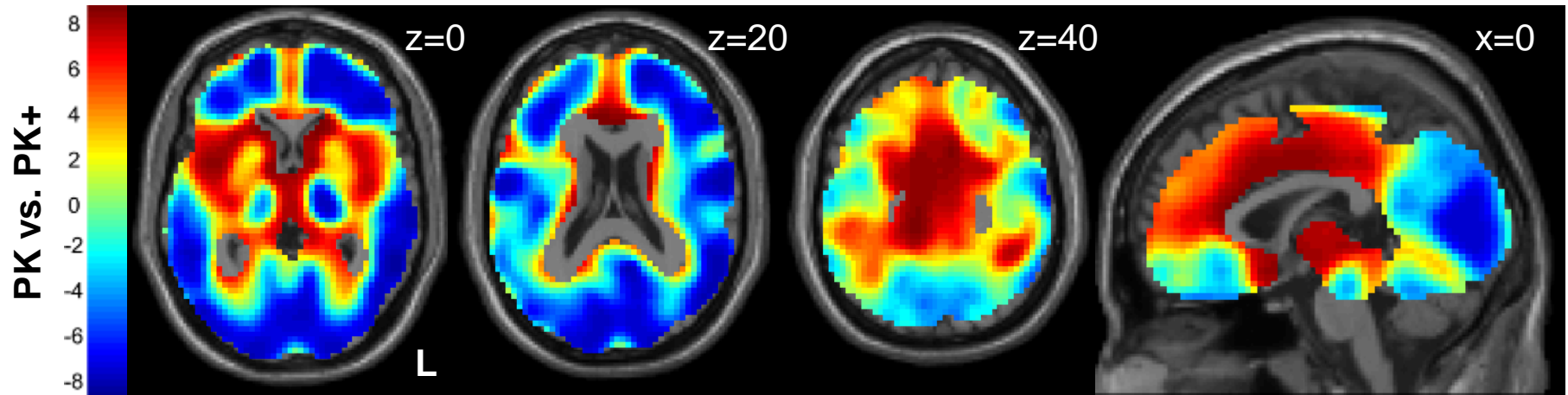
Méthode: reconnaissance de motifs



1. Déterminer les motifs discriminants
2. Tester la validité de ces motifs



Résultats: « motifs » discriminants



Résultats: matrice de confusion

Diagnostic du classificateur (IA)	Diagnostic final lors du suivi	
	PK	PK+
PK	39 (93)	13 (17)
PK+	3 (7)	65 (83)

Comparaison de la méthode d'IA (RVM) avec le diagnostic radiologique

	42 patients PK	78 patients PK+	Total 120 patients
Correct agreement	26 (62%)	63 (81%)	89 (74%)
Incorrect agreement	2 (5%)	1 (1%)	3 (3%)
Correct RVM, incorrect radiological	13 (31%)	2 (3%)	15 (13%)
Correct radiological, incorrect RVM	1 (2%)	12 (15%)	13 (11%)

« Profilage » du patient

Médecine personnalisée

