



L'imagerie *in vivo* pour le développement de nouveaux médicaments du cerveau

Luc ZIMMER

Université Claude Bernard Lyon 1 – Hospices Civils de Lyon

Centre de Recherche en Neurosciences de Lyon (CNRS UMR5292 - INSERM U1028)

CERMEP-Imagerie du Vivant



Hospices Civils de Lyon
Université Claude Bernard Lyon 1
INSERM
CNRS
CHU de Saint-Etienne
Université Grenoble Alpes

Cyclotron



Radiochemistry-Pharmacy



PET-CT Scanner



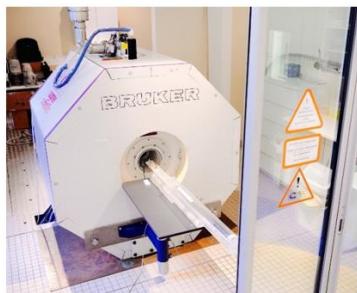
PET-MRI Scanner



Micro-PET Scanner



Micro-MRI Scanner



3T-MRI Scanner



1.5T-MRI Scanner



SCT Scanner



MEG Scanner





Le poids social et économique des pathologies psychiatriques en Europe

Disease category	DALYs lost (1000s)	% of total DALYs lost
Neuropsychiatric disorders	13,732	26.5
Depression	4117	8.0
Alzheimer and other dementias	1989	3.8
Cardiovascular disease	8838	17.1
Cancer	8549	16.5
Others	20,606	39.8
Total	51,725	100.0

DALYs
“Disability-Adjusted Life Years”
= années d’invalidité



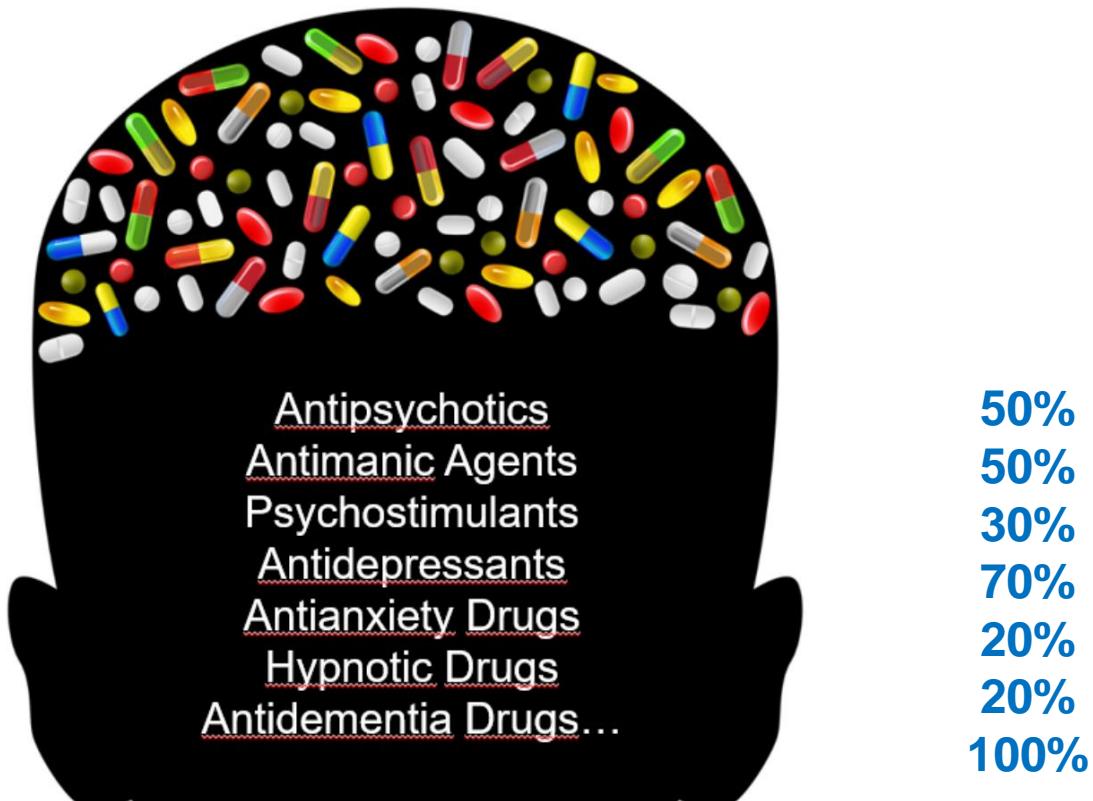
Psychotropic drugs

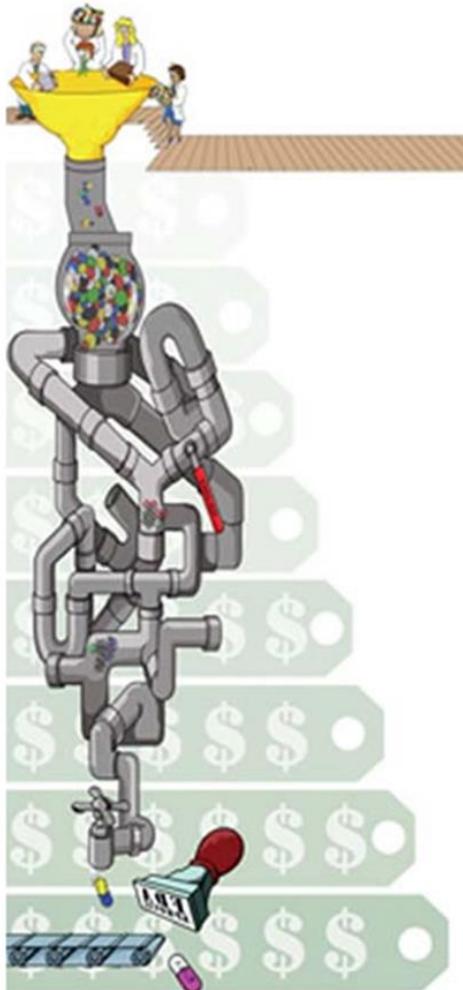
“Any drug capable of affecting the mind, emotions, and behavior”





Psychotropic drug **non-responders**





The Failure of Target-Oriented Drug Discovery

The crisis in CNS investment

CNS drug research: A dilemma
for big pharma companies

2010-2011

GlaxoSmithKline, AstraZeneca, Novartis,
MSD, Sanofi stop or limit their investments
in research in psychiatry



Using imaging biomarkers to accelerate drug development and clinical trials

Go/no go decisions

have to be earlier and with more certainty

- **Target engagement**
- **Drug exposure**
- **Pharmacological activity**



L'imagerie TEP

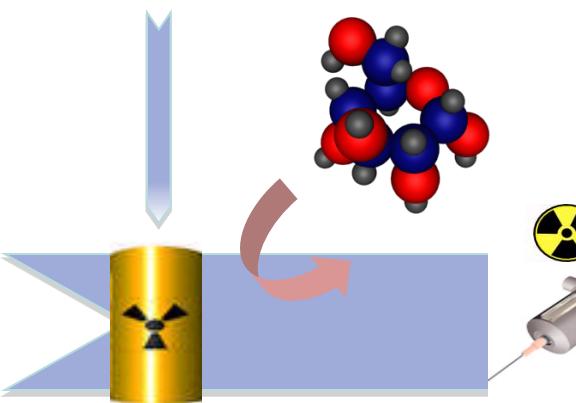
Radiochimie



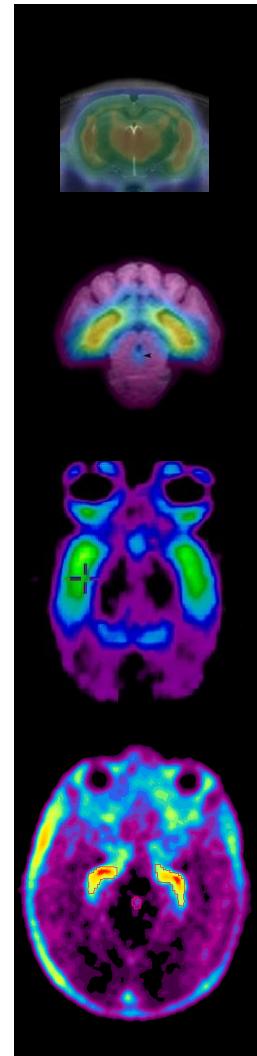
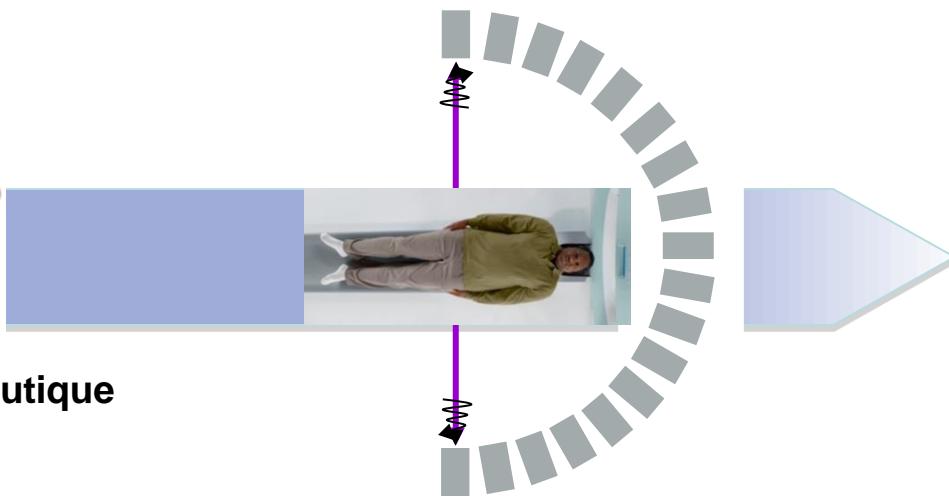
Radiopharmacie



Médecine nucléaire

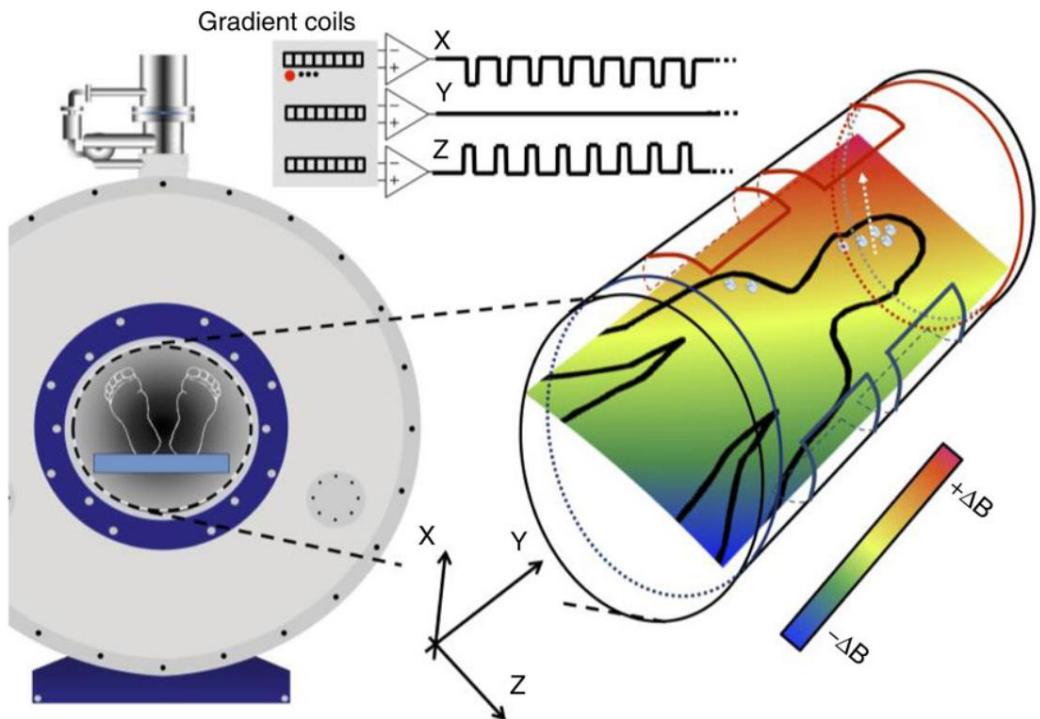


Radiopharmaceutique

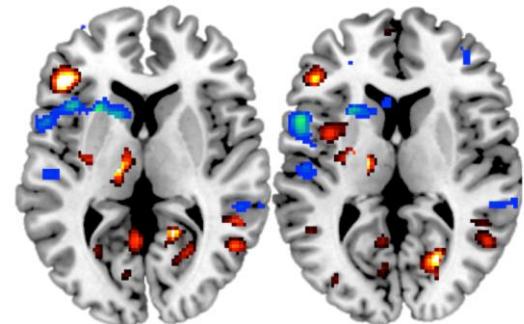




L'imagerie IRM



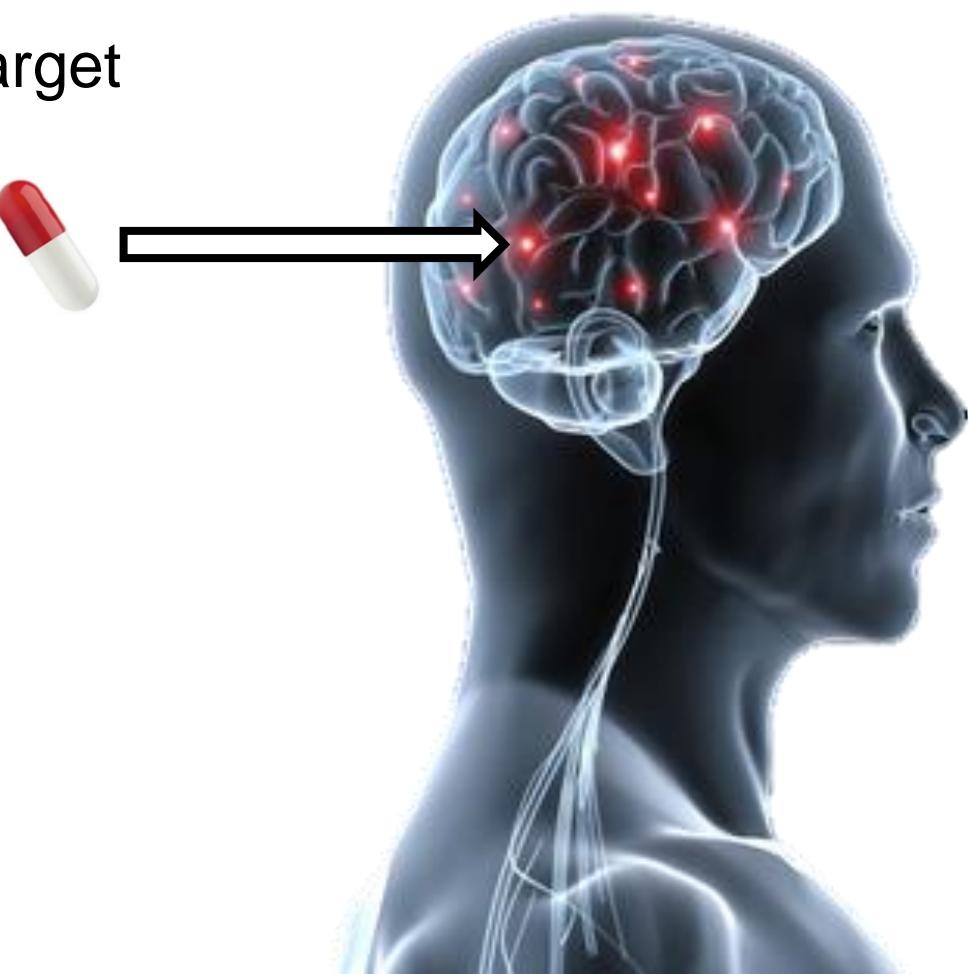
Imagerie anatomique
Imagerie fonctionnelle





1. Target engagement

Drug binding to the right target





Principle:

Each patient (or animal) is its own control (before/after treatment)

→ Comparison of PET brain scans, before/after treatment

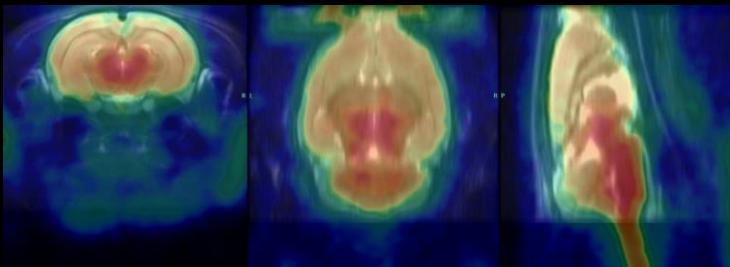
→ Percentage of receptor occupancy



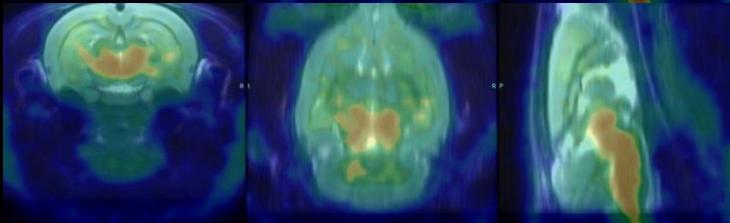


Target engagement of NLX-112 a novel treatment of L-DOPA-induced dyskinesia

[¹⁸F]-F13640 Control



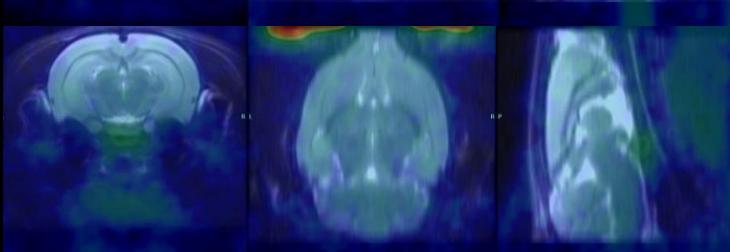
NLX-112 0.04 mg/kg



NLX-112 0.16 mg/kg

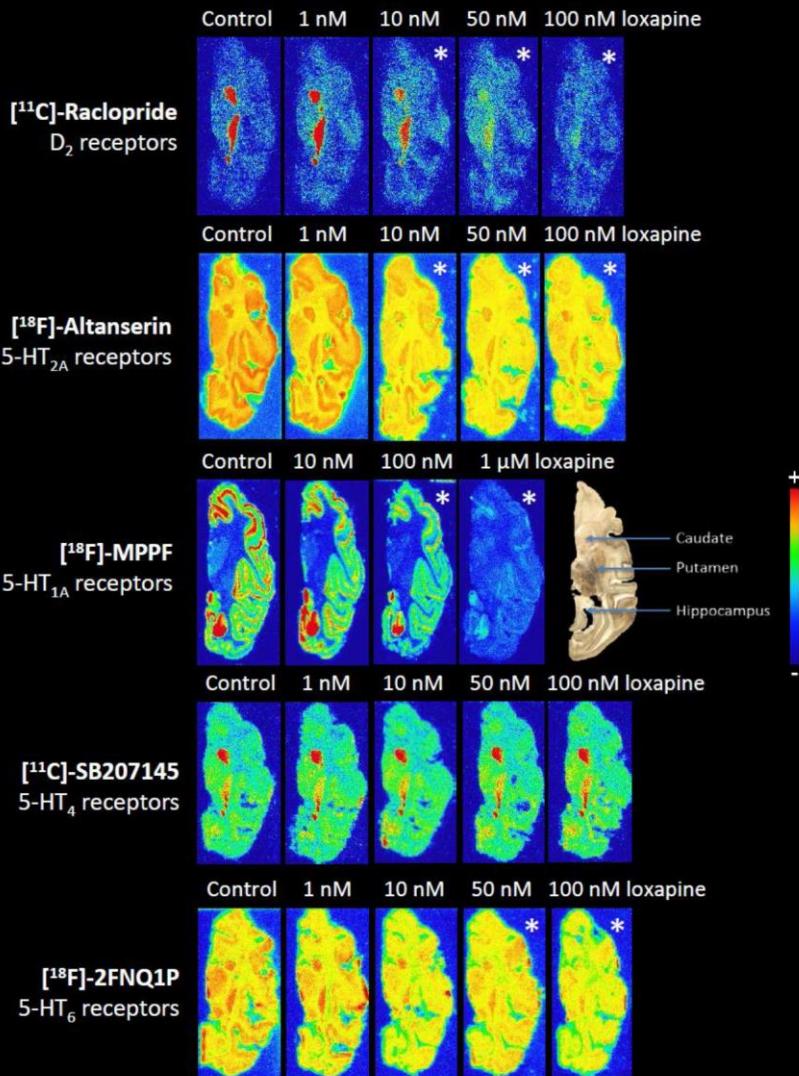


NLX-112 0.63 mg/kg





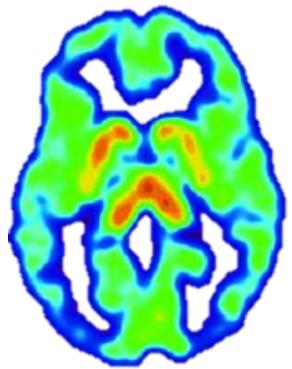
In vitro occupancy of loxapine on primate brain receptors



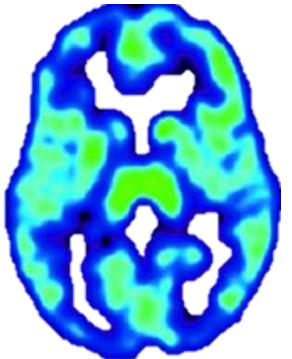


Example of antidepressants

PET imaging of serotonin transporter vs citalopram

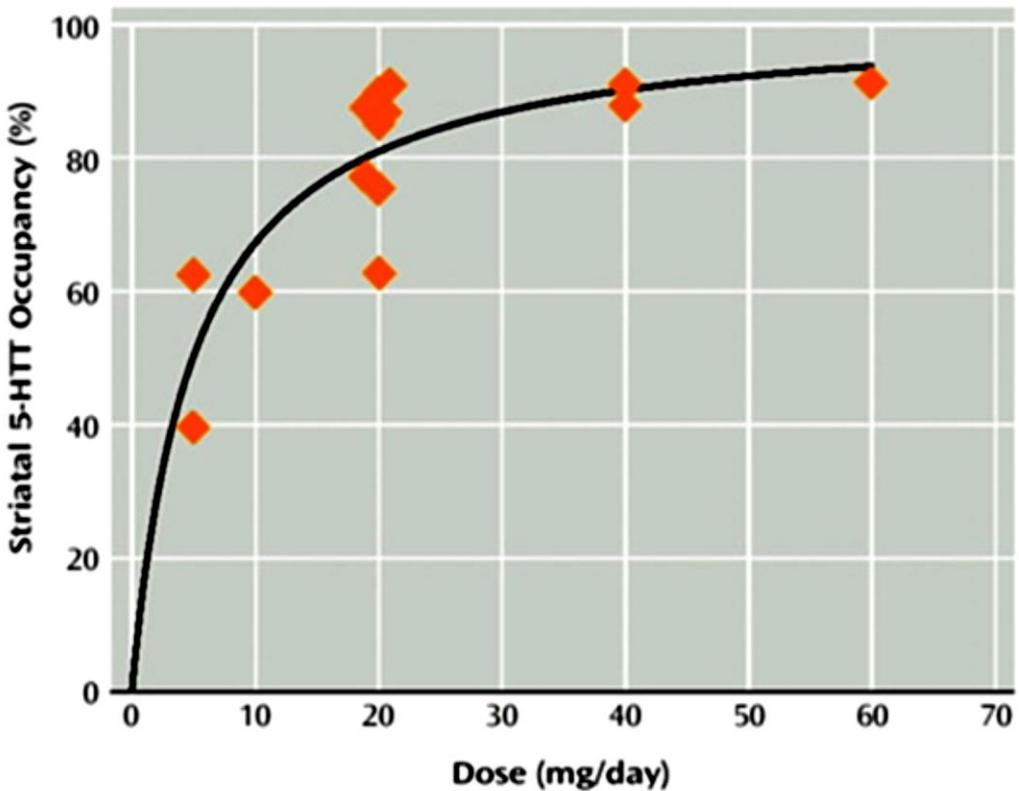


[¹¹C]-DASB before treatment



[¹¹C]-DASB after treatment

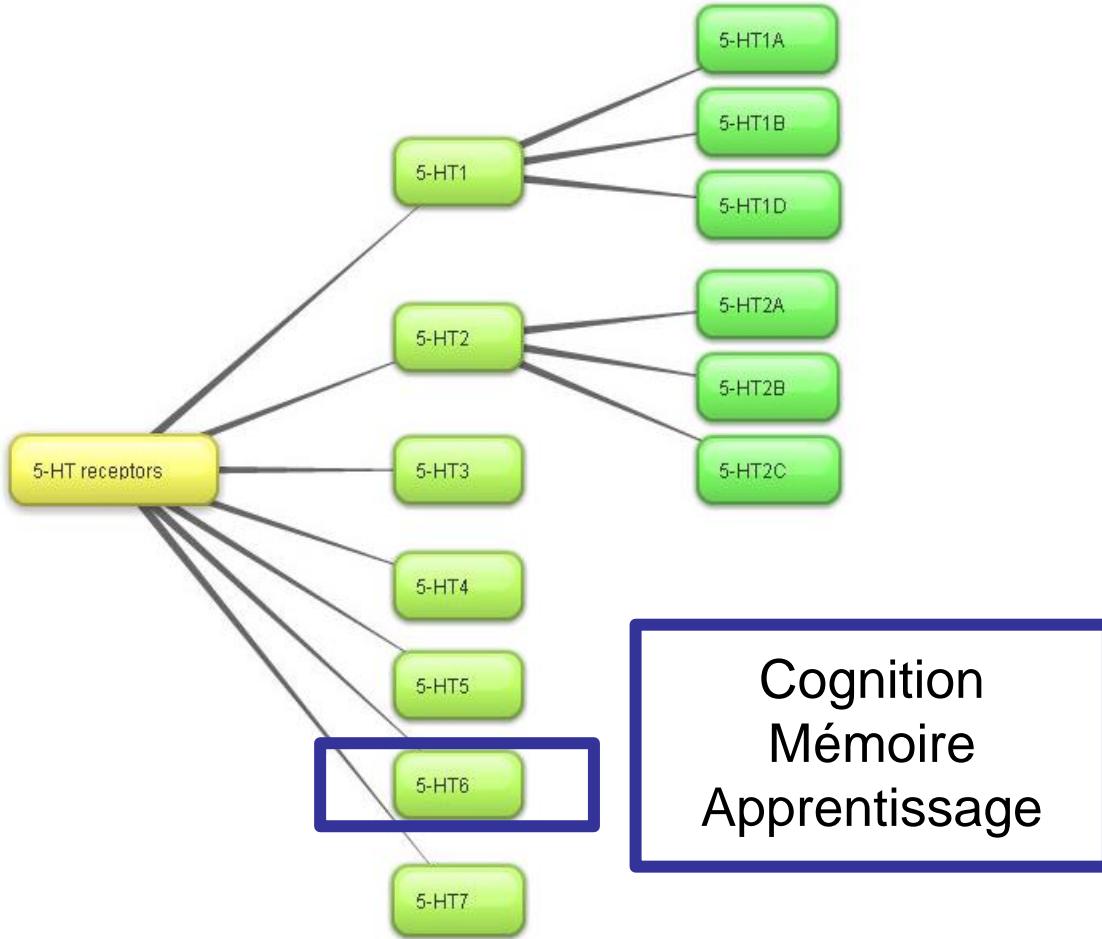
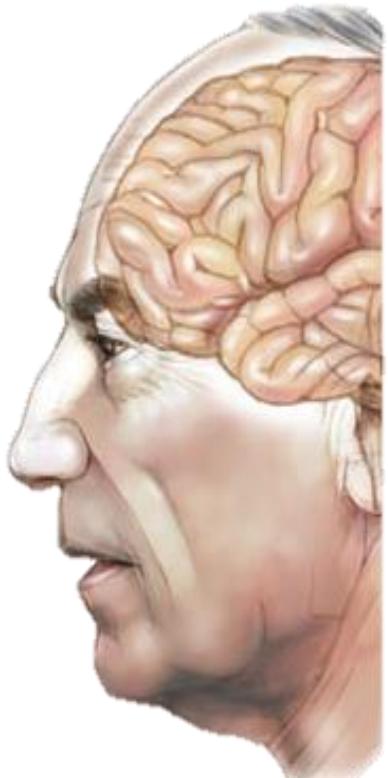
citalopram 20 mg/d, 4 weeks



Meyer et al, Am J Psychiatry 2011

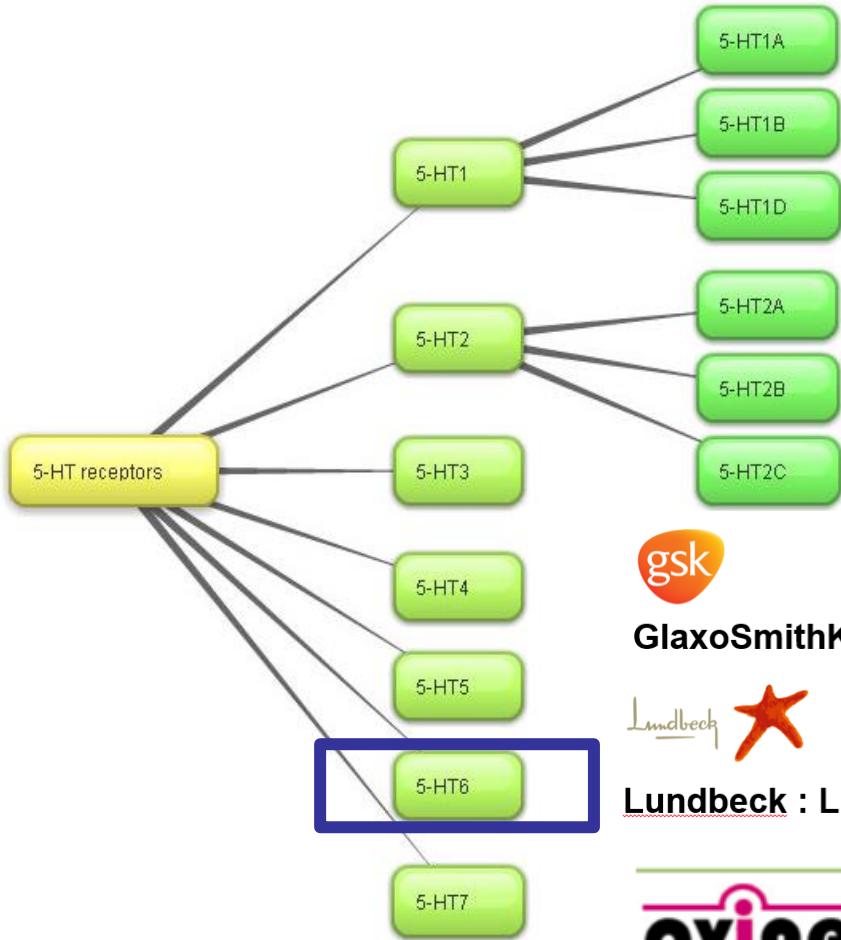
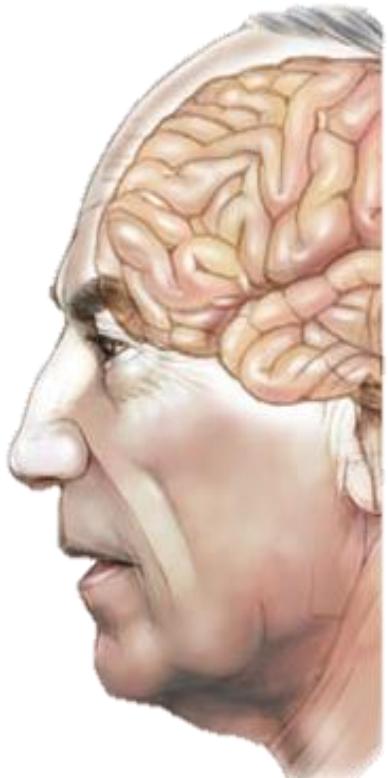


Les cibles sérotoninergiques dans la maladie d'Alzheimer





Les cibles sérotoninergiques dans la maladie d'Alzheimer



GlaxoSmithKline : SB-742457



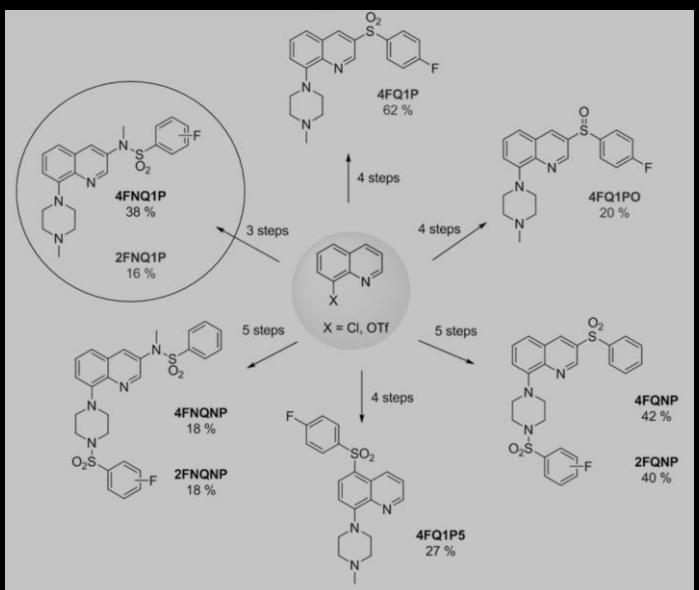
Lundbeck : Lu AE58054 (idalopirdine)



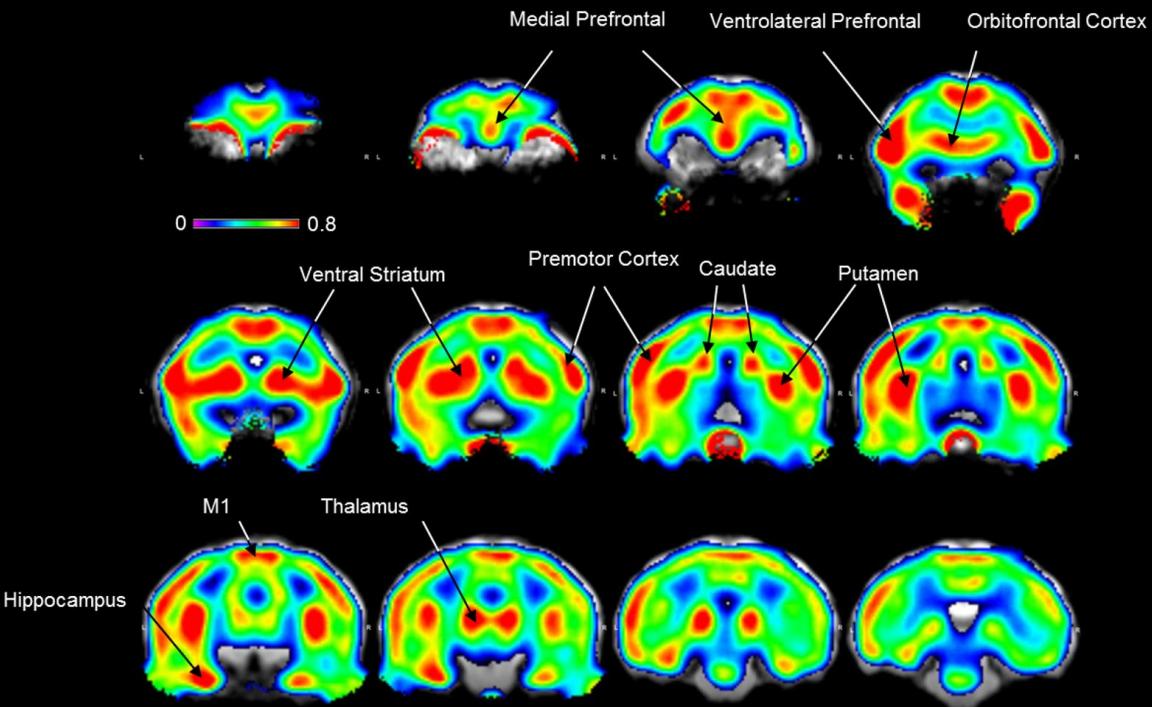


Vers un radiotraceur TEP des récepteurs 5-HT₆

Radiochimie → primate → vers « first-in-man »



T. Billard, ICBMS

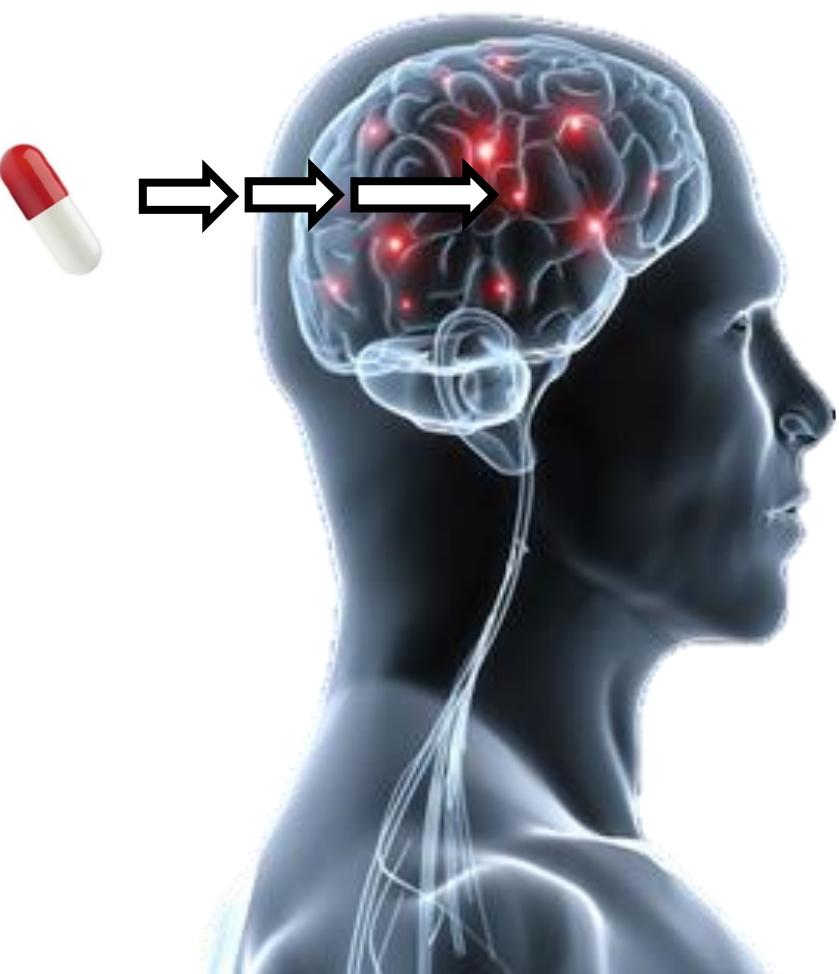




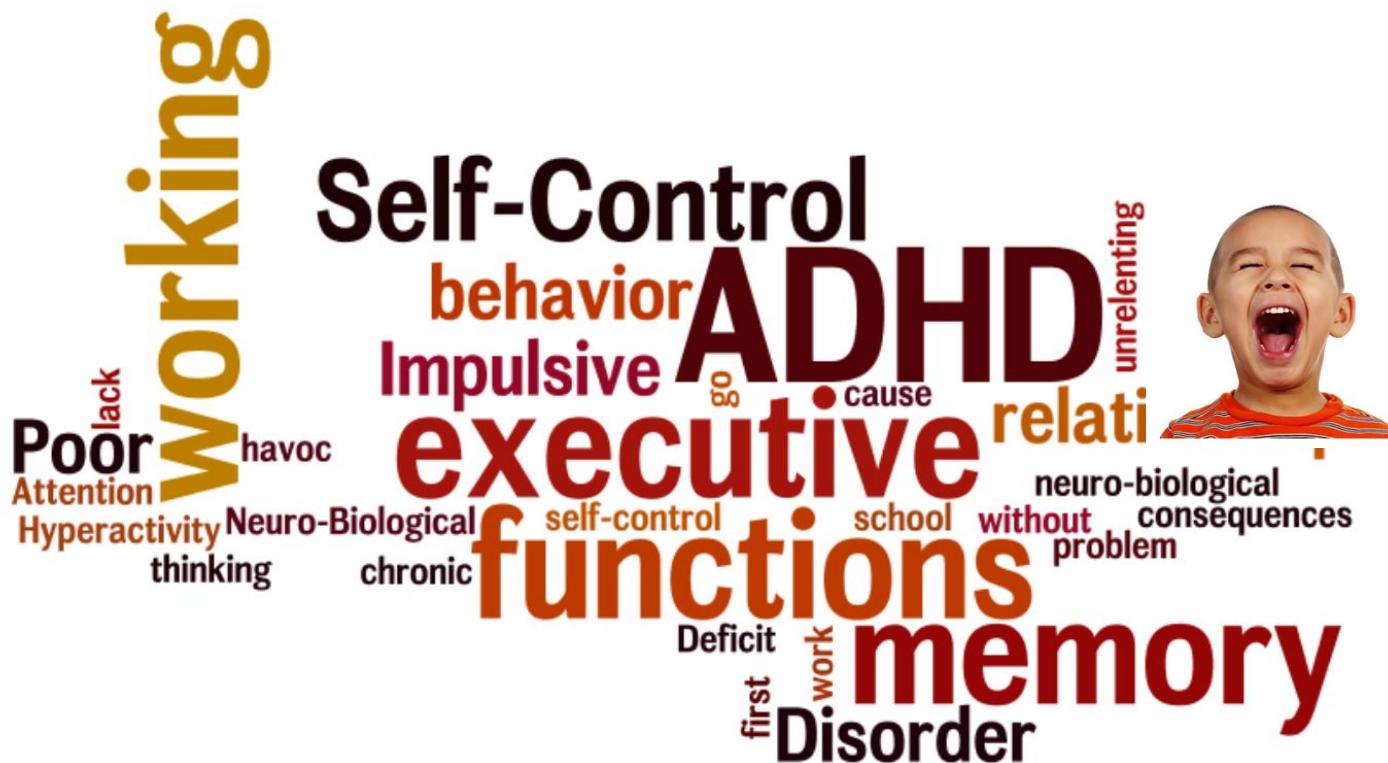
1. Target engagement

2. Drug exposure

At the target site of action
for the desired length of time



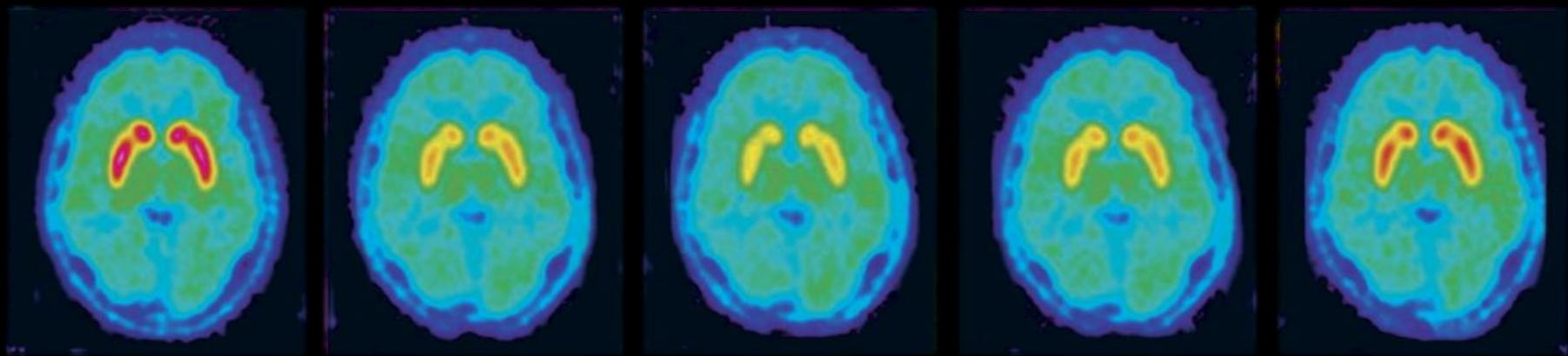
Attention deficit hyperactivity disorder (ADHD)



Pharmacological treatment (in France) : **methylphenidate** (Ritaline, Quasym, Concerta...)



In vivo occupancy of dopamine transporter
after immediate release methylphenidate administration



Before

+ 1h

+ 2h

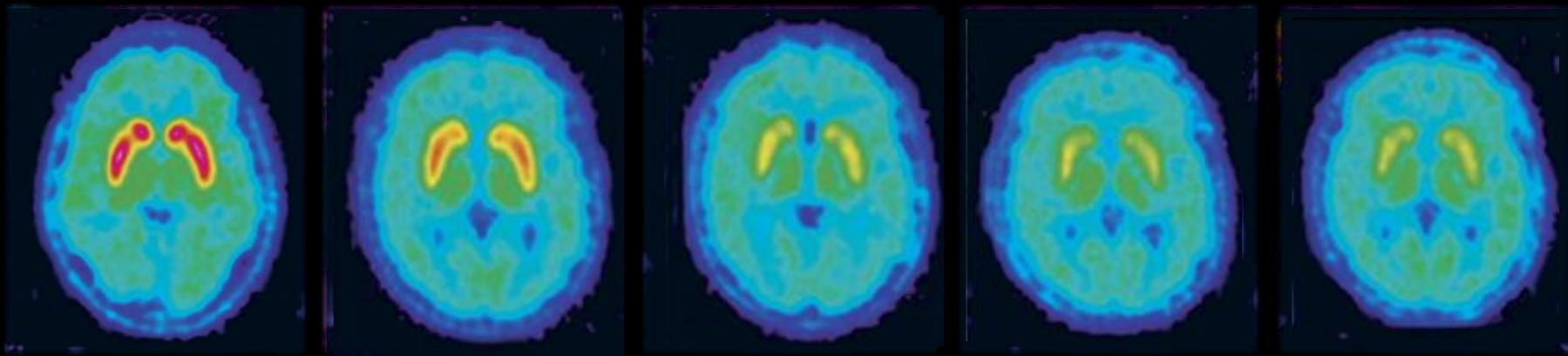
+ 3h

+ 4h

[¹¹C]altropane (DA transporter PET radioligand)



In vivo occupancy of dopamine transporter
after prolonged release methylphenidate administration



Before

+ 1h

+ 3h

+ 5h

+ 7h

[¹¹C]altropane (DA transporter PET radioligand)

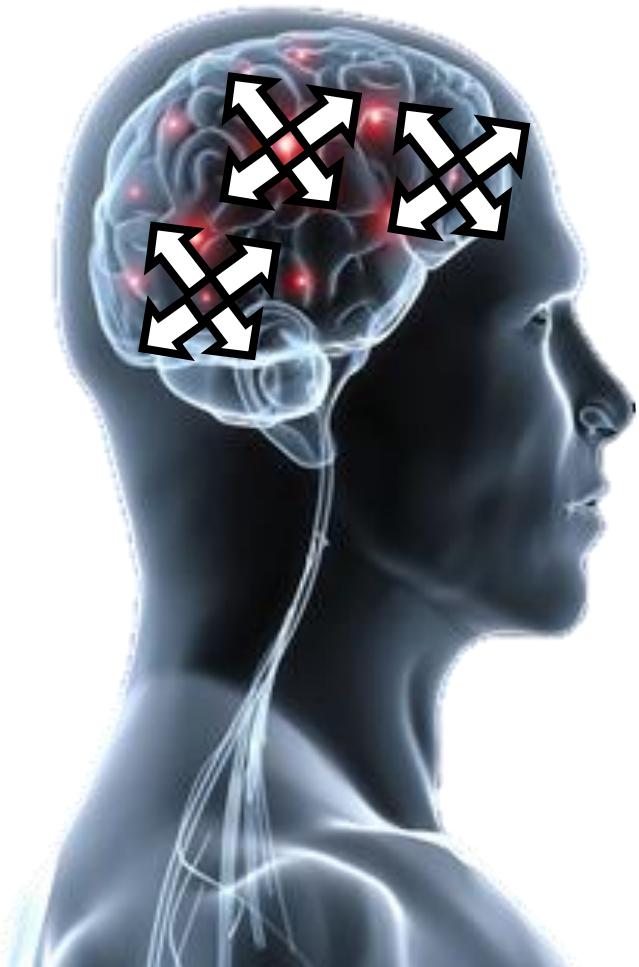


1. Target engagement

2. Drug exposure

3. Pharmacological activity

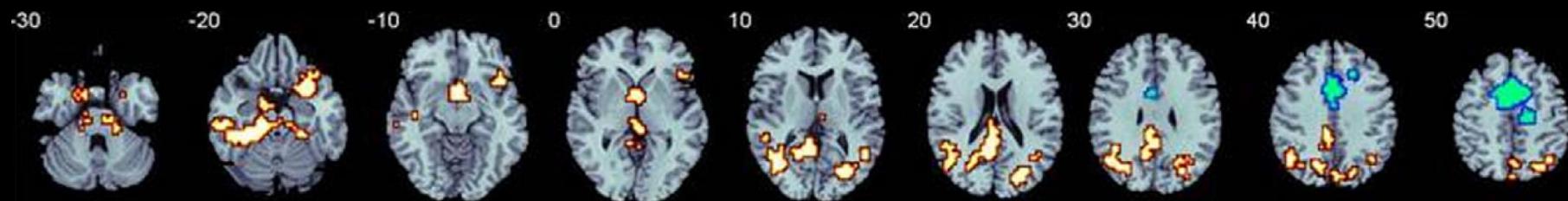
Proportional to the demonstrated target exposure and target binding



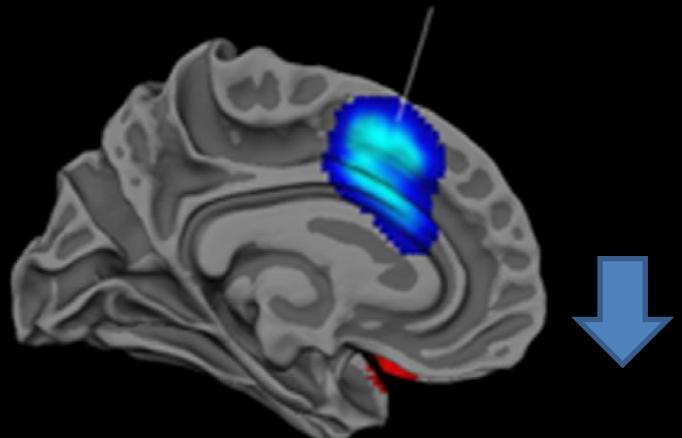


Pharmaco-MRI

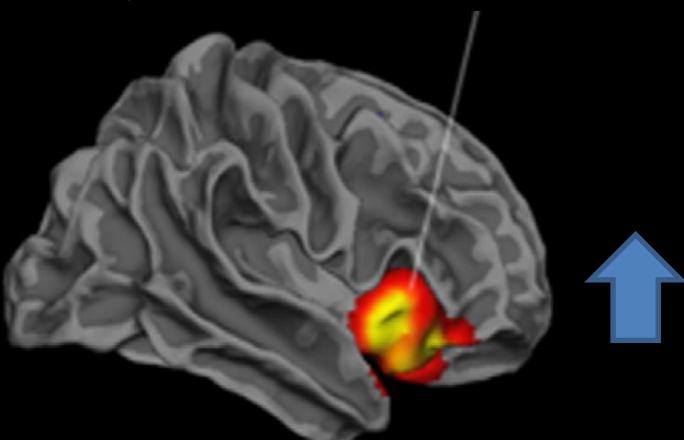
Pattern d'activation cérébrale du méthylphénidate



Cortex cingulaire antérieur
Aire motrice supplémentaire



Gyrus frontal inférieur droit

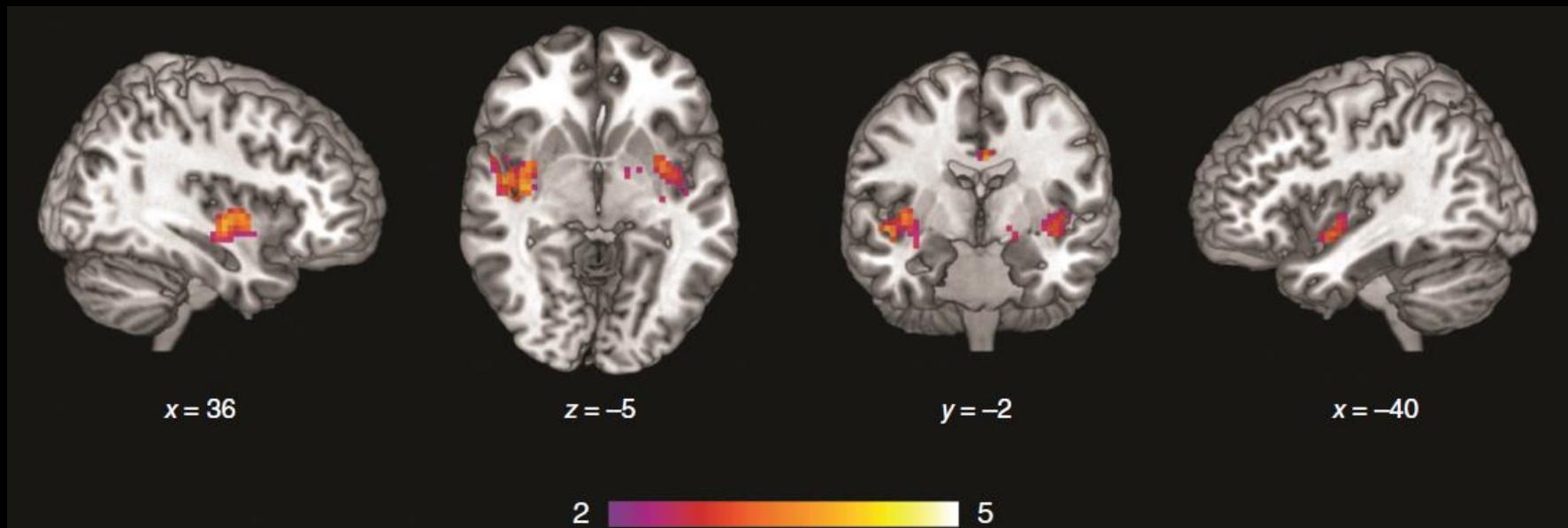


Rubia et al, Biol Psychiatry 2014



Pharmaco-MRI

Une différence de connectivité entre les répondeurs et les non-répondeurs ?

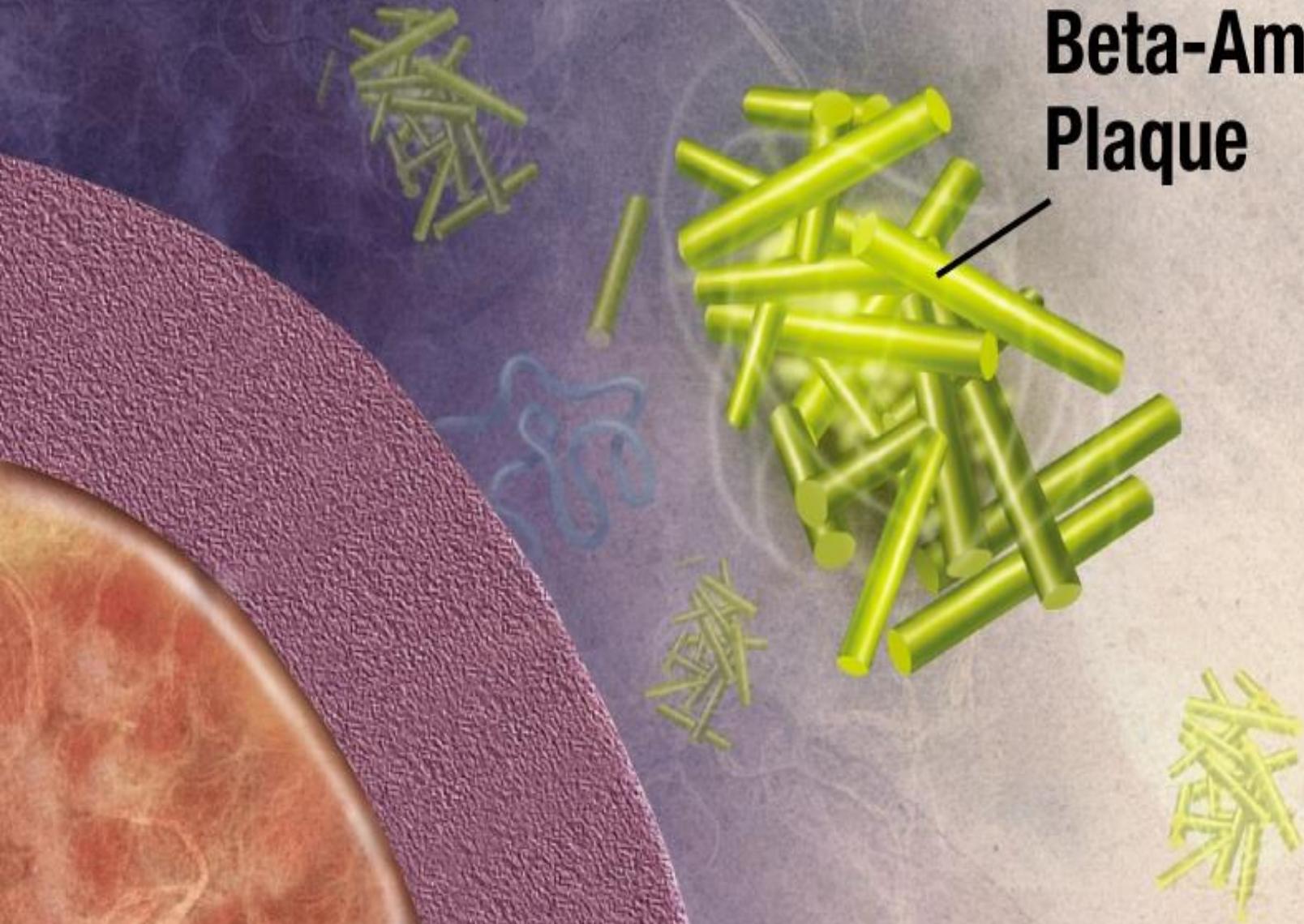


Hong et al, J Psychiatry Neurosci 2015



Alzheimer's Disease Pathophysiology

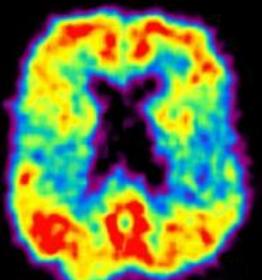
**Beta-Amyloid
Plaque**



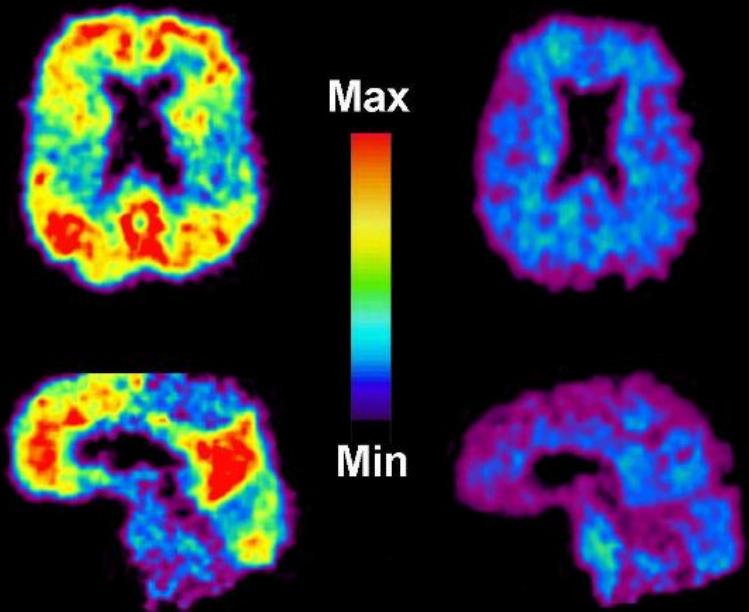


La visualisation des plaques amyloïdes

Alzheimer



Control



PiB PET SCANS



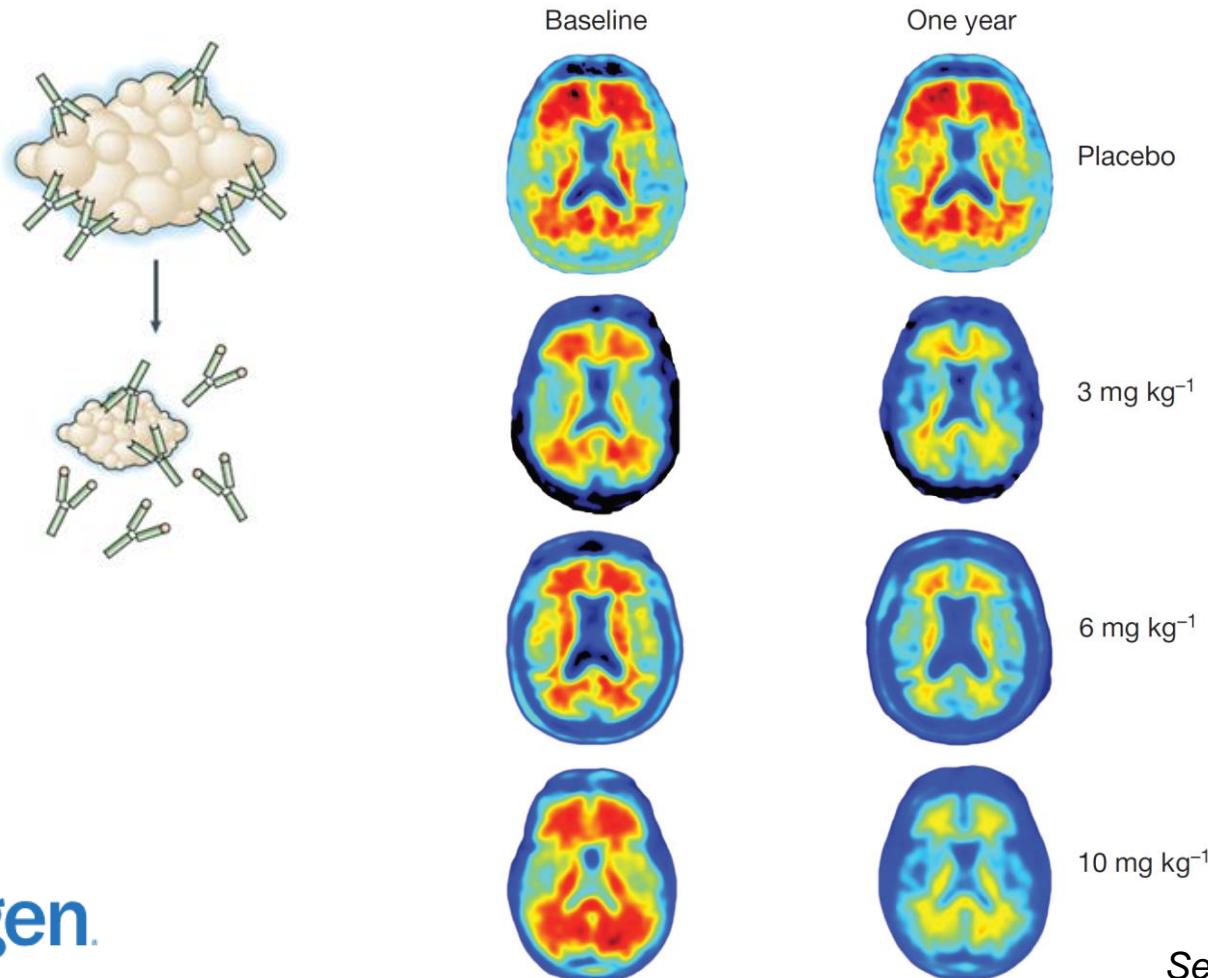
University of Pittsburgh
PET Amyloid Imaging Group



Failed clinical amyloid-targeting drug trials in Alzheimer's disease

Drug	Company	Development phase	Status
Alzhemed	Bellus Health	3	Failed
Avagacestat	Bristol-Myers Squibb	2	Failed
AN1792	Elan/Johnson & Johnson	2	Failed
Bapineuzumab	Elan/Johnson & Johnson	3	Stopped
ACC-001	Elan/Johnson & Johnson	2	Stopped
Avandia	GlaxoSmithKline	3	Failed
ELND005	Johnson & Johnson	3	Stopped
Semagacestat	Eli Lilly	3	Failed
m266	Eli Lilly	2	Stopped
Solanezumab	Eli Lilly	3	Failed
Dimebon	Medivation	3	Failed
Tarenfluril	Myriad Genetics	3	Failed
Tramiprosate	Neurochem	3	Failed
Huperzine	Neuro-Hitech	3	Failed
Lipitor	Pfizer	3	Failed
PBT2	Prana Biotechnology	2	Failed

Binding du [¹⁸F]florbetapir montrant la baisse de β-amyloïdes chez des patients MCI sous aducanumab (avec ralentissement du déclin cognitif !....)





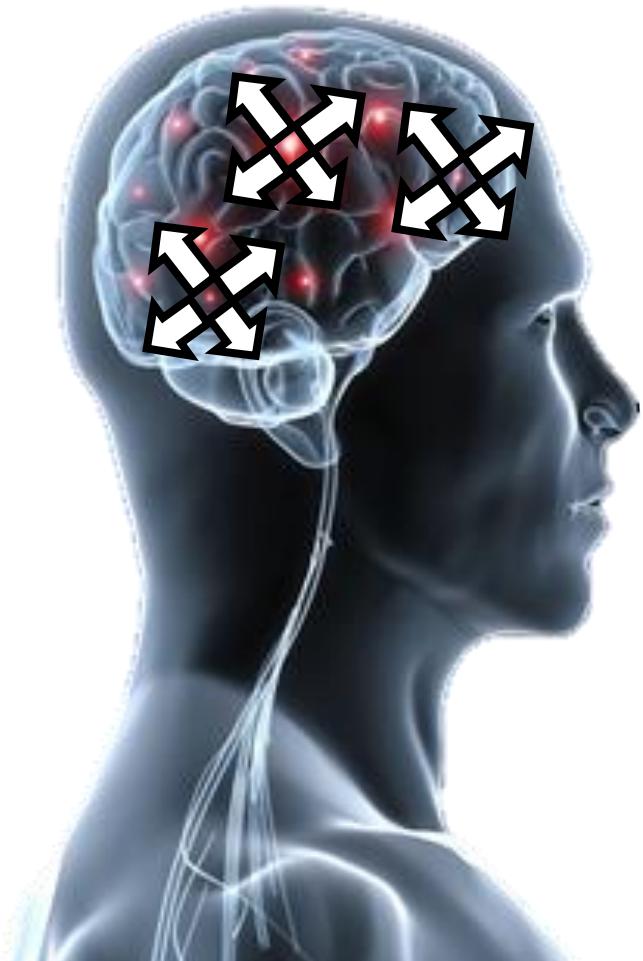
1. Target engagement

2. Drug exposure

3. Pharmacological activity

4. New pharmacological concepts

Biased agonists





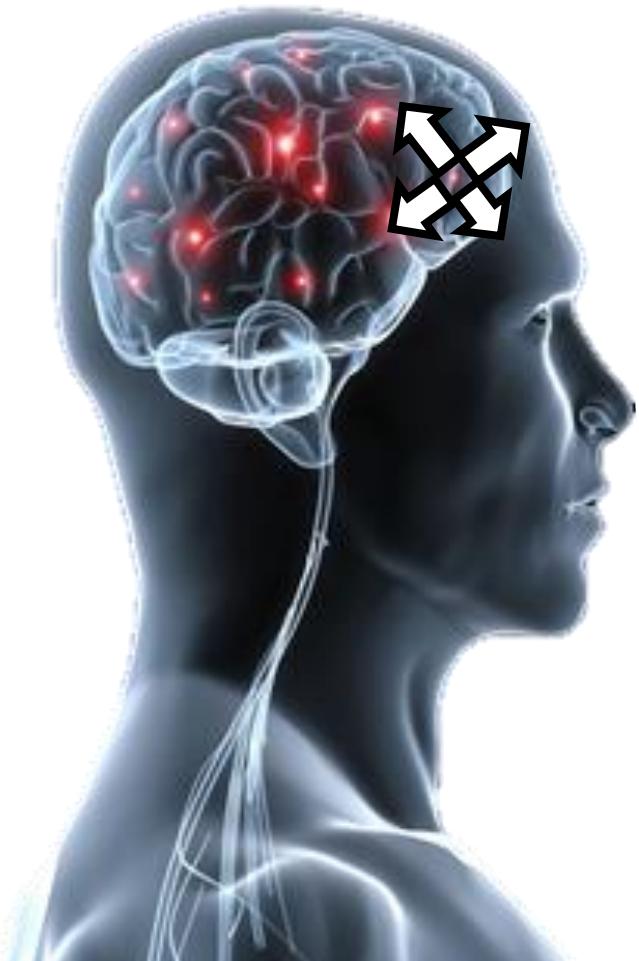
1. Target engagement

2. Drug exposure

3. Pharmacological activity

4. New pharmacological concepts

Biased agonists





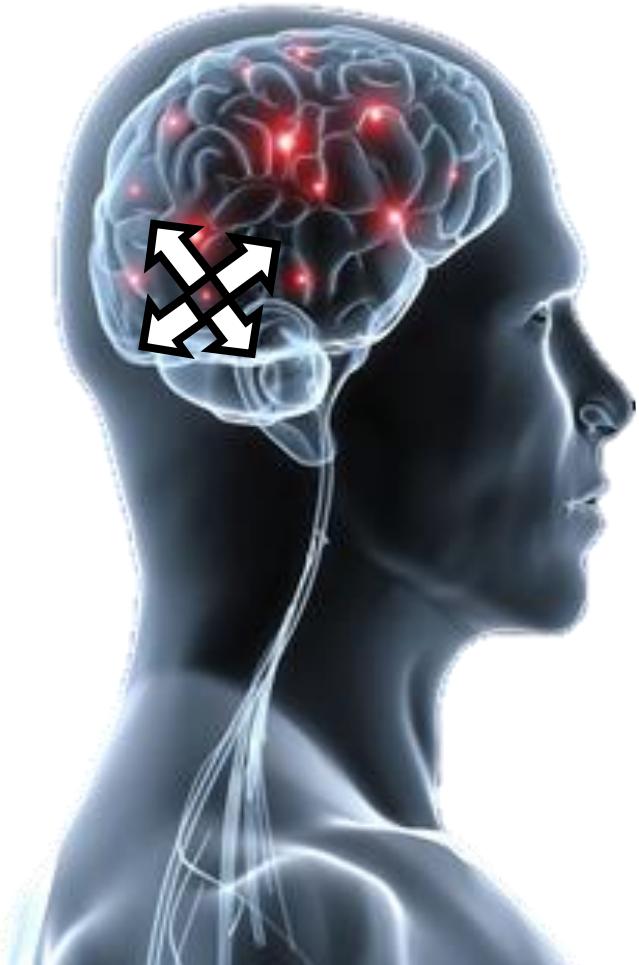
1. Target engagement

2. Drug exposure

3. Pharmacological activity

4. New pharmacological concepts

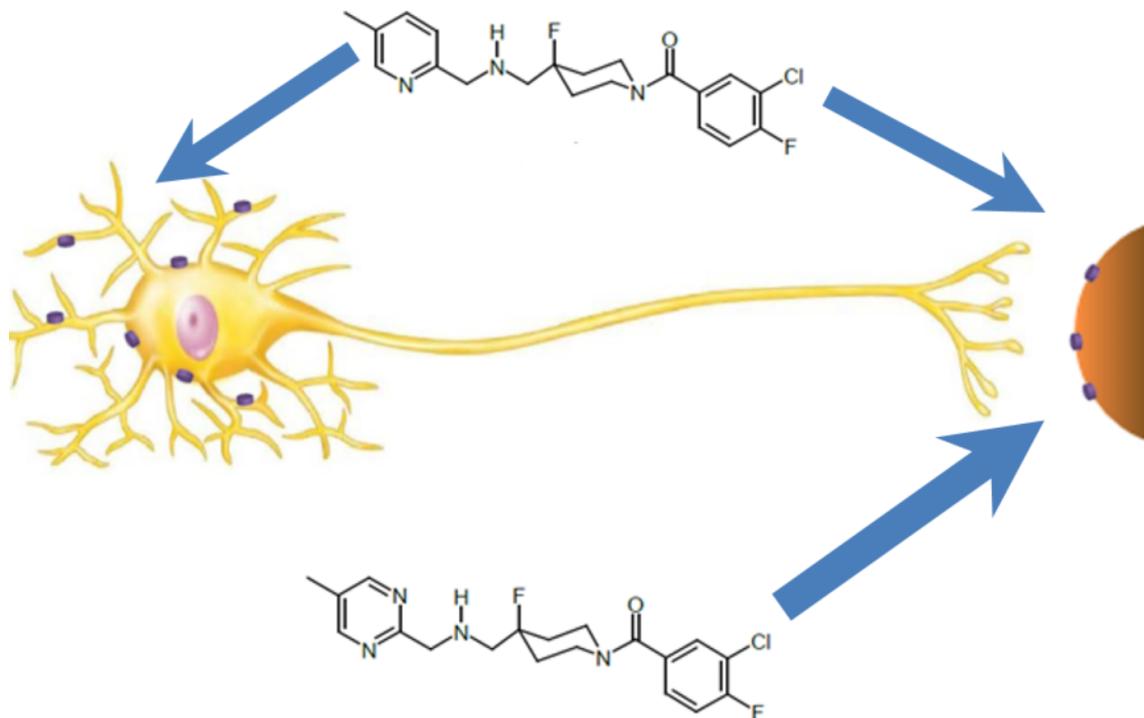
Biased agonists





5-HT_{1A} receptor biased agonists

F13640



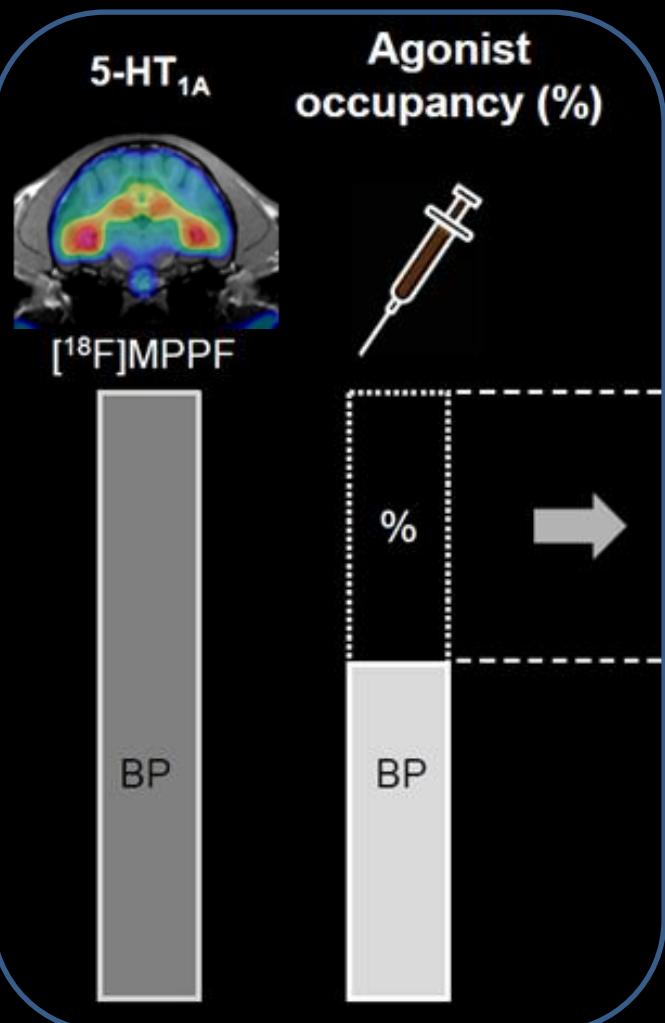
F15599



Benjamin Vidal

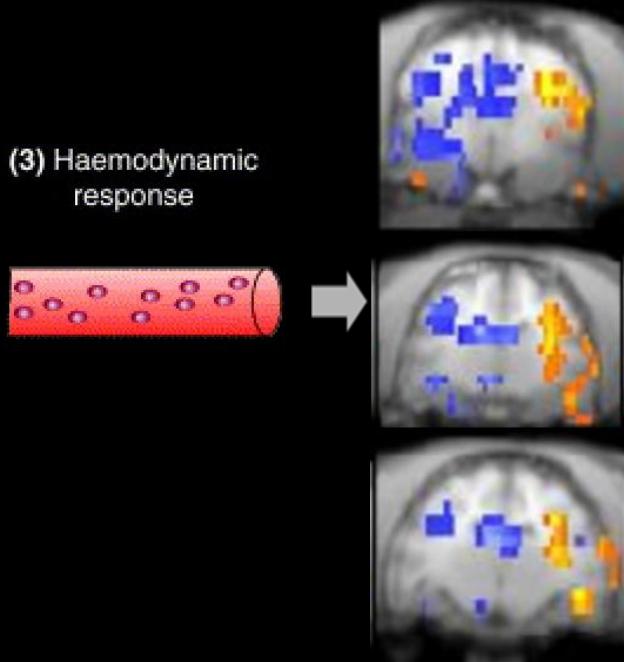


PET



fMRI

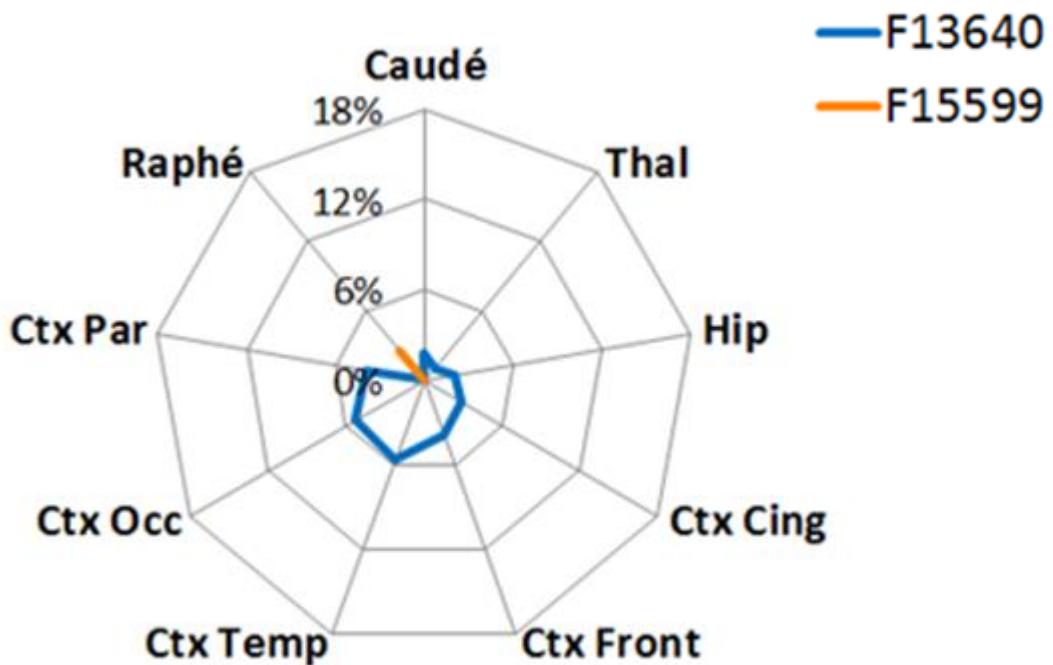
BOLD activation patterns





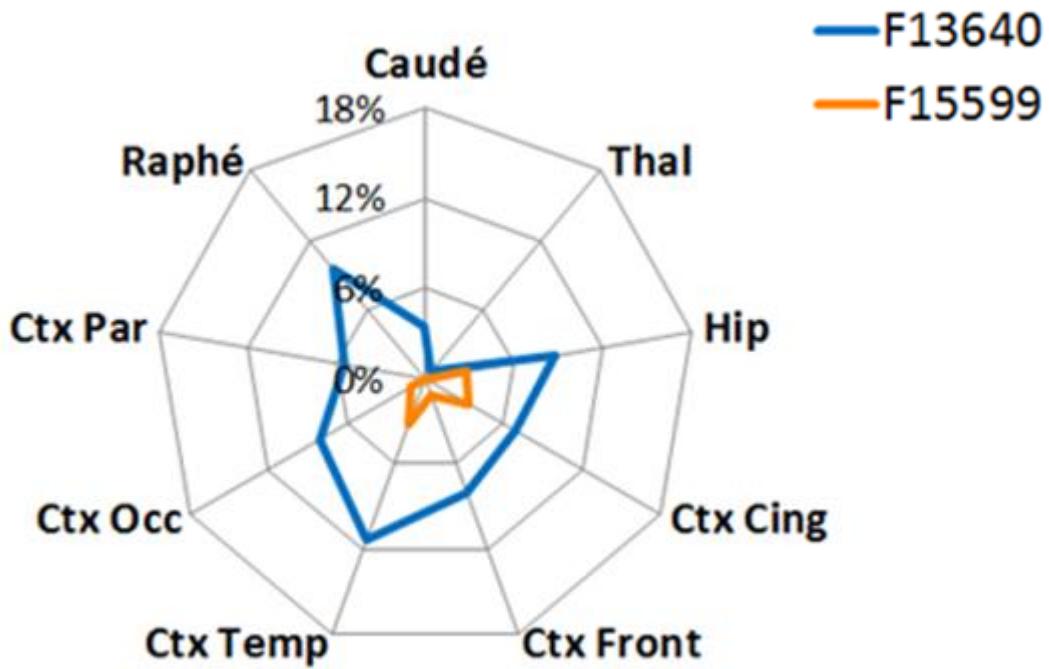
Occupation des récepteurs 5-HT_{1A} (TEP)

0,04 mg/kg



Occupation des récepteurs 5-HT_{1A} (TEP)

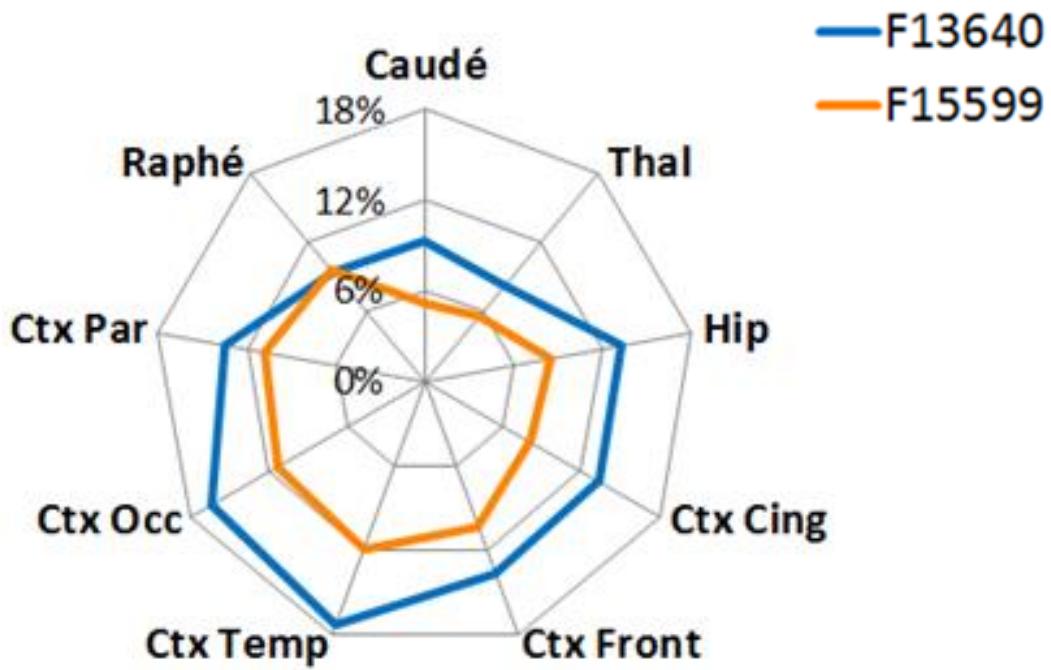
0,08 mg/kg





Occupation des récepteurs 5-HT_{1A} (TEP)

0,16 mg/kg

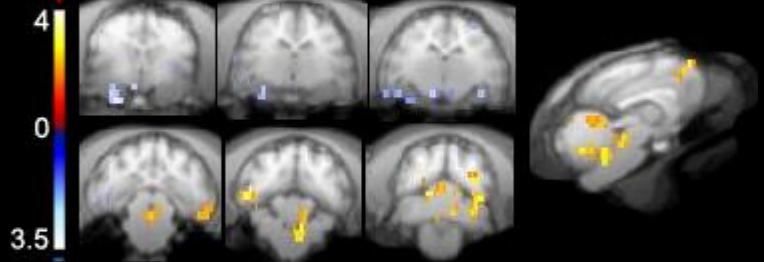
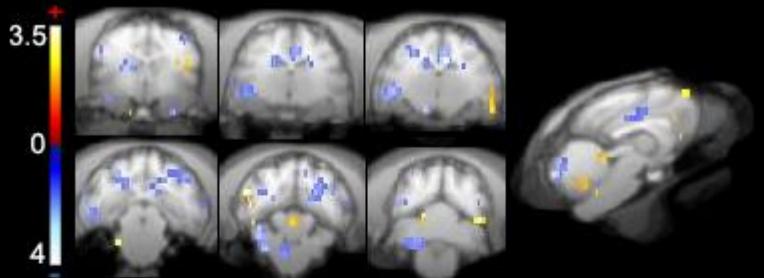




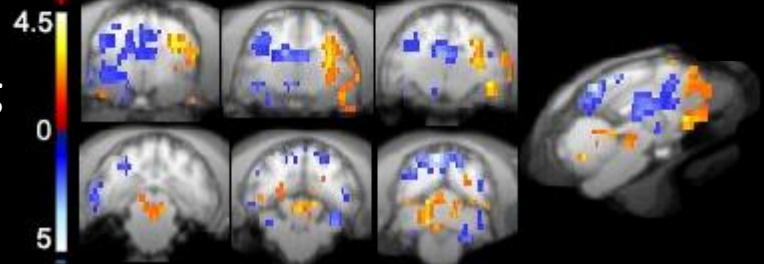
Activation cérébrale (IRMf, BOLD)

F13640

0,04 mg/kg



0,16 mg/kg

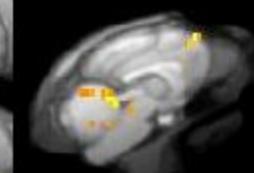
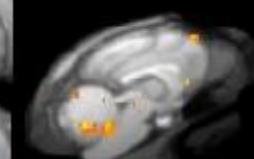
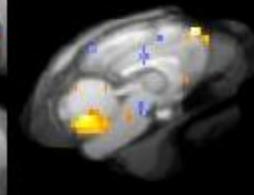


F15599

4
0
4

4
0
5

4
0
3



p<0,05

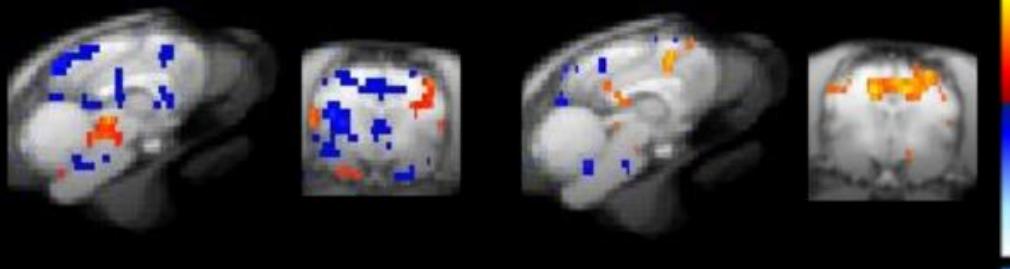


Carte de corrélation TEP/IRMf

F13640

F15599

p<0,05



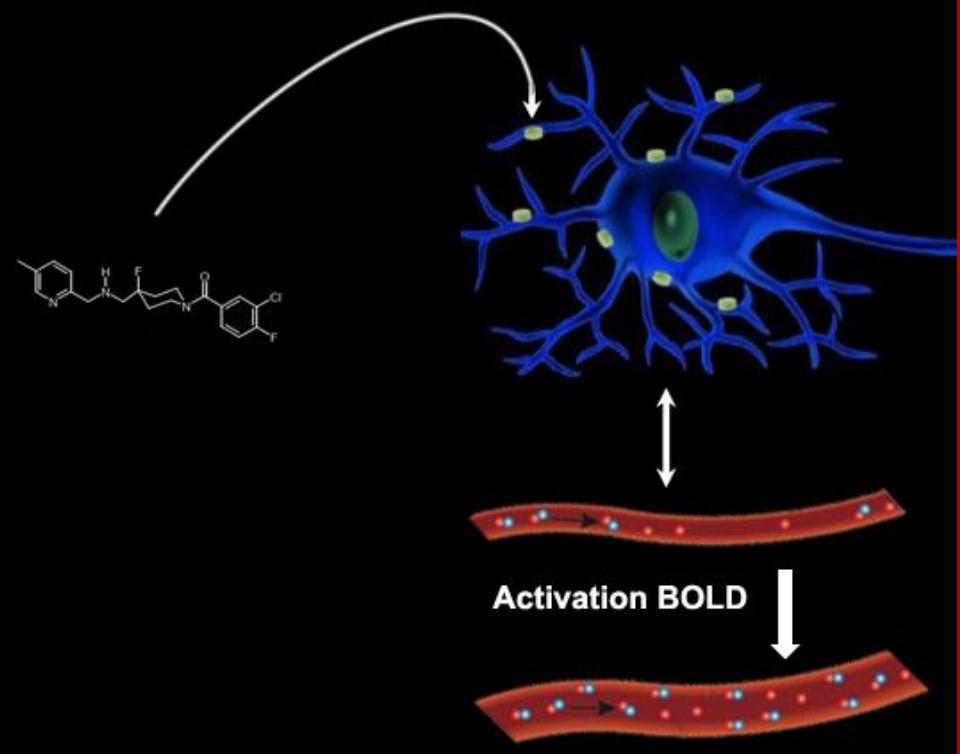
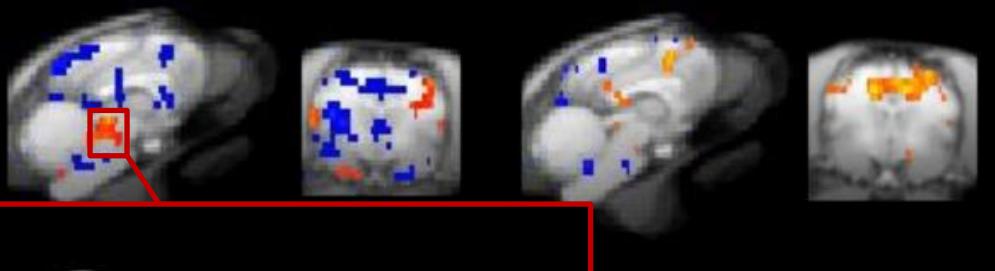


Carte de corrélation TEP/IRMf

F13640

F15599

p<0,05



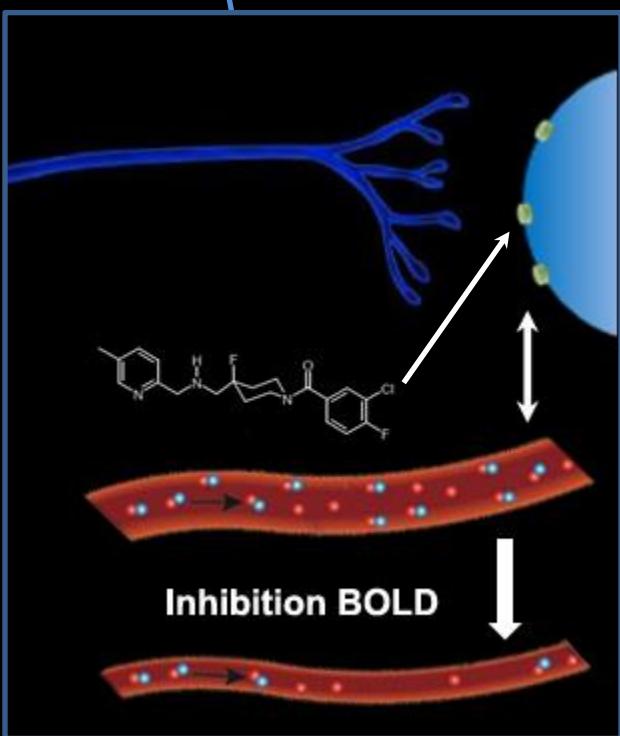
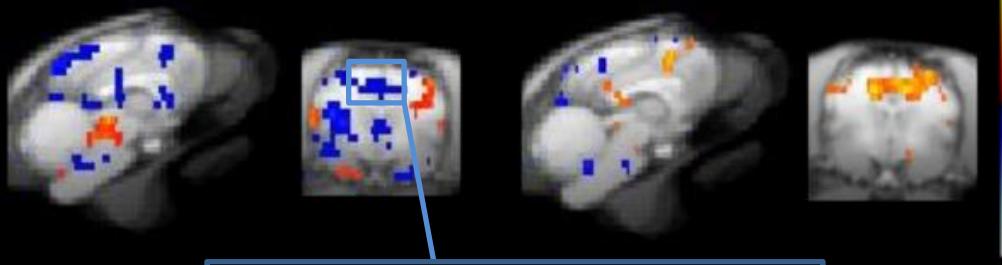


Carte de corrélation TEP/IRMf

F13640

F15599

p<0,05



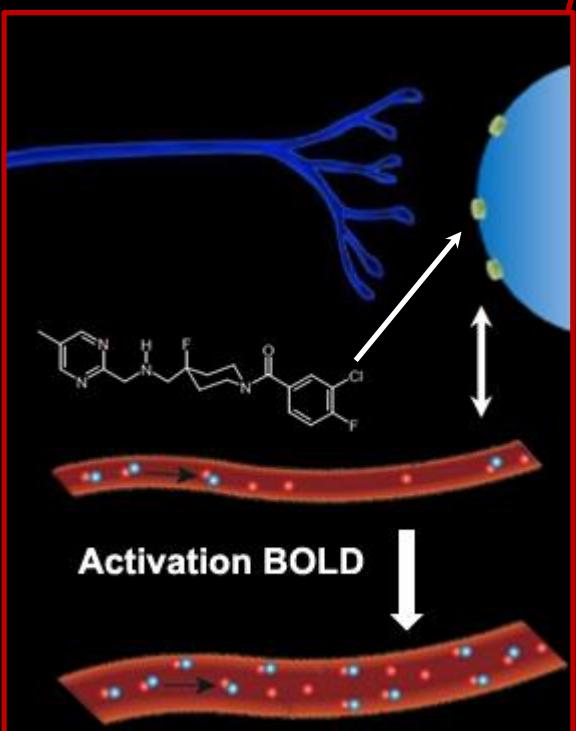
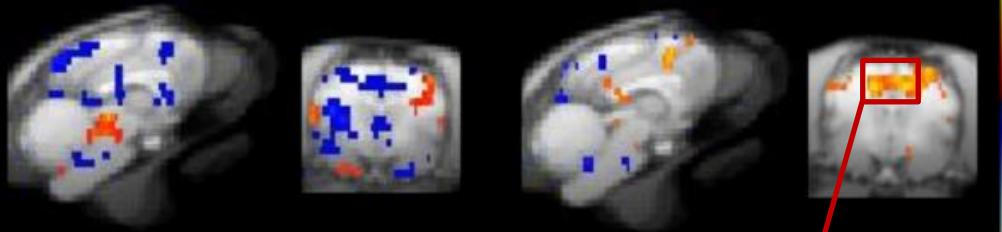


Carte de corrélation TEP/IRMf

F13640

F15599

p<0,05





Conclusions

L'imagerie *in vivo* pour le développement de nouveaux médicaments du cerveau

- lien direct (et rapide) entre la préclinique et la clinique
- quantification de cibles de médicaments
- biomarqueur de l'efficacité d'un médicament
- preuves de concept pharmacologiques