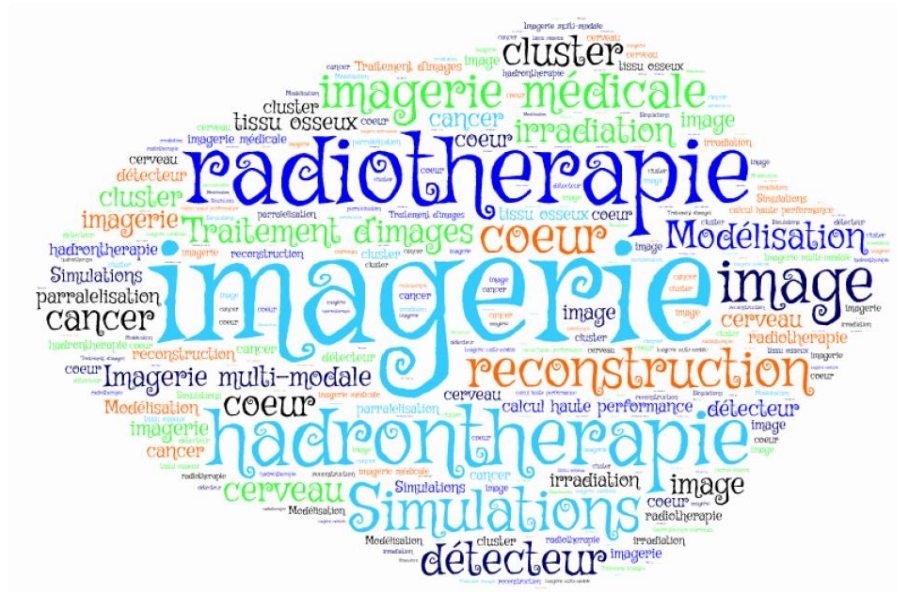
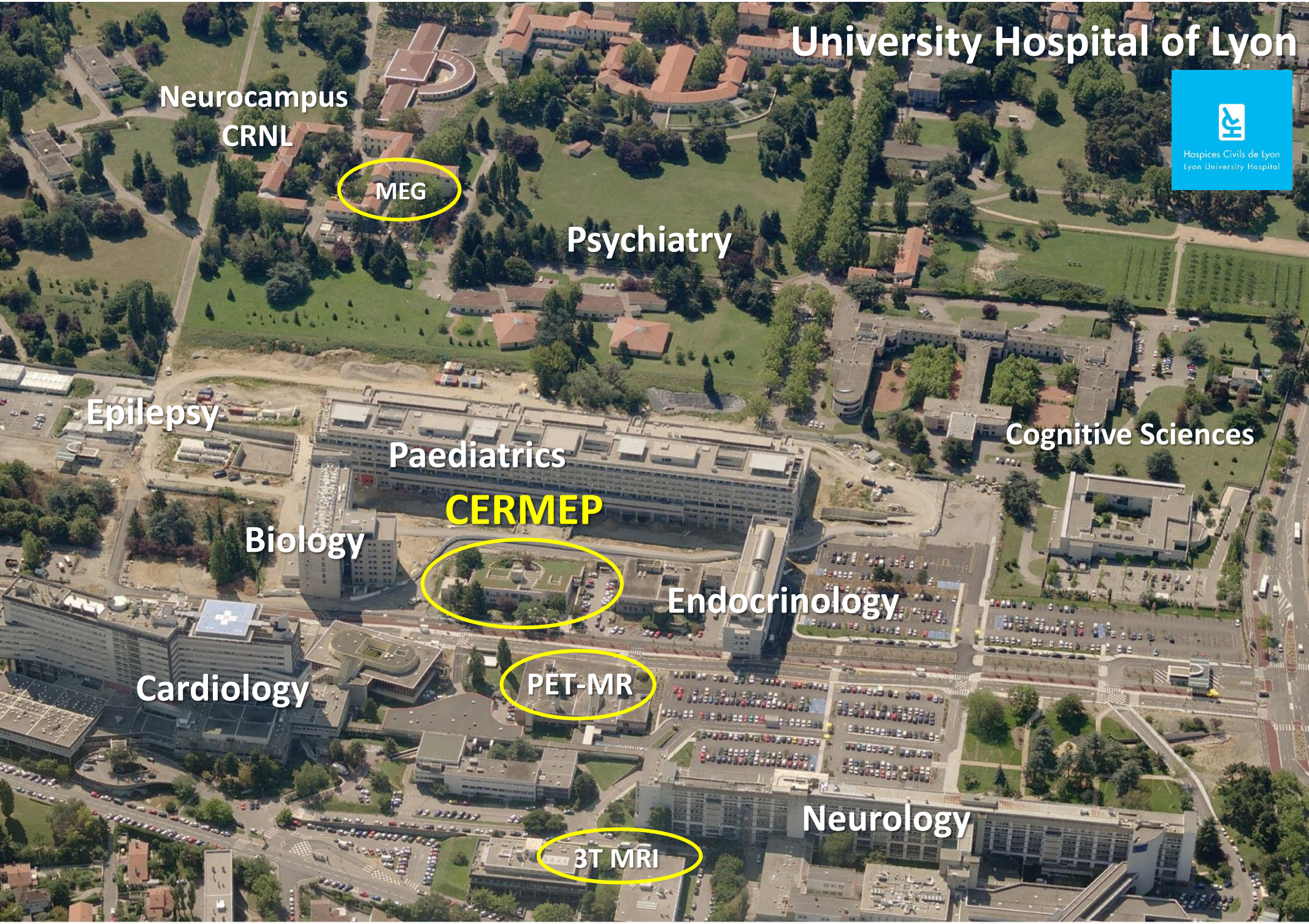
Hybrid PET/MR neuroimaging for CNS drug discovery

Luc ZIMMER

Université Claude Bernard Lyon1 & Hospices Civils de Lyon

BIORAN, Centre de Recherche en Neurosciences de Lyon
CERMEP-Imagerie du Vivant




University Hospital of Lyon
Hospices Civils de Lyon
Lyon University Hospital
Neurocampus
CRNL
MEG
Psychiatry
Epilepsy
Paediatrics
Cognitive Sciences
CERMEP
Biology
Endocrinology
Cardiology
PET-MR
Neurology
3T MRI

cermep
imagerie du vivant

A research imaging platform

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

Cyclotron

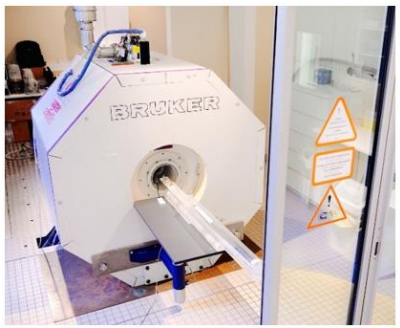
Radiochemistry-Pharmacy

PET-CT Scanner

PET-MRI Scanner

Micro-PET Scanner

Micro-MRI Scanner

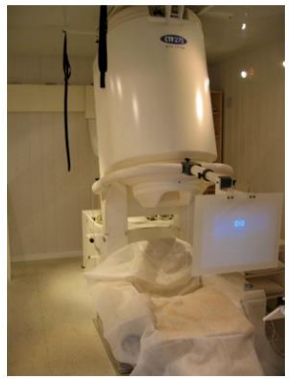


3T-MRI Scanner

1.5T-MRI Scanner

SCT Scanner

MEG Scanner

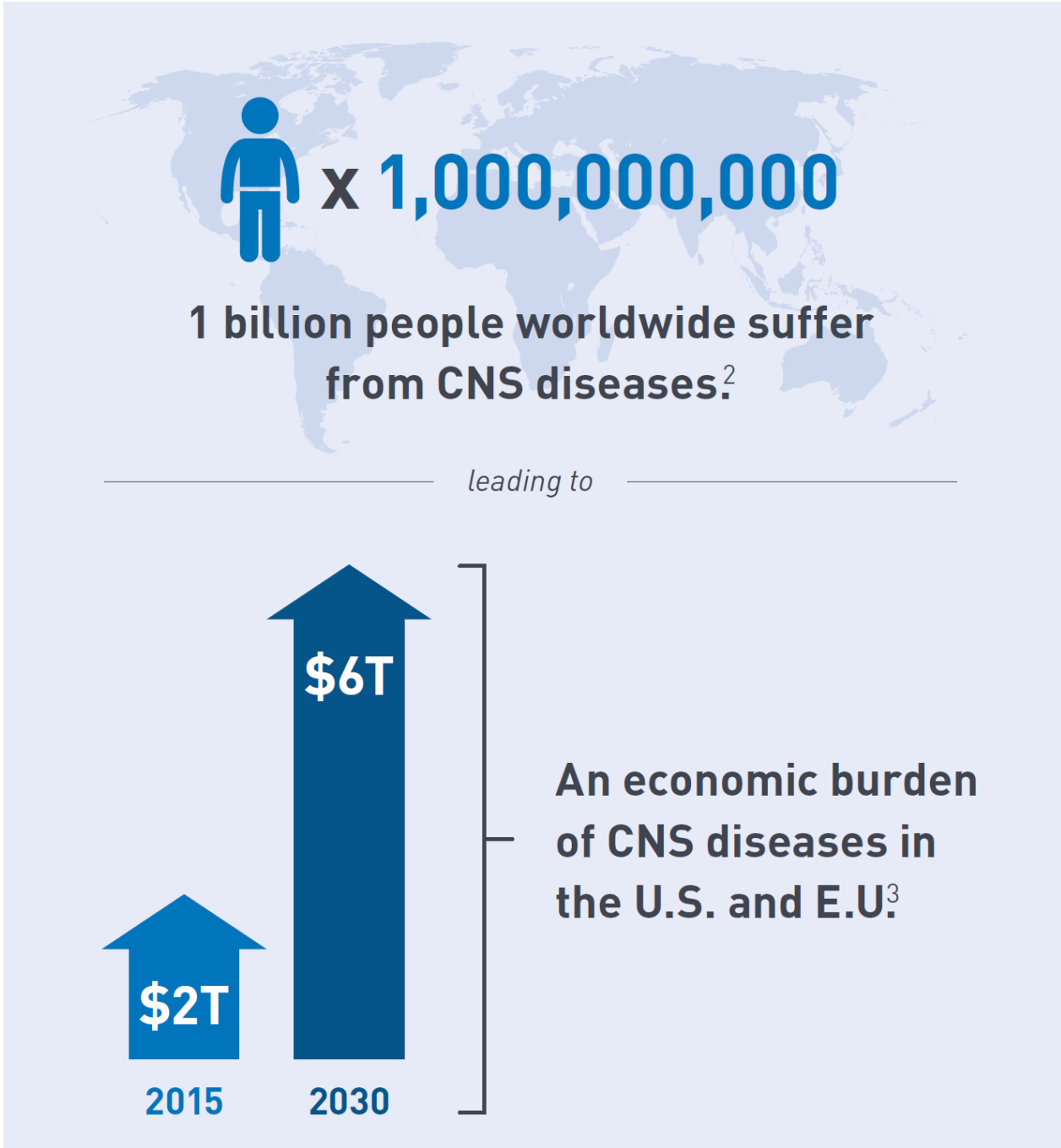


20 Engineers & Assistant Engineers

Radiopharmacology lab & Animal Facilities

ISO 9001 Quality Management & Good Clinical Practice standards

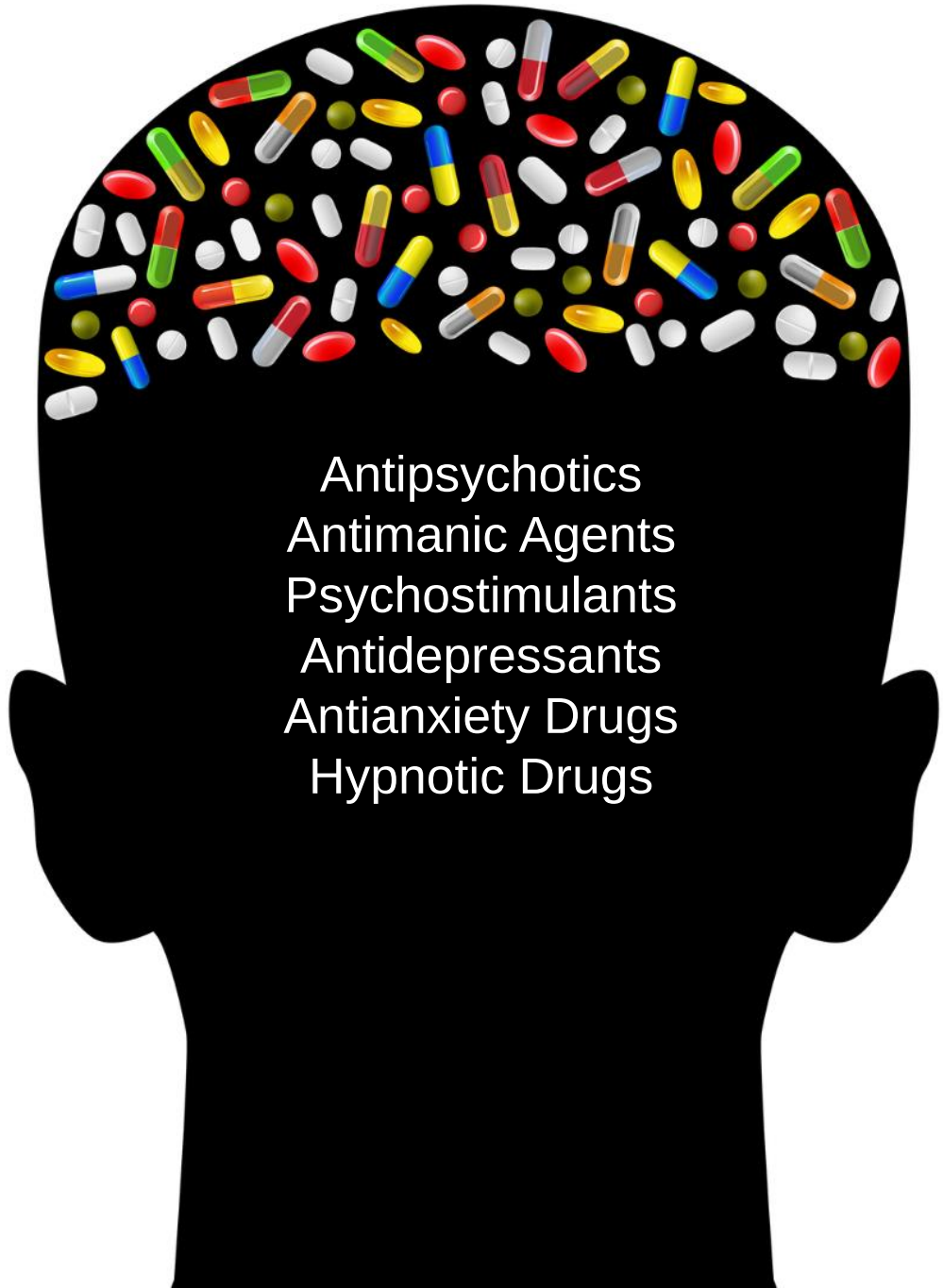
The current context of CNS drug discovery



Ereshefsky et al, Parexel 2015

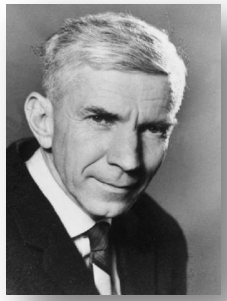
Psychotropic drugs

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



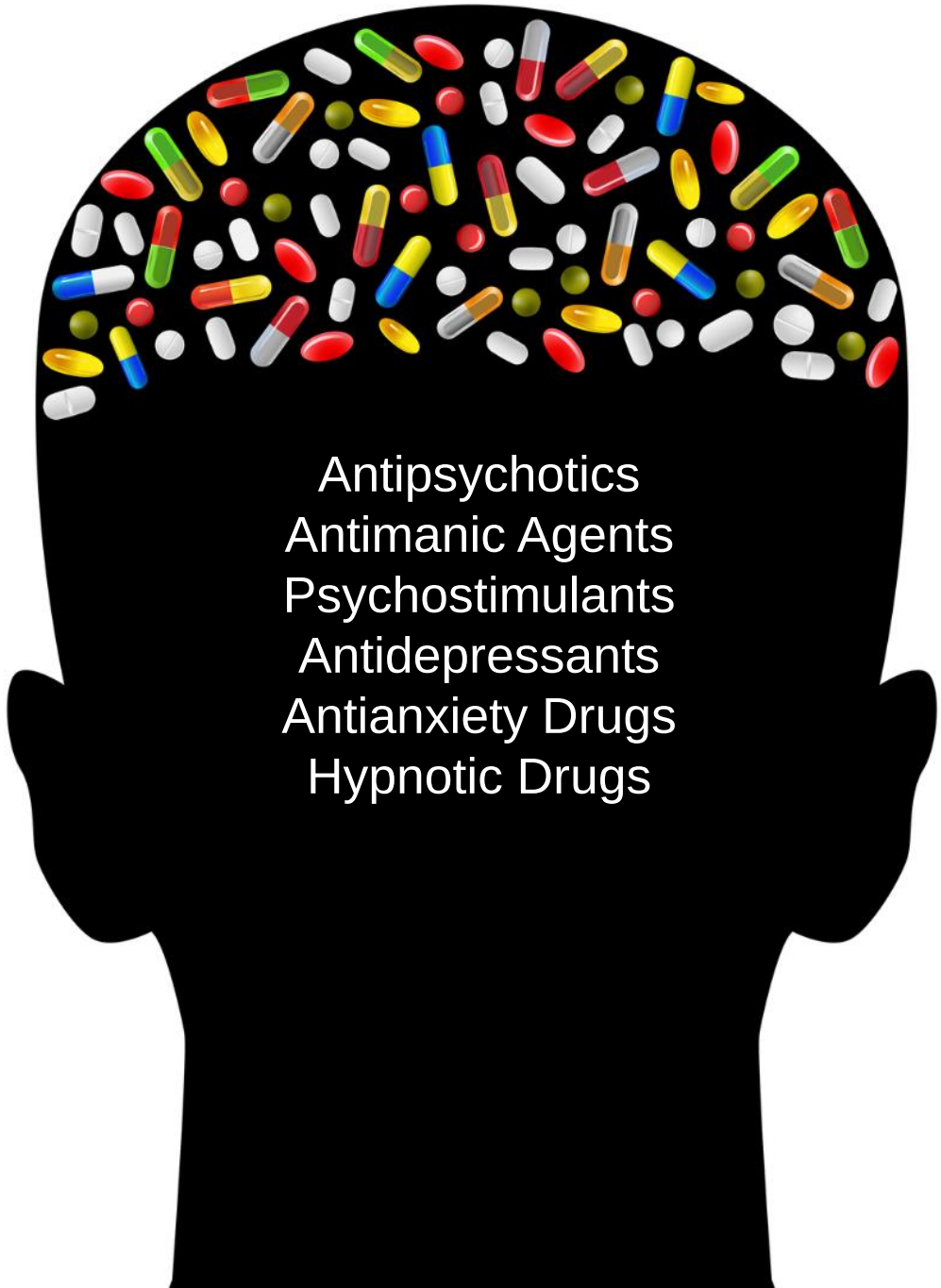
Psychotropic drugs were invented more than 40 years ago

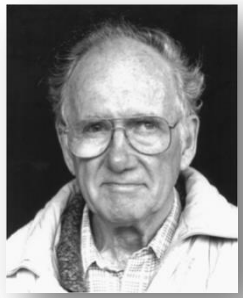
Delay & Deniker 1952



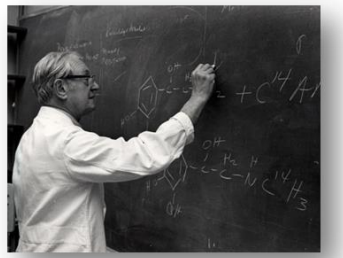
Kuhn 1957

Janssen, 1955

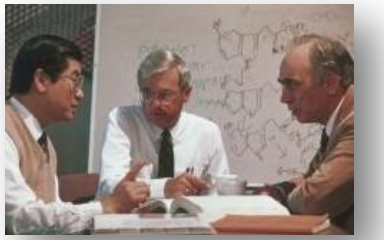




Schou, 1954

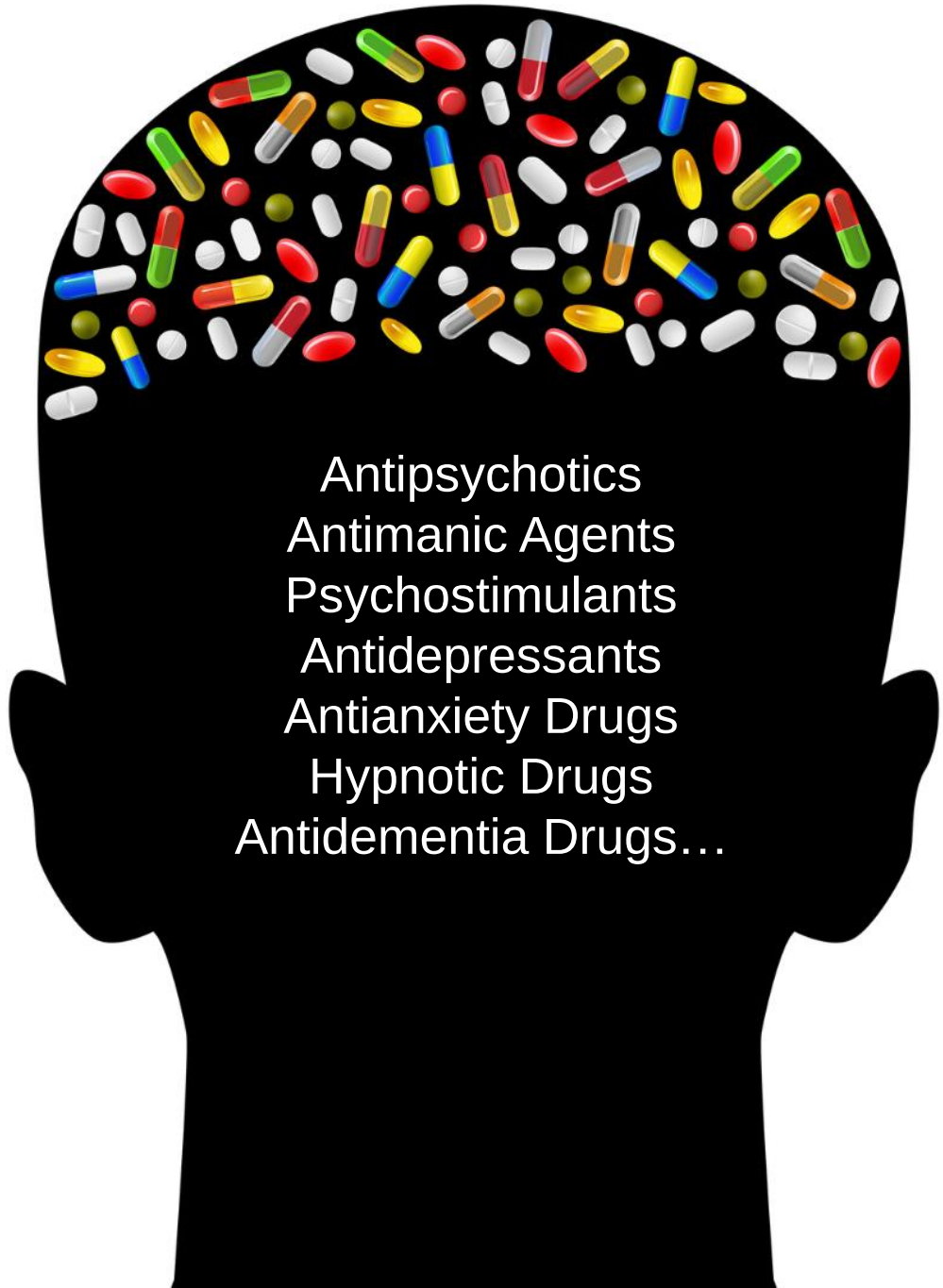


Axelrod 1970



Molloy, Fuller, Wong, 1970

Psychotropic drug non-responders



Antipsychotics	**50%**
Antimanic Agents	**50%**
Psychostimulants	**30%**
Antidepressants	**70%**
Antianxiety Drugs	**20%**
Hypnotic Drugs	**20%**
Antidementia Drugs…	**90%**

The Failure of Target-Oriented Drug Discovery

The crisis in CNS investment

CNS drug research: A dilemma for big pharma companies

Funding crisis threatens development of new treatments for mental illness – urgent action needed

PET/MR neuroimaging to de-risk novel CNS therapies

Go/no go decisions
have to be earlier and with more certainty

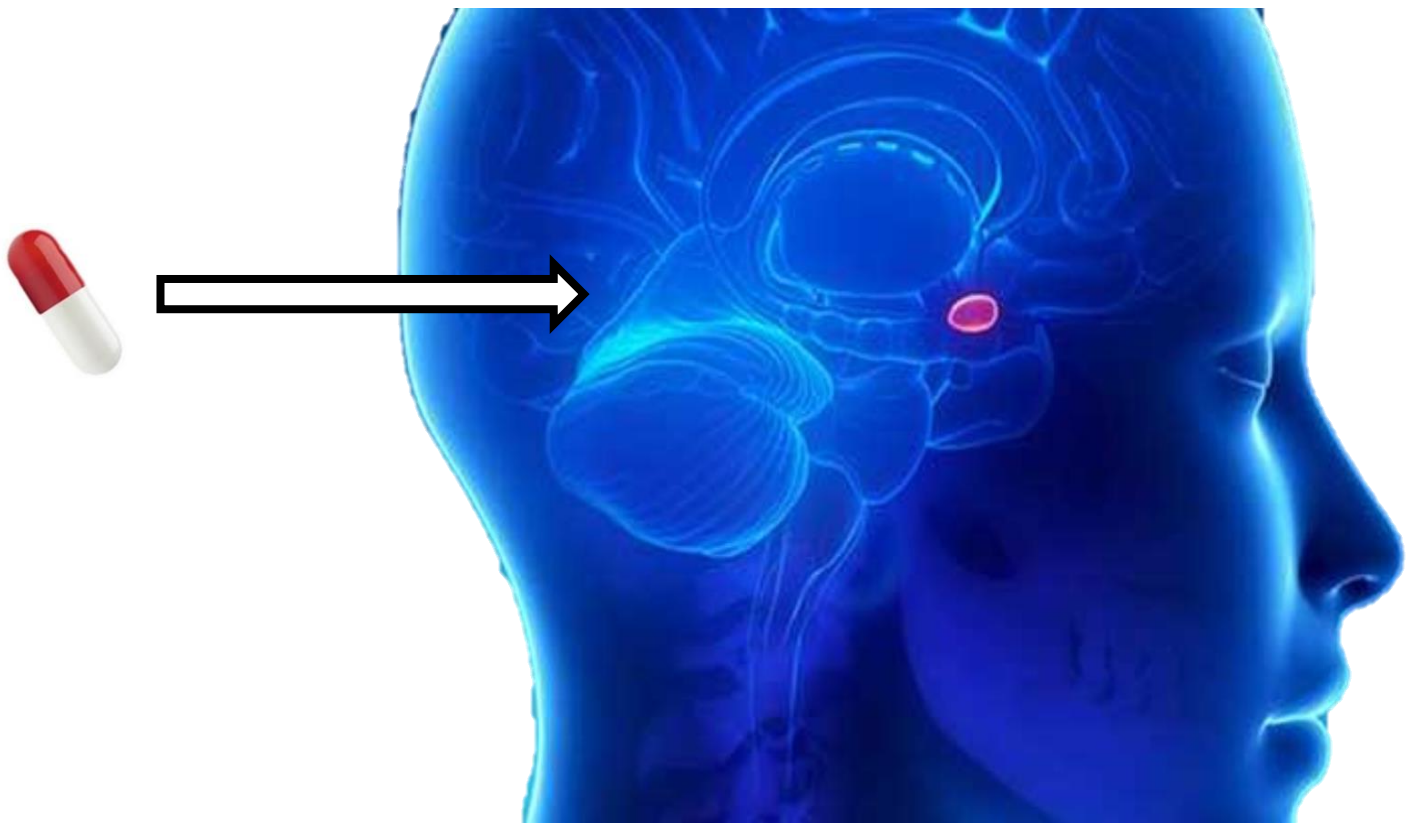
Gunn & Rabiner, Drug Discovery Today 2014

PET/MR neuroimaging to de-risk novel CNS therapies

Go/no go decisions
have to be earlier and with more certainty

Gunn & Rabiner, Drug Discovery Today 2014

1. Target engagement (PET)
Drug binding to the right target

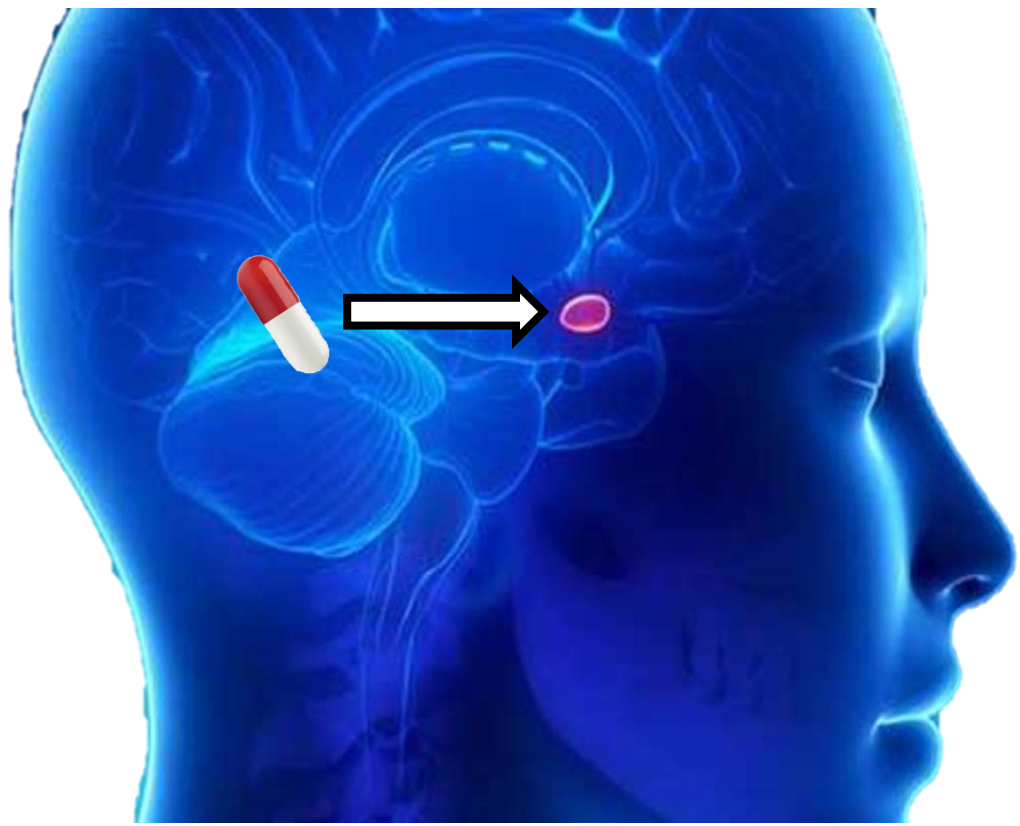


PET/MR neuroimaging to de-risk novel CNS therapies

Go/no go decisions
have to be earlier and with more certainty

Gunn & Rabiner, Drug Discovery Today 2014

2. Drug exposure (PET)
At the target site of action for the desired length of time

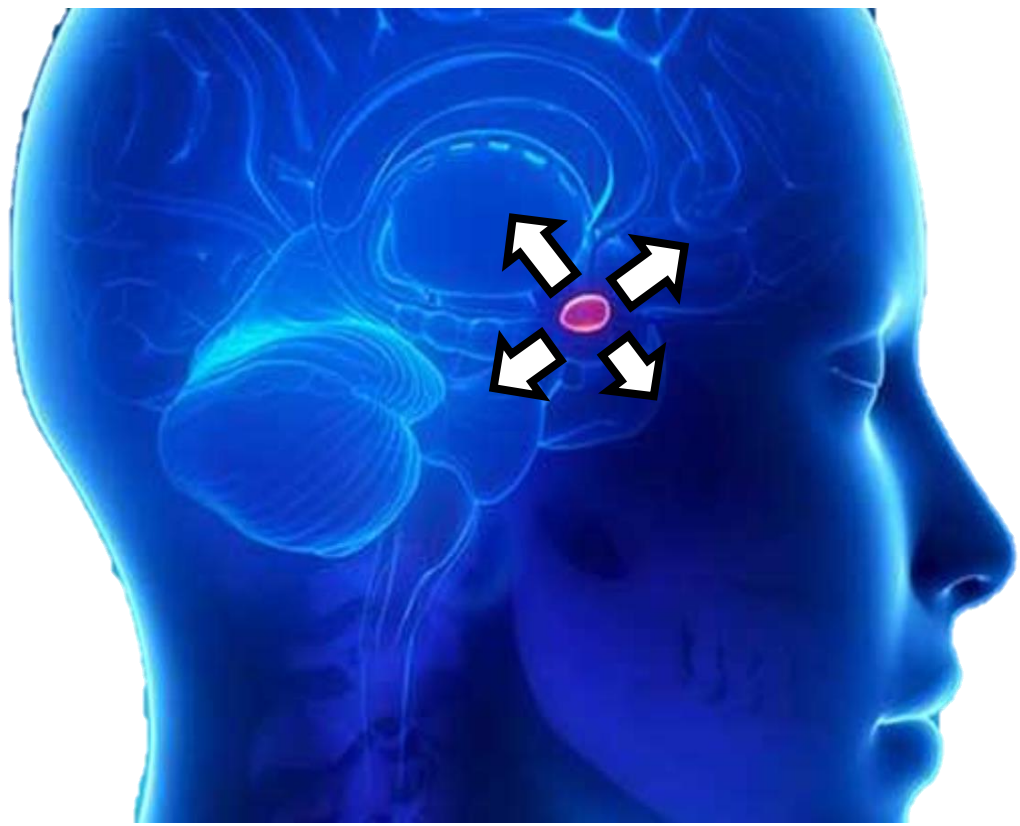


PET/MR neuroimaging to de-risk novel CNS therapies

Go/no go decisions
have to be earlier and with more certainty

Gunn & Rabiner, Drug Discovery Today 2014

3. Pharmacological activity (MRI)
Proportional to the demonstrated target exposure and target binding

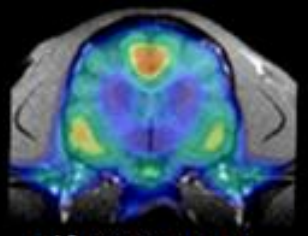


Neuropharmacology of serotonin agonists
(cats)

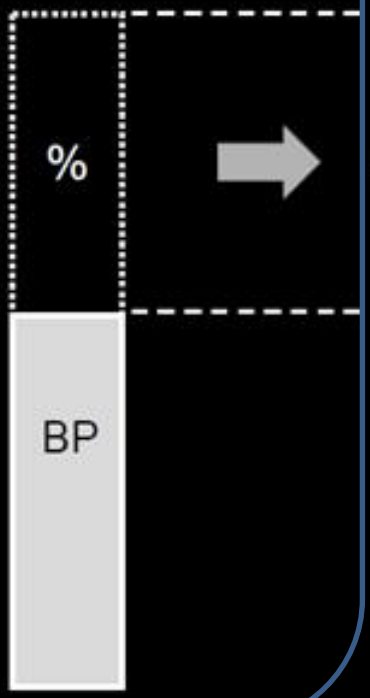
PET

5-HT$_{1A}$

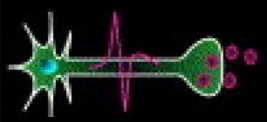
Agonist occupancy (%)



[^{18}F]MPPF



(1) Neuronal activity

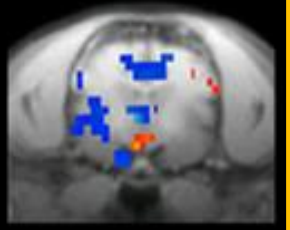


(2) Neurovascular coupling

fMRI

BOLD activation patterns

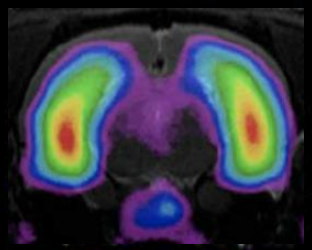
(3) Haemodynamic response



Neuropharmacology of antidepressants
(rats)

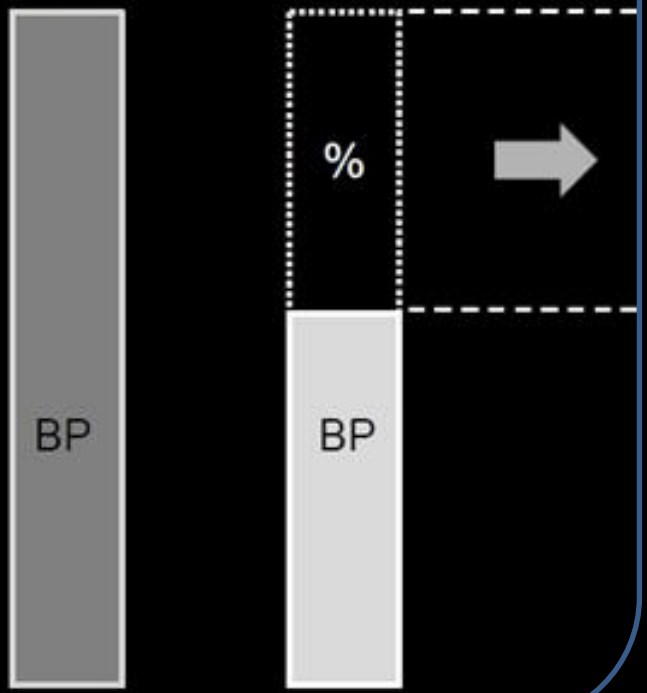
PET

5-HT$_{1A}$

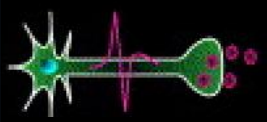


[^{18}F]MPPF

Drug occupancy



(1) Neuronal activity



(2) Neurovascular coupling

fMRI

BOLD activation patterns

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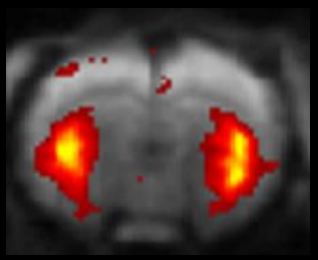
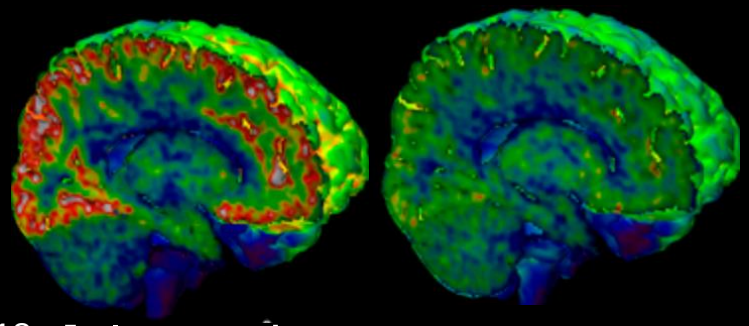


Neuropharmacology of antipsychotics
(human/non human primates)



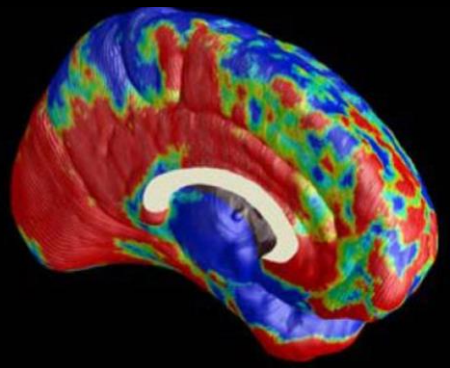
[^{18}F]altanserin

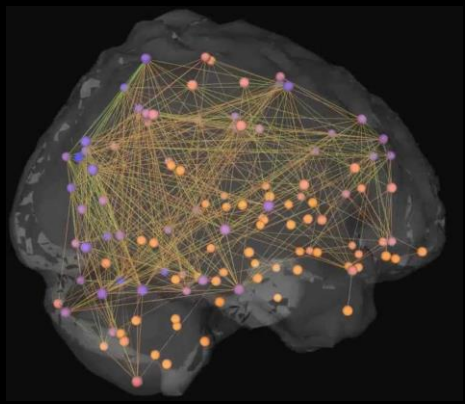
Drug occupancy

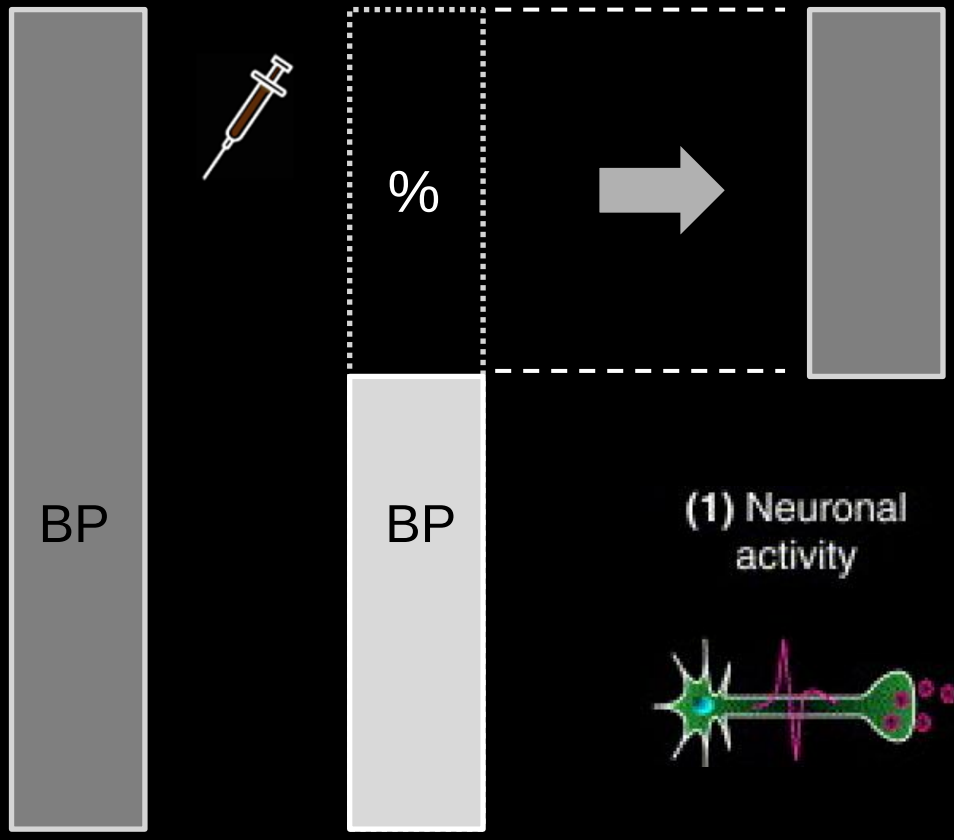
BOLD

Brain activation

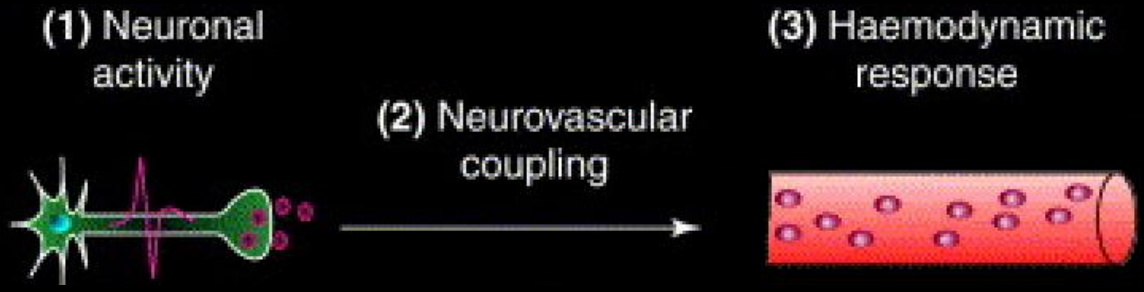
Functional connectivity







5-HT$_{2A}$ receptors



Conclusions

Hybrid PET/MR neuroimaging as a **unique tool** to explore in vivo

→ mechanism of action of CNS drugs

→ pharmacodynamic/pharmacokinetic relationships

→ translation from preclinical to clinical stages

→ new neuropharmacological concepts

zimmer@cermep.fr