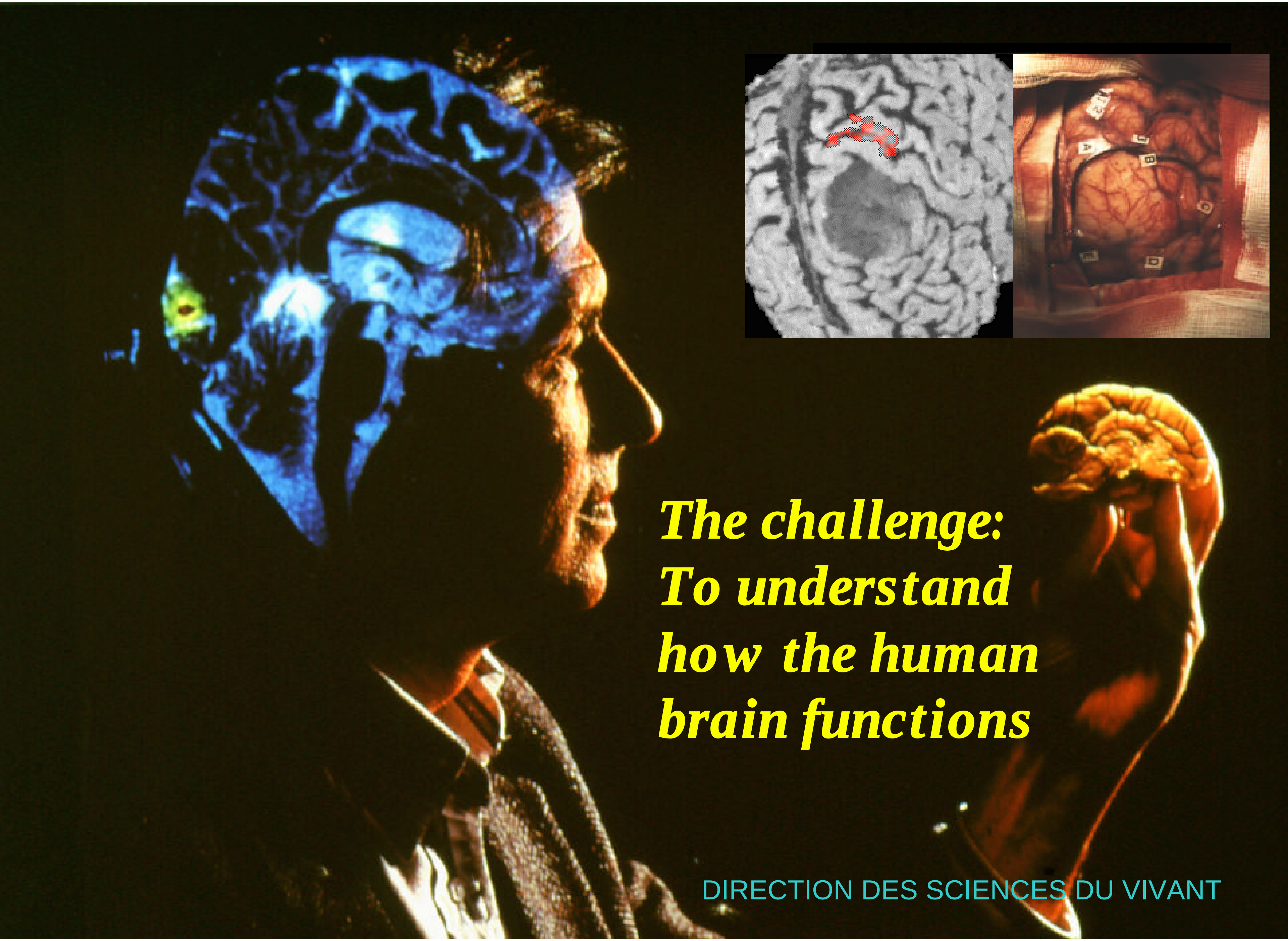
# **Use of antimatter for the *in vivo* investigation of the brain : *Positron Emission Tomography***

Pr A. Syrota

Matter-antimatter asymetry

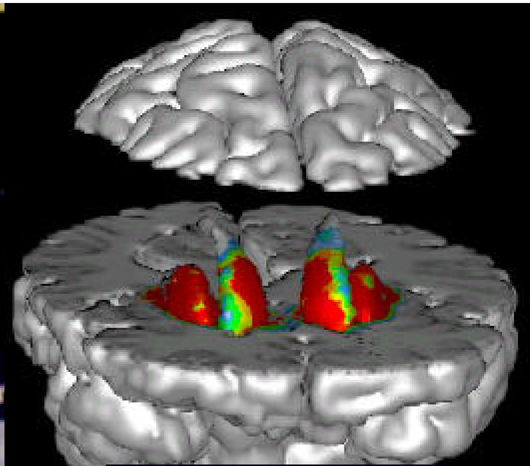
XIV$^{th}$ Rencontres de Blois

Blois, 18 june 2002

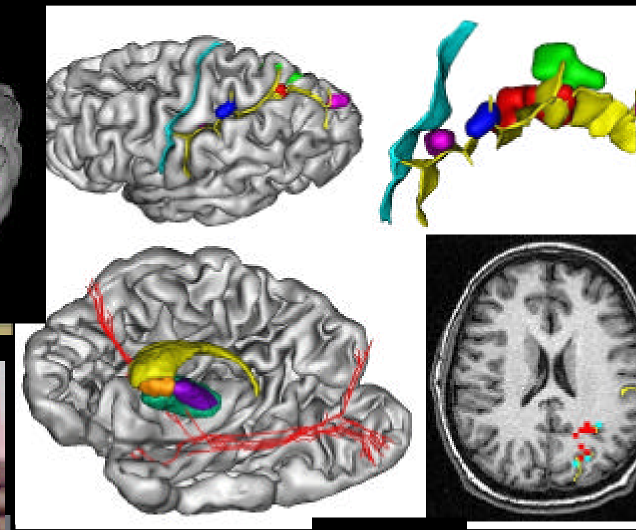


# *The challenge: To understand how the human brain functions*

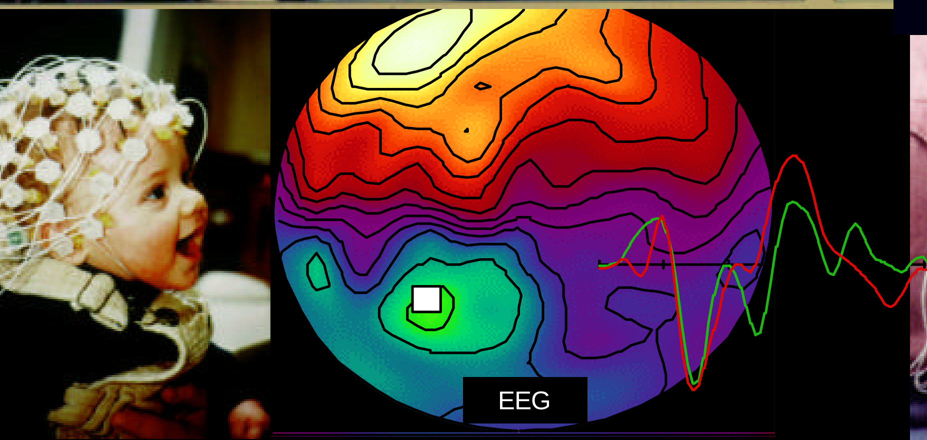
PET



D2 receptor distribution in the brain



fMRI



EEG

# NEUROIMAGING

**SPECT, TEP…**
**MRI, MRS…**
**EEG/ERPs, MEG…**
**Computers…**

# I - THE MARRIAGE OF THE TRACER METHOD AND OF THE ARTIFICIAL RADIOACTIVITY

George de Hevesy and Frédéric Joliot

# NUCLEAR MEDICINE
## *The tracer method*

- 1913 G.C. de Hevesy: description of the tracer method; using Radium D to monitor chemical changes in lead
- 1922 A. Lacassagne: the first autoradiography
- 1923 G.C. de Hevesy: using $^{212}Pb$ as a tracer to measure the absorption and transfer of lead in plants.
- 1934 G.C. de Hevesy: using $D_2O$ to measure water elimination in the human body

Institut du Radium, 1932
(électromètre Hoffmann)

# THE BASES OF NUCLEAR MEDICINE

*The tracer method*

- 1912 G. Hevesy : using radioactive elements as tracers

*Artificial radioactivity*

- 1934 I. and F. Joliot-Curie: discovery of artificial radioactivity (Nobel prize for Chemistry in 1935)
  - This was actually a double discovery:
    - artificial radioelements
    - $\beta^+$ radioactivity

*Instrumentation*

- 1930 E.O. Lawrence: the first cyclotron at Berkeley
- 1939 O. Hahn and M. Strassmann: fission of the nucleus
- 1942 L. Szilard and E. Fermi: the first self-sustained chain reaction in Chicago

# F. Joliot's work on radioactive tracers applications to biology

- 1934 Frédéric Joliot and Irène Curie: «Artificial production of a new kind of radio-element» (Nature)
- 1935 Frédéric Joliot: one should «think of using these radioactive elements as tracers to study the behavior of their inactive isotopes in certain chemical reactions or in biological phenomena»
- 1935 G.C. de Hevesy: utilization of Phosphorus-32
  «The formation of the bones is a dynamic process, involving continuous loss and replacement» (Nature)

# F. Joliot's work on tracers applications to biology

- *1937: report in support of the creation of the Laboratory of Atomic Synthesis* :
  - "The tracer method, using synthetic radioelements, will make it possible to study with greater ease the problems associated with the location and elimination of various elements introduced into living organisms.
  - In this case, radioactivity is used only to determine the presence of an element in a specific part of the organism.
  - Under such conditions, it is not necessary to introduce large quantities of the radioactive tracer."

# ACADEMY OF MEDECINE
## November 23, 1943

- “As soon as we had succeeded in preparing the first synthetic radioelements, we proposed that they be used for the investigation of certain chemical and biological problems…

- The radioactive tracer method is of long standing and was hitherto applied to natural radioelements. Hevesy” - *(Nobel prize for Chemistry, rewarding the whole of his work on tracers ,1943 ) -* “ and Paneth were the first to use it judiciously…"

***« SUR L'OBTENTION DE LA THYROXINE MARQUÉE PAR LE RADIOIODE ET SON COMPORTEMENT DANS L'ORGANISME »***

Frédéric JOLIOT, Robert COURRIER, Alain HOREAU et Pierre SÜE
*Comptes rendus des séances de l'Académie des Sciences* (1944)

( SYNTHESIS OF LABELED THYROXINE AND ITS DISTRIBUTION IN THE BODY )

# II - THE MARRIAGE OF PHYSICS AND COMPUTERS

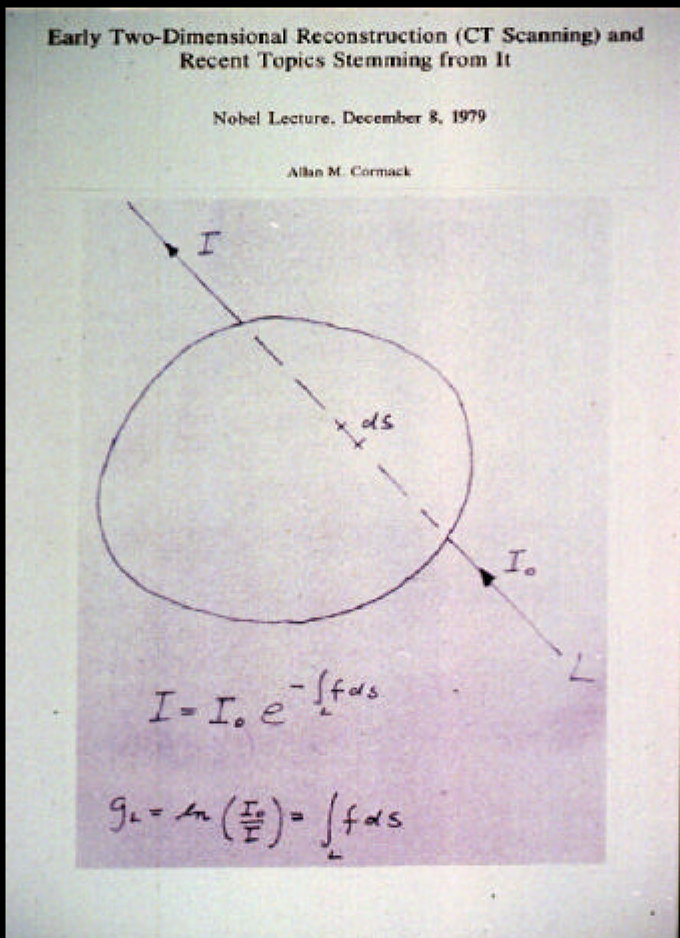
The computerized tomography

# TOMOGRAPHY

- Computerized tomography (CT)
  - 1961 W.H. Oldendorf : «isolated flying spot detection of radiodensity discontinuities displaying the internal structural pattern of a complex object»
  - 1963 D. Kuhl : «image separation radioisotope scanning»
  - 1964 A.M. Cormack : «representation of a function by its line integrals, with some radiological applications» (Nobel Prize 1979)
  - 1973 G.N. Hounsfield : «computerized transverse axial scanning (tomography) Part I. Description of system» (Nobel Prize 1979)

- Positron Emission Tomography (PET)
  - 1975 M.E. Phelps, M.M Ter-Pogossian, D.E. Kuhl : «application of annihilation coincidence detection to transaxial reconstruction tomography»

# Computerized tomography


Early Two-Dimensional Reconstruction (CT Scanning) and Recent Topics Stemming from It

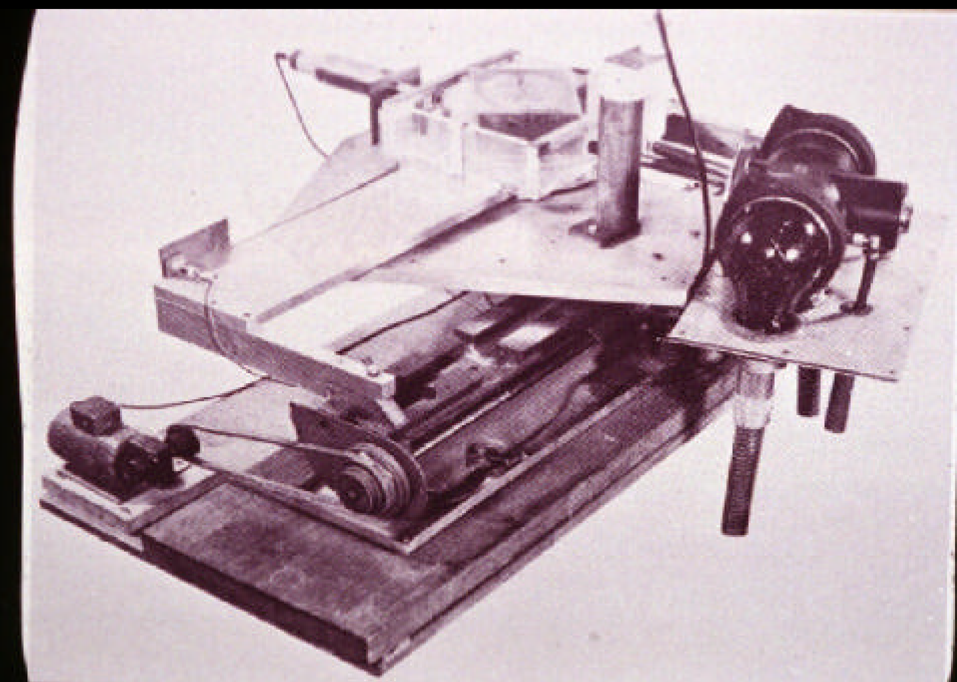
Nobel Lecture, December 8, 1979

Allan M. Cormack

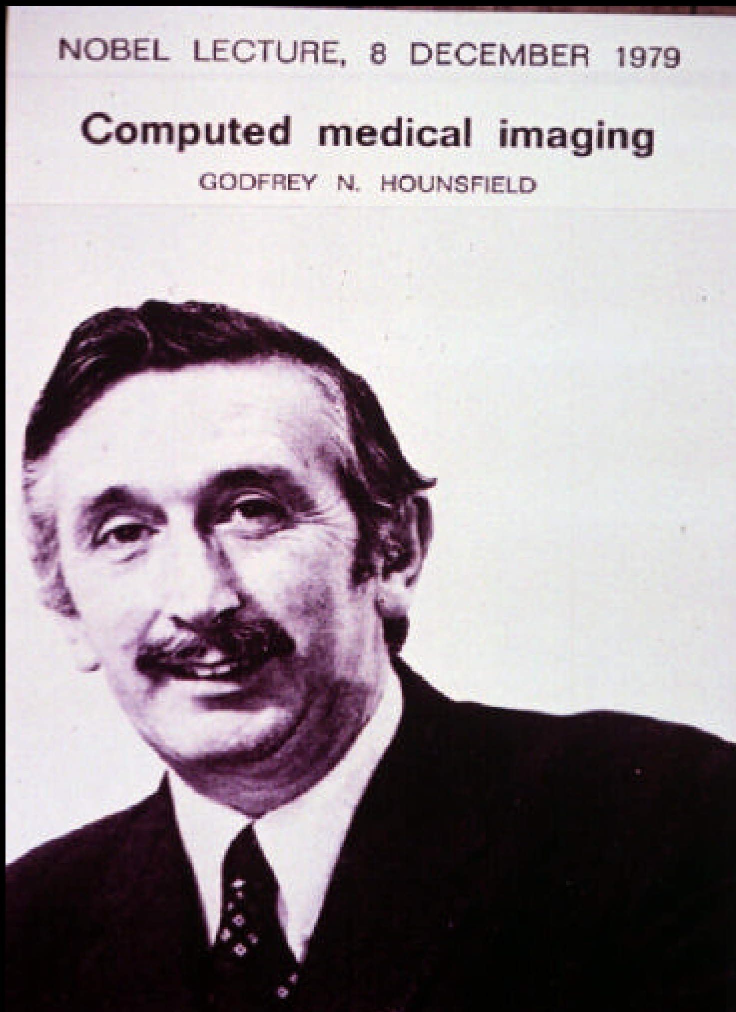


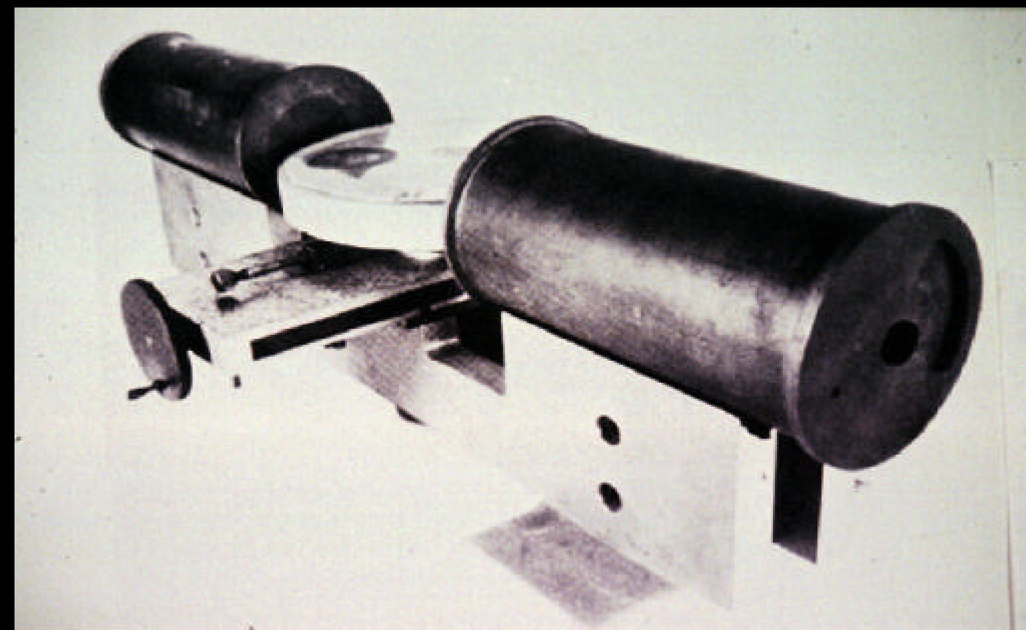
$$I = I_0 e^{-\int_L f\, ds}$$

$$g_L = \ln\left(\frac{I_0}{I}\right) = \int_L f\, ds$$



# Computerized tomography



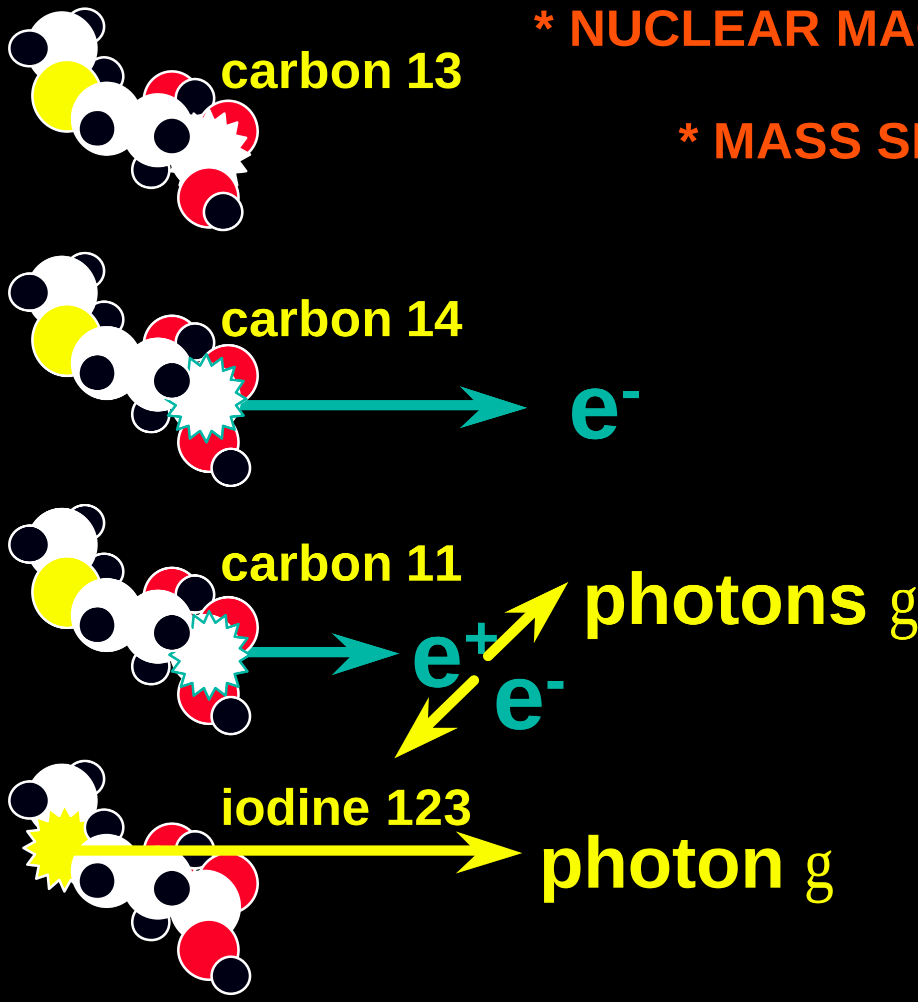
# ISOTOPIC TRACERS

**STABLE ISOTOPES**

**$b^{-}$ EMITTERS**

**$b^{+}$ EMITTERS**

**g EMITTERS**




* NUCLEAR MAGNETIC RESONANCE

* MASS SPECTROMETRY

*PHOTOGRAPHIC PLATE

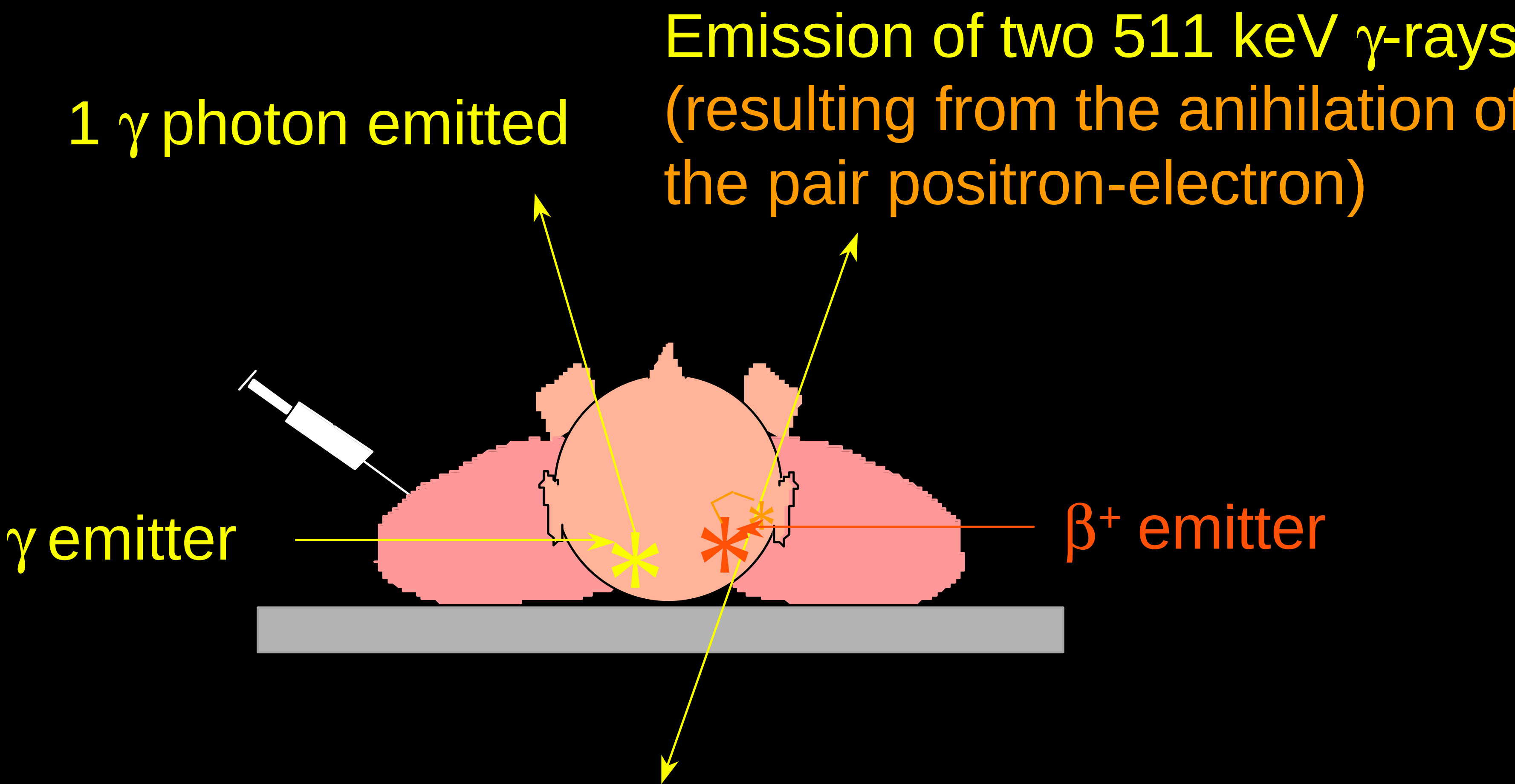
* SCINTILLATION DETECTORS

*PET
*SPECT

# III - IMAGING METHODS

- Single Photon Emission Computed Tomography (SPECT)
- Positron Emission Tomography (PET)
- Fonctional Magnetic Resonance Imaging (fMRI)
- *in vivo* NMR Spectroscopy
- Electro- and Magneto-encephalography (EEG and MEG)
- Optical methods in the near infra-red: spectroscopy (NIRS), transit time of photons

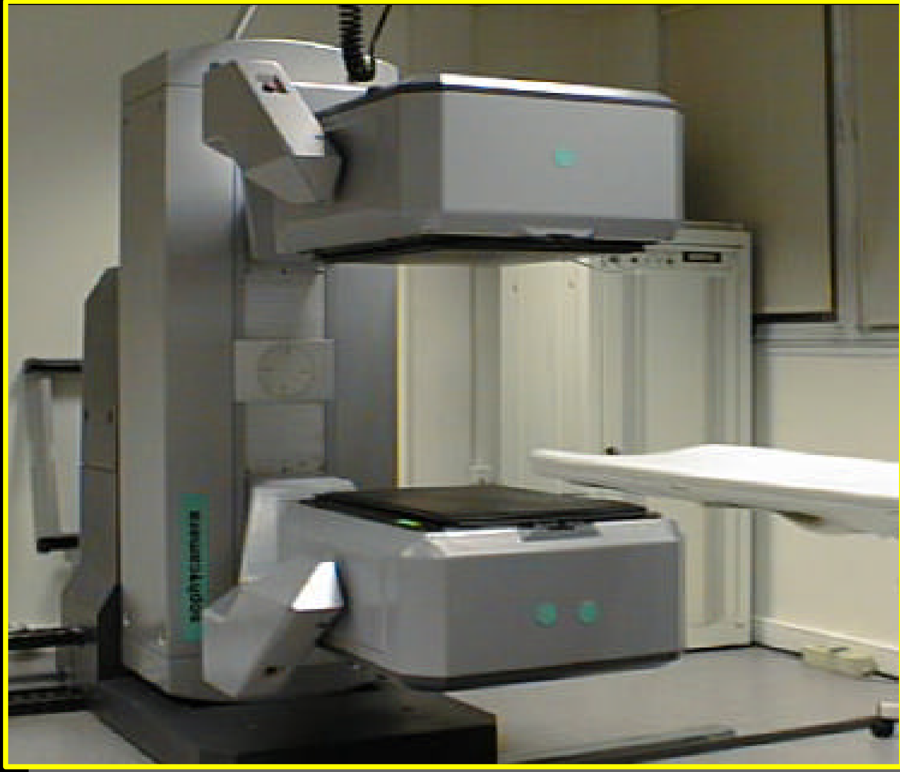
# Properties of g and b$^{+}$ isotopes



# NUCLEAR MEDECINE

*Progress in instrumentation*

- 1928 : H. Geiger and W. Müller : charged particle counter
- 1950 : manual scanner (Geiger-Müller counter then scintillation counter)
- 1951 B. Cassen : rectilinear scanner
- 1957 H.O. Anger : scintillation camera
- 1980 : SPECT (rotating camera)

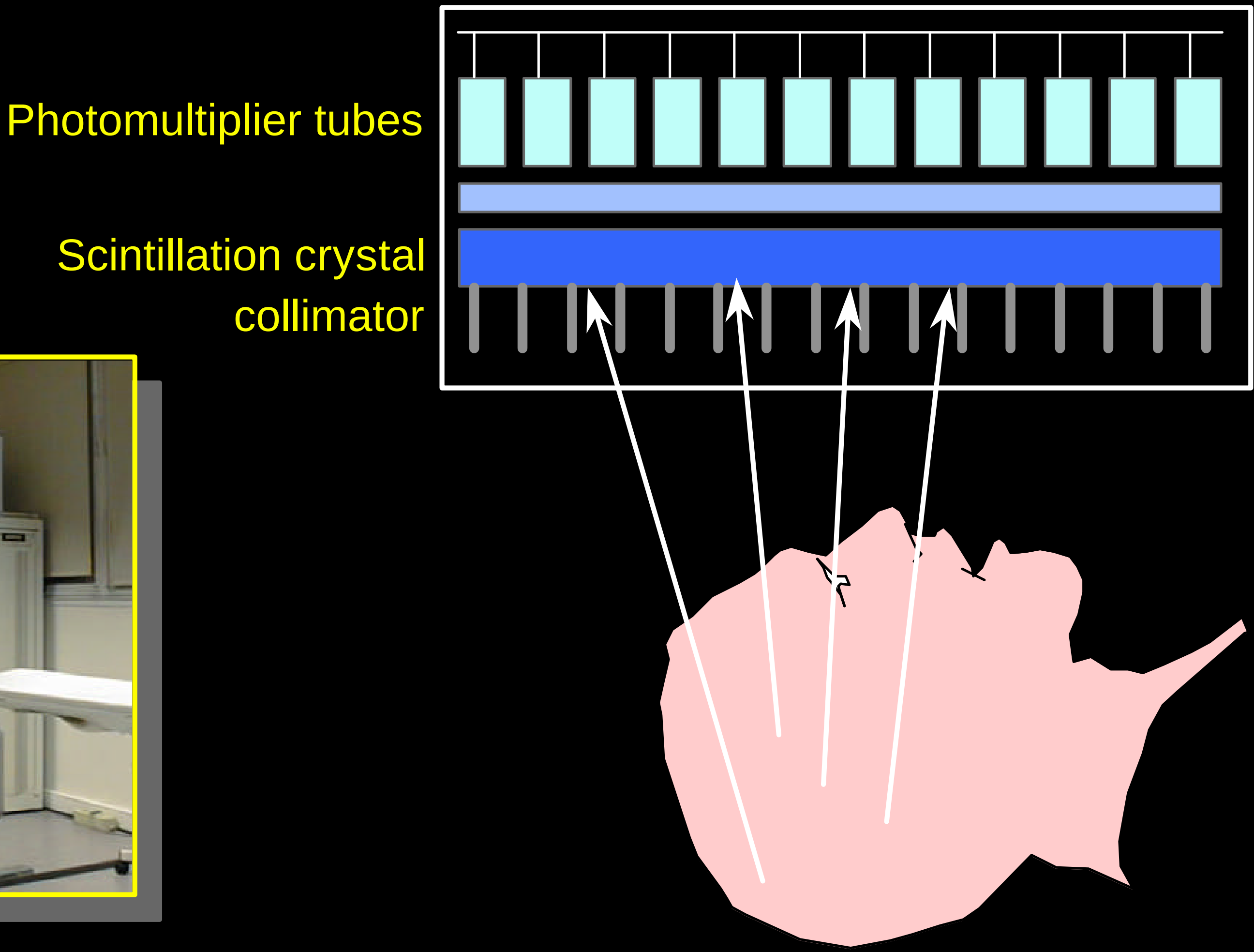


# Radiation detection
# Scintillation camera

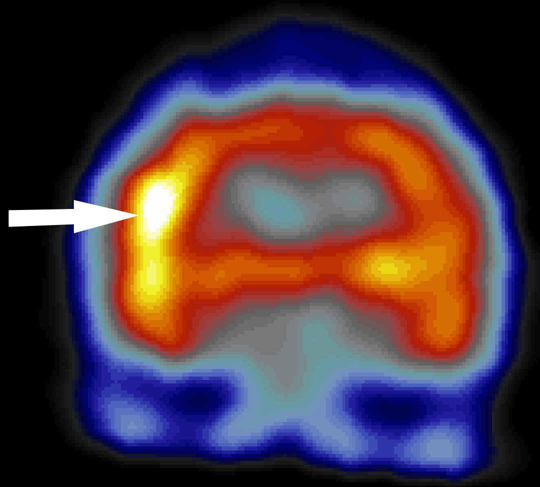
$^{99m}Tc$ : 140 keV, 6h

$^{123}I$ : 159 keV, 13 h

$^{201}Tl$ : 71 keV, 73 h

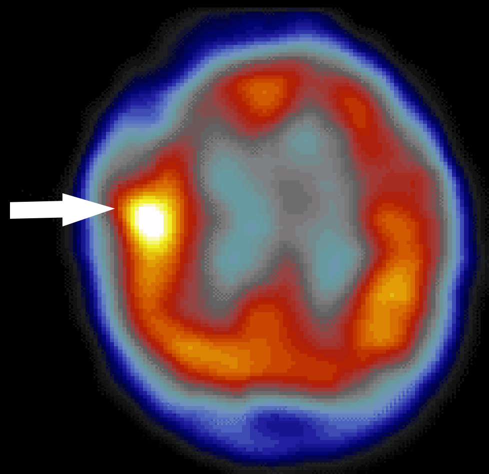


# Ictal SPECT
# in frontal lobe epilepsy



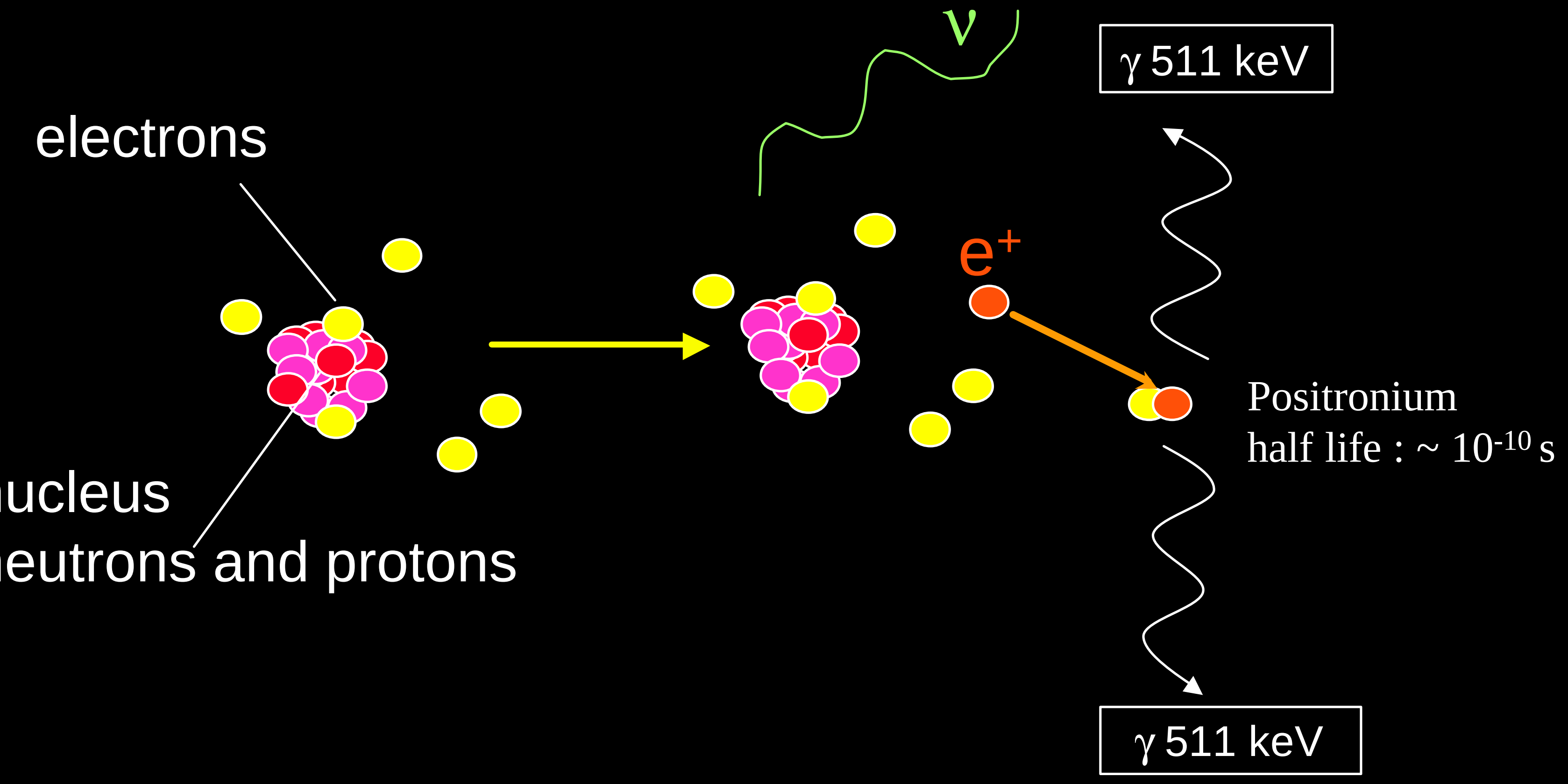
SPECT

MRI



SPECT

# Positron emission and annihilation



# Positron emitters widely used for clinical investigations

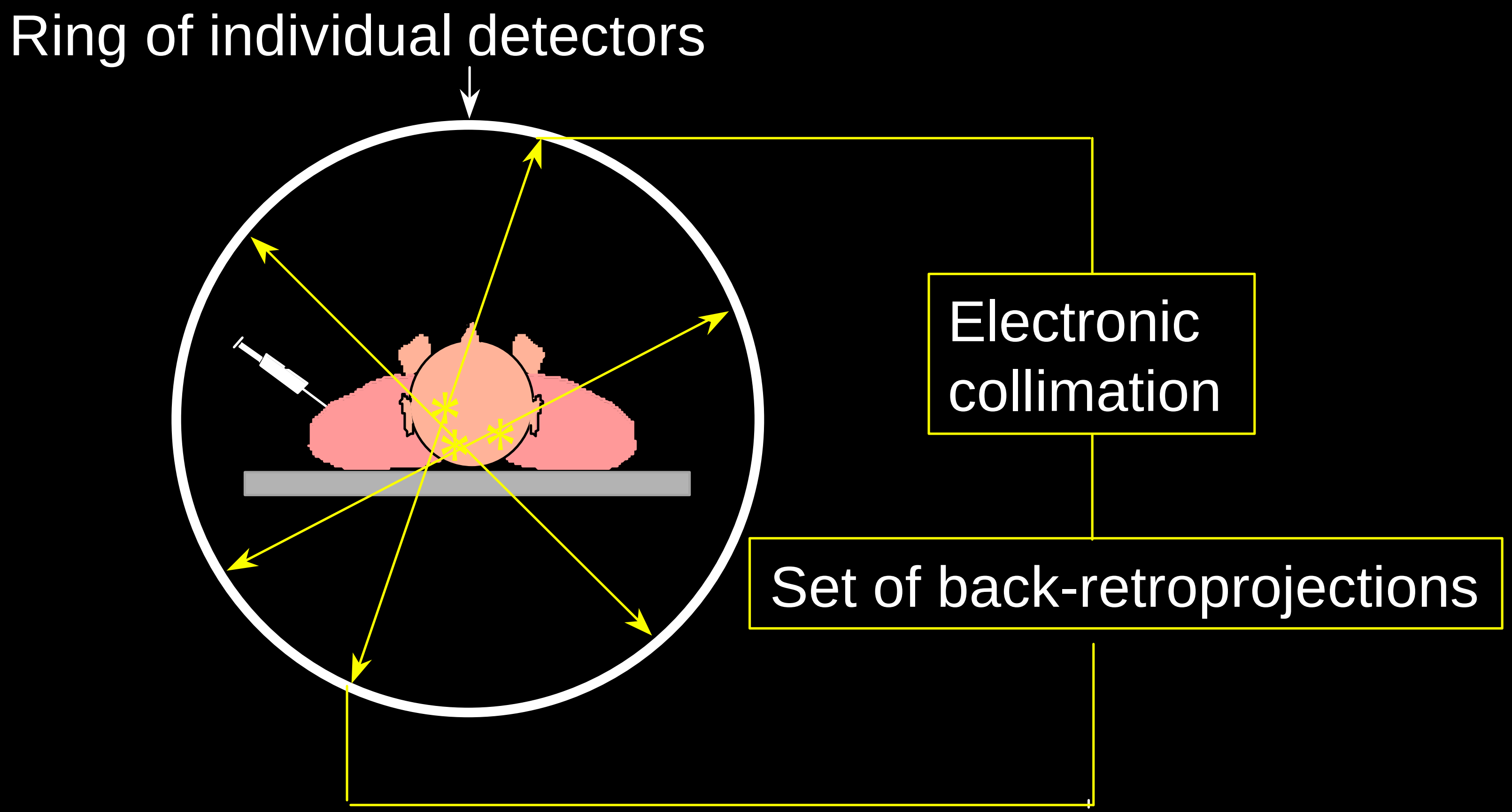
| Nuclide | Half-life | Daughter | # photons/100 disintegrations |
|---|---|---|---|
| C-11 | 20.4 min | B-11 | 200 |
| N-13 | 9.97 min | C-13 | 199.6 |
| O-15 | 2,05 min | N-15 | 190 |
| F-18 | 1,83 hr | O-18 | 200 |

- $^{11}C$, $^{13}N$, $^{15}O$ are isotopes of natural elements carbon, nitrogen and oxygen
- there are no positron emitting isotopes of hydrogen and phosphorus but they have a 1/2 spin and are detectable with NMR

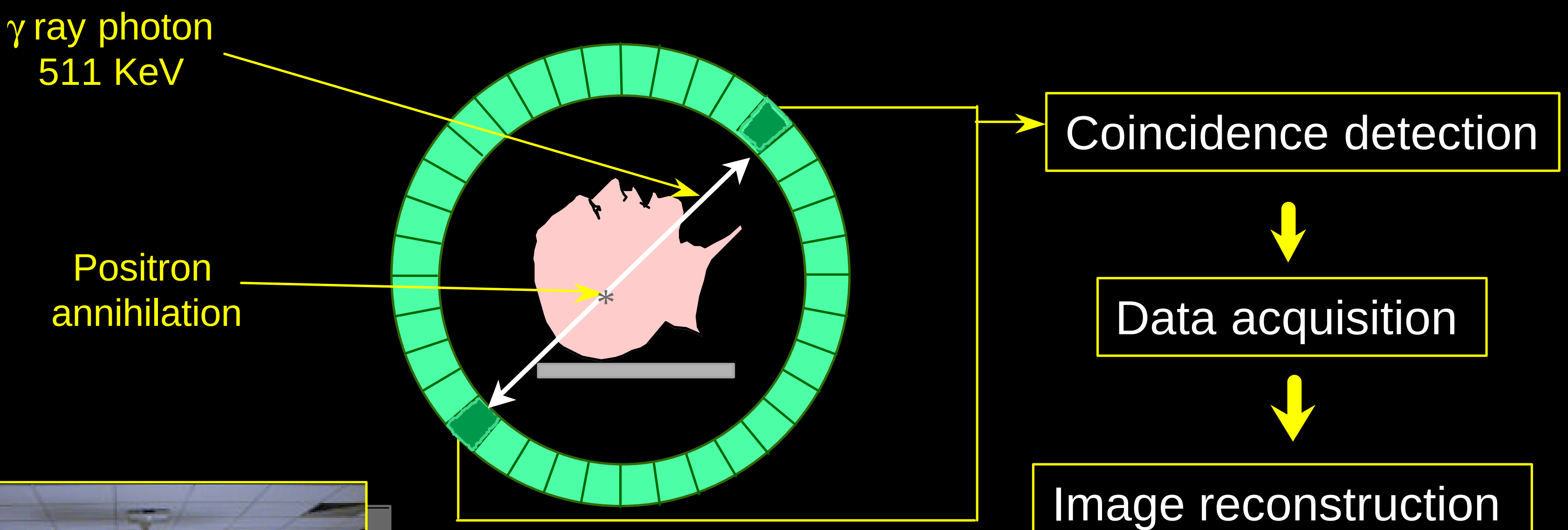
# Positron emitters useful for clinical investigations

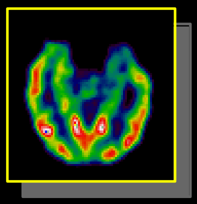
| Nuclide | Half-life | Daughter | # of photons/100 disintegrations |
|---|---|---|---|
| K-38 | 7.64 min | Ar-38 | 200 |
| Mn-52 | 5.59 days | Cr-52 | |
| Fe-52 | 8.3 h | Mn-52m | 100 / 112 |
| Co-55 | 17.5h | Fe-55 | 152 |
| Cu-61 | 3.41 h | Ni-61 | 122 |
| Cu-64 | 12.7 h | Ni64, Zn64 | 36 |
| As-72 | 1.08 days | Ge-72 | 176 |
| Br-76 | 16.2 h | Se-76 | 108 |
| Rb-82 | 75 s | Kr-82 | 190 |
| Sr-83 | 1.35 days | Rb-83 | 48 |
| Y-86 | 14.7 h | Sr-86 | 66 |
| I-124 | 4.18 days | Te-124 | 46 |

# Principle of PET
## coincidence detection



# Positron Emission Tomography



# PET imaging

**Cyclotron**

**Isotope production**

[ $^{11}C$ or $^{18}F$]

**$^{18}F$**

**$^{11}C$**

**radiochemistry laboratory**

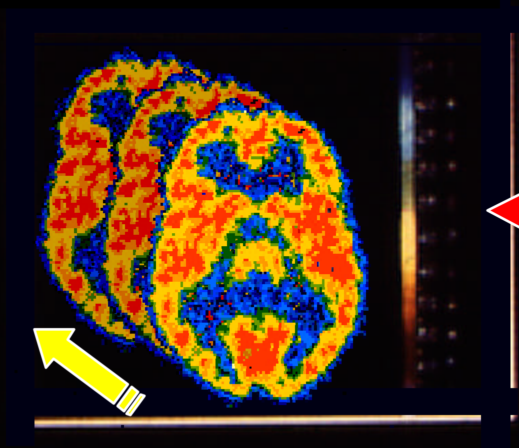
**Chemical précursor**

**Radiolabeled molecule**

**« radiotracer »**

**PET camera**

**Ligand distribution in the brain (tomographic images)**



## cyclotron

## radiochemistry

# Positron detection :
# positron emission tomograph

# III - PET : clinical applications

diseases of the Central Nervous System :

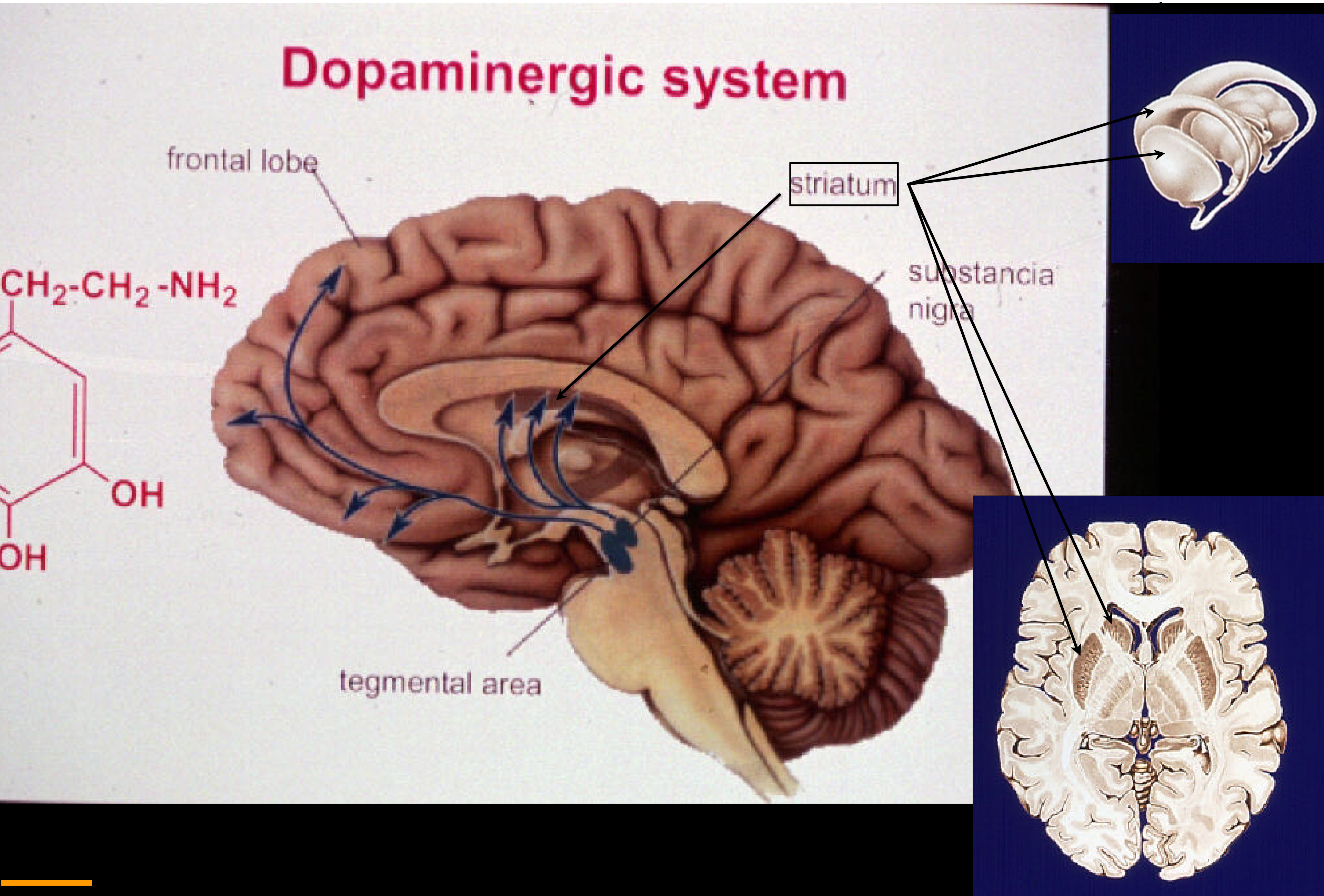
- Alzheimer 's disease
- Parkinson 's disease
- epilepsy
- stroke
- mental diseases
- ...

normal brain functions:

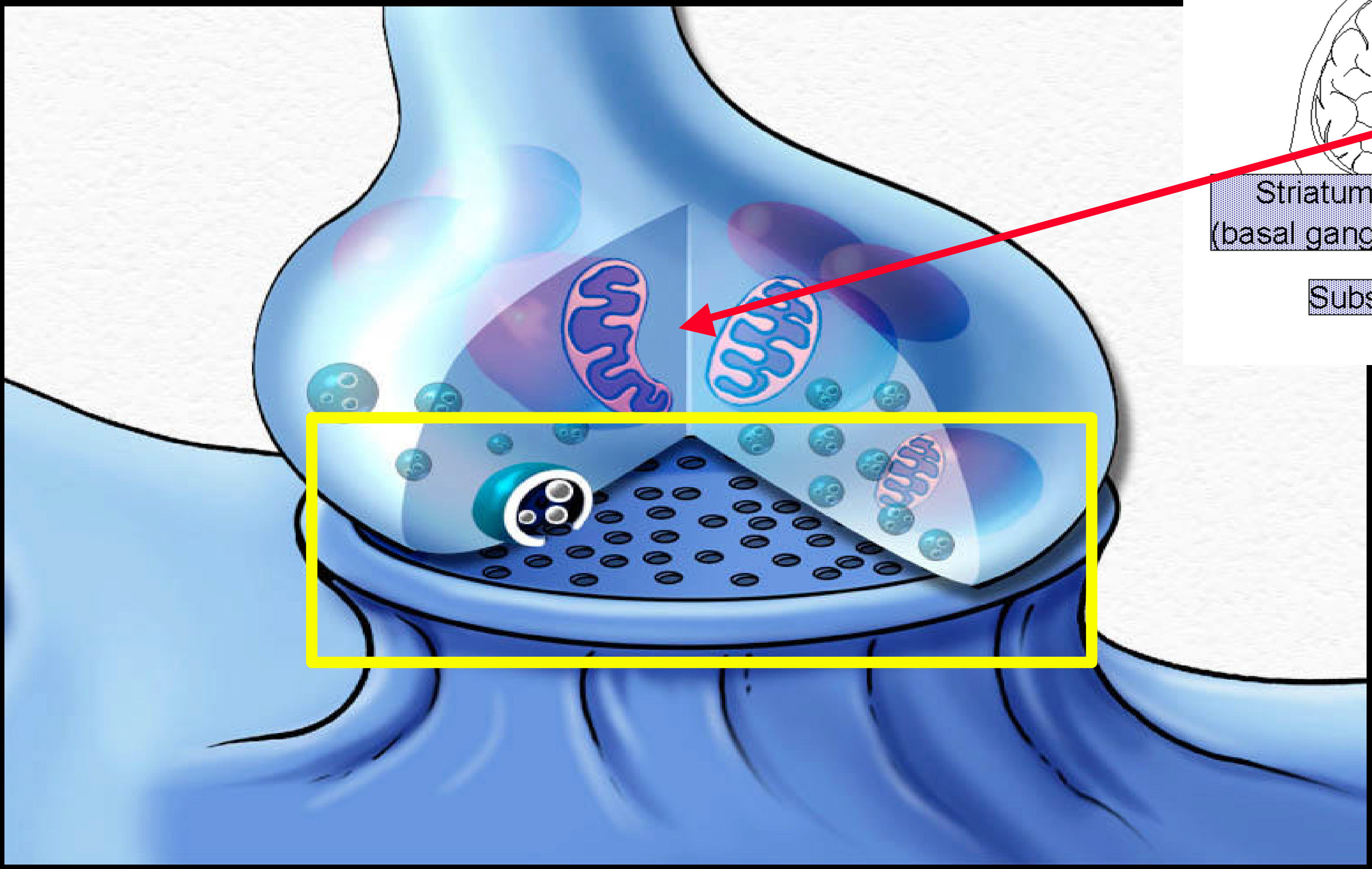
- vision
- language
- memory
- calculus
- consciousness

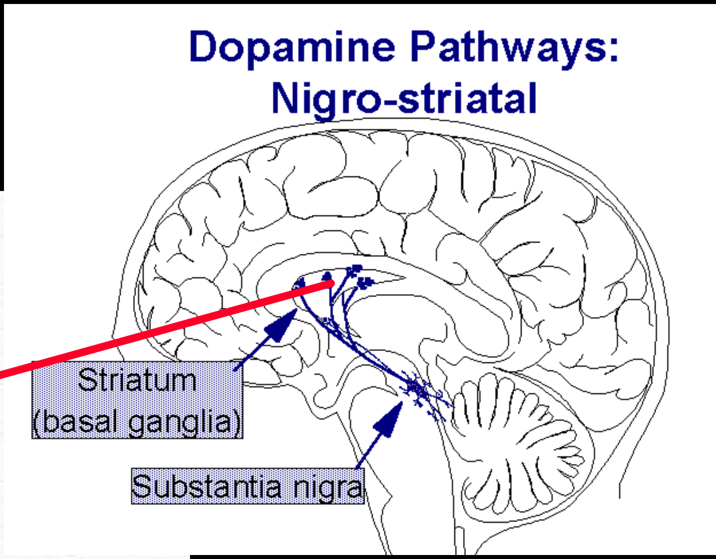
# Positron Emission Tomography Radiopharmaceuticals

| | Tracer | Half-life |
|---|---|---|
| • Metabolism | $^{18}F$-deoxyglucose | 110 min |
| • Blood flow | $^{15}O$-water | 2 min |
| • Benzodiazepine receptors | $^{11}C$-flumazenil | 20 min |
| • Dopamine synthesis | $^{18}F$-dopa | 110 min |


Dopaminergic system
frontal lobe
striatum
substancia nigra
tegmental area
CH2-CH2-NH2
OH
OH

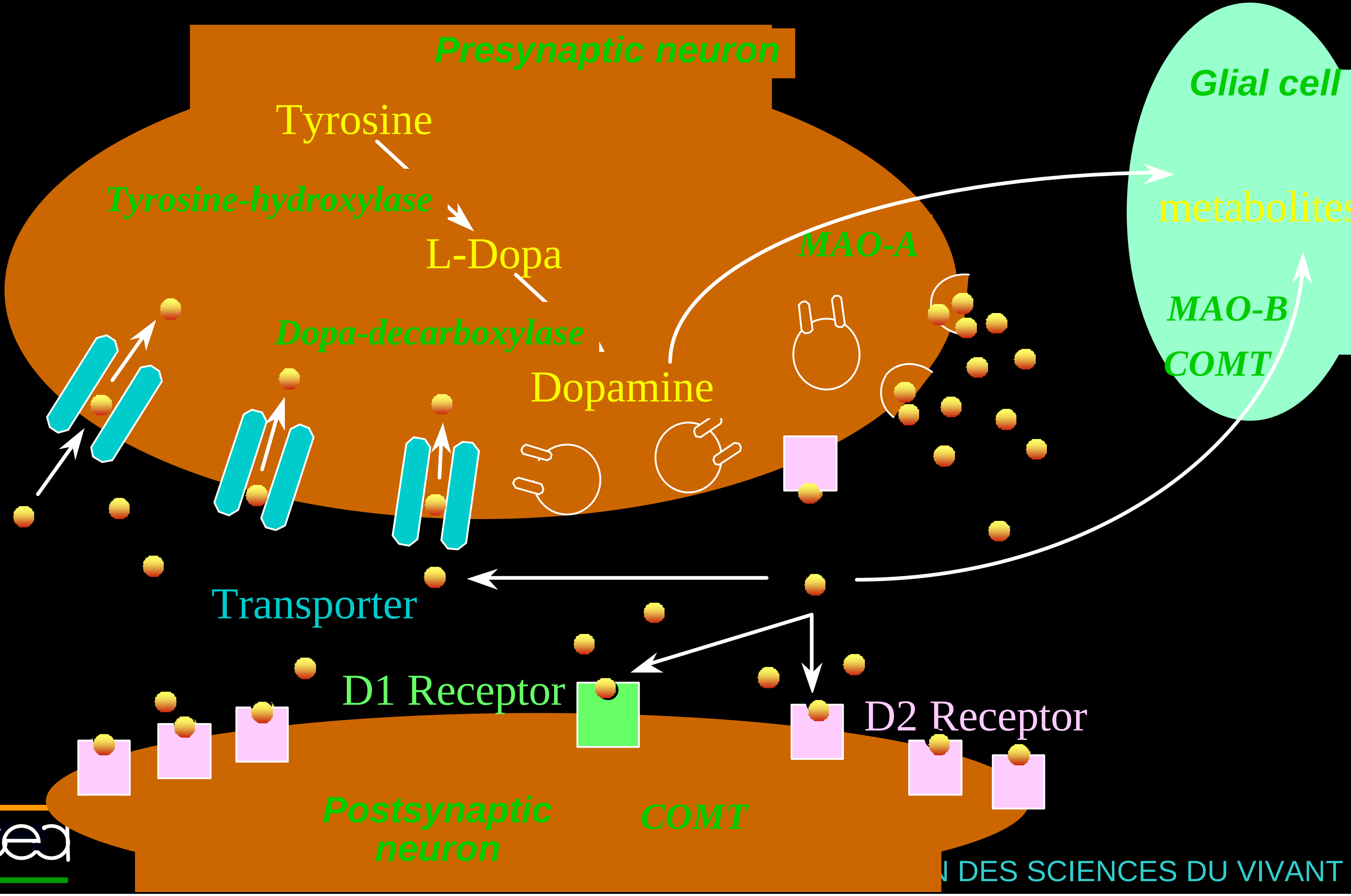
# Dopaminergic synapse





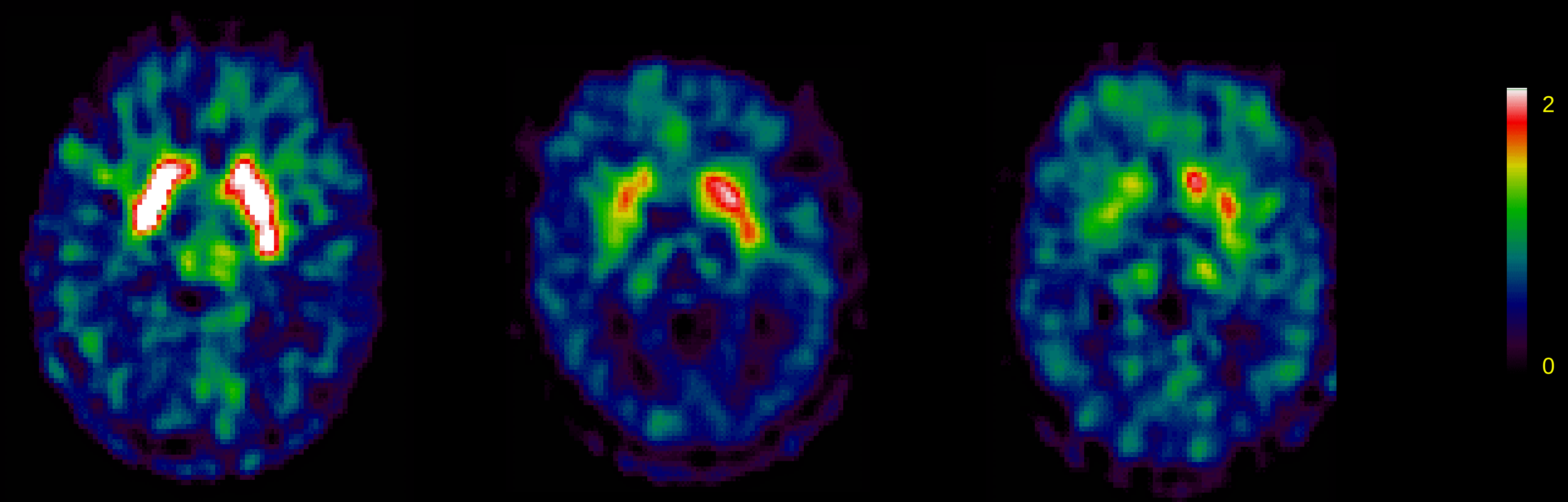

DIRECTION DES SCIENCES DU VIVANT

# Dopaminergic synapse

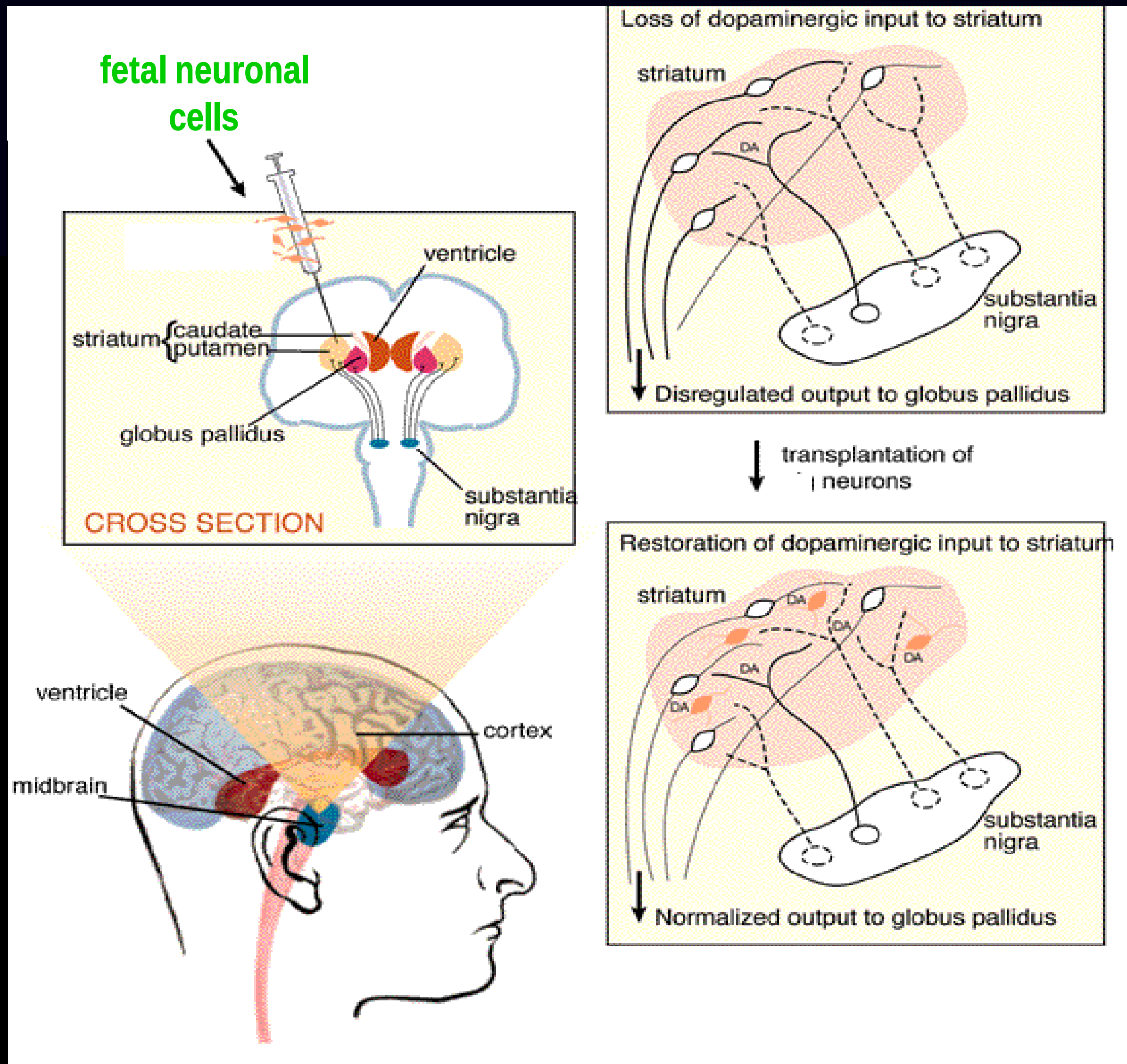


# Parkinson’s disease
# $^{18}$F-Fluorodopa and PET

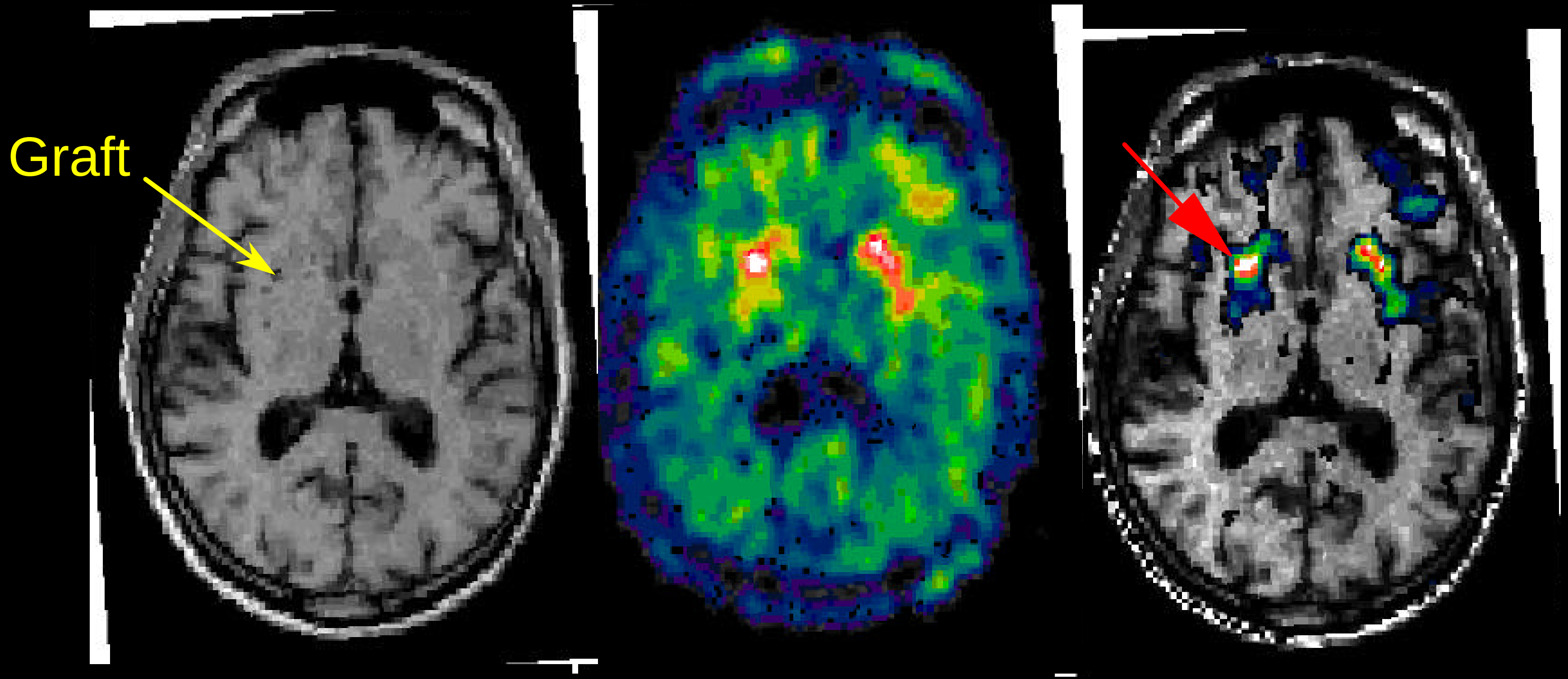
control early disease severe PD



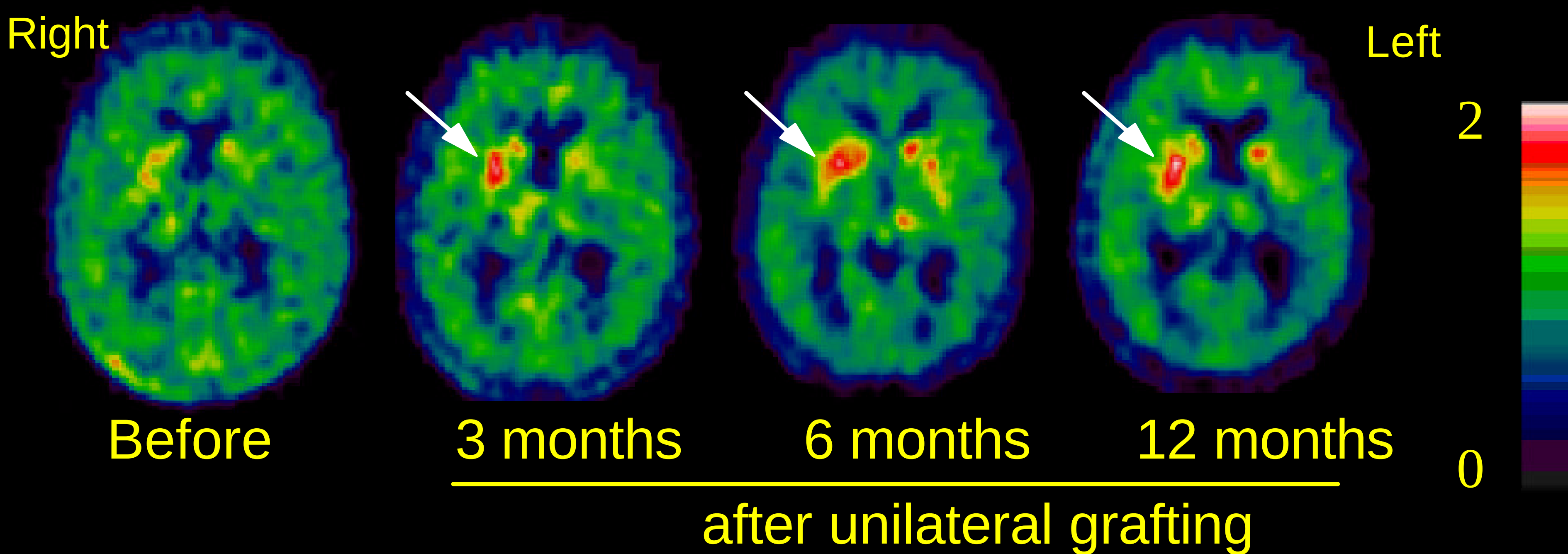
# Neuronal Transplantation



# Grafts in Parkinson's disease
# $^{18}$F-Fluorodopa and PET

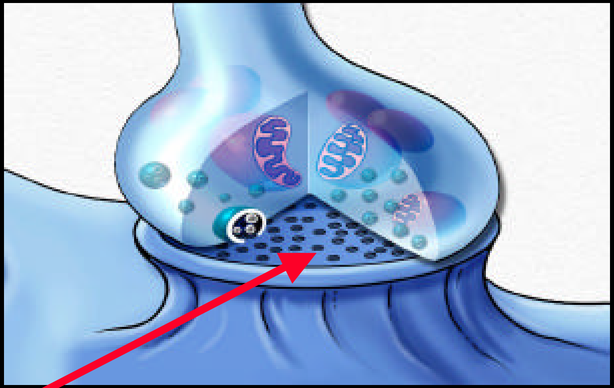


# Neurotransplantation in Parkinson 's disease

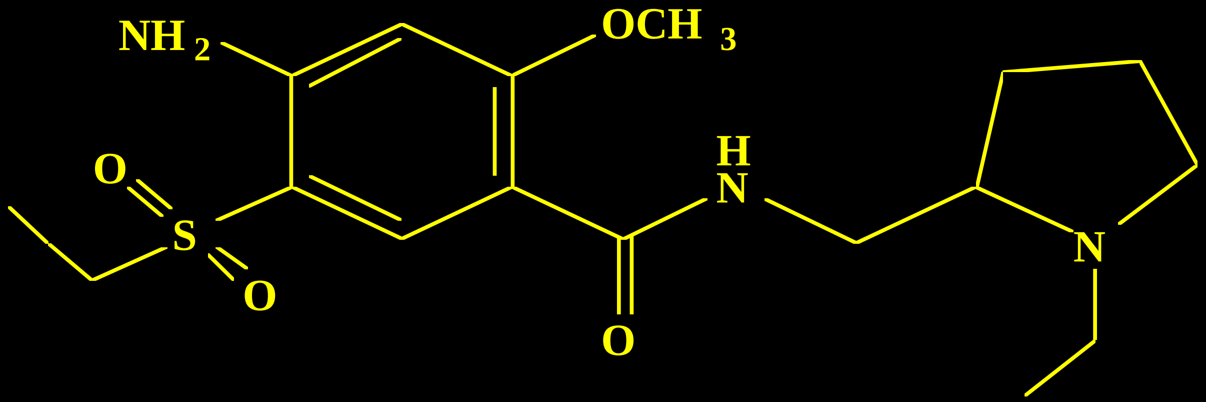



[$^{18}$F]-Fluorodopa

# AMISULPRIDE
## an antipsychotic drug

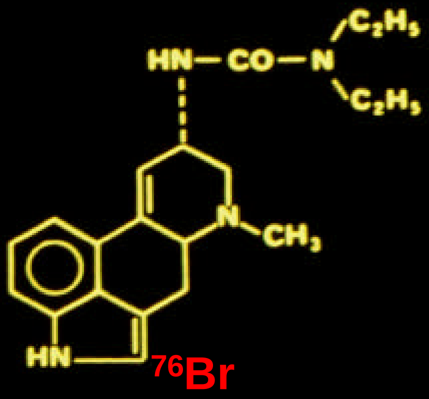


## D2 receptor occupancy in Schizophrenia

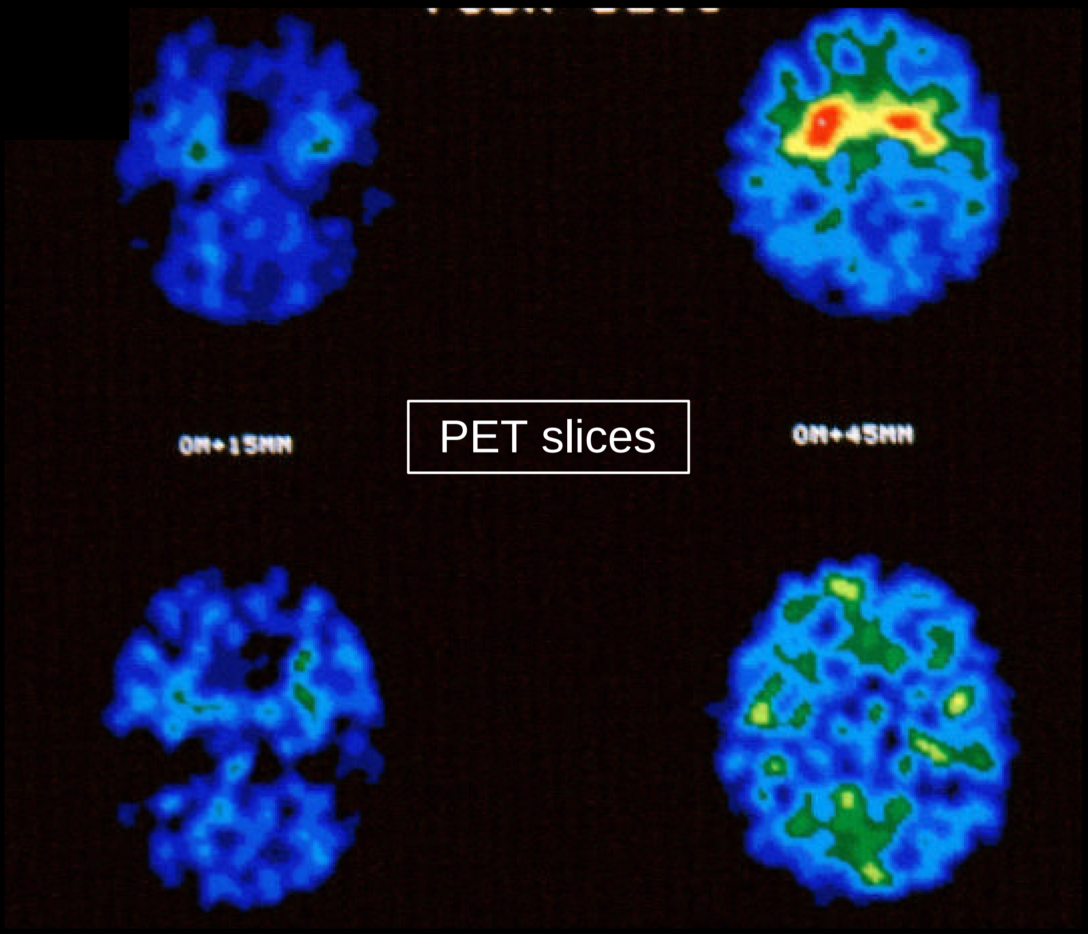



(+/-)-4-amino-N-{(1-ethyl-2-pyrrolidinyl)methyl}-5-ethylsulfonyl-2-methoxybenzamide

# $^{76}$Br-BromoLisuride



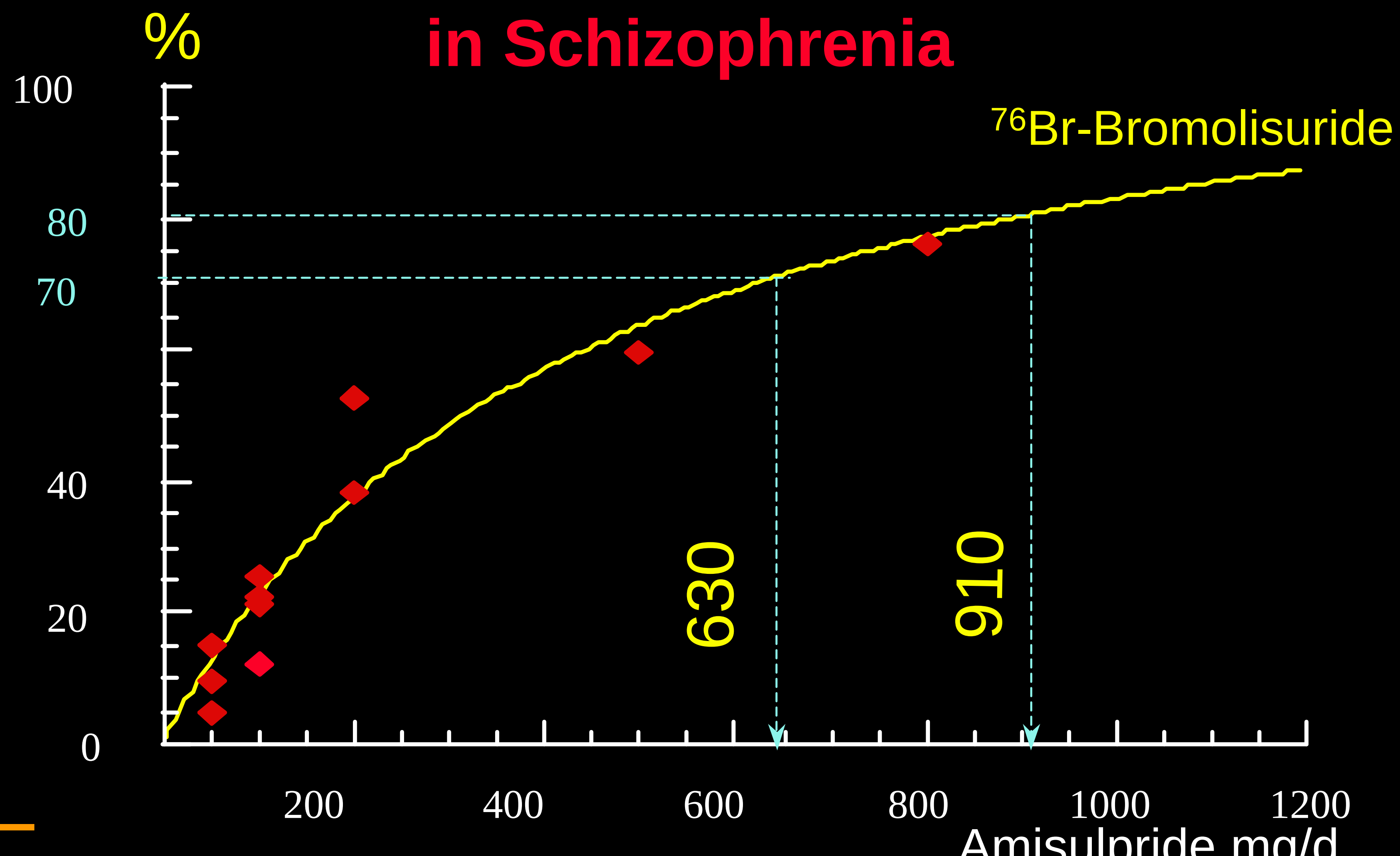

iv. injection




Control

Amisulpride
800 mg/d

# D2 receptor occupancy AMISULPRIDE in Schizophrenia




Martinot et al., 1995

# AMISULPRIDE
## in Schizophrenia

| Phase II and III trials | PET D2 receptor occupancy |
| --- | --- |
| Thousands of patients<br>8 years | 11 patients<br>2-3 months |
| Standard range doses : | Effective doses : |
| 600 -1200 mg/d | 630 - 900 mg/d |
| EPS incidence is high | Upper “safe” limit: |
| over 1200 mg/d | 1107 mg/d |

# CEREBRAL ACTIVATIONS

- Opening of ion channels (inflow of $Na^+$, outflow of $K^+$) and propagation of action potentials (a few ms)

→ **EEG, MEG**

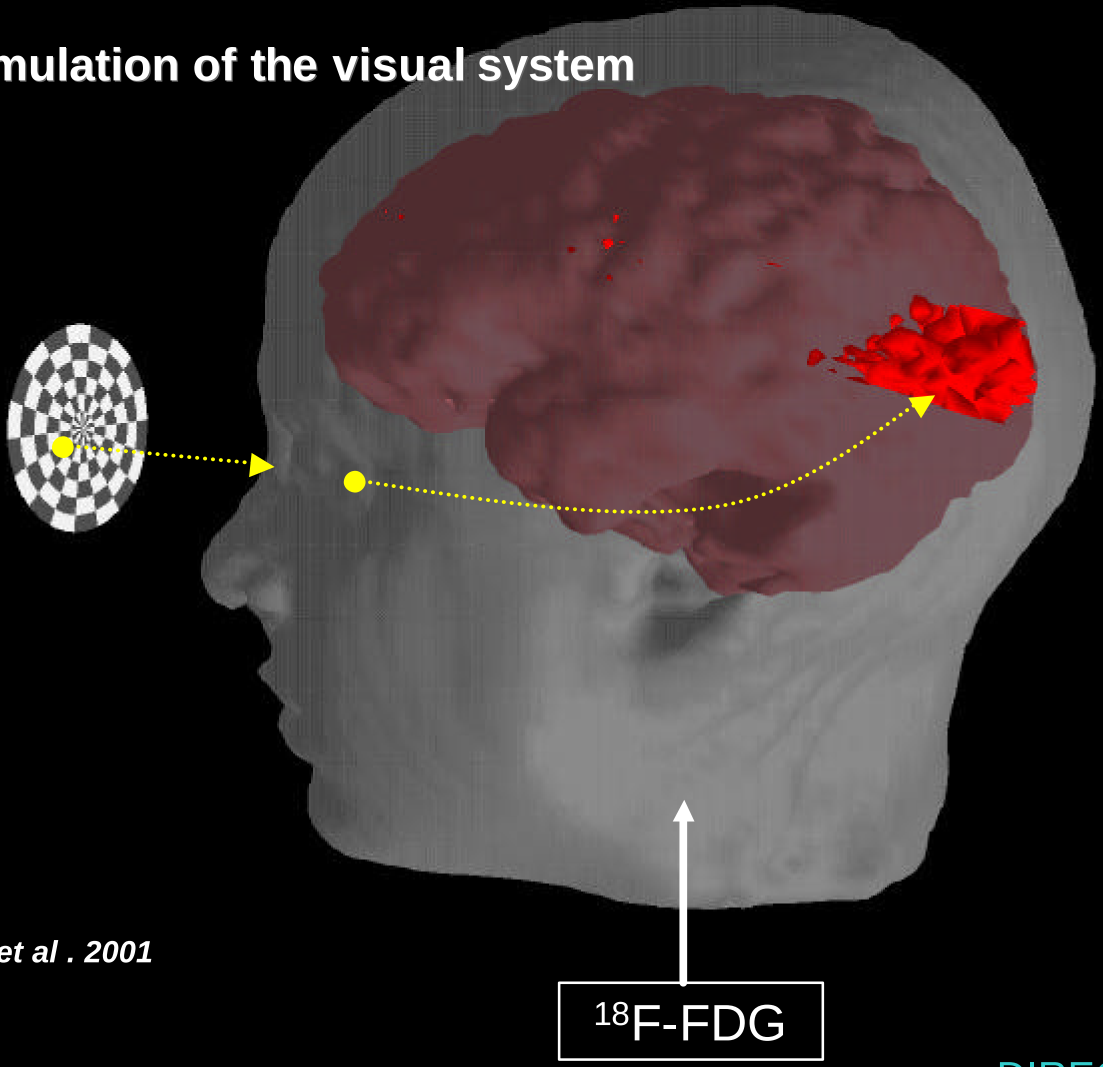
- Increased energy consumption (sec.) - ATP is needed for active transport of $Na^+$ and $K^+$ -
  - Increased regional cerebral blood flow
  - Increased regional cerebral blood volume
  - Few modifications of oxygen utilization

→ **PET, SPECT, fMRI, NIRS**

# Visual activation task

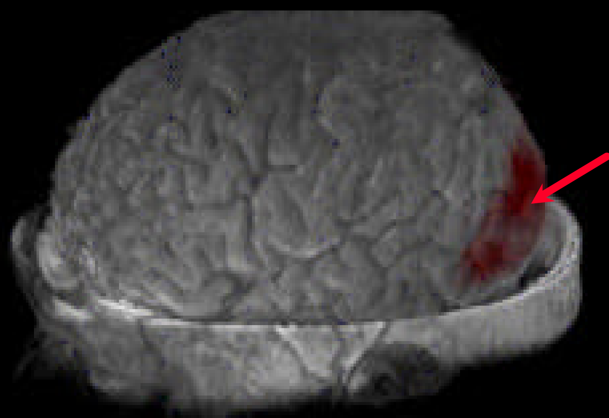
1- injection of an analogue of glucose labeled with $^{18}F$ ($^{18}F$-fluorodeoxyglucose)

2- stimulation of the visual system




Increased glucose consumption

visual cortex is activated

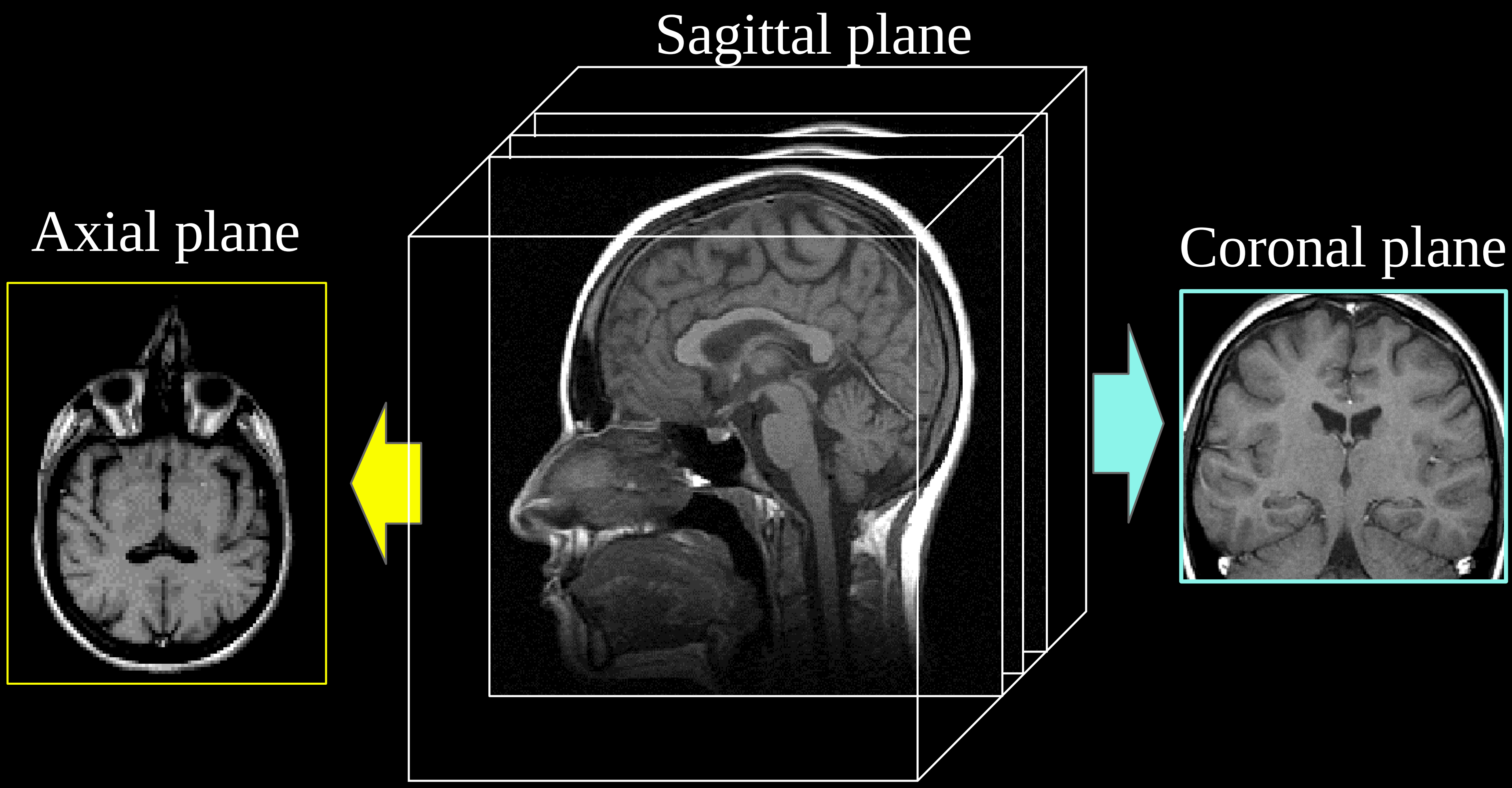


*Huettel et al . 2001*

# HISTORY OF NUCLEAR MAGNETIC RESONANCE

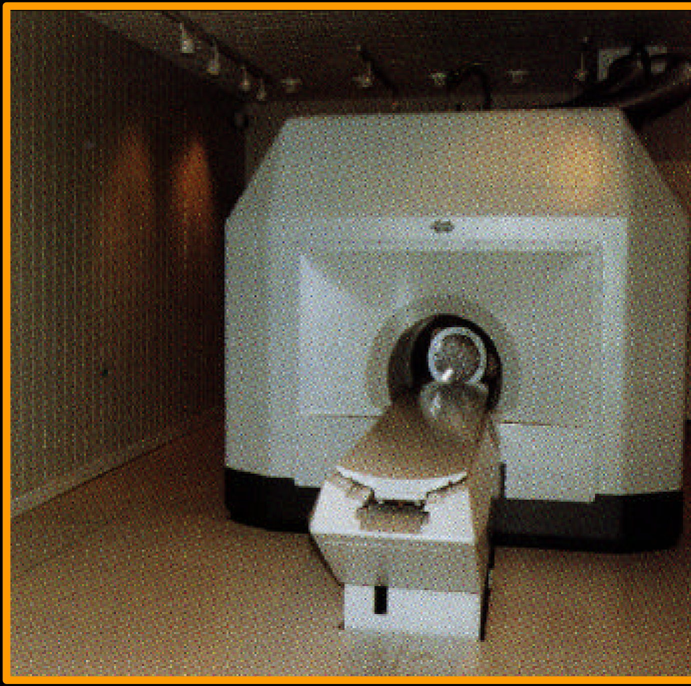
- 1946 F. Bloch: *Nuclear Induction*.
- 1947 E.M. Purcell: *Resonance Absorption by Nuclear Magnetic Moments in a Solid*.
- 1971 R. Damadian: *Tumor Detection by Nuclear Magnetic Resonance.*
- *1973* P.C. Lauterbur: *Image Formation by Induced Local Interactions: Examples employing Nuclear Magnetic Resonance.*

# Magnetic Resonance Imaging



# Functional Magnetic Resonance Imaging (fMRI)

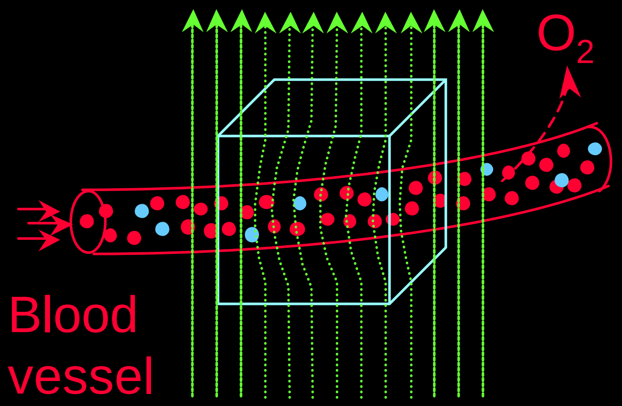
- 1991 J.W. Belliveau et al.: *Functional Mapping of the Human Visual Cortex by Magnetic Resonance Imaging.*
- 1992 Ogawa S. et al.: *Oxygenation - Sensitive Contrast in Magnetic Resonance Imaging of Rodent Brain at High Magnetic Fields (BOLD technique)*



SHFJ, whole body 3T magnet

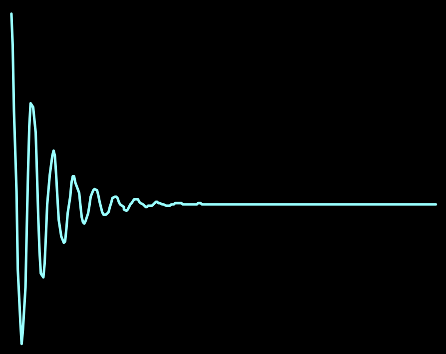
# Blood Oxygenation Level-Dependent (BOLD) fMRI

Voxel in the brain



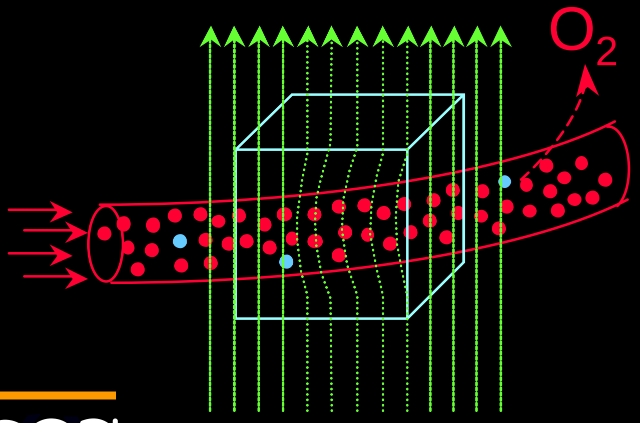

<u>Baseline condition:</u>

Local $B_0$ distorded by endogenous Hb



$B_0$

Time domain signal



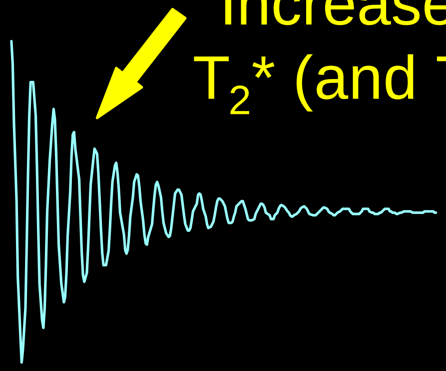

<u>Activation:</u>

↑↑↑ CBV and CBF

↑ $O_2$ extraction

Net ↓ in Hb

Improved local $B_0$ homogeneity



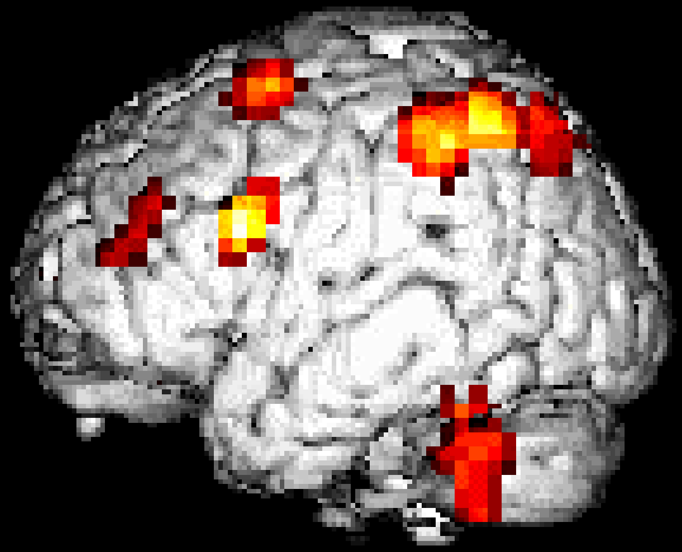
Increased $T_2$* (and $T_2$)

# CEREBRAL ACTIVATIONS and fMRI

- BOLD technique: Blood Oxygen Level Dependent
- hemoglobin of the rbcs is the endogen contrast agent
- increased oxyhemoglobin content results in an increase in $T_2^*/T_1$ signal
- 2%-5% changes at 1,5T and 10% to 15% at 4T
- changes in blood flow are visible but cannot be quantified in absolute values (ml/mn/g)
- spatial (anatomic) resolution is excellent

# Exact calculation and approximation

Exact Calculation

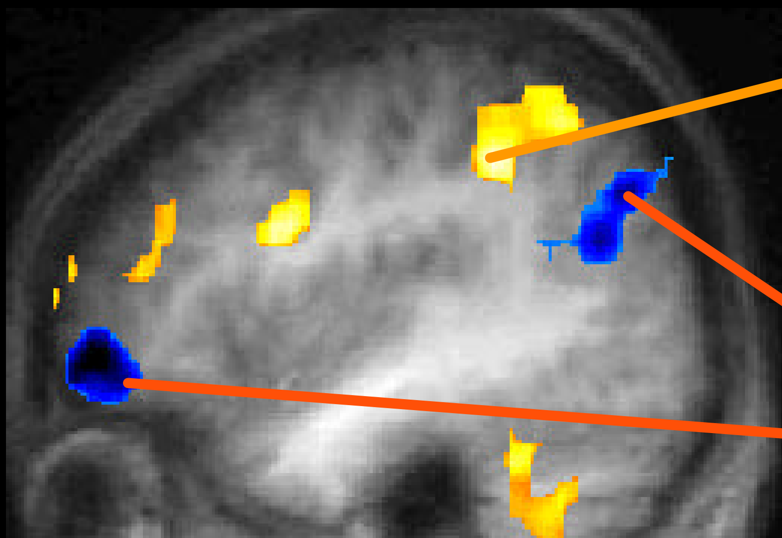


Approximation

Dehaene et al., *Science* May 7th 1999

Service Hospitalier Frédéric Joliot, CEA/DSV, Orsay, France

# Exact calculation and approximation



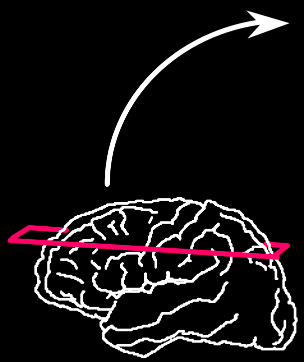
Approximation
Intraparietal Cortex

Exact Calculation
Angular Gyrus
and Inferior Frontal Cortex

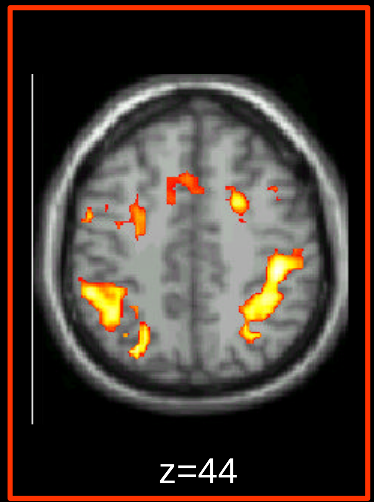
Dehaene et al., *Science* May 7th 1999

Service Hospitalier Frédéric Joliot, CEA/DSV, Orsay, France

# Number representation in the inferior parietal lobe

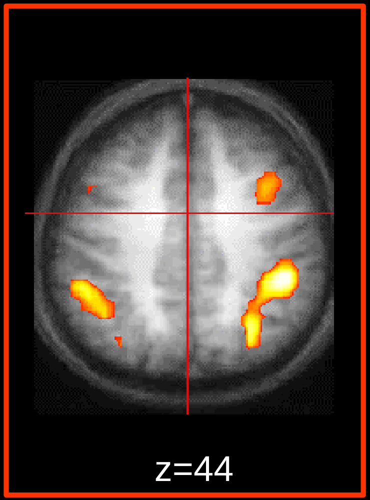


***Calculation - Letter naming***



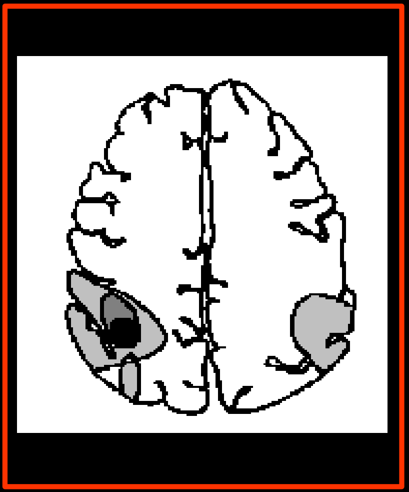

Chochon, Cohen, van de Moortele, & Dehaene (1999) *Journal of Cognitive Neuroscience*

***Approximation - Letter matching***



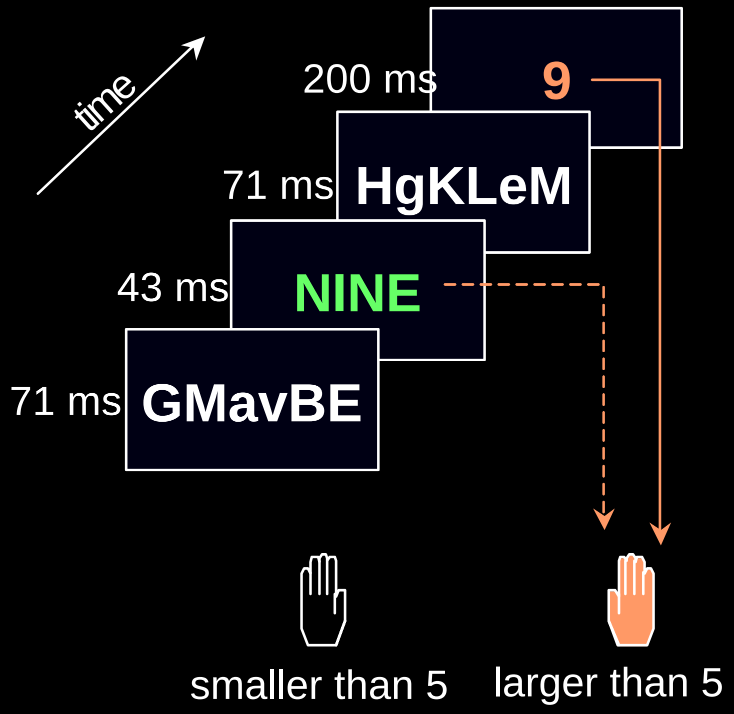

Dehaene, Spelke, Stanescu, Pinel & Tsivkin (1999) *Science, 284*, 970-974

***Lesions in 5 acalculic patients***

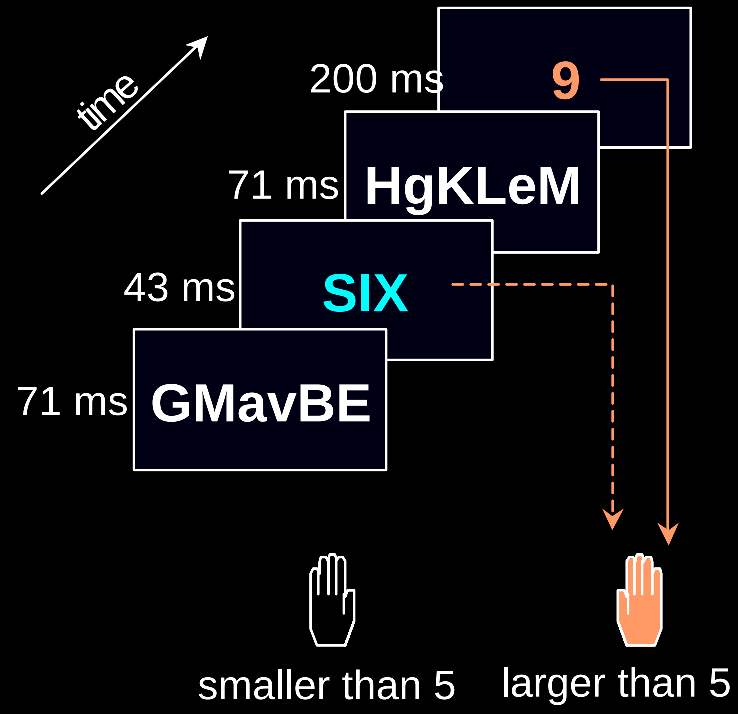


Dehaene, Dehaene-Lambertz, & Cohen (1998) *Trends in Neuroscience, 21*, 355-361.

# QUANTITY REPETITION PRIMING: A MARKER OF UNCONSCIOUS SEMANTIC PROCESSING?




**Same Response**
**Repeated Quantity**

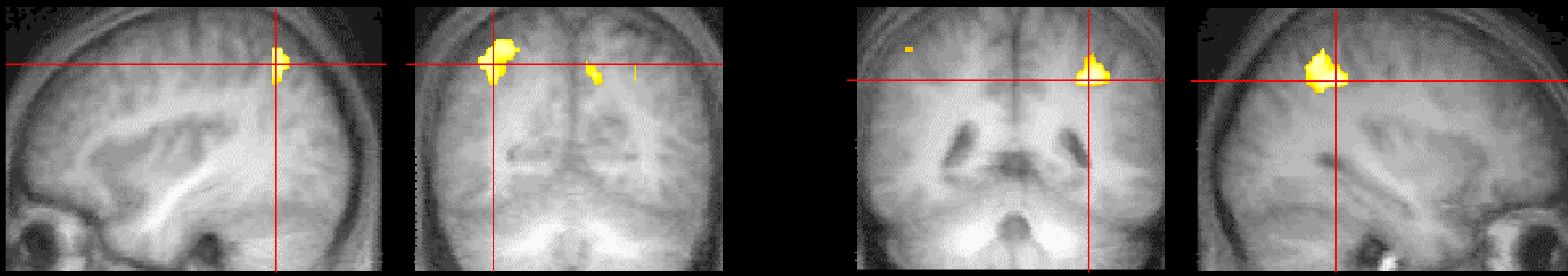



**Same Response**
**Different Quantity**

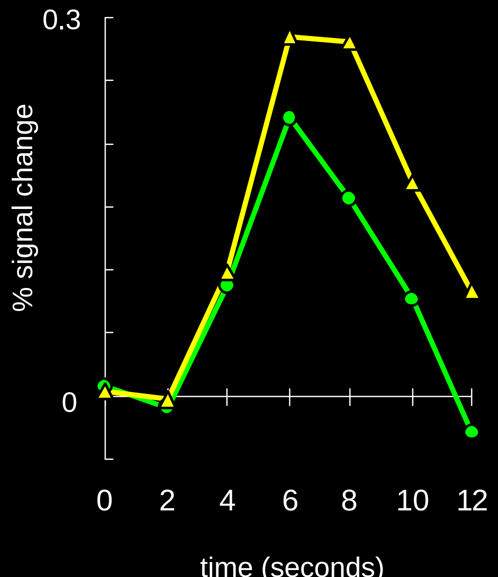
*Nature, 1998*

# A DIRECT IMAGE OF UNCONSCIOUS SEMANTIC PROCESSING

The intraparietal quantity system shows a notation-independent repetition effect



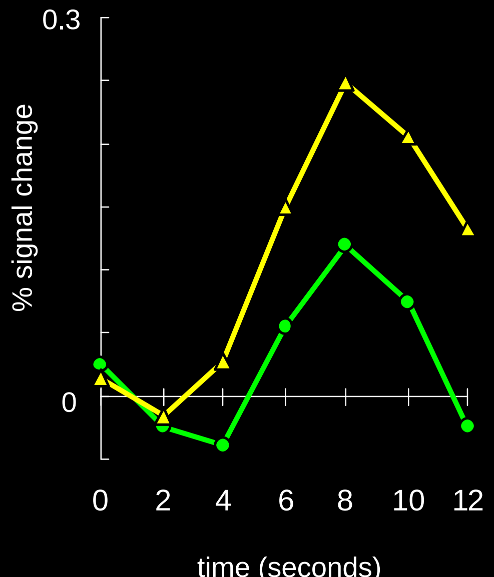
**Left Intraparietal**



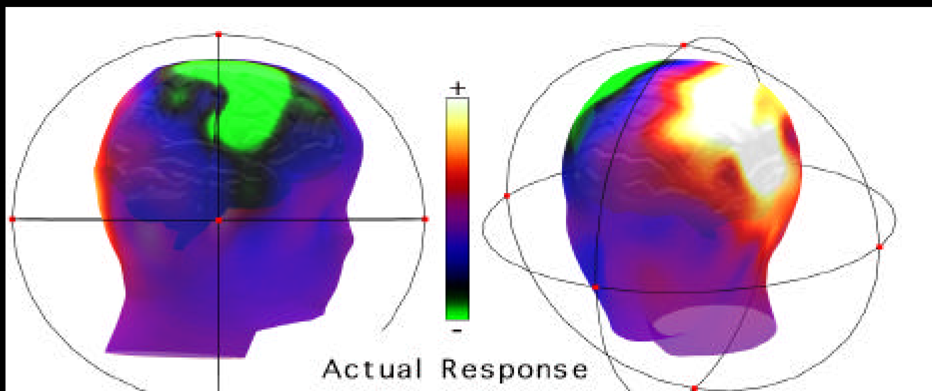

**Different Quantity**

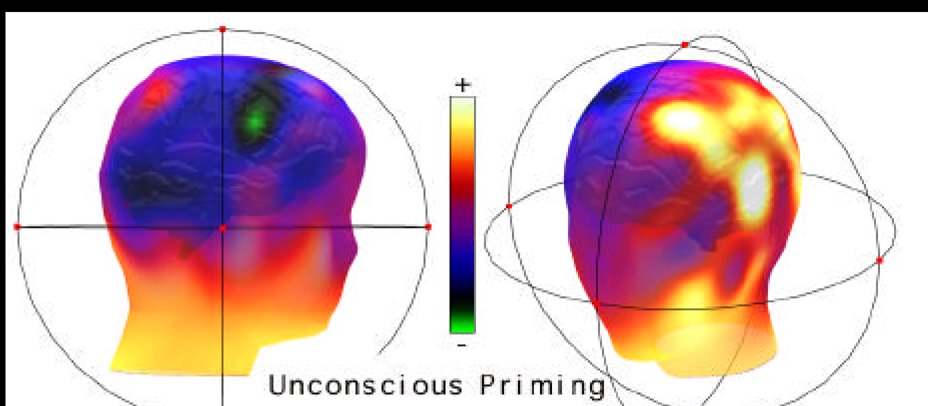
**Repeated Quantity**

**Right Intraparietal**



# Imaging cognitive functions : unconsciousness




Cerebral imaging confirms that our brain is able to process subliminal informations

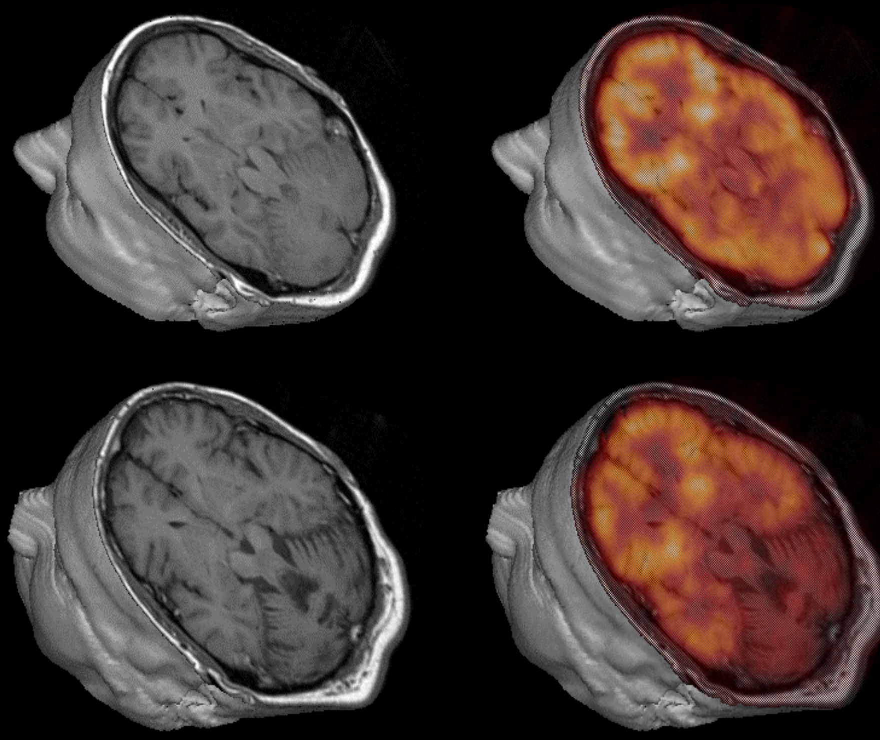
*Nature (1998)*

# THE SPIRITUAL FATHERS OF THE LOCALISTIC THEORY

- 1761 Giambattista Morgagni:  development of the anatomical concept of diseases
- 1801 Xavier Bichat:  the birth of modern medicine: «Cut open a few cadavers and any doubts that observation alone could not dispel will vanish instantly.»
- 1894 Rudolf Virchow: the  relationship between illness and the histopathological discovery of tissue anomalies
- 1895 Wilhelm Röntgen: display of the skeleton

# NUCLEAR MEDICINE AND FUNCTIONAL IMAGING

- 1950: first functional images of the thyroid
- 1970s: the CT scanner, ultrasonography, MRI..., endoscopy and biopsies..., even ECG are techniques which are interpreted in the same way as images
- 1990: Nuclear medicine aims at progressing beyond anatomy and histopathology to become a true molecular medicine



# SERVICE HOSPITALIER FREDERIC JOLIOT
# Orsay

DIRECTION DES SCIENCES DU VIVANT