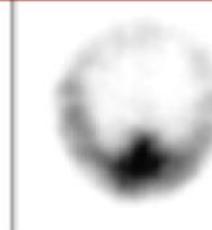
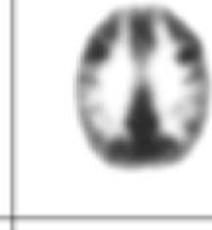
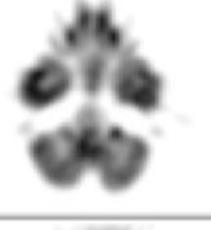
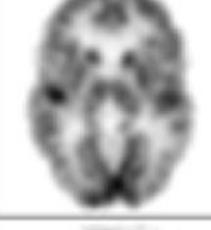
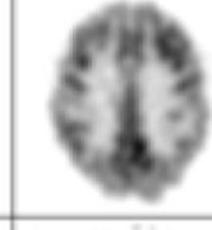
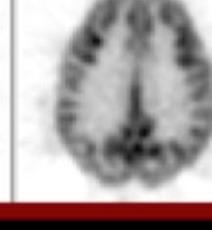


Positron Emission Tomography: Clinical and Research Applications



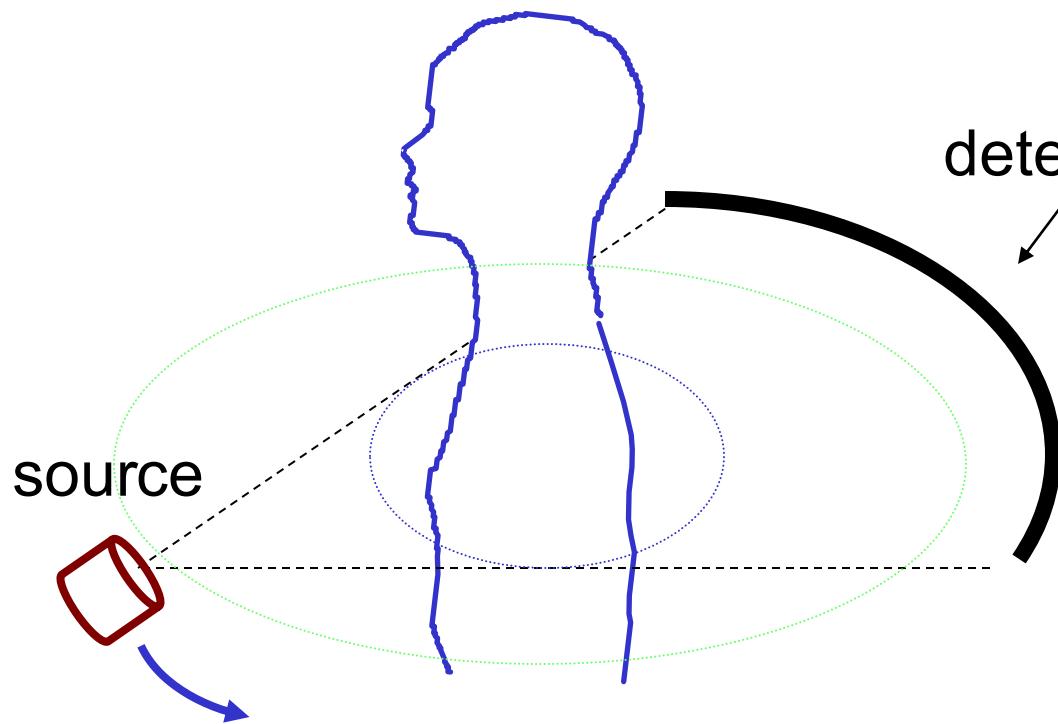


- 1975 the first commercial PET scanner was introduced
- 70s and 80s PET was mainly used for research
- 1990s being used in clinics regularly

			PET III 1975
			ECAT II 1977
			NeuroECAT 1978
			ECAT 931 1985
			ECAT EXACT HR ⁺ 1995

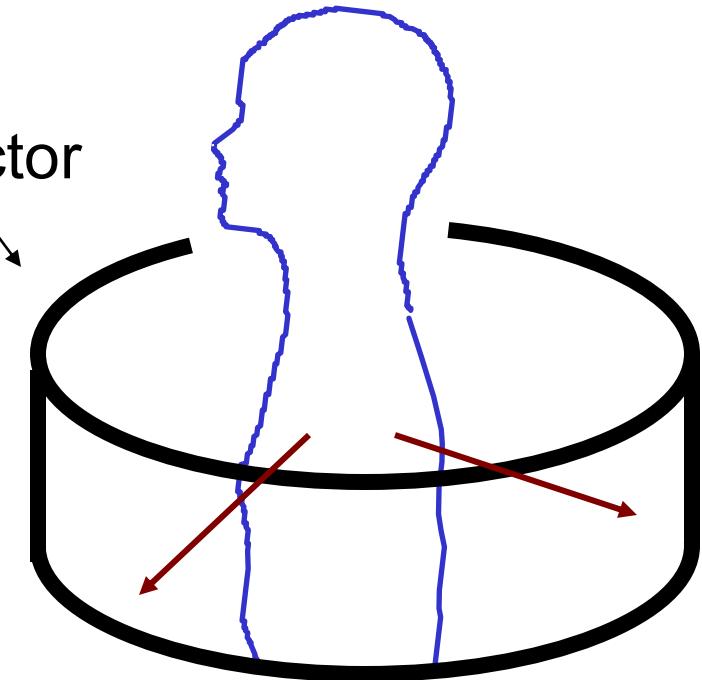
Two Types of Tomography

‘Tomo’ + ‘graphy’ = Greek: ‘slice’ + ‘picture’



CT: Transmission

detector



PET: Emission

Major Medical Imaging Modalities

<u>Modality</u>	<u>Resolution (mm)</u>	<u>TX or EM*</u>	<u>Mode</u>
X-ray	0.1 – 1.0	TX	Projection
Nuclear	10 – 20	EM	Projection
		Medicine	
X-ray CT	0.5	TX	Tomographic
Ultrasound	0.3	TX (sound)	Tomographic
MRI	1	EM (RF)	Tomographic
SPECT	10	EM	Tomographic
PET	5	EM	Tomographic

*(TX = transmission, EM = emission)

Positron Emission Tomography

- Positron-emitting short half-life (e.g., $^{18}\text{Fluoride}$, $^{15}\text{Oxygen}$) radionuclides to form labelled compounds as radiotracers

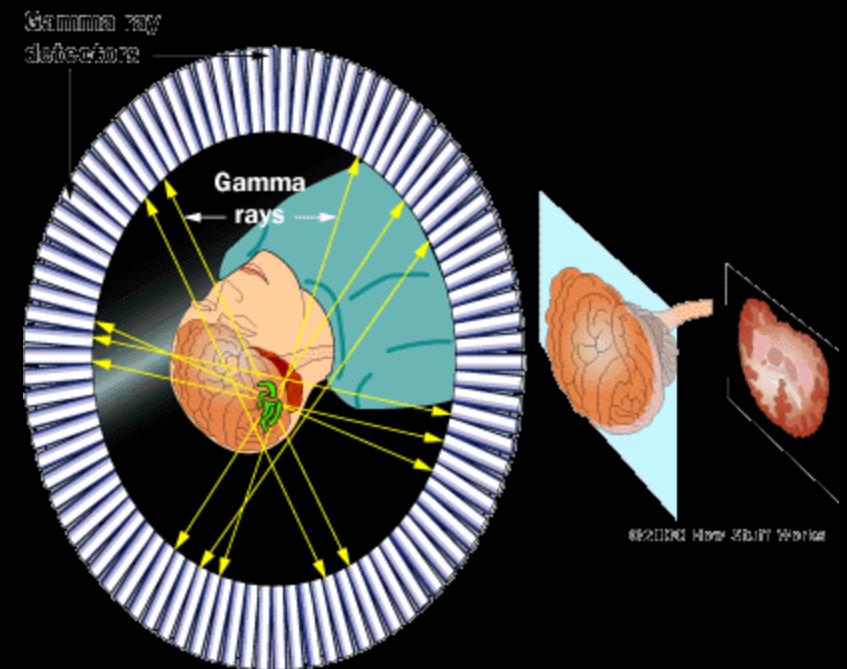
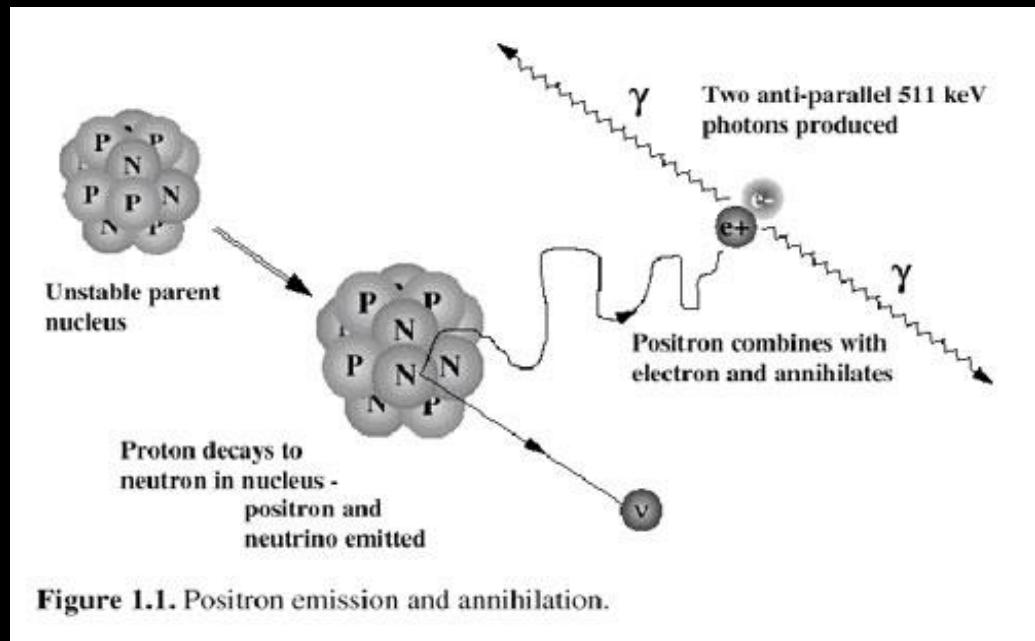
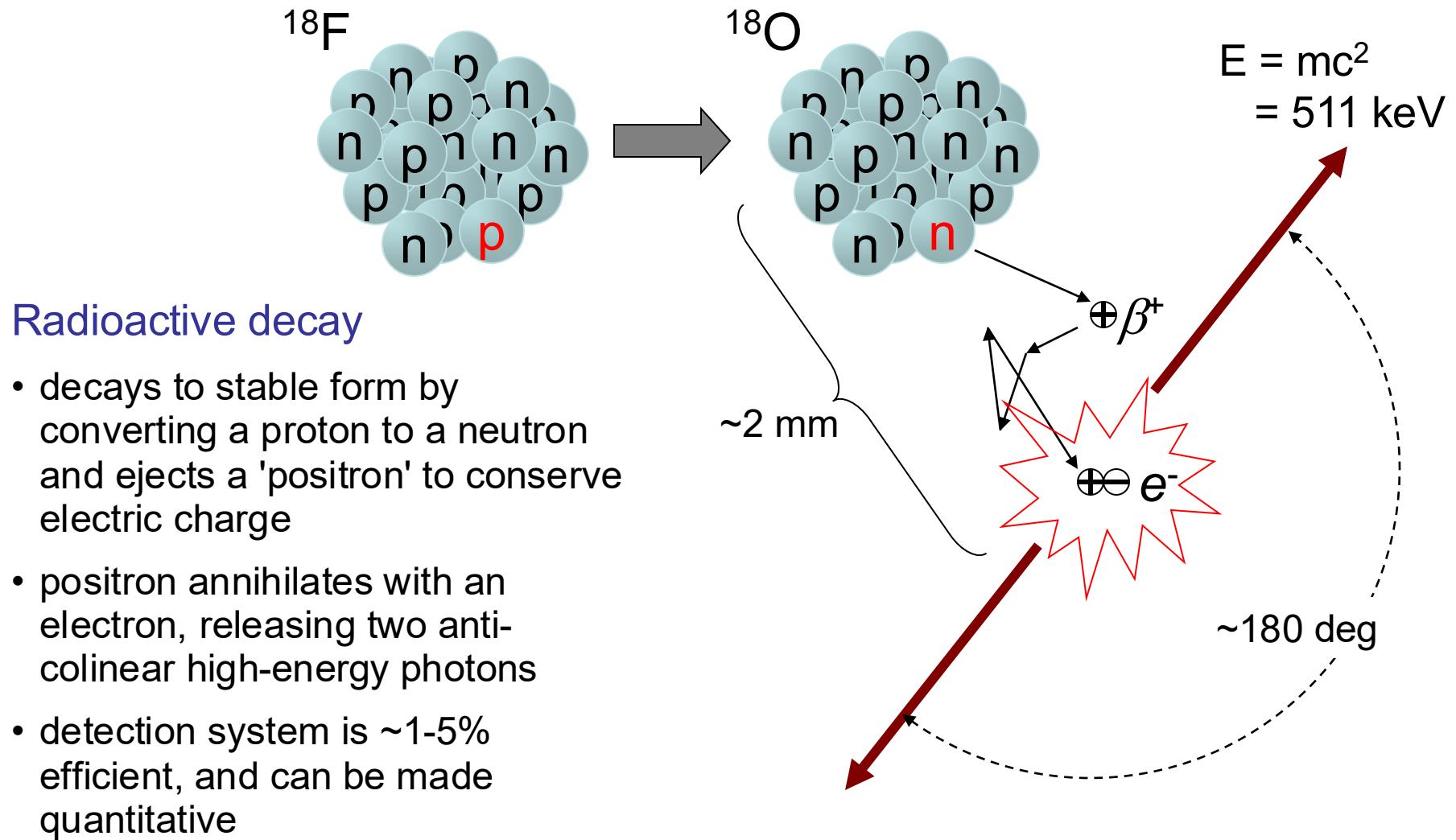
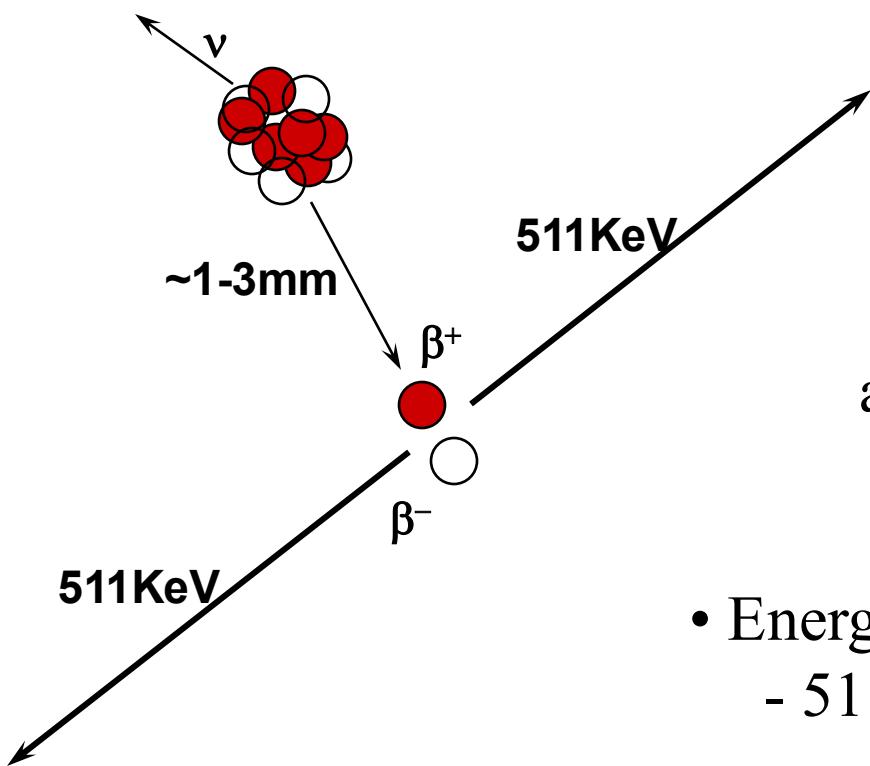


Figure 1.1. Positron emission and annihilation.

How it works: Positron Emission

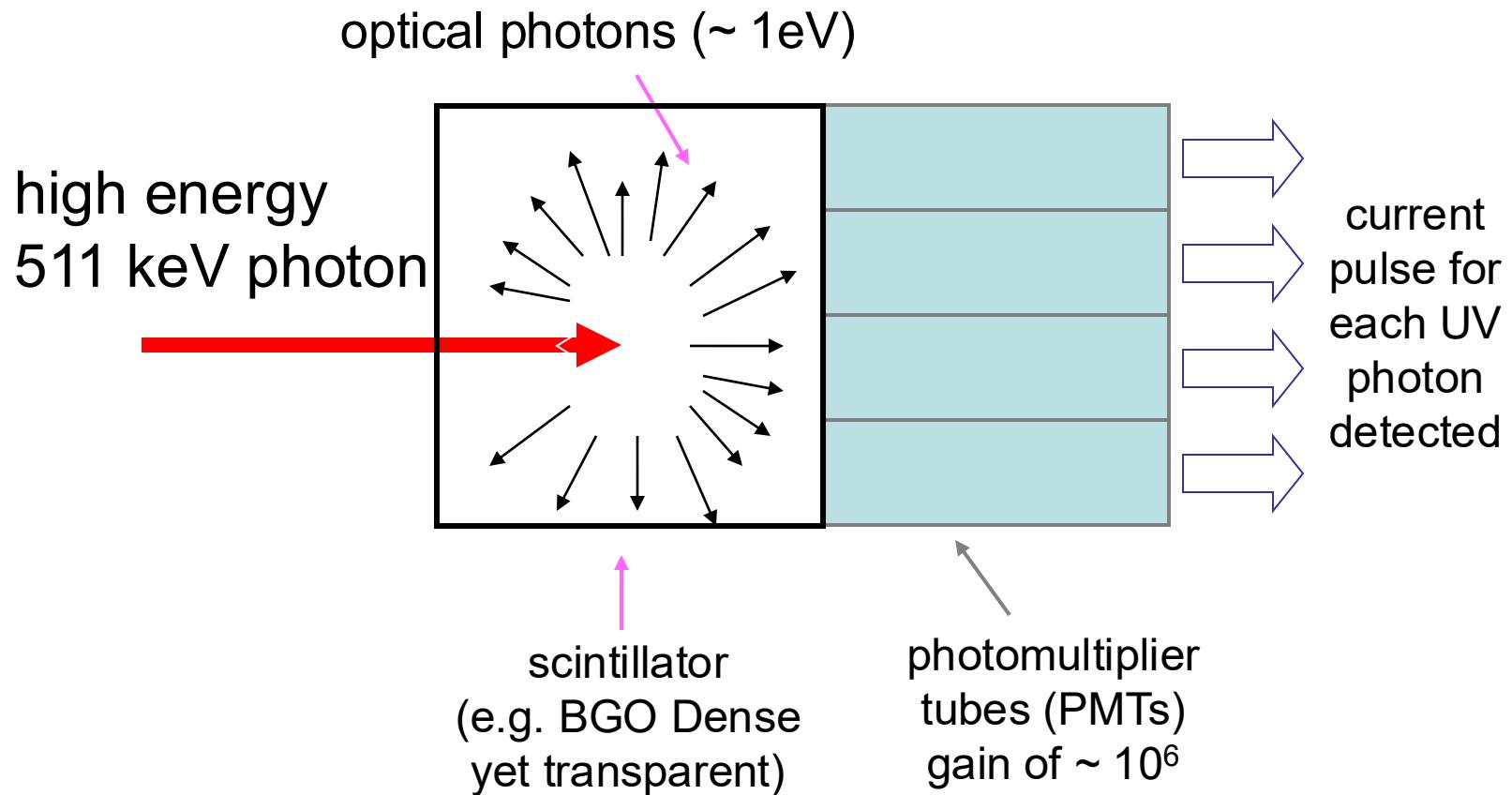


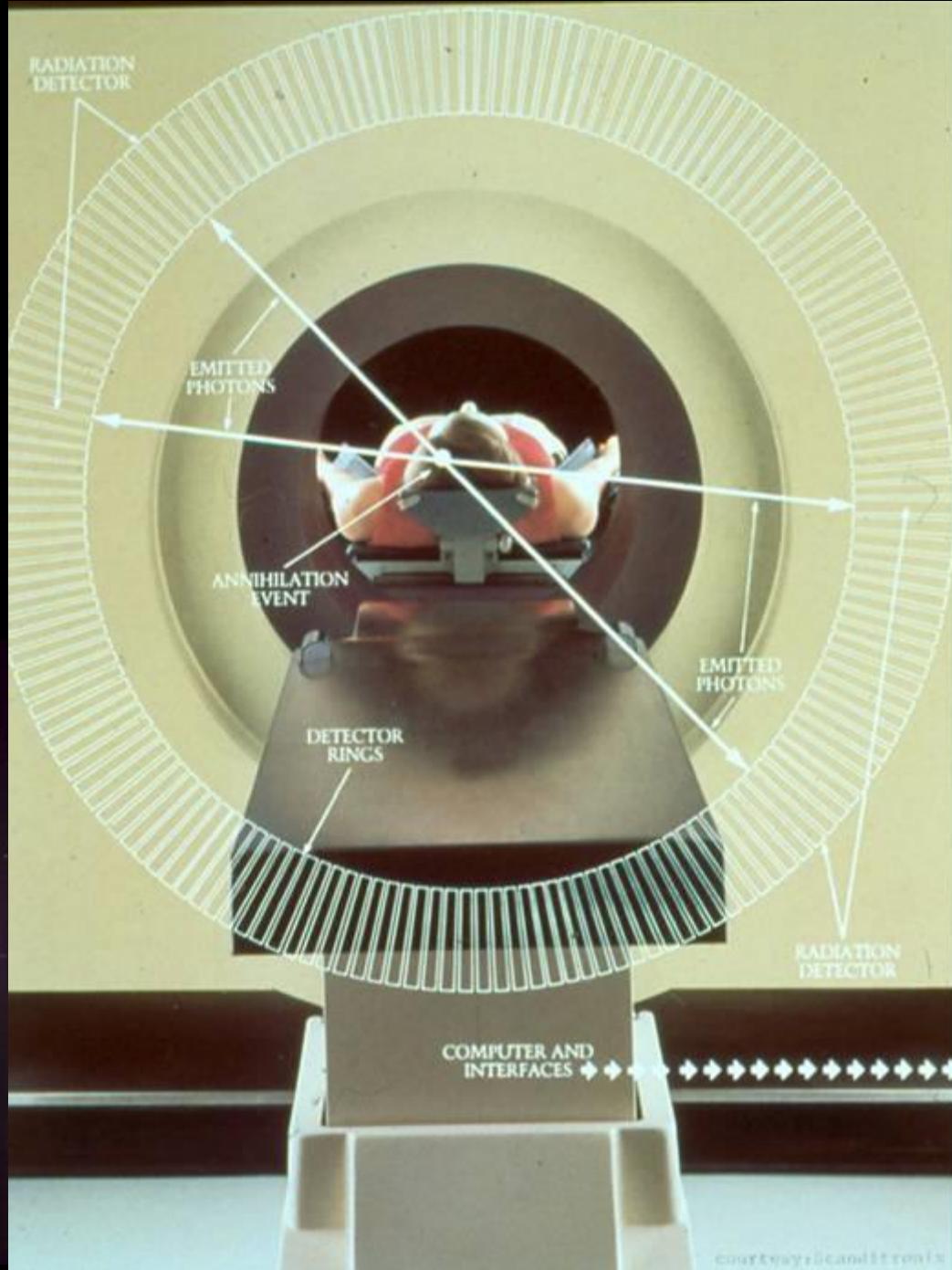
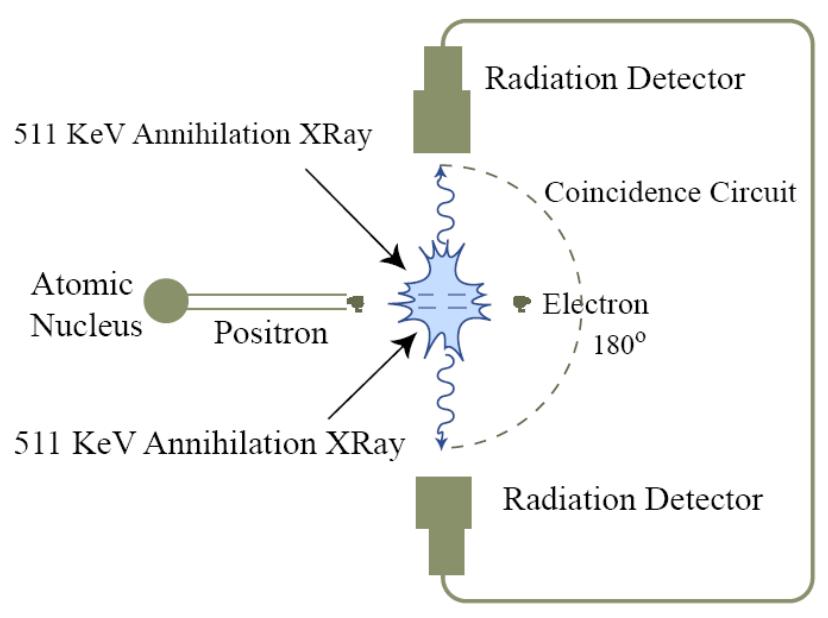
Basic Physics



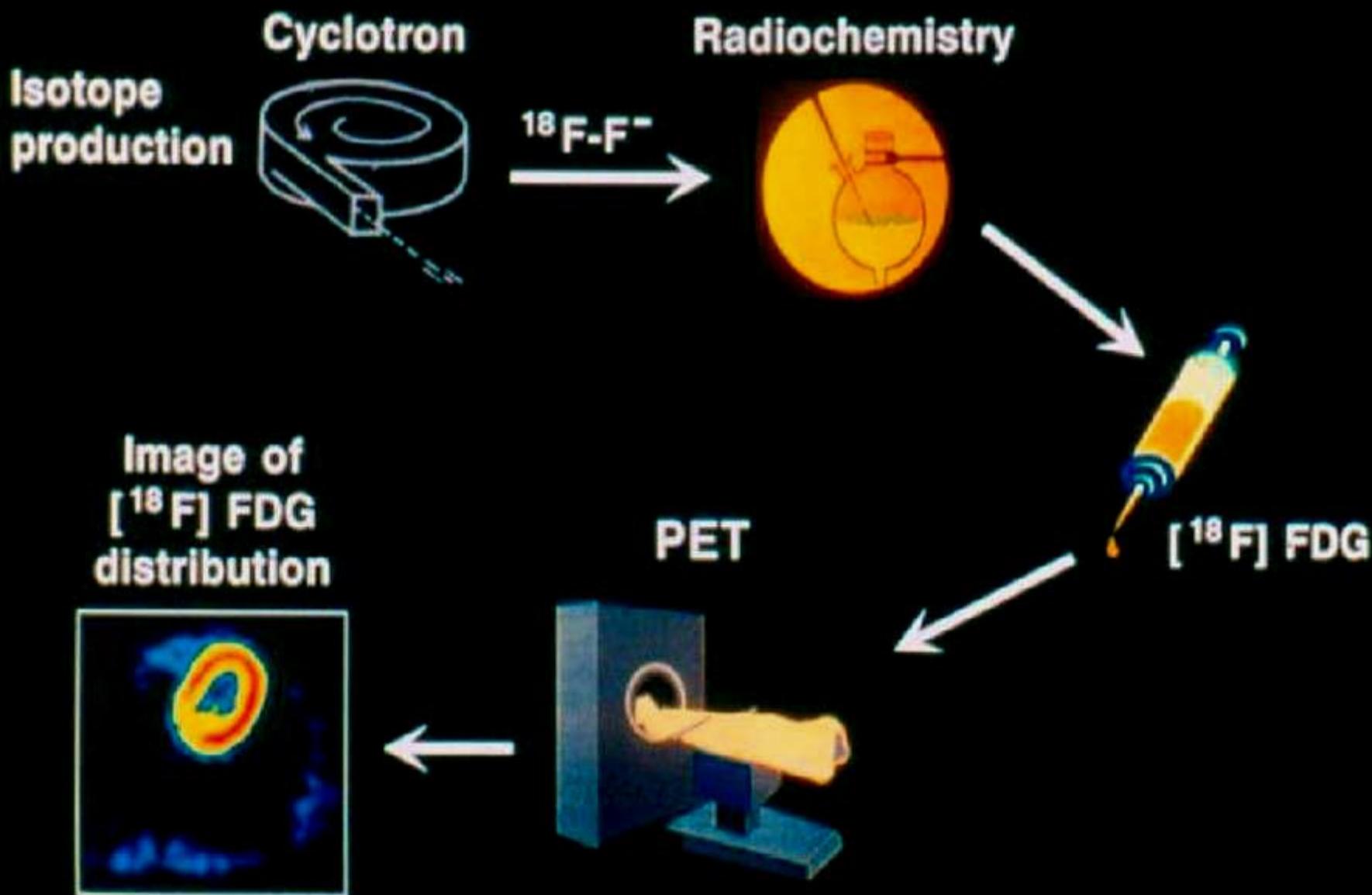
- Positron travels 1-3 mm before annihilation (depending on energy)
- Energy and Momentum conservation
 - 511 keV Photons and back-to-back
- **Simultaneous detection of two 511KeV photons →**
 - event along line between detectors

How it works: Scintillation

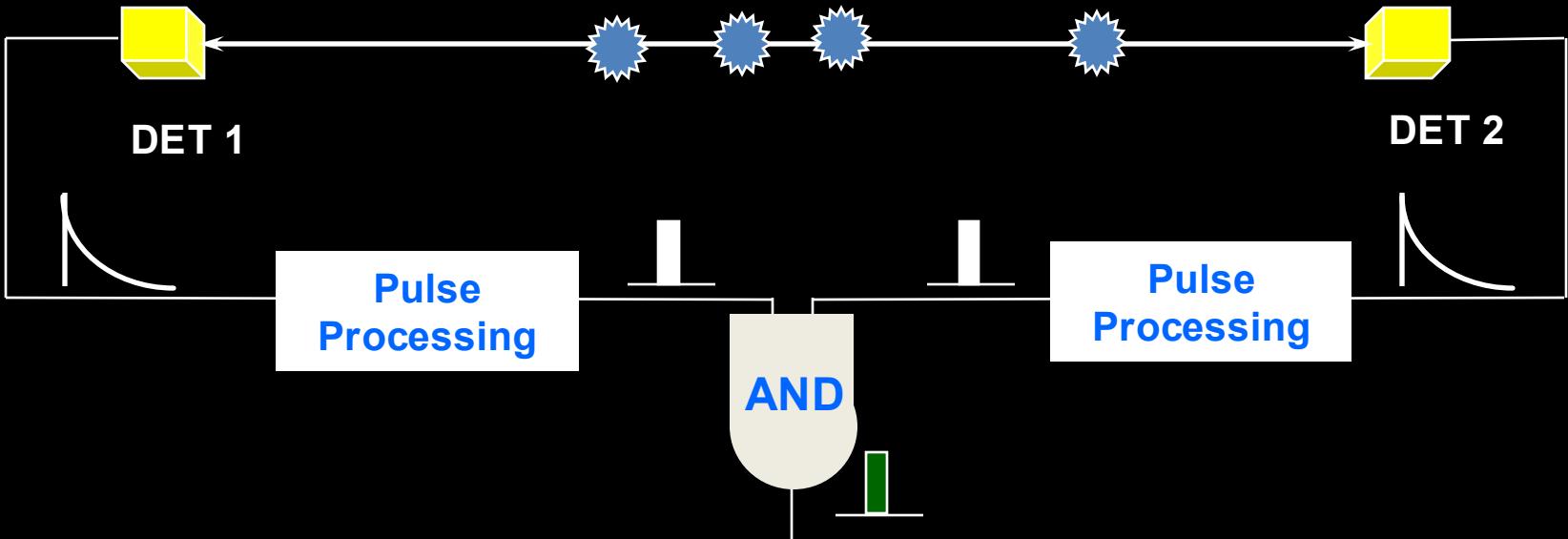




IMAGING OF GLUCOSE UPTAKE BY PET

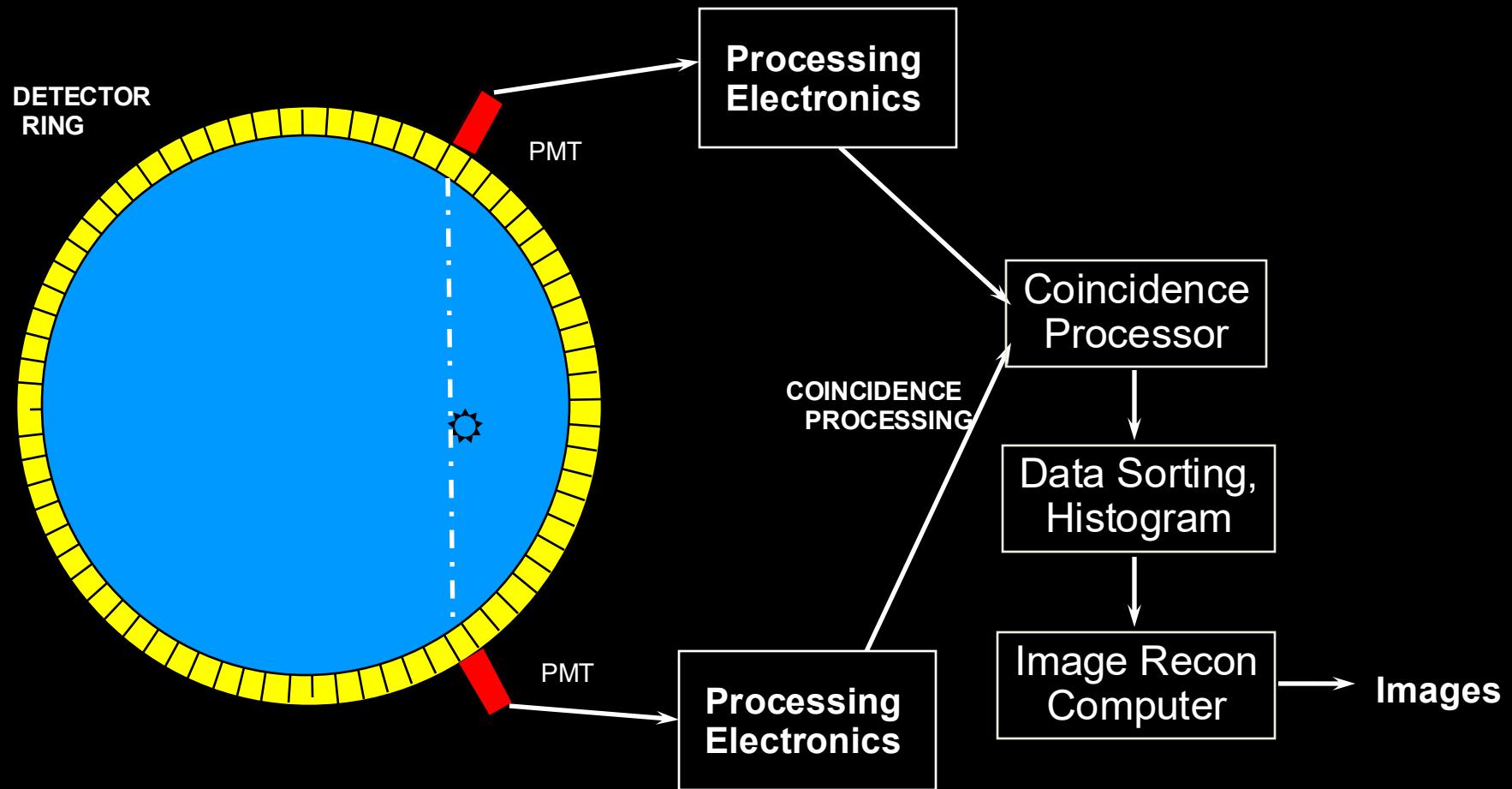


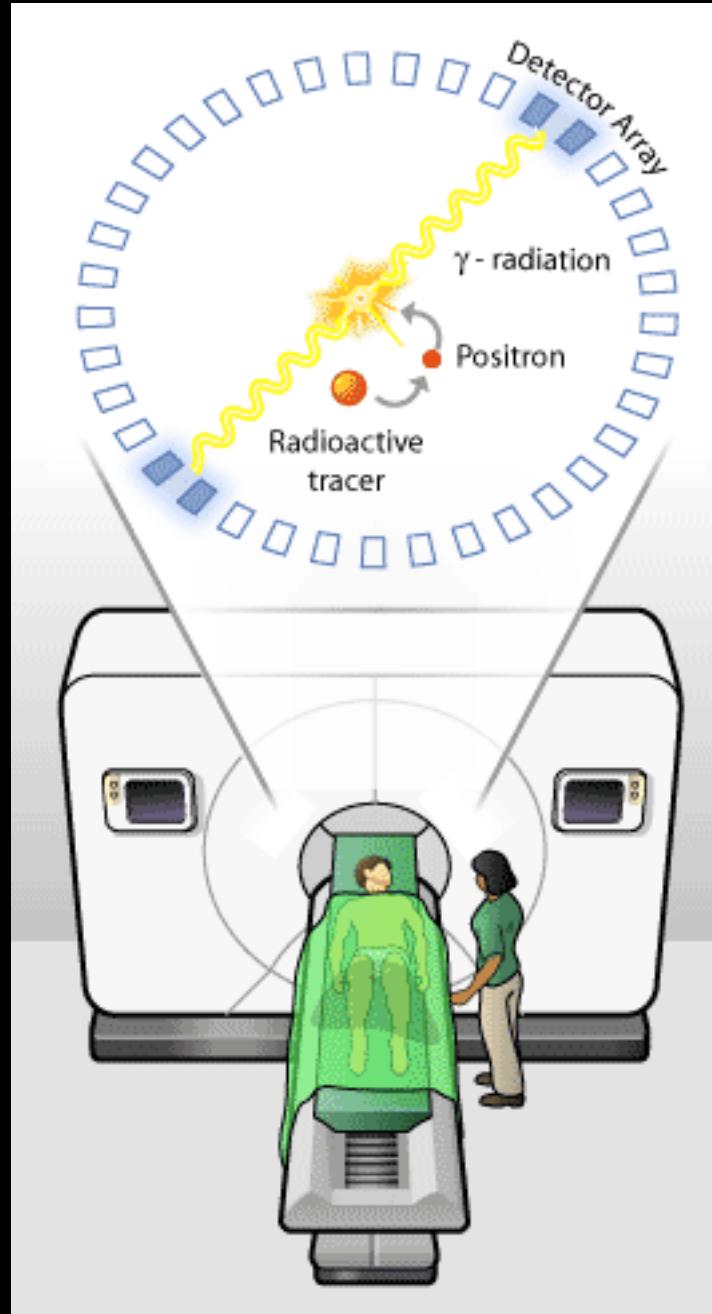
Coincidence Detection



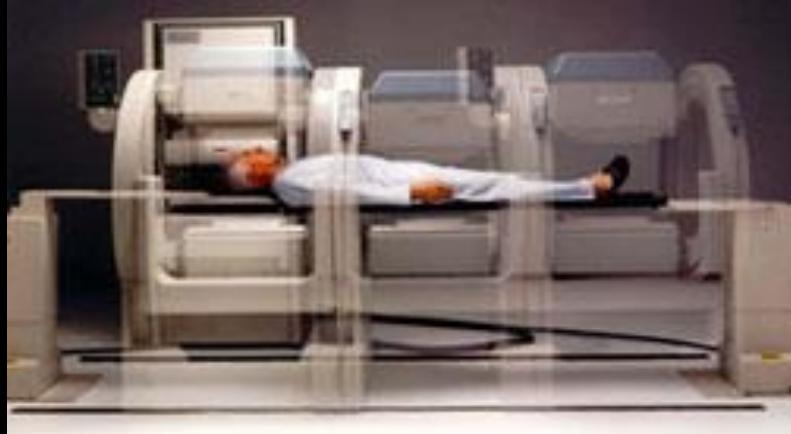
- Events occurring anywhere on line between detectors contribute coincidence counts to detector pair.
- Recorded counts are proportional to line integral of activity between the detectors.

Projection Data Collection





Positron Emission Tomography

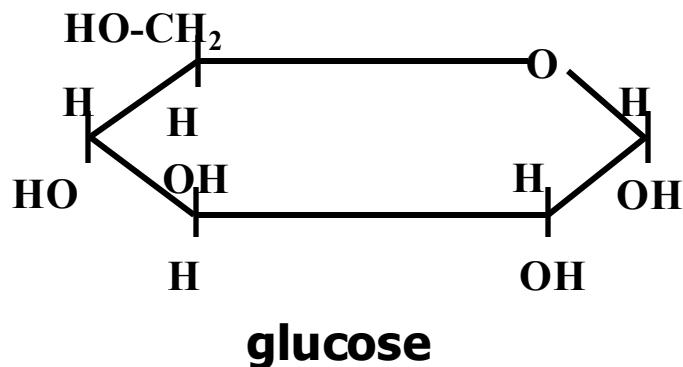
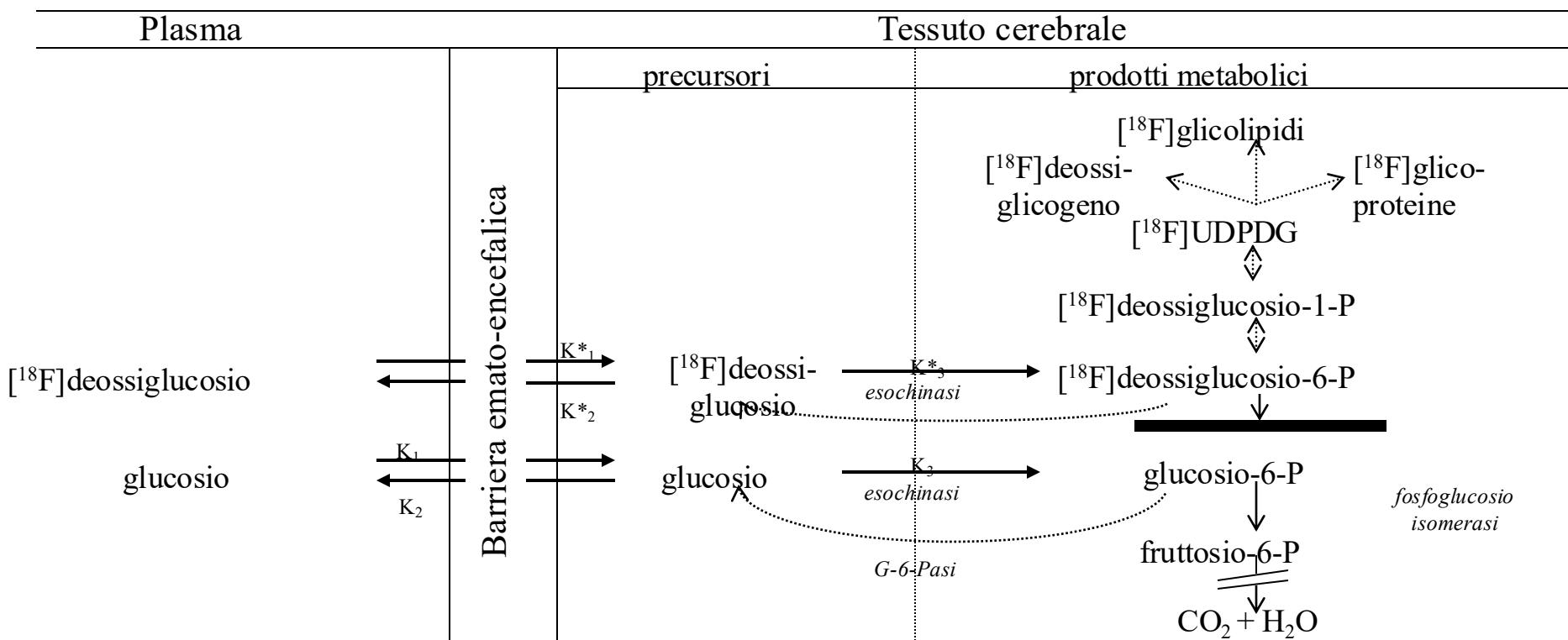


- Which molecular targets are we interested to label?
- Information on brain synaptic activity could be provided by:
- **^{18}FDG to characterize glucose metabolism**
- **H_2^{15}O to measure blood flow changes**

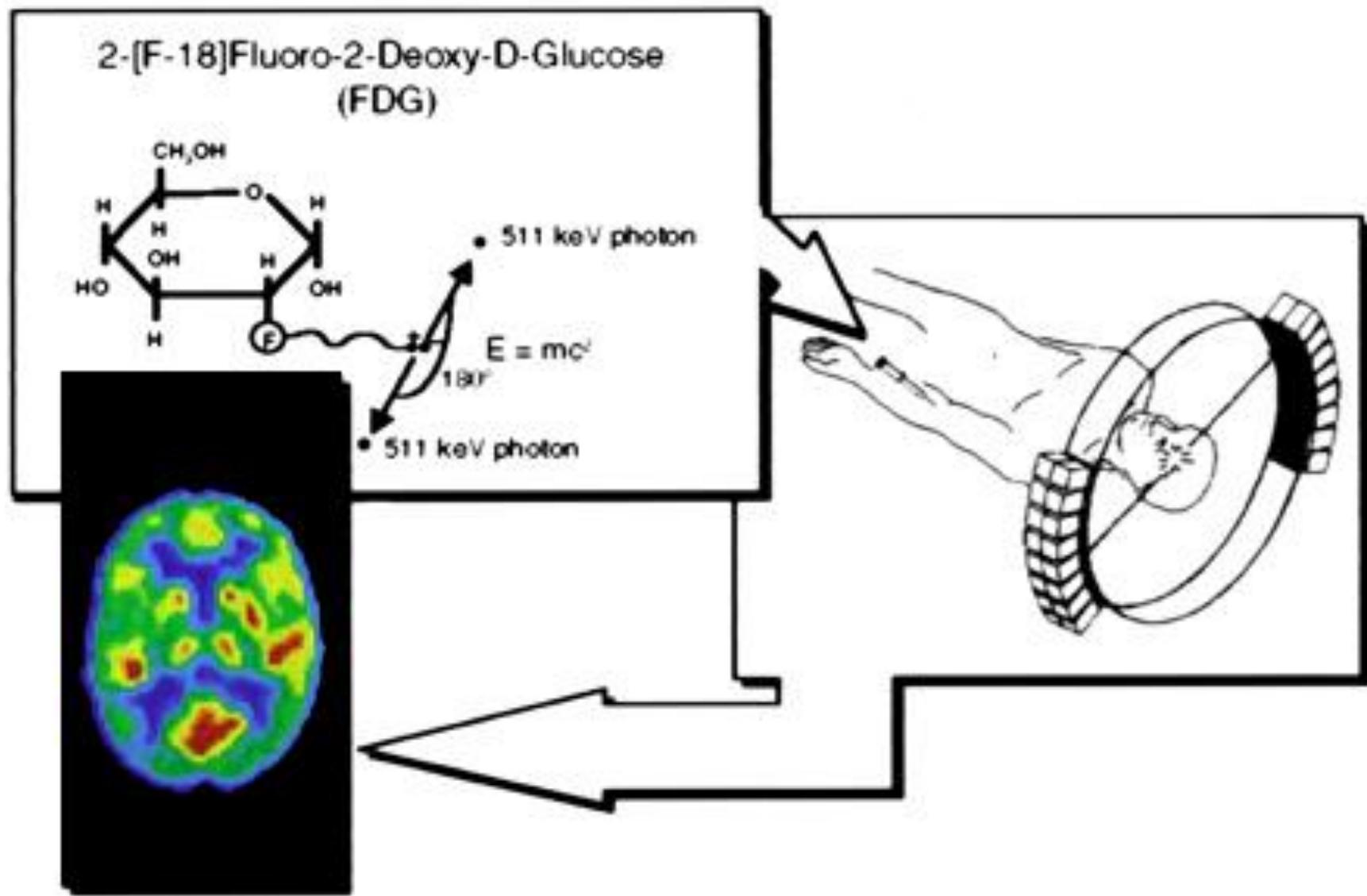
Distinctive features

	^{18}FDG	H_2^{15}O
• Half-life (min)	110	2
• Observation time (min)	45	1 - 4
• Single scanning session (min)	65	1 - 4
• Max number of image acquisition in a single session	1-2	> 10

The ^{18}F Fluoro-2-deoxy-D-glucose model for the *in vivo* assessment of cerebral glucose metabolism

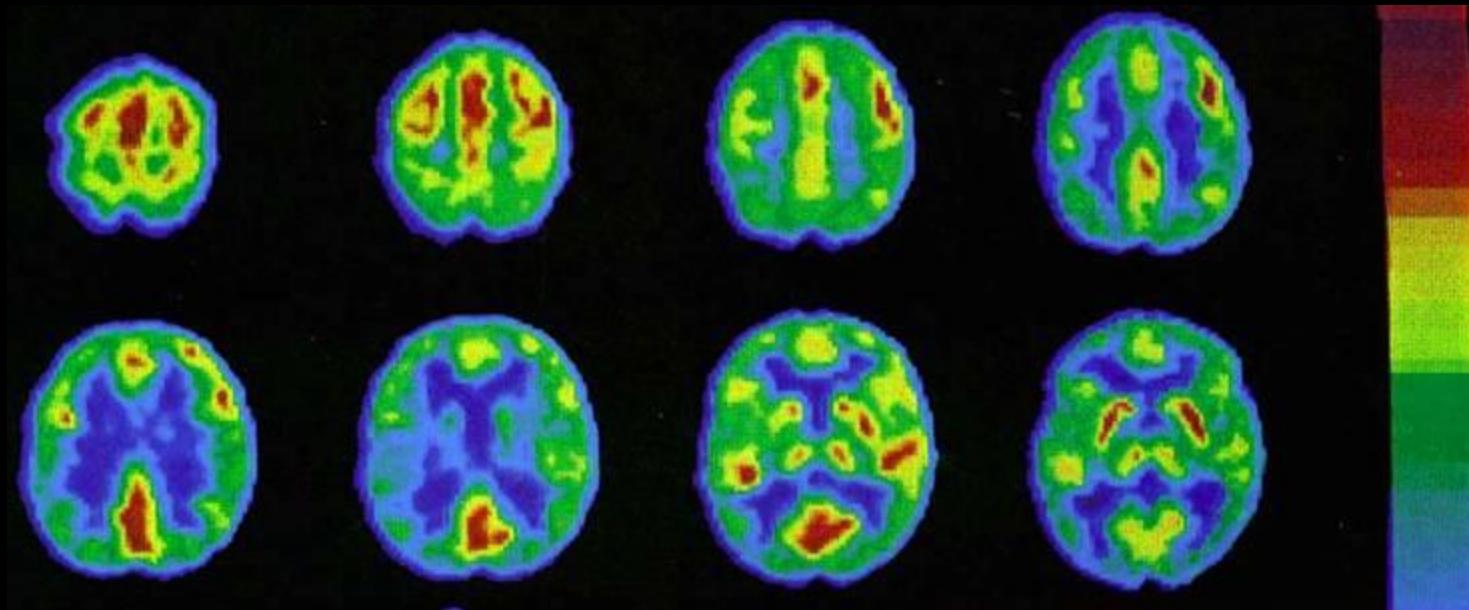


Positron Emission Tomography

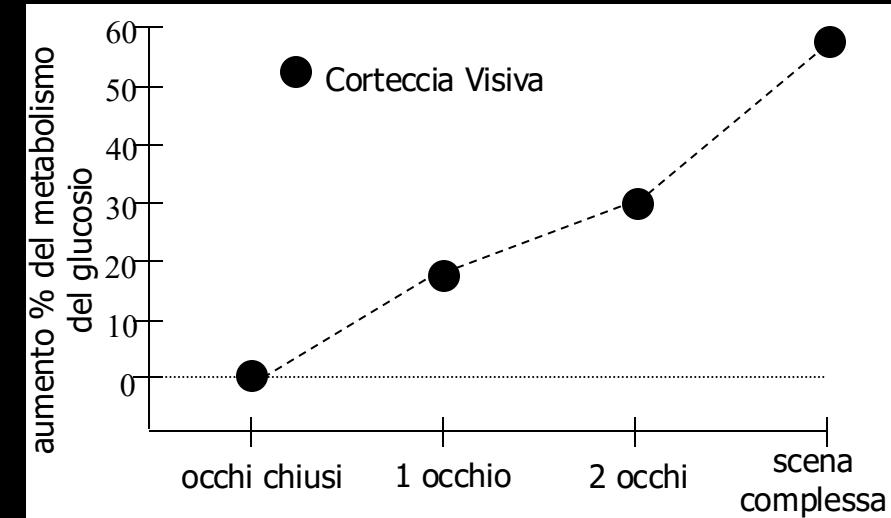
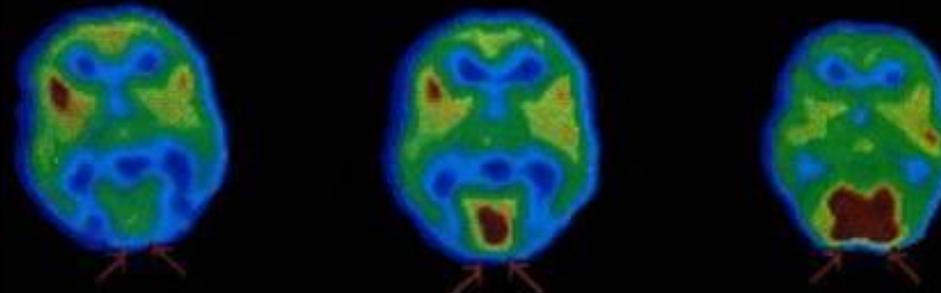


Positron Emission Tomography

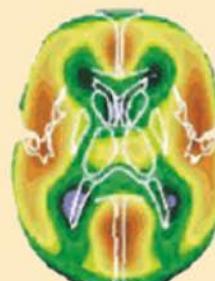
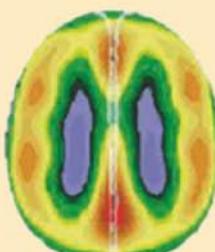
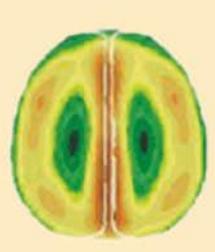
- Resting state



- Visual stimulation



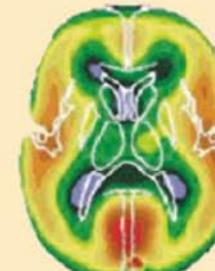
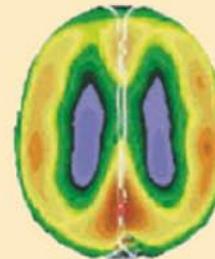
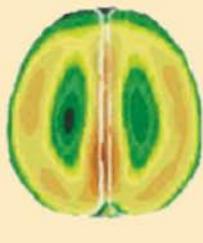
CBF



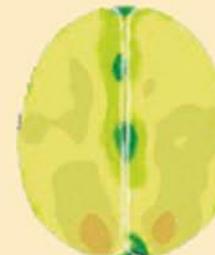
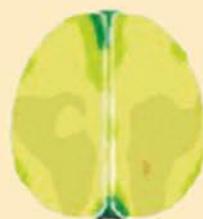
Maximum

Minimum

CMRO₂



OEF

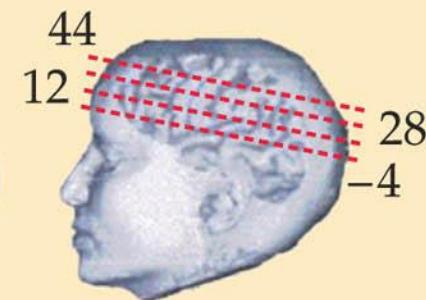


$z = 44$

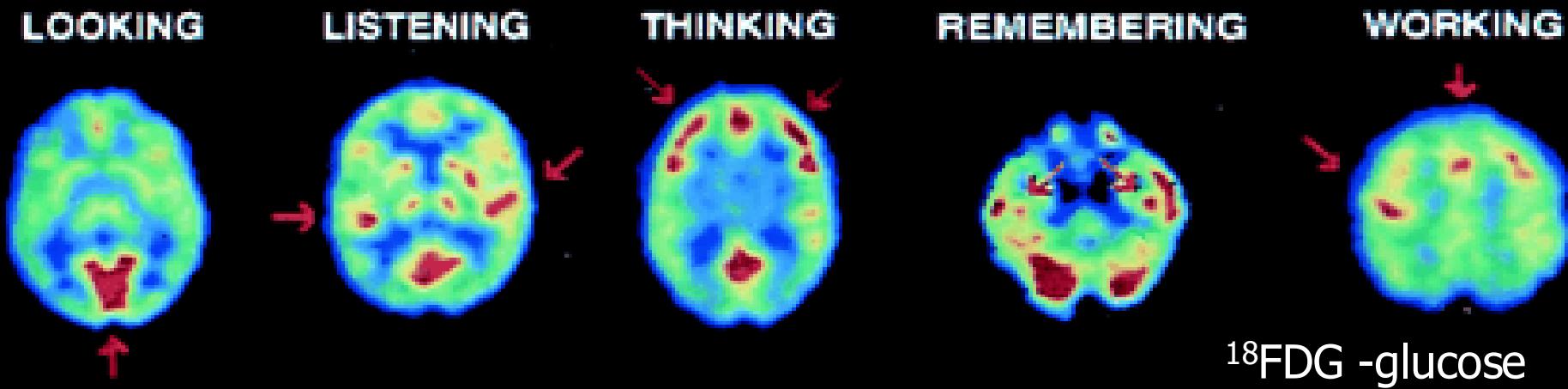
$z = 28$

$z = 12$

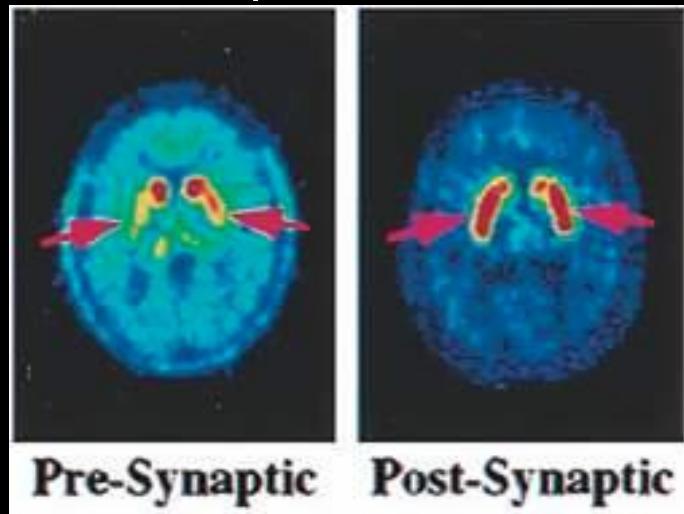
$z = -4$



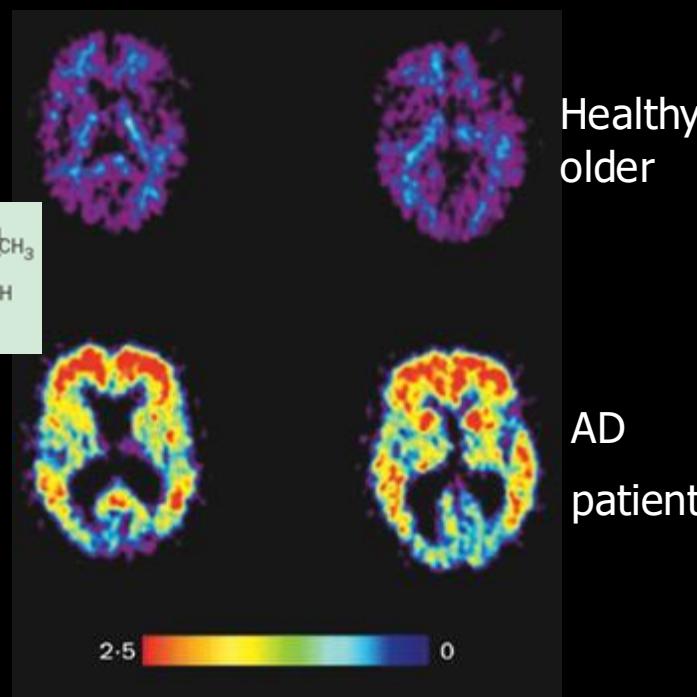
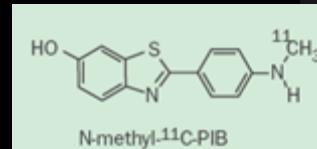
Positron Emission Tomography



^{18}F -fluorodopa



^{18}F -fluoroethylspiperone



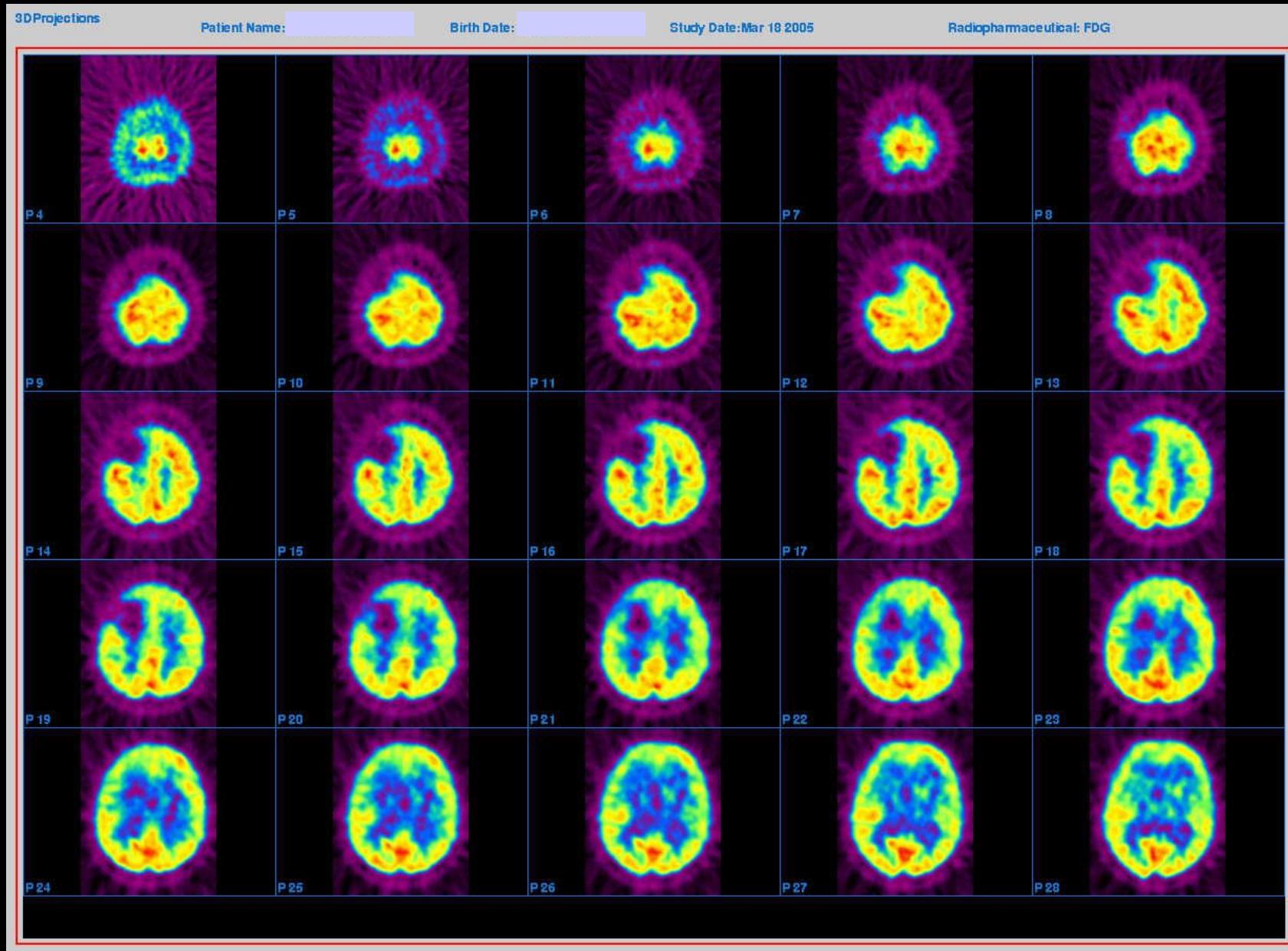
Positron Emission Tomography

- F-18
 - FDG
 - CFT
 - FTHA
 - F-Dopa
 - F-Atipamezole
 - F-F
 - L,-165
- O-15
 - Water
 - CO
 - O₂
- C-11
 - Acetate
 - CFT
 - Choline
 - CIT
 - Deprenyl
 - Dopa
 - FLB 457
 - Flumazenil
 - m-Hydroxyephedrine
 - MeAIB
 - Methionine
- MP4A
- NMSP
- NNC 756
- Palmitate
- Raclopride
- SCH 23390
- SCH 39166
- WAY 100635

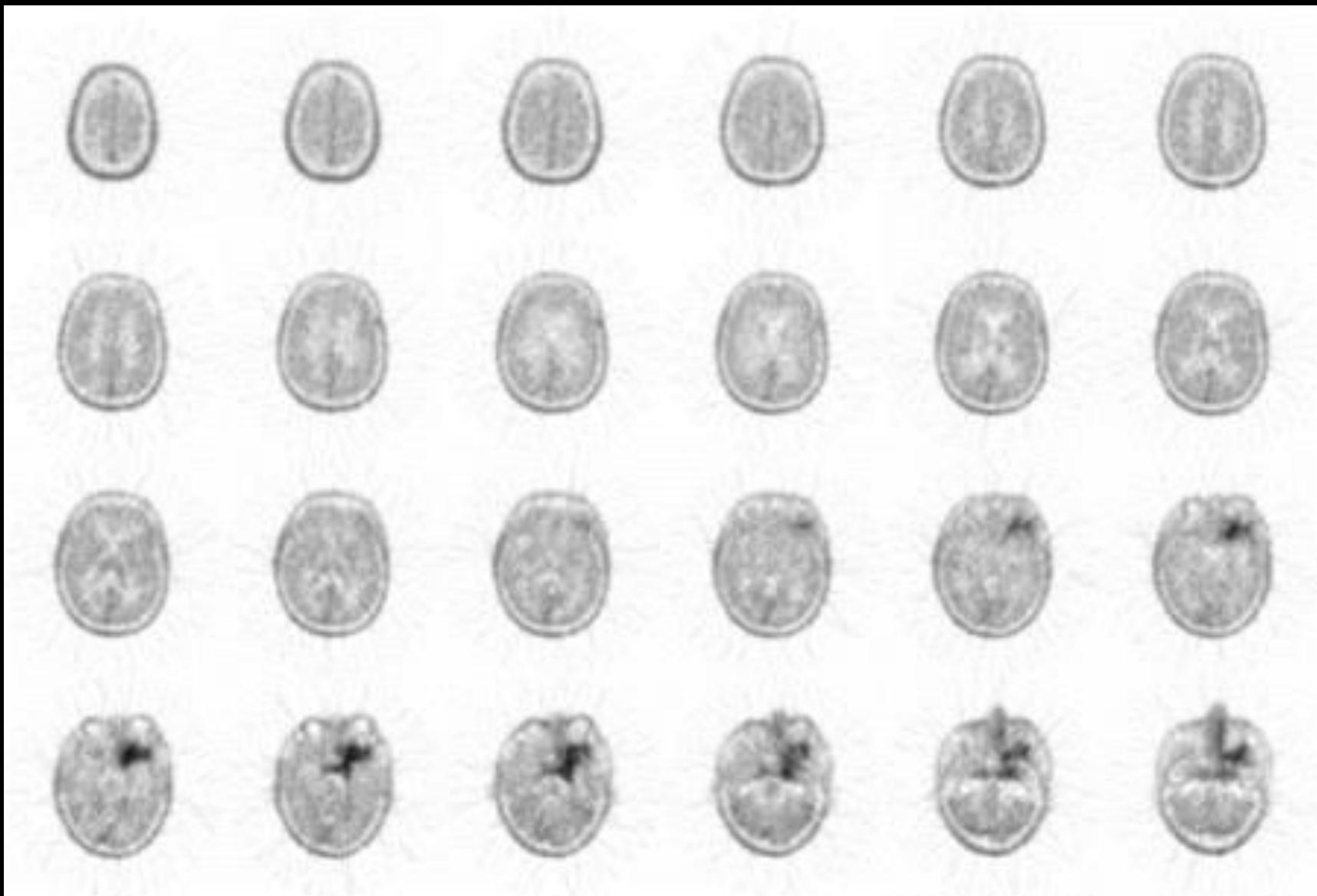
PET: Qualitative evaluation

- The most elementary approach to evaluation of the tracer distribution is visual inspection of the reconstructed tomographic images.
- “Static image” contains only one time frame, usually scanned a certain time after tracer injection (late-scan). This approach might be sufficient for many investigations, in particular for clinical diagnosis
- In many cases, deviations of the regional distribution of the radio-pharmaceutical from the distribution observed in a reference group occur. Detection of such deviations might suffice for diagnosis, therapy evaluation, or for the assessment of drug effectiveness.

PET: Qualitative evaluation



PET: Qualitative evaluation



PET: Qualitative evaluation

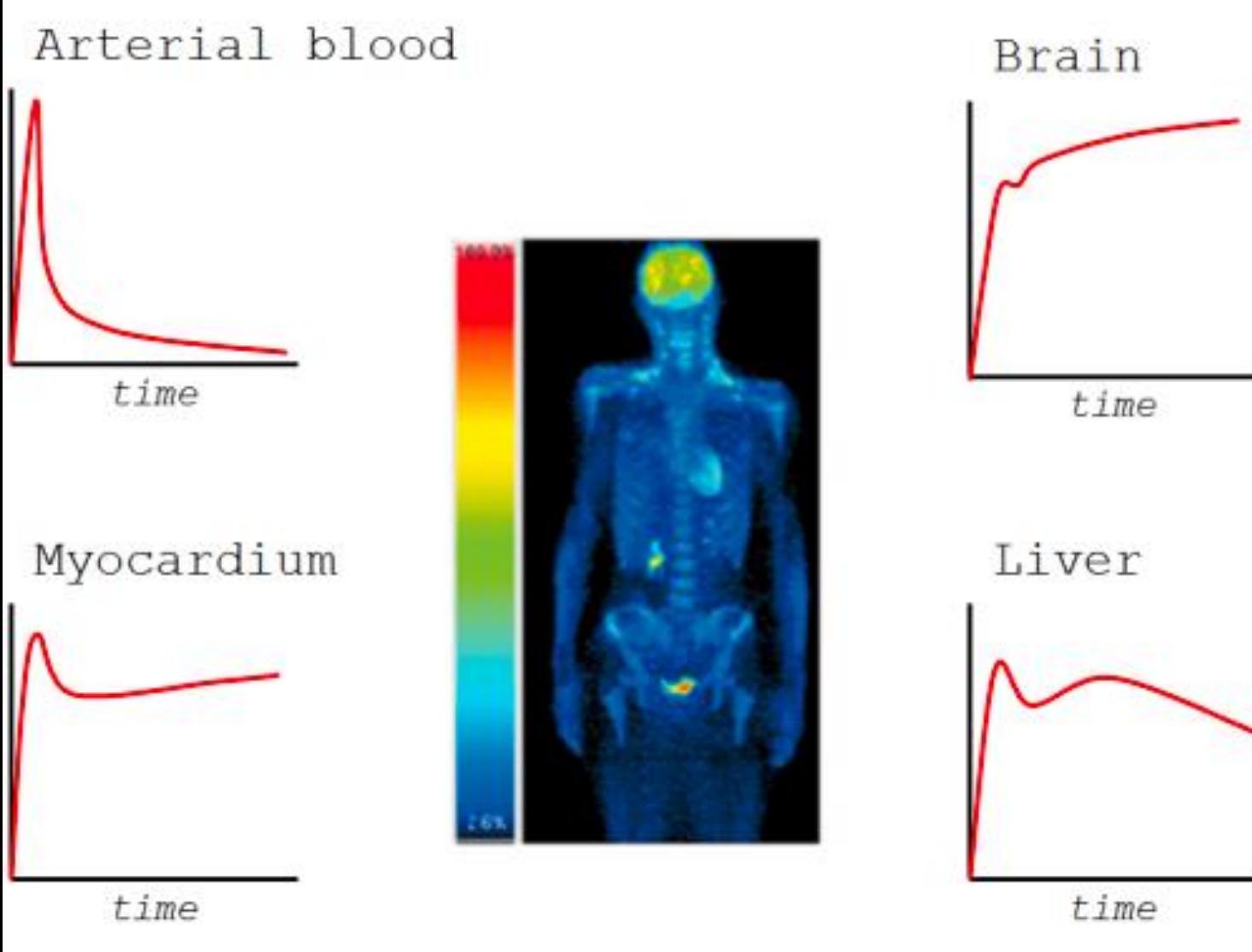
This is a serious shortcoming of the method:

- An increase of the image contrast of a target region relative to some “distant” reference region within the image volume may be caused by an increased tracer uptake in the target tissue or a reduction of uptake in the reference region or by a combination of both effects
- Global alterations of the uptake are not detectable at all by this approach. In order to improve the situation, visual analysis is often combined with simple quantitation procedures (but tissue concentration of a radiopharmaceutical is varying with time!)

PET: Normalizing tissue uptake

- To make the measured tissue concentration in one study comparable to measurements in other studies we have to normalize the tissue concentration at least to the administered dose, and preferably also to the weight of study subject or animal
- You get ***Standardized Uptake Values*** (SUVs), which are already fairly well comparable between studies and subjects
- There are several drawbacks in the SUV method, most importantly that SUV is time-dependent, and affected by different plasma clearance between subjects and study conditions:

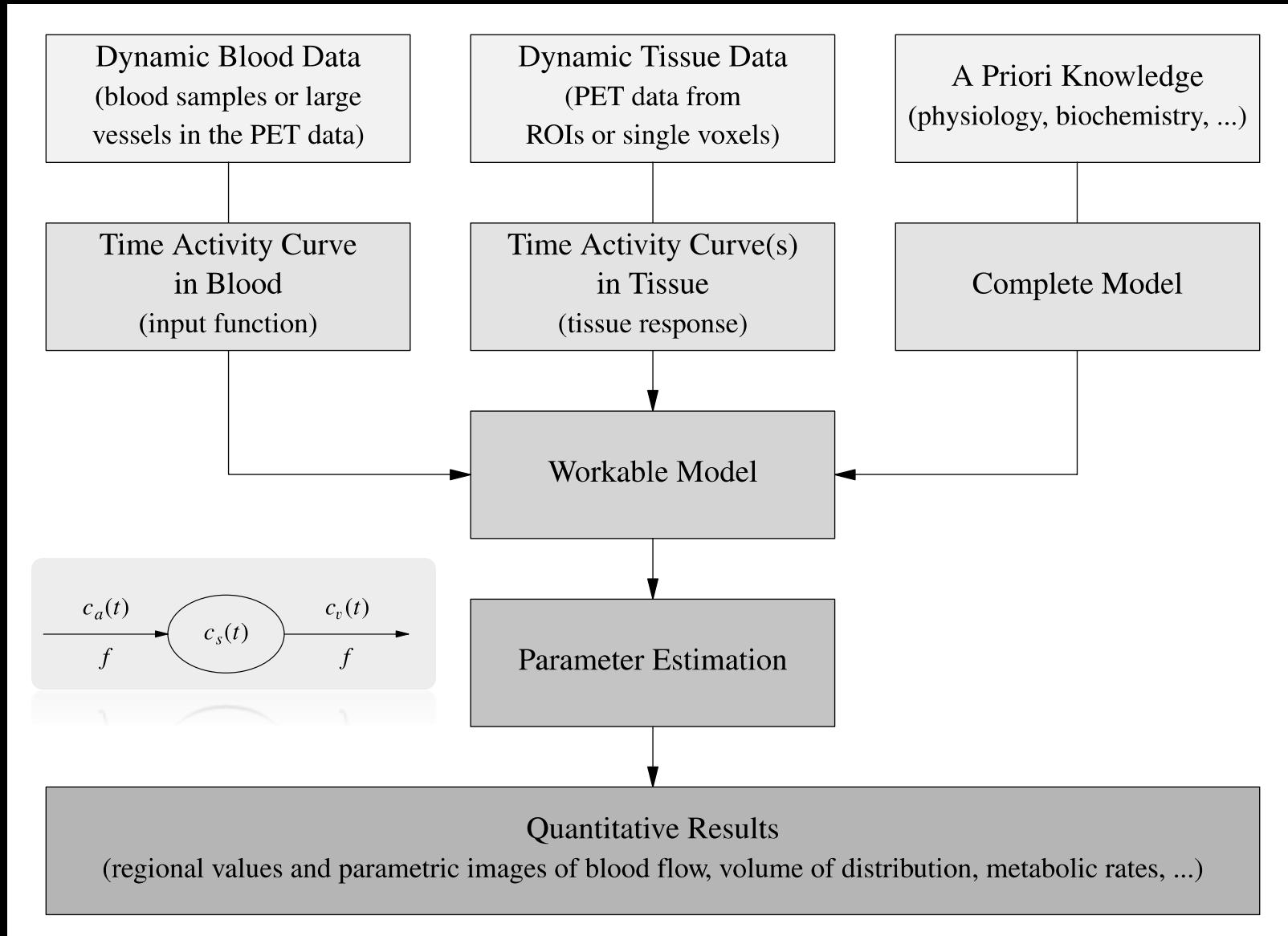
PET: Normalizing tissue uptake



PET: Normalizing tissue uptake

- In parametric image each voxel represents a value of some physiological parameter, for example perfusion or receptor binding potential, while the original PET image contains radioactivity concentrations.
- When traditionally modelling is done using regional time activity information, a parametric image is created so that the modelling is done separately in each voxel.
- In theory, it is also possible to apply the model to dynamic sinogram, and reconstruct parametric sinogram to parametric image.

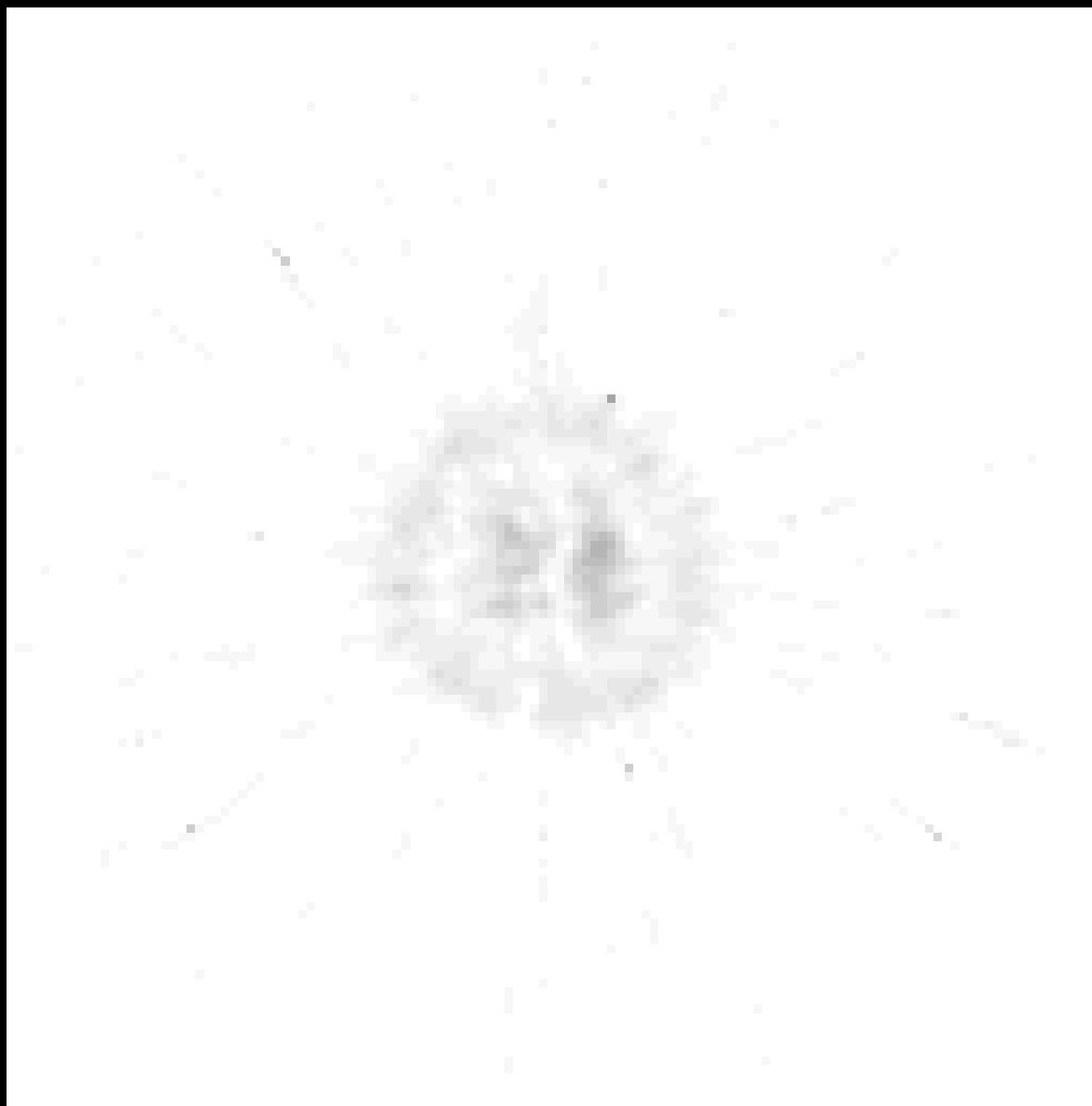
A model for PET



Quantitative PET

- The concentration of the unchanged (non-metabolized) tracer in arterial plasma (or blood, depending on the tracer) is the gold standard input function (IF) in PET data analysis: **plasma time-activity curve (PTAC)**
- Correction of vascular radioactivity requires the measurement of total radioactivity concentration in the blood.
- Arterial blood can be measured by manual or automated sampling of arterial blood: arterial catheterization is safe and reliable, but burdensome;
- Non-invasively from **dynamic PET image**, if heart, arch of aorta, abdominal aorta or other large artery is visible in the image;

Parametric mapping of PET images

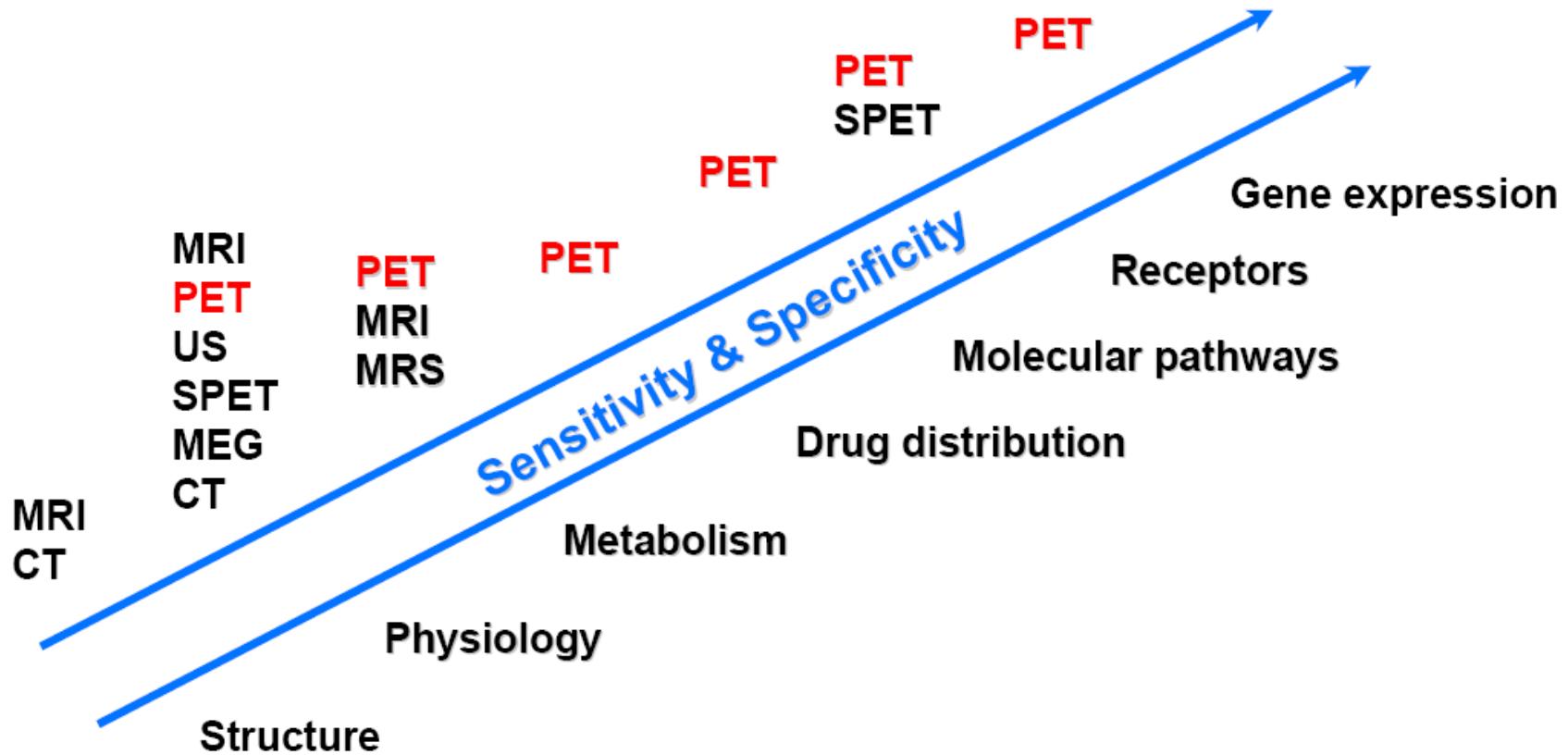


Why using PET currently?

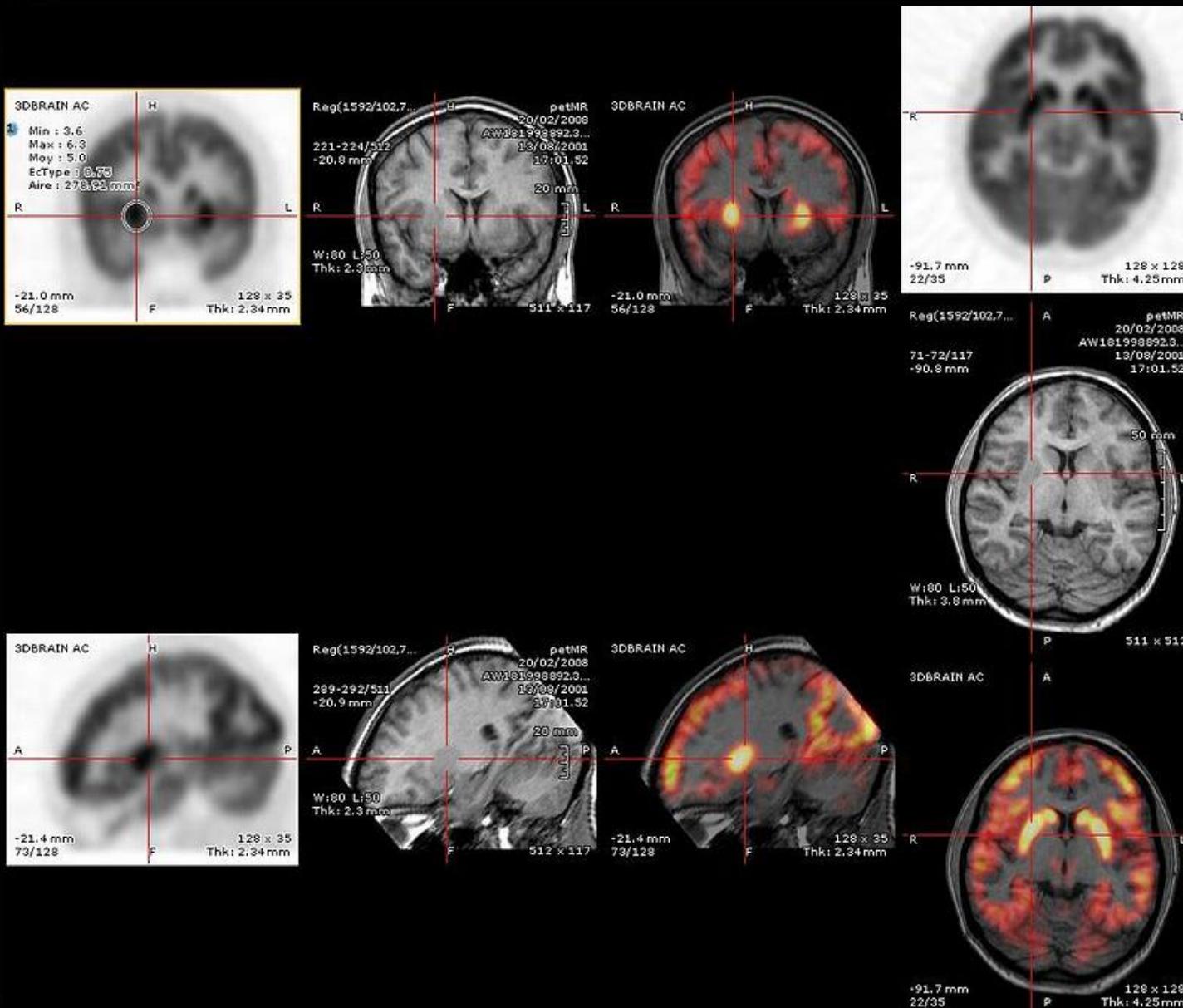
- **Endless number of possible tracers (i.e., chemical targets)**
- **Quantitative methodology!**
- **High sensibility**
- **Top 'chemical resolution'**
- **Good spatial resolution (2 mm)**

Why using PET currently?

The role of PET imaging in Medicine



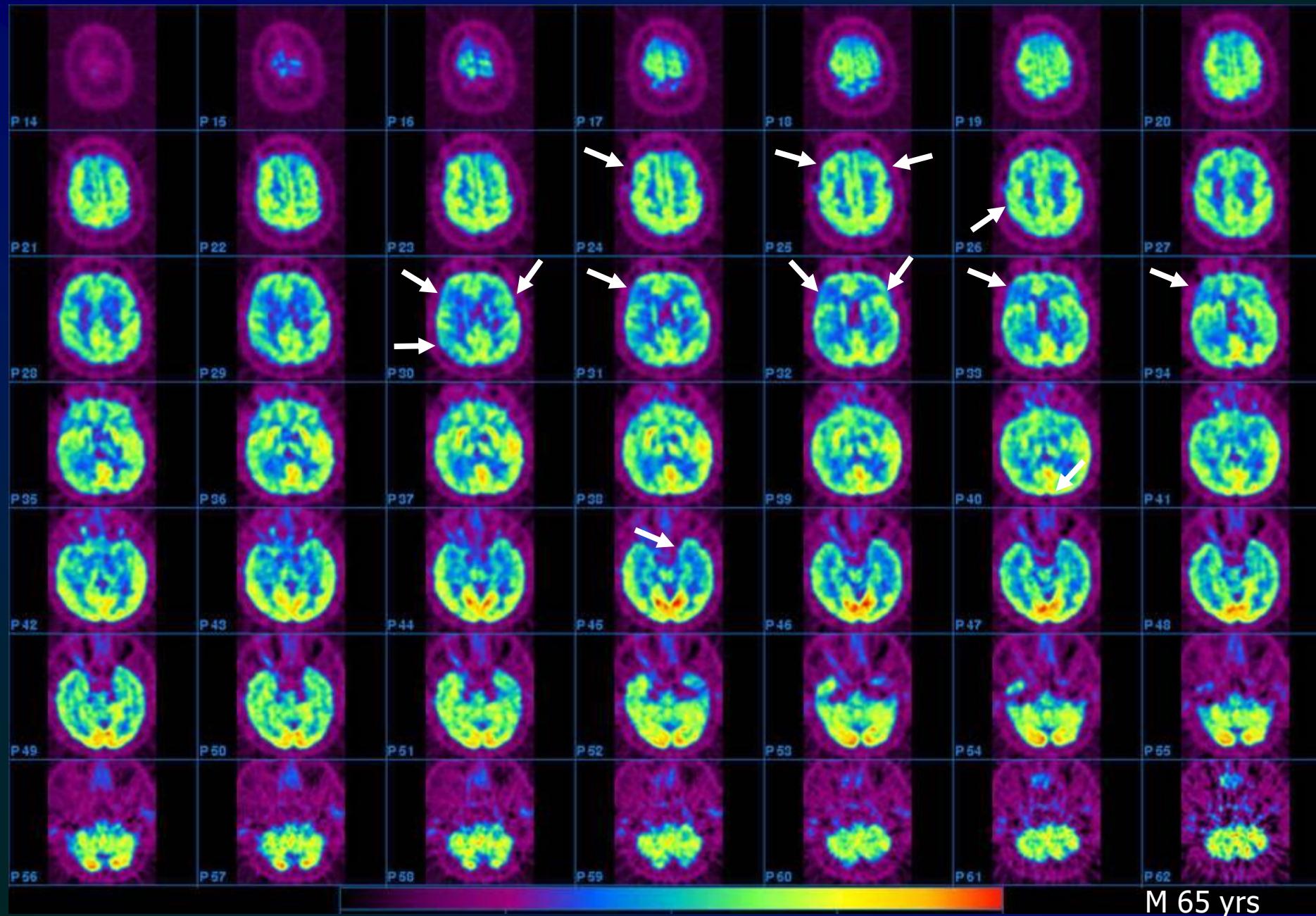
Combination of PET with CT or MRI



Clinical application of PET imaging

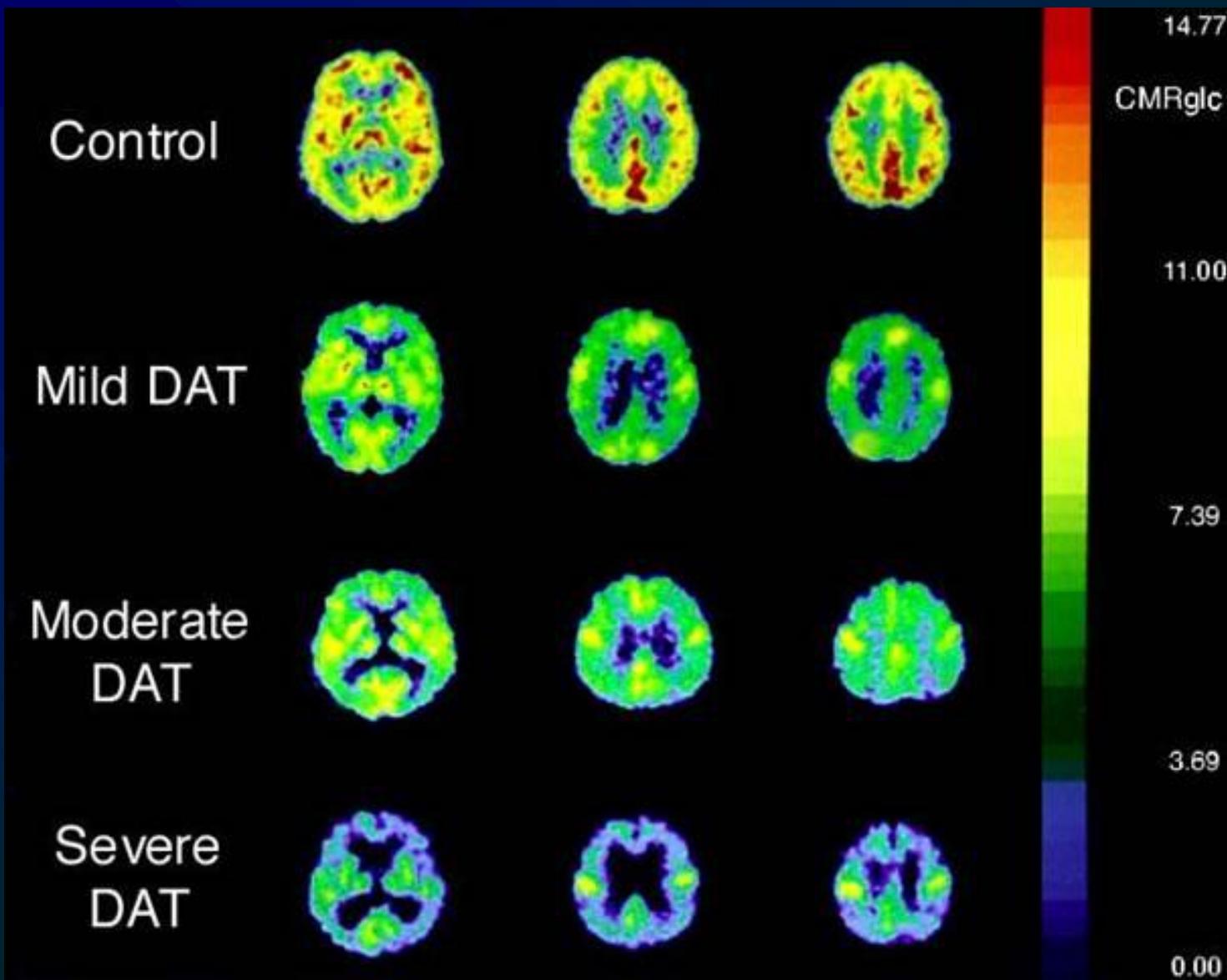
- Neurodegenerative disorders
 - Clinical characterization
 - Differential diagnosis
 - Evolution
- Tumors
 - Presence and Grading
 - Follow-up
- Epilepsy
- Chronic pain
- Movement disorders
- Trauma
- Stroke
- Infective disorders
- Presurgical functional mapping

Alzheimer's Disease: Diagnosis

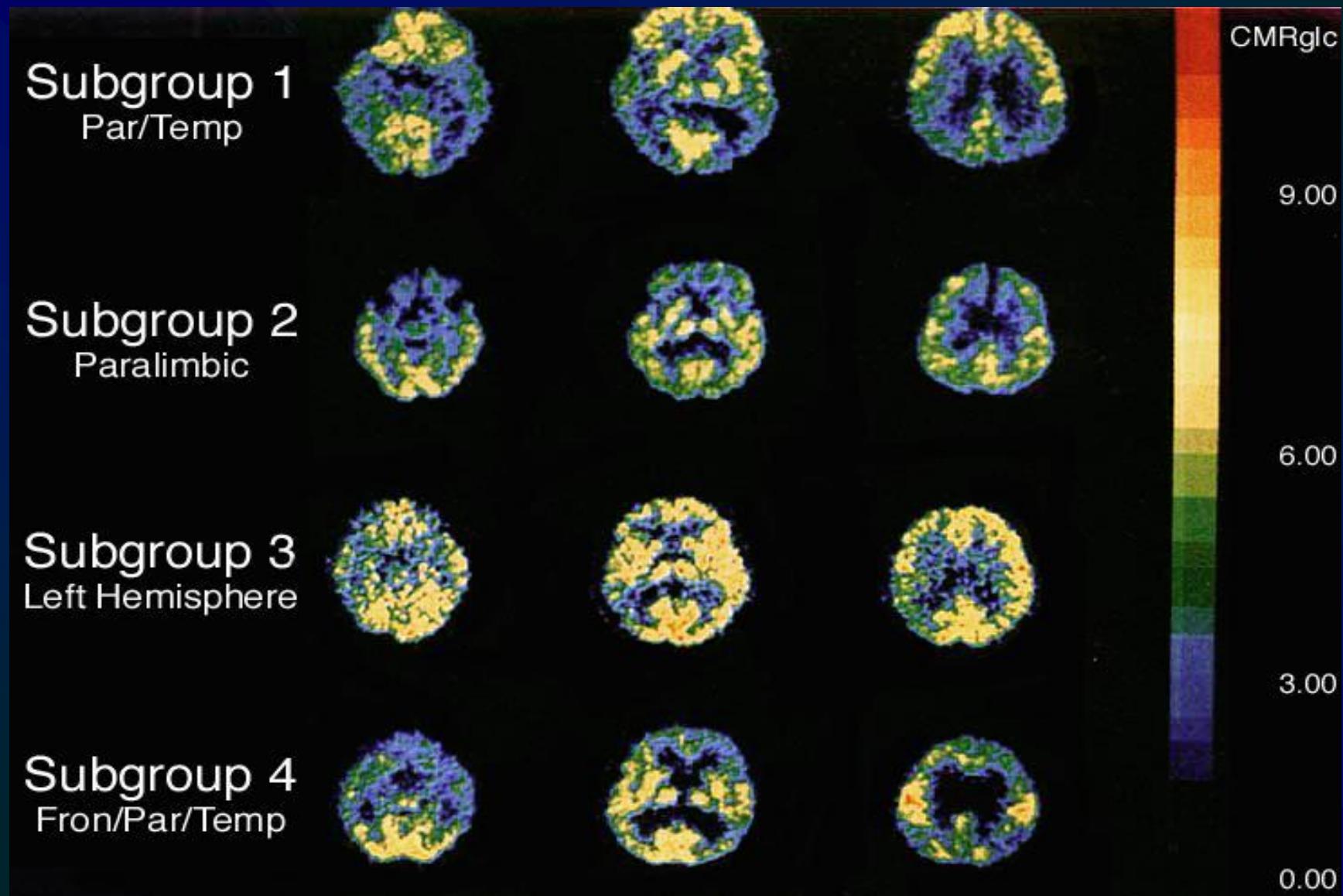


M 65 yrs

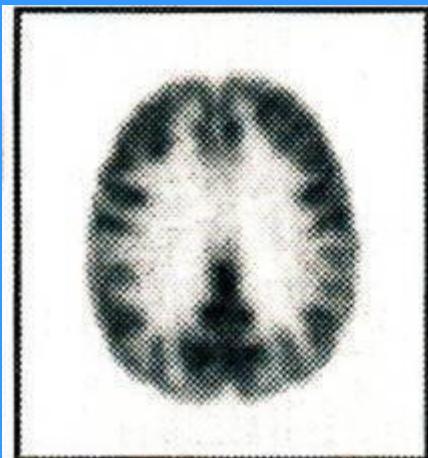
Alzheimer's Disease: Evolution



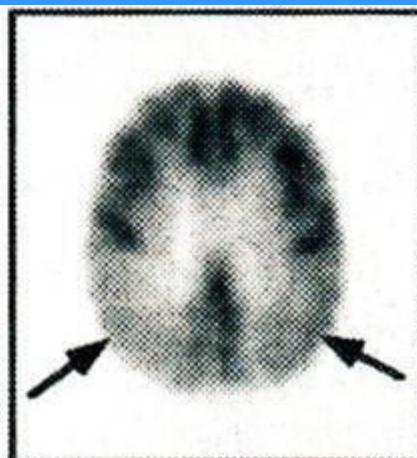
Alzheimer's Disease: Correlation with Clinical Symptoms



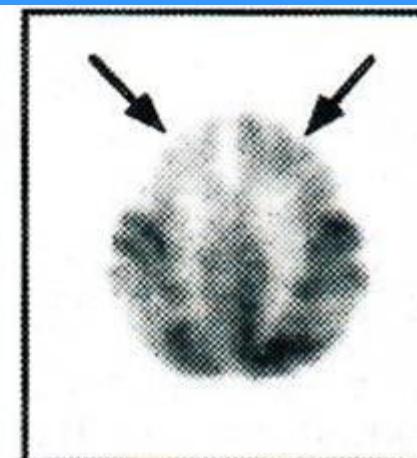
PET in the Evaluation of Dementia: Differentiating cognitive impairments



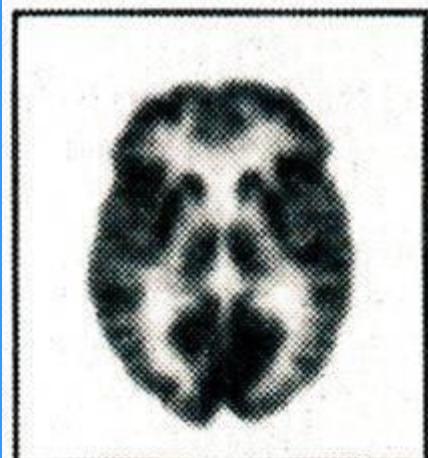
Normal



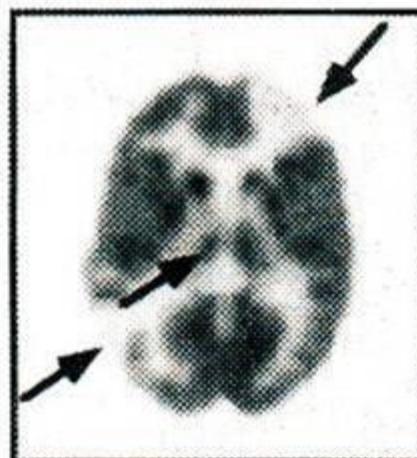
Alzheimer's



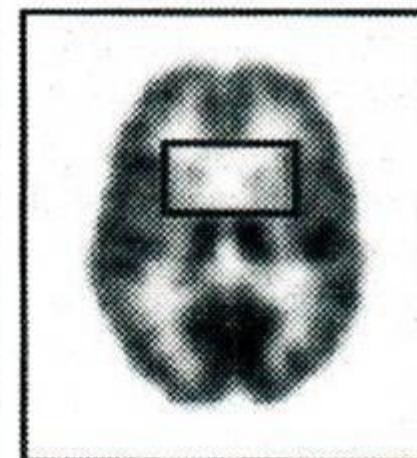
Pick's



Normal

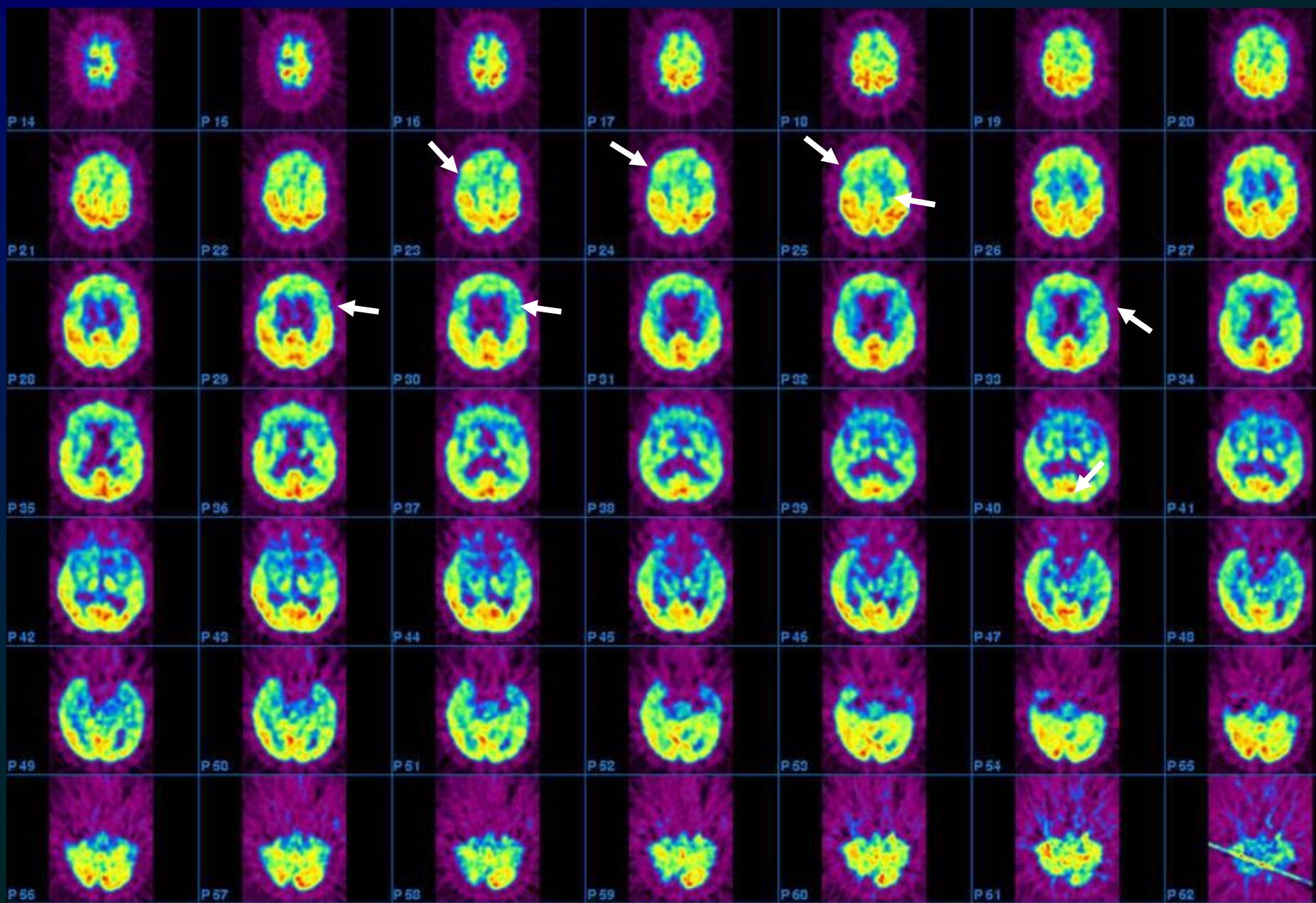


Multiple Infarct
Dementia



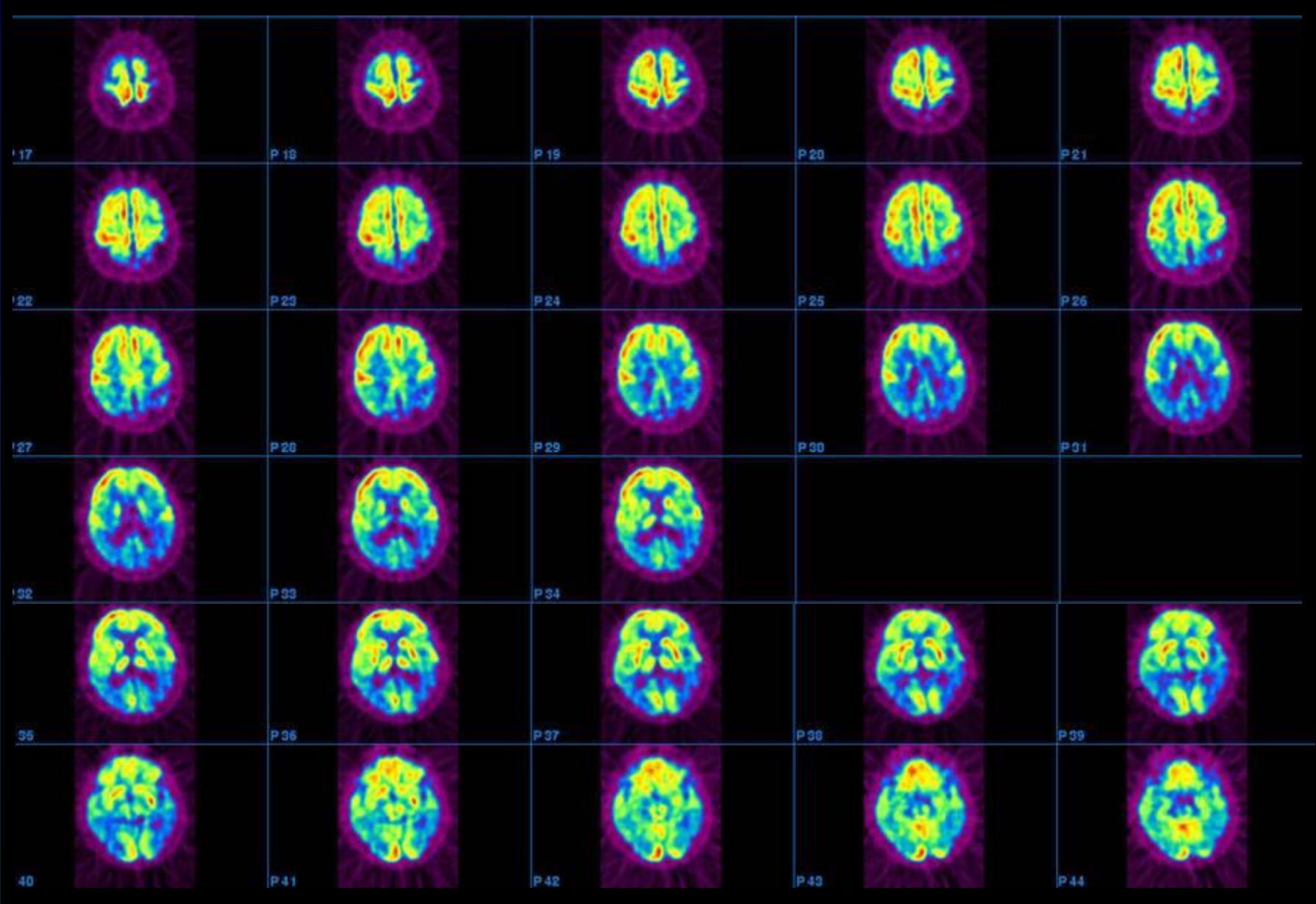
Huntington's

Fronto-temporal dementia



F 70 yrs

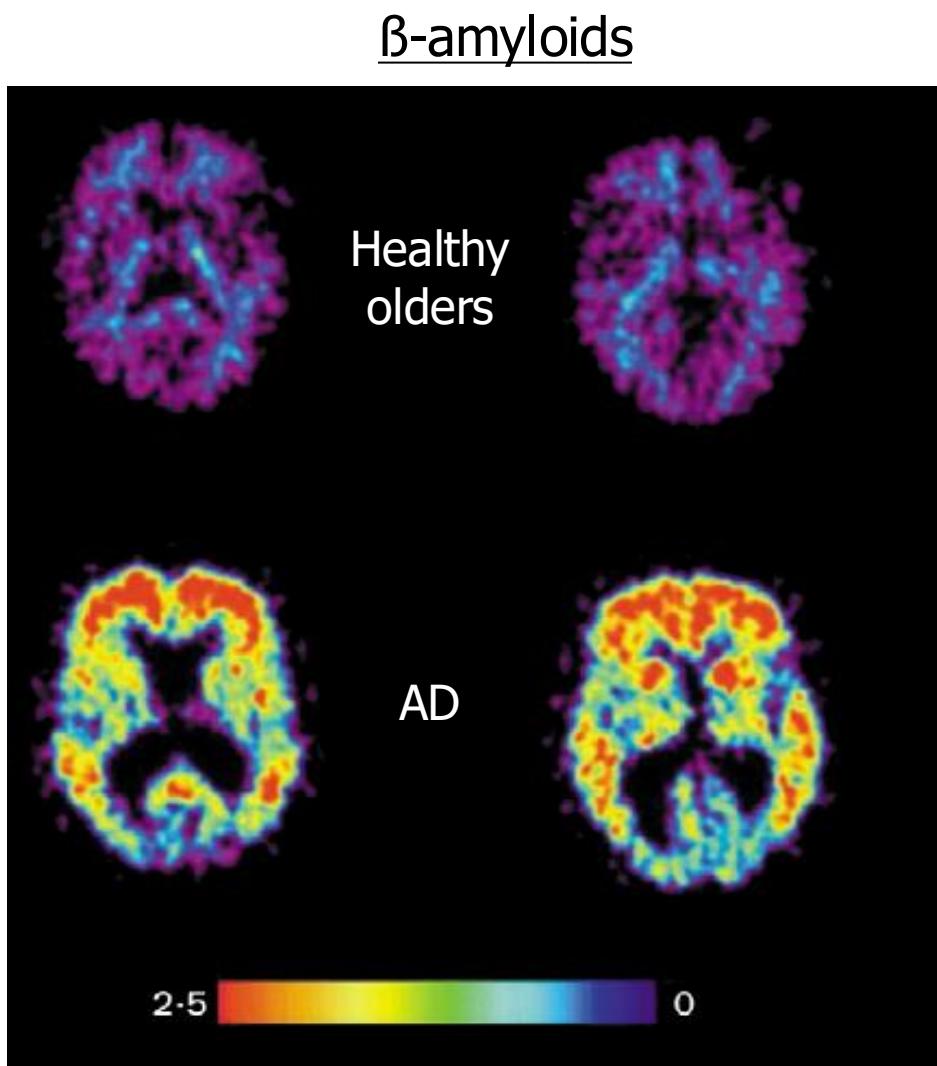
Visual Variant



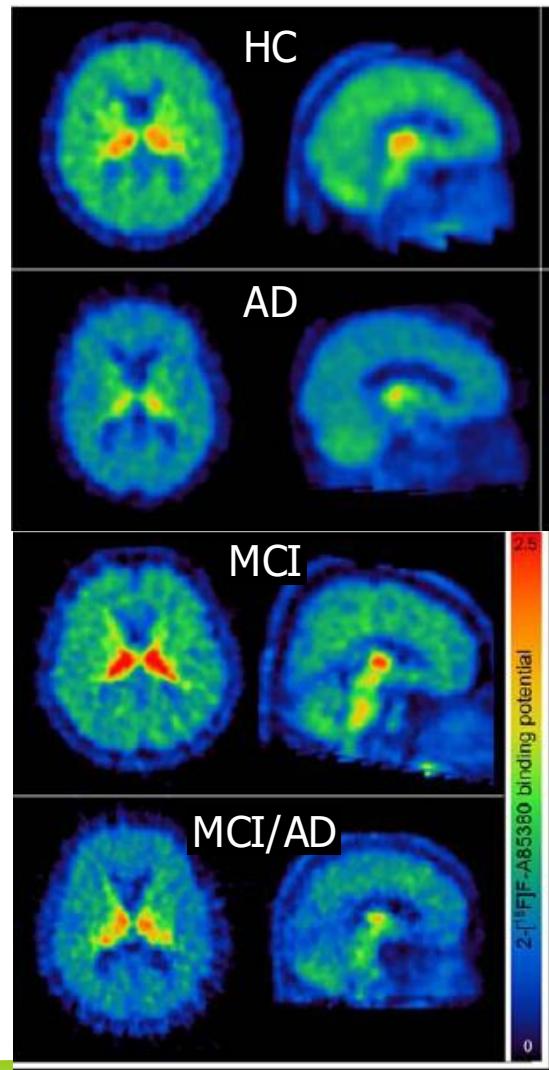
The role of *in vivo* brain functional exploration methodologies in understanding cognitive impairment during pathological aging

- Investigate the effects of neurodegenerative processes on:
 - Brain metabolism
 - Correlation between cognitive deficits, clinical evidences and metabolic changes
 - Clinical differentiation and evolution
 - Neurotransmitters
- Detect early evidence of cognitive impairment
 - Genetic risk for dementia
 - Stress test
 - Recovery
- Insight into neuropathology
- Understanding and following therapy

PET – New frontiers for neuropathology



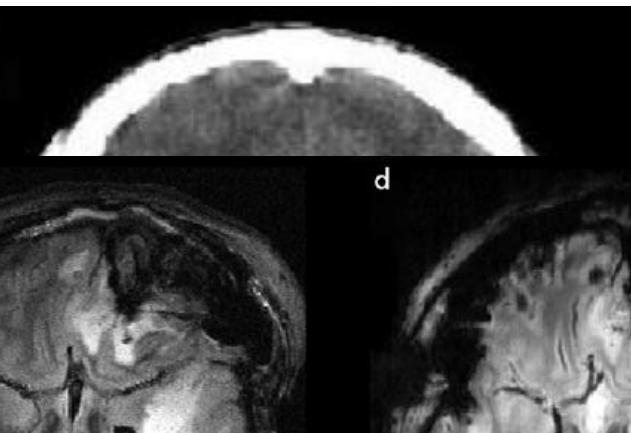
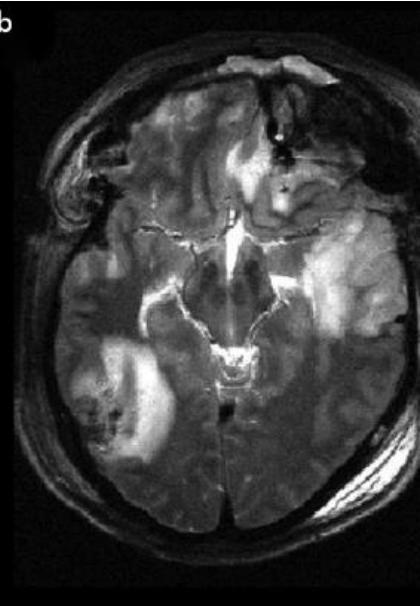
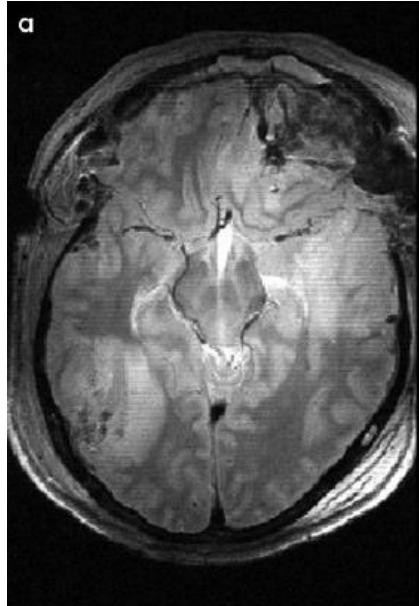
Nicotinic receptors



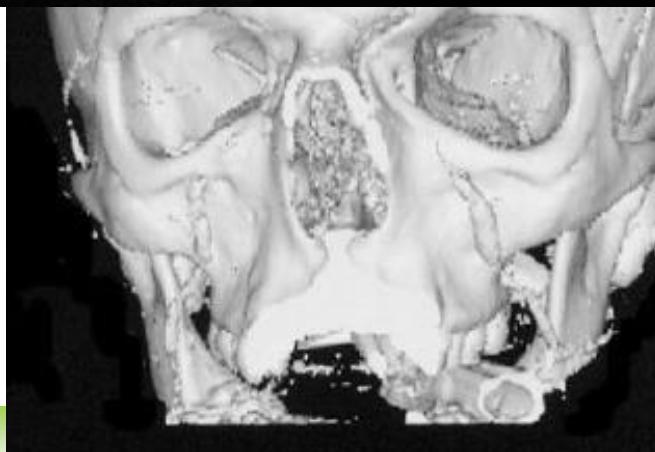
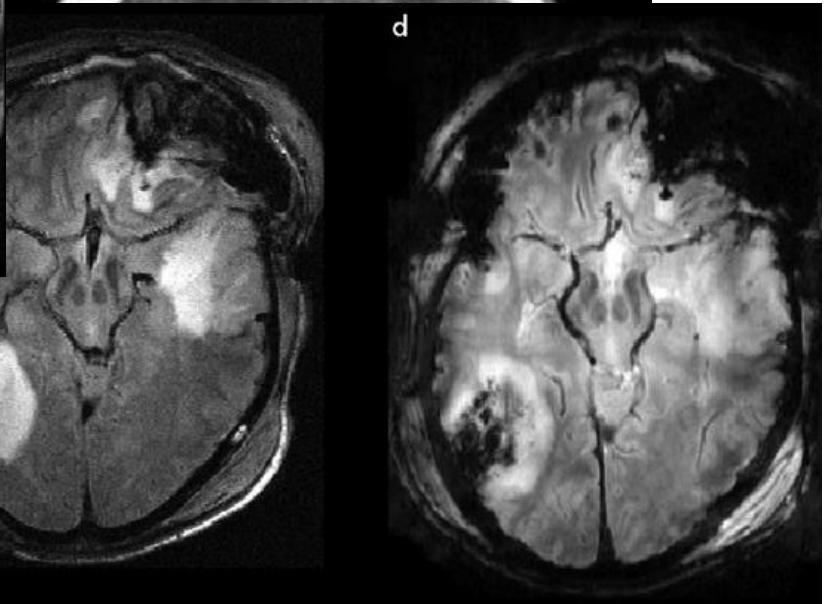
Nordberg A., *The Lancet Neurology*, 2004

Sabri O., *Eur J Nucl Med Mol Imaging*, 2008

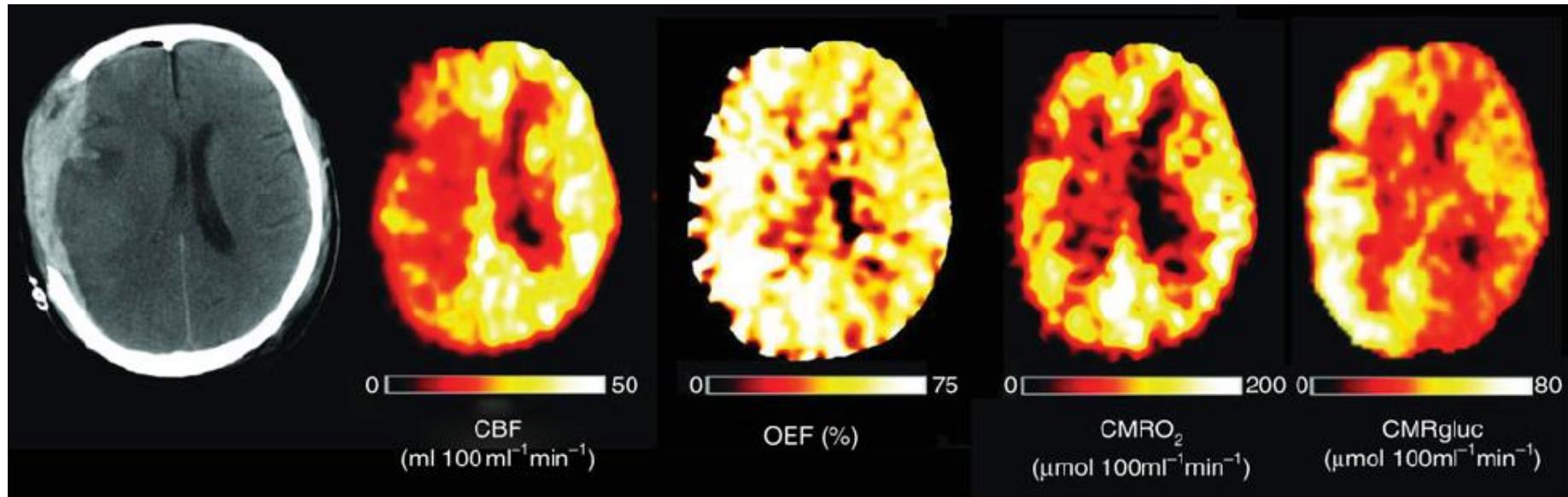
Trauma - CT and MRI



d

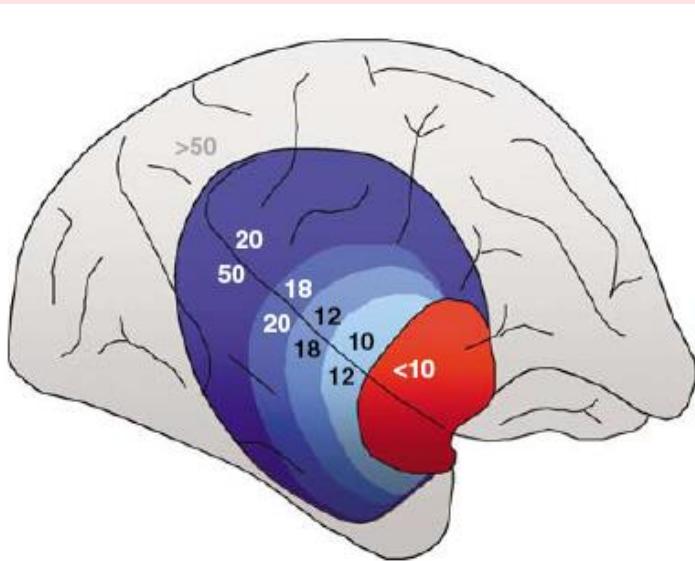


Trauma - DTI/PET/sRMN

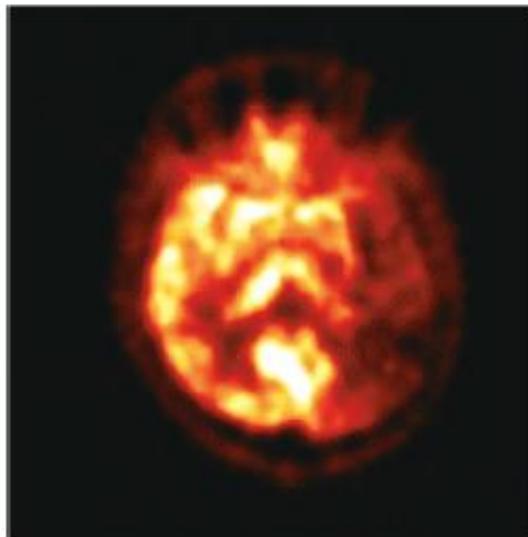


Stroke - PET

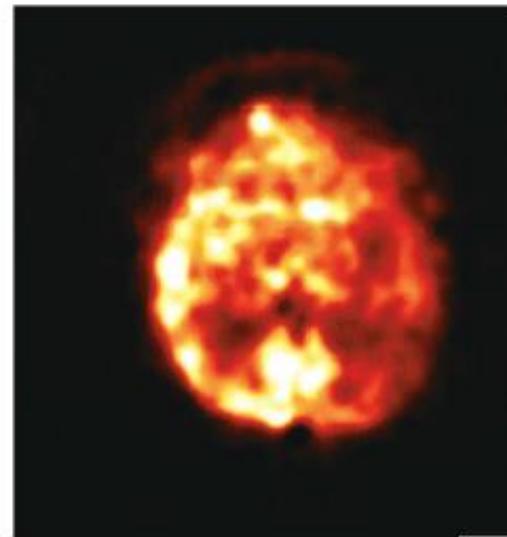
- Valutare la funzionalità residua di ogni paziente
- Comprendere i meccanismi d'azione delle varie terapie riabilitative o della risposta del paziente alle stesse al fine di una migliore scelta individuale



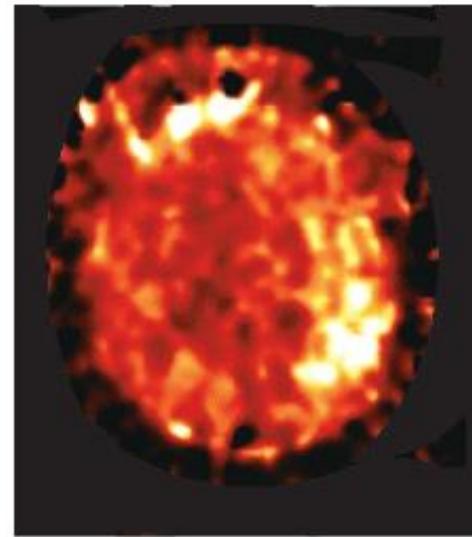
CBF



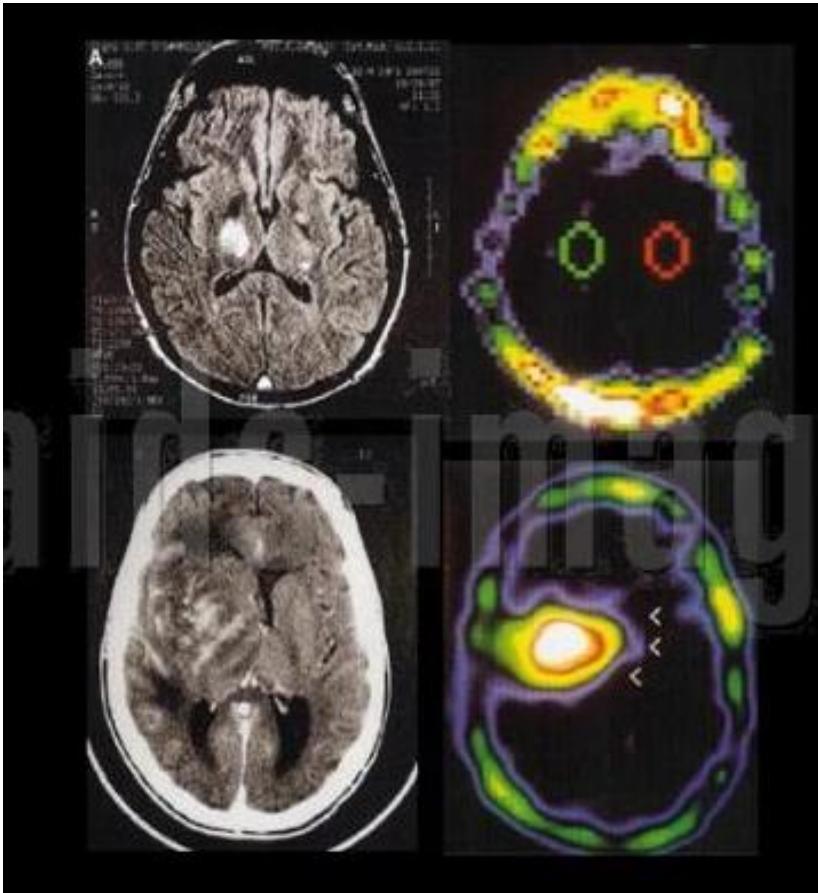
CMRO₂



OEF



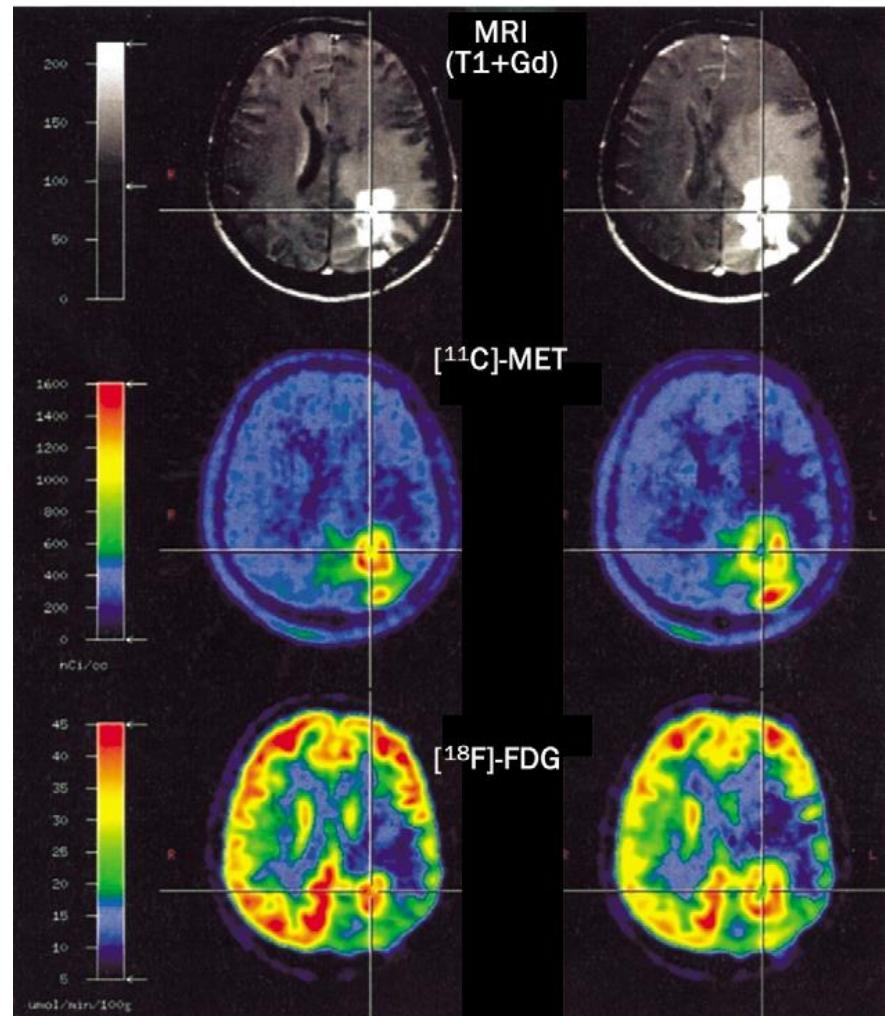
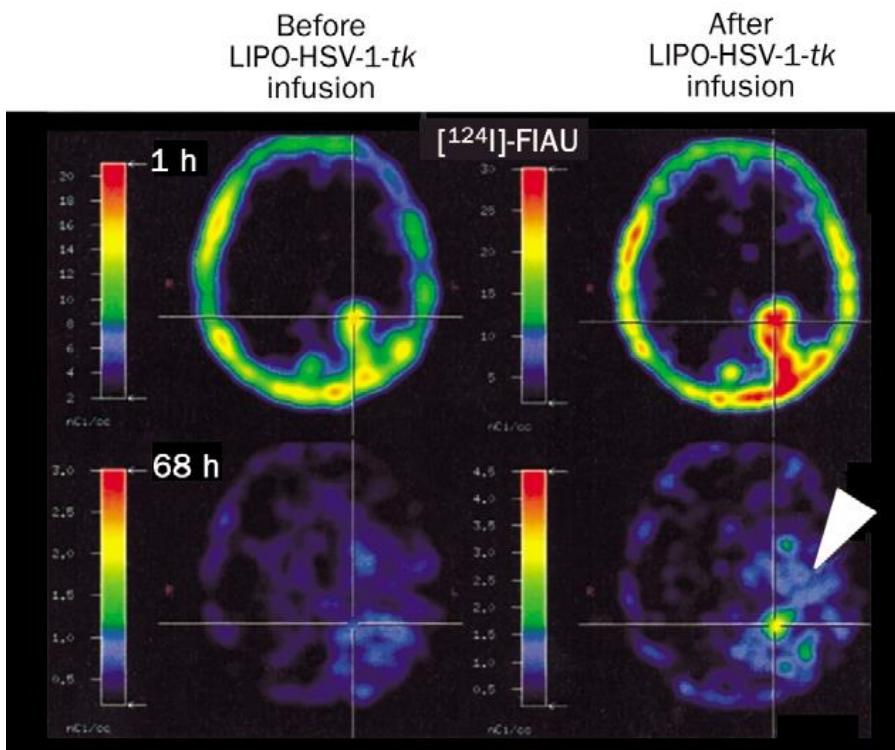
PET – infections



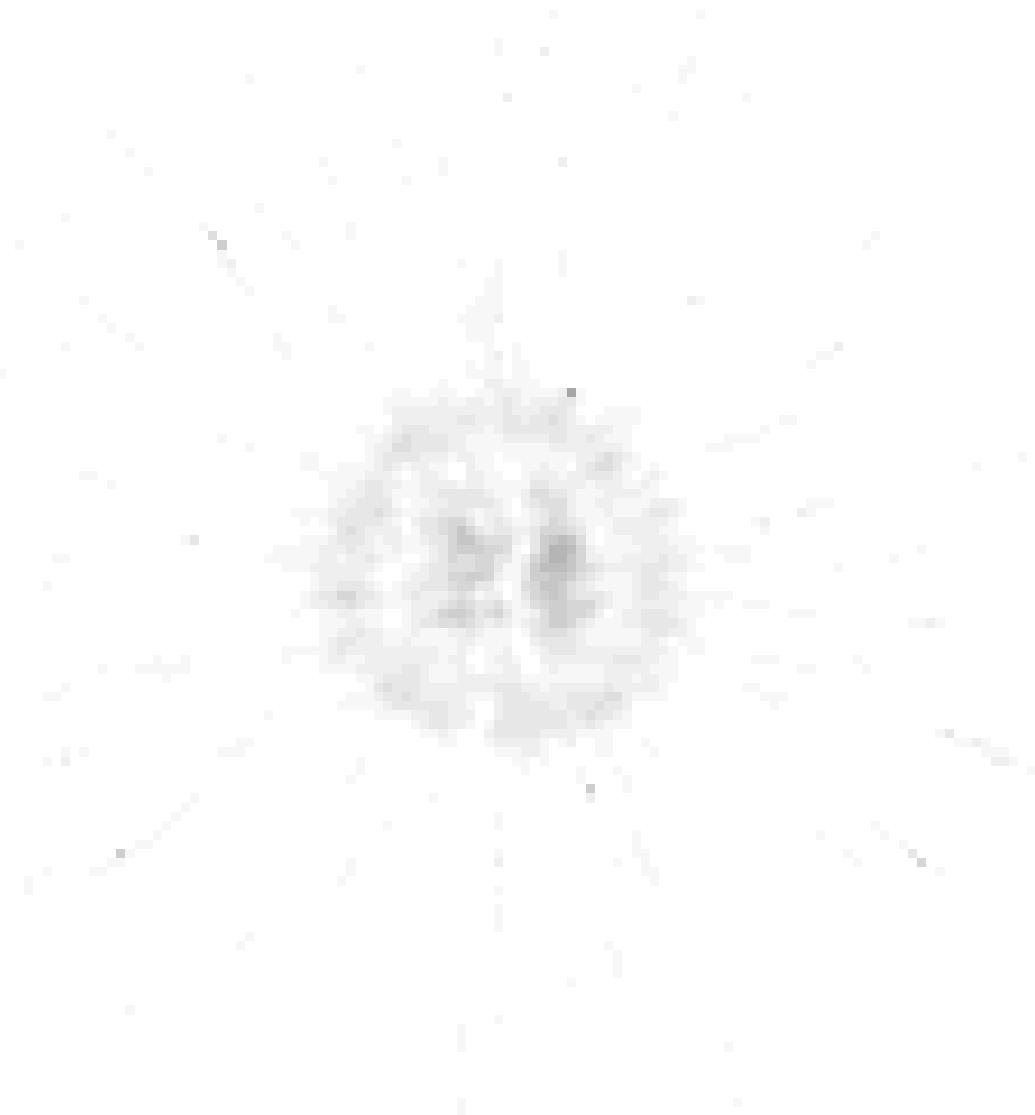
Toxoplasmosi

Linfoma

PET – genetics

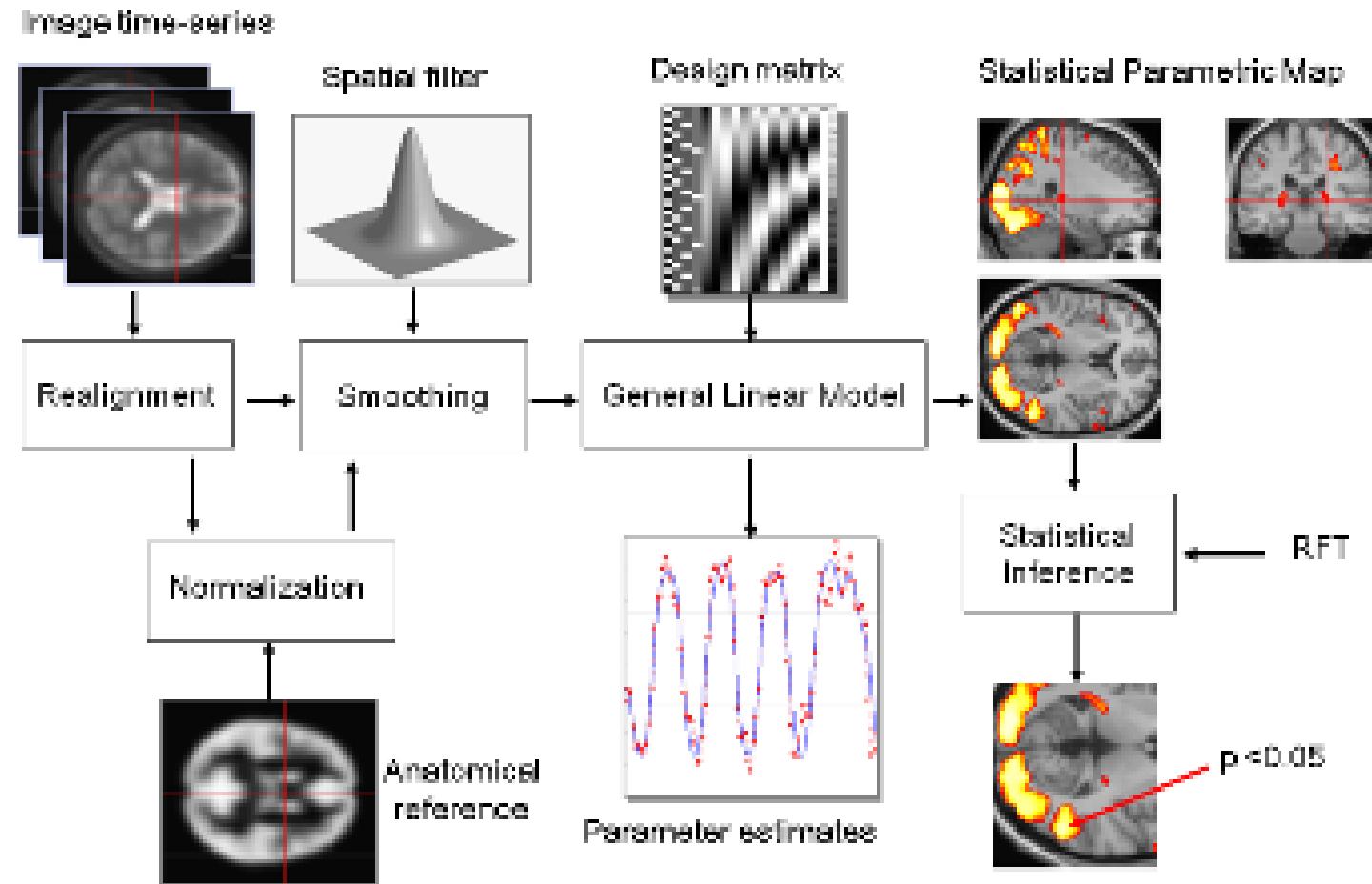


Parametric mapping of PET images

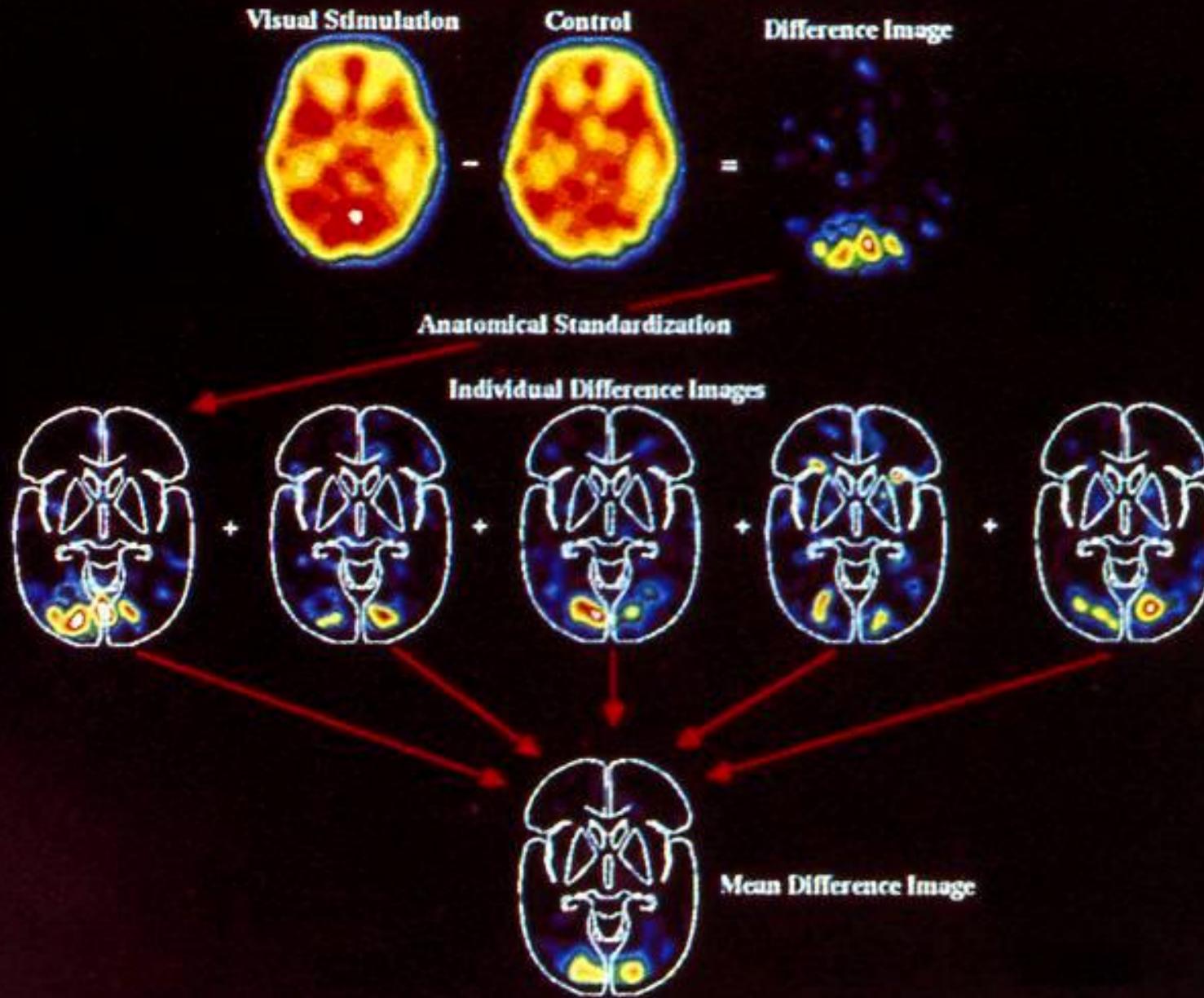


Standard PET preprocessing – minimal!

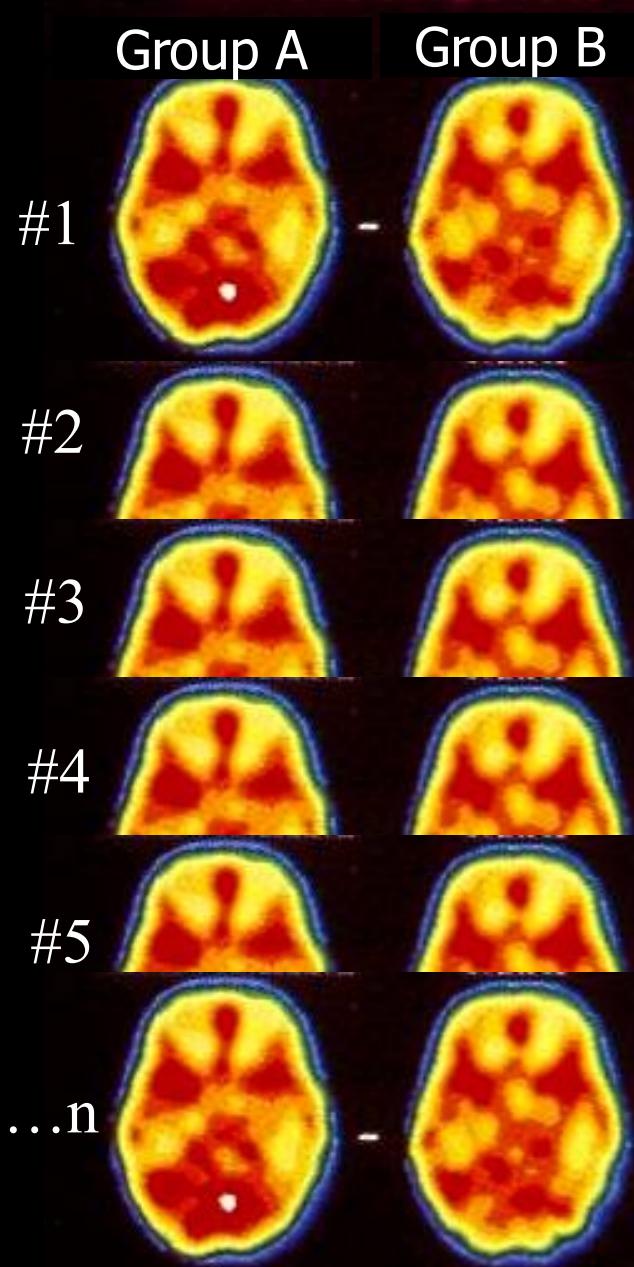
SPM



Parametric mapping: condition comparison



Parametric mapping: group comparisons



{ Spatial Normalization
(Talairach
&
Tournoux
Atlas)

{ Second-level
statistical
processing (e.g.,
GLM)



Group Results

Pure insertion, thus cognitive subtraction

- In functional neuroimaging studies, cognitive subtraction refers to an aspect of experimental design involving the comparison of two conditions or brain states that are presumed to differ in only one discrete feature (the independent variable)
- Pure insertion asserts that there are no interactions among the cognitive components of a task

NEUROIMAGE 4, 97–104 (1996)
ARTICLE NO. 0033

The Trouble with Cognitive Subtraction

K. J. FRISTON, C. J. PRICE, P. FLETCHER, C. MOORE, R. S. J. FRACKOWIAK, AND R. J. DOLAN

The Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom

Received January 18, 1996

Donders' Subtractive Methods

Donder's work attempts to describe the processes going on in the mind, by analyzing cognitive activity into separate stages (many scientists assumed that responding to a stimulus occurred instantaneously!)

Donder was particularly interested in "timing the mind" and used a subtraction technique to time the different mental processes that the brain goes through when faced with different tasks



F. C. Donders

Donders performed experiments using reaction time tasks in 1868:

1. a simple reaction time task - e.g. you are seated in front of a panel that contains a light bulb and a response button. When the light comes on, you must press the button.
2. a discrimination reaction time task - e.g. you are seated in front of a panel with 5 light bulbs and one response button. When the target light goes on you must press the button - but not if the 4 other lights come on.
3. a choice reaction time task - e.g. you are seated in front of 5 light bulbs, each with their own button. You must press the button corresponding to the appropriate light.

Levels of cognitive subtraction

Stronger Results

- **Basic cognitive subtraction:** Rational argument of validity
- **Cognitive conjunction:** Two cognitive subtraction designs show same activation difference
- **Parametric design:** Increasing levels of a factor correspond with increasing levels of activation

SPM
example

reconstruction
realignment
smoothing

Data analyses

How to build a (PET imaging) experiment



Experimental hypothesis



Subject selection,
screening, psychometric
evaluations, etc.



Experimental session and data
preprocessing

Experimental paradigm





Russian grandmaster Anatoly Karpov deep in thought at the FIDE competition against Jan Timman.

Perché gli scacchi?

- I problemi scacchistici sono complessi
- L'abilità dello scacchista è ben misurabile
- C'è una vasta letteratura sulla psicologia cognitiva degli scacchi

Compiti sperimentali

- **Discriminazione Bianco/Nero**
- **Discriminazione Spaziale**
- **Regole**
- **Scacco Matto**

Discriminazione B/N

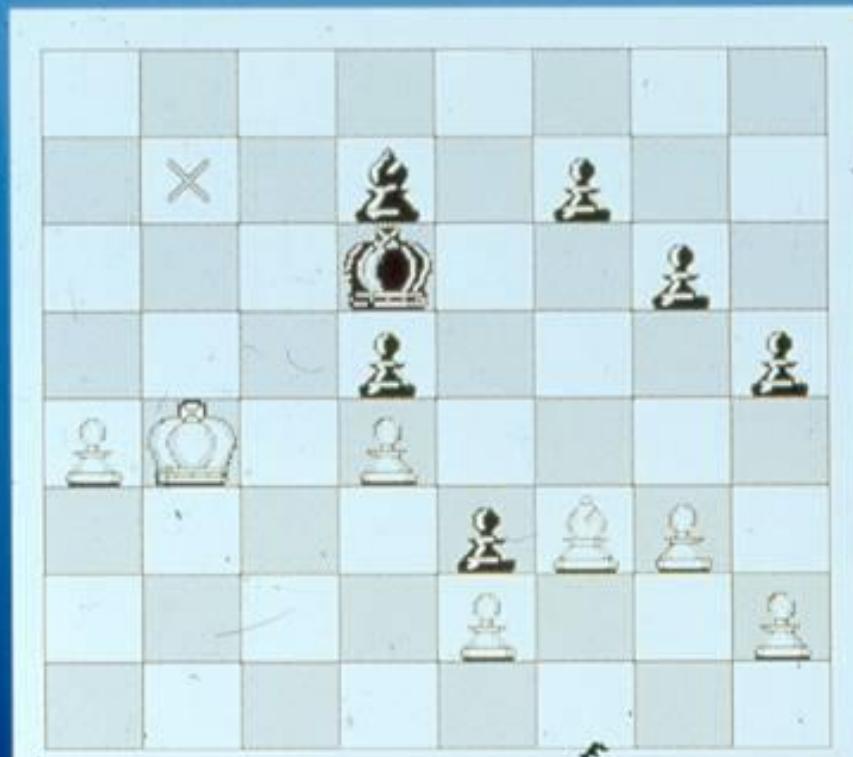


Ci sono pezzi BIANCHI sulla scacchiera?

Componenti della Discriminazione B/N

- Percezione della scena visiva
- Discriminazione Bianco/Nero
- Lettura
- Decisione
- Recupero della regola motoria
- Movimenti oculari
- Movimento del pollice

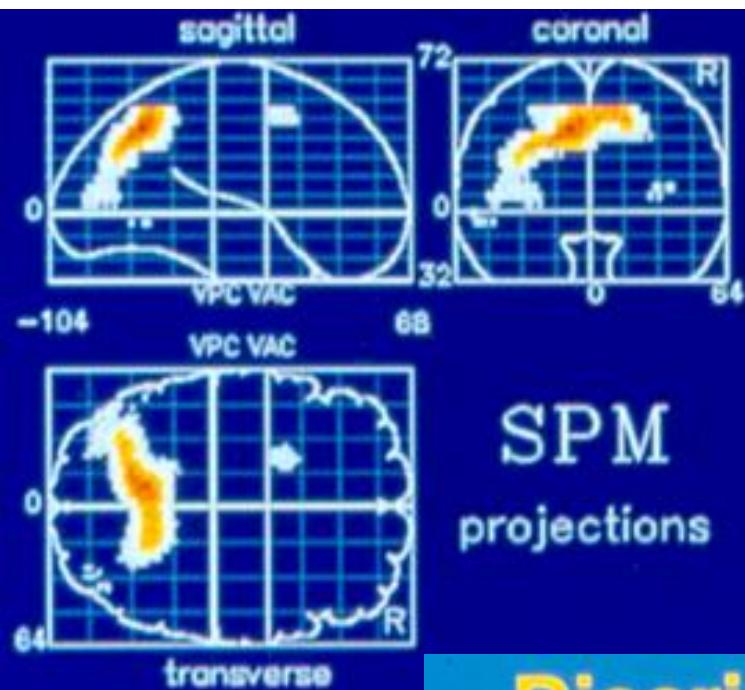
Spatial Discrimination



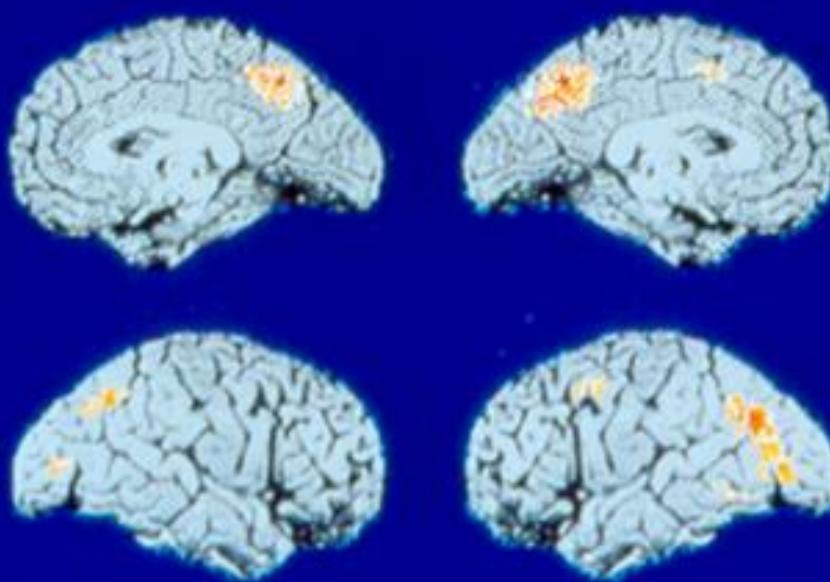
E' BIANCO il pezzo più vicino alla X?

Componenti cognitive introdotte dal compito di Discriminazione Spaziale

- **Attenzione spaziale**
- **Analisi spaziale statica**



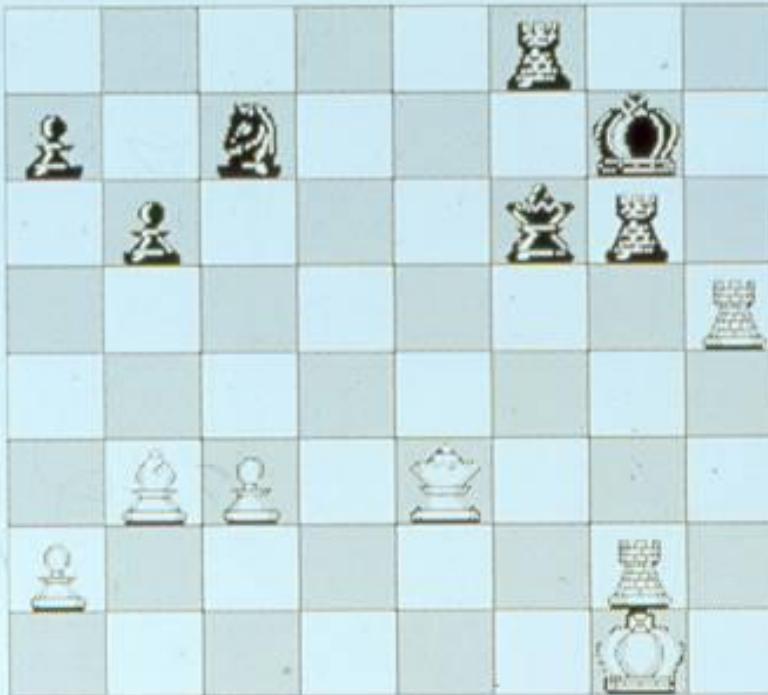
SPM
projections



Discriminazione spaziale - Discriminazione B/N

- Precuneo (sinistra e destra)
- Lobo occipitale (sinistra e destra)
- Lobulo parietale superiore (sinistra)
- Giro temporale medio (sinistra)
- Corteccia premotoria superiore (sinistra)

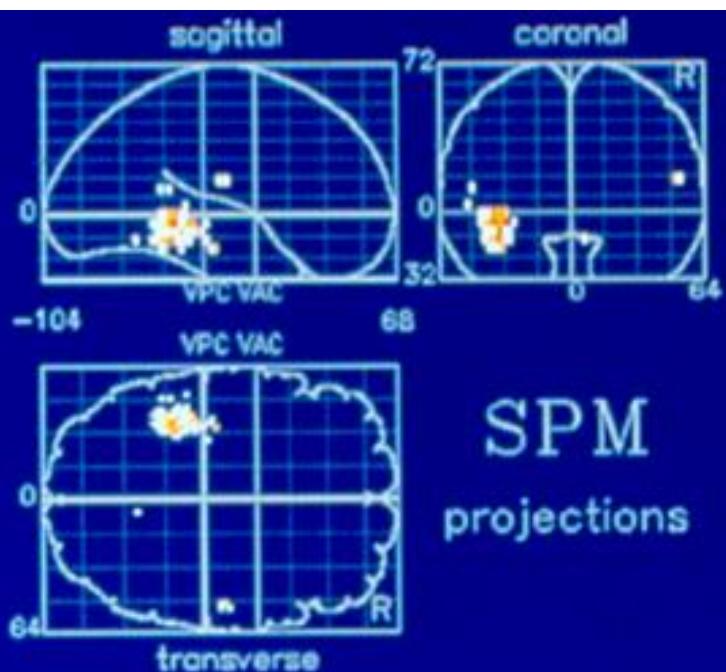
Regole



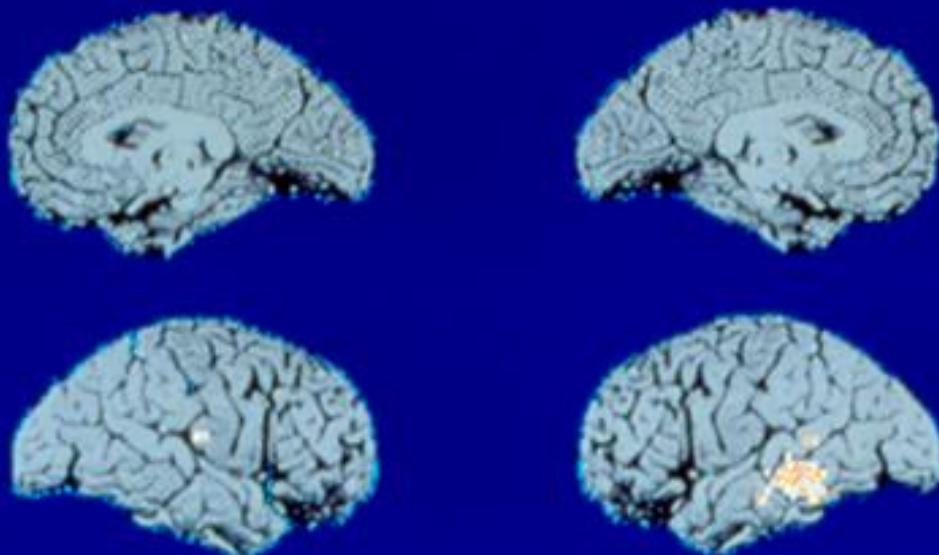
La REGINA BIANCA può catturare il PEDONE NERO?

Componenti cognitive introdotte da "Regole"

- Discriminazione del valore dei pezzi**
- Recupero delle regole (per un pezzo)**
- Analisi spaziale dinamica (per un pezzo)**



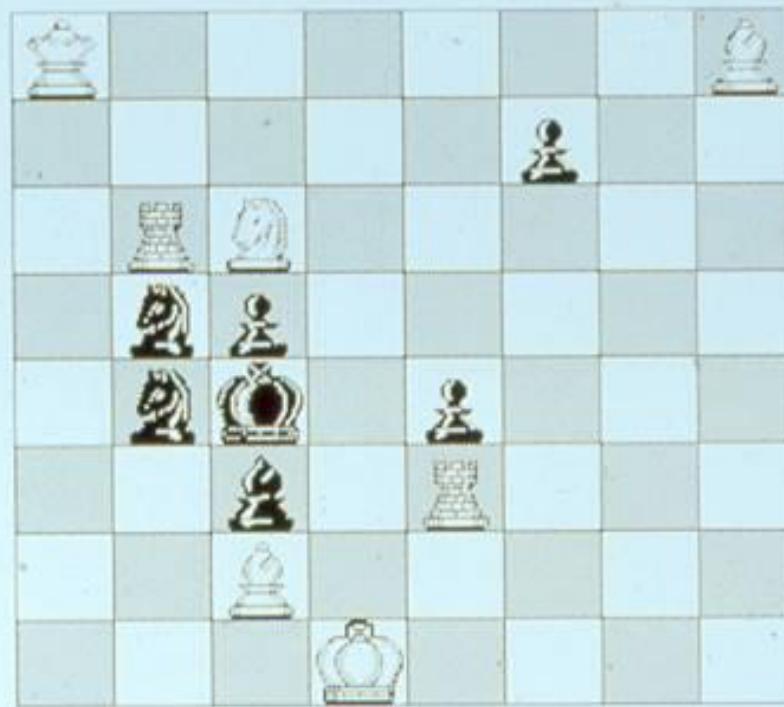
SPM
projections



Regole - discriminazione spaziale

- Ippocampo di sinistra
- Lobo temporale di sinistra (strutt. mediali)
- Giro temporale superiore di sinistra (terzo medio)
- Giro temporale medio di sinistra (terzo medio)
- Giro fusiforme di sinistra
- Cervelletto
- Giro post-centrale di destra

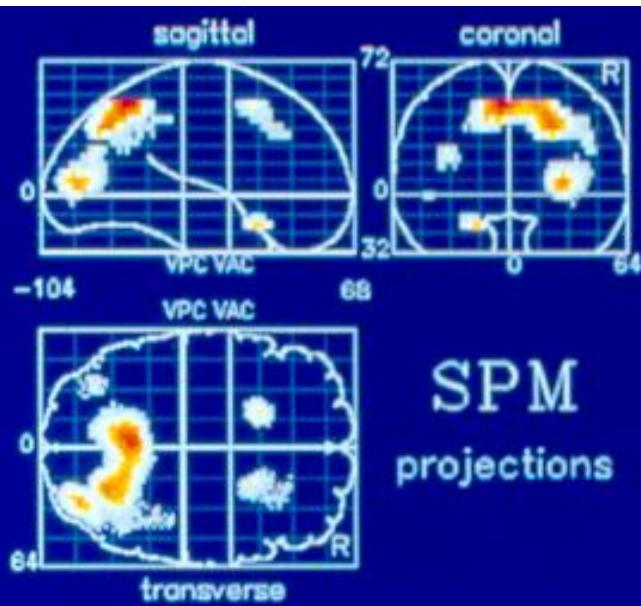
Scacco matto



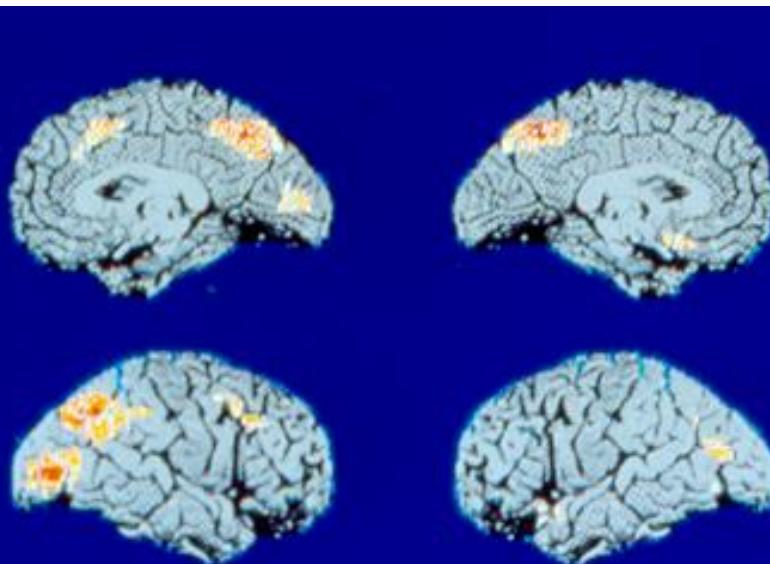
Può il BIANCO dare scacco matto con una mossa?

Componenti cognitive introdotte da "Scacco matto"

- Recupero delle regole del gioco (per tutti i pezzi)**
- Valutazione delle conseguenze di ogni mossa
(visualizzazione mentale)**
- Generazione di una sequenza di mosse
(pianificazione)**

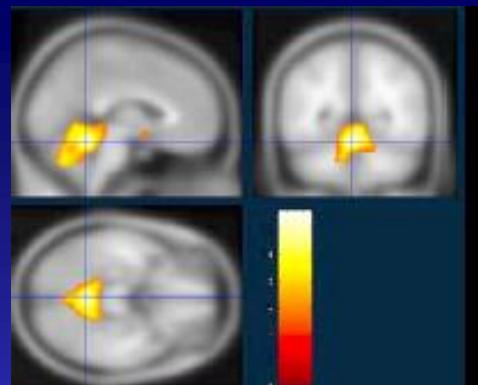


SPM
projections



Scacco matto - Regole

SPM
example



Results interpretation and discussion

reconstruction
realignment
smoothing

Data analyses

How to build a (PET imaging) experiment



Experimental hypothesis

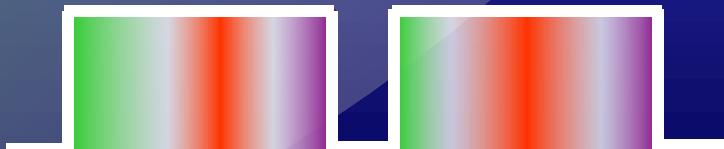


Subject selection,
screening, psychometric
evaluations, etc.



Experimental session and data preprocessing

Experimental paradigm



Neural correlates of face perception

- What do we mean for ‘face perception’
- The importance of:
 - Gender
 - Age
 - Gaze
 - Identity
 - Expression
 - Familiarity
 - Etc...



How to build a (PET imaging) experiment



Experimental hypothesis

Subject selection,
screening, psychometric
evaluations, etc.

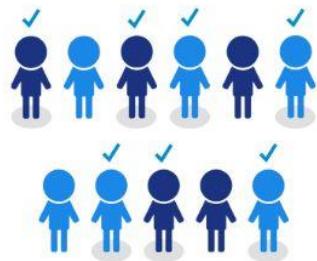
Neural correlates of face perception

- Which features should we take into account for subject selection relative to face perception?
- The role of:
 - Gender (and Sexual Orientation?)
 - Ethnicity
 - Age
 - Education, working job, other socio-demographic variables
 - Health status
 - Visual acuity
 - Drug-free
 - Psychometric characterization?
 - Possible selection bias?
 - Sampling Methodology?
 - Calculating sample size?

Neural correlates of face perception

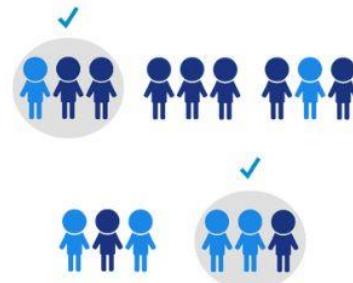
Probability Sampling Methodologies

1



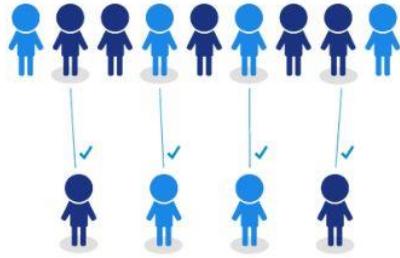
Simple Random Sampling

2



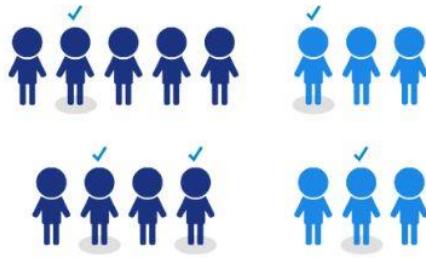
Cluster Sampling

3



Systematic Sampling

4

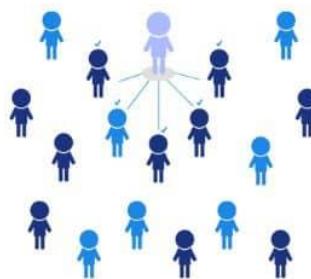


Stratified Random Sampling

Neural correlates of face perception

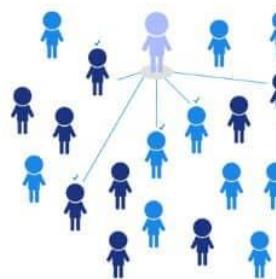
Non-probability Sampling Methodologies

1



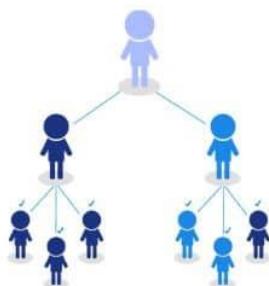
Convenience Sampling

2



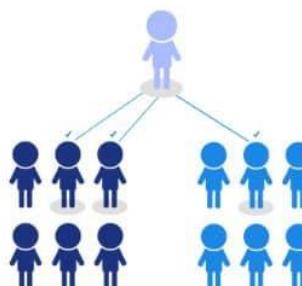
Purposive Sampling

3

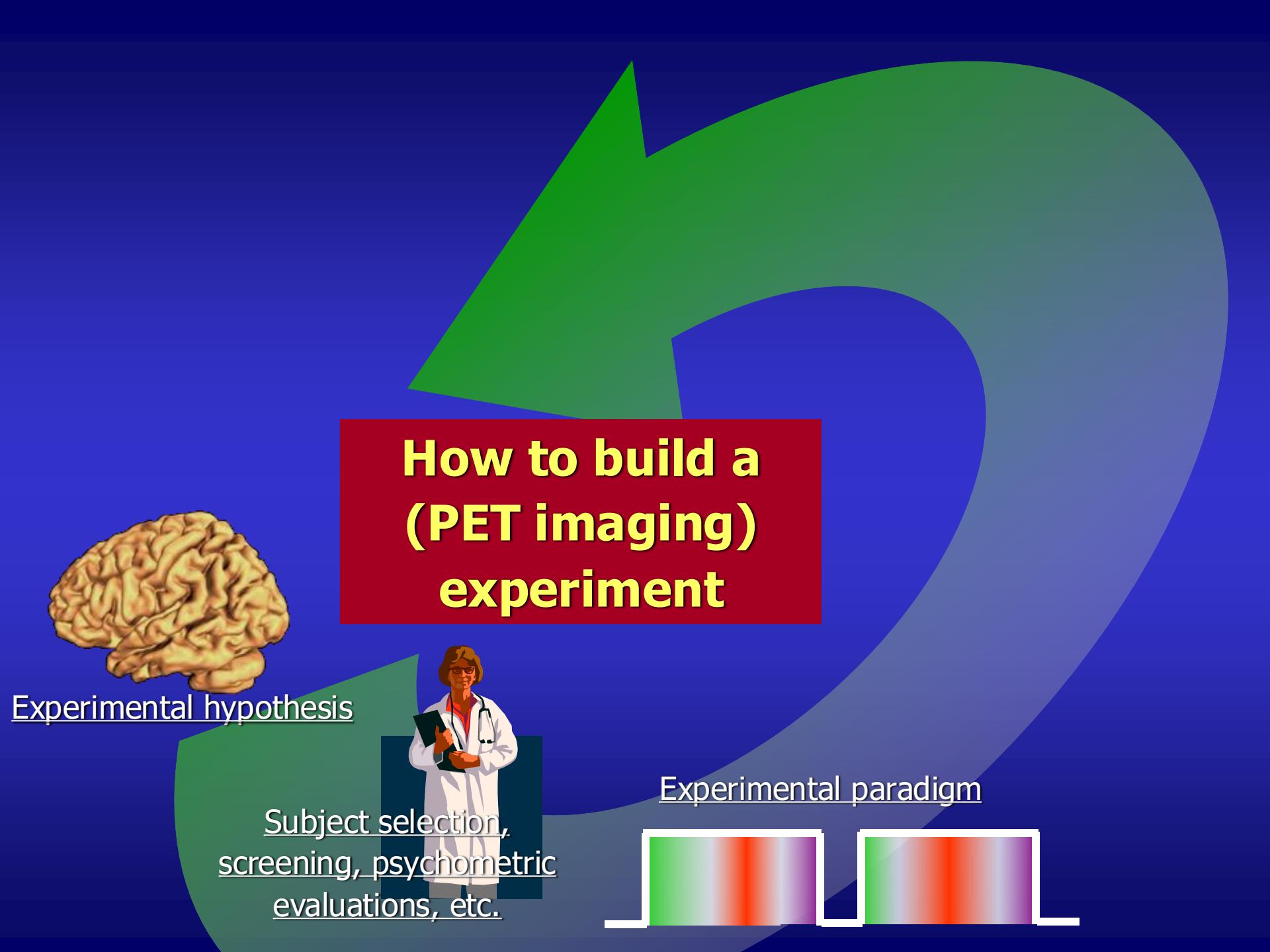


Snowball Sampling

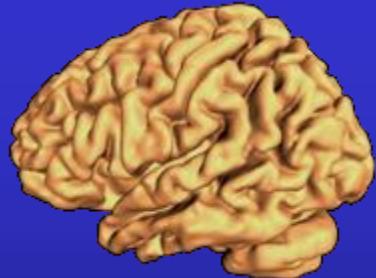
4



Quota Sampling



How to build a (PET imaging) experiment

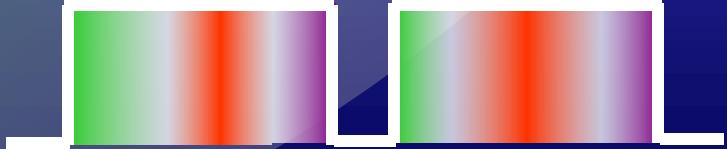


Experimental hypothesis



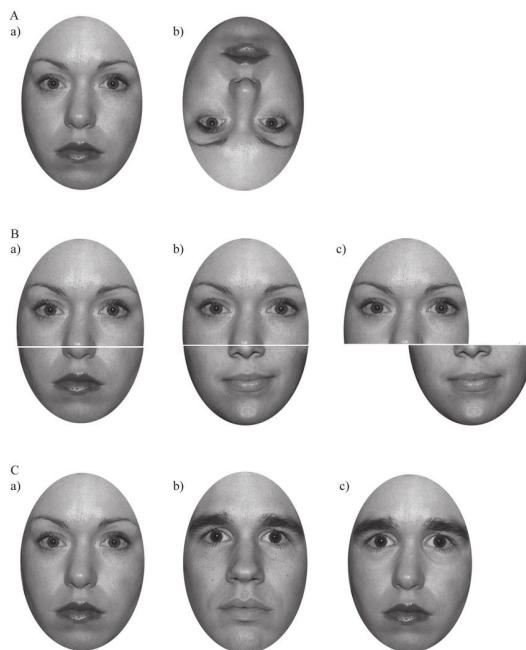
Subject selection,
screening, psychometric
evaluations, etc.

Experimental paradigm



Neural correlates of face perception

- Which *stimuli* to be selected?



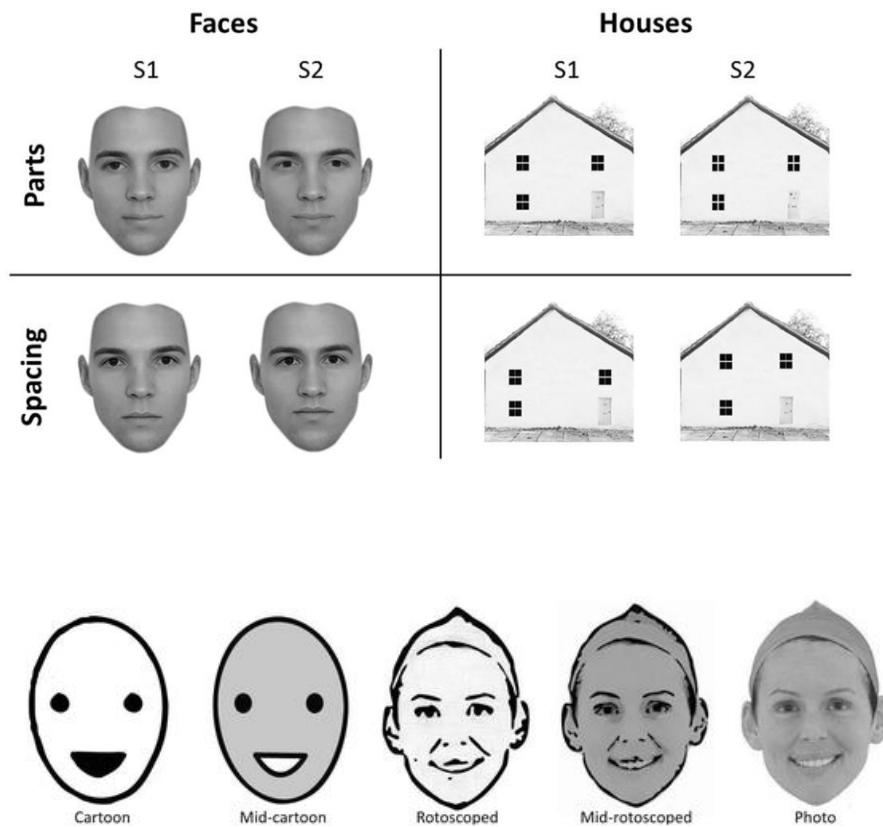
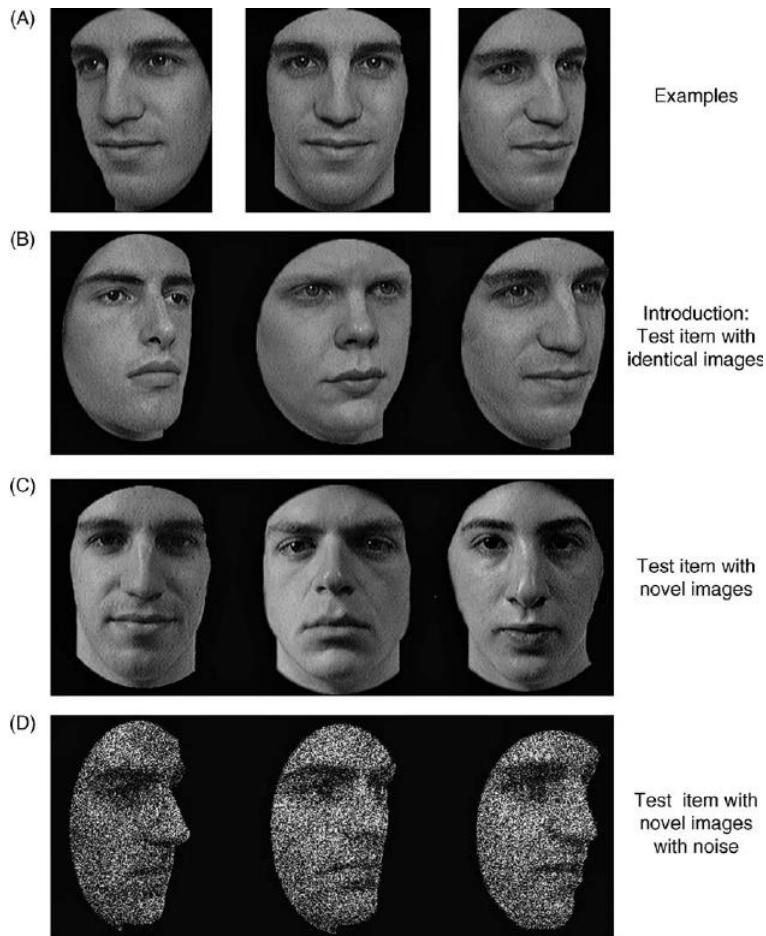
Mooney Faces stimuli:



Mooney Objects stimuli:

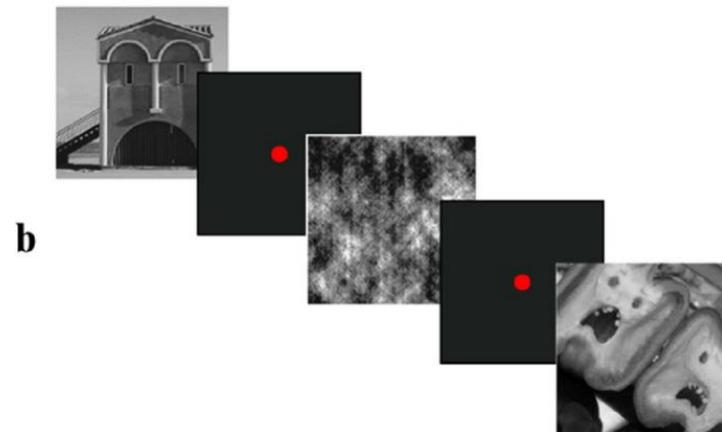
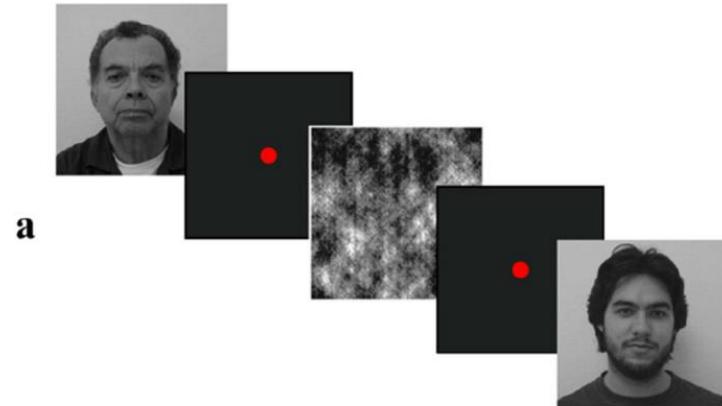
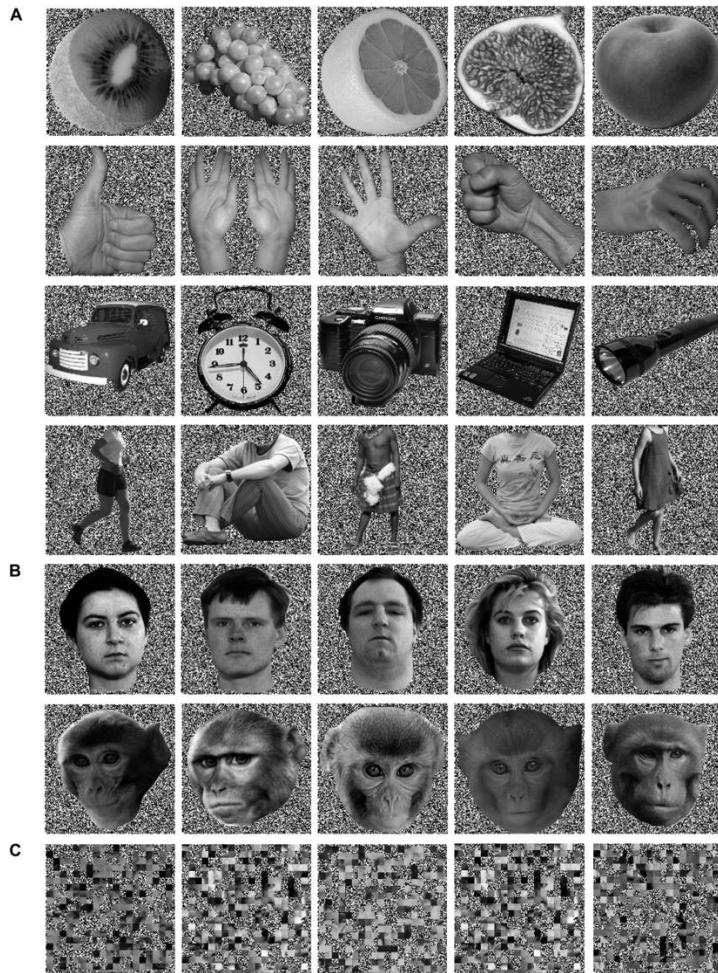
Neural correlates of face perception

- Which *stimuli* to be selected?



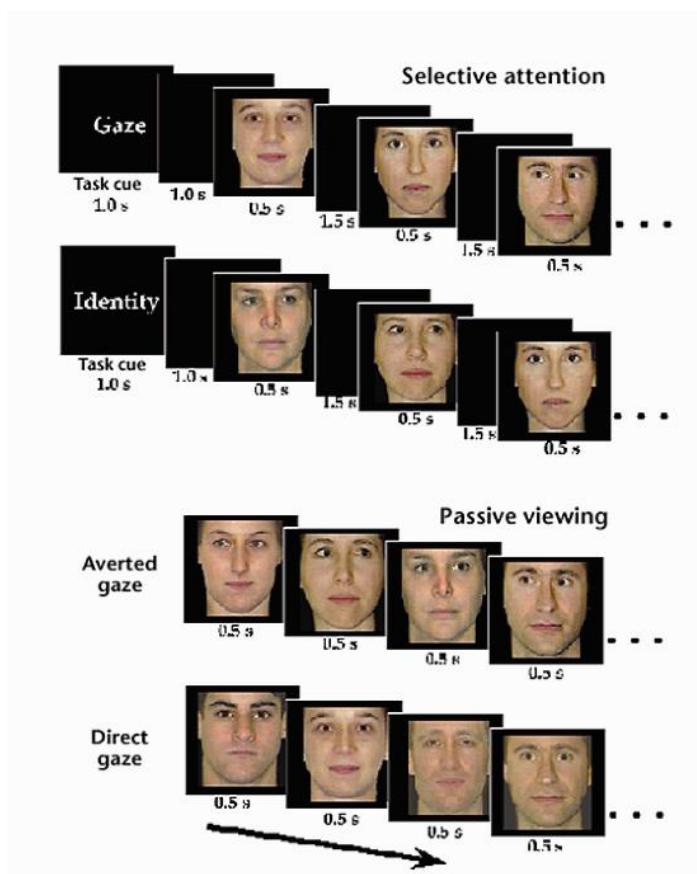
Neural correlates of face perception

- Which *stimuli* to be selected?



Neural correlates of face perception

- Which *task* to be selected?



Pharmakinetics

Clinical
experience

Epidemiology

Drug

Pharmacodynamics

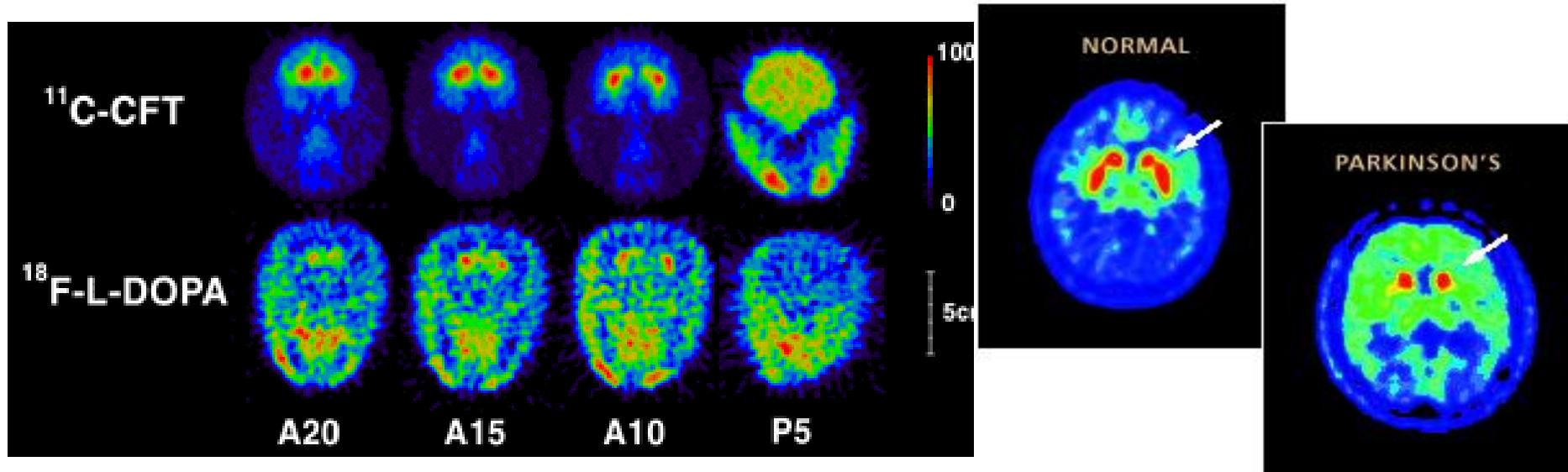
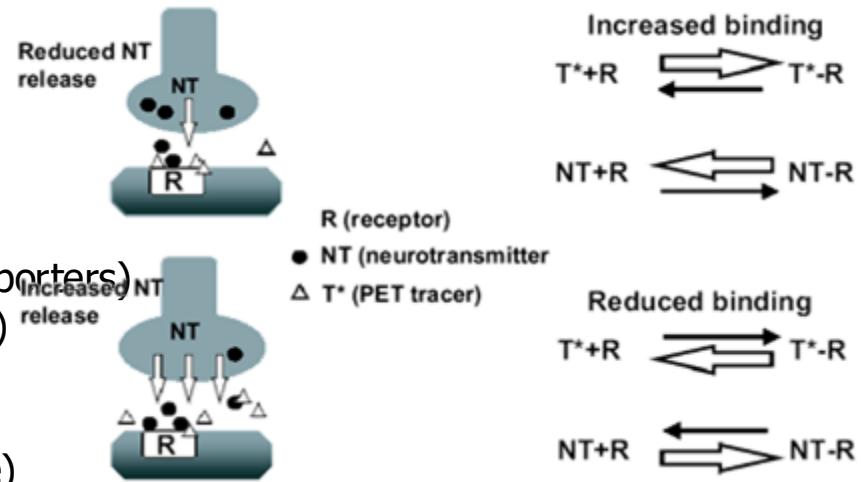
Functional sites of
drug action

Localization and
characterization of
receptors

Understanding drug action

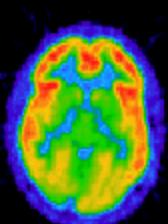
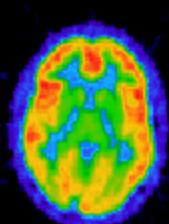
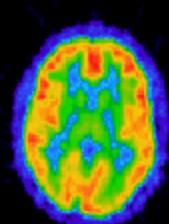
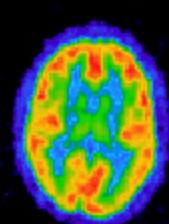
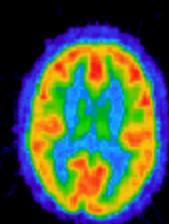
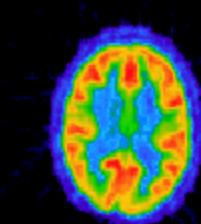
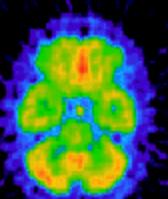
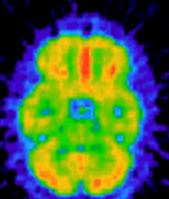
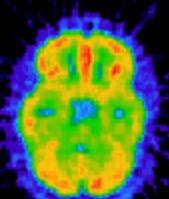
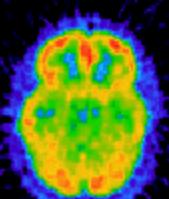
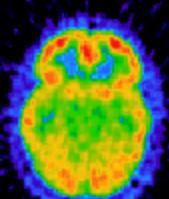
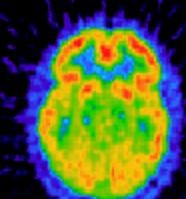
Isotopes used to visualize receptors or neurotransmitter release/uptake

- [¹¹C]acetate (metabolism)
- [¹¹C]methionine (amino acid utilization)
- [¹¹C]flumazenil (GABAA-benzodiazepine receptors)
- [¹¹C]raclopride (dopamine D2 receptors)
- [¹¹C]carfentanil (opiate receptors)
- [¹¹C]dihydrotetraabenazine (vesicular monoamine transporters)
- [¹¹C]hydroxyephedrine (cardiac adrenergic innervation)
- [¹¹C]epinephrine (cardiac adrenergic innervation)
- [¹¹C]phenylephrine (cardiac adrenergic innervation)
- [¹¹C]methylpiperidinyl propionate (acetylcholinesterase)



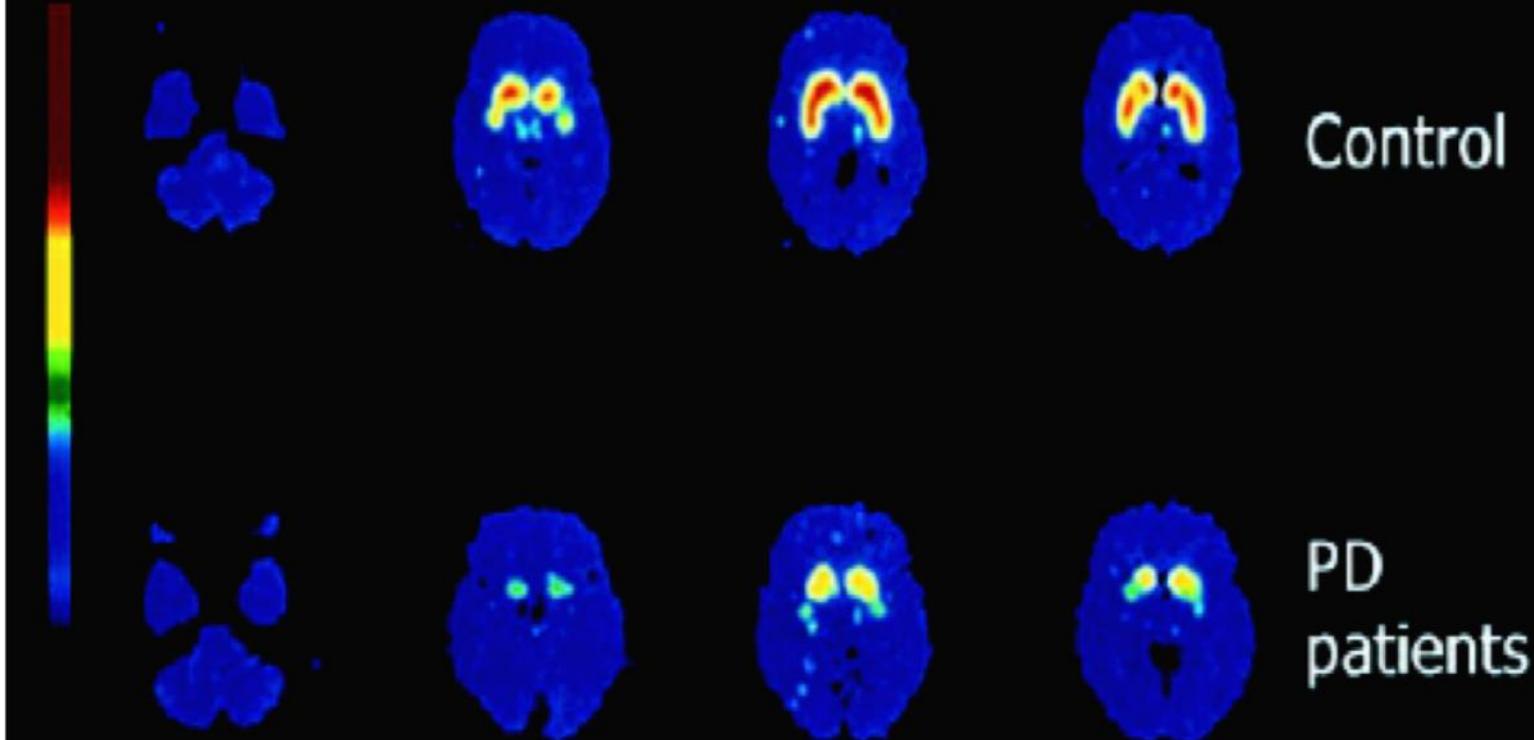
[¹¹C]MDL 10097 - PET

Flow dependent images



5HT_{2A} receptors images

DOPAMINE UPTAKE SITES [¹¹C]WIN 35,428



- Images of dopamine transporters in Parkinson's disease and a healthy control with a selective dopamine transporter ligand
- In PD there is a marked reduction in the right and left putamen and a smaller, but significant, reduction in both caudate nuclei

Drugs destroy dopamine balance

