PET – A new method to see the function of the brain

National /Turku PET Centre
at night

Staff > 100
3 cyclotrons
3 PET-scanners
PET/CT scanner (64 slice CT)
1.5T MRI

A Joint National Research Institute of
University of Turku,
Åbo Akademi University and
Turku University Central Hospital

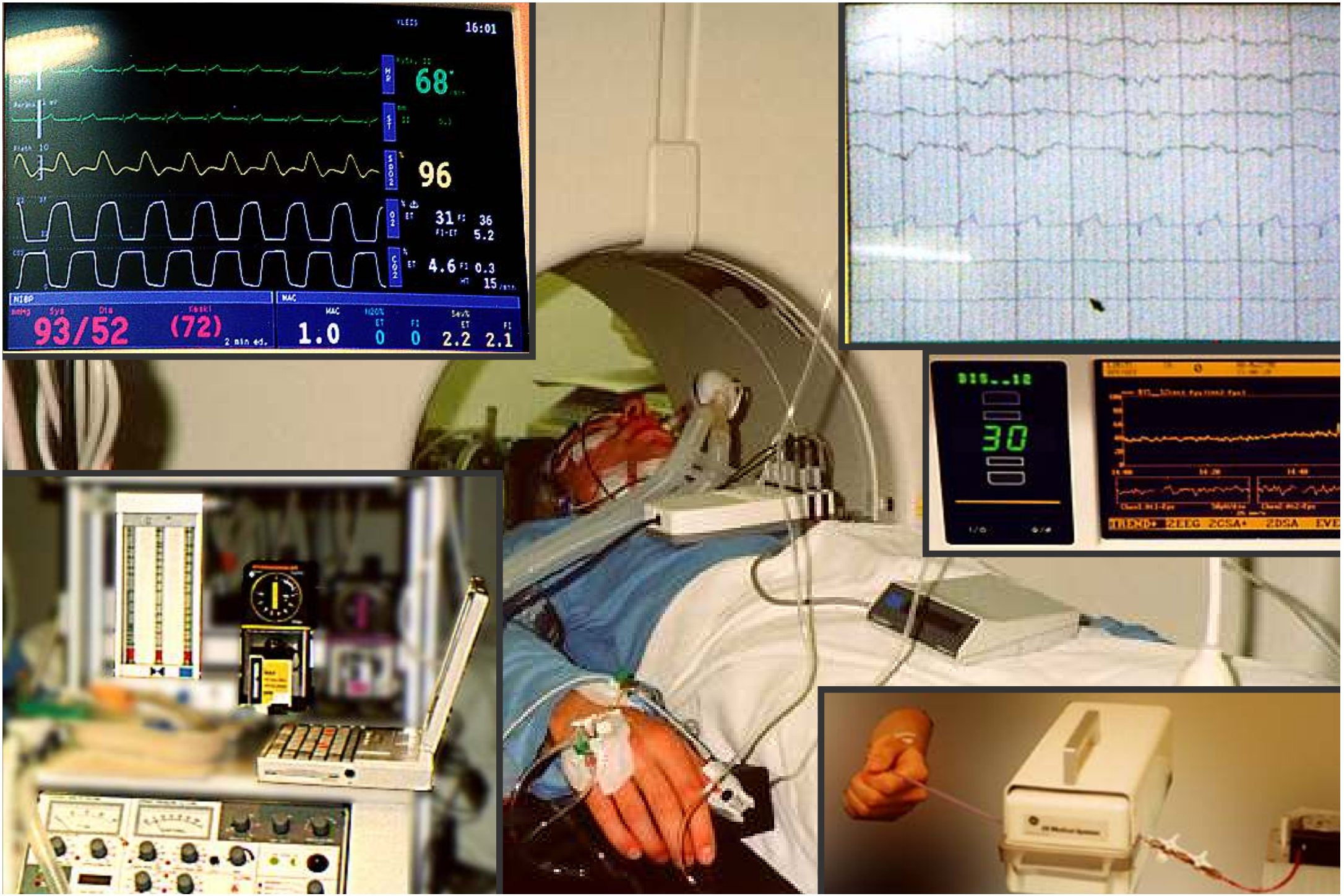
http://www.turkupetcentre.fi

PET – A new method to see the function of the brain

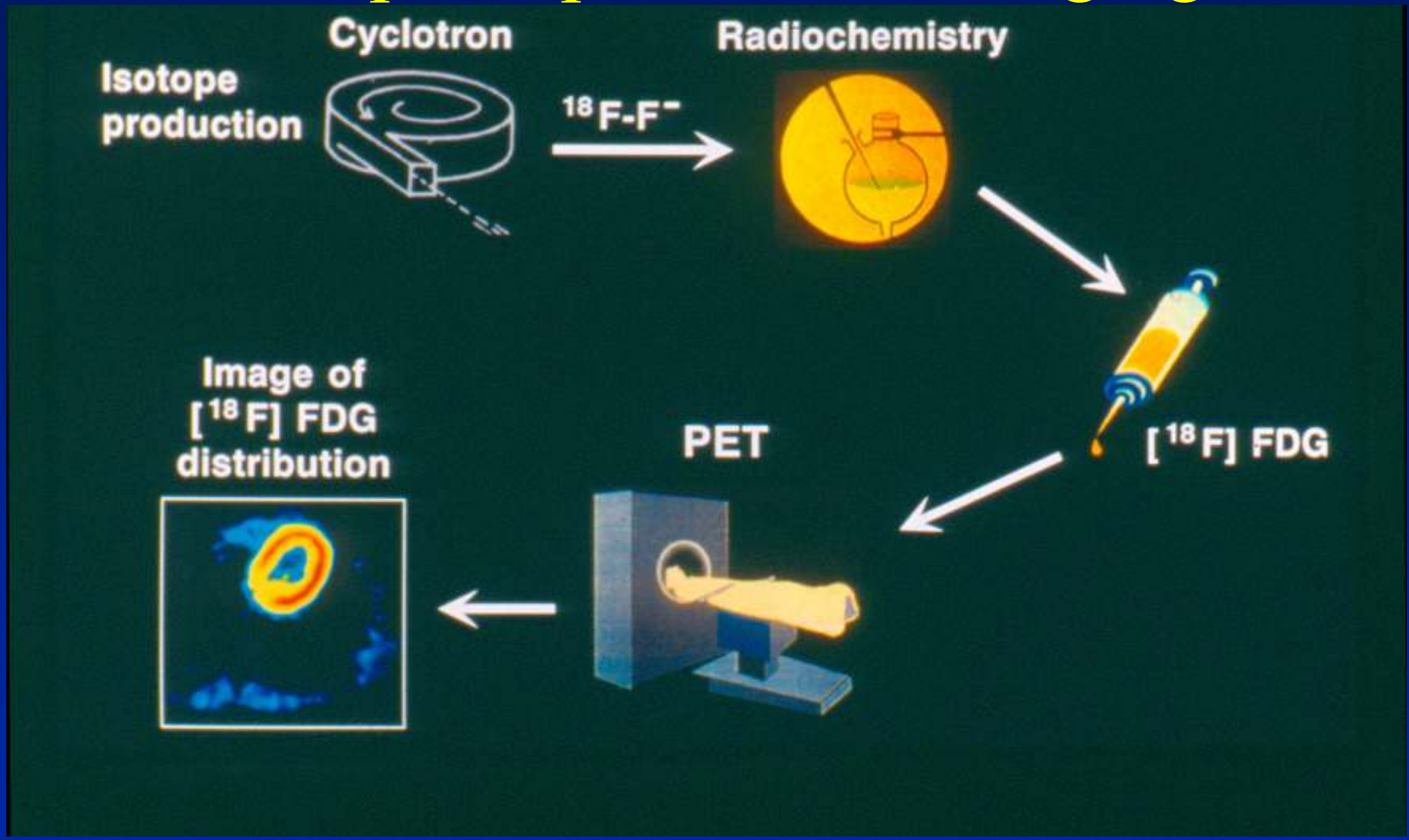
- Basic physics of PET method
- PET in neuro research and drug development
- Present and future trends in neuroPET

What is PET?

- PET= Positron Emission Tomography
- A computerized tomography employing short lived (2 min - 2 hour) radioactive isotopes (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{68}Ga)
- Enables noninvasive study of tissue molecular function

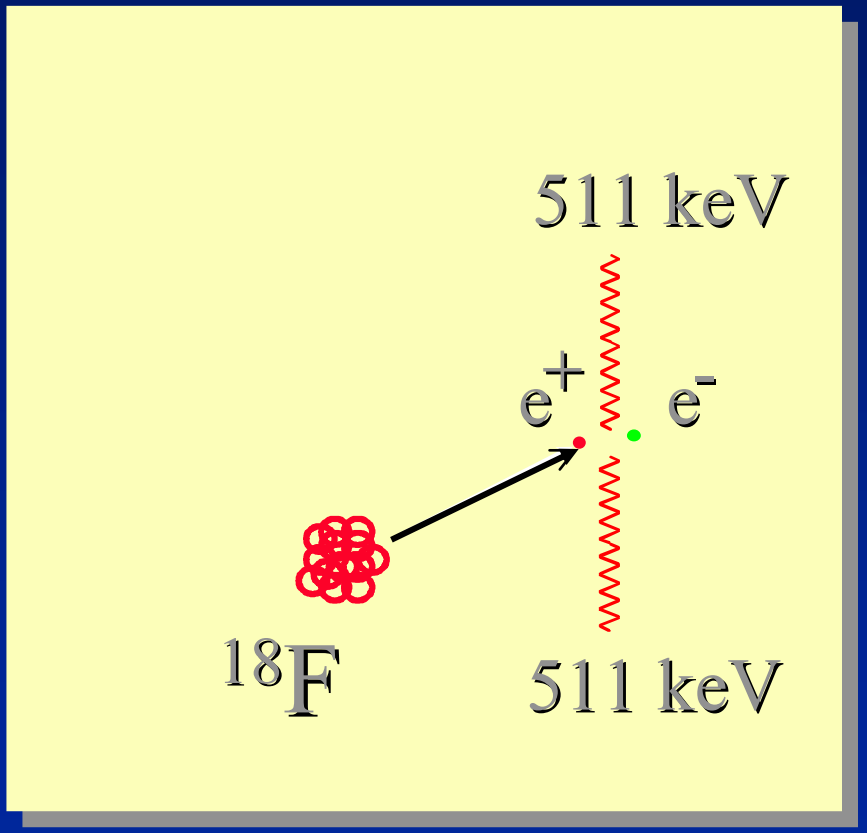

16:01
68
96
31
36
5.2
4.6
0.3
15
NIBP
93/52
(72)
MAC
1.0
30

The principle of PET imaging

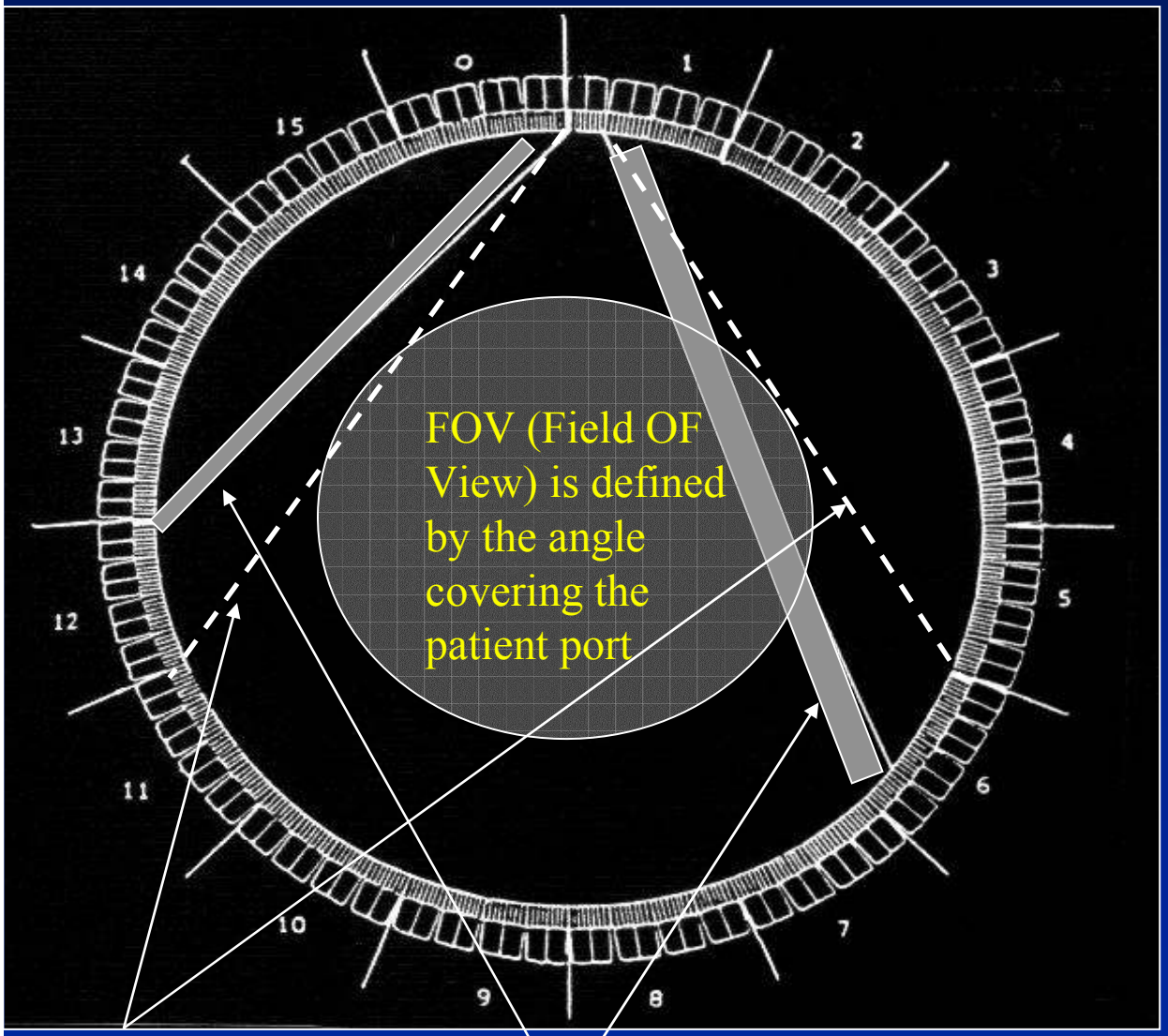


Common Positron Emitters

- $^{14}N(p,\alpha)^{11}C$ $T_{1/2} = 20.4$ min
- $^{16}O(p,\alpha)^{13}N$ $T_{1/2} = 10.0$ min
- $^{14}N(d,n)^{15}O$ $T_{1/2} = 2.05$ min
- $^{18}O(p,n)^{18}F$ $T_{1/2} = 109.8$ min

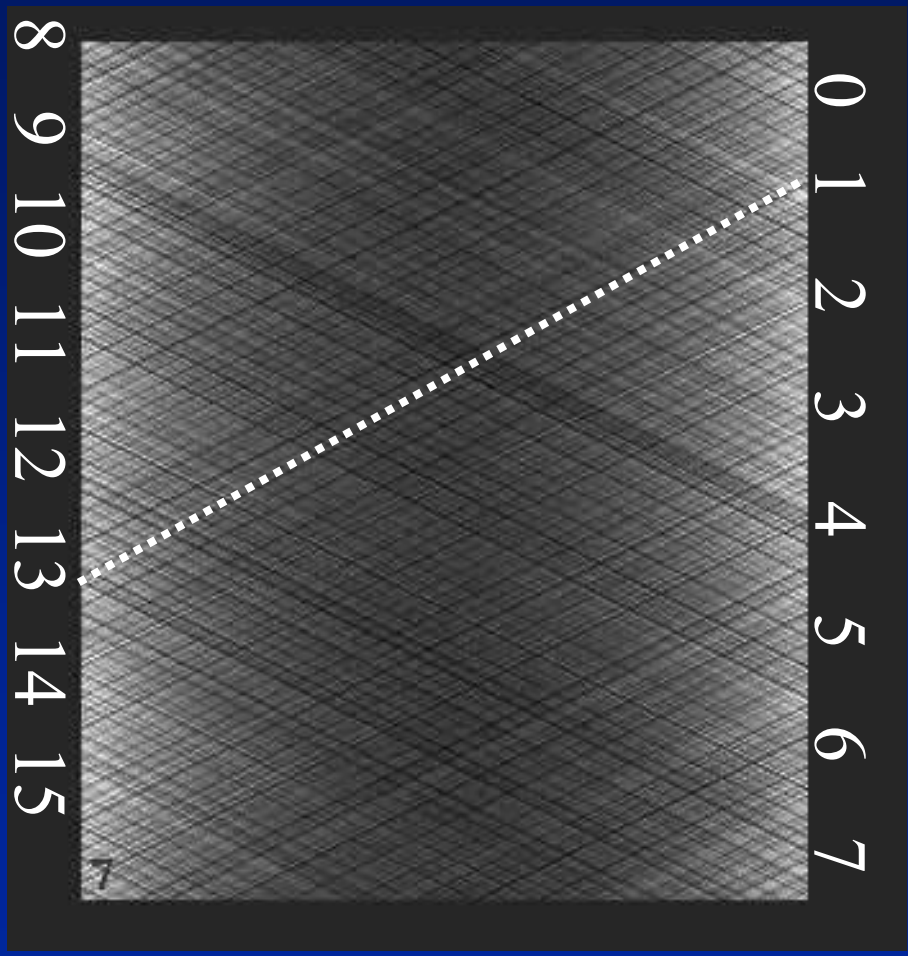


Need a cyclotron !



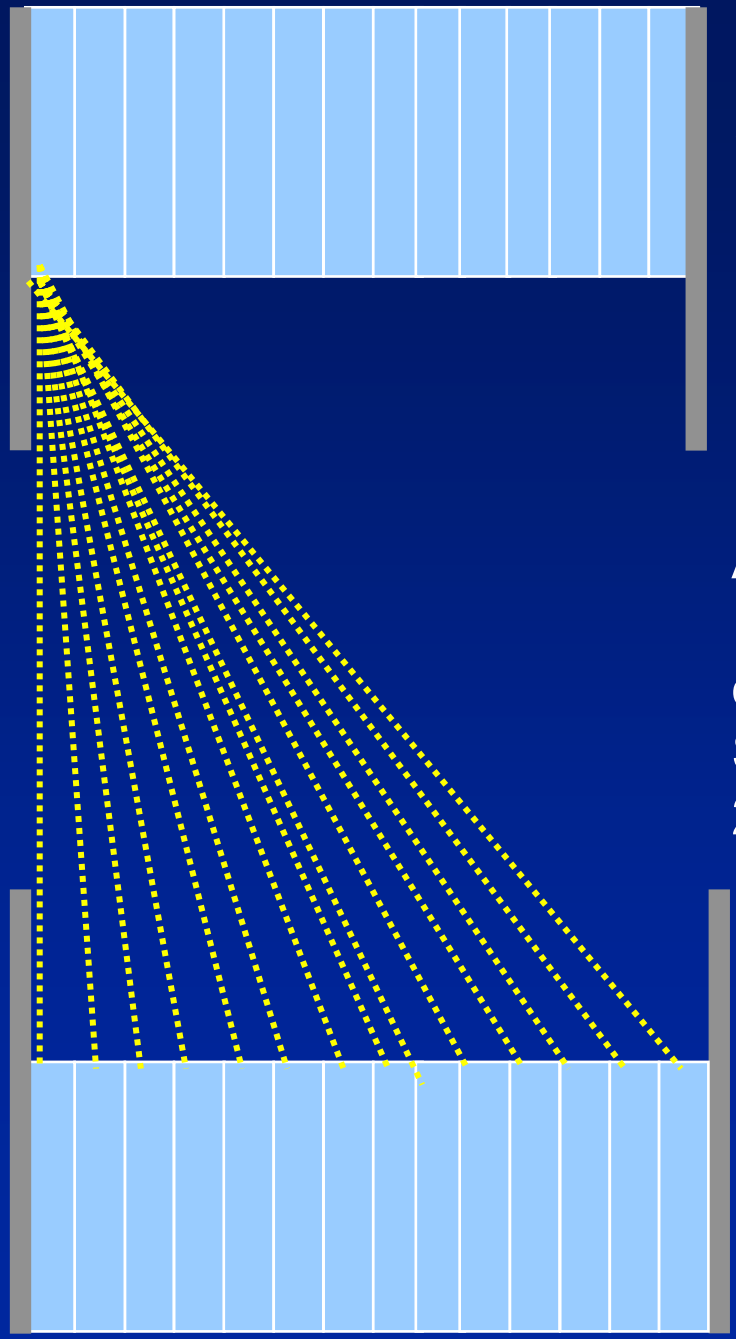
LOR (Line Of Response) is a line (or tube) between two opposing crystals. Tube diameter is angle dependent.

2D Sinogram



In the sinogram LOR is represented by one diamond

Turku PET Centre

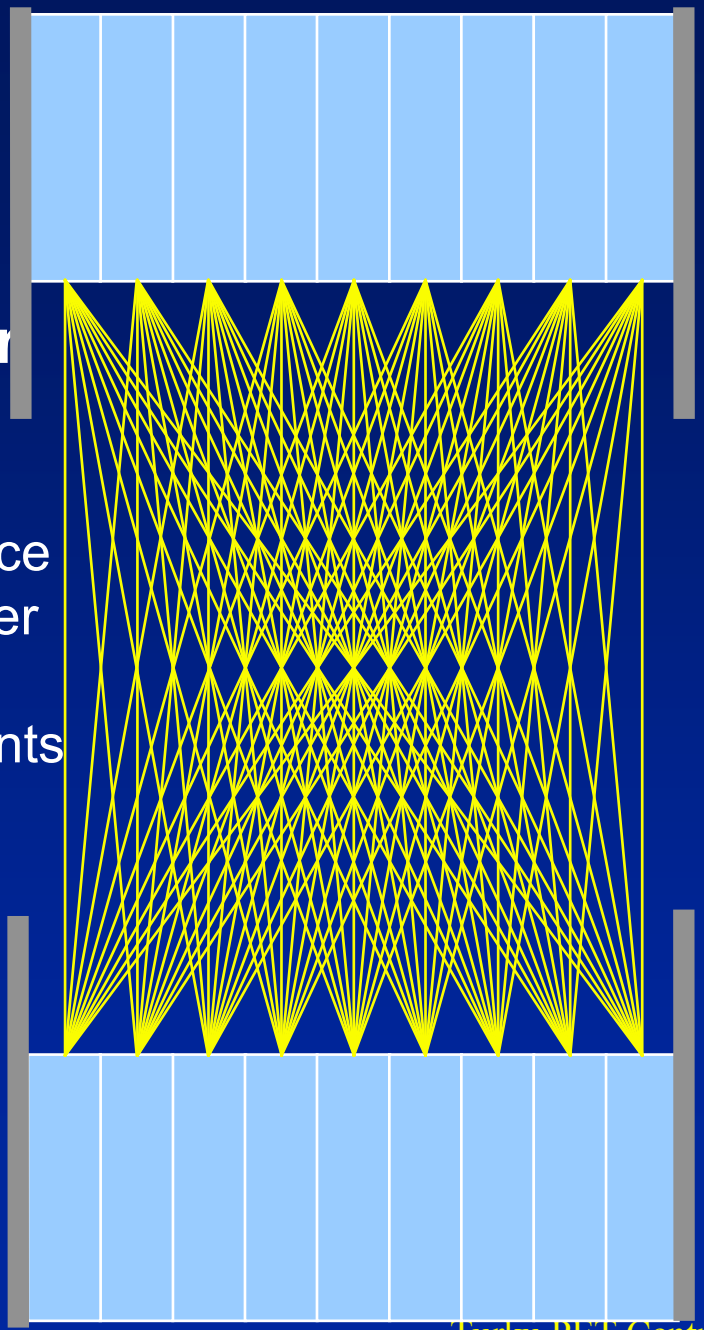


3D PET

no septa

→4 times better sensitivity

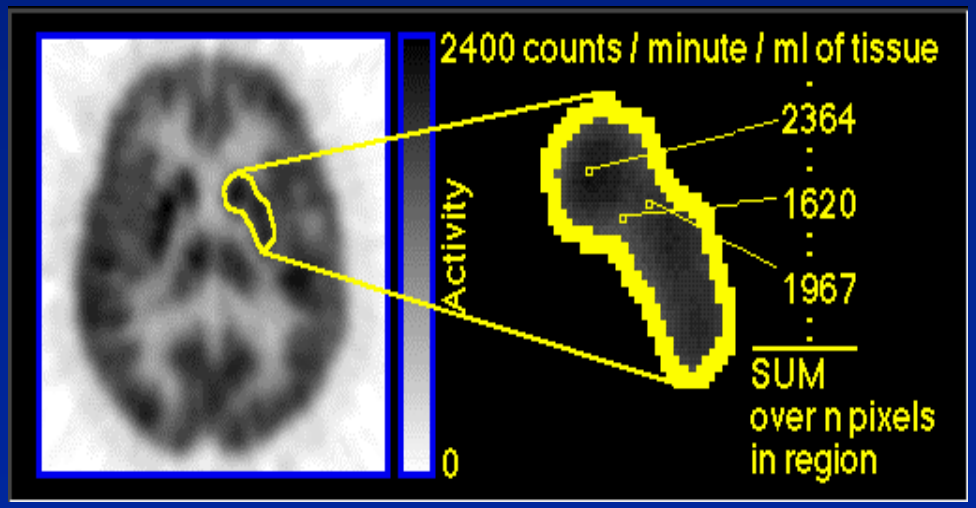
Axial plane difference Is defined by number of segments. Segment 0 represents 2D image



Analysis of PET Results (1)

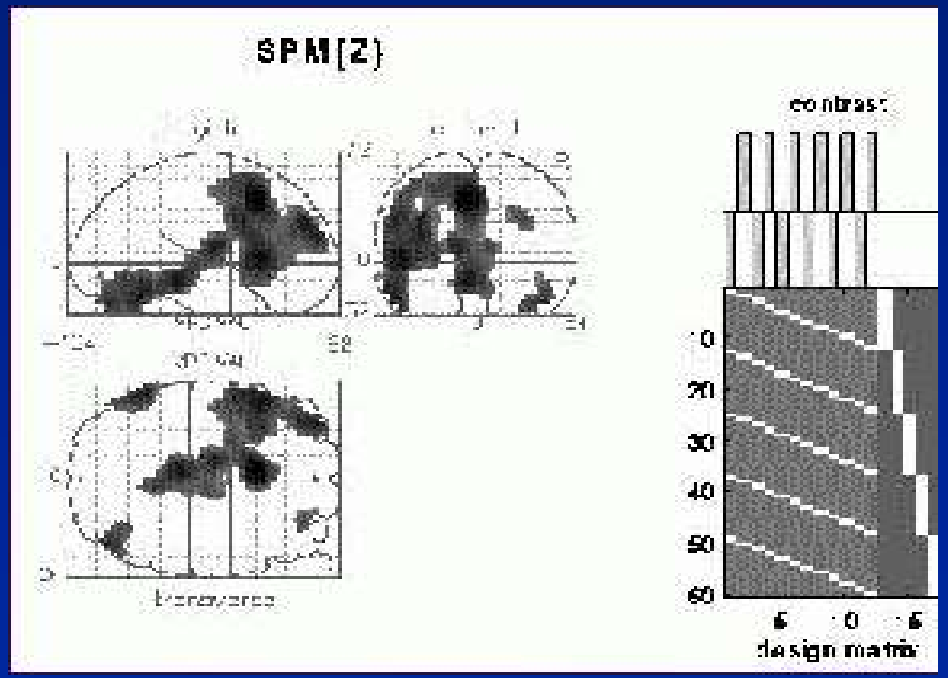
1) Absolute quantification

- *Draw ROIs on MRI images*
- *Mathematical modeling*
- *Blood samples usually needed*



2) 3D mapping of relative changes

- *Statistical parametric mapping (SPM)*



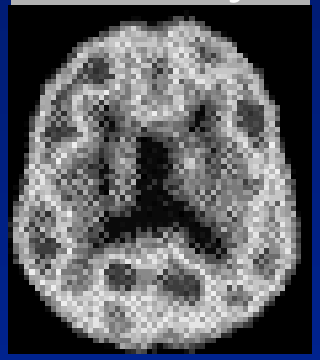
Analysis of PET Results (2)

Modelling

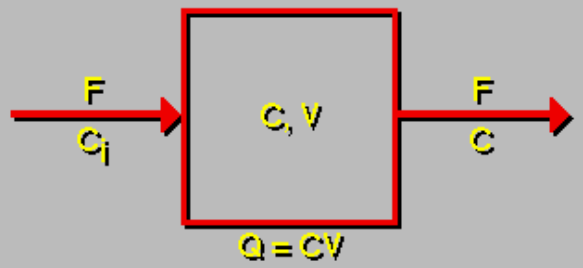
1) on-line arterial activity
2) dynamic 3D PET data
3) metabolite samples

=> *Model*
=> *Quantitative result*

2)Tissue activity

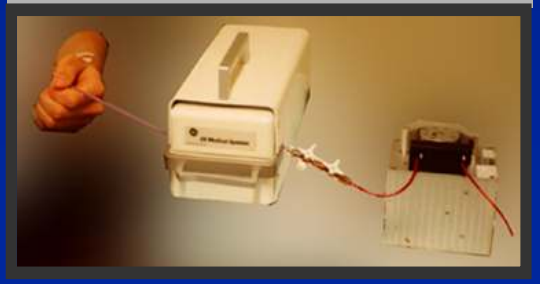


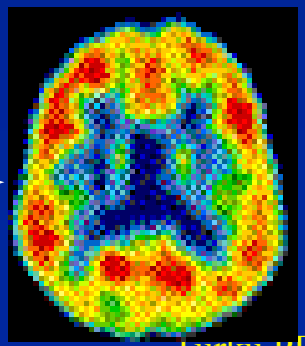
3)Tracer metabolite data



F = blood flow
C_i = arterial concentration of tracer
C = tissue concentration of tracer
V = distribution volume of tracer
= amount of tracer / g of tissue / amount of tracer / ml of blood

1)Arterial activity

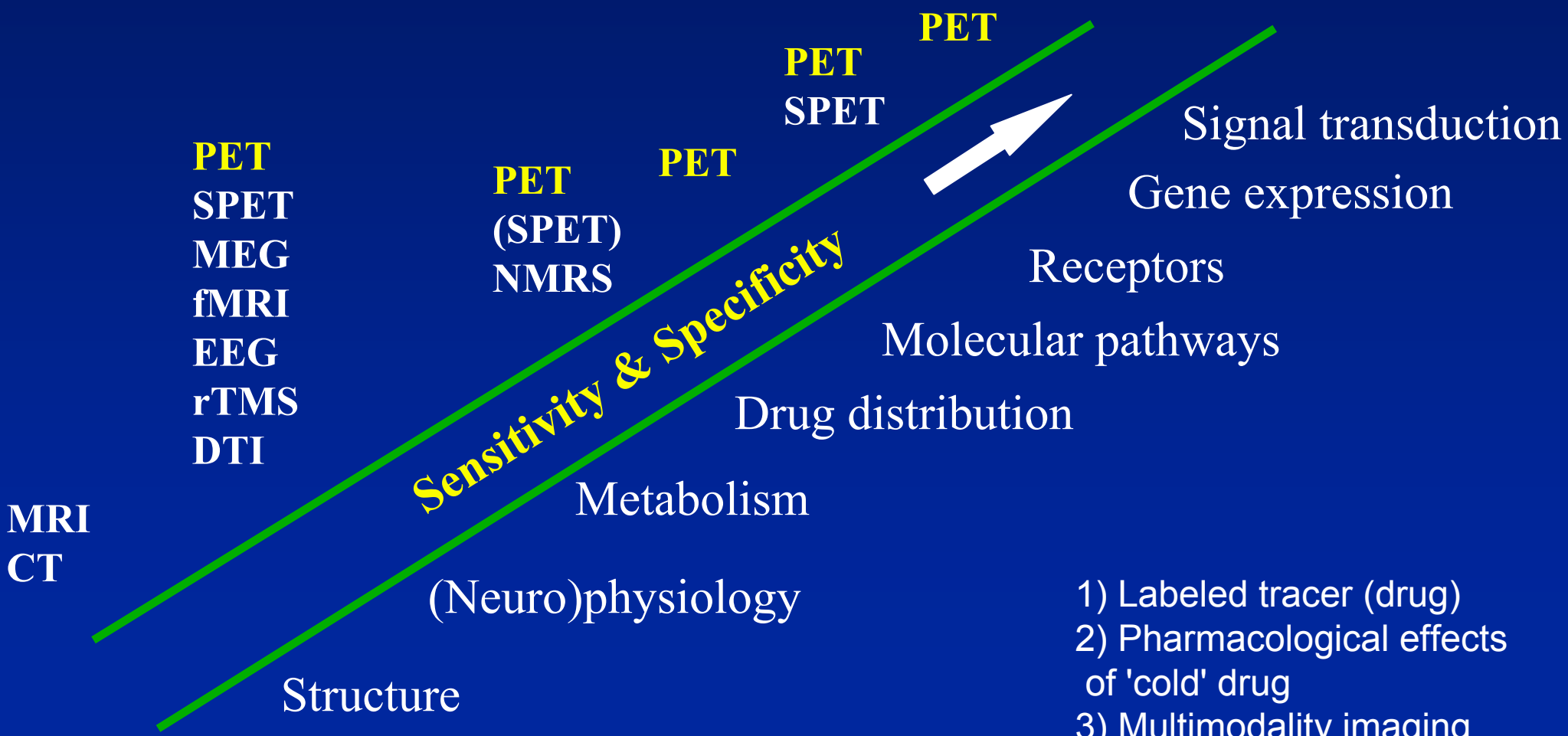




PET – A new method to see the function of the brain

- Basic physics of PET method
- PET in neuro research and drug development
- Present and future trends in neuroPET

The Role of PET in Brain Imaging



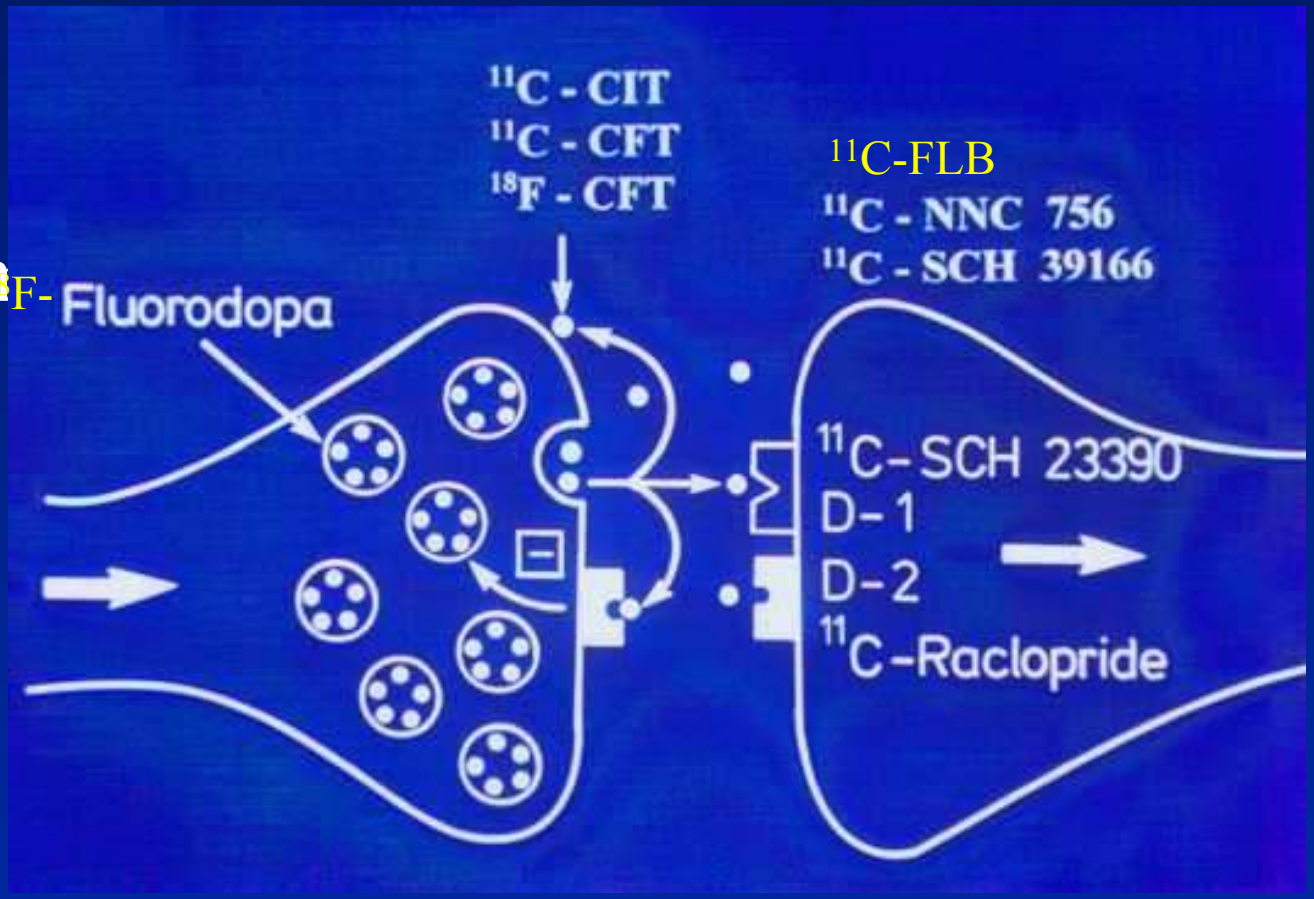
1) Labeled tracer (drug)
2) Pharmacological effects of 'cold' drug
3) Multimodality imaging

Advantages of PET in neurotransmitter studies

- PET is one of the few tools enabling investigation on neurotransmission in living human brain
- Wide selection of radiopharmaceuticals
- ”Biological” radiopharmaceuticals
- Quantitation

PET in neurotransmitter research: dopaminergic synapse

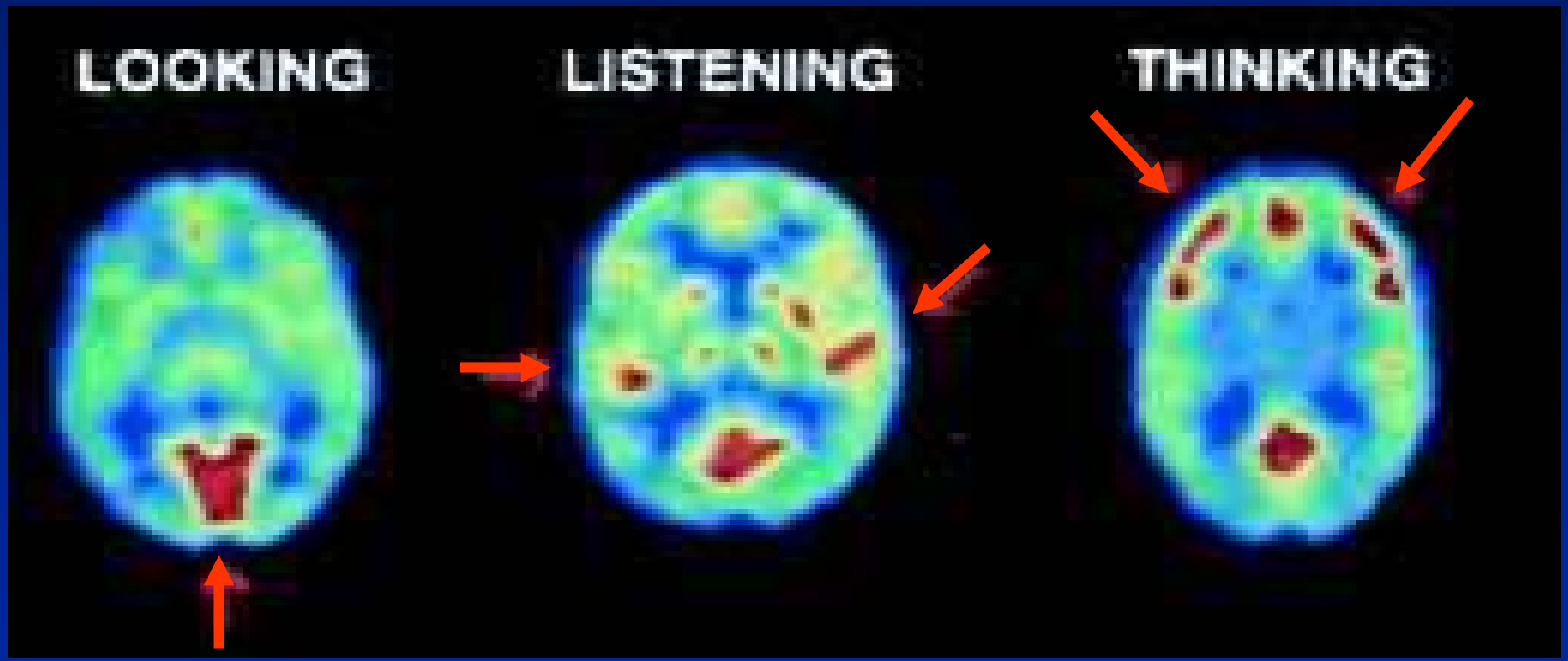
- Synthesis
- Metabolism
- Receptors
- Reuptake



Activation studies

- PET imaging during ”baseline” and ”task”
- ”Activation” = ”task” - ”baseline”
- ”Activation” is considered to represent increased neuronal function in brain areas involved in the task

Glucose metabolism



Visuospatial representations used by chess experts: A preliminary study

Pertti Saariluoma

Computer and Information Sciences, University of Jyväskylä, Finland

Hasse Karlsson

Department of Psychiatry, University of Helsinki, and PET Centre, University Central Hospital of Turku, Finland

Heikki Lyytinen

Department of Psychology, University of Jyväskylä, Finland

Mika Teräs and Fabian Geisler

PET Centre, University Central Hospital of Turku, Finland

Blindfold chess is played without the players seeing either the pieces or the board. It is a skill-related activity, and only very skilled players can construct the mental images required. This is why blindfold chess provides a good task with which to investigate the spatial memory and skilled mental images of expert players. In a PET investigation, we compared memory performance and problem solving in very experienced chess players with their performance in an attention task, in which the subjects classified the names of chess pieces. The memory task predominantly activated the temporal areas, whereas problem solving activated several frontal areas. The relevance of these findings to concepts such as general imagery, skilled imagery, apperception, and long-term working memory are discussed.

Correspondence should be addressed to Pertti Saariluoma, Computer and Information Sciences, University of Jyväskylä, Box 35, Jyväskylä, Finland. Email: psa@it.jyu.fi

This work was funded by the University of Helsinki for the first author, and by the Turku PET Centre. We would like to thank Steven Crawford for correcting the English. We also thank Michel Denis and two anonymous reviewers for very detailed and constructive comments.

http://www.tandf.co.uk/journals/pp/09541446.html DOI:10.1080/09541440340000501

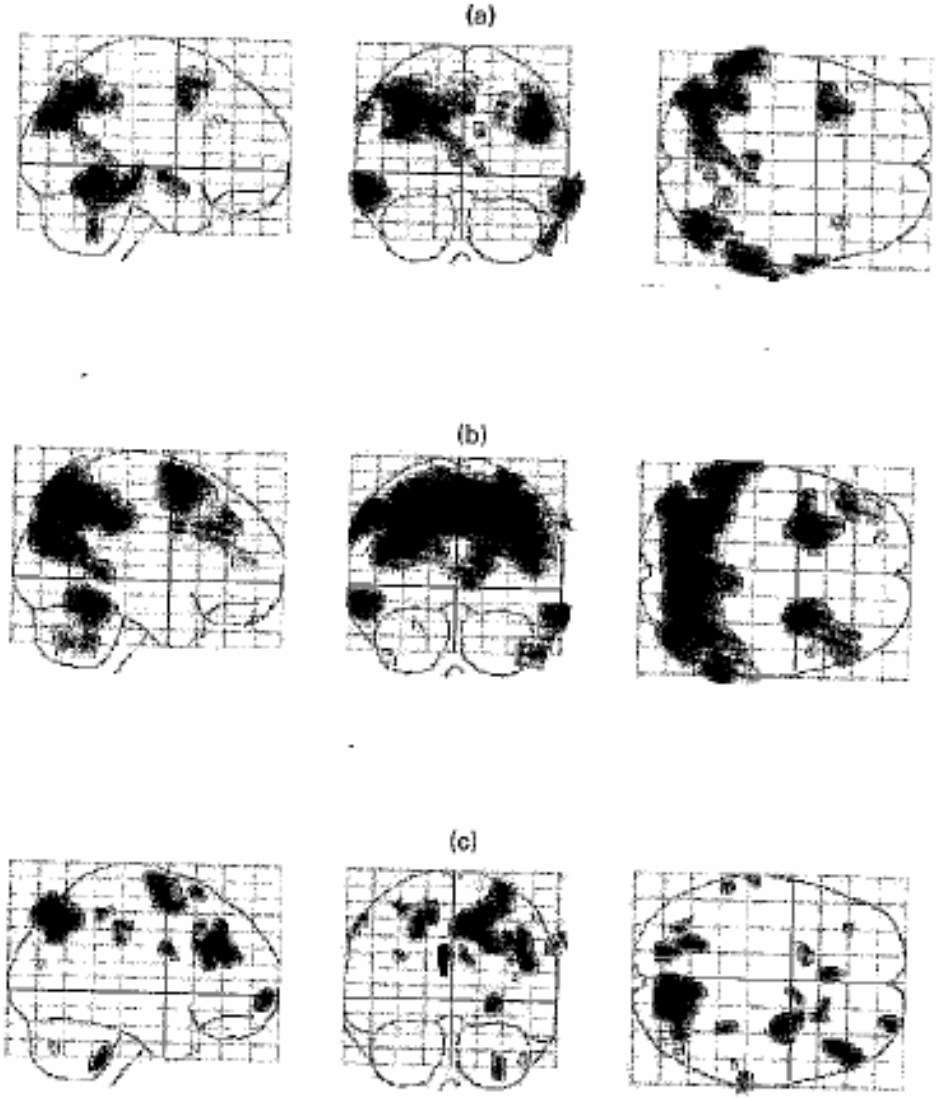
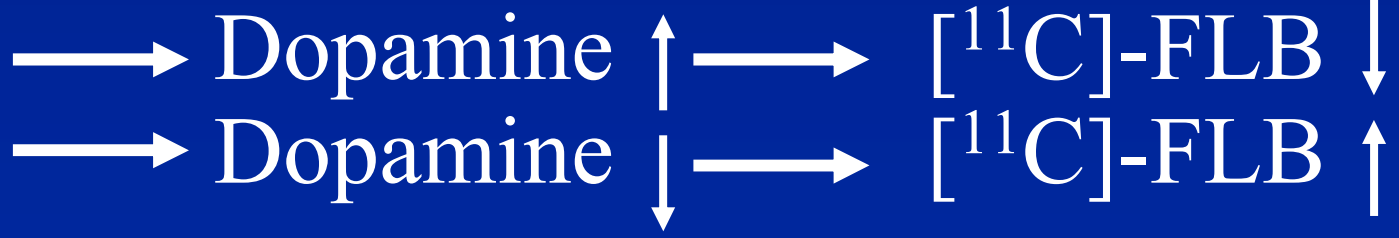


Figure 1. Brain regions associated with blindfold chess. **(a)** Memory – Attention; **(b)** Problem solving – Attention; **(c)** Problem solving – Memory.

Turku PET Centre

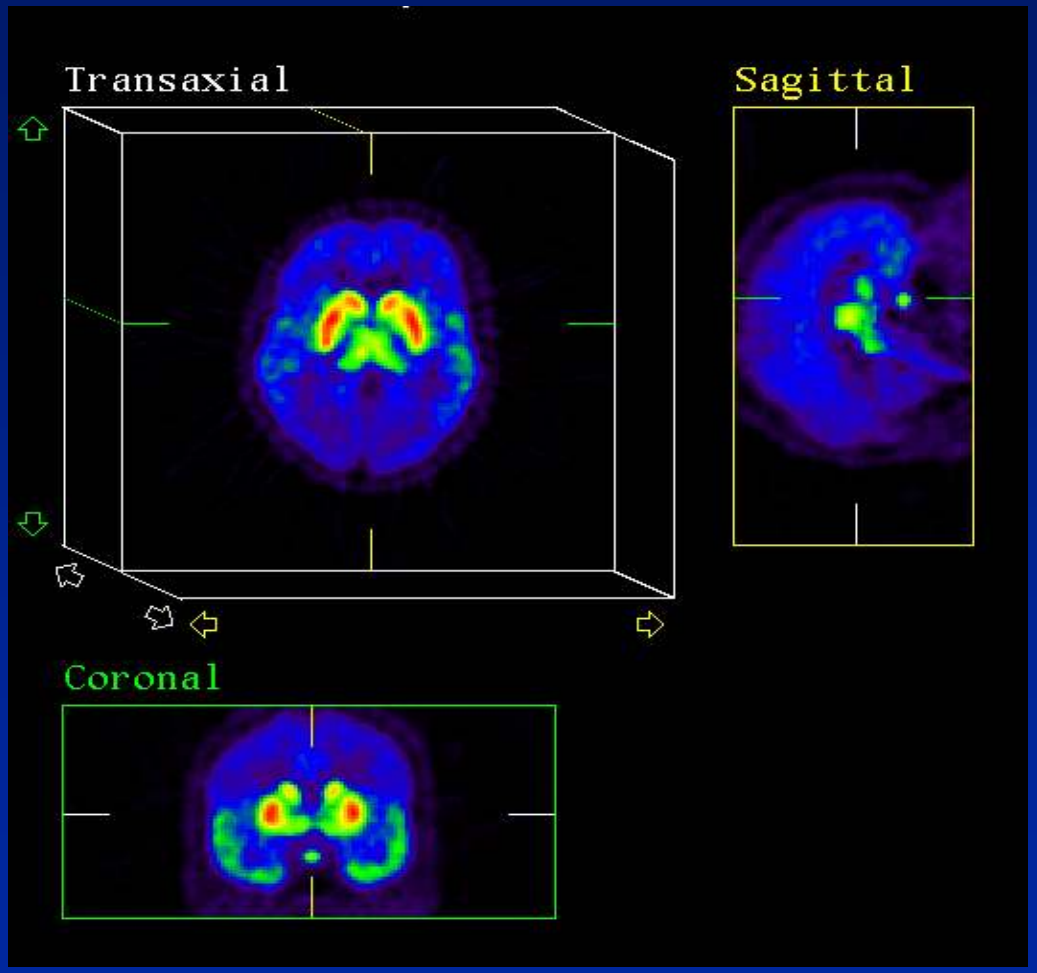
Activation studies: cortical dopaminergic system

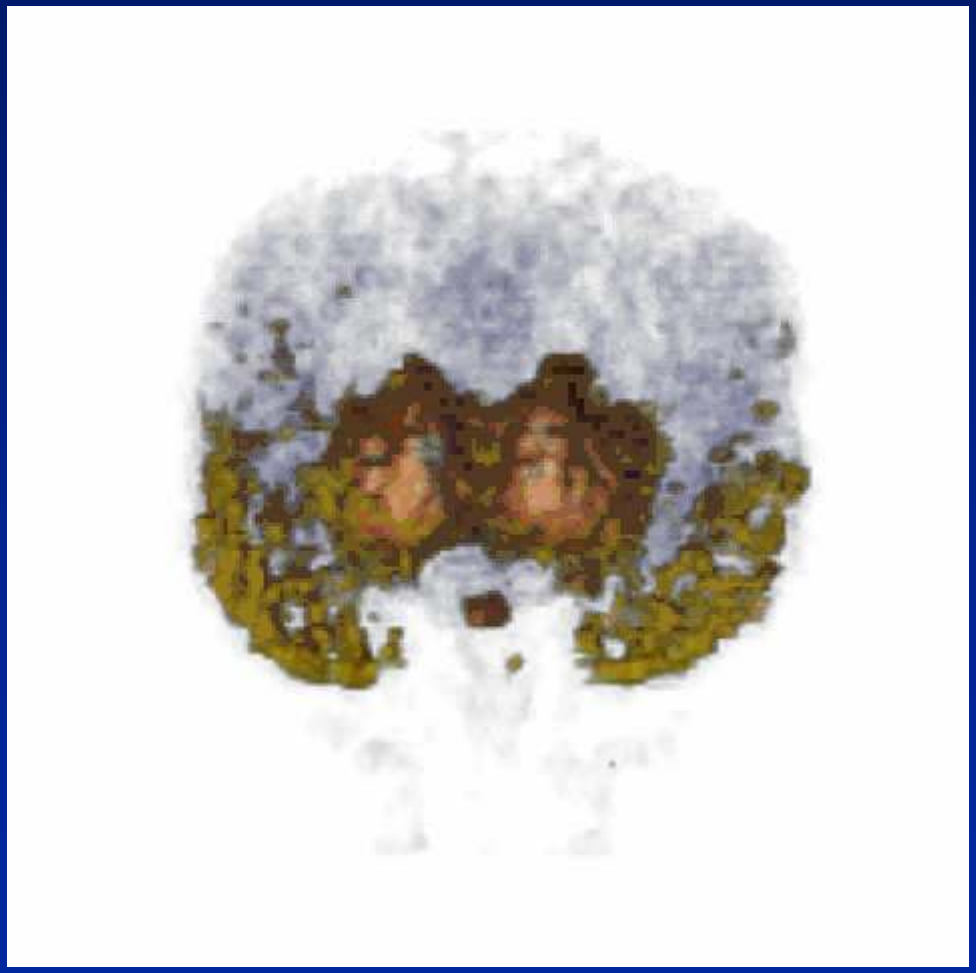
- [^{11}C] FLB 457
  - high affinity D_2 / D_3 antagonist
  - reversible binding
  - enables visualisation of cortical and extrastriatal dopamine receptors
  - competition with endogenous dopamine



[11C]FLB, a reversibly binding high affinity dopamine D2 receptor antagonist

Calculated binding potential images

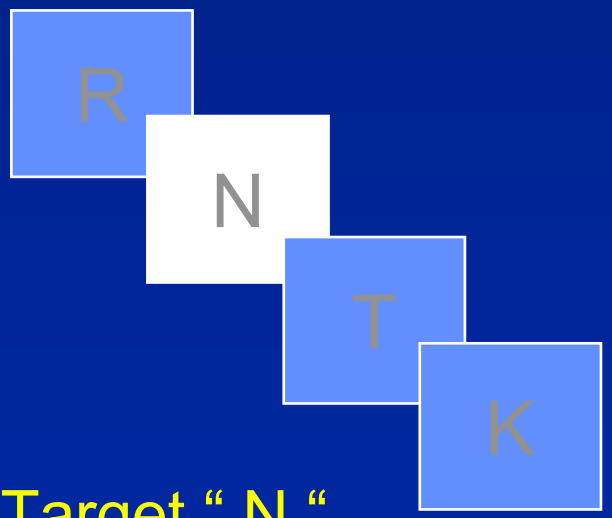




Activation studies: cortical dopaminergic system

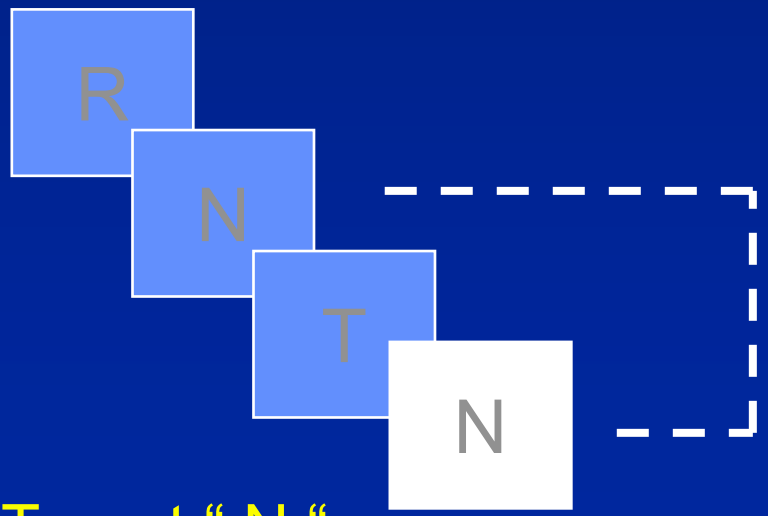
- Tasks
  - baseline
  - 0-back (”vigilance”)
  - 2-back (”working memory”)
  - single consonants were presented visually by a PC on a projector screen

0 - back



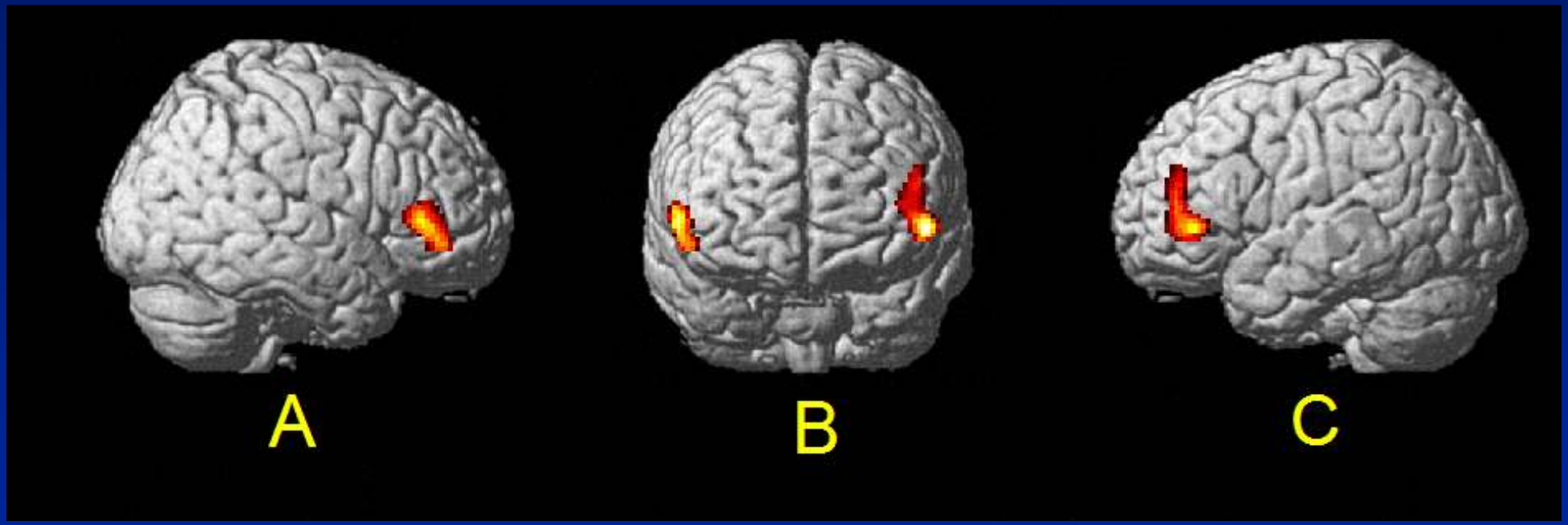
Target “ N “

2 - back



Target “ N “

Activation studies: cortical dopaminergic system



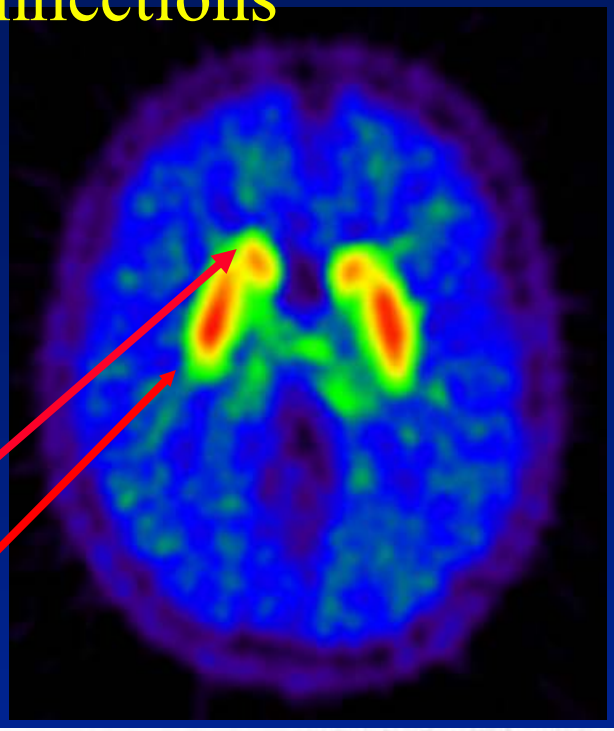
WM - vigilance

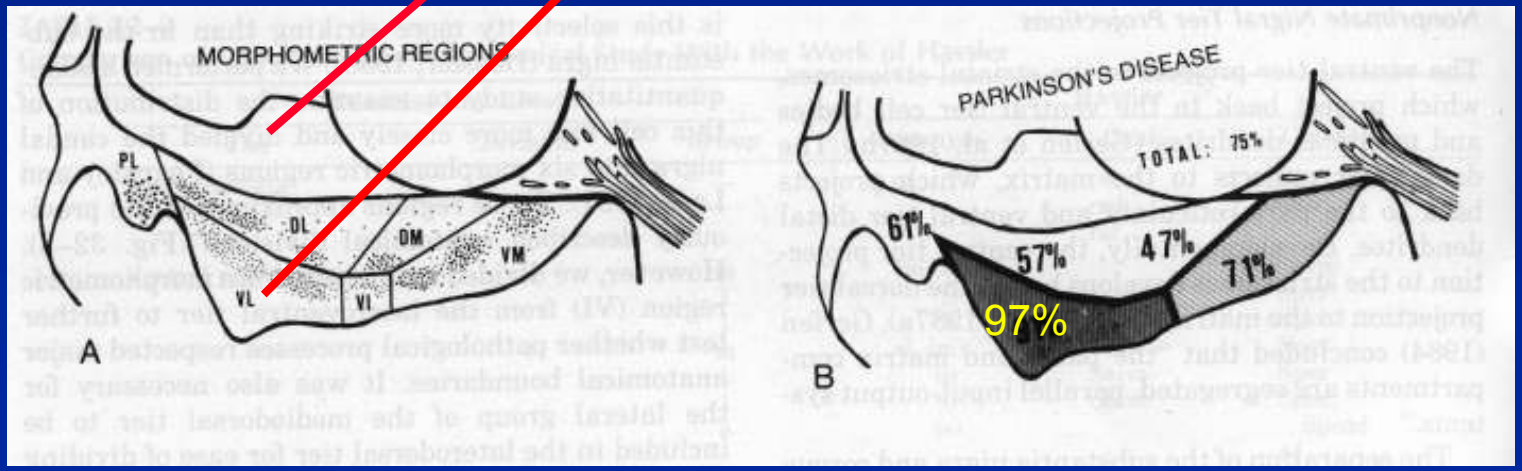
PET in brain diseases

- Diagnosis / differential diagnosis
- Follow-up
- Detection of asymptomatic cases
- Development of treatment
- Monitoring of treatment effects
  - drug treatment
  - lesions
  - stimulations
  - transplantation
  - gene teraphy
  - other teraphies

Organisation of Nigrostriatal dopamine interconnections

Pathophysiology of PD
Loss of dopaminergic neurons in the substantia nigra leading to dopamine deficiency in the basal ganglia

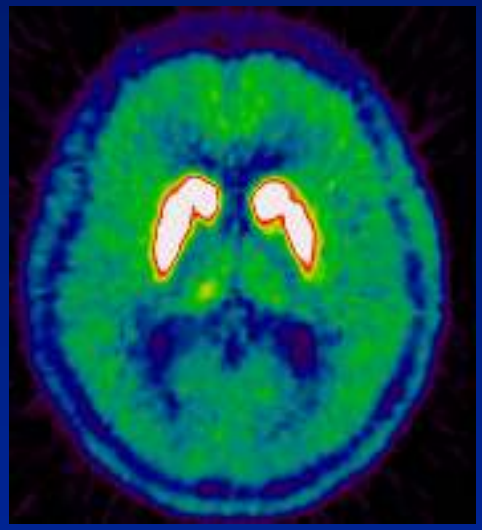




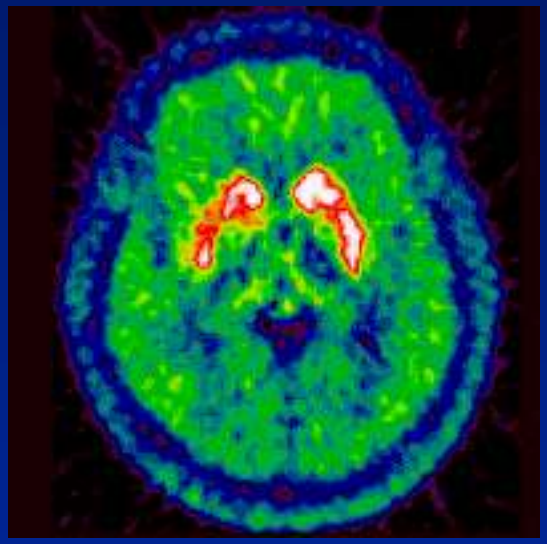
Degree of cell destruction

Turku PET Centre

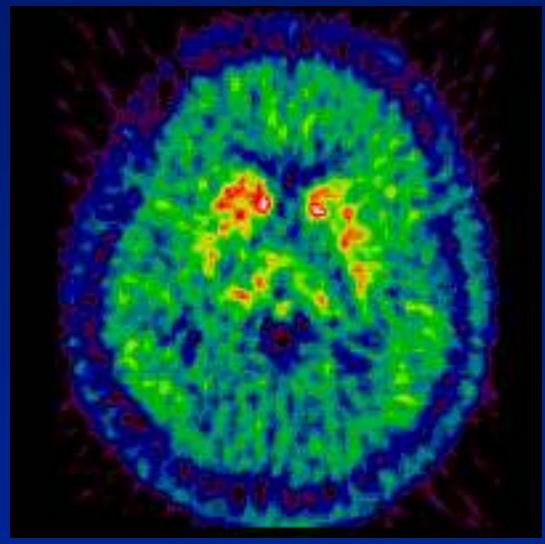
^{18}F-dopa PET: twin study



Control



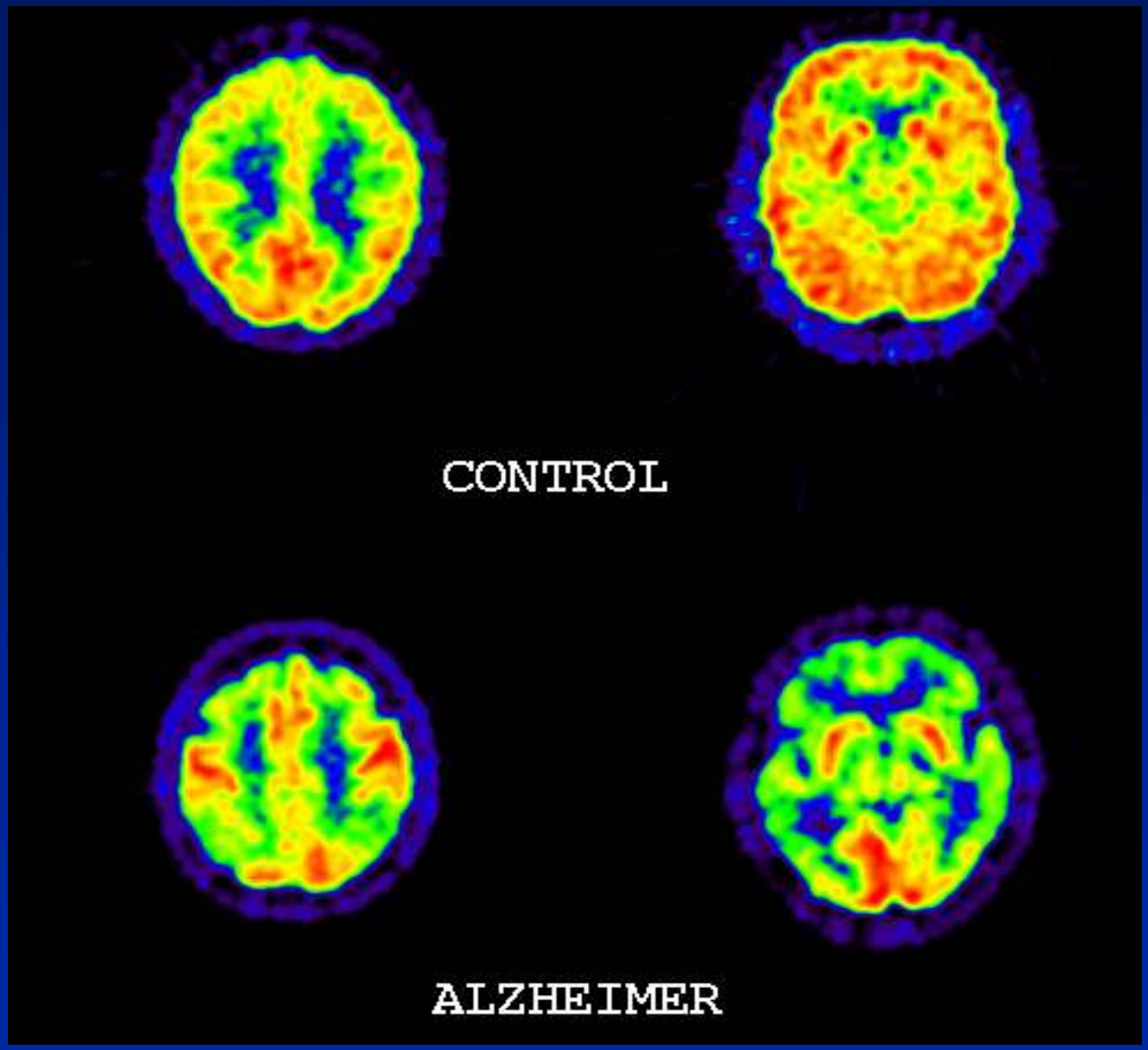
Healthy sibling of a monozygotic PD patient



Same person 5 years later, symptomatic

Turku PET Centre

Differential Diagnosis of Dementia

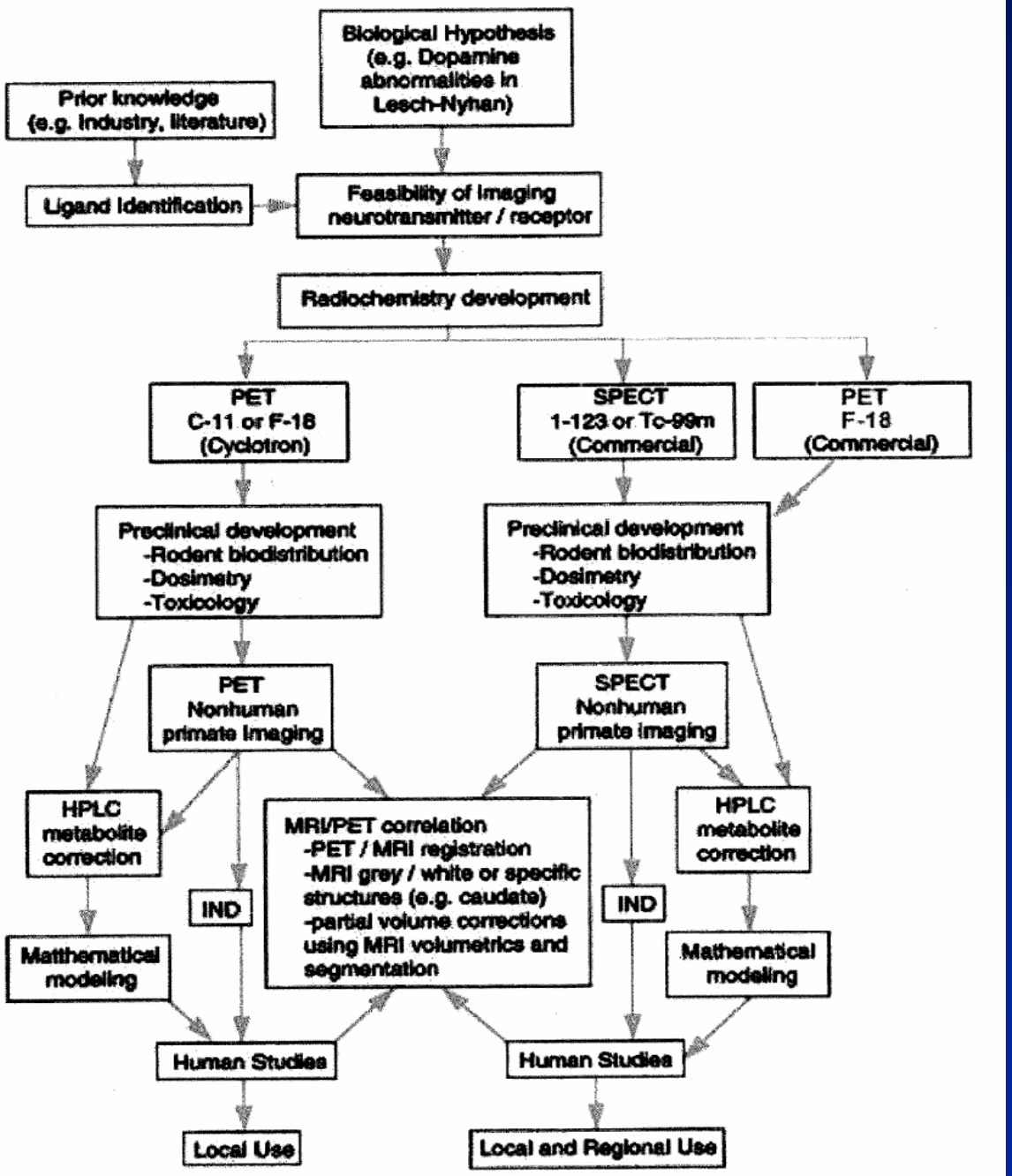


Turku PET Centre

Receptor occupancy studies with PET – implications for drug development

- 'Proof of concept'
- Enhancement of dose-finding procedures for further drug development

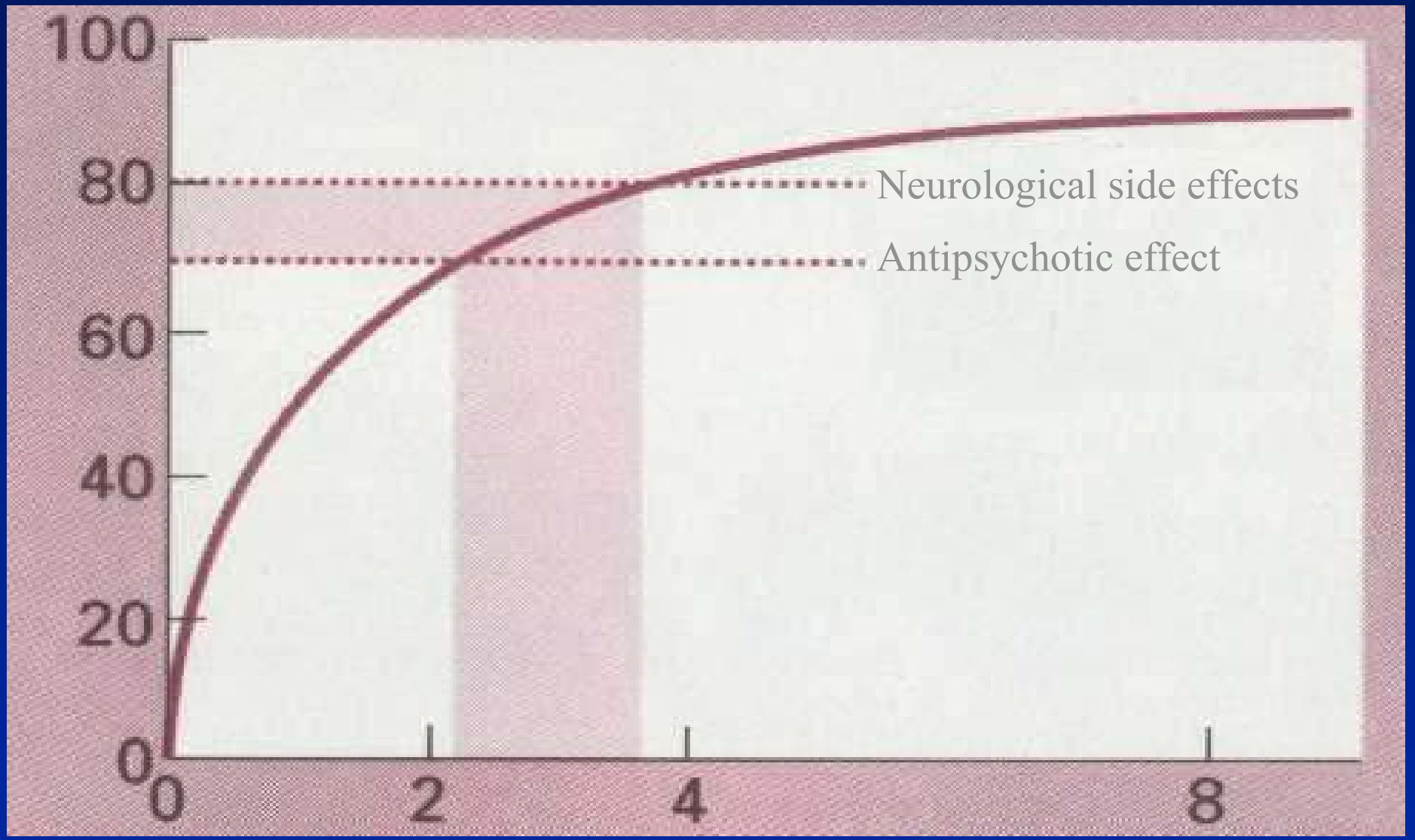
- Critical issues: Imaging methodology development and timing of PET studies in order to get maximal benefit


Biological Hypothesis (e.g. Dopamine abnormalities in Lesch-Nyhan)
Prior knowledge (e.g. Industry, literature)
Ligand Identification
Feasibility of imaging neurotransmitter / receptor
Radiochemistry development
PET C-11 or F-18 (Cyclotron)
SPECT 1-123 or Tc-99m (Commercial)
PET F-18 (Commercial)
Preclinical development -Rodent biodistribution -Dosimetry -Toxicology
Preclinical development -Rodent biodistribution -Dosimetry -Toxicology
PET Nonhuman primate imaging
SPECT Nonhuman primate imaging
HPLC metabolite correction
MRI/PET correlation -PET / MRI registration -MRI grey / white or specific structures (e.g. caudate) -partial volume corrections using MRI volumetrics and segmentation
HPLC metabolite correction
IND
IND
Matthematical modeling
Mathematical modeling
Human Studies
Human Studies
Local Use
Local and Regional Use

"Optimal" properties for a PET radiotracer for brain

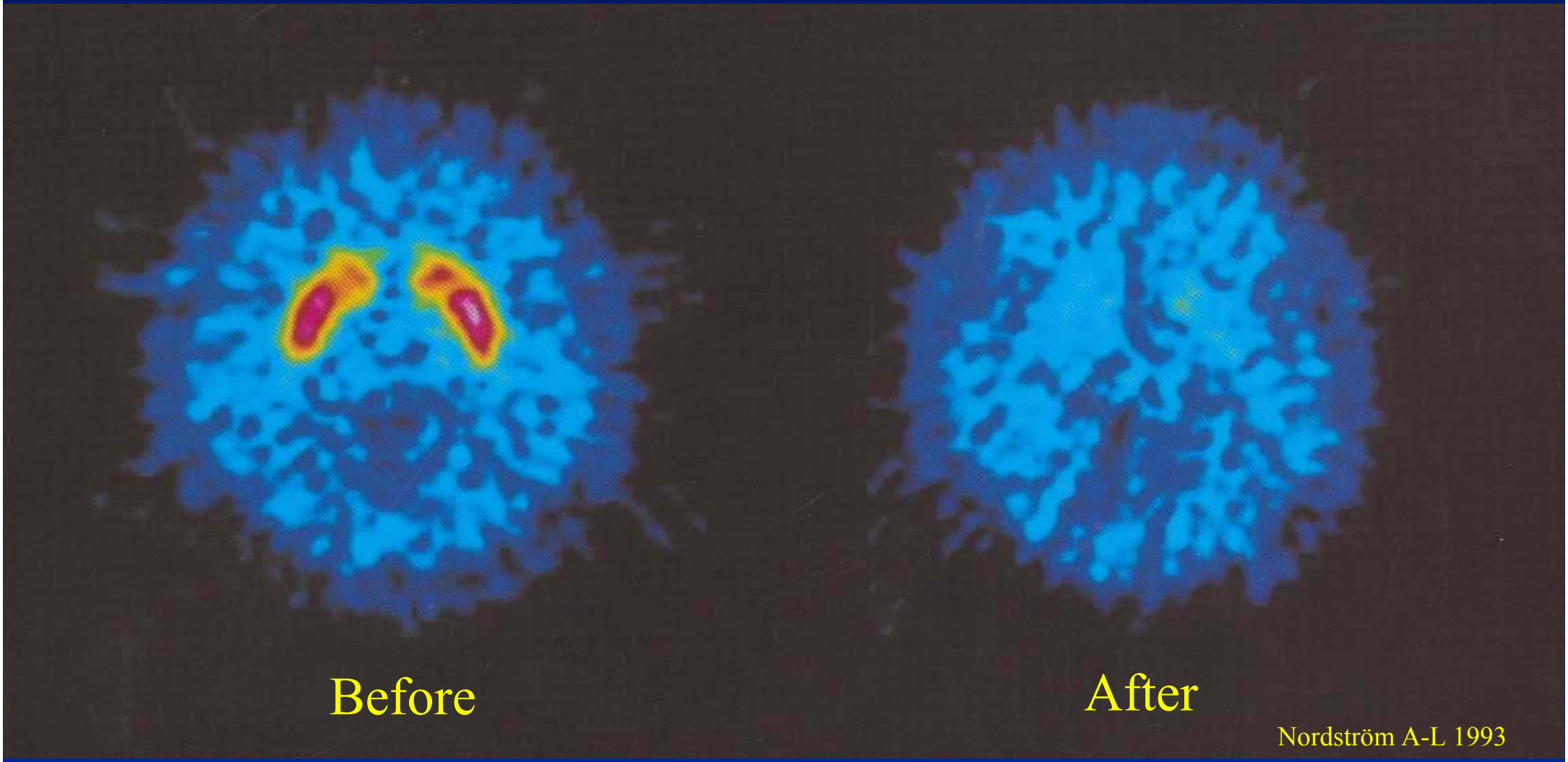
- Unfortunately, no absolute criteria ! Good drug ≠ good tracer
- Suitable for high specific radioactivity labelling (usually 11C or 18F)
- selective and specific ligand, affinity high but not too high (equilibrium within the scan time) – fast plasma clearance helps
- no radioactive metabolites entering the brain
- free fraction in plasma should be measurable (helps modelling)
- not toxic, appropriate radiation dosimetry
- Optimal lipophilicity; Log P < 3.5 but not too low as non-specific binding may increase limiting access to CNS (plasma proteins, lungs, liver, spleen)

D_2 receptor occupancy (%)



Modified from Syvälahti and Hietala 1998

Dopamine D_2 receptor occupancy



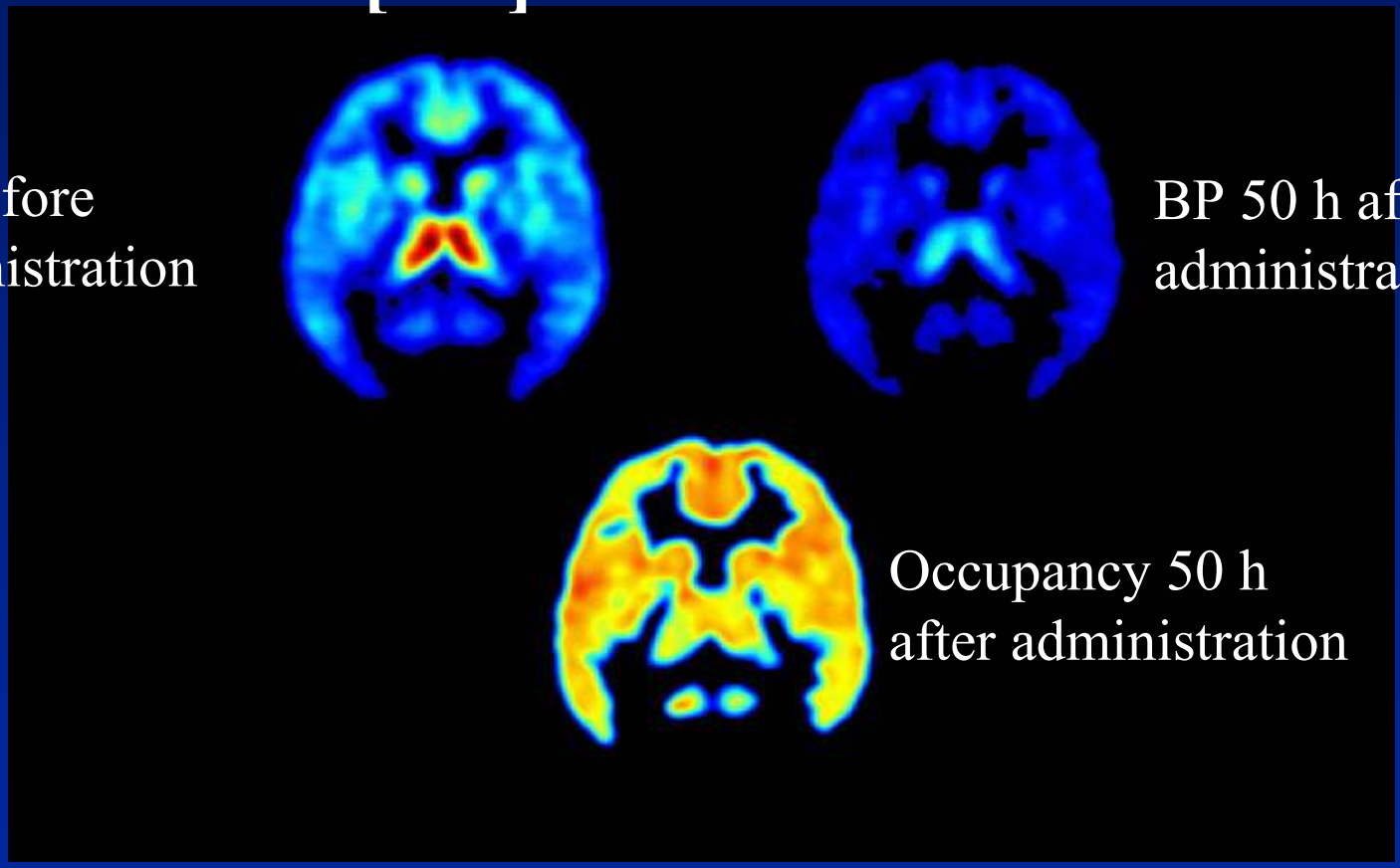
Nordström A-L 1993

Haloperidol

Turku PET Centre

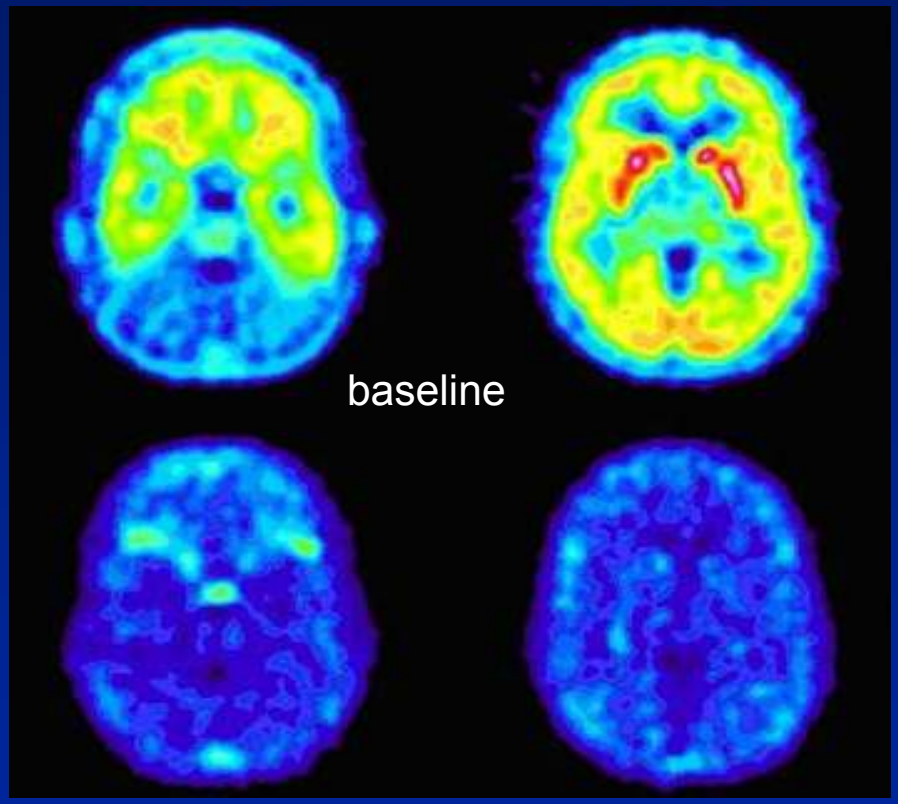
Occupancy of μ-Opioid Receptors by Nalmefene

[^{11}C]Carfentanil

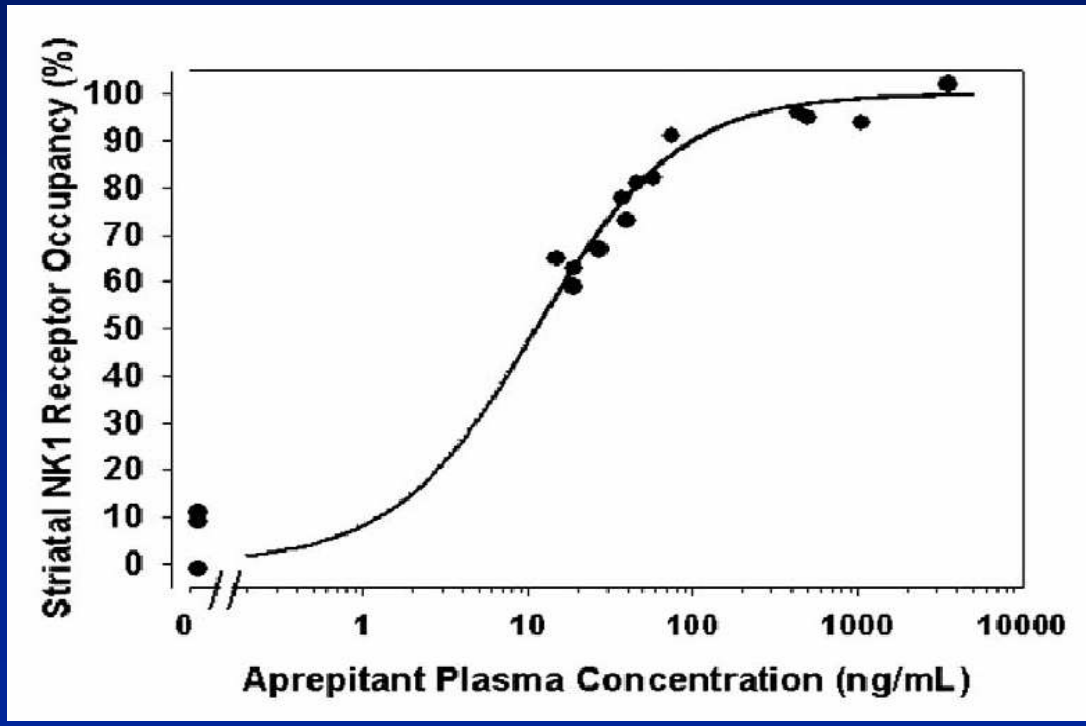


Ingman et al, 2005

NK1 receptor occupancy by a NK1 receptor antagonist, aprepitant



Aprepitant 100 mg, 2 weeks



Bergström M, *Hargreaves RJ, *Burns HD, *Goldberg MR, *Sciberras D, *Reines SA, *Petty KJ, *Ögren M, *Antoni G, *Långström B, Eskola O, Scheinin M, Solin O, *Majumdar AK, *Constanzer ML, *Battisti WP, *Brandstreet TE, *Gargano C, Hietala J. **(Biol Psy, 55:1007-1012, 2004)**

Turku PET Centre

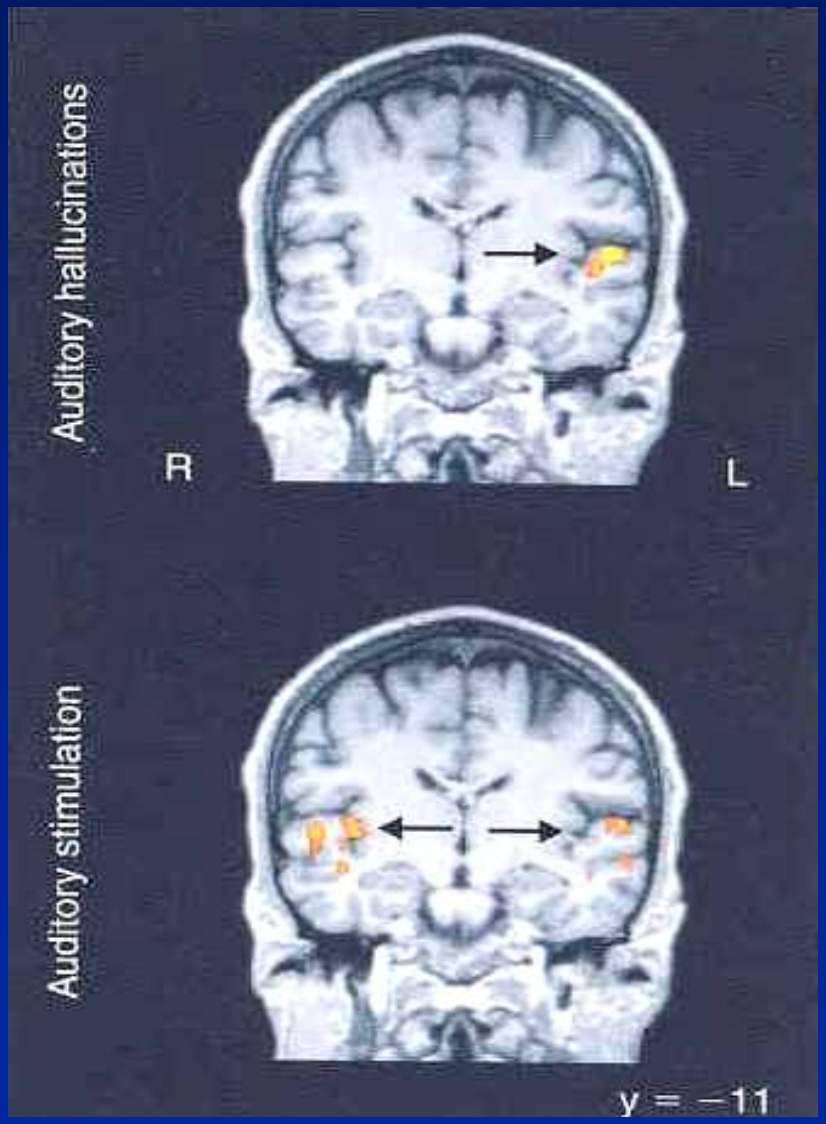
Conclusions

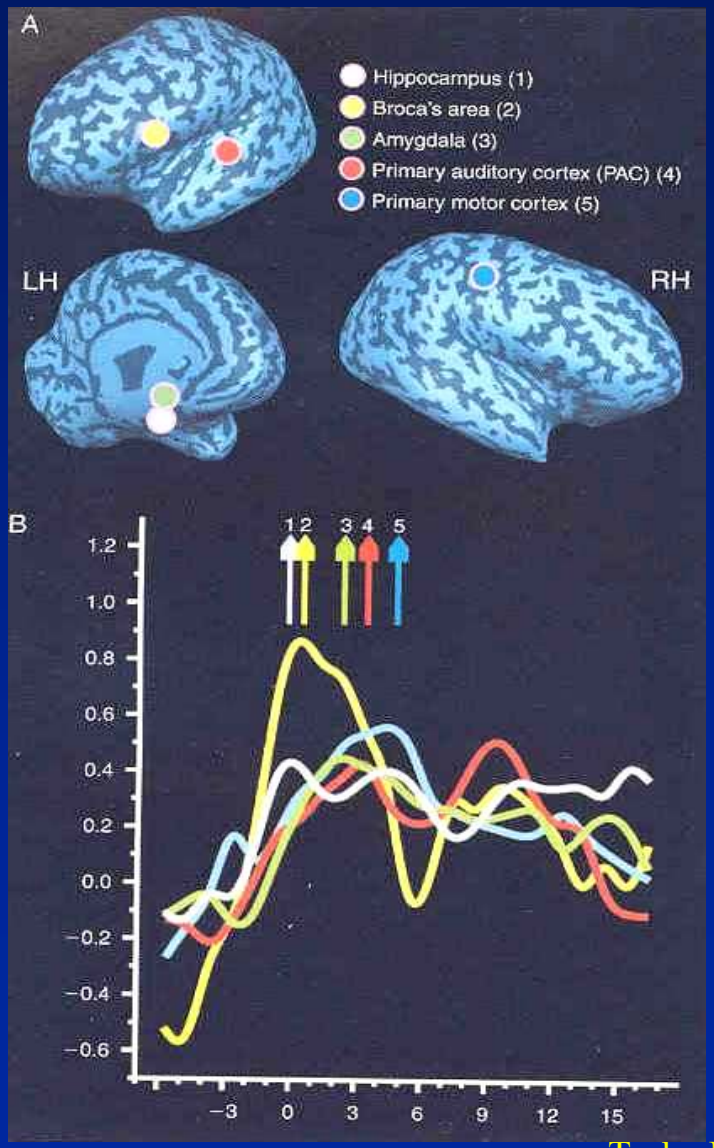
- PET is a versatile method to study the role of neurotransmitter systems in
  - Normal brain functions
  - Brain diseases
  - Drug development

but, keep in mind that

PET has poor temporal resolution

Auditory hallucinations in schizophrenia – fMRI study





Turku PET Centre

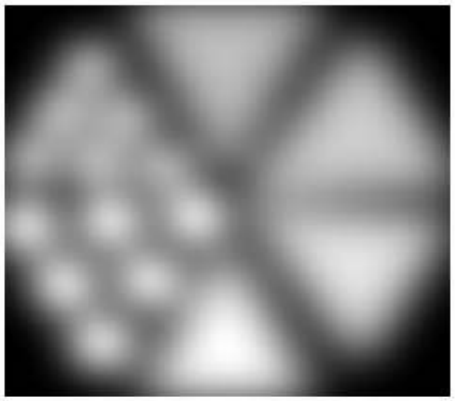
PET – A new method to see the function of the brain

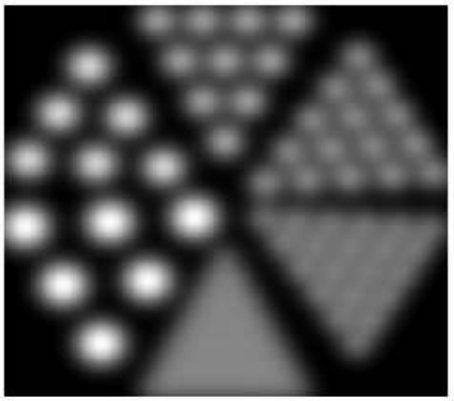
- Basic physics of PET method
- PET in neuro research and drug development
- Present and future trends in neuroPET

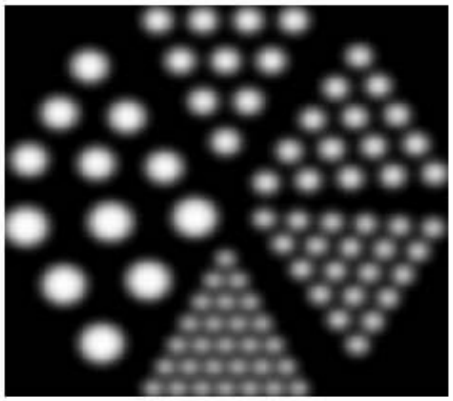
Micro PET

Effect of resolution

Simulated Phantom

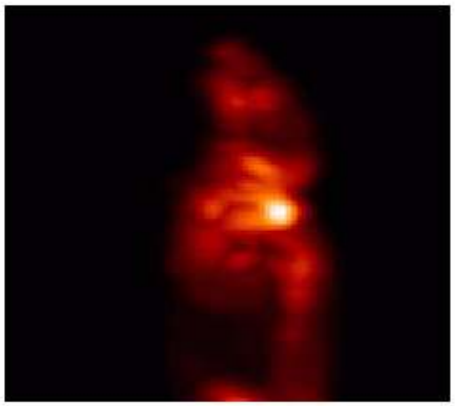


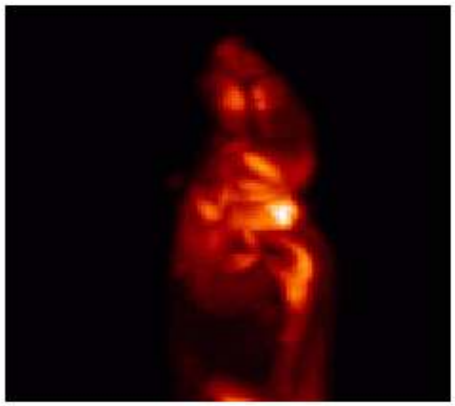




Resolution 4mm 2mm 1mm

30g Mouse Focus™ 120





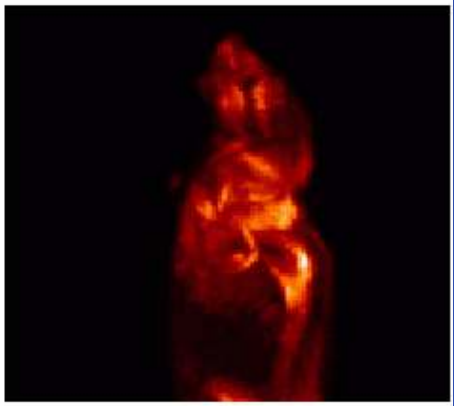
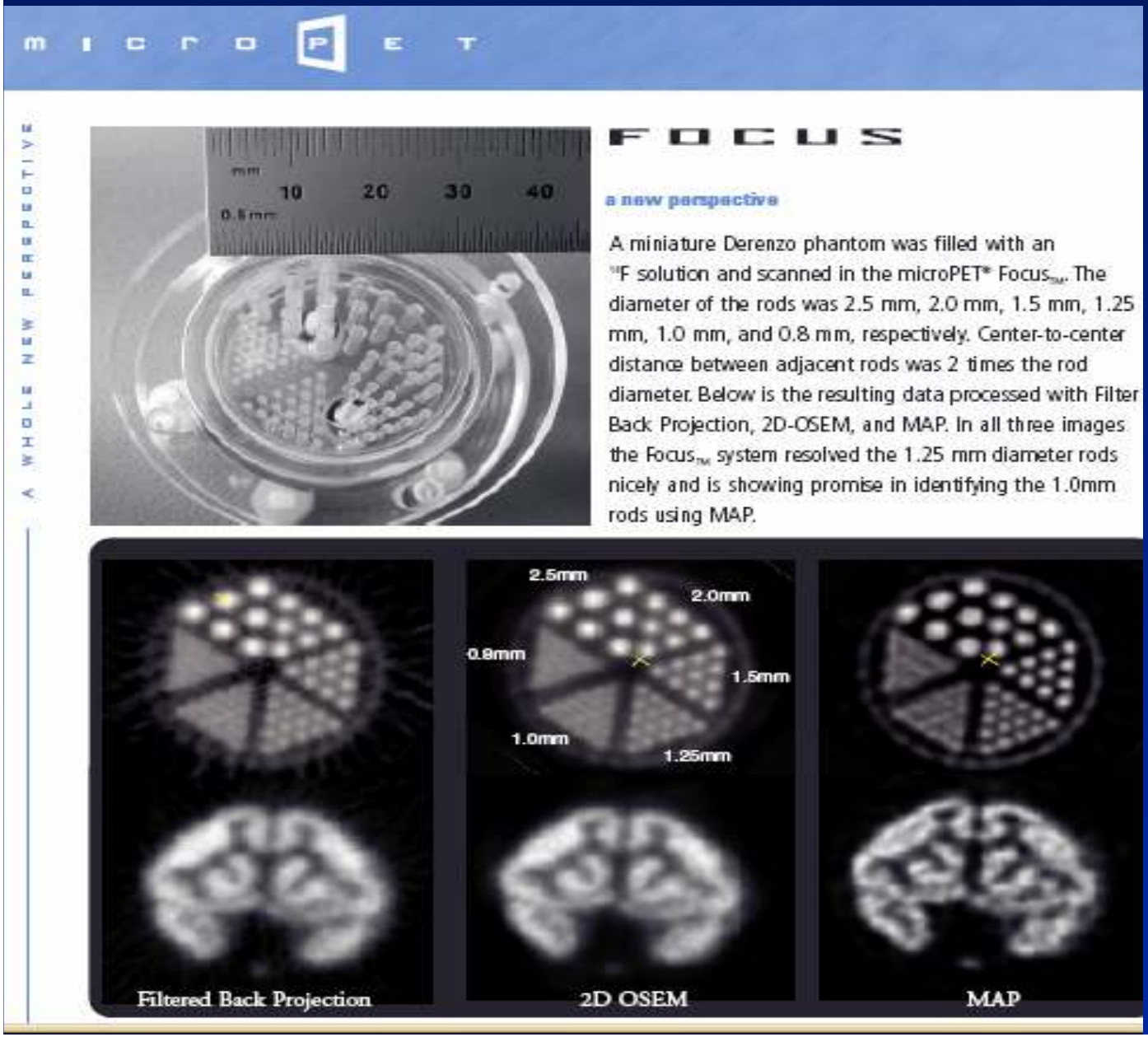


Image courtesy of The Universiry of Tennessee Medical Center

The effect of reconstruction method

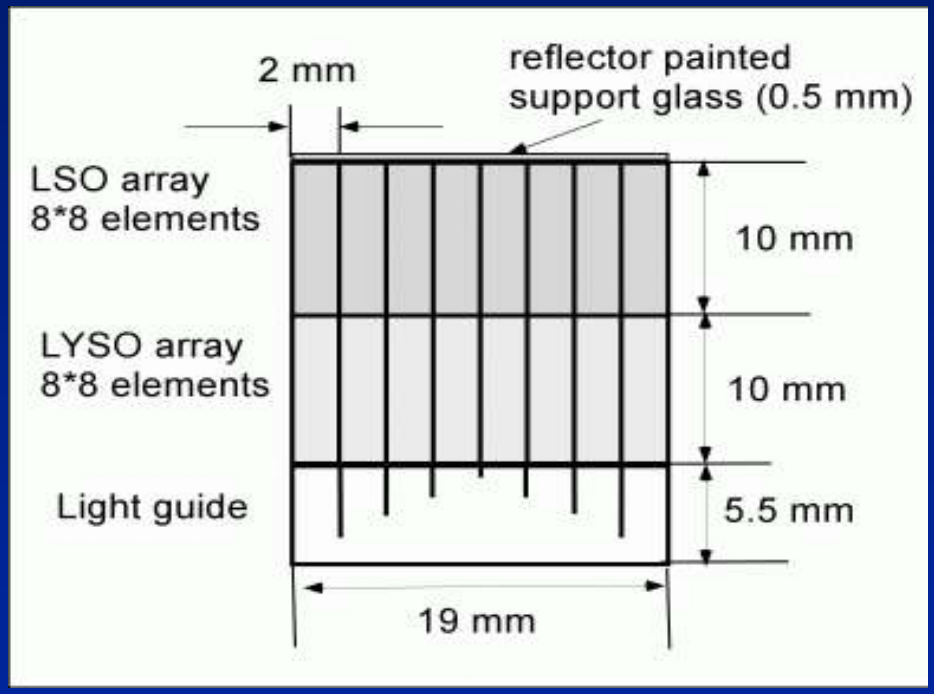


- Better resolution demand more attention to reconstruction parameters

Miniature Derenzo phantom

Monkey brain phantom

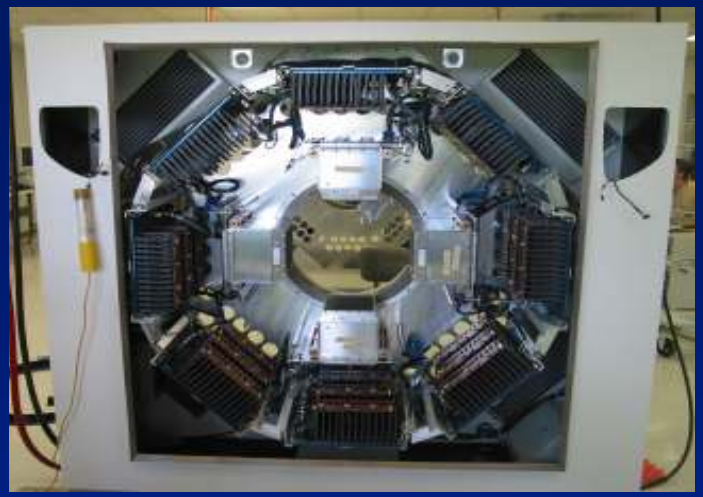
The Block detector
a LSO/ LYSO detector



coinc_eff(lso/lyso, 2 cm) = 1.23 *coinc_eff(lso/gso, 1.5 cm)
Total of 59 904 LSO and LYSO elements

HRRT

- High Resolution Research Tomograph
- High resolution (2.5 – 3 mm)
- 47-cm panel separation
- 25-cm axial FOV
- High sensitivity (5-6%)
- Phoswich detectors (LSO/LYSO 2x2x10 mm)
- List mode
- 119,808 crystals
- 4.5×10^9 LORs



Turku PET Centre

Comparison of PET scanners from different generations

	ECAT 931	**GE Advance**	**HRRT**
	2D	(2D /) **3D**	**only 3D**
Year of purchase	1988	1996	2003?
Number of rings	8	18	104
Slice Thickness (mm)	6,75	4,25	1,2
Crystal material	BGO	BGO	LSO/LYSO
Crystal size (mm)	5,6x12,5x30	4x8x30	2x(2,1x2,1x10)
Number of crystals	4096	12096	119808
Axial length (cm)	10	15	25
Patient port diameter (cm)	62	60	35
Spatial resolution (mm)	6	4	2,5
Sensitivity (kcps/uCi/ml)	100	1200	n. 2500
Size of a raw data frame (Mb)	2	50	326
Frame reconstruction time (min)	1	4	200, 30 w ith cluster

The second generation HRRT – a multi-centre scanner performance investigation

V. Sossi[1], H. W. A. M. de Jong[2], W. C. Barker[3], P. Bloomfield[4], Z. Burbar[5], M.-L. Camborde[6], R. E. Carson[7], C. Comtat[8], L. A. Eriksson[5], S. Houle[4], D. Keator[9], C. Knöß[10], R. Krais[11], A. A. Lammertsma[2], A. Rahmim[12], M. Sibomana[5], M. Teräs[11], C. J. Thompson[13], R. Trébossen[8], J. Votaw[14], K. Wienhard[10], D. F. Wong[12]

[1]Physics and Astronomy, University of British Columbia, Vancouver, Canada, [2]VU University Medical Center, Amsterdam, The Netherlands, [3]NIH Clinical Center, Bethesda, USA, [4]CAMH, Toronto, Canada [5]Siemens Medical Systems, Knoxville, USA, [6]PPRC, University of British Columbia, Vancouver, Canada, [7]Yale University New Haven, New Haven, USA, [8]Frédéric Joliot Hospital Facility, CEA/DSV, Orsay, France [9]Psychiatry & Human Behavior, University of California, Irvine, USA,[10]Max Planck Institute for Neurological Research, Cologne, Germany,[11]Turku PET Centre, Turku, Finland, [12]Radiology, The Johns Hopkins University School of Medicine, Baltimore, USA,[13]Montreal Neurological Institute, McGill University, Montreal, Canada,[14]Radiology and Physics, Emory University, Atlanta, USA

ABSTRACT

The high resolution research tomograph (HRRT-CTI PET Systems) is one of the most complex existing PET scanners:[1,2,3] it is the only human size scanner capable of decoding the depth of the gamma ray interaction (DOI) in the crystal, using an LSO/LYSO phoswitch detector arrangement, leading to a total of 119,808 detector crystals. In this study we determined basic scanner hardware characteristics, such as scanner data acquisition stability, and their variability across 11 centers. In addition a subset of the NEMA NU-2001 standards measurements was performed. We found (i) significant variability in the DOI decoding results between centers, (ii) a trend toward an increasing number of detected true coincident events as a function of elapsed time from scanner calibration likely due to a shifting energy spectrum, (iii) a count rate dependent layer identification (iv) scatter fraction ranging from ~ 42% to 54% where the variability was equally related to the shifting of the energy spectrum, (v) sensitivity ranging from ~5.5% to 6.5% across centers, (vi) resolution of ~ (2.5mm)³, fairly consistent across centers, (vi) image quality give results very comparable to other scanners.

INTRODUCTION

The high resolution research tomograph (HRRT –CTI PET Systems – fig. 1) is one of the most complex existing PET scanners: it is the only human size scanner capable of decoding the depth of the gamma ray interaction (DOI) in the crystal. **DOI determination** is achieved by means of a phoswitch detector utilizing crystals (Fig.2) with different decay times and subsequent pulse shape discrimination [4]: the first layer is **LSO** and the second layer is **LYSO** (Lu0.6Y1.4SiO5:Ce, i.e. 70 % YSO and 30 % LSO). The decay time of LSO is approximately 43-44 nsec, while that of LYSO is approximately 53 nsec.[5,3]

Figure 1 HRRT:
25 cm axial FOV
8 planar detectors
119,808 crystals
25 cm axial FOV
30 cm radial FOV

Figure 2 Detector block:
128 2.2x2.2x10 mm³ crystals
2.44 mm average crystal pitch

The ability to correctly identify the gamma interaction in each layer depends on several factors:

- the actual decay time separation between crystals,
- the accurate calibration of the photomultiplier tube gains
- timing alignment between signals coming from different crystals
- the count-rate to which the crystals are exposed during data acquisition
- stability of the hardware components over time

Each of these aspects is prone to some *uncertainty* and *variability*, for example:

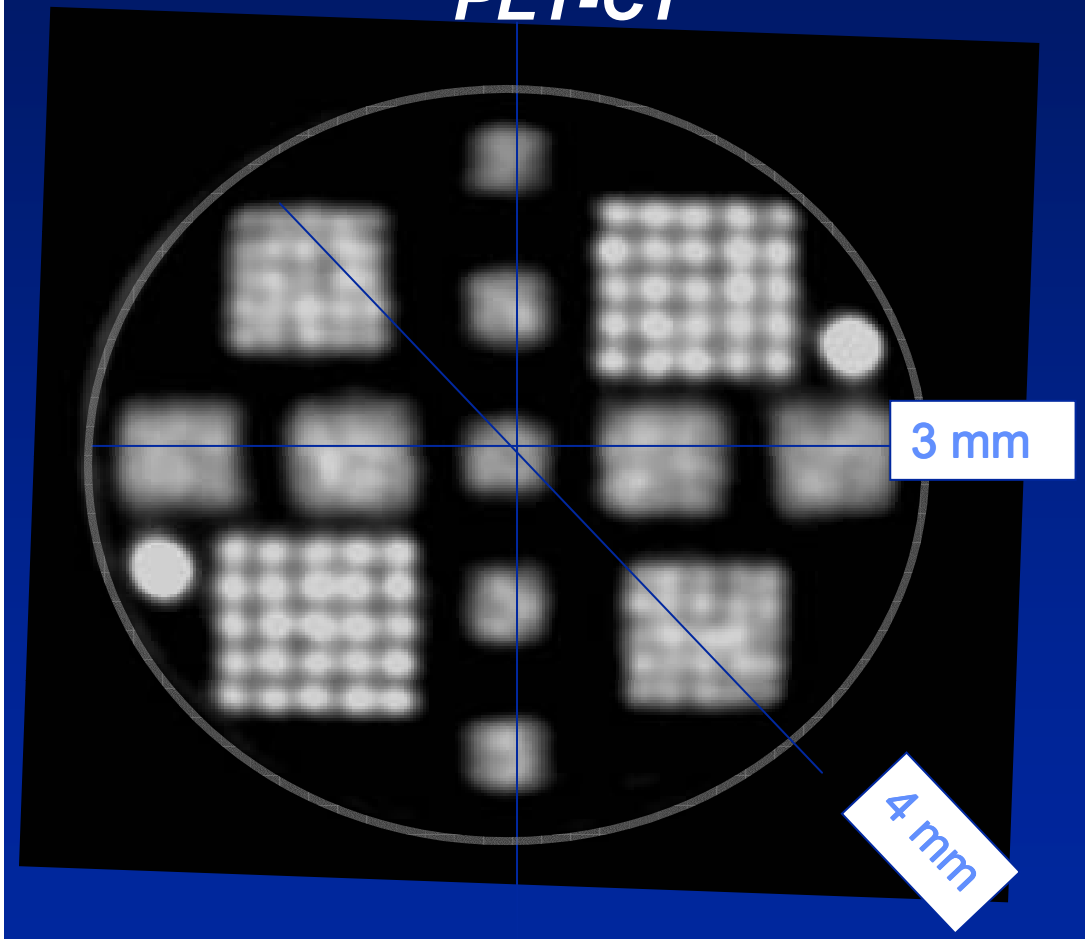
- the crystal manufacturing process does not consistently produce LSO and LYSO with exactly the same decay time,
- the detector set-up procedure is extremely complex, time consuming and requires manual intervention thus introducing some degree of operator dependency
- hardware can be influenced by aging and radiation exposure.

IEEE-MIC 2005

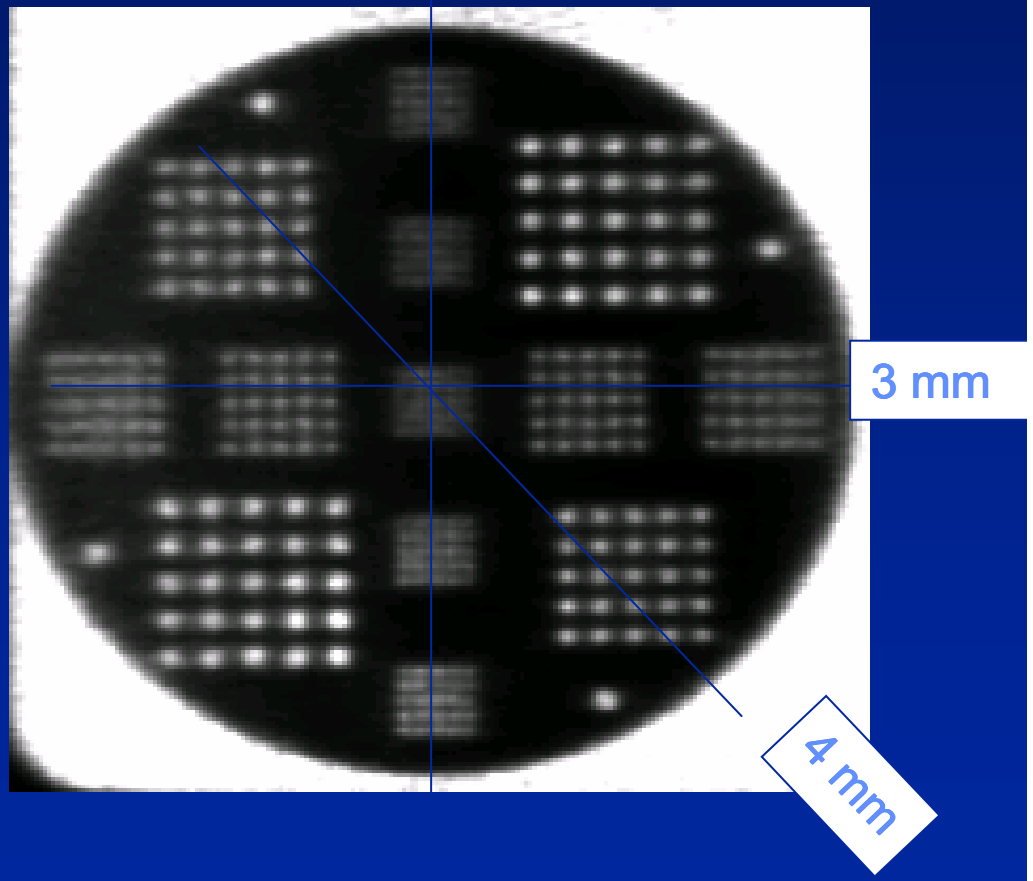
Turku PET Centre

Resolution Comparison

Commercial PET-CT



HRRT



Turku PET Centre

GE Advance PET camera

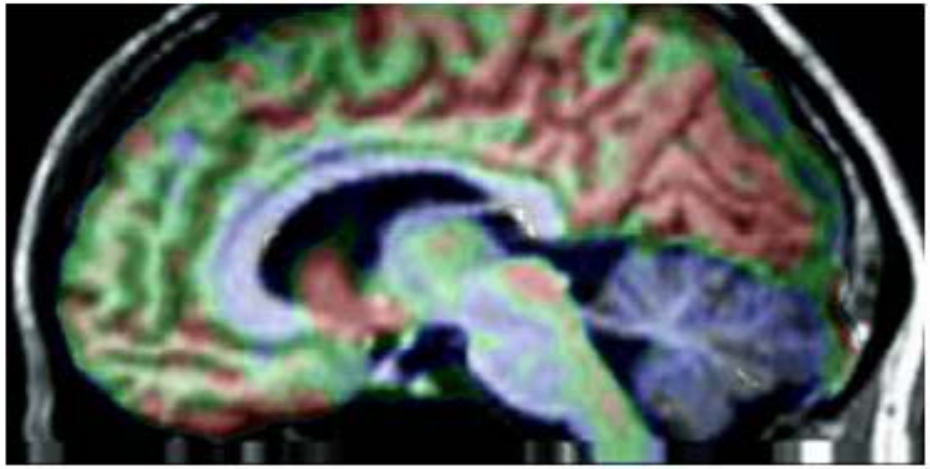
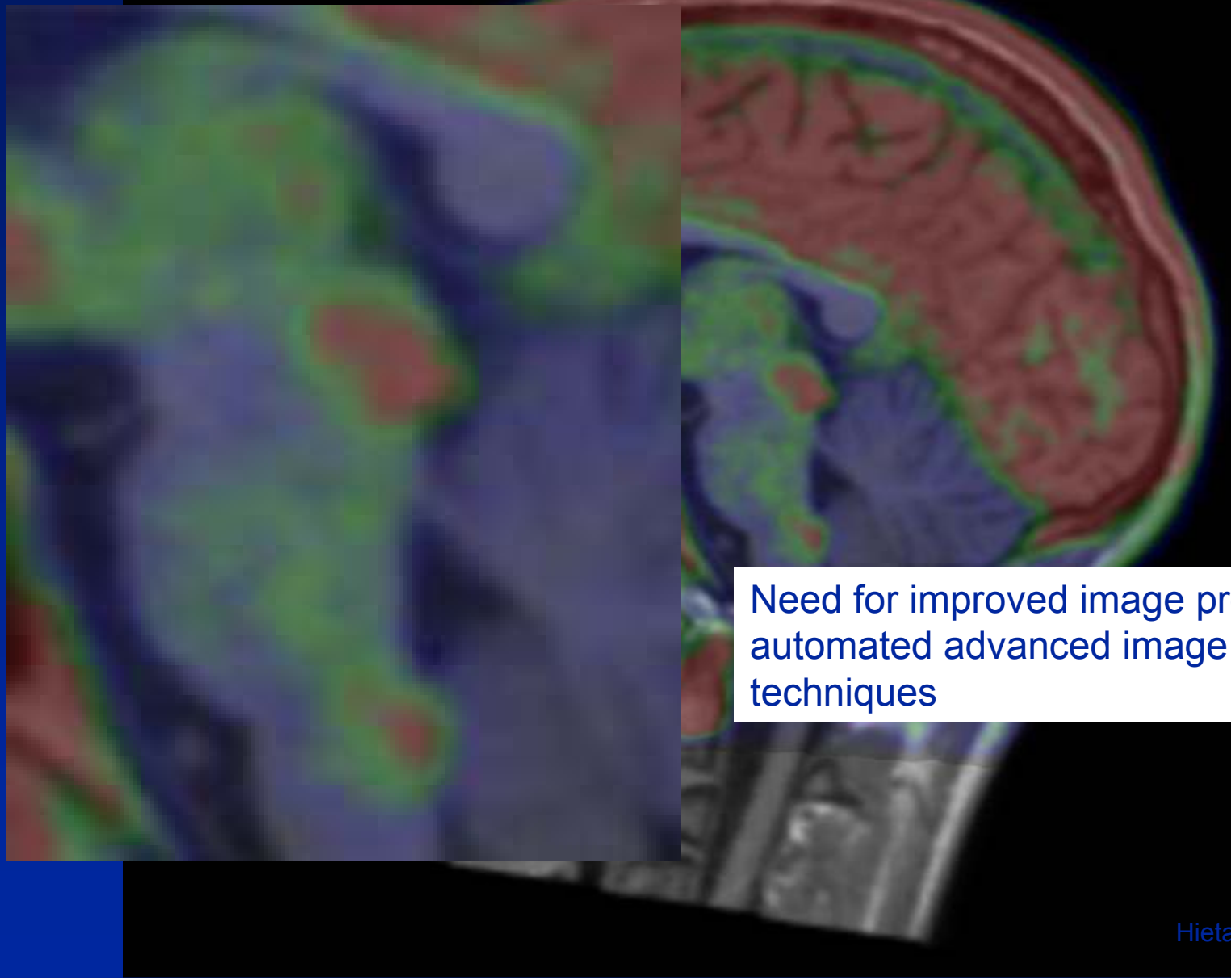


Fig. 7. Distribution of [F-18]SPA-RQ uptake in the midbrain–pons–medulla of a healthy male volunteer. Sagittal slice of an integrated image from 190 to 240 min is aligned with the structural MR image from the same subject. There is moderate uptake in the superior and inferior colliculi of the midbrain as well as in the nuclei group in medulla (e.g., nucleus solitaris, nucleus ambigus, and other nuclei of vagus, trigeminal nucleus, inferior salivary nucleus, and area postrema). In addition, there is some uptake in the pons representing tegmentum and possibly raphe nuclei. Because of limitations in resolution, these locations are tentative. Note also the high [^{18}F]SPA-RQ binding in ventral striatum and cortex, moderate binding in thalamic nuclei, and very low cerebellar uptake in this slice.

et al MIB 2005

High resolution PET and NK1 receptors, [^{18}F]SPA-RQ and ECAT HRRT



Need for improved image processing and automated advanced image analysis techniques

Comparison of Image Segmentation
For
CT vs. MRI

Axial View

MRI Image

MRI
Segmented Gray Matter

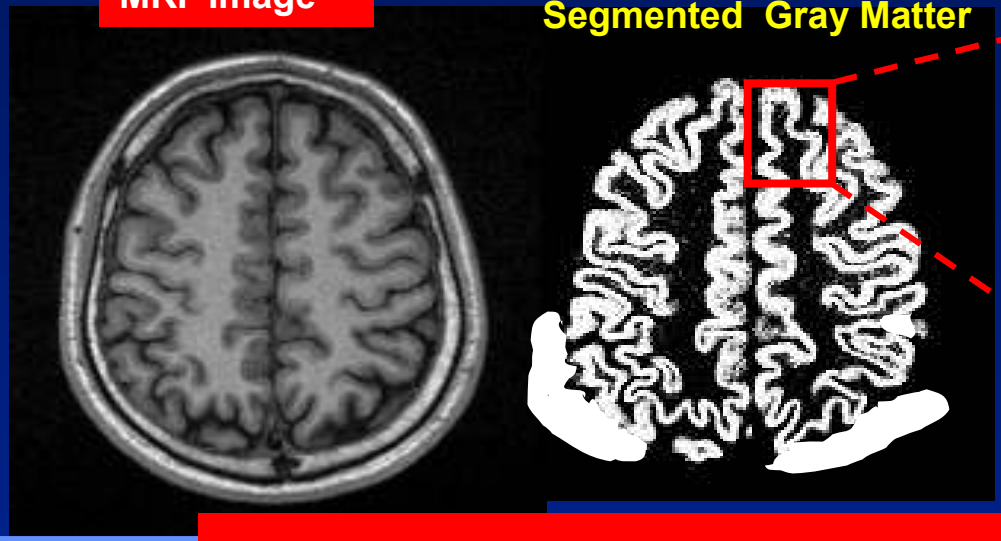
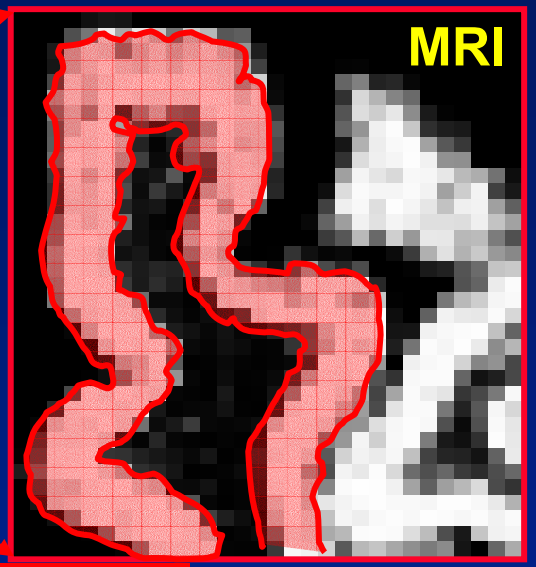
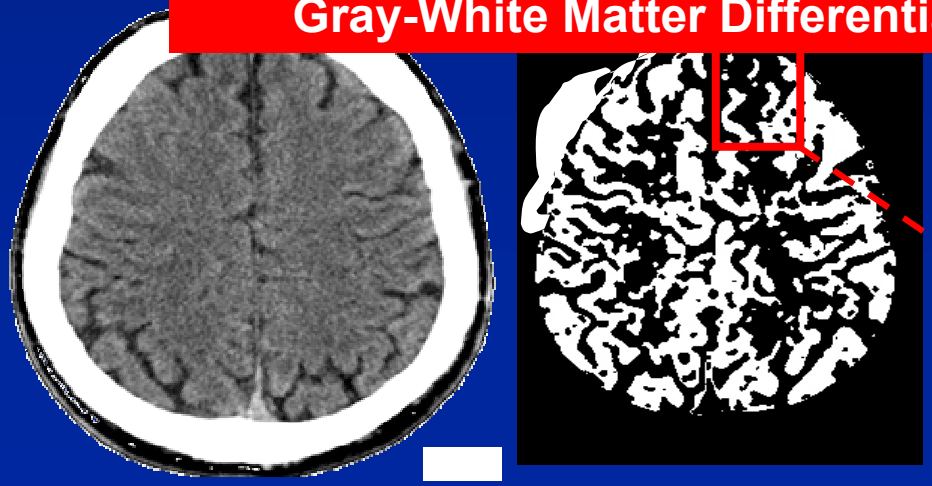


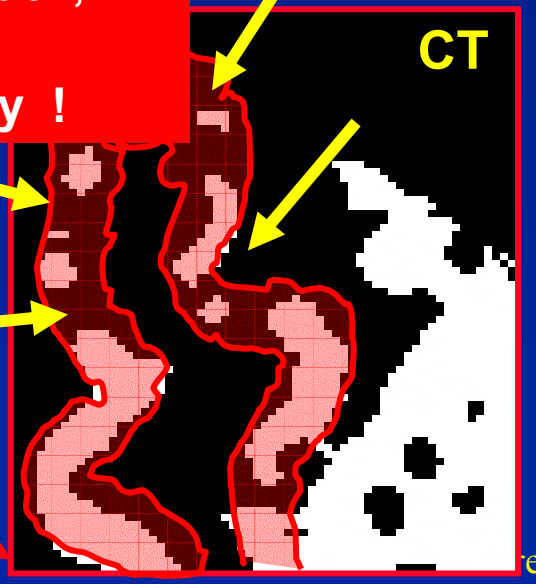
Image Segmentation



Beside X-ray Dose problem with improved resolution,
CT Simply Does Not Have
Gray-White Matter Differentiation Capability !

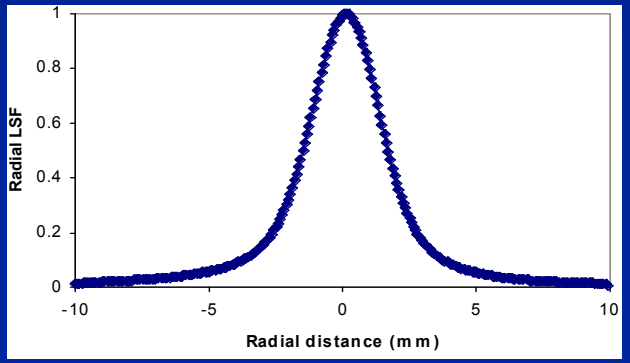
CT I





MOLAR

- Motion-compensation OSEM List-mode Algorithm for Resolution-recovery reconstruction
- All physical effects in the system model
- Exact LOR positioning
- Event-by-event motion correction (Polaris)
- System matrix computed on-the-fly
- LOR-based line spread functions
- Randoms estimation from singles
- Single scatter simulation model
- Component-based count-rate dependent normalization
- 256x256x207 images (1.2 mm/voxel)

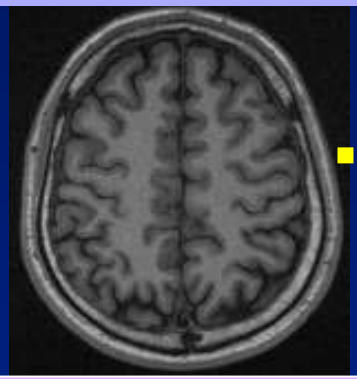


Turku PET Centre

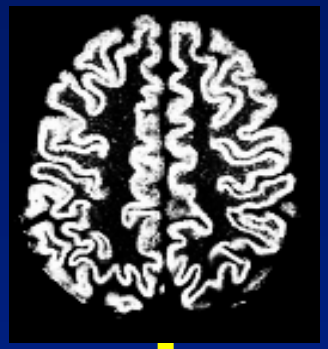
Multiparametric Image Fusion Algorithms – I

Z.H. Cho et.al.
Neuroscience Research Institute,
Gachon Medical University, Incheon, Korea

Original MRI Image

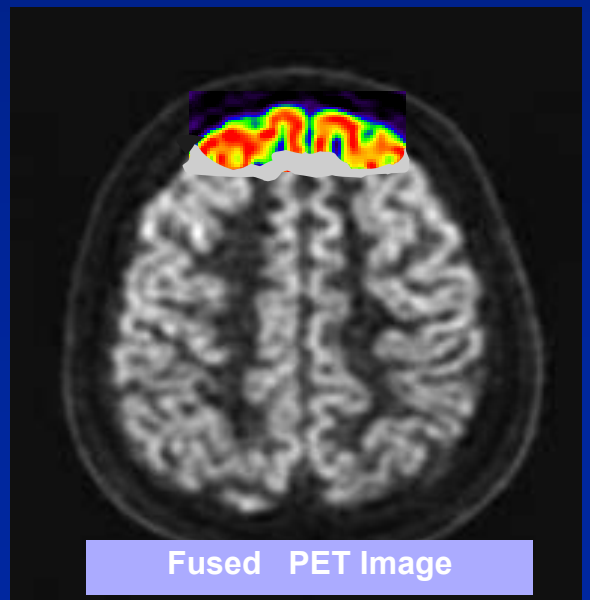


Segmented MRI Image

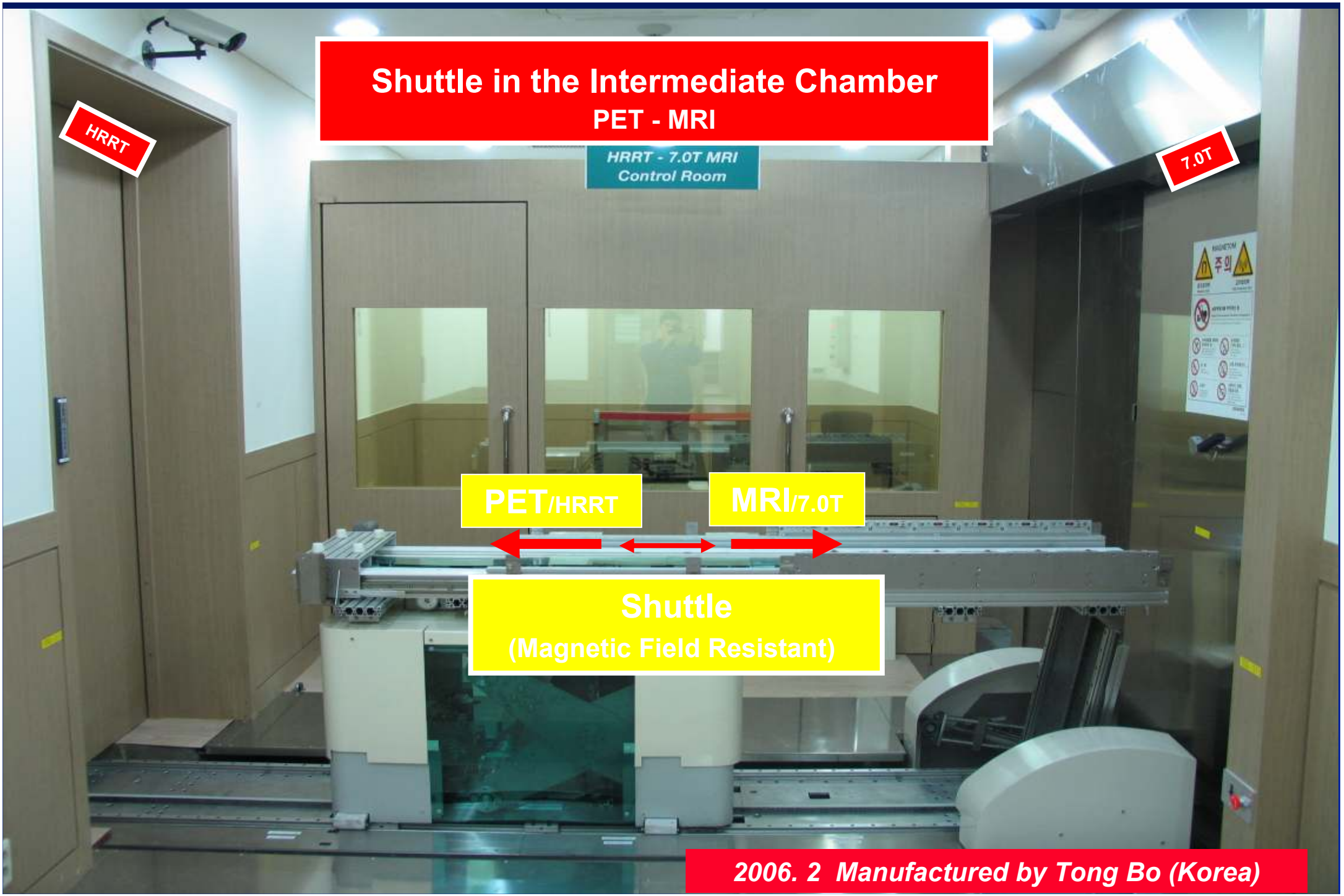


$$\lambda_j = f_j^G \lambda_j^G + f_j^W \lambda^{-W} + f_j^C \lambda^{-C}$$

Original PET Image



Fused PET Image


Shuttle in the Intermediate Chamber
PET - MRI
HRRT
HRRT - 7.0T MRI
Control Room
7.0T
PET/HRRT
MRI/7.0T
Shuttle
(Magnetic Field Resistant)
2006. 2 Manufactured by Tong Bo (Korea)

PET- MRI What is it ?

Max Planck Institute for Neurological Research

MAX-PLANCK-GESELLSCHAFT

with Klaus-Joachim-Zülch-Laboratories of the Max Planck Society and the Faculty of Medicine of the University of Cologne, Director Prof. Dr. D. Yves von Cramon

The Max Planck Institute for Neurological Research invites applications for four Group Leader positions

Selbständige Nachwuchsgruppe der Max-Planck-Gesellschaft (Independent Junior Research Group)

SCIENCE April 7, 2006

Currently, the following technologies / methods are available at the Institute: **human brain PET** (EXACT-HR, HRRT), **animal PET** (μPET) **and animal MRI** (4.7T, 7.0T, 11.7T), **optical imaging** (bioluminescence, fluorescence and laser scanning microscopy) **autoradiography, electron microscopy, histology, immunohistochemistry and invasive imaging / neuromonitoring** (microdialysis, subdural EEG). In 2006, a **combined human brain PET-MR-System** will be installed.

Thank you !

This review was done in collaboration with

- Professor Jarmo Hietala, Psychiatry
- Professor Juha Rinne, Neurology
- Professor Harry Scheinin, Drug development