# Combined PET and MRI Systems – Potential Neurological Applications

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# Outline

PET imaging basics.

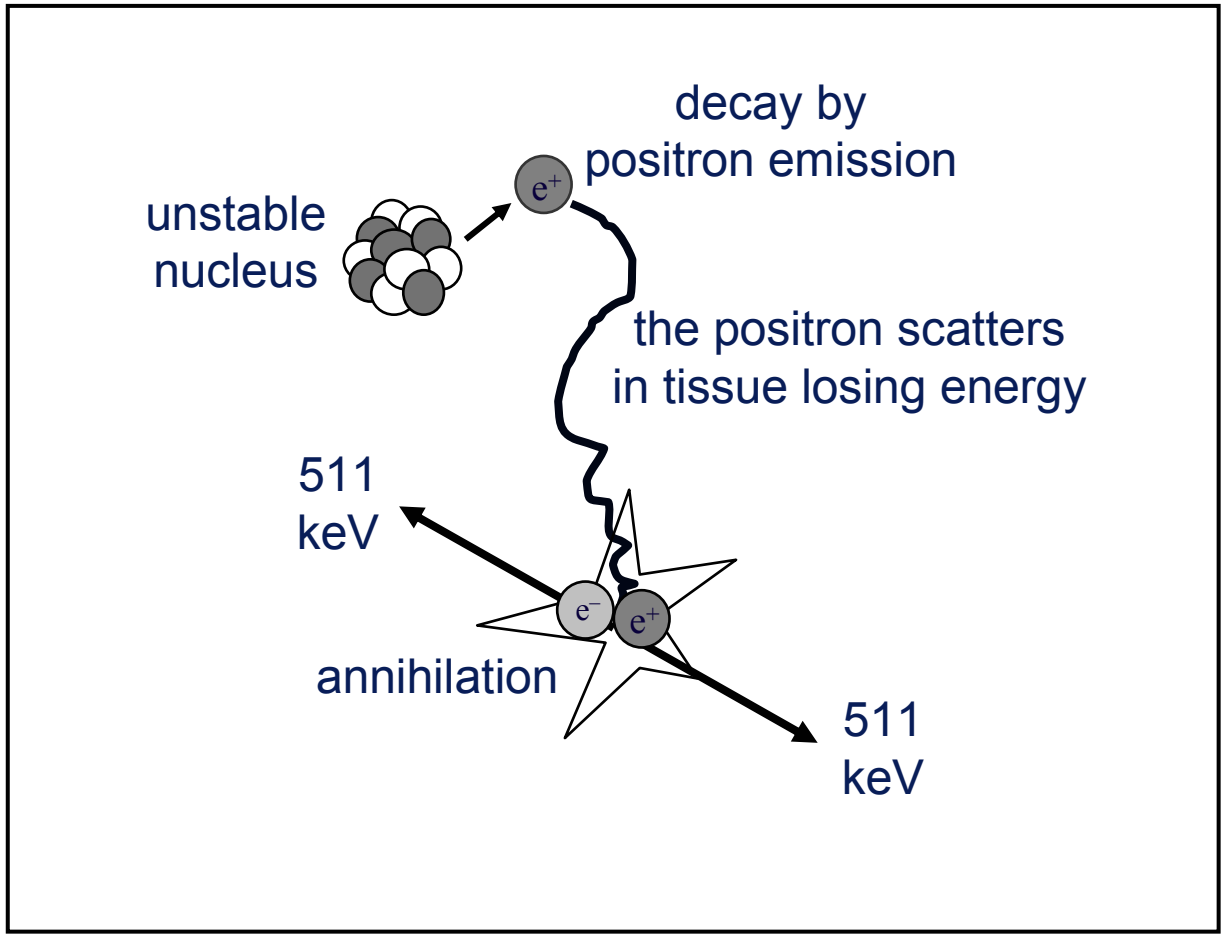
Integrated PET/MRI systems:

- Motivation.
- Challenges and limitations.
- Current state-of-the-art:
  - Small animal systems
  - Human system
- Opportunities/advantages:
  - “Technical” perspective
  - “Neurological” perspective

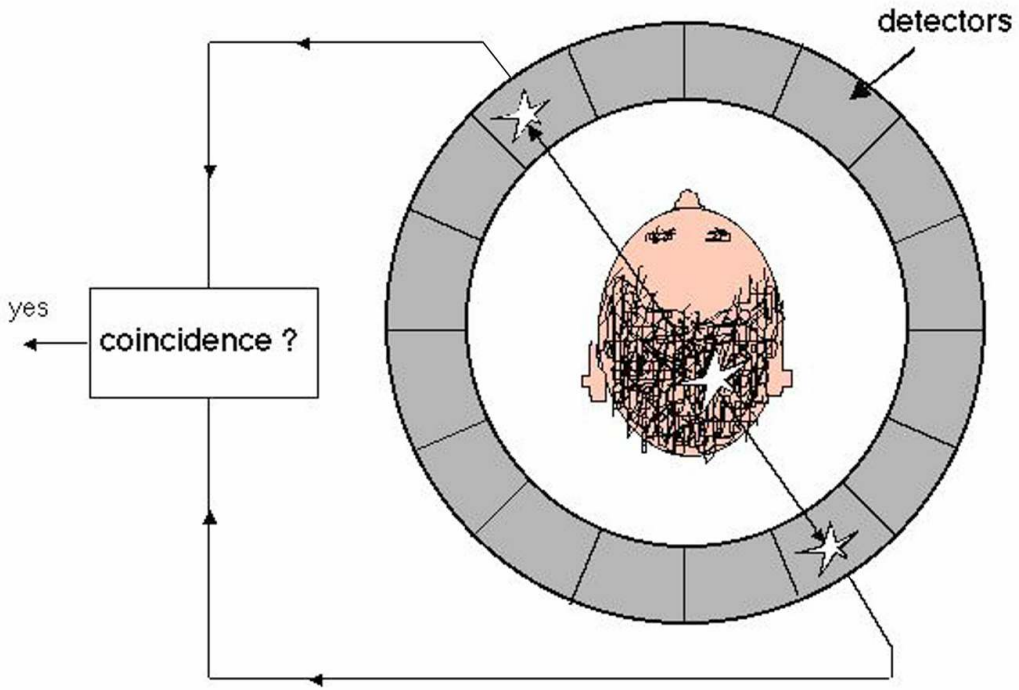
# Introduction

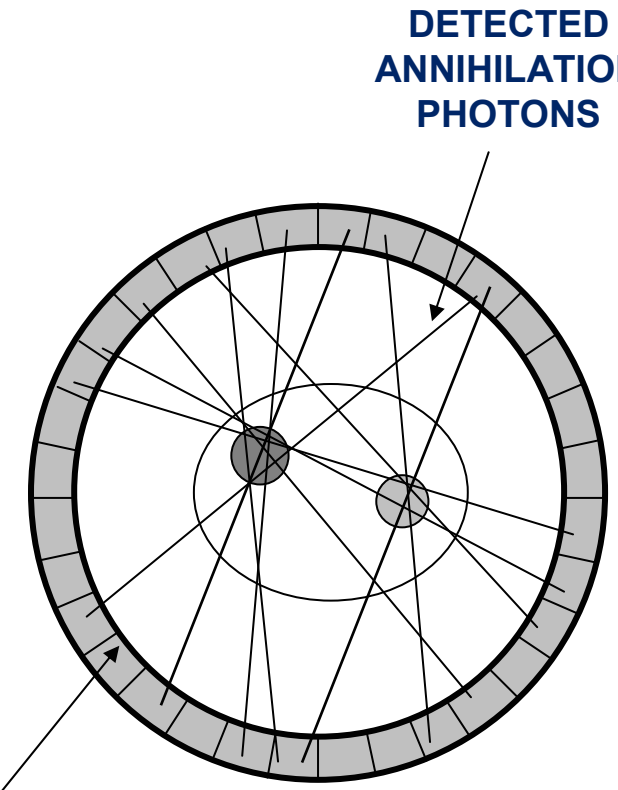
- Imaging techniques – important tools to investigate complex living systems.
- Each imaging modality measures fundamentally different information:
  - PET measures concentration of molecules labeled with positron-emitting radionuclides.
  - MRI measures proton density and tissue relaxation times.
- No imaging modality can provide information on all aspects of structure and function – ***multimodality imaging systems.***

# Positron Emission and Annihilation

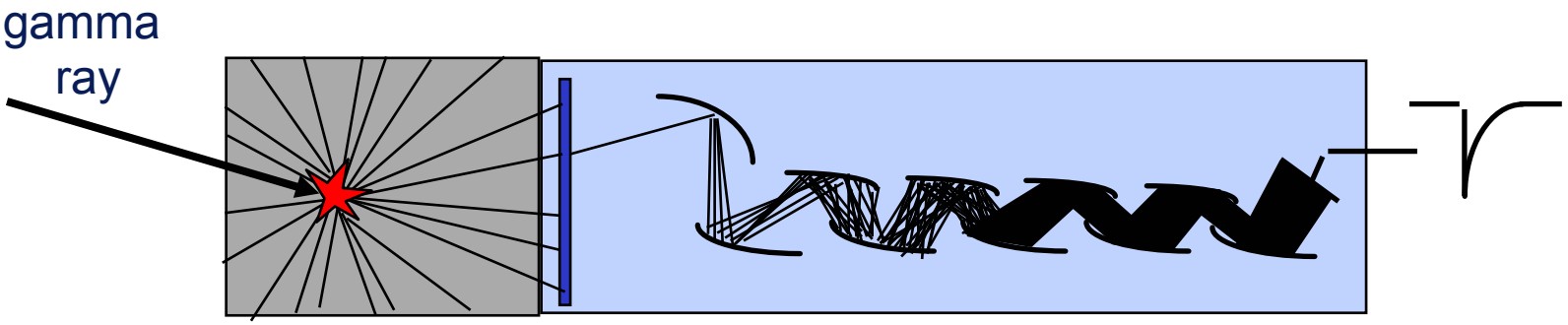


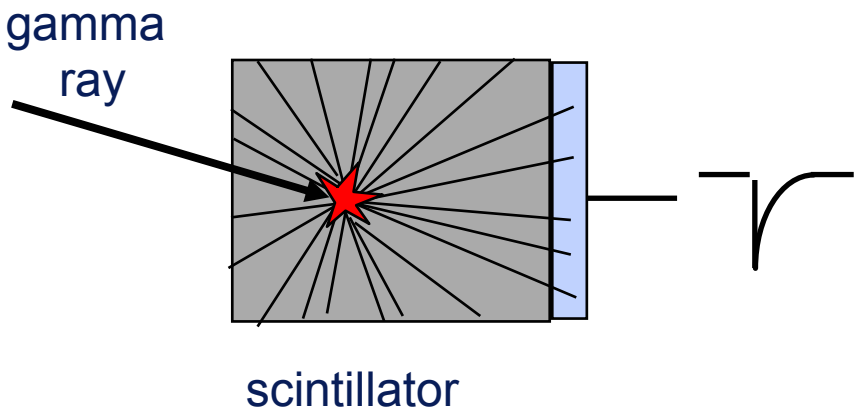
# PET Scanner Concept

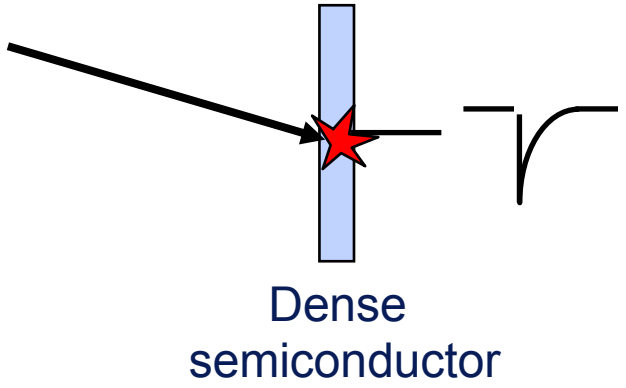


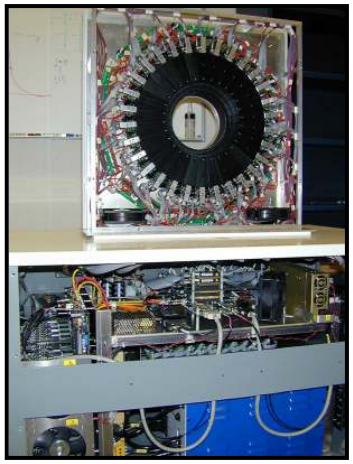
# PET Detector Basics



# PET Scanners



**Small animal imaging**

microPET II

GE Advance

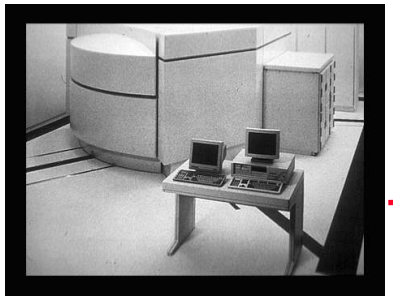
Siemens HRRT

**Clinical imaging**

# Positron Emitting Radionuclides

| Isotope | Half-life | $\beta^+$ fraction | Max. Energy | rms (mm) |
|---|---|---|---|---|
| **C–11** | **20.4 mins** | **0.99** | **0.96 MeV** | **0.4** |
| **N–13** | **9.96 mins** | **1.00** | **1.20 MeV** | **0.7** |
| **O–15** | **123 secs** | **1.00** | **1.74 MeV** | **1.1** |
| **F–18** | **110 mins** | **0.97** | **0.63 MeV** | **0.3** |
| Na–22 | 2.6 years | 0.90 | 0.55 MeV | 0.3 |
| Cu–62 | 9.74 mins | 0.98 | 2.93 MeV | 2.7 |
| Ga–68 | 68.3 mins | 0.88 | 1.90 MeV | 1.2 |
| Rb–82 | 78 secs | 0.96 | 3.15 MeV | 2.8 |
| I–124 | 4.18 days | 0.22 | 3.16 MeV | 2.8 |

# PET-labeled Radiopharmaceuticals

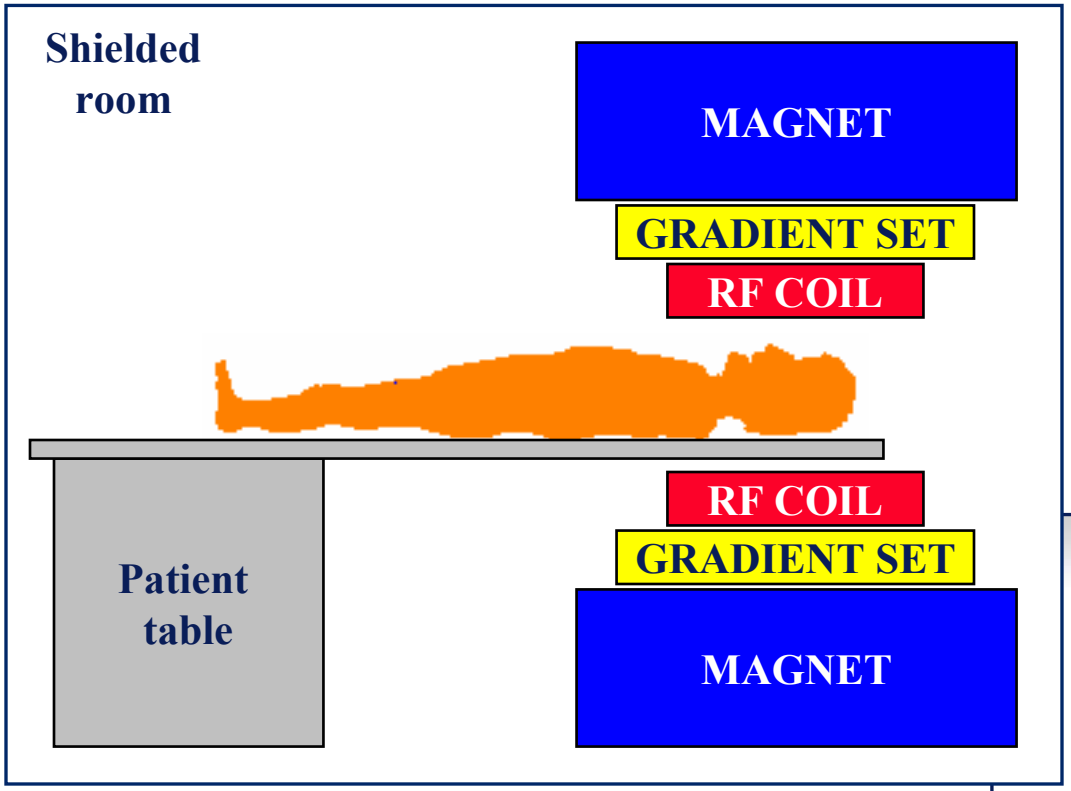


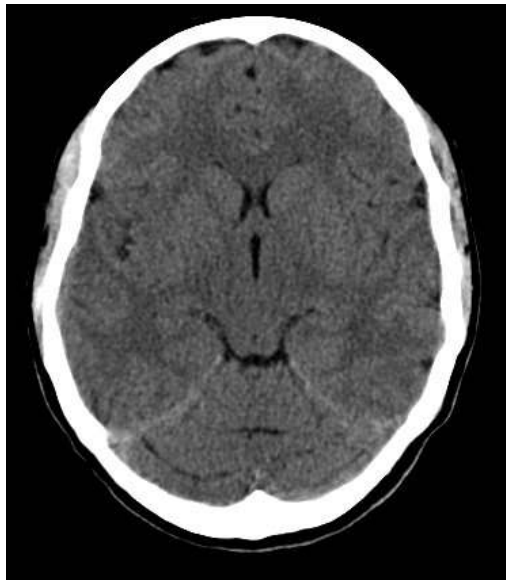
cyclotron

$^{11}C$, $^{13}N$, $^{15}O$, $^{18}F$

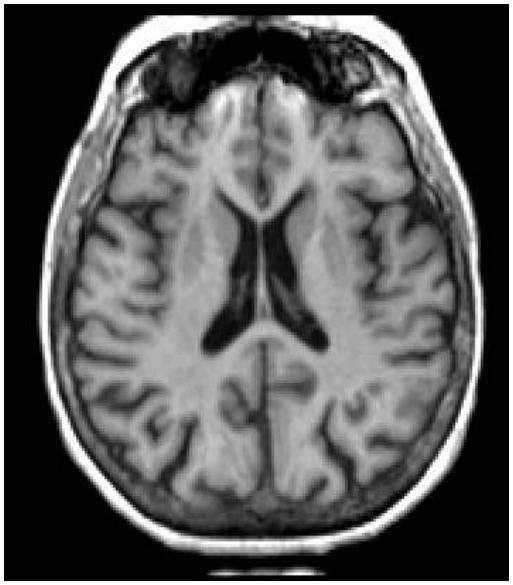
- hemodynamic parameters ($H_2{}^{15}O$, $^{15}O$-butanol, $^{11}CO$, $^{13}NH_3$.....)
- substrate metabolism ($^{18}F$-FDG, $^{15}O_2$, $^{11}C$-palmitic acid....)
- protein synthesis ($^{11}C$-leucine, $^{11}C$-methionine, $^{11}C$-tyrosine)
- enzyme activity ($^{11}C$-deprenyl, $^{18}F$-deoxyuracil...)
- drugs ($^{11}C$-cocaine, $^{13}N$-cisplatin, $^{18}F$-fluorouracil...)
- receptor affinity ($^{11}C$-raclopride, $^{11}C$-carfentanil, $^{11}C$-scopalamine)
- neurotransmitter biochemistry ($^{18}F$-fluorodopa, $^{11}C$-ephedrine...)
- gene expression ($^{18}F$-ganciclovir, $^{18}F$-antisense oligonucleotides...)
- .....

# MR Imaging Basics

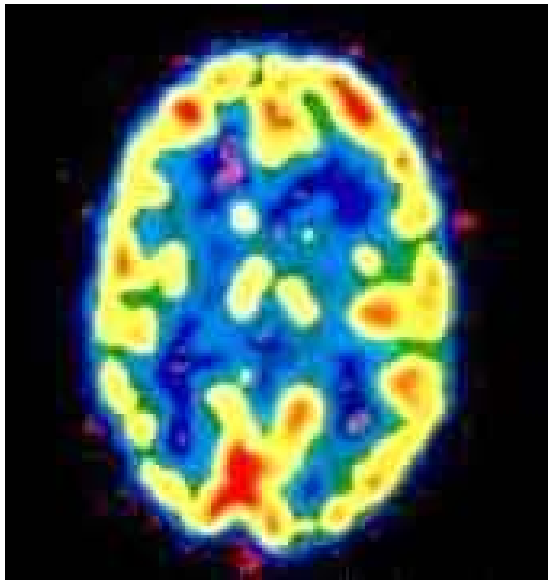


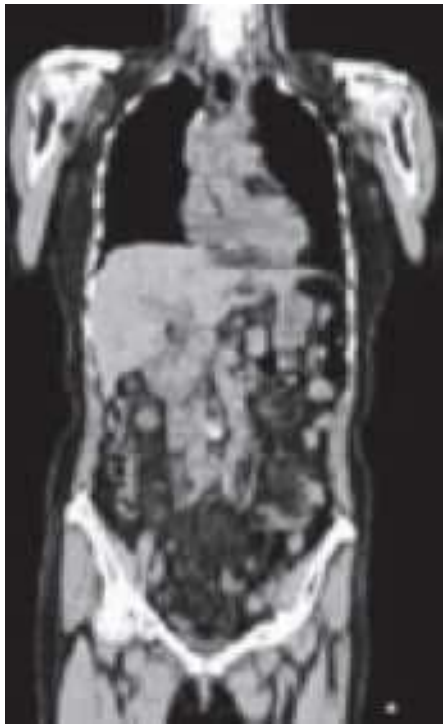
X-RAY CT

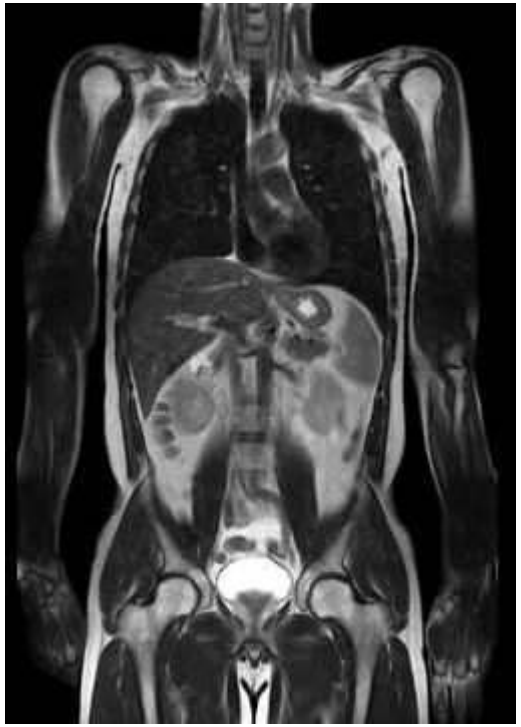


MRI



PET





# Combined PET and MRI – Why?

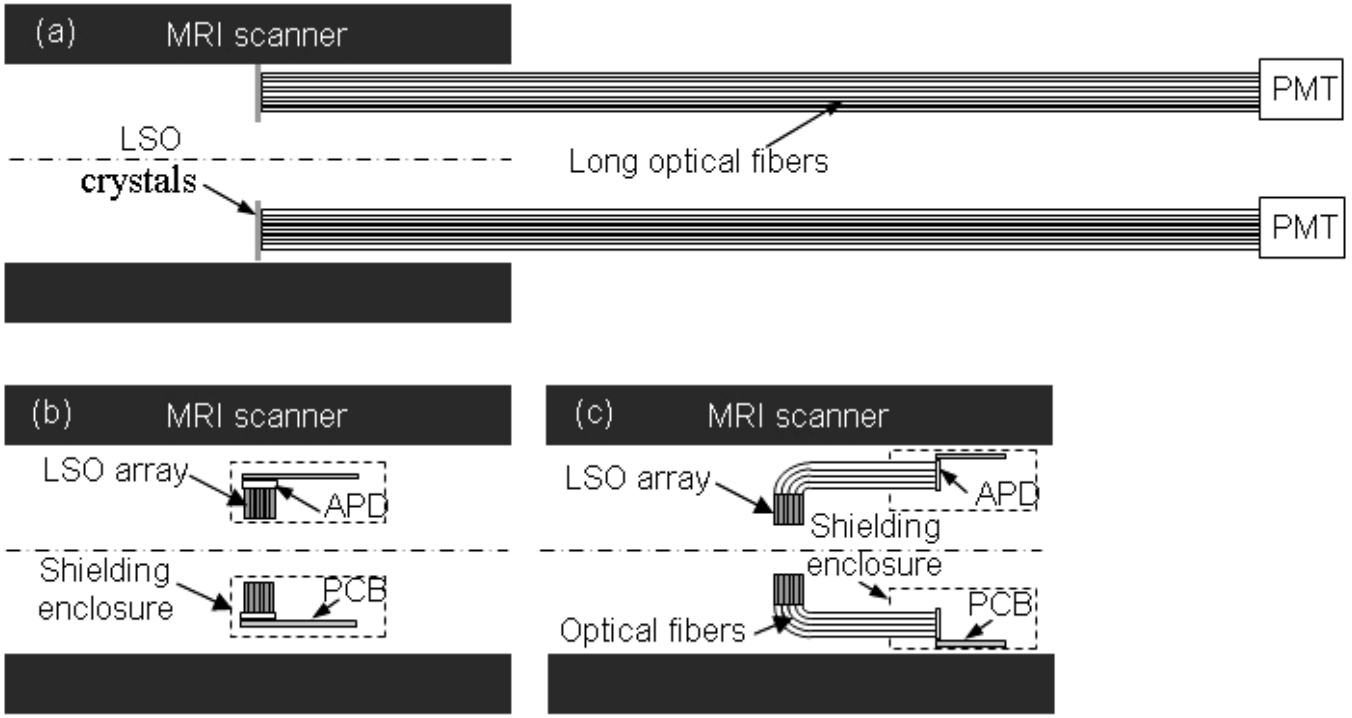
| | PET | MR |
|---|---|---|
| **PROs** | - Exceptionally sensitive assays of a wide range of biological processes<br>- Quantitative technique | - Exquisite high resolution anatomical information with excellent soft tissue contrast<br>- Physiological parameters<br>- Metabolic and biochemical information |
| **CONs** | - Poor spatial resolution<br>- Limited anatomic information<br>- Involves ionizing radiation | - Poor sensitivity<br>- Absolute quantification challenging |

# Challenges in Combining PET and MRI

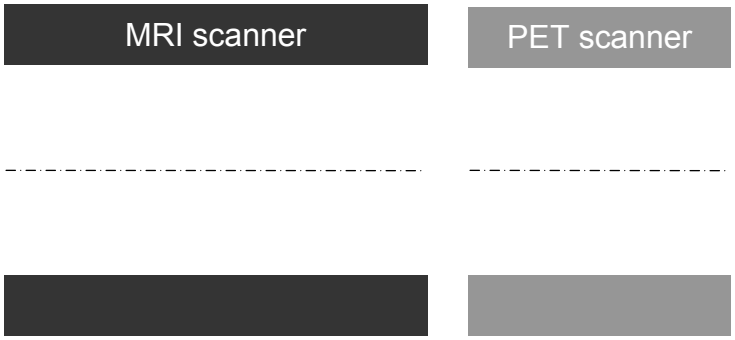
- Limited space available inside the MR scanner.
- No ferromagnetic components allowed.
- Homogeneity of the $B_0$ field.
- Radiofrequency interference (RFI) between the MR transmit/receive coils and the electronics of the PET system.
- Susceptibility artifacts and eddy currents related to the placement of materials inside the MR magnet.
- Photomultiplier tubes (PMTs) are very sensitive to magnetic fields.
- Effect of the magnetic field (both the static and switching gradient fields) on the PET (RFI, heating, vibrations, etc).
- Cost !

# Approaches for Combining PET and MRI

Simultaneous MR - PET




Sequential MR - PET



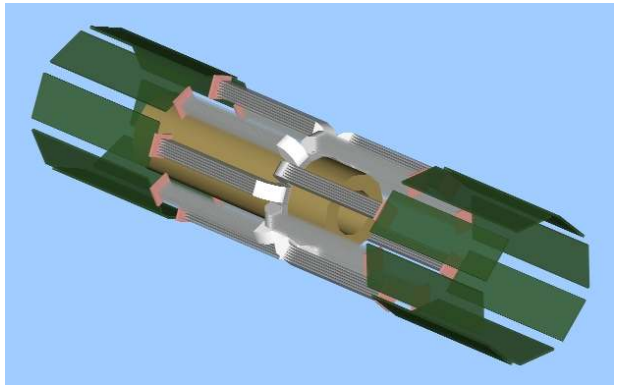
# Current State-of-the-art Systems

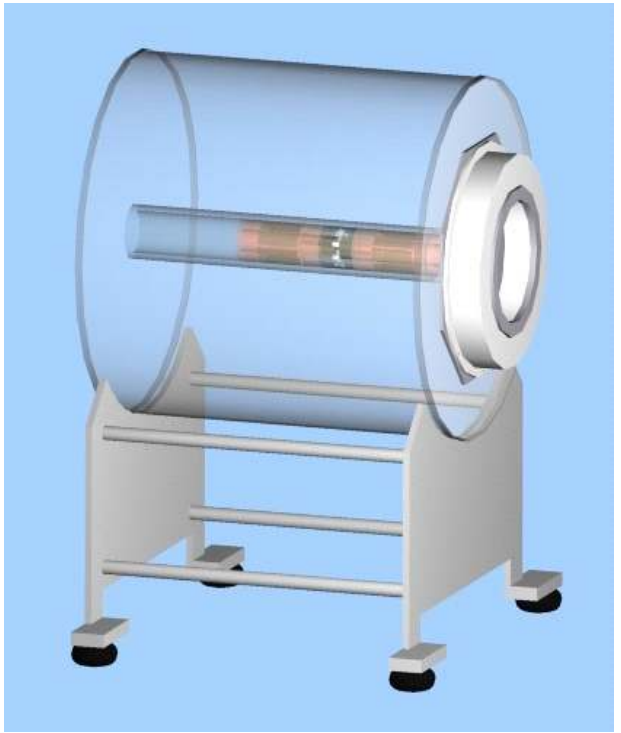
- Small animal imaging - PET/MR
  - University of California Davis
  - University of Tübingen
- Human imaging – MR-PET
  - BrainPET prototype (Siemens Medical Solutions) installed at MGH

# UC Davis PET/MRI Project

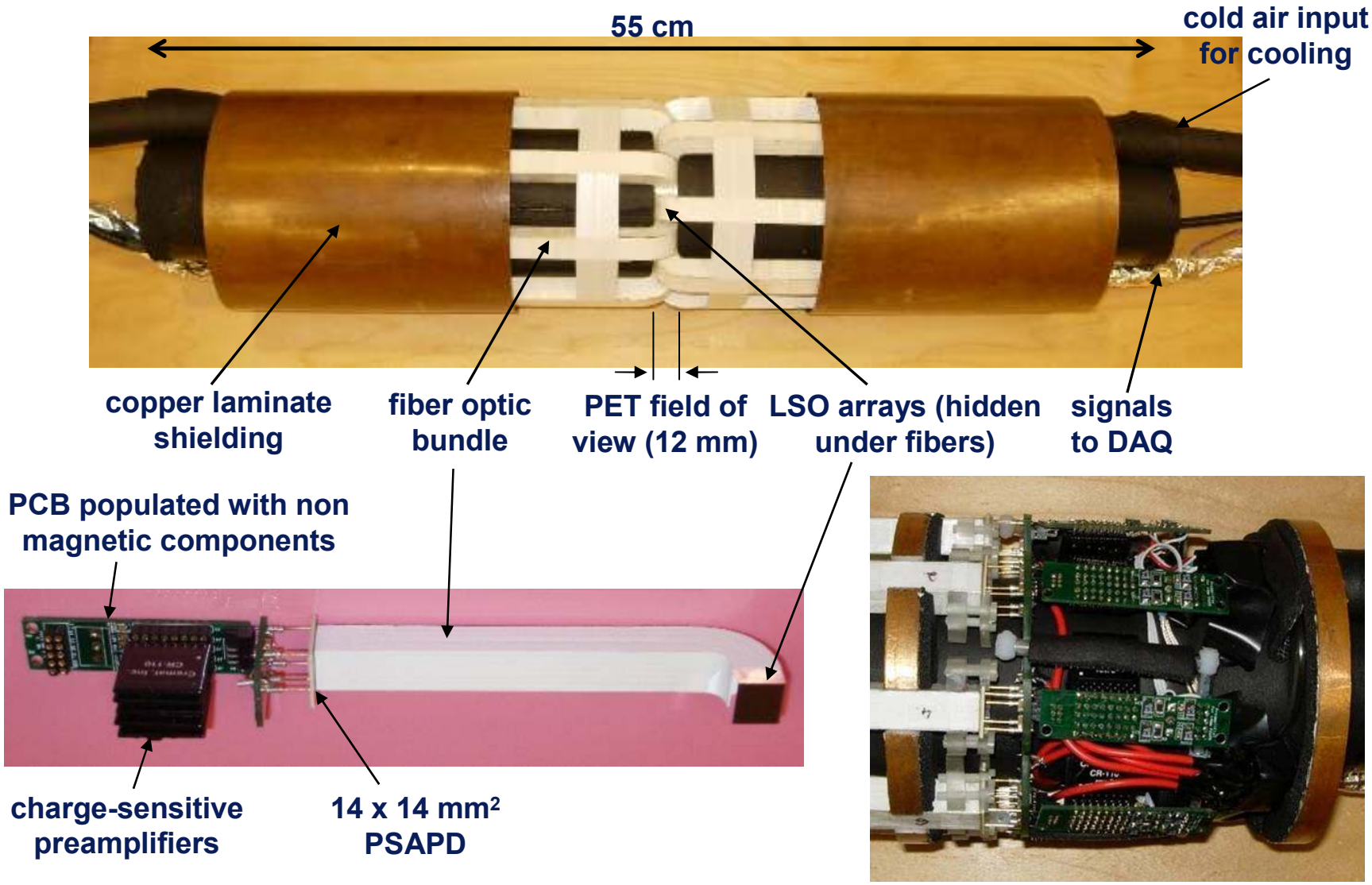
**Aims:**

- Design and build a high resolution, high sensitivity, multi-ring small-animal PET scanner integrated with a 7 Tesla small-animal MR system.
- Minimal interference between the two systems.

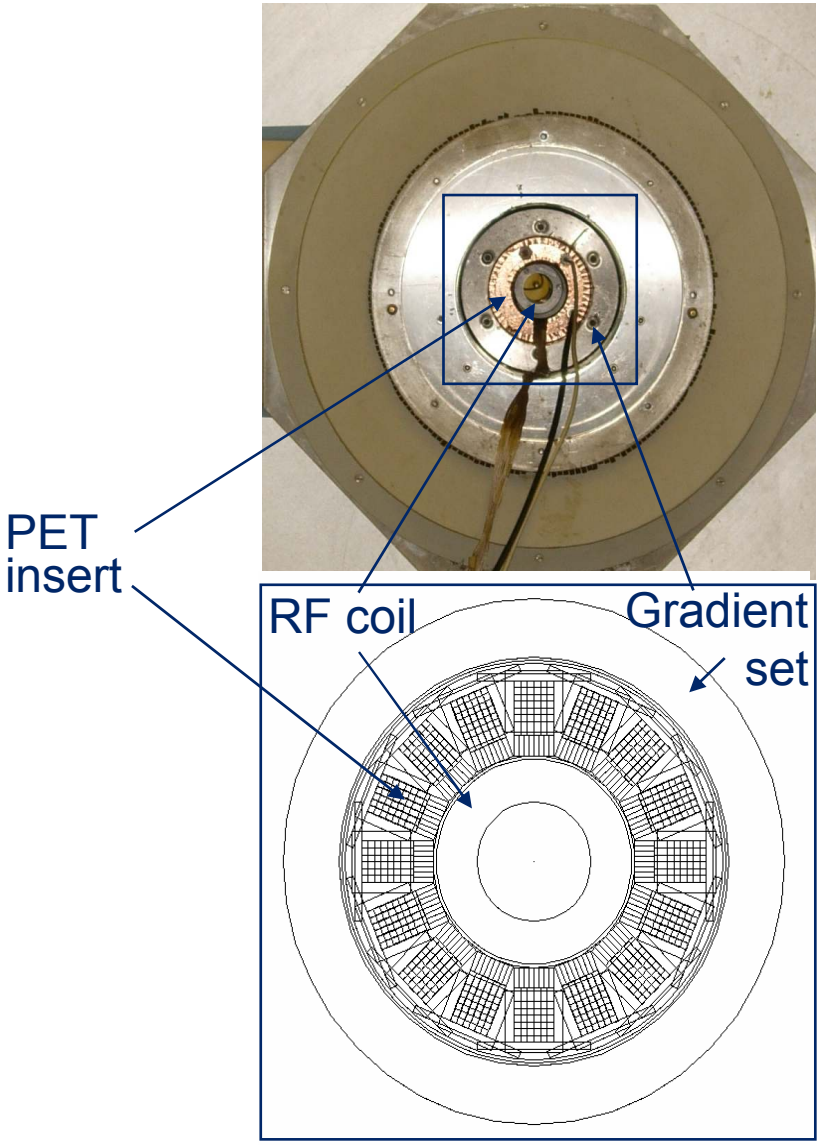




# UC Davis MR-compatible PET Insert



# UC Davis PET/MRI System




| Characteristic | Value |
|---|---|
| Crystal size | 1.43x1.43x6 $mm^3$ |
| Crystal pitch | 1.51 mm |
| Fiber size | 1.95x1.95 $mm^2$ |
| Fiber bundles' length | 10 cm |
| PSAPD size | 14x14 $mm^2$ |
| Number of modules | 16 |
| Ring diameter | 60 mm |
| Axial FOV | 12 mm |
| Transaxial FOV | 35 mm |
| Number of crystals | 1024 |
| Insert length | 55 cm |
| Insert outer diameter | 11.8 cm |

C. Catana et al., *J. Nuclear Medicine* 2006; 47(12): 1968-1976

# *In Vivo* Simultaneous PET/MRI

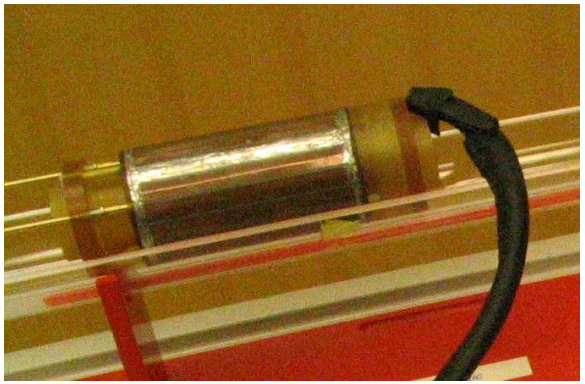
**PET**

- Insert temperature ~ –10ºC
- LLD set just above the noise level for each detector module.
- Timing window = 25 ns.
- Basic normalization using a uniform phantom.
- No other corrections applied.
- Fully 3D ML-EM reconstruction.

**MRI**

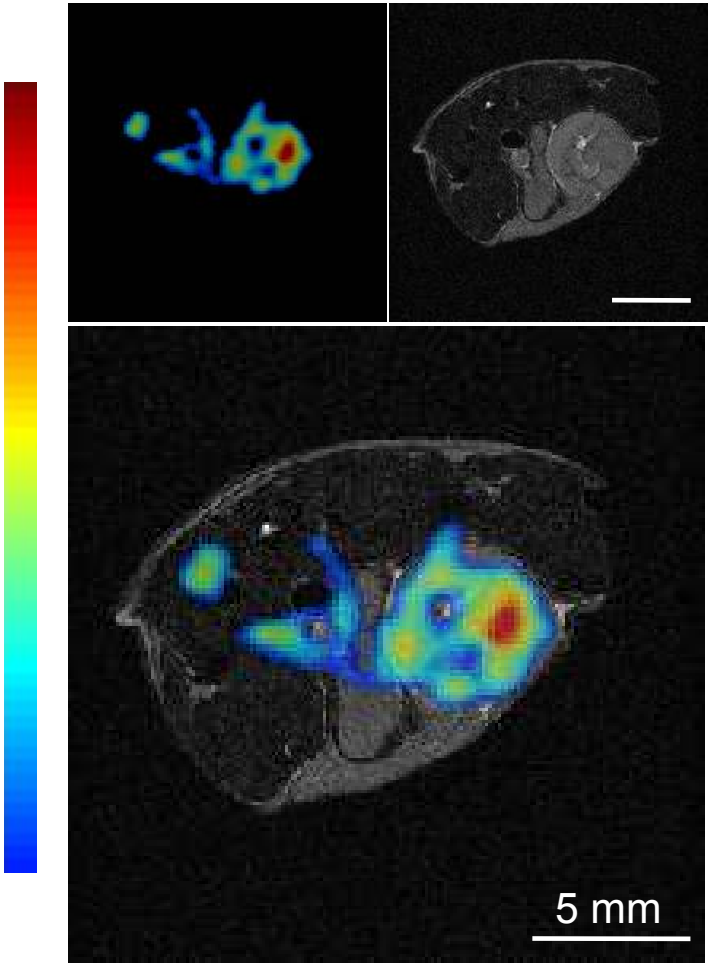
- Acquired simultaneously with the PET data.
- Custom-made brain and whole body RF coils with heating to maintain animal at 37°C.
- Tuning and matching.
- Automatic first order shimming.

Brain imaging coil



Whole body imaging coil

# *In Vivo* Simultaneous PET/MRI




**Mouse**
**FDG Tumor Imaging**

- $10^6$ MC38 cells
- 10 days post injection

**PET**

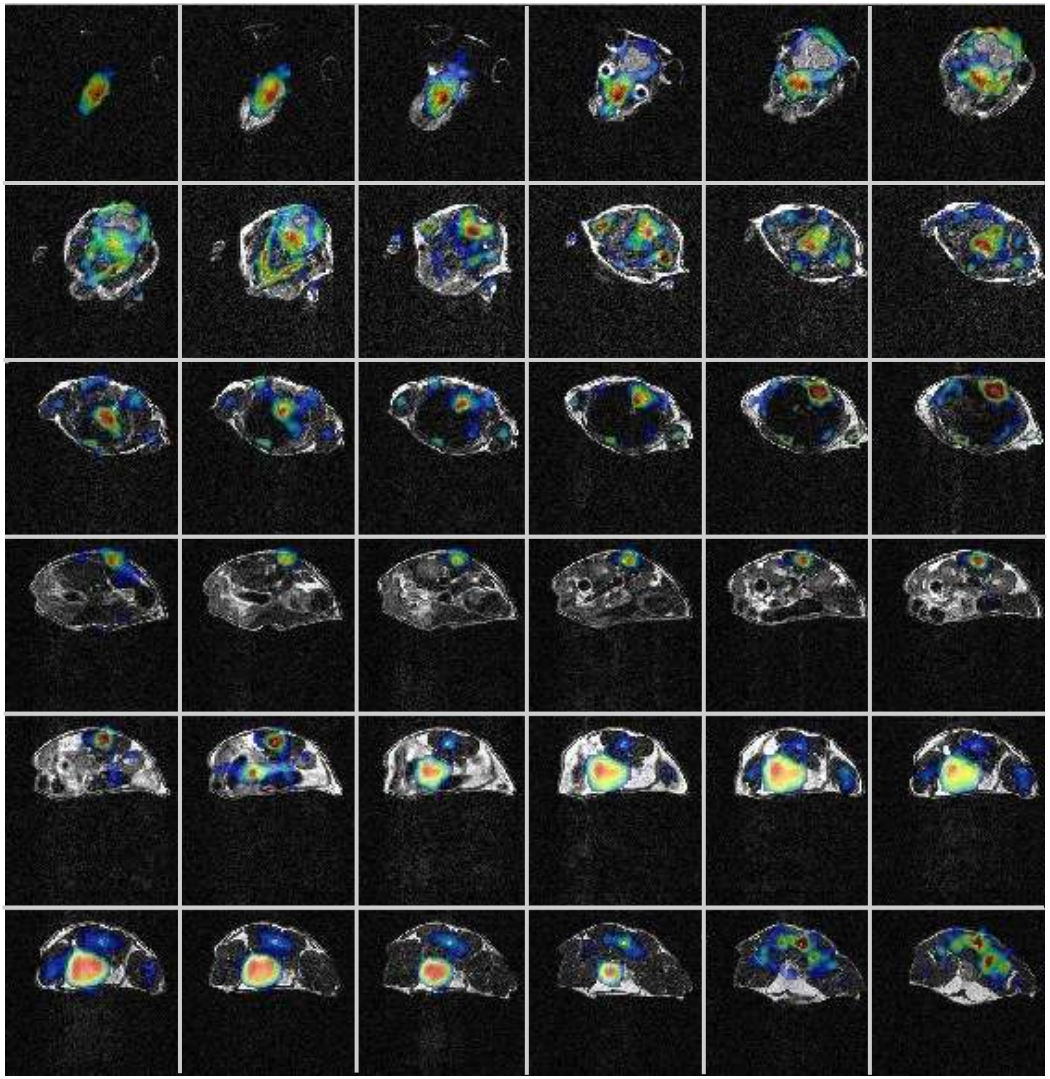
- ~200 µCi $^{18}$F-FDG
- Voxel size: 0.35 x 0.35 x 1.5 $mm^3$

**MR**

- RARE sequence
- Whole body imaging RF coil
- FOV=4 x 4 $cm^2$
- Matrix size 256 x 256

C. Catana et al *Proc. Nat. Acad. Sc. USA,* 2008; 105 (10): 3705-3710

# *In Vivo* Simultaneous PET/MRI



## Bone Scan Mouse Whole-Body

### PET

- ~200 μCi $^{18}F^-$
- 6 min scans for 8 bed positions covering a total axial FOV of 68 mm
- Voxel size: 0.35 x 0.35 x 1.5 $mm^3$

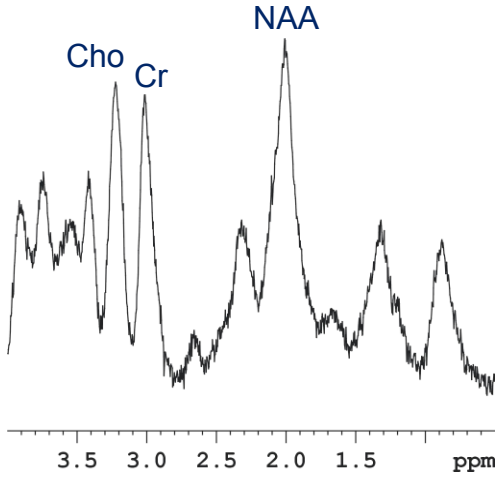
### MR

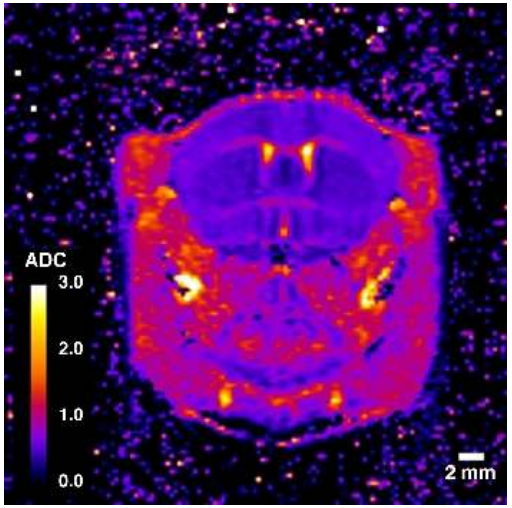
- RARE sequence
- Respiratory gating
- Whole body imaging RF coil
- FOV=4x4 $cm^2$
- Matrix size 256x256

# Beyond Morphological MRI

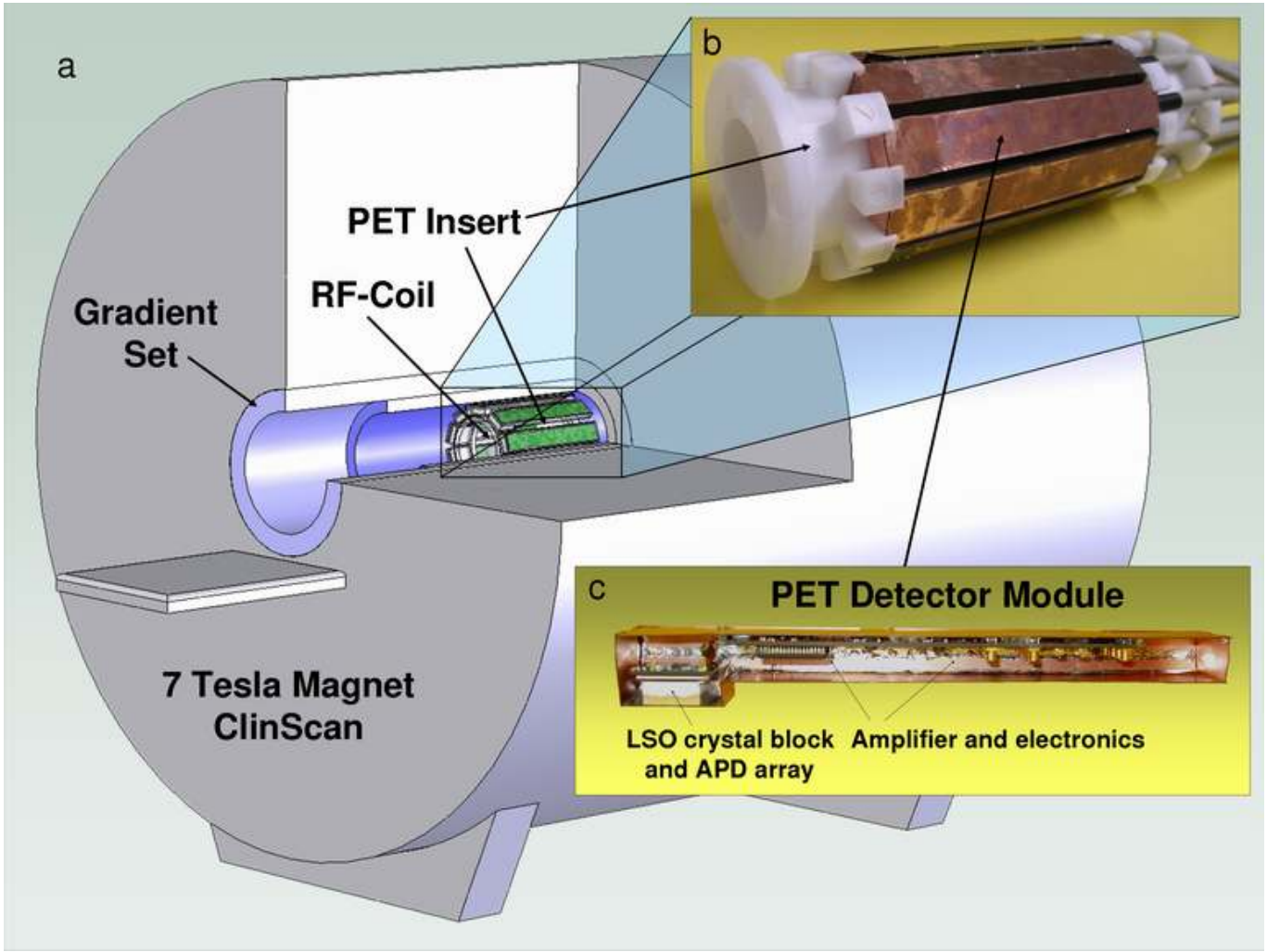
Advanced MR in the presence of the PET insert:

- ***In vivo* mouse brain MR spectroscopy**
  - Volume-selective *in vivo* $^{1}H$ spectroscopy
  - 3 x 3 x 3 $mm^3$ voxel positioned centrally in the mouse brain.
  - PRESS sequence (TR/TE=2500/12 ms)
  - Water suppression using a CHESS sequence.
- **DWI EPI**
  - 4 shot EPI (TR/TE = 2000/32 ms).
  - FOV = 1.92 x 1.92 $cm^2$, matrix size 128 x 128, slice thickness = 0.75 mm.
  - Diffusion: Δ=14 ms, δ= 7msec; b = 100, 200, 600, 800, 1400 sec/$mm^2$.

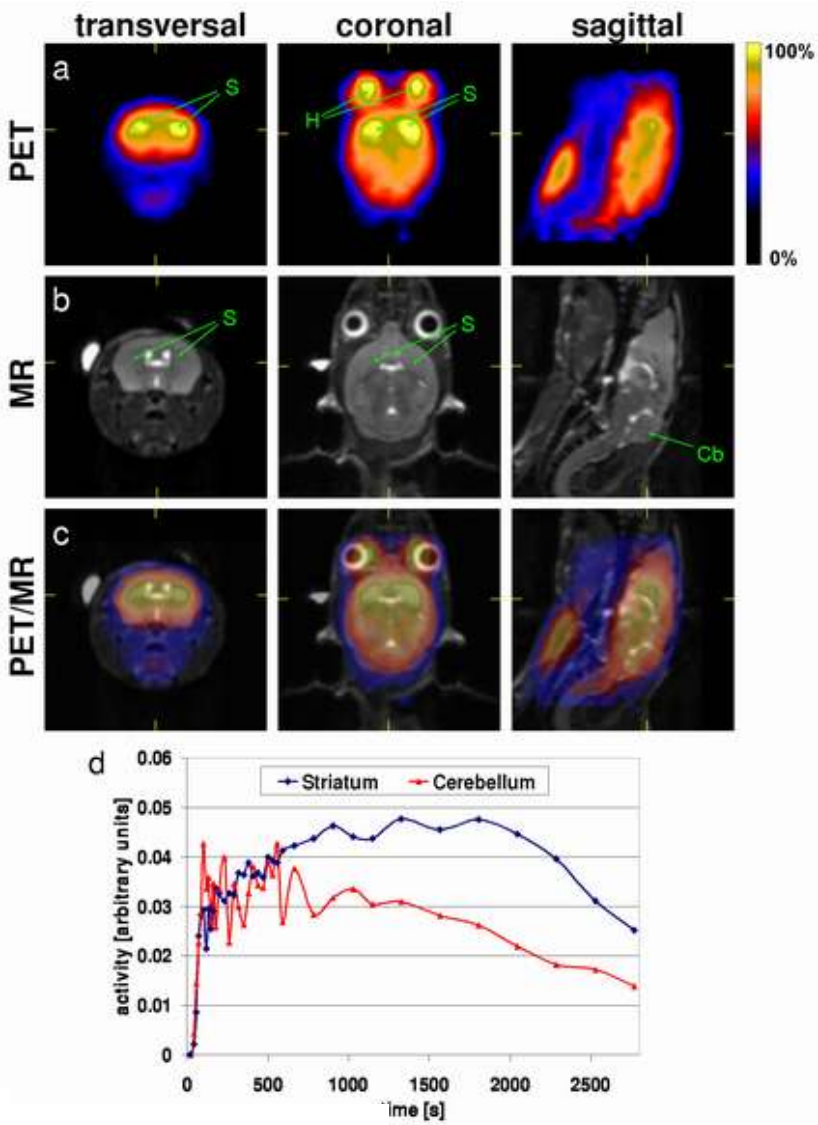


# Univ. of Tuebingen PET/MRI System



# *In Vivo* Simultaneous PET/MRI




(a) [$^{11}$C]-*d-threo*-Methylphenidate PET.

(b) 3D TSE MR sequence.

(c) Fused images.

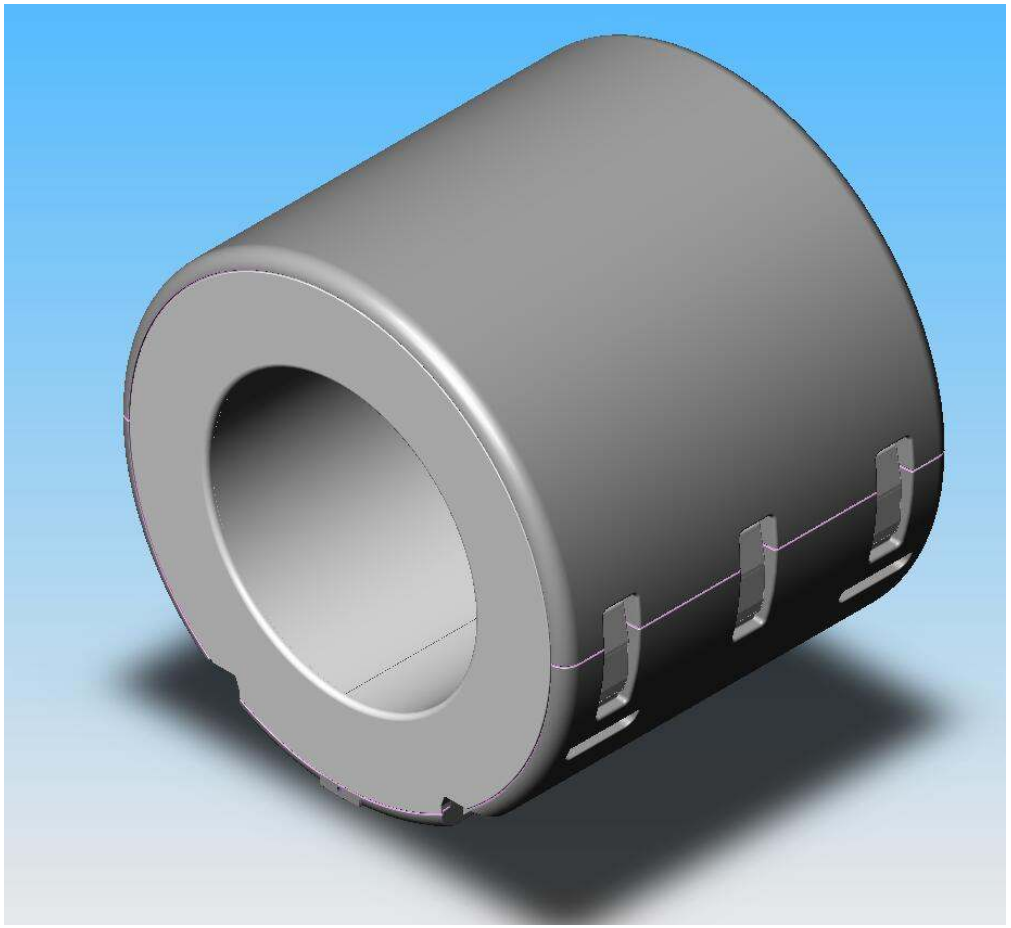
(d) Time activity curves derived from the dynamic PET data.

M.S. Judenhofer et al., *Nature Medicine*, 2008; epub March 23

# Clinical MR-PET

# Siemens BrainPET Prototype Design

- Standard  MR 3T tunnel (60 cm ID)
- BrainPET insert (35 cm ID)
- 32 Detector Cassettes
- 6 LSO Blocks/Cassette
  - crystal size 2.5 x 2.5 x 20 $mm^3$
  - 12 x 12 crystals/block
  - 3 x 3 array of Hamamatsu APDs
- 192 LSO Blocks total
- 1732 APDs total
- 19.25cm axial / 30cm transaxial
- Air/Water cooling



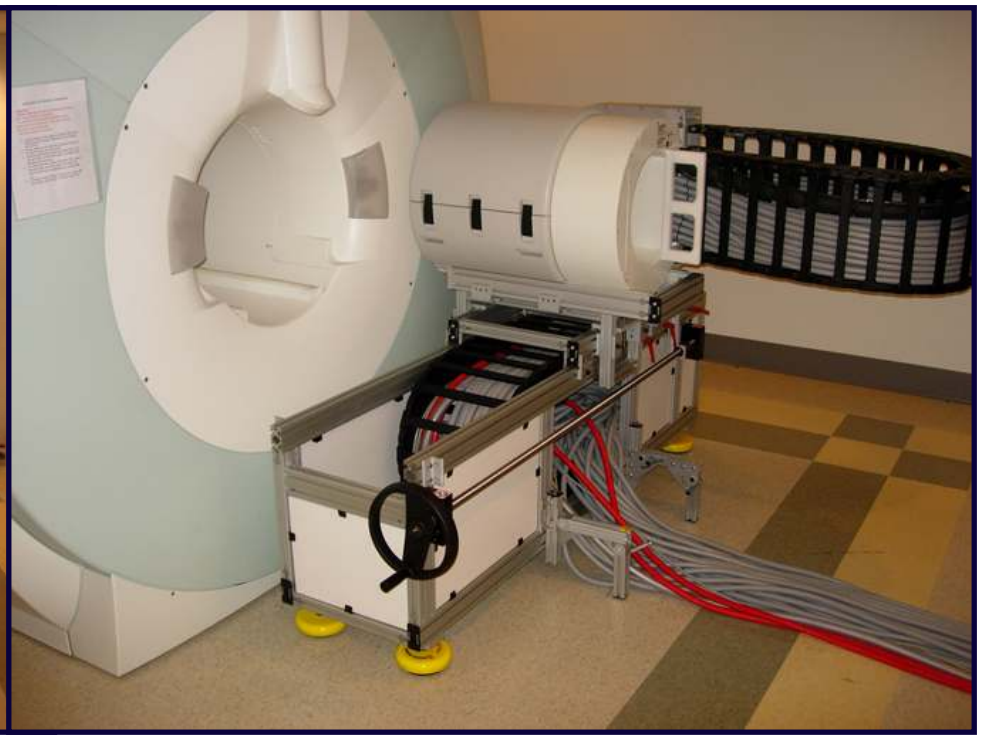
***Courtesy of Siemens Medical Solutions***

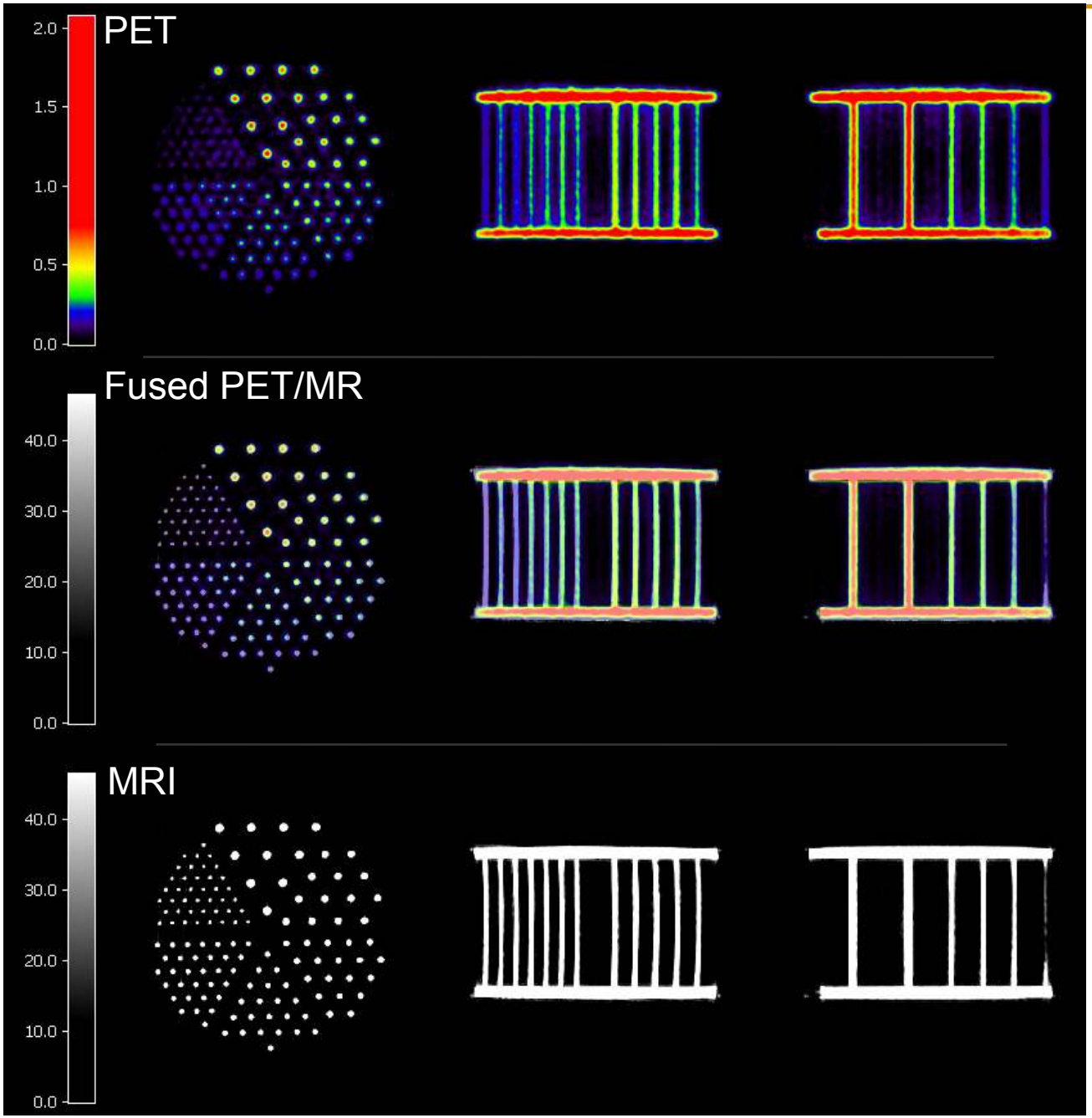
# BrainPET – Preliminary Results

- First APD-based PET scanner capable of imaging the human brain in one bed position
- First Performance Results:
  - Sensitivity: in stand alone PET mode ~25% higher than the HRRT [400-650 keV]
  - Spatial Resolution: <3 mm at 8 cm radius (cortex)
  - Timing Resolution: <6 ns (APD); timing window used is 12 ns
  - Scatter Fraction: ~40% (NU2-1994: 43.6% @ 0 cm, 40.9% @ 4 cm)

***Courtesy of Siemens Medical Solutions***

# Integrated MR-PET Scanner at **MGH**




# Simultaneous MR-PET Data Acquisition

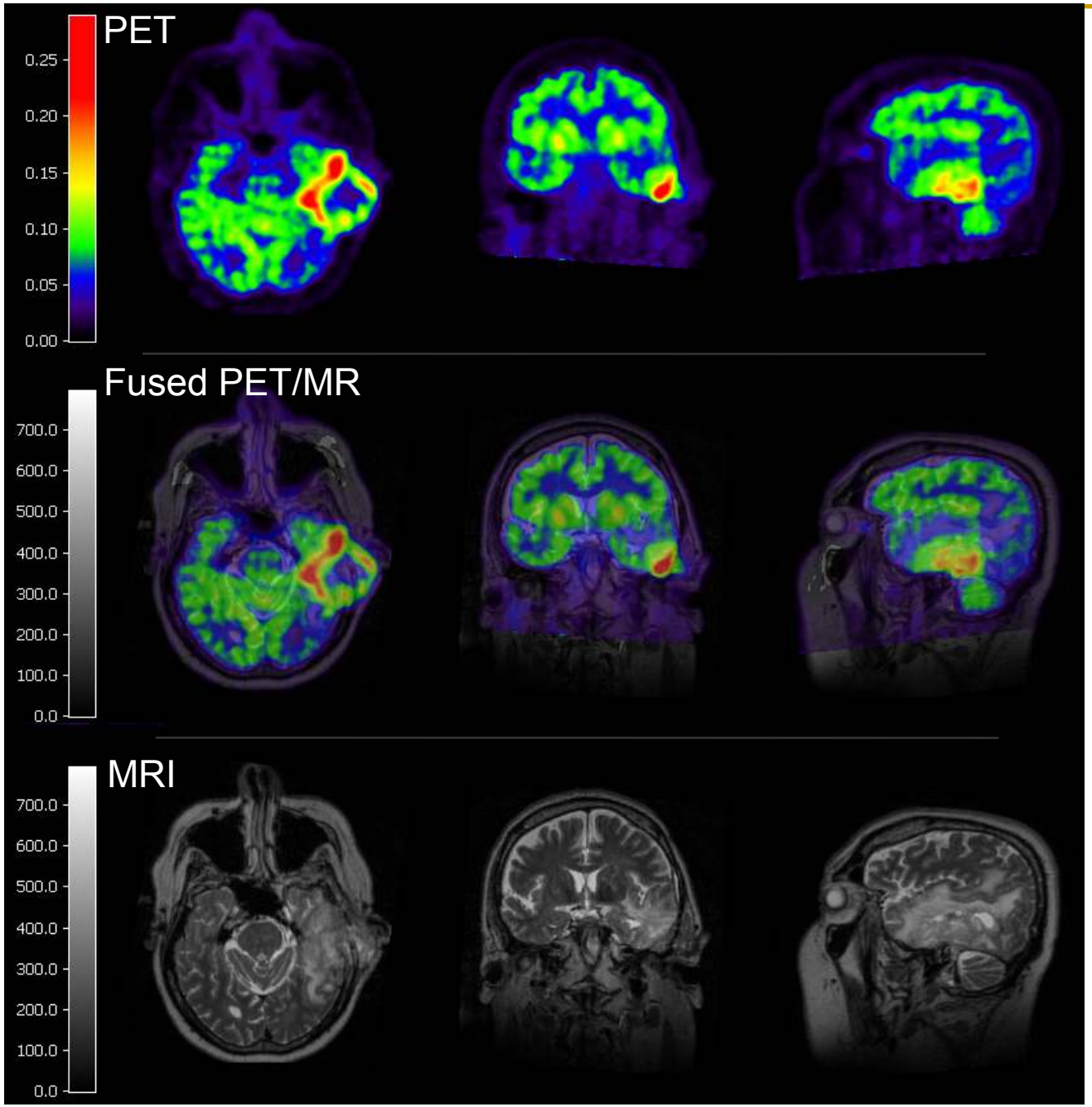
20 cm diameter phantom; hole size range 2.5 – 6 mm; center- to center=4 times hole diameter

**PET**

- 1.5 mCi F-18 water
- 20 min acquisition scan
- OSEM 3D reconstruction

**MR**

- FLASH (shown), TSE, MP-RAGE sequences run simultaneously
- CP coil




# Simultaneous MR-PET Data Acquisition

54 year old with malignant glioma and cutaneous extension

**PET**

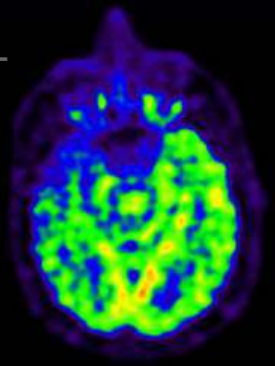
- 5.45 mCi FDG injected approx. 2.5 hours prior to data acquisition
- OSEM 3D reconstruction
- Attenuation correction performed based on the MR data

**MR**

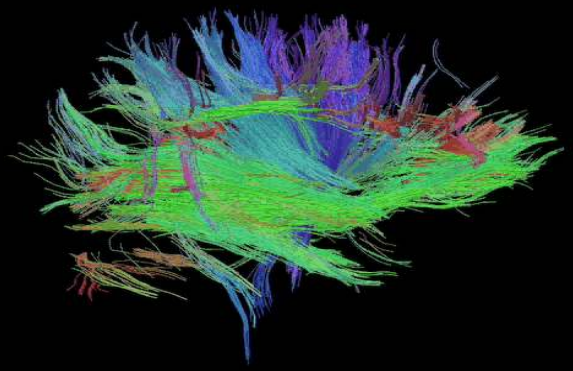
- T1 MP-RAGE, T2 SPACE (shown), FLAIR, DTI, CSI, SVS sequences run simultaneously
- CP coil

# Simultaneous MR-PET Acquisition

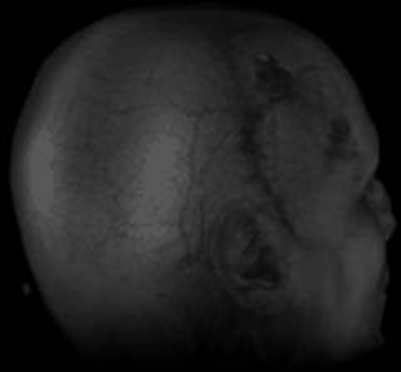
PET



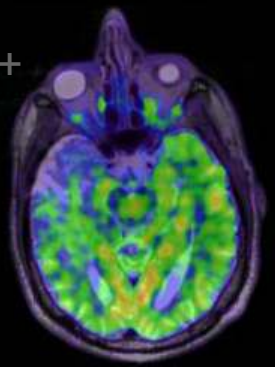
Diffusion Tractography



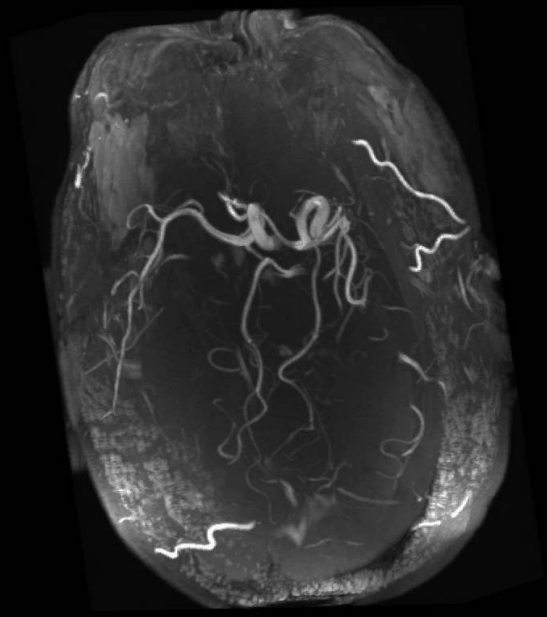
Surface Rendering



PET+ MR

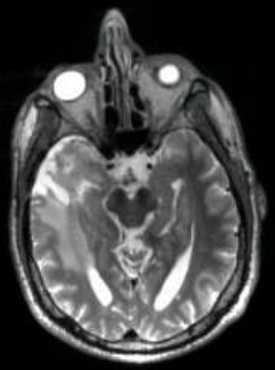


MRA



High Res Anatomy

MR



# Combined MR-PET – Opportunities

"Technical" perspective

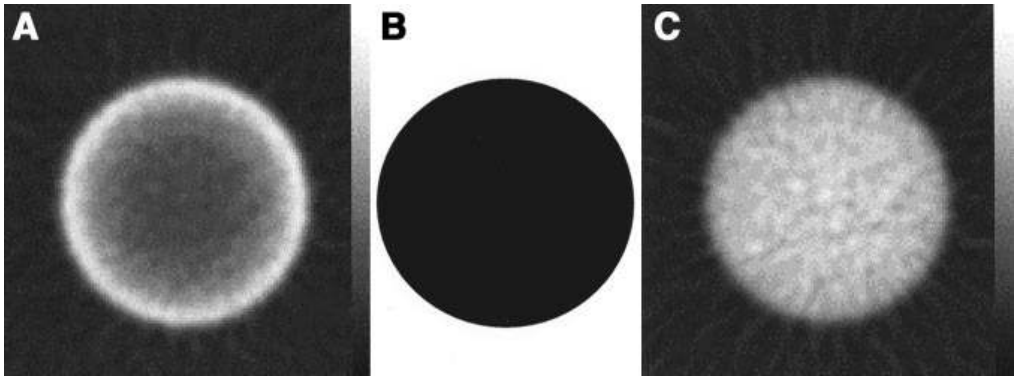
Neurological perspective

# Combined MR-PET – Technical perspective

## Improving the PET Data Analysis/Quantification

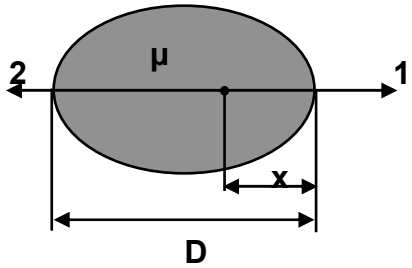
- Attenuation correction.
- Motion correction.
- Partial volume effect correction.
- Arterial input function estimation.
- PET image reconstruction.
- Spatial resolution – positron range effect.

# Attenuation Correction




$$I(x) = I(0)e^{-\mu x}$$

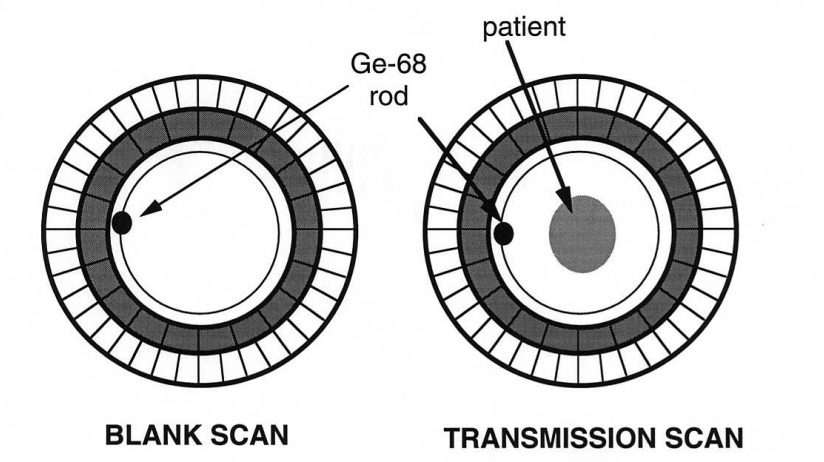
$$p_2 = e^{-\mu(D-x)}$$




$$p_1 = e^{-\mu x}$$

$$p_{coinc.} = p_1 p_2 = e^{-\mu x} e^{-\mu(D-x)} = e^{-\mu D}$$

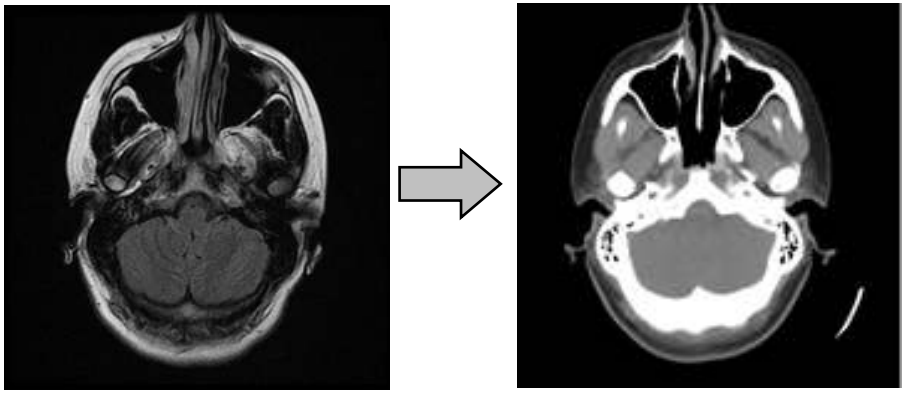
$$Atten.Corr. = e^{\mu D}$$



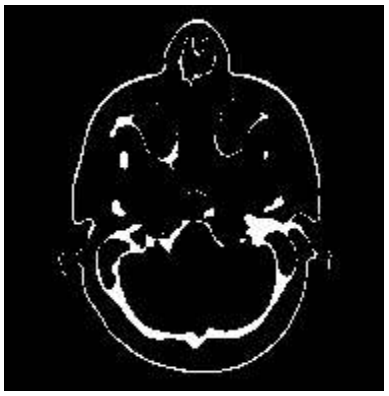

(Cherry SR, Sorenson JA, Phelps ME. *Physics in Nuclear Medicine*, 3rd ed.)

# Attenuation Correction

- Important for both qualitative and quantitative analysis.
- **MR-based attenuation correction:**
  - **Approach**:
    - MR image segmentation.
    - Assign known attenuation coefficients.
    - Calculate attenuation correction factors.
  - **Advantage:**
    - Reduced radiation dose and acquisition time.



MRI CT



MR-based
bone segmentation

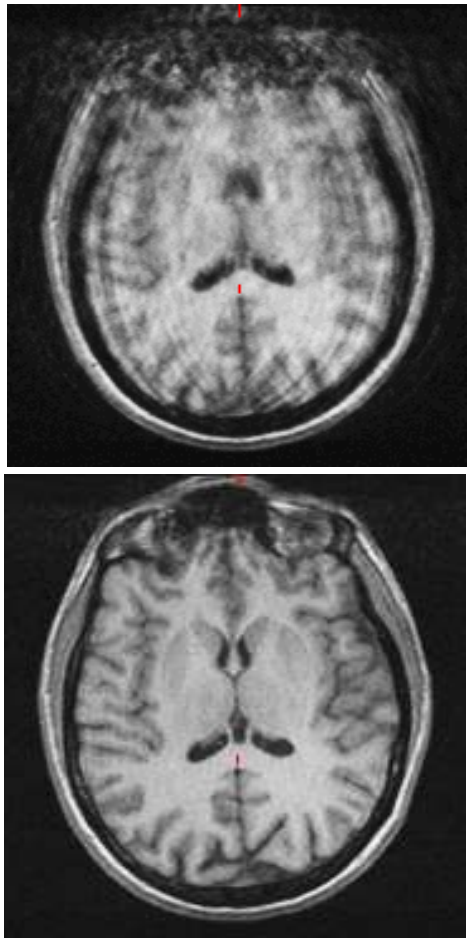
# Motion Correction

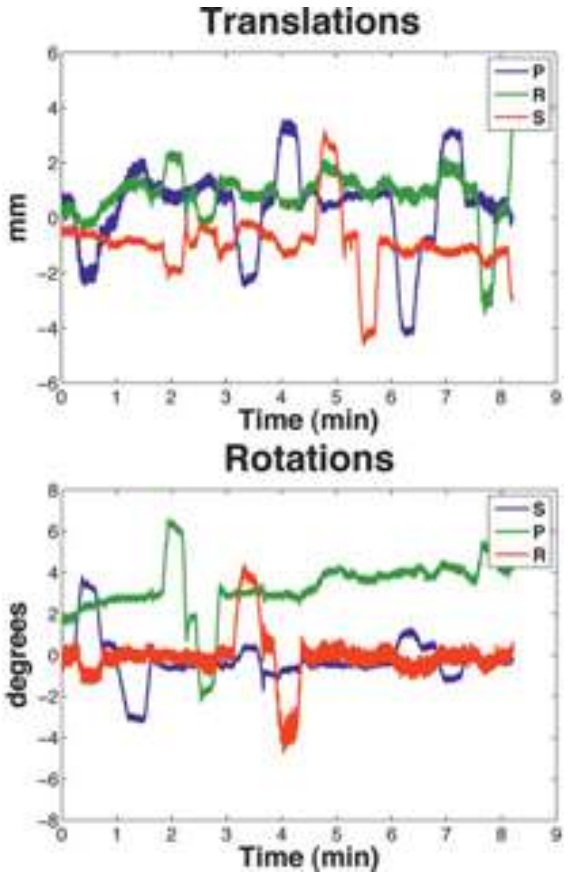
- Subject motion during the PET data acquisition can lead to image blurring or introduce artifacts.
- **MR-assisted motion correction**
  - **Approach:**
    - Acquire MR data repeatedly during the emission scan.
    - Generate motion log file.
    - Correct on an event-by-event basis before image reconstruction
  - **Advantage:**
    - Avoids mismatches between the transmission and emission data.
    - More accurate than optical tracking approaches.

# Motion Correction

No motion correction

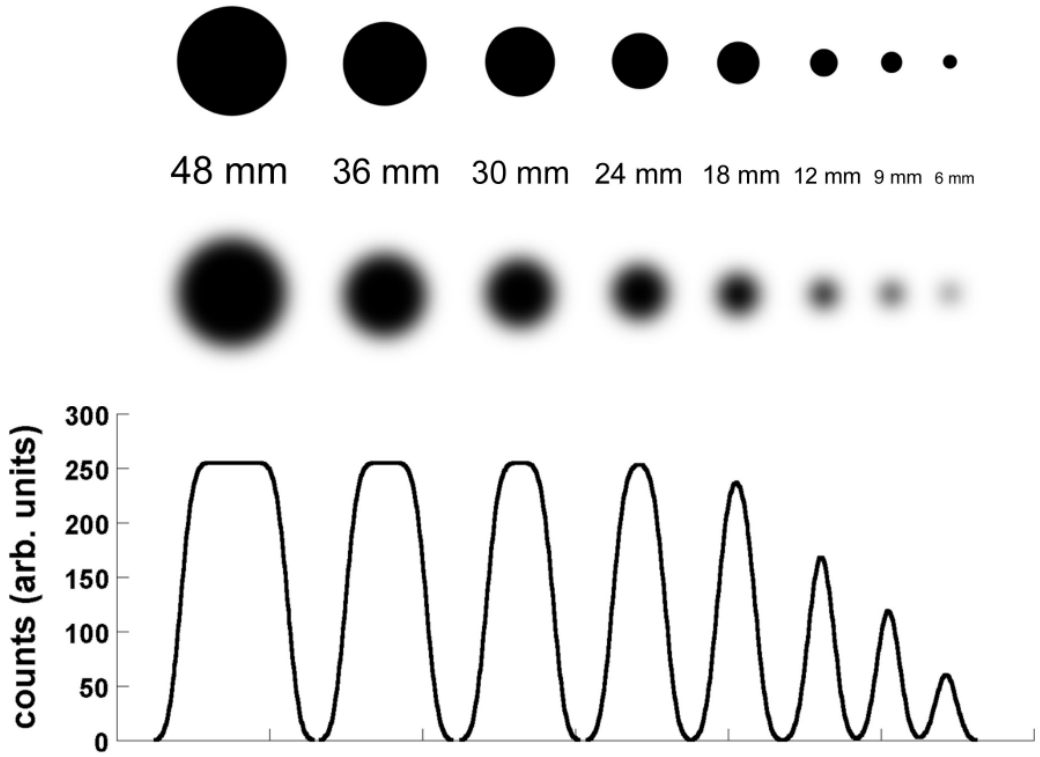
With motion correction






Andre J.W. van der Kouwe et al, Magnetic Resonance in Medicine 2006; 56: 1019-1032

# Partial Volume Effects



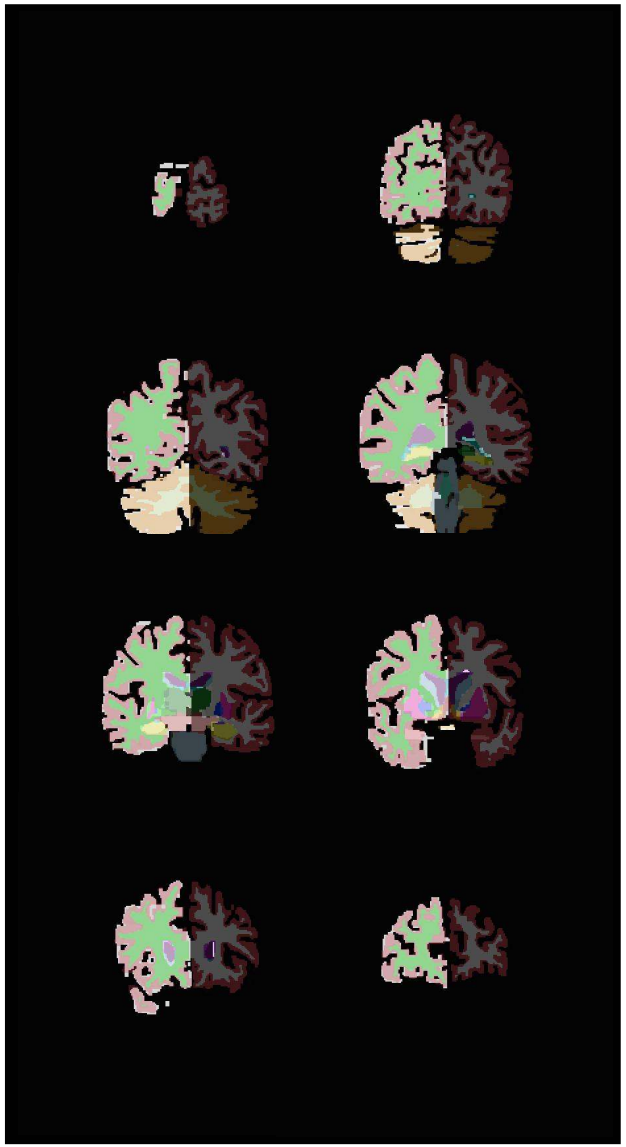

Camera FWHM = 12 mm

(Cherry SR, Sorenson JA, Phelps ME. *Physics in Nuclear Medicine*, 3rd ed.)

- Caused by the limited spatial resolution.
- Under- or overestimation of the tissue activity concentration
- To correct we need to know:
  - Size of the object
  - Reconstructed image resolution

# Partial Volume Effects

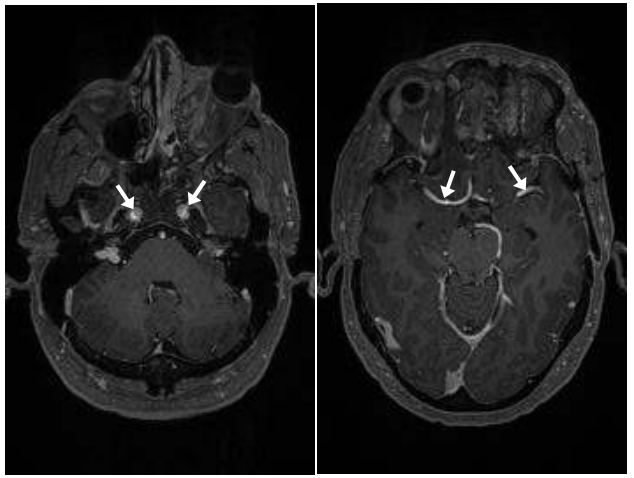
- **MR-based partial volume correction:**
  - Excellent soft tissue contrast.
  - Different segmentation task (i.e. white and gray matter, cerebrospinal fluid).
  - Combined MR-PET scanner:
    - Extremely accurate co-registration of the two data sets.

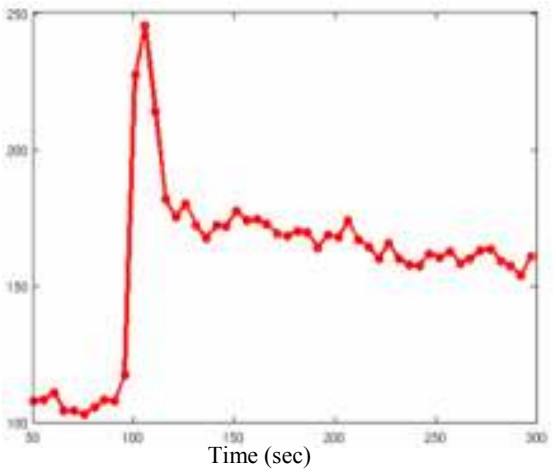


(Images courtesy of Andre J.W. van der Kouwe and Bruce Fischl, MGH)

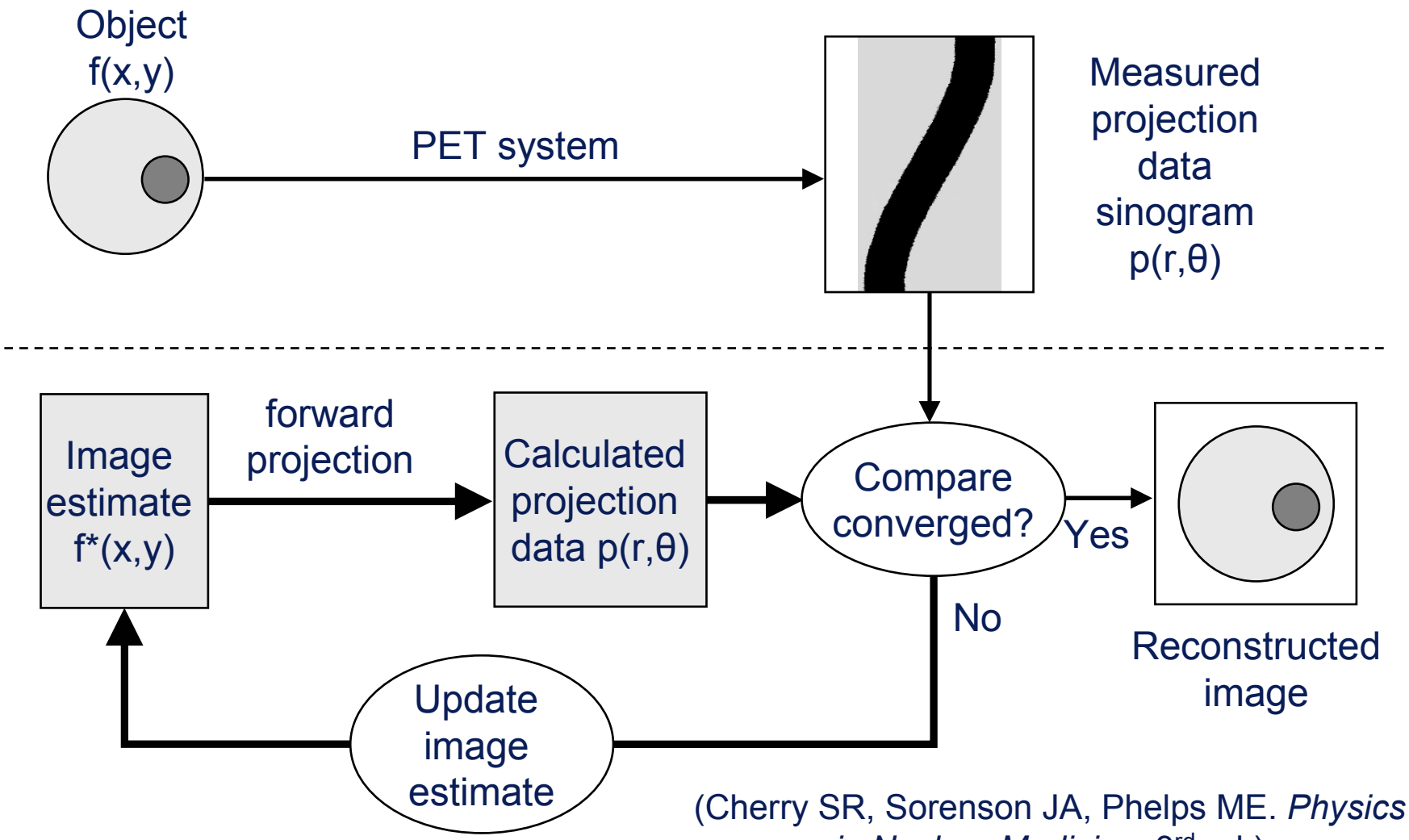
# Arterial Input Function Estimation

- PET data quantification:
  - Dynamic PET data acquisition.
  - Tracer compartment model.
  - Arterial input function (AIF).
    - "Gold standard" - arterial blood sampling.
- **MR-assisted AIF estimation:**
  - **Approach:**
    - Manually/automatically define a ROI across the vessel.
    - Obtain an average value for all the voxels in the ROI.
    - Correct for confounding effects (partial volume and spillover).
    - Regional CBF information.
  - **Advantages:**
    - Minimally invasive.
    - Regional vs global estimate.





# PET Iterative Reconstruction



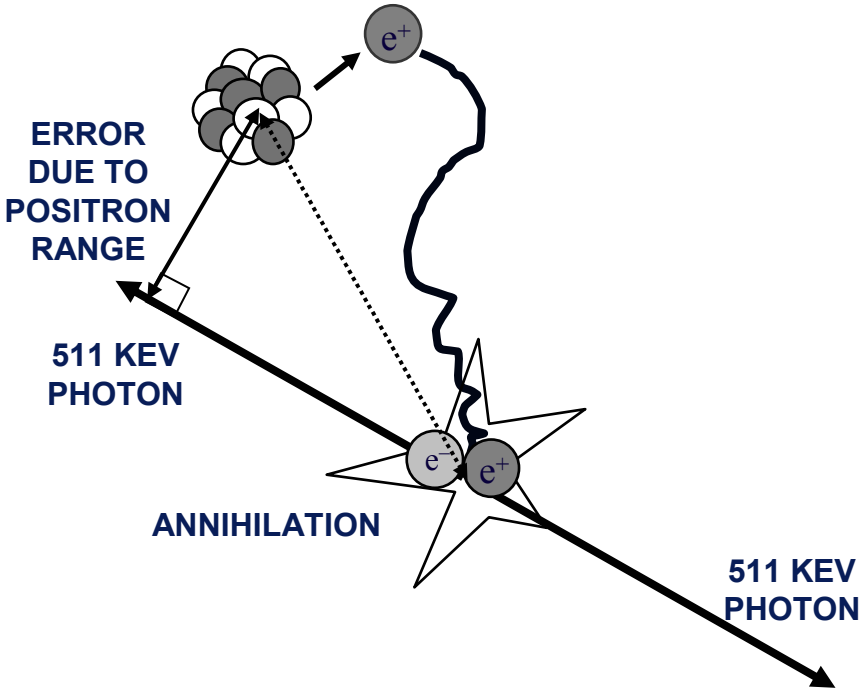

(Cherry SR, Sorenson JA, Phelps ME. *Physics in Nuclear Medicine*, 3rd ed.)

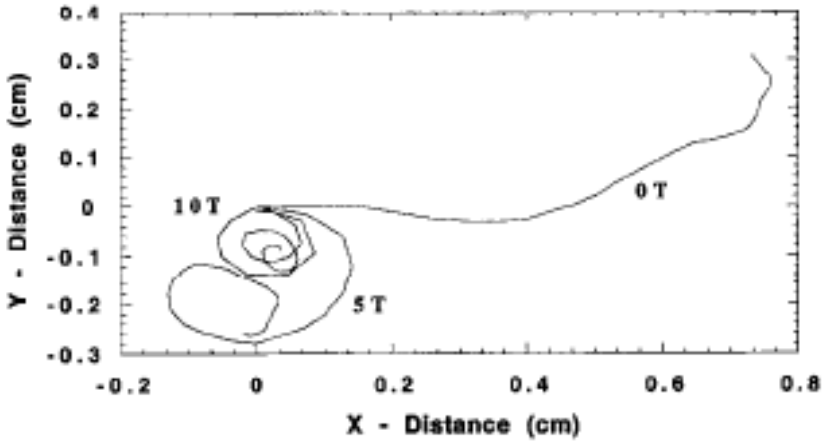
# Spatial Resolution – Positron Range

$$\vec{F}_{Lor} = q\vec{V} \times \vec{B}$$

$$R = \frac{0.334}{B}\sqrt{(2m_p E_t) + E_t^2}$$

V – positron velocity (vector)
B – magnetic field (vector)
q – particle charge
"x" – cross product operation
$E_t$ – component of the positron kinetic energy (MeV) perpendicular to the magnetic field
$m_p$ – rest mass of the positron




Representative paths in tissue of a 2 MeV electron (Raylman et al, Int. J. Radiation Oncology Biol. Phys 1997; 37, 5)

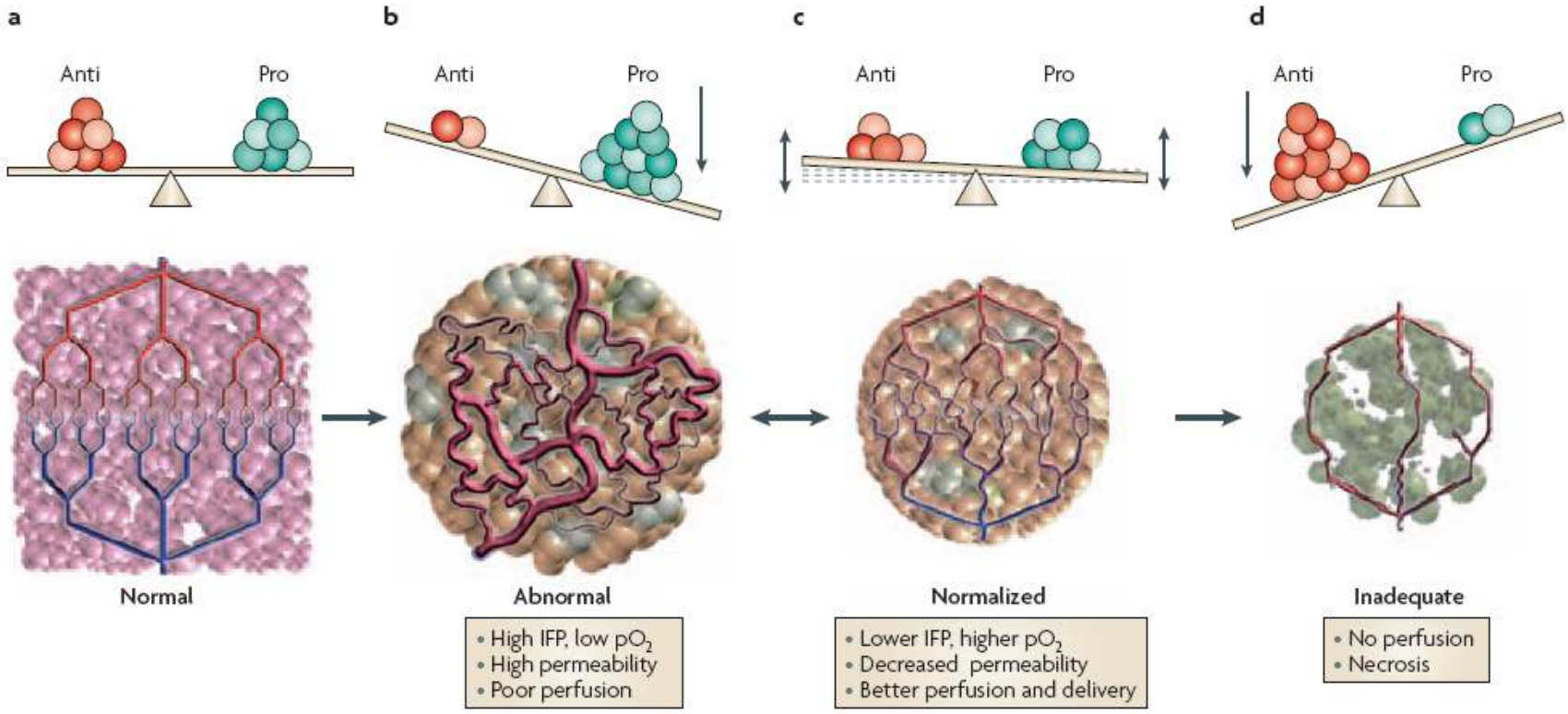
# Combined MR/PET – Neurological Perspective

- Brain Tumors – Glioblastoma Multiforme
- Dementias – Alzheimer's Disease
- Cerebrovascular Diseases – Ischemic Stroke
- …

# Glioblastoma Multiforme

- 40% of all primary malignant brain tumors.
- 13,000 persons/year in US.
- Average survival less than 1 year, <4% of patients survive 5 years or more.
- Standard initial therapy:
  - Maximal surgical resection;
  - Combined daily tomozolomide and radiation;
  - 6 monthly cycles of temozolomide.
- Pathological features:
  - Loss of BBB integrity;
  - Severe hypoxia with tumor necrosis;
  - Marked angiogenesis with microvascular proliferation.

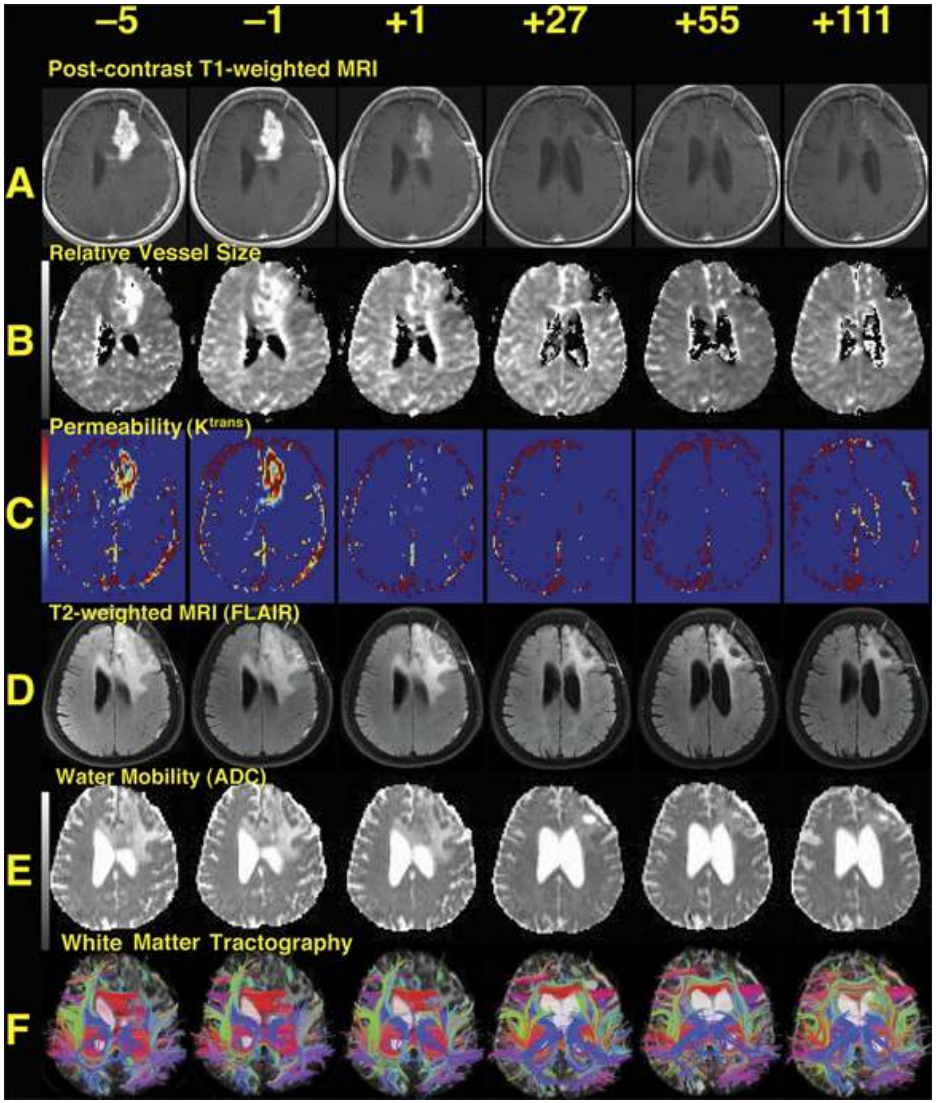
# Anti-angiogenic Therapy

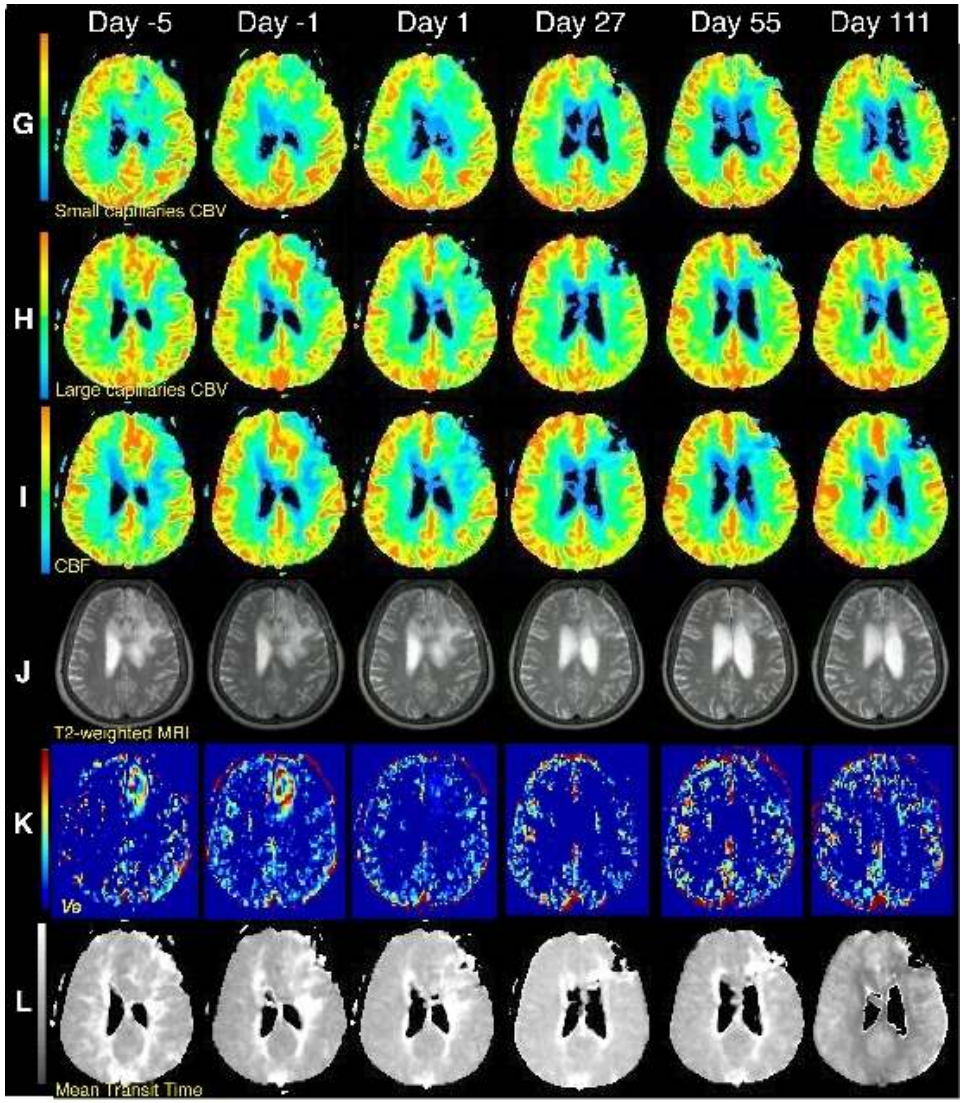



## Vascular Normalization Concept

(R.K. Jian et al; *Nature Reviews Neuroscience*, 2007, 8: 610-622)

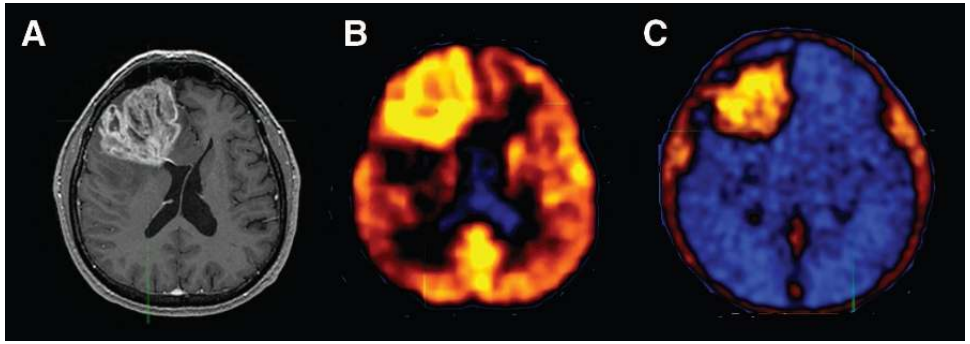
# Glioblastoma Multiforme – MRI



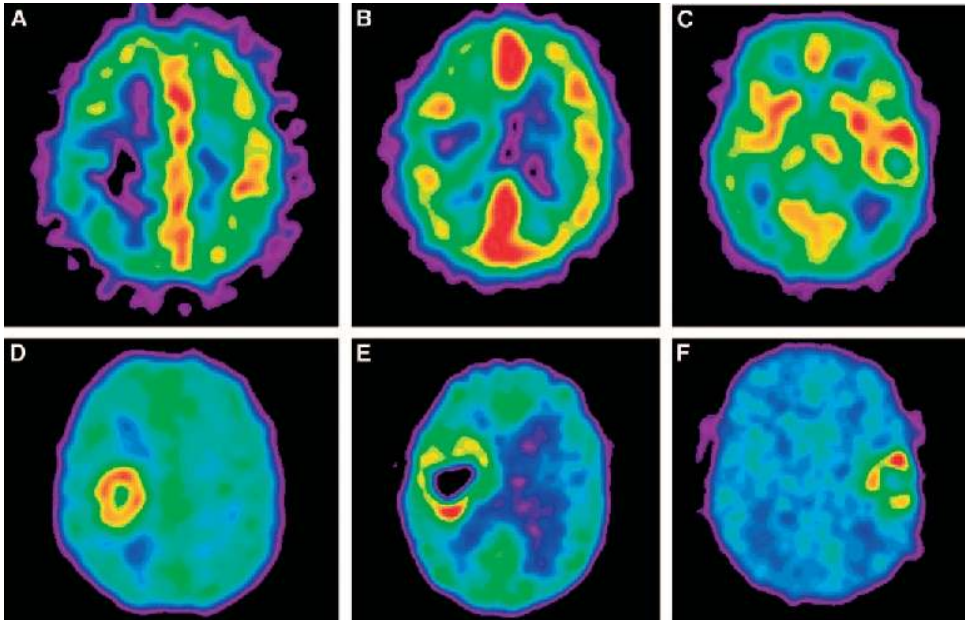

T.T. Batchelor, A.G. Sorensen et al; *Cancer Cell*, 2007, 11: 83-95

# Glioblastoma Multiforme – PET




(A) MRI (contrast-enhanced T1-weighted image), (B) $^{18}$F-FDG PET, (C) $^{18}$F-FLT PET

Chen et al, *J Nucl Med* 2005; 46:945-952




(A-C) $^{15}$O-$H_2O$ perfusion imaging

(D-F) $^{18}$F-FMISO hypoxia imaging

M Bruehlmeier et al; *J Nucl Med* 2004; 45:1851-1859

# Glioblastoma Multiforme – MR-PET

- Vascular permeability
- Blood volume
- Blood flow
- Mean transit time

} **MRI**

Anti-permeability or anti-tumor effects?

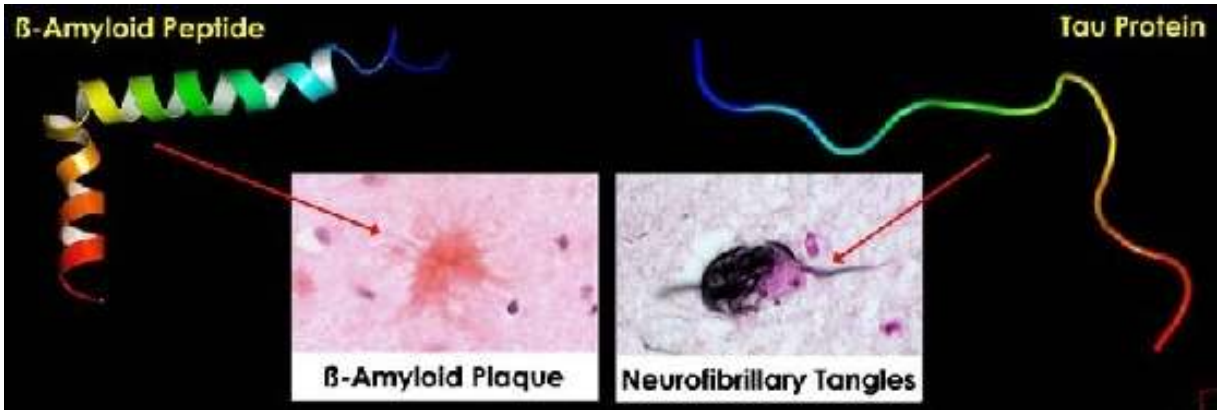
- Metabolism
- Proliferation
- Hypoxia

} **PET**

*Ideally: minimally invasive, quantitative, reproducible.*

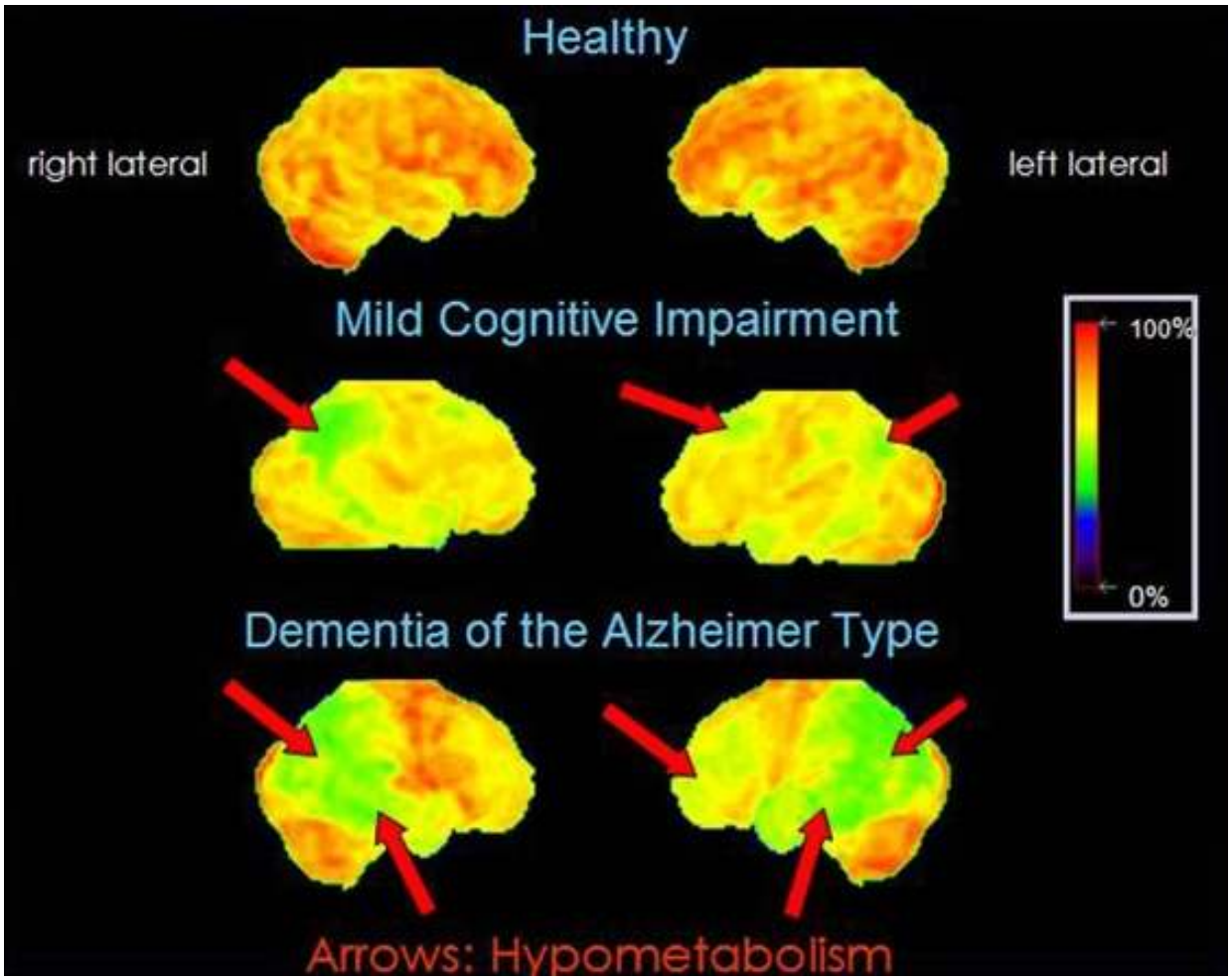
# Alzheimer's Disease

- 60-70% of all dementias.
- 4.5 million people in US (14 million by 2050).
- The cost for care ~$100 billion/year in US.
- Pathological features:
  - β-amyloid plaques
  - neurofibrillary tangles (NFTs)
- Current treatment – symptomatic.




J Reichert et al; *Nucleic Acids Res.* 2002; 30: 253-4; A. Drzezga et al; *Eur J Nucl Med Mol Imaging* 2008; 35 Suppl.1: S4-S11

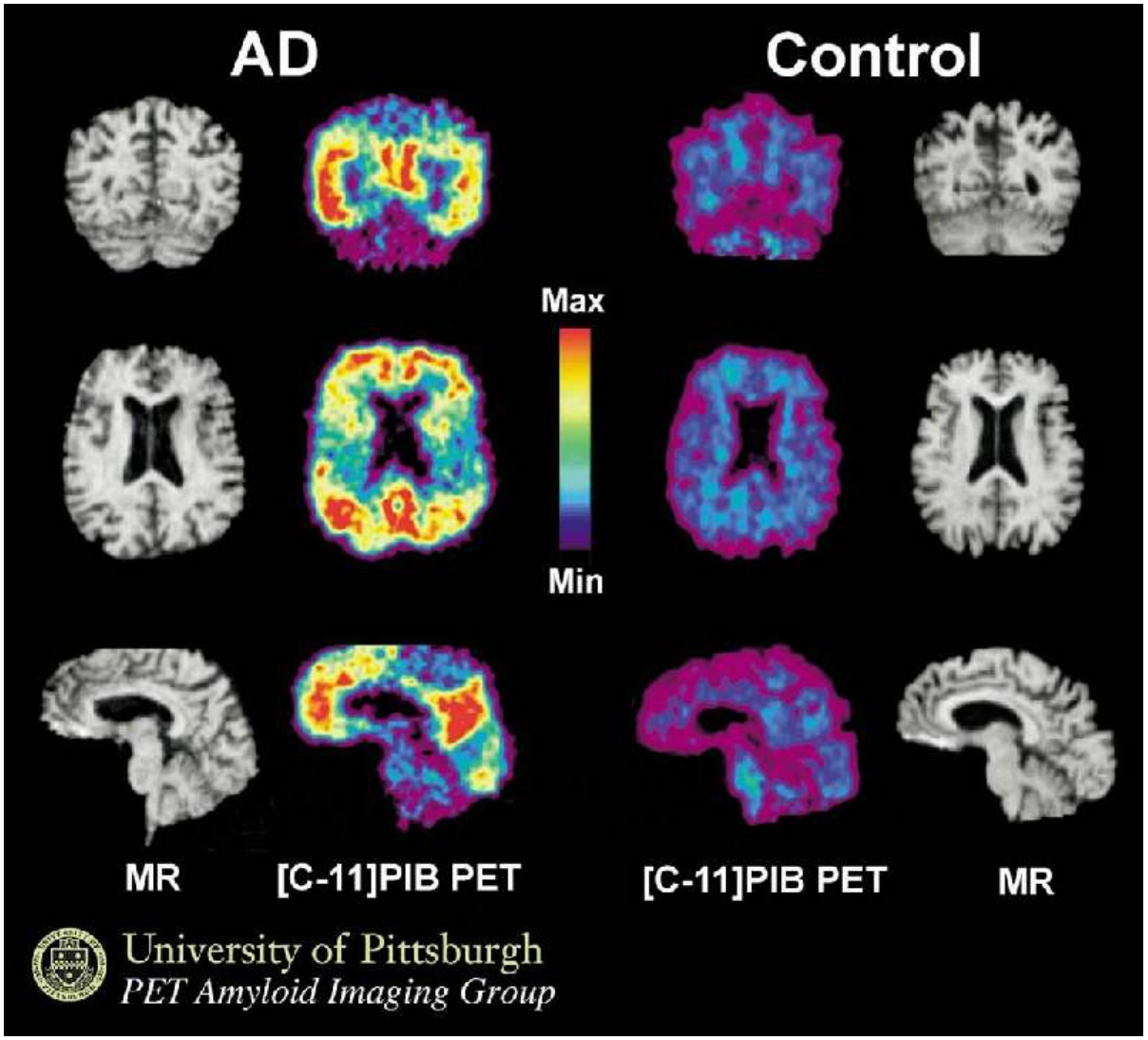
# Alzheimer's Disease – PET




$^{18}$F-FDG PET (glucose metabolism)

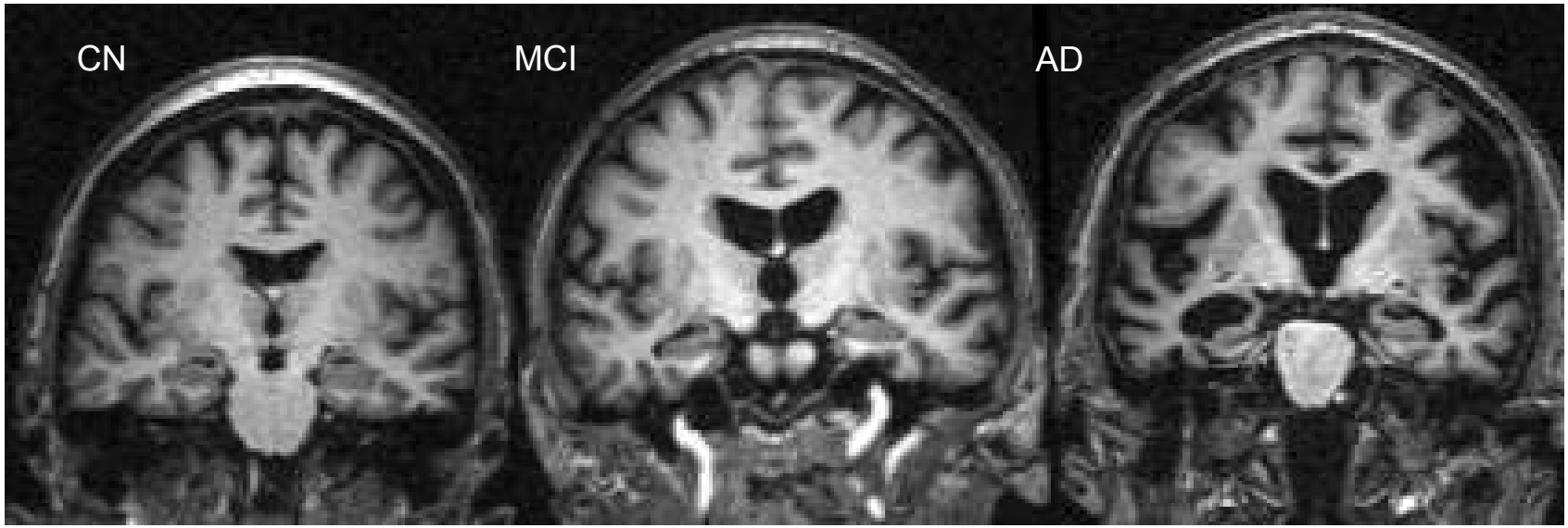
A. Drzezga; *Methods* 2008; 44: 304-314

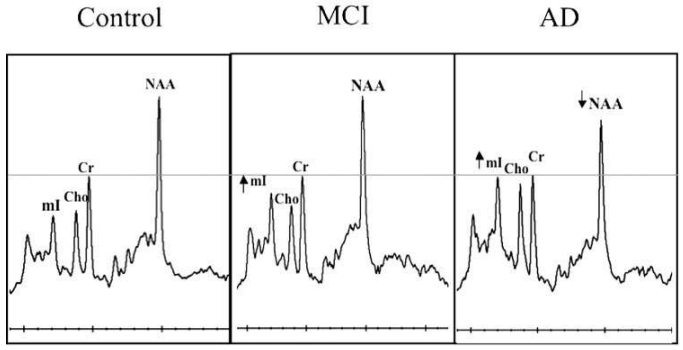
# AIzheimer's Disease – PET

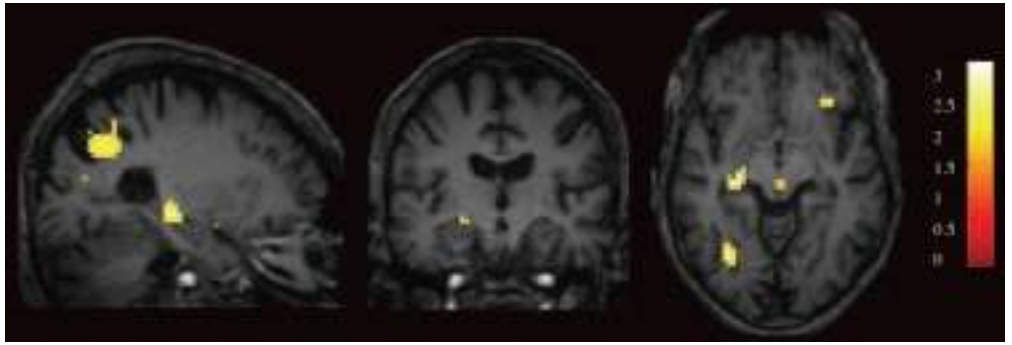



$^{11}$C-PIB PET (amyloid deposition)

# Alzheimer's Disease – MRI



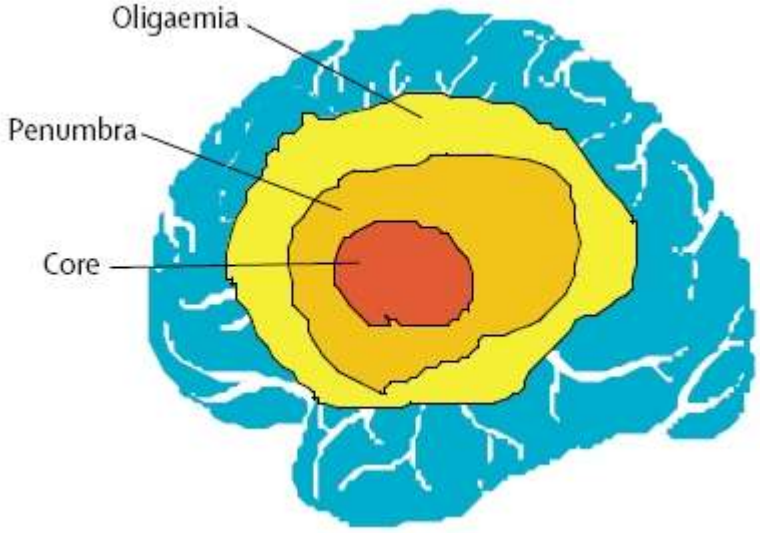
BC Dickerson and RA Sperling; *NeuroRx: J Am Soc Exp NeuroTherap* 2005; 2, 248-360

# Alzheimer's Disease – MR-PET

- Advantages:
  - Complementary information about brain anatomy, chemistry, physiology and pathology in a single imaging session.
  - Improved PET data quantitation (i.e. PVC, AIF estimation, motion correction).
- Potential applications:
  - Early diagnosis.
  - Patient stratification.
  - Assess the efficiency of disease modifying therapies (e.g. anti-amyloid agents).

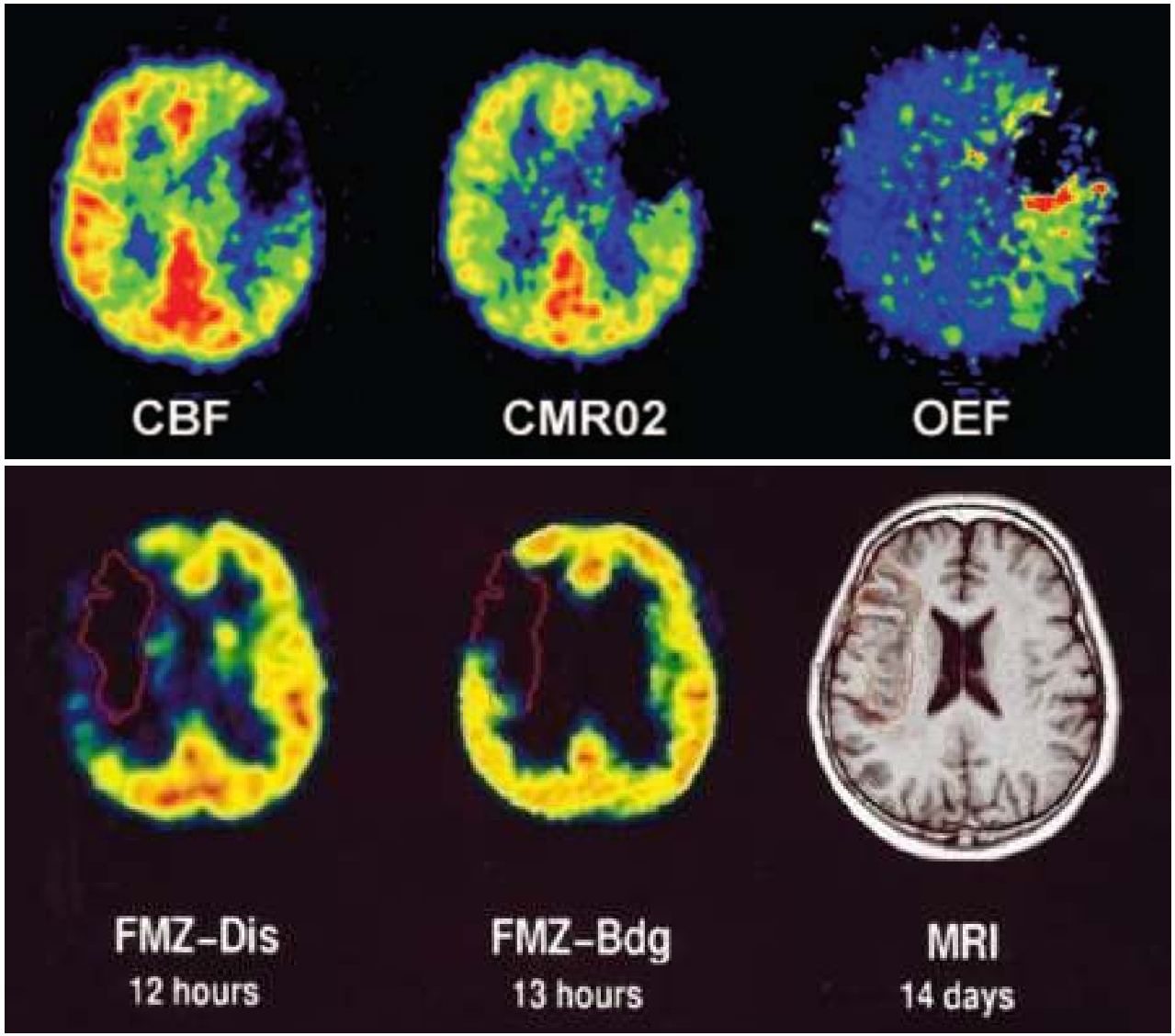
# Ischemic Stroke

- Stroke is the third leading cause of death in US (160,000) and first cause of adult disability;
- 85% of the 780,000 cases/year are ischemic.
- Three tissue compartments have been identified:
  - Core (irreversibly damaged tissue)
  - Penumbra (hypoperfused, at risk tissue)
  - Oligaemia (normal/slightly reduced perfusion)




KW Muir et al; *Lancet Neurol* 2006; 5: 755-768

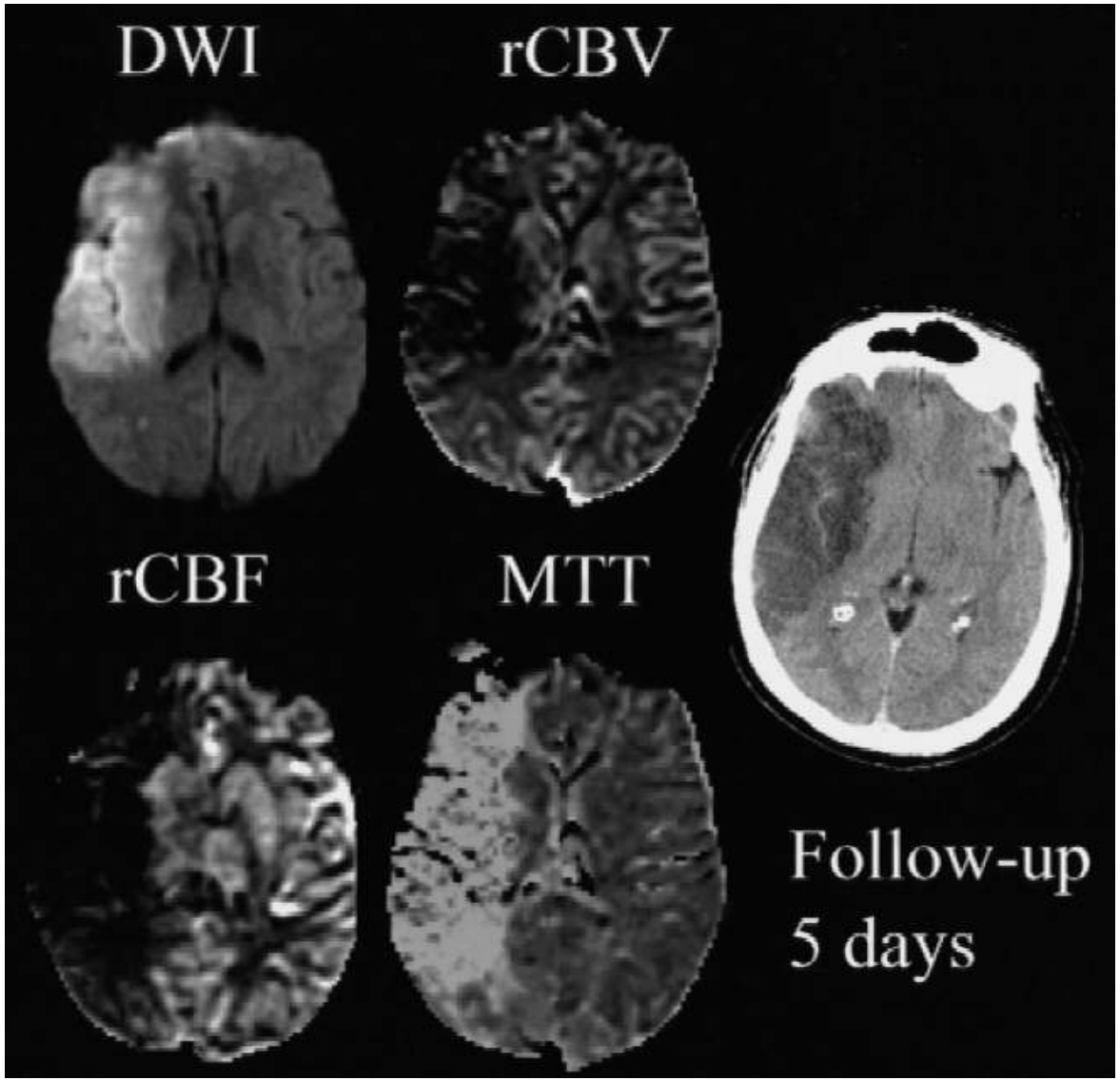
# Ischemic Stroke – PET




Sobesky et al; *Stroke* 2005; 36: 980-985

WD Heiss et al; *Stroke* 1998; 29: 454-461

# Ischemic Stroke – MRI

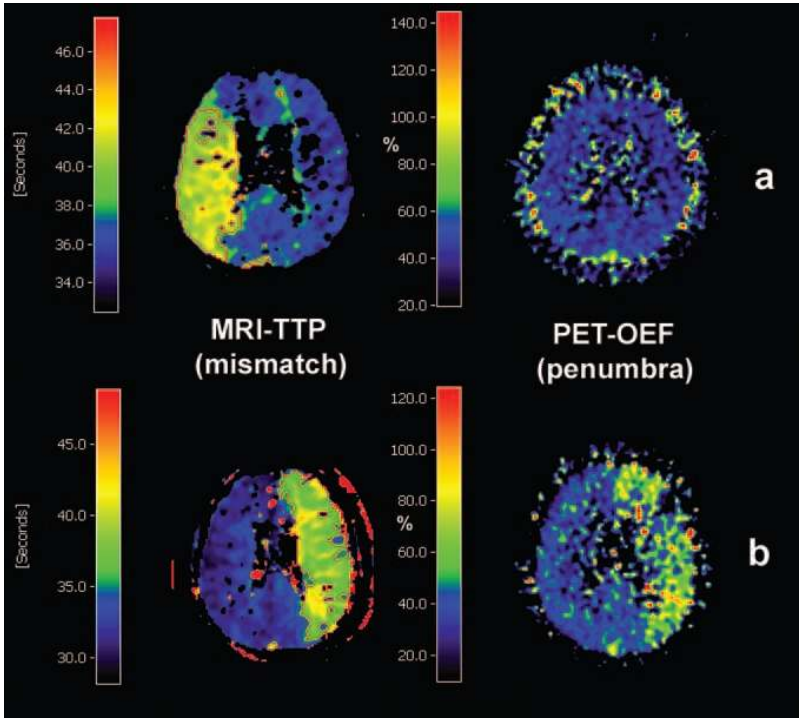



Perfusion-diffusion mismatch concept

Y Ozsunar and AG Sorensen et al; Topics in MRI 2000; 11(5): 259-272

# Ischemic Stroke – MR-PET

- Advantages:
  - Simultaneous measurements
- Potential applications:
  - Calibrate MRI on PET
    - Penumbra vs PWI-DWI mismatch
  - Better selection of patients that could benefit from thrombolytic therapy beyond 3 hours.
  - Follow-up.




Sobesky et al; *Stroke* 2005; 36: 980-985

# Conclusions

- MR compatible PET inserts were built and initial imaging tests were performed.
- *In vivo* simultaneous studies were successfully performed.

- The opportunities for PET/MRI are wide open.
- Existing neurological applications might benefit from this new technology.
- New molecular imaging applications will almost certainly emerge.

# New Technologies

"New directions in science are launched by new tools much more often than by new concepts.

The effect of a concept-driven revolution is to explain old things in new ways.

The effect of a tool-driven revolution is to discover new things that have to be explained."

**Freeman Dyson, Imagined Worlds**

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- **Siemens MRI**
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- **NCRR**