15th Topical Seminar on Innovative Particle and Radiation Detectors

IPRD19 – Siena (Italy)

14-17 October 2019

Positron Emission Tomography: alive and kicking after more than after 65 years on stage

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Contents

- A bit of history
- Molecular Imaging
- Preclinical Systems
- Hybrid Systems (PET-MR)
- Clinical Systems
- Conclusions
- Acknowledgments

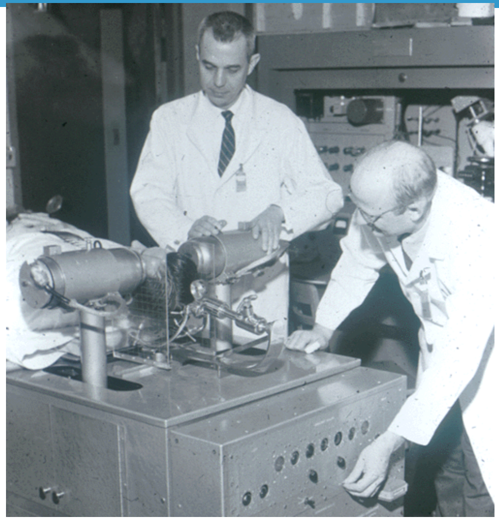
A bit of history

«Once Upon a Time….»

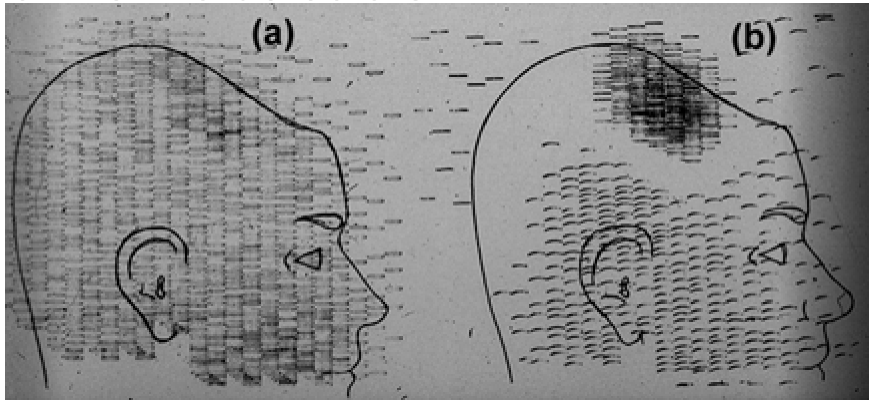
The first idea of PET (talk at MGH by William Sweet, May 16,1951

First Clinical Positron Imaging Device

1953 - This instrument followed the general concepts of the instrument built in 1951 but included many refinements. It produced both a coincidence scan as well as an unbalance scan. The unbalance of the two detectors was used to create an unbalance image using two symbols to record any unbalance in the single channel rates of the two detectors.



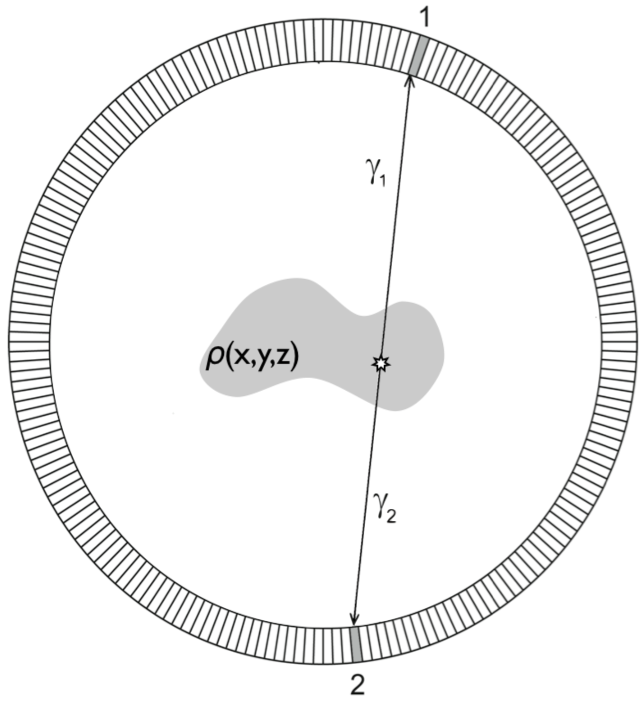
Dr. Brownell (left) and Dr.Aronow are shown with the scanner (1953).



Coincidence and unbalance scans of patient with recurring brain tumor. Coincidence scan (a) of a patient showing recurrence of tumor under previous operation site, and unbalance scan (b) showing asymmetry to the left. (Reproduced from Brownell and Sweet 1953).

A.Del Guerra et al., Rivista Nuovo Cimento [2016, Vol. 39(4), pp.155-223]

A learning paradigm: PET and its application



- RADIOISOTOPE decays, emitting β^{+}.

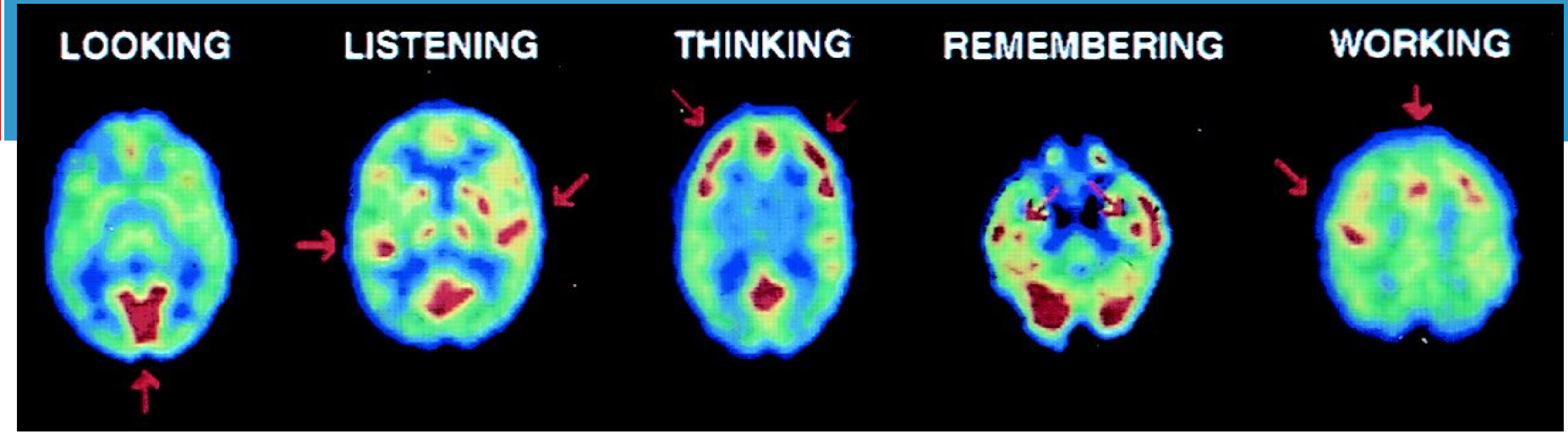
^{18}F	2 hour half-life
^{15}O, ^{11}C, ^{13}N	2–20 minute half-life

- β^{+} annihilates with e^{-} from tissue, forming back-to-back 511 keV photon pair.
- 511 keV photon pairs detected via time coincidence.
- Positron lies on line defined by detector pair (Line of FLIGHT =LOF ➔ LOR).
- The LOFs are collected by surrounding the object with a "ring" of detectors.

The activity distribution ρ(x,y,z) is measured in terms of projections ($N_{\gamma\text{-}\gamma}$) along lines L.
Each projection is obtained from the activity distribution with the line integral operator:

$$N_{\gamma-\gamma} = k\int_L \rho(x,y,z)\,dl$$

The first images in neurology (UCLA- Mike Phelps and Ed Hoffman) [late '70]



PET studies of glucose metabolism to map human brain's response in performing different tasks. Subjects looking at a visual scene activated visual cortex (arrow), listening to a mystery story with language and music activated left and right auditory cortices (arrows), counting backwards from 100 by sevens activated frontal cortex (arrows), recalling previously learned objects activated hippocampus bilaterally (arrows), and touching thumb to fingers of right hand activated left motor cortex and supplementary motor system (arrows). Images are cross-sections with front of brain at top. Highest metabolic rates are in red, with lower values from yellow to blue.

A.Del Guerra et al., Rivista Nuovo Cimento [2016, Vol. 39(4), pp.155-223

PET→Molecular Imaging

A visual ***representation, characterization, and quantification*** *of biological processes at the cellular and subcellular levels within intact living organisms."*

Sanjiv S.Gambhir

The main performance parameters of a PET scanner

- **Sensitivity**
- **Spatial resolution**
- **Time resolution**
- **Reconstruction Algorithm**
- **Correction and Quantitation**
- **Specificity of the radiotracer**

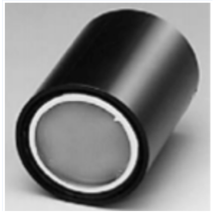
The evolution of the *Scintillators*
(sensitivity and time resolution)

	NaI	BGO	GSO	LSO	LYSO	LGSO	LuAP	YAP	$LaBr_3$
Light yield 10^3 ph/MeV	38	9	8	30	32	16	12	17	60
Primary decay time	250	300	60	40	41	65	18	30	16
ΔE/E (%) at 662 keV	6	10	8	10	10	9	15	4.4	3
Density (g/cm^3)	3.67	7.13	6.71	7.35	7.19	6.5	8.34	5.5	5.08
Effective Z_{eff}	50	73	58	65	64	59	65	33	46
1/μ @ 511 keV (mm)	25.9	11.2	15.0	12.3	12.6	14.3	11.0	21.3	22.3
PE (%) at 511 keV	18	44	26	34	33	28	32	4.4	14

[A.Del Guerra et al., Rivista Nuovo Cimento [2016, Vol. 39(4), pp.155-223]

The evolution of the *Photodetectors*
(spatial and time resolution)

- **PhotoMulTiplier (PMT)**
- **Position Sensitive PhotoMulTiplier (PSPMT)**



- Round 2” (e.g. R2486)

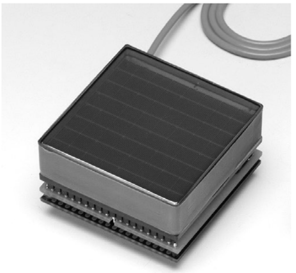
(proximity mesh dynodes and crossed wire anode)

- Square 1” (e.g. R7600-C8, R5900-C12)

(metal channel dynodes and crossed plate anode)

- Square 2” – Flat panel (e.g. H8500)

(metal channel dynodes and multi-anode)



- **Solid State Detectors (SSD)**

- Avalanche Photo-Diode (APD and PSAPD)

- Silicon Photo-MultiPlier (SiPM)

- Analog SiPM

- Digital SiPM

The evolution Time of flight PET: TOFPET (time resolution)

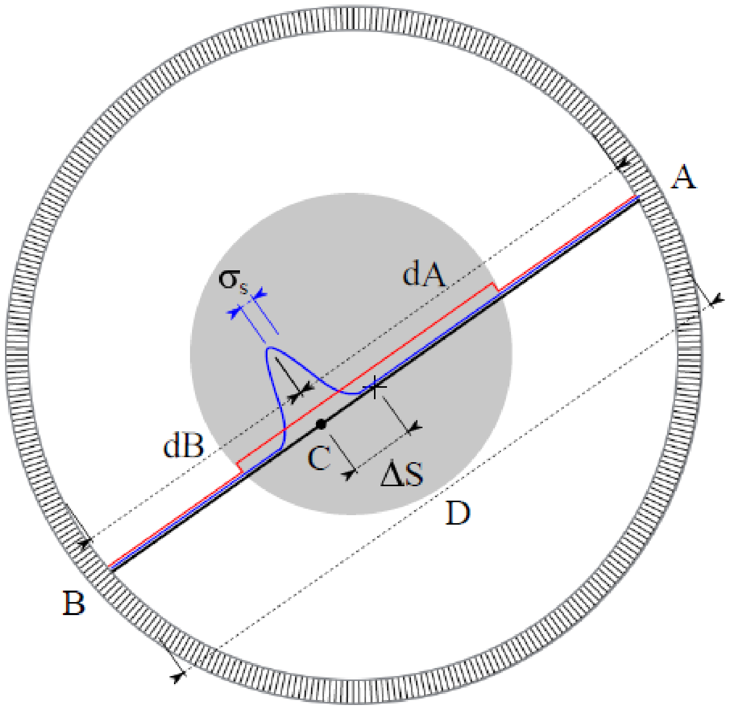


Figure 18.: The Time-of-Flight PET concept. The displacement of the annihilation point along the LOR (ΔS) is obtained by measuring the difference in arrival time ΔT (see text). Blue and red lines show how data are distributed along the LOR during the retroprojection step. Non-TOF data (red) are uniformily distributed along the LOR while TOF-data are distributed around the emission point thus increasing SNR in the reconstructed image.

[A.Del Guerra et al., Rivista Nuovo Cimento [2016, Vol. 39(4), pp.155-223]

The evolution of the *algorithms*

Analytical Methods

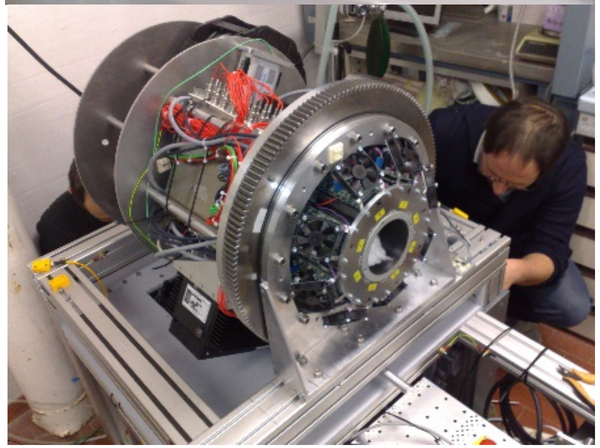
- **2-D: Filtered Back-Projection (FBP) [Shepp and Logan, 1974]**
  1. Unidimensional Fourier transform of each projection
  2. Filtering each projection in the unidimensional Fourier space by multiplying by the frequency filter (|ν| ,i.e.,Ram-Lak; Hamming; Shepp-Logan)
  3. Inverse unidimensional Fourier transform of each filtered projection
  4. Projecting backward the filtered projections
- **3-D: Single Slice Re-Binning (SRB);**
  Fourier Rebinning (FORE)
  3-D Filtered Back-Projection (FBP)

Iterative Methods (2D & 3D)

- **Maximum Likelihood Expectation Maximization (ML-EM) [Shepp and Vardi, 1982]**
- **Ordered Subsets Expectation Maximization (OSEM) [Hudson and Larkin, 1994]**

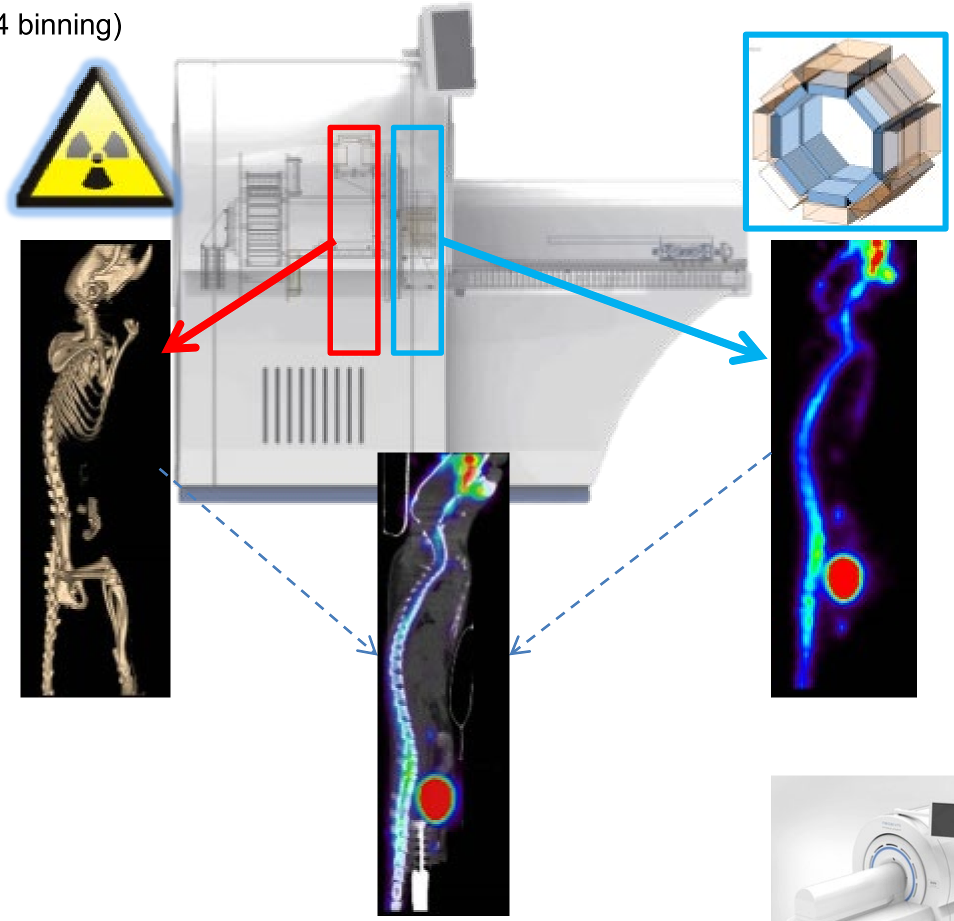
IRIS PET-CT

Laboratory of Imaging Biomarkers, CNR-IFC, Pisa, Italy



μCT
- X-ray tube: 80 kV, 80 W
- Min. scan time: 7 s
- Min. voxel size: 30 μm
- Limiting spat. res.: 74 μm (10% MTF)
- Axial FOV: 90 mm
- CMOS detector w/ max frame rate of 86 fps (4x4 binning)

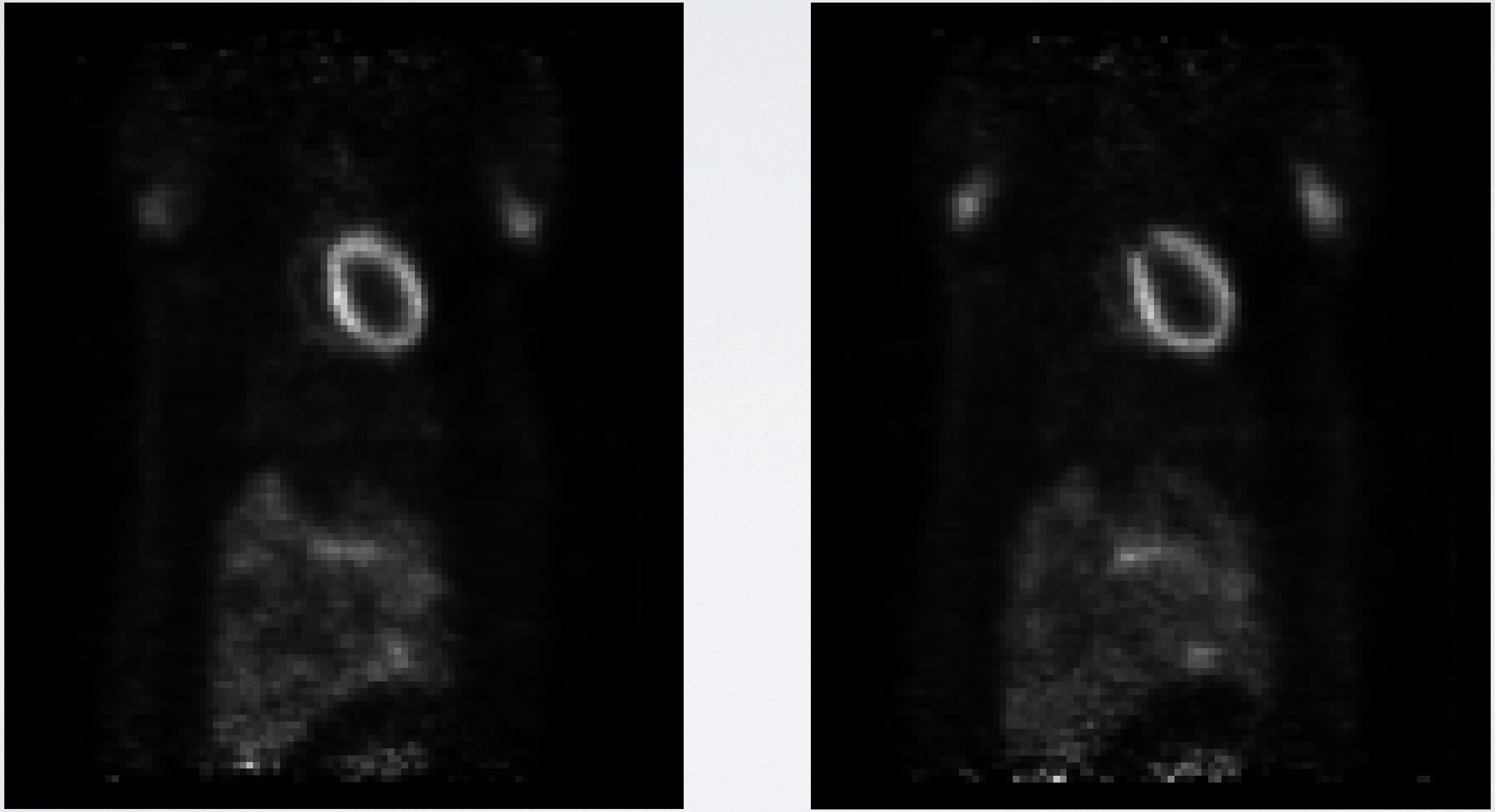
μPET
- Sensitivity = >9% [250 keV - 750 keV]
- Spatial resolution = 1.1 mm (MLEM)
- Axial FOV = 94 mm
- Transaxial FOV = 80 mm
- Energy resolution = ~13%
- Timing resolution = 1.8 ns



inviscan Imaging systems

N.Belcari et al., IEEE TRPMS, 2017, 1(4) pp.301-309

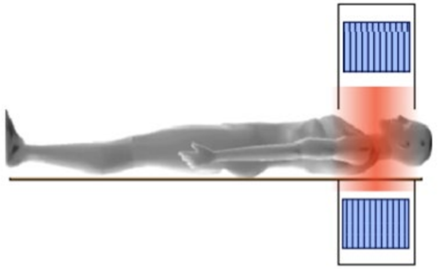
Cardiac (8 phases) and respiratory gating (binary) of a rat heart beating (18F-FDG)



Taken with IRIS PET/CT scan:Courtesy of David Brasse, CNRS, Strasbourg (2016)

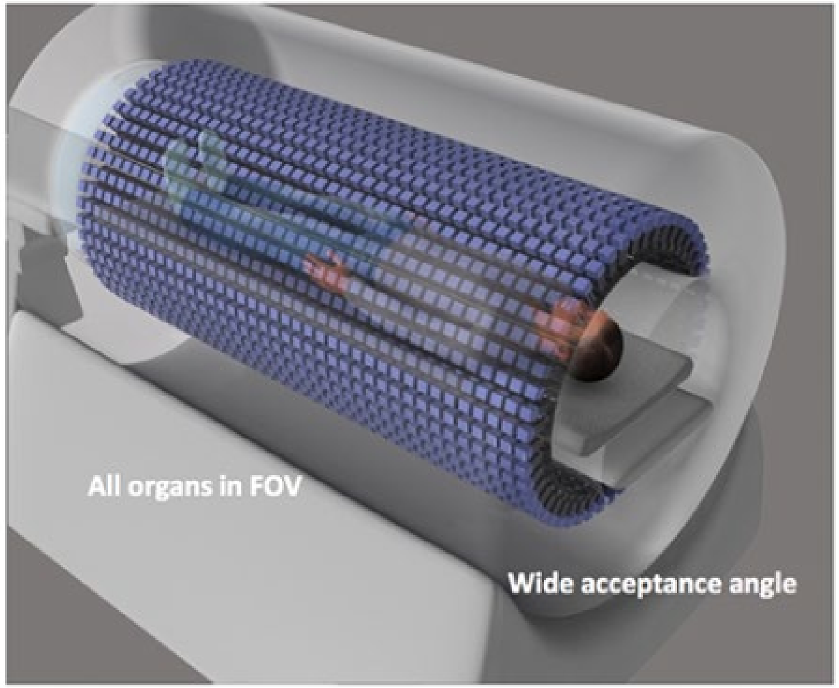
NEXT?

THE EVOLUTION OF AXIAL LENGTH :TOTAL BODY PET



Only about 1-2% of emitted signal is detected

Solution: Scanner covers the entire patient



- Superior image quality
- Shorter imaging time
- Reduced radiation dose
- Total body coverage

Cherry SR, Badawi RD, Karp JS, Moses WW, Price P, Jones T. Total-body imaging: transforming the role of positron emission tomography. Sci Transl Med. 2017;9

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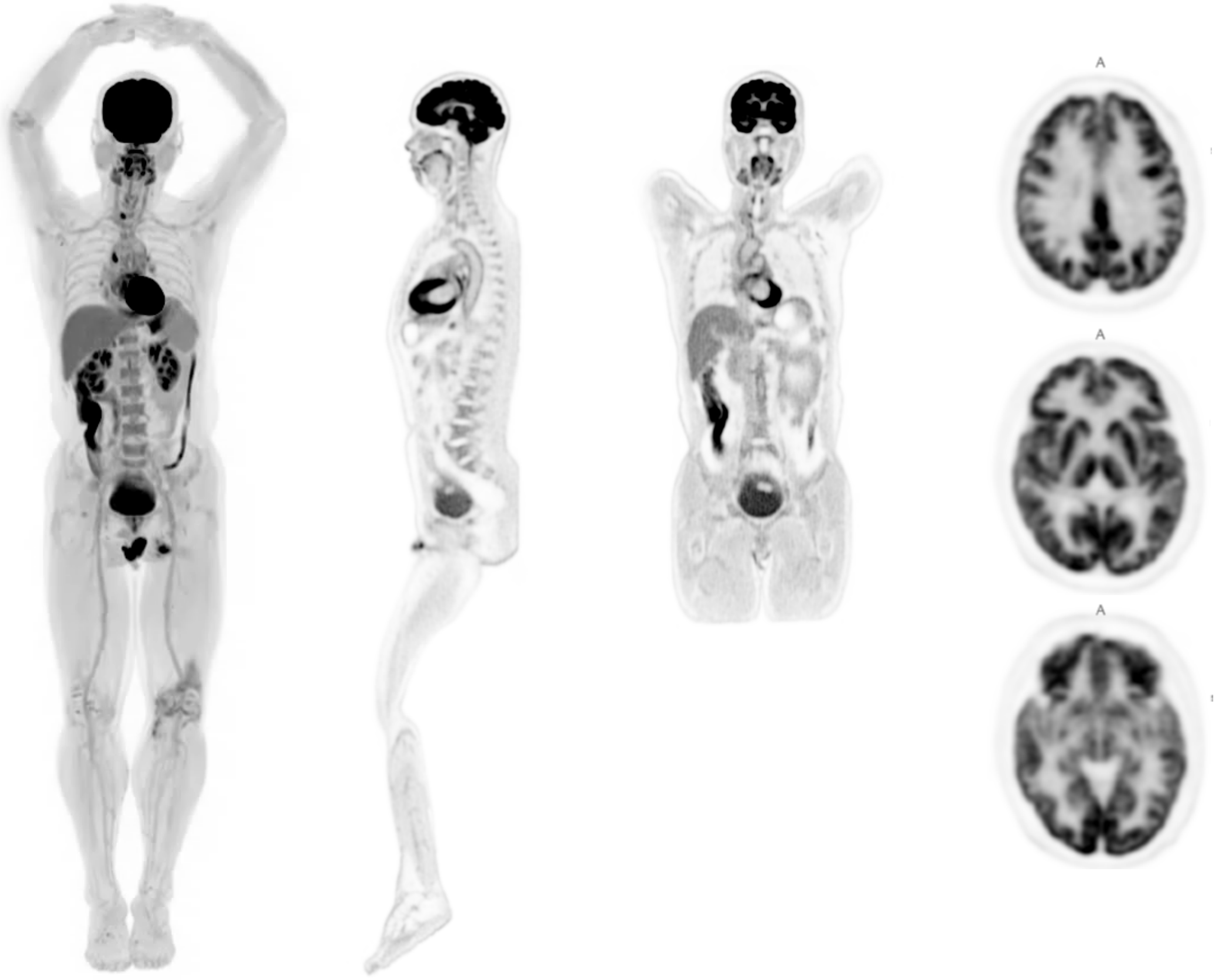
EXPLORER: First Human Images

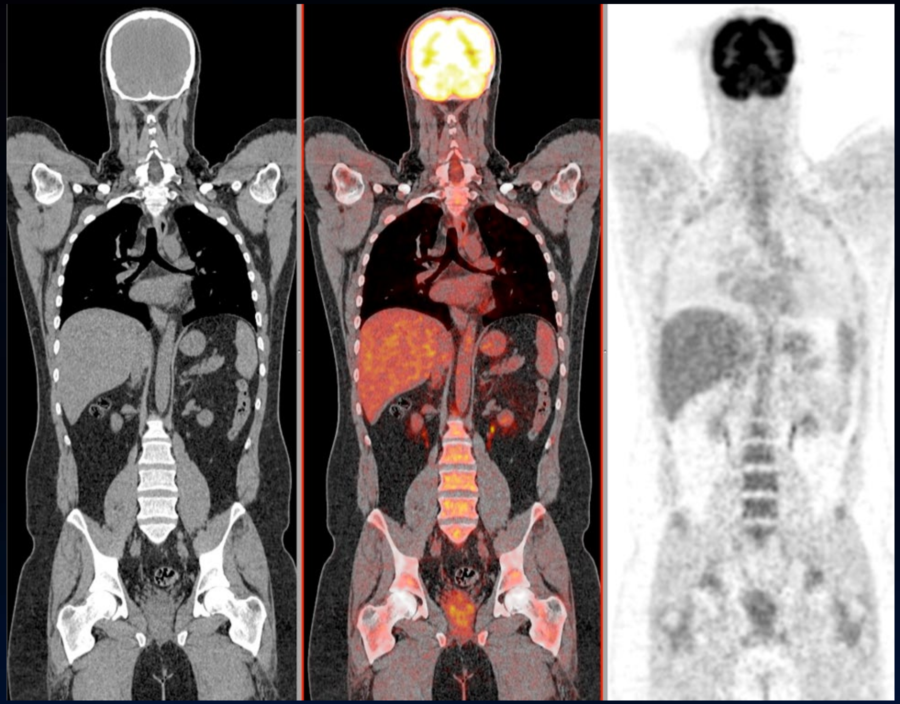


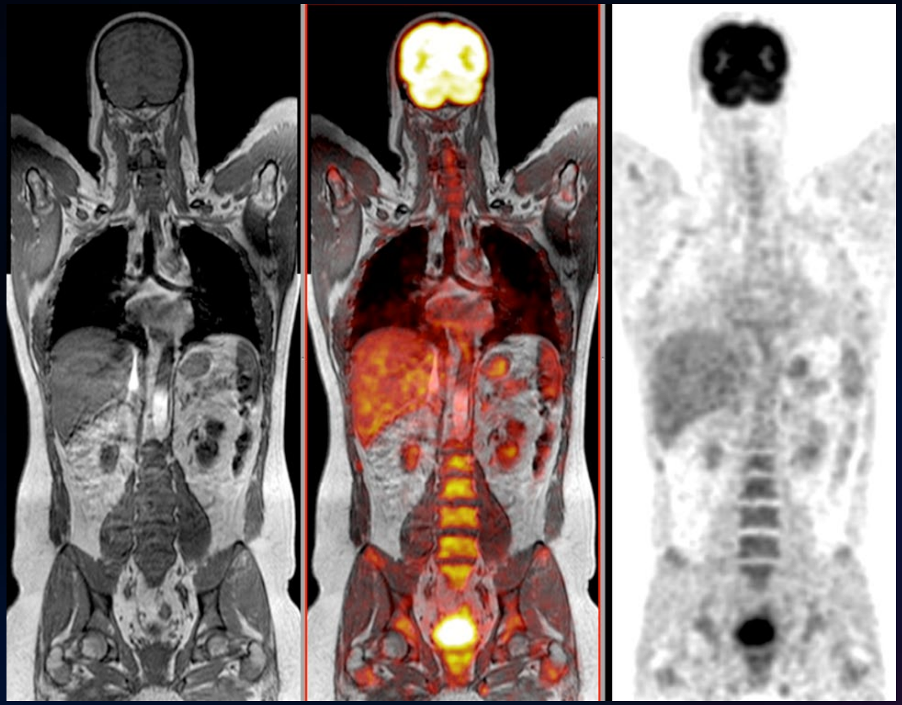
7.8 mCi FDG
65 kg subject
20 minute scan
1 bed position
90 mins post-injection
OSEM with PSF and TOF
20 subsets, 5 iterations
$1 \times 1 \times 1.425$ mm^3 voxels

Slide Courtesy of
UC Davis
United Imaging
Zhongshan Hospital

FROM PET-CT

TO PET-MR





Representative clinical PET-CT (left) and PET-MR (right) whole-body images of the same patient acquired sequentially (~60 min time difference) on two combined systems (Siemens Biograph Hirez TrueV and Philips Ingenuity TF PET-MRI, respectively) following injection of 370 MBq of 18F-FDG.

[H.Zaidi and A.Del Guerra, Medical Physics, 2011, 38(10),5667-5689]

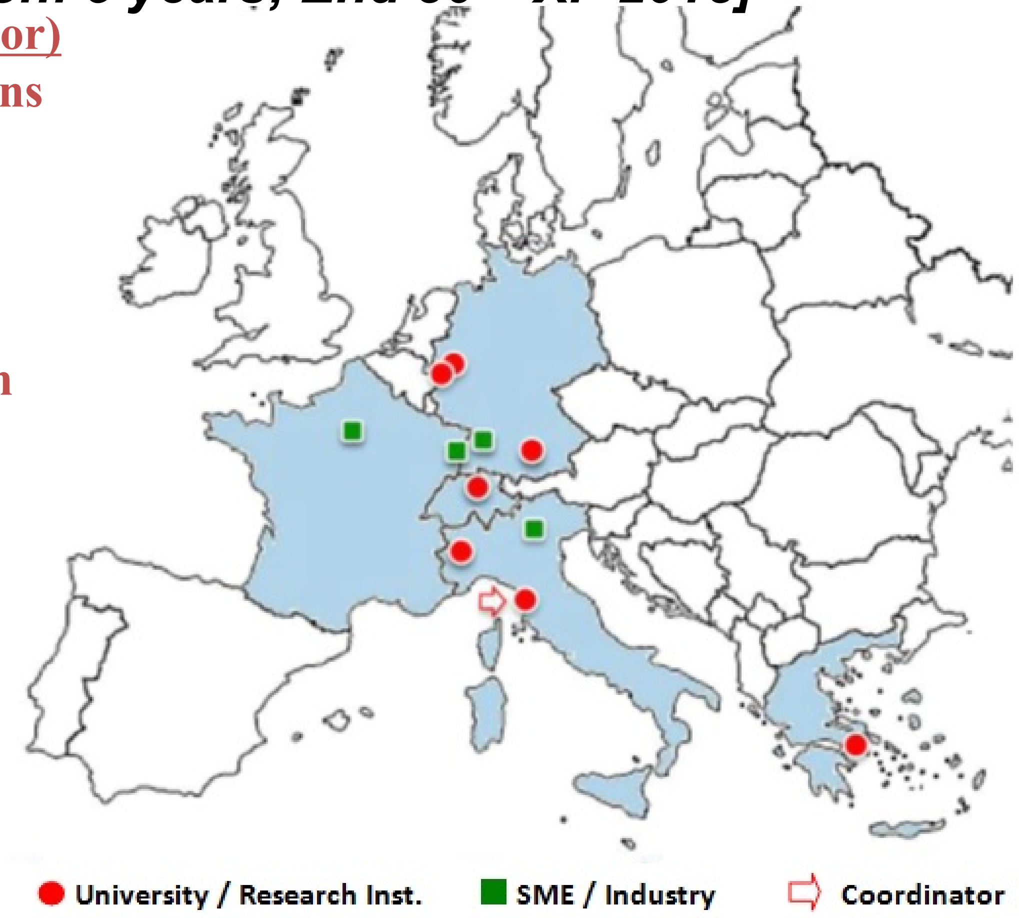
THE TRIMAGE PROJECT [11 beneficiaries]

"A dedicated trimodality (PET/MR/EEG) imaging tool for schizophrenia"

[Start: 1- XII -2013; Duration: 5 years; End 30 – XI -2018]

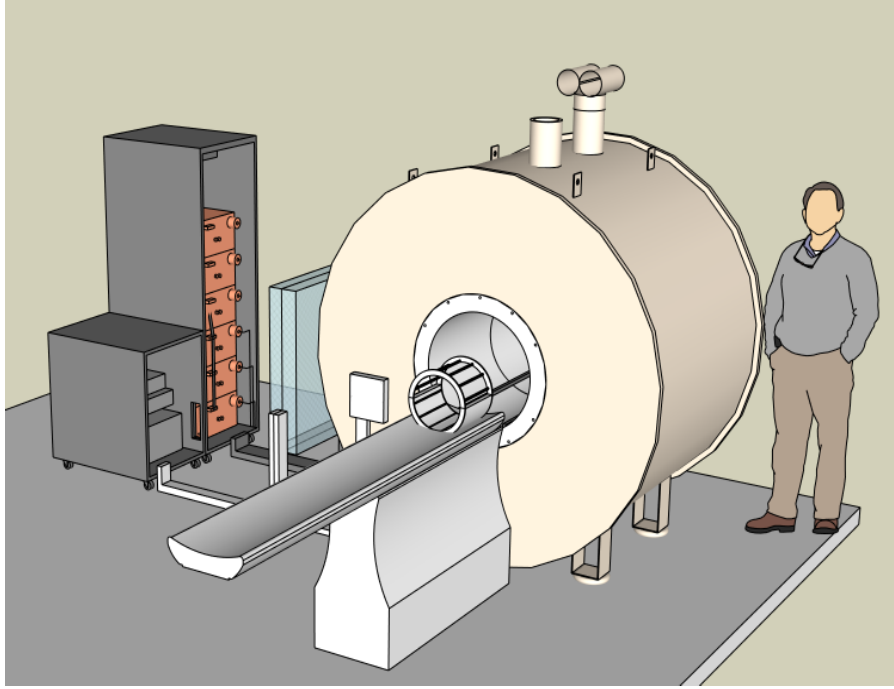
1. Dept of Physics, Pisa University (Coordinator)
2. Technological Educational Institute of Athens
3. INFN – Sez. di Torino
4. Technische Universitat Munich
5. Forschungszentrum Juelich GmbH
6. JARA BRAIN, Dept of Psychiatry, Psychotherapy and Psychosomatics, Aachen
7. Dept. of General and Social Psychiatry, Univ. of Zurich

1. AdvanSiD
2. WeeROC
3. Raytest GmbH
4. RS2D



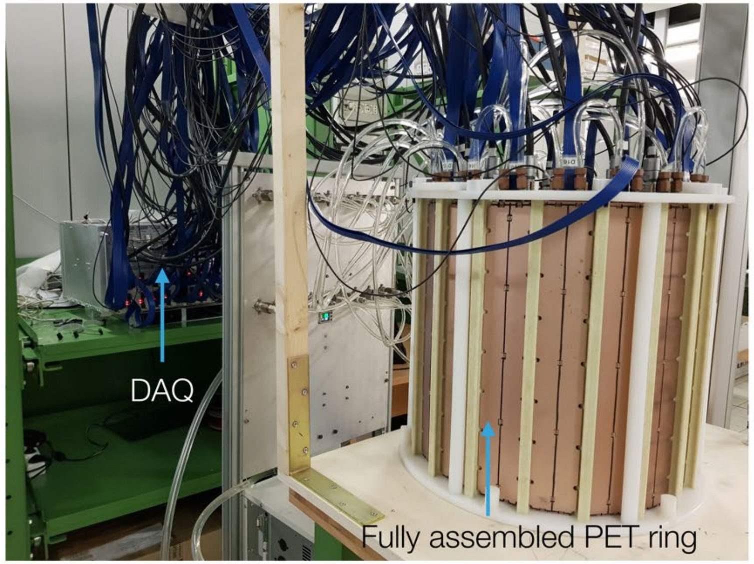
www. trimage.eu

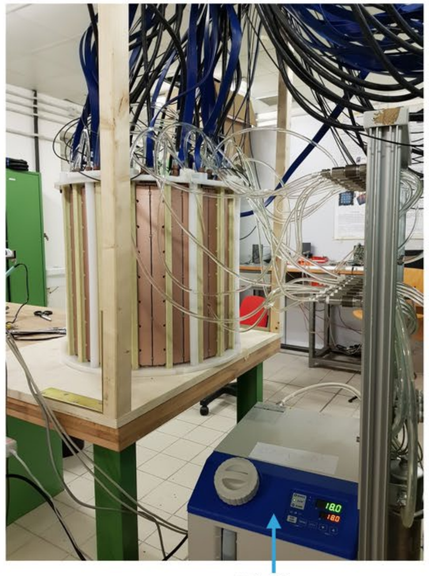
THE TRIMAGE SCANNER



Schematic drawing of the MR system

The MR under test at RS2D partner





🡐The TRIMAGE PET ring. Left: the fully assembled PET ring as installed in the laboratory environment where the characterization tests were performed. The PET ring is connected to the data acquisition system (DAQ). Right: picture of the ring where there is visible the water chiller, used for the stabilization of the SiPM temperature.

The evolution of the radiotracers
(specificity)

TABLE III.: Physical properties of the so-called physiological radioisotopes

Radioisotope	Half-life (min)	Positron average kinetic energy (MeV)	Positron kinetic energy endpoint (MeV)	Positron average range in water (mm)
^{11}C	20.4	0.385	0.960	1.2
^{13}N	10.0	0.491	1.198	1.6
^{15}O	2.0	0.735	1.732	2.8
^{18}F	109.8	0.242	0.633	0.6

RADIOTRACERS

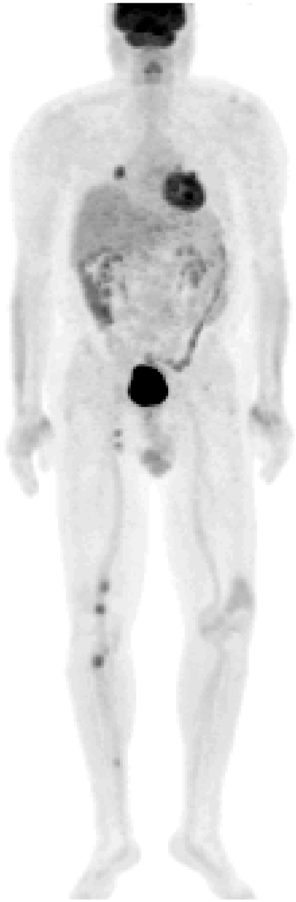
- ^{18}F based — ^{18}F-FDG: metabolism (a-specific)
  - ^{18}F-FLT: cell proliferation
  - ^{18}F-MISO: hypoxia
  - ^{18}F-DOPA: Parkinson... and more
- ^{11}C- based — ^{11}C-choline:prostate
  - PiB: Pittsburgh compound B (Alzheimer)... and more
- ^{13}N, ^{68}Ga, ^{64}Cu-based .. and more

[A.Del Guerra et al., Rivista Nuovo Cimento [2016, Vol. 39(4), pp.155-223]

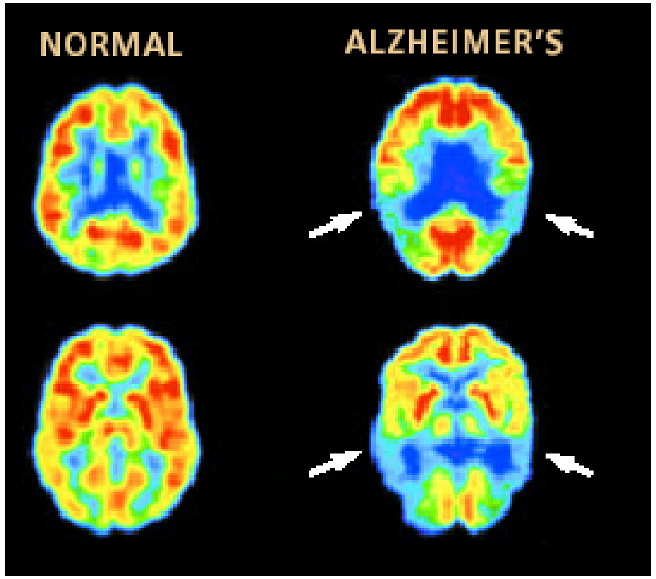
The evolution applied to Diagnostic

Oncology

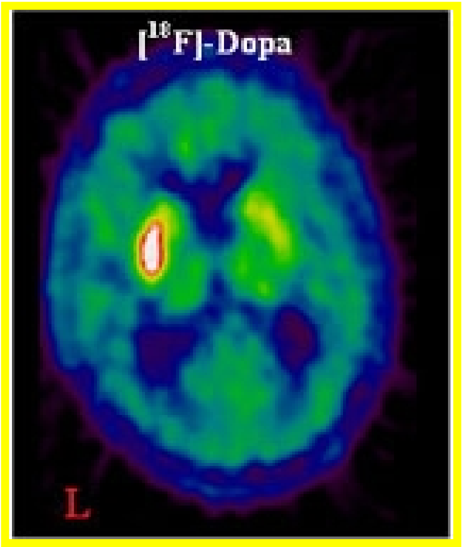
Neurology



^{18}F-FDG
Total body

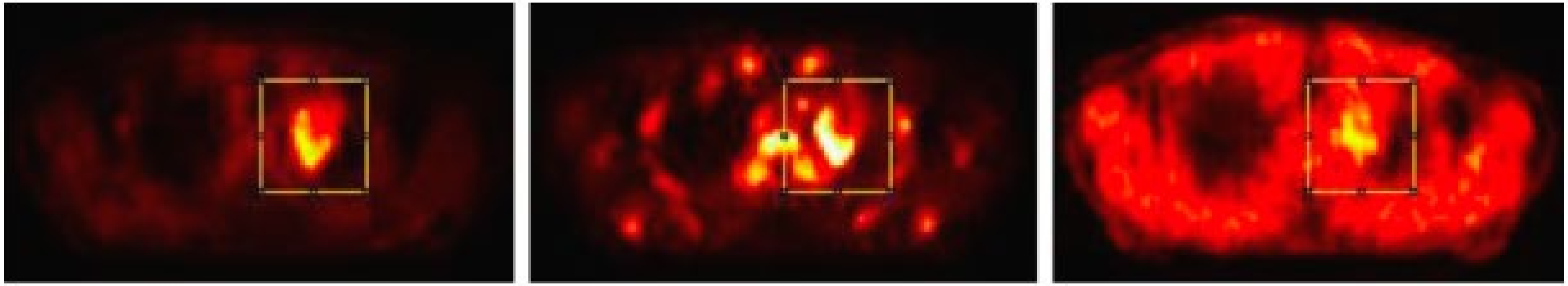


^{18}F-FDG
Brain study for
Alzhemeir's disease



^{18}F-DOPA
Brain study for
Parkinsons's disease

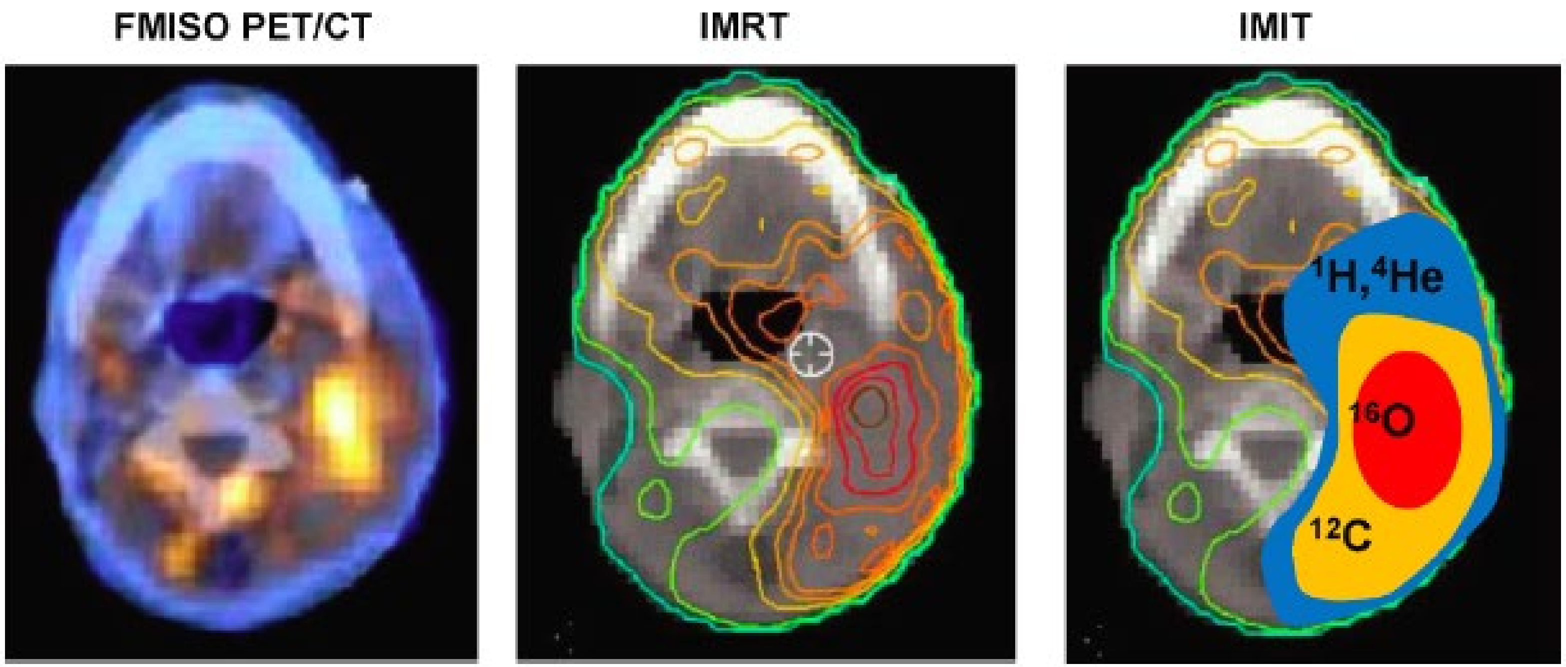
The evolution applied to oncology



(a) FDG (b) FLT (c) FMiso

Example of varying uptake (indicated by the yellow box) and background activity patterns in PET images of the same patient with a centrally located lung tumor, highlighting the different functional properties of the applied 18F-based tracers [(a) FDG, (b) FLT, and (c) FMISO]
[K.Parodi, Medical Physics, Vol. 42, No. 12, December 2015]

The evolution applied to treatment planning



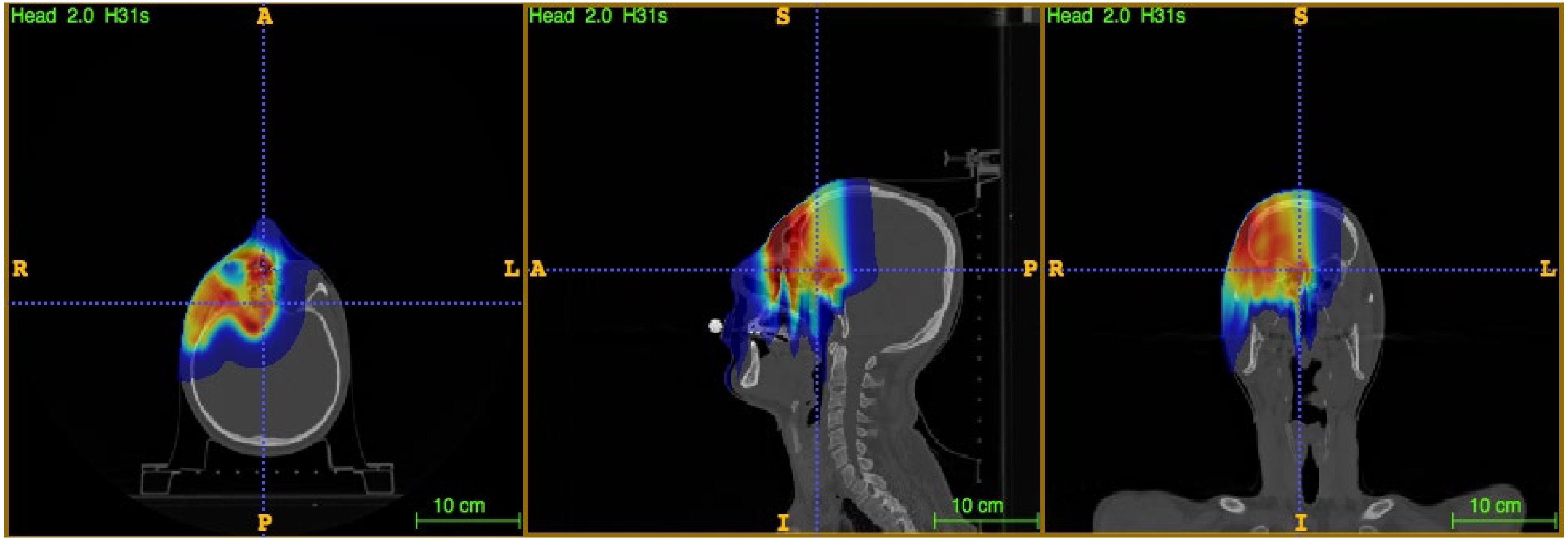
Example of hypoxia imaging based on FMISO PET/CT (left), and corresponding locally enhanced dose to hypoxic structures for dose painting in IMRT (middle), as well as illustrative implementation of radiation-quality-modulated dose painting in IMIT, targeting with heavier ions (16O, 12C) the most resistant (i.e., hypoxic) tumor subareas while keeping low-LET radiation in the surrounding tumor volume. Adapted with permission from: D.Thorwarth and M. Alber, Eberhard Karls University Tubingen (2011), “Implementation of hypoxia imaging into treatment planning and delivery,”

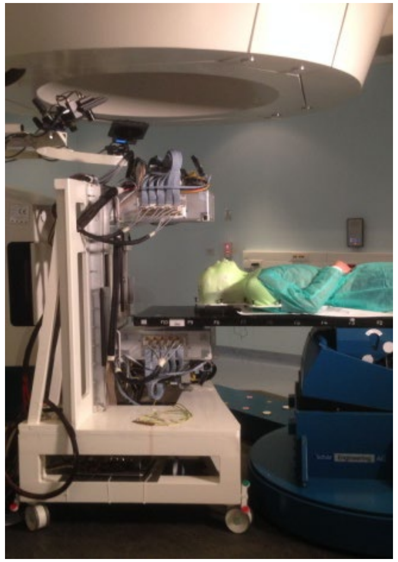
[K.Parodi,Medical Physics, Vol. 42, No. 12, December 2015]

First clinical test @CNAO, 1-2 Dec. 2016

Planned dose

240 s treatment + 30 s after-treatment of data acquisition





Carcinoma of the lacrimal gland: 3.7 10^{10} protons [66.3, 144.4] MeV/u
(28-29)/30 fractions, 2.2 GyE

Take home message

- **After 65 years PET is alive and kicking and it is fundamental for precision medicine.**

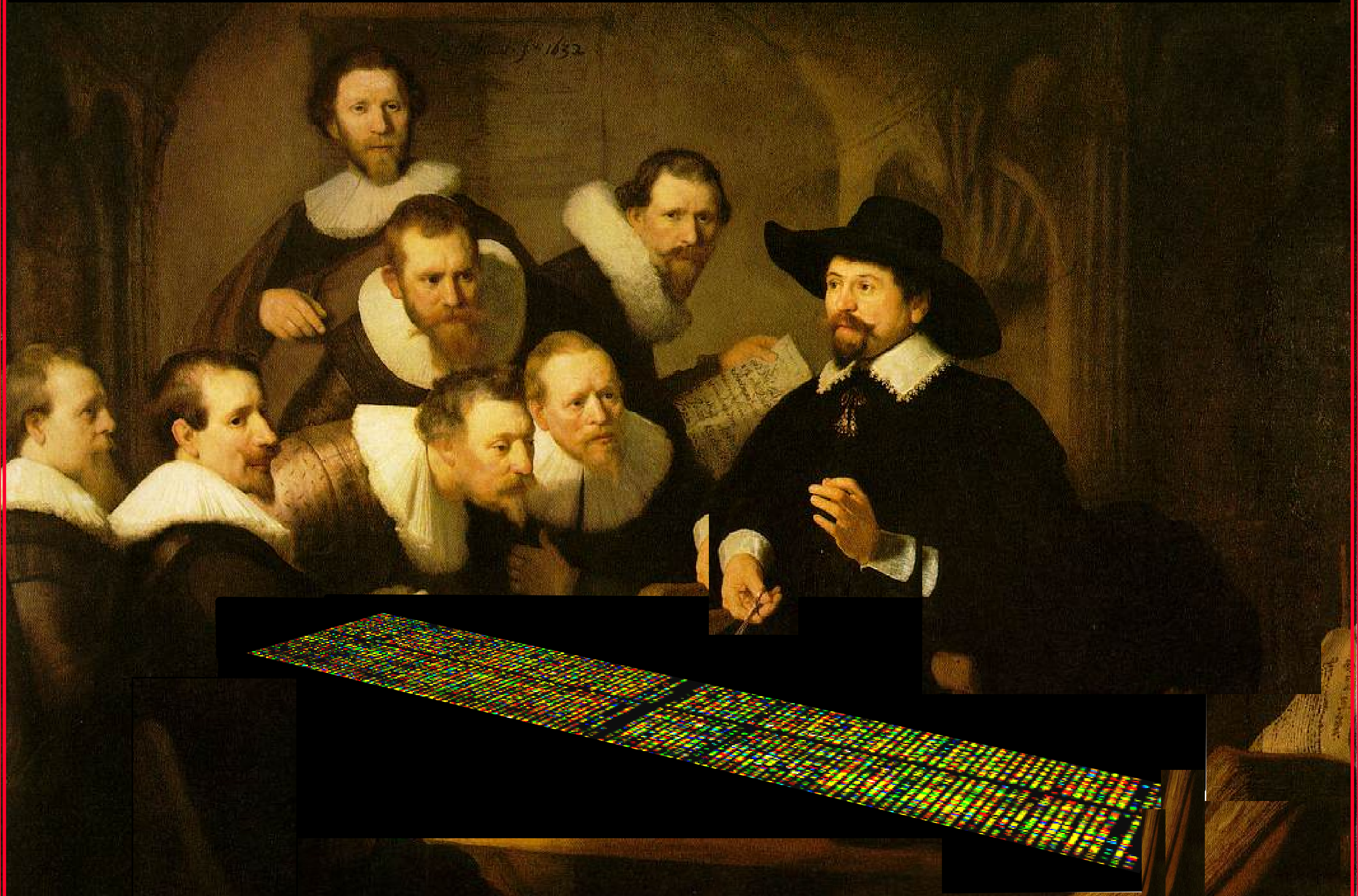
➔ It's no time for retirement! Not yet!

- **Organ specific PET devices are under development (whole body, breast, brain, prostate, pediatric PET, range in hadrontherapy..)**

- **Multimodality Imaging (PET-CT, PET-MR, PET-US,…and more)**

ANATOMY LECTURE ~ 2020

MOLECULAR Imaging➔ Precision Medicine



[Courtesy of Hedvig Hricak, Memorial Sloan-Kettering Cancer Center, ECR-2009]

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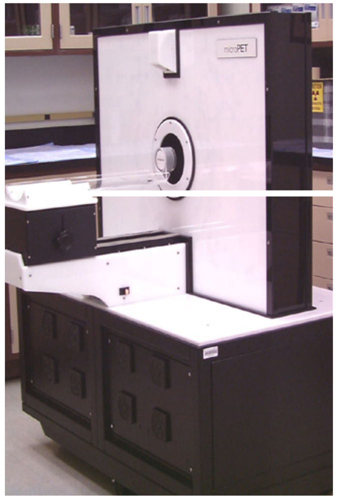
Matteo Morrocchi
Valeria Rosso
Giancarlo Sportelli
Stan Majewski
Simon Cherry
Stefaan Vanderberghe
George Loudos
The TRIMAGE collaboration
... and many more

THANK YOU!

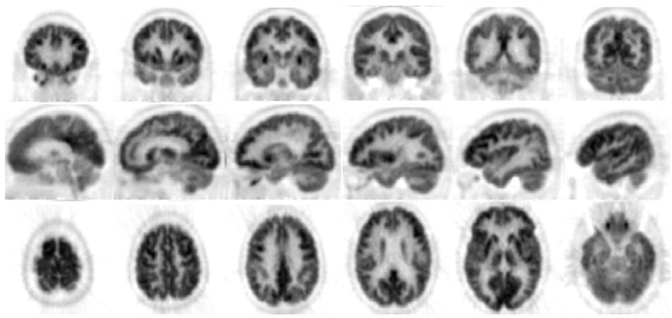
The evolution of the Preclinical Systems (since the mid '90)

Human PET

microPET



human

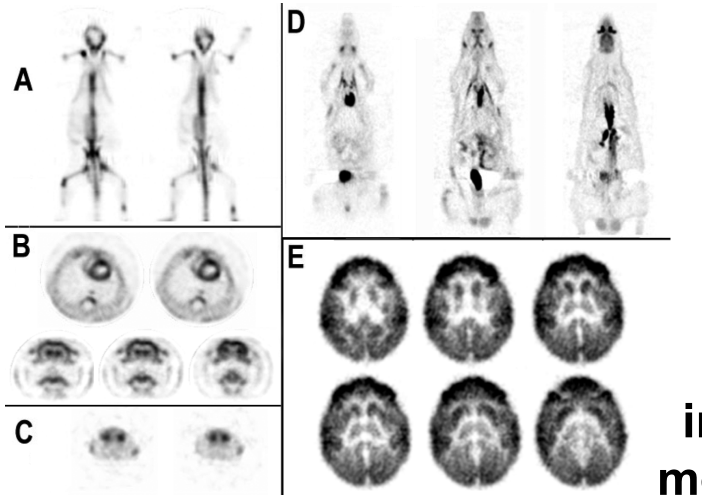


*Images courtesy of Simon Cherry, UCLA

mouse

rat

mouse



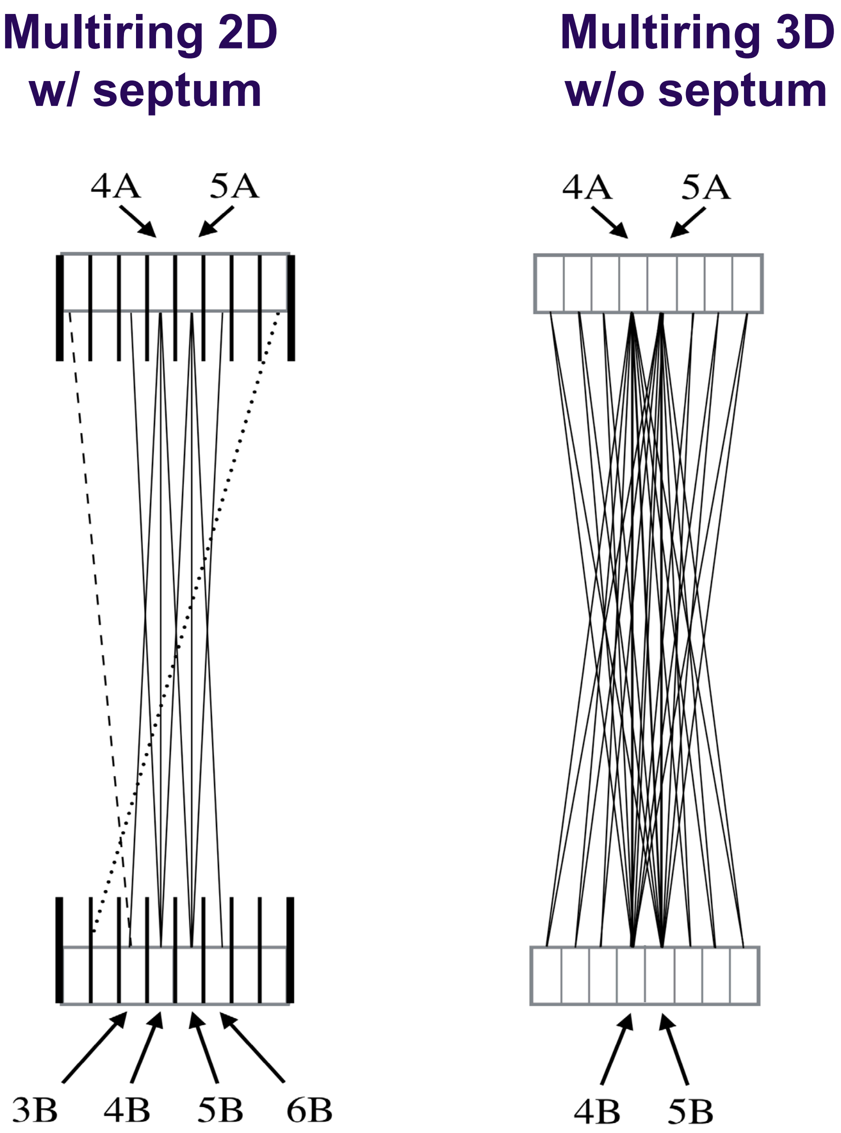
rat

infant monkey

The evolution of *PET scanner geometry*:
From Single Ring to Multiring → From 2D to 3D (sensitivity)

Single ring
4 cm - 6 cm
axially

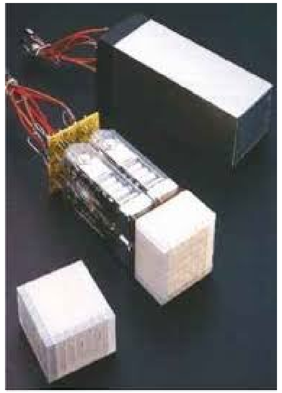
Multiring
Around 20 cm
axially



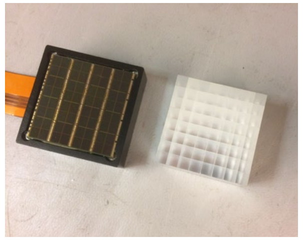
TRANSFER TO CLINICAL PET SYSTEMS

Spatial resolution

4-6 mm pixels with PMTs

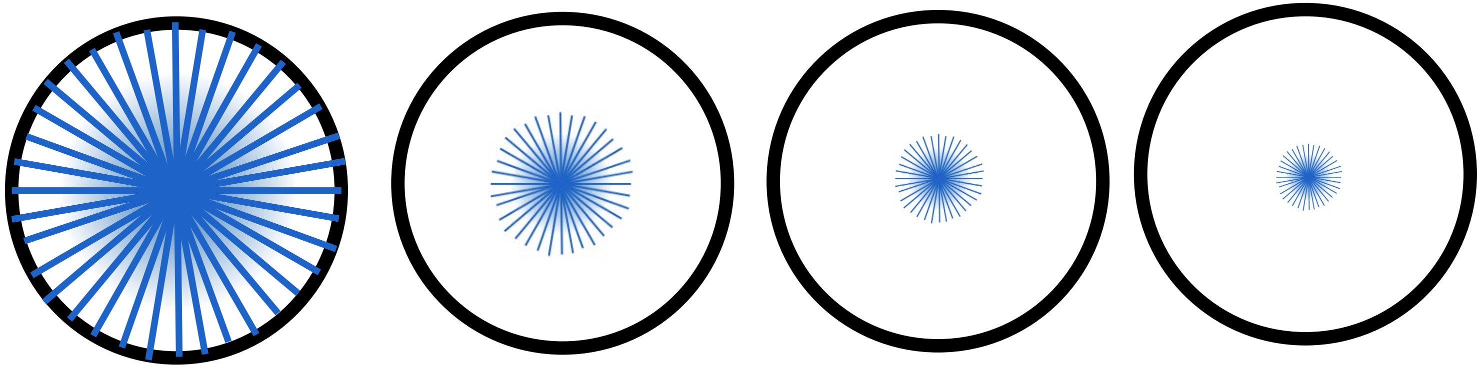


3-4 mm pixels with SiPMs



TOF

PET | 500-600 ps | 300-400 ps | 200-300 ps



2000-2010

2015-2020

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Courtesy of Stefaan Vanderberghe

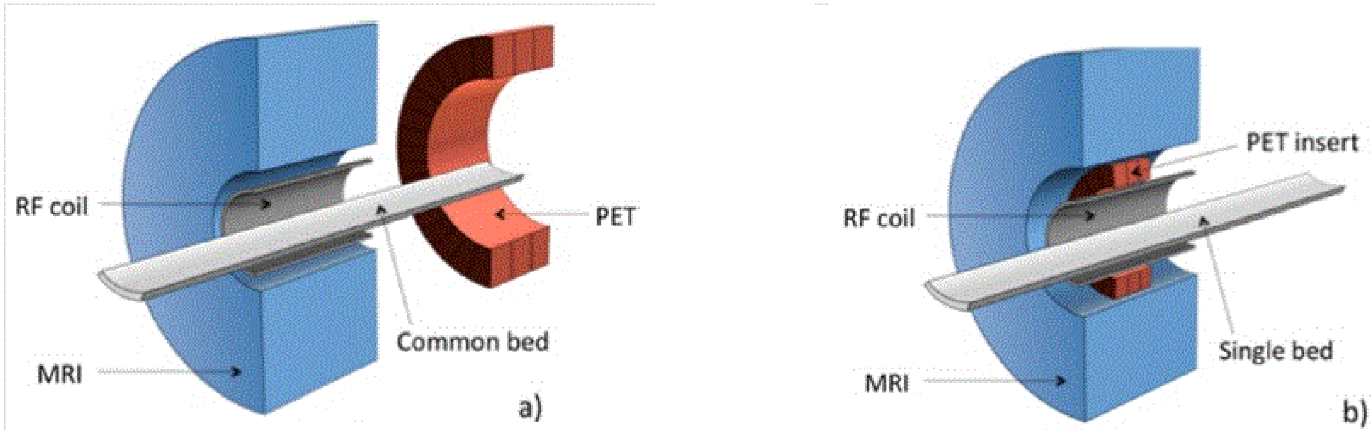
The Evolution of Brain Imaging (organ specific sensitivity)

Left: 1961 – Brookhaven's "Headshrinker", Center-Left: 2011 – "PET-Hat". Center-Right: 2013 – Hamamatsu's brain PET system, Right: 2015, "Helmet-Chin". None compact, one wearable. (Courtesy of Stan Majewski, 2016)

The evolution of Hybrid systems→PET/MR

Hybrid PET/MRI systems provide functional and morphological information *at the same time*:

- No image fusion required
- Space and costs saving
- Better soft tissue contrast
- Lower radiation doses



Tandem PET and MR configuration   Hybrid PET/MR scanner

[H.Zaidi and A.Del Guerra, Medical Physics, 2011, 38(10),5667-5689]