

## 2.3. Positron Emission Tomography

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Positron Emission Tomography ( PET ) is the most sensitive method to image trace amounts of molecules in vivo. Therefore this technique is used to measure in man or in the living animal biochemical and physiological processes in any organ with threedimensional resolution. The last 25 years have seen a rapid and still ongoing development in the production of positron emitters, radiochemical labelling techniques, tomograph technology and image reconstruction algorithms. This is driven by the manifold research applications of PET in the study of human disease and its possible treatment. Because of the possibility to see and measure quantitatively physiological disorders in an early stage, before permanent morphological damage has occurred, which will only then be visible in x-ray or magnetic resonance computer tomography, PET is finally finding its way from a sophisticated research tool into routine clinical diagnosis.

### The Method

The use of positron emitters for radioactive labelling offers important advantages compared to single photon emitters. Some of the physiologically most interesting chemical elements like carbon, nitrogen and oxygen have only positron emitting short-lived isotopes. This makes a detection device, which is sensitive to positron decay, highly desirable. The positron travels only a short distance in tissue, then it annihilates with an electron into two 511 keV gamma-quanta or photons which are emitted back to back. When these two gamma-quanta are detected by two detectors in coincidence then the decay event can be localized to the line connecting the two detectors. This "electronic collimation" allows to construct highly efficient detection systems, because there is no need for heavy collimators. Since both photons have the same energy the detection probability is almost independent from the point between the two detectors where the decay event originated. Therefore the corrections for attenuation in tissue, which are generally huge in these measurements, can be done very accurately.

Commercial tomographs consist of thousands of detectors, which are arranged in many rings surrounding the object. Each detector is connected in coincidence with opposing detectors. First this was restricted to opposing detectors in the same ring or in neighbouring rings with septa shields between the detector rings to get rid of unwanted scattered radiation. Then to increase sensitivity and make better use of the applied activity the septa were made removable and coincides between many rings were registered. Now the most advanced systems have no shielding at all between the detectors. The accepted solid angle is increased by extending the axial field of view with more detector rings and tightly packed detectors with a high stopping power are arranged in a compact geometry. This 3D or volume data acquisition, where all possible coincidence lines inside the detector volume are registered, induces besides higher count rates of true coincidences also a large increase of scatter coincidences and random coincidences. A scatter coincidence is an detected event where one or both photons were deflected by Compton scattering and are therefore assigned to a wrong coincidence line. Scattered coincidences may reach the same amount as true events and very elaborate correction algorithms have become necessary to subtract scatter contributions for accurate quantitative results. A random coincidence is an event where two photons from different decays are detected during the short coincidence time window. Random coincidences can be subtracted online using a second delayed coincidence window.

### New developments

Since the beginning it was a primary objective in PET to improve the spatial resolution of the tomographs. The early tomographs used NaJ(Tl) crystals as scintillation detectors. These were soon substituted by BGO (bismuth germanate)

crystals which have higher detection efficiency and are not hygroscopic. Commercial tomographs using BGO reached a spatial resolution of approximately 4 mm. Presently the first tomographs with a new scintillator LSO (lutetium oxyorthosilicate) are built. LSO has similar high detection efficiency as BGO, but with a five fold higher light output and an eight times faster light decay time. This allows to push spatial resolution close to its physical limit of 1-2 mm, which is determined by the positron range in tissue and the small noncollinearity of the annihilation photons. Increased spatial resolution requires smaller scintillation crystals. When the size of the photomultiplier tubes (PMT) became the resolution limiting element, the one-to-one coupling between crystal and PMT was given up and an Anger camera principle was applied in the block detector concept. For example 8x8 crystals were cut into a single scintillator block forming a light guide to 4 PMTs. By comparing the signals of the 4 PMTs the individual crystals are uniquely identified. An even more cost effective scheme, a quadrant sharing arrangement of PMTs (**Figure 1**) allows to further increase the number of crystals per PMT. This was quite recently realized in the first PET tomograph for neurological studies in humans with LSO scintillators, the High Resolution Research Tomograph (HRRT), manufactured by SIEMENS/CTI, Knoxville, TN, USA and installed at the Max-Planck-Institute for Neurological Research in Cologne. It consists of 120,000 single crystal elements, each 2.1 mm x 2.1 mm wide, arranged in 104 rings giving a reconstructed spatial resolution of less than 2.5 mm in a 20 cm diameter volume. This made it also necessary to measure the depth of interaction (DOI) of the incident photons in the 15 mm deep detectors to avoid ambiguities when photons penetrate several crystals by oblique incidence. From several ideas how to obtain DOI information, a scintillation phoswich with two crystal layers with different light decay times was chosen. Pulse shape discrimination allows then to separate scintillation events in the two layers.

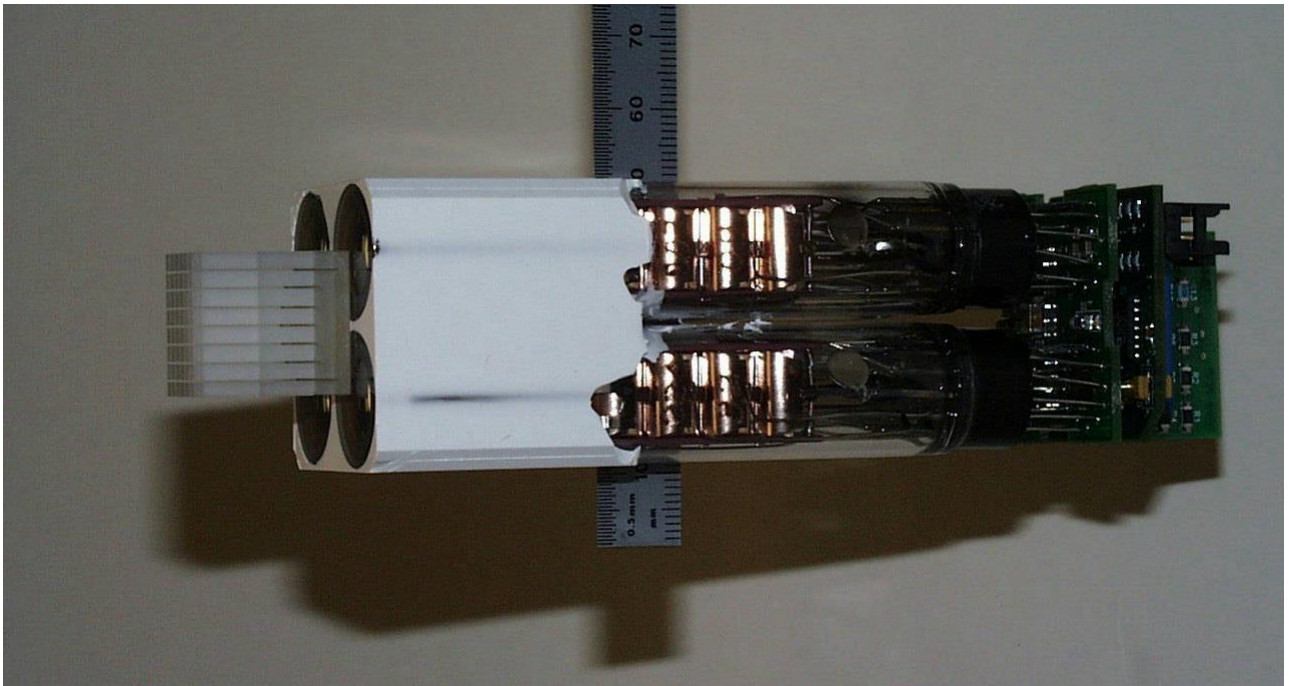


Figure 1 A LSO phoswich detector block on a set of 4 PMTs. The scintillator block consists of two LSO layers with different light decay times, which are cut into a 8x8 crystal matrix and glued on a light guide.

After correction for scatter and random events, attenuation and dead time an image of the activity distribution can be reconstructed. Originally this was done with standard 2D filtered backprojection algorithms giving a stack of transverse image slices. With 3D data acquisition this was extended to volume reconstruction, which required hours of computing time. Therefore the algorithms

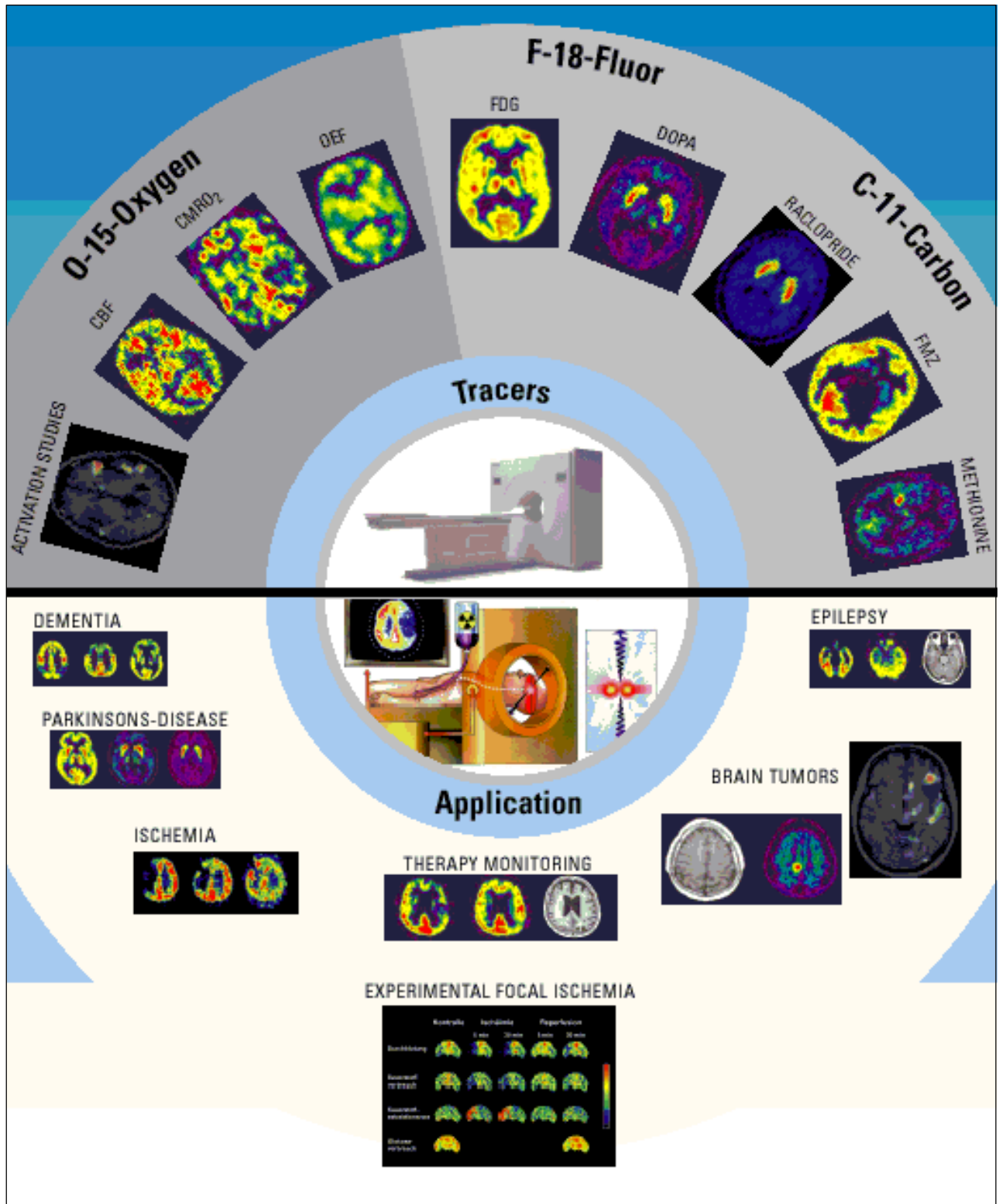


Figure 2 Overview of the PET method with brain images for common tracers in clinical applications

were parallelized and run on multiple processors. Only recently, with the rapid developments in computer hardware, iterative 3D reconstruction is becoming routinely feasible. The PET images can then be superimposed on higher resolution images from other modalities like MRI (magnetic resonance imaging) to relate the information in the moderate resolution PET images to morphology.

## Tracer production

The commonly used positron emitting nuclei in PET are  $^{11}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{O}$  and  $^{18}\text{F}$ . The first three are isotopes of the most abundant elements in organic compounds. This allows the labelling of naturally occurring biomolecules or drugs without altering the compounds defined courses in living systems.  $^{18}\text{F}$  can be used to substitute hydrogen or hydroxyl groups. Because of their short half-life, ranging from 2 min for  $^{15}\text{O}$  to 110 min for  $^{18}\text{F}$ , they have to be produced close to their application. Various small, compact cyclotrons specially constructed for the production of those isotopes in a hospital environment are commercially available. There are cyclotrons with external proton and deuteron beams, proton-only, self-shielding machines with internal targets down to 3 MeV beam energy for the exclusive generation of  $^{15}\text{O}$  and negative ion machines allowing simultaneous irradiations on separate target ports. They are equipped with targetry and remote systems for chemical precursor production like  $^{11}\text{CO}$ ,  $\text{C}^{15}\text{O}$ ,  $^{13}\text{NH}_3$ ,  $^{11}\text{CH}_4$  or  $\text{H}_2^{15}\text{O}$  in high yields of several curies. Computer controlled automated robot systems synthesize in heavily shielded hot cells radiolabelled compounds in optimized short times of few minutes, including purity controls. For  $^{18}\text{F}$ -labelled compounds, which can be shipped over considerable distances because of its 110 min half-life, a net of distribution centers has been built in several countries to deliver the radiotracers by car or plane to PET installations with no accelerator facility. This aided much to the recent expansion of PET in routine clinical diagnosis.

## Applications

The study of physiological parameters and their pathological variation with PET has found broad clinical applications in neurological disease, brain and body tumors and cardiac tissue viability. In addition the unique possibilities of PET methodology are being used to investigate brain function in normal volunteers, to develop experimental models for various human diseases, to study the in vivo pharmacokinetics of drugs and the efficacy of treatments of disease. Several hundred molecules have been labelled with positron emitters, but only few of them have found their way to clinical application so far. (**Figure 2**) gives a schematic overview of common tracers and some neurological applications. Short-lived  $^{15}\text{O}$  is mainly used to label water for bloodflow studies or oxygen gas to study oxygen metabolism. Because of its short half-life  $^{15}\text{O}$ -water injections can be applied in short time intervals repeatedly to measure bloodflow under various functional activation paradigms in normal or diseased brain (**Figure 3**). The combination of quantitative values for cerebral bloodflow (CBF), oxygen consumption ( $\text{CMRO}_2$ ) and oxygen extraction (OEF) give important information about the pathophysiological status in the acute phase of cerebral ischemia and can guide stroke therapy with early reperfusion by thrombolysis (**Figure 4**).

Fluorodeoxyglucose (FDG) is since more than 20 years the most widely used PET tracer, which is now also supplied routinely from many distribution centers. Its uptake in tissue can be easily quantified as glucose metabolic rate with a stable autoradiographic model developed by Sokoloff, which needs in addition to a single PET measurement only the time course of radioactivity in arterial blood. It has been broadly applied to image and to quantify metabolic disturbances in cardiology, oncology and in almost every neurologic disease or disorder.

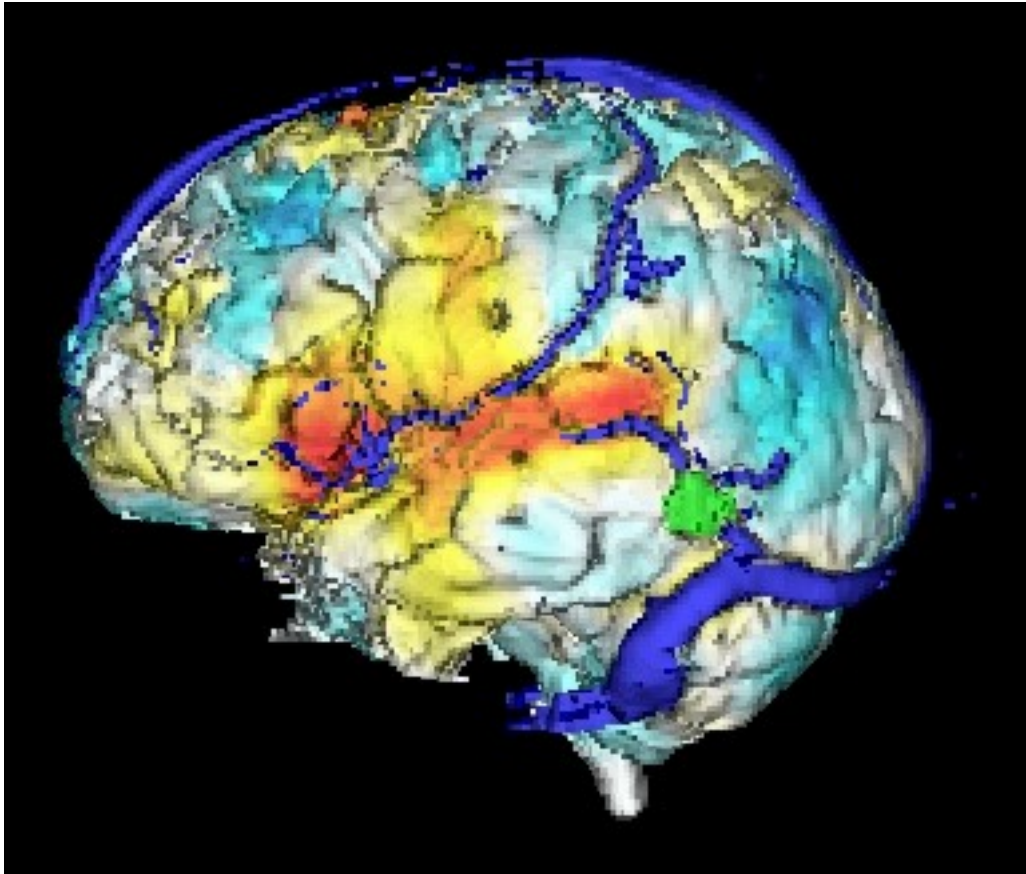


Figure 3 Blood flow changes under speech activation superposed on MRI brain volume. The location of the speech areas (red areas with increased blood flow) in relation to the brain tumor (shown in green) give important information to the neurosurgeon before surgical intervention.

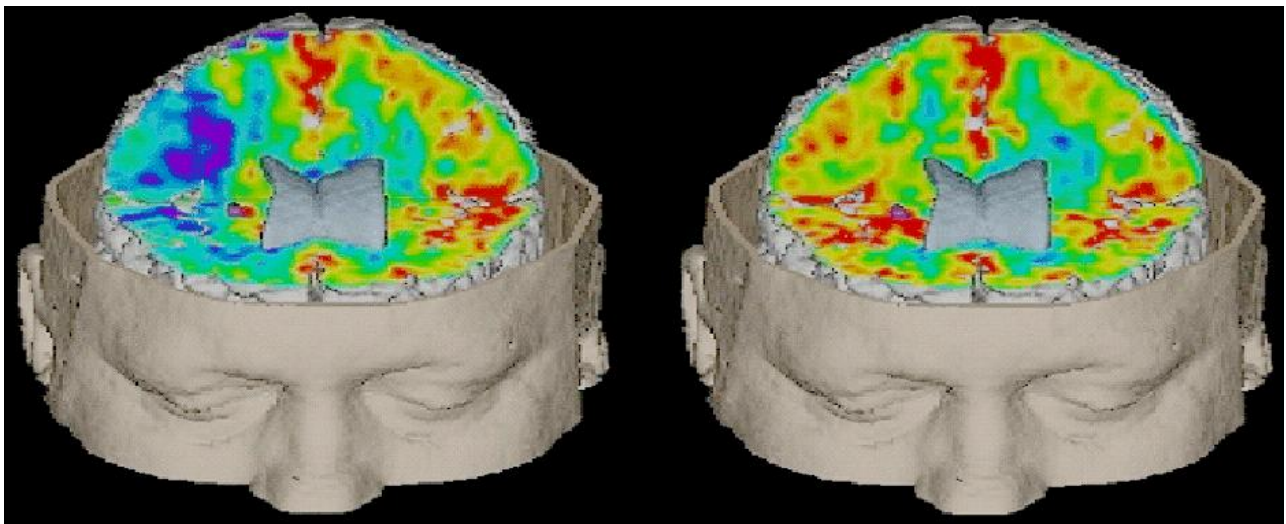


Figure 4 Left image shows the infarcted region with decreased blood flow in blue. After trombolysis therapy blood flow has recovered as shown in the right image. The cuts through the brain volume from MRI are overlaid with blood flow information from PET in color.

The study of the dopaminergic system with  $^{18}\text{F}$ -L-DOPA and raclopride allows to image disturbances on the transmitter and on the receptor side in movement disorders like Parkinsons disease. A labelled receptor ligand like raclopride enables to measure regional receptor densities or to observe changes in endogeneous dopamine levels caused by functional stimulations.

Flumazenil (FMZ) is a ligand binding to benzodiazepine receptors, which can be used to image neuronal integrity with applications for example in stroke and epilepsy.

With labelled amino acids, like methionine, amino acid transport, metabolism and protein synthesis can be studied under various conditions. Especially in brain tumors amino acid uptake in combination with FDG gives important information about tumor localization, extent and malignancy.

This short overview of some clinical applications shows only a small share of the potential of the PET method. Promising future applications emerge in drug development, psychopharmacology, visualisation of gene therapy and in experimental research with animals.

### References for further reading

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