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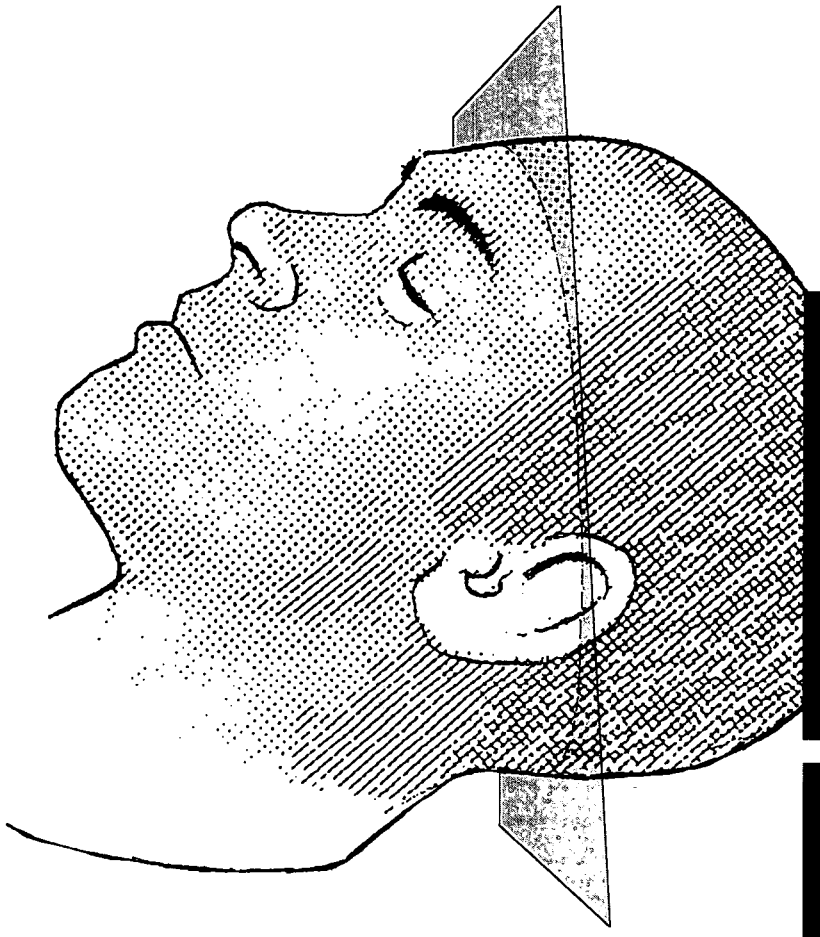
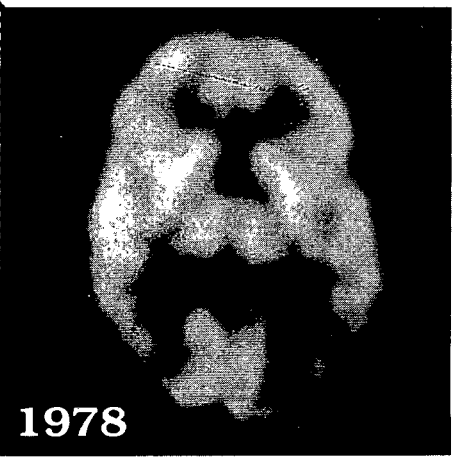
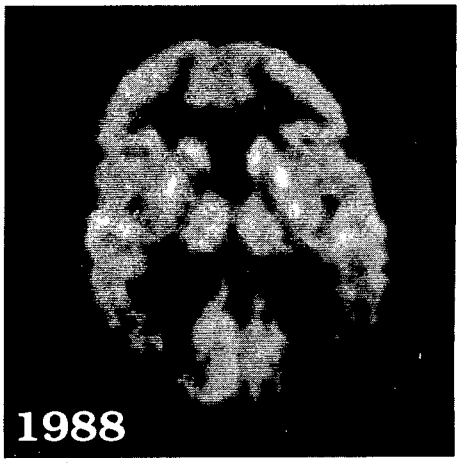
High-Resolution PET

for medical science studies







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High-Resolution PET for Medical Science Studies

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CONTENTS

A PET Primer 2
Positron Emission Tomography: Evolution of a Technology
¶ PET Theory: Emission, Detection, and Reconstruction

PET Instrumentation: Design Factors 4
Physical Factors Affecting Resolution ¶ Spatial Resolution and Accuracy ¶ Statistical Factors ¶ Innovation in Detector Design ¶ Sampling Strategies ¶ Attenuation and Localization

Clinical Studies 11
Alzheimer's Disease ¶ Tumors ¶ PET vs NMR in Tumor Studies ¶ Epilepsy ¶ Arteriovenous Malformations ¶ Treatment Planning with PET

Future Directions 16
Instrumentation for a Deeper Understanding of Neurophysiology

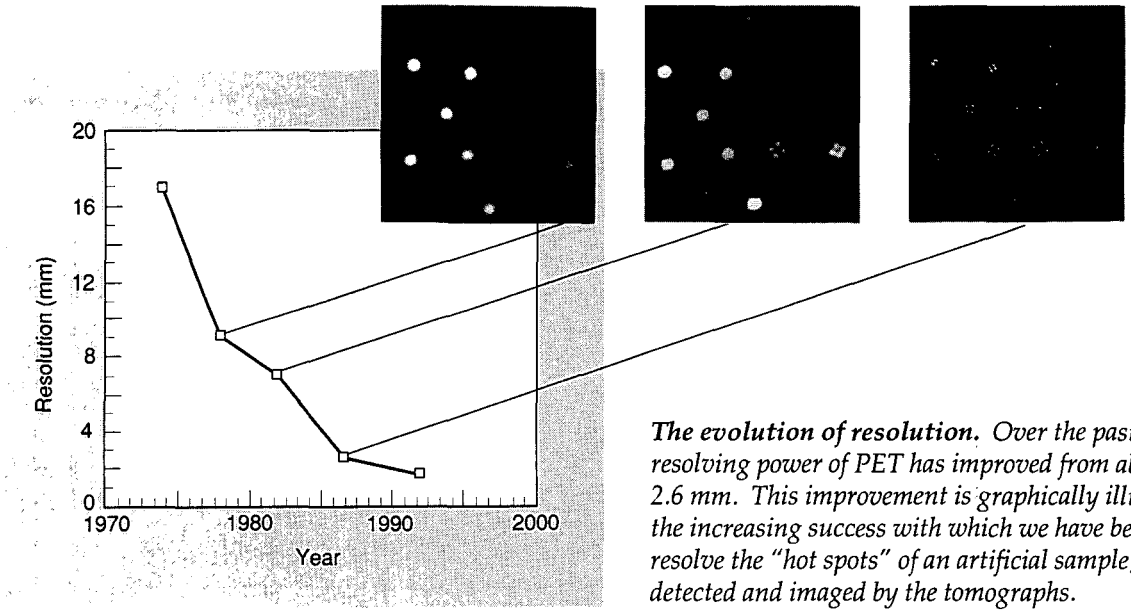
A PET PRIMER

Positron Emission Tomography: Evolution of a Technology

One of the unexpected fruits of basic physics research and the computer revolution is the noninvasive imaging power available to today's physician. Technologies that were strictly the province of research scientists only a decade or two ago now serve as the foundations for such standard diagnostic tools as x-ray computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), ultrasound, single photon emission computed tomography (SPECT), and positron emission tomography (PET). Furthermore, prompted by the needs of both the practicing physician and the clinical researcher, efforts to improve these technologies continue. This booklet endeavors to describe the advantages of achieving high resolution in PET imaging.

The history of PET can be traced to the early 1950s, when workers in Boston first realized the medical imaging possibilities of a particular class of radioactive substances. It was recognized then that the high-energy photons produced following the decay of positron-emitting isotopes could be used to describe, in three dimensions, the physiological distribution of "tagged" chemical compounds (see facing page). After two decades of moderate technological developments by a few research centers, widespread interest and broadly based research activity began in earnest following the development of sophisticated reconstruction algorithms and improvements in detector technology. By the mid 1980s, PET had become a practical tool for medical diagnosis and for dynamic studies of human metabolism. Today, because of its millionfold sensitivity advantage over MRI and its chemical specificity, PET is used to study Alzheimer's disease, Parkinson's disease, psychiatric disorders, epilepsy, tumors, and coronary artery disease. Its use has added immeasurably to our current understanding of flow, oxygen utilization, and the metabolic changes that accompany disease.

For the past 15 years, a team of physicists and physicians at the Donner Laboratory of the Lawrence Berkeley Laboratory has been devoted to advancing the power of PET imaging to its physical limits. A product of their research is today's most advanced instrument, the Donner PET-600, which has a resolution of 2.6 mm. Nonetheless, further improvements are vital if the full imaging potential and biomedical scientific advantages of PET are to be realized.

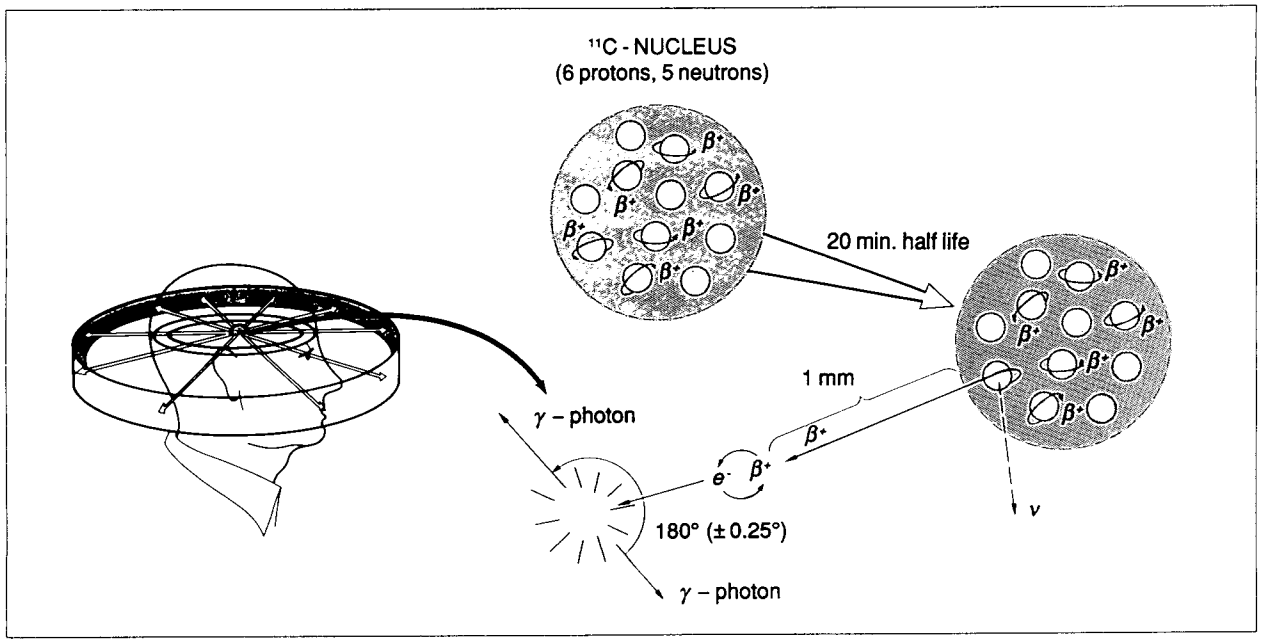


The evolution of resolution. *Over the past decade, the resolving power of PET has improved from about 9 mm to 2.6 mm. This improvement is graphically illustrated by the increasing success with which we have been able to resolve the "hot spots" of an artificial sample, which are detected and imaged by the tomographs.*

PET Theory: Emission, Detection, and Reconstruction

PET imaging begins with the injection of a metabolically active tracer — a biological molecule that carries with it a positron-emitting isotope (for example, ^{11}C, ^{13}N, ^{15}O, or ^{18}F). Over a few minutes, the isotope accumulates in an area of the body for which the molecule has an affinity. As an example, glucose labeled with ^{11}C, or a glucose analogue labeled with ^{18}F, accumulates in the brain, where glucose is used as the primary source of energy. The radioactive nuclei then decay, emitting positrons which immediately annihilate with nearby electrons (their antiparticles) to produce two 511-keV photons. These high-energy gamma rays emerge from the body in opposite directions, to be detected by an array of scintillator crystals and photomultiplier tubes. When two photons are recorded simultaneously by a pair of detectors, we conclude that the annihilation event that gave rise to them must have occurred somewhere along the line connecting the detectors. After 10,000 or more annihilation events are detected, the distribution of the photon-emitting tracer is calculated by tomographic reconstruction procedures: PET reconstructs a two-dimensional image from the one-dimensional projections seen at different angles.

The physical basis of positron emission tomography. *Positrons emitted by "tagged," metabolically active molecules annihilate with nearby electrons and give rise to a pair of high-energy photons. The photons fly off in nearly opposite directions, and thus serve to pinpoint their source. The biological activity of the tagged molecule can be used to investigate a number of physiological functions, both normal and pathological.*

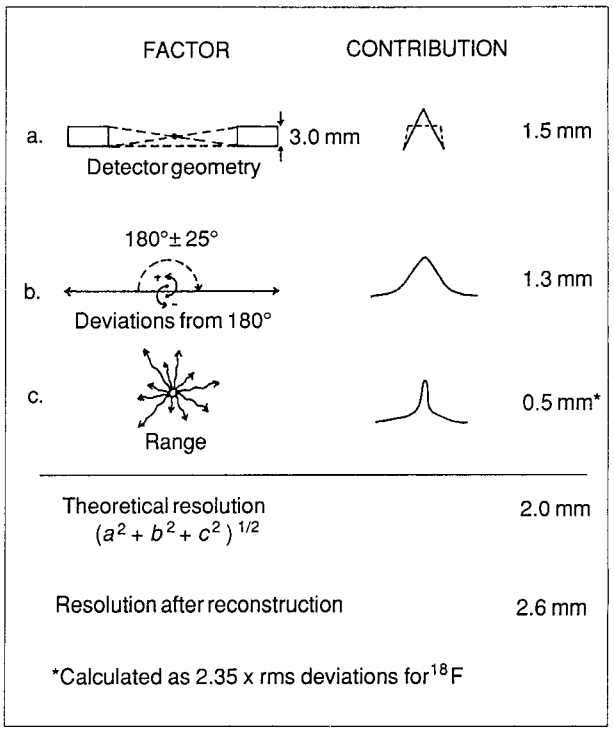


PET INSTRUMENTATION: DESIGN FACTORS

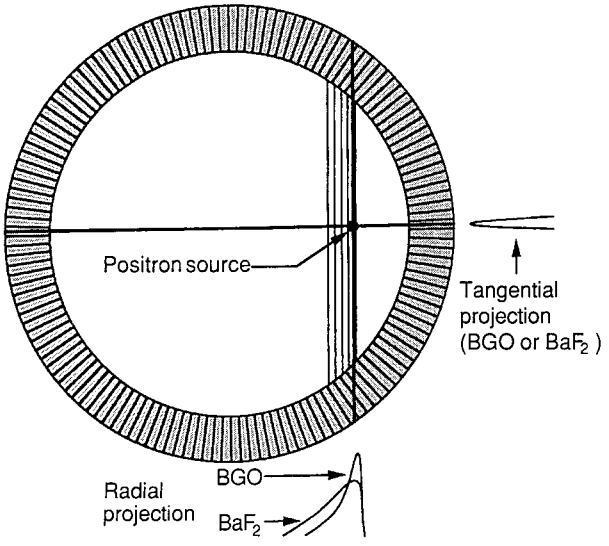
Physical Factors Affecting Resolution

As illustrated in the figure to the right, various factors affect the spatial resolution of PET tomographs: (a) The size of the detector is critical in determining the system's geometric resolution. (b) The angle between the paths of the annihilation photons can deviate from 180°, as a result of some residual kinetic motion at the time of annihilation. The effect on resolution of this deviation increases as the detector ring diameter increases, so that eventually this factor can have a significant effect. (c) The distance the positron travels after being emitted from the nucleus and before annihilation causes a deterioration in spatial resolution. This distance depends upon the particular nuclide. For example, the range of blurring for ^{18}F, the isotope used for deoxyglucose, is quite small compared with that of other isotopes. Combining values for these three factors for the PET-600 tomograph, we can estimate a detector-pair spatial resolution of 2.0 mm and a reconstructed image resolution of 2.6 mm.

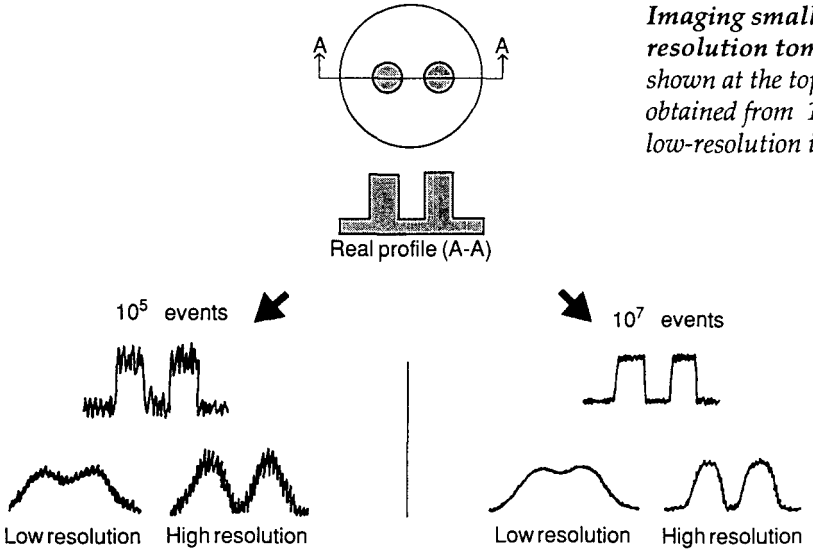
Furthermore, because the path of a photon from an "off-center" event typically traverses more than one detector crystal, the resolution often falls below the optimal value, especially at the edge of the imaging field. This phenomenon is illustrated below.



Factors contributing to the resolution of the PET-600 tomograph. *The contribution most accessible to further reduction is the size of the detector crystals.*



Resolution astigmatism in detecting off-center events. *Because annihilation photons can penetrate crystals to different depths, the resolution is not equal in all directions, particularly at the edge of the imaging field. This problem of astigmatism will be taken into account in future PET instrumentation (see page 8).*

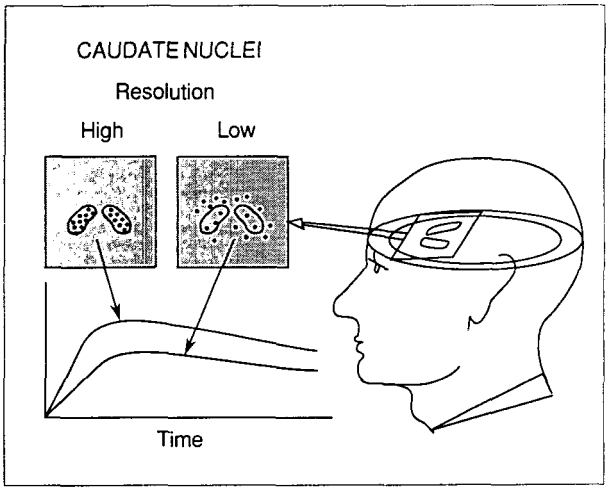


Imaging small features with high- and low-resolution tomographs. *For the activity profile shown at the top of the figure, a high-resolution image obtained from 10^5 events is more accurate even than a low-resolution image based on 10^7 events.*

Spatial Resolution and Accuracy

The quantitative accuracy of PET images is controlled by the sampling resolution. The uppermost diagram in the figure above shows the top view of a cylinder of activity marked by two "hot spots." The diagram immediately below it shows the resulting real profile of activity. The two figures in the third row show the profiles that would be reconstructed from 10^5 and 10^7 events, assuming an instrument with infinitely sharp geometric resolution. The bottom row shows the less ideal results obtained with tomographs of finite spatial resolution. In both low-resolution reconstructions, the two hot spots blend together, separated only by a shallow dip. The hot spots in the high-resolution reconstructions are separated by a much deeper dip. Thus, a low-resolution system, even one with the excellent statistics of 10^7 detected events, fails to show hot spots as accurately as a high-resolution system sampling only 10^5 events.

In addition, if the structure under examination is smaller than the instrument resolution, the concentration of labeled ligand will be less than the true value. Thus, as shown to the right, the time-activity curves depicting changes in concentration with time will be in error.



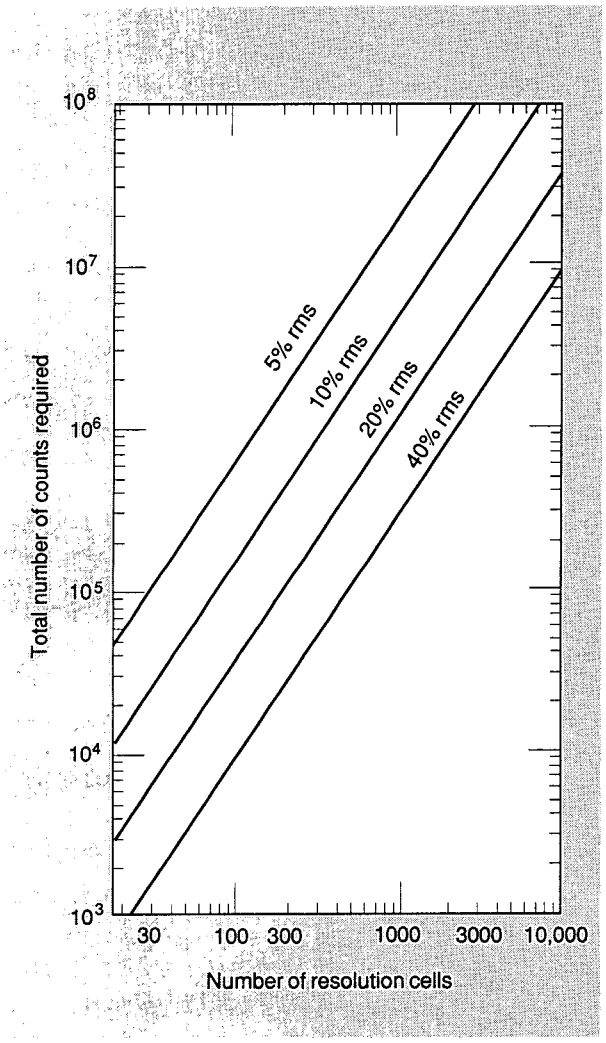
Measuring activity in small regions of the brain. *Low spatial resolution leads to an underestimation of metabolic activity and thus to erroneous dynamic activity curves.*

Statistical Factors

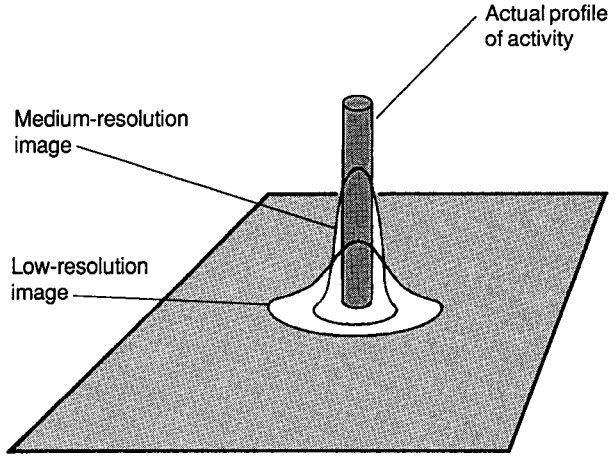
The ability to map quantitatively the spatial distribution of a positron-emitting isotope depends on adequate spatial resolution to avoid blurring. In addition, sufficient data must be acquired to allow a statistically reliable estimation of the tracer concentration. The amount of available data depends on the biomedical accumulation, the imaging system sensitivity, and the dose of injected radioactivity. The statistical requirements are closely related to the spatial resolution, as shown here.

For a given accuracy or signal-to-noise ratio for a uniform distribution, the ratio of the number of events needed in a high-resolution system to that needed in a low-resolution system is proportional to the 3/2 power of the ratio of the numbers of effective resolution elements in the two systems. The number of effective resolution elements is the sum of the occupied resolution elements weighted by the activity within each element.

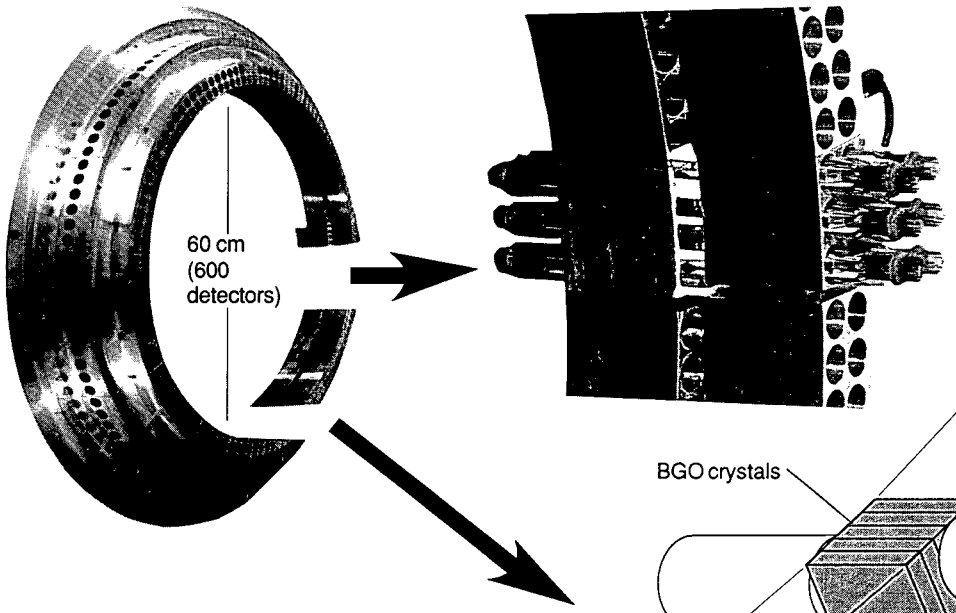
The reason better resolution gives improved results without the requirement for a drastic increase in the number of detected events is that the improved resolution increases contrast. (It is well known that the number of events needed to detect an object is inversely related to the square of the contrast.)



Statistical requirements and spatial resolution. *The general relationship between the detected number of events and the number of resolution elements in an image is graphed for various levels of precision. These are relations for planes of constant thickness.*



High spatial resolution and contrast enhancement. *The ability to see a feature on a uniform background is degraded when the instrument resolution broadens the feature and reduces its height relative to the background.*

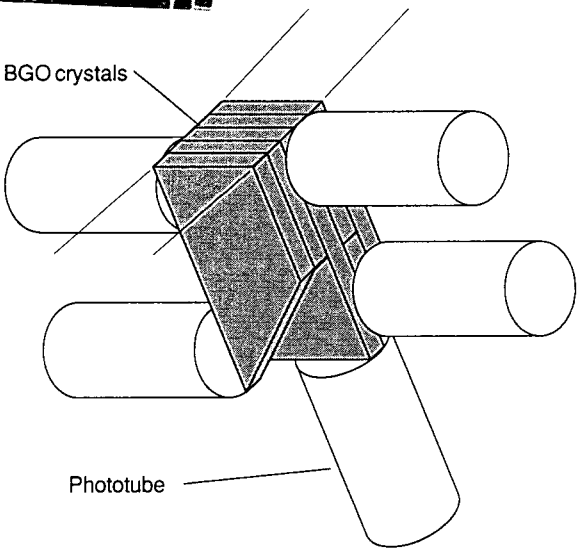


PET-600 Tomograph Design

The implementation of the PET-600 required special organization of the detectors. To achieve high spatial resolution and high efficiency, a ring of 3-mm-wide, closely packed crystals of the dense scintillator bismuth germanate (BGO) was desired. However, the smallest economical phototubes were 14 mm in diameter — too large for direct coupling to the crystals. A new design was developed that positioned the phototubes in alternating positions on several sides of the crystals, and the desired individual crystal-phototube coupling was achieved.

The individual coupling of each crystal to a photodetector results in the high spatial resolution, speed, and sensitivity of the system. High event rates are possible because the detector channels are in parallel. The efficiency of the detector depends on the density of the scintillation crystal, and BGO is the densest available material.

Efficient detection of the annihilation photons from positron emitters is provided by the combination of a crystal which converts the high-energy photons to visible-light photons. These photons

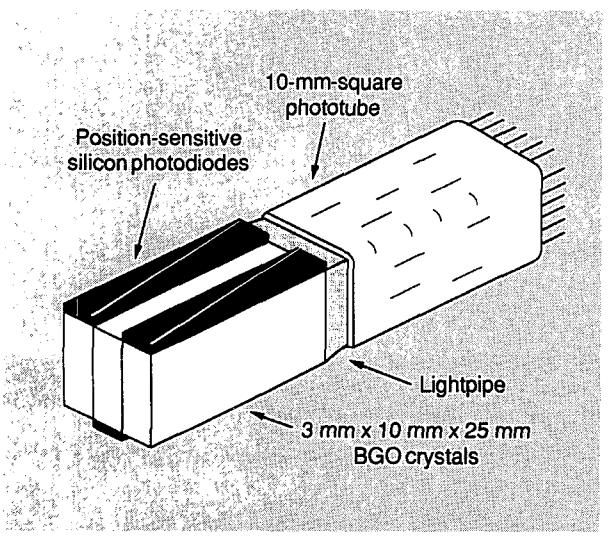


PET-600 detector geometry. *The directly coupled phototubes are arranged in different orientations around the 3-mm-wide scintillator crystals to permit the closest possible packing of the crystals*

are detected by a photomultiplier tube that produces an amplified electrical current pulse proportional to the amount of light emitted. The fact that the imaging system sensitivity is proportional to the square of the detector efficiency leads to a very important requirement that the detector be nearly 100% efficient. Thus, other detector systems such as plastic scintillators or gas-filled wire chambers, with typical individual efficiencies of 20%, would result in a coincident efficiency of only 4%.

Innovation in Detector Design

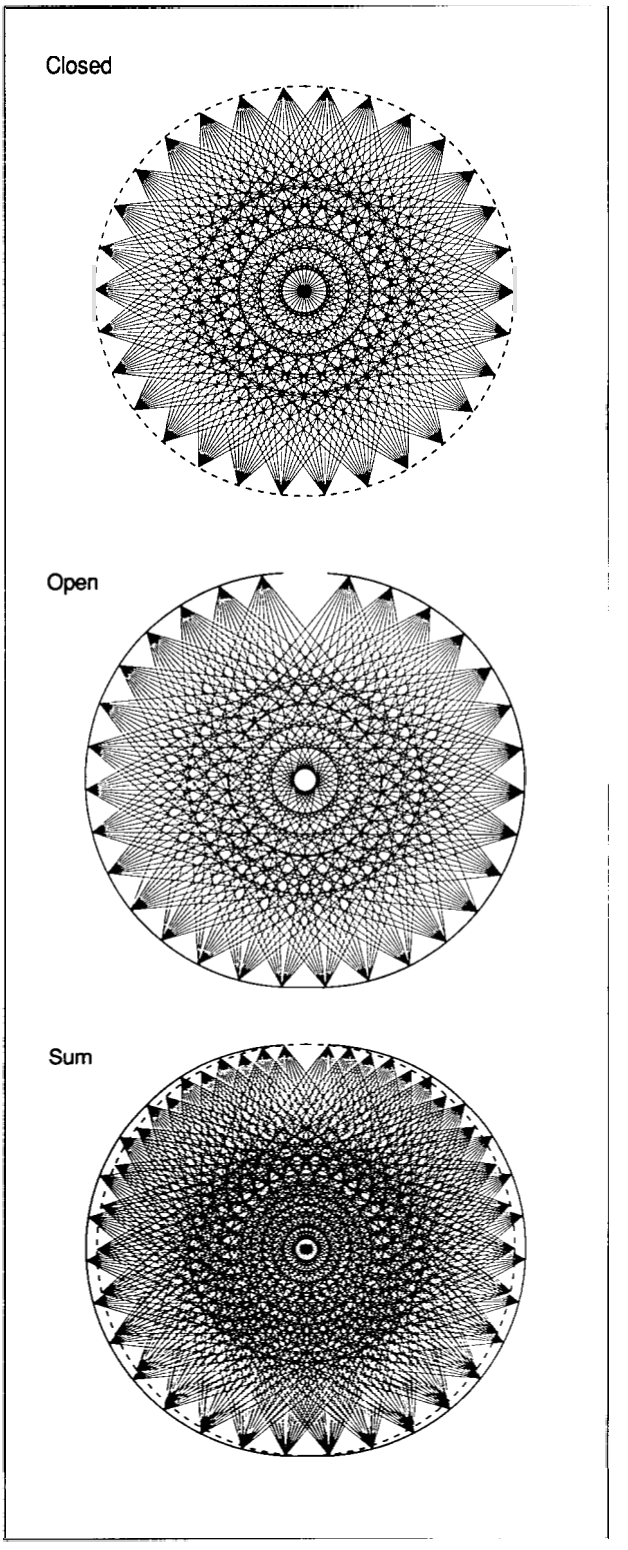
For future applications, such as the one described on page 16, we have proposed the detector shown in the figure below. It would consist of three or more optically isolated BGO crystals attached to a single 10.0-mm-square photomultiplier tube, which provides a fast timing pulse for the group. Each crystal is also individually coupled to a position-sensitive photodiode which identifies the crystal that stopped the annihilation photon and determines the depth of interaction. Prototypes of the detector system, the surface-mount charge amplifiers used to read out the position-sensitive photodiodes, and the associated digital circuits are now being developed. The objective is to build a tomograph capable of quantifying the energy metabolism and neurochemistry of regions of the brain such as the hippocampus, thalamus, hypothalamus, basal brain stem nuclei, and cerebellar nuclei. The sensitivity-resolution capabilities of this system are unique.



A detector design for still higher resolution. *The distribution of light between the two triangular segments of each photodiode establishes the depth of the scintillation event, thus reducing the astigmatism problem described on page 4.*

Sampling Strategies

As shown in the upper diagram to the right, spatial sampling by a stationary ring of detectors limits image uniformity and spatial resolution, because the lines of coincidence are coarsely spaced relative to the detector resolution. The sampling density can be improved by wobbling the detector assembly or, alternatively, by a subtle "clamshell" motion of the entire detector array. Clamshell sampling, a method developed at the Lawrence Berkeley Laboratory, employs a slight rotation of each half of the circular ring of 600 crystals in the PET-600. When the clam is shut and therefore has an even number of crystals, as in the top figure, the sampling lines between opposing detectors form concentric circles. The middle figure shows the clam in the open position, with, in effect, an odd number of detectors with one missing. The concentric rings formed by the sampling lines in this position lie between those produced when the clam is shut. Consequently, when data from both positions are combined, the sampling density is doubled, improving both uniformity and spatial resolution.



A clamshell sampling strategy. *Lines between pairs of detectors yield different sampling patterns, depending on whether the detector "shells" are closed or open. Combining data obtained in both positions maximizes sampling uniformity and spatial resolution.*

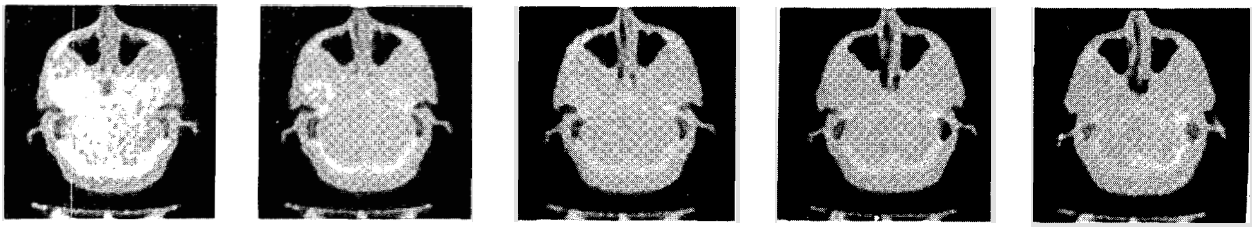
Attenuation and Localization

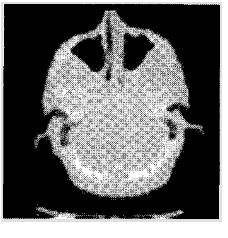
PET reconstruction requires a priori knowledge of the spatial distribution of attenuation coefficients in the imaging volume. We use the PET instrument to acquire an x-ray CT–like transmission image by positioning a positron-emitting source outside the patient. The transmitted fraction of 511-keV photons is detected for each angle around the patient. This method is analogous to x-ray CT, except instead of an x-ray tube rotating around the patient, we use a very strong radioactive source.

The rotating source technique is nearly ten times as efficient as distributed "hoop" sources commonly used in PET, because it allows one to overcome the problem of accidental coincidences, the rate-limiting factor in transmission data acquisition.

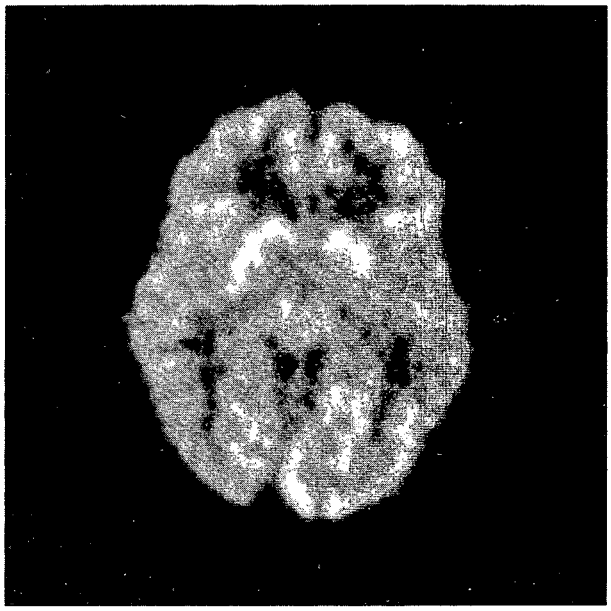
In addition to providing the attenuation coefficients needed for PET reconstruction, our transmission images are sufficiently accurate to allow image features to be related to anatomical structures. The bony characteristics of the skull and other parts of the body allow one not only to accurately determine the position of the emission section but also to reproduce patient placement for sequential follow-up studies.

PET transmission images for attenuation coefficients and patient repositioning. *Shown here is an example of a transmission study comprising five overlapping transverse sections, separated by 2 mm center-to-center. The single image at the bottom was acquired on a later occasion to verify the accurate repositioning of the patient.*

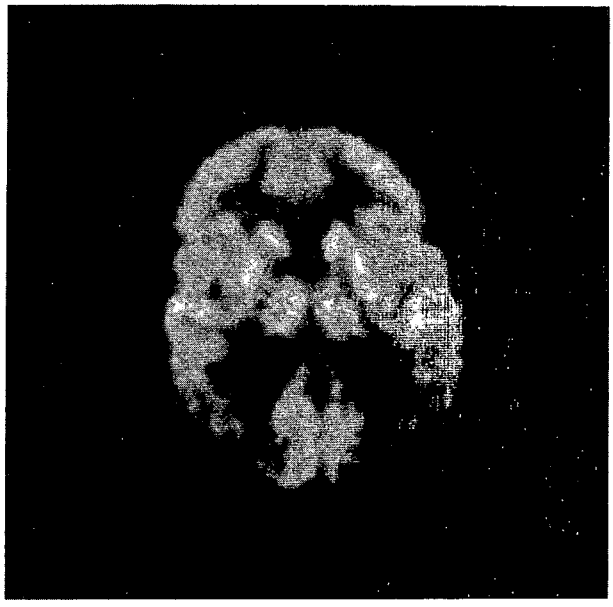




Alzheimer's Disease



Control

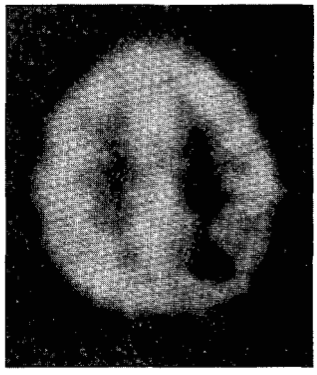


Alzheimer's disease

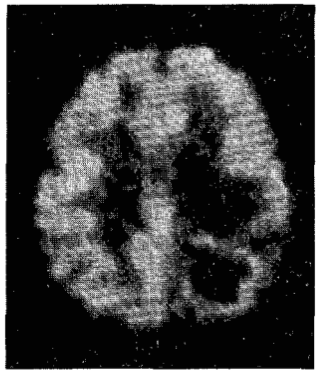
The adjacent figures show PET-600 brain images from a pair of age-matched subjects, one suffering from Alzheimer's disease and the other a control. The upper image shows the brain of the Alzheimer's subject; the low accumulation of glucose in the temporal and parietal regions is characteristic of the disease. The PET-600 allows improved visualization and quantitation of small details of subcortical regions of the brain, as well as improved differentiation of gray matter, white matter, and cerebrospinal fluid to account for the effects of atrophy. These measurements will improve our diagnostic ability and our understanding of the pathophysiology of the disease.

Tumors

Images of brain glucose metabolism of tumors were obtained from the same patient, using the low-resolution PET (upper image at right) and the high-resolution PET-600. A central region of necrosis can be seen in both images. However, the PET-600 image clearly shows a rim of high activity around the necrosis, which is not apparent in the low-resolution image. Detection of this rim of high metabolism around the necrosis leads to the proper diagnosis of recurrent tumor.



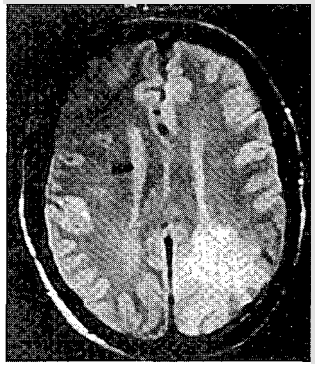
PET-280



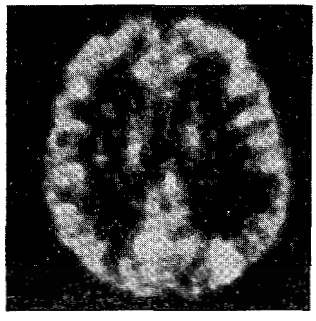
PET-600

PET vs NMR in Tumor Studies

Although in many cases, NMR and PET complement each other in imaging the body, PET's ability to image metabolic activity makes the technique particularly useful in studying recurrent tumors and the effect of radiation therapy. Unlike the image produced by NMR, at right, PET allows a distinction to be made between a region that has become cancerous again after radiation and a region that has undergone necrosis as a result of being exposed to radiation. The NMR image shows an intense region of signals consistent with either radiation necrosis or recurrent brain tumor. The PET image, on the other hand, specifically shows a region of high metabolic activity in the occipital cortex, indicating the presence of recurrent tumor. The higher resolution provided by the PET-600 permits the analysis of a smaller area of metabolism, thus increasing the method's utility as a diagnostic tool.



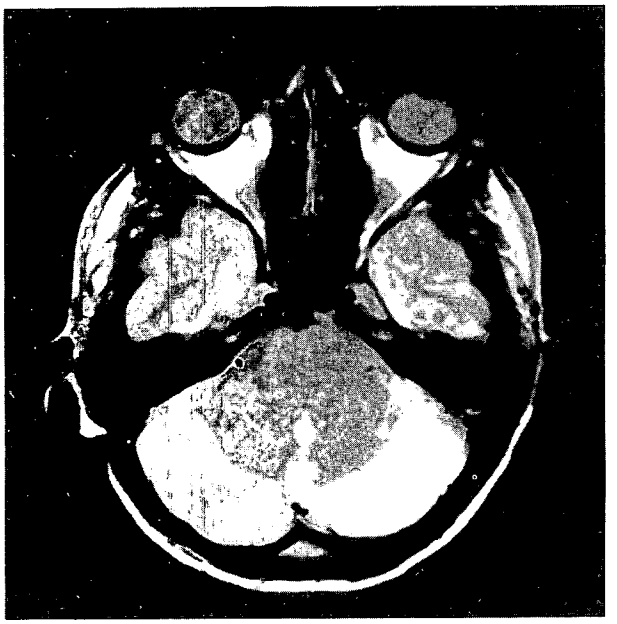
NMR



PET-600

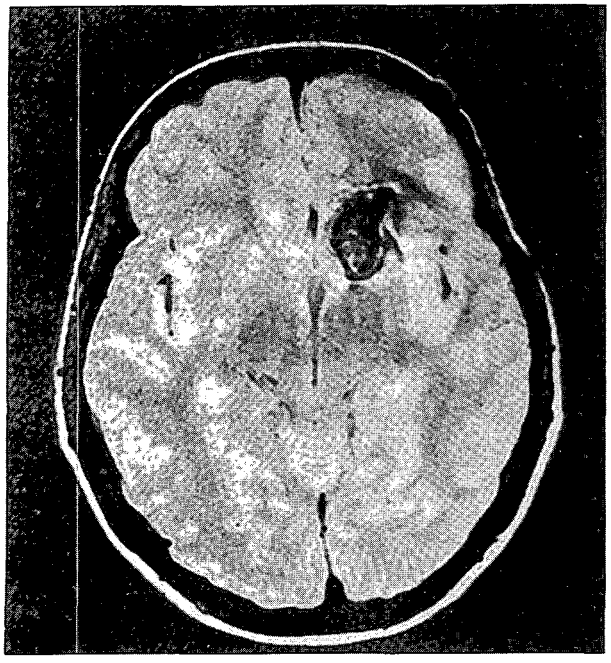
Epilepsy

Epileptic seizure foci are detected as areas of hypometabolism in PET glucose metabolism studies performed when the patient is not having a seizure. The adjoining image shows decreased metabolism in the temporal lobe in a patient with controlled partial complex epilepsy. The PET study was performed to localize the seizure focus prior to surgery. Localization of the epileptic foci with new tracers is a major potential of high-resolution PET.

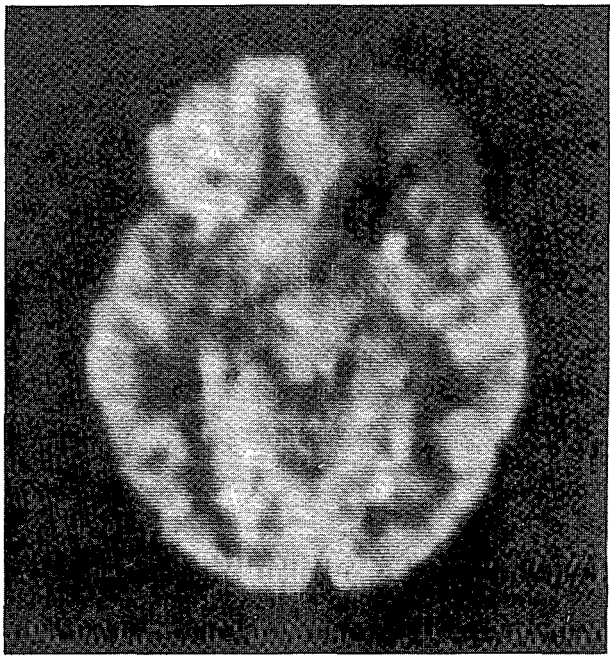


NMR

PET



NMR



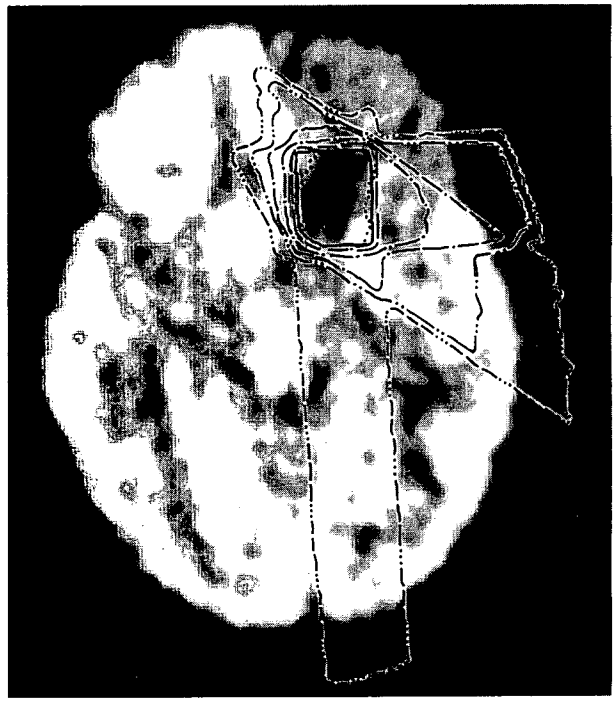
PET-600

Arteriovenous Malformations (AVMs)

The NMR image above shows the AVM as an area of signal loss due to blood flow. The PET image shows the AVM as a region devoid of glucose metabolism and also shows decreased metabolism in the adjacent frontal cortex. This is a metabolic effect of the AVM on the brain and may explain some of the patient's symptoms.

Treatment Planning with PET

Positron emission tomography depicts metabolic information which in many cases is not reflected in changes of the NMR signal or in structural changes that would be detected by x-ray CT. As a result, PET can play a critical role in treatment planning. For example, it is important to avoid further injury to tissues surrounding a tumor or an AVM, as those tissues are already being compromised by a shunting of blood flow or by pressure associated with the pathological condition. Shown here is an example of a treatment plan in which a criterion is the avoidance of the left frontal lobe tissues, which had a low metabolic rate as a consequence of a nearby arteriovenous malformation. In this particular case, the NMR image did not show a change in signal in the frontal lobe.

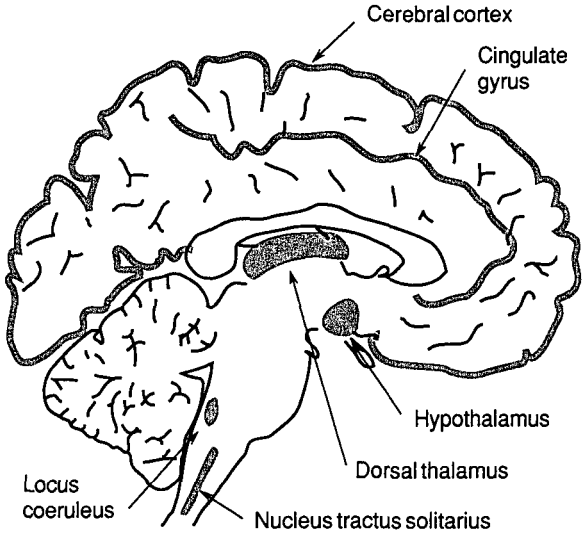


FUTURE DIRECTIONS

Instrumentation for a Deeper Understanding of Neurophysiology

With the technology embodied in the PET-600 tomograph, we are now able to visualize small structures in the brain and to reliably quantify activity there, as well as in the heart and in tumors throughout the body. The present resolution capabilities have the potential for delineating epileptic foci and for revealing normal and abnormal balances in brain neurochemistry. However, some physiological structures remain beyond the limits of even PET-600. In addition, metabolic studies are limited by the fact that we can acquire data from only one "slice" at a time, a limitation imposed by the detector configuration adopted to optimize the resolution. Medical problems that require a higher-resolution system with a "multislice" capability include the evaluation of major brain neurochemical regions such as the very thin ribbon of the frontal cortex where the excitatory α_2 adrenergic system neuroreceptors are found. Even with a suitable chemical tracer, our 2.6-mm-resolution system cannot accurately image this elusive region of metabolic activity. In addition, important control centers for memory, cardiovascular activity, and arousal, including the hippocampal gyri, the locus ceruleus, the nucleus tractus solitarius, and the basal forebrain nuclei (thought to play an important role in Alzheimer's disease) are too small to be imaged with the best of today's PET systems. Thus, the causative mechanisms of memory disorders, depression, and circulatory system abnormalities such as hypertension await development of PET instrumentation with a spatial resolution of 2 mm or less.

In light of this need, we are continuing to work toward a cost-effective detector system that would overcome the "single-layer limitation" and, at the same time, further improve resolution. By reducing the detector width to 2 mm, it is possible to build an instrument with a resolution of 2 mm. Furthermore, by using detectors such as those described on page 8, we can reduce the astigmatism associated with off-center annihilation events. Our current goal is to develop a 20-ring multislice positron tomograph with over 10,000 crystals and a 2.0-mm in-plane spatial resolution over 39 imaging planes. Such an instrument would open an entirely new era in neurophysiological research, offering for the first time an opportunity to do metabolic studies on a scale commensurate with the size of physiological control centers in the brain.



Frontiers of neurophysiology. *The α_2 system of adrenergic receptors, shown here in color, is believed to play a major role in the control of hypertension and perhaps coronary blood flow. A multilayer PET system with improved resolution is motivated in part by the potential it would provide for studying these very small or narrow clusters of specific neuroreceptors.*

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