# Functional Brain Imaging with Single Photon Emission Computed Tomography and Positron Emission Tomography

*a report by*
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## Introduction

In general, imaging can address two issues: structure and function. It is possible either to view structures in the body and image anatomy or view chemical processes and image biochemistry. Structural imaging techniques can image anatomy and include ultrasound, X-rays, computerised tomography (CT) and magnetic resonance imaging (MRI). Bone can be distinguished from soft tissue in X-ray imaging, and organs become delineated in CT and MRI imaging. Biochemical modalities – single photon emission computed tomography (SPECT) and positron emission tomography (PET) – differ from structural modalities in that they follow actual chemical substituents and trace their routes through the body. These methods give functional images of blood flow and metabolism that are essential to diagnoses and to research on the brain, heart, liver, kidneys, bone and other organs of the human body.

Since anatomical structures usually serve different functions and embody different biochemical processes, to some degree, biochemical imaging can provide anatomical information. However, the strength of these methods is to distinguish tissue according to metabolism not structure. For example, *Figure 1* shows a transaxial slice through the human brain (top row) acquired with different imaging modalities (bottom row), giving different information about the brain function and anatomy. Several clinical applications are associated to each imaging technique.

## Nuclear Medical Imaging

SPECT allows tomographic images to be reconstructed from projection data acquired at discrete angles around the object and has, in recent years, become one of the major tools for the *in-vivo* localisation of radiopharmaceuticals in nuclear medicine studies. Important clinical areas of SPECT imaging include cardiology, neurology, psychiatry and oncology. In conjunction with new and existing radiopharmaceuticals, quantitative SPECT may be used to measure non-invasively blood flow, metabolic function, receptor density and drug delivery. In oncology, it is important in radiation dosimetry and treatment planning for internal radionuclide therapy, in general, and radioimmunotherapy, in particular.

High resolution and great sensitivity are two paramount goals of SPECT imaging. Therefore, researchers must always consider this trade-off when working on new collimator designs. There have been several collimator designs in the past 15 years that have optimised the resolution/sensitivity inverse relation for their particular design. Converging hole collimators, for example fan-beam and cone-beam, have been built to improve the trade-off between resolution and sensitivity by increasing the amount of the Anger camera that is exposed to the radionuclide source. This increases the number of counts, which improves sensitivity.

More modern collimator designs, such as half-cone beam and astigmatic, have also been conceived. Sensitivity has seen an overall improvement by the introduction of multi-camera SPECT systems. A typical triple-camera SPECT system equipped with ultra-high-resolution parallel-hole collimators can achieve a resolution of between four to seven millimetres. Other types of collimators with only one or a few channels – pinhole collimators – have been designed to image small organs and human extremities such as the wrist and thyroid gland, in addition to research animals such as rats.

On the other hand, PET scanners' design has an interesting history. It includes early systems based on gamma cameras, the use of discrete detectors in opposing planar arrays and rings, the use of a variety of scintillators (for example, thallium-doped sodium iodide (NaI(Tl)), bismuth germanate (BGO), barium fluoride ($BaF_2$), plastic and lutetium orthosilicate (LSO)) and systems based on wire chambers and hybrids of wire chambers and scintillators. In 2000, some of the old technologies used in PET systems have re-emerged (for example, dual-head gamma cameras operated in coincidence mode) as well as new scintillators and new detector design directions (for example, layered crystals with pulse-shape discrimination). Wire chambers of various kinds are also still being developed for PET applications. Phoswich detectors, where a 'low-energy' detector (for example, yttrium oxyorthosilicate (YSO)) is placed in a front layer and is used for low-energy SPECT imaging, and a 'high-energy' detector (for example, LSO) in a second layer is used for PET imaging, are also receiving considerable attention for the design of dual-modality scanners (SPECT/PET). As PET has become of more interest for clinical practice, several different design trends seem to have developed. Systems are being designed for 'low-cost' clinical applications, very high-resolution research applications and almost everywhere in between.

All of these systems are undergoing revisions in both hardware and software components. New technologies that are emerging include the use of LSO and GSO as alternatives to BGO crystals, the use of layered crystals and other schemes for depth-of-interaction determination (for dedicated systems) and for hybrid SPECT/PET devices (for example, NaI(Tl)/LSO). In addition, high-resolution animal scanner designs are plentiful and two such devices are now being offered commercially. There are many different design paths being pursued that could be the mainstream of future research systems. The SPECT/PET systems are pushing ahead for higher count rate performance (still a major area of difference between hybrid and dedicated PET systems) and effective scatter and attenuation correction capabilities as well as combined functional and anatomic imaging (PET/CT and SPECT/CT). The dedicated systems seem to be splitting into two major design paths:

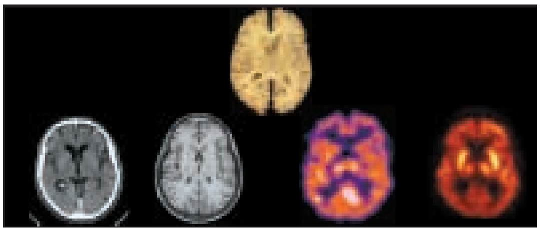
- lower cost yet higher performance whole body imaging systems; and
- very high spatial resolution systems aimed primarily at research applications.

The major technologies currently under development seem to be centred on improved, cheaper electronics and better scintillators. One technology that has yet to make a significant impact in this field is the use of solid-state devices – either for light collection or primary photon collection. The problem has usually been cost, but new technology may yet allow such devices to be considered for future SPECT/PET systems. It will be interesting, indeed, to see what technologies become the most popular in the future.

## Recent Advances in Image Correction and Reconstruction Techniques

Many mathematical approaches have been used for image reconstruction in SPECT and PET. Two broad categories have emerged that are referred to as analytic and iterative algorithms. The common characteristic of analytic methods is that they utilise exact formulae for the reconstructed image density. Historically, the most popular method is filtered back-projection where the acquired projection data is filtered with a ramp filter before being back-projected. The iterative approach is based on the process of matching the measured projections to the calculated projections. The calculated projections are determined from an initial reconstruction and are compared with the measured data. The difference between the two data sets is used to correct the calculated projections. This procedure is repeated until some predefined error level has been reached. Statistical reconstruction techniques such as the maximum likelihood expectation maximisation (ML-EM) algorithm seek a source distribution that will maximise the ML function relating the estimated and the measured projections.

***Figure 1: Transaxial Slice of the Human Brain (Top)***



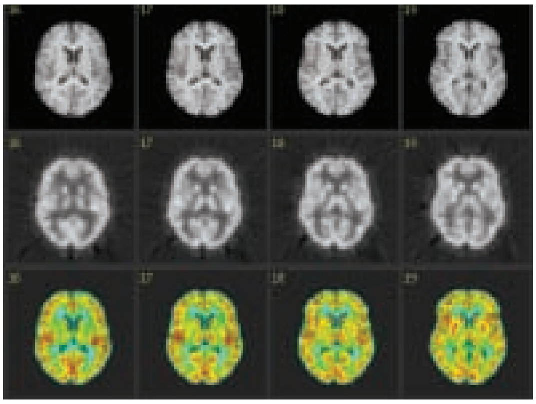
*Acquired with both morphological and functional imaging modalities (bottom); from left to right: X-ray CT, MRI, SPECT and PET.*

Modern image reconstruction methods involve two key components. The 'software' of image reconstruction is an objective function (the likelihood function) that describes the acceptability of an image solution. The 'hardware' is the algorithm for optimising the objective function to find the best solution. In recent years, 'hardware' components such as the ordered subsets expectation maximisation (OSEM) algorithm have been widely studied with an aim towards producing image reconstruction algorithms that will be practical in the near term. With advances in computer technology (for example, multiprocessor personal computers (PCs) and PC clusters) and optimisation techniques (for example, Monte Carlo Markov Chain methods), the machinery of optimisation will allow more complex objective functions to be used; thus, the software of image reconstruction will become the dominant open issue. The research community's relative lack of success in developing good Bayesian priors for image reconstruction is one explanation. Simple priors, or no priors at all, have often been preferred to sophisticated edge-preserving priors that tend to create unnatural image results.

The image quality and quantitative accuracy of SPECT and PET reconstructions is degraded by a number of physical factors including:

- the finite spatial resolution of the imaging system and the resulting partial volume effect;
- the attenuation of the photons travelling towards the detector elements;
- the detection of scattered photons;
- the limited number of counts that is able to be

***Figure 2: Transaxial Slices of a Clinical Brain Study***



*Acquired with both morphological and functional imaging modalities; from top to bottom: MR, PET and finally the fused MR/PET image.*

collected when imaging patients;

- physiological and patient motion; and
- the reconstruction algorithm.

While it is well accepted by the nuclear medicine community that the detection of Compton-scattered events degrades image quality, a common question asked by most nuclear medicine physicians concerns to what extent scatter affects image interpretation and clinical decision-making, whether it reduces diagnostic accuracy and what the real added value of scatter correction in clinical and research applications is. The physicists are convinced that attenuation and scatter corrections are vital components towards the production of artefact-free quantitative data.[1,2]

The major manufacturers of dedicated PET tomographs supply attenuation and scatter correction software to end-users, whereas the dual-head gamma camera market is still suffering in this respect. However, it is expected that commercial software for accurate quantitation will be available shortly. Quantitative nuclear imaging is an area of considerable research interest and many research groups are very active in this field, leading the nuclear medicine community to forecast promising progress during the next few years.

The collection of various data from anatomical and functional imaging modalities is becoming very common for the study of a given pathology, and its aggregation generally allows for a better medical decision in clinical studies. Multimodal data fusion appears more and more as a key element for the optimal use of images. The MR/PET fusion process is illustrated in one clinical case (see *Figure 2*).

## Clinical and Research Applications of Functional Brain Imaging

This section aims at providing a short overview of the applications of SPECT and PET techniques in cognitive studies as well as in some neurologic and psychiatric diseases. Both techniques (especially PET) have been employed extensively to identify the neuroanatomical basis of various cognitive functions such as memory, perception and attention. Generally, cognitive PET experiments have focused on cerebral blood flow, a measure that provides the most reliable index of moment-to-moment brain function[3], thus allowing the assessment of the whole network of brain areas involved by a certain behaviour. In brief, a standard cognitive PET study consists of several consecutive scans per subject, measuring blood flow changes in the brain that take place while the subject is engaged in some kind of cognitive task. By comparing the activation pattern associated with different conditions, it is possible to identify brain areas showing differential response in relation to a specific cognitive performance. These methods have, for example, allowed the study of the impact of age-related physiological changes in the brain on cognition, and determining how this activity differs between young and older people. The data usually shows that older people utilise different areas of the brain than young subjects when performing the same cognitive task at the same level of proficiency.[4] Grady[5] interpreted these differences in terms of functional reorganisation or functional plasticity.

These methods have also been employed widely in many neurologic conditions such as epilepsy, neurodegenerative disorders, cerebrovascular diseases, movement disorders and malignant brain tumours. SPECT brain scans can study perfusion in epilepsy patients, particularly those with focal epilepsy emanating from the medial temporal lobes and

1. *H Zaidi, "Scatter modelling and correction strategies in fully 3D PET",* Nucleur Medicine Communications*, 2001, vol. 22: pp. 1,181–1,184.*
2. *H Zaidi, M Diaz-Gomez, A E Boudraa and D O Slosman, "Attenuation correction for whole-body PET imaging using automated fuzzy clustering-based segmentation method",* Proceedings of the IEEE Nuclear Science Symposium and Medical Imaging Conference*, San Diego, in press, 2001.*
3. *M E Raichle, "Images of the mind: studies with modern imaging techniques",* Annual Review of Psychology*, 1994, vol. 45: pp. 333–356.*
4. *A R McIntosh, A B Sekuler, C Penpeci, M N Rajah, P J Bennett, C L Grady and R Sekuler, "Neural systems of visual memory in young and old observers",* Neuroimage*, 1998, vol. 7: pp. S526.*
5. *C L Grady, "Brain imaging and age-related changes in cognition",* Experimental Gerontology*, 1998, vol. 33: pp. 661–673.*

producing complex partial seizures.[6] Ictal, postictal and interictal studies allow identifying focuses of epileptic discharges that increase cerebral perfusion during seizures and reduce perfusion postictally and interictally. These studies are used as preoperative investigations and have become an important adjunct to clinical and electrophysiological evaluation of patients with epilepsy who are surgical candidates.

SPECT and PET brain scans have also been helpful in highlighting that hypometabolism occurs bilaterally in the parietal and posterior temporal lobes of Alzheimer's disease patients, in the frontal lobes extending to the cingulated gyrus in frontotemporal dementia and in Creutzfeldt-Jakob disease, for example. Scanning of patients using flurodeoxyglucose (FDG)-PET provided observations of hypometabolic regions in movement disorders, for example, in the striatum in Huntington's disease. [$^{18}$F]dopa-PET is the most commonly applied radiotracer for the study of presynaptic dopaminergic function in the basal ganglia in Parkinsonism. With recent advances in PET technology, this method has become more sensitive at identifying extrastriatal and preclinical changes in Parkinson's disease. Moreover, the pattern of [$^{18}$F]dopa in the striatum can be employed to differentiate between Parkinson's disease and two other diagnoses that can be difficult to separate clinically, namely supranuclear palsy and multiple system atrophy. Hypermetabolism occurs in cortical and subcortical regions in tardive dyskinesia and has been found in high-grade cerebral neoplasms such as glioblastoma multiform as well as in intracranial infections. Oxygen metabolism has been used extensively in evaluation of ischemic cerebrovascular disease to determine the 'cerebral perfusion reserve'.

In psychiatry, functional brain imaging studies have suggested the neural basis of several mental disorders such as schizophrenia and obsessive-compulsive disorder. Abnormal functional activity has been identified in prefrontal cortex, temporal lobes, thalamus and medial temporal lobe in patients with schizophrenia. The majority of findings suggest a disruption of frontotemporal integration that might underlie schizophrenia.[7] PET and SPECT data on obsessive-compulsive disorder have revealed abnormal regional cerebral blood flow and glucose metabolic rates, particularly in orbitofrontal and striatal areas in drug-free, non-depressed patients with obsessive-compulsive disorder. ■

6. *M D Devous, R F Leroy and R W Homan, "Single photon emission computed tomography in epilepsy",* Seminars in Nuclear Medicine*, 1990, vol. 20: pp. 325–341.*
7. *K J Friston and C D Frith, "Schizophrenia: a disconnection syndrome?"* Clinical Neuroscience*, 1995, vol. 3: pp. 89–97.*