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Positron Emission Tomography in the Study of Brain Metabolism in Psychiatric and Neuropsychiatric Disorders

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Positron emission tomography (PET) differs fundamentally from computerised tomography (CT) and magnetic resonance imaging (MRI) in that it is a method for measuring function as opposed to structure. It is the most powerful tool available for the measurement of *in-vivo* brain function. This review describes the basic principles of the technique and its application to the study of brain metabolism in neurological and psychiatric disorder. The development of resting-state metabolic studies by the application of specific activation paradigms, a major current focus of the technique, is discussed.

Principles

The feasibility of PET is dependent upon the availability of compounds that can be labelled with positron-emitting nuclides. The signal measured in PET is derived from the decay of those radioactive substances, which are introduced into the body either by intravenous injection or by inhalation. The most useful and most commonly used nuclides are oxygen-15, carbon-11 and fluorine-18 with half-lives of 2.1, 20.4 and 110 minutes respectively. These are essentially ideal in that their substitution into molecules of biological interest does not alter the behaviour of the compound in the body from that of the stable parent compound. Fluorine-18 usually substitutes for a hydrogen atom in a molecule that will normally contain no stable fluorine; even such relatively minor substitutions may subtly alter biological properties. The short half-lives of the commonly used tracers makes an on-site cyclotron a prerequisite for a PET centre. Recent developments of mini-cyclotrons and automated 'black-box' production of tracers may diminish the capital outlay necessary to perform PET at the expense of constraining the range of possible studies. The major advantage of using tracers with a short half-life is that this ensures a low radiation dose to the subject, enabling repeat studies, if necessary even within the same scanning session. This has particular relevance to the development of activation paradigms using dynamic estimations of blood flow.

Positrons, which are positively charged electrons, when emitted from decaying nuclei, travel a short distance (1–3 mm) in tissue until they interact with an electron, resulting in an anhihilation reaction. This reaction releases two gamma rays of equal energy (511 keV) which travel in exactly opposite directions. A detector system of high sensitivity placed circumferentially around the head can map the distribution of the positron-emitting nuclide. These detectors are electronically linked by coincidence circuits so that only the simultaneous arrival of gamma rays at two opposite detectors is registered as an 'event'. Using standard computerised reconstruction techniques, in conjunction with coincidence detection, it is then possible to map the spatial and temporal distribution of the positron-emitting nuclide (Ter-Pogossian & Phelps, 1975; Huang *et al*, 1979; Hoffman *et al*, 1979). Loss of signal due to attenuation by brain tissue can be corrected by performing a transmission scan, in which the subject is exposed to an external ring source of radioactivity located within the scanner, before the emission study. With the latest detector systems it is possible to obtain up to 31 contiguous slices of data from the 10.8 cm of the head scanned. In-plane resolution of the order of 5 mm has been obtained with scanners that are at the present limits of technological sophistication. Sensitivity of detection is exquisite, such that picomolar concentrations of radiolabelled substances can be measured. By comparison, magnetic resonance (MR) spectroscopy has a sensitivity in the tens to hundreds of millimolar range. With suitable calibration, the tissue tracer distribution can be recorded in absolute physical units of radioactivity (Ci/ml). The PET camera therefore is a measuring instrument in addition to an imaging device.

PET methods of measurement of brain metabolism

The data acquired in a PET study need to be understood and expressed in terms of some physiological, biochemical or pharmacological process. This is achieved using a model, which in its simplest form is a mathematical description of the biological process being measured in terms of the temporal and spatial fate of the tracer, such that the parameter of

interest can be derived. Mathematical models are generally used to incorporate known information about a process so as to provide a framework or representation that allows the interpretation of measurements. The simplest methods are those used to measure tissue metabolism. PET measurements of metabolism depend on the fact that in the adult brain functional activity is almost entirely dependent on oxidative metabolism requiring oxygen and glucose as substrates (Siesjo, 1978). Rates of metabolism can be determined by measuring the rate of utilisation of a substrate, as in the oxygen technique (Frackowiak *et al*, 1980), or the accumulation of a product, as in the deoxyglucose technique (Phelps *et al*, 1979; Reivich *et al*, 1979). The detail of these methods is beyond the scope of this review and the reader should refer to previous comprehensive reviews (Phelps *et al*, 1986; Baron *et al*, 1989).

Clinical application of PET

A PET scan can typically last between 45 minutes for a resting metabolic or flow scan and two or more hours for a study using a pharmacological tracer. Preparation for the scan involves fabrication of a head holder to ensure immobility during the scan, and insertion of a radial artery catheter. The latter is required to enable sampling of arterial blood during the scan, in order to measure the amount of tracer in the blood and accurately define the arterial input function to the brain. Maintenance of head position during the scan is of crucial importance in increasing the signal-to-noise ratio.

The use of a head holder inhibits gross movement within the scanner but finer movements are more difficult to control. The inherent intersubject variability in brain size and shape is a further important confounding variable in identification of the site of origin of a functional signal. These problems have been addressed in a number of ways. A structural (MR or CT) scan may be taken with an external frame of reference to allow cross-modal (structure–PET) matching. If this is not the case, then structures in the PET images have to be identified by inspection. This is justifiable in some PET images such as ^{18}F-DOPA images of the basal ganglia, but it is not an ideal approach to metabolic images. The method used at the MRC Cyclotron Unit at the Hammersmith Hospital involves the matching of each individual PET scan to a standard PET template in a least-squares sense. This template has a predetermined relationship (Friston *et al*, 1989) to a standard stereotactic space (Fox *et al*, 1988; Talairach & Tournaux, 1988). This avoids the need for a structural scan while maximizing the probability that a signal from the same place in two images relates to the same part of the brain. To illustrate the problem, and this solution, Plate VI shows two schizophrenic brains before and after elastic transformation into a standard reference space.

The confinements of the technique may lead to bias in patient selection, particularly where cognitive or perceptual disturbance leads to agitation, perplexity and behavioural overactivity. This has particular relevance for studies of dementing or psychiatric patients and is discussed in more detail below.

Data acquisition

The methods sections of many papers detail a number of technical specifications which relate to the nature of the images acquired. Many of these are of little importance, particularly with reference to established protocols such as for the estimation of regional cerebral blood flow (rCBF) and regional cerebral metabolic rate of glucose. One specification which should be noted is the number of planes acquired. This can vary from 3 to 31 and for values of less than 15 there is likely to be 'dead space' – interplane cerebral tissue not seen by the camera. In studies with small plane numbers, or those reporting a single plane at a time, the signal in a region of interest (ROI) (e.g. for the caudate) will reflect both the proportion of the total volume of the caudate represented within the plane and its activity. This extra source of error will predispose to type 2 errors.

The full width at half maximum (FWHM) is a measure of the camera's resolving power and is typically 8 mm. Studies on machines with a larger FWHM are as 'good' as 'high-resolution' PET. This is because all data analysis begins by 'smoothing' the images, either directly or, by definition, when using ROIs.

Changes in metabolism with ageing

Studies of normal ageing using PET have concentrated on defining the normal regional changes in cerebral metabolism (of oxygen and glucose) and haemodynamics. Measurements of glucose metabolic rate (Kuhl *et al*, 1982; Duara *et al*, 1983) have yielded less consistent results than measurements of oxygen metabolism in relation to blood flow, performed extensively using the steady-state oxygen inhalation technique (Frackowiak *et al*, 1980). The salient points of these studies are that there is an age-related decline in blood flow in grey matter but not white matter and that this is not paralleled by a decline in the

metabolic rate of oxygen. There is a trend towards increased oxygen extraction (OER) reflecting the maintenance of metabolism in the face of declining flow.

Dementia

Global changes

In contrast to the normal ageing process, patients with Alzheimer's disease (AD) have a progressive decline in both CBF and metabolic rate of oxygen in grey matter which correlates with the severity of cognitive impairment. This metabolic decline is also seen in white matter. In terms of global changes of metabolism, decreases of up to 50% of normal control values have been reported. The coupled relationship between CBF and metabolic rate of oxygen holds for both hemispheric and regional analysis, with emphasis on posterior temporal and parietal regions (Frackowiak *et al*, 1981). As yet, it remains uncertain whether the changes demonstrated reflect diminished neuronal numbers or diminished metabolism in numerically normal neurons. PET studies using fluorodeoxyglucose have also shown significant decreases in the metabolic rate of glucose in the same temporoparietal regions (Friedland *et al*, 1983).

For any condition studied, the interpretation of local changes in activity will be confounded by the global change. In most conditions what is of interest is the true regional change and its relationship to discrete symptoms, signs, or activation by specific neuropsychological or pharmacological paradigms. In order to delineate this regional effect, the global activity must be normalised. Methods of normalisation range from simple division by a global mean to *post-hoc* statistical adjustments (Friston *et al*, 1990). Whatever the method used it is important to bear in mind that statements about regional differences can only be relative. For example, hypofrontality may well be hyperoccipitality. If data have been normalised there is no way of distinguishing between the two. If no normalisation has been applied then regional differences will be confounded with global differences.

Morphological changes in dementia

Structural imaging has demonstrated gross morphological brain changes in AD, particularly cortical atrophy. These latter changes could introduce problems of quantification in PET, in that the presence of non-neural elements within the volume might influence functional measurements. As yet there are no entirely satisfactory methods for correcting for these partial-volume effects, although systematic correction of the PET image on a pixel-by-pixel basis with reference to high-quality MR imaging has been described (Videen *et al*, 1988). It can be assumed therefore that calculated values for energy metabolism reported in the literature are an overestimation of the true decrease in metabolism.

Focal changes

Oxygen and glucose methods have found similar patterns of regional pathophysiology in AD. Deficits in metabolism have an emphasis initially in the parietal and adjoining parts of the posterior temporal cortex and anterior occipital cortex. Progression of the dementia is associated with decreased frontal metabolism, but with relatively little further change in the temporoparietal regions. Characteristically the primary motor and sensory cortex and striatum are relatively spared (Frackowiak *et al*, 1981). Focal abnormalities have been correlated with clinically determined impairments (Chase *et al*, 1984*a*; Foster *et al*, 1984, 1986). In particular, aphasia, apraxia and visuospatial function have been correlated with changes in metabolism in the appropriate hemisphere. The levels of clinical effects correlating with decreased metabolism in AD have been reviewed by Huxley & Rapoport (1986). Firstly, reductions in whole-brain metabolism are related to overall severity of dementia. Secondly, regional hypometabolism in the association cortices exceeds that in primary sensorimotor cortex, corresponding to marked impairment of higher cognitive function. Thirdly, greater metabolic asymmetry is accompanied by disproportionate neuropsychological deficits in either language or visuospatial functions, depending on whether the hypometabolism is in the dominant or non-dominant hemisphere, respectively.

A group of conditions increasingly recognised clinically are the so-called focal degenerations which present initially with highly selective neuropsychological impairments, most commonly aphasia. Both clinical and neuropathological findings suggest that these are distinct conditions from Alzheimer's disease (Mesulam, 1982). Gross structural brain changes are not usually apparent in the early phase of these disorders, though PET can reveal alterations in metabolism before the development of structural change (Tyrrell *et al*, 1990). The pattern of altered metabolism is frequently highly focal and distinct from that seen in early AD. The ability to perform serial studies on these patients should help to clarify the nosological status of these conditions and the degree to which they are truly focal or generalised degenerations with an early focal emphasis.

Multi-infarct dementia and cerebrovascular disease

Pathological studies show that the substrate for vascular dementia is the cumulative effect of multiple ischaemic infarctions, usually with strategic placement and exceeding a threshold volume (Tomlinson *et al*, 1970). The pathophysiological sequence in the acute events is a fall in perfusion pressure and flow to below 50% of normal. At this stage oxygen extraction (OER) is maximal and the ischaemic threshold is crossed. Depending on the depth and duration of ischaemia, cell death and/or frank infarction will occur. This phase is characterised by a low oxygen metabolic rate with high OER which rapidly changes to low metabolic rate and low OER when neuronal damage occurs (Wise *et al*, 1983). At some time following a stroke, tissue reparative processes usually lead to recoupling of CBF and oxygen metabolic rate and normalisation of OER.

Multi-infarct dementia (MID) produces global reductions in cerebral metabolism but in addition there are focal and asymmetric areas of hypometabolism, not confined to any particular brain region. Various studies have demonstrated multiple lesions in cortex, deep nuclei, subcortical white matter and cerebellum (Frackowiak *et al*, 1981; Kuhl *et al*, 1985*a*,*b*). Typically, more widespread brain involvement is detected by PET than by CT, consistent with the finding that single lesions may have extensive and distant metabolic sequelae. Characteristically, increasing severity of dementia correlates with global hypometabolism and increasing involvement of the frontal cortex.

More striking examples of alterations in metabolism are seen in patients who have experienced isolated lacunar infarcts, detected by structural imaging, affecting cortical or subcortical grey matter. These discrete anatomical lesions frequently produce cerebral metabolic effects at sites distal to the ischaemic lesion, which are not detected by conventional imaging techniques. An example of this phenomenon is the contralateral cerebellar metabolic depression or cerebellar diaschisis, seen following cortical cerebral vascular lesions (Baron *et al*, 1981). Similar effects are seen with lacunar infarcts of deep grey matter. Baron *et al* (1986) demonstrated significant ipsilateral cortical hypometabolism affecting the entire cortical mantle following thalamic infarcts. A number of single case reports of isolated subcortical lesions, mainly thalamic, have demonstrated similar patterns of distal metabolic depression. These findings raise a number of important points, particularly relating to extrapolations from clinicopathological relationships, and are discussed further below.

Pick's disease and 'frontal' dementias

Pick's disease has a metabolic profile distinct from that of AD and MID, with marked bilateral frontal hypometabolism (Franck *et al*, 1986). 'Dementia of frontal lobe type', distinct from Pick's, has recently been described (Gustafson *et al*, 1985; Neary *et al*, 1988). Measurements from single-photon emission computerised tomography (SPECT) in these patients indicate reduced metabolism in the frontal lobes. It is of interest that both AD and MID show increasing 'frontality' in clinical terms and hypometabolism, as assessed by PET, with disease progression. Whether or not hypofrontality is an entirely specific finding, determined by local neuropathological changes, is open to question. It is possible that frontal areas are 'recruited' according to distribution of neurotransmitter systems that are primarily affected by degenerative change in crucial distant (subcortical) regions of origin. The finding of hypofrontality in functional psychiatric disorders and the effect of deep lesions in animal models lends validity to the non-specific notion of hypofrontality. For example, Kiyosawa *et al* (1987) showed significant metabolic depression in the ipsilateral frontotemporal cerebral cortex following electrocoagulation of the left nucleus basalis in five baboons. In addition, D'Antona *et al* (1985) found that eight patients with a presumed diagnosis of progressive supranuclear palsy had a highly significant decrease in glucose metabolism in the pre-frontal regions. These findings also question the validity of the clinical distinction between the cortical and subcortical dementias.

PET in psychiatric disorders

In psychiatric disorders, structural imaging studies have isolated subgroups of patients with non-specific brain changes, usually atrophic. However, the majority of patients with major psychiatric illness (schizophrenia or manic–depressive psychosis) have brains that appear normal with present structural imaging. Abnormalities in these disorders are likely to be functional, with symptoms generated by, or related to, the activity and integration of neural networks.

Patient selection is a major problem in psychiatric studies and bias may conceivably be introduced at at least two stages. Firstly, diagnostic criteria tend to emphasise 'positive' symptoms such as delusions and hallucinations, with the result that subsyndromes with

less florid symptoms may be under-represented in studies. This is a particular problem in studies of schizophrenic patients. Secondly, the confinements that scanning imposes (head mould, administration of radiopharmaceutical by inhalation or injection, arterial cannulation) are of critical importance in psychiatric patients who may be sensitive to external stresses and subject to abnormal beliefs and experiences. Therefore selection may occur at the scanning stage, with more disturbed patients unable to tolerate one or more of the procedures involved. It is with these problems in mind that increasing attempts are made to identify nosologically pure subgroups of patients. This may involve studying groups with identified biological markers such as neuroendocrine indices, genetic markers from molecular biology techniques or well circumscribed cognitive/neuropsychological deficits, in addition to initial diagnosis according to standardised diagnostic categories such as those from DSM–III (American Psychiatric Association, 1980) or Research Diagnostic Criteria (Spitzer *et al*, 1977). Once identified, specific activation paradigms, in terms of neuropsychological or neuropharmacological challenge, may be applied to these groups, with the anticipation that sensitivity and specificity of the functional scanning technique will be enhanced with respect to resting conditions.

In order to fulfil the potential of advances made in activation protocols, analysis of PET images needs to be standardised, with particular emphasis placed on moving away from the traditional ROI analysis. A pixel-by-pixel approach will enable both hypothesis-led and more speculative analysis to be made without the constraints of ROIs whose boundaries bear little relationship to functional neuroanatomy.

The following sections review findings from previous PET studies of psychiatric disorders, with emphasis placed on study design and data analysis.

Schizophrenia

Schizophrenia has been studied more than any other psychiatric disorder using PET but there have been very few consistent findings in the ten years PET has been used in this field. As with many other investigative approaches, this is probably due to the variability and multiple concomitants of schizophrenia. To complicate matters PET has evolved considerably in technical terms over the years and earlier results are difficult to compare with more contemporary findings.

The majority of studies have tried to find a regional cerebral dysfunction associated with schizophrenia. To this end small numbers of schizophrenic subjects have been scanned cross-sectionally and compared with normals. This class of study has, on the whole, lent support to the notion that schizophrenics evidence 'hypofrontality'. There are however many studies in which this is not the case. A smaller number of studies go further than this and relate regional dysfunction to a specific pharmacological or neuropsychological function. This has involved correlating indices of regional cerebral activity with dose of drug taken, psychological test performance, clinical ratings or, more recently using 'activation' designs.

Hypofrontality

The pioneering work of Ingvar (1974) and contemporaries, using xenon inhalation techniques to estimate blood flow, provided the first evidence for hypofrontality. Contemporary replications should be viewed in a more critical light. The concept of hypofrontality was based on empirical findings and constrained by the available techniques, which had very limited spatial resolution. Neuroanatomically or physiologically, the idea that the entire frontal lobes change metabolically as a single unit while the non-frontal regions remain a stable reference is not tenable. The pre-frontal cortices are diverse functionally and architectonically. They include both granular and agranular cortex with markedly different ontology, neural connections and functions. Medial cortices include SMA, the anterior cingulate, contigious paralimbic cortex and granular cortex. The lateral cortices include Brodmann's areas 46, 9 and 8 as well as pre-motor areas and area 44. The range of functions includes eye movements (frontal eye fields), and motoric speech (Broca's area). Psychiatric sequelae of lesions to the medial and lateral cortices are different and have formed the basis of classifications of frontal-lobe syndromes (Blumer & Benson, 1975). Work in our own unit, done in collaboration with Dr C. Frith, highlights this functional dissociation within the pre-frontal cortices. Plate VII shows images of the significance of cerebral activation associated with intrinsically generating words (verbal fluency) and intrinsically generating random motor responses. These images are pictures of significant cerebral blood-flow change induced by activation, superimposed on the Talairach proportional grid (Talairach & Tournaux, 1988) which describes the most commonly used anatomical reference space used in PET.

DeLisi *et al* (1985*a*) studied patients with chronic schizophrenia and matched controls. The patients met strict DSM–III criteria for schizophrenia and

were free of medication for at least two weeks before the study. Patients had significantly lower anterior: posterior ratios (8 of the patients had ratios less than 1). Cerebral atrophy determined by CT was not associated with this aberrant metabolic pattern. Gur *et al* (1987*a*,*b*) described abnormalities of the subcortico-cortical metabolic gradient in schizophrenic patients who were free of medication for at least a week. The duration of illness varied from 3 to 17 years. No evidence for hypofrontality was found. Finally, Szechtman *et al* (1988), in a controlled study, examined whether duration of neuroleptic treatment influenced the regional distribution of metabolism in patients meeting Research Diagnostic Criteria (RDC) for schizophrenia. The patient group was dichotomised according to treatment duration. Both groups had a greater anterior: posterior (hyperfrontality) ratio than controls, though this was less evident in the group with the longest exposure to neuroleptics.

Explanations for these apparently inconsistent results include the confounding effects of treatment and illness duration, differences in scanning procedure, especially correction for attenuation, and in image analysis. An important consideration is the relative preponderance of positive and negative symptoms in the groups studied. In this context Liddle (1987) has described three subsyndromes of schizophrenia which include a syndrome of 'psychomotor poverty' characterised by negative symptoms (flat affect and poverty of speech and spontaneous movement). Based on a comparison of signs and symptoms in focal brain lesions it is suggested that this syndrome is associated with impaired pre-frontal cortical function. The prediction that hypofrontality is associated with negative symptoms has received some support from PET studies. Delisi *et al* (1985*b*) reported that the only significant correlations between relative hypofrontality and symptom ratings were for emotional withdrawal, disorientation, distractability and helplessness/hopelessness. Kishimoto *et al* (1987) discriminated between three distinct types of metabolic pattern in chronic schizophrenic patients. Hypofrontal patients tended to show flat, blunted affect, and a hypoparietal group delusions and hallucinations.

Specific associations between symptoms and regional dysfunction are revealed by correlational analyses with the schizophrenic group. It is possible that comparing schizophrenics with schizophrenics, and avoiding uncontrollable confounding variables, will prove a fruitful strategy. This approach is best exemplified by the demonstration of three distinctive rCBF profiles in a group of 30 chronic schizophrenics split orthogonally, three ways, according to Liddle's subsyndromes (Liddle *et al*, 1990).

The possible relationships between negative symptoms, hypofrontality and putative abnormalities of the mesocortical dopaminergic system have been addressed from a number of perspectives. Animal studies using autoradiography have shown increased frontal and anterior cingulate metabolic response to the dopaminergic agonist apomorphine (McCulloch *et al*, 1982). Corresponding dopaminergic challenge in humans has yet to be established, although initial studies have been reported. Wolkin *et al* (1987) report decreased frontal, temporal and striatal glucose metabolism in schizophrenics and controls following *d*-amphetamine (0.5 mg/kg p.o.). Geraud *et al* (1987) report a reversible haemodynamic hypofrontality in young schizophrenics. Hypofrontality was seen in chronic patients whose disease had evolved over more than two years and this pattern disappeared during exacerbation of the symptoms. In a subgroup who had not been treated for several weeks, a weak dose of a dopaminergic agonist restored near-normal frontality. The authors conclude "this [dopamine hypersensitivity] may reflect either the role of neuroleptic washout or a primitive dopaminergic depletion as proposed by some authors in the chronic form of schizophrenia".

Therefore, hypofrontality is not always found and may critically depend on the type of schizophrenia being studied.

Cognitive/sensorimotor activation

Making PET a behaviourally or pharmacologically specific technique is the object of activation paradigms. Behavioural specificity can be achieved by using PET in conjunction with cognitive or sensorimotor activation. Regional deficits measured with PET can be seen as a common mediator of clinical and neuropsychological symptoms. The resting levels of regional blood flow or metabolic rate in psychiatric patients may not be markedly different from those of normals (Sheppard *et al*, 1983); however, the increase in cerebral activity brought about by a cognitive task may differ considerably. This increased sensitivity may reveal correlations between clinical ratings and cerebral activity that were previously hidden. Using ^{11}C deoxyglucose as a PET tracer, Volkow *et al* (1987) studied patients with chronic schizophrenia using a smooth-pursuit eye-tracking activation task. This task was chosen because performance is impaired in some schizophrenics and impairment is associated with dysfunction of the frontal cortex. Significant differences

between conditions were observed solely in the patients with positive symptoms. The authors note that there were more significant correlations between metabolic rate and clinical items during the task condition. In particular negative correlations were found between left frontal metabolic rate and some ratings on the Brief Psychiatric Rating Scale. This study illustrates how activation studies may increase not only the specificity but also the sensitivity of PET.

Cohen *et al* (1987) studied cerebral function during an auditory discrimination task designed to emphasise sustained attention. A direct relationship was found between metabolic rate in the pre-frontal cortex and accuracy of performance. In schizophrenics lower pre-frontal flow was unrelated to task performance.

Warkentin *et al* (1989), using a xenon inhalation measurement of rCBF, used a verbal-fluency task as a cognitive challenge. The most marked effect of the activation in normals was seen in the left prefrontal area, but in the schizophrenic group this increase was attenuated. The authors concluded "the controversy regarding frontal lobe dysfunction in schizophrenia is related to whether these areas are functionally challenged or not".

Specificity is implicit in the design of the activation. If impaired augmentation of regional cerebral activity is associated with a specific cognitive task, then the deficit has both a neuroanatomical and a functional specificity. Linking of cortical and neuropsychological dysfunction is illustrated by the work of Weinberger *et al* (1988). Using xenon-133 inhalation to measure rCBF, this group has shown that chronic schizophrenics fail to activate the dorsolateral pre-frontal cortex (DL-PFC) during the Wisconsin Card Sort Test (WCS). The baseline in these studies was a simple number-matching task. They extended the specificity of this "behaviour-specific hypofunction" by demonstrating significant correlations between DL-PFC rCBF during the WCS and cerebrospinal fluid levels of dopamine and serotonin metabolites.

Pharmacological activation

Short-term longitudinal studies in conjunction with pharmacological challenge permit the changes in cerebral activity following manipulations of specific neurotransmitter systems to be identified. Cleghorn *et al* (1990) have studied the effect of apomorphine on neuroleptic-naive first-episode schizophrenics and controls. They found a bilateral increase in the 'caudate' frontal area in the control group. At low doses McCulloch *et al* (1982) demonstrated increases in frontal gluclose metabolism in layers IV and VI in their autoradiographic studies in animals. A simple interpretation is a pre-synaptic hyperpolarising effect of apormorphine on ascending dopaminergic projections, resulting in an indirect disinhibition of cortical activity. In Cleghorn's study the schizophrenics failed to evidence increases in frontal metabolism, further implicating frontal dopaminergic projections in schizophrenia.

Future directions

There have been no long-term studies of schizophrenia. Activation studies involve repeated scanning in different brain states and represent short-term longitudinal designs which hold great promise. These studies require a method of rapid CBF estimation such as that described by Raichle *et al* (1983) and Lammertsma *et al* (1989). Other techniques suggest that combined activation studies are going to be an important area. Daniel *et al* (1990) have used SPECT to measure changes in rCBF in chronic schizophrenics while performing the WCS and a simple control task. These changes were measured in the presence and absence of dextroamphetamine using a double-blind, placebo-controlled, cross-over design. Amphetamine produced a task-independent reduction in global CBF. With amphetamine there was a significant activation of the left DL-PFC, while with placebo there was no such activation. Furthermore, WCS performance improved considerably in the drug condition. The authors conclude "these findings are consistent with animal models in which mesocortical dopamine activity modulates and enhances the signal to noise ratio of PFC activity". It is interesting that Pycock *et al* (1980) note "Lesions of either midbrain cell bodies in the VTA or of frontal cortical areas directly, with subsequent loss of DA terminals in the prefrontal cortex, induce hyperactivity in rats and enhanced behavioural responses to amphetamine".

Affective disorders

The aetiology of the affective disorders is still unknown. The efficacy of antidepressant medication implicates abnormal neural transmission in monoaminergic pathways in neural networks in critical brain regions involved with mood regulation. However, the specific anatomical regions involved have yet to be delineated. This failure has frequently been ascribed to the lack of direct measures of brain function *in vivo*.

In contrast to schizophrenia there have been relatively few studies of patients with affective disorders. The earliest study compared regional

cerebral metabolic rates of glucose in schizophrenia, affective disorder and control subjects using a somatosensory paradigm (1 Hz electric shocks to the right forearm) to attempt to control for ambient state across subjects (Buchsbaum *et al*, 1984). The affective patients showed a reduced 'anteroposterior (AP) gradient' in glucose metabolism compared with normal subjects, a finding that was repeated in the schizophrenic group. There were no differences between the affective and schizophrenic groups, which was explained on the one hand by small sample size (16 schizophrenics and 11 affectively disordered), diagnostic heterogeneity among both groups, and range of severity of the mood disturbance, and on the other hand by suggesting that the reduced AP gradient could be a generalised feature of both illnesses – a core biological feature of the psychoses. The order of magnitude of these changes was similar to that seen in multi-infarct dementia (Kuhl *et al*, 1985*b*).

Region-of-interest analysis was used in the above study and this has been the approach adopted to date in most PET studies. The problem with ROI analysis is simply that any results are in terms of the ROIs chosen. ROIs have little validity in terms of functional anatomy, and none in terms of cytoarchitectonics. Attempts to avoid subjective bias in selection of ROIs include use of computer algorithms to identify brain areas. Reiman *et al* (1984, 1986) used a stereotactic method of anatomical localisation in which co-ordinates from a stereotactic atlas and measurements from a lateral skull radiograph are entered into a computer program that generates the co-ordinates of the desired regions in the PET image. Data from these regions are recorded without visual inspection of the image and are thus free from observer bias. However, even if ROIs were partially validated in terms of gyral anatomy they will still fail to be proper topographic descriptions of distributed functional systems. Therefore a major development in analysis of PET data is the move towards pixel-by-pixel analysis. To this end, Fox *et al* (1988) have developed an automated data-analysis technique which identifies significant changes in rCBF in volumes of pixels (voxels). Pixel-by-pixel analysis is more valid primarily because the spatial extent and location of any change is constrained solely by the data. This is even more important in the study of neurotransmitter systems which are not subject to 'parcellation' or sulcal delimitation.

With these limitations in data analysis in mind, only one study of affective disorders to date has failed to report 'hypofrontality' (Kling *et al*, 1986). In this study only six "chronically depressed" patients were studied, with diagnostic criteria unspecified for one case. Further heterogeneity in this group included the presence of increased ventricular brain ratio (VBR) in four of the six patients.

A detailed series of studies has been reported by members of the group from the University of California, Los Angeles (UCLA) (Phelps *et al*, 1984; Baxter *et al*, 1985; Schwartz *et al*, 1987). In the earliest study, 14 patients with unipolar depression had scans, six being repeated after a pre-dose of 15 mg methylphenidate and four having a third scan when euthymic. Seven bipolar manic and five bipolar depressed patients were also studied, with three subjects rescanned in a euthymic state. Seven age-matched controls were scanned with and without methylphenidate. Overall, patients with bipolar depression had a highly significant decrease in hemispheric metabolic rate for glucose when compared with all other groups, including unipolar depressives. A subgroup of the unipolar depressives had asymmetries limited to frontal temporal cortex, most prominent in the postero-inferior portion of the frontal cortex and in the anterior superior portion of the temporal cortex. Within this group, the subgroup who showed asymmetric hypometabolism (left less than right) had a positive clinical response to methylphenidate which correlated with a normalisation of the baseline metabolic asymmetries.

In the second study of the series, cerebral glucose metabolic rate was examined in 11 patients with unipolar depression, five with bipolar depression, five with mania, three with mixed bipolar states and nine control subjects. Whole-brain glucose metabolic rate was decreased in bipolar depressed and mixed affective groups, with this change normalising in those groups on resolution of depression or mania. The unipolar depressed group showed a lower caudate:whole-brain ratio of metabolic rate when compared with normals and bipolar depressed. These data suggest, like the CBF studies with xenon (Uytdenhoef *et al*, 1987), that global hypometabolism in bipolar depressives may be state- rather than trait-dependent in view of the normalisation on elevation of mood.

Baxter *et al* (1989) further attempted to identify a metabolic profile common to three depressive subtypes. In a study of 10 unipolar depressives, 10 bipolar depressives, 24 patients with obsessive–compulsive disorder with ($n = 10$) or without ($n = 14$) depression, 6 bipolar manics and 12 normal controls they found a significant decrease in the ratio of glucose metabolic rate in the left dorsal anterolateral pre-frontal cortex to that in the whole hemisphere (ALPFC:Hem). Similar though less significant

changes were observed in the right ALFPC. Twelve patients were rescanned after antidepressant medication, and percentage increase in the left ALPFC: Hem ratio correlated with clinical improvement. The authors concluded that the data suggested a left-ALPFC abnormality in depression.

In a hypothesis-led study, Post *et al* (1987) investigated glucose utilisation in the temporal lobes of 13 patients meeting DSM–III criteria for primary affective illness. Five patients were depressed, six 'improved' or euthymic, and two were hypomanic. Data were compared with those obtained from 18 normal volunteers and from 17 schizophrenics. A somatosensory paradigm was used to attempt to control for ambient conditions between patients and subjects, and regional values were normalised to the maximum value for the relevant PET scan slice. In the depressed group the right and left temporal lobes revealed a relative hypometabolism, reaching statistical significance only on the right.

These studies illustrate the need to study larger numbers of well defined patients longitudinally and the need to develop regionally specific activation paradigms before final conclusions are made about focal abnormalities in metabolism. Cross-sectional designs include, for example, comparing depressives with non-depressives and depressives with depressives. The former design has been employed extensively and may be of limited use, particularly with small patient samples. The problems in cross-sectional studies are even more striking in schizophrenia. Confounding differences between schizophrenics and normals are innumerable: some of the more important include taking large amounts of drugs, differences in social class, pre-morbid adjustment, highest educational level, number of years in hospital, hostility, suspiciousness, and arousal. Some of these variables have been shown to affect regional cerebral activity, and those which have not would probably be interesting experiments in themselves. The main findings of 'patient–normal' comparisons are 'hypofrontality' and altered cortico-subcortical metabolic gradients. Neither of these are specific to affective disorders or schizophrenia, as previously discussed.

In conclusion, PET studies of affectively ill patients have consistently found decreased cerebral metabolism, most frequently located to the inferior frontal lobe, during the depressed state. ROI analysis may limit the extent to which these changes can be related to anatomical or monoaminergic theories of affective illness. The development of pixel-by-pixel analysis in association with specific activation paradigms, neuropsychological and neuropharmacological, should increase the sensitivity of the technique and allow identification of anatomical regions of abnormality and covarying brain regions, with an implicated relationship to connectivity and neural networks. The nosological status of clinically identified subsyndromes can then be validated by relationship to PET-determined functional changes.

Obsessional disorders

Obsessive–compulsive disorder (OCD) has traditionally been classified as a neurotic disorder, with an assumed psychological aetiology. OCD is perhaps the most disabling of the non-psychotic mental disorders and may occur in up to 1 in 200 teenagers (Flament *et al*, 1988). It is characterised by unwanted, persistent, recurrent intrusive thoughts which may be accompanied by ritualistic behaviour or compulsions. The similarity between compulsive behaviour and movement disorders has led to the hypothesis that OCD may be secondary to basal-ganglia dysfunction. PET can test this hypothesis directly.

Baxter *et al* (1987) studied 14 patients with OCD and compared them with 14 controls and 14 patients with unipolar depression. In OCD a significant elevation in metabolism was seen in the left orbital gyrus, with a non-significant elevation in the right orbital gyrus, and significant elevations bilaterally in caudate nuclei. These findings were related to mental state in that the orbital gyrus metabolism remained elevated even after successful drug treatment, whereas the caudate:hemisphere metabolic ratio increased from a normal level in the morbid state to an elevated level with improvement of symptoms after drug treatment. The authors hypothesised from these findings that in symptomatic OCD cortical activity, especially orbital, is elevated beyond the capacity of the caudate to maintain its integrative role; that is, orbital cortex is 'released'. With successful treatment the caudate re-establishes its processing capacity through an increase in its metabolic rate relative to functionally connected structures.

The limitations of this study in terms of heterogeneity of patient group were addressed subsequently (Baxter *et al*, 1988), when drug-free, non-depressed, right-handed patients with OCD were compared with a new group of matched controls. Similar results were found, with globally raised cerebral metabolic rates in addition to bilaterally raised metabolism in caudate nuclei, orbital gyri and orbital:hemisphere ratio. In the third study of this series (Baxter *et al*, 1989) OCD patients with and without depression were compared with unipolar and bipolar depressives and normal controls. In this study the OCD patients

with depression had significantly lower metabolic rates in the left ALPFC compared with OCD patients without depression. This metabolic pattern was also found in the primary-depression groups.

Swedo *et al* (1989) studied 18 adults with OCD of childhood onset and 18 matched controls. This group found significantly increased bilateral pre-frontal, left orbital frontal, left pre-motor and right sensorimotor metabolism and increased bilateral anterior cingulate metabolism. Increased caudate metabolism did not reach significant levels. Metabolic measures correlated with measures of clinical state and predicted response to clomipramine, with non-responders having the highest metabolic rates.

Martinot *et al* (1989) examined the relationship between regional metabolism and clinical and neuropsychological features of OCD in 16 non-depressed patients and eight controls. In all brain regions absolute metabolic rates were significantly lower in patients than in controls, not explained by the effect of concurrent medication in 10 out of 16 of the patients. No relationship was found between metabolic rates and clinical data but neuropsychological data revealed significant impairment of the OCD group in memory and attention tasks. When related to regional metabolism, absolute metabolic rates for lateral pre-frontal areas and for whole cortex were inversely correlated to Stroop-test subscores.

A single study of Gilles de la Tourette syndrome, which is invariably associated with obsessional features, has also reported increased metabolism in the basal ganglia (Chase *et al*, 1984*b*).

Thus PET studies lend support to the hypothesis that OCD is associated with a functional abnormality in the basal ganglia and frontal cortex. Further studies are underway to assess metabolic rates before and after psychological and pharmacological treatment and will affect the nosological status of OCD, previously considered a neurotic disorder with a psychological aetiology.

Anxiety states and panic disorder

Anxiety states are the most common psychiatric disorders. Within this group of disorders, one in particular, panic disorder (PD), has caught the attention of 'biological' psychiatrists. PD is characterised by recurrent, discrete attacks of extreme anxiety in the absence of a frightening stimulus. In a substantial subgroup of patients with PD, infusion of sodium lactate precipitates an anxiety attack. This rarely happens in normal controls, suggesting a neurobiological basis for this problem.

Reiman *et al* (1984) studied ten patients with panic disorder (seven lactate responders) and six normal controls, using ^{15}O-labelled water to measure CBF. Patients were studied resting. There were no differences in global or hemispheric values between groups, but ROI analysis revealed a significantly decreased left-to-right ratio in the parahippocampal gyrus of the PD patients who were lactate responders. In a further study (Reiman *et al*, 1986), which included increased numbers of patients and controls, the previous finding of hippocampal asymmetry in lactate-sensitive patients was replicated using measures not only of blood flow but also of blood volume and oxygen metabolism. The lactate-sensitive PD patients also had raised whole-brain oxygen metabolism.

This series was further extended (Reiman *et al* 1989*a*,*b*) to include studies of patients during a discrete panic attack and of normal controls during states of anticipatory anxiety, awaiting an unpleasant electrical stimulus. These studies represent a significant advance in terms of the data-analysis technique (Fox *et al* 1988). Firstly, global blood flow was normalised to 50 ml/100 g/min. Secondly, the population of regional changes in blood flow, as determined from subtracted PET images (i.e. test state minus rest state), were examined statistically for significant change. Finally, locations of the rCBF changes were established with reference to the stereotactically standardised data matrix. In the first study, during a lactate-induced panic attack, there were significant increases in rCBF in the temporal poles, insular cortex, claustrum, lateral putamen, the vicinity of the superior colliculus and in the vicinity of the left anterior cerebellar vermis. In the second study, during production of anticipatory anxiety, there were significant increases in rCBF in identical regions. The authors suggested a final common pathway for the expression of these two forms of anxiety involving the temporal poles. These findings relate well to the theory of Gray (1982) which implicates the hippocampus and its afferent and efferent connections in the neurobiology of anxiety.

A single study from another centre (Mountz *et al*, 1989) compared seven subjects with simple phobias of small animals with eight normal controls. Each subject received five PET scans in a fear–rest–fear repeated-measures paradigm. Although phobic stimuli produced a significant increase in state anxiety during fear and significant differences in peripheral physiological measurements between the fear and rest scans, any changes in global or regional CBF were found to be non-significant when the effects of hypocapnia due to anxiety-induced hyperventilation were taken into account. In view of these results the authors suggested that CBF changes induced by state anxiety are either not measurable by PET techniques

or else do not exist. They further concluded that the frequently voiced concerns of the confounding effect of subject anxiety on CBF measurements are overstated.

PET in neuropsychiatric disorders

Psychiatric morbidity is common in primary neurological illness. The presence of psychotic or non-psychotic symptoms in the presence of a demonstrable (focal) pathological process is clearly of great interest in the understanding of the generation of such symptoms. Earlier, restrictive approaches, in which disorders were thought to be either neurological (organic) or functional (psychiatric), have led to a limited understanding between the relationship of psychopathology and disturbance of regional brain function. PET studies have also been subject to this conflict of paradigms, with a few notable exceptions. The design of future PET activation studies will address similarities rather than differences between various neuropsychiatric disorders. A full review of PET in neuropsychiatric disorders is beyond the scope of this review: the following section illustrates the potential application of PET in neuropsychiatric research, with reference to two conditions, thalamic infarction and Parkinson's disease.

Thalamic infarction

Following isolated infarcts of the thalamus, a wide range of clinical manifestations are recognised. These include verbal and visual memory impairment, aphasia, neglect and behavioural change (Bogousslavsky *et al*, 1988). PET studies have shown that clinical symptoms in these patients seem to be the result of remote physiological effects rather than a direct consequence of the subcortical (thalamic) pathology. Baron *et al* (1986) described PET and neuropsychological findings in ten patients with unilateral vascular thalamic lesions demonstrated by CT. Neuropsychological testing focused on language and memory. Four patients were re-studied three to six months after the first study. In nine out of the ten patients there was significant ipsilateral cortical hypometabolism affecting the whole cortical mantle diffusely, this change tending to normalise with time after the stroke. A range of neuropsychological abnormalities were displayed in these patients, including language disturbance (incoherence, dysarthria, word-finding difficulties and impaired verbal fluency), memory impairment (visual and verbal memory) and disorientation for time and place. These findings also normalised with time. Kuwert *et al* (1989) demonstrated ipsilateral hypometabolic changes in five out of seven patients with unilateral thalamic infarcts. Areas affected included cerebellum (4/5), frontal cortex (3/5) and parietal cortex (5/5).

Parkinson's disease

Depressive symptoms are common in Parkinson's disease. The reported incidence varies between 40% and 50% (Schiffer *et al* 1988). The relationship between the two disorders is controversial, with the most frequently posited hypothesis being that depression is a psychological reaction to the motor disability. Brown & MacCarthy (1990) found an absence of somatic symptoms, negative self-referential ideation and suicidal thoughts or actions in a sample of patients with Parkinson's disease and suggested that this confirmed the more reactive nature of mood disturbance. Clinical impression, however, suggests that mood disorder may predate motor disorder in a significant number of cases. Mayberg *et al* (1989) investigated the relationship between mood disorder and cerebral glucose metabolism in eight patients with Parkinson's disease (three with major depression, two with minor depression and three non-depressed) and four normal volunteers. All patients were in the early stages of Parkinson's disease (Hoehn-Yahr scale range 1–3; North Western Disability Scale < 14) and were cognitively normal as assessed by the Mini Mental State examination. Significant differences between the groups were seen, with hypometabolism in orbital and inferior prefrontal cortex in the depressed patients (major and minor depression) compared with non-depressed Parkinsonian and control subjects. Severity of depression correlated with metabolic rate. This finding suggests that a specific neurochemical abnormality may underly this feature of Parkinson's disease, perhaps loss of extrastriatal ascending monoaminergic pathways. This has validity in terms of the previously discussed primate studies in which lesions of such pathways are associated with decreased frontal metabolism.

Conclusions

Positron emission tomography is the most powerful technique available for the investigation of brain function *in vivo*. The task of research workers is further refinement of the methodology involved, particularly in the fields of design of activation paradigms and data analysis, which will further increase the sensitivity and specificity of the method. To date, the majority of studies of patients with psychiatric disorders have been in the resting state. Regional abnormalities have been consistently found

in the major psychoses and there is some evidence for abnormalities specific to two neurotic disorders traditionally thought to have a psychological aetiology, namely panic disorder and obsessive–compulsive disorder. Future PET programmes will couple metabolic measures with pharmacological and cognitive activation of specific functional systems and studies using tracers for neuroreceptors will attempt to provide a parallel neurochemical basis for the metabolic profiles. In conjunction with delineation of clinical subsyndromes, these techniques should lead to significant advances in the understanding of the pathophysiology of the major psychoses.

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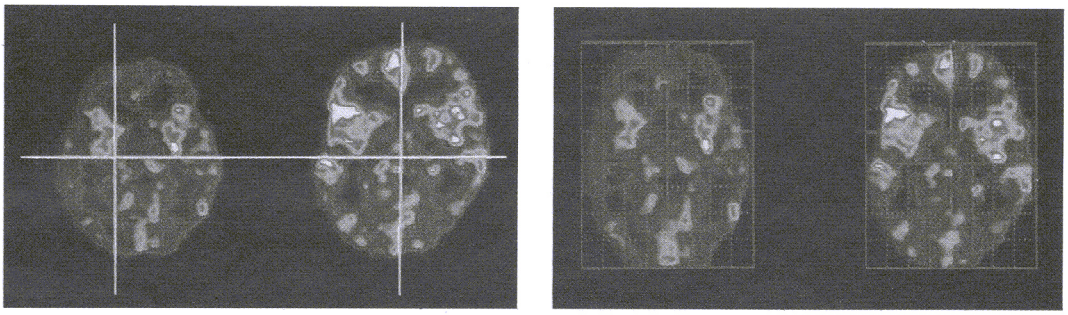
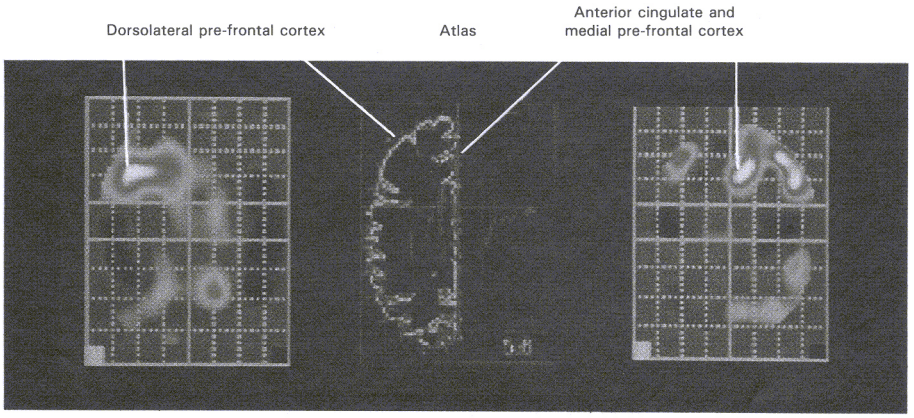


Before elastic transformation

After elastic transformation

PLATE VI (Bench *et al*) The effects of non-linear transformation on slices from two different brains of schizophrenic subjects. The grid corresponds to that used by Talairach *et al* (1988). Note the gross non-linear asymmetries before transformation.



Verbal fluency

Random movement

PLATE VII (Bench *et al*) Statistical parametric maps (SPMs) of focal activations observed when comparing brain states which involve intrinsic generation of words during a series of verbal-fluency activations (left), and during the generation of random finger movements (right). White areas are t values at $P<0.001$ (not Bonferroni corrected). The grid corresponds to that used by Talairach *et al* (1988). Note that lateral pre-frontal cortices are primarily involved in verbal fluency and medial cortices in random generation.