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EDITORIAL

PET scanning and schizophrenia – what progress?[1]

Positron Emission Tomography (PET) provides quantitative three-dimensional images of the physiological processes of the living brain. However, the disturbances of brain physiology in schizophrenia are likely to be subtle. Although recent neuropsychological studies have partially undermined the Bleulerian view that basic intellectual activities are undamaged in schizophrenia, it remains true that the majority of schizophrenic patients can perform within the normal range in most aspects of brain function. It is failure to integrate the separate elements of activity constructively that produces the most devastating effects of the illness. This suggests that the abnormalities of brain function involve the processes that generate and coordinate mental activity. What has PET contributed to the delineation of these putative abnormalities?

In view of the seminal role played by the hypothesis of dopaminergic overactivity in schizophrenia, there has been great interest in the use of PET to measure dopamine D_2 receptor density in the basal ganglia in untreated schizophrenic patients. Studies using selective D_2 ligands have yielded ambiguous results. Farde *et al.*, (1987) found no increase in D_2 receptor number in the putamen or caudate nucleus. Wong *et al.* (1989), who had found an increase in their initial study of schizophrenic patients, subsequently found a similar increase in patients with manic depressive psychosis, raising the possibility that an excess of D_2 receptors can be feature of psychotic illness in general.

Meanwhile there have been important advances in the use of PET to explore the subtle processes involved in the generation of activity. These developments have been dependent on refinement of PET techniques for measuring regional cerebral blood flow (rCBF). In the era before PET, Ingvar & Franzen (1974) used the xenon infusion technique to demonstrate a relative reduction in blood flow in the frontal lobes in schizophrenic patients. This finding was of great interest because of the role of the frontal lobes in the initiation and organization of mental activity. Subsequent PET studies of blood flow and of cerebral metabolism provided additional evidence of hypofrontality in at least some schizophrenic patients, but studies of unmedicated acute patients found no evidence of hypofrontality (Sheppard *et al.* 1983, Early *et al.* 1987).

Interest in rCBF as an index of disordered brain function in schizophrenia was revitalized when Weinberger *et al.* (1986) used the xenon inhalation technique to demonstrate that in some schizophrenic patients blood flow in the dorsolateral prefrontal cortex does not increase above resting levels during performance of the Wisconsin card sorting test, a task requiring flexibility in problem solving. In contrast, blood flow in that brain region does increase in normal individuals performing this task.

The physiological mechanisms regulating cerebral blood flow appear to be finely tuned to respond to the brain's requirements. Fox & Raichle (1986) found that rCBF in the sensorimotor cortex during somatosensory stimulation increased by 26%, while the rate of oxygen metabolism in the same region increased by 5%. A similar activation produced an 11% increase in the rate of glucose metabolism (Raichle *et al.* 1987). The change in rCBF during brain activation occurs within seconds of the onset of activity. Thus, rCBF can be a sensitive index of brain activity. However, various sources of confounding variation in rCBF measurements which must be taken into account. The major sources of variation are anatomical variation; fluctuation in global cerebral perfusion; idiosyncratic variation in brain activity; and clinical heterogeneity.

[1] Dr Peter F. Liddle, Department of Psychological Medicine, Hammersmith Hospital, DuCane Road, London, W12 0HS.

ANATOMICAL VARIATION BETWEEN SUBJECTS

There is considerable variation in the shape, size and gyral pattern of human brains, which confounds the averaging of focal changes in brain activity in groups of subjects. To deal with this problem, Fox *et al.* (1985) and Friston *et al.* (1991*a*) have developed techniques for transforming the brain image into one which matches a standard brain specified in the Talairach & Tournoux (1988) stereotactic atlas. It is then possible to perform pixel-by-pixel comparisons of rCBF patterns averaged over a number of subjects. It is appropriate to represent the changes in rCBF as a statistical parametric map depicting the location of all pixels for which the statistical significance of the change exceeds a specified threshold. The omnibus significance of the entire map can be tested by using the χ^2 test to determine the probability of occurrence of the observed number of suprathreshold pixels (Friston *et al.* 1991*b*).

VARIATION IN GLOBAL CEREBRAL BLOOD FLOW

There are substantial temporal fluctuations in global cerebral blood flow which tend to swamp variations in rCBF. If differences in regional flow between conditions were proportional to global flow, the effect of variation in global flow might be removed by dividing rCBF values by global flow. If on the other hand, the relevant differences in regional flow were unrelated to global variations, it would be more appropriate to employ analysis of covariance, treating the difference between conditions as the categorical variable and global flow as the covariate. Friston *et al.* (1990) have shown that in the case of rCBF changes associated with cognitive activation, the assumption of proportionality to global flow in invalid, while a pixel-by-pixel analysis of covariance produces a good fit to the observed data.

IDIOSYNCRATIC VARIATION IN BRAIN ACTIVITY

Because patterns of brain activity are complex and prone to vary between individuals, findings are more likely to be interpretable if the study is designed to compare rCBF patterns in states of brain activity that differ in a well controlled manner. This approach is well illustrated in the study by Peterson *et al.* (1988) of the brain activity involved in processing words in normal individuals. They measured rCBF during performance of each of a series of tasks of increasing complexity, each task differing from the preceding one in only one aspect of mental processing. Simple exposure to either written or aural presentation of words was associated with activation of the visual or auditory sensory cortex. As task complexity increased in a manner demanding higher levels of processing, anterior brain locations were recruited.

Controlled modification of brain activity can be produced by carefully designed behavioural tasks, or by drugs which modify neurotransmission. To exploit such strategies fully, it is necessary to make multiple measurements of rCBF during a single session. PET techniques using either intravenous $H_2{}^{15}O$ or inhaled $C^{15}O_2$ are ideally suited to such studies because an adequate image of rCBF can be obtained from infusion or inhalation lasting a period or order 2 minutes. Therefore, it is necessary to sustain the brain state of interest for only a brief period. Furthermore, because the half life of ^{15}O is only 2·1 min, no trace of the isotope can be detected after 10 min, and images of multiple distinct brain states can be obtained within an hour.

CLINICAL HETEROGENEITY

In so far as symptoms are a reflection of brain activity, heterogeneity of symptom profiles in schizophrenia is likely to reflect heterogeneity of brain activity. The appropriate approach to detecting the features of rCBF associated with a specific symptom profile is to examine the correlation between rCBF and severity of the relevant symptoms in a cohort of patients who are

relatively homogeneous with regard to other potentially confounding variables such as degree of chronicity.

Employing such a strategy, Liddle *et al.* (1990, 1992) found that each of three previously identified syndromes of persistent schizophrenic symptoms was associated with a distinct pattern of rCBF in paralimbic and/or multimodal association cortex and related subcortical nuclei. Psychomotor poverty (poverty of speech; flat affect; decreased spontaneous movement) was associated with decreased rCBF in the left prefrontal and parietal cortex, and with increased rCBF in the caudate nucleus. The most significant rCBF feature associated with the disorganization syndrome (disorders of the form of thought and inappropriate affect) was an increase in rCBF in the right anterior cingulate gyrus. Reality distortion (delusions and hallucinations) was associated with increased rCBF in the left parahippocampal gyrus and contiguous areas, while there were decreases in rCBF at several sites in the right hemisphere.

PSYCHOLOGICAL PROCESSES RELEVANT TO SCHIZOPHRENIA

Psychomotor poverty in schizophrenia is associated with poor performance in tasks such as word generation, which involve the internal generation of a plan for action; the disorganization syndrome is associated with difficulty in suppressing inappropriate responses and, in particular, is associated with poor performance in the Stroop test (Liddle & Morris, 1991). The brain sites involved in these psychological processes in normal individuals have been delineated by measurement of rCBF changes associated with these activities.

Frith *et al.* (1991) compared rCBF during articulation of an internally generated list of words with rCBF during articulation of a list of words provided by the experimenter. They found that internal generation of words by normal subjects was associated with activation of an area of the left dorsolateral prefrontal cortex. This area coincided with the area in which resting rCBF is decreased in schizophrenic patients with marked psychomotor poverty.

In the Stroop test, the subject names the colour of the print for each word in a list of colour names printed in ink of a colour differing from the colour name. This task requires the suppression of the tendency to respond to the colour name. Pardo *et al.* (1980) compared rCBF during the naming of the colour of print where print colour conflicted with colour names, with rCBF during a similar task in which there was no conflict between colour of print and colour name. They demonstrated that the brain site maximally activated during suppression of the competing response was in the right anterior cingulate cortex. This site coincided with the site of greatest increase in resting rCBF associated with the disorganizing syndrome in schizophrenic patients, indicating that patients with persistent symptoms of disorganization might engage in a sustained struggle to suppress inappropriate responses.

PHARMACOLOGICAL ACTIVATION

The use of PET measurements of rCBF to study changes in brain activity produced by drugs which modify neurotransmission is illustrated by the study by Friston *et al.* (1991*c*) of the effects of buspirone, a partial agonist at serotonin $5HT_{1A}$ receptors, in normal subjects. The study combined behavioural activation and pharmacological challenge to examine the effects of buspirone on the cerebral activity associated with a word-learning task. They found that a 30 mg oral dose of buspirone attenuated the increase in rCBF in the left parahippocampal gyrus associated with learning of words. This attenuation in rCBF increase was accompanied by impairment of performance in the word learning task.

Although the use of PET to measure the effects of pharmacological agents on rCBF in schizophrenic patients has not been reported, Cleghorn *et al.* (1991) have demonstrated that the dopamine agonist apomorphine produces a decrease in glucose metabolism in the caudate nucleus in schizophrenic patients, but not in normal subjects.

CONCLUSION

The use of PET to provide three-dimensional images of rCBF patterns associated with specific mental activities and to map the effects of drugs which modify neurotransmission offers a realistic prospect of delineating the pathophysiology of schizophrenia. Brain sites involved in the initiation of activity and in the suppression of interfering mental activity have been identified in normal individuals, and these sites coincide with the sites of abnormal rCBF in schizophrenic patients with syndromes in which these aspects of mental processing are implicated.

PETER F. LIDDLE

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