Structural and Functional Brain Imaging in Schizophrenia

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We present an evaluation of the contribution of structural and functional brain imaging to our understanding of schizophrenia. Methodological influences on the validity of the data generated by these new technologies include problems with measurement and clinical and anatomic heterogeneity. These considerations greatly affect the interpretation of the data generated by these technologies. Work in these fields to date, however, has produced strong evidence which suggests that schizophrenia is a disease which involves abnormalities in the structure and function of many brain areas.

Structural brain imaging studies of schizophrenia using computed tomography (CT) and magnetic resonance imaging (MRI) are reviewed and their contribution to current theories of the pathogenesis of schizophrenia are discussed. Positron emission tomography (PET) studies of brain metabolic activity and dopamine receptor binding in schizophrenia are summarized and the critical questions raised by these studies are outlined. Future studies in these fields have the potential to yield critical insights into the pathophysiology of schizophrenia; new directions for studies of schizophrenia using these technologies are identified.

Key Words: schizophrenia, computed tomography, magnetic resonance imaging, positron emission tomography, fluorodeoxyglucose, dopamine receptors

This paper critically reviews the contribution of structural and functional brain imaging to our current knowledge of schizophrenia. Studies involving computed axial tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) of brain metabolism and of dopamine receptors are examined. Methodological issues that influence the validity of the data generated by each method are considered first. Then the clinical correlates of brain measurements are analyzed. The reasons for inconsistent findings are explored and robust findings are identified. Finally, future directions are suggested, based on the lessons learned from collective experience with these new research technologies.

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STRUCTURAL BRAIN IMAGING STUDIES

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have provided contemporary psychiatry with the opportunity of investigating in vivo the gross structure of the brain in patients with schizophrenia. Together with advances in psychiatric diagnoses and research design, these non-invasive technologies have enhanced our ability to establish structural brain differences in patients with schizophrenia. Work in this field has been growing for the past fifteen years since the first CT report of ventricular enlargement by Johnstone et al, 1976. With over 50 controlled CT studies of ventricular size in schizophrenia (see reviews by Raz and Raz 1990 and Lewis 1990), it is valuable to ask what can be concluded from studies to date and what questions need to be addressed in future studies. This section will provide an overview of studies to date and trends in the CT and MRI literature so as to highlight potentially fruitful areas for future pursuits in this area. This review does not aim to be exhaustive or comprehensive. Other recent

reviews may provide complementary perspectives (Raz and Raz 1990; Lewis 1990; Pfefferbaum et al 1990; Pfefferbaum and Zipursky 1991; Shelton et al 1988; Waddington 1990).

Evidence for Ventricular and Sulcal Enlargement

The most basic question to be asked is whether the accumulated evidence for ventricular enlargement in schizophrenia is convincing. This has been the subject of a number of reviews and metaanalyses (Raz and Raz 1990; Lewis 1990; Pfefferbaum 1990; 1991; Shelton et al 1988; Waddington 1990). The results of controlled studies have not been entirely consistent in showing ventricular enlargement in schizophrenia. Even more recent studies which have addressed design problems encountered by earlier studies such as inadequate sample size and use of inappropriate control groups have yielded inconsistent results (see review by Lewis 1990). Settling the issue of whether CT and MRI studies support the view that there are structural brain differences in schizophrenia cannot, however, be settled merely by tallying up the number of controlled studies which do and do not support this claim (Raz and Raz 1988).

Raz et al (1988) have pointed out that whether a given study shows a statistically significant effect is a function not only of the magnitude of the group differences found but also on the sizes of the samples used. A study with a small number of subjects may find a substantial difference between patients and controls which nonetheless fails to reach statistical significance. Raz and Raz (1990) have dealt with this problem in their metaanalysis by calculating an effect size for each of the 53 controlled studies (CT and MRI) of ventricular size in schizophrenia. They define the effect size as the difference between the mean ventricular volume of the patient and control groups, divided by the pooled standard deviation. Using this methodology they have shown that a large majority of studies have effect sizes that fit a normal distribution curve with a mean effect size of approximately 0.57 - 0.70 standard deviations from the control mean. While such a difference is medium in size, it should be kept in mind that this is a description of a very crude measure of a very gross fluid volume. It is conceivable that with further methodological refinements this estimate will need to be revised upwards. In particular, the use of volumetric measures instead of area measures and the use of more rigorous models to control for the effect of age, may lead to revisions in the estimated magnitude of this effect.

In addition to reports of lateral ventricular enlargement in schizophrenia, there have been many reports of enlargement of the third ventricle, the cerebellar folia, the Sylvian fissures, as well as sulci in other cortical regions (see reviews by Raz and Raz 1990; Shelton et al 1988). While measurement of the ventricles has posed significant technical problems, these pale in comparison with the difficulty of measuring the cortical sulci (see review by Pfefferbaum et al 1990). Using a computerized semiautomated approach to identifying fluid pixels, Pfefferbaum et al reported that cortical sulci were increased in all major cortical regions surveyed (Pfefferbaum et al 1988); the mean effect size for the schizophrenic group was approximately one standard deviation from the mean of the controls. In their meta-analyses, Raz et al (1990) estimated the effect size for cortical sulcal enlargement to be 0.35. However, it is not clear whether this represents a significant difference from the mean effect size for the lateral ventricles or whether the cortical differences are obscured to a greater extent by larger measurement error (Raz and Raz 1990). They did report that across the 14 neuroimaging studies which provided regional measures of sulci, the effect sizes for anterior and posterior cortical sulci did not differ significantly nor did the effect sizes for the right and left hemisphere sulci (Raz and Raz 1990). This is consistent with the finding of Pfefferbaum et al (1988), that regional measures of cortical sulcal volume were both significantly increased and significantly intercorrelated.

It has been hypothesized that ventricular and sulcal enlargement may represent manifestations of separate pathophysiologic processes (Weinberger et al 1979). In the Raz and Raz (1990) metaanalysis, no association was found between measures of ventricular and sulcal size in patients with schizophrenia; however, this may well have been due to the use of relatively gross measures of the cortical sulci. Pfefferbaum et al (1988) did find a significant correlation between computer quantified volumetric measures of ventricular and sulcal size in the schizophrenic patients (rho = 0.62, $p < .001$) which remained highly significant after both CT measures were corrected for age (rho = 0.54, $p < .001$). This finding suggests that a single process may account for both findings. It could be, for example, that as a result of cortical atrophy, the sulci enlarge directly and the ventricles expand secondarily.

Most studies of ventricular size in schizophrenia have relied on the VBR (ventricle-brain ratio) (Syneck and Reuben 1976) which is defined as the ratio of the ventricular area to the intracranial area on the single CT section on which the lateral ventricles are largest. While area and volume measures have been found to be highly correlated (Reveley 1985), they are not equally sensitive to small changes in ventricular size (Raz et al 1987). Raz et al (1987) have shown that, in their hands, measuring the ventricles over multiple sections lead to an almost two-fold increase in the estimation of the effect size compared to the more traditional method of measuring the VBR on a single CT section using a mechanical planimeter.

It has also been appreciated that ventricular volume increases significantly with age and most recent studies have taken caution to control for the effect of age. Although earlier evidence had suggested that age effects on brain CSF measures could be assumed to be noncontributory as long as the patients were below the age of 60 years (Zatz et al 1982), more recent evidence suggests that even in the 20-45 year age range that age may account for up to 50% of the variance in cortical sulcal volume and in cortical grey matter volumes (Zipursky et al 1990a). If the within

group variance in schizophrenics in age-matched samples of schizophrenics and controls is very substantial, it is that much more difficult to establish between group differences. Use of analysis of covariance or age regression models (Pfefferbaum et al 1990; 1986; 1988) can be of great value in reducing age effects.

Clinical Correlates of Structural Brain Abnormalities

Attempts to relate ventricular enlargement to differences in clinical subtype, positive or negative symptoms, severity of illness, and medication responsiveness have not yielded clear results (see reviews by Lewis 1990; Raz and Raz 1990). Initial enthusiasm was great for the notion that ventricular enlargement might be associated with what has been described by Crow (1980) as Type II schizophrenia (ie. schizophrenia characterized by poor premorbid adjustment, cognitive impairment, poor response to medication and a predominance of negative symptoms). Very little support for this formulation has accumulated over the past ten years despite intensive investigation (Raz and Raz 1990; Lewis 1990). That significant clinical correlates of ventricular enlargement have been difficult to establish, is likely due in part to the methodological problems previously discussed and to the limitations of the clinical assessment instruments used. It might also be the case, however, that meaningful clinical correlates of ventricular enlargement do not exist. While it might be the case that the presence of certain types of brain abnormalities might predispose or directly lead to the development of schizophrenia, it may not be the case that the magnitude of any of the clinical symptoms is directly related to the magnitude of the brain abnormalities.

Raz and Raz (1990) have carried out a metaanalysis in which they have shown that larger numbers of hospitalizations are associated with greater ventricular effect sizes even though other measures of illness duration and severity were not consistently associated with ventricular enlargement. The explanation for this association is not clear. Raz and Raz (1990) suggest that this could be due to the effect of age, disease severity, institutionalization and treatment, or the effect of a progressive disease process. Although most studies have not been able to find a relationship between ventricular enlargement in schizophrenia and gender (see review by Goetz and Van Kammen 1986), evidence is accumulating that male patients with schizophrenia may be more likely to have ventricular enlargement. The elucidation of such relationships are limited not only by the previously described concerns about limitations in measurement and age effects but also by sample selection criteria. Whether this finding holds clues about the pathophysiology of schizophrenia or is an artifact of, for example, gender differences in age or alcohol use has yet to be determined.

Significance of Structural Brain Abnormalities

While it does not seem to be the case that clinical subtypes of schizophrenia can be differentiated on the basis of ventricular enlargement, the possibility that differences inventricular size amongst schizophrenics might reflect differences in etiology remains a possibility. It has been hypothesized that patients who develop schizophrenia on a genetic basis will not have structural brain changes whereas those with sporadic cases may have a structural brain abnormality to account for their developing schizophrenia (Reveley et al 1982). Exploration of this hypothesis has also lead to inconsistent results (Lewis 1990).

Twin and Sibling Studies

While the evidence is substantial that groups of patients with schizophrenia have enlarged ventricles compared with controls, it is still not clear whether this is due to a large effect in a few or a small to medium effect in many with the illness. There is very little evidence from the CT and MRI studies to date to suggest that there is a bimodal distribution of ventricular sizes; on the contrary, most studies have suggested that there is a continuous distribution. It could well be the case that all patients with schizophrenia have some degree of ventricular enlargement relative to what their ventricular size would have been given their individual genetic makeup. This possibility is very difficult to test in part because of the large normal variation of ventricular size both with age and at any given age. By studying siblings of patients with schizophrenia it is possible to reduce some of the variance in ventricular size which may be due genetic variation. Weinberger et al (1981) have reported that when they compared the VBRs of 10 chronic schizophrenics to 12 of their nonschizophrenic siblings, all schizophrenic patients had the largest VBR of their sibships. As a group, the schizophrenic patients had larger ventricles than their siblings and controls. However, the well siblings of the schizophrenics, whose VBRs were intermediate in magnitude between the patients and controls, also had larger ventricles than controls. Using a similar strategy, DeLisi et al (1986) studied the VBRs of schizophrenic patients who came from sibships where more than one member had schizophrenia. They compared these 26 patients who were from 12 different families, with 10 of their nonschizophrenic siblings and 20 volunteers. The patients with schizophrenia in this study had larger ventricles than the volunteers but were not significantly different from their nonschizophrenic siblings whose mean VBRs were approximately midway value between the patients' and volunteers' values. Together with the Weinberger et al (1981) study, these findings suggest that ventricular enlargement is not likely to be restricted to those without a familial disposition towards schizophrenia (as was suggested by Reveley et al 1982) and that even some unaffected siblings may have brain differences compared to normals.

To further clarify the role of genetics in the development of ventricular enlargement in schizophrenia, other investigators (Reveley et al 1982; Suddath et al 1990) have studied monozygotic (MZ) twins who are discordant for schizophrenia. If ventricular enlargement in schizophrenia is due to an underlying genetic difference, then MZ twins, whether

or not they are concordant for schizophrenia, would be expected to have ventricles of a similar size; on the other hand, if ventricular size is increased in schizophrenia because of some non-genetic insult to the brain, then it would be expected that the affected MZ twin in twin pairs discordant for schizophrenia would have the larger ventricles. Reveley et al (1982) found using CT that the schizophrenic twins had larger ventricles than their well co-twins in 6 of 7 cases but that the well co-twins also had ventricles that were larger than found in MZ twin pairs with no history of schizophrenia. Using MRI, Suddath et al (1990) also found that as a group the affected co-twins had larger ventricles than the group of unaffected co-twins and that MZ twins discordant for schizophrenia had larger intrapair differences in ventricular size than pairs of healthy MZ twins. On visual inspection of the images, the affected twin had larger ventricles in 12 of 15 pairs (a nonsignificant difference). However, no comparison of the discordant twins to normals was described. To fully interpret these findings, it would also have been valuable to know whether the magnitude of intrapair differences in MZ twins discordant for schizophrenia is different from that of MZ twins concordant for schizophrenia. If MZ twins concordant for schizophrenia have intrapair differences which are not different from those MZ twins who are discordant for schizophrenia, this would argue against concluding that the differences in VBR in discordant MZ twins are etiologically related to the development of schizophrenia in the affected twin.

There could be a number of possible explanations for the findings of Suddath et al (1990). The schizophrenic twins in these pairs may have been exposed to an environmental influence that lead to the brain differences; the unaffected co-twins may have also been exposed to the same influence but have had an insult of insufficient magnitude to lead to schizophrenia. Another possibility would be that both members of the twin pairs may possess an underlying structural vulnerability to schizophrenia but only the affected twin has been exposed to an additional environmental vulnerability factor. So as not to trivialize the methodological difficulties in carrying out such family and twin studies, it should at least be mentioned that among other problems it is critical to establish that the unaffected twins or siblings will not develop schizophrenia at some time subsequent to the study. We do not know this with certainty for the family and twin studies published to date. In the Suddath et al (1990) study, the mean age of the twins was 32 years while in the Reveley et al (1982) study the mean age was 38 years.

Is Ventricular Enlargement Progressive?

If one accepts that patients with schizophrenia as a group have enlarged ventricles, the question then arises of whether the process which leads to these differences is a progressive one. This issue has been explored using a number of different approaches: studies of patients early in their course of illness, follow-up studies and crossectional studies of patients with a range of illness durations. Ventricular enlargement has been found in most (Schulz et al 1983; Weinberger et al 1982; Turner et al 1986) but not all studies (Iacono et al 1988) which have looked at patients with schizophrenia of recent onset. Follow-up studies of 3 and 8 years duration by Nasrallah et al (1986) and Ilowsky et al (1988), respectively, have found no evidence for significant increases in ventricular size over these time periods. Most cross sectional studies have failed to find a relationship between illness duration and ventricular size (see review by Goetz and Van Kammen 1986; Lewis 1990). Taken together, these different lines of investigation suggest that the brain differences found in patients with schizophrenia are not progressive over the chronic course of the illness.

It remains to be determined when the differences found in patients with schizophrenia occur. Such differences could occur during prenatal development leaving the individual predisposed to schizophrenia. If this were the case, then follow-up studies involving individuals at high genetic risk for schizophrenia could determine whether significant differences are apparent early in life in these patients. Alternatively, these differences could occur during the early part of the illness, that is during the prodrome and initial acute episode. If they occur early in the course of the illness, one might be able to detect limited progression if it was possible to study patients in these early phases on the illness. That siblings and unaffected co-twins of schizophrenics have some degree of ventricular enlargement would suggest that the total extent of ventricular enlargement could not be due to the development of schizophrenia per se. Others have suggested that ventricular enlargement may be associated with birth injury (for review see Lewis et al 1990). Like the investigation of familial contributions to structural brain changes in schizophrenia, hypotheses about birth injury raise additional complex methodological considerations (Lewis 1990).

Differences in Intracranial Volume

If the brain abnormalities found in schizophrenia are due to an insult to the brain early in development, it might be expected that this would result in a reduction in the size of the adult brain in these patients. In as much as it is believed that brain growth drives skull growth (Davis and Wright 1977), one might expect head size to be reduced in some patients with schizophrenia if the process causing schizophrenia takes place prior to the completion of brain growth (approximately age 18) (Pfefferbaum and Zipursky 1991). This was initially reported by Andreasen et al (1986) and subsequently by Pearlson et al (1989) and Zipursky et al (1991) though others have not been able to find this effect (Weinberger et al 1987; DeLisi and Goldin 1987; Andreasen et al 1990). A number of factors may contribute to the inconsistencies in this finding which exist between studies: failure to control for body size and gender differences between groups, limitations in statistical power due to small sample sizes and the use of small numbers of CT sections

per subject. If it is the case that only some potential etiologies of schizophrenia result in smaller intracranial volumes, then differences in the population of schizophrenics sampled could also lead to such inconsistencies. The differences observed have been on the order of a 3-5% difference in intracranial volume in patients with schizophrenia as a group. It is conceivable that a difference of this magnitude could be due to an insult to the brain at any stage in its development including adolescence. For example, Feinberg (1983) has hypothesized that a defect in cortical synaptic pruning during adolescence could underly schizophrenia. This does lead to the question of whether those who develop schizophrenia after brain growth is completed may be more likely to have ventricular and sulcal enlargement rather than reduction in intracranial volume (Pfefferbaum and Zipursky 1991) whereas those who develop schizophrenia before brain growth is completed may show evidence of reduced brain volume rather than ventricular and sulcal enlargement. Determination of intracranial volume may, therefore complement the measurement of ventricular and sulcal volume in determining the onset of the brain abnormalities in schizophrenia.

In summary, evidence has accumulated from CT studies of schizophrenia that ventricles and cortical sulci are enlarged in patients with schizophrenia. Clearly these are nonspecific findings as they are present in many neurological illness (e.g. Alzheimers disease, Parkinson's disease, alcoholism, normal aging and perhaps other psychiatric illnesses (Raz and Raz 1990; Jernigan 1986). Since these findings are nonspecific, they are not helpful diagnostically. They may, however, provide clues to the pathophysiology of schizophrenia. It is assumed that the enlargement of ventricles and sulci in patients with Alzheimer's disease and alcoholism, for example, are a reflection of the underlying pathophysiology, even if there is a substantial overlap with normal as there is in both of these conditions. Presumably these findings, when seen in patients with schizophrenia, also hold clues to the etiology and pathophysiology of schizophrenia. Unlike the CT findings of Alzheimers and alcoholism which are progressive with the natural history of ongoing disease, the abnormalities in schizophrenia appear early in the illness and appear to parallel the normal aging curves. In addition, in the case of schizophrenia, the enlargement of ventricles and sulci may be associated with a slight reduction in intracranial size, suggesting that in at least some patients, the development of brain abnormalities may have occurred before brain growth had been completed. Whatever is causing this phenomenon is also likely affecting many cortical areas to a significant extent. The insight provided by CT into the brain abnormalities associated with schizophrenia have, therefore, been very valuable in terms of directing our thinking towards disturbances in brain development as possible explanations for the development of schizophrenia. The potential for CT to provide further insights into this field, however, is limited by the spatial resolution and lack of tissue contrast provided by CT.

MRI STUDIES OF SCHIZOPHRENIA

MRI became available in the mid-1980s and offers many advantages over CT scanning. Subjects are exposed to a very low degree of risk from the magnetic field and radiofrequency pulses compared to the ionizing radiation of CT. This is of particular importance in planning longitudinal studies involving many repeat scans. MRI also provides considerable tissue contrast within the brain, such that grey matter and white matter can be distinguished as can areas of fluid, infarction, and tumor. MRI also provides great flexibility in choosing the plane of acquisition so that sections can be acquired in axial, coronal, sagittal or oblique planes. In fact, with current technology, scans can be acquired volumetrically and sectioned into any plane following the scan. In vivo structural brain imaging has been significantly limited in the past by partial voluming over 5-10 mm thick sections, often with a gap being present between sections. Current technology now allows for section thickness approaching 1mm. In addition, the MRI acquisitions can now be done for the head as a volume rather than a finite number of sections. Large numbers of relatively thin (1 mm) sections can now be acquired that allow one to section the brain as a volume so that sections of different orientations can be used to address different questions (Pfefferbaum et al 1990). Beam hardening artifact, which is a major problem for CT studies in that it limits the resolution of cortical sulci and the visualization of the temporal lobes, is not a factor in MRI scanning. As a result, the temporal lobes can be clearly visualized with MRI, a feature which is of great importance for the study of schizophrenia.

At the same time as CT was beginning to provide a general picture of the types of gross brain abnormalities present in patients with schizophrenia, new evidence was emerging from neuropathological studies that pathology may be localized in the brains of schizophrenics to structures in the temporal lobes. Bogerts et al (1985), for example, have described reductions in volume of the hippocampus, amygdala and parahippocampal gyrus. Brown et al (1986) have reported that compared to the brains of patients with affective disorders, brains from patients with schizophrenia showed disproportionate enlargement of the temporal horns of the ventricles. Gliosis in limbic and basal ganglial areas have been described by Stevens (1982). Abnormalities in limbic regions have also been described in recent cytoarchitectonic studies (for review see Roberts et al 1990). The literature, however, has not been unanimous in reporting these abnormalities (Heckers et al 1990).

MRI studies have been in an excellent position to followup on these pathological studies in vivo. A number of MRI studies have now examined the temporal lobes in patients with schizophrenia. Suddath et al (1989) has described reduced temporal lobe volume as well as reduced temporal lobe grey matter in schizophrenia. MRI studies by Johnstone et al (1989) and Kelsoe et al (1988), on the other hand,

have not found reduced temporal lobe size. Reduced hippocampal volume in male schizophrenics on MRI scan has now been described by Bogerts et al (1990) while Barta et al (1990) has described reduced superior temporal gyrus volume and left amygdala volume. However, MRI studies to date have not been consistent in controlling rigorously for age effects, artifactual sources of asymmetry, differences in intracranial volume or the possibility that other brain regions may show similar effects (see review by Pfefferbaum et al 1990).

MRI studies to date have been quite consistent in documenting that patients with schizophrenia as a group have either gross or localized loss of temporal lobe volume or temporal lobe grey matter volume. Yet it remains unclear whether these types of differences are present in other brain regions. Zipursky et al (1990a) have conducted an MR study of 22 male patients with schizophrenia and 20 healthy controls, all between the ages of 20 and 45 years old. Summing over seven 5mm axial MRI sections, it was shown that grey matter volume but not white matter volume was significantly reduced in this sampling of the brain and that the schizophrenic group had less grey matter in all gross cortical regions measured. This finding suggests that schizophrenic patients may have widespread differences in grey matter volume and that this finding may underly the cortical sulcal and ventricular volume increases reported with CT. This finding is consistent with the gross neuropathological finding of Pakkenburg (1987) who found that the brains from patients with schizophrenia differed from control brains in total grey matter but not white matter volume. It is still conceivable that the temporal lobe differences are of greater magnitude than differences elsewhere in the brain or that they may be of more relevance to the clinical presentation of schizophrenia. It seems unlikely, however, that the structural brain abnormalities in schizophrenia are isolated to the temporal lobes, as it remains unclear how abnormalities localized to the temporal lobes could explain enlargement of the bodies of the lateral ventricles so frequently reported in patients with schizophrenia.

Quantification and comparison of grey matter and white matter volumes in multiple brain areas require that tissue contrast be consistent throughout the images analyzed. This is commonly not the case as a result of radiofrequency (RF) inhomogeneity within the field of view of the MRI scanner (Pfefferbaum et al 1990). Digital filtration approaches to this problem have been proposed and successfully implemented (Lim and Pfefferbaum, 1989).

MRI has also been helpful in clarifying the nature of the pathophysiologic process underlying schizophrenia. Any disease process in the brain which causes neuronal damage after the 6th month of gestation should result in a glial reaction which involves proliferation of glial cells (Roberts 1990). Areas of gliosis have been described in the temporal lobes of some patients with temporal lobe epilepsy using MRI (Kuzniecky et al 1987). In as much as a gliosis has been described in the brains of patients with schizophrenia postmortem (Stevens 1982), it was of great interest to see whether MRI studies of schizophrenia would show significant areas of gliosis within the brain. This has not in general been the case, a finding which is in accordance with recent postmortem studies (for review see Roberts 1990). Current evidence, therefore, favors the possibility that the brain abnormalities in schizophrenia may be due to a developmental rather than a degenerative or destructive process. Further research needs to be done to determine whether these differences are present at birth in patients at risk for schizophrenia or whether they occur at some later stage of brain development.

There has been considerable interest in the possibility that schizophrenia may be a manifestation of an underlying abnormality in cerebral asymmetry. A number of clinical observations has lead to this view. Among patients with temporal lobe epilepsy who develop schizophrenia-like syndromes, it is much more common for the primary seizure focus to be on the left than right side (Perez and Trimble 1980). The capacity for MRI to provide high resolution images of small grey matter nuclei raises the possibility that differences in the size of such structures may be detectable in patients with schizophrenia. In as much as this type of analysis requires structures to be measured on each side of the brain, the possibility frequently arises that differences may be present on one side of the brain but not on the other. Crow et al (1989) have even hypothesized that an anomaly in the development of cerebral asymmetry may underly schizophrenia. However, the interpretation of differences in cerebral asymmetry is difficult (Zipursky et al 1990b). Multiple sections need to be included in such analyses as there is often imperfect alignment of the hemispheres relative to each other such that a given section may sample the two hemispheres in nonequivalent anatomical areas. Imperfect alignment of the subjects' head in the scanner may also lead to artifactual asymmetries (Zipursky et al 1990b). Whether asymmetry is quantified and expressed as a ratio or as a difference score may also significantly affect interpretation of such data (Zipursky et al 1990b). What is very clear is that most studies have found evidence that both hemispheres are affected in schizophrenia. It remains to be determined whether asymmetries significantly different from those observed in normals can be consistently found in patients with schizophrenia.

Future Directions

MRI studies of schizophrenia are at a very early stage in their history. Evidence from recent structural brain imaging studies and neuropathological studies has lead to reconsideration of the possibility that schizophrenia may be a disease of brain development (see reviews by Roberts et al 1990; Weinberger et al 1987). Evidence to date of localized and widespread gray matter differences may be valuable clues to the pathophysiology of schizophrenia. Yet these studies do require replication and clinical correlates will need to be elucidated with larger sample sizes.

Which questions about the structural brain abnormalities are best addressed with MRI as opposed to neuropathological

studies? Clearly, neuropathological investigations are critical in elucidating the cellular basis for any gross brain abnormalities observed with MRI. By describing the underlying pathology, investigators move closer to identifying the sequence of pathophysiology which underlies schizophrenia. There are, however, many advantages to doing structural brain investigations with MRI rather than with postmortem samples (for review see Kirch and Weinberger 1986). These advantages are of major significance and include: 1) prospective evaluation of patients and controls; 2) avoidance of brain changes related to coexisting disease, agonal events and brain fixation; 3) ability to study otherwise healthy subjects; 4) ability to recruit large samples and; 5) use of samples across a wide age range including young subjects early in the course of their disease (Kirch and Weinberger 1986).

Postmortem studies tend to bias one to study older samples of patients. Many of the critical question in this field need to be asked about young patients early in their disease. When, exactly, can one detect significant abnormalities with MRI? Are these present in the prodrome or at the time of the first episode of psychosis? While the brain abnormalities of schizophrenia do not appear to be progressive over the long-term course of the illness, can it be shown that at some point in adolescence, a significant period of deviation from normal brain structure occurs and progresses for a finite period of time? Do individuals in families with a high risk for schizophrenia have significant abnormalities on MRI and do these occur only in affected members, those with schizophrenia spectrum disorders or totally asymptomatic relatives? Addressing these questions is critical to the development of a coherent theory of the pathogenesis of schizophrenia and will be helpful in guiding future neuropathological investigations.

There will also need to be much further work done to determine whether the brain abnormalities of schizophrenia are truly localized, asymmetric or perhaps widespread. Future studies will hopefullly optimize their ability to study tissue volumes rather than areas, use the most rigorous measurement techniques and control carefully for the effects of normal aging. MRI studies of schizophrenia should then be in an excellent position to guide future neuropathological investigations of schizophrenia.

FUNCTIONAL ANATOMIC STUDIES WITH POSITRON EMISSION TOMOGRAPHY (PET)

Our aim is to evaluate, methodologically and conceptually, what has been learned and to identify new opportunities. Pet studies in schizophrenia have been reviewed recently (Buchsbaum 1990 Wiesel 1989).

The majority of studies have examined functional anatomy by measuring the regional distribution of radioactively labelled 2-fluoro-2-deoxyglucose (FDG), an analog of glucose. The radioactive tracers used are Fluorine 18 [18F] or Carbon 11 [11C]. Glucose and 2-deoxyglucose are competitive substrates using the same carrier across the blood-brain barrier and are phosphorylated by the same enzyme, hexokinase, to glucose-6-phosphate or its analog deoxyglucose. Unlike glucose-6-phosphate, deoxyglucose-6-phosphate is not metabolized further in the glucolysis and it is trapped in the tissue. Thus, metabolic measures with PET in fact measure the uptake of [18F] FDG into the cells. This process is very closely coupled cerebral with blood flow. Regional changes in metabolism or blood flow reflect neuronal activity in the region of interest. However, a reduction of cortical tissue volume could underlie low blood flow and metabolism. Sensitive MRI or CT measures of sulcal volume are only now becoming possible (Pfefferbaum 1986; Lim and Pfefferbaum 1989). These measures will help determine the extent to which changes are structural or biochemical.

The resolution of PET cameras has been improving so that the new generation of cameras have a resolution of 3-5 mm which make it possible to study small structures in the limbic system, nuclei of thalamus and brain stem, whereas previously, measures had to be confined to larger regions — frontal, temporal, parietal and occipital cortices, and the basal ganglia were divided simply into the thalamus and striatum (caudate and putamen).

Anatomic Localization

PET can measure metabolic or neurochemical activity, and good anatomic localization of function is crucial. Functional regional abnormalities may indicate pathological tissue and raise questions that could be answered by structural imaging or neuropathological studies. Since PET provides functional metabolic maps of the brain, anatomical landmarks are difficult to identify. Most groups rely upon brain atlas approximations of anatomic structures, or on structural images from CT or MRI superimposed on PET images in subjects examined in comparable head positions. Most PET research groups define slice level according to standard anatomical or CT atlas (eg. Matsui and Hirano 1978), and visually identify regions of interest by inspection of each scan where this is possible and where it is not, by specified measurements from slice level to vertex and anterior to posterior poles. Fox et al (1988) use stereotactic coordinates based on an atlas and programmed in the tomograph. Gur et al (1987) use a standardized template programmed to all PET scans. Cleghorn et al (1990) have used stimulation maps for cortical areas related to language function, digitized them and transposed them into proportions to apply to PET images. All of these methods can be criticized for using an idealized image based on an atlas. This criticism may, however, not be crucial when dealing with large structures.

Friston et al (1989) have introduced a new method based on the proportionate distance of structures from the line between the anterior commissure and the posterior commissure (AC-PC) which bears a fairly constant relation to a line connecting the most anterior point of the glabella

to the mid point of the base of the inion (Fox et al 1985). This line in turn has a predictable relation to other brain structures and the contribution of individual differences to error is known. The technique was validated anatomically by predicting the location of focal activation of the sensory motor cortex. This location was compared to normal anatomy according to a standard atlas (Talairach and Tournoux 1988) which takes into account normal variation. Estimates of structural location, using this method in comparison with MRI, have an error whose SD is 3.54 mm which is less than normal anatomic variation (Friston et al 1989).

Some hold the opinion that each individual subject's brain should be outlined on an MRI image, which in turn should be superimposed on the PET image. However, as noted above, such precise measurements with MRI are themselves difficult. Moreover, cortical regions subserving specialized functions may be located in different gyri in different individuals (Goldman-Rakic, personal communication, 1991.

As with MRI, the exact positioning of the head is important and repeated measures are vulnerable to error due to tilting, particularly from the temporal lobe to the vertex. However, repeated measures show that cerebral glucose metabolic measurements are reproducible within 1-2%. Such reproducibility has been demonstrated in resting normal human subjects (Bartlett et al 1988), and in psychotic subjects re-examined within hours or days (Bartlett et al 1991). Precise reproducibility is, however, dependent upon utilizing relative rather than absolute measures. Relative measures utilize a value for a region of interest in ratio with a denominator, which can be the mean for either a tomographic slice, a hemisphere, or the whole brain. There is evidence that relative measures correspond better than absolute measures, to direct measures of brain tissue (Meyer et al 1989).

Absolute measures (CMR glu) vary markedly from day to day. Twofold individual differences in absolute cerebral metabolic rate for glucose from day to day have been reported. Such differences would obscure many experimental effects or effects related to disease. Between 57% and 17% of this variance is due to differences in brain size (Hatazawa et al 1987) (Yoshii et al 1988). Furthermore, when the effects of age and gender are considered in a study of mild brain atrophy, only 20% of the variance in CMR glu could be explained by atrophy. These data suggest that absolute values of CMR glu may lack sensitivity to the effects of disease. These problems may explain the fact that nine studies of schizophrenic subjects have reported low whole brain metabolism and seven have not (Buchsbaum 1990). The sources of artifact in PET measurements are becoming much better understood. Future studies will thus be more reliable.

Relative measures have the disadvantage of ambiguity as to whether a change in one region represents that region itself (represented by the numerator), or change in the opposite direction in the comparison region (represented by the denominator). Statistical methods, however, can determine the probability that the change in one region is dependant on change in another specific region or on widely distributed changes (Friston et al 1990). In addition, one can examine the relations of two functionally related parts such as frontal and parietal cortices as a frontal-parietal ratio. This ratio is functionally meaningful, since both structures subserve aspects of attention (Cleghorn et al 1989).

In addition, Friston (1991) has described a new method for localizing functionally meaningful differences in regional cerebral activity. A statistical parametric map (SPM) of the correlation between behavioral psychopathology scores and rCBF or CMR glu in each pixel can be calculated. The procedure transforms each brain into a standard stereotactic space and corrects for intersubject differences in whole brain, metabolic or blood flow values. Stereotactic normalization removes the variance due to anatomical variation by mapping each pixel to a standard stereotactic space, as defined by Talairach and Tournoux (1988). These images consist of the 26 planes which correspond to the horizontal sections of the above atlas. To accommodate variability in gyral anatomy between subjects and to increase the ratio of signal to noise, each image is smoothed with a Gaussian filter with a full width to half height of 10 pixels. Differences in global activity are removed using linear regression and normalized to the mean value for all patients. Then statistical parametric maps of correlations between behavioral ratings and cerebral activity values for all pixels are made for all planes (SPM). An estimate is then made of the probability that the observed pattern of correlations could have arisen by chance. The number of pixels for which a coefficient exceeded the value required to meet $P = .05$ is compared with the number of correlations of $p > .05$ as compared with those expected under the Null Hypothesis of zero correlation by Chi squared test. Taking each plane separately, the plane is considered to be significant if the probability of chance occurrence equals $p < .005$.

Frontal Lobes

Initial PET-FDG studies of schizophrenia focussed on the frontal lobes owing to the initial blood flow studies of Ingvar and Franzen (1974) who found a relative reduction of the normal hyperfrontal pattern in patients with schizophrenia. This has been called "hypofrontality," and a significant inverse correlation between frontal blood flow values and negative symptom intensity was proposed in chronic schizophrenics. Some acutely ill psychotic patients who were particularly alert actually showed the opposite, an exaggeration of the hyperfrontal pattern that is normal (Ingvar personal communication 1991). Other patients were not different than normal controls. Since the negative symptoms resemble a form of frontal lobe syndrome, it was logical for Buchsbaum's, (1982 and 1984) pioneering studies with PET and [18F] FDG to examine the frontal lobes. Buchsbaum and co-workers also found relative hypofrontality (relative to the occipital lobe which was used as a point of reference). A total of six studies have reported

low relative frontal metabolism (Buchsbaum 1982, 1984) (Farkas et al 1984) (Wolkin et al 1988) (Cohen et al 1987) and four have not (Sheppard et al 1983) (Jernigan et al 1985) (Kling et al 1986) (Wolkin et al 1985). One with neuroleptic naive subjects has reported exaggerated frontal metabolism (Cleghorn et al 1989). These differences are not precisely related to the intensity of negative symptoms as will be seen below. How then can the discrepancies be explained?

First, it is notable that Ingvar and Franzen's finding of hypofrontality was evident in a group of chronic schizophrenic patients, while acutely ill patients had a normal or exaggerated frontal blood flow. Thus, the findings of other investigators in young, never-treated patients do not contradict the earlier results. It must be concluded that schizophrenics display greater variability in frontal activity than do normal controls.

Neuroleptic treatment appears to lower frontal metabolism but not to a degree sufficient to explain several replications of hypofrontality. Furthermore, recent neuroleptic withdrawal has been found to be associated with hypofrontality (Cascella et al 1990) and most reports of hypofrontality have examined patients approximately two weeks after neuroleptic withdrawal. Hypofrontality is in no way specific to schizophrenia and is also found in affective disorders (Buchsbaum et al 1984) and can be caused by both frontal cortical and subcortical neurological lesions (D'Antona et al 1985). In our clinical experience, hypofrontality is found in patients who have an irreversible negativity syndrome, a lifelong history of asociality, anergia, anhedonia, perinatal brain damage and current evidence of a frontal lobe syndrome on neurocognitive testing. In addition, Volkow et al (1987) suggests that patients with predominantly negative symptoms are metabolically hypofrontal when compared with those who have predominantly positive symptoms. Most recently, Buchanan et al (1991) have reported that patients with an enduring deficit state have reduced glucose utilization in frontal and parietal cortices and in the thalamus. Future studies should determine whether hypofrontality is associated with evidence of perinatal brain damage, premorbid schizoid or schizotypical traits, MRI evidence of increased ventricular volume and sulcal widening, small temporal lobes, family history of schizophrenia and male gender. Such findings would add validity to Murray's proposal (Castle and Murray 1991) that there is a congenital form schizophrenia which is distinct from adult onset psychosis. Such severely compromised function might be reflected in a reduction of gray matter volume, which in turn could account for hypometabolism measured by PET.

In addition, Liddle and Barnes (1990) have recently confirmed the existence of two kinds of frontal syndrome in schizophrenia (Liddle 1987). One called psychomotor poverty, resembles the well known deficit state. Using Statistical Parametric Mapping (Liddle et al 1991) have found the poverty syndrome is associated with reduced blood flow measured by PET in dorsolateral prefrontal cortex mainly on the left. The other syndrome is called disorganization, an orbito frontal syndrome that includes formal thought disorder and inappropriate affect; it is associated with hypoperfusion of anterior cingulate and medial prefrontal cortex mainly on the right.

We have mentioned several possible substantive sources of discrepancies between studies of frontal metabolism in schizophrenia: differences in the degree to which positive or negative symptoms were evident, differences in conceptualizing symptoms, chronicity, neuroleptic treatment and withdrawal from treatment, and possibly reduced gray matter volume.

In addition, methodological issues may contribute to discrepancies. Investigators differ in the measurements of absolute versus relative measures (discussed above) and in the denominator used for relative measures: the mean for the tomographic slice, a hemisphere or whole brain value, or values for occipital or parietal lobes. Furthermore, some studies of the so called resting state utilize a standard sensory stimulus (Buchsbaum et al 1982, 1984), others do not.

Most of the above studies have been carried out in the resting state, in subjects experiencing psychotic symptoms. This approach has promised to reveal a metabolic functional anatomic map of the psychotic state, an approach which has only been partly successful owing to the many sources of variance pointed out above.

An experimental cognitive approach is more likely to reveal functional biological changes. Landmark studies have been carried out by Weinberger et al (1986) and Berman et al (1988) using xenon inhalation and measures of cerebral blood flow in response to tasks that do or do not demand frontal lobe activation. These studies revealed that both subjects treated with neuroleptics and those not treated fail to activate frontal blood flow when required to perform the Wisconsin Card Sort Test. They also perform poorly on the test. When asked to perform a test that does not require frontal function, namely Raven's Matrices, no difference between controls in rCBF or test performance and patients was observed. Most recently, these investigators have distinguished frontal gyri on PET by means of MRI and report that the main effect is in the inferior frontal gyrus (Berman et al 1991). Failure to show appropriate activation on the computerized EEG with the Wisconsin Card Sort Test has been demonstrated by Williamson et al (1989). Furthermore, Buchsbaum (1990) using the Continuous Performance Test as a cognitive challenge, has demonstrated that schizophrenics activated frontal and temporal-parietal cortex metabolism to a lesser degree than controls. These studies invite further analysis with specific cognitive challenges so that the deficit can be more precisely defined and localized than it can be using a task as complex as the Wisconsin Card Sort Test. For example, perseveration errors may reflect poor functioning of the dorsolateral prefrontal cortex, while inefficient sorting and non-perseverative errors may not (Sullivan et al 1991). In contrast, working memory (holding an item consciously in mind) depends on the integrity of a specific mid-prefrontal region

(Funahashi et al 1989). Considerable anatomical precision can be achieved with simpler tasks (Posner et al 1988).

It is likely that considerable complexity will emerge to muddy the apparently simple relationship between cognitive challenge and frontal lobe activity. Recently Wood and Flowers (1990) reported that a narrative prose recall task caused left hypofrontality on the first trial and right hypofrontality on the second, suggesting that the hypofrontality can be a state and not a trait phenomenon. Novelty may play an important role. The anterior cingulate may also be activated by novelty and not by task repetition (Berman et al 1991).

Temporal Lobe

Measures of temporal lobe metabolism are particularly vulnerable to head tilting. In addition, differences in the angle of the tomographic slice at different centers makes comparison of studies of this region particularly difficult. Computerized lateral reconstructions of the lateral and medial temporal lobes are now possible. In view of the cumulative evidence implicating the left temporal lobe in the positive symptoms of schizophrenia recently reviewed by Crow (1990), some PET workers have attempted to determine whether there is a significant difference in the left and right temporal laterality. DeLisi et al (1989) found temporal lobe lateralization to the left in schizophrenia and that this was in proportion to the severity of psychopathology measures, a finding which is consistent with observations by Gur et al (1987). Using a slightly different anatomical tomographic slice, we have been unable to confirm these observations (Cleghorn et al 1990; 1991). However, computer reconstruction of image data of the entire temporal cortex will help resolve these discrepancies. Considerable evidence for left temporal structural abnormalities is emerging (see below).

PET researchers have been reluctant to interpret differences in laterality because of methodological inconsistencies. In addition, stimuli which require the use of a specialized structure in one hemisphere may activate the homologous structure in the contralateral hemisphere, although the latter may not be absolutely required for performance of the task (Ojemann et al 1988) (Fried et al 1981). Thus, true differences in hemispheric specialization may be obscured.

Perhaps because of the methodological difficulties mentioned above, the results of studies to date have been inconsistent; seven studies have detected significantly lowered metabolic rates in the left temporal lobe but five have not (Buchsbaum 1990). Hypometabolism in the left temporal lobe would be consistent with the observation of a smaller volume of temporal lobe gray matter on MRI (Barta et al 1990) (Rossi et al 1990) and at autopsy (Bruton et al 1990).

Challenge studies using language tasks promise that much more can be learned about the left temporal lobe using PET. Wood and Flowers' PET studies (1990) have observed focal suppression of left hemisphere blood flow in Broca and Wernicke's Area during the process of recall in a verbal memory task. Cleghorn et al (1991) have observed relative hypometabolism in the posterior superior temporal gyrus region, part of Wernicke's Area, in neuroleptic naive subjects experiencing auditory hallucinations during 18F FDG uptake. This may be consistent with the observation that the size of the superior temporal gyrus, measured by MRI, correlated inversely with auditory hallucination scores (Barta et al 1990).

Parietal Lobe

Relative hypometabolism in two tomographic slices of the parietal region has been observed in neuroleptic treated (Szechtman et al 1988) and in drug naive patients (Cleghorn et al 1989). In addition, the frontal parietal ratio was significantly greater in patients than in controls. Very few studies have examined parietal metabolism but those which have supported this finding (Wiesel et al 1987, Kishimoto et al 1987). Buchanan et al (1991) have reported that low glucose utilization in parietal cortex is associated with an enduring deficit state.

Studies of the parietal lobes may be rewarding since activation of the right parietal lobe is crucial for sustained attention to sensory stimuli (Pardo et al 1991), and for the direction of attention to extra personal space (Mesulam 1985), functions which are frequently disordered in schizophrenia (Posner et al 1988) (Cleghorn 1988). Buchsbaum et al (1990) examined right and left parietal metabolism in patients and controls during performance of the CPT and found that the patients right sided activation was less in patients than controls and performance scores were poorer than controls.

The recognition of facial affect requires intact right parieto temporal function (Fried et al 1982) and is impaired in schizophrenia. Borod et al (1986) compared schizophrenic patients with other patients suffering from right hemisphere lesions and found both groups poor at voice and face recognition and the recognition of emotional expression in the voice and face. Data consistent with these findings (but without brain localizing data) have been presented by Feinberg et al (1986), Kolakowska et al (1985), Novic et al (1984), and Taylor and Abrams (1985). Electrocorticographic studies carried out on neurosurgical patients have implicated the parieto occipital junction, the posterior middle temporal gyrus and the homologue of Broca's area in the right hemisphere in facial affect recognition (Fried et al 1982). These regions can be examined by PET using appropriate challenge stimuli.

Neuroleptic Effects

Perhaps the most robust finding of PET studies in schizophrenia is that chronic neuroleptic administration is followed by an increase in basal ganglia metabolic rates (Buchsbaum 1987) (DeLisi et al 1985) (Wolkin et al 1985) (King et al 1986) (Szechtman et al 1988). Furthermore, the dopamine agonist apomorphine has the opposite effect and it reduces striatal metabolism to a significantly greater

extent in schizophrenic patients than in controls (Cleghorn et al 1991).

Most recently, Cleghorn et al (1991) have replicated their previous findings (Szechtman et al 1988) that schizophrenic patients examined two or more years, after chronic neuroleptic treatment had significantly elevated relative metabolism in the striatum but not in the thalamus. In addition, Cleghorn et al (1991) observed a decrease in the frontal parietal ratio ie. a significant decrease in relative frontal metabolism and an increase in relative parietal metabolism. There was a concomittant decrease in positive and negative symptoms and an increase in I.Q. after two and three years of neuroleptic treatment. The decrease in frontal parietal ratio is consistent with reports of declining frontal posterior (not specifically parietal) ratios by Wolkin et al (1985) and a similar finding by DeLisi et al (1985) which was observed only in those patients who improved with treatment. Revaluating that study, Buchsbaum et al (1987) did not find any significant changes in cortical metabolism following neuroleptic treatment. Gur et al (1987) found no change in cortical or subcortical values; however, three of the fifteen patients remained unmedicated. In addition, single values were given for subcortical structures. No significant effect on thalamus was reported; the increase in striatal metabolism reported in other studies may have been diluted by including the data from the thalamus.

Most recently, Warkentin et al (1990) has observed a significant reduction of the frontal occipital blood flow ratio following neuroleptic treatment and highly significant positive correlations between the degree of the behavioral disturbance and the right hemisphere ratios for frontal occipital and frontal parietal blood flow. Symptom changes were also associated with both the changes in frontal and parietal values separately, in the right hemisphere. These findings indicate that changes in the frontal parietal and striatal systems accompany recovery from psychotic symptoms. However, neuroleptic effect and symptomatic improvement remain confounded.

The relation of duration of disease and drug treatment was analysed in one study (Wiesel et al 1987). Duration of disease or age but not duration of neuroleptic treatment was related to reduced brain metabolism. Cleghorn et al (1991) have confirmed that duration of neuroleptic treatment was not related to measures of brain metabolism. In a sample of controls with an age range of 19-44 years, age was not significantly correlated with striatal metabolism but was significantly and inversely correlated with parietal lobe metabolism.

Future Directions

It is evident that consistent findings can emerge from cerebral metabolic studies using positron emission tomography in schizophrenia. This is illustrated by a reasonable degree of uniformity in results in different centers, when neuroleptic effects are examined. However, characterization of patients in the resting state shows discrepancies which probably cannot be solely attributed to the heterogeneity of schizophrenia. Severity and chronicity, reversibility by treatment, degree of neurocognitive impairment, prior treatment effects and duration of neuroleptic withdrawal, all need to be carefully controlled. Studies on neuroleptic naive subjects are particularly promising.

Most of the studies reported so far must be considered a first generation of PET studies in schizophrenia, whose methodologic and conceptual limitations have become evident. Localization of the disorder to one or other lobe or central gray structures is probably simplistic. Anatomic knowledge of cortical striate thalamic feedback loops has become available since the first PET studies were started (Alexander and Crutcher 1990). It is possible that the problems of cognitive integration that characterize schizophrenia may involve cortical basal ganglia limbic loops (Damasio and Damasio 1989). Integration of elements of experience is accomplished not only by frontal or anterior temporal cortices but by these widely distributed neuronal loops. Ablation of frontal and anterior temporal structures does not put an end to integrated experience and behavior. Zipursky's (1990a) report that anatomical abnormalities may involve much of the cortex is consistent with an analysis of the clinical, pathophysiological and pathological abnormalities identified in schizophrenia (Cleghorn and Albert 1990).

The implication of cortico-striate-thalamic loops introduces new complexities into design and data analysis. In addition, the comparison of syndromal groups may introduce variability that obscures important subtleties. The use of syndrome factors and statistical parametric mapping is promising. In addition, it may be wise to use within person designs in which a single experimental condition is varied, and the image of a stimulus condition is subtracted from a control condition (Posner et al 1988; Pardo 1991). This method permits examination of cerebral patterns of response within individual members of a group and for measurement of variability in the location and intensity of functional anatomic response within groups.

In addition, the relations between regions must be examined to fully explore the possibility that widely distributed brain systems may be abnormal in schizophrenia, taking suitable precautions to avoid type II errors (Cleghorn and Albert 1990). The stimuli in such studies can be cognitive or pharmacological, and the opportunity to examine brain function and dysfunction with these techniques is extensive (Cleghorn 1991 and 1991).

DOPAMINE RECEPTOR IMAGING

Direct imaging of D2 dopamine receptors in living human brain, provides the opportunity of extending in vitro dopamine receptor work into the clinical domain. In vitro work has provided strong evidence supporting D2 dopamine receptor blockade by neuroleptics as the mechanism for their antipsychotic action (Seeman 1987). In vitro findings of elevated D2 receptors in schizophrenia, however, have been more controversial (Seeman 1987; Reynolds 1989;

Kornhuber et al 1989). Conflicting PET studies have only further heated the debate over D2 receptor elevation in schizophrenia. PET dopamine receptor studies in other areas relating to schizophrenia, however, have been providing useful and more consistent information. These areas will be reviewed in this section.

Methodology of Dopamine Receptor Imaging Using PET

PET measurement of brain dopamine receptors in vivo must contend with many variables in addition to those encountered with in vitro binding techniques. In vivo, the amount of radioligand (ie, the receptor-labelling compound) that binds to brain receptors can be influenced by a number of factors: 1) blood brain barrier permeability of the radioligand; 2) the extent of plasma protein radioligand binding; 3) the rates of metabolism and elimination of the ligand; and 4) the confounding effects of radioactive ligand metabolite accumulation in the brain. The uptake of radioligand that one measures in brain tissue containing dopamine receptors (eg. striatum), will consist of both that which is bound to the receptor as well as non-specific tissue ligand uptake. This latter component must be 'subtracted off,' in order to obtain some quantitative measurement of receptor-bound ligand. PET studies often estimate the 'non-specific' component of binding from radioligand uptake measurements in cerebellum [a brain area essentially devoid of dopamine receptors (List and Seeman 1981)]. While this method is the easiest and most practical for clinical PET receptor measurements, cerebellar ligand uptake may not always be equivalent to the non-specific binding in dopamine receptor-rich regions such as the caudate and putamen (striatum) (Farde et al 1988; Bahn et al 1989; Logan et al 1987).

A single measurement of receptor binding reflects two parameters, the number of receptors present (Bmax), and their affinity (KD) for the radioligand used. In order to obtain separate estimates of these two parameters, measurements of specific binding must be made at varying radioligand concentrations, or levels of receptor occupancy. In man, practical and ethical considerations, however, can impose some constraints on this approach. Repeat experiments are limited by radiation exposure restrictions, and problems may be encountered in giving the large pharmacological doses of ligand required to produce significant receptor occupancy. While optimally one might like to obtain individual measurements of Bmax and KD, the importance of obtaining separate estimates can be over-emphasized. In vitro work, for example, has shown that observed binding changes in pathological states are usually due to Bmax changes with no alteration in KD (Seeman et al 1987). Such changes can be observed using a single radioligand concentration (Lee et al 1978) (even though no separate KD and Bmax determinations are possible under these conditions).

Much work in the PET dopamine receptor area has attempted to take into account the various factors influencing D2 ligand brain uptake and binding. This has been done by making detailed measurements and then using mathematical models to generate binding parameters (such as Bmax and KD, — or a combined constant referred to as k1 (Welch et al 1984) or k3 (Wong et al 1986), which is the product of Bmax and a binding association rate constant). Many have argued that such an approach is necessary to obtain meaningful measurements, that can be used for comparative purposes (Welch et al 1984; Wong et al 1986; Perlmutter et al 1989). Others have argued, however, that unless one has an accurate estimate of all important factors affecting ligand binding, including those factors in the overall calculations may actually introduce more error into the binding estimates (Smith et al 1988; Wienhard et al 1990). This argument suggests that simpler more directly measured values (eg. striatal to cerebellar ratio) may be preferable. Use of an independent method of receptor measurement would be useful in determining the utility of the two PET methods. For example, direct manipulation of receptors (by chronic neuroleptic treatment or by lesioning) could be performed in monkey, measured by PET, and then compared to in vitro receptor measurement in the same animals.

In the preceding discussion, caudate and putamen are cited as examples of D2 dopamine receptor-rich brain regions. Autoradiographic techniques and binding studies using tissue homogenates have also detected D2 receptors in limbic and cortical regions. Owing to limits in resolution, however, PET D2 studies have been mainly confined to caudate and putamen, and attempts to detect extrastriatal sites have failed (Farde et al 1988a). It is also known that the distributions of dopamine receptors in caudate and putamen are not homogeneous (Sokoloff et al 1990), nor are the neuronal projections, which differ significantly in caudal versus rostral areas of striatum (Graybiel 1990). The measures of whole caudate and putamen reported in PET D2 studies may thus not reflect regional dopamine receptor changes occurring in specific neuronal systems.

Investigation of Neuroleptic Drug Action at D2 Receptors Using PET

Studies have long demonstrated that in vitro affinities of neuroleptic drugs for D2 receptors correlate well with their clinical potencies in treating schizophrenia, thus supporting the D2 receptor as the site of action of antipsychotic drugs (Seeman 1987). PET studies have now begun to examine, in vivo, this correlation and related issues in schizophrenic patients under neuroleptic treatment.

The approach, in vivo, has been to estimate neuroleptic occupation of D2 receptors by measuring the extent of reduction in radioligand D2 receptor binding in subjects receiving neuroleptic medication compared to drug-free controls. D2 density in the medicated patients, however, may be higher than in the drug-free controls because chronic neuroleptic treatment can up-regulate D2 sites (List and Seeman 1979). Therefore, this strategy may lead to an underestimation of neuroleptic D2 receptor occupancy during

chronic neuroleptic treatment. This approach, however, has lead to the finding that chronic antipsychotic treatment in schizophrenia, regardless of the neuroleptic used, results in striatal D2 receptor occupancies of 65% - 80%, suggesting that antipsychotic efficacy of neuroleptics is achieved when this level of D2 receptors blockade is achieved (Farde et al 1988; Wolkin et al 1989). Observed occupancy levels for atypical neuroleptics such as clozapine and melperone have also fallen within the low end of this range. Such data refutes the notion that the reduced frequency of extrapyramydal side-effects with atypical neuroleptics is due to regionally selective D2 blocking activity which spares the striatum (Borison et al 1983). Further understanding of the differential effects of atypical neuroleptics may be gained from PET studies which image other neuroreceptor systems (Meltzer et al 1989), or other dopamine receptor subtypes [eg D1 (Farde et al 1987; Friedman et al 1985) or those newly identified through molecular cloning (Sokoloff et al, 1990; Van Tol et al, 1991; Sunahara et al, 1991)].

A number of studies have looked at the relationship between neuroleptic dose or blood level and D2 receptor blockade. A significant curvilinear relationship was seen between dose and striatal D2 binding inhibition in one individual whose antipsychotic medication (sulpiride) was gradually reduced on a weekly basis (Farde et al 1988). Another study (Baron et al 1989) showed a similar curvilinear relationship when looking at D2 binding inhibition in 11 patients (with a variety of diagnoses) receiving treatment with an assortment of neuroleptics at a wide range of dosages. An average ED50 for D2 receptor blockade (dose required to block 50% of receptors) was estimated to be 150 mg, in standardized chlorpromazine equivalents. One must be cautious about the accuracy of the ED50, however, due to many sources of error (eg. use of cerebellum baseline for non-specific binding; effect of neuroleptics on D2 density).

Neuroleptic non-responsiveness in schizophrenia has also been examined using PET. Wolkin et al (1989) found no difference in the degree of receptor blockade during neuroleptic treatment between those groups of schizophrenics that were responsive and non-responsive to medication. This would suggest that failure to respond clinically was not due to failure of neuroleptic to reach D2 receptor sites.

A number of studies have looked at neuroleptic withdrawal in relation to the time needed to clear neuroleptic from brain D2 receptors. Farde et al (1988), have observed in two patients (one taking haloperidol and the other taking sulpiride), that after drug discontinuation, serum levels declined much faster than did the D2 blocking effects. Others have looked at the time needed following neuroleptic discontinuation for D2 receptor binding to return to control levels. The time averaged 6 1/2 days in one study, where patients with schizophrenia had been treated with haloperidol (15 mg or 20 mg) for 1-3 weeks before discontinuation (Smith et al 1988). In another study using a diagnostically heterogeneous population, return to control levels of binding appeared to occur within 5-15 days (Baron et al 1989). As previously discussed, however, the use of binding measurements from drug-naive subjects to estimate baseline receptor binding levels in patients receiving neuroleptics, may make neuroleptic D2 occupancy levels appear lower than they really are. Thus, the time needed for complete neuroleptic washout from D2 sites may be underestimated in these studies. A more accurate estimate might be obtained by making all comparisons within individual patients (ie. D2 binding measurements while in the drug-free state, then while on medication, and then at intervals following drug withdrawal).

Dopamine Receptors and Tardive Dyskinesia

Dopamine receptor supersensitivity has been postulated as a pathophysiological mechanism underlying tardive dyskinesia (Klawans 1973). Two PET studies have looked at D2 receptors in patients with a variety of diagnoses who developed tardive dyskinesia following chronic neuroleptic treatment (Blin et al 1989; Andersson 1990). Neither study supports an association of D2 dopamine receptor elevation with tardive dyskinesia, although one study (Blin et al 1989) suggests D2 density may be associated with severity of oral dyskinesia. In both studies, however, numbers were small and there were substantial differences between controls and patients in addition to the presence or absence of tardive dyskinesia. Controls were neuroleptic-naive and relatively healthy compared to patients who suffered from chronic psychiatric illness or organic brain syndromes. One study (Andersson et al 1990) included a more representative comparison group (ie. previously medicated psychiatric patients without tardive dyskinesia), however, this consisted of only three patients. The nine day neuroleptic-washout time before PET scan in one study (Blin et al 1989) may not have been adequate, as residual neuroleptic in the brain could have interfered with the binding measurement.

As discussed, the effectiveness of current PET methods to detect receptor changes is unknown. It might thus be useful to make PET D2 measurements under conditions that are known to produce dopamine receptor changes, in order to determine whether such changes can be detected by PET. For example, D2 receptor elevation in animals (including primates) following chronic neuroleptic treatment is a consistent finding, and one would also expect to see this in man. After washout from chronic neuroleptic administration, a PET study showing increased D2 binding compared to pretreatment levels would help validate PET D2 quantitation methodology.

Dopamine Receptors in Schizophrenia

Postmortem studies on brain tissue from schizophrenics have shown elevated densities of D2 dopamine receptors (of 1.5 to 2-fold greater than controls) (Seeman 1987). There has been difficulty in interpreting these results, however, as most of the schizophrenics at some point had received neuroleptics, which can themselves cause D2 receptor elevation (List and Seeman 1979). In addition, one recent

postmortem study suggests no increase in D2 receptors in schizophrenics neuroleptic-free for at least three months before death (Kornhuber et al 1989). This question has now been directly addressed using PET techniques to measure D2 receptors in living schizophrenics known to have never received medication.

An early study in 1986 (Crawley et al 1986), (using a gamma camera with a gamma-emitting D2 receptor ligand, [77Br]bromospiperone) showed a small but significant increase (11%) in striatal/cerebellar activity in the schizophrenic group (n=12) compared to controls. However, less than a third of the schizophrenics were neuroleptic-naive. The patients were also quite heterogeneous with respect to age, sex and length and phase of illness.

In the same year a PET study from Johns Hopkins University (Wong et al 1986), using [11C]-N-methyl-spiperone, ([11C]NMSP) demonstrated a 2.5 fold increase in D2 receptor densities in schizophrenics compared to controls. In this study, comparisons made were between estimated Bmax values rather than between observed binding levels. As described, the estimation of Bmax requires two scans per subject performed at differing levels of dopamine receptor occupancy (which in this study consisted of one scan before and one scan after a dose of haloperidol). Interestingly, in this same study, binding levels (as measured by striatal: cerebellar ratios or k3 values) following single scans in the absence of haloperidol did not detect differences between controls and schizophrenics.

The following year Farde et al (1987) (Karolinska, Sweden), using [11C]raclopride at trace and high dose in a two scan experiment under equilibrium conditions (approximating an in vitro binding assay), were unable to find any differences in D2 receptor densities between controls and unmedicated schizophrenics. A more detailed recent study by this group confirmed their initial negative finding (Farde et al 1990). It was also shown that this study had sufficient statistical power to have detected receptor elevation in schizophrenics, if it were present.

Much discussion (Andreasen et al 1988; Zeeberg et al 1988; Seeman 1988; Seeman et al 1990; Seeman et al 1989) has focused on factors which might explain the widely discrepant results between the Karolinska and Johns Hopkins studies but as yet, the controversy remains. Differences between the studies can be found in both the patient characteristics and in the methods of D2 receptor measurement. The Johns Hopkins patients were older and more chronic, with an average length of illness of 5 years from psychosis onset, compared to 1.9 years from onset of prodromal symptoms in the Swedish group. The Johns Hopkins workers have suggested that there is a relationship between receptor elevation and length of illness. PET data from other groups as well as in vitro binding data, however, does not support such an association (Kornhuber et al 1989; Martinot et al 1989).

Many differences in the Johns Hopkins and Karolinska methodologies have been described in detail elsewhere (Andreasen et al 1988). These differences do not adequately account for the disparity between results. While [11C]raclopride and [11C]NMSP differ in their affinity and specificity for D2 receptors, in vitro data indicates that these ligands label the same population of D2 receptors (Hall and Wedel 1986). Spiperone derivatives can label sites other than D2. In striatum, however, binding is mainly dopaminergic especially at low ligand concentrations (as used in human PET studies) (List and Seeman 1981). Farde et al (1989) have also demonstrated that similar binding parameters can be obtained independent of whether measurements are made under equilibrium or non-equilibrium conditions. An erroneous use of cerebellum to estimate striatal non-specific binding has been implicated for the lack of observed D2 elevation in the Karolinska study (Seeman 1988; Seeman et al 1990). However, while the use of cerebellum is explicit in the Karolinska study, it also enters into the Johns Hopkins analysis, and thus does not likely account for the disparity in the results.

Inhibition of [11C]raclopride, but not [11C]NMSP binding, by endogenous dopamine, has also been proposed to explain the negative findings of the Karolinska group (Seeman et al 1990; 1989). In order for such an effect to confound in vivo comparisons of schizophrenic to control D2 densities, one would have to suppose that endogenous dopamine levels were different in these two groups. If this were the case, the D2 affinity constant for [11C]raclopride between the schizophrenics and controls should appear to be different and this was not observed (Farde et al 1987; 1990). Increased endogenous dopamine output is likely to occur in the middle of both the Karolinska and Johns Hopkins studies during the second PET scan when a large dose of neuroleptic is given (as neuroleptics are known to increase dopamine release). Such an effect might invalidate the assumptions used in calculating receptor densities in both studies.

Concerns have also focused on the methodology of the Johns Hopkins group. Firstly, it seems surprising that the two scan experiment, with its complex estimation of Bmax, detects 2-3 fold elevations of D2 receptors in schizophrenia, while simple striatal to cerebellar ratios or k3 values (a component of which is Bmax) obtained from single scan experiments do not suggest even a trend towards elevation in schizophrenia (Wong et al 1986; Zeeberg et al 1988). Wong et al (1986) have stated that these simpler methods are invalid when elevated levels of receptors are present as the rate of binding is then limited by blood flow (ie. ligand delivery) to the brain area. Studies from other groups, however, suggest that brain blood flow is not rate-limiting (Logan et al 1987; Welch et al 1984; Perlmutter et al 1989; 1986; Smith et al 1988; Wolkin et al 1989), and that if elevated densities were present, striatal to cerebellar ratios should still show a tendency to increase. As previously discussed, ratios studied in other situations have shown the direction of change that would be expected.

Another methodological issue of concern in the Johns Hopkins study relates to the use of haloperidol. For the purposes of the D2 density estimations, a number of halo-

peridol binding constants as well as brain concentrations for each subject need to be known. These cannot be measured directly and are therefore estimated indirectly from in vitro values or by making a number of assumptions of questionable validity. The association rate constant of haloperidol for D2 receptors is arbitrarily assumed to be the same as that measured for [11C]NMSP. Brain haloperidol concentrations are estimated by measuring plasma haloperidol levels and then assuming a blood-brain partition co-efficient identical to that measured for [11C]NMSP. No evidence is provided to demonstrate that haloperidol is identical to [11C]NMSP in its physical and biochemical behaviour. Furthermore, only the plasma free (not protein bound) haloperidol is likely to partition into brain. The fraction of free haloperidol in plasma was not determined in the Johns Hopkins study. Thus, significant differences in protein binding between individuals could alter apparent Bmax values and confound comparisons.

Also of concern in the Johns Hopkins study, is that their data analysis produces binding estimates for haloperidol that suggest it has a much lower affinity for D2 receptors in the schizophrenics compared to controls. Post-mortem studies do not show such alterations in D2 affinity for neuroleptic, neither does one see this under experimental conditions in animals. Wong et al (1988) have argued that estimates of haloperidol affinity are not very reliable and it would be a mistake to attribute much significance to them. Nevertheless, it is interesting to note that there appears to be an inverse correlation between the affinity and Bmax values, so that in terms of actual amount of binding observed, one parameter offsets the other.

Three other studies have looked at D2 receptors in schizophrenia. Lundberg et al (1989), using 11C-clozapine found no differences from control; however their sample was extremely small (n=3). Martinot et al (1989) using [76Br]bromo-spiperone and striatal to cerebellar ratios, found a non-significant trend towards D2 elevation in 12 schizophrenics. When the sample was subdivided after analysis into chronic patients versus those with an acute onset of psychosis, a 30% elevation over controls was seen for the latter but not the former group. This subdivision results in very small numbers per group, however, and it is not clear that this subdivision is clinically valid. A replication of this study using a further 19 unmedicated (including 10 drug naive) schizophrenics, and the more D2 selective ligand 76 Br-bromolisuride, again failed to detect significant overall D2 elevation in patients (Martinot et al 1991). Furthermore, in this latter study, no significant difference in D2 binding was observed between patient subgroups.

Only one study, therefore, from the Johns Hopkins group using the haloperidol method, demonstrates a substantial elevation of D2 receptors in schizophrenia. It should be noted that a power analysis by the Karolinska group shows that their study population was large enough to detect this elevation if it were present.

Some clarification of the discrepancies might occur if both the [11C]raclopride and the John Hopkins [11C]NMSP methods are performed in the same individuals drawn from both recent onset, as well as chronic groups of schizophrenics. It may be that PET receptor measurement methods have not yet been accurate enough to reliably answer this question due to limitations in resolution and in parameter estimation models.

Future Directions

Current techniques for measuring D2 dopamine receptors using PET have, however, been able to provide some consistent findings. This is evident in the similar observations across centers with respect to the relationship between D2 receptor occupancy and neuroleptic dosage. Further studies now need to explore in more detail the relationship between receptor occupancy and clinical response. For example, is there a group of patients who fail to respond to neuroleptics due to lack of D2 occupancy? Does receptor occupancy change with remission of symptoms or during psychotic relapse? Is there a relationship between receptor occupancy and neuroleptic induced extrapyramidal side-effects?

In contrast to drug occupancy studies, discrepancies between research groups continue to occur in the D2 receptor comparisons between schizophrenics and controls, as well as between those with and without tardive dyskinesia. Such comparisons likely require greater accuracy and sophistication of binding estimation than are required for drug occupancy studies. Pathological changes may effect not only receptor levels, but also ligand delivery to the receptors. Furthermore, differences in receptor binding in pathological states may be more subtle and may be localized to only sub-portions of brain regions. Improvement of receptor quantitation methods have focused on attempts to control for the pharmacokinetic factors which are felt to influence delivery of ligand to the receptor sites. Validity of the method is usually determined by comparing the absolute values of binding parameters estimated by PET, to previously determined in vitro values. Such comparisons are helpful in relating in vivo to in vitro work at the biochemical level. From the point of view of clinical comparisons, however, one is more interested in knowing whether a difference exists [and its magnitude and direction] between those with and without the disorder rather than obtaining absolute values of binding parameters. Thus, a useful direction for further validation of methods should involve examination of PET's ability to detect changes in D2 dopamine receptor levels under conditions where this is known to occur (eg. following chronic neuroleptic treatment).

While pathological changes in D2 receptors may be limited to specific regions of basal ganglia or may involve extra-striatal sites, thus far D2 binding measurements have been limited to whole caudate and putamen. The development of selective PET ligands with higher D2 receptor affinity (Halldin et al 1990) and improvements in the

resolution of positron cameras should allow the study of sub-portions of basal ganglia including nucleus accumbens. Hopefully this will also permit the detection of extrastriatal D2 sites including frontal and temporal cortical areas and substantia nigra.

The availability of D1 PET ligands will allow the study of D1/D2 interactions which have been reported as abnormal in postmortem brain tissue from schizophrenics (Seeman et al 1989). Molecular cloning has recently identified three new pharmacologically distinct dopamine receptor subtypes (D3, D4 and D5) (Sokoloff et al 1990; Vantoll et al 1991; Sunahara et al 1991). These sites may be helpful in the further understanding of pharmacological effects of antipsychotics and may provide clues regarding pathological mechanisms of schizophrenia and tardive dyskinesia. As yet, however, no specific ligands are available to label these sites.

Aside from refinements in PET methodologies for dopamine receptor measurement, heterogeneity in the patient population and the choice of appropriate controls remain ongoing issues. In looking at drug effects on receptors, prospective studies using within patient comparisons (ie before, during and after treatment), should help reduce potential confounding variables. With respect to dopamine receptor measurements of drug-naive schizophrenics and measurements in those with and without tardive dyskinesia, clinical variables including severity, length of illness and clinical features of illness must be carefully controlled for. Future studies will require larger sample sizes so that cases can be stratified on variables that may potentially influence dopamine receptor binding.

CONCLUSIONS

Structural and functional brain imaging studies of schizophrenia suggest that multiple cortical and subcortical brain areas are involved in the pathophysiology of this illness. The extent to which abnormalities are localized to specific structures or functional anatomic systems needs to be elucidated in future work.

Structural brain imaging studies and neuropathological studies suggest that schizophrenia has a neurodevelopmental origin. It is not yet known whether the brain abnormalities seen in schizophrenia develop prenatally, postnatally or coincide with the onset of illness. To this end, it will be very important to determine whether brain abnormalities are present in children at risk for schizophrenia and in unaffected family members. Fuller characterization of the brain abnormalities will enhance efforts to resolve these issues.

Metabolic studies utilizing PET provide the opportunity of detecting abnormal brain functioning in schizophrenia under a variety of physiologic and cognitive conditions. Such studies have the potential to detect abnormalities whether or not the gross structure of the brain is abnormal. Interpretation of future studies will need to take into account normal individual variation in brain structure. The extent to which abnormalities in function reflect structural abnormalities has not been determined. The use of MRI and PET on the same subjects promises to answer this question.

PET receptor studies in patients with schizophrenia are at a relatively early stage in their development. Current controversies about the integrity of the D2 system in schizophrenia has had the benefit of focusing attention on the critical methodological considerations that will need to be addressed in the next generation of PET receptor studies. The potential exists for this technology to provide critical insights into the pathophysiology of schizophrenia, extrapyramidal syndromes and the mechanisms of action of medications used in the treatment of schizophrenia. While PET receptor studies measure crucial drug effects, measures of blood flow or metabolism may reflect effects that are temporally and anatomically remote from receptor sites. Such studies may also shed light on abnormalities of brain function or structure.

Brain imaging studies of schizophrenia have provided important insights into the biological foundation of schizophrenia. Advances in these technologies and accumulating experience in dealing with the methodological issues posed by such studies will greatly increase the potential for these fields of research to yield new insights into the nature of schizophrenia.

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