From Syndrome to Illness: Delineating the Pathophysiology of Schizophrenia With PET

by Robert M. Cohen, William E. Semple, Michael Gross, and Thomas E. Nordahl

Abstract

The Section on Clinical Brain Imaging of the Laboratory of Cerebral Metabolism has been engaged in studying regional brain metabolism by positron emission tomography (PET) to establish the pathophysiology of schizophrenia. Recent studies have revealed that the fluorodeoxyglucose (FDG) PET methodology can be applied successfully to determine the anatomical substrata of directed attention. In normal controls, the metabolic rate in the middle prefrontal cortex, measured during the ongoing performance of auditory discrimination, is associated with their accuracy of performance. In unmedicated patients with schizophrenia, even those who performed as well as normals, the metabolic rate in the mid-prefrontal cortex was found to be significantly lower than normal. Further, this decreased metabolic rate was unrelated to performance. In medicated patients with schizophrenia, at least part of the metabolic deficit remains, but this deficit appears to be performance-related. These findings suggest several conclusions. The mid-prefrontal cortex and its dopamine neurotransmitter pathway input are important biological determinants of sustained attention. Two types of prefrontal metabolic deficits may contribute to dysfunctional goal-directed behavior and, more speculatively, vulnerability to psychosis in some patients with schizophrenia. One deficit is sensitive to neuroleptics, and thus presumably to a change in the balance of regional brain dopamine input. A second deficit is unaffected by neurolpetic treatment.

The path of medical knowledge of an illness begins with the description of a syndrome, followed by studies that foster understanding of etiology (causal factors), pathogenesis (how the causal factors produce the illness), and treatment. Although success in describing the syndrome of schizophrenia has been an important advance, facilitating the development of treatment, psychiatry's inability to delineate a pathophysiology for schizophrenia has been a stumbling block. Narrow, and presumably more successful, studies of etiology cannot be performed. Systematic approaches to treatment and prevention have been slowed, and, perhaps most importantly, the right to define the illness has been withheld.

At the Intramural Research Program (IRP) of the National Institute of Mental Health (NIMH), we have made a sustained effort to use positron emission tomography (PET) to help elucidate a pathophysiology for schizophrenia. We have made this commitment because we believe that PET, a brain-imaging technology of unsurpassed ability to localize and quantify tracers in space and thereby physiological processes in the human brain, offers the greatest promise for delineating the pathophysiology of schizophrenia. For a more detailed description of PET methodology, see Cohen et al. (1986).

We quickly recognized that defining pathophysiology required a

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clear understanding of the dimensions of normal physiology, i.e , we had to establish a range of values for the parameters of normal organ physiology In general, these normal values are defined in the context of organ function. For example, to understand whether the kidney is functioning properly may require observing electrolyte concentrations in the urine following abstinence from food and fluids. In the brain, these values are likely to be determined behaviorally. Thus, researchers in PET must choose both a tracer to study and thereby the physiological process to be measured, and a context, i.e., what the subject will be doing while the physiological process is measured Task choice can be predicated upon known behavioral deficits in an illness or upon the function of a brain region suspected or demonstrated to be involved in the pathophysiology.

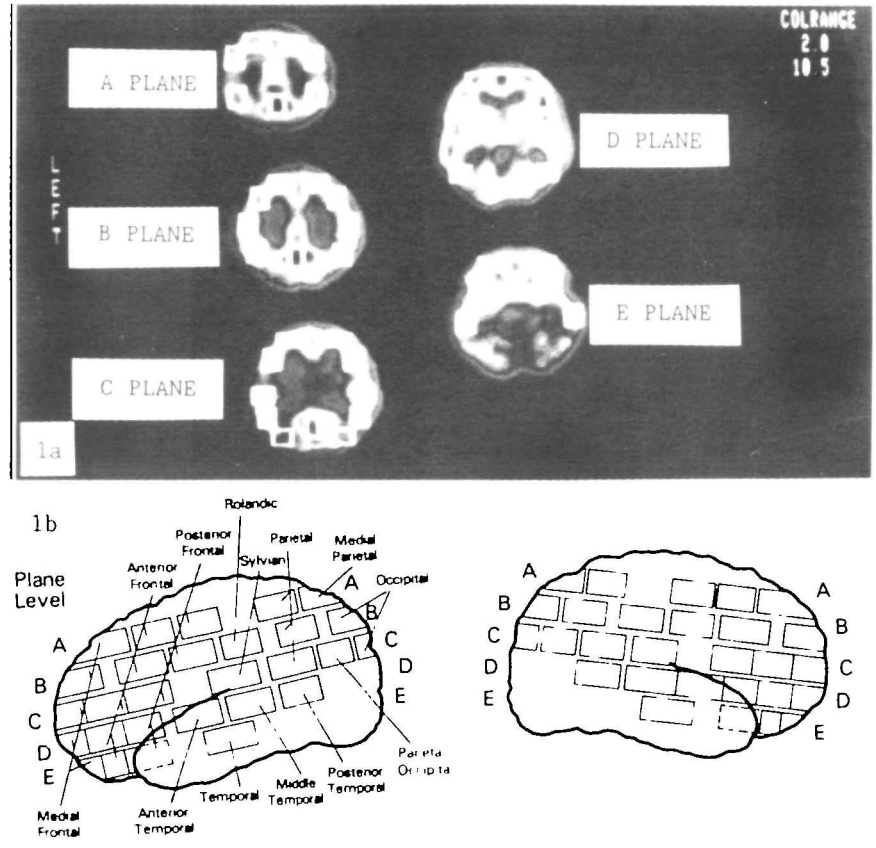
Prior PET Studies of Schizophrenia

To date, most studies of schizophrenia and PET have measured the anatomical determinants of the "resting" state or the state of the brain while an individual is experiencing somatosensory stimuli (meaningless, but sometimes painful electric shock to the forearm) The anatomy of function has been determined by measurements of regional blood flow or glucose metabolism The latter measurement, based on the accumulation of the radioactive tracer ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) was derived from the ^{14}C-deoxyglucose method of Sokoloff and his colleagues at the NIMH-IRP (1977)

Given that regional blood flow and metabolism are closely linked to regional brain functional activity, the use of these particular tracers in PET studies of schizophrenia was and is admirable. Their unambiguous physiological interpretation provides a strong scientific basis for studies of schizophrenia, and differs from the more common occurrence of new technologies being employed to study schizophrenia with dramatic initial results subsequently giving way to disappointment because of inadequate understanding of the meaning of the measurements obtained.

Although the resting state has proved to be a reasonable choice in studies of dementia, epilepsy, and tumors (Mazziotta and Phelps 1986), it appears unlikely that the exclusive study of patients in the resting state will prove sufficient

Figure 1. Five typical PET slices (top) and lateral surface schematic representations of same regions from left and right hemispheres (bottom)



The top portion shows 5 typical positron emission tomography (PET) slices that are obtained from subjects using the ECAT II scanner with the rectangular regions of interest (ROI) boxes overlaid on the images Below the actual slices is a lateral surface schematic representation of these same regions as sampled from the left and right hemispheres Regions labeled as medial, although sampled from the medial portion of the cortex, are represented as incomplete boxes on the lateral surface The boxes outlined by dashed lines are sampled from the surface of the frontal cortex, medial to the temporal cortex The region labeled as medial parietal is also referred to in the text as superior posterior parietal cortex

for the delineation of the pathophysiology of schizophrenia. In contrast to dementia, epilepsy, or tumors, the syndrome of schizophrenia is more difficult to discern in the resting or unconscious patient, or for that matter at postmortem. It is, however, readily recognizable in the patient in the context of interaction with his environment.

Nevertheless, some resting studies have revealed an apparent "hypofrontality" in schizophrenia. As noted initially by Ingvar and Franzen (1974) in their blood flow studies, higher functional activities are observed in the frontal cortex than in the more posterior areas of the brain in normal controls, but not in some patients with schizophrenia. It is the attenuation of this hyperfrontal pattern in schizophrenia that has also been observed by some PET investigators (see references in Cohen et al. [1986]). The frontal cortex is an area of the brain believed to be important for the performance of the highest integrative or executive functions of the brain. The more posterior areas of the brain are more closely associated with the receiving and processing of sensory stimuli. Therefore, these findings have, in general, been interpreted as supporting the hypothesis that a frontal cortex abnormality is responsible for those disorders of higher cognition associated with schizophrenia.

Because findings of hypofrontality in patients with schizophrenia at rest, however, were not robust, an attempt to increase frontal cortex activity with electric shock and thus increase frontal cortex differences between schizophrenic patients and normal controls was made. Observations of differences in the processing of painful stimuli in schizophrenia also contributed to the choice of this condition. The findings of hypofrontality with electric shock, however, were perhaps even weaker than those at rest (Buchsbaum et al. 1984). Our own recent investigation of the somatosensory condition in normals has suggested that electric shock is not associated with generalized activation of the frontal cortex, and in some regions of the frontal cortex may be associated with suppression of activity (Cohen et al., in press).

Functional Localization of Sustained Attention in Normals and in Patients With Schizophrenia

To remedy these problems, we began in the summer of 1983 to study frontal cortical function in schizophrenia in the context of a specific executive function, maintenance of directed attention. We chose to examine the functional localization of the ability to perform continuous auditory discrimination because consistent deficits in continuous performance had been reported in schizophrenia and in subjects at increased risk for schizophrenia (Mirsky 1969; Nuechterlein et al. 1984). Because sustained attention is also fundamental to the development and execution of "goal-directed" behavior, these defects may lie closer to the primary defects presumed to be associated with genetic errors than the overt symptomatology of schizophrenia (fully expressed phenotype). Furthermore, as the frontal cortex is quite large in man and consists of a number of functionally somewhat independent entities (Goldman-Rakic 1984), we elected to do a detailed anatomical examination of this area (figure 1).

A direct relationship between functional activity in the middle prefrontal cortex and the accuracy of performance was observed in normals, but not in patients with schizophrenia (table 1) (Cohen et al. 1987). We believe this to have been the first time that the metabolic activity of a brain region had been specifically linked to quantitative measures of actual ongoing performance in man. The metabolic rates in the middle prefrontal cortex of patients with schizophrenia, even those who performed as well as normals, were found to be significantly lower than normal. In contrast to the higher than resting glucose metabolic rates that had been observed only in the right mid-prefrontal cortex of Plane C in the normals performing discrimination, the area of lower metabolic rates in the mid-prefrontal cortex in schizophrenia was considerably larger and included both the left and right prefrontal cortex of Planes C and D (figures 2 and 3).

Although the mid-prefrontal cortex was the only area shown to have statistically higher metabolic rates in normals performing auditory discrimination compared to resting subjects, two other regions had lower metabolic rates in normals performing the discrimination task compared to those at rest. These regions encompassed a portion of the cingulate gyrus and the superior posterior parietal cortex.

That more than one cortical area would be associated with sustained attention is consistent with a network approach to behavior in which brain structures are components of semi-autonomous networks subserving different behavior. Further, lesions in all three of the regions, identified in our study as possibly important in the biological determination of

Table 1. Mid-prefrontal cortex glucose metabolic rate—performance associations

Brain region	Normal controls	Drug-free schizophrenic patients	Medicated schizophrenic patients
Plane C			
Medial	-.490[1] (.375)	.014 (-.067)	-.856[1] (.874[1])
Right anterior	-.454[2] (.264)	-.123 (.237)	-.742[2] (.671)
Left anterior	-.401[2] (.333)	-.259 (.041)	-.608 (.667)

Significant within-group Pearson product-moment correlations between regional glucose metabolic rates of the frontal cortex and performance are reported. Numbers not in parentheses represent correlations to the number of incorrectly identified distractors (false alarms), negative correlations indicated that higher metabolic rates in the region of interest (ROI) are associated with fewer errors. Correlations within parentheses are with the number of correctly identified targets (hits), positive correlations indicate that higher glucose metabolic rates in the ROI are associated with a greater number of hits. Statistically significant associations, uncorrected for number of comparisons, are as follows.

[1]$p < .01$
[2]$p < .05$

sustained attention, have been associated with unilateral neglect in man (Mesulam 1985).

As might be expected for dysfunction of this network, the schizophrenic patients had higher metabolic rates in the cingulate and the superior posterior parietal cortex, although only the latter reached statistical significance (see figure 2A). Thus, lower overall metabolic activities in the cingulate and superior posterior parietal regions may represent an improved signal-to-noise ratio for the relaying of specific sensory information within these two regions in normal controls. This improved signal-to-noise ratio may not occur, at least in the superior posterior parietal region, in some patients with schizophrenia. For example, in rats, stimulation of the locus ceruleus, with presumed concomitant norepinephrine release, was demonstrated to decrease the deoxyglucose uptake of the cingulate gyrus (Abraham et al. 1979). It was hypothesized that the release of the neurotransmitter norepinephrine in the cingulate gyrus reduces the effect of sensory input not significant for behavior while enhancing the effects of sensory input conveying information important for the determination of behavior.

Furthermore, in addition to those regions identified as important to the performance of auditory discrimination in normals by our own FDG-PET study, some areas of the temporal lobe, areas known by other methods to be important for information processing, show evidence of metabolic reduction in the schizophrenic patients studied.

Whether the sustained attention problems in schizophrenia arose from a specific defect in one or more of the brain structures, found to be biological determinants of sustained attention in these studies, or other brain structures not "visualized" in the PET procedure (see Cohen et al. 1986) remained unclear. Nor had we determined whether the observed metabolic deficits resulted from abnormalities in the functioning of neurotransmitter pathways in these regions.

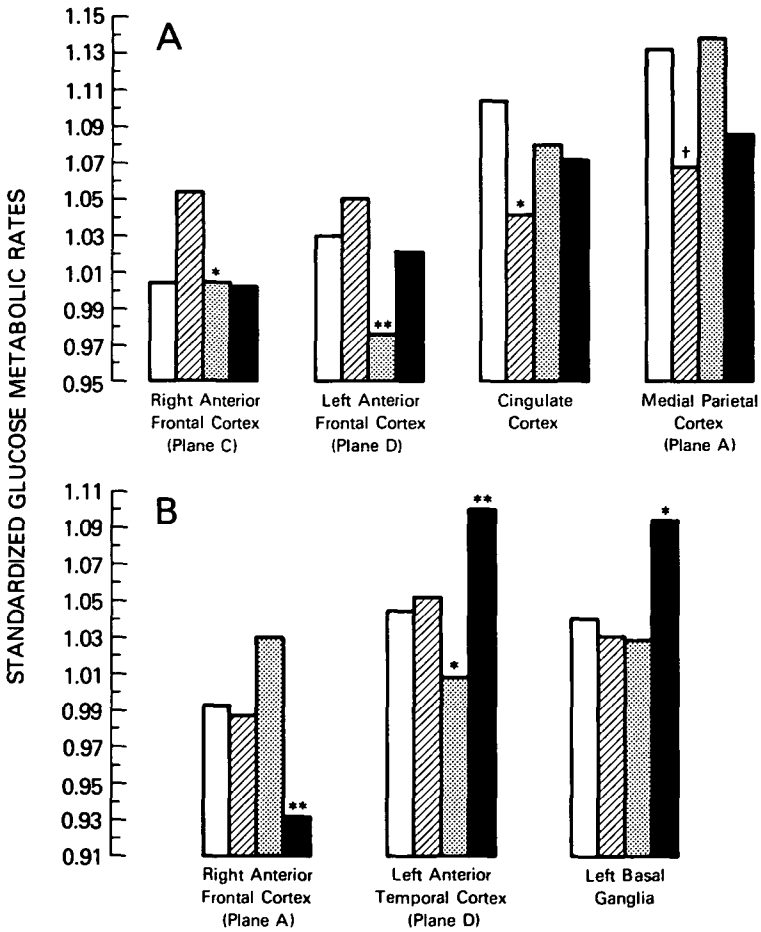
Evidence for Partial Neuroleptic Dependence of Prefrontal Cortex Dysfunction in Schizophrenia

To resolve some of these ambiguities, we examined patients receiving clinically titrated doses of neuroleptics. In a prior study using a within-subject design and somatosensory stimulation, neuroleptics appeared to induce an increase in hypofrontality. This finding failed, however, to reach statistical significance in the eight subjects evaluated (DeLisi et al. 1985). Rather, the largest changes observed were increases of metabolic rate in the basal ganglia and temporal lobes.

In the current study, a separate group of eight patients was examined with considerably greater anatomic detail. These patients did not differ in subtype, age, Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) measures of symptoms or in their performance on the auditory discrimination task from the 16 unmedicated patients studied. Differences in global glucose metabolism were not observed between the medicated and unmedicated patients.

Replicating the earlier work (DeLisi et al. 1985), significant and consistent findings of higher glucose metabolic rates in the medicated patients were observed in anatomic regions sampled from the anterior, middle, and posterior portions of the temporal cortex and

Figure 2. Bar graph of regional glucose metabolic rates of normal controls and schizophrenic patients at rest and performing auditory discrimination



The bar graph shows standardized regional glucose metabolic rates of (from left to right for each brain region) normal controls at rest (clear bars), n = 16; normal controls performing auditory discrimination (diagonally lined bars), n = 27; unmedicated patients with schizophrenia performing auditory discrimination (stippled bars), n = 16; and medicated patients with schizophrenia performing auditory discrimination (black bars), n = 8. The standardization procedure is designed to minimize the effects of individual variation in global glucose metabolism on regional comparisons by dividing an individual's glucose metabolic rate in a specific region by the individual's global glucose metabolic rate (Clark et al. 1985). The global glucose metabolic rate refers to the average value for glucose metabolism obtained for all the gray matter rich areas of the brain sampled. Whenever regional metabolic rates or functional activities are referred to in this article, we are actually referring to this transformed variable. The brain regions in figure 2A are representative of those regions associated with the performance of auditory discrimination in normal controls, and the regions in figure 2B are those not associated with cognitive performance in normals, but found to be sensitive to neuroleptics. Statistically significant findings as determined by 2-tailed t test are indicated by ** for p = < .01, * for p = < .05 and × for p = < .06 and are located above the stippled bars, representing the unmedicated patients when between unmedicated patients and normal controls performing auditory discrimination, and above the black bars, representing unmedicated patients, when differences are between unmedicated and medicated patients.

the basal ganglia. Further, higher values were observed also in the hippocampus and thalamus of the medicated patients.

Lower metabolic rates in the medicated patients were observed in the area of the superior prefrontal cortex that includes the premotor cortex and perhaps the superior portion of the mid-prefrontal cortex. These differences were apparent only because of the detailed regional analysis performed. Statistically significant differences were not observed in the 15 sampled regions of the parietal and occipital cortices.

Of the regions found to be of biological importance to the ability to perform the sustained attention task, metabolic differences were most apparent in the superior posterior parietal cortex, cingulate gyrus, and lower part of the mid-prefrontal cortex (Plane D). Although these differences were all in the direction of the medicated patients more closely resembling the normal controls, these differences did not reach statistical significance when medicated patients were compared to their drug-free counterparts. However, in contrast to the drug-free patients who differed from the normal controls in their frontal cortex metabolic rates in both Planes C and D, the medicated patients did not show statistically significant differences in their D plane frontal cortex metabolism when compared to the normal controls.

More important, the mid-prefrontal cortex in the medicated patients appeared closely coupled to the patients' performance accuracy. In the medicated patients, almost all of the regions of the mid-prefrontal cortex demonstrated strong correlations with the ability to perform the auditory discrimination

task in the expected direction of higher metabolic rates being associated with better performance (table 1).

Implications for the Pathophysiology of Schizophrenia

Although electrophysiological, neuropharmacological, and lesion studies have suggested that catecholamines play a critical role in the function of the prefrontal cortex in animals (Glowinski et al 1984; Goldman-Rakic 1984; and Sara 1985), we believe these results to be among the first in man to demonstrate an important function of the dopamine neurotransmitter pathway in the biological determination of sustained attention as mediated by the mid-prefrontal cortex Moreover, the data also imply that neuroleptics may modulate the directed attention deficit in schizophrenia through its effects on the prefrontal cortex

We are currently examining our data from the perspective of subtype, i.e., paranoid compared to undifferentiated schizophrenia, and have begun a replication of this study using a scanner with considerably higher resolution. Although the latter may make it possible to visualize other regional determinants of sustained attention and their neurotransmitter dependence, we might briefly speculate about the significance that these prefrontal metabolic deficits and their neuroleptic dependence may have for the pathophysiology of schizophrenia

First, at least two types of prefrontal cortex metabolic abnormalities are apparent One appears to respond to the administration of neuroleptics and a second does not. Our limited data also suggest that a similar prefrontal cortex abnormality may be present in manic-depressive illness, but not in other psychiatric disorders (e.g, obsessive-compulsive disorder), and and that these abnormalities are not directly related to clinical symptoms at the time of metabolic measurement.

Because the reduced frontal cortex metabolism in schizophrenia is found in the same brain area that the ability to sustain goal-directed behavior localizes to, the prefrontal cortex in this illness may be at a disadvantage with respect to the limbic cortex or other brain regions in capturing the motor system. This could be the cause of the difficulties schizophrenic patients have in directing behavior on behalf of long-range goals or "higher level" motivations. Hypothetically, this disadvantage could also be the metabolic representation of an individual's vulnerability to become psychotic since, in the broadest sense, psychosis is a state in which the proper integration of external stimuli with motivations, drives, and short- and long-term goals or rewards to produce behavior goes awry, e.g., the motor system comes under the primary direction of the limbic system (see, e.g., Stevens 1973)

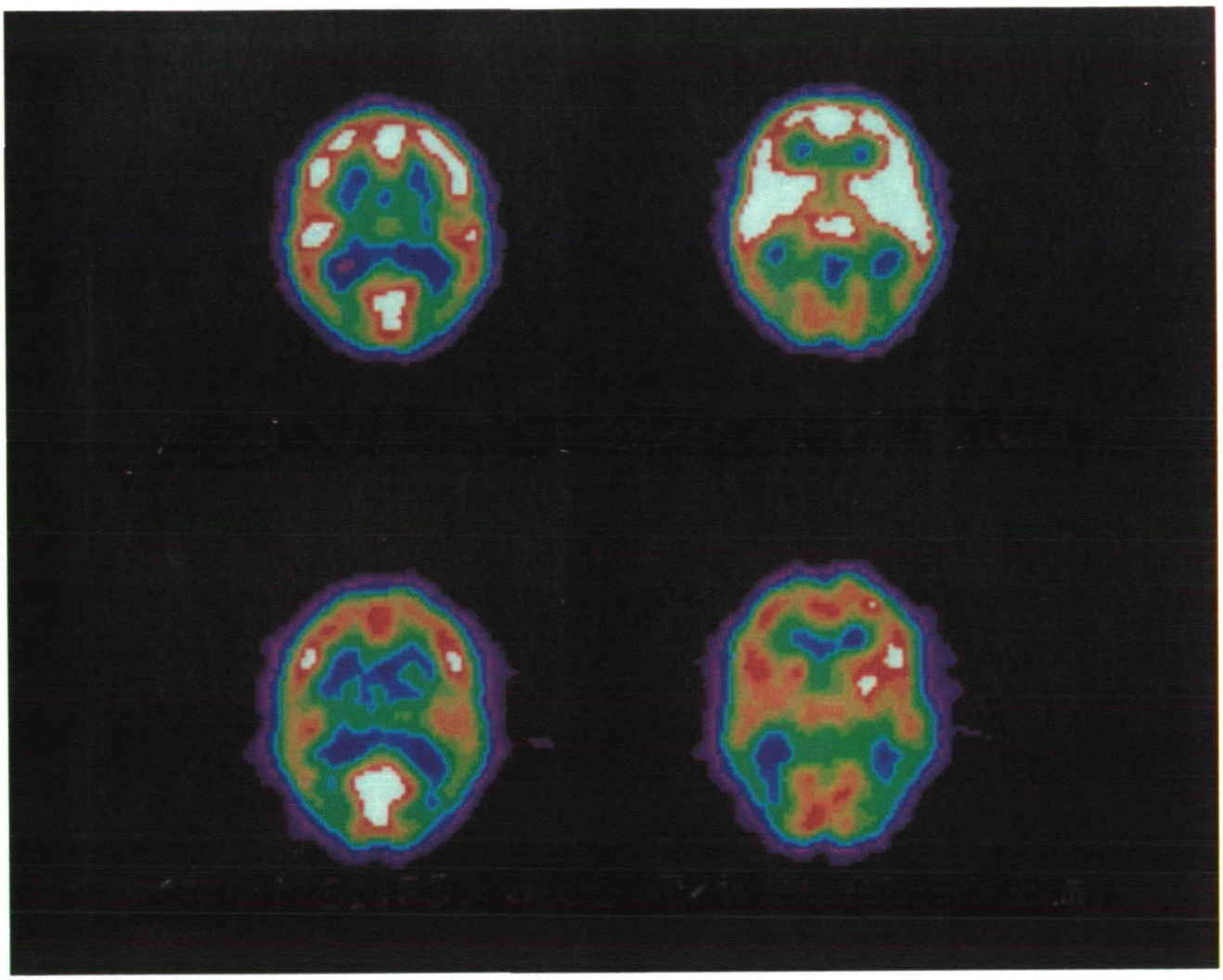
A rationale for the effect of neuroleptics is then readily apparent As the dopamine neurotransmitter system appears to serve an enabling or gating function, not only important in the initiation of motor behavior, but also facilitating the switching between channels of activity in given brain regions (Oades 1985; Fibiger and Phillips 1986, Mogenson 1987), blocking dopamine receptors with neuroleptics could provide the rapid remediation of psychotic symptoms That is, remediation could result from reducing the ability of all brain regions, including the limbic cortex, to capture the motor system. Over time, if the differential characteristics of dopamine neuron adaptation to neuroleptics observed in rodents and in nonhuman primates (Bacopoulos et al. 1978; Bannon et al. 1987) also occurred in man, this blockade would favor the prefrontal cortex over the limbic cortex. This preference would be attributable to the development of tolerance to the neuroleptic-induced increase in dopamine turnover in the striatum and limbic cortex, but not in the prefrontal cortex

Future Directions

Although the success we have had in understanding brain regional metabolism in the context of sustained attention and a component of its neurotransmitter dependence is gratifying, it is likely that the study of this one cognitive process will not be sufficient to define the pathophysiology of schizophrenia (Cohen and Campbell 1984). Just as no one phenomenological variable, such as hallucinations, is sufficient to delineate schizophrenia, we will probably need to evaluate brain activity and its neurotransmitter dependence with respect to a number of cognitive tasks Study of the other major component of behavior, emotion, is also needed if we are to arrive at a fuller understanding of schizophrenia.

For some of these studies, cerebral blood flow measurements by PET will offer the flexibility of evaluating localized functional brain activity during the relatively brief period of a minute. Because this methodology also facilitates the execution of and analysis of sequential studies of multiple tasks

Figure 3. Planes C and D, containing regions of the mid-prefrontal cortex, for a typical normal control (above) and a typical patient with schizophrenia (below)



The two subjects were chosen based on their approximation to the average of each group in their standardized metabolic rates. Metabolic rates are represented from low to high, respectively, by black, purple, blue, green, yellow, red, and white. The lower metabolic rates in the mid-prefrontal cortex (top of slice) are readily apparent.

in the same individual, these studies will be of particular utility in trying to divide complex behaviors into specific cognitive processes that can be associated with biological parameters. The 35-minute task period over which PET measurements of glucose metabolism are made, however, was ideal for our sustained attention task. The important determinants of this task were clearly detectable against the background of those brain regions that are important to the determination of non-"goal-directed behavior" but whose contributions are averaged out during the measurement period.

The central tenet of the laboratory is the belief that our increasing knowledge of the molecular genetics, biochemistry, and cytology of the central nervous system will fall short of allowing us a complete understanding of normal and abnormal behavior. Studies of the functioning brain system will be required to delineate the pathophysiology of schizophrenia regardless of the degree of sophistication that genetic probes and postmortem analyses achieve.

Such work should facilitate a reduction in the heterogeneity of patient samples by ensuring that patients who have the schizophrenia syndrome also share the same pathophysiology. This may be of particular importance to genetic studies. Furthermore, were a single gene found to be principally responsible for the genetic determination of schizophrenia before the elucidation of the pathophysiology, schizophrenia researchers would still need to develop information about the pathophysiology. This information is necessary to tackle the difficult problems of determining the mechanisms responsible for the development of the schizophrenia phenotype and to develop new treatment strategies. The latter development should benefit also from a more complete understanding of how the molecular mechanisms associated with neuroleptic efficacy lead to changes in brain function.

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Schizophrenia: Questions and Answers

What is schizophrenia? What causes it? How is it treated? How can other people help? What is the outlook? These are the questions addressed in a booklet prepared by the Schizophrenia Research Branch of the National Institute of Mental Health.

Directed to readers who may have little or no professional training in schizophrenia-related disciplines, the booklet provides answers and explanations for many commonly asked questions of the complex issues about schizophrenia. It also conveys something of the sense of unreality, fears, and loneliness that a schizophrenic individual often experiences.

The booklet describes "The World of the Schizophrenic Patient" through the use of analogy. It briefly describes what is known about causes—the influence of genetics, environment, and biochemistry. It also discusses common treatment techniques. The booklet closes with a discussion of the prospects for understanding schizophrenia in the coming decade and the outlook for individuals who are now victims of this severe and often chronic mental disorder.

Single copies of *Schizophrenia: Questions and Answers* (DHHS Publication No. ADM 86–1457) are available from the Public Inquiries Branch, National Institute of Mental Health, Room 15C–05, 5600 Fishers Lane, Rockville, MD 20857.

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Readers who wish to receive a copy of the **Special Report** should write to the **Schizophrenia Research Branch, NIMH, Rm. 10C-06, 5600 Fishers Lane, Rockville, MD 20857.**

NARSAD: The Momentum Grows

NARSAD (the National Alliance for Research on Schizophrenia and Depression) is a new collaborative effort of the National Alliance for the Mentally Ill, the Mental Health Association, the Schizophrenia Foundation, and the National Depressive and Manic Depressive Association. Working together, the citizens and professionals involved with NARSAD are marshaling support for research on psychiatric illness, primarily the schizophrenias and the affective disorders, but also—as the effort grows—other mental illnesses that cause major disability or dysfunction. The formation of this group coincides with the unprecedented promise offered by our current scientific armamentarium and reflects a burgeoning activism on the part of citizens' groups.

The primary goal of NARSAD will be to support the search for new information, new understanding, new ideas, and technological innovations that could shed light on the major mental illnesses. The ultimate goal is elimination of these illnesses through any and all efforts we can bring to bear. Many disciplines and approaches offer potential for better knowledge and improved methods of diagnosing, treating, and caring for our patients: genetics, biochemistry, pharmacology, neurobiology, epidemiology, psychiatry, psychology, physiology, and anatomy, among others. Within the framework of basic science, specific projects may have important implications for our biomedical, clinical, brain/behavioral, and therapeutic objectives—and such projects will be considered as well.

Grant applications for the first program of NARSAD have been reviewed, and the awards were made in April 1987. This program provides support for extension of research fellowship training. It is expected that as more resources become available, additional mechanisms will be supported. These may include faculty support, support for laboratory equipment, and other appropriate programs tailored to complement existing mechanisms available through the national institutes.

The Lieber Award, which was made in September 1987, is to further the research of an outstanding scientist carrying out work relevant to the causes, pathophysiology, treatment, and prevention of schizophrenia, depression, or other serious mental illness.

We are especially interested in fostering creative work and in minimizing the paper work and time usually expended responding to applications. We want to encourage young researchers entering the field or considering doing so, established scientists who have already been productive in these areas, and investigators using new or promising techniques that might be appropriate for psychiatric research or treatment. We are trying to use the knowledge and experience of our Scientific Advisory Board to avoid the problems known to accompany other support mechanisms.

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