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Donald P. Hall, Jr., M.D.
National Institutes of Health, Bethesda, Maryland

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Exploring Frontal Lobe Dysfunction in Schizophrenia with Positron Emission Tomography

Donald P. Hall, Jr., M.D.

Frontal lobe dysfunction in schizophrenic patients has been highly suspected for many years. Many psychiatrists and patients, however, are awaiting solid proof of a biological manifestation of this disease. While positron emission tomography does not uniformly demonstrate such a manifestation, it does demonstrate a prefrontal cortex deficit in most reported studies. Further, a localization of the attention deficit of schizophrenia, in the prefrontal cortex, is strongly suggested by some studies.

INTRODUCTION

Positron emission tomography (PET) has enabled investigators in modern clinical psychiatry to demonstrate that schizophrenia is, at least in part, a frontal lobe disorder. PET studies of many patients with schizophrenia exhibit a decreased level of metabolism in the frontal cortex. Other brain areas have also been investigated for their role in schizophrenia. These regions include the hippocampus (1), basal ganglia, limbic system, and other brainstem areas (2). This review, however, is limited to the deficit most consistently reported with PET brain metabolism studies—hypofrontality.

Frontal lobe dysfunction in schizophrenia has been suggested for many years by several research paradigms. Post-mortem studies have reported abnormal neurotransmitter receptor levels including serotonergic (3,4), muscarinic (5), GABAergic (6), and others. Histological abnormalities in the frontal cortex of schizophrenic patients, including decreased cortical cells (neurons > glia) in layer VI (7) and ultrastructural (EM) abnormalities in neurons (8), have been reported. Frontal lobe pathology has also been suggested by MRI studies, reporting significantly smaller frontal lobes in schizophrenics (9). Cognitive aspects of schizophrenia, including attention and vigilance, have been a continuing focus in the evaluation of this disease (10,11). A recent study of patients with frontal lobe lesions demonstrated that these patients also had a deficiency in maintaining tasks that require sustained attention (12). Frontal lobe dysfunction

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in schizophrenia has, therefore, been strongly suggested from several research paradigms. Recently, however, a localization of this deficit in a specific brain region has been demonstrated by functional imaging techniques.

Early functional imaging studies of cerebral metabolism utilized Xe [133] inhalation or carotid injection to examine relative blood flow rates. Ingvar and Frazen applied this technology to the study of schizophrenic patients and demonstrated a relative decrease in cerebral blood flow in these patients (13,14). They reported that normal persons demonstrated a relatively higher blood flow in the prefrontal cortex than in temporal or parietal cortices. In schizophrenic patients, however, this hyperfrontality was attenuated and the patients were described as hypofrontal. A review of attempts to replicate these findings is available (15). Cerebral blood flow studies using Xe [133], however, have several limitations, including lower spatial resolution and provision of only relative blood flow values. PET scan technology has been useful in confirming, and investigating more effectively, hypofrontality in schizophrenia. Recent advances in controlling the behavioral aspects of the scanning procedure and evidence of a more precise localization of the dysfunction in the mid-prefrontal cortex may permit significant advances in the understanding of schizophrenia (16).

PET TECHNOLOGY

PET scanning utilizes short lived, radioactively labeled biomolecules to study normal and diseased states in brain tissues. A positron emitting isotope is incorporated into metabolites, or drugs, by using a cyclotron which forms an unstable nucleus. Within the nucleus of the isotope, a proton transforms into a neutron. During this transformation, a positron is emitted. The positron then collides with an electron to produce two photons of light. A geometrical image of relative photon activity is then developed. A detailed review of PET technology is available (17).

One of the most useful compounds in psychiatric research has been F[18]-labeled 2-fluoro-2-deoxy-D glucose (FDG). The FDG tracer method, developed by Sokoloff, Reivich and coworkers (18-20), has been used to evaluate glucose metabolism in brain tissues. According to their 2-deoxyglucose model, FDG is transported into the cell and phosphorylated in a manner similar to glucose. However, unlike glucose, phosphorylated FDG is not a substrate for metabolism. Once transported into the cell, FDG is phosphorylated and degraded slowly enough to be considered essentially trapped during the scanning measurements. FDG is phosphorylated (the rate limiting step) based on metabolic needs and is, therefore, a good indicator of cellular activity. The functional imaging offered by PET opens new dimensions in the study of brain physiology. Although conventional imaging with x-ray technology has enabled visualization of structural changes (eg. ventricular enlargement) in schizophrenia, PET may detect biochemical changes at an earlier stage and provide more information about the pathophysiology.

TABLE 1.

Pet Studies of Frontal Cortex Metabolism in Schizophrenic Patients Off Medication

Study	S/C	Frontal Metabolism Differences
Farkas, et al, 1980 (21)	1/n.r.	decreased
Buchsbaum, et al, 1981 (22)	5/5	decreased
Buchsbaum, et al, 1982 (29)	8/6	decreased
Sheppard, et al, 1983 (30)	12/12	nonsignificant
Widen, et al, 1983 (31)	6/12	decreased
Brodie, et al, 1984 (32)	6/5	decreased
Buchsbaum, et al, 1984 (33, 34)	16/19	decreased
Buchsbaum, et al, 1984 (35)	4/19	decreased
DeLisi, et al, 1985 (36)	20/21	decreased
Jernigan, et al, 1985 (37)	6/6	nonsignificant
Wolkin, et al, 1985 (38)	10/8	nonsignificant
Sedvall, et al, 1986 (39)	13/10	increased
Volkow, et al, 1986 (40)	4/12	nonsignificant
Cohen, et al, 1987 (16)	16/27	decreased
Early, et al, 1987 (41)	10/20	nonsignificant
Gur, et al, 1987 (42)	12/12	nonsignificant
Wiessel, et al, 1987 (43)	10/20	decreased*
Wolkin, et al, 1987 (44)	6/9	decreased
Wolkin, et al, 1988 (45)	13/8	decreased
DeLisi, et al, 1989 (46)	21/9	nonsignificant
Gur, et al, 1989 (47)	20/18	nonsignificant

Symbols: S/C - Schizophrenic patients/control subjects; *only study reporting decreased frontal rate, yet increased A:P ratio; n.r. - not reported.

Notes: 1) All studies used age-matched controls except Buchsbaum, 1984 (quadruplet study - ages 51); Wolkin, 1985 (mean ages s/c - 38/27). Brodie, 1984, did not report ages. All remaining studies reported mean ages of 22-38.

2) Frontal metabolism differences include reported differences in absolute frontal rates; frontal: whole slice, frontal: whole brain or anterior:posterior ratios.

3) All studies used glucose ligands except Sheppard, 1984 (0[15] and C[15]02).

DEMONSTRATION OF HYPOFRONTALITY BY PET

A search of PET literature reporting on frontal lobe glucose metabolism in schizophrenic patients uncovered approximately thirty studies. The first PET report of hypometabolic activity in the frontal cortex of a schizophrenic patient was by Farkas, Reivich and coworkers in 1980 (21). Other early studies by Buchsbaum (22) and Widen (23) confirmed the evidence of hypofrontality. Studies using medicated schizophrenic patients have generally demonstrated hypometabolic activity in the frontal cortex (24-28). Table 1, above, however, presents a review of 21 studies using only unmedicated and never medicated patients, due to a concern of possible confounding effect by neuroleptic treatment. Review of these studies reveals some inconsistent findings. Several vari-

ables have been considered as possible sources for the discrepancy between these findings.

The variable which has received the most discussion in the literature has been neuroleptic treatment. Some investigators have questioned the validity of reports of hypometabolic activity in the frontal cortex of schizophrenics because of neuroleptic treatment concurrent with or preceding scanning procedures (30,41). These investigators suggest that hypofrontality findings may be an effect of treatment and not a manifestation of schizophrenia. This view is partly supported by findings of extended clinical and pharmacokinetic effects which persist following termination of medication (48,49). Additional support for their viewpoint comes from studies of never-medicated schizophrenics (30,31,40,41). These studies have consistently found no significant differences in frontal lobe metabolism in schizophrenic patients. However, these findings may be due to a biological difference between new-onset and chronic schizophrenia. A recent report by Wiessel and coworkers (43) indicated that duration of illness was directly correlated with degree of hypofrontality.

Due to the concern of possible frontal lobe changes with neuroleptic treatment, most studies have utilized patients which have been taken off medication prior to the scanning procedure (wash-out studies). Of the recent studies using nonmedicated patients (see table), most have used patients off neuroleptics for at least 13 days. Some studies have used wash-out periods of only 10 days (44,45). Others have used mixed samples with some patients that received limited dosages at least forty-eight hours prior to scanning (30) or some patients off neuroleptics for at least seven days (42). One study did not specify duration off medication (22).

Support for the validity of studies reporting hypofrontality in patients unmedicated prior to and during scanning procedures can be found in the reports of PET studies comparing metabolism before and during neuroleptic treatment. These reports have generally indicated that frontal glucose metabolism is either unchanged or increased, not decreased, during neuroleptic treatment (38-40,50-53). Changes in metabolism were studied with medication intervals ranging from 1 hour to 7.4 years. Further support for the validity of studies using previously medicated patients comes from dopamine receptor occupancy studies. Using Br[76] labeled bromospiperone binding to corpus striatum, Camdon and coworkers (54) found that after neuroleptic withdrawal, a return to 100% unoccupied receptors occurred within 7-12 days in the majority (6/8) of subjects tested. A final answer to this question of neuroleptic effects on frontal lobe metabolism may require a prospective study of metabolic rates before, during and following neuroleptic treatment, which demonstrates a complete return to baseline metabolism.

One variable of increasingly apparent importance, which remains less than optimally controlled in most experiments to date, is behavioral activity during PET scanning. Most studies of metabolic activity have used resting subjects. Many studies have taken measures to limit sensory stimulation of the patient

during scanning in order to provide a more uniform sensory environment. Other studies have used somatosensory stimuli in the form of mild electrical shock to the right forearm (33,34,36,50). Somatosensory stimuli have been used to maintain a uniform sensory environment between subjects and preferentially activate the frontal lobes (55,56). Xe [133] blood flow studies have reported attenuation of this activation in schizophrenic subjects (57). However, a recent PET study comparing sensory environments during scanning found that somatosensory stimulation is not an effective method of frontal cortex activation (58). In a study of 52 normal volunteers, Cohen and co-workers compared the effects of somatosensory stimulation, auditory discrimination and resting states on frontal metabolic activity. Increased metabolic rates were found in the right middle prefrontal cortex during the auditory discrimination task. This increased rate demonstrated a direct correlation with the accuracy of the subjects' performance, suggesting that this area may be very important in attention maintenance. The somatosensory stimuli, however, was not associated with generalized activation of the frontal cortex.

Continuous performance tasks, such as the auditory discrimination task, have also been used to study the attention deficits in schizophrenia. Continuous performance tasks have been shown to be highly sensitive to functional illness (59) and have been used to demonstrate attention deficits in schizophrenia (60). Their attention deficit is evident in several areas. They often fail to attend to novel stimuli (61). Once attention is attained, they often fail to maintain task performance. The frontal lobe appears to be involved in anticipatory responding. The frontal lobe deficit theory of schizophrenia, therefore, is supported by the patient's poor preparation for response. A study by Cohen (16) examining 16 schizophrenic patients, performing auditory discrimination tasks during PET scanning, demonstrated specific areas of deficient metabolism. Of the 55 specific regions examined, only the left anterior, medial and right anterior areas of the frontal cortex, in a single plane, demonstrated significant metabolic deficits. An earlier study by Jernigan and co-workers (37) also used an auditory discrimination task to study schizophrenic patients. Their finding of nonsignificant changes, however, may have been due to a limited sample size (6 patients) or the limited number of slices analyzed (1 slice).

CONCLUSIONS

Greater than 50% of the PET studies investigating frontal lobe metabolism have demonstrated decreased activity in schizophrenic patients. The variability of findings in the frontal cortex do not appear to be caused by neuroleptic medication. However, a prospective study of neuroleptic effects before, during and after medication may be useful. Some authors have suggested that the failure to consistently confirm frontal deficits may be due to different pathological groups of schizophrenics (eg. frontal and temporal lesions). Others have suggested that variance between studies may reflect the chronicity of the disease.

Additional sources of variance may include specificity of analysis (eg. whole frontal cortex slice vs. subdivided areas) and sample size. Frontal cortex activating tasks may also reduce the variability between studies by utilizing the recognized attention deficit seen in most of these patients.

In summary, an area of metabolic dysfunction in the prefrontal cortex of schizophrenic patients has been demonstrated through the use of positron emission tomography. The inconsistencies in the attempts to replicate these findings are probably due to multiple variables. The fact that 50% of the studies have succeeded in demonstrating a frontal lobe deficit is remarkable, given the lack of frontal activating tasks and limited subdivision of frontal areas in most studies.

In conclusion, PET technology is opening new dimensions to the study of psychiatric research. PET offers functional imaging not provided by previous analytical instruments and greater precision and depth than other newly developed techniques. Further refinement of nuclear and computer technology, and experimental methodology promise to make PET an invaluable tool in the study of schizophrenia and other mental diseases.

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