SCHIZOPHRENIA
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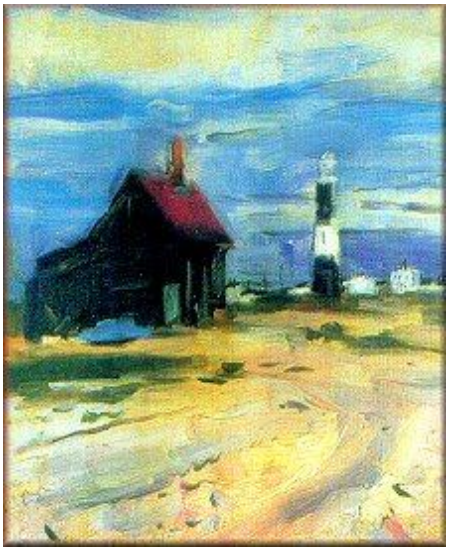

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FUNCTIONAL NEUROIMAGING IN SCHIZOPHRENIA

Functional brain imaging methods have been applied to the study of schizophrenia aiming at elucidating the neurobiology of this complex and heterogeneous disorder. These methods have included the 133Xenon technique for measuring cerebral blood flow (CBF); positron emission tomography (PET) for assessing metabolism, CBF and neuroreceptor functioning; single photon emission computerized tomography (SPECT) for studying CBF and neuroreceptors; and, more recently, functional magnetic resonance imaging (fMRI) for measuring changes attributable to cerebral blood flow. This chapter will review the application of this technology in schizophrenia research. Studies will be summarized and integrated with our current understanding of brain function in schizophrenia.

Links between clinical features of schizophrenia and brain function have been guided by hypotheses that relate behavior to specific brain regions and systems which are implicated in schizophrenia. These links are based on preclinical research and the emergence of symptoms, commonly seen in schizophrenia, that occur following brain lesions. Persistent negative symptoms have been related to frontal lobe dysfunction. Frontal lobe damage has neurobehavioral sequelae, such as impairment in abstraction, verbal fluency, mental flexibility and concept formation. Positive, productive symptoms (hallucinations and delusions) have been related to the temporo-limbic system, with evidence of impaired learning and memory. Subcortical regions, with special emphasis on the basal ganglia, have been examined in the context of the dopamine hypothesis. Across these dimensions, laterality measures of the relation between left and right hemispheric parameters have been compared in patients and normal controls. While necessarily simplistic and not reflecting on other brain systems that modulate normal and pathological psychotic behavior, these dimensions have generated hypotheses that can be examined with functional brain imaging. The application of neurobehavioral probes has enhanced our ability to evaluate brain systems that regulate specific processes in healthy people and in those affected by schizophrenia.

CEREBRAL METABOLISM AND BLOOD FLOW STUDIES

Studies of cerebral metabolism and blood flow (CBF) can be divided into those measuring the physiologic

parameters at a resting state and those introducing a perturbation, or challenge, in the form of a neurobehavioral probe or pharmacologic intervention. Initially, investigators assessed whether resting CBF and glucose metabolism differed between patients with schizophrenia and healthy controls. The topography of physiologic activity was examined along the dimensions stated above. This research is summarized in special reviews (15,38,53).

The frontal lobes were implicated in early physiologic studies of CBF in schizophrenia. Patients did not show the normal pattern of increased anterior relative to posterior CBF (45). This "hypofrontal" disturbance in the anterior-posterior gradient has been supported by some (e.g., 8,14,15,58,91), but not all (e.g., 17,35,37,39,41) studies of resting CBF(133Xenon and SPECT) and glucose metabolism (PET).

The relationship between this pattern of metabolic activity and clinical variables has also been examined (82). Decreased frontal metabolic activity has been associated with duration of illness; a longer duration was associated with negative symptoms (83) and a lower anteroposterior gradient (90). Liddle et al. (54) found that patients with poor performance on the Stroop test, which measures attention, had abnormal CBF in anterior cingulate cortex. Mozley et al. (60) noted that patients with poorer memory displayed greater mid-temporal glucose metabolism.

Differences in resting values between patients and controls were also found in laterality indices, suggesting relatively higher left hemispheric values in severely disturbed patients (40,77). Furthermore, improvement in clinical status correlated with a shift toward lower left hemispheric relative to right hemispheric metabolism (41). This supports hypotheses derived from behavioral data concerning lateralized abnormalities in schizophrenia (19), as well as perhaps the more specific form of the hypothesis which proposes that schizophrenia is associated both with left hemispheric dysfunction and overactivation of the dysfunctional left hemisphere (43).

The technology applied and definition of regional parameters in these reports varied. Most studies used regional ratios such as region/whole brain or anterior/posterior rather than absolute values of activity. Some of the inconsistencies in findings are likely related to sample heterogeneity, analytic approaches and the individual techniques employed. Most studies had relatively small numbers of patients, who varied in important clinical factors such as chronicity, symptom subtypes and severity, level of functioning and history of treatment. Furthermore, inclusion criteria were not consistent across studies. varied. A history of substance abuse comorbidity, or head trauma with loss of consciousness, can affect brain metabolism. In some studies, it was unclear whether hypofrontality was established. For example, Buchsbaum and colleagues considered their data to demonstrate hypofrontality. However, they also reported that increased activity in posterior regions, rather than reduced frontal activity, was responsible for the difference in the anterior-posterior gradient between patients and controls. Another potentially important source of variability in results is the definition of resting state. Investigators have been reluctant to include an unstructured resting state because of concern that such measures will be uncontrolled and therefore produce unreliable results. Some studies used partial sensory deprivation, while others used sensory stimulation in order to standardize this condition. However, several studies examined the reproducibility of resting baseline measures with relatively unstructured conditions (i.e. eyes open, ears unoccluded, ambient noise kept to a minimum). These studies found very high reproducibility among healthy subjects (41,85) and patients with schizophrenia (4).

Given the demonstrated reliability of the standardized, resting, baseline condition, we believe it is important to include such a condition in physiological neuroimaging studies. This serves three main purposes. First, it permits comparison across studies within a center as technology evolves and patient characteristics change. Without a common resting baseline condition it would be impossible to determine the source of differences in results. Second, it will permit comparability across centers. Imagine the need to explain why two centers using the same or similar tasks find evidence for different regional abnormalities in schizophrenia. If resting baseline values are available and are comparable in the two samples, different task effects could be legitimately attributed to theoretically meaningful sources, such as task condition or symptomatic variability. A third advantage of a standardized, resting baseline data is the provision of a reference point for evaluating whether a given task or condition has increased neural activity. In studies that have included such a condition, cognitive activation was shown to increase cortical activity consistently both in patients and controls (33,35,42). Using a resting, baseline condition enables the investigator to make much stronger statements when interpreting regional effects. Rather than being restricted to statements that a given region has changed in its activation relative to the remainder of the brain, resting baseline availability permits the investigator to state whether the task caused increased neural activity.

Regardless of one's position in the debate over the value of obtaining resting baseline measures, it is apparent that measures of CBF and metabolism during the performance of cognitive tasks tend to accentuate differences between patients and controls. Perhaps even more importantly, such measures are critical for establishing the link between behavioral deficits and the ability of brain regions to become activated in response to task demand. This expectation has been supported by studies that employed neurobehavioral probes (31). This approach begins with hypotheses, derived from neurobehavioral data, that associate behavioral measures with regional brain function. Task selection can be made to include a target task, where patients are expected to have differential deficit, and control tasks. The patterns of task-induced changes in regional brain activity are then compared between patients and healthy controls. This has now become the established research paradigm, and significant progress has been made since the early studies with 133Xenon.

In the first study, in which we compared medicated schizophrenic patients with sociodemographically balanced, healthy controls, we found no differences in overall or hemispheric CBF using the 133Xenon clearance technique. However, distinct abnormalities were seen in the pattern of hemispheric changes induced by verbal (analogies) and spatial (line orientation) tasks. Healthy controls showed the expected greater left hemispheric increase for the verbal and greater right hemispheric increase for the spatial task. However, patients with schizophrenia had a bilaterally symmetric activation for the verbal and greater left hemispheric activation for the spatial task. Thus, patients failed to show the normal left-hemispheric dominance for the verbal task, and instead showed left hemispheric over-activation for the spatial task.

Similarly, Weinberger et al. (88) found no regional abnormalities in resting CBF in patients with schizophrenia. However, distinct abnormalities were reported in the dorsolateral prefrontal region during activation with the Wisconsin Card Sorting Test of abstraction and mental flexibility, which is sensitive to frontal lobe damage (86). The application of this paradigm to the study of monozygotic twins discordant for schizophrenia (87) revealed that all affected twins had reduced dorsolateral prefrontal cortex CBF response, compared with discordant co-twins. These results have been corroborated by other investigators (48,71). Furthermore, negative symptoms, which have been related to frontal lobe dysfunction, showed a negative correlation with frontal CBF during performance of executive but not control tasks (81). This research paradigm has been applied to healthy people in PET studies (6). Probing brain systems with specific tasks has also been advanced in SPECT (3,49, 72) and in CBF studies with PET (30,59,66). These studies are illustrated in Figure 1.

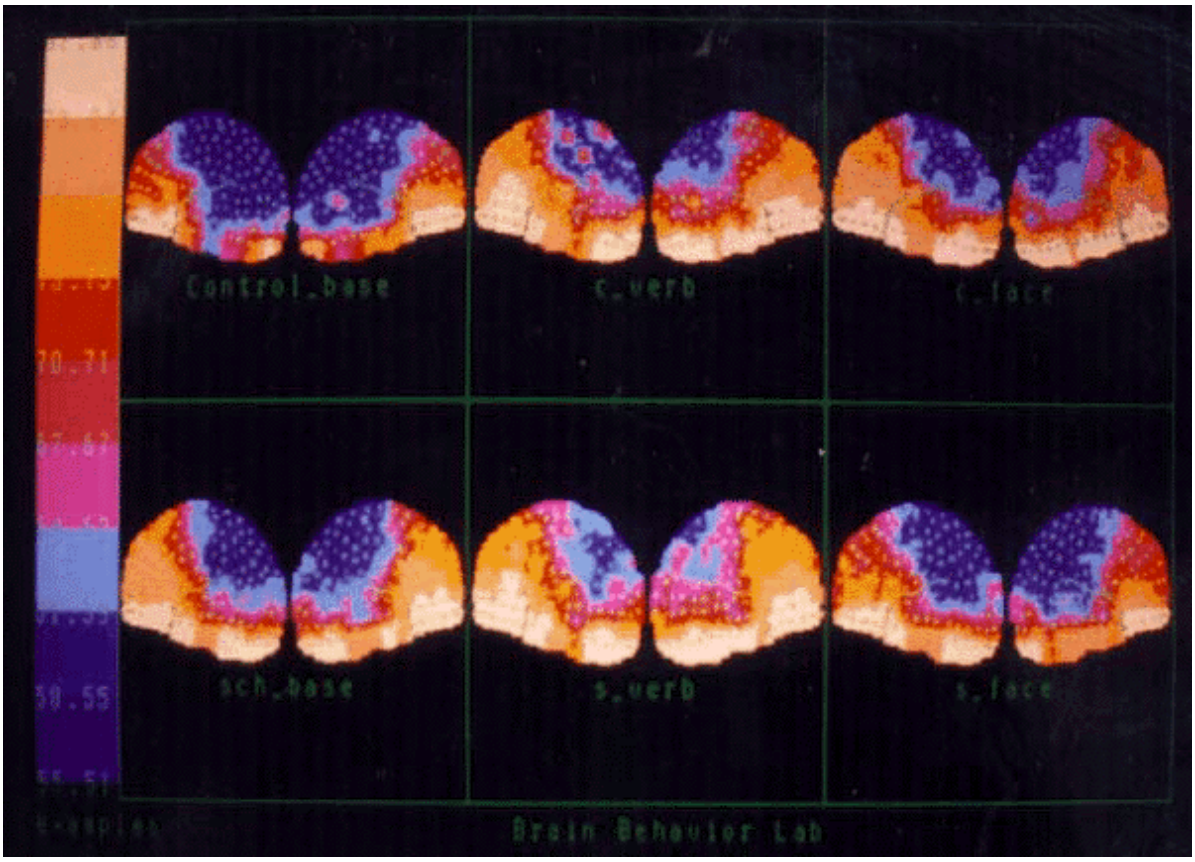

Figure 1. **Regional cerebral blood flow in two hemispheres of schizophrenics and matched controls when resting (R), solving verbal analogies (V), and performing spatial task (S). Normal control values are from earlier study for comparison with latest matched sample. A color-coded topographic display of the raw rCBF values in healthy controls (upper row) and patients with schizophrenia (lower row) for resting baseline (left column), verbal memory (middle column) and facial memory (right column). The color scale on the left shows the relative magnitude of values. Note the high flows anteriorly and in the visual cortex, and the overall increase during memory activation.**

Subsequent to assessing global, anterior/posterior and laterality dimensions, investigators have begun the study of functional changes in brain systems linked to other impaired behavior. Dysfunction in temporo-limbic structures, including the hippocampus as well as temporal cortex, is supported by neuroanatomic and neuropsychological studies (9,73). Lateralized abnormalities in these regions, with greater left than right hemispheric dysfunction, are implicated by characteristic clinical features of schizophrenia, such as thought disorder, auditory hallucinations, and language disturbances. PET studies of temporal lobe metabolism showed both increased (e.g., 21,37) and decreased glucose utilization. Decreased metabolism was also noted in hippocampus and anterior cingulate cortex (79). Studies in this region have been limited in part by instrument resolution.

Metabolism and flow patterns in temporo-limbic regions have also been related to symptoms. Liddle et al. (54) used 15O-labeled water with PET and described abnormal CBF in the parahippocampal gyrus that was associated with positive symptoms. Musalek et al. (63) found hallucinations to be associated with SPECT flow changes in hippocampus, parahippocampus and amygdala. There are conflicting reports of superior temporal gyrus functional changes in schizophrenia during active auditory hallucinations. Cleghorn et al. (18) suggested that patients with hallucinations have significantly lower relative metabolism in Wernicke's region. Anderson et al. (1) showed asymmetric temporal lobe perfusion (lower in the left than the right) in schizophrenic patients with auditory hallucinations. Delisi et al. (21) found greater metabolic activity in the left anterior temporal lobe, which was related to the severity of symptoms. This is consistent with Gur's (40,41) reported association between severity of symptoms and a relative increase in left hemispheric metabolism measured with PET.

Further research is indicated to elucidate the nature and extent of temporal lobe changes in schizophrenia. Given

that this region is linked to memory functions, an appropriate neurobehavioral probe would be aimed at memory (34,96). We have applied verbal and facial memory tasks in schizophrenia in association with the 133Xenon clearance method (34) The results are presented in Figure 2.

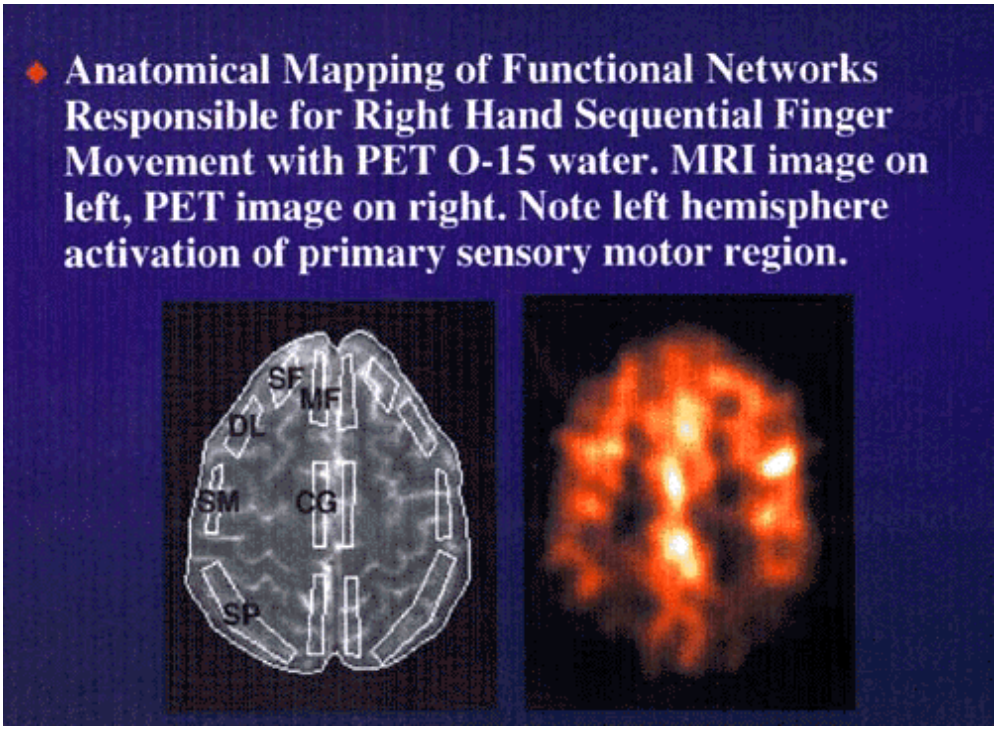

Figure 2. Transaxial sections of SPECT imaging of D2 dopamine receptors in normal brain after an iv injection of 5 mCi. of [^{123}I]-IBF. High accumulation was observed in basal ganglia area of the brain where D2 dopamine receptors are concentrated.

As can be seen, resting CBF values and topography were normal, but abnormalities in activation-induced changes were observed. These abnormalities were both in degree of activation and in lateralized changes as a function of whether the memory task required processing of words or faces. In healthy controls, the mid-temporal region was the only cortical area showing hemispherically appropriate changes (left > right for words; right > left for faces). By contrast, patients did not show a significantly lateralized response in this region and instead showed such responses in other regions.

Functional changes in the basal ganglia have been examined with PET and SPECT. Several PET studies implicated basal ganglia dysfunction in schizophrenia (11,22,39,41,51). The withdrawal-retardation factor (emotional withdrawal, blunted affect, and motor retardation) of the Brief Psychiatric Rating Scale, has been negatively correlated with PET basal ganglia metabolic activity (93). Neuroleptic-naive schizophrenic patients were reported to have relatively increased blood flow in left globus pallidus (24). Some PET studies reported decreased basal ganglia metabolism in schizophrenia (11,15), while others found increased basal ganglia metabolic rates following administration of neuroleptic medication (11).

Thus, while the contribution of PET metabolic and blood flow studies so far has been to add to the growing evidence implicating involvement of the basal ganglia in schizophrenia, the exact nature of the dysfunction remains unclear. In particular, the relationship between basal ganglia and frontal lobe activity in schizophrenia needs further scrutiny. Structural and functional imaging has revealed evidence of interrelationships between the various key regions. Rubin et al. (70) showed that patients with schizophrenia not only fail to activate dorsolateral prefrontal cortex in response to the Wisconsin Card Sorting Test, but they also fail to inhibit caudate activation. Hence, in schizophrenia, the basal ganglia continue to show relatively increased flow in caudate during performance of the task, as opposed to normal controls who seem to demonstrate a reciprocal relationship, in which a decrease in relative blood flow in the basal ganglia is associated with increased perfusion to the frontal region.

The pharmacologic status of patients undergoing metabolic and blood flow studies has varied. Research conditions have ranged from investigations in which neuroleptics were considered a variable that needed to be controlled to those in which pharmacologic intervention was introduced in a standardized fashion to examine treatment effects

on the regional metabolic landscape. The washout period in studies that wished to control the effects of neuroleptics on CBF and metabolism usually was short, ranging from 2–4 weeks. This represents a compromise between what is feasible and what is desirable. Siegel et al. (78) examined glucose activity in cortical-striatal-thalamic circuits in a large sample of unmedicated schizophrenic males and found low metabolic activity in medial frontal cortical regions and the basal ganglia, as well as impaired lateralization pattern in frontal and temporal regions. A strategy applied more recently, which is especially important in functional neuroimaging, is the study of neuroleptic-naive, first-episode patients. This population is particularly informative when the focus of the study is the effects of pharmacologic intervention. The study of neuroleptic-naive patients before pharmacologic intervention permits evaluation of the disease state separate from its treatment. A pattern of abnormalities is evident in first-episode patients across studies (14,37,80), indicating that disruption in normal brain processes is evident already at the presentation of illness and cannot be attributed to treatment or chronicity. While this is clearly an informative approach, progress can be made in metabolic studies using complementary methods that integrate pharmacologic probes with metabolic studies.

A repeated-measures design has been applied in a limited number of PET studies. In addition to examining the relationship between symptom severity and time (39,41), this paradigm is especially useful when pharmacologic intervention is standardized. Bartlett et al. (5) compared the effects of thiothixene and haloperidol in chronic schizophrenic patients who were scanned while off medication and after 4–6 weeks on medication. A different pattern of global and regional glucose metabolism was seen in the two groups. PET scans were obtained at weeks 5 and 10 of a double-blind, crossover trial of haloperidol and placebo in 25 patients with schizophrenia (13). Low relative metabolism in the striatum on placebo was associated with improved symptomatology. Responders had increased metabolism in the striatum after treatment. Nonresponders failed to show such a change and had more marked hypofrontality while on medication. In a subsequent study, 12 patients were scanned before and 4–6 weeks after treatment with clozapine or thiothixene (12). The drugs had a differential effect, with clozapine increasing and thiothixene decreasing metabolism in the basal ganglia, right more than left. Holcomb et al. (44), in a study using a repeated-measures design, evaluated glucose metabolism in 12 patients who were on a fixed dose of haloperidol, and again 5 and 30 days after drug withdrawal. No differences were observed between metabolism on medication and after 5 days of withdrawal. However, at 30 days, decreased metabolism was noted in the caudate, putamen and anterior thalamus, whereas the frontal cortex and anterior cingulate had increased metabolism. The authors concluded that the basal ganglia were the site of the primary antidopaminergic action of haloperidol, and that the other changes observed were mediated through the striato-thalamo-cortical pathways (78,79). The integration of pharmacologic and neurobehavioral probes is a potentially powerful approach. Dolan et al. (23) noted that there was enhanced activation of the anterior cingulate after administration of apomorphine to patients, suggesting a modulating role for dopamine.

The introduction of functional MRI (fMRI) is an exciting development in functional imaging research. The method is radiation-free and more amenable to repeated measures. The application of this technology to the study of schizophrenia is still in the early stages. Renshaw et al. (69) measured the relative magnitude of the change in image signal intensity caused by photic stimulation in eight patients and nine controls. The mean signal intensity change in the primary visual cortex was significantly greater in patients than in controls. Sensorimotor cortex and supplementary motor area (SMA) activation were examined in right-handed patients and controls during finger-to-thumb opposition. All subjects showed significant activation of the SMA and both ipsilateral and contralateral sensorimotor cortices. Compared with controls, patients showed a decreased activation of both sensorimotor cortices and SMA, as well as a reversed lateralization effect (89). Yurgelun-Todd et al. (97) examined 12 schizophrenic patients and 11 controls during performance of a word fluency task. Patients showed less left frontal activation and greater left temporal activation than controls. With increased understanding of the technology and elucidation of neural systems processing tasks in healthy people, our ability to apply the methodology to schizophrenia will also be enhanced.

NEURORECEPTOR STUDIES

The study of neuroreceptors provides another important window for assessing the nature of neurochemical abnormalities in schizophrenia. Since advances in elucidating the pathophysiology of schizophrenia require understanding of neurotransmitter function, the application of PET and SPECT to the study of receptor occupancy is an important research domain. These efforts have been guided both by an extensive

psychopharmacological literature and by advances in basic neuroscience with respect to neuroreceptor subtyping. Functional neuroimaging is the meeting ground of preclinical and clinical neuropharmacology. Human neuroreceptor PET studies have built on progress with *in vitro* binding measurements of receptor density and affinity and neuroreceptor autoradiography (75,95). Psychotic symptoms seen in schizophrenia have been associated with dysfunction of the dopaminergic system, and the dopamine hypothesis has undergone revisions (20,55).

The development of radioligands for PET studies first focused on the D2 receptor because of its clinical significance. The study of neuroleptic-naive patients could potentially differentiate attributes of the psychotic state before and after neuroleptic intervention. Two major methodologies for quantitative measurement have been developed and applied in the study of schizophrenia. Investigators at Johns Hopkins University applied 11C-N-methylspiperone (NMSP; 84) and reported that patients, compared with controls, had higher D2 Bmax values (67,95). Studies at the Karolinska Institute using 11C raclopride, reported similar Bmax and Kd values in patients and controls (27,28).

These apparent differences have been discussed and summarized extensively and are likely related to multiple factors, including patient variables, ligand properties and PET modeling methods (2,38). Since the ligands differ in binding properties and sensitivity to endogenous dopamine, studies permitting more direct comparisons will be particularly helpful. In such an effort, Nordstrom et al. (64) evaluated the reproducibility of the [11C]NMSP finding in a study of seven neuroleptic-naive patients and seven controls before and after administration of 7.5 mg of haloperidol. Consistent with previous quantitative PET studies of [11C]raclopride binding (27,28), no differences were observed between patients and controls pre-treatment; after haloperidol dosing, the specific binding of [11C]NMSP was reduced by 80–90%. More recently, investigators at John Hopkins (38) replicated the initial data in a new sample of drug-naive schizophrenic patients. Other data revealed that D2 density increased in psychotic but not in non-psychotic bipolar patients. The degree of increase was comparable to that reported in schizophrenia (94). This raises questions regarding the specificity of the dopamine hypothesis to schizophrenia versus other psychotic syndromes (38).

Martinot et al. (57) measured D2 striatal dopamine receptors using 76Br-bromospiperone in a PET study of 12 untreated schizophrenics and found no increase in patients relative to controls. In a subsequent study (56), 76Br-bromolisuride was applied to the measurement of striatal D2 receptors in 19 untreated patients and 14 controls. Again, no differences in striatum to cerebellum ratios emerged, and in both studies no relation to symptoms or subtypes was evident.

The study of neuroreceptors can also address issues related to the relationship between receptor function and signs such as akathisia, which are commonly observed in patients treated with neuroleptics. Farde (29) studied four control subjects who were given 11C-SCH 23390, a selective D1 dopamine receptor antagonist. Two PET studies, at low and high doses of the radioligand, were conducted per subject. Transient akathisia occurred only when binding in the basal ganglia was at a high level (45–59%) occupancy. The D2-dopamine receptor antagonist [11C] raclopride was measured in 20 controls and 13 patients. In patients and controls, akathisia was associated with maximal ligand binding in the basal ganglia. Wolkin et al. (92) found that neuroleptic-resistant schizophrenics did not differ from neuroleptic responders in degree of D2 receptor occupancy by the neuroleptics. The regional distribution and kinetics of haloperidol binding were studied with 18F-haloperidol in a PET study of five schizophrenics, examined while on haloperidol and after a drug washout, and nine controls (74). Wide regional distribution of the ligand was evident in the cerebellum, basal ganglia and thalamus, in contrast to the specific binding to the basal ganglia of 18F-N-methylspiroperidol. Thus, small structural differences among butyrophenones are associated with differences in kinetics and distribution.

PET neuroreceptor methodology has also been applied to the study of atypical vs. typical antipsychotic drugs. The properties of clozapine binding to D1 and D2 dopamine receptors were examined in an open study of five patients who received clozapine and 22 patients treated with typical neuroleptics (25,26). Clozapine induced lower D2 occupancy (38–63%), whereas D2 receptor occupancy with typical neuroleptics at conventional doses was 70–89%. Neuroleptic-induced extrapyramidal syndromes were associated with higher D2 occupancy. In a follow-up study, Nordstrom et al. (65) examined the relationship between D2 receptor occupancy and antipsychotic drug effect in a double-blind PET study using 11C-raclopride. Seventeen patients with schizophrenia were randomly assigned to

three groups and treated with a varied dose of raclopride. A PET study was conducted at steady-state on 13 patients during the third to fourth week of treatment. A curvilinear relationship between plasma concentrations of raclopride and D2 receptor occupancy was found. A significant relationship was noted between D2 receptor occupancy and percent changes in the Brief Psychiatric Rating Scale as a measure of outcome. The D2 receptor occupancy in patients who had extrapyramidal symptoms (EPS) was higher than in patients without EPS. Nordstrom et al. (64) examined D1, D2, and 5-HT2 receptor occupancy in 17 patients treated with clozapine (125–600 mg/day) after applying 11C-SCH23390, 11C-raclopride, and 11C-N-methylspiperone. D2 receptor occupancy (20–67%) was lower than for typical neuroleptics (70–90%), D1 receptor occupancy was higher (36–59%) than that reported for typical neuroleptics (0–44%), and 5-HT2 receptor occupancy was high (84–94%). Thus, clozapine shows a combination of relatively high D1, low D2, and very high 5-HT2 receptor occupancy values, with serum concentrations not predictive of the degree of receptor occupancy. In a PET study of [11C]raclopride, Kapur et al. (46) determined D2 receptor occupancy induced by 2 mg/day of haloperidol for two weeks in seven patients. High levels of D2 occupancy (53–74%) were noted with substantial clinical improvement. A similar investigation in nine patients receiving 2–6 mg/day of risperidone showed receptor occupancy (66–79%) similar to that of typical neuroleptics and higher than that of clozapine (47). These research paradigms illustrate the integration of functional neuroimaging with pharmacologic research. Clearly, incorporation of these strategies into psychopharmacologic studies of schizophrenia with available therapeutic agents can advance the field and guide treatment intervention.

The D2 receptor SPECT ligand IBZM (10) has been applied in studying dopamine D2 receptors in patients with schizophrenia (52). Fifty-six patients were evaluated and a semiquantitative analysis of D2 receptor binding (basal ganglia/frontal cortex) ratio of activity calculated. The basal ganglial frontal cortex ratios in patients taking typical neuroleptics were significantly lower than those in the neuroleptic-free subjects, but not lower than those in the patients taking atypical neuroleptics (clozapine, remoxipride). No overall elevation of D2 receptor binding was observed between 20 patients off medications and 20 controls (68), but in male patients a left lateralized asymmetry was found.

Kessler (50) has used epidepride, a D2 receptor antagonist, to explore extrastriatal D2 receptors in autoradiographic and *in-vivo* neuroimaging studies. Iodine-labeled epidepride may be a useful agent for exploration of D2 sites, since it labels receptors in prefrontal and cingulate cortex, as well as in the striatum. Subsequent developments introduced IBF, which has more specific affinity for D2 receptors with SPECT (61), as well as TISCH and FIDA (16,62). Figure 3 illustrates the application of such ligands in human studies.

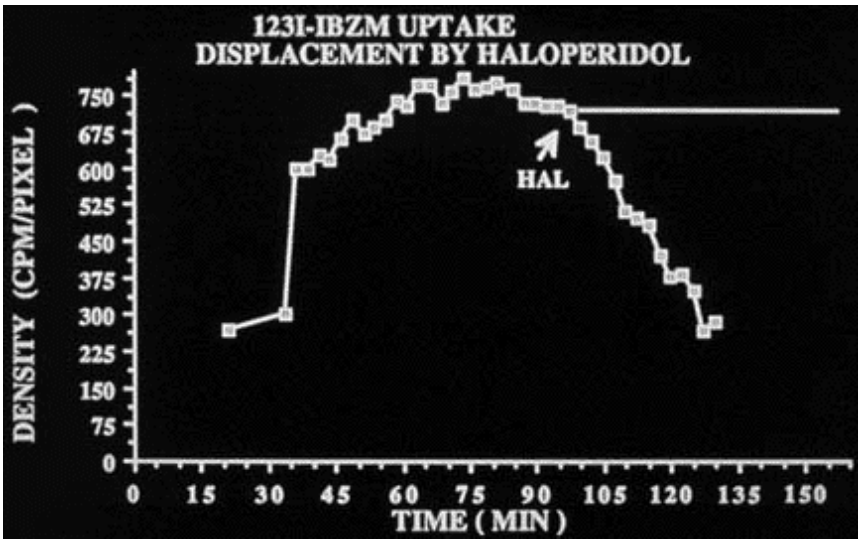

Figure 3. Time activity curves after 5 mci of ^{123}I-IBZM injection. The administration of halperidol resulted in IBZM displacement.

CONCLUSIONS

Functional neuroimaging research in schizophrenia has made progress in two areas: regional brain energy metabolism and blood flow and neuroreceptor studies. In a review of this field, Sedvall (76) concluded that major future advances in understanding the pathophysiology of schizophrenia will be achieved through advanced

resolution and development of new ligands for neurotransmitter systems. While the potential of these developments is undeniable, metabolic studies can also make unique contributions that will prove essential for finding the neural basis of schizophrenia and ultimately for improved treatment (36). Functional neuroimaging studies, in the context of the overall effort in neurobiologic research in schizophrenia, have contributed and will continue to advance the understanding of brain dysfunction related to neurobehavior and neuropharmacology. The field has reached some maturity in developing appropriate paradigms, and there is now a need for adequate sample size in patient and normal populations, with attention to clinical heterogeneity and variability in brain function in relation to gender and age.

Two complementary types of probes can enhance our understanding of brain function in schizophrenia. The first is the study of neuroreceptors, as described by Sedvall (76). The second concerns neurobehavioral probes (31), which provide a useful paradigm for metabolic studies. While there are a number of reports where glucose studies were undertaken during cognitive activation procedures (15,38), a better ligand for such studies is 15O-labeled water for measuring cerebral blood flow and fMRI. The short half-life of 15O-labeled water permits repeated measures under different task conditions. This strengthens the design by eliminating sampling error and enabling the demonstration of task X region interactions. Studies with other physiologic neuroimaging methods, such as the 133Xenon clearance technique, have used this approach profitably in the study of schizophrenia (7,35,88). These studies are now underway with PET and fMRI and require consideration of several factors: task appropriateness for the imaging environment, task difficulty, validity and reliability of tasks in relation to the concepts they measure, specificity of effect for task and population and availability of performance data that can be correlated with metabolism (32,34).

One of the major challenges in this research is the integration of neuroimaging data, across anatomic and functional measures, with clinical and neurobehavioral variables. A potential strength of functional neuroimaging is the integration of neuroreceptor and metabolic studies. Ultimately, dysfunctional neurotransmitter systems translate to aberrant metabolism. Since CBF and metabolism reflect neuronal activity, relating these domains is a prerequisite for understanding the neurobiology of schizophrenia. As new receptor subtypes are cloned and radioligands are developed and made available for human studies, it will be necessary to know which neuroreceptor measures result in increased neuronal activity and how regional activation relates to behavior.

Thus, while new receptor ligands and improved resolution are welcome and exciting, and to these one should now add the development of methods for magnetic resonance spectroscopy and flow measures, it is unlikely that finding the neural basis of schizophrenia will simply come as a product of applying the right method with sufficient resolution. Rather, it seems that we will have to undertake the harder and longer route of understanding the interaction between regional brain activity and neuroreceptors as it affects the clinical and neurobehavioral manifestations of schizophrenia. On the positive side, in the process of this examination, we will be in a position to find partial answers of immediate benefit for treatment. And, in the evolution of this work, we will systematically improve our ability to articulate a neuropsychiatric perspective of this devastating disorder.

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