Articles

Brain Imaging: Applications in Psychiatry

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Various brain imaging techniques have become available in the past decade. These include techniques to evaluate brain structure, such as computed tomography and magnetic resonance imaging, and techniques to assess functional activity, such as measurement of regional cerebral blood flow, single photon emission computed tomography, and positron emission tomography. These techniques can be used to map brain structure and function in normal human beings, and they have enlarged our knowledge of the pathophysiology of mental illnesses by demonstrating structural, metabolic, and neurochemical abnormalities in a wide range of mental disorders.

PSYCHIATRISTS HAVE KNOWN FOR AT LEAST 100 YEARS THAT mental illnesses must be fundamentally due to perturbations of normal neural activity in the brain. Emil Kraepelin is recognized by many as the founding father of modern psychiatry. He amassed in the Psychiatric Clinic of Munich University a group of distinguished brain scientists, including Alzheimer, Nissl, Brodmann, and Gaupp, to search for those perturbations. Through their basic work, they laid many of the foundations for the study of neuropathology and modern neuroscience. These scientists identified diseases such as schizophrenia and manic-depressive illness that form the basis of contemporary psychiatry nosology, and they isolated the neuropathology for the mental illness that bears Alzheimer's name. Yet this talented and dedicated group was unable to identify the neural mechanisms of other more complex mental illnesses.

Their failure to find lesions that could be seen clearly with the naked eye or with a microscope led some psychiatrists to conclude that there were no specific neural abnormalities. In retrospect, it is clear that Kraepelin and his fellow psychiatrist-neuroscientists of the early 20th century were on the right track. However, they lacked sufficiently sensitive tools to map and measure the complex aberrations of cognitive, perceptual, emotional, and motor functions that characterize major mental illnesses such as schizophrenia or the affective disorders. The development of the technology of brain imaging during the past 15 years has changed this situation significantly. The psychiatrist-neuroscientist of the 1980s has the opportunity to study brain anatomy in patients in exquisite detail, to observe shifts in metabolic activity as the brain responds to cognitive or perceptual challenges, and to measure quantitatively the neurochemical activity of a variety of neurotransmitter circuits in the brain. These brain imaging techniques may make it possible to identify the anatomic, metabolic, and neurochemical substrates of mental illnesses.

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Psychiatric Symptoms and Brain Mechanisms

The symptoms of mental illness can be put into two broad categories: those that represent an aberration or distortion of normal functions and those that represent a loss of normal functions. This distinction was originally made by Hughlings-Jackson, who called these two groups positive and negative symptoms. He believed that positive symptoms were due to irritative or release phenomena (hyperactivity) and negative symptoms were due to simple neuronal loss (hypoactivity) (*1*). Although this distinction is an oversimplification, it provides a useful preliminary model for conceptualizing psychiatric symptoms and relating them to underlying neural activity (*2*).

Positive symptoms include phenomena that are distortions or exaggerations of normal functions. Auditory hallucinations, for example, are frequently observed in patients with schizophrenia and manic-depressive illness. These hallucinations represent abnormal auditory perceptions: hearing voices or sounds when no external stimulus is in fact present. Since no external stimulus exists, these phenomena must arise spontaneously from abnormal neural activity within the brain. Delusions represent an abnormality in inferential thinking; the patient perceives stimuli in his environment accurately but makes erroneous or distorted inferences about their significance. For example, a patient may conclude that a red traffic light symbolizes danger from the enemies that persecute him or may make some other similar false inference. The psychiatric term "positive formal thought disorder" refers to abundant productive speech that is disorganized and difficult to understand and represents a distortion of normal verbal communication. Bizarre behavior includes domains such as motor activity and social interaction, and may be manifested as stereotyped behavior (for example, rocking), aggressive and agitated behavior, or inappropriate social or sexual behavior. Negative symptoms, on the other hand, represent a loss or diminution of functions that should be present. These include loss of the following characteristics: fluency and spontaneity of verbal expression (alogia), fluency of emotional expression (blunted affect), the ability to initiate and persist in completing various tasks (avolition), the ability to experience pleasure or form emotional attachments to others (anhedonia and asociality), and the ability to focus attention on some specific activity or task in a sustained manner (attentional impairment). Some neurotic symptoms, such as obsessions, compulsions, or anxiety, are also positive in the sense that they represent a distortion or exaggeration of normal functions, whereas others, such as depressed mood or loss of appetite, are negative.

Ultimately, all these types of symptoms must be understood in terms of the interaction of neural systems and neural circuits. The identification of the underlying neural mechanisms of clinical symptoms is a major goal of modern psychiatry. Auditory hallucinations, for example, may represent an abnormality in the perceptual and memory systems residing in various parts of the temporal lobes. When speech is heard normally in response to an external stimulus,

sound waves enter through the ears and are transduced through end organs in the cochlea, transferred by neuronal tracts to the auditory perceptual cortex in the temporal lobes, and then transferred to the auditory association cortex where the sounds are "associated" with a verbal meaning and recognized as words that both denote and connote. The auditory association cortex has input and output connections with other brain regions, including the amygdala and hippocampus, which are temporal lobe regions dedicated to encoding memories. Verbal stimuli heard and read in the past are stored in these temporal lobe gray matter nuclei. Theoretically, auditory hallucinations could arise from aberrations in any part of this neural system, or even in other systems connected to it such as the cingulate and frontal cortex. The kinds of aberrations could also vary and include possibilities such as an irritative lesion causing spontaneous neuronal discharges, inactivation of a regulatory center that then causes another center to become overactive, or a disconnection of the circuits that causes several centers to run freely in a disorganized manner.

Evidence from neuropathology implicates the hippocampal formation and perhaps the frontal and cingulate gyri as the areas responsible for these aberrations. Several independent neuropathological studies of postmortem brains have indicated either neuronal loss or abnormal patterns of substructure in the hippocampus and parahippocampal gyrus in patients suffering from schizophrenia (*3*). Whether these anatomical abnormalities lead to functional hyperactivity or hypoactivity is unclear. One possible hypothesis is that auditory hallucinations arise when auditory memories—fragments of speech read or heard in the past and stored in the amygdala and hippocampus—are released intermittently because of a lack of regulatory input from another brain region such as the frontal cortex.

Negative symptoms can be more easily explained by our knowledge of normal brain function, although the explanation is also only a hypothesis. The five negative symptoms described above that occur frequently in psychosis represent a loss of functions associated with various portions of the prefrontal cortex. The prefrontal cortex is the largest region in the human brain, and only the human species has such extensive development of the frontal lobes. The frontal lobes provide the capacity to think abstractly or creatively, to express language and feelings fluently, to form social judgements and read social situations, to form emotional attachments to others, to focus attention in a sustained manner, to initiate tasks and persist in them, to think serially and sequentially, to plan for the future, and to make adaptational changes in thinking and behavior when changing environmental demands require them (*4*). Many of these functions are lost as a consequence of frontal lobe injury. Thus, a decrease in the functional capacity of the frontal lobes may account for the prominent negative symptoms that occur so frequently in schizophrenia.

The above examples reveal several important points about the study of psychopathology in relation to neural mechanisms. First, although animal research can be useful (particularly to study neurochemical localization and neural circuits), there are no animal models for many cognitive and emotional functions of human beings. Human beings are the only animals who can communicate with one another in highly refined verbal languages. No other animals have such highly developed frontal lobes, and no other animals share our capacity for generating abstract and creative thoughts, complex social organizations and networks, long-term future plans, or many other "frontal" functions. Although some animals display neurotic behavior, psychotic behavior comparable to most positive symptoms appears to be rare or nonexistent. Thus, much of our study of mental illness must be limited to human beings. We can learn a great deal from the study of postmortem

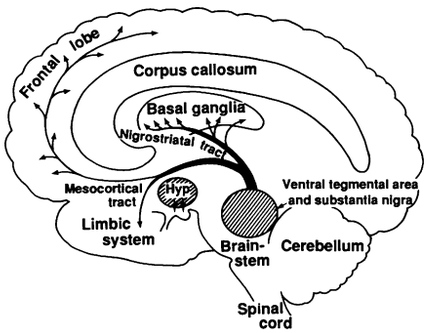

Fig. 1. Schematic drawing showing probable dopamine projections in the human brain. Two main projections arise in the ventral tegmental area. The nigrostriatal tract projects to the basal ganglia, while the mesocortical tract projects to the temporal and frontal lobes. Reciprocal connections are not shown. Hyp, hypothalamus.

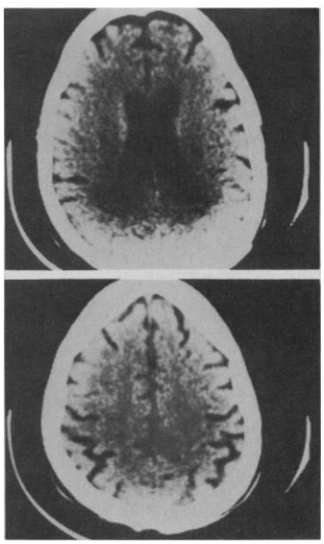

Fig. 2. CT scan from a patient suffering from schizophrenia, showing ventricular enlargement (**top**) and cortical atrophy (**bottom**). This patient was in his mid-30s when the scan was obtained.

human brains, but the optimal situation would be to study the living brain and to evaluate it while it is in the process of producing abnormal thoughts and behavior.

A second point is the importance of studying normal brain activity in addition to abnormal brain activity. Our knowledge about how the normal brain functions is scanty. Although we make global statements about the role of the prefrontal cortex in creative thought, the importance of the hippocampus and amygdala in storing memories, and the role of the association cortex in attributing meaning to language, most of the details of these regions and functions are as yet unmapped. Understanding how our brains generate the thoughts and feelings that make us uniquely human is one of the most exciting challenges of the final decades of the 20th century. Further, without knowing how the brain functions normally, it is difficult to identify the mechanisms that produce abnormal thinking, emotions, and behavior.

In clinical neuroscience this task is in fact more difficult and complex than the above discussion implies. Although it is important to identify the mechanisms that produce symptoms, in real life symptoms cluster together in patterns that psychiatrists recognize as syndromes and diseases. Any adequate explanatory model must not only account for the presence of particular symptoms but must account for the way they cluster together and even occur in paradoxical mixtures, as when positive and negative symptoms co-occur. Both clinical psychiatry and neuroscience are complex. We speak about brain systems and circuits as independent entities, yet this description undoubtedly represents an oversimplification that reduces the overwhelming complexity of the central nervous system to an understandable and workable level. The systems and circuits that we describe, be they anatomical (for example, frontal and limbic

systems) or neurochemical (for example, dopamine and serotonin systems), are not independent but interactive.

The Dopamine Hypothesis and Neural Mechanisms in Schizophrenia

The most widely accepted hypothesis concerning neurochemical mechanisms in schizophrenia is the "dopamine hypothesis," which suggests that symptoms of schizophrenia are at least partially caused by a functional hyperactivity in the dopamine system in the brain (*5*). The dopamine system originates in cell bodies in the ventral tegmental area and substantia nigra and projects in two principal tracts: the mesocortical system and the nigrostriatal system (Fig. 1). The mesocortical system projects to the limbic regions and to the prefrontal cortex, while the nigrostriatal system projects to the caudate, putamen, and globus pallidus. Although Fig. 1 does not show feedback loops between these various regions, the temporolimbic, prefrontal, and nigrostriatal systems are joined by reciprocal interconnections.

The dopamine hypothesis is based on several lines of evidence, derived principally from information concerning the mechanism of action of psychoactive drugs (*5*). Neuroleptic drugs decrease psychotic symptoms and produce dopaminergic blockade, whereas amphetamine-like compounds act as dopamine agonists and exacerbate the symptoms of psychosis.

Theoretically, the dopaminergic overactivity in schizophrenia could be due to a variety of mechanisms. Like all classic neurotransmitters, dopamine is synthesized in neurons, stored in synaptic vesicles, released into the synapse on activation, and thereafter either metabolized to homovanillic acid (HVA), returned to the transmitter neuron, or used to activate a receptor site on another neuron. Receptors are protein complexes in the cell walls of neurons. There are two major groups of dopamine receptors, D1 and D2. The D1 receptor is positively coupled to adenylate cyclase, one of the second messenger systems that carries messages within receptor neurons, and the D2 receptor is negatively coupled to adenylate cyclase.

Although excessive dopamine transmission could occur at any point in this series of steps, the bulk of the evidence appears to implicate abnormalities in receptor neurons rather than excessive production, failure to metabolize, or failure to reuptake the transmitter following its release at synapses. Studies designed to assess presynaptic dopaminergic hyperactivity by measurement of metabolic breakdown products (HVA) in the cerebrospinal fluid or plasma have largely been negative. In fact, there is some suggestion that patients with schizophrenia may have decreased HVA, which may be correlated with indices of cerebral atrophy such as ventricular enlargement and with negative symptoms, implying that some manifestations of schizophrenia may actually reflect hypodopaminergic activity (*6*). On the other hand, many studies have documented that patients with schizophrenia have increased numbers of D2 receptors in the basal ganglia and limbic regions (*7*). In interpreting these studies, however, the effects of previous treatment with antipsychotic drugs is a matter of concern because increased numbers of D2 receptors may be a consequence of D2 receptor proliferation in response to chronic blockade. Ideally, one needs information about the integrity and function of the dopamine system in patients with schizophrenia who have never been treated with neuroleptic drugs. However, postmortem studies include very few such patients.

In 1983, Bannon and Roth proposed a useful hypothesis that would explain the mixture of positive and negative symptoms in schizophrenia and the evidence for both increases and decreases in dopamine function (*8*). On the basis of animal studies indicating that selective prefrontal cortical dopamine lesions enhance subcortical dopamine transmission, they postulated that patients with schizophrenia may simultaneously have hypodopaminergic function in their prefrontal cortex and hyperdopaminergic activity in subcortical or limbic regions. The hypofrontal activity might be manifested as the classic negative symptoms of schizophrenia, while the increased subcortical or limbic activity would be reflected by movement abnormalities or positive symptoms such as hallucinations. This combination of symptoms could be explained by reduced prefrontal cortical dopamine, leading to relative activation of other dopamine systems in the basal ganglia or limbic regions that would normally be modulated by the prefrontal cortex.

In Vivo Brain Imaging

The above summary of the current state of knowledge concerning normal and abnormal neural activity in the brain and its relation to major mental illnesses is based primarily on postmortem studies, animal resarch, and the examination of peripheral metabolites in human beings. Each of these approaches has inherent limitations. Postmortem investigation of brain tissue is confounded by the aging process, the effects of various medications, and the changes produced by other diseases in addition to mental illness. Animal models

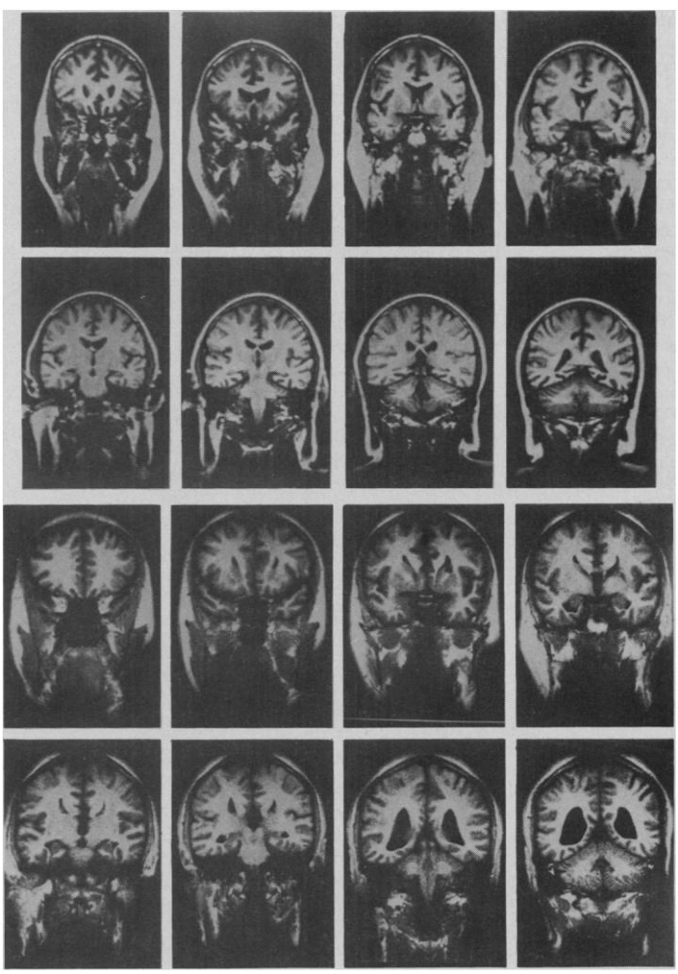

Fig. 3. A set of MRI scans in the coronal plane showing (**top two rows**) normal structure in a normal volunteer and (**lower two rows**) an abnormal scan from a patient with schizophrenia and nearly complete agenesis of the corpus callosum. In the abnormal scan, temporal lobes are also distorted, and the posterior ventricular horns are markedly enlarged.

do not permit the examination of distinctly human functions such as language or complex social interactions. The study of peripheral metabolites yields only oblique inferences about what might actually be happening in the brain itself. Ideally, we would like to bypass these difficulties and observe the structural, metabolic, and neurochemical characteristics of the human brain in relatively young mentally ill individuals whose clinical picture has not been clouded by secondary factors such as the effects of institutionalization or treatment with psychoactive drugs. In addition, we would like to map the vast range of cognitive functions that are distorted or diminished in the mentally ill by observing the structure and metabolic and neurochemical functions of the brains of normal individuals.

With in vivo brain imaging these things can be seen and measured. Brain imaging refers to a group of relatively new related techniques that permit direct observation of the brain in living human beings. The oldest technique, computerized tomography (CT), was developed in the early 1970s. Brain imaging techniques fall into two broad groups: techniques that measure structure and those that measure function. The former methods include CT and magnetic resonance imaging (MRI); these methods permit the study of brain anatomy and possible structural abnormalities. The latter include measurement of regional cerebral blood flow (RCBF), single photon emission computed tomography (SPECT), and positron emission tomography (PET). The techniques that measure function permit the study of the brain at work through the measurement of metabolic activity and neurotransmitter systems.

Computerized tomography. This was one of the earliest techniques to be applied to psychiatric patients. Johnstone *et al.* reported in 1976 that patients suffering from schizophrenia tended to have a significantly greater degree of enlargement in the ventricular system than did a matched control group (*9*). The ventricles are cavities in the brain filled with cerebrospinal fluid; enlargement of the ventricles is assumed to occur at the expense of neuronal tissue and thus is an indirect indicator of compromised brain function. Although this study was initially greeted with skepticism because the patients in the sample were relatively old and included many who had been institutionalized, these findings have subsequently been replicated in

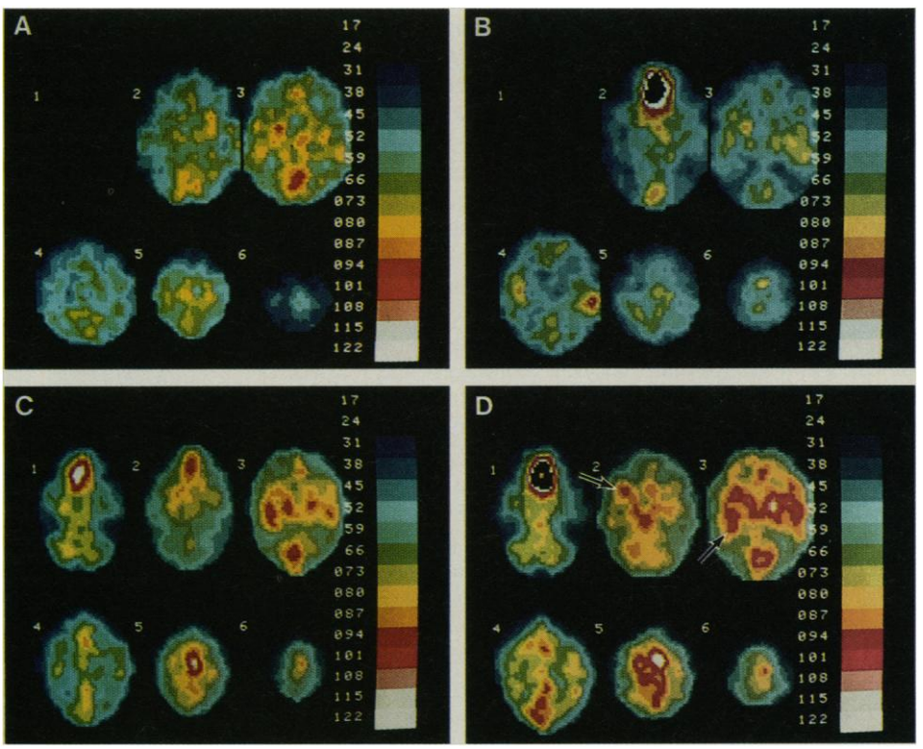

Fig. 4. A set of SPECT scans showing variations in regional cerebral perfusion. (**A**) A 68-year-old man who is not demented. (**B**) A 73-year-old man with Alzheimer's disease. Both studies were obtained at rest. Cuts B-2 and B-3 reveal areas of abnormally low activity in the posterior region of both hemispheres. These areas correspond to the posterior temporal and posteroinferior parietal cortices. There are no areas of abnormally low activity in (A). (**C** and **D**) A normal young, right-handed woman, obtained at rest (C) and during a language activation task (D). The overall activity increases during the task, and there are discrete areas where asymmetric changes can be noticed. The arrows in (D) point to areas of increased activity in the left frontal D-2 and left temporal D-3 regions, corresponding to Broca and Wernicke areas, respectively. Also of interest are the marked increases of activity in the right basal ganglia (white area on D-3), the right supplementary motor area (white area on cut D-5), and the left cerebellar hemisphere (cut D-2). These structures were engaged in the motor response (movement of left foot) used to monitor the language activation procedure (*45*). Scale shows relation between color and relative amount of radioactivity.

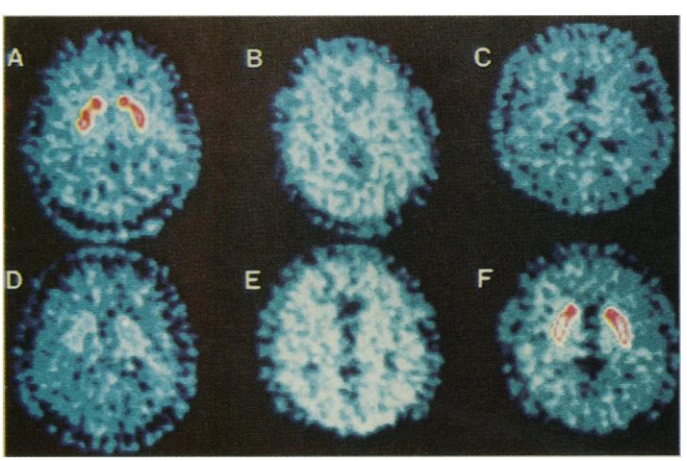

Fig. 5. A series of PET scans showing effects of various antipsychotic drugs on D2 receptor occupancy with ^{11}C-labeled raclopride, a ligand that specifically labels 2D receptors. (**A**) Healthy volunteer; (**B**) patient treated with haloperidol (8 mg/day); (**C**) patient treated with flupenthixol (100 mg/week); (**D**) patient treated with clozapine (600 mg/day); (**E**) patient treated with sulpiride (1600 mg/day); and (**F**) same patient as (E) 2 weeks after complete withdrawal of drug. The healthy volunteer shows high levels of ligand upake in the caudate and putamen. The treated patients (B through E) have complete receptor blockade as a consequence of neuroleptic treatment, thereby preventing ligand uptake. After drug discontinuation (F), receptors are unoccupied, and uptake and binding with [^{11}C]raclopride can occur. Images were obtained from research group of G. Sedvall, Karolinska Institute, Stockholm. [Reprinted from (*38*) with permission, copyright 1986, American Medical Association]

a large series of studies (*10–12*). The finding of ventricular enlargement in schizophrenia now has become one of the most consistently reproduced findings in psychiatry.

Studies with CT have indicated that patients suffering from schizophrenia (Fig. 2) may have one of a variety of abnormalities: ventricular enlargement evidenced by an increased ventricle to brain ratio, cortical atrophy as evidenced by sulcal widening, and cerebellar atrophy. Ventricular enlargement has been the abnormality most consistently replicated among these findings. Depending on the criterion used to define enlargement, frequency of abnormalities varies from study to study (*11*). If the criterion applied for ventricular enlargement is two standard deviations larger than the control mean, then the frequency in schizophrenia ranges from 6% to as high as 40%. The studies reporting higher rates appear to draw from populations with greater severity and chronicity of illness.

These rather consistent findings have had important implications for research in the mechanisms of schizophrenia. This illness clearly involves not only functional abnormalities, but perhaps abnormalities in brain structure. There is now a substantial impetus for investigating the pathological factors that could lead to structural abnormalities. For example, abnormalities indicated by CT have been observed in young, first-episode patients, suggesting that a pathological process may begin before the actual onset of symptoms of the illness (*12*). The abnormalities do not appear to progress excessively with age (*13*). Ventricular enlargement in schizophrenia may also be correlated with low birth weight and obstetrical complications, and it is more prominent in the ill twin in pairs of monozygotic twins who are discordant for schizophrenia (*14*). These latter findings suggest the importance of intervening environmental variables. Studies with CT have also explored the correlates of structural abnormalities. Some evidence suggests that abnormalities shown by CT may be related to poor premorbid adjustment, cognitive impairment, negative symptoms, and a poor response to treatment (*9, 10, 15*). Thus, structural abnormalities may begin early in life, and they may suggest a somewhat worse prognosis.

Abnormalities in CT scans are not specific to any type of mental illness, however, and therefore cannot serve as a specific diagnostic laboratory test for these illnesses. In addition to schizophrenia, abnormalities have been reported in bipolar disorder, depression, alcoholism, anorexia nervosa, Alzheimer's disease, and multi-infarct dementia (*16*). Although not diagnostically specific, a CT scan is sometimes clinically useful in differential diagnosis. For example, a CT scan showing ventricular enlargement in a young person suffering from psychotic symptoms who lacks a history of substance abuse provides some information consistent with a diagnosis of schizophrenia.

Magnetic resonance imaging. MRI has become widely available only in the past 3 to 4 years; it has a number of advantages over CT. Unlike CT, which is limited to imaging brain regions in a transverse plane, MRI can image in all planes, including sagittal and coronal as well as transverse. Coronal images are particularly useful for visualizing frontal and limbic regions (Fig. 3). This technique also produces superb gray-white resolution. Consequently, MRI permits an accurate three-dimensional reconstruction of brain structures. It does not use ionizing radiation and has minimal risk.

Because of its newness, few studies of psychiatric samples have been conducted with MRI yet. It has potential applications in four areas: morphometric studies of brain structure, assessment of tissue function and possible tissue pathology through measurement of T1 and T2 relaxation times, measurement of metabolic function through magnetic resonance spectroscopy, and assessment of blood flow and possibly metabolism through paramagnetic tracers. It is not yet clear whether all these applications will be useful in psychiatric samples.

The high degree of resolution, combined with the ability to see the brain in three dimensions, makes morphometric studies of structure potentially the most useful application. One study of 38 schizophrenic patients, who were compared to 45 normal controls by observing their midsagittal cut alone, has indicated that the patients had smaller frontal lobe size, as well as a decrease in cranial and cerebral size (*17*). The decreased frontal size is consistent with hypotheses concerning the importance of frontal dysfunction in schizophrenia. The decreased cranial size suggests that the occurrence of schizophrenia may be influenced by early developmental abnormalities, because cranial growth is largely complete during the first 2 years of life and is determined principally by cerebral growth. A second replication study from the same research group yielded somewhat different results; however, this appears to be due in part to a difference in the nature of the control group (*18*). Controls in the first study were drawn from hospital personnel, whereas controls in the second study were matched sociodemographically and educationally to the patients and also had somewhat smaller brain measurements in comparison with the first group of controls. This finding may suggest that the socioeconomic peers of the schizophrenic patients suffered from similar early disadvantages that produced a similar limitation in cerebral development. Some additional predisposing factor was, however, necessary to lead to an illness such as schizophrenia.

Other abnormalities in patients with schizophrenia have also been observed with MRI. For example, ventricular enlargement is consistently noted with MRI, and it appears to be more prominent in the frontal horns (*18*). Several patients with schizophrenia have midline developmental abnormalities leading to either complete or partial agenesis of the corpus callosum. Embryologic studies have shown that the corpus callosum and limbic structures such as the hippocampus and septal area are developmentally related (*19*). Clinically, these patients have tended to have prominent positive symptoms that resist treatment, a finding consistent with a possible relation between positive symptoms and temporolimbic abnormalities.

Morphometric studies of normal brains can also be conducted with MRI to examine structure-function relations in large samples of normal people. For example, a study by de Lacoste–Utamsing and Holloway of five female and nine male postmortem brains indicated differences in callosal size and shape between the two sexes (*20*). These researchers speculated that the callosum shows a characteristic sexual dimorphism, with females having corpora callosa consistent with less highly differentiated brain structure. A subsequent study with MRI scans from 40 male and 40 female subjects failed to confirm sex-related differences in the callosum (*21*). MRI scans in the transverse plane have confirmed the original observations of Geshwind whose postmortem study of brains demonstrated that the planum temporale and other left temporal brain regions controlling language function are larger on the left than the right in normal individuals (*22*).

Hypoplasia of cerebellar vermal lobules VI and VII have been observed in autism; these lobules are derived from the fastigial nuclei (*23*). If confirmed, these findings have implications for the role of embryological brain development in the genesis of autism.

MRI offers substantial advantages over CT because of its improved precision of visualization. Potentially, it lends itself to well-quantified morphometric studies of brain regions not easily visualized on CT, such as the corpus callosum, hippocampus, amygdala, and other temporolimbic structures. At this stage, however, more basic research is needed to determine whether MRI can identify structural abnormalities in mental illness that are either useful diagnostically or as a means for identifying underlying mechanisms.

Regional cerebral blood flow and single photon emission computed tomography. By means of RCBF measurements and SPECT, inves-

tigators can examine the brain at work. These techniques have been applied to the measurement of cerebral perfusion (Fig. 4) and more recently to the study of neurotransmitter systems. Blood flow has most often been measured from the rate of disappearance of inhaled xenon-133 as recorded by sodium iodide photon detectors placed around the head. Tomographic techniques for measuring cerebral perfusion with xenon are also available but have been less widely used. Cerebral perfusion can also be measured with other tracers, such as ^{123}I-labeled iodoamphetamine (^{123}I-IMP). With all these techniques, cerebral perfusion is assumed to provide an indicator of metabolic activity, with areas of hyperfusion reflecting an increase in cerebral metabolic activity.

Much basic scientific work has been done to refine the methodologies for the measurement of cerebral perfusion and to evaluate its relevance to a variety of conditions (*24*). Ingvar and Franzen observed abnormalities in blood flow in patients with schizophrenia (*25*). Their work indicated that some patients with schizophrenia had decreased perfusion in their frontal lobes, often referred to as "hypofrontality." This finding has been replicated by a number of investigators, but not by all (*26, 27*).

The study of resting perfusion has largely been superseded by the use of activation studies. One interesting application of blood flow measurement is to use stimuli and challenges to map patterns of metabolic activity in the normal brain. For example, this approach has been used to explore language processing in the normal brain, and it has been observed that normal individuals who listen to a series of words in order to identify a selected subset (for example, those that rhyme with a predetermined stimulus word) do indeed differentially activate specific language regions such as Broca's area (*28*). Alternately, several tasks have also been identified that activate the frontal lobes; these include the Continuous Performance Test, which requires sustained attention and pattern recognition, and the Wisconsin Card Sorting Test, which challenges the ability to think abstractly and to change a conceptual set in response to changed instructions and stimuli (*27, 29*). When normal individuals take these tests, which are designed to assess frontal lobe function, they appear to have increased blood flow in the frontal cortex. Once such tasks have been identified and found to produce specific patterns of activation in normal individuals, they can then be used to determine whether patients with mental illness can achieve similar cerebral activation. Inability to do so suggests a possible deficit in a specific brain region. To date, this paradigm has been applied to the study of both left hemisphere and frontal lobe function in schizophrenia. One study has demonstrated that patients with schizophrenia have a specific inability to activate their frontal lobes in response to a task that challenges the frontal lobe (*27*). This finding is consistent with the general hypothesis of frontal lobe dysfunction in schizophrenia. Left hemisphere abnormalities have also been observed, consistent with the language and auditory abnormalities observed in schizophrenia (*24*).

Most RCBF studies conducted to date have used the cortical probe technique. SPECT is a scanning technique that uses the computerized tomographic reconstruction method originally developed for CT and MRI in combination with the detection of single photons emitted through some exogenously administered tracer. Xenon is sometimes used with this technique, but its application is limited by its relatively low energy that produces low sensitivity for detection. An alternative technique involves the use of a rotating detector (gamma camera) and associated planimeter systems to collect information from multiple angular projections. This approach has the advantage of producing images in multiple planes and providing improved resolution. Several laboratories throughout the country are also working on the development of high-resolution SPECT systems that will bring resolution down to as low as 8 millimeters (full width at half maximum) in combination with three-dimensional image construction.

Several ^{123}I-labeled tracers, such as ^{123}I-IMP, are now available for clinical imaging trials in the United States. These tracers are ideal for labeling blood flow and may permit examination of perfusion in subcortical regions such as the basal ganglia and temporal lobe limbic structures. Further, radionuclides suitable for imaging neurotransmitter systems are being developed and may make it possible to monitor the effects of treatment and mechanisms of drug action by means of SPECT. Tracers for dopamine and acetylcholine receptors currently exist, and one report has indicated increased dopamine receptors in the basal ganglia that were observed with SPECT (*30*).

The strongest clinical application of SPECT to date has been in the study of Alzheimer's disease. Both SPECT and PET have shown a pattern of hypoperfusion in posterior temporoparietal regions that appear to be specific to and characteristic of this disease (*31*). Flow patterns in depression, on the other hand, appear to be different (*32*). If differences in flow patterns are clearly present in depression and Alzheimer's disease, the observation of blood flow could be very useful for the differential diagnosis of dementia versus depression in the elderly, one of the most difficult of the differential diagnoses that psychiatrists must make.

Since commercially available tracers are used for SPECT, and it does not require the on-site presence of a cyclotron or a team of physicists and chemists, it is a far less expensive technique than PET. Although its resolution is not equal to that achievable with PET, it may prove sufficient for many applications. Further developments of SPECT techniques over the next few years may make it practicable for use in smaller university centers and community hospitals unable to support the high cost of PET scanning. As a research technique, SPECT is an important complement to PET and permits the relatively rapid evaluation of large samples to test specific hypotheses about normal functional patterns and possible regional abnormalities in major mental illnesses.

Positron emission tomography: Metabolic and activation studies. PET is the most elegant of the available brain imaging techniques. While RCBF and SPECT studies rely on the detection of single photons, PET localizes activity by recording the position of two photons that are emitted (due to the law of conservation of energy) after a positron strikes an electron and produces an annihilation of both. Because this event can be detected with a two-point coincidence line, resolution is substantially better than when single photons are detected. Because PET requires the generation of positron-emitting isotopes, an on-site cyclotron is needed as well as a support team consisting of physicists, radiochemists, and experts in computer modeling. This combination of equipment and expertise makes PET expensive to acquire and to operate. However, it surpasses all other brain imaging techniques in sensitivity and flexibility.

Like SPECT, PET has two major groups of applications—the assessment of metabolic activity and the measurement of neurotransmitter function. In early PET studies, researchers focused on the measurement of cerebral metabolism with deoxyglucose, which could be labeled with ^{18}F or ^{11}C. These isotopes have half-lives of 110 and 20 minutes, respectively. With a half-life of only 2 minutes, ^{15}O is also available for PET imaging in order to measure perfusion and metabolism. Imaging with ^{15}O, although technically difficult, allows the completion of many relatively short studies within a brief time period, permitting a rapid comparison of cerebral metabolic activity in a variety of conditions. For example, the same subject can be evaluated at rest and thereafter with a series of cognitive challenge tasks designed to sequentially assess performance on several different aspects of language or frontal activity and to permit comparison with a matched control task. Multiple back-to-back studies of this type substantially improve the resolution of PET, since they permit

the subtraction of a paired control state image from the task state image, thereby removing areas not recruited by the task (*33*). Although the activation paradigm can also be used with [^{11}C]- or [^{18}F]deoxyglucose, this method is more cumbersome because a longer time interval must elapse between the studies, and factors such as possible changes in head position or in metabolism related to time of day or variation in mood or attention are potential confounders.

In early PET studies of major mental illnesses, investigators focused on the measurement of cerebral metabolism at rest and used deoxyglucose. Patterns of relative hypofrontality were observed in patients with schizophrenia and those with bipolar disorder, although, as in RCBF, this finding has not been consistently replicated (*34*). More recent work has explored frontal lobe activation in schizophrenia and documented an inability to activate frontal systems, as measured by PET as well (*29*). In addition, using both deoxyglucose and ^{15}O-labeled water, investigators have found a relative increase in metabolic activity in subcortical regions in schizophrenia, particularly the basal ganglia (*35*). This pattern of hypofrontality coupled with increased activity in subcortical regions in schizophrenia may be consistent with the model for the simultaneous generation of positive and negative symptoms previously described (*8*). However, some investigators who use PET have not always provided adequate descriptions of the clinical status of their samples or used appropriate controls.

Recently PET has also been used to study less severe mental illnesses, such as the neuroses. A specific area of hyperactivity has been identified in the right parahippocampal gyrus, reflecting susceptibility to lactate-induced panic attacks (*36*). Because this is an important region for encoding memory, this finding is particularly interesting, in that the experience of panic either may be triggered by old anxiety-producing memories or may involve the encoding of new memories that may later trigger subsequent panic attacks. This locus is thus consistent with the behavioral phenomenon recognized as stimulus generalization. In obsessive-compulsive disorder, patterns of increased metabolic activity have been observed in the frontal lobes and basal ganglia (*37*). These may represent a trait rather than a temporary phenomenon, because the increased activity tends to persist after the patients have been successfully treated and have a diminution in obsessional symptoms. Again, the localization of increased activity is consistent with current knowledge concerning the function of the frontal lobes. Patients with obsessive-compulsive disorder have a tendency to be overabstract and overintellectual, to worry and plan excessively for the future, and to repeat serial-sequential behaviors (that is, compulsions) as if locked in a "do-loop" that they are unable to escape.

PET: Study of neurotransmitter systems. Study of neurotransmitter systems in the brain is a particularly promising area for PET research. Ligands are currently available for the study of D1 and D2 dopamine receptors and for serotonin, benzodiazepine, opiate, and muscarinic receptors (*38*).

PET has been used most extensively to study dopamine D2 receptors (Fig. 5), which have obvious importance for understanding the pathophysiology of schizophrenia and the mechanism of action of neuroleptic drugs. Early studies demonstrated that D2 receptors could indeed be labeled, as evidenced by clear areas of uptake in the caudate and putamen (*38, 39*). Likewise, the mechanism of neuroleptic action was demonstrated through visual documentation of dopamine receptor blockade: when labeled neuroleptic was given to patients previously medicated with drugs believed to produce receptor occupancy and blockade, areas of uptake could no longer be demonstrated (*38, 40*). Neuroreceptor imaging has quickly passed, however, from the simple visualization of receptor occupancy to quantitative methods for measurement of actual numbers of D2 receptors in neuronal membranes. Three alternative methods for such measurement are available. Each uses different ligands and different models and measures different things. Two dynamic models have been proposed for the measurement of receptors with derivatives of spiperone; these models involve three to four compartments and are an extension of the Sokoloff model (*41*). Alternatively, an equilibrium model has been proposed for ^{11}C-labeled raclopride that permits a direct measurement of B_{max} (maximal number of binding sites) and K_d (dissociation constant) (*38, 42*).

To test directly the hypothesis that D2 receptors are increased in patients suffering from schizophrenia, first-episode patients who have never been medicated must be studied because treatment with neuroleptic drugs can potentially increase the number of D2 receptors by inducing receptor proliferation as a compensatory mechanism in response to chronic blockade. Two studies examining D2 receptor density in never-medicated schizophrenic patients have been conducted. One study used the dynamic model with spiperone and the other used the equilibrium model with raclopride (*43, 44*). However, the results of these two studies conflict. Using the dynamic model, Wong *et al.* reported an increase in D2 receptor density (*43*), but Farde *et al.* reported normal receptor density with the equilibrium model (*44*). Because the two groups used ligands that differ in their specificity for labeling D2 receptors, different models to measure receptor density, and somewhat different groups of patients, the reasons for the conflict are probably methodological. On the basis of in vivo imaging, the role of the D2 receptor in schizophrenia as yet remains unclear. Nevertheless, continued PET research is the best method for determining its role.

Over the long term, the study of neurotransmitters and neuroreceptors by means of PET imaging should increase steadily in importance. PET imaging of neurotransmitter systems permits clinicians and investigators to bypass peripheral measures and study the brain directly. Operationally, this means that direct measurement of receptor occupancy could supersede attempts to measure serum blood levels as indicators of the presence of drugs in the brain. With PET, the effects of various medications on receptor plasticity can be examined. These results may improve our understanding of troublesome side effects such as tardive dyskinesia and perhaps ultimately permit the identification of preclinical cases of this disorder. The identification of abnormalities in specific neurotransmitter systems or of subsystems within specific brain regions may permit the development of more specific pharmacologic agents for treatment.

Conclusion

Brain imaging offers psychiatry a broad range of investigative techniques that fulfill the popular fantasy of being able to "read the mind," albeit in the form of "seeing the brain" both structurally and functionally. At present, brain imaging provides a modest amount of information that is useful in differential diagnosis, as in distinctions between depression and dementia. It has provided more information about possible pathophysiological mechanisms of major mental illnesses, including structural abnormalities in some forms of schizophrenia. Metabolic abnormalities, such as hypofrontality in schizophrenia or hyperfrontality in obsessional disorder, have also been observed. The long-term promise of brain imaging is substantial. It will permit the mapping of cerebral function in normal individuals so that we can achieve a better understanding of normal brain structure, physiology, chemistry, and functional organization. On the basis of this knowledge, the abnormalities underlying the major mental illnesses can also be mapped.

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