Neuroimaging in Psychiatry: An Update

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Cover Illustration by Christie Grams
INTRODUCTION

Psychiatrists have tried for generations to understand the causes of mental disorders. In the last third of the 20th century, technological advances in the biological, medical, and psychological sciences have allowed for more direct and sophisticated study of the brain than was previously conceivable.

This paper addresses the state of neuroimaging in psychiatry. Current imaging methods are described, followed by a discussion of imaging applications in clinical practice. A comprehensive review of neuroimaging research findings in psychiatry is beyond the scope of this paper. However, the major findings in schizophrenia are reviewed in order to illustrate the potential these methods have for advancing psychiatric knowledge.

IMAGING METHODS

All modern neuroimaging methods are based upon the ability of a detector to measure high-energy photons coming from the brain. The data obtained by the detector is processed using computer algorithms that construct 2- or 3-dimensional images of the brain for visual interpretation or that allow for quantitative data analysis. Brain imaging methods include structural and functional imaging techniques. In a structural scan, a static image of brain anatomy is generated without providing any direct information about current physiological function. A functional study provides information about cerebral blood flow, cerebral metabolism, or receptor populations in the brain.

COMPUTED TOMOGRAPHY

In computed tomography (CT) scanning, a collimated beam of x-rays produced by a rotating assembly passes through the brain of the subject. The x-rays are differentially attenuated based on the radiodensity of the tissue, with bone the most radiopaque (ie, appearing white on film or screen) and air the least radiopaque. The attenuated beam is recorded by a detector (ie, a scintillation crystal); a computer algorithm reconstructs the data into a series of 2-dimensional images. The spatial resolution of this technique is high (1 to 2 mm), and excellent images of the skull, ventricles, and sulci can be obtained.

CT scanning has several limitations. Because the radiodensities of gray matter and white matter differ by only a small margin, gray matter/white matter resolution is only fair, and the ability of CT scanning to discriminate small or deep brain structures is limited. The contents of the posterior fossa (ie, brainstem, cerebellum) are particularly difficult to visualize because of the thick bone surrounding that region of the brain. Finally, only transverse sectioning of the brain is possible with CT scanning.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) exploits the phenomenon of nuclear magnetic resonance. Atoms with an odd number of protons have paramagnetic properties. These protons, when placed in a static magnetic field, will align and spin, or resonate, in relationship to the axis of the field. When the proton is exposed to a brief radiofrequency pulse oriented transverse to the axis of the field, it absorbs energy, causing a change in the proton’s orientation. Termination of the pulse results in realignment within the static magnetic field, a process known as T₁ relaxation, or longitudinal relaxation. The accompanying release of energy, or realization, produces a detectable signal. An additional signal can be detected immediately after the radiofrequency pulse before realignment occurs. The rapid decay of this signal is known as T₂ relaxation, spin-spin relaxation, or transverse relaxation.

Hydrogen nuclei in water molecules are the chief source of MRI signals in biological tissues. Differential relaxation rates in different tissues are used to distinguish structures of the brain. MRI provides far better soft tissue resolution than CT, and gray matter/white matter differentiation is outstanding. The cerebellum, brainstem, and deep subcortical structures may be clearly visualized. Images can be generated in the transverse, coronal, and sagittal planes. Precise volumetric analysis of small brain structures and regions is possible. (In contrast, quantitative measurement, or morphometric, capabilities of CT are principally limited to cerebral ventricular volume and ventricular brain ratio.)

Depending on the clinical or research application, various pulse and detection algorithms and image
acquisition techniques may be used to produce $T_1$, $T_2$, mixed-, spin density-, diffusion-, or proton density-weighted images. The clinician or investigator selects the technique most likely to provide optimum information in a given circumstance. As a general rule, for instance, $T_2$-weighted images provide outstanding anatomic detail, whereas $T_1$-weighted images have superior sensitivity for many types of lesions. Overall, MRI produces the best resolution and contrast for structural imaging (Figure 1).

Clinical MRI magnets are generally capable of generating a field strength of 1.5 T. A number of research centers have obtained machines with field strengths of 3 T, and MRI machines generating field strengths of up to 6 T have been developed and are available for human use. This trend toward stronger field strengths should produce better spatial resolution, and therefore greater investigatory capability in future research. These advances will ultimately result in more sensitive clinical diagnostic capabilities as well.

Diffusion tensor imaging (DTI) is a relatively new MRI-based structural imaging method that uses the properties of water diffusion in tissues to study white matter tract architecture. This method permits the identification of abnormal white matter organization even in the absence of demonstrable white matter volume deficits, thus identifying white matter pathology with greater diagnostic sensitivity and detail.

**FUNCTIONAL MAGNETIC RESONANCE IMAGING**

Functional MRI (/MRI), presently a research tool, generally refers to an application of MRI based on the magnetic properties of deoxyhemoglobin. This method, in which deoxyhemoglobin essentially acts as an endogenous contrast agent, is also known as blood oxygenation level-dependent (BOLD) imaging.

Cerebral neuronal activity results in increased regional cerebral blood flow (rCBF), a relationship that was first hypothesized by Roy and Sherrington and was later demonstrated using a xenon-based method for measuring cerebral blood flow. Increased neuronal activity results in a greater proportional increase in rCBF compared to the increase in metabolism (which results in hemoglobin desaturation), so the local concentration of deoxyhemoglobin is decreased when activity increases. /MRI permits the measurement of rCBF when the subject is at rest, and again when the subject is engaged in a cognitive challenge task. The resultant images are compared to determine patterns of change in rCBF during the activity. The response patterns of ill subjects and controls may be compared to infer the presence of deficits associated with the mental disease.

/MRI is completely noninvasive and exposes the subject to no ionizing radiation. /MRI, like magnetic resonance spectroscopy (MRS), is performed using the same machines as are used to perform structural MRI. Structural images can be obtained simultaneously, allowing more precise correlation of rCBF to specific brain regions or structures.

**MAGNETIC RESONANCE SPECTROSCOPY**

MRS permits the in vivo study of tissue metabolism and biochemistry using the physical principles of nuclear magnetic resonance. Each compound found in brain tissue produces a signature spectral peak. Examination of the spectra allows the investigator to identify and quantify the concentration of multiple chemical species within the region. MRS data is most commonly depicted graphically, although images can be constructed to illustrate the distribution of a compound in the brain.

The current threshold for detection is in the millimolar range, imposing a limitation on which compounds can be studied. Naturally occurring nuclei that can be studied with MRS include proton ($^1$H), phosphorus 31, fluorine 19, lithium 7, sodium 23, carbon 13, and potassium 39.

Phosphorus or hydrogen spectroscopy (ie, proton spectroscopy) are the most often performed MRS studies. Neuronal metabolites commonly measured by /MRS include N-acetyl-aspartate, creatine, glutamate, glutamine, and choline. Compounds measured with $^{31}$P-MRS include adenosine triphosphate (ATP), phosphocreatine, phosphomonoesters and phosphodiesters (indicators of membrane synthesis), and inorganic phosphate. Volumes as small as 1 cm$^3$ may be studied using $^1$H-MRS. $^{31}$P emits a lower signal strength than $^1$H, so $^{31}$P-MRS requires larger volumes of brain tissue.

MRS has been used in research applications to study psychiatric disorders$^4$, including schizophrenia, affective disorders, neurodevelopmental and childhood disorders, dementias, alcoholism, cocaine abuse, anxiety disorders, and eating disorders, as well as normal brain function$^5$ and changes associated with normal development$^6$.

**SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY**

Increased regional activity in brain is associated with enhanced perfusion, and decreased activity with relative hypoperfusion. Single photon emission computed tomography (SPECT) provides a measure of cerebral perfusion, and by inference, brain activity, by following the disposition of an intravenously injected radiotracer in the brain. High-energy photons emitted from the tracer are detected and converted into an electric signal
Figure 1. Axial views of MRI study (left) compared to single photon emission computed tomography (SPECT) (right). Notice the large defect visible on the SPECT image, which shows no perfusion in the medial frontal region. This scan also depicts white matter shear injury in several places between the border of white and gray matter as well as old hemorrhage in left frontal region. (Adapted from Weight DG, Bigler ED. Neuroimaging in psychiatry. Psychiatr Clin North Am 1998;21:725–59, Color Plate: Figure 2 with permission from Elsevier Science.)

Figure 2. Brain slices from 18F-fluorodeoxyglucose positron emission tomographic scans taken at different times in the same patient, a 39-year-old woman with recurrent major depression. On the left is her scan while she was depressed but medication-free. On the right is a scan of the same slice after she recovered from her depressive episode; she was again medication-free during this scan. (Adapted from Kotrla KJ. Functional neuroimaging in psychiatry. In: Yudofsky SC, Hales RE, editors. The American Psychiatric Press textbook of neuropsychiatry. 3rd ed. Washington (DC): American Psychiatric Press; 1997:255. www.appi.org Figure courtesy of George MS, Ketter TA, Willis M, Post RM. Biological Psychiatry Branch, National Institute of Mental Health.)

Figure 3. Monozygotic twins discordant for schizophrenia were studied during the Wisconsin Card Sorting Test using 15O-water positron emission tomography. Red represents greater blood flow. As seen at the arrows, the twin with schizophrenia is less able to increase prefrontal blood flow during the task. (Adapted from Kotrla KJ. Functional neuroimaging in psychiatry. In: Yudofsky SC, Hales RE, editors. The American Psychiatric Press textbook of neuropsychiatry. 3rd ed. Washington (DC): American Psychiatric Press; 1997:260. www.appi.org Figure courtesy of Berman KF, Weinberger DR. Clinical Brain Disorders Branch, National Institute of Mental Health.)
SPECT images can be superimposed (i.e., co-registered) for camera assembly that rotates around the subject’s head, generating multiple images that are reconstructed using computer programs. Various quantitative and semiquantitative strategies are used to analyze the data, and mathematical filtering techniques that cancel background noise allow the creation of visual images. In recent years, radiolabeled neuropeptide ligands have been used in SPECT for the study of neuropeptidergic receptors.

Single photon emitters used in SPECT are compound from technetium 99m, iodine 123, or xenon 133. These substances are generally taken up into cells within minutes of injection and are subject to very slow washout. Therefore, the resultant images represent a relative “snapshot” of brain perfusion (i.e., receptor binding) within a short interval of injection, as opposed to the more dynamic “real time” images obtained with positron emission tomography (PET). Injection may be done when the subject is at rest or during cognitive activation.

Radiotracers used in SPECT have half-lives long enough for them to be acquired from commercial radiopharmaceutical suppliers, rather than the expen- soraneous, on-site production generally required for PET. The most commonly used tracer for measuring blood flow is technetium Tc 99m d, i-l-hexamethylpropyleneamino xime (HMPAO).

SPECT is widely available in most hospital nuclear medicine departments. The cost of a study is comparable to a structural MRI scan. The spatial resolution (6 to 8 mm), although somewhat inferior to PET, especially for deeper structures, is adequate to provide highly useful data in many clinical and research applications (see Figure 1).

**POSITRON EMISSION TOMOGRAPHY**

Although it is primarily a research tool at present, PET is the gold standard for functional neuroimaging. This method differs in many ways from SPECT. PET radiotracers emit a positron during the decay process. After traveling a short distance (1 to 2 mm), the positron collides with an electron, producing an annihilation event. The collision produces 2 high-energy photons, which travel away from one another at an angle of approximately 180 degrees. Nearly simultaneous scintillations of equivalent energy oriented 180 degrees apart (detected by opposing PET cameras) are assumed to emanate from the same annihilation event. Three-dimensional localization of tracer is thus permitted. The photons are of higher energy than those produced by single photon emitters, contributing in part to PET’s superior resolution (4 to 6 mm) over SPECT. PET and SPECT images can be superimposed (i.e., co-registered) over structural MRI images, enhancing the localization of functional findings to specific brain structures.

PET tracers are based on oxygen 15, nitrogen 13, carbon 11, or fluorine 13, and have much shorter half-lives than SPECT tracers. Consequently, PET tracers must generally be compounded shortly before the study. This requires an on-site cyclotron and radiopharmaceutical laboratory as well as an on-site radiochemist and other technically skilled support staff. These factors contribute to the high capital cost and per-study cost of PET and explains the relatively small number of PET-equipped hospitals or labs around the country. Centers which have PET capability for research have been able to utilize it clinically in a number of roles. However, PET has been utilized less in psychiatry than in neurology, neurosurgery, and other fields of medicine.

PET has a broader scope of application than does SPECT, and can provide direct data about cerebral metabolism in addition to rCBF and receptor density. 18F-fluorodeoxyglucose PET is used to study cerebral glucose metabolic rates (Figure 2). Additionally, the relatively “real time” images obtained with PET offer a greater flexibility in performing studies on brain function while the subject is at various degrees of rest or cognitive activation. The relative intracellular stability of SPECT tracers does not provide such flexibility. A comparison of PET and SPECT is summarized in Table 1.

**CLINICAL APPLICATIONS IN PSYCHIATRY**

Two questions face the psychiatrist in regard to clinical neuroimaging. First, is a neuroimaging study indicated in a given clinical circumstance? Secondly, if imaging is indicated, which technique would provide the most clinically useful information? The answers to these questions are dynamic—determined by the state of psychiatric sciences both in terms of the imaging methods available and the degree to which research findings have been translated into clinically practical treatment strategies. The clinical utility of any diagnostic test is the “bottom line” in deciding whether to order the test. For example, even if an imaging tool has consistently demonstrated a specific disease-related abnormality, that study will remain clinically unnecessary unless the imaging information leads to a specific diagnosis, and even then, only if that diagnosis leads to specific management strategies. The costs, inconveniences, discomforts, and risks associated with the imaging study must be justified by the likelihood of obtaining information that is important to the patient—that is, guidance toward effective treatment or meaningful diagnostic or prognostic information that
would otherwise be unavailable. Unfortunately, such a standard has not yet been reached for most mental disorders. While imaging research findings continue to fill psychiatric journals, these exciting results have generally not offered sufficient practical use to justify clinical imaging on a large scale.

The most common and justifiable use of clinical imaging in psychiatry remains the same as it has been for many years: to rule out nonpsychiatric causes of mental disturbances. In other words, imaging is most often done to rule out unlikely intracranial pathology (eg, tumor, cerebrovascular event, trauma, malformation) rather than “rule in” a likely primary psychiatric diagnosis based on the demonstration of characteristic findings.

**APPLICATIONS OF STRUCTURAL IMAGING**

**Computed Tomography**

A number of studies have retrospectively reviewed the diagnostic yield of structural neuroimaging in psychiatric patients. McClellan et al\(^\text{10}\) reviewed the findings of all head CTs done on psychiatric inpatients at their hospital over a 3-year period. Patients with previously diagnosed medically or surgically treatable central nervous system (CNS) lesions, and those with focal neurologic deficits or clinical findings highly suggestive of intracranial pathology (eg, seizures, papilledema, intractable headaches) were excluded from the study, leaving only those studies performed for routine screening. Of 261 patients studied, 230 (88.1%) had normal studies. Another 27 (10.4%) had a finding of atrophy, 2 had nonspecific basal ganglia calcifications, 1 had an old lacunar infarct, and 1 had an osteoma. The authors concluded that there was no justification for routine CT scanning of the head as a screening procedure.\(^\text{10}\)

Goodstein\(^\text{11}\) recommended the following general criteria for CT imaging of psychiatric patients in order to increase the diagnostic yield and obtain a justifiable result in terms of costs and benefits:

- Symptoms do not fit a classic pattern (ie, atypical presentation)
- High suspicion of focal brain lesion due to clinical findings
- CT results will affect treatment (ie, not simply satisfy academic curiosity)

**Magnetic Resonance Imaging**

MRI studies have demonstrated structural abnormalities, particularly nonspecific white matter lesions, more commonly than have CT studies. The clinical significance of these findings remains unclear. Interpretation is further complicated by the high incidence of such abnormalities in normal individuals (eg, up to 30% of nondepressed elderly have nonspecific white matter lesions demonstrated by MRI). Nonetheless, the introduction of MRI marked a dramatic advancement in the ability of psychiatrists to identify anatomic brain lesions and has proven to be of great value. Although structural MRI, in its clinical role, remains a

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**Table 1. Comparison of Single Photon Emission Computed Tomography and Positron Emission Tomography in Neuroimaging**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>SPECT</td>
<td>Widely available</td>
<td>Spatial resolution modestly inferior to PET (6–8 mm)</td>
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<tr>
<td></td>
<td>Far less expensive than PET</td>
<td>Cannot directly measure glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>Less technically complex than PET</td>
<td>Intracellular stability of radionuclide precludes certain applications</td>
</tr>
<tr>
<td></td>
<td>Cyclotron not required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uses commercially available radionuclides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intracellular stability of radionuclide facilitates some studies</td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>Superior spatial resolution (4–6 mm)</td>
<td>High expense</td>
</tr>
<tr>
<td></td>
<td>Good imaging of deep structures</td>
<td>On-site cyclotron, radiochemist, laboratory facilities required</td>
</tr>
<tr>
<td></td>
<td>Measures cerebral glucose metabolism in addition to rCBF and receptor density</td>
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</tr>
<tr>
<td></td>
<td>More flexible for cognitive challenge studies</td>
<td></td>
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<tr>
<td></td>
<td>Superior quality of receptor studies</td>
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</tbody>
</table>

*PET = positron emission tomography; rCBF = regional cerebral blood flow; SPECT = single photon emission computed tomography.*
tool relegated to ruling out gross CNS lesions, it performs this task with far greater sensitivity than CT and is preferred in most circumstances in which structural imaging is indicated. An exception is in the detection of acute CNS hemorrhage or trauma. CT remains the study of choice in these cases, although diffusion-weighted MRI may replace CT for these applications in the future. A comparison of CT and MRI is summarized in Table 2.

A study concerning the diagnostic yield of MRI led researchers at McLean Hospital in Belmont, Massachusetts to review all head MRI studies performed on psychiatric inpatients over a 5-year period. In more than 6200 studies, unexpected, potentially treatable findings were found in 99 cases (1.6%). These conditions included (in descending order of frequency): multiple sclerosis, hemorrhage, temporal lobe cyst, tumor, vascular malformation, and hydrocephalus.12

The Massachusetts General Hospital Psychiatry Neuroimaging Group13 developed guidelines for the use of structural imaging studies with psychiatric patients (Table 3). They have determined that if the guidelines are followed, abnormal findings are likely to be found in 10% to 45% of cases, and findings that would lead to specific medical intervention are likely to occur in 1% to 5% of cases.

### Correlation with Treatment Response

A number of studies have attempted to correlate anatomic variants with antipsychotic treatment response. Cazzulo published a report in 196314 in which pneumoencephalography was used to demonstrate that patients with enlarged lateral ventricles responded more poorly to antipsychotic drugs than did patients with normal anatomy. The additional presence of abnormal electroencephalographic (EEG) findings predicted an even worse response. Friedman et al15 performed meta-analysis on 33 studies and concluded that anatomic changes did not significantly predict treatment response across all subject populations. However, several factors that did predict a significant correlation between structural abnormalities and poor treatment response were identified: increased age, increased illness duration, increased duration of antipsychotic treatment, early age of onset, and the presence of marked structural abnormalities (ie, values greater than 2 standard deviations from control values). Structural MRI abnormalities in schizophrenia have been associated with a longer recovery time in patients experiencing their first psychotic episode.16 As the pathophysiology of schizophrenia and other mental disorders are deciphered, predictors such as these will create an expanded role for imaging in basic disease management beyond the role of the organic work-up.

### Table 2. Comparison of Computed Tomography and Magnetic Resonance Imaging in Neuroimaging

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Most widely available imaging tool</td>
<td>Relatively contraindicated in pregnant women and children due to radiation exposure*</td>
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<tr>
<td></td>
<td>Less expensive than MRI</td>
<td>Contrast medium: high rate of adverse reactions (5%), especially in patients with allergies or renal disease</td>
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<tr>
<td></td>
<td>Procedure of choice for acute central nervous system trauma, hemorrhage, or calcified lesions</td>
<td>Transverse images only</td>
</tr>
<tr>
<td></td>
<td>Less patient discomfort than MRI</td>
<td>Limited morphometric use</td>
</tr>
<tr>
<td></td>
<td>Short scan time (5–10 min)</td>
<td>Poor visualization of posterior fossa and deep structures</td>
</tr>
<tr>
<td>MRI*</td>
<td>Superior lesion sensitivity</td>
<td>Availability is limited relative to CT</td>
</tr>
<tr>
<td></td>
<td>Superior gray-white differentiation</td>
<td>Longer scan time (30–50 min)</td>
</tr>
<tr>
<td></td>
<td>No exposure to ionizing radiation</td>
<td>Claustrophobia common</td>
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<tr>
<td></td>
<td>Transverse, coronal, and sagittal images possible</td>
<td>More expensive than CT</td>
</tr>
<tr>
<td></td>
<td>Excellent views of deep structures and posterior fossa</td>
<td>Contraindicated if implanted metal (eg, clips) or certain devices (eg, pacemaker) are present</td>
</tr>
<tr>
<td></td>
<td>Excellent morphometric capabilities</td>
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</table>

*Safety of MRI is not fully established in pregnant women, and should be used judiciously.
APPLICATIONS OF FUNCTIONAL IMAGING

Information from functional imaging is qualitatively distinct from that provided by structural studies. Functional brain scans can provide diagnostically and therapeutically useful information in a narrow—but expanding—assortment of neuropsychiatric disorders.

Differential Diagnosis of Dementia

The differential diagnosis of dementia based on clinical features has always challenged psychiatrists and neurologists. However, unless a reversible cause of dementia was detected (eg, hypothyroidism, vitamin deficiency), little in the way of treatment could be offered, making a precise diagnosis nonessential. However, diagnosis-specific (rather than syndrome-specific) treatment tools are or will soon be available, which will make correct specific diagnoses critical.

Structural imaging methods have played a limited role in this diagnostic challenge. CT and MRI may demonstrate evidence of old or new infarcts, pointing to a diagnosis of multi-infarct dementia. Dementia may be secondary to normal-pressure hydrocephalus, which produces dramatic enlargement in the ventricular system and is well visualized using CT or MRI.

Functional imaging methods currently may be used to make a more precise diagnosis and, in fact, many insurance companies will now pay for these studies as part of a dementia evaluation. Various causes of dementia produce characteristic perfusion defects demonstrable through 99mTc-HMPAO SPECT. Alzheimer’s disease characteristically produces bilateral temporoparietal hypoperfusion, with frontal involvement late in the clinical course. Frontotemporal perfusion defects are seen with the frontal lobe dementias (eg, Pick’s disease). Multi-infarct dementia, as would be predicted, demonstrates a patchy distribution of perfusion defects. Dementias secondary to Huntington’s and Parkinson’s disease, either of which may develop before clinically obvious movement disturbances are noted, are evidenced by caudate abnormalities and diffuse cortical involvement, respectively. Depression, which may present as dementia in elderly patients, shows inconsistencies, ranging from normal findings to diffuse, symmetrical prefrontal cortical abnormalities which improve with treatment.

Localization of Epileptic Foci

Epilepsy, which may have neuropsychiatric consequences, has been widely studied using PET and SPECT, and clinically useful applications of both are in current practice. EEG has good sensitivity for detecting superficial cortical foci if the patient is studied during the seizure. However, the ability of EEG to locate deep subcortical epileptic foci, or to locate foci between ictal events, is limited. SPECT and PET imaging techniques may be used to locate seizure foci in these circumstances. Radiotracer studies typically show ictal hyperperfusion and interictal hypoperfusion at the focus. Rowe et al conclude that postictal SPECT has a positive predictive value for the correct localization of a unilateral focus of 97%. These techniques are also used to delineate the boundaries of involved brain parenchyma in preparation for the surgical management of intractable epilepsy.

Evaluation of Traumatic Brain Injury

Traumatic brain injury commonly causes a wide variety of neuropsychiatric syndromes, often with disabling or even dangerous behavioral or cognitive consequences. In some cases, functional imaging demonstrates superior sensitivity to structural imaging; showing perfusion defects in the absence of abnormal CT or MRI findings. This may be of value in forensic as well as clinical settings.

NEUROIMAGING RESEARCH IN SCHIZOPHRENIA: A REVIEW OF THE LITERATURE

Schizophrenia has been more widely studied using neuroimaging techniques than any other mental disorder.
A brief review of major research findings provides an excellent illustration of the remarkable potential offered by these methods. An exhaustive review of the literature, even in schizophrenia alone, is beyond the scope of this monograph. If the reader wishes to delve further into this literature, excellent comprehensive reviews of structural and functional imaging research findings in schizophrenia are available.

STRUCTURAL BRAIN IMAGING

The demonstration of anatomical brain abnormalities has contributed to the collapse of psychologic causal explanations for schizophrenia over the past 3 decades. A huge body of CT and MRI research literature demonstrates quite conclusively that subtle structural abnormalities are associated with schizophrenia.

Ventricles and Sulci

The most consistent neuroanatomic finding in schizophrenia is that of enlarged cerebral ventricles and sulci relative to normal controls. Johnstone et al first demonstrated this finding using CT. This finding has since been replicated by dozens of investigators on the basis of visual inspection, planimetric or volumetric analysis, or ventricular brain ratio (VBR) calculation, and relatively few studies have yielded negative findings. The MRI literature has generally been consistent with the CT literature regarding ventricular and sulcal enlargement.

Andreasen et al reviewed 49 blinded, controlled CT studies of lateral VBR in schizophrenic subjects and normal controls, with positive results outnumbering negative results by a ratio of approximately 3 to 1. Abnormal VBRs (defined as VBRs greater than 2 standard deviations larger than the control mean) were demonstrated in 5% to 53% of schizophrenic subjects.

Van Horn and McManus conducted a multivariate meta-analysis of 39 studies of ventricular size in schizophrenia that assessed VBR. They found that although there was a significant positive correlation between schizophrenia and VBR, this correlation was smaller than had previously been believed. They concluded that although the presence of increased VBRs in schizophrenics is of great research interest, the difference is too small to have practical diagnostic utility.

The significance of increased VBRs in patients with schizophrenia remains controversial. Some authors have pointed out that although the mean VBR of schizophrenic populations is indeed larger than that of unaffected controls, many schizophrenic subjects have a VBR within—or even below—the normal range. These discrepancies raise the question of whether subtle anatomical findings are an occasional or consistent pathologic correlate of schizophrenia. The remarkably wide, overlapping ranges of values for subjects and controls across all studies seems to make this question unanswerable.

Weinberger’s group at the National Institute of Mental Health conducted an elegant study in which MRIs of 15 monozygotic twin pairs discordant for schizophrenia (ie, one affected and one unaffected twin) were examined, both by visual inspection and by computerized volumetric analysis (Figure 4). Scans were analyzed by investigators who were blinded as to the psychiatric condition of each subject. In 12 of the 15 twin sets, the affected twin was accurately identified by visual comparison of MRI images, even if the ventricles of the affected twin were small. Volumetric measures of lateral and third ventricles were significantly larger in the affected twins, and hippocampal volumes were smaller in affected twins. The authors concluded that if appropriate controls are available (eg, an identical twin), subtle anatomical changes can be detected in most patients with schizophrenia and are probably characteristic of the disease.

Weinberger’s group found no correlation between anatomical measures and age, duration of illness, or extent of exposure to neuroleptic drugs. On the other hand, Garver posited clinically distinguishable schizophrenic subtypes, one of which is characterized neuroanatomically by progressive atrophic changes (ie, relative brain enlargement during acute psychotic exacerbation followed by incremental shrinkage with each recovery). Other subtypes had relatively normal ventricular and sulcal anatomy.

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**Figure 4.** Paired MRI scans from a set of monozygotic twins discordant for schizophrenia. Note that the affected twin demonstrates greater ventricular size than does the unaffected twin. (Reprinted with permission from Weinberger DR. From neuropathy to neurodevelopment. Lancet 1995;346(8974):552–7. Copyright The Lancet Ltd.)
Regional Structural Abnormalities in Schizophrenia

Until the advent of MRI, precise in vivo anatomic and morphometric studies in schizophrenia, beyond the study of large structures such as lateral ventricles, were not technically feasible. The advantages of MRI promoted a major advance in the neuroanatomic study of schizophrenia (Table 2). These efforts have focused predominantly on the temporal and frontal lobes, thalamus, and the basal ganglia.20,21 Although many subtle abnormalities have been demonstrated, none yet appear to be pathognomonic for schizophrenia. Findings are inconsistent across studies, although varying methodologies and heterogenous study populations almost guarantee mixed results that cannot be completely reconciled at this time.

Temporal lobe abnormalities of many types have been widely reported, including those involving general reduction in temporal lobe volume, decreased volume of discrete structures, and focal asymmetries. Total temporal lobe volume appears to be reduced by approximately 8% in patients with schizophrenia, with similar reductions in volume of the amygdala and hippocampus. Volume loss and abnormal asymmetry of the transverse temporal gyrus and superior temporal gyrus have been described as well. The latter have been correlated with thought disorder29 and auditory hallucinations.30 Temporal lobe asymmetries have also been associated with negative symptom subgroups.32 Many studies have found temporal lobe abnormalities to be more prominent in the left hemisphere.

Studies of the frontal lobes have focused on the prefrontal cortex and results are highly mixed. Total frontal lobe volume losses of 6% to 8%, prefrontal total and white matter volume losses, and selective gray matter losses have all been reported.

Andreasen et al33 and Buchsbaum et al34 have reported decreased thalamus volume, the latter study also using PET to demonstrate decreased thalamic metabolism. The authors speculate that these findings may relate to the sensory information filtering difficulties seen in patients with schizophrenia.

Enlargement of the caudate has been reported, although 2 studies have demonstrated a reduction in caudate size after patients were switched from traditional neuroleptics to clozapine.35,36 Whether anatomic abnormality of the caudate is associated with the pathophysiology of schizophrenia or is merely a treatment effect remains to be seen.

An exciting application of DTI, a relatively new imaging method, has been the demonstration of abnormal white matter organization occurring diffusely throughout the brain1 and in the corpus callosum37 of schizophrenics. The unequaled ability of DTI to study white matter architecture offers extraordinary possibilities in schizophrenia research.

FUNCTIONAL BRAIN IMAGING

All of the functional imaging techniques described in earlier sections of this monograph have been applied to schizophrenia research. As with structural imaging, many inconsistencies exist in the literature of functional imaging in schizophrenia. However, common findings have emerged that have dramatically expanded our understanding of schizophrenia.

Frontal Lobe Studies

Clinical evidence, including neuropsychological and clinical findings of similarities between people with frontal lobe injuries and those with schizophrenia, led investigators to study frontal lobe function in schizophrenia. Hypoactivity of the frontal lobes (particularly the dorsolateral prefrontal cortex), also known as “hypofrontality,” is the most characteristic functional imaging finding associated with schizophrenia. When subjects are studied at rest, generally using 18F-fluorodeoxyglucose PET or 99mTc-HMPAO SPECT, this abnormality has been weak and inconclusive.35 Patients with chronic disease and prominent negative symptoms are more apt to show hypofrontality at rest, but even in this setting results are inconsistent. Part of the inability to consistently demonstrate abnormal frontal lobe function at rest may lie with the uncontrollable nature of the internal milieu when subjects are mentally unfocused.

Hypofrontality is a robust finding when schizophrenic subjects are challenged with a prefrontally related task, such as the Wisconsin Card Sorting Test. This finding has been replicated repeatedly, irrespective of the phase of the illness or medication status. Hypofrontality has been demonstrated during psychotic exacerbation and during relative remission, on antipsychotic medication or off. Studies with negative results do exist, however, pointing to either methodological problems or the possibility that certain schizophrenic patient populations may have different underlying pathophysiology. Berman and Weinberger mount a balanced and convincing argument in favor of the fundamental nature of this deficit in schizophrenia,22 in part based upon the rCBF results derived from their study of monozygotic twins, both discordant and concordant for schizophrenia.39,40 In that study, as with the companion study of anatomic findings mentioned earlier,38 there was a wide range of data among the subjects. However, in almost all cases, frontal activation was higher in the unaffected twin than in the schizophrenic twin (Figure 3, page 4).
Other Functional Imaging Studies

Temporal lobe abnormalities have been less consistently demonstrated than hypofrontality. The most commonly reported temporal abnormality has been overactivity, although some studies have shown normal findings or even temporal hypoactivity. Cingulate underactivation and cortical-striatal-thalamic circuit abnormalities have been described as well. Investigations of the basal ganglia have been quite mixed, and neuroleptic medication is an obvious potential confounder.

fMRI has great potential to further this body of research, possessing certain advantages over radiotracer methods. For example, repeated studies in a short period of time may allow for more complex experimental designs. The greater sensitivity of fMRI to movement-related artifact and other uncontrollable subject factors remains limiting.

Researchers have attempted to make clinicopathologic correlations based on the above data and general knowledge of functional neuroanatomy. For example, Liddle et al proposed that psychomotor poverty may be associated with dorsolateral prefrontal cortex hypoactivation, disorganization with increased activity in the right anterior cingulate gyrus, and reality distortion with medial temporal lobe hyperactivation.

MRS has been widely used to study neurochemical abnormalities in patients with schizophrenia. 31P-MRS studies reveal abnormal phosphate concentrations in the prefrontal cortex, including a reduction in membrane building blocks (ie, phosphomonoesters), an increase in membrane products (ie, phosphodiester), and abnormal utilization of high-energy phosphates (ie, ATP). These findings indicate abnormal membrane phospholipid metabolism in the prefrontal cortex; this disturbance has not been observed in the temporal lobes. The authors speculate that this represents a primary pathophysiologic event and may be related to an exaggeration of the normal synaptic pruning process that occurs during early adolescence.

Another application of PET and SPECT in schizophrenia research is in receptor studies. Dopamine receptors, especially D2 receptors, have been most widely studied, although other receptors (eg, serotonin, glutamate) are under investigation as well. A number of methodologic limitations have contributed to inconclusive results; improved ligands and methods may yield more useful studies in the near future.

CONCLUSION

Neuroimaging has grown from a field with fairly narrow clinical and research applications in psychiatry to a veritable fountain of knowledge about schizophrenia and many other mental disorders. Although psychiatric neuroimaging is still most relevant to research, the development of clinical applications is inevitable. The efforts of clinicians and trainees to meet the educational challenge required to use these tools appropriately will benefit patients immeasurably.

REFERENCES


