Brain Magnetic Resonance Imaging: Approaches for Investigating Schizophrenia

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Abstract

Magnetic resonance imaging (MRI) offers the potential for identifying, in vivo, specific brain abnormalities associated with schizophrenia. The detection of small morphological differences in areas such as the prefrontal cortex, limbic structures, and basal ganglia requires attention to a number of technical and methodological details. The effects of age, height, sex, head size, and overall tissue loss are of particular concern and are discussed. MRI acquisition and processing techniques for improving gray/white tissue contrast and image resolution are described, as are techniques for quantitative, volumetric measurement of localized regions of interest and specific brain structures as well as of the brain as a whole. Techniques for evaluating frontal lobes, temporal lobes, and basal ganglia integrity are reviewed, and recent observations on these brain regions in patients with schizophrenia are described.

One conclusion that can be drawn from the large number of published computed tomographic (CT) studies of schizophrenic patients is that the structural brain abnormalities of schizophrenia are elusive. While clinical, biochemical, and neuropathological data have implicated specific neuroanatomical regions such as the prefrontal cortex (Weinberger 1987), the limbic structures (e.g., Flor-Henry 1969; Stevens 1973), and the basal ganglia (e.g., Carlsson 1988) in the pathophysiology and etiology of this disorder, CT studies have provided little evidence to support a specific neuroanatomical pathophysiology. The superior resolution and greater flexibility of magnetic resonance imaging (MRI) have raised expectations that this modality will provide a more powerful tool for uncovering regionally specific brain abnormalities associated with schizophrenia. However, several important methodological and technical issues need to be addressed before these expectations can be met.

It has been approximately 15 years (Johnstone et al. 1976) since psychiatrists first used CT images for in vivo investigation of the brains of psychiatric patients. During this time, tremendous improvements have occurred in the capability of CT technology for producing higher quality images and minimizing artifacts, as well as for displaying, analyzing, and quantifying the numerical data underlying the filmed or printed brain image. Analyses of CT images were initially performed using the X-ray film, with qualitative estimates, rating scales, and linear or area measurements, typically confined to one or two sections. Thus, very limited data were used to estimate the size of three-dimensional structures such as the lateral ventricles. With access to image processing software and hardware, investigators are now able to analyze not just the filmed or printed image, but rather the matrix of numbers underlying such images. Computerized analysis enables classification of pixels as tissue or cerebrospinal fluid (CSF), and integration of information over multiple sections, to produce volumetric measures of proportions of CSF and tissue in anatomically defined regions of interest. With MRI, the approach can be

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extended to allow differentiating gray matter from white matter. In addition, MRI offers greater opportunities for characterizing tissue quality and delineating specific substructures. In this article, we describe techniques for the in vivo acquisition and computerized analysis of volumetric measures of neuroanatomical regions of interest and specific brain structures using MRI.

Methodology and Study Design

The elusiveness of CT findings in schizophrenia may be attributed partially to the small size of the effect and partially to the failure to control adequately for other variables affecting brain morphology. Brain morphology is strongly affected by several variables that are relatively independent of schizophrenia (such as age, sex, and height), as well as others that might be associated with schizophrenia, such as alcohol consumption, educational status, and handedness. Whether the imaging modality is CT or MRI, these variables must be taken into consideration and appropriate controls implemented so that inferences about schizophrenic pathophysiology can be properly drawn.

Sources of Normative Data and Other Comparison Groups

There has been lively discussion about whether the use of medical patients with “normal” scans rather than healthy community members as controls influences the outcome of CT studies of schizophrenia (Smith and Iacono 1986; Raz et al. 1988; Smith et al. 1988). The use of scans from patients referred for a CT evaluation but read as “normal” as controls for schizophrenic patients has been quite popular and motivated by two considerations: reluctance to expose healthy subjects to unwarranted radiation, and the convenience and economy of using readily available data. While MRI obviates the first consideration, the second is still very relevant. Smith and Iacono (1986) compared several CT studies of the ventricle-brain ratio (VBR) and concluded that outcome regarding enlarged VBR in schizophrenic patients was more a function of control values than of patient values. A prospective comparison of VBRs from 30 schizophrenic patients, 30 normal control subjects, and 30 medical control subjects revealed no significant difference between schizophrenic patients and normal control subjects, but a significant difference between schizophrenic patients and medical control subjects (Smith et al. 1988).

In a critique of the Smith and Iacono (1986) analysis, Raz et al. (1988) compared effect size between 14 studies of VBR in schizophrenia which used normal control subjects and 27 studies which used medical, neurological, or nonpsychotic patients as controls and found no significant difference. While effect size rather than dichotomous outcome is indeed a better statistic for this type of comparison, it should be noted that both analyses were limited to published studies and thus probably underestimate negative results. Regardless of study outcome, medical patients with “normal” scans are less desirable as controls for schizophrenic patients than healthy community members, because the former inevitably underrepresent the variability existing across apparently healthy subjects. MRI studies should use healthy community members rather than medical patients to provide normative reference data. In addition to comparisons with normative data, comparisons between schizophrenic patients and other pathological groups are also necessary, especially if claims of diagnostic specificity for a finding are to be made. The choice of a comparison group depends on the hypothesis being tested, and might include patients with well-documented abnormalities in the anatomical region(s) being investigated in schizophrenic patients. For example, patients with Parkinson’s disease are particularly relevant for studies investigating the role of basal ganglia structures in schizophrenia; patients with temporal lobe epilepsy or Alzheimer’s disease for studies investigating the role of limbic structures in schizophrenia; patients with alcoholism for studies investigating the role of frontal lobe structures in schizophrenia; and patients with affective disorders for studies investigating alterations in hemispheric symmetry.

The use of patients with disorders that typically occur at an older age than schizophrenia poses specific problems, which are discussed in greater detail below.

Age Effects. Morphological brain differences seen in cross-sectional studies of healthy community members spanning the adult age range far exceed any differences reported between schizophrenic patients and control subjects. Observations of a marked acceleration of age-related changes in ventricular and sulcal size on CT scans of subjects over the age of 60 years (e.g., Zatz et al. 1982) have tended to divert attention from changes
occurring before this age. In our CT studies of volumetric measures of ventricular and sulcal fluid, this model was consistent with small but significant changes occurring from the twenties, with age accounting for 30 to 50 percent of the variance over the adult age range, 20 to 80 years (Pfefferbaum et al. 1986). More recently, in an MRI study of schizophrenic and control subjects (aged 23 to 45 years), we found that among the controls, age accounted for approximately 20 percent of the variance in cortical sulcal volume and 40-60 percent of the variance in gray matter volumes (Zipursky et al. 1989). While schizophrenia is typically a disease of young adulthood, it is crucial to take normal aging effects into account before comparing schizophrenic patients with control subjects, because small but significant group differences may be obscured by the normal change that occurs across the age range sampled.

A number of approaches have been used to control for the effects of age. The popular "age-matched" group design avoids rather than investigates the influence of age. Individual age-matching and pair-wise comparison can have the disadvantage of reducing statistical power, depending on the amount of variance accounted for by age, not to mention the constraints placed on control recruitment. For either approach, it is necessary to determine whether age contributes significantly to any variance found and, if necessary, to remove this influence, being careful to do so in a way that does not exclude important information. We have found the age-regression model to be a particularly powerful and flexible approach for dealing with age effects in CT studies (Pfefferbaum et al. 1986, 1988a, 1988b). To apply this model, data from healthy community members at each decade of the adult age range are regressed on age to derive age norms (mean and standard error of the regression at each age). Data for individual patients can then be expressed as Z-scores (the difference between their data and the mean for their age, divided by the standard error of the regression for their age) to allow analysis of pathological changes independent of age effects. Z-scores have the added advantage of allowing comparisons between individuals and groups of different ages.

**Height and Sex.** On average, the heads and brains of women are smaller than those of men, attributable to the fact than women, on average, are smaller (i.e., are shorter and weigh less) than men (Gould 1981). Whether there are meaningful differences in brain size after accounting for body size is not yet agreed upon, in large part because there is no generally acceptable means of fully correcting brain size for body size. What is clear (and will be described further below) is that it can be expected that women will have smaller brains before and perhaps after correcting for height, and one can therefore expect most brain structures to be proportionately smaller in women. It is critical, in a study including both sexes, that this source of variation in brain size across subjects be taken into account. Furthermore, even within a single-sex study, differences in height can contribute to differences in brain size (Gould 1981).

If a brain is small because of agenesis or atrophic processes, it is reasonable to assume some functional consequence. It is important to note, however, that the size of a healthy brain, per se, has little predictive value regarding function. For example, Hatazawa et al. (1987) demonstrated that the regional metabolic activity of the brain is inversely proportional to brain size and total metabolic activity is similar across individuals, independent of the size of the brain.

**Alcohol and Drug Use.** The extent to which alcohol and drug use may contribute to the brain differences found between schizophrenic patients and control subjects is not clear. In a population of alcoholic patients, we found a relationship between the extent to which patients deviated from age norms for ventricular and sulcal enlargement and their lifetime alcohol consumption (Pfefferbaum et al. 1988a), suggesting that the high levels of alcohol consumption in this group played a role in the diffuse morphometric changes observed. While most studies of brain structure in schizophrenia screen alcohol- and drug-dependent patients from their sample, the contribution of alcohol or drug consumption in schizophrenic patients, albeit at lower levels than in alcoholic patients, is rarely addressed (see Turner et al. [1986] for an exception). An explicit investigation of alcohol consumption as a continuous quantitative variable is needed to resolve the issue.

**Handedness Differences.** There has long been interest in the possibility that a higher incidence of left-handedness and other manifestations of altered lateralization of brain function in schizophrenic patients compared to the population at large may be a clue to potential etiological subtyping (Wexler 1980; Merrin 1981). However, the extent to which
differences in brain anatomy in general, or cerebral asymmetries in particular, can be attributed to handedness differences and the importance of controlling for this variable in MRI studies of schizophrenia are not yet clear. A volumetric CT analysis of hemispheric asymmetry was consistent with the notion that left-handed people may have significant differences in brain hemispheric symmetry compared to right-handed people (Zipursky et al. 1990). As with the variables of age and alcohol consumption discussed above, continuous quantitative (rather than dichotomized) measures are probably needed for a sensitive investigation of the issue. A continuous measure of handedness, such as the Crovitz scale (Crovitz and Zener 1962) would be a valuable addition to MRI brain scan studies, particularly when hypotheses regarding lateralized differences in brain structure (e.g., that proposed by Crow et al. 1989) are being investigated.

**Education and Socioeconomic Status.** Some recent CT and MRI studies have noted a relationship between social class or educational status and brain structural variables (Pearson et al. 1989, Andreasen et al. 1990), and advocate matching between patients and controls on such variables. This type of matching is particularly problematic, since both of these variables are profoundly influenced by the disease itself. For example, if a sample of schizophrenic patients is found to have a very low average level of education, selecting controls to match this level will possibly draw from a population with other subtle forms of brain dysfunction. At the very least, assessment of socioeconomic class should be based on class of origin. Assessment of educational status might better be served by a general measure of premorbid intelligence, such as the National Adult Reading Test (NART; Nelson 1982), than by years of schooling completed. The most parsimonious explanation for any apparent relationships between brain size and education and socioeconomic class is that such differences are mediated by class differences in stature and associated head size (Zipursky et al., in press). A variety of techniques have been adopted to enable comparison of brain morphometric variables across individuals with varying head sizes, and these are discussed in greater detail below.

**Heterogeneity Within Schizophrenic Populations.** Failure to replicate studies or to find differences between schizophrenic patients and control subjects, however carefully matched, may be attributable to heterogeneity among the sample of schizophrenic patients, all of whom meet formal diagnostic criteria. However, though variables such as age of onset, length of illness, drug responsiveness, symptom pattern, clinical subtype, presence of tardive dyskinesia, presence of neurological abnormalities, family history of schizophrenia, and season of birth have all been considered to explain differences in the ventricular enlargement observed on CT (Sheraton and Weinberger 1986), no clear pattern of association between clinical and brain variables has emerged. Whether the more specific aspects of brain morphology measurable on MR images will reveal a neuroanatomical basis for the observed heterogeneity of schizophrenia remains to be determined. At this time, it is not clear which clinical features are more likely to be associated with specific structural brain changes. All schizophrenic subgroups will therefore need to be investigated.

**Magnetic Resonance Imaging**

MRI has proved to be the superior modality for neuroanatomical imaging. In addition to its lack of ionizing radiation, permitting repeat scans and acquisition of normative data from healthy subjects, MRI provides superior tissue contrast, high resolution, and a flexible plane of acquisition. These advantages can be put to good use in the study of schizophrenia. For example, while CT studies have documented larger ventricles and sulci in schizophrenic patients than controls, they have not allowed a determination of whether the greater amount of CSF is preferentially at the expense of white matter or gray matter. Furthermore, CT images are affected by spectral shift artifact which distorts signals at the skull boundary, particularly at higher and lower sections. This has limited the accuracy with which outer brain margins can be identified in the apical cortex and the temporal lobes. Finally, the identification and measurement of specific subcortical structures such as those of the limbic system and basal ganglia are limited on CT by poor in-plane resolution and volume averaging, usually over 8- to 10-mm-thick sections.

**Image Acquisition**

Introduction to the Physics of MRI. Several excellent descriptions of the principles of MRI are available in the literature (Morris 1986; Oldendorf and Oldendorf 1988), to which the
reader is referred for more indepth treatment. Atomic nuclei with an odd number of protons or neutrons behave as spinning tops with an electrical charge, and thus they produce a magnetic field, oriented along the axis of rotation of the nucleus. These atomic species possess a magnetic moment and are said to exhibit nuclear magnetism. When these nuclei are exposed to a magnetic field, they align either parallel or antiparallel with the field—that is, either in a high or low energy state—with a slight preponderance in the parallel or low energy state. Each atomic species exhibiting nuclear magnetism has a unique spin or rotational frequency that is a function of the strength of the external magnetic field to which it is exposed. MRI is most often applied to hydrogen atoms (protons), the most abundant element in biological tissue.

When further exposed to electromagnetic radiation at the appropriate frequency, the spin system absorbs energy, and a resonance condition is created. When pulsed with electromagnetic radiation (e.g., radiofrequency [RF] waves) at the resonant frequency (the Larmor frequency), some of the nuclei are moved out of alignment with the static magnetic field (i.e., out of the parallel low energy state into a higher energy state). When the radio waves are turned off, the nuclei return to equilibrium, and the amount of energy given off provides a measure of the number of nuclei stimulated (i.e., the proton density [PD] for hydrogen MRI). T1 is the exponential time constant which describes the return to equilibrium and realignment with the static magnetic field (spin-lattice relaxation time). After a group of nuclei absorb energy at their resonant frequency, they will oscillate in phase briefly. They soon begin to oscillate out of phase as a result of local fluctuations in the magnetic field caused by movement of other oscillating nuclei. When the nuclei oscillate out of phase (i.e., dephase) the signals cancel out. T2 is the exponential time constant describing signal loss due to this dephasing in the transverse plane (spin-spin relaxation time). The intensity of any voxel in the resultant image can be described as a function of the three parameters (T1, T2, PD) and the timing of RF pulses (the repetition rate [TR]) and signal acquisition time (echo time [TE]). The application of additional magnetic gradients in the three orthogonal axes provides the spatial encoding necessary for expressing this information as MR images.

Figure 1. Change in signal intensity of CSF, gray matter, and white matter over different TEs with a T2-weighted sequence (TR = 1,000 ms)

CSF = cerebrospinal fluid, TE = echo time, T2 = exponential time constant describing signal loss due to dephasing in transverse plane (spin-spin) relaxation time, TR = repetition rate.
For example, midsagittal images provide a more reproducible guide for positioning of the patient in the scanner, as it is in CT, but can be determined by programming the magnetic gradients. Conventional orientations are in the axial, sagittal, and coronal planes. Each orientation provides a different view of the brain and is the optimal orientation for visualizing different structures. For example, midsagittal images provide clear delineation of the prefrontal cortex and the corpus callosum, coronal images provide views of the hippocampus and limbic structures over several sections, and axial images provide a good view of basal ganglial structures such as the putamen, globus pallidus, caudate, and substantia nigra. To compare neuroanatomical structures across subjects, however, it is critical that the images be acquired in a standardized orientation. External landmarks, such as the canthomeatal line, are not optimal for this task, as considerable variation may exist in the relationship of such external landmarks to internal brain structures (Talairach et al. 1987). Internal landmarks provide a more reproducible guide for image orientation. The anterior and posterior commissures provide two such internal landmarks, and serve to define a plane passing through them, perpendicular to the sagittal plane (Vanier et al. 1987), which corresponds to the plane used in some anatomical atlases (Talairach and Szikla 1967). Once defined, this plane can be used to standardize both coronal (perpendicular) and axial (parallel) imaging orientations. To implement this technique, a sagittal image must first be acquired, on which the anterior and posterior commissures are identified and the plane defined. Axial and coronal images can then be acquired at orientations parallel and perpendicular to this plane (figure 2).

For studies where asymmetry of brain structures is of interest, the correct alignment of the subject's head with regard to planes of acquisition is of critical importance. On CT scans, where the plane of image acquisition is defined by the position of the patient in the scanner, tilting of the head can produce artifactual asymmetries. With MR, a bias in the plane of acquisition can also occur, even with careful attention to correct alignment of acquisition plane (Zipursky et al. 1990).

Image Resolution, Signal to Noise, and Section Thickness. Image resolution is affected both by in-plane resolution and by section thickness. An in-plane resolution of 1 mm means that each pixel in the image matrix represents 1 mm². However the 5-mm section, typical of many MRI protocols, means that each image data point (voxel) represents the average of 5 mm³. To optimize quantitative volumetric measurements, one wants high in-plane resolution and as thin sections as possible. However, technical factors such as gradient strength and the amount of RF energy used to excite the object limit the thinness effectively available. In addition, because there is less material producing the signal in a thin section, signal-to-noise ratio is reduced. Thin sections also require longer scanning time to encompass an equivalent volume of the brain, with attendant disadvantages for scanning restless psychiatric patients.

Section thickness using the standard selective excitation methods is generally limited to 3 mm because of RF power and gradient strength limitation. Section profiles are not perfectly rectangular but have broad shoulders that may extend each edge by as much as 25 percent. If adjacent sections are too close to each other, their profiles can overlap, resulting in a mixing of signals from one section into another, an artifact called "cross-talk." The most common way to avoid cross-talk is to leave a gap between sections. In a protocol acquiring sections representing...
Figure 2. Mid-sagittal image with arrows indicating location of the anterior commissure (AC) and posterior commissure (PC). A plane passing through the AC and PC, and perpendicular to the sagittal plane, determines the neuroanatomic reference plane. Reprinted, with permission, from Lim et al. (1990).
5.0-mm-thick sections of brain, a 2.5-mm gap is typically left between sections (or a 1.0-mm gap between 3.0-mm sections). This means that up to 33 percent of the portion of the brain being imaged is excluded from the data set. Such an omission may be acceptable for global estimates of volumes of CSF, white matter, and gray matter over broadly defined neuroanatomical regions, but significantly reduces the accuracy with which the volume of small specific structures can be measured. An alternative technique, that allows collection of data from directly adjacent sections is section interleaving. The region to be imaged is divided into adjacent sections, but the scan is accomplished in two passes. On the first pass, data are collected from the first, third, fifth sections, etc. On the second pass, data are collected from the intervening second, fourth, sixth sections, etc. The disadvantage is that the imaging time is doubled.

Artifact Minimization. MR images are susceptible to various types of artifact; some types can be minimized during image acquisition (e.g., cross-talk noted above), and others can only be remedied during data analysis. Physiological sources of artifact are pulsation of blood and CSF through regions of the brain being imaged. The limbic system is particularly vulnerable to this artifact because of its proximity to the ventricular system and the carotid arteries. Cardiac-gating (Enzmann et al. 1987) and flow-compensated pulse sequences (Quencer et al. 1988) can help reduce these sources of movement artifact, as is illustrated in figure 3, which shows images collected without and with flow compensation and cardiac gating. However, they are not without cost. Because more gradients are used, the minimum TE is lengthened and the maximum number of slices that can be acquired is reduced.

Calibration Using Quality-Assurance Phantom. The accuracy and reproducibility of image data are directly related to the stability of the imaging hardware, especially the magnetic field gradient systems, the main magnetic field, and the RF pulse system. In a recent study, we monitored image quality by scanning the manufacturer’s quality assurance phantom in three orthogonal planes on every scan day. We measured four distance markers in each of the four planes and found that the standard deviation of the linear measurement amounted to only 0.19 percent in our scanner (Lim et al. 1990). Nonetheless, we recommend doing this routinely to provide a standard against which any image data appearing spatially aberrant or distorted can be checked.

Imaging Time. A recurring theme in any discussion of MRI data acquisition for clinical studies is the constant tradeoff an investigator must make between resolution of the image and time of the subject in the scanner. Optimal image acquisition parameters for specific studies need to be determined empirically and will vary depending on the structure being imaged and the clinical context.

Figure 3. Effect of artifact reduction techniques on temporal lobe
characteristics of the subjects being studied. Image acquisition time has become a major concern in designing an MRI study. If images are acquired in more than one orientation, thin sections are interleaved, and cardiac gating and flow compensation techniques employed, the entire acquisition session can easily exceed 1 hour. Reductions in scanning time may be at the cost of poorer image resolution and contrast. Even with cooperative and relaxed patients, involuntary head movements during a lengthy scan session can be a problem. Head restraints provide one solution (Evans et al. 1988). A complementary approach, adopted by some research groups, involves administering a sedative hypnotic, adequate to calm the patient or put him to sleep.

Image Analysis

General Considerations in Image Analysis. Interpretation of structural brain-imaging studies is not only affected by the clinical design of the study and the quality of the images collected but also by the approach to measurement adopted and the criteria used to define areas of interest. MR images may be analyzed in different forms. Measurements can be done on radiographs, on tracings of overhead projections of radiographs, at the scanning console, from photographs of the images, or from computer consoles to which the original digital image data have been transferred. Use of radiographic films is limited by the window settings chosen at the time the films are made (Zatz and Jernigan 1983) and may affect the extent to which partially volumed structures can be demarcated. The greatest flexibility is afforded by systems that allow the digital data to be transferred directly to a computer so that images can be processed in a consistent and reliable manner. An important principle of brain morphometrics is that any particular part of the brain should not be viewed in isolation, but compared with other parts or regions.

"Blindness" to Group in Scan Assessment. Assessments based on rating scales, rankings, or even manual planimetry or linear measurements involve considerable subjective judgment, particularly if images are of poor resolution or have much volume averaging. Most computerized quantitative image-processing systems require that an investigator manually establish a threshold differentiating CSF from tissue or identify specific neuroanatomical boundaries. These tasks should be performed without knowledge of the diagnostic group to which the scan belongs. This is best accomplished by masking all identifying information from the image and ensuring a good mix of cases from all groups being investigated. For asymmetry studies, "blindness" to left and right can be accomplished by randomly reversing left or right orientation on film or console.

Volumetric vs. Area Measures. The size of brain structures can be estimated using linear, area, or volumetric measurements. In the CT literature on ventriculomegaly in schizophrenia, planimetric (area) measures have been used most commonly, applied to one or two sections where the lateral ventricles were most extensive. This approach has the merit of being accessible to investigators without computerized image-processing facilities, but it sacrifices information about the dimensionality and anatomical structure of this complex CSF-filled space. While it has been shown that linear and planimetric measures of the lateral ventricles from CT scans are highly correlated with volumetric measures (Zatz and Jernigan 1983; Reveley 1985; Raz et al. 1987), some studies have demonstrated the superior sensitivity of volumetric over area measures (Gado et al. 1982; Raz et al. 1987) in detecting small group differences—perhaps because random measurement errors are more likely to cancel each other out in volumetric measures, leading to greater reliability and validity of the measure (Raz et al. 1987). With the advent of MRI, in which specific neuroanatomical structures appear in great detail over numerous thin consecutive sections, the selection of single sections for linear or area measurements can be arbitrary and inconsistent across subjects, and the merits of volumetric measurement are even more apparent. Use of thin sections minimizes the error of estimating volume over multiple sections (Filipek et al. 1989).

Volumetric measurements are particularly important if the left-right asymmetry of structures is to be investigated (Zipursky et al. 1990). Relatively small brain structures such as the amygdala may not be located in a perfectly parallel position relative to one another in each hemisphere. The section in which a given structure appears largest on one side of the brain may not be the section in which the contralateral structure also appears largest. This applies to both axial and coronal sections. For irregularly shaped brain structures, there is little reason to expect that the left/right asym-
metry measured on a given section is representative of overall asymmetry of that structure. A volumetric measurement of the structure in each hemisphere is needed for the reliable determination of lateralized size differences. Single section measurements of structural asymmetry are also much more vulnerable to the effects of tilting of the head or misalignment of the head in the scanner. It is possible to determine the degree of angulation of a head in the scanner to assess whether asymmetry is real or artifactual (see Zipursky et al. 1990).

Accounting for Head Size. Given the existence of nonspecific differences in head size between individuals, it is important to demonstrate that any difference in the size of specific brain structures is independent of such differences. Ratio measures, such as the VBR, take head size into account, as do analyses of covariance (Zatz and Jennigan 1983). Now that a number of investigators have described reduced intracranial volume in patients with schizophrenia (Andreasen et al. 1986; Pearson et al. 1989; Zipursky et al., in press), the issue has become more complicated. If schizophrenia, which is hypothesized to affect the brain before it has completed its growth (e.g., age 15-20 [Dekaban and Sadowsky 1978]), does indeed lead to diminished brain size and, as a result, diminished skull size, the correction of all structural brain measures for intracranial volume could obscure pathologically relevant information. The possibility of significant differences in intracranial volume between schizophrenic patients and control subjects should always be tested. Once this has been done, the critical question is still whether particular brain structures are disproportionately reduced in schizophrenia, a question that will require controlling for differences in intracranial volume.

Accounting for Generalized Tissue Loss. A similar consideration exists for taking into account generalized morphological differences in the brains of schizophrenic patients compared to control subjects. If after controlling for the effect of intracranial volume, one is able to show that there is a significant reduction in the size of a particular brain area, it may still be the case that the reduction in size of the specific brain region is proportional to the generalized reduction in tissue volume. Our data suggest that schizophrenia is characterized by generalized ventricular and cortical sulcal enlargement (Pfefferbaum et al. 1988b), as well as a diffuse loss of gray matter (Zipursky et al. 1989). Therefore, it is necessary to demonstrate a disproportionate loss of localized tissue before concluding that a specific brain structure is uniquely affected by the disease. For example, before being able to interpret the MRI findings of reduced gray matter volume in the hippocampus (DeLisi et al. 1988; Suddath et al. 1989) and in the temporal lobe (Suddath et al. 1989), it is critical to determine whether similar gray matter reduction exists in other cortical areas.

Our working hypothesis regarding these generalized structural abnormalities of schizophrenia is that if the process causing brain structural abnormalities begins before and continues after final maturation of the brain is achieved, it will result in some reduction in intracranial volume with attendant reduction in head size as well as reduction in brain tissue and increase in CSF. If this process begins after full brain size is achieved, head size will not be affected, but there will be a reduction of brain tissue and increase of CSF. Thus, the increase in CSF seen in schizophrenia, especially in cortical sulci, represents tissue loss from the previously attained maximal tissue volume.

Specific Procedures. Brain morphometric assessment might include the following components: image-artifact minimization; assessment of total intracranial volume; differentiation of CSF, white matter, and gray matter; identification of broadly defined, anatomically meaningful regions of interest; and delineation of specific small neuroanatomical structures. We have recently developed approaches to each of these components, which are described below.

Preprocessing. The first step is to identify all the pixels which represent brain and CSF, so that intracranial size can be estimated. While bone is readily identifiable on CT because of its characteristic large signal, it can easily be confused with CSF and tissue in many MRI acquisition sequences. We use late-echo images from a spin-echo sequence in which CSF has a long T2 and thus a higher signal than bone, providing the sharp transition necessary for automatically identifying skull margins. Once identified, pixels representing skull and scalp can be stripped away from the image, and the information about skull boundary locations transferred to images obtained with sequence parameters on which CSF/bone contrast is not available (Lim and Pfefferbaum 1989).

The next step is to differentiate pixels representing CSF from those
representing white matter and gray matter. Attempts to differentiate tissue from CSF or white matter from gray matter by setting a single threshold for an entire brain section are hampered by the influence of nonuniform RF coil to transmit and receive characteristics on signal intensity. This RF inhomogeneity can introduce a low-frequency gradient of signal intensity across a given image. While the human visual system can maintain contrast detection in the face of this artifact, automated thresholding techniques assume a constant baseline level. Figure 4 illustrates the problem. Figure 4a presents an image with a typical RF inhomogeneity intensity gradient. Figure 4b illustrates how a single CSF/tissue threshold for this image, set in the frontal pole, fails completely to differentiate these compartments in the posterior pole. Homomorphic filtering (Lim and Pfefferbaum 1989) is one solution to this problem.

Thresholding. Many current quantitative image analysis systems rely on a combination of automation, using mathematical algorithms, and human input. One approach uses edge-detection algorithms, aided by human interaction, to draw contours around like tissue types (e.g., Filipek et al. 1989; Suddath et al. 1989). Filipek et al. (1989) illustrate the application of border-definition algorithms to outline a range of individual gray-matter structures as well as white-matter tracts. Another approach involves identifying pixel-intensity values that differentiate CSF from tissue, and white matter from gray matter (setting a threshold), and using this criterion to classify all pixels in a section into one of three compartments (e.g., Lim and Pfefferbaum 1989; Jernigan et al. 1990).

Our approach to three-compartment segregation of MR images involves the use of combination images (figure 5). Segregation is a two-stage process. At each stage, a two-compartment model is assumed. For the first stage, an early-minus late-echo combination image (which optimizes CSF/tissue contrast) is used. Once CSF pixels have been identified, an early-plus late-echo image (which optimizes white-gray matter contrast) is used. Fluid pixels are masked out, and the remaining gray and white matter pixels are differentiated. Compartmentalization can be performed interactively, by adjusting a one-bit image until it most closely approximates its full gray-scale version (Lim and Pfefferbaum 1989) or can be performed automatically, using algorithms that identify the intensity value above which any pixel is considered to be tissue and below which any pixel is considered CSF on the first pass, and differentiates white matter from gray matter on the second pass. Figure 6 illustrates the image segmented into three compartments.

Tissue-segmentation algorithms work best when applied to healthy tissue. One challenge currently facing image analysis is how to characterize the quality, as well as the quantity, of white and gray matter regions of the brain, and how to develop segmentation algorithms that work well in the face of focal abnormalities. One group has recently developed a "signal-hyperintensity" compartment in their segmentation procedure (Jernigan et al. 1990). Using this approach, they confirmed clinical observations of an increase in "signal hyperintensities" with age. However, their procedure appears to overrepresent the phenomenon on some regions while underrepresenting it in other brain regions, and could not differentiate between the hyperintensity "capping" frontal
Figure 5. Image combination to enhance fluid/tissue and white/gray contrast

Early (A) and late (B) echo images from the same section. The combination early plus late-echo image (C) enhances white/gray matter contrast, while the early minus late-echo image (D) enhances fluid/tissue contrast. Reprinted, with permission, from Lim and Pfefferbaum (1989).

horns of the ventricles, which is often considered "normal" by clinicians, and other "abnormal" hyperintensities.

Gliosis, edema, and demyelination produce changes in white and gray matter signal intensity, perhaps reflecting the altered properties of tissue water resulting from these pathologies. Regardless of the physiological basis for changes in signal intensity, current efforts to characterize them generally consist of scales rating the extent of hyperintensities, counts of their frequency, or measurements of their size. Figure 7 illustrates an axial scan with both deep white matter and periventricular hyperintensities.

There are numerous other physiological causes of changes in signal intensity, many of which are poorly understood. It has been suggested that iron may decrease MRI signals, probably by local ferromagnetic effects, allowing in vivo investigation of the neuropathologically reported increased iron concentration in basal ganglial structures in patients with movement disorders. Figure 8 illustrates an area of decreased signal in the putamen, especially on the late echo. MRI studies of patients with movement disorders (Drayer et al. 1986a, 1986b; Rutledge et al. 1987; Heinz et al. 1988; Braffman et al. 1989) using various qualitative ratings have not obtained consistent results. Whether this reflects inadequacy of the assessment technique or the absence of a bona fide effect is not clear. It should be noted, however, that a recent study of cadaver brains from neurologically intact individuals found no relationship between MRI-signal intensities of the brains and their tissue concentrations of iron (Chen et al. 1989).

Delineation of regions of interest.
Specific subregions of the brain, such as prefrontal cortex, various limbic structures, and basal ganglial structures, have been hypothesized to play a specific role in the pathophysiology of schizophrenia. How can the borders of these structures be reliably identified on MR images so that they can be accurately measured? Even though the resolution of MR images is excellent, it does not yet approach that provided from post-mortem specimens. In addition, the fit between structures as visualized on an MRI scan and as represented in a pathological specimen neuroanatomical atlas will be affected by the thickness of the MRI section and the extent to which the planes of view match. Because of the problems in reliably and validly identifying poorly visualized neuro-
anatomical boundaries, one approach to anatomical analysis is to develop a schematic model with geometrically defined regions encompassing multiple structures. This approach can be combined with thresholding CSF, white matter, and gray matter to identify changes in the relative proportions of these three compartments in the region of interest.

It should be reemphasized here that neuroanatomical structures and regions of interest generally extend across multiple MRI sections, and should be identified and measured as extensively as possible, rather than on a single "best view" section.

For axial MRI scans, we have developed a series of regions of interest based on those previously developed for analysis of CT data (Pfefferbaum et al. 1988a). First, left and right hemispheres are separated on each section by connecting midline points identified by a trained operator. Then, landmarks that will optimize delineation of different cortical regions are identified and the sections divided into segments based on the position of these landmarks (figure 9). Selected segments are then combined over sections to produce regions of interest encompassing particular neuroanatomical regions, such as the prefrontal cortex, the occipital lobes, and the temporal lobes.

Another example of rough outlining, focused on a specific brain region, is provided by Awad et al. (1989), who used postoperative MRI scans to evaluate the extent of resection performed in temporal lobectomies for intractable seizures. They developed a model in which five coronal sections, anchored to fixed points of the mesencephalon, are each further divided subjectively into superior and inferior lateral, basal, and medial quadrants. Regionalized resection, as assessed in this model, correlated well with success of surgery and also, to some extent, with loss of memory abilities (Katz et al. 1989).
Figure 7. Axial image illustrating various hyperintensities in a 70-year-old subject


separating frontal lobes from parietal lobes. The collection parameters of the MR image and the plane of view will determine the ease with which these landmarks can be identified. Estimates of frontal lobes have been made from sagittal (Andreasen et al. 1986, 1990), coronal (Kelsoe et al. 1988), or axial images. The extent to which measures obtained in each orientation correspond with each other has not, to our knowledge, been assessed.

In one of the earliest reports of MRI changes in schizophrenic patients, Andreasen et al. (1986) measured the frontal lobes on a single parasagittal section. Images were enlarged and projected on a screen. Boundaries consisting of the central sulcus, margins of the corpus callosum and cingulate gyrus, and marrow line of the diploic space (an alternative to inner margin of the skull) were traced and the area measured with a planimeter. In this first study, frontal lobes were smaller in schizophrenic patients, even when controlling for the smaller overall cranial area, but a recent replication study (Andreasen et al. 1990) failed to confirm this finding. Using coronal scans, Kelsoe et al. (1988) measured the volume of the prefrontal lobes by summing the area of all sections anterior to the genu of the corpus callosum separately for left and right hemispheres. They found no difference between schizophrenic patients and control subjects on this measure, with or without covarying for total brain volume.

We have recently developed the following procedure for delineating prefrontal lobes, based on axial sections: the most anterior point of the genu of the corpus callosum is defined as the posterior boundary of the prefrontal cortex. A coronal plane is constructed at this point, perpendicular to a line passing through the anterior and posterior commissures. All brain tissue anterior to the plane is defined as prefrontal cortex (Figure 9). Definition of more specific frontal brain areas, such as the dorsolateral frontal lobe or motor strip, is hampered by difficulties in identifying their specific sulcal boundaries on MRI. However, an extension of the
geometric segmentation approach, analogous to that developed for the temporal lobe by Awad et al. (1989), is currently being developed in which coronal sections are divided into pie-shaped wedges, based on estimated location of boundary markers.

**Temporal Lobes.** Temporal lobes are well delineated on coronal images with their Sylvian fissure boundary clearly apparent throughout much of their extent. An excellent parametric study by Jack et al. (1988) describes anatomical criteria for defining the extent and boundaries of the temporal lobes, though this particular approach has not yet been used in any of the clinical reports of temporal lobe changes in schizophrenia. Some studies of the temporal lobe in schizophrenia have been volumetric (e.g., Johnstone et al. 1989; Suddath et al. 1989). Others have selected one or two “best view” sections (e.g., Rossi et al. 1990). Some studies have attempted to define an anatomical boundary of the upper extent of the temporal lobe (e.g., Kelsoe et al. 1986), while others have simply drawn a straight line connecting some point of the Sylvian fissure to some medial landmark (e.g., Suddath et al. 1989; Rossi et al. 1990). Scorers were not blind to left and right hemisphere in any of these studies. Johnstone et al. (1989) standardized temporal lobe measurements for individual differences in overall brain size. Some studies report smaller temporal lobes in schizophrenic patients (Suddath et al. 1989; Rossi et al. 1990) while others find this effect absent (Kelsoe et al. 1986) or weak (Johnstone et al. 1989). Suddath et al. (1989) differentiated between white and gray matter volume within the temporal lobes and reported that schizophrenic patients had less gray matter than control subjects but no differences in white matter.

Deep within the temporal lobe lie certain limbic structures, including the hippocampus and the amygdala which have been postulated to play a role in the pathogenesis of schizophrenia. Post-mortem studies of
these structures have suggested loss of volume (Bogerts et al. 1985; Brown et al. 1986). The first anatomical examination of the hippocampus and related structures using in vivo MRI was reported by Naidich et al. (1987a, 1987b). In this study, coronal and sagittal MR images of the hippocampus and related structures were compared to cryomicrotome- and formalin-fixed sections of brains, selected to illustrate these structures. A spin-echo pulse sequence with TR = 400-750 ms and TE of 25-30 ms was used on a 1.5 Tesla system. Five-mm coronal sections were obtained and the "gyri and sulci of the inferomedial temporal lobe and the gross anatomic features of the major gray and white components of the hippocampal formation [were] displayed well" (Naidich et al. 1987a, p. 747). No quantification of the MR image was reported.

Several studies have since used MRI in an attempt to quantify specific limbic structures, in vivo, in schizophrenic patients (Delisi et al. 1988; Kelsoe et al. 1988; Johnstone et al. 1989; Suddath et al. 1989), in patients with Alzheimer's disease (Seab et al. 1988), and in patients with amnestic syndrome (Press et al. 1989). Each of these studies has used a different acquisition sequence and a different approach to identifying and measuring the structures of interest. The first study of schizophrenia to be published obtained T1-weighted images using a 600-ms inversion-recovery imaging protocol on a 0.5 Tesla scanner (Kelsoe et al. 1988). Up to 13 coronal sections (10-mm), laser-oriented to the can-thomeatal line, were obtained from each subject. Images were displayed on the computer console, where brightness and contrast were adjusted individually to optimize anatomical boundaries. Images were enlarged and investigators used a joystick-controlled cursor to outline structures of interest. Several structures, including the amygdala-hippocampal complex, were outlined on each section on which they appeared, and a volume was computed by summing these area measurements. Left- and right-sided structures were measured and analyzed separately. Investigators were not blind to subject identity or laterality. This study failed to obtain statistical differences on hippocampal measures between the 14 control subjects and 24 schizo-
phrenic patients from whom usable data were collected. A subsequent study from the same group of investigators, which included some of the same patients (Suddath et al. 1989), reports that the overall reduction in temporal lobe gray matter volume in schizophrenic patients was greatest in the medial sections, which are believed to encompass the amygdala and the anterior hippocampus.

MRI scans obtained as part of a study of familial schizophrenia were analyzed by Delisi et al. (1988) for evidence of differences in limbic system structures. Full details of the imaging protocol used in this study were not provided. Data analysis consisted of selecting two sequential coronal sections clearly demarcating the hippocampus, amygdala, and parahippocampal gyrus, enlarging the images, and measuring areas of interest by manual planimetry. These areas were expressed as a ratio of overall cranial area on that section to control for intersubject differences in head size. The investigators report a significant reduction in overall limbic area between 24 schizophrenic patients (11 sibling pairs and 2 unrelated cases) and 18 unrelated control subjects.

Two other approaches to direct measurement of the hippocampus have recently been described and applied to patients with Alzheimer's disease (Seab et al. 1988) and amnesia (Press et al. 1989). Seab et al. (1988) used a phase-corrected inversion recovery (TR = 2000 ms, TI = 500 ms, TE = 33 ms) acquisition sequence, with 5-mm sections. Hippocampal measurements were made on a single coronal section, with geometric calculations done to correct for variations in image-plane orientation. Hippocampal values were normalized by expressing them relative to the size of the lenticular nucleus, as measured on the same section. The lenticular nucleus was chosen because it is believed not to be affected in Alzheimer's disease. A 40-percent reduction in the hippocampus in Alzheimer's disease patients relative to age-matched controls, with no overlap between patients and controls, was found.

Press et al. (1989) used a T1-weighted (TR = 400 ms, TE = 20 ms) spin-echo, coronal sequence to acquire six interleaved 5-mm-thick sections in a plane perpendicular to the long axis of the hippocampus. Subjects' heads were tilted back, and a sagittal view was made first to ensure this acquisition plane. Exceptionally good detail of the structures of the hippocampus was obtained. Three sections, beginning with one located at the same rostrocaudal level in each subject, were selected for quantification which consisted of outlining the hippocampal formation on each section and taking the average. The area of the hippocampal formation in the patients was 49 percent of that in the control subjects, and calculating this area as a percent of the area of the temporal lobe did not affect the results. T2-weighted images, acquired as part of the same protocol, were used to identify areas of abnormal signal intensity.

Johnstone et al. (1989) present another approach to analyzing temporal lobe structures. CSF areas of the right and left temporal horns of the lateral ventricles were measured at every section on which they appeared. The temporal horn measure, covaried for temporal lobe area, was smaller in schizophrenic patients (n = 16) than in control subjects (n = 15) when only males were considered. There was a diagnosis x side interaction for temporal lobe measures in which schizophrenic patients had smaller left than right temporal lobes, but control subjects had smaller right than left temporal lobes. The approach to "temporal lobe structure" assessment adopted in this study—measurement of the readily visualizable CSF-filled temporal horns—is one that is certainly accessible, and has also been applied to CT images (e.g., Kido et al. 1989). Because of the indirect nature of this approach, it is generally not interpreted as a measure of hippocampal change, but rather an index of temporal lobe atrophy. However, the assumption that increase in the temporal horn is solely a consequence of a decrease in temporal lobe tissue is not established with certainty.

We have recently designed an imaging sequence for visualization of the temporal lobes, in particular the hippocampus and its adjacent limbic structures (Lim et al. 1990). Key elements include the use of the internal anatomical reference plane, acquisition of two sets of thin (3-mm) interleaved sections, and use of gating and flow compensation software during acquisition to reduce movement artifact. Data analysis involves first magnifying and smoothing the image to display the temporal lobe (figure 10). Then, CSF areas of the temporal horn are delineated automatically by thresholding the images in a manner that still maintains the gray scale in tissue areas. Finally, structured criteria are applied to delineate a boundary for the hippocampal-amygdaloid complex. Since the boundary of the amygdala is intrinsically indistinct, and further obscured by partial voluming, separate delineation of hippocampus and amygdala is not attempted. An estimate of the volumes of the temporal horn and the hippocam-
ROI = region of interest. TR = repetition rate. TE = echo time (reprinted, with permission, from Lim et al. 1980).

Basal Ganglia. Many individual structures of the basal ganglia, including the caudate, putamen, the globus pallidus, and the substantia nigra, can be fairly reliably identified on axial and coronal images (figures 11a and 11b). MRI reports on these structures have principally been in patients with movement disorders, and have generally been based on axial scans (Drayer et al. 1986a, 1986b; Rutledge et al. 1987; Heinz et al. 1988; Braffman et al. 1989). As stated above, one focus for these structures has been the changes in signal intensity, perhaps attributable to alterations in tissue iron concentrations. Other changes, such as narrowing of the pars compacta of the substantia nigra, have been more consistently (Duguid et al. 1986; Braffman et al. 1989; Stern et al. 1989), but not universally (Huber et al. 1989) noted.

Techniques for measuring the volume of specific basal ganglial structures, based on our approach for measuring the hippocampus, are currently under development in our laboratory. Gross assessment, measuring the gray matter compartment in a broad region of interest encompassing a number of these structures, is also possible.

Three-Dimensional Image Acquisition. While current two-dimensional MRI technology has enabled significant progress in investigating structural brain abnormalities in psychiatric patients, the delineation of fine
neuroanatomical detail is limited by available section thickness and problems in defining plane of acquisition. Conventional two-dimensional MRI acquisition techniques collect data from predetermined sections through the brain by specifically exciting each section with a selective RF pulse in the presence of a magnetic gradient. Paradoxically, it requires more RF power to excite a thinner section, limiting section thickness on most scanners to about 3 mm. Steps to remedy these limitations frequently come at the cost of longer scan times. New approaches to image acquisition, especially three-dimensional imaging, offer particular promise for neuroanatomical localization.

With three-dimensional MR image acquisition, the magnetic gradient is used to code the information for each section spatially, with a nonselective, lower power RF pulse. After image data have been collected, a Fourier transform decodes section positions from the entire data set. These section data are then further reconstructed into the final image. This technique has numerous advantages of great potential value to psychiatric applications. First, three-dimensional imaging offers improved signal to noise ratio over two-dimensional imaging, since the entire volume of the brain is sampled during each excitation, rather than a limited section. Second, section thickness is no longer limited by RF power limits. Submillimeter section thicknesses are theoretically possible. Third, three-dimensional data are amenable to postacquisition reformatting in any plane. This eliminates the need for selecting a particular slice orientation during image acquisition. Finally, acquisition time is substantially reduced.

We have recently implemented three-dimensional imaging using a 1.5 Tesla clinical imager (General Electric Signa 4.0, Milwaukee). A "spoiled grass" three-dimensional imaging sequence was used with the following imaging parameters: TR = 23 ms, TE = 5 ms, Flip Angle = 40°, Number of Excitations = 1, Field of View = 24 cm, and image matrix = 256-196. The image was reconstructed to 124 slices, 1.3-mm thick, with 0.9 mm in-plane resolution. Image collection time was less than 10 minutes. Image data were transferred from the scanner to the laboratory minicomputer (Sun 3/260C, Sun Microsystems, Mountain View) via magnetic tape. The entire image data set was loaded into a TACC-1 application accelerator for visualization using the Sun-provided software package "Voxvu."

This software and hardware combination permits the near real time manipulation of the image data, including the interactive selection of slices in any arbitrary plane. Thus, even though the data set was originally collected in a sagittal orientation, images can be reconstructed in the orientation that provides best visualization for the structure of interest. For example, temporal lobe structures can be seen in excellent detail when axial sections are oriented negatively to the canthomeatal line. Figures 12 and 13 illustrate some of the possible planes of postacquisition sectioning.

Conclusions

The superior resolution and greater flexibility of MRI offer the hope that this modality will enable identification of any regionally specific brain abnormalities that might be associated with schizophrenia. However, several important methodological and technical issues need to be addressed before these expectations can be met. In addition, it is important for data to be collected and analyzed in such a way that specific hypotheses about particular regions of morphological changes in the brain can be tested within the context of the brain as a whole.
Figure 12. Three-dimensional images illustrating various planes of visualization
Figure 13. Two views from 3-dimensional image illustrating specified structures


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