Structural Brain Abnormalities as Indicators of Vulnerability to Schizophrenia

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Abstract

The literature on structural brain abnormalities in schizophrenia is examined to determine whether these abnormalities represent viable candidate markers of vulnerability to the disorder. A majority of studies agree in finding that schizophrenia patients as a group have significantly larger ventricles and smaller limbic brain structures than normal control subjects, but about 50 percent of patients fall within the range of control subjects on these measures. This result has been interpreted to suggest that structural abnormalities characterize only a subgroup of patients. However, given the substantial degree of normal variability in brain structure between families, the use of biologically unrelated individuals as controls is misleading. Studies that have compared schizophrenia patients with their unaffected first-degree relatives have found a much higher sensitivity rate for ventricular enlargement and reduced limbic volumes (i.e., 70%-100%). This high within-family sensitivity, together with evidence from meta-analytic reviews of a substantial relationship between ventricular enlargement and severity of illness, argues in favor of a continuous distribution of the brain pathology in schizophrenia and against a model in which the pathology characterizes only a subgroup of patients. The structural abnormalities observed in both younger and older patients have been found to be highly correlated with familial risk for schizophrenia and obstetric complications, suggesting that some part of the deviance may be present in the premorbid state and that it may reflect both genetic and environmental etiologic processes. The evidence for specificity of the deficits to schizophrenia is equivocal, but no study has yet compared the within-family sensitivities of morphological measures among the major psychiatric conditions. Additional studies using first-degree relatives and well-defined neuroanatomical measurements are needed to determine which brain regions have the highest sensitivities as indicators of schizophrenia in families.


In the past two decades, over 200 postmortem and neuroimaging studies have documented the presence of structural brain pathology in schizophrenia patients. The most consistently replicated findings are limbic system pathology and enlargement of the third and lateral ventricles (Raz and Raz 1990; Bogerts 1991; Cannon 1991b). There are two major competing perspectives on the significance of structural brain deficits in schizophrenia. First, some or all of the brain deviance may originate before symptom onset and may mark or directly contribute to vulnerability to the disorder. Evidence supporting this hypothesis includes the finding of heterotopic displacement of neurons in limbic regions consistent with a disruption of brain development during gestation (e.g., Arnold et al. 1991), the finding of ventricular enlargement in first-episode patients (e.g., Iacono

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et al. 1988), and the finding of greater brain pathology in individuals at elevated genetic risk for schizophrenia (e.g., Cannon et al. 1989, 1993). Second, the brain changes may be nonspecific (or nonpathogenic) consequences of illness or of psychiatric treatments. Evidence supporting this hypothesis includes correlations between brain abnormalities and duration of illness (e.g., Pandurangi et al. 1988) and the finding of similar brain abnormalities in other psychiatric conditions (e.g., Rossi et al. 1989).

Thus, while there is little doubt that structural cerebral pathology exists in schizophrenia, controversy remains as to the roles of the abnormalities in the etiology and pathophysiology of the disorder. In this review we consider the recent evidence bearing on the issue of whether measures of structural brain pathology represent viable candidate markers of vulnerability to schizophrenia. This article is not intended to serve as a comprehensive review of the brain-imaging and neuropathology literatures.

Rather, we focus on structural deficits that have been examined in a large number of studies using designs necessary to assess their status as vulnerability indicators (e.g., within- and between-family comparisons, longitudinal assessments). Our discussion is thus addressed primarily to the marker status of ventricular enlargement and limbic system pathology, for which at least preliminary information based on these designs is available. Following the scheme suggested by the guest editors of this issue, we organize our discussion around the following issues: (1) reliability and validity of neuromorphological assessment procedures; (2) nature and localization of the deficits observed in schizophrenia; (3) methodologic parameters influencing detection of the abnormalities; (4) sensitivity and specificity of morphologic measures as illness indicators; and (5) relationships of the abnormalities to familial risk, temporal course, and phenomenologic dimensions of the illness.

Assessment

The two most widely used techniques for visualizing the structure of the brain in living subjects are computed tomography (CT) and magnetic resonance imaging (MRI). These techniques are based on different physical principles of image acquisition. In CT, x-ray technology is used to image contrast between bone, brain tissue, and cerebrospinal fluid (CSF). In MRI, a magnetic field applied to the brain produces radiofrequency signals that reflect different properties of the underlying tissue. By manipulating parameters of the eliciting pulse, one can optimize contrast between brain and CSF and between gray and white matter.

For both of these techniques, regional and whole-brain measurements can be obtained directly from the digitized computer image or by manual planimetric analysis of the developed films. Computerized analysis is generally preferred because the semiautomated procedures available for tissue segmentation remove a major share of the operator-related measurement error. The most commonly used measurement in imaging studies of schizophrenia subjects is the ventricle-brain ratio (VBR), which is the area of the lateral ventricles expressed as a percentage of total brain area. Volumetric measures can be obtained from either procedure by integrating area measurements from multiple contiguous slice levels. Width measurements and pathology ratings of various regions of interest (ROIs) are also sometimes used.

Computer-assisted measurements of brain and CSF obtained from either procedure yield interrater reliability estimates at or above 0.9; the reliabilities for corresponding manually generated measurements are typically in the 0.6 to 0.9 range. The validity of CT-based measurements is limited by signal distortions caused by the beam-hardening effect of calvarial bone and by partial-volume averaging due to the relatively large slice thicknesses (e.g., 10 mm) employed with this procedure. MRI has greater spatial and contrast resolution than CT, and the images can be acquired and reconstructed in three dimensions, providing for more valid estimates of the volumes of cerebral structures. Recent work has demonstrated that the reliability and validity of MRI measures of brain and CSF volumes can be maximized by combining information on two independent properties of the image (proton density and T2) in the pixel classification algorithm. These procedures yield estimates within 1.6 cc of the actual volumes of agarose-graphite phantoms (Kohn et al. 1991). Interrater reliability estimates obtained with these procedures on human subjects are in the 0.95 to 0.99 range (Gur et al. 1992). Similar validation and reliability studies are now under way for regional gray and white matter volumes.

Nature of Deficits

Our brief summary of the nature of structural brain abnormalities in schizophrenia is based on several
recent reviews of the neuroimaging and postmortem literatures (Raz and Raz 1990; Bogerts 1991; Breslin and Weinberger 1991; Cannon 1991b). We do not attempt a complete integration of these literatures in this article; rather, we highlight the major findings and trends, which serve to establish the regions that can be considered as candidate markers of schizophrenia in the discussion that follows.

The most consistently replicated findings in CT and MRI studies of patients with schizophrenia are enlargement of the third and lateral ventricles and increased prominence of the cortical sulci and fissures. In 86 percent (24/28) of the studies reviewed in Cannon (1991b), schizophrenia patients were found to have significantly larger third ventricles than control subjects; in 76 percent (55/72) of the studies, schizophrenia patients were found to have significantly larger lateral ventricles; and in 61 percent (19/31) of the studies, schizophrenia patients were found to have significantly greater cortical sulcal prominence.

Ventriculomegaly and cortical sulcal prominence are general, nonspecific signs of brain pathology. Since these measures are typically expressed as percentages of whole brain volume or area, it is unclear whether the changes reflect proximal or distal tissue reductions. Studies that have directly examined this ambiguity in interpretation have found evidence that ventricular enlargement in schizophrenia is associated with cell loss in periventricular regions. Lesch and Bogerts (1984) found that third ventricle enlargement was accompanied by reduced thickness of the diencephalic periventricular gray matter. Similarly, reduced volumes of limbic structures, particularly the parahippocampal gyrus, appear to be correlated with enlargement of the temporal horns of the lateral ventricles (Brown et al. 1986). Also supporting this interpretation is the consistency with which postmortem and MRI studies have been able to detect abnormalities in periventricular structures. In a recent review of the postmortem literature, Bogerts (1991) concluded that “all qualitative and quantitative investigations of the medial temporal lobe structures (i.e., the hippocampal formation, including the dentate gyrus, parahippocampal gyrus which contains in part the entorhinal cortex, and amygdala) and of the cingulate gyrus (which is functionally closely related to them) found structural abnormalities of one or several of these limbic brain parts in a substantial proportion of schizophrenics” (pp. 163–164).

There is a similar degree of consistency among MRI studies of the limbic system (e.g., DeLisi et al. 1988; Bogerts et al. 1990, 1991; Suddath et al. 1990) and among MRI and postmortem studies investigating thalamic pathology (Nieto and Escobar 1972; Dom et al. 1981; Stevens 1982; Lesch and Bogerts 1984; Andreasen et al. 1990; Pakkenberg 1990).

The interpretation of the specific neuroanatomical deficits associated with increased cortical sulcal prominence is less ambiguous than interpretation of deficits associated with ventriculomegaly and depends primarily on the regional specificity of the measurements used. CT studies have typically found evidence of generalized enlargement of the cortical sulci and fissures; however, these studies have rarely differentiated cortical CSF measurements by lobe. More refined analyses of postmortem sections and MRI measurements of regional gray matter volumes generally point to anatomical localization of cortical changes in schizophrenia in the temporal lobes (Johnstone et al. 1989; Suddath et al. 1989; Dauphinais et al. 1990; Rossi et al. 1990, 1991; DeLisi et al. 1991; but see Kelsoe et al. 1988). Whether structural pathology of the frontal lobe exists in schizophrenia remains controversial (see Benes et al. 1986, 1991; Andreasen et al. 1990).

It is also important to note that structural pathology in schizophrenia patients is generally found to be either more pronounced in the left hemisphere (e.g., Brown et al. 1986; Losonczy et al. 1986; Bogerts et al. 1990; Crow 1990; DeLisi et al. 1991; Shenton et al. 1992) or equivalent in the two hemispheres (see Suddath et al. 1990).

**Methodologic Issues**

While the finding of structural brain pathology in schizophrenia appears to be reliable, it is important to assess whether differences between schizophrenia patients and control subjects are robust with respect to variations in study design, sample characteristics, scanning methodology, and so on. That is, can we conclude that purely random influences account for the failure to observe differences between schizophrenia patients and control subjects in the minority of studies? This issue has been adequately investigated only with respect to ventricular enlargement.

Smith et al. (1988) reviewed imaging studies investigating ventriculomegaly in schizophrenia and found that significant pathology in the schizophrenia patients was reported in a higher percentage of
studies using medical patients as controls than studies using normal volunteers as controls. This result suggested that the stringent exclusion criteria used for medical patients (i.e., prescreening of brain scans for evidence of pathology) may result in a selective sample with smaller ventricles. However, tallying results according to the level of significance obtained in individual studies ignores differences in sample size (i.e., statistical power) and other methodologic aspects of the studies. To control for these factors, Raz et al. (1988) examined the mean effect size (i.e., the standardized degree of difference between patients and controls) in studies using medical patients as controls and in studies using normal volunteers as controls. The effect sizes were equivalent, indicating that once differences in statistical power are accounted for, type of control group does not influence the degree of difference found between schizophrenia and control samples in neuroimaging studies. Raz et al. (1988) also noted that although medical patient controls did in fact have smaller ventricles than normal volunteer controls, the schizophrenia patients in studies using medical patients as controls had smaller ventricles than the schizophrenia patients in studies using normal volunteers as controls. This correspondence accounted for the stable effect size between the two types of studies.

If nature of the control group is not a significant factor influencing the findings of neuroimaging studies of schizophrenia, then perhaps individual or subgroup differences within the schizophrenia samples play a role. Although a few studies have reported ventricular enlargement exclusively in male patients (Flaum et al. 1990), there is no systematic pattern of degree of difference between the patient and control groups as a function of gender (Raz and Raz 1990). The mean age of the patient groups contributes to the variability in effect size between studies (Raz and Raz 1990), but age does not explain the finding of structural abnormalities in schizophrenia, since patient and control samples are almost always matched for age. (We consider the relationship of age and duration of illness to structural abnormalities in greater detail in the “Temporal Course” section.) In two recent quantitative reviews (Raz and Raz 1990; Cannon 1991b), the only subject characteristic found to have a major influence on the VBR distribution of schizophrenia patients and the magnitude of the effect size was severity of illness as indexed by cumulative length of hospitalization. The correlation between mean VBR and mean length of hospitalization in the schizophrenia samples was 0.78. The correlation between effect size and mean length of hospitalization was 0.69. These correlations remained significant and substantial after accounting for the mean ages of the patient samples, indicating that the relationship between severity of illness and ventricular enlargement is present in both younger and older subjects. The relationship is also likely to be independent of exposure to physical treatments, since differences between schizophrenia patients and control subjects have been detected in studies of first-episode patients and in patients with little or no exposure to neuroleptics or electroconvulsive therapy (e.g., Iacono et al. 1988; Cazullo et al. 1989).

It is also noteworthy that variations in scanning methodology do not significantly influence the findings of neuroimaging studies of schizophrenia patients. Raz and Raz (1990) found no differences in effect size as a function of scanner resolution and scanning angle. In addition, abnormalities have been detected with all of the available approaches to quantification. There is, however, a relative sensitivity difference related to type of measurement; for most ROIs, volumetric measures are associated with larger effect sizes than are area measures, which are associated with larger effect sizes than are linear measures (Raz et al. 1987; Raz and Raz 1990).

**Sensitivity**

The foregoing discussion indicates that the finding of structural brain pathology in schizophrenia patients is highly replicable and, at least with respect to ventriculomegaly, robust with respect to variations in most aspects of study methodology. However, we have not yet addressed the more basic issue of how many schizophrenia patients show deviance on these measures. Some studies have approached this issue by defining values at or above one or two standard deviations (SDs) from the control mean as pathologic and values below these levels as normal. There are two major problems with this approach: (1) there is no objective basis for determining the abnormality threshold of a quantitative morphological measure such as VBR, and (2) the sensitivity of a given threshold fluctuates as a function of the range of control values, which are known to be quite variable.

An alternative approach is to estimate the sensitivity of the brain...
measurements as illness indicators from the effect size. Sensitivity can then be expressed as the percentage of nonoverlap between the patient and control distributions. Because the findings of all available studies can be integrated into a single sensitivity estimate, this approach eliminates the threat of a spuriously small or large estimate due to sample fluctuations. Again, an adequate number of studies is available only for ventricular enlargement, which will serve as our primary example. In their review of 93 neuroimaging studies, Raz and Raz (1990) determined that the mean effect sizes for lateral ventricle enlargement, third ventricle enlargement, and sulcal prominence were 0.70, 0.66, and 0.35, respectively. An effect size of 0.70 indicates that there is a 43 percent nonoverlap between the distributions of the schizophrenia and control samples. There is, of course, variability in the distribution of effect size, which places upper and lower confidence limits on the degree of nonoverlap of the two distributions. The 43 percent rate is, however, a measure of the central tendency of the studies, and this is the figure we will use to focus the following discussion.

A 43 percent nonoverlap between schizophrenia patients and control subjects on VBR suggests that the sensitivity of this measure as a marker of schizophrenia is rather poor. An important conceptual question has not yet been addressed, however: How are we to interpret the 57 percent overlap with the normal distribution? One explanation is that the overlapping and nonoverlapping patients represent different populations of schizophrenia patients. This position was advocated by Crow (1989), who proposed that structural abnormalities may characterize an etiologically distinct subgroup of schizophrenia patients with poor premorbid adjustment, cognitive impairment, poor response to neuroleptics, and prominent negative symptoms. There are two major problems with this interpretation. First, there are no robust clinical differences between schizophrenia patients with larger and smaller ventricles, an issue we will examine in greater detail in the “Functional Expression” section. Second, the distribution of ventricular size and other structural measures in schizophrenia is not bimodal, as would be expected if the measures defined biologically distinct subgroups. Rather, the distributions are unimodal with a significant positive skew. Weinberger (1987) suggested that these distributional characteristics may indicate a more homogeneous underlying process than is commonly presumed (see also Harvey et al. 1990).

The alternative explanation is that VBR and other neuromorphological measures represent illness markers in the general population of schizophrenia patients. In this case, heterogeneity within and between samples of schizophrenia patients would most likely result from individual differences and nonrandom sampling with respect to a major phenomenologic correlate of brain pathology—for example, severity of illness. That is, the selection criteria for patients in different studies would produce samples with varying average levels of severity, resulting in varying degrees of overlap between the neuromorphological distributions of patients and controls. As we have seen, differences in severity of illness do in fact account for a large share of the variability in effect size in the neuroimaging literature. However, we are still left with the question of how to interpret the cases that overlap with the normal distribution. If there is a continuous severity–brain pathology distribution in schizophrenia, even patients at the low end of the continuum should be classified as deviant on these measures.

Is it possible to reconcile the overlap between the neuromorphological distributions of patients and controls with the continuum model’s prediction that all schizophrenia patients have some degree of brain pathology? The answer lies in the fact that biologically unrelated individuals are not the most appropriate basis of comparison for considering the proportion of schizophrenia patients who are deviant on a particular morphological indicator. The practice of matching a patient to an unrelated normal individual on characteristics such as age, gender, and social class does not ensure that morphological differences between the two individuals are related only to factors that predispose to or result from illness in the patient. In fact, the major source of variation between the two individuals is that they are biologically unrelated to each other. In monozygotic (MZ) twins discordant for schizophrenia, interpair (i.e., between-family) differences account for over 90 percent of the overall variability in VBR (Reveley et al. 1982). The percentage is somewhat higher among normal MZ twins. In view of the substantial variability in VBR related to family membership, the value obtained for a given schizophrenia patient may fall well within the range of an unrelated normal control group but at the same time...
be classified as deviant when compared with the distribution of the patient's normal relatives.

What do within-family comparisons tell us regarding the sensitivity of brain deviance as an indicator of schizophrenia? The results of the four published studies comparing VBR measurements in schizophrenia subjects and their relatives are summarized in table 1. The average sensitivity estimate obtained in these studies is 84 percent (range 71%-100%), indicating that about five of every six schizophrenia patients in these studies had larger VBRs than their unaffected first-degree relatives. The magnitude of these differences is not trivial (see the last column of table 1). In studies of discordant siblings, the mean pairwise difference between the affected and unaffected siblings is on the order of 100 percent. In studies of discordant MZ twins, the mean pairwise difference is on the order of 50 percent. The smaller magnitude of difference between discordant MZ twins than between discordant siblings is accounted for by the fact that there is no within-family genetic variability in the MZ twins, while in siblings this variability is on average 50 percent. In addition, there is less variability related to intrauterine conditions in twins than in siblings. The within-family sensitivity of specific regional measurements is equally impressive. In nearly all of the schizophrenia twins in Suddath et al.'s (1990) study, MRI measures of hippocampal volume were reduced bilaterally compared with those of their unaffected cotwins (13/15 and 14/15 for the right and left hemispheres, respectively).

**Specificity**

The utility of neuromorphological measures as illness indicators is also dependent on their ability to discriminate schizophrenia patients from patients with other psychiatric disorders. The evidence on the specificity of general measures such as VBR is mixed. In direct comparisons, schizophrenia patients tended to have larger ventricles than patients with bipolar and unipolar affective disorders, but the differences were not always statistically significant (e.g., Yates et al. 1987; Rossi et al. 1989; Swayze et al. 1990). In their quantitative review, Raz and Raz (1990) examined the difference in mean effect sizes for VBR in studies comparing patients with affective disorders with normal controls and in studies comparing schizophrenia patients with normal controls. The degree of nonoverlap with the normal distribution was found to be less pronounced in affective disorders than in schizophrenia, providing modest support for the specificity of VBR as an indicator of schizophrenia (compared with affective disorders).

As mentioned earlier, ventricular enlargement is a general measure of brain pathology that can reflect both local (i.e., periventricular) and distal tissue reductions and that can result from a variety of etiologies (e.g., birth trauma, alcoholism, and head injury). Ventriculomegaly per se would therefore not be expected to show a high degree of specificity to schizophrenia when considered against the full range of disorders with organic features. Studies examining the specificity of regional gray matter volumes are much more consistent in indicating a significant reduction in limbic and paralimbic nuclei in schizophrenia compared with affective disorders (e.g., Johnstone et al. 1989; Rossi et al. 1991). A more powerful test of specificity would be a comparison of the within-family sensitivity rates for morphological traits such as hippocampal volume.

### Table 1. Results of studies examining differences in ventricle-brain ratio between schizophrenia probands and their unaffected first-degree relatives

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging method</th>
<th>Type of relatives</th>
<th>No. of probands</th>
<th>No. of relatives</th>
<th>Sensitivity (%)</th>
<th>Pairwise difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinberger et al. (1981)</td>
<td>CT</td>
<td>Siblings</td>
<td>10</td>
<td>12</td>
<td>100</td>
<td>122</td>
</tr>
<tr>
<td>DeLisi et al. (1986)</td>
<td>CT</td>
<td>Siblings</td>
<td>25</td>
<td>10</td>
<td>71</td>
<td>76</td>
</tr>
<tr>
<td>Suddath et al. (1990)</td>
<td>MRI</td>
<td>MZ twins</td>
<td>15</td>
<td>15</td>
<td>80</td>
<td>-1</td>
</tr>
<tr>
<td>Reveley et al. (1982)</td>
<td>CT</td>
<td>MZ twins</td>
<td>7</td>
<td>7</td>
<td>86</td>
<td>47</td>
</tr>
</tbody>
</table>

*Note.* —Sensitivity refers to the percentage of patients with more deviant values than their unaffected relatives. Pairwise difference indicates the magnitude of difference (expressed as a percentage of relative's value) between each patient and each relative, averaged across pairs. CT = computed tomography; MRI = magnetic resonance imaging; MZ = monozygotic.

1 Data necessary to perform the calculation were not presented in the referenced paper.
as hippocampal volume among the major psychiatric conditions; this test awaits the collection of neuroimaging data on family members of affective disorder probands.

Genetic Contributions

We have discussed the implications of within-versus between-family comparisons for estimating the sensitivity and specificity of morphological measurements as illness indicators. What do these factors tell us about the genetic determination of VBR and other structural traits? Reveley et al. (1982) found that the heritability coefficients for VBR in normal MZ twins, normal dizygotic (DZ) twins, and MZ twins discordant for schizophrenia were 0.98, 0.70, and 0.87, respectively. These heritability coefficients suggest that VBR (and, most likely, other neuromorphological characteristics) are under a substantial degree of genetic control. At the same time, the large between-family variation in VBR indicates that there must be considerable heterogeneity in the genetic determinants of brain structure in the general population. A question of major importance is thus whether the genetic mechanisms contributing to more deviant values on morphological traits such as VBR are related to the genetic mechanisms that predispose to schizophrenia.

The most commonly used approach to this issue in the neuroimaging literature is the family history (FH) method. In this approach, one first identifies a patient sample and then interviews each patient, some relatives, or both regarding the presence of psychopathology among family members. Patients with a positive FH are then compared with patients with a negative FH on morphological characteristics such as VBR. The results of studies using this approach are quite varied. Among the 13 FH studies of VBR published before 1991 that used formal diagnostic criteria and provided details of the assessment methods, 3 found larger ventricles in patients without a positive FH, 2 found larger ventricles in patients with a positive FH, and 8 found no relationship (see Cannon 1991a, for references). The mixed results of these studies are not very surprising in view of several methodologic weaknesses of the FH method. The most important of these is that in a disorder with a nontrivial environmental component and with partial penetrance at a major locus, multiple gene effects, or both, a large proportion of family members who do not manifest the phenotype will in fact be genotypically at risk. False negatives may also result from small family size or systematic evasion of the diagnostic process by affected relatives (DeLisi et al. 1986). The predominant trend of the FH studies (i.e., no significant differences between FH+ and FH− patients) is readily explained by a false-negative bias. In addition, some of the FH studies were vulnerable to a high rate of false positives because they defined familial risk on the basis of any major psychiatric diagnosis in the relatives, which is a dubious basis from which to infer genetic risk for schizophrenia.

An alternative strategy is to study the offspring of parents that have schizophrenia. This approach minimizes the false-negative bias because any two offspring from families of comparable size and with comparable severity of illness in the affected parent will have the same degree of empirical risk for schizophrenia and thus will manifest illness markers in equivalent proportions. In addition, because the risk rate of offspring of two affected parents is approximately double that of the offspring of one affected parent (Gottesman and Shields 1982), there should be a commensurate degree of difference in the incidence of an illness marker between the two types of offspring. Only one such parent–offspring high-risk study has examined structural brain pathology as an indicator of genetic predisposition to schizophrenia. In this study, 207 children of mothers with schizophrenia and 104 children of normal parents were initially examined in 1962, when they averaged 15 years of age (Mednick and Schulsinger 1965). Most of the subjects were reexamined between 1986 and 1989 with psychiatric interviews and CT scans. Because diagnostic assessments were obtained on both parents, it was possible to classify each offspring into one of three levels of risk, depending on whether neither (n = 60), one (n = 72), or both (n = 25) of the parents were diagnosed with schizophrenia-spectrum disorders. It was found that cortical and ventricular CSF-brain ratios increased in a stepwise linear fashion with increasing level of genetic risk for schizophrenia. That is, individuals with two affected parents evidenced greater ventricular and sulcal enlargement than those with one affected parent, who in turn evidenced greater ventricular and sulcal enlargement than those with no affected parent. An additional share of the variance in ventricular CSF-brain ratio was accounted for by the interaction of genetic risk for schizophrenia and obstetric complications. These effects were
significant when age, gender, history of substance abuse, and history of organic brain syndromes and head injuries were controlled for (Cannon et al. 1993). The results replicated the findings of an earlier pilot study from this project (Cannon et al. 1989).

Cannon et al. (1993) used a parent-offspring (i.e., vertical) high-risk design to examine whether structural abnormalities aggregate in the families of schizophrenia patients. Other studies have used a sib-sib (i.e., horizontal) high-risk design to examine this issue. Weinberger et al. (1981) found that both schizophrenia patients and their unaffected siblings had significantly larger ventricles than normal controls, suggesting a familial or genetic component of increased ventricular size in schizophrenia. DeLisi et al. (1986) studied 34 affected and unaffected individuals from 11 different families and found a significant association between ventricular size and schizophrenia within families, even after the contributions of several environmental sources of brain pathology were partialled out. Revelley et al. (1982) found a similar pattern of results in a study of MZ twins discordant for schizophrenia, but the differences between the unaffected cotwins of schizophrenia patients and the normal control twins, although moderately large (effect size = 0.8), failed to reach statistical significance. There was, however, a significant increase in ventricular size in the twins with schizophrenia compared with the unaffected cotwins, which necessarily reflects the influence of different environments.

Taken together, the evidence available from vertical and horizontal high-risk studies supports the hypothesis that structural brain abnormalities aggregate in the families of persons with schizophrenia. This aggregation seems to reflect (at least in part) a genetic mode of transmission, since the pathology increases linearly with the number of affected relatives. However, high-risk and twin studies also indicate that, like schizophrenia itself, some part of the brain deviance in these patients must be environmentally determined (Revelley et al. 1982; Cannon et al. 1989, 1993; Suddath et al. 1990).

Temporal Course

An issue of central theoretical and practical importance to the marker status of brain abnormalities in schizophrenia is whether the abnormalities index vulnerability to the illness, progression of the disease process, or both. The finding of a greater degree of ventricular enlargement in the unaffected relatives of schizophrenia patients than in normal controls argues in favor of the status of brain abnormalities as vulnerability indicators. More direct support for the vulnerability perspective would be provided by evidence that brain abnormalities precede the development of the disorder. Although no such prospective study has been conducted, several studies have found evidence of brain abnormalities in first-episode patients and in teenagers with schizophrenia-spectrum disorders (e.g., Iacono et al. 1988; Hendren et al. 1991).

There is indirect evidence that some part of the brain deviance may originate quite early in life. As noted above, Cannon et al. (1989, 1993) found that enlargement of the CSF spaces in adulthood was predicted by the unique and interacting influences of genetic risk for schizophrenia and obstetric complications. The fact that these associations were independent of several secondary sources of brain pathology (e.g., age, gender, substance abuse, and head injury) suggests that the genetic influence on brain morphology in schizophrenia is expressed at least in part during the development of the brain. The obstetric effect also clearly suggests that some share of the pathology originates early in development. This interpretation is also supported by the results of several recent postmortem studies that have found evidence of ectopic changes in the brains of schizophrenia patients attributable to genetic or teratogenic disturbances during gestation. These findings include (1) disturbances of pyramidal cell orientation in the anterior and medial portions of the hippocampus (Kovelman and Scheibel 1984); (2) heterotopic displacement of pre-alpha cell groups in the rostral entorhinal region of the parahippocampal gyrus (Jacob and Beckmann 1986; Falkai et al. 1988; Arnold et al. 1991); (3) reduced depth of the granule cell layer in the dentate gyrus (McLardy 1984); and (4) disturbed arrangement of neurons in the anterior cingulate gyrus (Benes 1987). These findings imply a disturbance of one or more of the basic processes of neural development during gestation: proliferation, migration, and differentiation (Nowakowski 1991b). Nowakowski (1991a) has demonstrated that similar patterns of ectopia (i.e., disturbances of cellular orientation and laminar organization in the hippocampal formation) are heritable in mice. Viral exposure during pregnancy represents another possible source of the ectopic changes (Mednick et al. 1986; Nowakowski et al. 1986; No...
1988), although it is unclear whether viral exposure is associated with the development of schizophrenia especially or only among individuals with a genetic predisposition to the disorder.

It is possible, however, that abnormalities originating during the development of the brain also progress over time. If this is the case, one would expect significant correlations between length of illness and structural indicators such as VBR. Such correlations have been a minority finding in the neuroimaging literature (Cannon 1991b). In studies that have reported significant associations between ventricular enlargement and duration of illness, there have also tended to be significant correlations between ventricular enlargement and age. This result suggests that the associations between ventricular enlargement and duration of illness found in these studies were not independent of age. All of the studies that examined this implication statistically found that duration of illness made a negligible and nonsignificant contribution to ventricular size once age was controlled (Andreasen et al. 1982; Mathew et al. 1985; Pandurangi et al. 1988; Schwarzkopf et al. 1990). In addition, in the two recent quantitative reviews, duration of illness was found to be uncorrelated with patients' mean VBRs (Cannon 1991b) and with effect size (Raz and Raz 1990) after the effect of age was partialled out.

A stronger basis for considering the possible progression of brain pathology in schizophrenia is provided by studies that have obtained multiple scans on the same patients over time. In three of the five such longitudinal studies conducted to date, there was a modest degree of variability but no significant increase in the ventricular values of schizophrenia patients over a period of 2 to 8 years (Nasrallah et al. 1986; Illowsky et al. 1988; Vita et al. 1988). In two other studies, however, schizophrenia patients evidenced significantly more progression in ventricular size over 1 to 4½ years compared with age-matched normal controls, suggesting that the progression observed in schizophrenia is greater than that found in normal aging (Kemali et al. 1989; Woods et al. 1990).

Postmortem studies have examined the issue of degeneration by determining the extent of glial scarring in the regions showing reduced volume in schizophrenia patients. Although some qualitative postmortem studies reported evidence of gliosis in the hippocampus, basal nucleus, and periventricular brainstem and diencephalic structures, in all of the controlled, quantitative postmortem studies there was no evidence of increased glial cell density in the medial temporal lobe structures, cingulate gyrus, or diencephalic periventricular regions of schizophrenia patients (see Bogerts 1991 for a review). However, the sensitivity of the staining methods in these studies remains in question (Stevens et al. 1992).

Thus, the preponderance of evidence suggests that at least some part of the brain pathology in schizophrenia is neurodevelopmental in origin and may index a relatively stable underlying vulnerability to the disorder. Given the moderate degree of progression found in two of the longitudinal studies, however, we cannot rule out the possibility that some degree of deterioration is associated with chronicity of the disease.

Functional Expression

As noted previously, much of the work on structural brain pathology in schizophrenia has been motivated by an interest in delineating subtypes of the disorder with different underlying pathophysiology. Crow (1989) suggested that structural anomalies may characterize a form of schizophrenia with poor premorbid adjustment, intellectual deficits, poor response to neuroleptics, and prominent negative symptoms. However, studies that have compared symptomatology, premorbid behavior, cognitive functioning, and treatment response in patients with "enlarged" and "not enlarged" ventricles have obtained contradictory findings. Cannon (1991a) reviewed 20 imaging studies examining ventricular enlargement in relation to positive and negative symptoms and found that although schizophrenia patients with enlarged ventricles evidenced significantly more negative symptoms than those without enlarged ventricles in 7 of the studies, there were no significant differences in the remaining 13 studies. There is a comparable degree of inconsistency with respect to the other illness dimensions (see Raz 1989, and Cannon 1991a for reviews).

The inconsistent findings are probably accounted for by several methodological and theoretical difficulties of the subgroup approach. In most of the studies, patients were divided into those with and without ventricular enlargement on the basis of arbitrary cutoff values or the distribution of an unrelated normal control group. All such studies are vulnerable to a false-negative bias because most or all of the patients classified as having normal ventricles may well be de-
viant when compared with their unaffected first-degree relatives. The strong correlation between ventricular enlargement and severity of illness observed across studies, combined with the high sensitivity rate of structural measures as illness indicators within families, argues for a continuous severity of illness–brain pathology distribution in this disorder. If this model is correct, any clinical, cognitive, or treatment differences between patients at the upper and lower ends of the pathology continuum would be simply a matter of degree and would not be meaningful from a subtyping perspective.

The effort to elucidate relationships between underlying brain pathology and clinical features of schizophrenia is complicated by several factors. First, given the considerable variability in illness expression in individual patients, it is unlikely that reliable relationships between phenomenologic variables and brain deviance will be found in studies employing a single, cross-sectional assessment of symptoms or cognitive function. Second, it is necessary to achieve a higher degree of neuroanatomical specificity in our morphological measurements before a less ambiguous assessment of their potential associations with functional impairments is possible. Third, because within-family variability in brain morphology appears to be most useful in marking the presence of schizophrenia, it is this variability that is most likely to bear a meaningful relationship to clinical dimensions of the illness. If this interpretation is correct, one would expect that the degree of difference between a patient and his or her unaffected relatives on a morphologic indicator would be more highly correlated with any functional impairments attributable to the lesion than the patient’s morphological value itself.

**Summary and Conclusions**

We have reviewed evidence that measures of brain pathology are highly sensitive indicators of illness expression within families and that some of the increase in brain pathology among schizophrenia patients and their unaffected relatives, compared with unrelated normal control subjects, is likely to be related to a genetic predisposition to the disorder. The results of twin and high-risk studies indicate that an additional share of the increase in brain pathology in schizophrenia patients is likely to be due to environmental insults such as obstetric complications. Taken together, these observations support the status of ventricular enlargement and limbic system pathology as markers of vulnerability to schizophrenia. However, several substantive questions remain to be addressed. Prospective neuroimaging studies are needed to determine conclusively whether the pathology is present in most patients premorbidly. Further longitudinal work is needed to assess whether and how the pathology may deteriorate over time. A clearer picture of the sensitivity and specificity of regional morphological variables as indicators of schizophrenia would emerge from studies employing first-degree relatives as controls for both schizophrenia and non-schizophrenia psychiatric probands. Our understanding of the role of brain abnormalities in the pathophysiology of the disorder is at this point quite limited, but it will be helped by the use of more specific neuroanatomical measurements, longitudinal assessments of phenomenologic and clinical variables, and family study designs that permit control for between-family variability in brain morphology.

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Announcement

The Western Psychiatric Institute and Clinic and the American Association of Community Psychiatrists will sponsor a conference on A New Look at Community Psychiatry: Confronting the Challenges of Our Times to be held at the Sheraton Hotel at Station Square, Pittsburgh, Pennsylvania, February 3-4, 1994. At the close of the program, participants will be able to discuss new developments in diagnosis and treatment of major mental illnesses, including substance abuse; access how reform in mental health service may affect the public patient; understand the evolving role of community psychiatrists in the mental health system; and understand the mental health aspects of the Public Health Service Plan, Healthy People 2000. For further information about the conference, please contact:

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