Temporal Lobe Asymmetries as the Key to the Etiology of Schizophrenia

by Timothy J. Crow

Abstract

With evidence that determinants of psychosis are present early and influence brain development, and in the absence of a significant environmental contribution, schizophrenia may be regarded as a genetic encephalopathy. Morphological abnormalities are particularly apparent in the temporal lobe and on the left side of the brain, and in a number of studies significant diagnosis × side interactions have been detected. Such interactions suggest an intimate relationship between the disease process and the mechanisms that determine asymmetrical brain development. These mechanisms presumably relate to the human capacity for speech and communication, and they may have played a critical role in the evolution of the human brain. A candidate locus for an asymmetry determinant and the psychosis gene within the exchange region of the sex chromosomes is proposed. Some sex differences in schizophrenia (e.g., with respect to age of onset and brain structure) may relate to subtle differences in the rate of asymmetry development in the two sexes.

It is often believed that there must be both genetic and environmental determinants of etiology in schizophrenia. However, the increasing strength of the evidence for the genetic contribution, the finding that onset is determined by developmental timing rather than extrinsic insult, and the lack of evidence for plausible environmental precipitants suggest that an exclusively genetic etiology cannot be ruled out. Such a view is supported by the following considerations: (1) Adoption away from a family that includes individuals suffering from schizophrenia does not reduce the risk of illness (Karlsson 1970). (2) Onset of illness in pairs of siblings occurs at the same age, and not at the same time as might have been expected if onset were related to an encounter with an environmental precipitant (Crow and Done 1986). (3) Incidence is approximately the same in countries with widely differing social, geographical, and industrial environments (Sartorius et al. 1986).

It is difficult to envisage an environmental factor consistent with each of these observations that could make a significant contribution to causation. The single finding that convinces many observers that the environment must contribute is discordance for illness in monozygotic (MZ) twins. It is not clear, however, that discordant MZ twins have fewer affected individuals among their relatives than do concordant pairs (McGuffin et al. 1987), as would be expected if the affected twin suffered from a nongenetic form of illness. It is also apparent that the unaffected twin sometimes has personality traits that resemble those seen in the disease. Therefore, discordance for psychosis in MZ twins is less decisive evidence for an environmental factor than is at first apparent; it has to be considered that MZ discordance represents a difference in gene expression that has an intrinsic ("epigenetic") and developmental origin instead of reflecting an environmental influence. Consistent with such an origin...
is Boklage’s (1977) observation that discordance for psychosis in MZ twins is related to discordance for right-handedness, although it should be noted that later studies by Luchins et al. (1980) and Lewis et al. (1989) have yielded more complex and somewhat differing findings.

Parfitt (1956) referred to the disease as a genetic encephalopathy and considered it to be an inborn defect of those parts of the brain that are characteristically human. According to him, onset is sometimes heralded by a heightening of function, followed by dysfunction and then in most cases by abrogation of function and a form of mental defect. The nature of episodes of illness is one of the more enigmatic aspects of the problem, although it is assumed that the identity of the psychosis gene may be found in the morphological brain changes now known to be present. Here it is suggested the disease is an anomaly of expression of the gene or genes that determine the development of asymmetry in the human brain.

The Nature of the Morphological Changes

A degree of enlargement of the lateral ventricle was first demonstrated by computed tomography (CT) by Johnstone et al. (1976) but earlier suggested by air encephalography (e.g., Haug 1962). The finding is now generally accepted in schizophrenia, particularly in studies that have included patients with chronic and deteriorating forms of illness. The meaning of these changes—in particular, at what stage of the disease they occur (i.e., whether they precede the onset of illness or progress during its course)—has been unclear. The suggestion that they are a result of physical treatments is ruled out by observations that they are as marked in patients without such treatments as in those who have had substantial amounts (Johnstone et al. 1976; Weinberger et al. 1979) even when the groups are carefully matched for other relevant variables (Owens et al. 1985).

In a recent CT study (Johnstone et al. 1989a), three distinct structural changes were detected as shown in table 1.

Lateral and third ventricular enlargement have been noted in a number of studies. A reduction in brain area has not previously been emphasized. The magnitude of the change was small but significant at the 1-percent level. Apparent reductions in brain size have been reported in two recent studies. In a CT scan study (Pearson et al. 1989), a reduction in brain slice area was found in schizophrenic patients relative to normal subjects that could not be explained on the basis of body height. In a magnetic resonance imaging (MRI) study (Nasrallah et al. 1990), a significant reduction in brain volume was observed. While ventricular enlargement might be a consequence of degeneration, a reduction in brain area or volume (unless the loss of brain substance is large) is less likely; such a reduction is more likely to be due to a failure of development. Thus, morphological changes in schizophrenia are present early and include a global component.

Asymmetries of Brain Structure in Schizophrenia

Air Encephalography (AEG) Studies (tables 2 and 3). Ventricular enlargement in schizophrenia was first reported on AEG (e.g., Jacobi and Winkler 1927). In a number of these studies, enlargement was reported to be greater on the left than on the right side. In their original study, for example, Jacobi and Winkler reported that the left ventricle was larger than the right in 9 of 19 cases while the right was larger in only one case. Lewis et al. (1962) reported that the enlargement was sometimes unilateral and in most cases on the right side. In his study, Haug (1982) found ventricular size to be greater in cases of chronic as compared to acute schizophrenia, although whether this difference relates to progression or intrinsic differences between the groups cannot be determined from assessments at a single timepoint. The changes in patients with chronic schizophrenia in this study show a degree of selectivity to the left temporal horn (table 2).

CT Scan Studies (table 3). In our patients with chronic schizophrenia, we found (Johnstone et al. 1989a) that when other relevant variables (e.g., age and duration of illness) were controlled, age of onset predicted a number of aspects of outcome. Thus, patients who were first hospitalized at an age below the mode for the group as a whole were more likely than those who were

Table 1. Schizophrenic (n = 127) vs. nonschizophrenic psychiatric patients (n = 45)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Ventricle-brain ratio</td>
<td>Increased by 10%</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Third ventricular area</td>
<td>Increased by 16%</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Brain area</td>
<td>Decreased by 3%</td>
<td>p &lt; 0.01</td>
<td></td>
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Table 2. Evidence from air encephalography of ventricular enlargement in chronic vs. acute patients with schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Acute schizophrenia</th>
<th>Chronic schizophrenia</th>
<th>Relative Increase</th>
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<tbody>
<tr>
<td></td>
<td>(n = 38)</td>
<td>(n = 101)</td>
<td></td>
</tr>
<tr>
<td>Third ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell media Right</td>
<td>12.4</td>
<td>14.1</td>
<td>13</td>
</tr>
<tr>
<td>Cell media Left</td>
<td>12.1</td>
<td>14.5</td>
<td>20</td>
</tr>
<tr>
<td>Temporal horn Right</td>
<td>2.8</td>
<td>3.6</td>
<td>29</td>
</tr>
<tr>
<td>Temporal horn Left</td>
<td>3.0</td>
<td>4.8</td>
<td>60</td>
</tr>
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</table>

*From Flaug (1982).*

first admitted at a later age to show negative symptoms, intellectual impairment (e.g., age disorientation), and behavioral deterioration. It might be expected that age of onset would predict whether or not structural change was present. Surprisingly, we found that the three measures (lateral ventricular area, third ventricular area, and total brain area) that distinguished patients with schizophrenia from other subjects did not separate those with early age of onset from those with late age of onset. However, a further structural index—the difference between the widths of the two sides of the brain in the posterior segments—did distinguish the groups. Patients with early onset had significant (p < 0.001) reductions in the width of the left hemisphere in measures taken in the occipital and temporal regions (Crow et al. 1989b). It seemed that early onset had arrested the development of the normal asymmetries in the posterior part of the brain.

Evidence for a loss of asymmetry in the occipital region in schizophrenia has also been reported in a CT scan study by Daniel et al. (1989). These authors found significant relationships between brain parenchymal and skull asymmetries: asymmetry of occipital skull measures was found to be less in a group of schizophrenic patients (with right-hand and -eye dominance) than in control subjects.

There is other CT scan evidence of a relationship between brain asymmetry and the schizophrenic disease process. In an investigation of MZ twins discordant for schizophrenia, Revely et al. (1987) demonstrated a reduction in scan density (which may indicate enlargement of cerebrospinal fluid spaces) on the left side in the ill twin. In another CT scan study, Keefe et al. (1987) reported that cases of "Kraepelinian" (poor outcome) schizophrenia had significantly greater ventricular enlargement on the left than other patients with schizophrenia.

Conflicting findings with respect to cerebral asymmetry were recorded in earlier CT studies. Luchins et al. (1982) reported that "reversals" of asymmetry (i.e., brain width wider on the right in the occipital region and wider on the left in the frontal region, by contrast with the normal findings) were more commonly found in patients with schizophrenia than in normal control subjects, and that this change was present in those patients whose ventricles were not enlarged. Although some studies (e.g., Tsai et al. 1983; Lee et al. 1985) reported similar findings, others (e.g., Andreasen et al. 1982) did not, and Luchins (1983) later concluded that "the better controlled studies have been negative" (p. 625). "Reversal" of asymmetry was not present in a study (Crow et al. 1989b) that showed reduced asymmetry in cases with early onset; in this case, arrest of development of the left hemisphere in the posterior (i.e., temporal and occipital) segments could account for the findings. It has to be considered that a failure to develop asymmetry (which is seen in changes on the later developing left side) instead of a reversal of asymmetry characterizes the schizophrenic disease process. Attempts to assess this possibility need to take handedness into account. In two studies (Crow et al. 1989b; Daniel et al. 1989), the exclusion of nonright-handers revealed stronger evidence for loss of posterior cerebral asymmetry, and in two studies (Andreasen et al. 1982; Katsanis and Iacono 1989), ventricular enlargement was found to be greater in left-handed patients with schizophrenia. Thus, left-handed schizophrenic patients may be anomalous.

MRI Studies (table 3). Recent MRI studies have reported lateralized changes in both the temporal lobe and the ventricles. With respect to temporal lobe area, Johnstone et al. (1989b) found a relative reduction (with a diagnosis × side interaction) on the left in patients with schizophrenia by comparison with those with affective disorders and age-matched control subjects. Rossi et al.
Table 3. Asymmetries of brain structure in schizophrenia

<table>
<thead>
<tr>
<th>Technique</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Air encephalography</strong></td>
<td></td>
</tr>
<tr>
<td>Jacobi &amp; Winkler (1927)</td>
<td>L&gt;R ventricle in 9 of 19 cases; R&gt;L in 1 case</td>
</tr>
<tr>
<td>Hunter et al. (1966)</td>
<td>Ventricular enlargement when unilateral left-sided</td>
</tr>
<tr>
<td>Haug (1982)</td>
<td>Temporal horn enlargement greater on L side in patients with chronic vs. acute schizophrenia</td>
</tr>
<tr>
<td><strong>Computed tomography</strong></td>
<td></td>
</tr>
<tr>
<td>Crow et al. (1989b)</td>
<td>Occipital asymmetry less in early onset cases of schizophrenia</td>
</tr>
<tr>
<td>Daniel et al. (1989)</td>
<td>Sagittal suture more symmetrical in right-handed schizophrenic patients</td>
</tr>
<tr>
<td>Keefe et al. (1987)</td>
<td>Poor outcome (Kraepelinian) cases have greater ventricular enlargement on L side</td>
</tr>
<tr>
<td>Reveley et al. (1987)</td>
<td>Scan density decreased on L in affected twin in discordant MZ pairs</td>
</tr>
<tr>
<td><strong>Magnetic resonance imaging</strong></td>
<td></td>
</tr>
<tr>
<td>Temporal lobe size</td>
<td></td>
</tr>
<tr>
<td>Johnstone et al. (1989b)</td>
<td>Relative reduction in temporal lobe area on L side in schizophrenic vs. affective patients &amp; controls</td>
</tr>
<tr>
<td>Rossi et al. (1990a, 1990b)</td>
<td>L temporal lobe area reduced</td>
</tr>
<tr>
<td>Coffman et al. (1989)</td>
<td>Temporal lobe size reduction greater on L side</td>
</tr>
<tr>
<td>Delisi et al. (1990)</td>
<td>Temporal lobe reduction in chronic patients (L&gt;R)</td>
</tr>
<tr>
<td><strong>Lateral ventricular size</strong></td>
<td></td>
</tr>
<tr>
<td>Kelsoe et al. (1988)</td>
<td>Ventricular enlargement greater in posterior regions on L side</td>
</tr>
<tr>
<td>DeGreef et al. (1990) &amp; Bogerts et al. (1990)</td>
<td>Lateral ventricular enlargement in 1st episode cases in body, occipital and temporal horns on L side</td>
</tr>
<tr>
<td>Schwarzkopf et al. (1990)</td>
<td>Left VBR and third ventricle enlargement in “sporadic” cases</td>
</tr>
<tr>
<td>Superior temporal gyrus volume</td>
<td></td>
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<tr>
<td>Barta et al. (1990)</td>
<td>Superior temporal gyrus volume reduced (L&gt;R); L gyrus volume inversely correlated with hallucinations</td>
</tr>
<tr>
<td><strong>Post-mortem findings</strong></td>
<td></td>
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<tr>
<td>Brown et al. (1986)</td>
<td>Parahippocampal gyrus width decreased on L side in schizophrenic patients relative to patients with affective disorder</td>
</tr>
<tr>
<td>Crow et al. (1989a)</td>
<td>Temporal horn enlargement in schizophrenia, but not in Alzheimer-type dementia, is selective to L side</td>
</tr>
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Note.—L = left; R = right; MZ = monozygotic. VBR = ventricle-brain ratio.

(1990a, 1990b) found significant reductions in temporal lobe area on the left but not on the right side in young patients (mean age of onset = 22 years) compared to normal control subjects. Coffman et al. (1989) observed a reduction in temporal lobe size, significantly greater on the left than on the right side, in their group of schizophrenic patients by comparison with normal control subjects, and DeLisi et al. (1990) reported similar findings in a group of patients with chronic (but not in those with acute) schizophrenia.

Kelsoe et al. (1988) found lateral ventricular area to be enlarged, particularly in the posterior (temporal and occipital) coronal sections, and those sections in which differences were seen, their significance was greater on the left side. In a study of 25 patients with first episodes of schizophrenia, DeGreef et al. (1990) and Bogerts et al. (1990) found enlargements that were significant on the left but not on the right side for the body and occipital and temporal horns, with enlargement of the anterior portion of the temporal horn being present only on the left. Schwarzkopf et al. (1990) factor-analyzed their assessments of ventricular size in 36 schizophrenic males and identified a factor of third ventricle and left lateral ventricular enlargement that was greater in patients without than in patients with a family history of schizophrenia.
A potentially interesting finding in a group of 15 male schizophrenic patients (Barta et al. 1990) is a reduction in the volume of the superior temporal gyrus, present on both sides but greater on the left. In this study, left superior temporal gyrus volume was inversely correlated with severity of hallucinations.

**Post-Mortem Studies** (table 3, figures 1-4). The nature of the brain changes and their location is further elucidated by two recent post-mortem studies. The first study (Brown et al. 1986) compared patients with schizophrenia with those with affective disorder who had died in the same institution. Brains were excluded from both groups if there was identifiable microscopic pathology (e.g., Alzheimer-type change or vascular disease). Brain structures were assessed on a photograph of a coronal section at the level of the interventricular foramina. The main findings were that when age, sex, and year of birth were controlled, (1) brain weight was reduced (by 5-6%) in the patients with schizophrenia; (2) lateral ventricular area was modestly (by 15%) but not significantly increased; (3) temporal horn area was significantly (p < 0.01) increased, the relative increase being over 80 percent; and (4) the width of the parahippocampal gyrus was reduced (p < 0.01). Of particular interest was a diagnosis x side interaction, with the differences between the groups being significantly (p < 0.02) greater on the left side (figure 1a and 1b); see figures 2a and 2b for areas assessed.

The second post-mortem study (Crow et al. 1989a) further emphasizes the relevance of asymmetry. Brains of patients with schizophrenia were compared with brains of age-matched controls. The components of the lateral ventricle were assessed on X-ray images following infusion of radio-opaque medium into the ventricular spaces after formalin fixation.

The area of the posterior and particularly the temporal horn of the lateral ventricle was increased in patients with schizophrenia—the temporal horn by a factor of 80 percent relative to the control group (figure 2a). In cases of Alzheimer-type dementia studied at the same time, ventricular enlargement was more general, affecting the anterior horns and body as well as the temporal and posterior horns (figure 2b). Of particular interest was the finding that the change in schizophrenia was selective to the left side of the brain (analysis of variance, p < 0.001), while in the Alzheimer cases there was no such lateralization (figure 3). Selectivity for the left side was present in both males and females, and was unaffected by inclusion or exclusion of brains in which histopathological changes could be detected.

The question raised is whether laterality of change relates to the disease process or to the normal asymmetries in the human brain— that is, do the findings indicate that the disease process itself is lateralized, or do they reflect an interaction between a bilateral process and normal anatomical and chemical asymmetries? The second post-mortem study (Crow et al. 1989a) addresses this question. Temporal horn enlargement is present in Alzheimer-type dementia, but it is not lateralized; when present in schizophrenia, it is selective to the left hemisphere. The findings rather strongly support the view (Crow 1984) that the disease process in schizophrenia is in some way associated with the mechanisms that determine the asymmetries in the human brain.

**Are There Significant Diagnosis x Hemisphere Interactions?**

The key issue is whether the apparent asymmetry in schizophrenia reflects more than that the human brain is itself an asymmetrical structure. Could it be argued that as a consequence of this fact differences are more likely to be observed on the left side? If, on the contrary, there is a relationship between the disease process and the mechanisms of determination of cerebral asymmetry, significant interactions between diagnosis and hemisphere will be expected. Some but not all the above studies give evidence of such interactions. The data from AEG have not been assessed from this point of view. Among CT scan studies, significant diagnosis x side interactions were present in the MZ twin study of Reveley et al. (1987), and among MRI studies, in those of Johnstone et al. (1989b) and Rossi et al. (1990a, 1990b). In addition, in the study of Coffman et al. (1989), right-left difference scores for the temporal lobe area were significantly (p < 0.02) greater in schizophrenic patients than in control subjects.

Perhaps the clearest evidence comes from the Northwick Park post-mortem studies. In the first (Brown et al. 1986), a diagnosis x hemisphere interaction (p < 0.02) was present for the width of the parahippocampal gyrus, and in the second (Crow et al. 1989a), such an interaction (p < 0.002) was observed for temporal horn area (assessed from the lateral aspect) and for measures of the height of the temporal and occipital
horns measured along the axis of the brainstem.

Thus, there is moderately compelling evidence that the structural changes in the brains of schizophrenic patients are lateralized, and there is some evidence from the second study that the asymmetry is specific to schizophrenia (figure 3).

The NIMH Neuroscience Center Study of Discordant MZ Twins

An MRI study recently reported from the National Institute of Mental Health (NIMH) Neurosciences Center by Suddath et al. (1990) provides an important test of the laterality hypothesis. These authors examined brain structure in MZ twin pairs discordant for schizophrenia and have drawn attention (Weinberger et al. 1990) to the fact that with respect to some of the comparisons (e.g., the volumes of the lateral ventricle, the hippocampus, and the anterior temporal gray matter), consistent differences between ill and well twins are present on both sides of the brain.

This finding establishes beyond a reasonable doubt that major changes associated with the schizophrenic disease process are present on both sides of the brain. However, volume measurements of total gray matter in the temporal lobe (reported in the paragraph entitled “Global Volume Measurements” on p. 791 of Suddath et al. [1990]) reveal a quite striking difference between ill and well twins only in the middle (in the anteroposterior dimension) segment. This segment includes particularly the isthmus, that part of the corpus callosum which, according to Witelson (1989), carries the fibers that connect those regions of the temporal lobe in which asymmetries are present.

The Meaning of Cerebral Asymmetry

Interest in the left brain in schizophrenia in recent years dates from Flor-Henry’s (1969) report that when psychotic changes are seen in association with temporal lobe epilepsy, the form of the psychosis is schizophrenia-like if the focus is on the left side. However, the concept has a history that extends back to not long after Broca’s confirmation (1861) of Dax’s (1865) localization of speech to the left hemisphere. Thus, Crichton-Browne (1879) wrote that “the cortical centers which are last organized, which are the most highly evolved and voluntary, and which are supposed to be located on the left side of the brain, might suffer first in insanity…” (p. 42), and Southard (1915) summarized his own studies of the pathology of schizophrenia as showing that “the atrophies and aphasias when focal show a tendency to occur in the left cerebral hemisphere” (p. 662). He added that “Aside from the left-sidedness of the lesions very striking is the preference of these changes to occupy the association centers of Flechsig” (p. 663) and “for this there is probably good a priori reason in the structure, late evolutionary development, and consequent relatively high lability of these regions” (p. 663).

Table 4. Monozygotic twin pairs ($N = 15$) discordant for schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
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<tbody>
<tr>
<td><strong>Anterior temporal gray matter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well twin</td>
<td>7.86 ± 1.20</td>
<td>8.47 ± 1.27</td>
</tr>
<tr>
<td>Ill twin</td>
<td>7.61 ± 1.36</td>
<td>8.57 ± 1.33</td>
</tr>
<tr>
<td><strong>Total temporal gray matter</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well twin</td>
<td>28.43 ± 5.99</td>
<td>30.53 ± 6.24</td>
</tr>
<tr>
<td>Ill twin</td>
<td>26.77 ± 5.37</td>
<td>30.21 ± 4.97</td>
</tr>
<tr>
<td>$p &lt; 0.002$</td>
<td></td>
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</table>

1From Suddath et al. (1990)
The anatomical basis of the asymmetries has been much clarified by Geschwind and colleagues. They found that in most people, particularly right-handers, the lateral sulcus extends back further on the left than on the right side of the brain (Geschwind and Levitsky 1968). This reflects the fact that there are structures in the left temporal lobe—for example, including the planum temporale, which forms part of the superior temporal gyrus—that are larger on the left than on the right. These encompass those areas of association cortex, including Wernicke’s area, that are responsible for speech and communication.

The gene controlling cerebral dominance is among those that particularly distinguish man from other primates. The cerebral dominance gene or right-shift factor is known from the studies of Annett (1985), McManus (1985), and others on handedness. It is transmitted as an autosomal dominant, although its location is unknown. Of the 30,000 genes that are said to be expressed in the brain, the cerebral dominance gene seems the best candidate for the psychosis gene that we now have.

### Location of the Cerebral Dominant Gene

A clue to the location of the cerebral dominance gene comes from the studies of the neuropsychology of Turner’s and Klinefelter’s syndromes that have been conducted by Netley and Rovet (1982, 1987). Turner’s syndrome cases lack an X chromosome and Klinefelter’s have an extra X chromosome. Netley and Rovet found that on IQ tests they have reciprocal deficits (table 5); in Turner’s syndrome, there is a performance deficit (Netley and Rovet 1982), and in Klinefelter’s syndrome, there is a verbal deficit (Netley and Rovet 1987). The obvious interpretation is that Turner’s syndrome is characterized by a right-hemisphere deficit and Klinefelter’s syndrome by a left-hemisphere deficit. Thus, some factor located on the X chromosome is responsible for the relative development of the two hemispheres. However, because in normal females one X chromosome is inactivated, abnormalities in Turner’s syndrome are attributable to those parts of the X chromosome that are not inactivated. These include, particularly, the pseudoautosomal or exchange region (Ferguson-Smith 1965), suggesting that the cerebral dominance gene is either in the pseudoautosomal region or in some other part of the X chromosome that is not inactivated (Crow 1989).

The pseudoautosomal region is that distal segment of the short arms of the X and Y chromosomes within which recombination occurs in male meiosis (Burgoyne 1986). Within this region there is strict homology of genes on the two sex chromosomes, although outside it there is divergence. Because in male meiosis a single obligatory crossover occurs within the region, there is a high rate of recombination here relative to other parts of the genome. Another peculiarity is that the region is not subject to inactivation in the female. Characteristic of pseudoautosomal transmission is concordance by sex—that is, that within a sibship affected individuals will be more often than otherwise would be expected of the same sex. This arises because when a gene within the region is passed from a father, it travels either on the X chromosome to daughters or on the Y chromosome to sons. When passed from a mother, it travels on the X chromosome without association to the sex of the children. Therefore, for a pseudoautosomal gene, concordance by sex is associated with paternal transmission. Evidence that this prediction holds for pairs of siblings with psychosis has recently been presented (Crow et al. 1989c, 1990).

### Sex x Diagnosis Interactions and Their Possible Significance

A curious but well-documented feature of the epidemiology of schizophrenia is earlier onset in males (Hafner 1987; Lewine 1988). Sex differences have also been apparent in some recent morphological studies: (1) Andreasen et al. (1990) reported that ventricular enlargement in a series of 55 patients with schizophrenia was significantly greater in males than...
in females. (2) In an MRI study, Nasrallah et al. (1990) found a reduction in brain volume in 20 patients with schizophrenia by comparison with normal control subjects that was greater in females than in males, with a significant diagnosis x sex interaction. (3) In an MRI study, Raine et al. (1990) found the corpus callosum to be thicker in females than in males—the findings being the reverse of those in normal subjects.

It seems worth considering whether an explanation of these sex differences may be found in the sexual dimorphism that is present in brain asymmetry. In a post-mortem study, Witelson (1989) has described a sex difference in the isthmus of the corpus callosum—that part which carries fibers from cortical areas that are asymmetrically distributed, females having larger isthmus area than males. According to DeLacoste and Woodward (1988), sex differences in the corpus callosum in primates are closely related to the evolution of cerebral asymmetries.

One can envisage that some aspect of the development of brain asymmetry is different in the two sexes and that this might relate to sex differences in age of onset and brain morphology in schizophrenia. For example, if as is sometimes suggested the brain is more lateralized in males than females, one might suppose that the process of lateralization proceeds faster in males. In this case, if there is an anomaly of the gene that controls lateralization, this would become manifest earlier, and if such manifestation were associated with arrest of development, the effects on ventricular and brain size in the two sexes might be different.

**Evolutionary Origins**

What is the evolutionary significance of the cerebral dominance gene?

In his book entitled *Evolution of the Brain and Intelligence*, Jerison (1973) includes a figure (reproduced here as figure 4) to show the relationship between brain weight and body size among primates. The point is that in species of the genus Homo, brain size has developed out of proportion to body size. Jerison (1973) has no doubt about the origin of these developments:

> We need not look far for special selection pressures toward the major enlargements of the brain within the genus Homo. The socialized life of a predacious primate is so obviously benefited by linguistic skills, and language is so manifestly the peculiarly human development, that change in the brain to permit that advantageous supplement to perception and communication would have had obvious selective advantages throughout the period of hominid evolution. [p. 465]

Levy (1977) spelled out the benefits of having the two hemispheres perform different functions:

> Bilateralization of function arose in response to specifically human pressures, occurring in a socially organized species, the members of which were mutually interdependent... [p. 271]

The significance of the cerebral dominance gene, then, is that it permitted new evolutionary developments, and the significance of psychosis may be that it reflects the disadvantageous spinoff of this essentially human evolutionary development.

**Conclusion**

With a strengthening case that determinants of psychosis are present early and influence brain development, and in the absence of evidence of a significant environmental contribution, it must be assumed that the etiology of schizophrenia is primarily genetic. Perhaps, to adopt Parfitt's (1956) suggestion, the disease should be referred to as a genetic encephalopathy.

Morphological abnormalities in the temporal lobe, as detected by AEG, CT scan and MRI, as well as in post-mortem studies, are seen particularly on the left side. Diagnosis x side interactions have been demonstrated a number of times: in one post-mortem study, enlargement of the temporal horn (viewed from the lateral aspect), present on both sides in Alzheimer-type dementia, was confined to the left in schizophrenia. The conclusion appears inescapable that there is a close relationship between the disease process and those genes that determine the development of asymmetry in the human brain.

Cerebral asymmetry relates to the capacity for speech and communication, and to handedness, a characteristic that may be transmitted as a simple Mendelian dominant. A possible location for the cerebral dominance gene or right-shift factor is within the pseudoautosomal or exchange region of the sex chromosomes. Therefore, this is a candidate locus for the psychosis gene.

Some sex differences in schizophrenia (e.g., with respect to age of onset and brain changes) may be explicable on the basis that the development of cerebral asymmetry proceeds at a slightly different rate in the two sexes. It is suggested that this mechanism has played a fundamental role in the evolution of the human brain.
Figure 1a. Diagram of a coronal section of the brain at the level of the interventricular foramen to indicate areas of cortex assessed.

Figure 1b. Widths of cingulate gyrus, insula-opercular cortex, and parahippocampal gyrus on the 2 sides of the brain in patients with schizophrenia (colored columns) and affective disorders (open columns).

**Areas assessed**

- Caudate nucleus (C)
- Corpus callosum (CC)
- Lateral globus pallidus (L)
- Medial globus pallidus (M)
- Putamen (P)
- Sylvian sulcus (S)
- Temporal lobe (T)
- Ventricle (V)
- Third ventricle (III)

**Average cortical thickness**

- Cingulate gyrus
- Insula-opercular cortex
- Parahippocampal gyrus

Bars indicate standard errors. For the parahippocampal gyrus, there is a significant (p < 0.01) reduction in width in schizophrenia and a diagnosis x side (p < 0.02) interaction (adapted, with permission, from Brown et al. 1986).

Cingulate gyrus (green), insula-opercular cortex (yellow), and parahippocampal gyrus (red).
Figure 2. Enlargement of the components of the lateral ventricle in (a) schizophrenia and (b) Alzheimer-type dementia, relative to age-matched controls.

Ventricular components are defined by vertical lines and are color-coded: anterior horn—green, body—yellow, posterior horn—orange, and temporal horn—red (adapted, with permission, from Crow et al. 1989a).

Lateral ventricular components
Percentage increase in schizophrenia as compared with normal controls.
Figure 3. Enlargement of the temporal horn on the two sides of the brain in Alzheimer-type dementia and schizophrenia.

By analysis of variance there is a diagnosis x side interaction ($p < 0.001$) (adapted, with permission, from Crow et al. 1989a).
Figure 4. Relationship between brain size and body weight in primates

\[
\text{Brain weight (g)} \quad \text{Body weight (kg)}
\]

- S = H. sapiens
- E = H. erectus
- H = H. habilis
- Z = A. boisei
- A = A. africanus

Dotted lines indicate the expected allometric relationship between brain and body weight in species with a similar degree of encephalization (adapted from Jerison 1973).
References


Johnstone, E.C.; Owens, D.G.C.; and their cerebral correlates.

Johnstone, E.C.; Owens, D.G.C.; Crow, T.J.; Frith, C.D.; Alexan-

logical Medicine,

Cerebral ventricular size and structural brain changes in schizo-

Bydder, G.M.; Colter, N.; Crow, T.J.; and Frith, C.D. The spectrum of structural brain changes in schizo-


Lee, J.H.; Lee, Y.J.; and Oh, S.W. Schizophrenia and cerebral lateral-


Netley, C.T. Summary overview of behavioral development in indi-


Sartorius, N.; Jablensky, A.; Korten, A.; Emberg, G.; Anker, M.; Cooper, J.E.; and Day, R. Early manifestations and first contact incidence of schizophrenia in different cultures. Psychological Medicine, 16:909-928, 1986.


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