Abstract

Asymmetries of the brain have been known about for at least a century, but they have been explored in detail only relatively recently. It has become clear that, although different asymmetries are common throughout the animal kingdom, they are most marked in the human brain. Disturbances in asymmetry are particularly striking in patients with schizophrenia and perhaps all psychotic illnesses, and may provide the neurological substrate for the etiology and clinical manifestations of the illness.

Key words: Structural asymmetries, functional asymmetries, laterality.


The two hemispheres of the human brain and their interactions have intrigued scientists and philosophers for centuries. Although functional asymmetries—the simplest being handedness—have been known for millennia, it is only within the last 150 years that it has gradually become clear that there are also structural differences between the two sides of the brain. However, as recently as 1929, a comparative study of endocranial casts (endocasts) of modern and prehistoric man and of anthropoid apes found no marked cerebral asymmetries (Weil 1929). Until relatively recently, it was usually held that only humans exhibited structural asymmetries, but increasing evidence indicates that structural lateralization is common among such disparate nonhuman species as birds, monkeys, and apes (for a review, see Bradshaw 1991). Furthermore, there is impressive evidence that structural asymmetries are to be found far back in evolution: studies of a 600-million-year-old Cambrian fossil, the calcichordate Placocystites forbesianus—a primitive forerunner of some vertebrates—appear to show clear evidence of caudal asymmetry (Jefferies and Lewis 1978). Indeed, it may be that asymmetry is the rule. However, it is also clear that the greatest degrees of structural laterality are to be found in the human brain. Presumably, this increase in the degree of asymmetry is what misled earlier investigators to think that asymmetry of the nervous system was not present in other organisms. (Other asymmetries—for instance, one claw of the blue crab being larger than the other—have long been known.) It has also become clear that asymmetry is not found only in the cortex, but also in many subcortical structures, presumably reflecting their close interrelationships.

The apparent ubiquity of cerebral asymmetry among animal species raises a number of important questions, a detailed discussion of which lies outside the scope of this article. Similarly, we must omit an exploration of the possible reasons for these asymmetries. For the interested reader we recommend a recent review by Lent and Schmidt (1993).

The objective of this article is to examine the current evidence concerning the normal structural asymmetries of the brain, then move to a discussion of the disturbances of these structural asymmetries in schizophrenia. While this review deals with the evidence concerning structural asymmetries that have been revealed by neuroimaging, in normal individuals and in those with schizophrenia, the data must clearly be placed in the broader context of asymmetries discovered from other sources, including anatomy, paleontology, and biochemistry. We would also stress at the outset that the unbridled enthusiasm of the 1970s for unequivocal differentiation of hemispheric structure and function has given way to an appreciation of the fundamental reciprocity between the hemispheres (Gruzelier 1981; Nass and Gazzaniga 1989; Efron 1990).

Gross Anatomical Asymmetries

The developing brain already shows marked asymmetries by the second trimester of pregnancy. The cortical fissures are consistently found to appear earlier in the right hemisphere (Dooling et al. 1983; Nowakowski 1987), and the

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most marked asymmetry in the brain, that of the planum temporale, has been identified in fetal brains (Wada et al. 1975; Chi et al. 1977) and in the majority of infants (Witelson and Pallie 1973). This structure is of great importance in health and perhaps also in schizophrenia.

The earliest studies of structural asymmetries of the brain concentrated on indices such as the weight and volume of the hemispheres, the relative proportions of gray and white matter, and the differences in the thickness and folding of the cortex on the two sides. Perhaps because of the limited technologies employed, few differences were found. However, there were some reports of reproducible asymmetries. Eberstaller (1884) and Cunningham (1892) both described asymmetries in the posterior ends of the Sylvian (lateral) fissures, the left reaching further back and being more horizontal. These findings have been confirmed using arteriography (LeMay and Culebras 1972) and computed tomography (CT) scanning (Rubens et al. 1976; LeMay and Kido 1978). It has also become clear that the distribution of this asymmetry is related to handedness (Hochberg and LeMay 1975).

Before these contemporary confirmations, it had been assumed that the longer left Sylvian fissure was a consequence of larger temporal and parietal opercula, which form, respectively, the floor and roof of the posterior fissure. This was partially confirmed by Pfeiffer (1936), who demonstrated a larger left temporal operculum. Additionally, he made the observation that the left planum temporale (PT) was larger on the left. The PT is a triangular area lying on the superior surface of the superior temporal gyrus, between Heschl’s transverse gyrus (the primary auditory area) and the most posterior portions of the Sylvian fissure. This finding was confirmed in elegant studies that also showed the left PT to be larger on the left side in 65 percent of brains, approximately equal in 24 percent and larger on the right in 11 percent (Geschwind and Levitsky 1968). This distribution of PT asymmetry has since been confirmed many times (Teszner et al. 1972; Witelson and Pallie 1973; Wada et al. 1975; Kopp et al. 1977).

With the advent of sophisticated neuroimaging techniques, it has proven possible to identify the PT on magnetic resonance imaging (MRI) scans, and once again the asymmetry has been confirmed (Steinmetz et al. 1989), together with the new observation that the relative dimensions of the PT on the two sides are related to handedness (Steinmetz et al. 1991; Barta et al. 1997). The left PT may be as much as 10 times larger than the right, greater than any other asymmetry anywhere else in the human brain and far outstripping any asymmetries observed in other species so far examined. There are other differences in the PT on the two sides, the most striking being the existence of one or more additional transverse gyri (Pfeiffer 1936; Campain and Minckler 1976). These findings have been confirmed in the fetus: The PT develops between the 29th and 31st weeks of gestation (Chi et al. 1977).

There is ample reason for taking a special interest in this region of the brain. Not only is it the most highly lateralized so far identified, but it also contains a portion of the heteromodal association cortex responsible for the comprehension and generation of language (Galaburda et al. 1978, 1987, 1990; Galaburda and Sanides 1980; Leinonen et al. 1980; Galaburda 1993). This same system is involved in a number of other major cognitive functions, including working memory (Mesulam 1985; Goldman-Rakic 1987, 1990). The PT is also the typical site of injury in patients with Wernicke’s aphasia.

Taken together, these observations suggest an intimate association between the anatomical asymmetry of this discrete region of the brain and the functional localization of much language activity to the left hemisphere. Attention has also been drawn to the incidence of asymmetries of the PT and the incidence of hand skill in the population (Annett 1992). It is of note that similar asymmetries in this region have been identified in the chimpanzee (Yeni-Komshian and Benson 1976). One major problem remains, however, that is of general importance in any discussion of sizes and volumes of structures in the brain. It is the problem of generating a precise definition of what constitutes the PT. This point has recently been explored in some detail (Galaburda 1993; Barta et al. 1995).

In the frontal lobe, the size of the regions involved in language are, in both fetal and adult brains, paradoxically smaller in the left hemisphere than in the right, if measured only according to the visible surface area (Wada et al. 1975). However, over a century ago, Eberstaller (1884) noted that regions around the frontal operculum, a component of Broca’s (the anterior language) area, are more convoluted—hence, probably larger—on the left. These findings have received support using contemporary methodologies (Falzi et al. 1982).

A number of other asymmetries have been noted in the brain, particularly through the use of radiological methods. Furthermore, the study of “endocasts”—the impression that the brain leaves on the inner surface of the skull—has made it possible to make inferences about the shape of the brain of ancient man and nonhuman anthropoids. Thus it has become feasible to make deductions about the evolution of cerebral dominance. This is significant, because the structural organization of the brain is of greater importance than just its size (Holloway 1968). The endocast of a Neanderthal dated at approximately 50,000 years old showed the pattern of Sylvian fissure asymmetry characteristic of modern man (Boule and Anthony 1911; LeMay and Culebras 1972). More re-
markable still is a similar finding in Peking Man dated over 500,000 years ago (Shellshear and Smith 1934). If we remember that the common explanation for the differences between the two sides is that it resulted from the growth of areas of the brain responsible for language, a possible implication is that language may have developed earlier in evolution than is normally assumed (Kochetkova 1978).

There are no clear effects of ethnic origin on brain asymmetries (Hrdlicka 1907). In a study of 297 East African skulls, the right frontal and left occipital regions of the brain protruded beyond the corresponding structures on the opposite sides (Gundara and Zivanovic 1968). These protrusions are known as petalias. The most characteristic pattern, a more protruding right frontal lobe, is termed right fronto-petalia. It is typically associated with a greater protrusion and width in the left occipital lobe—left occipito-petalia. This protrusion in normal adults is a reflection that the left occipital lobe and the right frontal lobes are larger than their counterparts in the opposite hemisphere (LeMay and Kido 1978; Pieniadz and Naeser 1984). This is referred to as “counterclockwise” or “Yakovlevian” torque, and it is most marked in right-handers. These characteristics are certainly present at 32 weeks gestation (LeMay 1984) and are reflected in gross volumetric measures of the frontal and occipital regions (Weinberger et al. 1982). In studies of the brains of early humans, it appears that this characteristic pattern was also present 100,000 years ago.

The most marked asymmetries of the cerebral hemispheres are found posteriorly. This is the major component of the normal torque. Associated with this is usually a greater protrusion of the outer margin of the left occipital bone, compared with the right (Smith 1907). In association with this greater left-sided posterior extension, the ipsilateral thalamus and choroid plexus (when it can be seen due to calcification of the glomus) also lie posterior to those on the right (LeMay 1976). The left occipital petalia is associated with a more posterior positioning of the splenium, longer temporal horn, and cerebellar protrusion, all on the same side (Hadziselimovic 1980). Since the early part of this century, attempts have been made to relate the shape of the head, and particularly of the petalias, to handedness (Smith 1907, 1908), but with only limited success. The development of progressively more sophisticated methods of analyzing MRI data (e.g., Falk et al. 1991) is revealing a number of patterns that appear to be typical. In addition to the now familiar counterclockwise torque, there appears to be a leftward asymmetry of the temporal back of the caudal portion of the infra-Sylvian surface. This is balanced by a rightward asymmetry of the parietal bank (Loftus et al. 1993). The pattern can be best visualized in three dimensions as a “balanced asymmetry” in the horizontal plane. Apart from the association of the normal torque pattern and handedness and the “balanced asymmetry,” other gross morphological asymmetries are associated with some measures of functional asymmetries, notably speech lateralization and handedness both in vivo (Ratcliff et al. 1980) and at postmortem (Witelson 1983; Witelson and Kigar 1992).

Similar asymmetries are also seen in apes and to a lesser degree in some monkeys (LeMay 1976; Holloway and De La Coste-Lareymondie 1982). In a study of photographs of 28 higher apes, the human pattern with a higher right Sylvian fissure was present in 16 and the higher left in only 1 (LeMay and Geschwind 1981). Similarly, an examination of ape and monkey endocasts has shown that the apes resemble humans, as, to a lesser extent, did Old World monkeys. However, there were few asymmetries in New World monkeys, with the exception of the protrusion of the left occipital region relative to the right (LeMay 1976).

With the advent of radiological techniques, it has become clear that there are a number of asymmetries in the brain. The first to be identified were ventricular asymmetries, shown by pneumoencephalography (PEG). The left lateral ventricle is usually (in ~ 70%) wider than the right, particularly anteriorly and in the tips of the temporal horns (LeMay 1984). Earlier observations derived from casts of the ventricles made after death had shown the left lateral ventricle to be larger in only 48 percent (Last and Thompset 1953). However, for purely technical reasons it is likely that the higher value would be correct. Indeed, a study of computed tomography (CT) scans of 100 normal adults again showed the left lateral ventricle to be wider than the right in 62 percent, with the right wider in 32 percent. In addition, males showed a greater difference between the measurements on the two sides (Gyldensted 1977).

Both the shape and the size of the lateral ventricles, particularly the occipital horns, show a correlation with the shape and size of the brain and the skull (Bailey 1936; Berg and Lonnun 1966). When fetal brains were examined at post mortem, it was found that the occipital horns occupied a much larger proportion of the overall ventricular volume than they do later in life (Curran 1909). It appears that as the brain increases in size, even after birth, the occipital horns become relatively smaller and more asymmetrical. Ventricular asymmetries are quite clear by the end of the first year of life (Lodin 1968), although there are no data on whether there are gender differences in the magnitude or timing of the development of this asymmetry. In a PEG study of 100 right-handed adults, the left occipital horn was longer in 60 percent, and the right in 31 percent (McRae et al. 1968). When the same
investigators examined a group of patients with epilepsy, they found a striking deviance from the normal pattern, with equal lengths in 60 percent of right-handers and 38 percent of left-handers, suggesting an abnormality of brain development or possibly some other insult to the brain. Similar findings were reported in young children. The left occipital horn was longer in 60 percent, but in those who had developed epilepsy before the age of 1 year, the two sides were either symmetrical or the right was longer (Strauss and Fitz 1980).

The association of structural and functional asymmetries has received increasing attention. We have already referred to the typical Yakovlevian torque being more accentuated in right-handers and to the interactions between handedness and the structure of the corpus callosum (Witelson 1989) and the Sylvian fissure (Witelson and Kigar 1992). Frequently, however, there have been limitations in the analysis of handedness (Chapman and Chapman 1987; Bryden and Steenhuis 1991), in the interpretation of structural data, or in controlling for gender or for the presence of diseases that might affect the brain. Clearly, there are also individual differences in brain asymmetries and fiber composition in the corpus callosum, implying the need for large studies to segregate the relationships between handedness and callosal structure (Aboitiz et al. 1992). A CT study of children, 71 percent of whom had epilepsy, clearly demonstrated significant structural asymmetries, but these did not correlate with measures of handedness (Deuel and Moran 1980). However, examination of the presented data reveals technical difficulties in the interpretation of the scans, and as we have already seen, epilepsy may be associated with a disturbance of the normal pattern of brain asymmetry.

In addition to these regional differences, there are more generalized interhemispheric differences. The ratio of gray to white matter is smaller in the right hemisphere. The greater amounts of gray matter on the left are primarily in the motor, premotor, and primary sensory area (Gur et al. 1980). These findings are consistent with the assertion that the left hemisphere is focally organized, whereas the right is more diffusely organized (Semmes 1968). Data from a variety of sources indicate that hemispheric differences can be best understood in terms of specific principles that are relevant to defined cognitive functions. So the left hemisphere is superior at encoding visual categories, but the right is better at representing overall visual patterns (Brown and Kosslyn 1993).

Gender and Asymmetries of the Nervous System

That there are hormonal influences on the brain is not in doubt. A more challenging question is whether hormones themselves or the sex chromosomes may affect the structure of the brain. In 1879, Crichton-Browne wrote that "the tendency to symmetry in the two halves of the cerebrum is stronger in women than in men" (p. 53). Although there are wide variations, there does indeed seem to be a true sexual dimorphism in the asymmetry of the brain (Bear et al. 1986). The hypothesis that prenatal exposure to testosterone could be responsible for differential rates of brain maturation and asymmetry has, as intended, generated considerable interest and debate, although no firm conclusions (Geschwind and Galaburda 1984).

The gross structure of the brain appears to be the same in males and females, with the exception of size differences, which appear themselves to be a function of height rather than gender (McGlone 1980; Janowsky 1989). However, a number of lines of evidence indicate gender differences in the maturation of the fetal and young child’s brain. Furthermore, there is some evidence of gender differences in a number of neuropsychological tasks ascribed to different hemispheres (for a review see Halpern 1992). There is evidence in favor of these differences being genetically determined. On tests of intelligence, patients with Turner's syndrome (XO) have performance deficits relative to verbal, which are consistent with right hemisphere dysfunction (Netley and Rovet 1982), and maldevelopment of heteromodal association cortex in the right hemisphere (Christensen and Nielsen 1981). By contrast, patients with an extra X chromosome—Klinefelter’s syndrome—and triple X syndrome have verbal deficits or delays, while their performance IQ tends to be in the normal range, suggesting left hemisphere dysfunction (Netley 1986).

The most important conclusion from a number of studies has confirmed Crichton-Browne’s observation that the male brain is indeed more symmetrical than the female. It has also become clear that the corpus callosum is larger in women, particularly in its more posterior parts (Witelson 1989; Kimura 1993), and that there are, in the callosum, marked interactions between gender and handedness (Cowen et al. 1993). It has been suggested that a larger corpus callosum is associated with better interhemispheric transfer of information, which might contribute to the statistically superior verbal fluency in women (Hines 1990). This gender difference in the corpus callosum may be relevant to the symptomatology of schizophrenia and the different clinical expressions of the disease in men and women. There are structural abnormalities in the corpus callosum in schizophrenia (Woodruff et al. 1993), although it is not yet known whether these abnormalities are modulated by gender. Several authors have found evidence of abnormalities in callosal transfer in schizophrenia, but the precise nature of this remains the subject of
considerable debate. Although there does appear to be good evidence of structural difference in male and female brains, particularly in more asymmetrical structures, this theory has not found universal acceptance. For instance Janowsky (1989) has argued that we do not know enough about the composition of neural networks to conclude that these structures are actually different in males and females.

One of the most contentious issues in neurobiology is the reported association between sexual orientation and brain structure. For instance, Allen and Gorski (1991, 1992) have reported that the size of the anterior commissure varies with sexual preference. A further interesting report showed an alteration of functional cerebral asymmetry during the menstrual cycle (Heister et al. 1989). Dopamine is lateralized, and it is also modulated by estrogens; this may indicate a relationship between structure, neurochemistry, and hormones that could be relevant to the differing clinical presentations of schizophrenia in men and women. It may also be relevant that there are structural and functional neuroendocrine asymmetries in the brain (Witling and Schweiger 1993), as well as an interrelationship between cortical and autonomic asymmetries, both of which may have structural as well as physiological bases (Gallhofer et al. 1993; Shannahoff-Khalsa 1993; Velikonja et al. 1993). These observations may be significant in view of the frequent observations of disturbances in autonomic, endocrine, and immunological function in schizophrenia.

An interaction between sex hormones and laterality was first suggested by Geschwind and Galaburda (1984; pp. 211–224). A later, refined version of this hypothesis posits that lower amounts of testosterone in the fetal female brain lead to less regression in the tempo-parietal region of the left hemisphere, with a consequently larger callosal isthmus. This, in turn, results in less functional asymmetry (Witelson 1991).

Crow (1993) has woven a number of different observations into an ingenious hypothesis linking the different ages at onset of schizophrenia in males and females with, among other things, the gender differences in asymmetry. He has also correctly predicted that normal asymmetry would be disturbed in schizophrenia. These concepts are very important and will be discussed in greater detail later.

### Asymmetries of the Cellular Organization of the Brain

Many architectonic asymmetries have been identified in the brain. While an examination of these lies outside our immediate field of interest, it is important to be aware that the most consistent asymmetries have been identified in regions of heteromodal association cortex involved in language. For instance, von Economo and Horn (1930) showed that left-sided auditory association cortex, which lies largely within the PT, is consistently larger on the left side. A series of studies by Galaburda and his collaborators have confirmed and extended these findings (Galaburda et al. 1978, 1987, 1990; Galaburda and Sanides 1980; Galaburda 1993). These asymmetries are not confined to histology. In area Tpt, which occupies a major portion of the PT and of the adjacent superior temporal gyrus, there is a consistent increase in the amount of choline acetyltransferase on the left (Amaducci et al. 1981). Further left-preponderant asymmetries have been identified in the inferior parietal lobule, another portion of the heteromodal association cortex with prominent language functions (Eidelberg and Galaburda 1984).

As might be anticipated, there is also an asymmetry of regions of the brain that enjoy close connections with these language-specific regions. The posterior thalamus appears to be relevant to language functions (Bell 1968; Geschwind and Galaburda 1984; Ojemann 1991). It is usually the pulvinar that is implicated, but adjacent nuclei probably also participate in language. One of these—the lateralis posterior nucleus of the thalamus—is larger on the left, but only in individuals with a larger left PT (Eidelberg and Galaburda 1982). This nucleus does project to the inferior parietal lobule (Geschwind and Galaburda 1984). More recently a unique population of large neurons has been identified in the left hemisphere. These lie in layer III of the anterior language area (Brodman’s area 45), providing further support for a structural asymmetry in a region with marked functional lateralization (Hayes and Lewis 1993).

It is striking that the most marked asymmetries are found in the PT and planum parietale (Jancke et al. 1994) and in parts of the dorsolateral prefrontal cortex. All of these lie within one of the most phylogenetically recent portions of the brain: a widely distributed but highly interconnected system—the heteromodal association cortical regions of the cerebral cortex. These appear to provide the neurological substrate for higher functions of language, thinking, and ideation.

### Structural Asymmetries Below the Tentorium

It has become quite well recognized that asymmetries are found at several levels of the nervous system. The decussation of the pyramids is asymmetrical in both fetal (Yakovlev and Rakic 1966) and adult human brains (Kertesz and Geschwind 1971). A further common asymmetry has been described in the lower medulla: an aberrant circum-olivary bundle that may be involved in the innervation of some muscles of articulation (Smith 1904).
Neurochemical Asymmetries. We have already referred to the asymmetry of choline acetyltransferase activity in the superior temporal gyrus (Amaducci et al. 1981). In addition, the left pulvinar contains more norepinephrine than the right (Oke et al. 1978). Postmortem analysis of neurotransmitters is notoriously difficult. Nevertheless, studies have indicated further left-right asymmetries in the content of dopamine, glutamic acid decarboxylase, and gamma aminobutyric acid in the basal ganglia (Glick et al. 1982). Possible doubt about the validity of these findings has been allayed by discoveries of similar biochemical asymmetries in the rat (Carlson and Glick 1989). These asymmetries, particularly an increased content of dopamine in the left globus pallidus, could have significant behavioral consequences. It has been suggested that these asymmetries in rats may be related to paw preference and hemiorientation (Carlson and Glick 1989). There are some data to suggest that behavioral lateralization of neonatal rats is related to asymmetries in cerebral dopamine (Afonso et al. 1993). In a more indirect, but potentially important study, children with early treated phenylketonuria, which is associated with developmental dopamine depletion, were studied on tasks of visual attention. The boys showed clear evidence of left-hemisphere dysfunction, but the girls did not (Craft et al. 1992). If confirmed, this finding may well have far-reaching consequences for our understanding of the development of gender differences in functional, and perhaps also in structural lateralization. It is now clear that dopamine turnover in the right and left nigrostriatal pathways is reciprocally regulated (Glowinowski et al. 1984). A further famous and potentially behaviorally significant experiment involved the administration of lysergic acid diethylamide (LSD-25) to patients before and after temporal lobectomy. It was shown that ablation of the right temporal lobe is associated with a disappearance of the perceptual effects of the drug (Serafetinides 1965), implying an asymmetry of 5-hydroxytryptamine type 1A and 2 receptors—the main site of action of LSD.

It is valuable to consider the interrelationships of structural and biochemical asymmetries. The latter appear to be a real phenomenon, not simply a reflection of increases or decreases in local tissue mass. However, the precise interactions among structure, biochemistry, and function remain obscure. There are, however, some data to suggest that antipsychotic medications do have a lateralized effect. Acute treatment with haloperidol has lateralized effects on dopamine turnover in the rat brain (Jerussi and Taylor 1982). Furthermore, treatment is associated with a small but significant shift in electroencephalography (EEG) voltage to the left (Serafetinides 1973) and with lateralized alterations in visual evoked responses (Myslobodsky et al. 1983). This notion is buttressed by the observation that unmedicated patients perform poorly on tasks typically ascribed to the right hemisphere, such as sorting shapes. However, treatment reverses the side of the deficit (Tomer and Flor-Henry 1989). These observations are suggestive of an antipsychotic-induced inhibition of function in the right hemisphere.

Schizophrenia

The possibility of a relationship between disturbances in cerebral asymmetry and psychosis was first raised almost 120 years ago (Crichton-Browne 1879). Other articles in this issue of the Schizophrenia Bulletin deal with components of cerebral asymmetry. We shall not reiterate information in them, other than to point out that data derived from several different types of studies have indicated abnormalities in the left hemisphere. These studies include neuropsychological testing (for a review see Nasrallah 1986); attention (Posner et al. 1988); auditory acuity (Mathew et al. 1993); brain electrical activity mapping (Morihisa et al. 1983); recordings of the P300 potential (Morstyn et al. 1983; Holinger et al. 1992; Faux et al. 1990, 1993); EEG (Morrison et al. 1991; Koukkou et al. 1993); positron emission tomography (Gur et al. 1987; Berman and Weinberger 1990; Friston et al. 1992; Wilson and Mathew 1993); single photon emission tomography (SPECT) (Suzuki et al. 1993); and biochemistry (Reynolds 1983; Kerwin et al. 1988). With so much evidence pointing toward the left hemisphere and/or an imbalance between the two sides, it is not surprising that a great deal of effort has been expended on the search for structural asymmetries in schizophrenia. We must, however, mention that although there is much to suggest left hemisphere dysfunction in schizophrenia, some evidence suggests that dysfunction in the right hemisphere, with a diminution of activity, is the key abnormality (Cutting 1990, 1992, 1994; Persaud and Cutting 1991). These models, however, are not necessarily mutually exclusive. The normal state of affairs is a functional balance between and within each hemisphere. For virtually every task there is a potential contribution from each hemisphere, although some tasks tend to be preferentially mediated by one hemisphere or the other.

What has become known as the "typical" pattern of anatomical asymmetry—a predominance of the left parieto-occipital regions—was described in the early years of this century and was speculated to be related to the functional specialization of the hemispheres (Smith 1907). The possibility that mental disturbances might be related to some derangements of the normal pattern of asymmetry of the brain had been raised by the detailed studies of Southard (1915) and subsequently by Inglessis (1925). However, in
both cases, the findings were not conclusive and were largely ignored during the years when psychological and social theories supplanted biological observations.

Southard's articles now appear prescient. Not only did he comment on ventricular enlargement (which he termed "internal hydrocephalus"), but he stated quite clearly that "the atrophies and aplasias when focal show a tendency to occur in the left cerebral hemisphere" (p. 662). Finally, he also pointed out the predilection for the pathological lesion to affect the "association centers of Flechsig" (Flechsig 1908, 1920), which we would identify as the interlinked system of heteromodal association cortex, which has recently been strongly implicated in the pathology of schizophrenia (Schlaepffer et al. 1994). More recently, interest in comparing the two hemispheres was rekindled by the observations and subsequent theorizing of differential behavioral effects of lesions in each hemisphere, leading to a redistribution of the normal balance between the two hemispheres (Flor-Henry 1969, 1976, 1983). Flor-Henry reported that when psychosis developed in association with an epileptic focus in the left hemisphere, it tended to be schizophrenia-like, while a focus in the right hemisphere is more likely to be associated with an affective psychosis. While initially these observations were thought to be relevant only to epilepsy, it was not long before a potential link to schizophrenia itself was being considered.

An early investigation using air encephalography had reported ventricular enlargement restricted to the left side in 9 of 27 chronic psychotic patients (Hunter et al. 1968). In two CT scan studies, it was reported that "density" of the left hemisphere was reduced on the left side in patients but not in controls (Golden et al. 1981; Largen et al. 1983). This observation was subsequently replicated in one study of chronic schizophrenia patients (Coffman et al. 1984) and in another of monozygotic twins discordant for schizophrenia (Reveley et al. 1987).

Although the suggestion that asymmetry of the hemispheres may play some role in schizophrenia is normally assumed to be a modern concept, the idea that disturbances within the corpus callosum resulting in aberrant intrahemispheric communication might underlie psychotic illnesses was first proposed by Wigan in 1841 (Clarke 1987). A development of the idea was proposed by Jaynes (1977) in his well-known book, in which he proposed that many of the symptoms of schizophrenia could be ascribed to a relative overactivity in the right hemisphere of the brain, such that the experience of auditory hallucination actually represented the reception by the left hemisphere of verbal activity by the right. Contemporary observation of reversal of the normal asymmetry of the planum temporale may provide some support for this thesis, if indeed this structure is active in the right hemisphere. Over the years, a number of studies have examined the function of the corpus callosum in schizophrenia, with interesting, but still inconclusive results (David 1987, 1993; Doty 1989; Raine et al. 1989).

The most consistent in vivo finding in schizophrenia is enlargement of the lateral ventricles, although a recent meta-analysis has revealed that the degree of this enlargement is much smaller than previously thought, and like some other findings, the differences between normal controls and patients have tended to become smaller as more studies have been performed (Van Horn and McManus 1992). The finding, however, remains robust, and in some reports the enlargement has been found to be asymmetric, the enlargement of the left being greater (Crow et al. 1988, 1989b; Crow 1990a; DeLisi et al. 1991, 1992). This preferential enlargement of the left lateral ventricle has also been found in postmortem study (Brown et al. 1986; Crow et al. 1989a). This investigation also convincingly demonstrated that this asymmetrical enlargement was found only in patients with an antemortem diagnosis of schizophrenia, but not in roughly matched patients with Alzheimer's disease, in whom the enlargement was the same on the two sides. This enlargement either reflects atrophy, or an arrest of brain growth, with a consequent failure of the brain to attain the adult proportions of brain to ventricular volumes. One of the key inquiries in research examining the neurobiological basis of schizophrenia is directed at establishing whether these brain abnormalities are progressive. It is also now emerging that ventricular enlargement is most pronounced in the temporal horns, again mainly on the left (Brown et al. 1986), and is associated with schizophrenia symptoms (Degreene et al. 1992; Kawasaki et al. 1993). The presence of enlarged ventricles has received such detailed examination because it may be a marker of a particular subtype of schizophrenia. Certainly, enlargement of the lateral ventricles is associated with an earlier age at onset (DeLisi et al. 1991, 1992). Enlargement of the third ventricle has been associated with neuropsychological deficit (Bornstein et al. 1992).

In addition to the asymmetries in the ventricular system, temporal lobe size itself is reduced in patients with schizophrenia, again more on the left than the right (Bogerts et al. 1990; Dauphinais et al. 1990). In two postmortem studies, the normal asymmetry of the lateral (Sylvian) fissure (left longer and flatter than the right) was found to be lost in schizophrenia (Crow et al. 1992; Falkai et al. 1992). However, it remains uncertain whether the reduction in temporal lobe volume is already present at the time of the onset of the illness (DeLisi et al. 1991, 1992). There has also been debate about whether both gray and white matter are decreased (Suddath et al. 1989; Zipursky et al. 1992) or whether the reduced volume is
localized to only some regions of the temporal lobe, such as the superior temporal gyrus (Barta et al. 1990; Shenton et al. 1992); the PT (Hoff et al. 1992; Rossi et al. 1992; Bilder et al. 1993; Petty et al. 1995); or the medial parts of the temporal lobe, specifically the hippocampus and amygdala (DeLisi et al. 1986; Bogerts et al. 1990). The left hippocampus is usually reduced in volume in patients compared with controls (Breier et al. 1992). The left parahippocampal region has been found to have a reduced volume compared with matched controls (Young et al. 1991; Kawasaki et al. 1993). More recently, DeLisi et al. (1994) examined the temporal lobes of a large group of patients with schizophrenia and demonstrated a reduction in the normal pattern of asymmetry in more anterior parts of the temporal lobes and, in females only, a trend toward less asymmetry posteriorly. They were unable to find reductions in the volume of the anterior portions of the left temporal lobe. However, as the authors themselves acknowledge, there were technical limitations in this study: 5 mm slices were used with 2 mm gaps—far larger than those used in studies reporting positive findings.

As work on brain structure in schizophrenia has progressed, further efforts have been made to relate deviations of symmetry to specific clinical features. Hoff et al. (1992) found anomalous asymmetry of the Sylvian fissure, particularly in women. Interestingly, it was negatively associated with cognitive dysfunction. This is surprising, given the prevailing view that cognitive dysfunction is more likely to be associated with aberrant neurodevelopment (Buckley et al. 1993; Buckley and O'Donovan 1994). In another study, increased volume of the Sylvian fissure was found, but only in male schizophrenia patients (Ron et al. 1992). Finally, two studies have found clear associations between alterations in the normal asymmetry of the PT and thought disorder (Rossi et al. 1994; Petty et al. 1995).

We are obviously still at an early stage of the investigation of structural asymmetries. While we have mentioned several studies in which clear asymmetries have been identified, others have failed to make the same observations. It is important to point out these negative reports. For instance, Bartley et al. (1993) and Kulynych et al. (1993) performed careful studies of 10 patients with schizophrenia who had unaffected monozygotic twins and 10 with dizygotic twins; they were unable to detect differences in normal asymmetries in the schizophrenia-affected twins. Similarly, Kleinschmidt et al. (1994) were unable to demonstrate a deviance of normal asymmetry in first-episode schizophrenia patients. Other studies directed toward different cortical and subcortical structures have failed to detect consistent asymmetries (Casanova et al. 1990; Jernigan et al. 1991; Degre et al. 1992; Levy et al. 1992). There are a number of reasons for these different results. The most important reflect the populations selected: Most have studied chronic male patients, and, as we have seen, there are good reasons for examining males and females separately. Furthermore there continue to be different technologies in use. It also has proven difficult to directly compare MRI analysis programs developed in different centers.

There are two major reasons for the concentration on the temporal lobes in schizophrenia. One is the association between temporal lobe epilepsy and schizophrenia-like psychoses. The second is the association between schizophrenia and disorders of language (Andreasen 1979a, 1979b), because the many regions of the brain involved in the reception and production of language lie in the superior portions of the temporal lobe.

Reduced asymmetries of the length of the PT have been reported in individuals with developmental dyslexia (Geschwind and Galaburda 1984; Larsen et al. 1990). Several studies have shown clear disturbances of the normal asymmetry of the planum temporale in patients with schizophrenia. Two were postmortem studies (Crow et al. 1992; Falkai et al. 1992), and five were in vivo (Hoff et al. 1992; Rossi et al. 1992; DeLisi et al. 1994; Kleinschmidt et al. 1994; Petty et al. 1995). All but the DeLisi group study showed reduction in the normal asymmetry of the area, and the degree of reduction appears to be related to the resolution of the methodology employed. Petty and colleagues used perhaps the highest resolution SPGR scans yet employed in studies of the region and found not just a loss of normal asymmetry but a complete reversal, in a small study of 14 patients. However, the power of this study was amplified by the use of extremely rigorous matching of controls to patients.

In 1979, Luchins et al. reported reversal of the normal asymmetries of the occipital and frontal lobes in some patients with schizophrenia; that is, the patients had wider right occipital lobes than left, and their left frontal lobes were smaller than the right. Subsequently, Naeser et al. (1981) and Tsai et al. (1983) reported reversals of asymmetry in the occipital but not the frontal lobe, and Luchins et al. (1981) replicated their earlier finding of reversal of occipital lobe asymmetry. However, the situation became much less clear as a number of negative reports began to appear (Andreasen et al. 1982; Jernigan et al. 1982; Nyback et al. 1982; Weinberger et al. 1982; Luchins and Meltzer 1983). In a critical review, Luchins (1982) himself concluded that the only significant and consistent finding was larger right frontal and left occipital brain regions in normal as well as affected individuals. An analysis of all the studies published up until 1983 demonstrated the familiar observation that in biological measurement the size of the effect tends to diminish as a function of the level of experimental control.
During the 1980s, Timothy Crow developed an ingenious hypothesis linking the neurological lesions of schizophrenia to the development of cerebral asymmetry, and he and his collaborators embarked on a number of investigations to test this hypothesis. At its simplest, the hypothesis proposes that schizophrenia is a disorder of the genetic mechanisms that control the development of cerebral asymmetry. The prediction from this theory is that the greatest disturbances will be seen in regions that normally show the highest degrees of asymmetry, such as the planum temporale. This prediction has subsequently been borne out. Furthermore, as additional studies have been performed, more data have supported the contention that the normal torque to which we referred earlier is diminished or absent in schizophrenia (Falkai et al. 1992). This loss of torque can be detected in groups with an early onset (Crow et al. 1989b) and in individuals experiencing a first episode (Bilder et al. 1993, 1994). An alternative explanation for the association between left-hemisphere lesions and schizophrenia relates to the differential maturation of the right and left hemispheres, which renders the left hemisphere more vulnerable to potential insults in the second trimester of pregnancy. Thus it would follow that structural asymmetries are an artifact of the timing of the insult (Bracha 1991).

CT and MRI studies have shown remarkable agreement with results obtained from postmortem studies. Most authors, as we have seen, have reported that the PT is larger on the left and that the Sylvian fissure extends farther back on the left and rises more steeply on the right. However, the volume of the temporal lobe is on average larger on the right (LeMay 1986). In a group of 25 healthy individuals, Jack et al. (1988) found temporal lobe volumes to be an average of 15.7 percent greater on the right side. However, a considerable range in the values was reported with no attempt to examine the potential effects of gender or handedness. Studies that have reported temporal lobe volumes in patients with schizophrenia have found that this right-greater-than-left asymmetry is maintained, although the degree is reduced. Thus, Suddath et al. (1989) found right temporal lobe volumes 15.5 percent greater than the left in controls, but only 12.5 percent greater in patients. In a further study the increased volume of the right was 13.6 percent in controls and 8.6 percent in patients (Harvey et al. 1993).

Although some MRI studies have not shown a significant asymmetry of temporal lobe volume in schizophrenia patients or controls (Shenton et al. 1992), a reversal of the normal pattern of asymmetry (i.e., left larger than right) has been reported in some patients with schizophrenia (Luchins and Meltzer 1983; Tsai et al. 1983). In a large study of patients with late paraphrenia (late-onset psychosis), Howard et al. (1994) found temporal lobe volume to be greater on the right in elderly controls (2.6%), in schizophrenia patients (5.9%), and in patients with delusional disorder (8.4%). This asymmetry was significant in both the schizophrenia and delusional disorder patients, but not in the controls. These results appear to be the reverse of the situation reported in young people with schizophrenia. The explanation is not readily apparent, particularly because there are so few normative data pertaining to brain volume measurements in the elderly. It may be, as the Howard group speculates, that normal aging is associated with a gradual loss of the asymmetry of brain volumes seen in younger adult life. Persistence of this asymmetry could then be a risk factor for the eventual development of schizophrenia or delusional symptoms. Considerable data collected in a variety of studies indicate that there is normally a balance between the activity of the two hemispheres, and convincing arguments have been advanced to suggest that schizophrenia symptoms may be linked to a predominance of right hemispheric activity (Cutting 1990) or left hemispheric underactivity (Gur 1979). The Howard group previously found an asymmetrical dilatation of the lateral ventricles, with significantly greater dilatation on the left, in patients with both delusional disorder and late-onset schizophrenia, compared with controls (Howard et al. 1994). This presumably reflects either arrested development of the left temporal lobe or, alternatively, increased loss of tissue on this side of the brain. Whichever explanation proves to be correct, this finding is consistent with that reported by Crow et al. (1988, 1990a, 1990b).

The precise delineation of the frontal lobes presents a number of technical difficulties that have hindered progress in this area. However, as we discussed earlier, at postmortem the total volume of the right frontal lobe is about 13 percent larger than the left (Weinberger et al. 1982). The direction and approximate magnitude of this asymmetry have been confirmed using CT in normal individuals (LeMay and Kido 1978; Chui and Damasio 1980). In MRI studies, there does not seem to be a significant difference in the relative sizes of right and left prefrontal regions when controls and schizophrenia patients are compared. Both show right side enlargement (Suddath et al. 1989). However, the situation appears to be different in the elderly. The volume of the right frontal lobe exceeds the left by 1.7 percent in controls, by 0.3 percent in patients with late-onset schizophrenia, but by 8.5 percent in patients with delusional disorder (Howard et al. 1994). It may be of interest that Swayze et al. (1992), while still finding the right temporal lobe to be larger than the left in schizophrenia patients, found small reduction compared with controls but also found that right and left temporal lobes were of equal volume in females with
bipolar disorder, once again demonstrating the importance of gender as an independent variable.

The comparison of early- and late-onset schizophrenia may present a useful avenue for further exploration, as more sophisticated attempts are made to relate symptoms to the neurobiological substrates of these illnesses. However, such a comparison is not without its problems. With increasing age there appears to be a progressive increase in interindividual differences in brain appearance (Jacoby et al. 1980). Therefore, the demonstration of minor structural abnormalities in the brains of older psychiatric patients becomes difficult, when compared with age-matched elderly controls. Thus, some of the subtle MRI findings reported in early-onset schizophrenia patients may be difficult to detect in the elderly, and the consistent findings in the temporal lobes, particularly in elderly patients with delusional disorder, are therefore likely to be robust.

One of the more interesting approaches to the study of the organic substrate in schizophrenia is the attempt to associate structural and functional abnormalities. There have been several recent attempts to do this. In a study of 31 schizophrenia patients and 33 volunteer controls, auditory P300 event-related potential and smooth pursuit eye movement abnormalities were associated with structural brain changes measured using MRI. In the schizophrenia group, P300 latency correlated negatively with the area of the right and left cingulate cortex and positively with the difference in size of the right and left amygdala. The results were more marked in the more severely affected individuals. In those schizophrenia patients whose P300 latency was greater than two standard deviations above the control mean, the area of the left cingulate cortex was significantly smaller than in controls, and the absolute right-left difference in the area of the amygdala was significantly increased. Eye-tracking dysfunction in schizophrenia was not related to changes in the amygdala or cingulate cortex, but it was significantly correlated with enlargement of the lateral ventricles. There was no specific association with enlargement of one side or the other. Schizophrenia subjects with poor eye-tracking had significantly larger lateral ventricles than controls. Eye-tracking dysfunction, but not P300 abnormality, was correlated with the severity of both positive and negative symptoms of schizophrenia (Blackwood et al. 1991). McCarley et al. (1991, 1993) have identified a clear association between reductions of the volume of the left posterior temporal gyrus and abnormalities of the auditory P300 potential. Because this is the same region of the brain associated with thought disorder (Shenton et al. 1992; Rossi et al. 1994; Petty et al. 1995), the obvious implication is that this lateralized neurophysiological measure is providing information about the substrate of disturbances in communication. What these data appear to be telling us is that more severe deviations of normal cerebral asymmetry are associated with more marked disturbances in one particular measure of neurological dysfunction in schizophrenia. This may be of importance in view of the data suggesting an association of handedness with tardive dyskinesia (McCreadie et al. 1982; Barr et al. 1989; Joseph 1990), even though handedness is, as we have discussed, a poor indicator of structural asymmetry.

We have referred to possible dynamic changes in functional laterality during the menstrual cycle. In one interesting study, sadly not replicated, a dichotic listening task showed a close relationship between disturbance of laterality and psychotic symptoms: When the patient was most ill, laterality was most disturbed, and recovery was associated with a return to near normal laterality (Wexler and Heninger 1979). It is tempting to speculate that the better prognosis of females with schizophrenia is associated with the female brain being more plastic in contrast to the greater structural asymmetries found in males, which have the effect of forcing a functional laterализation.

In our view, structural and functional asymmetries, and particularly their integration with clinical measures, still have much to teach us about schizophrenia.

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