Atypical Handedness in Schizophrenia: Some Methodological and Theoretical Issues

by Paul Satz and Michael Foster Green

Abstract

An updated review of the literature strongly supports the view that in schizophrenia there is an atypical leftward shift in the handedness distribution that, while comprising different subtypes, is characterized by a more variable and less completely lateralized pattern of manual preference, referred to as mixed handedness (MH) or ambiguous handedness (AH). Only two studies revealed an increased prevalence of left-handedness suggestive of pathological left-handedness (PLH). This article also examines the current status of neurodevelopmental factors and mechanisms in schizophrenia that purport to explain these pathological shifts in handedness (PLH, MH, AH). Different theoretical positions were evaluated, each involving some aspect of left hemisphere insult (unilateral or bilateral). Finally, it was shown that these shifts predict certain key symptoms and neural substrates in schizophrenia including thought disorder, negative symptoms, neuropsychological impairment, family history, and brain anatomy. These subtypes may represent neurodevelopmental markers of insult during intrauterine life that are nongenetic in origin.

Key words: Handedness, laterality, neuropsychological impairment.


A well established fact about schizophrenia is that first-degree relatives have an increased risk of the disorder. Few now doubt that schizophrenia has a genetic basis, yet its mode has to be explained. Even the identical twin [of an individual with schizophrenia] stands a better than 50% chance of escaping the illness. Genetic factors are not the whole story. [Murray and Lewis 1987, p. 681]

In the past decade, interest has increasingly focused on the role of neurodevelopmental factors as independent or aggregated effects of genetic and environmental burdens in the etiology of schizophrenia (Weinberger 1987; Murray et al. 1992a, 1992b). One behavioral index has gradually emerged as a potential marker of a neurodevelopmental insult in a subgroup of schizophrenia patients, namely, atypical handedness.

The purpose of this article is threefold. First, we review the current status of atypical handedness in schizophrenia to determine whether a leftward shift in the distribution of handedness exists. Second, we examine the current status of neurodevelopmental factors and mechanisms in schizophrenia that might, in part, explain this pathological shift, including both left-handedness and mixed handedness (MH). Finally, we determine whether this lateral shift is associated with or predicts certain key symptoms and neural substrates in the disorder (e.g., thought disorder, negative symptoms, neuropsychological impairment, family history, and brain anatomy).

Atypical Handedness: Is There a Shift in the Distribution?

The last and most comprehensive review of this literature was reported by Green et al. (1989b). Although the studies varied widely in terms of methodology, procedures, and results, the predominant finding was a shift in the distribution away from right-handedness. This finding was based on a majority of the studies (9 positive, 5 null, 2 paradoxical), which included some of the methodologically stronger and more recent studies. Interestingly, this leftward shift in the distribution, which deviated from the typical J-shaped distribution long reported in the normal population (Annett 1972), was composed of two rather distinct subtypes, one left-handed and the other mixed-handed. The assessment methods used to measure and classify these two subtypes will be described below.

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Since our last review (Green et al. 1989b), 19 additional studies have addressed the association between handedness and schizophrenia. Seven of the studies examined the prevalence of different handedness subtypes (left or mixed) to determine whether a shift in handedness distribution exists in a subgroup of schizophrenia patients (Nelson et al. 1993; Clementz et al. 1994; Manoach 1994; Cannon et al. 1995; O'Callaghan et al. 1995; Taylor and Amir 1995; Malesu et al. 1996). The studies used a variety of methods to assess and classify handedness, ranging from self-reports and multiple-item questionnaires to demonstration methods. Four of the seven studies showed a leftward shift in the handedness distribution (all except for O'Callaghan et al. 1995; Taylor and Amir 1995; and Malesu et al. 1996). However, in the Malesu et al. study (1996) a trend toward increased MH was in the hypothesized direction. The remaining studies addressed the association between non-right-handedness (left or mixed) and other behavioral, cognitive, neurological and brain imaging abnormalities in schizophrenia that will be discussed later in this review.

Because a similar shift in the distribution of non-right-handedness was found in the majority of the earlier and current reviews, we decided to pool data across studies and tally the overall box score outcomes. The results (14 positive, 7 null, 2 paradoxical) provide some support for a leftward or atypical shift in the handedness distribution. We then examined each study to determine the nature of the leftward bias in terms of subtype frequency (i.e., left or mixed). In the vast majority of studies reporting prevalence data, the leftward shift was due to an increase of MH compared with normal or patient controls. Only two studies reported an increase in left-handedness (Gur 1977; Manoach et al. 1988). To interpret these subtype findings, it is important to describe some of the key methodological issues related to the assessment and classification of handedness in these studies.

First, two studies (Gur 1977; Manoach et al. 1988) used observed writing hand or self-report as the sole basis for assessment and classification, which permits only a dichotomous outcome (left-handed or right-handed). In such cases, reports of an increased prevalence of left-handedness could be misleading if some subjects turned out to be mixed-handed. The latter determination would require a questionnaire or observed demonstration procedure. A similar issue arises when right-handedness is classified by self-report or observed writing hand, because the majority of mixed-handers, when assessed by multiple-item questionnaires, use the right hand for writing (Annett 1972). Also, if one attempts to determine the prevalence of left-handedness in schizophrenia patients, one would need to conduct a large-scale or epidemiologic survey because of the low base rate frequency of left-handedness in the normal population (writing hand 10%-12%, questionnaire 5%). These problems will be discussed later in this review.

Second, while most of the studies on prevalence used a variety of questionnaire formats, they differed markedly in terms of items and number. This is important because the larger the number of items used, the greater the chance of finding some mixed-handed preferences (Harris and Carlson 1988). In other words, an inverse relationship exists between the number of items and MH or left-handedness.

Third, the criterion used to classify handedness varied across studies. Studies using a more conservative criterion (100%) were more likely to find an increase in MH, especially if many items were employed in the questionnaire (Annett 1972). For example, while the prevalence of right-handedness is approximately 90 percent in the normal population (based on self-report or writing hand), this prevalence drops to approximately 65 percent when a multiple-item preference questionnaire is used (Annett 1972). Using a 12-item questionnaire, one typically finds the following distribution of handedness subtypes in the normal population: left 5 percent, mixed 30 percent, right 65 percent (Annett 1972).

Fourth, although the number of potential items (tasks) used to assess handedness is endless, given man's complex motor programming and output functions, only a few tasks are differentially sensitive to hemispheric dominance. Steenhuis and Bryden (1989) have shown that those manual tasks that require chaining of complex motor sequences (proximal and distal) are represented on a general laterality factor whose neural substrate is hemispherically specialized. In contrast, discrete lateral movements (e.g., picking up a pin) may be less lateralized.

Fifth, the assessment used to classify handedness can be based on a multiple-item preference questionnaire (self-report) or a multiple-item demonstration test. The demonstration approach allows a more direct measure (observation) of hand preference than the preference approach, and it determines the status of within-task consistency on individual items. The demonstration approach has revealed that a subgroup of mixed-handed institutionalized patients have no consistent directional asymmetry on a given task and should be differentiated from the larger population of mixed-handers who, while variable in hand preference between tasks, are not inconsistent within tasks. We have labeled the former subgroup as having ambiguous handedness (AH) because of the near-randomness of their manual preference.

Although the presence of these atypical handedness subtypes in schizophrenics, as well as in other brain disorders, signals some type of pathological shift in the distribution of handedness, the neural substrates or mechanisms...
that underlie these subtypes have been less clear, especially in psychiatric studies of schizophrenia. For this reason, the next section has a brief review of some neurodevelopmental factors in the etiology of some schizophrenia subgroups, with particular focus on specific brain substrates or mechanisms that are hypothesized to account for these atypical handedness subtypes.

Neurodevelopmental Factors in the Etiology of Schizophrenia. The neurodevelopmental model of schizophrenia has received considerable support from both empirical and conceptual sources (Weinberger 1987; Murray et al. 1992a, 1992b). Empirical support for the neurodevelopmental model is difficult to obtain because of a thorny methodological obstacle: The onset of symptoms in schizophrenia typically occurs in early adulthood, so the time period of interest (usually prenatal or perinatal) occurs decades before the data collection. Several creative approaches have been applied to circumvent this problem.

Epidemiologic studies have evaluated whether naturally occurring influenza epidemics increase the risk that a fetus will develop schizophrenia as an adult. In a well-conducted and frequently cited study, Mednick et al. (1988) considered the effects of a relatively brief and fairly widespread A2 influenza epidemic in the Helsinki area in 1957. This study examined the rates of schizophrenia in adulthood for individuals who were presumably exposed to the A2 influenza virus while in utero compared with controls who were born in the same hospitals during the same months in previous years. The individuals who were exposed to the influenza virus while in the second trimester of fetal development (but not the first or third trimester) had higher rates of schizophrenia than control subjects. Hence, a virus may have disrupted some aspect of fetal neurodevelopment, which in turn increased the risk for schizophrenia. This finding, while not entirely consistent across studies (Kendell and Kemp 1989; Bowler and Torrey 1990; Crow et al. 1992) has generally been replicated (Barr et al. 1990; O’Callaghan et al. 1991b). Part of the difficulty in replicating the finding is the somewhat unexpected possibility that the increased risk may be largely limited to females (Takei et al. 1994).

Another approach to the neurodevelopmental model has used neurohistology. These studies, while using substantially different methods, have generally supported the epidemiological studies by finding abnormalities in cell orientation and cell placement that likely reflect disruption during the second trimester. For example, Scheibel and colleagues (Kovelman and Scheibel 1984; Conrad and Scheibel 1987) found that in the brains of schizophrenia patients the pyramidal cells of the hippocampus showed directional disorientation compared with those of controls. The finding of disorientation strongly suggests that the problems arose during cell migration, because these cells cannot change their orientation after this phase. Although the studies initially involved only the left hemisphere, a subsequent study also found comparable cell disorganization in the right hemisphere (Conrad et al. 1991).

Akbarian and colleagues (1993a, 1993b) stained cells for the enzyme nicotinamide-adenine dinucleotide phosphate-diaphorase in the prefrontal and temporal regions of schizophrenia patients and matched controls. In both of these regions, the cells of the patients were located in deeper layers compared with controls. The interpretation is that the abnormal cell placement reflects abnormalities in cell migration. Interestingly, cell migration occurs during the second trimester, a time period that was implicated by the epidemiological studies.

An “archival-observational” approach has been used by Walker and colleagues (Walker and Lewine 1990; Walker et al. 1993) to study the neurodevelopment of schizophrenia. They obtained childhood home movies from families in which at least one child subsequently developed schizophrenia and at least one did not. In the initial study, raters were able to identify the pre-schizophrenic child significantly above chance. Although the raters in this initial study were not given any specific instructions on how to select the pre-schizophrenic child, subsequent studies have found that the pre-schizophrenia siblings showed greater negative emotions (Walker et al. 1993) and a higher rate of neuromotor dysfunction (Walker et al. 1994).

The approach most relevant for the current discussion has been the search for markers of abnormal neurodevelopment in adult schizophrenia patients. These markers are usually measurable characteristics in adults that reflect abnormal neurodevelopmental processes which occurred before or shortly after birth. Markers of abnormal development have included dermatoglyphic signs (Bracha et al. 1991, 1992; Mellor 1992) and minor physical anomalies (Gualtieri et al. 1982; Guy et al. 1983; Green et al. 1989a, 1994a, 1994b; O’Callaghan et al. 1991a; Lohr and Flynn 1993).

Dermatoglyphic procedures with schizophrenia patients have suggested two types of abnormalities: changes in total finger ridge counts (TFRC) and increased dermatoglyphic asymmetry. Recent studies of TFRC have used a powerful design involving monozygotic twins, only one of whom is diagnosed with schizophrenia. Results revealed that one subgroup of schizophrenia patients had lower ridge counts (perhaps due to ischemia during the second trimester) than their twins, whereas a second subgroup showed higher ridge counts than their twins (perhaps indicating edema during the second trimester) (Bracha et al. 1992).
A second dermatoglyphic finding in schizophrenia is increased dermatoglyphic asymmetry (also called fluctuating asymmetry; see Markow and Wandler 1986; Markow and Gottesman 1989; Mellor 1992), which is considered a sign of possible disturbances in fetal neurodevelopment or a lower neurodevelopmental stability (Mellor 1992).

Minor physical anomalies (MPAs) are minor abnormalities of the head, face, hands, and feet (e.g., high-steepled palate, epicanthal folds, gaps between toes). The studies that have compared MPAs in patients with schizophrenia with normal controls have all found an excess of MPAs in schizophrenia (Gualtieri et al. 1982; Guy et al. 1983; O’Callaghan 1991a; Lohr and Flynn 1993; Green et al. 1994a), which does not seem to be an artifact of socioeconomic status (Green et al. 1994a). More recently, O’Callaghan et al. (1995) failed to find a relationship between MPAs and ventricular brain volumes in schizophrenia patients using magnetic resonance imaging (MRI). Although MPAs were previously thought to reflect processes from the first trimester, data suggest that second trimester events are relevant to the development of MPAs (Green et al. 1994a, 1994b).

It is our view that atypical handedness, like abnormal dermatoglyphics and MPAs, is a marker of problems in neurodevelopment. As such, we expect elevated rates of atypical handedness in schizophrenia. In fact, it would be a problem for a neurodevelopmental model of schizophrenia to incorporate the absence of a shift in the handedness distribution.

The neurohistological studies suggest that early problems in cell migration are not restricted to a particular lobe or to one hemisphere. Why then does a neurodevelopmental abnormality that is most likely diffuse or multifocal yield a shift in handedness that is unidirectional? The next section will address some of the mechanisms and neural substrates known or hypothesized to underlie different pathological shifts in the handedness distribution.

Neurodevelopmental Mechanisms in Subtypes of Atypical Handedness.

Pathological left-handedness (PLH). Although an increased prevalence of this subtype would lend additional credence to those who postulate a left hemisphere substrate in schizophrenia (Posner et al. 1988; Crow et al. 1989; Posner and Early 1990; Bracha 1991), only two studies have reported such an association (Gur 1977; Manoach et al. 1988). As noted earlier, even these results could have been biased by the absence of an assessment for MH. Despite these problems, the tendency in psychiatric studies has been to associate all forms of atypical handedness with left-handedness:

It is typically stated that schizophrenics are more frequently left-handed than other groups. Although this is probably true, the more general finding is that schizophrenics are less frequently unambiguously dextral. In order to maintain consistency with previous literature and to improve this article’s readability, we frequently use the term ‘left-handed’ to refer to nondextral subjects. [Clementz et al. 1994, p. 400]

An increased incidence of PLH has long been reported in other clinical disorders with known early focal brain insult (e.g., epilepsy, stroke, hemiplegia, hemispherectomy; see Harris and Carlson 1988 for a review). PLH refers to a subset of natural right-handers who, because of early brain injury to the left hemisphere (before age 6), suffer a hypofunction of the right hand (often transient), which in turn causes a shift to preference for the left hand. The model advanced by Satz (1972, 1973) computes the proportion of natural right-handers with left-sided brain insult who would have to shift handedness to account for a raised incidence (above the population base rate) in any clinical disorder. According to Harris and Carlson (1988), there are two basic assumptions in the model. The first is that the location of the brain lesion is random, just as likely to strike the left hemisphere as the right. Thus, in statistical terms, the brain lesion is a binomial function. The second assumption is that left hemisphere lesions lead to a greater incidence of switched-handedness because of the predominance of right-handers in the general population (approximately 90%). Consequently, when early focal brain injury causes a shift in handedness, the result will almost always be PLH rather than pathological right-handedness (PRH). The PRH subtype, the result of right brain insult in a natural left-hander, is seldom discussed because of its relative infrequency compared with PLH (approximately 11:1; Satz 1972). The Satz model also postulates two types of manifest left-handedness in the general population: (1) a natural group whose hand preference springs from genetic and/or environmental factors and (2) an aetiogenic pathological group whose hand preference springs from early brain injury primarily to the left hemisphere. This model contrasts with other positions that view all forms of manifest left-handedness as pathological—both prenatal and postnatal (Bakan 1971; Geschwind and Galaburda 1985). These latter views, however, have not received much empirical support in recent years (Harris and Carlson 1988; Bishop 1990).

If PLH represents a smaller subset of the general population of manifest left-handers, then how can the two handedness subtypes be differentiated? It has recently been shown that the lesion that produces the shift in manual preference may also produce other alterations in lateral development, including hemispheric speech (right or
bilateral), cognition (relatively preserved language, but impaired visual-spatial ability [i.e., crowding effect]), and limb length (right hemihypoplasia), that constitute elements of a clinical syndrome (Satz et al. 1985; Strauss et al. 1990). Although hemihypoplasia (hand and/or foot length) was first observed by Penfield and Robertson (1943), its correlation with other elements of the syndrome was recognized only recently. The potential use of this index as a biological marker of PLH (and early left hemisphere insult) was replicated on a sample of children with unilateral vascular injuries related to cardiac catheterization (Aram et al. 1986). All but one of the children with right hemihypoplasia (and left-brain injury) were left-handed, whereas none of those with left hemihypoplasia (and right-brain injury) were left-handed.

A second biological marker of PLH was reported by Bishop (1980, 1984), who hypothesized that marked inferiority in hand skill for the nonpreferred hand would constitute a unilateral “soft” neurological sign in otherwise nonsymptomatic samples. Her reasoning was that PLH could also be the result of a brain abnormality too mild to produce clinical symptoms (e.g., epilepsy, mental retardation, or hemiplegia) but sufficient to make the genotypically preferred hand clumsy, thus forcing a preference for the other hand. In three separate studies (Bishop 1980, 1984; Gillberg 1983), children showing the poorest nonpreferred hand performance (left or right) were significantly more likely to be left-handed and to have speech problems. However, these subjects showed no impairment in their preferred hand. These findings are provocative because they suggest that “even so mild a dysfunction as clinically asymptomatic clumsiness of the right hand may be sufficient to induce preference for the left hand” (Harris and Carlson 1988, p. 356). The results also strengthen other reports of PLH in patients with very mild left focal injury without any clinical signs of hemiplegia or motor impairment (Varga-Khadem et al. 1985). In fact, Varga-Khadem et al. noted that very early and consistent preference for the left hand (before age 6) was often associated with PLH and early left brain insult, because normal hand preference is typically unstable during this developmental period (Satz 1988).

The preceding findings strongly suggest that the neural substrate in PLH is associated primarily with a left-sided focal brain insult during the prenatal or postnatal period up to age 6. Further, this insult may vary from a mild injury involving no clinical symptoms (other than PLH) to a more severe injury involving changes in brain organization and cognition (PLH syndrome). In the latter case, the symptom pattern is marked by differential sparing as well as impairment due to functional reorganization during this early period of brain plasticity. An important point to note, however, is that this functional reorganization is not possible if the brain insult is early but diffuse, as in closed head injury (Ewing-Cobbs et al. 1987; Levin et al. 1987). In such cases, the symptoms are more general and symmetrical with no alteration in handedness, even when the injuries occurred before age 6 (Levin et al. 1987).

What implications do these findings on PLH have for schizophrenia, in which evidence of diffuse ectopic changes in cell migration are known to occur in some subgroups during prenatal development? The initial conclusion is none. The neurodevelopmental factors in schizophrenia are most probably diffuse and nonfocal and, therefore, unlikely to produce marked asymmetries in lateral preference such as PLH. This conclusion is further buttressed by the infrequency of empirical reports of left-handedness in schizophrenia, as noted above. At the same time, alternative views that postulate a left hemisphere substrate in schizophrenia (Posner et al. 1988; Crow et al. 1989; Posner and Early 1990; Bracha 1991) could challenge the preceding conclusions. For this reason, the PLH construct may still have relevance to schizophrenia. These views will be addressed below.

Mixed-handedness (MH) and ambiguous handedness (AH). In contrast with PLH, studies lend support for a raised incidence of MH in some schizophrenia groups. We suggest that the term “mixed-handedness” refers to a more heterogeneous population of subjects who are less lateralized and who, by definition, vary in their manual preference for different tasks (e.g., ambidexters). However, it has traditionally been assumed that this variation in manual preference among tasks is at least consistent within tasks. This assumption proved false when put to empirical test. By varying the method typically used in the assessment of human handedness, we developed the Hand Preference Demonstration Test (HPDT), in which subjects were asked to demonstrate their manual preference for eight simple items requiring skilled movement of predominantly distal musculature (e.g., picking up a spoon and a dime, using a crayon or a hammer). The items were administered three times in quasi-random order within one session or within two sessions spaced a week apart to determine within-task consistency.

In a series of studies with autistic patients (Satz et al. 1985; Soper et al. 1986) and nonautistic, mentally retarded institutionalized patients (Soper et al. 1987), we found an increased incidence of MH (approximately 50%) in these patients. However, when consistency of within-task responses was examined, we found that the vast majority of these mixed-handers had no consistent directional preference for most tasks. In fact, many of their responses seemed almost random. We referred to this subgroup as AH.

Although this assessment procedure has not been used with the developmentally disabled before, other
investigators have also reported a subgroup of autistic patients (approximately 40%) whose hand preference has been labeled incomplete, not established, or mixed (Colby and Parkison 1977; Barry and James 1978; Tsai 1982; Fein et al. 1984). In more recent studies using the HPDT procedure, results have confirmed the more frequent presence of an AH subtype in two cohorts of mentally retarded patients (Morris and Romski 1993; L. Vermue and H. Van der Vlught, personal communication 1989).

More recently, the AH subtype has been found in a subset of hospitalized schizophrenia patients in two separate studies using the HPDT procedure (Green et al. 1989b; Nelson et al. 1993). These findings were somewhat unexpected in patients without severe mental retardation or autism. Although there was also an increased prevalence of MH in both schizophrenia groups (40% compared with 15% in controls), approximately half of the mixed-handers met the criteria for AH (i.e., inconsistent on at least two tasks).

What mechanism might account for this atypical form of manual preference or dominance? We had earlier suggested (Soper and Satz 1984) that the AH subtype represents a third pathological phenotype that, unlike PLH or PRH, arises from early brain damage of such severity that neither side of the brain is sufficiently intact for the expression of manual (or cerebral) dominance. Interestingly, in our autism study (Soper et al. 1986) we found that this subtype achieved significantly lower IQ scores than did the two lateralized groups (left and right). Similar results have also been observed for the MH subtype by other autism investigators (Tsai 1982; Fein et al. 1984).

Although a bilateral hemispheric insult represents a likely substrate for AH because of the well-documented diffuse and multifocal neurodevelopmental abnormalities in a subset of schizophrenia subjects, this hypothesis fails to explain why the shift is unidirectional and leftward in cases of AH as well as MH including AH. In some respects, the distinction between AH and MH is arbitrary except for the distinction between within-task and between-task consistency. Otherwise, AH represents a specific subgroup of MH. As such, the mechanisms likely to induce a leftward shift in handedness, given an underlying bilateral or diffuse prenatal insult, are most probably the same in both cases, except perhaps in their severity.

**Left Hemisphere Lag Hypothesis.** This hypothesis states that during normal development of the fetal brain, the left hemisphere lags behind the right in intrauterine growth, causing the left hemisphere to be smaller than the right hemisphere throughout the early and mid-prenatal period (Bracha 1991):

By the end of the second trimester, the right hemisphere has achieved almost full-term; thus second-trimester injuries affecting, that is, anoxic, ischemic, toxic, or infectious insults that are systemic and bilateral, will affect the left hemisphere more than the right hemisphere. [p. 551]

This hypothesis is based on earlier postmortem studies of nonschizophrenia subjects that suggested that the left hemisphere matures more slowly than the right hemisphere during the early and mid-prenatal periods, which increases the window of vulnerability to epigenetic events (Fontes 1944; Chi et al. 1977). Also, because the left temporal region is hypothesized to be the last cortical area to complete neuronal migration, it is especially vulnerable to injury.

If this delay hypothesis were true, it would fit nicely with developmental positions that state that the immaturity of a system (prenatal or early postnatal) is a predictor of its vulnerability to birth stress (Bradley and Mistretta 1975). Similar outcomes have also been reported in head injury, in which those developmental skills in ascendency are more vulnerable to trauma than those skills already established (i.e., later in development; Ewing-Cobbs et al. 1987).

Interestingly, the lag hypothesis represents one of the main postulates of Geschwind and Galaburda’s (1985) theory of dyslexia, which attempts to link left hemisphere insult, left-handedness, and immune disorder in dyslexia. Unfortunately, the left hemisphere lag hypothesis has received little empirical support and some serious challenges (see Best 1988 and Bishop 1990 for reviews). In fact, Bishop (1990) states that this hypothesis is one of the most confusing parts of the Geschwind and Galaburda (1985) theory and should be abandoned. For example, if the left hemisphere delay leads to shifts in language (right) and handedness (left) (i.e., because of right hemisphere acceleration, which they regard as the norm), then according to Bishop (1990), “this would seem to entail that left-handedness and right hemisphere language representation should be the normal state of affairs, which clearly is not the case” (p. 151). Another major problem for the hypothesis is that, while there is some evidence to suggest that the right planum temporale develops about the 30th week of gestation, just a week to 10 days before the left (Chi et al. 1977), they also note that a larger Sylvian fissure is present on the left side as early as 16 weeks’ gestation. This latter structure includes Wernicke’s association area, which is the critical substrate for receptive language. A time window differential of 10 days hardly warrants the status of a vulnerability lag. Finally, the lag hypothesis, as noted by Bishop (1990), is diametrically opposed to reviews by Annett (1985) and Morgan and Corballis (1978).
Bracha's (1991) use of the lag hypothesis provides an interesting attempt to explain reports of structural brain asymmetry in the presence of bilateral prenatal insults. In fact, he suggests that "the asymmetry may be merely an artifact of the timing of the insult and may be most useful as a marker of the timing of the insult (i.e., second trimester)" (p. 551). Unfortunately, this position rests on the somewhat tenuous claim of a differential lag in left hemisphere growth. Also, the hypothesis makes no clear predictions on cognitive (i.e., linguistic) or motor (hand preference) sequelae that would result from a left temporal lobe abnormality.

Another variant of the left hemisphere lag hypothesis has been proposed by Crow et al. (1989). However, in contrast with Bracha's (1991) position, Crow et al. (1989) hypothesize that this lag is primarily due to a unilateral mechanism that is genetic and that is responsible for both schizophrenia and cerebral dominance. Crow et al. (1989) suggest three possible explanations for the structural brain changes in schizophrenia:

1. normal brain development proceeds in a sequence in which growth in temporal and occipital structures is completed relatively late; (2) growth continues later on the left than on the right side; and (3) if there is arrest of the sequence, this is seen most clearly in left temporo-occipital structures and is more easily detected as a change in ventricular size than brain substance. [Crow et al. 1989, p. 1149]

Crow et al.'s (1989) reformulation of the lag hypothesis makes a clear and compelling argument for a unilateral defect in the left hemisphere, and they report postmortem anatomical and computed tomography (CT) data to support their claim that the left temporal horn enlargement in schizophrenia reflects an arrest in intrauterine brain growth that is under genetic control. This position, along with Bracha's (1991), provides a heuristic framework for other positions that advocate a left hemisphere substrate in schizophrenia (Flor-Henry 1976; Posner et al. 1988; Posner and Early 1990).

Unfortunately, this reformulation again rests, in part, on the controversial assumption of a lag in left hemisphere neuronal migration. Furthermore, Crow et al. (1989) make some additional claims that could prove troublesome. First, they eschew any role for exogenous trauma factors (epigenetic) that are known to occur in some patients with schizophrenia during the prenatal or perinatal periods and may result in more diffuse or multifocal insult. As such, the theory implies that schizophrenia is etiologically a homogeneous disorder (under unspecified genetic control) without different subgroups of "sporadic" cases induced by trauma. Also, the assumption that the defect in cerebral dominance is unilateral conflicts with considerable other CT and postmortem anatomic evidence of bilateral (symmetric) ventricle-brain ratio (VBR) enlargement in schizophrenia (see Pearlson et al. 1989 for a review). A final problem in this otherwise provocative hypothesis is that, like Bracha (1991), it makes no clear predictions about cognitive (i.e., linguistic) or motor (hand preference) sequelae that would result from a defect in cerebral dominance involving the left temporal cortex.

In summary, both views of the lag hypothesis, while innovative, have problems, and neither position has yet collected data on handedness or language function that, if altered, could provide some additional support for both views. Such support remains unlikely at the present time, based on the scarcity of studies showing an increased incidence of left-handedness in schizophrenia. A final comment concerns the lag hypothesis. If Bracha (1991) dropped this assumption, which may contain unnecessary surplus meaning anyway, then his position acknowledging a bilateral or multifocal insult due to epigenetic factors would be compatible with the two hypotheses that follow.

Left Hemisphere Vulnerability Hypothesis. The left hemisphere vulnerability hypothesis, which has not been addressed in schizophrenia to date, suggests that the left hemisphere may be more vulnerable to prenatal or perinatal insults because of inherent differences in its vascular or metabolic properties, not because of its rate of maturation. The primary evidence in support of this hypothesis is based on studies of severely premature infants with very low birth weights (Guzzetta et al. 1986; Raz et al. 1994). The most common cerebral lesion in these premature neonates is the intracranial hemorrhage of subependymal origin (Volpe 1989). Using ultrasound scans, the investigators found that cerebral insults caused by intracranial bleeds affected the cerebral hemispheres unevenly. In a majority of cases the bleeds were unilateral (3:1 on the left), but in cases of bilateral hemorrhage the pattern was also asymmetric, with a similar ratio of left hemisphere involvement (3:1) (Raz et al. 1994).

More difficult to explain are the possible mechanisms that might underlie this vulnerability. Although it has been suggested that the germinal matrix in the left hemisphere (a richly vascularized region overlying the head of the caudate nucleus) is exhausted at a slower rate, thereby requiring relative augmentation of vascular support (Taylor 1969), other explanations have suggested that developmental asynchronies in hemispheric vascularization may be involved or that a relative increase of germinal cells in the left hemisphere may require relative amplification in blood supply to this region (see Raz et al. 1994 for a review). Carmon et al. (1972) have also suggested that the right hemisphere might enjoy greater vas-
cular supply than the left hemisphere, which would provide more protection from adverse metabolic events.

Although these explanations are speculative, the fact remains that the left hemisphere is more vulnerable to adverse hypoxic events in very low birthweight infants. However, only a minority of premature births are in this category of bleeds, and the association between birth complications and schizophrenia, while present, confers only a small relative risk (Goodman 1988). Also, the hemispheric vulnerability hypothesis faces the same basic problem as the lag hypothesis, namely, accounting for the increased incidence of MH in schizophrenia.

One possible clue to this phenomenon would be to assume that in a subset of patients with schizophrenia, certain sporadic exogenous events (e.g., infections or bleeds) traumatized the genetically predisposed fetus at some critical time, leading to diffuse and multifocal brain insult. In such cases, the insult would further increase the left hemisphere’s predisposed vulnerability, thereby shifting manual preference leftward. However, the presence of a diffuse insult including the right brain would inhibit a more extreme shift to the left (PLH), as with a focal left-sided lesion. This explanation would be strengthened if one could link the co-occurrence of atypical handedness with diffuse structural brain insult in schizophrenia.

Five studies provide support for this key association, although in four of them the term “left-handedness” was based either on writing hand (Katsanis and Iacono 1989), convenience (Clementz et al. 1994), or not defined (Pearson et al. 1989; O’Callaghan et al. 1995). Pearson et al. (1989) showed that a history of abnormal birth stress and the presence of left-handedness were significant predictors of an enlarged VBR on multiple regression analysis. Katsanis and Iacono (1989) found enlargement of the lateral ventricles (based on CT) in a subgroup of left-handers with schizophrenia, but not right-handers. Also, the former group had more neuropsychological test impairment. Clementz et al. (1994) also found a similar VBR enlargement in left-handed versus right-handed patients with schizophrenia, but no VBR enlargement or excess of left-handedness was found in a group of patients with affective disorders. O’Callaghan et al. (1995) investigated the association between handedness and ventricular brain volume (using MRI) in a small sample of patients with schizophrenia, nine of whom (20%) were left-handed based on an unspecified dichotomous classification using the Edinburgh inventory (1971). Results showed a bilateral increase in ventricular volume in the non-right-handed male patients. However, among female patients, non-right-handedness was associated with lower premorbid intelligence.

The fifth study (Satz et al. 1990), reported MRI data on a small sample of lateralized (n = 10) chronic schizophrenia patients using the HPDT, in which the lateralized group was classified based on consistent preference in the same direction (right in all but one patient) for all tasks across repeated presentations. The MRI scans were also compared with those from a normal control group (n = 25). This is the only study to date to show an association between VBR asymmetry and atypical handedness. Nine of the 10 nonlateralized schizophrenia patients had larger left versus right VBRs compared with none of the lateralized schizophrenia patients or controls. Interestingly, though unclear, was the finding of a structural asymmetry on the left, which would be compatible with the views of Bracha (1991) and especially Crow et al. (1989), except for the unnecessary and probably false assumption of a lag in left hemisphere maturation. However, the enlarged left VBR was associated with an increase in MH, not left-handedness. In fact, while 2 of the 10 subjects wrote with the left hand, they were clearly MH or AH.

Hemispheric Specialization Hypothesis. The final hypothesis on the putative mechanism underlying MH in schizophrenia, the hemispheric specialization hypothesis, makes no implicit assumption regarding a predisposed left hemisphere vulnerability in either maturation rate or metabolic constraints. However, it again introduces the concept of a left hemisphere factor—but as a necessary, though insufficient, explanation of PLH and MH.

The hypothesis states that in the vast majority of humans there is a biological substrate for hemispheric specialization in which the left hemisphere plays a dominant role in the mediation of speech, language, and related analytic functions (Molfese and Segalowitz 1988). This asymmetry, regardless of acceleration rate, is structurally evident early in intrauterine life, as well as electrophysiologically and behaviorally during early postnatal life.

The primary anatomical evidence for this substrate concerns asymmetries in the planum temporale. The horizontal bank of this structure underlies auditory association cortex and is posterior to the Heschl’s gyrus, which is primary auditory cortex. Geschwind and Levitsky (1968) reported the first documentation based on measurements of planum length in 100 postmortem brains: 65 percent of the plana were longer on the left, 24 percent were symmetrical, and only 11 percent were longer on the right. This leftward asymmetry was later confirmed in newborn (Witelson and Pallie 1973), infant (Wada et al. 1975), and fetal brains (Chi et al. 1977). Additional anatomic evidence for this hypothesis is based on the role of the left inferior frontal convolution in language production and the left posterior temporal cortex in language comprehension (Geschwind and Galaburda 1985).
Other investigators have suggested that this hemispheric asymmetry (i.e., cerebral dominance), while probably under genetic control, induces a contralateral bias for both motor (handedness) and attentional processes (e.g., the rightward shift bias; Annett 1972). It has also been suggested that the left cerebral hemisphere may play a dominant role in the innervation of dopaminergic activity (Tucker and Williamson 1984), which may provide a neurochemical substrate for both manual laterality and contralateral hemiattentional orientation (Glick and Russ 1981; Kinsbourne 1988; Posner et al. 1988).

To date, this hypothesis has provided a reasonable explanation for alterations in manual laterality when the left hemisphere is injured focally during prenatal or early childhood life (as noted earlier). The critical issue, however, concerns the conditions under which this construct could account for an increased incidence of MH. The explanation is rather straightforward and parsimonious if one assumes that a proportion of schizophrenia patients have bilateral brain damage, whether genetically or exogenously induced. Rather than postulating a left hemisphere vulnerability predisposition (even if true), one would merely have to state that the presence of a diffuse insult (including the right hemisphere) would shift one's manual preference in a leftward, though incomplete, direction, resulting in MH or AH. This explanation avoids the assumptions necessary in the preceding two hypotheses without challenging either of them.

It should be clear from the preceding comments that atypical handedness, whether expressed as PLH, MH, or AH, represents a potential biological marker of an underlying neurodevelopmental insult that occurred much earlier during prenatal development. If so, these markers could represent potential signs of nongenetic cases of schizophrenia. However, this latter interpretation could be challenged if it were shown that alterations in handedness were also under genetic control. Such a finding would not change the role of atypical handedness as a neurodevelopmental marker, only its reference to genetic versus epigenetic events.

Are There Clinical and Cognitive Correlates of Atypical Handedness?

Recent studies have addressed the association between non-right-handedness (left or mixed) and other behavioral, cognitive, neurological, and brain-imaging abnormalities in schizophrenia. Five of these studies also reported data on prevalence, as noted earlier in this review (Clementz et al. 1994; Manoach 1994; Cannon et al. 1995; O’Callaghan et al. 1995; Taylor and Amir 1995). The remaining studies were Katsanis and Iacono 1989; Pearlson et al. 1989; Barr et al. 1990; Joseph 1990; Satz et al. 1990; Faustman et al. 1991; Kern et al. 1991; Brown et al. 1992; Tyler et al. 1995; Manschreck et al. 1996; Morgenstern et al. 1996; Hayden et al. 1997. Most of these studies were not addressed in the original review by Green et al. (1989b) because of its focus on assessment methodology and prevalence.

In terms of clinical correlates, some studies have considered the relationship between handedness and formal thought disorder in schizophrenia (Taylor et al. 1982; Manoach et al. 1988; Manoach 1994; Taylor and Amir 1995; Manschreck et al. 1996). Taylor et al. (1982) evaluated the relationship between handedness and a range of psychotic symptoms in a large sample (n = 232) of schizophrenia patients. A series of 15 contrasts were performed by dividing patients into groups by symptom and then comparing the handedness distributions of the groups. Only one symptom—the presence of formal thought disorder—was associated with left-handedness and MH. This finding came from the male patients: of the 88 male patients with thought disorder, 47 percent were mixed- and left-handers. In contrast, of the 44 patients without thought disorder, 23 percent were mixed- or left-handers. In a curious interpretive twist, the authors concluded that the group without thought disorder formed the most pathological group. The reason for this unexpected interpretation is that the authors were viewing the results within a perspective of abnormal dextrality in schizophrenia because they had previously found a paradoxical shift toward dextrality in schizophrenia (Taylor et al. 1980). Naturally, we view the results as supporting a relationship between thought disorder and atypical shift away from dextrality.

Subsequent interest in the relationship between formal thought disorder and handedness stemmed from the notion that atypical handedness may reflect an underlying disruption in the dominant hemisphere and that this disruption may also result in reduced hemispheric specialization for linguistic processes. Manoach et al. (1988) evaluated handedness and formal thought disorder in 58 male schizophrenia patients. They determined handedness only by writing hand. As noted earlier, a more comprehensive handedness assessment likely would have revealed that a number of the left-handed subjects actually had MH. In this initial study, the left-handers had higher rates of formal thought disorder.

A later study (Manoach 1994) with both normal and psychiatric controls and using a dimensional handedness assessment yielded similar results. Sinistrality was associated with increased thought disorder for male schizophrenia patients (there were too few females to analyze separately). This relationship between sinistrality and thought disorder may have been linked to either left-
handedness or MH; the results in this regard were unclear. In addition, a variability index of hand proficiency (based on the standard deviation of various proficiency tests) was related to both thought disorder and language functioning for the combined male and female schizophrenia sample, but not for the normal or psychiatric controls. The results from the two Manoach studies were interpreted as evidence for a disruption in the establishment of hemispheric dominance that resulted in both impaired language functioning and increased sinistrality.

Similar findings were reported in a study by Manschreck et al. (1996) that also investigated the association between left-handedness and memory and thought disorder in schizophrenia. Using a single item from Annett's (1972) handedness inventory, 21 right-handed and 21 left-handed patients selected from a larger patient pool were assessed on an experimental memory task and for the presence and severity of thought disorder (e.g., derailment, illogicality, and poverty of speech content). The two groups of patients were individually matched on word recall ability, age, sex, and education. Results showed that the left-handed patients were less able to take advantage of increasing context to assist in word recall and had more symptoms of disorder.

Tyler et al. (1995) also showed an increased prevalence of persistent auditory hallucinations in a sample of 94 left-handed versus 595 right-handed schizophrenia patients whose relatives were members of the United Kingdom National Schizophrenia Fellowship. Handedness was dichotomized on a single variable from an unspecified handedness questionnaire. This study also found that the left-handed patients had more cognitive and behavioral abnormalities in childhood than did the right-handed patients.

In contrast with the preceding findings, Taylor and Amir (1995) failed to find an association between left-handedness or MH and thought disorder, mania, depression, or emotional blunting. Results also failed to show an increase of non-right-handedness in the schizophrenia group. This study used Oldfield's (1971) assessment battery to classify handedness groups in a large sample of patients with DSM-III (American Psychiatric Association 1980) schizophrenia (n = 163), affective patients (n = 103), and normal controls (n = 112). However, as in most of the other studies, the criteria for subtype classification was not specified.

Moving from symptomatic to demographic and familial correlates, Cannon et al. (1995) evaluated 96 patients with schizophrenia for an association between handedness and clinical features such as age at onset, chronicity, family history, and gender. They reported a prevalence of mixed handedness of 36.4 percent, which is almost identical to the 38.7 percent rate reported by Green et al. (1989b) using a different handedness assessment. Cannon et al. (1995) found that MH was significantly associated with greater chronicity of illness, and there were trends (p < 0.1) associating it with a negative family history for schizophrenia and with being male. Handedness was not associated with age at onset in this study. These qualities (i.e., chronic, male, early onset, and negative family history) have been suggested as characteristics of a "neurodevelopment" type of schizophrenia (Murray et al. 1992a, 1992b). The patients with MH in this study shared most of these characteristics, suggesting that atypical handedness may be a reflection of this proposed subtype of schizophrenia.

The connection between MH and negative family history for schizophrenia (p = 0.06) is noteworthy because it suggests that MH is associated with factors that are independent of the genetic diathesis for schizophrenia. Family history is a rather imprecise method; however, the notion that atypical handedness is related to non-genetic factors received more direct support in a study by Clementz et al. (1994) that failed to find any increased non-right-handedness in the relatives of schizophrenia patients.

As mentioned earlier, several studies have found an association between handedness and increased VBRs in schizophrenia (Katsanis and Iacono 1989; Pearlson et al. 1989; Satz et al. 1990; Clementz et al. 1994). It would be reasonable to expect that the relationships between atypical handedness and neuroanatomy would be mirrored by associations between handedness and neurocognition. In fact, they appear to be.

Some studies have found evidence of neuropsychological impairment in left-handed schizophrenia patients. Katsanis and Iacono (1989) compared 51 right-handed subjects with 12 left-handed subjects in a fairly comprehensive neuropsychological battery. The left-handed patients performed worse than right-handed patients across most tests of the neuropsychological battery, regardless of the particular cognitive process assessed by the test. The differences between handedness groups reached significance for the Wisconsin Card Sorting Test (Heaton 1981) and the performance IQ on the Wechsler Adult Intelligence Scale—Revised (Wechsler 1981).

In a similar study, Faustman et al. (1991) compared left- and right-handed schizophrenia patients (n = 24 per group), and left- and right-handed controls (n = 15 per group) on selected measures from the Luria Nebraska Neuropsychological Battery (Moses et al. 1983). Instead of examining a range of abilities, the authors selected measures that they considered to be sensitive to cognitive dysfunction in schizophrenia based on their previous research. The measures included rhythm, memory, intellectual processes, and global score. While the left- and right-handed controls did not differ in these measures, the
left-handed schizophrenia patients performed worse than right-handed patients in rhythm and memory.

These studies suggest greater cognitive compromise in left-handed patients. A limitation of both studies is that handedness was determined only by writing hand. As mentioned earlier, when handedness is defined only by writing hand, the left-handed group probably includes a subgroup of individuals who would have been considered mixed-handed if a dimensional handedness assessment had been used. This inherent heterogeneity in comparing left- with right-handers creates more difficulty in interpreting study results. It is conceptually more direct to compare subjects who have atypical handedness to those who are lateralized.

In a recent study from our laboratory (Hayden et al. 1997), we specifically evaluated differences in memory between two groups of patients: those with AH (i.e., within-item inconsistency; n = 19) and those who were lateralized (n = 39). The patients had various forms of chronic mental illness, with schizophrenia being the most common diagnosis. The patients received a battery of tests that included measures of verbal memory, executive functioning, and motor performance. The AH group performed significantly worse on measures of verbal memory and manual dexterity. The groups, however, did not differ on a measure of motor learning.

Taken together, these studies argue that the abnormalities in neurodevelopment may also be associated with certain symptoms (especially those that are heavily dependent on language functioning) as well as with other neurocognitive sequelae.

A final correlate of particular interest concerns the relationship between non-right-handedness and tardive dyskinesia (TD). Two early studies (McCreadie et al. 1982; Joseph 1990) reported an association between left-handedness and TD. These early studies, which employed dichotomous measures of handedness, have been challenged in more recent studies (Barr et al. 1990; Kern et al. 1991; Brown et al. 1992; Morgenstern et al. 1996). In fact, the latter studies have shown just the opposite effect—that non-right-handedness is a protective factor against TD, regardless of whether patients were inpatients or outpatients. The most compelling support for this view is based on the recent Yale University TD study, a prospective cohort investigation of 362 psychiatric outpatients in New Haven, Connecticut (Morgenstern et al. 1996). Hand preference was assessed with a 17-item laterality questionnaire. Pure left-handers and mixed-handers were pooled and showed lower rates of TD compared with predominately right-handed patients (42% with schizophrenia). The University of California Los Angeles study (Kern et al. 1991) hypothesized that the seemingly paradoxical protective effect was due to early diffuse insult, which not only induced a leftward shift in manual laterality, but also probably rendered primary dopaminergic receptors in the left hemisphere (Tucker and Williamson 1984) less sensitive to the chronic antidopaminergic effects of neuroleptics.

Conclusions

The results reviewed in the preceding sections provide some reasonable support for the view that, in schizophrenia, there is an atypical leftward shift in the handedness distribution. This shift is largely characterized by a more variable and less completely lateralized pattern of manual preference, namely, MH or AH. While one typically uses the term "left-handed," to refer to these nondextral subtypes (Clementz et al. 1994), it was shown that this term is potentially misleading and probably incorrect. The two studies reporting an increased incidence of left-handedness used writing hand as the sole basis for classification. This approach unfortunately prevents a determination of the proportion of MH and consequently lowers the overall rate of non-right-handedness in a sample. Another point to note is that while a majority of the studies reported a leftward shift in the distribution (2:1), there was sufficient variability to warrant more large-scale epidemiological research on this topic. One likely explanation for this variability is the marked differences in the assessment and classification of handedness across studies.

It was also suggested that the different types of atypical handedness (MH, PLH, and AH) represent neurodevelopmental markers of an early brain insult, probably diffuse or multifocal, during prenatal life; they also predict other key symptoms and neural substrates in the disorder. Studies reporting these pathological links to non-right-handedness in schizophrenia have marshaled compelling evidence for this hypothesis, which should be viewed as complementary to the prevalence findings noted earlier. While prevalence estimates have varied, probably as a function of differences in study procedures and methodology, results have been consistent in linking deviations in manual laterality to other clinical and neurological aspects of the disorder.

Finally, it was suggested that these deviations in lateral preference be viewed as epigenetic events that, when aggregated with genetic factors, may result in more severe forms of schizophrenia (Murray et al. 1992a, 1992b). However, this interpretation rests on the assumption that deviations in hand preference are induced only by exogenous, not genetic, events, which may not be true. Although current evidence favors the former view, more research should focus on whether atypical deviations in
hand preference may occur in schizophrenia in the absence of any known prenatal exogenous insult.

Different hypotheses were reviewed that purport to explain different subtypes of atypical handedness (PLH, MH, AH) in schizophrenia, with particular attention to MH. Although each hypothesis addressed some aspect pertaining to the left hemisphere (lag, vulnerability, hemispheric specialization), it was shown that a more parsimonious explanation could result by avoiding surplus meaning associated with concepts of unilateral insult or vulnerability of the left hemisphere and postulating that an early bilateral or multifocal brain insult would be necessary and sufficient to alter the left hemisphere’s control over cognitive (language) and contralateral motor (handedness) functions leading to a less complete and more variable form of MH. However, alternative explanations favoring a focal left hemisphere insult in utero, while still of potential merit and appeal, still lack sufficient support that shows a more extreme leftward shift in the handedness distribution. We hope this review will encourage future studies of this issue.

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**Announcement**

The *13th International Symposium for the Psychotherapy of Schizophrenia (ISPS)* will be held in Stavanger, Norway, June 4–9, 2000. A call for papers will be ready in the autumn of 1998. The theme of the symposium is “Schizophrenia and Other Psychoses: Different Stages—Different Treatment?” Registration will be on Sunday, June 4th, and the official opening will begin Monday, June 5th. Some of the topics to be discussed are: Monday—“The Nature of Psychosis” and “History of Psychotherapy”; Tuesday—“What Kind of Psychotherapy for Which Patient? Phase-Specific Treatment,” “Cognition and Psychotherapy,” and “Therapeutic Alliance and Psychotherapy”; Wednesday—“Early Intervention in Psychosis” and “Personality and Psychosis”; Thursday—“Integrated Treatment” and “Guidelines: New Antipsychotics and the Combination With Other Therapies”; and Friday—“Research in Psychotherapy” and “Models for Training and Competence Building.”

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