Laterality in Animals: Relevance to Schizophrenia

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Abstract

Anomalies in the laterality of numerous neurocognitive dimensions associated with schizophrenia have been documented, but their role in the etiology and early development of the disorder remain unclear. In the study of normative neurobehavioral organization, animal models have shed much light on the mechanisms underlying and the factors affecting adult patterns of both functional and structural asymmetry. Nonhuman species have more recently been used to investigate the environmental, genetic, and neuroendocrine factors associated with developmental language disorders in humans. We propose that the animal models used to study the basis of lateralization in normative development and language disorders such as dyslexia could be modified to investigate lateralized phenomena in schizophrenia.

Key words: Animal models, laterality in animals, functional and structural asymmetry, language, hand preference.


Throughout the history of the brain and behavioral sciences, it has been largely accepted that cerebral lateralization was a unique feature of the human brain, particularly for functions underlying language and hand preference (Glick et al. 1979; MacNeilage et al. 1987; Denenberg 1988). However, accumulated evidence now supports the existence of lateralization at the structural and functional levels in a range of species. A portion of the literature on animal laterality will be discussed in this article, but the reader is referred to a number of recent, comprehensive reviews for more detailed coverage of functional, anatomical, and neurochemical asymmetries in nonhuman species (Denenberg 1984; Diamond 1984; Gerendai 1984; Goldman-Rakic and Rakic 1984; Bianki 1988; Springer and Deutsch 1989; Ward 1991; Hellige 1993; Hiscock and Kinsbourne 1995).

Despite the large and growing literature describing behavioral, neuroanatomical, and neurophysiological asymmetries in nonhuman species, research on animal laterality has not been well integrated into the mainstream of human brain research. Nevertheless, a few investigators have demonstrated success in applying animal models of laterality to the study of human brain development and behavioral disorders. For example, Denenberg, Fitch, Rosen, and colleagues have used rodents to model the anomalous laterality patterns associated with developmental dyslexia and language impairment (Rosen et al. 1989, 1995; Denenberg et al. 1991a, 1991b, 1996; Fitch et al. 1993, 1994, 1997). In addition, many of the basic principles involved in the normal organization and development of brain asymmetries and related behavior have been conceptualized through the use of animal models (Collins 1977, 1985; Nordeen and Yahr 1982; Lipp et al. 1984, 1996; Galaburda et al. 1986; Diamond 1991; Rosen et al. 1992; Waters and Denenberg 1994; Riddle and Purves 1995). Advancements in the areas of developmental learning disabilities and basic neuroscience strongly suggest that the field of neuropsychiatry may also benefit from studies of laterality in animals.

Abnormalities in behavioral and neurobiological laterality have been widely documented in studies of schizophrenia (see Flor-Henry and Gruzelier 1983; Kovelman and Scheibel 1986; Nasrallah 1986; Takahashi et al. 1987 for reviews). Yet very few experiments have been specifically designed to study these phenomena in nonhuman species. Numerous animal models of schizophrenia have been proposed and implemented in recent years (see Lyon 1990, 1991 for reviews), but most have focused on neurotransmitter systems and the behavioral pharmacology related to this psychiatric disorder. These models have not addressed right-left differences (e.g., Hafner et al. 1991, 1993; Lewis et al. 1992; Schwartzkopf et al. 1992; Lipska

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et al. 1993; Lipska and Weinberger 1994, 1995; Moghaddam et al. 1997). Thus, connections between investigations of laterality in nonhuman species and research on neurobehavioral asymmetries in patients with schizophrenia can be made only indirectly. The objective of this article is to draw together and present the laterality findings from the seemingly distant areas of clinical research in humans and basic neuroscience research in animals. Toward this end, we will review the neuropsychiatric and animal literature on laterality to lay the groundwork for further discussion. Then, we will integrate examples of lateralized systems that have been studied in both animals and in schizophrenia patients to demonstrate the feasibility and importance of bridging these research fields. The topics discussed are not meant to be exhaustive of either literature, but rather indicative of lateralized phenomena exhibited by schizophrenia patients, phenomena that also occur in neural or behavioral systems that have been studied in animals.

Material on human and animal laterality from three major areas of neuroscience will be covered: (1) behavioral and cognitive, (2) neuroanatomical, and (3) neurophysiological and biochemical. The primary emphasis will be on behavioral laterality, although related asymmetries in brain structure and function will be covered briefly as well. Some of the developmental factors that affect the expression of these neurobiological measures will also be addressed. Our aim is to demonstrate how overlaps and links between the study of neurobiological asymmetries in animals and humans may inform both the study of schizophrenia and the direction of future neuropsychiatric research.

We have attempted to be sensitive to the limitations of cross-species comparisons and acknowledge that it is virtually impossible to operationalize the many clinical manifestations of schizophrenia into straightforward animal experiments. Conversely, we recognize that data derived from animal models must often be applied in a conceptual rather than in a literal sense to the study of schizophrenia. We do not intend to suggest that lateralized neurobehavioral measures in humans and animals necessarily have common evolutionary (homologous) or functional (analogous) bases. We designed the comparisons simply to elucidate general issues important to the development and organization of brain and behavior laterality in schizophrenia patients and in nonhuman species and to point out areas of convergence between these traditionally disparate fields of research.

Laterality in Animals and in Schizophrenia Patients

Behavioral and Cognitive Laterality.

An overview of anomalous behavioral and cogni-
**An overview of functional laterality in animals.** Laterized behaviors have been studied extensively in animals, either to model basic neurobehavioral principles or to provide insights into pathological neurodevelopmental processes. Some of the earliest reports of functional lateralization in nonhuman species derived from Nottebohm's work showing that control of song production was lateralized to the left hypoglossal nucleus of male canaries (Nottebohm and Nottebohm 1976; Nottebohm 1977). Asymmetries have been also reported in the sensory (Heffner and Heffner 1984; Zappia and Rogers 1987; Rogers 1990), motor (Lehman 1980; Glick and Ross 1981; Camp et al. 1984; Dewberry et al. 1986; Fagot and Vauclair 1991; Waters and Denenberg 1994; Bulman-Fleming et al. 1997), affective (Rogers 1982; Crowne et al. 1987; Maier and Crowne 1993), and cognitive (Zimmerberg and Riley 1988; Adelstein and Crowne 1991; Crowne et al. 1992; King and Corwin 1992; Fenton and Bures 1993; Fitch et al. 1993; Cowell et al. 1997) aspects of avian, rodent, and primate behavior.

The hormonal and environmental conditions that affect the organization of functional asymmetries have been investigated in developmental studies of animals, particularly rodents (Denenberg et al. 1978, 1986; Sherman et al. 1980; Rogers 1982, 1990; Garbanati et al. 1983; Camp et al. 1984; Lipsey and Robinson 1986; Zappia and Rogers 1987; Zimmerberg and Riley 1988; Alonso et al. 1991; Fitch et al. 1993; Maier and Crowne 1993; Cowell et al. 1997). The specific measures employed and the direction of the effects often distinguish behavioral asymmetries observed in animals from those seen in humans, making direct comparisons across species difficult. Despite these limitations, researchers will find it useful to turn to the animal literature to obtain theoretical context for, or gain better understanding of, the results from human studies, which typically examine developmental processes indirectly (i.e., with data from interview questionnaires or obstetric records). By looking to animal studies of behavioral asymmetry, we hope to shed light on some of the environmental conditions and developmental mechanisms that influence the origins and expressions of anomalous laterized behaviors seen in patients with schizophrenia.

**Converging lines of research on behavioral laterality in animals and in patients with schizophrenia.** Few behavioral modalities have been studied within all three of the following paradigms: (1) functional laterality in patients with schizophrenia, (2) functional laterality in animals, and (3) animal models of lateralized behavioral systems in schizophrenia. Of the many laterized phenomena cited in the preceding sections, research on asymmetries in motor behavior provides the broadest basis for comparison across all of the above three research paradigms. In addition, studies of functional asymmetries in language and language-related processes have been examined in the first research paradigm listed above and have been modeled in animals using tests of auditory discrimination. These studies provide another context from which to address laterality issues in schizophrenia. Therefore, two in-depth sections—one on behavioral motor asymmetries and the other on language, language-related processes, and auditory discrimination—will discuss specific connections between animal laterality and schizophrenia research.

**Asymmetries in motor behavior.** Motor asymmetries in patients with schizophrenia. One notion that emerged from early behavioral studies of schizophrenia was that patients' left hemispheres appeared to be dysfunctional or "overactivated." Patients were shown to exhibit more leftward patterns of circling behavior and eye, foot, and hand movements than controls (Gur 1977, 1978; Bracha 1987). Results from such investigations of motor asymmetries have been interpreted in various ways, which were not necessarily mutually exclusive but were certainly difficult to confirm on the basis of behavior alone. One view was that primary disruptions in the left hemisphere were accompanied by shifts of motor lateralization to the right hemisphere, whereas others attributed similar results to increased activation of dopaminergic systems in the right hemisphere (Gur 1977, 1978; also see Gruzelier and Flor-Henry 1979; Bracha 1987). Recent research on functional magnetic resonance imaging (MRI) suggests that disturbances in lateralized movements involve complex interactions of activity in both right and left sensorimotor cortices (Wenz et al. 1994). However, the underlying basis of even straightforward behavioral asymmetries, such as hand preference or body movements, are still not clearly understood from a neurodevelopmental basis.

The study of individual differences in motor function has revealed an even more complex and heterogeneous view of laterality in schizophrenia. For example, various studies of hand preference have shown patients with schizophrenia to have higher, lower, or equal percentages of non-right-handedness as compared with controls (Boklage 1977; Fleming et al. 1977; Taylor et al. 1980; Torrey et al. 1993; Cannon et al. 1995; Sakuma et al. 1996) and patients with bipolar disorder (Lohr and Caligiuri 1995). The direction and degree of various motor asymmetries have been shown to vary as a function of clinical subgroup, severity of illness, family history of psychosis, and sex (Fleminger et al. 1977; Manoach 1994; Cannon et al. 1995; Tyler et al. 1995). In general, findings support the view of Nasrallah (1986, p. 160), who theorized that "inconsistent findings in handedness research in schizophrenia may in large part be due to the
different subtype and gender compositions of the various samples reported.” The effects of such differences on variation in neurobehavioral asymmetries in schizophrenia are further complicated by “the combined effect of the disease and the neuroleptic medication” (Wenz et al. 1994, p. 975). Therefore, animal models that allow researchers to experimentally control or manipulate neuropharmacology, environment, genetics, and developmental conditions are particularly essential in unraveling the intricacies of neurocognitive laterality in this disorder.

Motor asymmetries in animals. Evidence of motor asymmetries in a variety of nonhuman species has been clearly demonstrated (Collins 1985; Glick et al. 1987; Bradshaw 1989; Carlson and Glick 1989). Evidence of population bias in nonhuman species has also been studied (Glick and Ross 1981; Alonso et al. 1991; Waters and Denenberg 1994; see also MacNeilage et al. 1987). As is the case with humans (Healey et al. 1986; Peters 1990, 1991), side preference appears to depend partly on the nature of the task used for measurement (Camp et al. 1984; Fagot and Vauclair 1991; Waters and Denenberg 1994; Bulman-Fleming et al. 1997) and the neurobiological systems involved (Whishaw et al. 1986; Barneoud et al. 1990; Cabib et al. 1995).

In the process of trying to investigate the basis and role of functional laterality in schizophrenia, continued research has uncovered a highly heterogeneous set of behaviors with anomalous asymmetry patterns. In the animal literature on lateralized motor behavior, the array of asymmetries is equally broad and complex, but somewhat better understood in terms of developmental principles. Studies of open-field activity, swimming rotation, T-maze side preference, and paw preference have revealed that direction and degree of motor laterality are influenced by multiple developmental factors, including early environment (Sherman et al. 1980; Camp et al. 1984; Alonso et al. 1991), genetics (Collins 1977; Waters and Denenberg 1994), hormonal milieu (Robinson et al. 1980; Ross et al. 1981; Sherman et al. 1983), neuropharmacology (Brass and Glick 1981; Jerussi and Taylor 1982; Rodriguez et al. 1994), immune status (Neveu et al. 1988; Denenberg et al. 1991b, 1996; Neveu 1992; Delrue et al. 1994), and neonatal cortical injury (Rosen et al. 1995). By exploring these factors, it may be possible to develop novel frameworks for couching both conceptualizations of, and research directions for, schizophrenia laterality research.

The classic work of Glick and colleagues, describing brain asymmetries and right-sided population bias in amphetamine-induced rotation in the rat, stimulated much research into the factors and conditions involved in the organization and expression of these and other similar asymmetries in motor behavior (Glick et al. 1979; Glick and Ross 1981). It was found that many measures of motoric and postural laterality (e.g., rotation behavior and side bias in the open field) were different in males and females and were affected by early environmental conditions. For example, females exhibited more amphetamine-induced rotation in adulthood and a greater degree of lateralized spatial preference in the open field than males (Robinson et al. 1980; Ross et al. 1981; Denenberg et al. 1982; Rosen et al. 1983). In addition, neonatal handling was found to enhance lateralization of spatial preference differently in male and female rats (Sherman et al. 1980, 1983). Furthermore, the effects of postnatal handling (Camp et al. 1984), prenatal stress (Alonso et al. 1991), and prenatal alcohol (Zimmerberg et al. 1988) on lateralized motor and postural behaviors were shown to differ as a function of sex.

Convergence of human and animal motor asymmetry research. Studies of motor behavior in patients with schizophrenia have not focused simultaneously on sex differences, perinatal development, and laterality. Ethical standards for human research practice, combined with the cost and time scale of studying human development, present major obstacles to the investigation of phenomena routinely examined in animals. Investigators must resort to very large-scale studies and intricate statistical methods to pull apart the sources of variance presented to them in clinical human data bases. Turning to the study of comparable phenomena in animals is another way to triangulate information, and as will be described later, some of the hormonal, environmental, and developmental factors that appear to affect lateralized behavior in schizophrenia also appear to play a role in the organization of motor asymmetries observed in animals.

The finding that a higher proportion of men than women with schizophrenia were left-handed writers (Fleminger et al. 1977), more sinistral on manual proficiency measures (Manoach 1994), and afflicted with subtle deficits in lateralized motor function (Goldstein et al. 1994) provides indirect evidence for sex differences in this patient population's expression of anomalous behavioral asymmetries. Looking to research on sex differences in animals, one finds support for the notion that the heterogeneous array of asymmetry effects observed within and between human patient groups depends in part on the ratio of male to female patients comprising the subject group. Animal studies also indicate that the varied patients' perinatal histories and genetic backgrounds may contribute further to different expressions of functional laterality and, thus, exacerbate inconsistencies in the literature.

Examining sex differences in patients' motor asymmetries, together with reports of sex differences in similar types of measures in animals (Fleminger et al. 1977; Robinson et al. 1980; Brass and Glick 1981; Ross et al.
include collecting detailed information on family and clues for designing future studies in humans that investi-
gplex interaction between genetic background and other Overall, the animal literature suggests that the develop-
and immune status of the mother and developing fetus. 
patients with schizophrenia may be influenced by a com-
developed in the uteri of non-autoimmune mothers. 
Denenberg et al. 1991ft), which had been transferred and 
depended on the specific strain of mouse examined. 
strains of mice (different strains from those used in 
Denenberg et al. (1996) showed that absolute asymmetry 
in offspring. Embryos from an autoimmune mouse strain 
were transferred into the uteri of non-autoimmune mice; 
and other mice from these two strains were not transferred (Denenberg et al. 1991b). Females whose gestation occurred in autoim-
une uteri had greater absolute paw asymmetry than 
those who developed in non-autoimmune uteri, but males 
were unaffected. If one views prenatal exposure to 
autoimmunity as a stressor, the results of this study 
together with those of Alonso et al. (1991) suggest that 
the developing functional asymmetries of males and 
females are differentially sensitive to stressful events 
during the prenatal period.

More recent work has found that the profile of lateral-
ized behavior, and whether sex differences were present, 
depended on the specific strain of mouse examined. 
Denenberg et al. (1996) showed that absolute asymmetry 
in swimming rotation was increased in two autoimmune 
strains of mice (different strains from those used in 
Denenberg et al. 1991b), which had been transferred and 
developed in the uteri of non-autoimmune mothers. 
Overall, the animal literature suggests that the develop-
ment of anomalous motor asymmetry patterns seen in 
patients with schizophrenia may be influenced by a com-
plex interaction between genetic background and other 
perinatal factors, including stress levels, hormonal milieu, 
and immune status of the mother and developing fetus.

The animal literature reviewed earlier may provide 
clues for designing future studies in humans that investi-
gate the neurodevelopmental basis of motor asymmetries 
in patients with schizophrenia. Future research would 
include collecting detailed information on family and medical history, plus considering demographic variables 
such as sex and age. Multiple measures of behavioral lat-
erality would also need to be assessed, since animal stud-
ies indicate that measures of motor laterality, such as paw 
preference and swimming rotation, are associated with 
asymmetries in different brain areas (Whishaw et al. 
1986; Barneoud et al. 1990; Cabib et al. 1995). Applying 
a research approach similar to the one described above 
would allow heterogeneity in motor asymmetries to be 
studied with respect to variation in specific developmental 
and neurobiological characteristics seen in patients with 
schizophrenia.

Language asymmetry in neurodevelopmental dis-
orders: Research links to the study of behavioral asym-
metry in schizophrenia. Language and language-
related processes in patients with schizophrenia. Many 
measures of lateralized language processing have been 
shown to differ between patients with schizophrenia and 
controls. Verbal memory deficits indicating dysfunction in 
left temporal and frontal regions are notable neuropsycho-
logical characteristics of schizophrenia (Saykin et al. 1991, 
Language dysfunction is present early in the course of the 
disease (Saykin et al. 1994) and has been shown to be 
related to formal thought disorder and atypical patterns of 
behavioral asymmetry (Manoach 1994; Sakuma et al. 
1996). Reversal or absence of the normative patterns of 
left-hemispheric lateralization in verbal processing has 
been noted in the visual and auditory modalities (Gur 
1978; Gur et al. 1983, 1985, 1994). Decreased left frontal 
and increased left temporal lobe activity have also been 
reported during verbal fluency activation in patients 
(Yurgelun-Todd et al. 1996). Furthermore, tests of 
dichotic listening have revealed that abnormal patterns of 
language asymmetry are associated with auditory halluci-
nations in schizophrenia (Green et al. 1994). It appears 
that disruptions in functional language asymmetry have 
important associations to cognitive and clinical aspects of 
schizophrenia.

The investigation of normative sex differences in lan-
guage asymmetry has contributed greatly to the general 
understanding of lateralized functions in the human brain. 
This research also has the potential to reveal which factors 
may be involved in the anomalous development and 
the expression of the functional laterality associated with 
schizophrenia. Early evidence for sex differences in func-
tional asymmetry of language processing was derived 
from research showing that women exhibited significantly 
better recovery of language following damage to the left 
hemisphere than men (Kimura and Harshman 1984). 
These findings supported the view that there may be a 
greater degree of functional language symmetry in the 
brains of women (see McGlone 1980, for review). Sex
differences have also been reported in the interhemispheric patterns of cerebral blood flow during the performance of verbal tasks (Wood et al. 1991), in neurophysiological asymmetry as measured by functional MRI during verbal tasks (Shaywitz et al. 1995), and in structural asymmetry as measured by right and left planum temporale size in men and women (Kulynych et al. 1994). These results support the notion of sex differences in the cerebral organization of language and are consistent with long-standing, although somewhat controversial, evidence of normative sex differences in the magnitude of the right ear advantage (REA) for discriminating verbal material in tests of dichotic listening (Lake and Bryden 1976; Bryden 1979; Hiscock et al. 1994).

The normative data suggest that controversy over the presence of REA reversal or attenuation in patients with schizophrenia (Gur 1978; Colbourn and Lishman 1979; Bruder 1983; Ragland et al. 1992; Grosh et al. 1995; Sakuma et al. 1996) may be due in part to the confounding effects of sex. Recent findings from neuropsychological studies reveal sex differences in performance on verbal memory and other language-related measures of performance (Goldstein et al. 1994; Gruzelier 1994; Lewine et al. 1996). Using latent class analysis, Goldstein et al. (1994) identified a subgroup of patients characterized by previous history of developmental learning problems. This subgroup, subsequently found to exhibit deficits in neuropsychological tests of verbal function, consisted entirely of male patients. This research provides further supporting evidence for unique profiles of lateralized cognitive ability and impairment in men and women with schizophrenia.

Research has demonstrated that functional lateralization for speech is directly dependent on the temporal (i.e., time-relevant) parameters of acoustic stimuli, regardless of linguistic content, both at the behavioral level, as measured by dichotic listening (Schwartz and Tallal 1980), and at the neurophysiological level, as measured by positron emission tomography activation during verbal, phonological, and nonverbal discrimination tasks (Fiez et al. 1995). These findings are consistent with evidence of language dysfunction in children with auditory discrimination deficits (Tallal et al. 1993), a population shown to exhibit atypical cerebral asymmetry (Jernigan et al. 1991). Conceptualizing language in terms of discrete auditory stimuli has enabled researchers to operationalize both language processing and language-processing deficits into tests suitable for animal studies. The following sections will explore how animal research on behavioral laterality has informed the study of developmental language disorders in humans and how it may also provide clues to some of the anomalous patterns of functional asymmetry in patients with schizophrenia.

Animal models of laterality in language-related processes. The notion that lateralization of speech depends on left-hemisphere specialization for the processing of rapidly changing auditory information is consistent, in turn, with animal studies demonstrating left-hemisphere specialization for auditory temporal processing (Dewson et al. 1970; Dewson 1977; Petersen et al. 1978, 1984; Heffner and Heffner 1984; Ehret 1987; Gaffan and Harrison 1991). Thus, monkeys, mice, and rats appear to exhibit patterns of lateralization for complex auditory discrimination similar to those seen for speech and complex nonspeech auditory processing in humans.

It has also been shown that male, but not female, rats exhibit an REA for the processing of rapidly presented tone sequences (Fitch et al. 1993), a finding that is consistent with studies of humans (Brown et al., in press). These data support the view that there are parallels between human and animal species with respect to lateralized gender differences in the neurobiological systems underlying language. As such, using animal models to address these and similar issues opens the door to research questions that are sometimes impossible to address in human clinical research. For example, in human research it is often difficult to demonstrate directly that sex differences in behavioral laterality result from perinatal hormonal exposure.

However, a considerable literature revealing the importance of early hormonal milieu in establishing sexually dimorphic neurobehavioral asymmetries in animals has accumulated (Robinson et al. 1980; Brass and Glick 1981; Ross et al. 1981; Camp et al. 1984; Zimmerberg et al. 1988; Alonso et al. 1991; Denenberg et al. 1991b; Fitch et al. 1993). Thus, animal models can help us understand how and why the brains of men and women differ and moreover may help us understand the mechanisms that underlie the development of anomalous patterns of lateralized behavior in schizophrenia.

Convergence of human and animal research on language-related processes. Crow and colleagues have explored the notion that disruptions of neurobiological asymmetries during fetal life are related to the emergence of schizophrenia in adulthood (Crow et al. 1989; Crow 1990). It has been suggested (Crow 1990, p. 433) that there is an "intimate relationship between the disease process and the mechanisms that determine asymmetrical brain development." Although epidemiological studies have demonstrated relationships between environmental and genetic risk factors and schizophrenia (Lewis and Murray 1987; Cannon et al. 1989; Bracha et al. 1992; Susser and Lin 1992; Verdoux and Bourgeois 1993), the connections between these developmental influences and atypical patterns of laterality have not been clearly established. Preliminary evidence suggests that certain devel-
opmental delays in neurobehavioral laterality may be inte-
grally linked to the emergence of schizophrenia (Crow et al. 1996). However, other aspects of anomalous asymmetry,
such as delays in neural processing of auditory stimuli
(Javitt et al. 1993), may not be unique to schizophrenia,
but may also accompany neurodevelopmental language
and learning disorders (Stein 1994).

That neurobehavioral asymmetries in verbal memory
and language comprise the essential core of the disease
process in schizophrenia seems unlikely. However, ani-
mal and normative human research indicate that asymme-
tries of language and language-related processes in
patients with schizophrenia may provide the backdrop for,
and interact with, numerous other complex cognitive and
clinical characteristics. The use of animal models, such as
those used by Fitch and colleagues (1993, 1994, 1997) to
study language disorders, could provide the field of schiz-
ophrenia research with information on the contributions
of sex hormones to developing asymmetries in language.
Further research could also shed light on the degree of
shared developmental history between language laterality
and other neurobiological traits specific to the etiology of
this disorder.

Neuroanatomical Asymmetries.

An overview of neuroanatomical asymmetries in
patients with schizophrenia. Abnormalities in neu-
roanatomical asymmetries have been found to differenti-
ate the brains of schizophrenia patients from those of con-
trols (Barta et al. 1990, 1997; Young et al. 1991; Breier et al.
1992; Falkai et al. 1992; Hoff et al. 1992; Rossi et al.
1992; Shenton et al. 1992; Bilder et al. 1994; Seidman et
al. 1994; Petty et al. 1995; Wible et al. 1995; Pearlson et
al. 1997), and to distinguish among clinical subtypes of
schizophrenia patients (Turetsky et al. 1995). Some of
the most reliable effects have been decrements in the size of
structures within the left temporal lobe, including the hip-
pocampus and amygdala (Barta et al. 1990; Young et al.
1991; Breier et al. 1992), the parahippocampal region
(Young et al. 1991), and the superior temporal gyrus,
Sylvian fissure, and planum temporale (Barta et al. 1990,
1997; Falkai et al. 1992; Hoff et al. 1992; Rossi et al.
1992; Shenton et al. 1992; Petty et al. 1995; Pearlson et
al. 1997). Recent reports have also begun to focus on the
contribution of the larger right planum temporale area in
patients to the reversed asymmetry effects observed in
this region (Petty et al. 1995; Barta et al. 1997).

Clinical (Barta et al. 1990; Shenton et al. 1992; Petty
et al. 1995) and cognitive measures (Hoff et al. 1992;
Seidman et al. 1994; Nestor et al. 1995) have been corre-
lated with anatomical features in an asymmetric fashion.
Most notably, decrements in left superior temporal gyrus
and left planum temporale were found to correlate with
severity of auditory hallucinations (Barta et al. 1990) and
thought disorder (Shenton et al. 1992; Petty et al. 1995). Additionally, Turetsky et al. (1995) showed a correlation
between severity of negative symptoms and asymmetry of
the temporal lobe.

Sex differences have been reported in the expression
of several neuroanatomical asymmetries in patients with
schizophrenia. Cowell et al. (1996) found that degree of
deviation from the normal pattern of anatomical asymme-
try was sexually dimorphic and due primarily to decre-
ments in left temporal lobe volume in male patients.
Other laboratories have reported that the normal left-
greater-than-right asymmetry of the Sylvian fissure was
present in men, but not women, with first-episode schizo-
phrenia (Hoff et al. 1992; DeLisi et al. 1994). By contrast,
Falkai et al. (1992) showed that the left Sylvian fis-
sure was more symmetrical relative to the right in male,
but not female, patients with schizophrenia whose average
duration of illness was 20 years. Several groups have
failed to find any disturbances in the structural laterality
patterns of their patient samples (Bartley et al. 1993;
Kleinshmidt et al. 1994; Kulynych et al. 1995; Becker et
al. 1996). As seen in the review of behavioral and cogni-
tive asymmetries, inconsistencies in the neuroanatomical
literature suggest that complex interactions among sex
hormones and the other developmental factors contribut-
ing to variation in clinical severity and subtype may lead
to real differences in lateralized brain structure across
samples of patients with schizophrenia.

An overview of neuroanatomical asymmetries in
animals. One of the best known studies of neuro-
anatomical asymmetry in nonhumans is Diamond's report
of laterality in the cortical thickness of the rat (Diamond
et al. 1981). Specifically, this study reported that certain
regions of the cerebral cortex were significantly thicker in
the right hemisphere than in the left. Kolb and colleagues
provided evidence of similar patterns of cortical thickness
asymmetry in rats (Kolb et al. 1984) and in other species,
including cats and rabbits (Kolb et al. 1982). Asymmetries
have also been shown in the medial and orbital prefrontal
reviewed cortical asymmetries in non-
human primates, based on skull size and other attributes.
Length of the Sylvian fissure in monkeys appeared to
show a left-greater-than-right asymmetry (Galaburda
1985a), and asymmetry of the Sylvian fissure in cats has
more recently been shown to vary as a function of sex and
paw preference (Tan and Kutlu 1993). It is interesting to
note that sex differences in associations between Sylvian
fissure asymmetry and hand preference have been
reported in humans as well (Witelson and Kigar 1992).

Early in the study of neuroanatomical asymmetries in
animals, researchers noted that the asymmetry patterns
differed between males and females. The right-thicker-than-left pattern observed in rats was seen only in the male cortex, whereas a trend toward asymmetry in the opposite direction was seen in females (Diamond et al. 1981). The association between hormonal exposure and laterality was further supported by animal research showing that patterns of cortical asymmetry were affected by manipulations of gonadal steroids in early development (see Diamond 1984 for review; Stewart and Kolb 1988), and were further differentiated by exposure to prenatal stress (Fleming et al. 1986; Stewart and Kolb 1988). Recent research with animal models of neurodevelopmental disorder has shown that microgyric lesions performed in infancy disrupt auditory temporal processing in adult male, but not female, rats (Fitch et al. 1994, 1997). This finding further supports an association between hormonal exposure and brain injury in disabilities involving language impairment.

Convergence of neuroanatomical research in animals and in human populations with neurodevelopmental disorders including schizophrenia. The etiology and developmental processes underlying the various manifestations of neuroanatomical laterality in men and women with schizophrenia are not well understood. However, there are many studies of both normal and abnormal neurodevelopmental processes in humans and animals from which general principles can be extrapolated to the study of laterality in schizophrenia. For example, injury of the left temporal lobe during development has been put forth as an important etiologic feature in dyslexia (Geschwind and Galaburda 1985a, 1985b; Galaburda 1993). Similar hypotheses have been put forth to account for the relationship between anomalous neurobehavioral asymmetries and schizophrenia (Crow 1990; Stein 1994). To outline possible parallels between the development of anomalous structural asymmetries in language disability and schizophrenia, the body of human and animal research devoted to the understanding of laterality in normal and disordered language development is discussed below.

As observed in many studies of patients with schizophrenia, normal asymmetries in the brain structures subserving language (Geschwind and Levitsky 1968; Witelson and Pallie 1973; Wada et al. 1975; Aboitiz et al. 1992; Kulynych et al. 1994) appear to be absent or even reversed in the majority of adult dyslexics (Galaburda et al. 1985b, 1994; Humphreys et al. 1990; Larsen et al. 1990; Duara et al. 1991) and language-impaired children (Hynd and Semrud-Clikeman 1989; Jernigan et al. 1991; Filipek 1996 for review). Observations comparing dyslexic and nondyslexic brains revealed a greater incidence of symmetry in the planum temporale, a part of the temporal lobe normally found to show a left-greater-than-right asymmetry (Geschwind and Levitsky 1968; Kulynych et al. 1994). The notion that disruptions in the early organization of cerebral asymmetries were central to the pathology of development dyslexia was a primary tenet of Geschwind's theory. He proposed that systematic variation in the size of the left temporal lobe during normal development, mediated in part by prenatal exposure to testosterone, determined the degree of this structure's asymmetry (Geschwind and Behan 1982; Geschwind and Galaburda 1985a, 1985b).

Through a combination of human and animal studies, it was determined that the total volume of asymmetric cortical regions was smaller than the total volume of symmetric brain regions, not larger as would have been predicted by Geschwind's theory. Re-examination of previously collected human data determined that in the normally developing planum temporale, asymmetries were more closely related to systematic variation of the "smaller" (usually the right) rather than the "larger" (usually the left) side (Galaburda et al. 1987). Studies in rodents uncovered a similar phenomenon whereby more symmetry was associated with larger total volume of cortical regions (Rosen et al. 1989). However, mice with neurodevelopmental abnormalities failed to show this systematic relationship, revealing important clues as to possible mechanisms involved in the development of anomalous neuroanatomical asymmetries (Rosen et al. 1989). Thus, in patients with clinical disorders involving dysgenesis of the left hemisphere, the disrupted relationship between brain asymmetry and brain volume may be developmentally linked to the presence of other more focal neural anomalies, including aberrations in early neuronal migration patterns (Rosen et al. 1992; Galaburda 1993).

The research of Galaburda, Rosen, and colleagues has focused on dyslexia, but its theoretical framework and experimental hypotheses may be applicable to other disorders, such as schizophrenia, that involve aberrant neurodevelopmental histories and abnormal neuroanatomical asymmetries. Indeed, researchers in the field of schizophrenia are turning to concepts that were used to explain anomalous cerebral laterization in developmental language disorders. For example, Barta et al. (1997, p. 666) have adopted Galaburda's (1991) notion of "lack of elimination [of neurons]" to explain phenomena such as the larger right planum temporale area that contributed to the reversed asymmetry in their sample of patients with schizophrenia.

The existence of focal neural anomalies in the cerebral cortex and thalamic nuclei has been demonstrated in adults with dyslexia (Galaburda et al. 1985b; Humphreys et al. 1990). Particularly noteworthy is the fact that ectopias were found more frequently in the left than in the right cerebral hemisphere of dyslexics (Galaburda et al. 1990).
Focal and laminar cytoarchitectural abnormalities, representative of disturbances in neural migration during development, have also been found in the brains of patients with schizophrenia (Benes et al. 1986; Jakob and Beckman 1986; Arnold et al. 1991; Benes 1995; Arnold and Trojanowski 1996). Consistent with Galaburda et al.'s study of dyslexics (1985b), Jakob and Beckman (1986) found more disturbances in the distribution of cortical neurons of the left hemisphere than in the right in postmortem specimens of patients with schizophrenia.

Current animal research is addressing the questions of how focal neural anomalies arise, how they relate to atypical asymmetry, why behavioral deficits associated with language disorders and dyslexia occur more frequently in males than females, and how the neural anomalies translate into behavioral deficits. For example, ectopias that naturally occur in the brains of certain inbred mouse strains and that have been surgically induced in neonatal rodents have been related to patterns of spatial navigation performance (Denenberg et al. 1991a, 1991b; Rosen et al. 1995; Waters et al. 1997), lateralized paw preference (Rosen et al. 1995), and sex differences in auditory processing similar to those observed in humans with developmental reading and language impairments (Fitch et al. 1994, 1997). This body of animal research supports the generalizations that (1) at least some neurodevelopmental disorders are characterized by perinatal insult to the brain, (2) the incidence of focal injury may in turn influence or be associated with atypical asymmetry, and (3) males appear to be at greater risk for these insults and their behavioral consequences (Gualtieri and Hicks 1985; Liederman and Flannery 1993; Goldstein et al. 1994).

Thus, considerable overlap between the constellations of neurobehavioral traits associated with developmental language disorders and schizophrenia can be seen (e.g., elevated incidence of perinatal brain insult, sex differences in the expression of the disorder, cytoarchitectural and neuromigrational disturbances, anomalous symmetry in language regions of the brain, and abnormal patterns of lateralized brain activity in language regions). Therefore, animal models used to study these phenomena in language disabilities could be modified to shed much light on the study of neurodevelopmental processes specific to disrupted laterality in schizophrenia.

**Neurochemical and Neurophysiological Asymmetries.**

An overview of neurochemical and neurophysiological asymmetries in patients with schizophrenia. Analysis of postmortem brains showed that dopamine concentrations in the left amygdala of patients with schizophrenia were elevated compared with controls (Reynolds 1983; Reynolds and Czudek 1987), thus providing a potential neurofunctional correlate of previously studied behavioral asymmetries. With the development of modern neuroimaging techniques, researchers have access to an even broader methodological base from which to collect data on neurochemical and neurophysiological laterality. Lateralized neurophysiological disturbances have been noted from the level of blood flow and brain metabolism (Calabrese et al. 1992; Siegel et al. 1993; Al-Mousawi et al. 1996; Harper Mozley et al. 1996) to the level of neurotransmitter binding (Joyce et al. 1992; Pedro et al. 1994; Pilowsky et al. 1994). Consistent with evidence from behavioral studies that suggested dysfunction of the left temporolimbic system (Flor-Henry 1976; Gur 1977, 1978; Bracha 1987; Cannon et al. 1994; Saykin et al. 1994), much neurophysiological work has also demonstrated abnormalities in left temporal lobe structures (Reynolds and Czudek 1987; Calabrese et al. 1992; Faux et al. 1993; Javitt et al. 1993; Nishino et al. 1993; Siegel et al. 1993).

Studies of neurotransmitter function have located abnormal asymmetries in striatal dopamine D₂ receptor binding in male patients with schizophrenia (Pilowsky et al. 1994). Pedro et al. (1994) demonstrated that asymmetry of striatal D₂ receptor binding levels was correlated with neuropsychological measures of stereotypy in patients with schizophrenia, but not in controls. In addition to lateralized abnormalities in resting brain activity (Early et al. 1987; DeLisi et al. 1989; Gur et al. 1989; Wilson and Mathew 1993), abnormal patterns of asymmetry in task-activated blood flow have also been demonstrated (Gur et al. 1983, 1985, 1994; O'Leary et al. 1996). Studies have revealed abnormal patterns of asymmetrical brain activity in language regions of patients experiencing hallucinations (Cleghorn et al. 1992). In addition, anomalous lateralized brain activity has been associated with measures of clinical severity (Mathew et al. 1982; Gur et al. 1989; Shenton et al. 1989), verbal ability (Harper Mozley et al. 1996), auditory attention deficits (O'Leary et al. 1996), and therapeutic response to clozapine (Molina Rodriguez et al. 1996). As with the behavioral and neuroanatomical asymmetries, there appears to be evidence of complex clinical and cognitive relationships among lateralized neurophysiological phenomena in schizophrenia. Not surprisingly, sex differences have been found in lateralized brain activity using measures of task-activated blood flow (Gur et al. 1983, 1985; Gur and Gur 1990) and MRI (Reite et al. 1997).

An overview of neurochemical and neurophysiological laterality in animals. A broad range of lateralized neurochemical and neurophysiological phenomena have been investigated in animals. Asymmetries in brain dopaminergic systems have been studied with respect to various dimensions of lateralized behavior in rodents
behavioral and neurochemical asymmetries. Hafner's not investigate the relationships between these effects and behaviors in female rats (Hafner et al. 1991, 1993) but did been studied in rats to specifically model mechanisms behavioral response to amphetamine in female, but not modulatory effect of estrogen on dopamine and related rats of the mammalian brain. The interactive effects of sex hormones on dopamine-induced rotational asymmetries and related neurochemistry has been demonstrated in the female rat. Becker and colleagues (Becker and Cha 1989; Castner and Becker 1990) reported that endogenous, or exogenously administered, pulsatile estrogen potentiated the dopaminergic and behavioral response to amphetamine in female, but not male, rats. This sex difference appeared to emerge at puberty through changes in the response of female striatal tissue to estrogen and provides some insight as to the possible mechanisms that may contribute to sex differences seen in lateralized neurocognitive relationships in patients with schizophrenia. The interactive effects of sex hormones on dopamine-induced behaviors and D₂ receptor sensitivity have also been studied in rats to specifically model mechanisms underlying sex differences in patients with schizophrenia (Hafner et al. 1991, 1993). The authors showed a strong modulatory effect of estrogen on dopamine and related behaviors in female rats (Hafner et al. 1991, 1993) but did not investigate the relationships between these effects and behavioral and neurochemical asymmetries. Hafner's model would provide an excellent animal preparation for studying the effects of hormones on the behavioral and neuropharmacological asymmetries associated with schizophrenia.

A convergence of neurochemical and neurophysiological asymmetry in animals and in patients with schizophrenia. The studies of the Gurs and their colleagues have focused on how asymmetries in resting and task-activated blood flow vary as a function of sex in schizophrenia (Gur et al. 1983, 1985; Gur and Gur 1990). They found that verbal and spatial processing differentially activated the left and right hemispheres in male and female patients. In anterior cortical regions, men with schizophrenia had higher left-hemisphere activity than control men at rest and during a verbal task. Male patients also lacked the overall increase and right-hemisphere lateralization in brain activity during a spatial task. Male patients also lacked the overall increase and right-hemisphere lateralization in brain activity during a spatial task. In the posterior cortical regions, control women had symmetric resting activity, greater left activity for the verbal task, and greater right activity for the spatial task, whereas women with schizophrenia had higher activity in the left hemisphere for all three conditions. Furthermore, lateralized effects of medication were noted only in men (Gur et al. 1985). The complexity of results from such studies demonstrates the need for animal experiments that address and manipulate the neurodevelopmental and neuropharmacological factors underlying sexually dimorphic asymmetries in the brain-behavior relationships associated with schizophrenia.

Many of the behavioral and cognitive measures used to study lateralized brain function in men and women with schizophrenia have parallels in the study of neurobehavioral asymmetries in animals. The following studies elucidate behaviors that could be applied toward the development of animal models for investigating lateralized neurocognitive function in human patients. With respect to lateralized verbal processing, research with nonhuman primates has shown left-hemisphere specialization for discriminating species-specific coo sounds (Petersen et al. 1978, 1984; Heffner and Heffner 1984) and matching noise and tone bursts of varying duration and spoken words to visual stimuli (Dewson et al. 1970; Dewson 1977; Gaffan and Harrison 1991). In mice, a left-hemisphere advantage for discriminating ultrasonic pup calls from ultrasonic noise bursts has been reported (Ehret 1987), and in rats, left-hemisphere specialization for discriminating two-tone sequences has been demonstrated for males but not females (Fitch et al. 1993). With respect to visuospatial processing, preliminary evidence of right-hemisphere specialization has been found in monkeys by using tachistoscopic tests of line abstraction (Hopkins et al. 1990) and in dolphins by using reaction time to objects presented to the right versus the left eye (Morrel-Samuels et al. 1990). Furthermore, superior per-
formance in spatial navigation has been associated with use of the right hemisphere in male rats (Crowne et al. 1992; King and Corwin 1992; Maier and Crowne 1993; Cowell et al. 1997). These primate and rodent experiments could be adapted to model the lateralized task-activated brain activity seen in humans. The obvious advantage of animal studies is that the effects of early brain insult, perinatal risk, genetics, immune status, and hormone exposure could be systematically altered. Such studies would be ideal for gaining insight into the developmental, hormonal, and neurochemical factors that differentiate the lateralized patterns of task-activated brain activity in schizophrenia patients from those of normal controls.

With respect to neurochemical correlates of schizophrenia, most animal models have not addressed the issue of laterality. One study that did study right-left differences found that haloperidol had asymmetrical effects on rotation-related nigrostriatal dopamine metabolite concentrations in rats (Jerussi and Taylor 1982). These authors suggested that by "dampening excess dopaminergic activity in the dominant hemisphere or increasing activity of the other, neuroleptics may restore a normal balance, or imbalance, between the two halves of the brain" (Jerussi and Taylor 1982, p. 73). A similar notion has been applied to interpret the influences of drug treatment on the brain-activation patterns of patients with schizophrenia. For example, clozapine has been shown to normalize striatal and frontal lobe asymmetries in resting glucose metabolism by increasing activity of the right basal ganglia and by decreasing the activity of the left frontal lobe (Potkin et al. 1990). Also, regional brain perfusion patterns of patients who responded to clozapine treatment differed in a lateralized fashion from their own pretreatment patterns and also from perfusion patterns of normal controls and clozapine nonresponders (Molina Rodriguez et al. 1996). Rodent models have been used to study the neuropharmacology of haloperidol and clozapine (Lipska and Weinberger 1994; Moghaddam 1994) and would provide ideal preparations for investigating the lateralized effects of such drugs.

Lipska and colleagues (1993) have used rats to study the development of the neurochemical, neuropharmacological, and behavioral phenomena that emerge after puberty following neonatal lesions to the ventral hippocampus. These experiments were designed to investigate a "constellation of major phenomena associated with schizophrenia" (Lipska et al. 1993, p. 67) by modeling the anomalous development of behavioral hyperresponsiveness to stress, related changes in the mesocorticolimbic dopaminergic system, and the differential effects of genetic background, haloperidol, and clozapine on these neurobehavioral measures (Lipska et al. 1993; Lipska and Weinberger 1994, 1995). The findings of this research suggest that medial prefrontal involvement after puberty is a delayed effect of neonatal hippocampal lesions. However, laterality effects were not systematically examined (Lipska et al. 1993; Lipska and Weinberger 1994, 1995).

The paradigms used by Lipska and colleagues, which model schizophrenia using a developmental design and multidimensional biobehavioral approach, could serve as the basis for future investigations of laterality. Such research would involve prepubertal and postpubertal assessments of lateralized behavior and brain function in rats that were given left, right, or bilateral hippocampal lesions in early life. The results could then be used to draw parallels with patterns observed in samples of patients with schizophrenia. The behavioral battery might incorporate techniques used by researchers such as Cabib, Carlson, and colleagues (Cabib et al. 1995; Carlson et al. 1996), who have investigated the contributions of asymmetries in brain dopamine systems to both lateralized and nonlateralized behaviors. This type of detailed study could help elucidate some of the complex relationships among the various measures of abnormal behavioral asymmetry seen in schizophrenia (Sakuma et al. 1996). Lipska and colleagues' developmental lesion model could be further applied to the study of the lateralized "language-related" and visuospatial processing measures discussed earlier in this section. Groups of animals that varied as a function of sex, early hormone manipulations, prenatal stress, early environment, and genetic factors could be systematically studied. Neuropharmacological manipulations, such as those applied by Lipska and Weinberger (1994), could then be examined with respect to laterality, developmental history, and individual differences.

Conclusions

The animal literature strongly supports the view that both normal and disrupted patterns of functional and structural laterality observed in adulthood have their basis in early development. Given the parallels between the anomalous laterality patterns in the brains and behaviors of patients with schizophrenia, and animals exposed to certain early environmental conditions, it is surprising that animal models have not been used more frequently to study the lateralized neurobehavioral systems involved in this disorder. Changes in neurobehavioral laterality may seem trivial in comparison to the vast number of complex clinical and neurobiological disturbances associated with schizophrenia. Despite the possibility that basic neurobiological asymmetries may have profound influences on other more complex functions, many researchers continue to examine higher order neurocognitive functions in patients with
schizophrenia without regard for the influence of laterality effects. Although our understanding of the interactions between laterality, hormonal exposure, genetics, immune status, and neurodevelopmental disorders is by no means complete, the research described herein demonstrates that animal research can provide important insights into some of the environmental conditions and developmental mechanisms that may influence the origins and expressions of anomalous lateralized phenomena seen in patients with schizophrenia.

References


Fenton, A.E., and Bures, J. Place navigation in rats with unilateral tetrodotoxin inactivation of the dorsal hippocampus: Place but not procedural learning can be lateralized to one hippocampus. *Behavioral Neuroscience*, 107:552–564, 1993.


Geschwind, N., and Behan, P. Left-handedness: Association with immune disease, migraine, and developmental learning disorder. *Proceedings of the National Academy of
Schizophrenia Bulletin, Vol. 25, No. 1, 1999

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Wada, J.A.; Clarke, R.; and Hamm, A. Cerebral hemispheric asymmetry in humans. Cortical speech zones in 100 adults and 100 infant brains. *Archives of Neurology*, 32(4):239–246, 1975.


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