



# Childhood laterality and adult schizophrenia spectrum disorders: a prospective investigation

Jason Schiffman<sup>a,\*</sup>, Sarah Pestle<sup>a</sup>, Sara Mednick<sup>b</sup>, Morten Ekstrom<sup>c</sup>,  
Holger Sorensen<sup>c</sup>, Sarnoff Mednick<sup>d,e</sup>

<sup>a</sup>Department of Psychology, University of Hawaii at Manoa, 2430 Campus Rd., Gartley Hall 110, Honolulu, HI 96822-2216, USA

<sup>b</sup>Salk Institute, La Jolla, CA, USA

<sup>c</sup>Danish Epidemiology Science Center, Institute of Preventive Medicine, Copenhagen University Hospital, Denmark

<sup>d</sup>Social Science Research Institute, University of Southern California, Los Angeles, CA, USA

<sup>e</sup>Institute of Preventive Medicine, Copenhagen University Hospital, Denmark

Received 30 September 2003; received in revised form 6 January 2004; accepted 7 April 2004

Available online 17 June 2004

## Abstract

Left or mixed-handedness, footedness, and eye dominance are thought to indicate abnormalities in lateralization related to schizophrenia. Increased left or mixed-dominance in schizophrenia suggests possible hemispheric abnormalities associated with the disorder. A related body of research suggests that some indications of lateralization abnormalities may be evident prior to the onset of schizophrenia, suggesting that disruptions in lateralization are inherent to the developmental course of the disorder. We attempted to replicate and extend upon findings indicating differences in lateralization between children who later developed a schizophrenia spectrum disorder ( $n=26$ ) and those who did not develop a schizophrenia spectrum disorder ( $n=216$ ), among a high-risk and control, longitudinal sample. The rate of left or mixed-footedness, eye dominance, and any anomalous lateralization, but not handedness, discriminated between those who developed schizophrenia spectrum disorders and those who did not. Left or mixed-laterality appears to signal neurological disruption relevant to the development of schizophrenia spectrum disorders.

© 2004 Elsevier B.V. All rights reserved.

*Keywords:* Schizophrenia spectrum; Laterality; Prospective

## 1. Introduction

### 1.1. Laterality and adult schizophrenia

Laterality correlates with cerebral dominance and has been investigated as a proxy for neurological

abnormalities in schizophrenia. Many studies investigating handedness and schizophrenia report an excess of left or mixed-handedness in patients with schizophrenia (e.g., Green et al., 1989; Cannon et al., 1995; Orr et al., 1999). Several studies report mixed-handedness correlating with higher scores on a schizotypal scale administered to non-patients (Chapman and Chapman, 1987; Kim et al., 1992). Further, related studies indicate an excess of non-right-handedness in first-degree relatives of persons with schizophrenia

\* Corresponding author. Tel.: +1-808-956-6267; fax: +1-808-956-4700.

E-mail address: [schiffma@hawaii.edu](mailto:schiffma@hawaii.edu) (J. Schiffman).

(Orr et al., 1999; Giotakos, 2002; Sommer et al., 2001). The literature regarding the relation between handedness and schizophrenia is as yet inconclusive, as other studies suggest no significant relation between handedness and the disorder (Taylor and Amir, 1995; Buijsrogge et al., 2002). The preponderance of evidence, however, supports the hypothesis that schizophrenia patients are more often left or mixed-handed compared to controls. Left or mixed-handedness in schizophrenia may indicate abnormalities in neurological structure or functioning.

Researchers also investigate eye dominance, or the preference for using one eye over the other in tasks requiring only one eye, as an indication of laterality in schizophrenia. Six studies have reported increased left-eye dominance among adult schizophrenia patients (Gur, 1977; Piran et al., 1982; Merrin, 1984; Shan-Ming, 1985; Gureje, 1988; Giotakos, 2002). Although the exact significance of these findings is unclear, left or mixed-eye dominance likely signifies an increased probability of disruption in fetal neural development.

### *1.2. Laterality in children who develop schizophrenia in adulthood*

The majority of studies revealing mixed dominance in schizophrenia are based on examination of individuals with full-blown schizophrenia in adulthood. These studies preclude the possibility of determining if differences in laterality precede schizophrenia or if they are a byproduct of the disease onset. Some behavioral and clinical deficits may be due to brain disturbances associated with the onset, and possible toxic effects, of psychosis (Madsen et al., 1999; Wyatt and Henter, 2001). Neuroleptic medication might also result in behavioral deficits (Marsden, 1982). Studies examining individuals before they develop schizophrenia provide evidence for neurological deficits preceding psychosis, and suggest that deficits are inherent to the natural course of the disorder. Existing prospective studies support a nonspecific but significant link between childhood neurological deficits and adult schizophrenia (e.g., Erlenmeyer-Kimling et al., 2000; Jones and Tarrant, 2000; Rosso et al., 2000).

Several cohort studies have measured childhood laterality as it relates to later risk for schizophrenia (e.g., Crow et al., 1996; Cannon et al., 1997). Crow

et al. investigated handedness in the National Child Development Survey, a study assessing all individuals born in the United Kingdom during a single week in 1958. Mothers of children who later developed schizophrenia were more likely to rate their children as ambidextrous at age 7 as compared to mothers of children who did not develop schizophrenia. Additionally, children who eventually developed schizophrenia were less strongly right-handed than controls at age 11.

Cannon et al. (1997) studied laterality in a total population of 5362 children born in England, Scotland, and Wales during one week in March 1946. Results indicated that at age 11, children who later developed schizophrenia showed a significant excess of mixed-eye dominance as compared to the remainder of the cohort. The authors failed, however, to detect a significant difference in hand preference between children who later developed schizophrenia and children who did not. Nevertheless, Cannon et al. interpreted their eye dominance findings as an indication that lateralization might play a role in the pathogenesis of schizophrenia.

### *1.3. Present investigation*

Using prospective assessments of laterality through handedness, footedness, and eye dominance, the present investigation attempts to replicate and extend upon research indicating differences in laterality among schizophrenia spectrum subjects as compared to control subjects. It was hypothesized that (1) left or mixed-handedness, left or mixed-footedness, left or mixed-eye dominance, and any anomalous lateralization (i.e., at least one left or mixed-dominant modality) would differentiate between those who developed a schizophrenia spectrum disorder in adulthood and the remainder of the sample (i.e., schizophrenia spectrum versus no mental illness and other psychopathology outcomes combined). We also hypothesized that (2) left or mixed-laterality would differentiate between those who developed a schizophrenia spectrum disorder and those who developed other psychopathology, and that (3) left or mixed-laterality would differentiate between those who developed a schizophrenia spectrum disorder and those who did not develop a psychiatric disorder of any kind in adulthood (i.e., an outcome of no mental illness). We used the more inclusive schizophrenia

spectrum group, as opposed to schizophrenia only, to increase sample size for analyses.

## 2. Methods

The current study is part of a larger longitudinal high-risk project investigating the precursors of schizophrenia. The design of the study, the subject characteristics, and the premorbid and follow-up diagnoses are described in greater detail elsewhere (Schiffman et al., 2002).

### 2.1. Subjects

Subjects were drawn from a Danish birth cohort consisting of all children born between September 1, 1959, and December 31, 1961, at Rigshospitalet in Copenhagen (Zachau-Christiansen and Ross, 1975). In 1972, a sample of 265 children from this cohort was intensively examined (Mednick et al., 1971). Two hundred forty-two were available for follow-up examinations in 1992. All children whose mothers or fathers had a psychiatric hospital diagnosis of schizophrenia comprised the first group ( $N=90$ ). A group of matched controls consisted of children who had at least one parent with psychiatric records other than schizophrenia ( $N=93$ ). The remaining subjects were matched controls with no parental records of psychiatric hospitalization ( $N=82$ ). Both control groups were matched with the high risk for schizophrenia birth cohort for gender ratio, mother's marital status at the time of conception, pregnancy number, social class, mother's height and weight, and mother's and father's age (Mednick et al., 1971).

### 2.2. Measures

#### 2.2.1. Laterality

Laterality was assessed in 1972, during an intensive examination. Subjects were 11–13 years of age. An experienced Danish pediatric neurologist administered a detailed analysis of dominance to all subjects. The examination included assessment of hand, foot, and eye dominance.

Handedness was assessed through the administration of Annett's Questionnaire, a 12-item self-report measure. The questionnaire asked subjects which hand

they would use for the following items: dealing cards, unscrewing a jar, shoveling, sweeping, threading a needle, striking a match, using scissors, hammering, using a racket, writing, throwing, and using a toothbrush (Annett, 1970). Responses were scored for each item (1 = left, 0 = right), and scores were summed to give a total handedness score for each subject. A higher score indicated a greater degree of left-handedness.

Footedness was assessed by asking subjects to kick a ball, balance, and hop on one foot. The foot used for each task was noted and scored (1 = left, 0 = right), and scores were summed to give a footedness score for each subject. A higher score indicated a greater degree of left-footedness. Seven subjects did not receive footedness evaluations.

Eye dominance was measured based on three tests: Crider's Ring, Crider's Card, and Crider's Box (Crider, 1944). In Crider's Ring Test, subjects were asked to pick up a curtain ring in one hand and look through it at the examiner's nose. They were then asked to switch hands and repeat. In Crider's Card Test, six cards of two different types were used; one type with a single hole punched in the middle, and a second type with a colored spot in the middle. Subjects were asked to look through a card with a small hole in it at the spot in the middle of the latter type of card, first up close, and then at a slight distance. The task was repeated with the remaining card pairs. Crider's Box Test uses a small open-ended cardboard box, with a white pipe cleaner emerging from one end and a black pipe cleaner emerging from the other. Subjects were asked to pick up the box using both hands, hold it 6 to 8 in. from their face, and align the two pipe cleaners. Responses for each task were scored (1 = left, 0 = right) and scores were summed to give a total eye dominance score for each subject. A higher score indicated a greater degree of left-eye dominance. Upon completion of the laterality examination, subjects were asked if either of their parents was left-handed. The neurologist assessed the subjects under standardized conditions, blind to psychiatric risk status, and blind to eventual psychiatric outcome in adulthood.

#### 2.2.2. Diagnostic assessment

In 1992, when the subjects were 31–33 years of age, their psychiatric status was ascertained. A psychiatrist administered two structured clinical psychiatric interviews, the Structured Clinical Interview

for DSM-III-R (SCID; Spitzer et al., 1990) and the psychosis section of the Present State Examination (PSE; Wing et al., 1974). These interviews yielded DSM-III-R diagnoses. In addition, Danish psychiatric hospital records of subjects were examined. Based on interview and/or hospital records, we obtained adult diagnostic outcomes for 242 of the 265 subjects (Table 1). A senior Danish psychiatrist supervised all the interviews and diagnoses. After complete description of the study to the subjects, written informed consent was obtained.

### 2.3. Statistical analyses

Given the limited number of schizophrenia spectrum subjects and the uniqueness of these data, we were more concerned with Type II Error (not detecting a significant difference when a significant difference exists) than with Type I Error (detecting a significant difference when one does not exist). Consequently, rather than employing omnibus tests to assess for overall group differences, and rather than correcting significance levels to reflect multiple tests, we used uncorrected-planned chi-square analyses. While these practices minimize the chances of Type II Error, they increase the risk for Type I Error.

Subjects' total laterality scores for each modality (handedness, footedness, and eye dominance considered separately) were divided into two categories: (1) right dominance, or (2) left or mixed-dominance. We set the criteria for the left or mixed-dominance groups as follows: for handedness, an Annett score from 3 to

11; for footedness, a score from 1 to 3; and for eye dominance, a score from 3 to 7. Additionally, in view of limitations of power, we created a categorical variable combining laterality data from the hand, foot, and eye measures. The "any anomalous lateralization" variable consisted of two categories: (1) subjects showing left or mixed-dominance in at least one modality (i.e., hand, foot, or eye), and (2) subjects showing complete right dominance (i.e., right dominant on hand, foot, and eye).

Our first set of chi-square analyses (one-tailed; two-by-two table; odds ratios reported) compared the rates of left or mixed-dominance in each modality (handedness, footedness, eye dominance, and any anomalous lateralization) among the schizophrenia spectrum outcome group to rates among the remainder of the sample (i.e., schizophrenia spectrum outcome group versus other psychopathology and no mental illness outcome groups combined). Follow-up chi-square analyses compared rates of left or mixed-dominance in each modality among the schizophrenia spectrum outcome group to rates among the other psychopathology outcome group and the no mental illness outcome group considered individually (i.e., schizophrenia spectrum outcome group versus other psychopathology outcome group and, separately, schizophrenia spectrum outcome group versus no mental illness outcome group; Fisher's exact test were reported for these analyses as well).

To assess specificity further, a chi-square analysis compared the rates of left or mixed-handedness, footedness, eye dominance, and any anomalous lateralization among the other psychopathology outcome group to rates among the no mental illness outcome group (i.e., other psychopathology outcome group versus no mental illness outcome group; two-tailed; two-by-two table).

In addition, to explore the possible impact of varying genetic risk for psychopathology on laterality, we compared the rate of left or mixed-handedness, footedness, eye dominance, and any anomalous lateralization between the following groups: subjects who had at least one parent with schizophrenia, subjects who had at least one parent with a nonpsychotic disorder, and subjects who had parents with no mental illness (chi-square; two-tailed; two-by-three table). These groupings were made regardless of subjects' adult diagnostic outcomes.

Table 1  
Adult outcome diagnoses

Schizophrenia spectrum disorders	Schizophrenia	16
	Schizotypal personality disorder	3
	Any psychosis or delusional disorder	5
	Paranoid personality disorder	2
Other psychopathology	Nonpsychotic mood or anxiety disorder	19
	Nonpsychotic alcohol/drug abuse	33
	Non-hospitalized minor axis I disorder	1
	Borderline personality disorder	5
	Schizoid personality disorder	1
	Antisocial personality disorder	1
	Personality disorder NOS	4
	Other personality disorder	6
No mental illness	No diagnosis	146
Total subjects		242

Table 2  
 Laterality in schizophrenia versus all others

		Schizophrenia spectrum <i>n</i> (%)	All others <i>n</i> (%)	Odds ratio (95% c.i.)	$\chi^2$ ( <i>df</i> )	<i>p</i> (one-tailed)
Hand preference	R	22 (84.6)	187 (86.6)	1.17 (0.45–3.04)	0.08 (1)	0.39
	M/L	4 (15.4)	29 (13.4)			
Foot preference	R	12 (52.2)	151 (71.2)	2.27 (1.09–4.71)	3.54 (1)	0.03
	M/L	11 (47.8)	61 (28.8)			
Eye dominance	R	10 (38.5)	125 (57.9)	2.20 (1.09–4.43)	3.54 (1)	0.03
	M/L	16 (61.5)	91 (42.1)			
Any anomalous laterality	R	5 (19.2)	95 (44.0)	3.30 (1.41–7.71)	5.86 (1)	0.01
	M/L	21 (80.8)	121 (56.0)			

To investigate the effect of an interaction between laterality and genetic risk on schizophrenia spectrum outcome, we compared (among the subjects with a parent with schizophrenia only) rates of left or mixed-dominance between the schizophrenia spectrum group and the combined other psychopathology and no mental illness group. We used chi-square analyses (one-tailed; two-by-two table; odds ratios and Fisher's exact test were reported).

### 3. Results

As sex differences in laterality have been found in previous studies (Cannon et al., 1995), we tested for potential confounding effects of sex on our measures of laterality. Males and females did not significantly differ in rates of left or mixed-handedness, footedness, eye dominance, or any anomalous lateralization. This pattern of no significant sex differences remained when analyzing subjects grouped separately for psychiatric risk (i.e., among subjects with a parent with schizophrenia only, among subjects with a parent with a nonpsychotic disorder only, and among subjects with parents without a disorder only). Subsequently, we combined males and females in all of our analyses.

Our first hypothesis was that the rate of left or mixed-handedness, left or mixed-footedness, left or mixed-eye dominance, and any anomalous lateralization would differentiate between those who did and those who did not develop a schizophrenia spectrum disorder in adulthood. We ran two (score: right versus left and mixed) by two (diagnosis: schizophrenia spectrum disorder versus other psychopathology and no mental illness combined) chi-square analyses to

test this hypothesis for handedness, footedness, eye dominance, and any anomalous lateralization. The rate of left or mixed-footedness, left or mixed-eye dominance, and any anomalous lateralization, but not handedness, discriminated significantly between groups (Table 2).

Guided by our second hypothesis, we ran individual two-by-two chi-square analyses to determine if rates of left or mixed-footedness, left or mixed-eye dominance, and any anomalous lateralization differentiated between subjects with schizophrenia spectrum disorders and subjects with no mental illness and other psychopathology separately.<sup>1</sup> As seen in Table 3, a higher rate of left or mixed-footedness, eye dominance, and any anomalous lateralization was significantly associated with a schizophrenia spectrum disorder outcome relative to an outcome of no mental illness. Neither a higher rate of left or mixed-footedness nor eye dominance significantly differentiated between an outcome of schizophrenia spectrum disorder and an outcome of other psychopathology. A higher rate of any anomalous lateralization was, however, significantly associated with a schizophrenia spectrum outcome relative to another psychopathology outcome.

Although the finding was not significant, the schizophrenia spectrum disorder subjects tended to have a higher rate of left or mixed-footedness (and to a lesser extent left or mixed-eye dominance) than did subjects with nonpsychotic disorders. The smaller number of subjects in the other psychopathology

<sup>1</sup> We did not analyze handedness as we had failed to find a significant effect for handedness between schizophrenia spectrum and the remainder of the control subjects. It appeared that the handedness variable lacked sufficient range to detect differences.

Table 3  
 Laterality comparisons across diagnostic outcome groups

		Schizophrenia spectrum <i>n</i> (%)	No mental illness <i>n</i> (%)	Odds ratio (95% c.i.)	$\chi^2$ ( <i>df</i> )	<i>p</i> (one-tailed)	Fisher's (one-tailed)
Foot preference	R	12 (52.2)	103 (72.0)	2.36 (1.11–5.01)	3.67 (1)	0.03	0.05
	M/L	11 (47.8)	40 (28.0)				
Eye dominance	R	10 (38.5)	89 (61.0)	2.50 (1.22–5.13)	4.57 (1)	0.02	0.03
	M/L	16 (61.5)	57 (39.0)				
Any anomalous laterality	R	5 (19.2)	66 (45.2)	3.47 (1.46–8.21)	6.14 (1)	0.01	0.01
	M/L	21 (80.8)	80 (54.8)				
		Schizophrenia spectrum <i>n</i> (%)	Other psychopathology <i>n</i> (%)	Odds ratio (95% c.i.)	$\chi^2$ ( <i>df</i> )	<i>p</i> (one-tailed)	Fisher's (one-tailed)
Foot preference	R	12 (52.1)	48 (70.0)	2.10 (0.93–4.71)	2.30 (1)	0.07	0.10
	M/L	11 (47.8)	21 (30.0)				
Eye dominance	R	10 (38.5)	36 (51.4)	1.69 (0.78–3.66)	1.28 (1)	0.13	0.18
	M/L	16 (61.5)	34 (48.6)				
Any anomalous laterality	R	5 (19.2)	29 (41.4)	5.94 (2.39–14.76)	4.08 (1)	0.02	0.04
	M/L	21 (80.8)	41 (58.6)				

outcome group relative to the no mental illness outcome group reduced power and may account for the lack of a statistically significant difference between the subjects with other psychopathology and those with a schizophrenia spectrum disorder on the individual measures of laterality. The odds ratio for the footedness comparison shows that subjects with schizophrenia spectrum disorders were 2.3 times more likely than those with other psychopathology to be left or mixed-footed. As an additional test of specificity, we compared rates of left or mixed-footedness, eye dominance, and any anomalous lateralization between the other psychopathology and no mental illness groups. Our measures of laterality did not significantly differentiate between these two groups suggesting similarity in rates of left or mixed-dominance among

the other psychopathology outcome group and the no mental illness outcome group (other psychopathology versus no mental illness; footedness,  $\chi^2(1)=0.14$ ,  $P=0.71$ ; eye dominance,  $\chi^2(1)=1.76$ ,  $P=0.18$ ; any anomalous lateralization,  $\chi^2(1)=0.27$ ,  $P=0.60$ ).

We were also interested in the relation between laterality and genetic risk for psychopathology based on parental diagnosis, regardless of the subjects' diagnostic outcomes. We ran a two (score: right versus left or mixed) by three (genetic risk: parent with schizophrenia, parent with other psychopathology, neither parent with a diagnosis) chi-square analysis to assess possible differences in laterality based on parental diagnosis. Our analysis failed to detect any significant differences between the three groups on our measures of laterality (Table 4).

Table 4  
 Laterality comparisons across genetic psychiatric risk groups

		Parent with schizophrenia <i>n</i> (%)	Parent with other psychiatric diagnosis <i>n</i> (%)	Parents without diagnosis	$\chi^2$ ( <i>df</i> )	<i>p</i>
Hand preference	R	70 (86.4)	73 (83.9)	66 (89.2) 8 (10.8)	0.95 (2)	0.62
	M/L	11 (13.6)	14 (16.1)			
Foot preference	R	51 (67.1)	58 (67.4)	54 (74.0) 19 (26.0)	1.06 (2)	0.59
	M/L	25 (32.9)	28 (32.6)			
Eye dominance	R	44 (54.3)	49 (56.3)	42 (56.8) 32 (43.2)	0.11 (2)	0.95
	M/L	37 (45.7)	38 (43.7)			
Any anomalous laterality	R	30 (37.0)	37 (42.5)	33 (44.6) 41 (55.4)	0.99 (2)	0.61
	M/L	51 (63.0)	50 (57.5)			

We also investigated a possible interactive effect of laterality and having a parent with schizophrenia on later development of schizophrenia spectrum disorders. It is possible that among individuals having a parent with schizophrenia, abnormal laterality will signify a stressor contributing to schizophrenia spectrum disorders. We therefore assessed whether individuals with a parent with schizophrenia with left or mixed-dominance would be more likely to have a schizophrenia spectrum outcome compared to other outcomes.

For these analyses, we selected only subjects with a parent with schizophrenia. This constraint limited the number of subjects ( $N=81$ ). As a comparison group, we combined the subjects with no mental illness and those with other psychopathology who had a parent with schizophrenia ( $N=64$ ); these subjects did not significantly differ from each other on any measure of laterality (other psychopathology versus no mental illness; handedness  $\chi^2(1)=0.03$ ,  $P=0.86$ ; footedness,  $\chi^2(1)=0.06$ ,  $P=0.81$ ; eye dominance,  $\chi^2(1)=0.03$ ,  $P=0.88$ ; any anomalous lateralization,  $\chi^2(1)=0.14$ ,  $P=0.71$ ). We conducted chi-square analyses among subjects with a parent with schizophrenia to assess whether measures of laterality would differentiate between those with schizophrenia spectrum disorders and those with either other psychopathology or no mental illness. As seen in Table 5, the rate of left or mixed-footedness and any anomalous lateralization, but not handedness and eye dominance, discriminated significantly between groups.

To account for the effects of family history of left dominance, we ran the above analyses excluding individuals who reported having a left-handed parent. Findings excluding subjects with a left-handed parent exhibited a pattern similar to findings employing the entire sample.

#### 4. Discussion

Similar to results reported by Cannon et al. (1997), we found that children who developed schizophrenia in adulthood were more than two times as likely as controls to show left or mixed-eye dominance. The odds ratio for both studies was 2.2. Additionally, we found a significant relation between schizophrenia spectrum disorders and left or mixed-footedness, a less frequently investigated measure of laterality than handedness. Significant differences in footedness, eye dominance, and any anomalous lateralization were found between the schizophrenia spectrum and the no mental illness outcome groups. We also detected a significant difference between the schizophrenia spectrum and other psychopathology outcome groups in combined dominance. Furthermore, we did not find a significant difference between the no mental illness group and the other psychopathology outcome groups in left or mixed-dominance on any measure of laterality.

These findings suggests a specific relation between global deficits in lateralization and schizophrenia spectrum disorders. Individual measures of laterality for the other psychopathology outcome subjects tended (nonsignificantly) to fall in between the scores of the schizophrenia spectrum and no mental illness outcome subjects. Given the significant difference observed between the schizophrenia spectrum group and the other psychopathology group on the any anomalous lateralization variable (a variable created to increase power), lack of power likely contributed to the nonsignificant differences found for footedness and eye dominance between the schizophrenia spectrum and other psychopathology outcome groups.

Table 5  
Laterality in schizophrenia versus all others among subjects with a parent with schizophrenia

		Schizophrenia spectrum <i>n</i> (%)	All others <i>n</i> (%)	Odds ratio (95% c.i.)	$\chi^2$ ( <i>df</i> )	<i>p</i> (one-tailed)	Fisher's (one-tailed)																												
Hand preference	R	15 (88.2)	55 (85.9)	.81 (0.21–3.21)	0.06 (1)	0.40	0.58																												
	M/L	2 (11.8)	9 (14.1)					Foot preference	R	7 (46.7)	44 (72.1)	2.96 (1.12–7.82)	3.54 (1)	0.03	0.06	M/L	8 (53.3)	17 (27.9)	Eye dominance	R	7 (41.2)	37 (57.8)	1.96 (0.79–4.87)	1.50 (1)	0.11	0.17	M/L	10 (58.8)	27 (42.2)	Any anomalous laterality	R	3 (17.6)	27 (42.2)	3.41 (1.10–10.50)	3.47 (1)
Foot preference	R	7 (46.7)	44 (72.1)	2.96 (1.12–7.82)	3.54 (1)	0.03	0.06																												
	M/L	8 (53.3)	17 (27.9)					Eye dominance	R	7 (41.2)	37 (57.8)	1.96 (0.79–4.87)	1.50 (1)	0.11	0.17	M/L	10 (58.8)	27 (42.2)	Any anomalous laterality	R	3 (17.6)	27 (42.2)	3.41 (1.10–10.50)	3.47 (1)	0.03	0.05	M/L	14 (82.4)	37 (57.8)						
Eye dominance	R	7 (41.2)	37 (57.8)	1.96 (0.79–4.87)	1.50 (1)	0.11	0.17																												
	M/L	10 (58.8)	27 (42.2)					Any anomalous laterality	R	3 (17.6)	27 (42.2)	3.41 (1.10–10.50)	3.47 (1)	0.03	0.05	M/L	14 (82.4)	37 (57.8)																	
Any anomalous laterality	R	3 (17.6)	27 (42.2)	3.41 (1.10–10.50)	3.47 (1)	0.03	0.05																												
	M/L	14 (82.4)	37 (57.8)																																

As with the study conducted by Cannon et al. (1997), all measures for this study were prospective; data were gathered years before diagnosis. Laterality studies investigating adults with schizophrenia potentially suffer from experimenter bias, as person-to-person contact can offer examiners clues to diagnosis. Our method of data collection reduced the likelihood of the adult clinical picture influencing measurement of laterality. Results from our prospective study provide evidence that neurological deficits of dominance precede symptom onset, and are most likely inherent to the course of the schizophrenia spectrum disorders, rather than a disease byproduct.

We did not find a significant difference in handedness between children who later developed schizophrenia and those who did not. Similarly, Cannon et al. (1997) failed to detect a significant relation between schizophrenia and handedness. At the time of our assessment in 1972, handedness in Denmark may have been subject to environmental influences (e.g., parents teaching their children to use their right hand to avoid social stigma; desks, scissors, and other devices designed for right-handed children). Footedness and eye dominance, however, may draw less attention, and are less likely subject to environmental influences. Additionally, although well validated and widely used, our measure of handedness was in questionnaire form. The neurologist did not actually observe individual hand preference as he did with footedness and eye dominance. Therefore, our measure of handedness might lack the validity of the foot and eye measures. Our footedness and eye dominance measures may more accurately assess innate lateralization than handedness.

Premorbid left or mixed-footedness may indicate hemispheric abnormalities related to psychosis. Footedness is similar to handedness in that left or mixed-footedness indicates disrupted hemispheric lateralization. Elias et al. (1998) argued that cerebral lateralization may actually relate more to footedness than to other lateral preferences. The functional significance of eye dominance, however, remains more ambiguous. Cannon et al. (1997) questioned a direct association between eye dominance and cerebral dominance, noting that input from either eye reaches both hemispheres. Cannon et al. did suggest, however, that left-eye dominance is associated with developmental disorders, and likely signifies disrupt-

tions in developmental processes. Gureje (1989) also suggested that left-eye dominance indicates neurodevelopmental deficits, and concluded that these deficits predate the onset of schizophrenia. Our findings based on premorbid children corroborate this conclusion.

Rather than being from a general population birth cohort, the subjects in this sample, apart from the no mental illness control group, were specifically selected because of their increased genetic risk for psychopathology (i.e., parental diagnosis). This design allowed us to investigate the role of genetic risk for psychopathology in measures of laterality. Traits elevated in first-degree relatives of people with schizophrenia indicate a genetic liability for the disorder. We did not detect significant differences in lateralization between offspring of a parent with schizophrenia (first-degree relatives) compared to offspring of parents with another disorder, or compared to offspring of parents with no psychiatric diagnosis. These results add to the mixed research regarding whether abnormal laterality is a part of a genetic liability for schizophrenia. In keeping with some studies (e.g., Cannon et al., 1995; Clementz et al., 1994), and conflicting with others (e.g., Hallett et al., 1986; Orr et al., 1999), our findings of no significant differences between risk groups tentatively suggest that laterality is not part of a direct genetic liability for the disorder.

We also examined the interaction of abnormal laterality and genetic risk for schizophrenia for developing a schizophrenia spectrum disorder. Among subjects with a parent with schizophrenia (i.e., genetic risk for schizophrenia), we found increased rates of childhood left or mixed-footedness and combined left or mixed-dominance (but not handedness or eye dominance) among the schizophrenia spectrum outcome group compared to the other psychopathology/no mental illness outcome group. Similar to results we recently reported regarding the interactive effect of minor physical anomalies and genetic risk for the development of schizophrenia spectrum disorders, our laterality results fit within the context of a “two-hit” model for schizophrenia (Schiffman et al., 2002). The two-hit model suggests that a “first hit” (in this case genetic disruption of fetal neural development) interacts with a “second hit” (in this case an event causing abnormal hemispheric lateralization) to increase risk for schizophrenia.

Typically, second hits are thought to be stressors that are (1) environmental (nongenetic), and that (2) occur later in life (e.g., obstetrical complications, unstable family environment). Consistent with a second hit we did not find an elevation of left or mixed-dominance in our sample of offspring of a parent with schizophrenia, indicating that abnormal lateralization might be an environmental contributor to schizophrenia. Unlike typical second hits that occur later in life, teratogenic events that cause abnormal lateralization likely occur very early in development. Fetuses as young as 10 weeks of gestational age demonstrate hand preference, suggesting that hemispheric lateralization may be vulnerable to teratogens at an early stage (Hepper et al., 1998). The possible early timing of factors leading to abnormal hemispheric development puts abnormal lateralization in a class of “second hits” similar to that of minor physical anomalies. Abnormal lateralization and minor physical anomalies most likely result from prenatal disturbances experienced in the first or second trimester of fetal development. Therefore, these correlates of schizophrenia may mark the occurrence of a prenatal second hit. The mechanisms explaining the relation between genetic risk and abnormal laterality, as well as other early “second hits”, warrant further study.

This study suffers from notable limitations. The low number of subjects with a schizophrenia spectrum disorder in this investigation limits statistical power and the ability to draw strong conclusions. Given our small sample size, we may lack sufficient power to detect a significant difference between schizophrenia spectrum and non-spectrum subjects on handedness. As expected, increasing power by incorporating all of our measures of laterality (i.e., the any anomalous lateralization variable) revealed the most significant differences between diagnostic groups.

The sample for this study was selected for increased genetic risk for psychopathology; thus, generalization may be another limitation. The majority of the schizophrenia subjects in this report have a parent with schizophrenia. Gottesman and Erlenmeyer-Kipling (2001) noted that because only a minority of individuals with schizophrenia have an identifiable parent with schizophrenia, high-risk samples might not represent the majority of people with a schizophrenia spectrum disorder. We contend, however, that most cases of schizophrenia are genetically influenced

through parental genotypic risk that fails to manifest phenotypically (Cannon et al., 1996). Therefore, we argue that high-risk samples like the one from this study do generalize to individuals developing a schizophrenia spectrum disorder who do not have a parent with the illness.

Additionally, we conducted our follow-up assessment when subjects were 31–33 years of age. We cannot generalize our findings to those who develop a spectrum disorder later in life. Despite these limitations, our findings of increased left-eye dominance, left-footedness, and any anomalous lateralization among children who later develop a schizophrenia spectrum disorder contribute to the body of research supporting the involvement of abnormal lateralization in a neurodevelopmental theory of schizophrenia.

### Acknowledgements

This work was supported by an NIMH Research Scientist Award (MH-00619) to Dr. Mednick and NIMH Grant MH-37692.

### References

- Annett, M., 1970. A classification of hand preference by association analysis. *Br. J. Psychiatry* 61, 303–321.
- Buijsrogge, J.J.A., Benali, K., Brazo, P., Dollfus, S., 2002. Sinistrality in schizophrenia. *Schizophr. Res.* 55, 303–306.
- Cannon, M., Byrne, M., Cassidy, B., Larkin, C., Horgan, R., Sheppard, N.P., O’Callaghan, E., 1995. Prevalence and correlates of mixed-handedness in schizophrenia. *Psychiatry Res.* 59, 119–125.
- Cannon, T.D., Mednick, S.A., Parnas, J., Shulsinger, F., 1996. “Developmental brain abnormalities in schizophrenia: contributions of genetic and perinatal factors”: reply. *Arch. Gen. Psychiatry* 52, 157–159.
- Cannon, M., Jones, P., Murray, R.M., Wadsworth, M.E.J., 1997. Childhood laterality and later risk of schizophrenia in the 1946 British birth cohort. *Schizophr. Res.* 26, 117–120.
- Chapman, J.P., Chapman, L.J., 1987. Handedness of hypothetically psychosis-prone subjects. *J. Abnorm. Psychology* 96, 89–93.
- Clementz, B.A., Iacono, W.G., Beiser, M., 1994. Handedness in first-episode psychotic patients and their first degree biological relatives. *J. Abnorm. Psychology* 103, 400–403.
- Crider, B., 1944. A battery of tests for the dominant eye. *J. Gen. Psych.* 31, 179–190.
- Crow, T.J., Done, D.J., Sacker, A., 1996. Cerebral lateralization is delayed in children who later develop schizophrenia. *Schizophr. Res.* 22, 181–185.

- Elias, L.J., Bryden, M.P., Bulman-Fleming, M.B., 1998. Footedness is a better predictor than is handedness of emotional lateralization. *Neuropsychologia* 36, 37–43.
- Erlenmeyer-Kimling, L., Rock, D., Roberts, S.A., Janal, M., Kestenbaum, C., Cornblatt, B., Adamo, U.H., Gottesman, I.I., 2000. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York high-risk project. *Am. J. Psychiatry* 157, 1416–1422.
- Giotakos, O., 2002. Crossed hand-eye dominance in male psychiatric patients. *Percept. Mot. Skills* 95, 728–732.
- Gottesman, I.I., Erlenmeyer-Kimling, L., 2001. Family and twin studies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. *Schizophr. Res.* 51, 93–102.
- Green, M.F., Satz, P., Smith, C., Nelson, L., 1989. Is there atypical handedness in schizophrenia? *J. Abnorm. Psychology* 98, 57–61.
- Gur, R.E., 1977. Motoric laterality imbalance in schizophrenia: a possible concomitant of left hemispheric dysfunction. *Arch. Gen. Psychiatry* 34, 33–37.
- Gureje, O., 1988. Sensorimotor laterality in schizophrenia: which features transcend cultural influences? *Acta Psychiatr. Scand.* 77, 188–193.
- Gureje, O., 1989. Correlates of positive and negative schizophrenic symptoms in Nigerian patients. *Br. J. Psychiatry* 155, 628–632.
- Hallett, S., Quinn, D., Hewitt, J., 1986. Defective interhemispheric integration and anomalous language lateralization in children at risk for schizophrenia. *J. of Nerv. Ment. Dis.* 174, 418–427.
- Hepper, P.G., McCartney, G.R., Shannon, E.A., 1998. Lateralised behaviour in first trimester human foetuses. *Neuropsychologia* 36, 531–534.
- Jones, P.B., Tarrant, C.J., 2000. Developmental precursors and biological markers for schizophrenia and affective disorders: specificity and public health implications. *Eur. Arch. Psychiatry Clin. Neurosci.* 250, 286–291.
- Kim, D., Raine, A., Triphon, N., Green, M.F., 1992. Mixed handedness and features of schizotypal personality in a nonclinical sample. *J. of Nerv. Ment. Dis.* 180, 133–135.
- Madsen, A.L., Karle, A., Rubin, P., Cortsen, M., Anderson, H.S., Hemmingsen, R., 1999. Progressive atrophy of the frontal lobes in first-episode schizophrenia: interaction with clinical course and neuroleptic treatment. *Acta Psychiatr. Scand.*, 367–374.
- Marsden, C.D., 1982. Motor disorders in schizophrenia. *Psychol. Med.* 12, 13–15.
- Mednick, S.A., Mura, E., Schulsinger, F., Mednick, B., 1971. Perinatal conditions and infant development in children with schizophrenia. *Soc. Biol.* 18, S103–S113 (Supplement).
- Merrin, E.L., 1984. Motor and sighting dominance in chronic schizophrenics: relationship to social competence, age at first admission, and clinical course. *Br. J. Psychiatry* 145, 401–406.
- Orr, K.G.D., Cannon, M., Gilvarry, C.M., Jones, P.B., Murray, R.M., 1999. Schizophrenic patients and their first-degree relatives show an excess of mixed-handedness. *Schizophr. Res.* 39, 167–176.
- Piran, N., Bigler, E.D., Cohen, D., 1982. Motoric laterality and eye dominance suggest unique pattern of cerebral organization in schizophrenia. *Arch. Gen. Psychiatry* 39, 1006–1010.
- Rosso, I.M., Bearden, C.E., Hollister, J.M., Gasperoni, T.L., Sanchez, L.E., Hadley, T., Cannon, T.D., 2000. Childhood neuro-motor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr. Bull.* 26, 367–378.
- Schiffman, J., Ekstrom, M., LaBrie, J., Schulsinger, F., Sorensen, H., Mednick, S.A., 2002. Minor physical anomalies and schizophrenia spectrum disorders: a prospective investigation. *Am. J. Psychiatry* 159, 238–243.
- Shan-Ming, Y., 1985. Imbalance of hemispheric functions in the major psychoses: a study of handedness in the People's Republic of China. *Biol. Psychiatry* 20, 906–917.
- Sommer, I., Aleman, A., Ramsey, N., Bouma, A., Kahn, R., 2001. Handedness, language lateralisation and anatomical asymmetry in schizophrenia. *Br. J. Psychiatry* 178, 344–351.
- Spitzer, R.L., Williams, J.B., Gibbon, M., 1990. *User's Guide for the Structured Clinical Interview for DSM-III-R*. American Psychiatric Press, Washington, DC.
- Taylor, M.A., Amir, N., 1995. Sinister psychotics: left-handedness in schizophrenia and affective disorder. *J. of Nerv. Ment. Dis.* 183, 3–9.
- Wing, J.K., Cooper, J.E., Sartorius, N., 1974. *The Measurement and Classification of Psychiatric Symptoms*. Cambridge Univ. Press, London.
- Wyatt, R.J., Henter, I., 2001. Rationale for the study of early intervention. *Schizophr. Res.* 51, 69–76.
- Zachau-Christiansen, B., Ross, E.M., 1975. *Babies: Human Development During the First Year*. Wiley, New York.