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Handedness in Boys with Gender Identity Disorder

Kenneth J. Zucker, Nicole Beaulieu, Susan J. Bradley, Gina M. Grimshaw, and Anne Wilcox

Centre for Addiction and Mental Health–Clarke Division and University of Toronto, Toronto, Canada

Handedness preference was assessed in 205 boys with gender identity disorder and 205 clinical control boys referred for other reasons. Boys with gender identity disorder were significantly more likely to be left-handed than the clinical control boys (19.5% vs. 8.3%, respectively). The boys with gender identity disorder, but not the clinical control boys, also had a significantly higher rate of left-handedness compared to three independent, general population studies of nonreferred boys (11.8%; $N = 14{,}253$) by Hardyck, Goldman, and Petrinovich (1975), Calnan and Richardson (1976), and Eaton, Chipperfield, Ritchot, and Kostiuk (1996). Left-handedness appears to be a behavioral marker of an underlying neurobiological process associated with gender identity disorder in boys.

Keywords: Gender identity disorder, handedness, sex differences.

Abbreviations: CAH: congenital adrenal hyperplasia; CAMH: Centre for Addiction and Mental Health; CBCL: Child Behavior Checklist; DES: diethylstilbestrol; DI: developmental instability; GID: gender identity disorder; HY: Y-linked minor histocompatibility; MHC: major histocompatibility complex.

Introduction

There are two well-established epidemiological aspects of handedness, i.e., an individual's preference for using the right hand or the left hand in unimanual skilled activities, such as writing: first, hand preference is strongly skewed—about 90% of people show a preference for the right hand and about 10% show a preference for the left hand; second, around this approximate distribution, there is a modest sex difference, with a greater percentage of left-handed males than females (Clark, 1957; Perelle & Ehrman, 1994; Seddon & McManus, 1991).

In modern society, prejudice against left-handers has diminished markedly and there is considerably less social pressure to perform unimanual behavioral tasks, particularly writing, with the right hand (Teng, Lee, Yang, & Chang, 1976). The fading of this bias has made it easier to explore the determinants of hand preference, which most researchers agree are largely biological in nature.

One line of research implicates a genetic influence (e.g., Annett, 1973; Saudino & McManus, 1998). Another line of research has been guided by the notion that the normal distribution of right- and left-handedness can be altered by putatively pathological prenatal or perinatal events (Satz, 1972, 1973). Accordingly, many studies have assessed whether or not there is an elevated rate of left-handedness (and, commonly, mixed or ambiguous handedness) among individuals exposed to some kind of presumed adversity or disruption during prenatal or perinatal development (e.g., prenatal exposure to neurotoxins, ultrasound, maternal smoking or alcohol use, severely premature birth, and birth stress). Along similar lines, researchers have also examined the relation between handedness and demographic variables (e.g., maternal age, birth order, and season of birth) on the grounds that such variables might be associated with underlying biomedical risk factors. Although it is beyond the scope of this article to consider these studies in detail (for reviews, see Bishop, 1990; McManus, 1983; Previc, 1996), it should be noted that the general view in the literature is that the pathological model of left-handedness has received mixed support: Some studies find evidence for a relation between an elevation in left-handedness and putative prenatal adversity whereas others do not. There are, of course, various reasons that might account for this inconsistency, including methodological issues, such as insufficient sample sizes (Coren, 1993) and the possibility that the putative markers of adversity were not particularly good ones.

Because an individual's preference for using the right or left hand has long been viewed as an index of functional cerebral asymmetry, many studies have examined the behavioral correlates of hand preference, such as cognitive ability patterns (e.g., Halpern, Haviland, & Killian, 1998) and occupational talents (e.g., O'Boyle & Benbow, 1990). In addition, researchers have explored the relation between handedness and several child psychiatric disorders, including autism (e.g., Cornish & McManus, 1996), hyperactivity (Biederman et al., 1994), and conduct disorder (e.g., Feehan, Stanton, McGee, Silva, & Moffitt, 1990; Gabrielli & Mednick, 1980), as well as mental retardation (e.g., Batheja & McManus, 1985; Flannery & Liederman, 1995) and developmental learning disabilities (e.g., Bishop, 1990).

The present study continued this last research strategy by examining the relation between handedness and gender identity disorder (GID) in boys. In the following section, we review the rationale that guided this empirical effort.

Requests for reprints to: Kenneth J. Zucker, PhD, Child and Adolescent Gender Identity Clinic, Child Psychiatry Program, Centre for Addiction and Mental Health–Clarke Division, 250 College St, Toronto, Ontario M5T 1R8, Canada
(E-mail: Ken_Zucker@camh.net).

Handedness and Psychosexual Differentiation

Boys who meet the DSM-IV diagnostic criteria for GID (American Psychiatric Association, 2000) display an array of behaviors suggestive of marked cross-gender identification, including cross-gender toy play, roles in fantasy, dress-up play, and peer affiliation preference. Such boys also show a marked rejection of culturally typical masculine interests and an avoidance of rough-and-tumble play. In addition, these boys often express the desire to be girls or, in some instances, an insistence that they are girls. As well, some of these boys express a marked dislike of their sexual anatomy and fantasize about having the sexual anatomy of girls. Follow-up studies of boys with GID suggest that a small minority persist in their desire to be girls and will seek out physical sex-transformation procedures in adolescence or adulthood; however, the majority of boys followed prospectively develop a homosexual sexual orientation, without co-occurring gender dysphoria (Green, 1987; Zucker & Bradley, 1995). Thus, at different phases of the life cycle, boys with GID show atypical psychosexual development with regard to three parameters: gender identity, gender role, and sexual orientation.

Perhaps the most prominent biological theory invoked to account for the development of GID concerns the role of prenatal sex hormones. From animal experiments, it has been well established that manipulation of the prenatal or perinatal hormonal milieu can alter postnatal sex-dimorphic behaviors, i.e., behaviors that, on average, show sex differences. Thus, for example, prenatal hormonal exposure to male-typical levels of androgens masculinizes the postnatal sex-dimorphic behavior of female offspring whereas underexposure to male-typical levels of androgens demasculinizes or feminizes the postnatal sex-dimorphic behavior of male offspring, a finding that has been demonstrated in many animal species, including the nonhuman primate (e.g., Dixson, 1998; Wallen, 1996).

In humans, the role of the prenatal hormonal environment has been opportunistically studied in children with physical intersex conditions (Collaer & Hines, 1995). For example, among genetic females with congenital adrenal hyperplasia (CAH), who are exposed prenatally to high levels of adrenal androgens, it has been found that they show postnatal behavioral masculinization, particularly with regard to gender role behavior and sexual orientation (e.g., Berenbaum & Hines, 1992; Zucker et al., 1996). In boys with GID, however, there is no evidence of gross somatic intersexuality, which would implicate the presence of a prenatal hormonal anomaly; however, experimental studies with female rhesus monkeys suggest that it is possible to induce postnatal behavioral masculinization without concomitant genital masculinization, at least for some behaviors that, on average, show a normative sex difference (Goy, Bercovitch, & McBrair, 1988). This behavioral-genital *dissociation* may serve, therefore, as a model for understanding psychosexual differentiation in boys with GID. It is possible that hormonal factors operating prenatally affect CNS differentiation that demasculinize or feminize postnatal sex-dimorphic behavior without affecting the configuration of the external genitalia.

There are several reasons for studying handedness in relation to GID in boys. As noted earlier, there is the normative sex difference in hand preference. Given that boys with GID are behaviorally feminized, it follows that their hand preference might also be shifted in the female-typical direction, i.e., an increased rate of *right-handedness*. Interestingly, however, studies of adult males with a homosexual orientation and of adult males with GID have found the opposite, i.e., an increased rate of *left-handedness* or *nonconsistent right-handedness*[1].

Regarding the relation between handedness and sexual orientation, Lalumière, Blanchard, and Zucker (2000) found, in a meta-analytic review, that homosexual men and women were significantly more likely to be non-consistently right-handed than were heterosexual men and women, respectively. In 20 studies comparing heterosexual ($N = 14{,}808$) and homosexual ($N = 6182$) men, the average odds ratio was 1.34; in 9 studies comparing heterosexual ($N = 1615$) and homosexual ($N = 805$) women, the average odds ratio was 1.91.

In five samples of adult females with GID, there was a consistent pattern of an elevated rate of left-handedness (Table 1). In six samples of adult males with GID, four studies appeared to find an elevated rate of left-handedness, but two others did not (Table 2). There are, however, several methodological issues that call for some caution in appraising the findings: (1) In the study by Orlebeke, Boomsma, Gooren, Verschoor, and Van den Bree (1992), the method of assessment differed between the probands and the controls, thus rendering the between-groups comparison suspect. (2) Among adult males with GID, it is important to subgroup the probands by their sexual orientation (in relation to their birth sex). Unlike adult females with GID, who are predominantly homosexual, adult males with GID show a more even distribution between a heterosexual and a homosexual sexual orientation and there is considerable evidence that the two sexual orientation subgroups differ with regard to a number of etiologically relevant parameters, including a childhood history of extensive cross-gender behavior, family demographic variables (e.g., sibling sex ratio and birth order), a history of transvestic fetishism, and so on (Zucker & Blanchard, 1997). In three of the handedness studies of males (Herman-Jeglinska, Dulko, & Grabowska, 1997; Orlebeke et al., 1992; Watson & Coren, 1992), the data were not analyzed separately by sexual orientation, thus making it difficult to interpret the findings. (3) None of the studies attempted to rule out any possible confounding or mediating variables between the probands and the controls. For example, because psy-

[1] There are several assessment strategies regarding both the measurement and the classification of handedness (see Bryden & Steenhuis, 1991). One approach, which we regard as the most conservative, classifies individuals as right-handed or left-handed as a function of which hand is used to perform a specific unimanual task, such as writing or drawing. A second approach assesses hand preference for a series of unimanual tasks (via questionnaire or behavioral demonstration) and then classifies individuals as exclusively right-handed or as nonconsistently right-handed. Individuals are classified as exclusively right-handed only if all tasks are performed with the right hand and as nonconsistently right-handed if at least one of the tasks is performed with the left hand (e.g., McCormick, Witelson, & Kingstone, 1990). A third approach is a variant of the second approach. Based on visual inspection of subjects' responses across an array of unimanual tasks, a cut-point is identified to distinguish predominantly right-handed responders from non-consistently right-handed responders. Last, handedness has been measured as a continuous variable (e.g., by summing hand preference, or degree of hand preference, across a series of unimanual tasks).

Table 1
Handedness Preference in Adult Females with Gender Identity Disorder

Study	Right-handed *N* (%)	Mixed *N* (%)	Left-handed *N* (%)
Orlebeke et al. (1992)			
Patients	34 (77.3)	2 (4.5)	8 (18.2)
Controls[a]	4236 (88.8)	NA	533 (11.2)
Herman-Jeglinska et al. (1997)			
Patients	70 (82.4)	—	15 (17.6)
Controls[b]	302 (91.2)	—	29 (8.8)
Cohen-Kettenis et al. (1998)			
Patients	31 (70.4)	4 (9.1)	9 (20.5)
Controls	ND	ND	ND
Slabbekoorn et al. (2000)			
Patients[c]	69 (74.1)	10 (10.8)	14 (15.1)
Controls[d]	86 (91.5)	1 (1.1)	7 (7.4)
Green & Young (in press)			
Patients[e]	58 (81.7)	5 (7.0)	8 (11.3)
Controls[b]	110 (88.7)	3 (2.4)	11 (8.9)

NA = Not assessed; ND = no data.
[a] Males and females combined because the data were not available separately by sex (L. J. G. Gooren, personal communication, May 8, 2000).
[b] Females only.
[c] Only patients with a homosexual sexual orientation are included. Patients with a heterosexual, bisexual, or "unknown" sexual orientation ($N = 17$) were excluded.
[d] Only heterosexual adult females are included. Data from girls ($N = 77$) were excluded because the method of assessment differed from that of the patients and adult controls. Raw data were provided by D. Slabbekoorn (personal communications, May 5 and 24 and July 25, 2000).
[e] Only patients with homosexual sexual orientation are included. Patients with a heterosexual, bisexual, or asexual sexual orientation ($N = 24$) were excluded. Raw data were provided by R. Green (personal communication, April 5, 2001).

Table 2
Handedness Preference in Adult Males with Gender Identity Disorder

Study	Right-handed *N* (%)	Mixed *N* (%)	Left-handed *N* (%)
Orlebeke et al. (1992)			
Patients	72 (77.4)	3 (3.3)	18 (19.3)
Controls[a]	4236 (88.8)	NA	533 (11.2)
Watson & Coren (1992)			
Patients	19 (64.4)	—	16 (35.6)
Controls[b]	199 (88.4)	—	26 (11.6)
Herman-Jeglinska et al. (1997)			
Patients	12 (80.0)	—	3 (20.0)
Controls[b]	129 (87.2)	—	19 (12.8)
Cohen-Kettenis et al. (1998)			
Patients	43 (93.5)	—	3 (6.5)
Controls	ND	ND	ND
Slabbekoorn et al. (2000)			
Patients[c]	89 (83.9)	6 (5.7)	11 (10.4)
Controls[d]	73 (84.9)	3 (3.5)	10 (11.6)
Green & Young (in press)			
Patients[e]	95 (85.6)	4 (3.6)	12 (10.8)
Controls[b]	124 (93.9)	0 (0.0)	8 (6.1)

NA = not assessed; ND = no data.
[a] Males and females combined because the data were not available separately by sex (L. J. G. Gooren, personal communication, May 8, 2000).
[b] Males only.
[c] Only patients with a homosexual sexual orientation are included. Patients with a heterosexual, bisexual, or "unknown" sexual orientation ($N = 79$) were excluded.
[d] Only heterosexual adult males are included. Data from boys ($N = 70$) were excluded because the method of assessment differed from that of the patients and adult controls. Raw data were provided by D. Slabbekoorn (personal communications, May 5 and 24, 2000).
[e] Only patients with a homosexual sexual orientation are included. Patients with a heterosexual, bisexual, or asexual sexual orientation ($N = 345$) were excluded. Raw data were provided by R. Green (personal communication, April 5, 2001).

chiatric comorbidity among adults with GID is common (American Psychiatric Association, 2000), the use of a clinical control group could help gauge the extent to which the handedness effect is specific to GID or characteristic of clinical populations in general. (4) Last, it should be noted that various methods were used to assess handedness, and different classification rules were used to assign individuals to handedness categories, so it is difficult to make precise comparisons across these studies.

Geschwind and Galaburda (1985) advanced one biological explanation to account for both the normative sex difference and the sexual orientation effect in hand preference. They posited that high levels of fetal testosterone might damage or slow the development of the normally dominant left hemisphere, allowing the right hemisphere to become equal or predominant and hence causing both handedness and language lateralization to shift from the left hemisphere to bilaterality or the right hemisphere. Geschwind and Galaburda argued that the normative sex difference in the fetal production of testosterone (see Forest, 1989) explained, in part, why males are more likely than females to be left-handed and also why males are more likely to suffer from learning disorders involving language (for critical overviews of the model, see Bryden, McManus, & Bulman-Fleming, 1994; McManus & Bryden, 1991).

Based on the Geschwind-Galaburda model, the relation between handedness and sexual orientation in females is straightforward: An overexposure to testosterone, as predicted by the prenatal androgen exposure theory (Meyer-Bahlburg, 1984), predisposes them to homosexuality and to non-right-handedness, i.e., a shift to the male-typical pattern of sexual attraction to females and increased non-right-handedness. The Lalumière et al. (2000) meta-analysis supported the prediction of increased non-right-handedness in homosexual women. Three other studies of women, unselected for sexual orientation and therefore likely to be predominantly heterosexual, found an association between masculinized gender role behavior and left-handedness (Casey & Nuttall, 1990; Nicholls & Forbes, 1996; Santhakumari, Kurian, & Rao, 1994). Although these two lines of research are consistent with the possibility of sex-atypical prenatal exposure to androgens, direct evidence is lacking (cf. McFadden & Pasanen, 1998). It is of interest, therefore, that four studies of girls and women with CAH, for whom there is incontrovertible evidence for sex-atypical exposure to adrenal androgens during fetal development, have reported higher rates of non-right-handedness than unaffected controls (Helleday, Siwers, Ritzen, & Hugdahl, 1994; Kelso, Nicholls, Warne, & Zacharin, 2000; Nass et al., 1987; Tirosh, Rod, Cohen, & Hochberg, 1993), and three studies of women whose mothers had been prenatally exposed to diethylstilbestrol (DES), a masculinizing synthetic hormone, also had higher rates of non-right-handedness than unaffected controls (Schachter, 1994; Scheirs & Vingerhoets, 1995; Smith & Hines, 2000); however, one study of 25 girls, for whom prenatal levels of testosterone were obtained in the second trimester via amniocentesis, found that higher levels of testosterone were associated with a greater degree of right-handedness (Grimshaw, Bryden, & Finegan, 1995).

In males, the Geschwind-Galaburda model is more complex and there have been two versions of it. If homosexuality in men is due to an underexposure to testosterone, as predicted by the prenatal androgen exposure theory (Meyer-Bahlburg, 1984), then there should also be a shift to a more female-typical pattern of increased right-handedness. However, Geschwind and Galaburda modified their original prediction based on Ward and Weisz's (1980) study of stressed pregnant rats, in which male fetuses responded with an initial rise and then a permanent drop in testosterone, followed by more postnatal "homosexual" behavior (increased lordosis) than in controls. They then referred to a study by Dörner, Schenk, Schmiedel, and Ahren (1983) on the putative greater prenatal stress experienced by the mothers of homosexual men than by the mothers of heterosexual men. Citing these observations, James (1989) surmised that "it seems reasonable to suggest that prenatal stress is associated with both high and low levels of foetal testosterone (at different stages of pregnancy) and thus … with both left-handedness and homosexuality in the same individual" (p. 179). Although the meta-analytic data on handedness and sexual orientation in males are consistent with the second model (Lalumière et al., 2000), there is no direct evidence that homosexual men have been exposed to sex-atypical levels of prenatal testosterone and the evidence linking prenatal stress and sexual orientation in males is, at best, equivocal (see Bailey, Willerman, & Parks, 1991). In the Grimshaw et al. (1995) study, no relation was found between prenatal levels of testosterone and handedness in 28 boys.

Given the relation between GID in childhood and a later homosexual sexual orientation or with GID in adulthood (homosexual subtype), the present study tested the hypothesis that left-handedness would be overrepresented in boys with GID. We tested this hypothesis by comparing the rate of left-handedness in the probands with two reference groups: (1) boys and girls from three large-scale quasi-epidemiological studies, and (2) a diagnostically heterogeneous group of clinic-referred control boys.

Method

Subjects

The probands were 205 boys, ages 3–12 years, referred clinically for concerns about their gender identity development. All probands were assessed in the Child and Adolescent Gender Identity Clinic, which is housed in the Child Psychiatry Program at the Centre for Addiction and Mental Health (CAMH)–Clarke Division, in Toronto, Canada. Based on clinical interview data, primarily obtained from the parents, 140 (68.3%) boys were classified as meeting the complete DSM criteria for GID. The remaining 65 (31.7%) boys did not meet the complete diagnostic criteria for GID and thus were considered subthreshold for the diagnosis. All of the subclinical cases had at least some of the behavioral characteristics associated with GID and the majority met the complete criteria when they were younger. Table 3 shows proband characteristics for five variables: age at assessment, IQ, parent report of behavioral psychopathology on the Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983), parents' marital status, and season of birth (Martin & Jones, 1999).

The first comparison group consisted of nonreferred boys and girls who were participants in three different studies: Niswander and Gordon (1972), Hardyck et al. (1975; see also Hardyck, Petrinovich, & Goldman, 1976), and Calnan and Richardson (1976). The subjects in Niswander and Gordon were part of the National Collaborative Perinatal Project on perinatal health and subsequent developmental outcome. Pregnant women who sought care in various medical centers in the United States and their children were studied longitudinally

Table 3
Sample Characteristics

	Gender identity disorder			Clinical controls			
Variables	Mean	(*SD*)	*N*	Mean	(*SD*)	*N*	*p*
Age (in yrs)	6.8	(2.4)	205	8.6	(1.9)	205	< .001
Verbal IQ[a]	102.3	(16.1)	193	96.0	(18.1)	204	< .001
Performance IQ[a]	103.9	(16.6)	195	100.0	(20.1)	204	.036
Full Scale IQ[a]	103.3	(16.4)	201	97.9	(18.7)	205	.002
Child Behavior Checklist							
Sum of items	45.5	(26.0)	203	67.0	(28.0)	204	< .001
Internalizing T	61.4	(10.8)	203	65.7	(10.8)	204	< .001
Externalizing T	60.3	(11.4)	203	67.6	(10.2)	204	< .001
Parent's marital status (%)							
Two-parent	71.7	—	147	47.8	—	98	< .001
Other	28.3	—	58	52.2	—	107	
Season of birth (%)[b]							
March–July	43.9	—	90	43.4	—	89	n.s.
August–February	56.1	—	115	56.6	—	116	

p values are from either *t*-tests or a chi-square test.

[a] An IQ score was not available for two probands. For the remaining 203 probands, 195 were administered either the WPPSI or the WISC. Of these, Verbal IQ was not available for two probands who did not speak English. The remaining eight probands were administered another intelligence test, such as the Stanford-Binet or the Leiter. For the clinical controls, all were administered either the WPPSI or the WISC.

[b] Per Martin and Jones (1999). A 2 (group) × 12 (month) chi-square test was also not significant.

following pregnancy. In this study, handedness data were obtained when the children were all 7 years of age (see Eaton et al., 1996; McManus, 1979). The subjects in Hardyck et al. were from a total population of school children, grades 1–6, from Berkeley, California (U.S.A.). The subjects in Calnan and Richardson were part of the National Child Development Study, a longitudinal investigation of all children born in England, Scotland, and Wales in one week of March 1958. Handedness data were obtained when the children were 11 years of age.

We chose these comparison groups for two reasons. (1) The sample sizes were all very large and thus there would be little concern about nonrepresentativeness that might occur in obtaining handedness data from a concurrent sample of nonreferred children (e.g., from a local school district) for whom "active" parental consent is required for participation. (2) When active consent is required, which is the usual procedure mandated by Institutional Review Boards, the participation rate is typically low (see, e.g., Crawford, Kaplan, & Kinsbourne, 1994). Given that left-handedness is an atypical behavioral trait, one concern is that parents of children who are left-handed might be more motivated to allow their child to participate than parents of children who are right-handed (see Cornell & McManus, 1992; Seddon & McManus, 1991).

The second comparison group consisted of 205 clinical control boys who were referred for assessment to the Child Psychiatry Program at the CAMH and who were subsequently seen for psychological testing. The reasons for referral varied and thus the control boys were diagnostically heterogeneous. This comparison group was used to control for the probands' route of entry into the study, namely that they were brought for clinical assessment because of something atypical in their behavior. Other than sex, we made no effort to match the probands and controls on the demographic and behavioral measures. Table 3 also shows the demographic and behavioral characteristics of the clinical controls. With the exception of season of birth, it can be seen that the two groups differed significantly on all of the other measures.

Measure

For the probands and the clinical controls, hand preference (right or left) was classified on the basis of which hand was used during a unimanual behavioral task (e.g., completion of the Coding and Mazes subtests on the WISC-III or the WPPSI-R, respectively). For 178 probands and 40 clinical controls, hand preference was also measured by a 12-item behavioral task derived from Bryden, MacRae, and Steenhuis (1991). One item required that the subject either write his name or to draw a circle. For these subjects, the preferred hand matched the preferred hand used on the Coding or Mazes subtest in all cases.

In Niswander and Gordon (1972), each child was asked to make an "X" three times, each time with a different colored pencil. Children who used the same hand on all three trials were classified as either right-handed or left-handed; children who switched hands on at least on trial were classified as mixed-handed (see Eaton et al., 1996). In Hardyck et al. (1975), each child was asked to write his or her name and, on this basis, was classified as either right-handed or left-handed. In Calnan and Richardson (1976), children were classified as right-handed, left-handed, or mixed-handed based on maternal report. Because the sample sizes were large, we assumed that the distributions in handedness would be relatively impervious to method variance in assessment.

Results

Table 4 shows the percentage of right-handed and left-handed children, by sex, in the Hardyck et al. (1975), Calnan and Richardson (1976), and Eaton et al. (1996) studies. In each study, a significantly greater percentage of boys than girls were left-handed, as was the case when the subjects were collapsed, $\chi^2(1) = 58.0, p < .00001$. The percentage of girls who were left-handed did not differ significantly across the three samples, $\chi^2(2) = 1.5$; however, there was a significant difference among the three samples of boys, $\chi^2(2) = 10.1$, $p = .006$. The percentage of left-handed boys was significantly lower in the Hardyck et al. study than in the Calnan and Richardson, $\chi^2(1) = 9.9$, $p = .001$, and Eaton et al., $\chi^2(1) = 3.9$, $p = .047$, studies, respectively.

Of the 205 boys with GID, 40 (19.5%) were left-handed whereas of the 205 clinical control boys, only 17 (8.3%) were left-handed, a significant difference, $\chi^2(1) = 9.9$, $p = .00169$. The odds ratio was 2.68 (95% CI 1.46 to

Table 4
Handedness Classification by Sex in Three General Population Studies

	Boys				Girls			
	Right-handed		Left-handed		Right-handed		Left-handed	
Study	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Hardyck et al. (1975)[a]	3543	(89.5)	417	(10.5)	3404	(91.3)	324	(8.7)
Calnan & Richardson (1976)[b]	4700	(87.3)	682	(12.7)	4828	(91.1)	472	(8.9)
Eaton et al. (1996)[c]	4327	(88.1)	584	(11.9)	4428	(90.6)	460	(9.4)
Total	12570	(88.2)	1683	(11.8)	12660	(91.0)	1256	(9.0)

The required data from Eaton et al. (1996) were provided by W. O. Eaton (personal communication, February 18, 2000). For Eaton et al., boys ($N = 92$) and girls ($N = 85$) classified as mixed-handed were excluded. For Calnan and Richardson, boys ($N = 384$) and girls ($N = 250$) classified as mixed-handed were also excluded.

[a] $\chi^2(1) = 7.2$, $p < .01$.
[b] $\chi^2(1) = 38.9$, $p < .00001$.
[c] $\chi^2(1) = 15.6$, $p < .0001$.

4.91), meaning that the probands were more than 2.5 times likely to be left-handed than the controls.

Compared to the percentage of left-handed boys in each of the three general population studies (see Table 4), the percentage of left-handed boys with GID was significantly greater: with Hardyck et al., $\chi^2(1) = 15.2$, $p < .0001$; with Calnan and Richardson, $\chi^2(1) = 7.6$, $p < .01$; with Eaton et al., $\chi^2(1) = 10.0$, $p < .002$. The odds ratios were 2.06 (CI 1.44 to 2.95), 1.66 (CI 1.17 to 2.38), and 1.80 (CI 1.26 to 2.56), respectively[2].

Compared to the percentage of left-handed boys in each of the three general population studies (see Table 4), the percentage of left-handed clinical control boys did not differ significantly: respective $\chi^2(1) = 0.81, 3.07$, and 2.12, all $ps > .05$. The odds ratios were 0.76 (CI 0.46 to 1.28), 0.62 (CI 0.38 to 1.03), and 0.67 (CI 0.40 to 1.11), respectively.

Because the probands differed significantly from the clinical controls on several demographic and behavioral measures (see Table 3), a logistic regression was performed in which these measures, along with group (probands vs. controls), were entered as predictor variables. The equation was built using forward stepwise regression (due to missing data, 14 subjects were lost for this analysis). The only variable that entered the regression equation was group. Thus, the results were comparable to the chi-square analysis reported above.

Collapsed across the probands and the clinical controls, there were no significant differences between right-handers and left-handers for the demographic and behavioral measures listed in Table 3. Within the GID group, 10 additional variables were also examined for handedness effects: whether or not the proband met the complete DSM criteria for GID, birthweight, singleton vs. twin births, whether or not the proband was adopted, maternal age at the time of the proband's birth, ethnicity (Caucasian vs. non-Caucasian), number of older brothers, number of older sisters, number of older siblings, and parents' social class (Hollingshead, 1975). None of these variables were related to the probands' handedness classification.

Discussion

The present study found that boys with GID had a significantly higher rate of left-handedness than did a diagnostically heterogeneous control group of clinic-referred boys and three independent samples of non-referred boys, with odds ratios ranging from 1.66 to 2.68. In contrast, the rate of left-handedness did not differ between the clinical control group and the three samples of nonreferred boys. Before considering possible interpretations of the data, several methodological issues will be discussed.

Each of the three samples of nonreferred boys had a significantly higher rate of left-handedness than did the three samples of nonreferred girls, a finding that is consistent with, and representative of, the broader literature on sex differences in handedness (Seddon & McManus, 1991). Across the three samples, the age at assessment differed: Grades 1–6 in Hardyck et al. (1975), age 7 in Eaton et al. (1996), and age 11 in Calnan and Richardson (1976). Given that age was unrelated to handedness classification in the GID and the clinical control groups and the more general observation that hand preference is established quite early in development (Bishop, 1990), it is unlikely that this variation in age is of particular importance. Among the nonreferred samples, the percentage of left-handed boys was significantly lower in the Hardyck et al. study than in the Eaton et al. and Calnan and Richardson studies, respectively; however, the percentage difference across the three samples was relatively small (2.2%). In any case, the finding that the boys with GID differed significantly from each of the comparison samples, whereas the clinical control boys did not, suggests that the effect was reasonably robust.

It will be recalled that the boys with GID differed significantly from the clinical controls on several demographic and behavioral measures (Table 3). At the time of assessment, the boys with GID were younger, had higher IQs, had fewer behavioral problems on the CBCL, and were more likely to come from intact families. However, none of these variables were related to handedness

[2] In Eaton et al., we excluded those subjects who were classified as mixed-handed. If the boys classified as mixed-handed are added to the left-handed group, the difference between the probands and the Eaton et al. boys remained significant, $\chi^2(1) = 5.48$, $p < .02$. We also excluded the mixed-handed subjects in Calnan and Richardson; however, in this study it is not clear if maternal report of mixed-handedness was based primarily on writing behavior. Thus, we did not conduct any additional analyses on these data.

classification (right- vs. left-handed) when the two groups were collapsed and none of these variables entered into the regression equation. Thus, there is no reason to believe that the between-groups difference on these variables contaminated or confounded the between-groups comparison for handedness.

A potential limitation of the present study is that the clinical control group of boys was diagnostically heterogeneous. This raises the question of whether or not a more diagnostically homogeneous group of clinical controls of a particular type would have yielded an elevation in left-handedness comparable to that of the GID boys. Unfortunately, the literature on the prevalence of left-handedness among some of the more common child psychiatric disorders is either nonexistent (e.g., with regard to the anxiety disorders) or inconsistent (e.g., with regard to conduct disorder and attention deficit hyperactivity disorder) (see, e.g., Biederman et al., 1994; Feehan et al., 1990; Gabrielli & Mednick, 1980). Even for autism, for which a connection to handedness has been studied most extensively, the literature is inconsistent and Bishop (1990) concluded that there does not appear to be an elevation in left-handedness per se, but rather evidence for ambiguous or mixed-handedness (see also Satz & Green, 1999). Bishop (1990) reached a similar conclusion regarding the relation between handedness and developmental learning disorders.

Although the present study cannot answer the question of diagnostic specificity with precision and this is, therefore, a matter that should be explored in subsequent studies, the present study did show that an elevation in left-handedness was not a characteristic of clinic-referred boys in general. Even if subsequent studies show that other diagnostic groups have a comparable elevation in left-handedness, the reason why boys with GID have an elevation in left-handedness probably requires an explanation in its own right.

In the very early literature on the development of hand preference, direct instruction was postulated as the main reason why most people are right-handed (see Hardyck & Petrinovich, 1977). For various reasons, most contemporary handedness researchers have dismissed this as a plausible explanatory mechanism. Regarding boys predisposed to develop GID, there is certainly no compelling reason to believe that they have been socialized in a manner that would result in an elevated rate of left-handedness. Accordingly, parsimony would dictate that the elevation is best accounted for by biological influences. What, then, might be the candidate explanations?

One possibility is a genetic effect, i.e., that there is also an elevation in left-handedness among first-degree relatives (see, e.g., McKeever, 2000). Unfortunately, we did not collect hand preference data for either the parents or the siblings of boys with GID, so a genetic-familial pattern of transmission cannot be either confirmed or ruled out. If such a pattern of transmission existed, it would then become necessary to explain why an elevation in left-handedness is over-represented in the families of boys who later develop a GID.

As noted in the Introduction, the prenatal androgen exposure theory connects psychosexual differentiation and hand preference. For both homosexual men and adult men with GID, however, the higher rate of non-right-handedness (or left-handedness proper) runs counter to the original hypothesis advanced by Geschwind and Galaburda (1985), since an underexposure to prenatal androgens would predict a higher rate of right-handedness (Berenbaum & Denburg, 1995). The elevation in left-handedness in boys with GID in the present study also runs counter to this prediction. Thus, unless one accepts the fluctuating testosterone hypothesis advanced by James (1989), for which there is no confirming or disconfirming evidence, or even the idea that *high* levels of prenatal testosterone in males have "paradoxical" effects, i.e., demasculinized behavior (see Berenbaum & Denburg, 1995), the prenatal androgen exposure theory appears to be wanting, at least for males, in trying to bridge atypical psychosexual differentiation and left-handedness.

In contrast to the data on males, the prenatal androgen exposure theory has better support in females. Elevated rates of left-handedness or nonconsistent right-handedness have been observed in women with either a homosexual orientation or GID (homosexual subtype) and in women exposed to sex-atypical levels of prenatal androgen (CAH and DES). Unfortunately, we were not able to assess patterns of handedness in girls with GID because they are referred at a much lower rate than are boys with GID (Zucker, Bradley, & Sanikhani, 1997) and thus our present database would have lacked adequate statistical power.

Given the dubious status of the prenatal hormonal theory linking handedness and psychosexual differentiation in males, Lalumière et al. (2000) considered two other biological accounts that might account for the relation. One account is that the linkage is mediated by immunological phenomena, specifically by the major histocompatibility complex (MHC), a set of closely linked genes present in all vertebrate species. There is some evidence for an association between left-handedness and specific MHC alleles (Gangestad et al., 1996). It has been hypothesized that atypical psychosexual differentiation in males, including homosexuality, might be related to specific MHC alleles via the mechanism of maternal antibodies to Y-linked minor histocompatibility antigens (HY antigens) by which the sexual differentiation of the fetal brain is diverted from the male-typical pattern. This "maternal immunoreactivity" hypothesis has been used to account for the fact that both GID and homosexuality in males is associated with an individual's number of older brothers, but not with number of older sisters (Blanchard & Klassen, 1997; Blanchard, Zucker, Cohen-Kettenis, Gooren, & Bailey, 1996; Green, 2000; Zucker, Green, et al., 1997). Perhaps there is some overlap between those MHC alleles that correlate with left-handedness and those that render HY antigens more visible (i.e., antigenic) to the maternal immune system. Alternatively, perhaps there is some overlap between those MHC alleles that correlate with left-handedness and those that render HY antigens less visible to neighboring neurons in the fetal brain, thus diminishing a signal that contributes to the sexual differentiation of the brain in the male-typical pattern (Ohno, 1977). Of course, these explanations are speculative since, at present, there is no direct evidence that maternal antibodies of HY antigens contribute to either GID or homosexuality in males, let alone evidence that the MHC background affects this process.

The other account considers left-handedness under the broader rubric of developmental instability (DI), which refers to an organism's degree of vulnerability to generic and environmental stressors during development. DI has been associated with various indicators of Darwinian

fitness (e.g., disease resistance, growth rate, and reproduction) across a variety of species (Thornhill & Møller, 1997). Yeo and Gangestad (1998) have noted that left-handedness or mixed-handedness is associated with indicators of reduced Darwinian fitness, including lower birthweight (e.g., O'Callaghan, Burn, Mohay, Rogers, & Tudehope, 1993) and various neurodevelopmental disorders, such as intellectual retardation and autism. In some respects, the phenomenon of DI is consistent with the more narrow concept of "pathological" left-handedness as discussed by Satz (1972, 1973). It is plausible, therefore, that left-handedness in boys with GID represents a marker that signifies an early instability in neurodevelopment more generally. If this is the case, then one would expect to find other markers of DI in boys with GID, including fluctuating asymmetry and minor physical anomalies, which are quite amenable to empirical investigation.

Elsewhere, we have examined one of these markers—birthweight—in boys with GID and found that they weighed significantly less than a diagnostically heterogeneous group of clinical control boys (Zucker et al., 1999). Although we did not detect birthweight differences by handedness among the probands in the present study, it is possible that, with a larger sample, a birthweight-handedness association would emerge. Because DI can be caused by a variety of environmental factors, this framework can consider disruptors not inherent to the fetus, but by other factors as well, including stress experienced by the mother during pregnancy. Given Coates' (1985) observation that mothers of boys with GID often experience extreme psychosocial stress when the probands are young, it would be important to explore whether such stress also occurred during the prenatal period as well.

In conclusion, the results from the present study suggest that an atypical hand preference may be a behavioral marker of an underlying neurobiological mechanism associated with GID in boys. It is, of course, recognized that it is a weak marker given that only a minority of the probands were left-handed. Nonetheless, it is hoped that the findings will provide leads to a better understanding of the biological diathesis involved in the differentiation of this relatively uncommon psychiatric disorder of childhood.

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