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Androgenic influences on neural asymmetry: Handedness and language lateralization in individuals with congenital adrenal hyperplasia

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Summary This study tested the hypothesis that prenatal androgen levels influence hand preferences and language lateralization, two manifestations of neural asymmetry. Participants were individuals with congenital adrenal hyperplasia (CAH, a genetic disorder that results in excess adrenal androgen production beginning prenatally) (40 females; 29 males) and their unaffected relatives (29 females; 30 males) who ranged in age from 12–45 years. The Edinburgh-Crovitz Inventory and the performance of five simple tasks (the Handedness Activities Test) were the measures of hand preferences, and a dichotic listening task composed of consonant-vowel nonsense syllables was the measure of language lateralization. No sex differences were observed among relative controls in hand preferences or language lateralization. Male participants with CAH were less consistently right-handed for writing than unaffected male relatives, when those who had been forced to switch writing hands from left to right were considered with left-handers as being not consistently right-handed. There were no other significant differences between individuals with CAH and unaffected relatives. These results do not support the hypothesis that prenatal androgens influence language lateralization, nor do they support the Geschwind-Behan-Galaburda model that posits a key role for testosterone in the development of cognitive problems in males, secondary to changes in hemispheric development and cognitive lateralization. Hormonal influences on handedness, although not always consistent, may be more likely. However, given that sex differences in both language lateralization and handedness are small, it is possible that limited sample size precludes the detection of consistent group differences.
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1. Introduction

Most people are right-handed for skilled manual tasks, such as writing. However, there is a greater

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incidence of left-handedness for writing in men than in women. Women also are more likely to use their right hands for performing a greater variety of tasks than are men (Oldfield, 1971; Calnan and Richardson, 1976; Schachter et al., 1987; Lansky et al., 1988). Most right-handed humans are left hemisphere dominant for language as reflected in a greater accuracy at reporting verbal information presented to the right than the left ear (Kimura, 1961a, b). This left hemisphere dominance for language is not as pronounced in left-handers—a greater proportion of whom (compared with right-handers) have either bilateral or right hemisphere language representation. There is also a small sex difference such that on average men are more left lateralized for verbal materials than are women (Bryden, 1979, 1982; Voyer, 1996). Thus, motoric lateralization is more pronounced in women and language lateralization is more pronounced in men. Whether these are primarily differences in direction or degree is not known.

One hypothesis regarding the development of sex differences in language lateralization and handedness relates to the differing gonadal hormone milieus experienced by males and females during development. There are two periods during early human development when males are exposed to much higher levels of androgens than are females (Smail et al., 1981). The first period begins between gestational weeks 8–10 when the testes start secreting testosterone and peaks around 13–15 weeks. Levels of testosterone then decline in males but are still elevated (compared to females) until gestational week 24 by which age both sexes have comparable testosterone levels. The second period occurs in the first six months of postnatal life when there is a second testosterone surge in males.

Two lines of evidence support the hypothesis that androgens and/or their metabolites (including estrogens) acting prenatally and/or neonatally are responsible for neurobehavioral characteristics that show sex differences: First, in a range of non-human species, these hormones have dramatic effects on behavior during early critical periods when testosterone levels are normally high in males. Thus, females treated with testosterone (or estrogen) during these critical periods show more male-typical behavior and less female-typical behavior as adults (Goy, 1968; Phoenix, 1974; Beach, 1975; Beatty, 1979; Goy and McEwen, 1980). Second, studies of humans exposed to unusual hormonal environments early in development (e.g., individuals with congenital adrenal hyperplasia (CAH), and individuals exposed prenatally to diethylstilbestrol (DES), a synthetic estrogen) have shown that some sex-typical behaviors are influenced by these alterations (Collaer and Hines, 1995).

Most cases of CAH result from a genetic deficiency of the enzyme 21-hydroxylase that is required for cortisol synthesis (New, 1998). Consequently, beginning prenatally, the precursors of cortisol are overproduced. These precursors are shunted into the androgen pathway leading to the overproduction of testosterone and other adrenal androgens. CAH due to 21-hydroxylase deficiency occurs in two forms—the simple virilizing form and the salt losing form, with the salt-losing form generally considered to be more severe (New, 1998). Female fetuses with CAH are exposed to higher than normal levels of androgens, especially testosterone (Pang et al., 1980; Wudy et al., 1999). Testosterone levels generally appear to be normal in male fetuses with CAH (Pang et al., 1980; Wudy et al., 1999), although a minority may have elevated testosterone, and levels of a less potent androgen, androstenedione, also may be elevated in male fetuses with CAH (Wudy et al., 1999).

Girls with CAH are more male-typical than other girls in regard to some sexually differentiated behaviors including toy, playmate and activity preferences (Ehrhardt et al., 1968; Ehrhardt & Baker, 1974; Slijper, 1984; Dittman et al., 1990; Berenbaum & Hines, 1992; Zucker et al., 1996; see Hines, 2004, for a review). Boys with CAH have not been studied as extensively as girls, and, when they have been studied, psychological outcomes have been inconsistent. Often no alterations in toy or playmate preferences are seen (Ehrhardt and Baker, 1974; Berenbaum and Hines, 1992; Hines and Kaufman, 1994). However, one study reported enhanced (more male-typical) activity levels in boys with CAH (Ehrhardt and Baker, 1974). In contrast, reduced male-typical behavior, particularly ''rough-and-tumble'' play, has been reported in some studies of males with CAH (Hines and Kaufman, 1994; Slijper, 1984), as has reduced performance on spatial tasks, such as mental rotations, at which males typically excel (Hampson et al., 1998; Hines et al., 2003).

Previous studies of handedness and language lateralization in individuals with CAH have yielded inconsistent results. Nass et al. (1987) found increased left-handedness in females with CAH but not in males with CAH (compared to unaffected same sex siblings), while Kelso et al. (1999, 2000) found increased left-handedness in females and males with CAH combined (compared to controls matched for age, sex and socio-economic status). In contrast, Helleday et al. (1994) found no differences in language lateralization or handedness between females with CAH and controls matched for age and region of birth. However Tirosh et al. (1993) found individuals with CAH, particularly females, to show an increased degree of language lateralization compared to right-handed, but not left-handed, matched controls. They also found that 20% of males and females with CAH were left-handed. Although they did not analyze these data on handedness statistically, they assumed this was higher than the incidence of left-handedness in the population at large.

Studies of females exposed prenatally to DES also address the issue of hormonal influences on handedness and language lateralization. With respect to language lateralization, one study found male-typical patterns of left hemisphere dominance for language in DES-exposed women when compared to their unexposed sisters (Hines and Shipley, 1984), whereas another found no differences between DES-exposed women and their unexposed sisters (Smith and Hines, 2000). The evidence for hormonal influences on handedness in women exposed to DES is more consistent. Two studies found reduced right hand preferences (Schachter, 1994; Scheirs and Vingerhoets, 1995) while a third found increased left-handedness for writing (Smith and Hines, 2000).

The present study was designed to provide additional evidence regarding androgenic influences on handedness and language lateralization, by looking at a larger sample of CAH individuals than was available for prior studies. If androgens are responsible for increased left handedness in males, then females exposed to exceptionally high levels of androgens during fetal life, because of CAH, should show more left handedness. Similarly for language lateralization—if the greater left lateralization for language in males reflects the prenatal action of testosterone, then females who have been exposed to unusually high levels of androgens early in development should show greater language lateralization to the left hemisphere than females do ordinarily. Finally, given that females exhibit greater right hand preferences than males, the androgen effect could make females with CAH less strongly right handed. Thus, we predicted that females with CAH would show increased left-handedness, increased left-hemisphere dominance for verbal materials and weaker right hand preferences when compared to unaffected female relatives. Predictions for males with CAH could not be made with similar confidence for three reasons: 1. it is not clear that males with CAH experience elevated levels of testosterone prenatally (Pang et al., 1980; Wudy et al., 1999); 2. Males with CAH have not typically been found to show increased male-typical behavior (Collaer and Hines, 1995) and sometimes have been found to show reduced male-typical behavior (Slijper, 1984; Hines and Kaufman, 1994; Hampson et al., 1998; Hines et al., 2003); and 3. In rodents, when androgen is administered to developing males it has variable effects, sometimes increasing, sometimes reducing and sometimes having no influence on sex-typical behaviors (Diamond et al., 1973; Baum and Schretlen, 1975; Dohler et al., 1984).

2. Method

2.1. Participants

The 128 participants in this study belonged to one of four groups: (1) Females with CAH (n = 40); (2) males with CAH (n = 29); (3) unaffected female relative controls (n = 29) and (4) unaffected male relative controls (n = 30).

Individuals with CAH were recruited through consultant endocrinologists at Middlesex Hospital, London (n = 35; 22 female, 13 male) and through a national CAH Support Group in the UK (n = 34; 18 female, 16 male). Unaffected relatives were recruited through the families of participants with CAH. This unaffected relative control group was composed of unaffected siblings (n = 57) and first cousins (n = 2).

All the CAH families were European except for one whose ethnicity was Asian (Indian, Pakistani or Bangladeshi). Information on fathers' and mothers' educational background was available for 50 and 60 participants with CAH, respectively. This information was classified on a scale of 1–5, with 1 representing the lowest level (no secondary school diploma) and 5 the highest level (education beyond the Batchelor's degree). The numbers (and percentages) of fathers in the five categories were (1) 10 (20%), (2) 14 (28%), (3) 4 (8%), (4) 10 (20%) and (5) 12 (24%). The numbers (and percentages) of mothers in the five categories were (1) 14 (23%), (2) 24 (40%), (3) 6 (10%), (4) 6 (10%) and (5) 10 (17%).

The participants were between 12 and 45 years old. The ranges in age for the four groups were: (1) females with CAH: 12–44 years (median = 17, M = 19.5, SD = 7.3); (2) males with CAH: 12–40 years (median = 17, M = 20.27, SD = 8.43); (3) unaffected female relative controls: 12–32 years (median = 19, M = 19.26, SD = 5.95) and (4) unaffected male relative controls: 12–45 years (median = 16, M = 18.00, SD = 6.81).

Sixty seven of the 69 participants with CAH had 21-hydroxylase enzyme deficiency. Medical records for the remaining two did not specify the enzyme deficiency. 60 were salt losers and four were simple virilizers. Medical records indicating salt losing status were not available for the remaining five participants. Written consent was obtained from all participants. Written parental consent also was obtained for those participants under the age of 18 years. Participants received £50.00 and travel expenses for completing the test battery.

2.2. Materials and procedure

A six-hour battery of cognitive, motor, physical and personality tests was administered. In this paper we report data on language lateralization and handedness. Other measures are being reported separately. Handedness was measured using the Edinburgh-Crovitz Handedness Inventory (Crovitz and Zenner, 1962; Oldfield, 1971) and five simple motor tasks. Language lateralization was measured using a dichotic listening task.

2.2.1. Handedness

The Edinburgh-Crovitz Handedness Inventory (Crovitz and Zenner, 1962; Oldfield, 1971) contains 15 questions about activities that can be performed with either the left or the right hand. Participants indicate the hand they use to perform each activity on a five-point scale where 1 = always right hand and 5 = always left hand. Scores range from 15 (all activities performed exclusively with the right hand) to 75 (all activities performed exclusively with the left hand). For the second measure of handedness (the Handedness Activities Test), the participants performed five simple tasks as instructed below:

- Pick up the pencil and write this sentence, ''The cow jumped over the moon.''
- Pick up the toothbrush as if you were going to brush your teeth.
- Take the scissors and cut a square around the sentence you just wrote.
- Pick up the pencil and draw a 'happy face' on this piece of drawing paper.
- Pick up the ball and gently throw it to me.

For each activity, right hand performance received a score of one and left hand performance a score of two. Total scores ranged between five and 10 with five indicating right-hand performance on all tasks and 10 indicating left-hand performance on all tasks. Composite handedness scores were calculated by averaging the standardized scores of the Edinburgh-Crovitz Inventory and the Handedness Activities Test.

Participants also completed a questionnaire that included the yes–no item: ''Were you ever forced to learn to write with your right hand (for example, by a teacher or parent) or have you ever switched your dominant hand?'' Thirty eight females with CAH, 27 relative control females, 25 males with CAH and 26 relative control males completed this item.

2.2.2. Dichotic listening

The dichotic listening task consisted of 120 pairs of consonant-vowel syllables (Berlin et al., 1973) presented in four sets of 30 pairs. The six stimuli were the consonants 'b', 'd', 'g', 'p', 't', and 'k' each followed by the vowel 'a'. In each presentation two syllables from among the six (ba, da, ga, pa, ta and ka) were presented simultaneously, one to each ear. Syllables were presented in random order and within each set, each syllable was presented to each ear an equal number of times and was paired with each other syllable an equal number of times. In addition, initial headphone position was randomly assigned and the participants reversed their headphones after the first 60 presentations.

Participants were instructed to attend to both ears and to record both sounds heard. To compute indices of ear advantage, a count was made of the number of times that the subject correctly identified the stimulus presented to each ear. Because information from the right ear has preferential access to the left hemisphere and information from the left ear has preferential access to the right hemisphere, language lateralization is reflected in the difference between scores on items presented to the right and left ears. The raw difference score is usually adjusted for overall performance. As there is no general consensus that one type of adjustment is better than others (Kuhn, 1973; Birkett, 1977; Zaidel, 1979; Hellige et al., 1981; Springer, 1986), the following three indices were calculated:

- Percent right correct-percent left correct (PRC-PLC);
- An index of ear advantage computed according to the formula $(R - L)/(R + L) \times 100$ (Studdert-Kennedy and Shankweiler, 1970)
- The 'phi' coefficient $(R - L)/((R + L)(2T - (R + L))^{1/2}$ (Kuhn, 1973).

Participants also underwent an audiometric examination. Ascending and descending thresholds at 250, 500, 1000, 2000, 4000 and 8000 Hz were assessed to determine the comparability of hearing in both ears. Data from participants whose mean right versus left ear thresholds differed by more than 15dB were excluded from analyses.

2.3. Statistical analyses

Where possible, two-way ANOVAs were used to evaluate main effects of sex and diagnosis and their interaction. In addition, planned comparisons were conducted to evaluate specific hypotheses. These compared: 1. unaffected males to unaffected females to assess sex differences in handedness and language lateralization; 2. female participants with CAH to unaffected females to determine if prenatal exposure to high levels of androgen produced more male-typical patterns of handedness or language lateralization; and 3. male participants with CAH to unaffected males to determine if CAH influenced handedness or language lateralization in males. These planned comparisons, and other analyses where two-way ANOVAs were not possible, used one-way ANOVAs, *t*-tests, Chi-square, or Fisher's Exact test, depending on the nature of the data.

3. Results

3.1. Handedness (See Table 1)

3.1.1. Hand writing

Although more participants with CAH (10% female and 17.2% male) were left handed for writing than unaffected relatives (6.9% female and 6.7% male), differences among the groups were not statistically significant (using Fisher's Exact test): For unaffected female versus male relatives, $p = 1.00$ on both handedness measures; females with and without CAH, $p = 1.00$ on both handedness measures; and for males with and without CAH, $p = 0.145$ on the Edinburgh-Crovitz Inventory and $p = 0.254$ on the Handedness Activities Test. However, 16% of male participants with CAH had been forced to switch from left-handed to right-handed writing as children, and when those who used their left hands for writing were included with those who had been forced to switch from the left hand, significantly more males with than without CAH were not consistently right handed ($p = 0.042$). Female participants with CAH did not differ from unaffected relative control females on this combined measure ($p = 0.69$), nor did unaffected males and unaffected females differ ($p = 1.00$).

3.1.2. Mean handedness (scores on inventories)

Patterns of results for each of the two handedness inventories analysed independently were the same as for the composite score and only results for the composite are reported here (except for the direction of handedness results, see below). Two-way ANOVA yielded no significant main effects or interactions for handedness ($F_{(1,124)} = 0.78$, $p = 0.380$ for sex; $F_{(1,124)} = 1.80$, $p = 0.183$ for diagnostic category; and, $F_{(1,124)} = 0.007$, $p = 0.933$ for the interaction). Although control females were slightly more left handed than control males, and both females and males with CAH were slightly more left-handed than unaffected relative controls of the same sex (effect sizes (*d*) = 0.177, 0.258 and 0.239, in order), planned comparisons showed that none of the differences was statistically significant (unaffected male and female

Table 1 Handedness measures and effect sizes in female and male participants with CAH and unaffected female and male relative control participants

	Hand used for Writing[a]		% Switching writing hands[b]	Edinburgh-Crovitz Inventory[c] Mean ± SD	Handedness Activities Test[c] Mean ± SD	Composite[c,d] Mean ± SD
	%RH	%LH				
(1) CAH female	90.0	10.0	2.6	1.69 ± 1.0	1.11 ± 0.09	0.038 ± 1.10
(2) Control female	93.1	6.9	0.0	1.52 ± 0.65	1.04 ± 0.16	−0.190 ± 0.67
(3) CAH male	82.8	17.2	16.0	1.87 ± 1.12	1.15 ± 0.31	0.213 ± 1.22
(4) Control male	93.3	6.7	3.9	1.67 ± 0.85	1.07 ± 0.25	−0.046 ± 0.957
d (2) & (4)				−0.200	−0.146	−0.177
d (1) & (2)				0.206	0.560	0.258
d (3) & (4)				0.203	0.286	0.239

[a] Assessed using the Handedness Activities Test.

[b] Group *n*s are 38, 27, 25 and 26 for (1)–(4) in order; for all other measures, group *n*s are 40, 29, 29 and 30 for (1)–(4) in order.

[c] Higher score indicate greater left-handedness.

[d] Composite scores are the average of standardized Edinburgh-Crovitz Inventory and Handedness Activities Test scores.

relatives ($F_{(1,57)}$ = 0.45, p = 0.506), females with CAH and unaffected female relatives ($F_{(1,57)}$ = 0.97, p = 0.328), and males with CAH and unaffected male relatives ($F_{(1,57)}$ = 0.825, p = 0.367).

A previous study (Nass et al., 1987) found significant differences in handedness using paired comparisons of females with CAH versus their own unaffected female relatives, even though group analyses yielded no differences. Therefore, we conducted a second ANOVA with diagnosis as a repeated measures factor on the subset of 22 participants with CAH (11 females and 11 males) who had a relative of the same sex (see Table 2). This analysis also yielded no significant main effects or interactions ($F_{(1,20)}$ = 0.810, p = 0.379 for sex, $F_{(1,20)} < 0.001$, p = 1.000 for diagnostic category, and $F_{(1,20)}$ = 1.537, p = 0.220 for the interaction). Planned comparisons within each sex also produced no significant differences ($F_{(1,10)}$ = 1.676, p = 0.225 for females; $F_{(1,10)}$ = 0.499, p = 0.496 for males).

3.1.3. Direction versus degree of handedness

The above analyses, using mean scores on inventories, do not distinguish degree of handedness from direction of handedness (for a discussion of this issue, see McManus, 1983). For example, a neutral mean score on a handedness inventory could indicate either that all activities are performed without preference by both hands or that half the items are performed exclusively by the right hand and the other half exclusively by the left.

Direction: To establish whether the groups differed in the direction of handedness, each item on the two measures was coded as having been performed by the right hand exclusively or not. The resulting data were analysed using Fisher's Exact tests (p values reported) and Chi-square (where participant numbers permitted). No significant differences were found in direction of handedness between unaffected male and female relatives (p = 0.731 for Edinburgh-Crovitz Inventory; p = 1.000 for Handedness Activities Test), females with CAH and unaffected female relatives (χ^2 = 1.474, df = 1, p = 0.225 for Edinburgh-Crovitz Inventory; p = 0.453 for Handedness Activities Test), or males with CAH and unaffected male relatives (p = 1.000 for Edinburgh-Crovitz Inventory; p = 0.181 for Handedness Activities Test).

Degree: To determine if the degree of handedness varied with sex and diagnosis, absolute values of scores were analysed. Two-way ANOVAs showed no significant main effects or interactions ($F_{(1,124)}$ = 0.23, p = 0.631 for sex; $F_{(1,124)}$ = 2.45, p = 0.120 for diagnostic category; and, $F_{(1,124)}$ = 0.04, p = 0.840 for the interaction). Planned comparisons yielded no significant differences between unaffected males and females ($F_{(1,57)}$ = 0.324, p = 0.571), females with and without CAH ($F_{(1,67)}$ = 2.049, p = 0.157), or males with and without CAH ($F_{(1,57)}$ = 0.715, p = 0.401).

3.2. Language lateralization

Means and standard deviations for the variables derived from the dichotic listening task are presented in Table 3. Four participants (two females with CAH, one unaffected male relative and one unaffected female relative) were excluded from the analyses because of disparity in right and left ear thresholds.

3.2.1. Ear scores

The four groups showed the expected right ear (left hemisphere) advantages. For the comparison of right and left ear scores, $t_{(37)}$ = 3.348, p = 0.002, for females with CAH; $t_{(28)}$ = 2.403, p = 0.023, for males with CAH, $t_{(27)}$ = 3.722, p = 0.001, for

Table 2 Handedness measures in female and male participants with CAH and their matched unaffected same sex relatives

Group	*n*	Handedness Measures					
		ECI		HAT		Composite	
		M	SD	M	SD	M	SD
Females							
CAH	11	1.21	0.21	1.00	0.00	−0.32	0.12
Control	11	1.79	0.95	1.11	10.26	0.065	0.97
Males							
CAH	11	1.79	1.18	1.16	0.37	0.32	1.35
Control	11	1.61	0.96	1.09	0.30	−0.07	1.05

ECI = Edinburgh-Crovitz Inventory, HAT = Handedness Activities Test, Composite = mean of standardized ECI and HAT scores. Higher scores indicate more left-hand preferences.

unaffected female relatives; and $t_{(28)} = 3.291$, $p = 0.003$ for unaffected male relatives.

3.2.2. Asymmetry indices

For all analyses involving asymmetry indices, results are reported for (R − L)/(R + L) × 100 because in all cases results were highly similar for the other two indices and in no case would significance be changed by using either of the others. This particular dichotic listening measure was selected because prior work suggested that it revealed a large sex difference (Hines and Shipley, 1984). Two-way ANOVAs yielded no significant main effects or interactions ($F_{(1,120)} = 0.045$, $p = 0.832$ for sex, $F_{(1,120)} = 0.281$, $p = 0.597$ for diagnostic category, and, $F_{(1,120)} = 0.017$, $p = 0.895$ for the interaction). Planned comparisons also yielded no significant differences between unaffected female and male relatives ($F_{(1,55)} = 0.004$, $p = 0.952$), females with and without CAH ($F_{(1,64)} = 0.092$, $p = 0.763$), or males with and without CAH ($F_{(1,56)} = 0.190$, $p = 0.665$).

Analyses conducted on the sub-sample of participants with CAH matched one to one with relative controls of the same sex showed the same pattern of results (See Table 4). Neither females nor males with CAH differed from their same sex siblings on asymmetry indices ($F_{(1,10)} = 0.030$, $p = 0.866$ and $F_{(1,9)} = 0.025$, $p = 0.879$, respectively). (This analysis includes one fewer pair of males than the similar analysis of handedness, because the unaffected male with asymmetrical hearing was the brother of a male with CAH).

3.2.3. Direction versus degree of language lateralization

Standard methods for analysing dichotic listening data, like those for analyzing data from handedness inventories, confound direction and degree of asymmetry. Therefore, additional analyses examined differences in direction and degree of lateralization separately. These were based on the directions and the absolute values of the normalized asymmetry index ((R − L)/(R + L) × 100) scores.

No significant differences were observed in direction of laterality for unaffected female versus male relatives ($\chi^2 = 1.442$, df = 1, $p = 0.230$), females with and without CAH ($\chi^2 = 1.648$, df = 1, $p = 0.199$) or males with and without CAH ($\chi^2 = 0.621$, df = 1, $p = 0.431$). Two-way ANOVAs yielded no significant main effects or interactions for degree of asymmetry ($F_{(1,120)} = 0.656$, $p = 0.420$ for sex, $F_{(1,120)} = 0.889$, $p = 0.348$ for diagnostic category, and $F_{(1,120)} = 3.023$, $p = 0.085$ for the interaction). Planned comparisons also yielded no significant differences in degree of laterality for unaffected female and male relatives ($F_{(1,55)} = 0.481$, $p = 0.491$), for females with and without CAH ($F_{(1,64)} = 0.339$, $p = 0.562$), and for males with and without CAH ($F_{(1,56)} = 3.359$, $p = 0.072$).

Correlations among the three lateralization indices and the two handedness measures and between the lateralization indices and handedness measures are presented in Table 5. The negative correlations between handedness and language lateralization for unaffected male and female controls are in the expected direction (Kimura, 1961a, b; Smith and Hines, 2000). In contrast, for males and females with CAH correlations between

Table 3 Right-and left-ear scores, asymmetry indices, and effect sizes in female and male participants with CAH and unaffected female and male relative controls

Group	*n*	Score				Asymmetry index					
		PRC		PLC		PRC-PLC		(R−L)/(R+L) × 100		phi	
		M	SD	M	SD	M	SD	M	SD	M	SD
CAH females (1)	38	51.18	16.41	45.22	12.06	5.96	10.98	5.19	10.52	0.06	0.11
Con females (2)	28	54.64	18.57	46.43	11.10	8.21	11.68	6.01	11.29	0.08	0.12
CAH males (3)	29	44.31	18.12	38.97	13.16	5.35	11.98	4.49	13.67	0.05	0.12
Con males (4)	29	52.53	18.49	45.69	13.54	6.84	11.19	5.85	9.78	0.07	0.12
d (2) & (4)		0.11		0.06		0.12		0.02		0.08	
d (1) & (2)		−0.20		−0.11		−0.20		−0.08		−0.17	
d (3) & (4)		−0.45		−0.50		−0.13		−0.12		−0.17	

PRC and PLC are percent correct right-ear and left ear, respectively.

Table 4 Right-and left-ear scores and asymmetry indices in female and male participants with CAH and their matched unaffected same sex relatives

Group	*n*	Score				Asymmetry index					
		PRC		PLC		PRC-PLC		(R−L)/(R+L) × 100		phi	
		M	SD	M	SD	M	SD	M	SD	M	SD
Females											
CAH	11	53.18	15.15	45.69	10.19	7.50	10.44	6.66	10.30	0.08	0.11
Control	11	56.82	19.24	46.82	11.26	10.00	14.74	7.39	14.36	0.10	0.15
Males											
CAH	10	35.92	15.89	34.42	11.16	1.50	10.89	0.09	16.20	0.01	0.12
Control	10	43.25	19.86	41.17	14.98	2.08	13.41	0.99	11.19	0.02	0.14

PRC and PLC are percent correct right-ear and left ear, respectively.

language lateralization and handedness were positive. However, none of these correlations was statistically significant. In addition, there were no group differences in correlations between either of the handedness measures (ECI or HAT) and the asymmetry index, $(R - L)/(R + L) \times 100$) (in all cases $p > 0.05$): For unaffected relative female and male relatives, zs = 0.054 and 0.005, respectively; for females with and without CAH zs = 0.044 and 0.03, respectively; and for males with and without CAH zs = 0.002 and −0.019, respectively. As in prior studies, the different lateralization indices correlated highly with one another (Hellige et al., 1981; Hines et al., 1992; Smith and Hines, 2000). The two handedness measures also correlated highly.

4. Discussion

This study addressed the hypothesis that exposure to high levels of androgens prenatally promotes male-typical patterns of handedness and language lateralization. The specific predictions were that, compared to unaffected female relatives, females with CAH would show (1) increased left-handedness for writing, (2) decreased overall right hand preferences and (3) increased left hemisphere dominance for verbal materials. No specific predictions were made regarding handedness and language lateralization in males with and without CAH, because prenatal androgen levels in male fetuses with CAH are not completely understood (Pang et al., 1980; Wudy et al., 1999), and because although males with CAH do not show behavioral differences in most respects (Ehrhardt and Baker, 1974; Berenbaum and Hines, 1992), they have sometimes been found to show reduced male-typical behavior (Slijper, 1984; Hines and Kaufman, 1994; Hampson et al., 1998; Hines et al., 2003) or increased male-typical behavior (Ehrhardt and Baker, 1974).

4.1. Handedness

Contrary to our predictions, handwriting, mean handedness, direction of handedness and degree of handedness did not differ in female participants with and without CAH. However, male participants with CAH were less likely to be consistently right-handed for writing compared to unaffected male relatives, although they did not differ in mean handedness, or in direction or degree of handedness.

The lack of significantly increased left-handedness in females with CAH resembles the findings of Helleday et al. (1994) who also did not find differences in hand preferences between females with and without CAH. However Nass et al. (1987) found increased left-handedness in females with CAH, and Kelso et al. (1999, 2000) reported a similar increase in males and females combined. The present results for females also contrast with studies showing increased left handedness in women exposed to DES (a non-steroidal synthetic estrogen) prenatally (Schachter, 1994; Scheirs and Vingerhoets, 1995; Smith and Hines, 2000).

The reduced number of consistent right handers in males with CAH in this study agrees with Kelso et al.'s (2000) finding of increased left-handedness in males and females with CAH combined. In addition, our observation that 17% of males with CAH were left-handed for writing is similar to that of Tirosh et al. (1993) who found a figure of 20%. However Nass et al. (1987) did not find any differences in handedness for males with and without CAH.

The reasons for these inconsistent findings are unclear. Chances of detecting existing differences

Table 5 Correlation among lateralization indices and handedness measures in female and male participants with CAH and unaffected female and male relative controls

	1 PRC-PLC	2 LI-2	3 phi	4 EC
1. PRC-PLC				
CAH females	–			
Control females	–			
CAH males	–			
Control males	–			
2. LI-2				
CAH females	0.98**	–		
Control females	0.98**	–		
CAH males		0.96**	–	
Control males	0.97**	–		
3. phi				
CAH females	1.00**	0.98**	–	
Control females	1.00**	0.98**	–	
CAH males		0.99**	0.97**	–
Control males	0.99**	0.97**	–	
4. EC				
CAH females	0.18	0.21	0.18	–
Control females	−0.18	−0.20	−0.18	–
CAH males	0.10	0.12	0.10	–
Control males	0.09	0.11	0.10	–
5. HAT				
CAH females	0.16	0.18	0.16	0.86**
Control females	−0.11	−0.14	−0.12	0.91**
CAH males	0.04	0.07	0.05	0.92**
Control males	−0.09	−0.07	−0.09	0.90**

PRC and PLC are percent correct right-ear and left ear, respectively; LI-2 represents (R−L)/(R+L) × 100; EC represents Edinburgh-Crovitz Inventory scores; HAT represents Handedness Activities Test scores.
** $p < 0.01$. *n*s = 38 CAH females, 28 control females, 29 CAH males and 29 control males.

increase with sample size, but the numbers of females with CAH in the studies that found increased left-handedness were smaller (*n* = 18 in Nass et al., 1987, *n* = 7 in Kelso et al., 1999 and *n* = 10 in Kelso et al., 2000), than in the studies where no increase was found (*n* = 22 in Helleday et al., 1994 and *n* = 40 in the current study). Nevertheless, a larger sample yet might yield the predicted results. Other explanations for inconsistent results could include differences in the ages of participants, the types of control participants, the proportions of participants with CAH who were salt wasting versus simple virilizing, and differences in the acceptance of left-handedness in the countries where the research was conducted.

Age differences do not appear to clarify the inconsistent results. Increased left-handedness was found in CAH females with mean ages of 11.6 years (Nass et al., 1987), 16 years (Kelso et al., 1999) and 22.3 years (Kelso et al., 2000), whereas left-handedness was not increased in those with a mean age of 22.7 years (Helleday et al., 1994) or 19.1 years (the current study).

The inconsistencies are also unlikely to relate to the type of control group used. For instance, left-handedness runs in families, raising the possibility that using relatives as controls precluded detection of increased left-handedness in females with CAH. However Nass, et al. (1987) found increased left-handedness only when females with CAH were matched one to one with same sex siblings controls. Moreover, of the studies using matched controls, two found increased left-handedness (Kelso et al., 1999, 2000) and one did not (Helleday et al., 1994).

One difference between the studies that found increased left-handedness in females with CAH (Nass et al., 1987; Kelso et al., 2000) and the two that did not (Helleday et al., 1994; current study) is the number of salt wasters versus simple virilizers studied, although this seems unlikely to explain the pattern of results. Fewer salt wasters were included in the first two studies (66.7% and 60%) than the second two (86.4% and 94.4%) and Kelso et al. (1999) did not report this information.

The salt-wasting form of the disorder is considered to be the more severe form, and so salt-wasters might be expected to be more, not less, likely to show altered hand preferences. In addition, if left-handedness reflects pathological neural organization (Satz et al., 1985), salt wasters might be expected to show more left-handedness than simple virilizers because of the greater likelihood of brain damage in salt wasters (during salt wasting crises). However, there is an absence of increased left-handedness in studies where there is an over representation of participants with salt wasting CAH.

Variability in cross-cultural tolerance of left-handedness could contribute to the inconsistent results. The three studies that found increased left handedness were performed in the USA (Nass et al., 1987) and Australia (Kelso et al., 1999; Kelso et al., 2000), whereas the Helleday et al. (1994) study that failed to find increased left handedness was conducted in Sweden. In the present study (conducted in the UK), increased left-handedness was observed for handwriting in male participants with CAH only when those participants who had been forced to switch to writing with the right hand were coded as left handed. Therefore, it is possible that pressures exerted by parents and/or teachers resulted in fewer left-handed participants with CAH in our study. This interpretation is made plausible by previous work demonstrating that cultural factors influence handedness (Provins, 1997).

4.2. Language lateralization

All four groups of participants in the current study showed the expected right ear (left hemisphere) advantage on the dichotic listening task. However, like Helleday et al. (1994) we found no differences between females with CAH and matched controls in patterns of performance on the task. We also found no differences between males with and without CAH.

Our failure to detect masculinized patterns of language lateralization in females with CAH may suggest that prenatal androgens do not influence this characteristic. However, stronger left hemisphere language lateralization has been demonstrated in healthy girls with higher levels of testosterone in second-trimester amniotic fluid than in girls with lower levels (Grimshaw et al., 1995). Moreover, Tirosh et al. (1993) found enhanced language lateralization in individuals, particularly females, with CAH. Similarly, one study found male-typical language lateralization in women exposed to DES prenatally (Hines and Shipley, 1984), whereas a second did not (Smith and Hines, 2000). Meta-analysis suggests that effect sizes for sex differences in language lateralization are small (Voyer, 1996), and in the current study the effect size for male versus female controls was negligible (d = 0.02–0.12, depending on the specific asymmetry index). Thus, extremely large samples may be needed to provide enough statistical power to detect gonadal hormone influences on language lateralization conistently, assuming that they exist.

4.3. The relationship between handedness and lateralization

None of the groups showed the expected significant negative correlation between hand preferences and language lateralization. However, in males and females with CAH this correlation was positive rather than negative. The expected negative relationship between language lateralization and hand preferences was found to be disrupted in females exposed to DES prenatally, but not in their unexposed sisters (Smith and Hines, 2000). This is consistent with the possibility that hormones influence at least one of these characteristics, thus disrupting the relationship that would normally be seen between them.

4.4. Implications

The reduced right hand preference in males with CAH is an enhanced male-typical pattern, since males generally show weaker right hand preferences than females (Hines and Gorski, 1985). Although prior studies generally have not found the behavior of males with CAH to be even more male-typical than controls, there is evidence that they show an enhanced male-typical pattern in a sexually differentiated physical characteristic. The ratio of the length of the index finger to the ring finger is smaller in men than in women (George, 1930; Manning et al., 2000), and is smaller yet in males with CAH compared to unaffected male relatives (Brown et al., 2002).

Research on DES-exposed women suggests that hormonal influences on hand preferences occur early, prior to week 10 of gestation (Smith and Hines, 2000). Finger length ratios also are determined early, probably sometime between weeks 8 and 14 of gestation (Garn et al., 1975). Thus, males with CAH may show more male-typical hand preferences and finger length ratios because they experience elevated androgens early in gestation. In CAH, the adrenal glands begin to produce excess androgen prior to week 13 of gestation (Wudy et al., 1999). Androgens may be elevated as early as five weeks of gestation because evidence from clinical practice highlights the importance of starting dexamethasone treatment from this age to prevent genital virilization of females with CAH (Dorr and Sippell, 1993). The testes in male fetuses begin to produce testosterone later—by about week 8 of gestation (Smail et al., 1981), and neural feedback mechanisms that allow them to reduce testicular androgen production in response to the high levels of androgen are operational prenatally (Brown-Grant et al., 1975). This could explain the normal levels of testosterone seen in most male fetuses with CAH later in gestation (Pang et al., 1980; Wudy et al., 1999), as well as the general absence of enhanced male-typical development of sex-related behavioral characteristics in males with CAH (Collaer and Hines, 1995).

Therefore, it is conceivable that male fetuses with CAH experience an initial rise in androgens above normal levels (before testicular androgen production or neural feedback mechanisms are in place), masculinizing physical and motor characteristics that develop early in gestation, such as hand preferences and finger length ratios. Neural systems underlying sex-related behaviors such as toy and playmate preferences probably develop later in gestation, when androgen levels are normal in males with CAH because of feedback inhibition. As a consequence, males with CAH could be hyper-masculinized in regard to hand preferences and finger length ratios, but not in regard to some aspects of childhood play behaviors. Of course, confirmation of these speculations awaits future research providing more detailed information on hormone levels in male fetuses with CAH. The behavioral demasculinization of males with CAH (of rough and tumble play behavior (Hines and Kaufman, 1994; Hines et al., 2003) and spatial abilities (Hampson et al., 1998) may reflect the severity of the illness that may override the influence of androgens (Hines and Kaufman, 1994), or androgen deficits at later points in time (Hines et al., 2003).

In summary, we found some evidence that prenatal exposure to higher than normal levels of androgens reduces right handedness in males. However we did not find a similar effect in females, nor was there evidence indicating that androgen influenced language lateralization in either males or females with CAH. Like prior studies, this provides weak but inconsistent support for a role for androgen in the development of hand preferences in humans, and little or no support for hormonal influences on language lateralization. In addition, our results do not support the Geschwind-Behan-Galaburda model in which fetal testosterone levels are hypothesized to influence development of the cerebral hemispheres, thus leading to altered language lateralization and cognitive problems in males (Geschwind and Behan, 1984; Geschwind and Galaburda, 1987). Other investigators also have questioned the usefulness of this model (McManus and Bryden, 1991; Bryden et al., 1994).

Finally, the lack of consistent effects in this and other studies of hormones and lateralization may relate to the small size of sex differences in language lateralization and handedness ($d = 0.073$ for language lateralization, $d = -0.177$ for hand preferences in the current study and $d = 0.062$ for verbal measures of language lateralization in Voyer's (1996) meta-analysis). Based on these figures, samples of over 500 (for language lateralization) and 175 (for hand preferences) per group would be required to have conventional levels of confidence (80%) of detecting group differences, even if these exist (Cohen, 1988). Given the small sex differences and the general lack of consistent effects in this and other studies, hormones would not appear to be a major determinant of individual variability in either hand preferences or language lateralization.

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References

Baum, M.J., Schretlen, P., 1975. Neuroendoctine effects of perinatal androgenization in the male ferret. Progress Brain Res. 42, 343–355.

Beach, F.A., 1975. Hormonal modification of sexually dimorphic behavior. Psychoneuroendocrinology 1, 3–23.

Beatty, W.W., 1979. Gonadal hormones and sex differences in nonreproductive behaviors in rodents: Organizational and activational influences. Horm. Behav. 12, 112–163.

Berenbaum, S.A., Hines, M., 1992. Early androgens are related to childhood sex-typed toy preferences. Psych. Sci. 3, 203–206.

Berlin, C.I., Lowe-Bell, S.S., Cullen, Jr.., J.K., Thompson, C.L., Loovis, C.F., 1973. Dichotic speech perception: An interpretation of right-ear advantage and temporal offset effects. J. Acoustic Soc. Am. 53, 699–709.

Birkett, P., 1977. Measures of laterality and theories of hemispheric processes. Neuropsychologia 15, 693–696.

Brown, W.M., Hines, M., Fane, B.A., Breedlove, S.M., 2002. Masculinized finger length patterns in human males and females with congenital adrenal hyperplasia. Horm. Behav. 42, 380–386.

Brown-Grant, K., Fink, G., Greig, F., Murray, M.A.F., 1975. Altered sexual development in male rats after oestrogen administration during the neonatal period. J. Reproduction Fert. 44, 25–42.

Bryden, M.P., 1979. Evidence of sex-related differences in cerebral organization. In: Whittig, M., Peterson, A.C. (Eds.), Sex-related Differences in Cognitive Functioning. Academic Press, New York, pp. 121–143.

Bryden, M.P., 1982. Laterality: Functional Asymmetry in the Intact Brain. Academic Press, New York.

Bryden, M.P., McManus, I.C., Bulman-Fleming, M.B., 1994. Evaluating the empirical support for the Gaschwind-Behan-Galaburda model of cerebral lateralization. Brain Cog 26, 103–167.

Calnan, M., Richardson, K., 1976. Developmental correlates of handedness in a national sample of 11-year-olds. Ann. Human Biol. 3, 329–342.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Erlbaum, Hillsdale, NJ.

Collaer, M.L., Hines, M., 1995. Human behavioral sex differences: A role for gonadal hormones during early development? Psychol. Bull. 118, 55–107.

Crovitz, H.F., Zenner, K., 1962. A group test for assessing hand- and eye-dominance. Am. J. Psychol. 75, 271–276.

Diamond, M., Llacuna, A., Wong, C.L., 1973. Sex behavior after neonatal progesterone, testosterone, estrogen, or antiandrogens. Horm. Behav. 4, 73–88.

Dittman, R.W., Kappes, M.H., Kappes, M.E., Borger, D., Stegner, H., Willig, R.H., Wallis, H., 1990. Congenital adrenal hyperplasia I: Gender-related behavior and attitudes in female patients and sisters. Psychoneuroendocrinology 15, 401–420.

Dohler, K.D., Hancke, J.L., Srivastava, S., Hofmann, C., Shryne, J.E., Gorski, R.A., 1984. Participation of estrogens in female sexual differentiation of the brain: Neuroanatomical, neuroendocrine and behavioral evidence. Prog. Brain Res. 61, 99–117.

Dorr, H.G., Sippell, W.G., 1993. Prenatal dexamethasone treatment in pregnancies at risk for congenital adrenal hyperplasia dur to 21-hydroxylase deficiency: effect of midgestational amniotic fluid stedoid levels. J. Clin. Endocrinol. Metab. 76, 117–120.

Ehrhardt, A.A., Baker, S.W., 1974. Fetal androgens, human central nervous system differentiation, and behavior sex differences. In: Friedman, R.C., Richart, R.M., Van de Wiele, R.L. (Eds.), Sex differences in behavior. Wiley, New York, pp. 33–51.

Ehrhardt, A.A., Epstein, R., Money, J., 1968. Fetal androgens and female gender identity in the early-treated androgenital syndrome. Johns Hopkins Med. J 122, 160–167.

Garn, S.M., Burdi, A.R., Babler, W.J., Stinson, S., 1975. Early prenatal attainment of adult metacrpal-phalangeal rank and proportions. Am. J. Phys. Anthropol. 43, 327–332.

George, R., 1930. Human finger types. Anat. Rec. 46, 199–204.

Geschwind, N., Behan, P.O., 1984. Laterality, hormones and immunity. In: Geschwind, N., Galaburda, A.M. (Eds.), Cerebral Dominance. Harvard University Press, Cambridge, MA, pp. 211–224.

Geschwind, N., Galaburda, A.M., 1987. Cerebral Lateralization. MIT Press, Cambridge, MA.

Goy, R.W., 1968. Organizing effects of androgen on the behavior of rhesus monkeys. In: Michael, R.P. (Ed.), Endocrinology and Human Behavior. Oxford University Press, London, pp. 12–31.

Goy, R.W., McEwen, B.S., 1980. Sexual Differentiation of the Brain. MIT Press, Cambridge, MA.

Grimshaw, G.M., Bryden, M.P., Finegan, J.K., 1995. Relations between prenatal testosterone and cerebral lateralization in children. Neuropsychology 9, 68–79.

Hampson, E., Rovet, J.F., Altmann, D., 1998. Spatial reasoning in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Dev. Neuropsychol. 14, 299–320.

Helleday, J., Siwers, B., Ritzén, E.M., Hugdahl, K., 1994. Normal lateralization for handedness and ear advantage in a verbal dichotic listening task in women with congenital adrenal hyperplasia (CAH). Neuropsychologia 32, 875–880.

Hellige, J.B., Zatkin, J.L., Wong, T.M., 1981. Intercorrelation of laterality indices. Cortex 17, 129–134.

Hines, M. 2004. Brain Gender. Oxford University Press, New York.

Hines, M., Chiu, L., McAdams, L.A., Bentler, P.M., Lipcamon, J., 1992. Cognition and the corpus callosum: Verbal fluency, visuospatial ability, and language lateralization related to midsagittal surface areas of callosal subregions. Behav. Neurosci. 106, 3–14.

Hines, M., Fane, B.A., Pasterski, V.L., Mathews, G.A., Conway, G.S., Brook, C., 2003. Spatial abilities following prenatal androgen abnormality: Targeting and mental rotations in individuals with congenital adrenal hyperplasia. Psychoneuroendocrinology, (in press).

Hines, M., Gorski, R.A., 1985. Hormonal influences on the development of neural asymmetries. In: Benson, D.F., Zaidel, E. (Eds.), The Dual Brain: Hemispheric Specialization in Humans. Guilford Press, New York, pp. 75–96.

Hines, M., Kaufman, F.R., 1994. Androgen and the development of human sex-typical behavior: Rough-and-tumble play and sex of preferred playmates in children with congenital adrenal hyperplasia (CAH). Child Development 65, 1042–1053.

Hines, M., Shipley, C., 1984. Prenatal exposure to diethylstilbestrol (DES) and the development of sexually dimorphic cognitive abilities and cerebral lateralization. Dev. Psychol. 20, 81–94.

Kelso, W.M., Nicholls, M.E.R., Warne, G.L., 1999. Effects of prenatal androgen exposure on cerebral lateralization in patients with congenital adrenal hyperplasia (CAH). Brain Cog. 40, 153–156.

Kelso, W.M., Nicholls, M.E.R., Warne, G.L., Zacharin, M., 2000. Cerebral lateralization and cognitive functioning in patients with congenital adrenal hyperplasia. Neuropsychology 14, 370–378.

Kimura, D., 1961a. Cerebral dominance and the perception of verbal stimuli. Can. J. Psychol. 15, 166–171.

Kimura, D., 1961b. Some effects of temporal lobe damage on auditory perception. Can. J. Psychol. 15, 156–165.

Kuhn, G.M., 1973. The phi coefficient as an index of ear differences in dichotic listening. Cortex 9, 450–457.

Lansky, L.M., Feinstein, H., Peterson, J.M., 1988. Demography of handedness in two samples of randomly selected adults (*N* = 2083). Neuropsychologia 26, 465–477.

Manning, J.T., Barley, L., Walton, J., Lewis-Jones, D.I., Trivers, R.L., Singh, D., Thornhill, R., Rohde, P., Bereczkei, T., Henzi, P., Soler, M., Szwed, A., 2000. The 2nd: 4th digit ratio, sexual dimorphism, population differences, and reproductive success evidence for sexually antagonistic genes?. Evol. Human Behav. 21, 163–183.

McManus, I.C., 1983. The interpretation of laterality. Cortex 19, 187–214.

McManus, I.C., Bryden, M.P., 1991. The Geschwind-Galaburda theory of cerebral lateralization: Developing a formal causal model. Psychol. Bull. 110, 237–253.

Nass, R., Baker, S., Speiser, P., Virdis, R., Balsamo, A., Cacciari, E., Loche, A., Dumic, M., New, M., 1987. Hormones and handedness: Left-hand bias in female congenital adrenal hyperplasia patients. Neurology 37, 711–715.

New, M.I., 1998. Diagnosis and management of congenital adrenal hyperplasia. Annu. Rev. Med. 49, 311–328.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia 9, 97–113.

Pang, S., Levine, L.S., Cederqvist, L.L., Fuentes, M., Riccardi, V.M., Holcombe, J.H., Nitowsky, H.M., Sachs, G., Anderson, C.E., Duchon, M.A., Owens, R., Merkatz, I., New, M.I., 1980. Amniotic fluid concentrations of delta-5 and delta-4 steroids in fetuses with congenital adrenal hyperplasia due to 21-hydroxylase deficiency and in anencephalic fetuses. J. Clin. Endocrinol. Metab. 51, 223–229.

Phoenix, C.H., 1974. Prenatal testosterone in the nonhuman primate and its consequences for behavior. In: Friedman, R.C., Richart, R.M., Van De Wiele, R.L. (Eds.), Sex Differences in Behavior. Wiley, New York, pp. 19–32.

Provins, K.A., 1997. Handedness and speech: A critical reappraisal of the role of genetic and environmental factors in the cerebral lateralization of function. Psych. Rev. 104, 554–571.

Satz, P., Orsini, D.L., Saslow, E., Henry, R., 1985. The pathological left-handedness syndrome. Brain and Cognition 4, 27–46.

Schachter, S.C., 1994. Handedness in women with intrauterine exposure to diethylstilbestrol. Neuropsychologia 32, 619–623.

Schachter, S., Ransil, B.J., Geschwind, N., 1987. Associations of handedness with hair color and learning disabililites. Neuropsychologia 25, 269–276.

Scheirs, J.G.M., Vingerhoets, A.J.J.M., 1995. Handedness and other laterality indices in women prenatally exposed to DES. J. Clin. Exp. Neuropsychol 17, 725–730.

Slijper, F.M.E., 1984. Androgens and gender role behavior in girls with congenital adrenal hyperplasia (CAH). In: De Vries, G.J., De Bruin, J.P.C., Uylings, H.B.M., Corner, M.A. (Eds.), Progress in Brain Research. Elsevier, Amsterdam, pp. 417–422.

Smail, P.J., Reyes, F.I., Winter, J.S.D., Faiman, C., 1981. The fetal hormone environment and its effect on the morphogenesis of the genital system. In: Kogan, S.J., Hafez, E.S.E. (Eds.), Pediatric Andrology. Martinus Nijhoff, The Hague, pp. 9–19.

Smith, L.L., Hines, M., 2000. Language lateralization and handedness in women prenatally exposed to diethylstilbestrol (DES). Psychoneuroendocrinology 25, 497–512.

Springer, S.P., 1986. Dichotic listening. In: Hannay, H.J. (Ed.), Experimental Techniques in Human Neuropsychology. Oxford University Press, New York, pp. 138–166.

Studdert-Kennedy, M., Shankweiler, D., 1970. Hemispheric specialization for speech perception. J. Acoustic Soc. Am. 48, 579–594.

Tirosh, E., Rod, R., Cohen, A., Hochberg, Z., 1993. Congenital adrenal hyperplasia and cerebral lateralizations. Ped. Neurol. 9, 198–201.

Voyer, D., 1996. On the magnitude of laterality effects and sex differences in functional literalities. Laterality 1, 51–83.

Wudy, S.A., Dörr, H.G., Solleder, C., Djalali, M., Homoki, J., 1999. Profiling steroid hormones in amniotic fluid of midpregnancy by routine stable isotope dilution/gas chromatography-mass spectrometry: Reference values and concentrations in fetuses at risk for 21-hydroxylase deficiency. J. Clin. Endocrinol. Metab. 84, 2724–2728.

Zaidel, E., 1979. On measuring hemispheric specialization in man. In: Rybak, B. (Ed.), Advanced Technology: Proceedings of the NATO Advanced Study Institute on Advanced Technobiology Paris, France, June 30–July 12, 1978. Nijoff and Noordhoff, Alphen aan den Rijn, Netherlands, pp. 365–403.

Zucker, K.J., Bradley, S.J., Oliver, G., Blake, J., Fleming, S., Hood, J., 1996. Psychosexual development of women with congenital adrenal hyperplasia. Horm. Behav. 30, 300–318.