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Spatial abilities following prenatal androgen abnormality: targeting and mental rotations performance in individuals with congenital adrenal hyperplasia

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Abstract

In most mammals, behaviors that show sex differences are influenced by androgen during early life. In the current study, the hypothesis that androgen influences the development of human spatial abilities was investigated. Participants included 40 females and 29 males with congenital adrenal hyperplasia (CAH), a genetic disorder that causes overproduction of adrenal androgens beginning prenatally, and 29 unaffected female and 30 unaffected male relatives of individuals with CAH. Participants ranged in age from 12–45 years. Measures of spatial abilities included two mental rotations tasks and two targeting tasks, all of which showed large sex differences favoring males in the unaffected relative controls. Females with CAH (exposed to higher than normal levels of androgen prenatally) performed better than unaffected females on the targeting tasks, and resembled unaffected males and males with CAH in this respect. However, females with CAH did not perform better than unaffected females on the measures of mental rotations abilities. Males with CAH showed unaltered performance on the targeting tasks, and impaired performance on the mental rotations tasks. Results are discussed in terms of differences in experiential and hormonal contributions to different spatial abilities, as well as in terms of possible differences in critical periods for hormonal influences on targeting versus mental rotations abilities. Specifically, we speculate that, although androgen may influ-

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ence targeting abilities prenatally, if hormones influence the development of mental rotations ability, they do so at some other time, perhaps during the first six months of postnatal life.

Keywords: Spatial abilities; Androgen; Sex differences; Targeting; Mental rotations; CAH; Critical periods; Development; Behavior; Gender

Although males and females do not differ in general intelligence, there are sex differences in specific aspects of cognitive performance, including some spatial and mathematical abilities at which males excel on average, and verbal fluency at which females excel on average (Collaer and Hines, 1995; Halpern, 2000). The largest differences are those in certain spatial abilities, particularly mental rotations ability (the ability to rotate figures rapidly and accurately in the mind) and targeting performance (the ability to aim projectiles accurately at a specified point in space).

The magnitude of sex differences in human behavior can be described using standard deviation ("*d*") units. Group differences in behavior, including sex differences, are considered large if d is 0.8 or greater, moderate if *d* is about 0.5 and small if *d* is 0.2 or less (Cohen, 1988). Meta-analytic studies suggest that the sex difference in three-dimensional mental rotations performance is large ($d = 0.9$), whereas that for two dimensional performance is small to moderate ($d = 0.3$–0.5) (Linn and Petersen, 1985; Voyer et al., 1995). The sex difference in targeting appears to be larger than that on either type of mental rotations task ($d = 1.3$–1.9) (Jardine and Martin, 1983; Watson and Kimura, 1991). Sex differences in other aspects of spatial abilities, such as spatial perception (the ability to position stimuli (e.g., lines) accurately, despite distracting information (e.g., a tilted frame)) and spatial visualization (the ability to use analytic strategies to manipulate spatial information) are smaller (d = 0.38–0.56 for spatial perception and $d = 0.16$, for spatial visualization) (Linn and Petersen, 1985; Voyer et al., 1995), as are sex differences in mathematical reasoning ($d = 0.32$) (Hyde et al., 1990) and verbal fluency (the ability to produce words with certain characteristics rapidly) ($d = 0.33$–0.53) (Kolb and Whishaw, 1985; Hyde and Linn, 1988; Spreen and Strauss, 1991).

It has been suggested that sex differences in spatial abilities may relate in part to the early hormone environment, particularly to levels of androgens prenatally (Hines, 1990; Kimura, 1992, 1999), but see also Hines (2002) for a revised perspective based on more recent findings. The original suggestion linking hormones to spatial abilities derives from evidence that the early hormone environment has dramatic influences on the development of behaviors that show sex differences in other mammals. For instance, female rats and rhesus macaques exposed prenatally or neonatally to higher than normal levels of androgens show more male-typical play behavior as juveniles and more male-typical sexual behavior as adults (Goy and McEwen, 1980; Meaney and Stewart, 1981). Spatial abilities have not been studied as extensively as play behavior and sexual behavior. However, male rats perform better than female rats on some spatial tasks, and females exposed to elevated levels of androgen or its metabolites during early development show enhanced performance on these tasks,

whereas males exposed to reduced levels of androgens show impaired performance (Williams and Meck, 1991).

Evidence regarding similar hormonal influences on human spatial abilities has come from studies of individuals exposed to abnormal levels of androgens beginning before birth (e.g., because of genetic disorders), and from studies relating normal variability in hormones during early development to subsequent spatial performance.

The genetic disorder, congenital adrenal hyperplasia (CAH), causes overproduction of adrenal androgens beginning prenatally. The underlying problem is deficiency in an enzyme, usually 21 hydroxylase (21-OH), needed to produce cortisol (New and Levine, 1984). As a consequence of the deficiency, precursors to cortisol are shunted into the androgen pathway, causing overproduction of testosterone and other androgens, and higher than normal levels of androgens in developing female fetuses (Pang et al., 1980). Testosterone levels in male fetuses generally are not elevated (Pang et al., 1980; Wudy et al., 1999), perhaps because the testes can decrease hormone production in response to the adrenal excess. Girls with CAH show increased male-typical toy, playmate and activity preferences (Ehrhardt et al., 1968; Ehrhardt and Baker, 1977; Slijper, 1984; Dittmann et al., 1990; Berenbaum and Hines, 1992; Zucker et al., 1996), suggesting that their prenatal exposure to elevated androgen has influenced these aspects of their sex-typical behavior.

Studies of spatial abilities in females with CAH have produced inconsistent outcomes. Some have reported that they show improved (i.e., more male-typical) performance compared to matched controls of the same sex or to unaffected sisters or female cousins (Perlman, 1973; Resnick et al., 1986; Hampson et al., 1998). However, other studies have found no differences between females with CAH and same sex siblings or matched controls on spatial tasks (Baker and Ehrhardt, 1974; McGuire et al., 1975; Helleday et al., 1994) or have even found impaired spatial performance in the CAH group (Helleday et al., 1994). Studies of males with CAH have generally found no differences from controls in spatial performance (Baker and Ehrhardt, 1974; McGuire et al., 1975; Resnick et al., 1986), although one study reported impaired spatial performance in CAH boys (Hampson et al., 1998). These differences in outcomes do not relate systematically to the age of the participants, the type of control group (matched versus relatives) or to the specific measures of spatial ability that were used (see Table 1). However, all the studies used small samples, ranging from 7–22 females and 5–16 males with CAH.

Studies relating normal variability in the early hormone environment to spatial ability have also produced inconsistent results. Androgen in umbilical cord blood at birth has been found to relate negatively in six year old girls to a composite spatial ability score based on four tests (Jacklin et al., 1988). Similarly, testosterone in amniotic fluid has been found to relate negatively to performance on a block-building task in four-year-old girls (Finegan et al., 1992). These results are the opposite of prediction, assuming that spatial ability is something at which males excel. However, the measures of spatial ability used in the studies did not show sex differences, and so might not have been appropriate measures of hormonal influences (Collaer and Hines, 1995). The same children who were studied at age 4 years by Finegan et al. (1992), were studied again at age 7, and testosterone in girls related positively to

Table 1
Studies of spatial abilities in individuals with Congenital Adrenal Hyperplasia (CAH)

Source	Participants CAH	Control	Age in years	Findings and type of task
Perlman, 1973	11F	11 (MT)	3–15	CAH F better (a)
Baker and Ehrhardt, 1974	13F, 8M	11F, 14M (RL)	4–26	No differences M or F (a,c)
McGuire et al., 1975	15F, 16M	31 (MT)	5–30	No differences M or F (a)
Resnick et al., 1986	17F, 8M	13F, 14M (RL)	11–31	CAH F better on 3 (a,c,c), but no different on 2 (a,a). CAH M no differences
Helleday et al., 1994	22F	22 (MT)	17–34	CAH F worse on 1 (b), but no different on 3 (a,a,c)[a]
Hampson et al., 1998	7F, 5M	5F, 4M (RL)	8–12	CAH F better, CAH M worse on 1 (a)

Note. M = Males. F = Females. (MT) = Matched. (RL) = Relative. (a) Spatial Visualization Tasks. (b) Spatial Perception Task. (c) Mental Rotations Task.

[a] For example, CAH F worse on 1 (b), but no different on 3 (a,a,c) means that CAH females performed worse than controls on a spatial perception task (b), but no different from controls on three other tasks, two of which were spatial visualization tasks (a,a) and one of which was a mental rotations task (c).

speed of mental rotations, but not to accuracy. Findings for boys were less clear, but suggested that higher testosterone predicted slower performance (Grimshaw et al., 1995).

No studies have investigated relationships between the early hormone environment and targeting in either individuals with CAH or healthy individuals.

Thus, studies relating prenatal hormones to spatial abilities in individuals with CAH, as well as studies relating normal variability in hormones to subsequent spatial performance, have produced inconsistent results, perhaps owing to methodological problems. In the current study, we attempted to address these problems by recruiting a large sample of individuals with CAH and by using measures of spatial abilities that show large and reliable sex differences.

1. Method

1.1. Participants

One hundred and twenty eight participants, 40 females and 29 males with CAH, and 29 unaffected female and 30 unaffected male relatives of individuals with CAH, took part in the study. Participants ranged in age from 12–45 years. Ages of groups (in years) were as follows: females with CAH (Range = 12–44, median = 17, M = 19.50, SD = 7.30), unaffected female relatives (Range = 12–32, median = 19, M = 19.26, SD = 5.95), males with CAH (Range = 12–40, median = 17, M = 20.27, SD = 8.43) unaffected male relatives (Range = 12–45 years, median = 16,

M = 18.00, SD = 6.81). All participants were European with the exception of one male with CAH and his unaffected sister, who were Asian (Indian, Pakistani, or Bangladeshi).

Participants with CAH were recruited through endocrinologists at Middlesex and Great Ormond Street Hospitals, London (n = 35; 22 female, 13 male) or via a CAH Support Group in the UK (n = 34; 18 female, 16 male). Unaffected relatives were recruited through the families of individuals with CAH. Sixty-six of the 69 patients with CAH were deficient in the enzyme 21-hydroxylase. Sixty-two had the salt-losing form of the disorder and 4 did not. For the remaining three participants with CAH, medical records confirming 21-OH deficiency and salt losing status were not available. Unaffected siblings (n = 57) and first cousins (n = 2) served as controls. Written consent was obtained from participants. For those under the age of 18 years, parents also provided consent.

1.2. Measures

Because prenatal exposure to androgen would be expected to influence behaviors that show sex differences, we selected measures of mental rotations and targeting ability that show substantial sex differences. To increase reliability of measurement, we used two measures of each ability. Data were analyzed for individual measures, as well as for composites of the two measures. (Composite scores were formed by calculating z scores based on the sample of 128 participants for each of the two measures and then averaging them.) In addition to these dependent measures that were hypothesized to relate to prenatal androgen exposure, measures of general intelligence and age were included for control purposes (i.e., to ensure that any observed group differences in mental rotations or targeting performance did not reflect underlying differences in intelligence or age). A measure of childhood gender role behavior was also administered to determine if our sample showed the expected sex differences and CAH-related differences in this respect.

1.2.1. Spatial tasks

1.2.1.1. 3-D mental rotations The revised Vandenberg and Kuse (1978) Mental Rotations Test (Peters et al., 1995) provided a measure of three-dimensional mental rotations ability. This paper and pencil test is based on the experimental stimuli of Shepard and Metzler (1971) and requires participants to rotate objects mentally in three-dimensional space. It consists of 4 practice items followed by 24 test items, divided into two sets. Three minutes are allowed for each set of 12 items, with a 1 min rest between them. For each item, the target stimulus is presented on the left and participants must determine which two of four stimuli to the right are rotated versions of the target (as opposed to different shapes). Each item has two correct answers and a point is given only if both correct answers are provided. The maximum possible score is 24.

1.2.1.2. 2-D mental rotations The Spatial Relations sub-test of the Primary Mental Abilities Test (Thurstone, 1963) provided a measure of two-dimensional mental

rotations ability. This paper and pencil test requires participants to rotate objects mentally in two-dimensional space. It consists of 4 practice items followed by 30 test items. Each item includes a two-dimensional target figure on the left and five rotated figures on the right, each either identical to, or a mirror image of, the target. For each target there are 1–3 correct matches. There is a seven-minute time limit for the test, and the score is the number of correct matches minus the number of incorrect matches. The maximum possible score is 70.

1.2.2. Targeting tasks

1.2.2.1. Ball throw For the ball throw task, the target consisted of a 90 cm × 90 cm plastic target covered with black Velcro, with a white dot in the center. Participants stood 3 m from the target, and threw ping-pong balls, covered with fabric designed to stick to Velcro, at the center dot using the hand with which they were most comfortable. All throws were overhand. Participants were given 4 practice throws followed by 10 test throws.

1.2.2.2. Dart throw The dart throw task was the same as the ball throw task except that the board was made from white polystyrene, the center dot was black, and darts were used to aim at the board.

For both targeting tasks, the dependent measure was the mean distance in centimeters from the center dot for the ten test throws. For both tasks, data were transformed prior to analysis, by subtracting the mean distance from the maximum possible, to make higher scores reflect better performance.

1.2.3. Control measures

1.2.3.1. Vocabulary Vocabulary sub-tests of the Wechsler Intelligence Scale for Children (WISC-III) (for 12–15 year olds) and the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (for those 16 years and over) provided estimates of general intelligence. The dependent measure was the age-scaled vocabulary score.

1.2.3.2. Age The age of each participant at the time of testing was recorded.

1.2.3.3. Childhood gender role behavior The pre-school activities inventory (PSAI) was used to assess childhood gender role behavior (Golombok and Rust, 1993a, 1993b). This standardized inventory includes 24 items measuring frequency of play with respect to a variety of sex-typed toys, games and activities. Higher scores on the inventory represent more male-typical behavior. The PSAI is usually completed by parents describing the behavior of their 2–7 year old children. Participants in our study completed the inventory to describe their own behavior retrospectively, for the period when they were between the ages of 2 and 7 years. We mailed the PSAI to participants after the rest of the study had been completed. It was returned by 35 females and 26 males with CAH and by 23 unaffected female and 26 unaffected male relatives.

1.3. Statistical analyses

Analyses of covariance (ANCOVAs) were used to examine the effects of sex (male, female) and diagnosis (CAH, unaffected relative) on task performance. In addition, planned comparisons were used to evaluate specific hypotheses. These compared: 1. unaffected females to unaffected males, to verify the existence (or absence) of sex differences on tasks; 2. females with CAH to unaffected females to determine if prenatal exposure to high levels of androgen enhances performance on tasks at which males generally excel; and, 3. males with CAH to unaffected males to determine if prenatal exposure to excess adrenal androgen either enhances or impairs performance on tasks at which males generally excel. An alpha level of 0.05 was used and all comparisons were two-tailed. Probability levels as well as effect sizes (d) are reported for the planned comparisons.

2. Results

2.1. Initial analyses

Two-way (Sex × Diagnosis) analyses of variance (ANOVAs) were used to determine if there were group differences on the control variables, vocabulary and age (see Table 2). There were no significant main or interaction effects for vocabulary ($F(1, 124) = 0.006$, $p = 0.937$, $F(1, 124) = 0.223$, $p = 0.637$ and $F(1, 124) = 1.54$, $p = 0.217$ for the main effects of sex and diagnosis and the interaction, in order) or for age ($F(1,124) = 0.036$, $p = 0.851$, $F(1, 124) = 0.951$, $p = 0.331$ and

Table 2
Age, vocabulary, mental rotations, targeting and recalled childhood gender role behavior in females and males with CAH and in unaffected relatives

	Females Unaffected (*n*=29)	CAH (*n*=40)	Males Unaffected (*n*=30)	CAH (*n*=29)
Age	18.74 (5.91)	19.07 (7.39)	17.57 (6.68)	19.86 (8.48)
Vocabulary	9.31 (2.41)	8.52 (2.52)	8.77 (2.24)	9.10 (2.66)
3-D, MR	7.31 (3.47)	8.00 (4.53)	11.27 (5.47)[a]	8.31 (4.22)
2-D, MR	34.55 (11.78)	36.40 (18.47)	43.63 (15.13)[a]	37.34 (14.38)
Dart Throw	44.63 (9.84)[b]	49.33 (4.79)	51.08 (7.19)	49.77 (8.05)
Ball Throw	42.40 (8.17)[b]	45.77 (6.15)	49.88 (5.97)	48.11 (5.82)
PSAI[c]	31.42 (15.49)[b]	57.68 (14.94)	73.13 (9.44)	69.79 (8.49)

Note. Data are Means (SDs). 3 - D=3 - Dimensional. 2 - D=2 - Dimensional. MR = Mental Rotations. PSAI = Preschool Activities Inventory.

[a] Unaffected males score significantly higher than all other groups.

[b] Unaffected females score significantly lower than all other groups.

[c] $N = 110$ for the PSAI: 35 females and 26 males with CAH; 23 female and 26 male controls.

F (1, 124) = 0.626, $p = 0.430$ for the main effects of sex and diagnosis and the interaction, in order).

Correlations between control variables and spatial measures were also examined. Both three-dimensional and two-dimensional mental rotations, as well as the mental rotations composite, correlated positively with vocabulary scores ($r = 0.233$, $p = 0.008$, $r = 0.336$, $p < 0.001$, and $r = 0.321$, $p < 0.001$, in order), but not with age ($r = 0.004$, $p = 0.968$, $r = -0.089$, $p = 0.318$ and $r = -0.048$, $p = 0.589$, in order). In contrast, performance on both the ball and dart throw tasks, as well as the targeting composite, correlated significantly with age ($r = 0.189$, $p = 0.033$; $r = 0.297$, $p < 0.001$; $r = 0.280$, $p < 0.001$, in order), but not vocabulary ($r = 0.089$, $p = 0.32$; $r = 0.128$, $p = 0.15$; $r = 0.125$, $p = 0.16$, in order).

We also calculated correlations between the two measures comprising each composite. The two measures of mental rotations correlated ($r = 0.571$, $p < 0.001$) as did the two measures of targeting ($r = 0.499$, $p < 0.001$).

2.2. Mental rotations abilities

Two way (Sex×Diagnosis) ANCOVAs were carried out on each of the two measures of mental rotations ability and on the mental rotations composite (see Table 2 and Fig. 1). Because vocabulary correlated with the mental rotations measures, it served as the covariate in these analyses. In addition to these ANCOVAs, the three planned comparisons (relative females versus relative males, females with CAH versus relative females, and males with CAH versus relative males) were carried out, again using vocabulary as a covariate.

For the Mental Rotations Test, there was a significant main effect of sex (F (1, 123) = 7.480, $p = 0.007$) and a significant sex by diagnosis interaction (F (1, 123) = 7.143, df (1, 119), $p = 0.009$), but no main effect of diagnosis (F (1, 123) = 1.742, $p = 0.189$). The planned comparisons revealed that unaffected males performed better than unaffected females (F = 12.245, df (1, 56), $p = 0.001$, $d = 0.89$), females with CAH and unaffected females performed similarly (F = 0.924, df (1, 66), $p = 0.340$, $d = 0.17$), and males with CAH performed worse than unaffected males (F = 6.701, df (1, 56), $p = 0.012$, $d = 0.58$).

For the Spatial Relations Test, there were no main effects of sex or diagnosis (F (1, 123) = 3.696, $p = 0.057$ and F (1, 123) = 0.441, $p = 0.508$, in order), but there was an interaction (F (1, 123) = 4.196, $p = 0.043$). The planned comparisons revealed that unaffected males performed better than unaffected females (F = 8.425, df (1, 56), $p = 0.005$, $d = 0.68$), females with CAH and unaffected females performed similarly (F = 0.740, df (1, 66), $p = 0.393$, $d = 0.12$) and males with CAH performed worse than unaffected males (F = 4.289, df (1, 56), $p = 0.043$, $d = 0.42$).

For the mental rotations composite, the two way ANCOVA indicated a main effect of sex (F (1, 123) = 7.235, $p = 0.008$), an interaction between sex and diagnosis (F (1, 123) = 7.413, $p = 0.007$), and no main effect of diagnosis (F (1, 123) = 1.314, $p = 0.254$). The planned comparisons revealed the same pattern of results as for the individual measures. Unaffected males performed better than unaffected

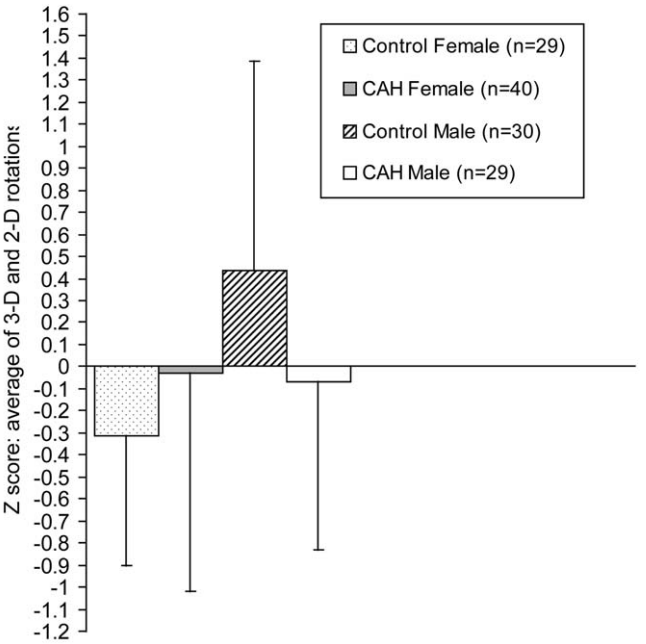

Fig. 1. Mental rotations performance in males and females with and without CAH. The pictured data are means and standard deviations for averaged Z scores for performance on a two-dimensional mental rotations task and a three-dimensional mental rotations task. Unaffected relative controls show the predicted sex difference in performance ($p < 0.001$). However, females with CAH do not differ from unaffected female relatives, and males with CAH perform worse than unaffected male relatives ($p = 0.008$).

females (F = 14.397, df (1, 56), $p < 0.001$, $d = 0.92$), females with CAH and unaffected females performed similarly (F = 1.057, df (1, 66), $p = 0.308$, $d = 0.16$) and males with CAH performed worse than unaffected males (F = 7.658, df (1, 56), $p = 0.008$, $d = 0.58$).

Finally, because of the large age range in our sample, and because most studies of sex differences in mental rotations performance have focused on those 30 years of age or younger, we conducted the same analyses on the 117 participants in this age range (i.e., ≤30 years). Results were identical to those reported above in terms of significant and insignificant effects.

2.3. Targeting abilities

Similar two-way ANCOVAs and planned comparisons to those used for mental rotations abilities were used to analyze data for targeting. However, because age, but not vocabulary, correlated with targeting performance, these analyses included age as the covariate (see Table 2 and Fig. 2).

For dart throwing, the ANCOVA indicated a main effect of sex (F (1, 123) = 7.684, $p = 0.006$), and an interaction between sex and diagnosis (F (1, 123) = 6.864, $p = 0.010$), but no main effect of diagnosis (F (1, 123) = 0.981, $p = 0.324$).

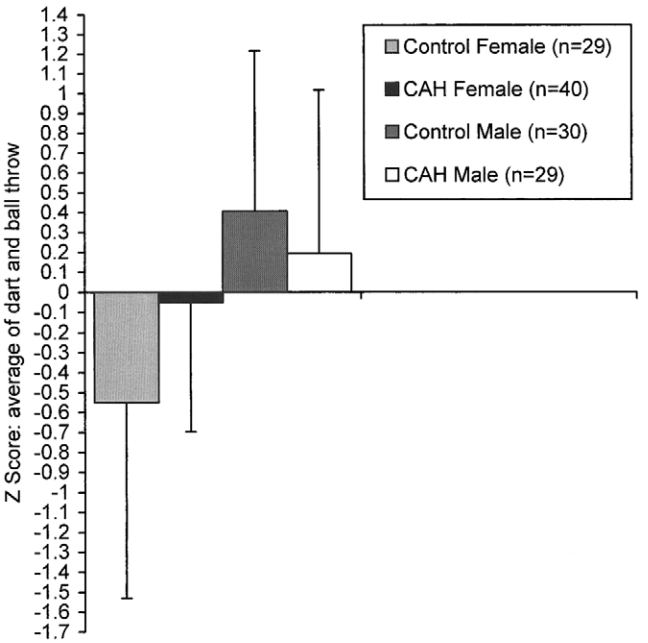

Fig. 2. Targeting performance in males and females with and without CAH. The pictured data are means and standard deviations for averaged *Z* scores for performance on a dart throw task and a ball throw task. Unaffected relative controls show the predicted sex difference in performance ($p < 0.001$). In addition, females with CAH perform better than unaffected female relatives ($p = 0.009$). Males with CAH do not differ from unaffected male relatives.

The planned comparisons indicated that unaffected males performed better than unaffected females (F = 11.625, df (1, 56), $p = 0.001$, $d = 0.76$), females with CAH performed better than unaffected females (F = 7.802, df (1, 66), $p = 0.007$, $d = 0.64$), and males with CAH performed similarly to unaffected males (F = 1.549, df (1, 56), $p = 0.218$, $d = 0.17$).

For ball throwing, there was again a main effect of sex (F = (1, 123) = 18.657, $p < 0.001$), an interaction between sex and diagnosis (F (1, 123) = 5.820, $p = 0.017$), and no main effect of diagnosis (F (1, 123) = 0.216, $p = 0.643$). The planned comparisons indicated that unaffected males performed better than unaffected females (F = 19.377, df (1, 56), $p < 0.001$, $d = 0.78$), the difference between females with CAH and unaffected females approached significance (F = 3.745, df (1, 66), $p = 0.057$, $d = 0.47$), and males with CAH did not differ from unaffected males (F = 2.325, df (1, 56), $p = 0.133$, $d = 0.30$).

Results for the targeting composite resembled those for the individual measures. There was a main effect of sex (F (1, 123) = 17.997, $p < 0.001$), and an interaction between sex and diagnosis (F (1, 123) = 9.019, $p = 0.003$), but no main effect of diagnosis (F (1, 123) = 0.750, $p = 0.388$). The planned comparisons indicated that unaffected males performed better than unaffected females (F = 22.823, df (1, 56), $p < 0.001$, $d = 1.07$), females with CAH performed better than unaffected females

(F = 7.151, df (1, 66), $p = 0.009$, $d = 0.67$) and males with CAH did not differ from unaffected males (F = 2.469, df (1, 56), $p = 0.122$, $d = 0.26$).

As for mental rotations, analysis of targeting data for those participants 30 years of age or younger produced the same pattern of significant and insignificant results.

2.4. Childhood gender role behavior

A two-way ANOVA on data for recalled childhood gender role behavior indicated significant main effects of sex (F (1,106) = 121.954, $p < 0.001$), and diagnosis (F (1, 106) = 22.123, $p < 0.001$), as well as a significant interaction (F = (1, 106) = 36.906, $p < 0.001$). Planned comparisons indicated that unaffected males scored higher (i.e., in a more male-typical direction) than unaffected females (F (1, 47) = 132.963, $p < 0.001$, $d = 3.35$), females with CAH scored higher than unaffected females (F (1, 56) = 41.652, $p < 0.001$, $d = 1.73$) and males with CAH did not differ from unaffected males (F (1, 50) = 1.803, $p = 0.185$, $d = 0.38$).

3. Discussion

We observed very different relationships between CAH and the two types of spatial abilities hypothesized to relate to prenatal androgen exposure (mental rotations and targeting). For mental rotations, males with CAH showed impaired performance, whereas the performance of females with CAH was unaffected. This outcome is not consistent with the hypothesis that prenatal androgen exposure enhances this aspect of spatial ability in females. In contrast, data for targeting were consistent with the hypothesis, with CAH females outperforming unaffected females and CAH and unaffected males performing similarly.

The outcomes for targeting abilities are similar to those seen in numerous prior studies of childhood play behavior (Ehrhardt et al., 1968; Ehrhardt and Baker, 1977; Slijper, 1984; Dittmann et al., 1990; Berenbaum and Hines, 1992; Zucker et al., 1996). In those studies, toy, playmate and activity preferences have been found to be more male-typical in girls with CAH than in unaffected relatives or matched controls, while boys with CAH usually have been found to behave similarly to unaffected boys. No prior studies have looked at targeting abilities in males and females with CAH, however. Thus, our data extend previously observed influences of prenatal androgen exposure on human behavior to include one aspect of spatial abilities, that is, targeting. However, because targeting performance involves muscle systems as well as neural systems, we cannot rule out the possibility that the action of androgen is on the developing musculature rather than on the developing brain. Studies using measures of targeting ability, independent of muscle strength, e.g., computerized tasks, could help evaluate this possibility.

The lack of a relationship between CAH and mental rotations performance in females, and the impaired performance in males with CAH were not predicted. However, neither outcome is unprecedented. One prior study of five boys with CAH reported impaired spatial performance compared to four unaffected male relatives

(Hampson et al., 1998). In addition, some prior studies have reported enhanced performance in CAH females on some spatial tasks (Perlman, 1973; Resnick et al., 1986; Hampson et al., 1998), but others have not (Baker and Ehrhardt, 1974; McGuire et al., 1975), or have even found impaired performance (Helleday et al., 1994). All of these prior studies had methodological limitations, notably small samples, or the use of measures that do not show large sex differences.

Our study had a markedly larger sample than any prior study. In addition, both of the mental rotations tasks used in our study showed substantial sex differences. Thus, the current report is not subject to these particular methodological limitations. It also seems unlikely that our sample of CAH patients and relatives is atypical, given that they showed the predicted pattern of results for targeting abilities, and the previously observed pattern of results for recalled childhood play behavior. Thus, it would seem that although the elevated androgen experienced prenatally by girls with CAH contributes to more male-typical childhood play and targeting performance, it does not cause more male-typical mental rotations performance. In addition, in males, CAH appears to be associated with impaired mental rotations performance, but not with alterations in targeting or childhood play.

One question raised by our results and those of prior studies is why increased spatial performance in females with CAH is sometimes, but not always, observed. One possible explanation relates to the tendency for positive results to be published, whereas negative results are not (Maccoby and Jacklin, 1974). It is a popular supposition that androgen relates to spatial abilities (e.g., Kimura, 1992, 1999), and many researchers with access to relatively small samples of patients might examine this possibility. However, those finding no relationship between CAH and spatial performance would be unlikely to publish their results, because the lack of an effect could be attributed to the small sample. In contrast, those finding a difference would find publication easier. Alternatively, differences in outcomes could relate to the use of different measures of spatial abilities in different studies, particularly given that the results of the current study suggest that mental rotations and targeting abilities show very different relationships to the early hormone environment. Additional studies, using a range of measures in large samples of individuals with CAH, would help resolve this issue.

It might be suggested that differences in adult hormone levels could have influenced our results, particularly for mental rotations performance. For example, some studies have found differences in spatial abilities at different phases of the menstrual cycle, and have suggested that high levels of circulating estrogen impair these abilities (Hampson, 1990; Phillips and Silverman, 1997). However, in some cases mental rotations performance has not been found to relate to menstrual cycle phase (Gordon et al., 1986; Gordon and Lee, 1993; Epting and Overman, 1998; Peters et al., 1995; Phillips and Silverman, 1997), or to other causes of variability in estrogen (Miles et al., 1998; Liben et al., 2002). Similarly, some studies suggest that high testosterone levels in adulthood improve spatial performance (Janowsky et al., 1994), whereas others suggest that androgen does not influence mental rotations (Alexander et al., 1998; O'Connor et al., 2001). Regardless, even assuming that estrogen impairs mental rotations performance and testosterone enhances it, explanation of our results in

terms of differences in circulating hormone levels would require either that estrogen levels were systematically higher, or testosterone levels systematically lower, in CAH than unaffected individuals. It is unlikely that either is the case. Nevertheless, additional research may be needed to resolve this issue completely. One approach would be to study children with CAH, who are not yet subject to the hormonal changes of puberty.

Finally, what could explain the difference in our results for targeting versus mental rotations abilities? It is possible that, unlike targeting, mental rotations ability is not related to the early hormone environment. Instead, sex differences could result entirely from other factors, including, (in addition to possible effects of adult hormone levels) differential education, socialization and life experiences of girls and boys. For instance, mental rotations performance relates to academic specialization, with mathematics and physical science majors outperforming humanities and social sciences majors (Casey and Brabeck, 1989; Peters et al., 1995). Also, there are practice effects on mental rotations performance that generalize to other versions of the test, suggesting that prior experience with this type of task may improve performance (Casey and Brabeck, 1989; Peters et al., 1995). Playing with boys and engaging in boy typical activities also has been associated with enhanced spatial abilities in girls (Serbin and Connor, 1979; Sprafkin et al., 1983), suggesting that sex differences in mental rotations performance could arise from sex differences in childhood play experiences. However, in our sample, mental rotations performance and male-typical activities in childhood were clearly dissociated in some groups. For instance, both females and males with CAH recalled high levels of male-typical activities, but did not show enhanced mental rotations performance. This suggests that engaging in male-typical activities as a child, at least as assessed by the PSAI, does not necessarily improve this particular aspect of spatial ability.

Although our results suggest that prenatal androgen elevation does not enhance mental rotations performance in females, other early hormone influences cannot be ruled out. Androgen levels are elevated in developing males not only prenatally, but also during the first six months of postnatal life (Smail et al., 1981). It is possible that this postnatal elevation influences mental rotations abilities. This would imply that hormones influence different spatial abilities at different times during development, perhaps relating to differences in the time when the relevant neural systems are at a critical stage. In rats and rhesus monkeys, different behaviors are influenced by androgen at slightly different times (Christensen and Gorski, 1978; Goy et al., 1988). In female rhesus monkeys, for instance, testosterone treatment early in gestation masculinizes some aspects of social behavior, such as grooming their mothers, but does not influence rough-and-tumble play. In contrast, the same hormonal treatment late in gestation masculinizes rough-and-tumble play without influencing maternal grooming (Goy et al., 1988).

The hormonal abnormality in females with CAH is confined largely to the prenatal period. Postnatally, hormone levels are regulated by treatment with corticosteroids. It is possible that the neural (or other e.g., muscular) systems underlying targeting develop prenatally, while those underlying mental rotations performance develop during the early postnatal period. In this case, improved targeting, but not mental

rotations, in girls with CAH could be explained. This explanation also could account for the deficit in mental rotations, but not targeting, in boys with CAH. In boys with CAH, it appears that testosterone is usually not elevated prenatally (Pang et al., 1980; Wudy et al., 1999). In addition, males with CAH typically do not show increased male-typical behavior; in fact, there are occasional reports that they show reduced male-typical behavior (e.g, Hines, 2002). One possible explanation is that feedback mechanisms normalize androgen levels during some periods of development in males with CAH, but produce reduced androgen levels during others. Specifically, after an initial increase in adrenal androgens, the testes may reduce androgen production to compensate for the increased adrenal output, thus preventing elevated androgens during most of prenatal development in CAH males. After birth, testicular androgen production may remain low, while corticosteroid treatment reduces adrenal androgen, producing lower than normal levels of androgen neonatally in boys with CAH (Pang et al., 1979). Therefore, boys with CAH may miss all or part of the androgen surge that normally occurs during the first six months of life (Smail et al., 1981), thus affecting steroid sensitive neural systems undergoing critical developmental processes at that time. There is insufficient evidence to pinpoint the time when neural systems involved in mental rotations performance develop, but the relevant circuitry includes portions of parietal cortex (e.g., Jordan et al., 2001; Just et al., 2001; Vingerhoets et al., 2001), and cortical systems continue to develop postnatally in humans, with parietal areas among the last to mature (Spreen et al., 1995). Thus, although this explanation is speculative, boys with CAH may show reduced mental rotations abilities, because they do not experience the same postnatal surge in androgen as other boys. Studies relating levels of hormones during infancy to subsequent mental rotations ability would be useful to help evaluate this possibility.

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