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Motor development in individuals with congenital adrenal hyperplasia: Strength, targeting, and fine motor skill

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Summary

This study investigated early androgen influence on the development of human motor and visuomotor characteristics. Participants, ages 12 to 45 years, were individuals with congenital adrenal hyperplasia (CAH), a disorder causing increased adrenal androgen production before birth (40 females, 29 males) and their unaffected relatives (29 females, 30 males). We investigated grip strength and visuomotor targeting tasks on which males generally outperform females, and fine motor pegboard tasks on which females generally outperform males. Physical characteristics (height and weight) were measured to explore whether body parameters could explain differences in motor skills. Females with CAH were stronger and showed better targeting than unaffected females and showed reduced fine visuomotor skill on one pegboard measure, with no difference on the other. Males with CAH were weaker than unaffected males in grip strength but did not differ on the targeting or pegboard measures. Correction for body size could not explain the findings for females, but suggests that the reduced strength of males with CAH may relate to their smaller stature. Further, the targeting advantage in females with CAH persisted following adjustment for their greater strength. Results in females support the hypothesis that androgen may masculinize, or promote, certain motor characteristics at which males excel, and contribute to

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Conflicts of Interest

All authors declare that they are free of conflicts of interest regarding this research.

Contributors

The contributions of each of the authors to the paper were as follows: Dr. Collaer analyzed the data and co-authored the paper. Drs. Brook, Conway, and Hindmarsh contributed to participant recruitment, served as medical and endocrine consultants, and co-authored the paper. Dr. Hines designed the study, obtained funding, supervised data collection, and co-authored the paper.

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defeminization of certain fine motor characteristics at which females excel. Thus, these data suggest that organizational effects of androgens on behavior during prenatal life may extend to motor characteristics and may contribute to general sex differences in motor-related behaviors; however, alternative explanations based on activational influences of androgen or altered experiential factors cannot be excluded without further study. **KEYWORDS:** congenital adrenal hyperplasia (CAH), androgen, sex, motor, strength, targeting

Although it can be argued that human males and females are more similar behaviorally than they are different (Hyde, 2005), the two sexes differ on average for certain behaviors, with reliable differences seen in aspects of childhood play, gender identity, sexual orientation, aggression, some visuospatial skills, muscle strength, and fine motor and perceptual speed (Halpern, 2000; Hines, 2004). A variety of factors appear to contribute to these behavioral differences, and one productive line of research has explored how sex steroid exposure during early (prenatal) life may contribute to sex-typed human development (Collaer & Hines, 1995; Cohen-Bendahan et al., 2005). Although early steroid influences have been investigated for many behaviors that show sex differences, there is relatively little information on their potential contributions to sex-typed human motor abilities or to tasks with a significant motor component, such as visuomotor ability.

Males and females differ at numerous levels of the motor system, from obvious peripheral differences in adult musculature and strength, through central differences in the molecular and anatomical substrates of motor or sensorimotor cortex. Central sex differences have been observed in the concentration of neurotransmitter-related metabolites in sensorimotor cortex, an area involved in perceptual processing and motor execution (Grachev & Apkarian, 2000), in the organization of motor cortex (Amunts et al., 2000), and in the brain activity associated with visuomotor movements (Gorbet & Sergio, 2007). Behavioral evidence suggests that sex differences in human movement exist as early as the first months of life (Piek et al., 2002) and may emerge throughout life for a variety of reasons, including differences in the integration of visual information used to guide certain motor or praxic processes (Chipman et al., 2002; Chaudhury et al., 2004) or differences in other processes, such as aspects of “postural support and movement organization” (Field & Pellis, 2008, p. 37). Given that all observable behavior funnels, ultimately, through motor systems, a clearer understanding of potential influences on motor and motor-related processes in the sexes would be valuable.

Considerable evidence suggests that sex steroids contribute to sex-typed neurobehavioral characteristics. Androgens and their metabolites are suggested to drive male-typical development of both the nervous system and behavior, presumably by acting on aspects of neural differentiation, such as cell survival, or by influencing neural function (Goy & McEwen, 1980; Breedlove, 1992). There is some evidence from humans that early sex steroids may influence sex-typed development (Collaer & Hines, 1995; Cohen-Bendahan et al., 2005), however the most rigorous support for this hypothesis comes from true experiments in nonhuman species in which sex steroid exposure can be manipulated. When females of various rodent species and nonhuman primates are treated with androgens during early life, specific aspects of their nervous systems, and adult behaviors, including reproductive behaviors (e.g., mounting frequency) and nonreproductive behaviors (e.g., maze learning and the execution of certain movements), are masculinized; additionally, these females generally fail to develop certain characteristics that are typically observed in control females (e.g., they show reduced capacity for lordosis/sexual receptivity and reduced open-field activity) (Goy & McEwen, 1980; Williams et al., 1990; Hines, 2004; Field & Pellis, 2008). Similarly, males deprived of early androgen exposure through castration or antiandrogen treatment fail to show normal male-typical neural characteristics and

behavioral development, regardless of adult hormonal exposure (Goy & McEwen, 1980; Hines, 2004). Thus, early male-typical levels of androgens or their metabolites are suggested to promote male-typical and/or decrease female-typical aspects of neurobehavioral development but their contributions to motor development, especially in humans, are relatively unexplored.

For ethical reasons, investigation of these questions in humans generally depends upon nonexperimental study designs involving patients with early-onset endocrine disorders. Patients with congenital adrenal hyperplasia (CAH) have been one of the most informative and frequently studied endocrine populations. In the most common form of CAH, a deficiency of the enzyme 21-hydroxylase leads to deficient production of cortisol and often of mineralocorticoids (Merke & Bornstein, 2005). Due to the negative feedback properties of the hypothalamic-pituitary-adrenal (HPA) axis, the cortisol deficiency leads to increased levels of its normal precursors which also function as precursors in the adrenal androgen pathway and result in overproduction of adrenal androgens beginning prenatally. In female fetuses, this elevates testosterone and other androgens to abnormal levels (Pang et al., 1980) and typically causes virilization of the external genitalia; however in developing males, although the relatively weak androgen, androstenedione may be elevated prenatally, other androgens, including testosterone, apparently are not (Pang et al., 1980; Wudy et al., 1999) presumably because high adrenal androgens are offset by a compensatory reduction in testicular production.

Females with CAH have been found to show aspects of behavioral masculinization or defeminization; for example, they are more likely to engage in male-typical childhood play, and express reduced heterosexual interest and reduced satisfaction with the female sex of assignment (Dittmann et al., 1990; Zucker et al., 1996; Hines et al., 2004; Pasterski et al., 2005). Evidence is less consistent concerning alteration of cognitive characteristics that show sex differences, such as selected visuospatial or mathematical abilities, in females with CAH (see Hines, 2004 for a review). For example, some studies have suggested that CAH females show enhanced male-typical cognitive abilities (Resnick et al., 1986; Hampson et al., 1998), while other studies have found no differences, inconsistent results, or even reduced male-typical abilities in females with CAH (Baker & Ehrhardt, 1974; McGuire et al., 1975; Helleday et al., 1994; Hines et al., 2003; Malouf et al., 2006). However, one of the studies that did not find alterations on a paper-and-pencil visuospatial measure of mental rotation, still found that females with CAH showed enhanced visuospatial/visuomotor targeting (i.e., throwing balls or darts at a bulls-eye; Hines et al., 2003). The possibility that androgens may produce more pronounced effects on motor or visuomotor skills than on more “cognitive” visuospatial abilities, even ones that show large sex differences, suggests the importance of investigating behaviors with large or prominent motor aspects in females with CAH. In contrast, studies of males with CAH have not generally shown consistent differences from control males (McGuire et al., 1975; Resnick et al., 1986), although some studies have suggested impaired visuospatial abilities (Hampson et al., 1998; Hines et al., 2003).

This study investigates the potential for sex steroid influence on the development of motor and visuomotor characteristics by studying patients with CAH in comparison with their relatives without CAH (unaffected relatives). Motor development has not been thoroughly investigated in CAH, although effects on it could have ramifications for other behavioral outcomes. In this study, we focus on three motor tasks that show sex differences: grip strength and visuomotor targeting that favor males, on average (Thomas & French, 1985; Watson & Kimura, 1989, 1991; Miller et al., 1993; Strauss et al., 2006), and fine motor pegboard tasks that favor females, on average (Yeudall et al., 1986; Strauss et al., 2006). Although differences in targeting have been reported previously for this sample (Hines et al.,

2003), we extend this analysis to explore whether differences in physical strength might influence the targeting findings.

Adult males and females differ in physical size, with males being taller and heavier, on average, than females (Ogden et al., 2004). Previous research also indicates that both males and females with CAH tend to be shorter than expected compared to population norms or predictions based on parental heights (Van der Kamp et al., 2002; Merke & Bornstein, 2005). In CAH patients treated with glucocorticoids, height may be reduced due either to corticoid overtreatment which inhibits growth and/or to undertreatment or poor compliance, producing elevated adrenal androgens which encourage premature epiphyseal closure (Stikkelbroeck et al., 2003; Christiansen et al., 2004). Therefore, because motor characteristics can relate to physical body size (Strauss et al., 2006), we also measured height and weight to investigate whether differences in physical size might explain any obtained motor results.

In line with results from experimental studies in nonhuman species, we hypothesize a dissociation, such that females with CAH will show increased (masculinized) grip strength and targeting and decreased (defeminized) fine motor ability compared to same-sex relative controls. Further, we hypothesize, based on population norms, that within unaffected controls, males will show higher grip strength and targeting and lower fine motor skill than females. However, because of the inconsistency of prior outcomes for males with CAH and for nonhuman male animals exposed to altered prenatal androgens, predictions for males with CAH are less clear and, thus, not directional. We hypothesize, in a more exploratory vein, that statistical control for height and weight, or for strength in the case of targeting results, will not alter the pattern of findings.

Methods

Participants

The study included 40 females and 29 males with CAH, and 29 females and 30 males who were unaffected relatives of individuals with CAH. Age ranges were 12 to 44 years for females with CAH, 12 to 40 years for males with CAH, 12 to 32 years for unaffected females, and 12 to 45 years for unaffected males. Table 1 presents means and standard deviations for age. Participants were European with the exception of one male with CAH and his unaffected sister, who were South Asian (Indian, Pakistani, or Bangladeshi).

Participants with CAH were recruited through endocrinologists at University College London and Great Ormond Street Hospitals in London ($n = 35$; 22 females, 13 males) or a support group for CAH patients in the UK ($n = 34$; 18 females, 16 males). Unaffected controls were recruited from the families of participants with CAH ($n = 57$ siblings and 2 first cousins) regardless of the sex of the relative. In five families, a patient with CAH (3 males and 2 females) contributed one unaffected sibling of each sex; in three families (each being a male patient with CAH), two unaffected sisters participated, and in one of those families an unaffected brother also participated; one other family contributed two females with CAH and one unaffected sister. Effects sizes and patterns of significant findings were essentially identical, both when control siblings of the same sex were averaged within families and when they were included separately. Therefore, results are presented for the full, unaveraged sample, as done in prior reports on other behavioral outcomes in this same sample (Hines et al., 2003; Mathews et al., 2004). Sixty-six of the 69 patients were deficient in the enzyme 21-hydroxylase. Sixty-two had the salt-losing form of the disorder and four did not. Medical records addressing 21-hydroxylase deficiency and salt-loss were not available for the remaining three patients recruited through the support group; however, these patients were taking medications that indicated the salt-losing form of CAH. Written

consent was obtained from participants and from the parents of those under the age of 18 years.

Participation rates were not calculated for two reasons. First, the names of individuals who were invited to participate were not retained, in order to eliminate any possible coercion to take part, and second, we did not have access to mailing lists from which letters to potential participants were sent, because of data protection considerations. Regardless, this study presents one of the larger samples in a behavioral investigation of CAH, and includes two different sources of participants, treating physicians and a support group, increasing the diversity of the sample.

Behavioral Measures

Grip strength—Grip strength (kg) was assessed using a hand dynamometer. The grip strength of each hand was measured three times, and three measures were derived: the mean strength of each hand (right and left grip strengths) and the average across the two hands (average grip strength). Grip strength shows a large male advantage in the normal population, with large effect sizes (*ds* of 1.5 to 2.5) for the older adolescents and adults in the age range of this sample (Thomas & French, 1985; Miller et al., 1993; Strauss et al., 2006).

Targeting—We previously reported group (sex by diagnosis) differences for this sample in the visuospatial/visuomotor task of targeting (Hines et al., 2003), using a composite measure of scores on ball and dart throw tasks (10 trials for each, using the hand with which participants were most comfortable). Balls were thrown overhand at the marked center of a plastic (90 × 90 cm) board and adhered to the surface by using mating Velcro surfaces on the ball and target. Darts were thrown overhand at the marked center of a polystyrene board. For each task, participants stood 3 m from the target, and the score was the mean distance of ten throws from the target's center. For both, data were transformed by subtracting the mean distance from the maximum possible distance, so that higher scores reflected better performance. Targeting accuracy shows large sex differences, with *ds* ranging from 1.1 to 2.0 (Jardine & Martin, 1983; Watson & Kimura, 1989, 1991).

Purdue Pegboard—On this speeded fine motor task, participants worked quickly to manipulate and position small objects (Tiffin, 1968; Strauss et al., 2006). Participants were asked to use their (self-identified) dominant hand to put pegs in holes as quickly as possible (two trials, 30 seconds each), and then repeated this with their nondominant hand. On the third task, participants used both hands in a specific, alternating motor sequence to create assemblies of simple, four item objects involving pegs, collars, and washers (for two trials, 60 seconds each). The two trials in each condition (dominant, nondominant, and assembly) were averaged. The assembly condition is somewhat more cognitively complex than the single-hand (dominant and nondominant) tasks (Schmidt et al., 1993; Strenge et al., 2002), perhaps due to its motor sequencing demands. In the normal population, the Purdue Pegboard (PP) shows small to moderate effects favoring females (*ds* = −0.52, −0.44 and −0.54 for the dominant, nondominant, and assembly conditions, respectively) in 15 to 40 year olds (Yeudall et al., 1986; Strauss et al., 2006).

Physical Measures

Height and weight were measured in the laboratory.

Control Measures

Intelligence and age were assessed as control measures. Intelligence was estimated using the Vocabulary subtest of the age-appropriate Wechsler Intelligence scale. The subtest from the

Wechsler Intelligence Scale for Children-III (WISC-III, Wechsler, 1991) was used for ages 12 to 15 years, while the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) was used for ages 16 and older.

Statistical Analyses

Two-way analyses of covariance (ANCOVAs) were used to examine the relationship of sex (male, female) and diagnosis (CAH, unaffected relative) to the dependent motor measures. Age and/or estimates of IQ were entered as covariates into analyses when they correlated with the specific dependent measure of interest. In addition, ANCOVAs were followed by planned (post hoc) comparisons using Fisher's Least Significant Difference (LSD) tests to investigate whether: 1. the sexes differed on the dependent motor measures (by comparing unaffected females to unaffected males); 2. prenatal exposure to elevated androgens promoted male-typical development or reduced female-typical development in females (by comparing females with CAH to unaffected females); and 3. CAH altered performance on sex-typed measures in males (by comparing males with CAH to unaffected males). For planned comparisons, effect sizes (*ds*) are reported based on covaried means and standard deviations. An alpha level of .05 was adopted, and one-tailed tests were used to evaluate clearly directional hypotheses (i.e., that control males score higher than control females for grip strength and targeting, but lower on Purdue Pegboard measures; that females with CAH score higher compared to unaffected females on grip strength and targeting, but lower on Purdue Pegboard measures). Two-tailed tests were used for nondirectional hypotheses (i.e., comparisons between males with CAH and their unaffected male relatives).

Results

Descriptive statistics for dependent measures, unadjusted for covariates, are provided in Table 1, and descriptive statistics following adjustment for covariates are provided for the dependent motor measures in Table 2.

Grip strength measures were positively skewed; thus, square root transformations were applied. These transformed scores were used in all statistical analyses; however, untransformed values are reported for the descriptive statistics.

The three grip measures (right, left, and average) correlated strongly with one other: correlation of right to left grip strength, $r(122) = 0.95$, right to average, $r(123) = 0.99$, and left to average, $r(122) = 0.99$, all $ps < .001$. Thus, results are presented for the average of the two hands.

The single-handed PP means (PP-Dominant and PP-Nondominant) also correlated strongly: $r(125) = 0.70$, $p < .001$; thus, these measures were averaged to form a single measure, PP-Single-hands. PP-Assembly scores correlated only moderately with the single-hand PP measures [with PP-Dominant, $r(125) = 0.54$, and with PP-Nondominant, $r(125) = 0.55$, both $p's < .001$], and so this measure was analyzed separately.

Grip measures were not collected (due to experimental error) for three females: two with CAH and one unaffected relative. Also, one male (unaffected relative) had a hand injury that prevented meaningful grip or pegboard assessment involving his left hand; thus, his averages for these measures are based on his uninjured hand, and he did not contribute a score to the PP-Assembly analyses.

Motor Strength

Two-way ANCOVA on average grip strength (square root transformed) using age as a covariate showed a main effect of sex, $F(1,120) = 36.24$, $p < .001$, and a significant

interaction, $F(1,120) = 10.76, p = .001$, with no main effect of diagnosis. Planned comparisons indicated that unaffected males were stronger than unaffected females, $F(1,120) = 40.58, p < .001, d = 1.67$; females with CAH were stronger than unaffected females, $F(1,120) = 3.79, p = .027, d = 0.49$; and males with CAH were weaker than unaffected males, $F(1,120) = 7.16, p = .008, d = 0.70$.

Targeting

Two-way ANCOVA on the composite targeting score using the covariate of age showed a main effect of sex, $F(1,123) = 18.19, p < .001$, and an interaction of sex and diagnosis, $F(1,123) = 9.21, p = .003$, but no main effect of diagnosis. Planned comparisons showed that unaffected males targeted better than unaffected females, $F(1,123) = 24.98, p < .001, d = 1.30$, and females with CAH targeted better than unaffected females, $F(1,123) = 8.24, p = .003, d = 0.70$; however, males with CAH did not target differently from unaffected males ($d = .39$, with CAH males scoring nonsignificantly lower).

Fine Motor Control

For PP-Single-hands, two-way ANCOVA, using age as a covariate, showed a main effect of sex, $F(1,123) = 10.31, p = .002$, and a main effect of diagnosis, $F(1, 123) = 4.31, p = .040$, but no interaction. Planned comparisons indicated that unaffected females were faster than unaffected males, $F(1,123) = 3.66, p = .029, d = 0.50$, but there was no significant difference between patients with CAH and unaffected, same-sex controls ($d = 0.30$ for females; $d = 0.44$ for males, with controls being nonsignificantly faster in both cases).

For PP-Assembly, two-way ANCOVA, using age and IQ as covariates, produced a main effect of sex, $F(1,121) = 7.42, p = .007$, but no main effect of diagnosis and no interaction. Planned comparisons indicated a sex difference in unaffected relatives, $F(1,121) = 5.92, p = .008, d = 0.64$, with females faster than males. Females with CAH were slower than unaffected females, $F(1,121) = 3.83, p = .027, d = 0.48$, but there was no significant difference between males with CAH and unaffected males, $d = 0.17$ (with CAH males nonsignificantly slower than unaffected males).

Relationship of Motor Variables to Height and Weight

If differences in height or weight contribute to differences in motor abilities, then covarying these factors could help to explain obtained results. Because height and weight correlated with grip strength and targeting, but not with pegboard performance, this section explores body size only in relation to the two gross motor skills. Two-way ANCOVA on grip strength (again using square root transformed values in analyses), with height and weight as covariates in addition to age, showed that the main effect of sex was still significant, $F(1,118) = 13.55, p < .001$, as was the interaction of sex and diagnosis, $F(1, 118) = 10.20, p = .002$, and there continued to be no main effect of diagnosis. Planned comparisons showed that unaffected males continued to be significantly stronger than unaffected females, $F(1, 118) = 22.61, p < .001, d = 1.26$, and females with CAH continued to be stronger than unaffected females, $F(1,118) = 7.40, p = .004, d = .67$; however, males with CAH were no longer significantly weaker than unaffected males, $F(1,118) = 2.72, p = .102, d = .42$.

Additionally, because males attain peak muscle strength later than females due to differences in pubertal timing (Tanner, 1962), grip strength was reanalyzed to control for potential age-related confounds. Analyzing males aged 16 years and older and females aged 14 years and older separately did not alter the pattern of significant findings above.

Two-way ANCOVA on the targeting score, with height and weight as covariates in addition to age showed a main effect for sex, $F(1, 121) = 6.57, p = .012$, and an interaction of sex and

diagnosis, $F(1, 121) = 7.95, p = .006$, but no main effect of diagnosis. Planned comparisons showed that, even controlling for height and weight, unaffected males targeted better than females, $F(1, 121) = 13.65, p < .001, d = 0.97$, females with CAH targeted better than unaffected females, $F(1, 121) = 9.53, p = .002, d = 0.74$, and males with CAH, while scoring lower, did not differ significantly from unaffected males, $d = 0.20$.

Relationship of Motor Strength to Targeting Ability

Partial correlations controlling for age were computed between targeting ability and average grip strength to understand whether the greater muscle strength reported in this study for CAH females (compared to unaffected females) and for unaffected males (compared to both males with CAH and unaffected females) might contribute to the targeting findings reported previously (Hines et al., 2003). Targeting and average grip strength correlated moderately, $r(122) = 0.55, p < .001$, in the sample as a whole, and also correlated significantly (or approached significance) for every group except females with CAH (for males with CAH, $r(26) = .57, p = .002$; for unaffected females, $r(25) = .36, p = .066$, for unaffected males, $r(27) = .66, p < .001$; however for females with CAH there was no significant correlation, $r(35) = .12, p = .48$).

To further explore the relationship of motor strength and targeting ability, we conducted a two-way ANCOVA on targeting, covarying age and grip strength. Although neither the main effect of sex or diagnosis was significant, the interaction of the two approached significance, $F(1, 119) = 3.59, p = .061$. Planned comparisons controlling for strength as well as age showed the same pattern of findings as originally reported by Hines et al. (2003). Unaffected males still targeted better than unaffected females, $F(1, 119) = 4.33, p = .020, d = .59$, females with CAH continued to target better than unaffected females, $F(1, 119) = 6.12, p = .008, d = .60$, and males with CAH did not differ significantly from unaffected males, $F(1, 119) < 1, p = .741, d = .09$, being nonsignificantly lower.

Effect Sizes

Effect sizes obtained in this study for sex differences between unaffected males and females were examined to allow comparison to prior findings. Effect sizes for sex differences in grip strength, targeting, PP-Single hands and PP-Assembly (not covarying height, weight, or grip strength) were 1.67, 1.30, 0.50, and 0.64, respectively, and agree reasonably well with prior findings (see Methods). Further, to the degree that androgens may be one of many contributors to behavioral differences, the effect size for CAH females compared to unaffected females would be expected to be smaller than that observed for the overall sex difference. The effect sizes (again without height, weight, or grip strength covariates) for the variables showing significant motor differences in CAH females versus unaffected controls (grip strength, targeting, and PP-Assembly) agree with this expectation, producing ds of 0.49, 0.70, and 0.48 respectively, constituting 29%, 54%, and 75% of the sex effect, in the same order.

Discussion

The hypothesis that prenatal androgens may influence human motor development was supported by the finding that females with CAH showed enhanced performance on motor and visuomotor tasks demonstrating large sex differences favoring males and reductions for one aspect of fine motor control, a characteristic demonstrating a small- to moderately-sized sex difference favoring females. Results for males with CAH revealed only one effect, reduced grip strength versus unaffected male relatives, and this effect was eliminated after controlling for height and weight. Prior research on males with CAH also has generally

reported either no alteration in behavior, or more occasionally, a reduction in male-typical characteristics (Collaer & Hines, 1995).

Motor Development in Females with CAH

Females with CAH were stronger than unaffected females as assessed by overall grip strength and targeted better using a composite measure of throwing tasks. These differences remained after controlling for height and weight, or in the case of targeting, for the greater motor strength of CAH females. Simple fine motor control requiring the rapid, repetitive placement of pins in holes with a single hand (PP-Single hand) was not significantly altered in females with CAH compared to unaffected females; however, in contrast, when fine motor control was assessed using a task with somewhat more complex cognitive sequencing (PP-Assembly) and involving faster overall manipulations (a greater number of items positioned per second), females with CAH were slower than controls. The specific fine motor measure that provided the stronger evidence of defeminization in females with CAH, also showed the larger sex difference in unaffected relatives.

Few previous studies have examined development of motor characteristics in individuals with CAH, although Dittmann (1992) found that females with CAH showed more masculine motor postures and movements than typical females. Also, Rodda et al. (1987) reported increased muscle (quadriceps) strength in a younger group of girls with CAH (aged 4 to 12 years), although this was most pronounced in girls with later diagnoses (ages 5 to 6 years, as opposed to infancy) or poorly controlled treatment. In comparison, all the female participants in our study were diagnosed in infancy.

Strength

If androgen exposure is responsible for the increases in muscle strength, there are several potential routes, direct and indirect, by which this effect could occur in females with CAH. First, elevated prenatal androgens might directly enhance strength through permanent organizational effects on neural or neuromuscular development; second, prenatal androgens might indirectly enhance strength by increasing preferences for activities that promote muscular development; or third, current adult (and adolescent) androgens might be elevated in females with CAH, despite treatment, and might function directly and activationally (rather than organizationally) to promote muscle development. Each of these possibilities will be considered below.

The sexes generally differ in overall strength (Miller et al., 1993), and differ specifically in grip strength not only in adulthood but also prepubertally (Neu et al., 2002). Differences in muscle strength are suggested to reflect factors such as differential muscle cross sectional area, muscle fiber size, and varying differentiation fates of precursor cells (Miller et al., 1993; Neu et al., 2002). Androgens are one potential cause of neuromuscular sex differences as they can stimulate myogenesis by influencing many of the aspects above (Herbst & Bhasin, 2004; Sinha-Hikim et al., 2004).

First, for androgens to organizationally enhance strength, two criteria must be met: neuromuscular tissues must be sensitive to androgens during early life and permanent developmental changes must be possible due to androgen exposure. Although there apparently are no directly relevant data from fetal humans, results from a hypogonadal mouse model suggest that early androgens, or their loss, exert effects on skeletal muscle development, and these effects do not appear to be identical to those achieved through later manipulations (Sciote et al., 2001). Also, exposure of males or females to androgens during a restricted critical period of early life permanently masculinizes the development of certain muscles (e.g., the levator ani) and associated motor neurons in the rat (Breedlove &

Hampson, 2002). Although the levator ani and related muscles are highly sensitive to androgens, reflecting elevated expression of androgen receptors (Monks et al., 2004), some degree of androgen sensitivity appears to be a general characteristic of skeletal muscle (Herbst & Bhasin, 2004). Thus, androgen exposure may produce more subtle effects in other muscle groups.

Also supportive of the possibility of early androgen effects is the finding of prepubertal sex differences in grip strength as early as six years of age (apparently the earliest it can be reliably measured) and in cross sectional muscle area (Neu et al., 2002). Muscle and grip strength differences during a period of sex steroid “quiescence” (Forest, 1979) indicate that such sex differences in strength are not due solely to differences in circulating androgens, and that other factors, perhaps including early androgen exposure, are influential.

Rather than exerting direct organizing effects on muscle, androgens could influence muscle strength indirectly by altering preferences for and participation in activities with muscular consequences. Engagement in physical activity during childhood has been shown to enhance muscular strength or factors related to muscle development such as amount of lean body mass (Morris et al., 1997; Chromiak et al., 2004; Annesi et al., 2005). There is strong evidence that females with CAH are masculinized in childhood toy and activity preferences, including higher levels of rough-and-tumble play, and in gender role behaviors, presumably reflecting prenatal androgenization of the brain (Money & Ehrhardt, 1972; Berenbaum & Hines, 1992; Hines et al., 2004; Pasterski et al., 2005). Thus, early exposure to androgens may enhance muscle development because females with CAH are more likely to engage in physical activities that foster development of muscle mass and strength.

Third, given the well-established association between circulating androgen levels and muscle development (Herbst & Bhasin, 2004), females with CAH might simply have higher current (adult and adolescent) androgen levels than unaffected females due to undertreatment or inconsistent medication compliance, and this may directly stimulate greater muscle mass and strength. However, a number of studies suggest that females who are treated for CAH are likely to have subnormal or normal, rather than elevated, levels of androgens, presumably as a result of glucocorticoid treatment (Helleday et al., 1993; Guo et al., 1996; Berenbaum et al., 2000; Hagenfeldt et al., 2000; Ogilvie et al., 2006), making this explanation questionable. Because circulating levels of adult/adolescent androgens are not available for our participants, however, this possibility cannot be ruled out.

To help distinguish among these possible reasons for enhanced strength in females with CAH, it would be useful to assess neuromuscular development during early life. Although assessment of grip strength requires a certain level of maturity, cross sectional muscle area can be assessed earlier using relatively noninvasive imaging techniques (Neu et al., 2002). Knowledge of whether muscle cross sectional area differs in females with CAH compared to unaffected controls, combined with androgen measures in adulthood, and activity preferences would help to determine whether strength shows a stronger relationship with prenatal or adolescent/adult androgens, or whether physical activity choices are more relevant.

Targeting

The ball and dart targeting measures explored in this study involved visuospatial as well as visuomotor abilities. Thus, the targeting advantage seen in unaffected males and in females with CAH (compared to unaffected females) could reflect group differences in either underlying skill or both. Males and females still differed in targeting ability after removing the effect of muscle strength. Consequently, it appears that males' greater average physical

strength is not responsible for their targeting advantage, suggesting differences exist in other skills underlying targeting ability.

Like unaffected males, females with CAH targeted better and also were stronger than unaffected females, but these two were not related to each other, and therefore, one variable cannot explain the other. Consequently, for both unaffected males and for females with CAH, enhanced targeting could reflect a masculinizing influence of early androgens on the neural regions that subserve visuomotor or general sensorimotor functions or effects on activity preferences and resultant practice effects.

Fine Motor Skill

Females with CAH performed somewhat less well on one fine motor task (PP-Assembly) at which females typically excel. Helleday et al. (1994) examined speeded visuomotor performance in a group of girls and women with CAH and controls (aged 17 to 34 years) as part of a larger battery, using the Trail Making Tests, Parts A and B, and the Wechsler Digit Symbol subtest. In that study, females with CAH also displayed lower (slower) performance on one of these three visuomotor tasks: Trail Making, Part B, the most cognitively demanding of the three. Differences in fine motor skills could reflect direct prenatal, defeminizing effects of androgen on the neural development of regions underlying the control of fine motor skills. Although a mechanism for such potential effects is speculative, aspects of cortical connectivity underlying primary motor functions appear to be relatively more sensitive to testosterone than some other cortical areas (e.g., primary visual cortex) (Venkatesan & Kritzer, 1999). Alternatively, just as early androgen exposure may indirectly improve muscle strength by fostering participation in strength-building physical activities, it might reduce participation in activities that normally promote fine motor skills in females. Alternatives to hormonal explanations for the sex difference in pegboard performance also exist, however, with factors related to men's larger finger size also suggested to impair their performance on fine motor tasks requiring manipulation of small objects (Peters et al., 1990).

Motor Development in Males with CAH

Concerning motor development in males with CAH, as noted earlier, predictions are less clear, and we were unable to locate other studies investigating muscle strength, targeting, or fine motor control in males with CAH. In the current study, males with CAH did not differ from unaffected males in fine motor control or targeting. In contrast, they displayed reduced muscle strength (an effect of moderate size); however, when the variables of height and weight were statistically removed from the analysis, CAH males no longer differed significantly from unaffected males. Possible interpretations are that males with CAH are less strong due to their smaller physical size or that they are less strong as a function of other variables that covary with CAH, such as reduced levels of physical activity, with implications for muscle development. It also is possible that the reduced muscle strength results from general effects of a chronic illness or glucocorticoid treatment, although, if so, such factors did not similarly diminish the muscle strength of females with CAH.

In summary, we found that females with CAH showed decreased performance on a visuomotor task at which females typically excel (fine motor skill) and increased performance on motor tasks at which males normally excel (grip strength, targeting). In addition, improved performance on grip strength and targeting remained when differences in height and weight were controlled, and the improved targeting performance persisted following adjustment for differences in grip strength. These results suggest that the alterations in motor performance reflect neural effects rather than more peripheral physical effects. Androgen during prenatal development could influence these abilities either by

acting directly on neural regions regulating them, or by altering interests and activities, such as in sports. Males with CAH showed reduced grip strength but no alterations in targeting or fine motor skill, and the difference in grip strength did not persist when height and weight were covaried. These results extend prior findings of behavioral alteration in females with CAH to include masculinization and defeminization of motor characteristics. We found no evidence of altered motor behavior beyond that attributable to changes in height or weight in males with CAH.

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Table 1

Means and standard deviations for physical and behavioral measures unadjusted for covariates

	Females With CAH (n=40)		Unaffected Females (n=29)		Males with CAH (n=29)		Unaffected Males (n=30)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	19.50	7.30	19.26	5.95	20.27	8.43	18.00	6.81
Vocabulary Scaled Score	8.52	2.52	9.28	2.36	9.10	2.66	8.77	2.24
Height (m)	1.57	.074	1.61	.075	1.65	.103	1.71	.115
Weight (kg)	67.99	15.70	59.73	13.39	64.77	14.85	63.66	14.13
Grip Strength –Average of hands (kg)	26.47	7.08	22.88	7.84	31.71	10.70	36.84	13.72
Targeting accuracy (z score)	-.016	.644	-.560	.976	.179	.821	.390	.808
Purdue Pegboard –Single hand (no. of pegs placed)	14.41	1.81	14.91	1.69	13.36	2.05	13.95	1.63
Purdue Pegboard – Assembly (no. of items placed)	35.65	5.95	39.04	7.02	34.12	6.18	34.66	6.09

Table 2

Means for motor measures after adjustment for covariates

Dependent Measure and Covariate(s)	Females With CAH (n=40)	Unaffected Females (n=29)	Males with CAH (n=29)	Unaffected Males (n=30)
	<u>Mean</u>	<u>Mean</u>	<u>Mean</u>	<u>Mean</u>
Grip Strength (kg) ^a Covary age	26.40 [†]	22.77 ^{*†}	31.03 [†]	37.68 ^{*†}
Grip Strength (kg) ^a Covary age, height, & weight	28.79 [†]	24.18 ^{*†}	30.31	34.04 [*]
Targeting accuracy (z score) Covary age	-.03 [†]	-.56 ^{*†}	.14	.44 [*]
Targeting accuracy (z score) Covary age, height, & weight	.09 [†]	-.50 ^{*†}	.10	.26 [*]
Targeting accuracy (z score) Covary age & grip strength	.13 [†]	-.30 ^{*†}	.07	.13 [*]
Purdue Pegboard – Single hand (no. of pegs placed) Covary age	14.40	14.91 [*]	13.28	14.05 [*]
Purdue Pegboard – Assembly (no. of items placed) Covary age & intelligence	35.87 [†]	38.77 ^{*†}	33.85	34.90 [*]

* Indicates a planned comparison showing a significant sex difference between unaffected males and females.

[†] Indicates a planned comparison test showing a significant difference between CAH patients and controls of the same sex.

^a Tabled grip strength values present descriptives that have been adjusted for covariates rather than values that have undergone the square root transformation used in statistical analyses.