Published in final edited form as:

Psychoneuroendocrinology. 2016 February ; 64: 164–173. doi:10.1016/j.psyneuen.2015.11.010.

Reduced short term memory in congenital adrenal hyperplasia (CAH) and its relationship to spatial and quantitative performance

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Abstract

Girls and women with classical congenital adrenal hyperplasia (CAH) experience elevated androgens prenatally and show increased male-typical development for certain behaviors. Further, individuals with CAH receive glucocorticoid (GC) treatment postnatally, and this GC treatment could have negative cognitive consequences. We investigated two alternative hypotheses, that: (a) early androgen exposure in females with CAH masculinizes (improves) spatial perception and quantitative abilities at which males typically outperform females, or (b) CAH is associated with performance decrements in these domains, perhaps due to reduced short-term-memory (STM). Adolescent and adult individuals with CAH (40 female and 29 male) were compared with relative controls (29 female and 30 male) on spatial perception and quantitative abilities as well as on Digit Span (DS) to assess STM and on Vocabulary to assess general intelligence. Females with CAH did not perform better (more male-typical) on spatial perception or quantitative abilities than

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Contributors

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

Conflict of interest statement

All authors declare that they have no conflicts of interest.

control females, failing to support the hypothesis of cognitive masculinization. Rather, in the sample as a whole individuals with CAH scored lower on spatial perception ($p = .009$), a quantitative composite ($p = .036$), and DS ($p = .001$), despite no differences in general intelligence. Separate analyses of adolescent and adult participants suggested the spatial and quantitative effects might be present only in adult patients with CAH; however, reduced DS performance was found in patients with CAH regardless of age group. Separate regression analyses showed that DS predicted both spatial perception and quantitative performance (both $p = .001$), when age, sex, and diagnosis status were controlled. Thus, reduced STM in CAH patients versus controls may have more general cognitive consequences, potentially reducing spatial perception and quantitative skills. Although hyponatremia or other aspects of salt-wasting crises, or additional hormone abnormalities cannot be ruled out as potential contributors, elevated GCs appear to be the most likely contributor to reductions in STM. Additional efforts to monitor GC administration protocols may help achieve optimal cognitive outcomes. Educational intervention for individuals with CAH might also be useful.

Keywords

congenital adrenal hyperplasia (CAH); digit span; spatial perception; quantitative; short term memory; glucocorticoid

1. Introduction

Classical congenital adrenal hyperplasia (CAH) is a genetic disorder marked by reduced adrenal synthesis of glucocorticoids (GCs), and often mineralocorticoids, typically resulting from deficiency of the synthetic enzyme 21-hydroxylase (White & Speiser, 2000).

Glucocorticoid deficiency and the absence of negative feedback signals cause excessive concentrations of precursors to be shunted into the intact adrenal androgen pathway. Consequently, individuals with CAH experience elevated adrenal androgens beginning prenatally, and girls with CAH are typically born with some degree of genital virilization (Pang et al., 1980; White & Speiser, 2000). Boys with CAH are thought to experience prenatal testosterone concentrations largely in the high normal range (Pang et al., 1980) as elevated adrenal production appears to be offset by compensatory reductions in testicular production. Postnatally, individuals with CAH are treated with GC replacement which ideally terminates the elevated concentrations of adrenal androgens; however postnatal concentrations of GCs and androgens still may be abnormal for a variety of reasons (White & Speiser, 2000).

Experimental studies demonstrate that androgen exposure during early critical periods masculinizes numerous neural and behavioral characteristics in non-human mammals, including rodents as well as nonhuman primates (Arnold, 2009). In line with findings in nonhumans, females with CAH show increased male-typical behavior in regard to a number of traits such as childhood play, sexual orientation, core gender identity and aggression (Hines, 2011). These findings suggest that certain aspects of neurobehavioral development in females with CAH may be altered in a male-typical direction through early exposure to elevated androgens. In contrast to the suggestion of masculinization of these traits in females

with CAH, males with CAH, who experience largely male-typical androgen exposure prenatally, do not show increased masculinization in these domains (Collaer et al., 2009).

Despite well-established masculinization of certain traits in females with CAH, cognitive abilities in the visuospatial and quantitative realms do not necessarily follow this pattern. Focusing specifically on the visuospatial task of mental rotation which typically shows one of the largest cognitive sex difference favoring males (Voyer et al., 1995), results have been inconsistent. Mental rotation ability was not altered in prior analyses from our sample of females with CAH (Hines et al., 2003) nor was it altered in three other studies of girls or women with CAH (Baker & Ehrhardt, 1974; Helleday et al., 1994; Malouf et al., 2006); however, three studies have found enhancement of mental rotation, although in some cases this was restricted to females with the more severe, salt-wasting form of CAH (Berenbaum et al., 2012; Hampson & Rovet, 2015; Resnick et al., 1986). In addition, in one of the studies (Hampson & Rovet, 2015) the effect was found only when a subgroup of female participants with CAH, deemed to show “questionable neurological status” perhaps related to the consequences of salt-wasting crises, was removed from the analyses. Visuospatial abilities other than mental rotation also have sometimes been found to show no differences for girls and women with CAH compared to controls or to show reduced performance (Baker & Ehrhardt, 1974; Helleday et al., 1994; Hines, 2011; McGuire et al., 1975; Perlman, 1973), although enhanced performance also has sometimes been reported for these measures in females with CAH (Berenbaum et al., 2012; Hampson et al., 1998; Mueller et al., 2008). Inconsistencies in results could reflect the use of small samples, differences in the matching of controls or in the specific measures of spatial ability, or genuine differences in the cognitive profiles of the various samples. Similarly for males with CAH, some studies show no differences in visuospatial abilities compared to controls (Baker & Ehrhardt, 1974; McGuire et al., 1975; Resnick et al., 1986) while others show reduced spatial, or specifically mental rotation, abilities (Berenbaum et al., 2012; Hampson et al., 1998; Hines et al., 2003). We have not found any studies showing elevated visuospatial skills in males with CAH.

Certain quantitative or mathematical abilities also show sex differences and represent another domain of potential interest in individuals with CAH. Tasks involving problem solving or mixed quantitative abilities favor males, with effect sizes ranging from small to moderate, depending on the specific measure and sample, while other quantitative skills show either no or negligible sex differences, or in the case of arithmetic calculation during childhood, a small to negligible sex difference favoring girls (Hyde et al., 1990). As with visuospatial abilities, enhanced quantitative skills might be predicted for females with CAH on tasks that favor males. Instead, a number of studies, again often based on small samples, suggest quantitative reductions for individuals with CAH (Baker & Ehrhardt, 1974; Perlman, 1973; Sinforiani et al., 1994).

We have recently found that children with CAH show lowered performance on digit span and have suggested this may result from elevated GC exposure (Browne et al., 2015). Digit span, a standard component of many intelligence and neuropsychological tests, is variously conceptualized as tapping short term memory (STM), working memory, and/or attention. It measures the amount of verbal information that can be processed and retained within a brief period of time (Lezak, 1995). For conciseness, we will refer to it here as a measure of STM.

Because the ability to attend and to remember recent material relates to numerous other cognitive abilities (Ackerman et al., 2005), reduced STM could have consequences for more complex cognitive skills. STM reductions, perhaps related to GC treatment, might contribute to quantitative or other cognitive challenges in individuals with CAH. For example, patients with Cushing's disease, marked by elevated endogenous GCs, show deficits in attention, spatial processing, and memory, including digit span (Forget et al., 2000; Martignoni et al., 1992), and the cognitive decrements resulting from GC excess may persist for years after treatment (Tiemensma et al., 2010).

Here we assess two alternative hypotheses regarding cognitive development in a relatively large sample of individuals with CAH. The hypothesis that spatial perception and mathematical tasks that show sex differences favoring males are improved by prenatal exposure to androgens would suggest that females with CAH should show enhanced performance compared to same-sex controls, while males with CAH should not differ from male controls. We also sought to replicate our finding of reduced STM (digit span) in patients with CAH, and secondarily hypothesized that such decreases may limit performance on cognitive tasks that relate to STM (Ackerman et al., 2005), including spatial and quantitative tasks. As a control, we also investigated whether general intelligence, as assessed by Vocabulary, varied between groups and whether reduced intelligence, perhaps caused by salt-wasting crises as suggested by Hampson & Rovet (2015), might also influence our findings. Vocabulary, considered to be a measure of crystallized rather than fluid intelligence, does not rely substantially on STM (Hayslip & Kennelly, 1982).

2. Methods

2.1 Participants

Participants included 69 individuals with CAH (40 female, 29 male), and 59 related controls (29 female, 30 male). The age range was 12 to 45 years (See Table 1 for means and standard deviations; there were no significant age differences between groups). Participants were part of a larger project examining a range of gender-related behaviors in individuals with CAH (Collaer et al., 2009; Hines et al., 2004; Hines et al., 2003; Knickmeyer et al., 2006; Mathews et al., 2009; Mathews et al., 2004). Participants were of European descent, other than one male with CAH and his unaffected sister who were South Asian (Indian, Pakistani, or Bangladeshi).

Recruitment of participants occurred through endocrinology clinics at University College London and Great Ormond Street Hospitals in London (n=35; 22 females, 13 males), as well as a support group for CAH patients in the UK (n=34; 18 females, 16 males). Control participants were unaffected siblings (n=57) or first cousins (n=2) of patients with CAH. The vast majority of patients (66 of 69) were deficient in the enzyme 21-hydroxylase, and 62 had the salt-wasting form of CAH, while four had the simple-virilizing form. Medical records indicating CAH variant were not available for three patients who were recruited via the support group, but their medications indicated that they had the salt-wasting variant. Participants and their parents, for those under the age of 18 years, provided written consent to take part in the study.

2.2 Materials and Procedure

Participants were tested in a six-hour session with frequent breaks for rest, lunch, and other nutrition. Tasks were presented in four different orders, and mentally demanding measures were intermixed with less demanding ones, such as motor tasks and surveys, to minimize fatigue. Although several studies on this cohort have been published previously, none of the measures reported here have been published, with the exception of the Vocabulary score which is included in many articles for control purposes. Further no new participants have been added to the cohort since completion of the project. The participants in this report are identical to those in four of the six other articles based on this cohort (Hines et al., 2003; Mathews et al., 2004; Collaer et al., 2009; and Mathews et al., 2009). Participant numbers differ in the two other studies because Hines et al. (2004) examined measures of sexuality, and so included only participants aged 18 years or older and who were tested when these measures were part of the battery (some participants had been tested prior to adding these measures), and who agreed to complete the sexuality measures. The sixth previously published article based on this cohort, Knickmeyer et al. (2006), included measures that were collected via mailed surveys rather than as part of the in-lab testing session and had fewer participants due to the return rate of these materials.

2.2.1 Spatial Perception Tasks

Judgment of Line Angle and Position-13 (JLAP): Participants match spatial attributes of target lines to 13 comparison lines. This task shows a large sex difference favoring males (Collaer & Nelson, 2002).

Water Level: Participants draw an imagined water line in bottles tipped at various angles, with error measured as the deviation from horizontal. This task shows a small to moderate sex difference favoring males (Voyer et al., 1995).

Rod-and-frame: Participants adjust a rod to vertical despite distracting information provided by a surrounding tilted frame, again producing an error score. This task shows a small to moderate sex difference favoring males (Voyer et al., 1995).

2.2.2 Quantitative Tasks

Scholastic Aptitude Test (SAT)-Math: This task measures the application of mathematical concepts to problem solving, and emphasizes algebra, geometry, and numerical operations (Lawrence et al., 2002). The test, designed for secondary school students, was administered to the 74 participants who were 16 years of age or older. It shows a small to moderate gender difference favoring males (Hyde et al., 1990).

Arithmetic Aptitude: This test of arithmetic word problems shows a small to moderate sex difference favoring males (Ekstrom et al., 1976).

Numerical Ability: This subtest of the Differential Aptitude Tests requires completion of specific calculations. Due to time considerations, the number of items and time were reduced by half. This task shows a negligible sex difference (Feingold, 1988).

2.2.3 Short Term Memory

Digit Span: On this subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), participants repeat series of digits either in the same order (digit span-forward) or in reverse order (digit span-backward) and the number of successful trials is counted. We also computed the sum of these two scores (digit span-total). This task shows a negligible sex difference (Jensen & Reynolds, 1983).

2.2.4 General Intelligence

Vocabulary: As a control measure for general intelligence, the scaled Vocabulary subtest score from the age-appropriate Wechsler Intelligence Scale was obtained. This test shows a negligible sex difference (Jensen & Reynolds, 1983).

2.3 Statistical Analyses

Analyses were conducted with SPSS using two-tailed tests and an alpha level of .05. The cognitive dependent variables (DVs) of spatial perception, quantitative ability, vocabulary, JLAP, and digit span were analyzed using two-way analysis of covariance (ANCOVA) with independent variables (IVs) of sex (male vs. female) and diagnosis (CAH vs. control) and age as the covariate. The distribution of Vocabulary scaled scores was additionally compared for patients and controls using Chi Square tests of independence with diagnosis as one factor and Vocabulary scaled score as the other. Task interrelationships were assessed using Pearson correlations. To further investigate unique predictive value of STM for both spatial and quantitative performance, two multiple regression analyses were performed including age, sex, diagnosis, and a sex X diagnosis interaction variable as predictors in the first block, with digit span added in a second block to assess unique variance explained when the other factors were controlled.

Effect sizes were calculated using Cohen's *d* which provides an index of the magnitude of the difference in group means versus score variability (standard deviation). Effect sizes of 0.2, 0.5 and 0.8 are considered small, medium, and large, respectively (Cohen, 1988). To put these in context, these effect sizes would correspond to mean group IQ differences of 3, 8 and 12 points.

3. Results

3.1 Cognitive composites and tasks in the sample as a whole

Tasks measuring spatial perception included the JLAP, water level, and rod-and-frame, all of which were expected to show sex differences favoring males. The score distributions for water level and rod-and-frame were skewed; therefore, these scores were transformed using log10. Because the spatial tests inter-correlated (*r* values ranging from .418 to .525, all *ps* < .001), a composite spatial perception measure was computed by averaging their standardized scores, reversing error z scores in sign so that higher scores indicated better performance. See Table 1 for composite means and standard deviations. The spatial perception composite showed main effects of sex, $F(1,123) = 5.67, p = .019, d = .42$, with males scoring higher than females, and of diagnosis, $F(1,123) = 7.05, p = .009, d = .47$, with controls scoring higher than individuals with CAH (Fig.1). There was no significant interaction of the IVs.

Tasks measuring quantitative skill included the SAT, Arithmetic Aptitude, and Numerical Ability. Because the quantitative tests inter-correlated (r values ranging from .610 to .762, all $ps < .001$); a quantitative composite measure (quantitative composite 1) was computed by averaging their standardized scores; however, because only a subset of participants was old enough to complete the SAT, the composite for participants under 16 years comprised the two remaining tasks. This quantitative composite showed a main effect of diagnosis that approached significance, $F(1,122) = 2.91, p = .091, d = .30$, with controls tending to score higher than individuals with CAH (Fig.1). There was no main effect of sex and no interaction of the IVs.

Because androgen effects would be predicted only for tasks that show sex differences, we also computed a composite for the two quantitative tasks on which males and females were expected to differ (SAT and Arithmetic Aptitude, when available, or just Arithmetic Aptitude for younger participants, quantitative composite 2). Quantitative composite 2 showed a significant main effect for diagnosis, $F(1,122) = 4.49, p = .036, d = .38$, with controls outscoring individuals with CAH. There was no main effect of sex and no interaction of the IVs.

To further examine possible androgenic influences on task performance, we compared control males and females to determine which individual measures showed significant sex differences in individuals without CAH, and so would be hypothesized to be influenced by androgens. Only the JLAP showed a significant sex difference in controls, $F(1,56) = 7.88, p = .007, d = .73$. We then tested for potential androgenic influences in the full sample by examining performance on the JLAP alone. Significant main effects on the JLAP were observed for sex, $F(1,123) = 7.39, p = .008, d = .50$, with males scoring higher than females, and diagnosis, $F(1, 123) = 6.14, p = .015, d = .45$, with controls scoring higher than patients with CAH. There was no interaction of the IVs. Because the JLAP showed a substantial sex difference for controls, we also conducted t-tests comparing females with and without CAH. There was no significant difference, $t(67) = 1.07, p = .29, d = .26$, with control females scoring nonsignificantly higher than females with CAH.

In contrast to tasks expected to show sex differences, Vocabulary scaled scores, as a measure of general intelligence, showed no significant main effects and no interaction (Fig. 2). Further, when the distribution of scaled scores was analyzed in relation to diagnosis using Chi Square, no significant differences existed between controls and patients with CAH for the sample as a whole or for males and females analyzed separately.

Finally, to investigate whether intellectual deficiency in some CAH patients, hypothetically due to salt-wasting crises, might mask androgen effects (see Hampson & Rovet, 2015), analyses on the spatial and on both quantitative composite scores were rerun after restricting the sample to those with estimated IQs of 70 points or greater (Vocabulary scaled scores of 7 or more), a typical cut off for intellectual disability (Schalock et al., 2007). The pattern of significant findings remained the same for the spatial and first quantitative composite. For the second quantitative composite, the reduced quantitative performance observed in this smaller sample for patients with CAH no longer passed the alpha level of .05 but the effect size was similar to that seen in the full sample, $F(1,105) = 2.70, p = .057, d = .36$.

To summarize, in the sample as a whole, there was no evidence suggesting (given the lack of significant interactions) that females with CAH showed enhanced (more male-typical) spatial perception or quantitative performance. Individuals with CAH, as a whole, scored lower (less masculine) or showed trends in that direction compared to control participants on measures expected to favor males. Thus, rather than cognitive masculinization in females with CAH, the results suggest spatial and quantitative performance decrements for patients with CAH with no evidence that this effect varied by sex. These findings occurred despite a lack of differences in general intelligence.

3.2 Cognitive composites and tasks for younger and older participants

We investigated whether the observed effects might vary for participants of different ages. Using a cut off of 20.0 years as suggested by a reviewer, analyses for the specific measures were recomputed for subsets of younger (adolescent) and older (adult) participants. This included splitting into a group of 88 adolescents below 20.0 years of age (49 CAH [30 female, 19 male], 39 controls [16 female, 23 male]), and 40 adults older than 20.0 years (20 CAH [10 female, 10 male], 20 controls [13 female, 7 male]). See Table 1 for means and standard deviations for the younger and older groups of participants.

For the spatial perception composite, the younger group showed no significant main effects of sex or diagnosis and no interaction, while the older group showed an effect of sex, $F(1,35) = 19.18, p = .001, d = 1.00$, with males scoring higher than females, and of diagnosis, $F(1,35) = 16.45, p = .001, d = .99$, with controls scoring higher than individuals with CAH. There was no significant interaction of the IVs.

For quantitative composite 1, the younger group showed no significant main effects of sex or diagnosis and no interaction, while the older group showed an effect of sex, $F(1,35) = 4.34, p = .045, d = .49$, with males scoring higher than females, and of diagnosis, $F(1,35) = 7.98, p = .003, d = .89$, with controls scoring higher than individuals with CAH, but no significant interaction of the IVs. For quantitative composite 2, again the younger group showed no significant main effects or interactions, while the older group showed a main effect of sex, $F(1,35) = 4.80, p = .035, d = .50$, with males scoring higher than females, and an effect of diagnosis, $F(1,35) = 11.76, p = .002, d = .95$, with controls scoring higher than individuals with CAH. There was no significant interaction of the IVs.

Exploring performance on the JLAP alone, the younger group showed no main effects of diagnosis or sex, and no interaction, while the older group showed a main effect of diagnosis, $F(1,35) = 8.51, p = .006, d = .74$, with controls scoring higher than patients with CAH, and a main effect of sex, $F(1,35) = 8.71, p = .006, d = .77$, with males scoring higher than females, but no interaction. In addition, because the JLAP showed a substantial sex difference for controls in the full sample, we conducted t-tests comparing females with and without CAH in adolescents and adults separately. There was no significant difference for adolescent females with and without CAH, $t(44) = 0.20, p = .85, d = .06$. Among adults, control women scored significantly higher than women with CAH on the JLAP, $t(21) = 2.49, p = .021, d = 1.05$. For the dependent measure of Vocabulary scaled score, there were no significant main effects of sex or diagnosis or interactions for either the younger or older groups.

3.3 Digit span performance and its relation to spatial and quantitative performance

Given the potential for STM to relate broadly to cognition (Ackerman et al., 2005), we explored whether this variable, as indexed by digit span, differed between patients and controls, and explored its potential contributions to performance on spatial perception and quantitative measures. Analyzing digit span-forward and backward scores separately, each showed a significant main effect of diagnosis: forward, $F(1,123) = 13.36$, $p = .001$, $d = .65$, and backward, $F(1,123) = 11.26$, $p = .001$, $d = .60$, but no main effects of sex and no interactions. Further, the forward and backward digit span scores correlated significantly, $r(126) = .554$, $p = .001$. Because they correlated, they were combined into a single variable – digit span total. Considering the sample as a whole, digit span total showed a main effect of diagnosis, $F(1,123) = 16.28$, $p = .001$, $d = .72$, with control participants scoring higher than individuals with CAH, but no significant main effect of sex and no interaction (Fig. 2). Restricting analyses to participants with estimated IQs over 70 points, the pattern of significant findings for digit span total was unaltered.

Analyzing digit span in the younger and older subgroups separately, both age groups showed a main effect of diagnosis, $F(1,83) = 4.69$, $p = .033$, $d = .36$ for the adolescent group, and $F(1,35) = 18.46$, $p = .001$, $d = 1.29$ for the adult group, with controls outperforming patients with CAH in both groups. Neither the younger nor older groups showed a main effect of sex or an interaction of sex and diagnosis.

Multiple regression—For both composite variables, spatial perception and quantitative performance, we conducted multiple regression in two blocks (Model 1 and Model 2), with age, sex, diagnosis, and a sex X diagnosis interaction variable as predictors in Model 1, and adding DS in Model 2 to assess unique predictive value. Tables 2 and 3 show R^2 , R^2 change, F change and effect sizes (Cohen's f^2) for the two analyses. For the spatial perception composite, Model 1 was significant ($R^2 = .119$, $p < .01$, $f^2 = 0.14$) with diagnosis accounting for significant variance ($p < .05$). When DS was added in Model 2, the model was significant ($R^2 = .210$, $p < .01$, $f^2 = 0.27$). Furthermore, F change was significant ($p < .001$), DS accounted for significant unique variance ($p < .001$, Beta = .328) and DS was the only significant predictor after age, sex, diagnosis and sex X diagnosis were controlled.

For the quantitative composite, Model 1 was not significant ($R^2 = .060$, $p = .109$, $f^2 = 0.06$). However, when DS was added in Model 2, the model was significant ($R^2 = .310$, $p < .001$, $f^2 = 0.45$). F change was significant ($p < .001$) and DS was the only significant predictor ($p < .001$, Beta = .541). Finally, statistics for tolerance (all values > 0.2) and variance inflation factor (VIF; all values < 5.0) showed that effects were not due to multi-collinearity in either regression analysis (spatial perception or quantitative performance).

4. Discussion

This study did not find evidence to support the hypothesis that elevated prenatal androgen exposure enhances or masculinizes spatial perception or quantitative abilities in females with CAH. Instead, results suggested that spatial perception and quantitative abilities may be reduced in some individuals with CAH. This reduction was seen for the sample as a whole and for adults, but not adolescents, with CAH, when the sample was subdivided by age.

Similarly, analyses comparing females with and without CAH showed no significant enhancement on JLAP in the CAH group, even though JLAP shows a substantial sex difference favoring males.

In addition, reductions in short term or working memory were consistently observed in patients with CAH compared to controls. This reduction was seen for the sample as a whole as well as in both adolescents and adults. Further, regression analyses showed that STM had significant and unique predictive value for both spatial and quantitative performance when age, sex, diagnosis, and the interaction of sex and diagnosis were controlled. This suggests that reduced STM performance in patients with CAH might, therefore, contribute to other cognitive challenges, including spatial and quantitative performance, particularly in adults.

The lack of masculinization of spatial perception and quantitative tasks in females with CAH, as well as a lack of masculinization of mental rotation in an earlier report on this cohort (Hines et al., 2003) can be juxtaposed with our previously published findings from this same cohort in other behavioral domains showing masculinization or defeminization. These include play, core gender identity, sexual orientation (Hines et al., 2004), targeting ability (Hines et al., 2003), aspects of personality (Knickmeyer et al., 2006; Mathews et al., 2009), and motor strength and some fine motor skills (Collaer et al., 2009). These prior findings suggest this group of patients is typical of girls and women with CAH in terms of showing increased masculinization for these other aspects of behavior, as has also been found by other researchers (Berenbaum & Hines, 1992; Dittmann, et al., 1992; Dittmann, 1992; Frisen et al., 2009; Helleday et al., 1993; Meyer-Bahlburg et al., 2006; Meyer-Bahlburg et al., 2008; Servin et al., 2003).

While evidence of masculinization in females with CAH is well-established for domains such as play, core gender identity, sexual orientation, and aggression, less agreement exists regarding spatial skills. Although the current study found no evidence for significantly enhanced spatial performance in females with CAH, some other studies have reported superior mental rotation or other spatial skills, such as virtual navigation, in females with CAH (Berenbaum et al., 2012; Resnick et al., 1986) or in females with the salt-wasting form of the disease (Hampson & Rovet, 2015; Mueller et al., 2008).

It appears unlikely that reductions in intelligence due to salt-wasting or hypoglycemic episodes are masking masculinizing effects of androgens on cognition in this sample, as has been suggested for another sample (Hampson & Rovet, 2015) because intelligence, as estimated by Vocabulary scores, did not differ in mean or overall distribution for patients with CAH compared to controls. Further, when analyses were restricted to participants with estimated IQs over 70 points, the patterns of results for the spatial and quantitative composites and short term memory were unchanged.

The studies finding enhancement of spatial skills in females with CAH have been conducted with participants in North America (Canada and the United States), while our study was conducted with participants in the United Kingdom; however, some other studies from North America have also failed to find spatial enhancement in females with CAH (Baker & Ehrhardt, 1974; Malouf et al., 2006; McGuire et al., 1975). Further, our finding that patients

and controls under 20.0 years of age showed no differences in spatial (or quantitative) performance, while patients over 20.0 years performed lower on these skills compared to relative controls was unexpected. These findings may reflect genuine differences in patients with CAH versus controls as a function of age, but they also could reflect reduced sample sizes and lowered power for the analyses broken down by age. Additional research could help determine if disorder-related cognitive effects vary reliably with age in CAH. If yes, age-related alterations could reflect contributions of the underlying disease process, a cumulative effect of treatment, such as prolonged exposure to GCs, the use of different treatments, such as specific GCs, or some combination of these.

The moderate to large reduction in short term or working memory found in this sample of adolescents and adults with CAH ($d = .72$) resembles findings from a separate sample of 7 to 11 year old children with CAH ($d = .70$) from our laboratory (Browne et al., 2015) as well as with limited data from Lewis et al. (1968; also see Nass and Baker, 1991). Because the ability to attend effectively is a prerequisite for success on many cognitive tasks, reduced short term or working memory could have a negative impact on other aspects of cognition (Unsworth & Engle, 2007), including spatial and quantitative abilities (Ackerman et al., 2005; Ashcraft and Krause, 2007; Silver & Goodman, 2008; Unsworth & Engle, 2007). Results of our regression analyses, showing that digit span significantly predicted spatial and quantitative performance, suggested that reduced short term or working memory could lead to reduced spatial or quantitative performance. This predictive relationship between STM and spatial or quantitative performance (from regression analyses) which holds for the sample as a whole and when other factors were controlled, combined with the finding (from our ANCOVA analyses) that patients with CAH demonstrated significantly reduced digit span, could help explain why some patients with CAH show reduced spatial or quantitative performance (also revealed in the ANCOVA analyses) in this study. Other studies also have demonstrated reduced performance for some patients with CAH on quantitative (Baker & Ehrhardt, 1974; Perlman, 1973) or spatial abilities (Berenbaum et al., 2012; Hampson et al., 1998).

A variety of mechanisms could explain the reduced STM in individuals with CAH. These include endogenous prenatal or postnatal hormonal factors that characterize the disease, neural consequences of these factors, or side effects of treatment. The androgen excess during prenatal life seems an unlikely mechanism, given the lack of cognitive masculinization observed and the pattern of reduced STM, a trait that does not generally show a sex difference. Although other prenatal hormone differences, such as elevated corticotropin releasing factor or adrenocorticotrophic hormone (ACTH) or deficient GCs, could conceivably alter development and, thus, explain our findings, little evidence supports their role, although their effects on human cognition are not well studied.

Perhaps the most likely explanation for reduced STM in CAH is glucocorticoid treatment. This treatment generally tends toward calculated overtreatment to adequately suppress ACTH and adrenal androgens, but it can be difficult to control, with patients often balanced imperfectly between high and low GCs. Even with multiple daily administrations to try to mimic the normal circadian rhythm, treatment 'frequently results in over- or under-replacement' (Debono et al., 2009, p. 223). Because cortisol may have an inverted-U shaped

relationship with cognition (Lupien & Lepage, 2001), either elevated or deficient GCs could theoretically impair cognitive abilities, but the body of evidence supports more deleterious effects of elevated GCs. Further, distinct from issues of general under- or over-dosing, STM could potentially be disrupted due to a temporal mismatch between the normal circadian rhythm of endogenous GCs compared to doses administered exogenously.

GCs influence neural function via effects on a number of neuropeptide and neurotransmitter systems that are critical to cognitive skills such as attention, perception, and memory, and while short term elevations can be beneficial to these functions, longer term elevations are considered to have detrimental effects (Erickson et al., 2003; Sapolsky, 2000). Potential reasons for GC-induced alteration of neural tissue or function are diverse, complex, and remain an area of active investigation. Disruptive effects of GCs could involve acute functional changes or long-term structural changes, with potential mechanisms including alterations in monoamines, decreased glucose transport, or increased vulnerability of neurons to insults (Erickson et al., 2003; Sapolsky, 2000). The observed consequences of long-term cortisol elevation include atrophy of regions of the hippocampus and prefrontal cortex (Erickson et al., 2003).

Digit span performance relies on a network of brain areas with prominent contributions from the prefrontal cortex (Aleman & van't Wout, 2008), an area containing substantial numbers of receptors for GCs (Wolf, 2003). Tasks involving short term or working memory and that rely on prefrontal cortex are known to be especially sensitive to interference from excessive GCs (Lupien et al., 1999). Cortisol administration has been found to acutely reduce digit span performance (Wolf et al., 2001) and chronic administration of hydrocortisone for 10 days has been found to impair performance on other tests with frontal lobe sensitivity (Young et al., 1999). Patients with Cushing's disease who present a model of chronic overexposure to GCs also show diminished attention and memory, including digit span (Forget et al., 2000; Martignoni et al., 1992; Tiemensma et al., 2010; Wolf, 2003). Also, participants showing elevated cortisol response to a challenging mental situation have been reported to show reduced attentional abilities (Bohnen et al., 1990).

Alternatively, our results may relate to possible brain damage due to adrenal crises associated with CAH. Individuals with the salt-wasting variant of CAH are at risk of these crises involving hyponatremia, hyperkalemia, and potentially hypoglycemia; and diffuse brain injury and cognitive disruptions may result from these episodes (Johannsen et al., 2006; Nass & Baker, 1991; White & Speiser, 2000). All but four of our patients had the salt-wasting form of CAH, preventing meaningful group comparisons to determine whether reductions in STM or other cognitive abilities were higher in patients with the salt-wasting than the simple virilizing form of CAH.

Strengths of the current study are its sample size, including the largest number of individuals with classical CAH in whom gender-related cognition has been assessed, as well as the use of unaffected relative controls. Weaknesses include an inability to analyze results in relation to several medical background factors, such as GC medication history, current hormone levels, genotype, or salt-wasting crises. Additional studies monitoring GC dosage, specific medication and timing of administration, compliance, and hormone concentrations could

clarify potential causal relationships between medical history variables and STM, or other cognitive outcomes, as well as the reason for variable group differences with age.

Regardless of the reasons for their emergence, the potential negative implications of reduced STM, or other cognitive abilities in individuals with CAH suggest that monitoring such individuals for educational challenges might be useful, so that remediation, if needed, can be offered early. In addition, if additional research confirms that glucocorticoid treatment, although life-saving, contributes to reduced STM or other cognitive difficulties, additional efforts to monitor administration protocols may be beneficial.

5. Conclusions

In this study, spatial perception and quantitative skill were not enhanced (i.e., made more male-typical) in females with CAH, providing no support for the hypothesis that prenatal androgen exposure enhances these abilities. Instead, individuals with CAH, particularly those aged 20 years and older, showed weakened performance in these domains, although this effect may be limited to participants over 20 years. Also, STM reductions as indexed by digit span were found in both adolescent and adult patients with CAH, and regression analyses showed that STM predicted spatial perception and quantitative performance in our sample independent of age, sex, and diagnosis effects. The most likely explanation of the reduced STM in patients with CAH is elevated GCs, although further research is needed to confirm this, and to explore possible contributions of other hormone imbalances, or brain insults from salt-wasting crises. If GCs are confirmed to contribute, treatment protocols and their success in achieving optimal control may benefit from continued scrutiny. In addition, educational interventions might be of use for individuals with CAH.

Acknowledgements

Research reported in this publication/press release was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under award number R01HD024542 to MH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We thank the families, children, and adults whose participation made this research possible. We also thank Dr. Caroline Brain and Dr. Leah Charmandari for referring patients to the study and Mrs. Sue Elford and others in the CAH support group for their help in recruiting participants.

Role of Funding Sources

The funding agencies played no role in study design; in the collection, analysis, or interpretation of data; or in the writing of the report or the decision to submit it for publication.

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Highlights

- Individuals with CAH show cognitive reductions in spatial and quantitative skills, although this may be limited to adult vs. adolescent participants
- Performance was also reduced on digit span, a measure of short term memory (STM)
- Digit span scores predicted performance in the spatial and quantitative domains
- Glucocorticoid treatment may lower STM with implications for other cognitive skills

Figure 1.
The spatial perception and quantitative composite scores for individuals with CAH and controls ($\pm$ standard error of the mean).

Figure 2. Digit Span and Vocabulary scores for individuals with CAH and controls ($\pm$ standard error of the mean).

Table 1

Means and standard deviations for each sex and diagnosis group

Measure	Female				Male			
	CAH (n=40)		Controls (n=29)		CAH (n=29)		Controls (n=30)	
Whole sample	M	SD	M	SD	M	SD	M	SD
Age	19.49	7.30	19.26	5.95	20.27	8.43	18.00	6.81
Spatial perception composite ^{a,b}	-0.30	0.92	0.02	0.63	0.00	0.77	0.37	0.71
Quantitative composite 1 ^c	-0.11	0.79	0.05	0.86	-0.17	0.84	0.13	1.02
Quantitative composite 2 ^a	-0.21	0.79	0.12	0.92	-0.17	0.89	0.14	1.10
JLAP ^{a,b}	9.55	4.13	10.62	4.08	10.83	3.85	13.17	3.71
Vocabulary	8.53	2.52	9.28	2.36	9.10	2.66	8.77	2.24
Digit Span ^a	12.35	3.41	14.83	3.43	12.21	3.80	14.73	4.46
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Younger (< 20.0 yrs) subsample	(n=30)		(n=16)		(n=19)		(n=23)	
	M	SD	M	SD	M	SD	M	SD
Age	16.03	2.17	14.70	2.47	15.39	2.30	15.15	2.38
Spatial perception composite	-0.16	0.94	-0.25	0.64	-0.21	0.76	0.20	0.69
Quantitative composite	-0.03	0.86	-0.17	0.88	-0.28	0.75	-0.19	0.67
Quantitative composite 2	-0.12	0.86	-0.09	1.03	-0.27	0.84	-0.17	0.86
JLAP	10.13	4.13	9.88	4.54	10.37	4.09	12.74	3.71
Vocabulary	8.67	2.81	9.44	2.87	8.89	2.49	8.65	2.23
Digit Span ^a	12.33	3.74	13.75	3.13	11.84	3.69	13.13	3.00
<hr/>								
Older (> 20.0 yrs) subsample	(n=10)		(n=13)		(n=10)		(n=7)	
	M	SD	M	SD	M	SD	M	SD
Age	29.88	7.51	24.87	3.66	29.54	8.03	27.37	8.37
Spatial perception composite ^{a,b}	-.72	.75	0.36	0.43	0.40	0.65	0.93	0.44
Quantitative composite 1 ^{a,b}	-0.34	0.51	0.32	0.79	0.04	0.99	1.19	1.29
Quantitative composite 2 ^{a,b}	-0.47	0.53	0.37	0.73	0.03	0.99	1.15	1.25
JLAP ^{a,b}	7.80	3.80	11.54	3.38	11.70	3.37	14.57	3.60
Vocabulary	8.10	1.37	9.08	1.61	9.50	3.06	9.14	2.41
Digit Span ^a	12.40	2.32	16.15	3.44	12.90	4.12	20.00	4.55

Notes: JLAP = Judgment of Line Angle and Position test. The table presents raw means and standard deviations (SDs). The spatial and quantitative composites are averages of standard scores (see text for details).

^a Main effect of diagnosis, with controls outperforming individuals with CAH, $p < .05$

^b Main effect of sex, with males outperforming females, $p < .05$

^c Trend for a main effect of diagnosis, with controls tending to outperform individuals with CAH, $p < .10$

Table 2

Summary of Multiple Regression Analysis for Variables Predicting the Spatial Perception Composite

N = 128	R ²	R ² Change	F Change		Standardized Coefficients		
			F	p	Beta	t	p
Model 1 ($p = .003$, $f^2 = 0.14$) [†]	.119	.119	4.16	.003 ^{**}			
Age					.166	1.95	.054
Sex					.230	1.85	.067
Diagnosis					.254	2.03	.044 [*]
Sex × Diagnosis interaction					.051	0.32	.750
Model 2 ($p = .005$ ^{**} , $f^2 = 0.27$) [†]	.210	.091	14.10	.000 ^{***}			
Age					.092	1.10	.274
Sex					.227	1.92	.057
Diagnosis					.137	1.11	.268
Sex × Diagnosis interaction					.039	.258	.797
Digit Span - total					.328	3.75	.000 ^{***}

*
 $p < .05$ **
 $p < .01$ ***
 $p < .001$ [†] Effect size is Cohen's $f^2 = R^2 / 1 - R^2$ (Cohen, 1988).

Table 3

Summary of Multiple Regression Analysis for Variables Predicting the Quantitative Composite

N = 128	R ²	R ² Change	F Change		Standardized Coefficients		
			F	p	Beta	t	p
Model 1 ($p = .109$, $f^2 = 0.06$) [†]	.060	.060	1.93	.109			
Age					.203	2.30	.023*
Sex					-.066	-.513	.609
Diagnosis					-.208	-1.607	.111
Sex × Diagnosis interaction					.105	.639	.524
Model 2 ($p = .000^{***}$, $f^2 = 0.45$) [†]	.310	.250	43.82	.000***			
Age					.082	1.04	.298
Sex					-.062	-.559	.577
Diagnosis					-.014	-.122	.903
Sex × Diagnosis interaction					.081	.574	.567
Digit Span - total					.541	6.62	.000***

** $p < .01$ * $p < .05$ *** $p < .001$ [†] Effect size is Cohen's $f^2 = R^2 / 1 - R^2$ (Cohen, 1988).