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# Spatial Ability and Prenatal Androgens: Meta-analyses of CAH and Digit Ratio (2D:4D) Studies

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## Abstract

Hormonal manipulations indicate that early androgens organize sex differences in spatial ability in animal models. In humans, spatial ability is also sexually dimorphic, and information about the effects of prenatal androgens on spatial ability can be obtained from studies of congenital adrenal hyperplasia (CAH) and the ratio of the second and fourth finger lengths (2D:4D). CAH is a condition characterized by prenatal overproduction of adrenal androgens, and several lines of evidence suggest that 2D:4D reflects prenatal androgen exposure. Some studies have found that these proxy measures of prenatal androgenization predict spatial ability, others have found no significant relationship, and yet others have obtained results in opposite directions. In light of these mixed findings, we conducted meta-analyses of published literature and unpublished results to determine if, across studies, either of these indications of prenatal androgens predicts spatial ability. In addition, we applied a trim and fill analysis to the data in search of asymmetry that might be an indication of publication bias. Results indicate that females with CAH have significantly better spatial abilities, and CAH males have worse spatial abilities, than do controls. Little or no relationship exists between 2D:4D and spatial ability. Implications for possible hormonal contributions and the developmental timing of sex differences in spatial cognition are discussed.

### Keywords

androgens; congenital adrenal hyperplasia; digit ratio; spatial ability; 2D:4D

## INTRODUCTION

The largest known human cognitive sex differences are found in the domain of spatial ability (Maccoby & Jacklin, 1974), with three-dimensional mental rotation tasks showing the largest effect sizes in meta-analytic studies (Voyer, Voyer, & Bryden, 1995). Mental rotation ability is the ability to imagine objects from a perspective other than the one depicted. Sex differences in mental rotations have been observed in African (Mayes & Jahoda, 1988; Owen & Lynn, 1993), East Indian (Owen & Lynn, 1993), and Asian (Mann, Sasanuma, Sakuma, & Masaki, 1990) populations, as well as in Western cultures. Recently, sex differences in spatial ability greater than those observed in mental rotations have been reported for virtual water mazes, computerized versions of mazes used in animal models (Astur, Ortiz, & Sutherland, 1998).

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Because virtual water maze and mental rotation performance correlate (Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005), and because males outperform females on water mazes in both humans (Astur et al., 1998; Driscoll et al., 2003; Driscoll et al., 2005) and laboratory rats (Jonasson, 2005), rats are likely to represent useful models for possible hormonal contributions to sex differences in human spatial abilities. In rats, spatial ability is masculinized perinatally by testicular hormones. Several studies have shown that neonatal castration impairs maze learning in males (Dawson, Cheung, & Lau, 1975; Isgor & Sengelaub, 2003; Joseph, Hess, & Birecree, 1978; C. L. Williams, Barnett, & Meck, 1990), and neonatal testosterone treatment improves maze performance in females (Dawson et al., 1975; Isgor & Sengelaub, 1998, 2003; Joseph et al., 1978; Roof, 1993; Roof & Havens, 1992; Stewart, Skvarenina, & Pottier, 1975). However, there may be an optimal level of early androgen exposure beyond which spatial ability declines. Early androgen treatment improves spatial ability in female rats, but impairs it in gonadally intact males (Roof, 1993; Roof & Havens, 1992).

Some evidence suggests that early androgens also masculinize human spatial ability (reviewed in Puts, Gaulin, & Breedlove, in press). This evidence includes reported relationships between spatial ability and congenital adrenal hyperplasia (CAH), a condition characterized by elevated prenatal androgen levels. In CAH, an enzyme deficiency causes precursors of cortisol to be shunted down the androgen pathway, leading to an overproduction of adrenal androgens (Pang et al., 1980). Although the hormonal abnormalities of CAH are treated shortly after birth, girls with CAH show signs of elevated prenatal androgen exposure (for example, virilized genitalia) and tend to be masculinized along several behavioral dimensions (Berenbaum, 1999). Some studies have found CAH females to exhibit masculinized spatial abilities (Hampson, Rovet, & Altmann, 1998; Hines et al., 2003; Perlman, 1973; Resnick, Berenbaum, Gottesman, & Bouchard, 1986), although others have not (Baker & Ehrhardt, 1974; Helleday, Bartfai, Ritzen, & Forsman, 1994; Malouf, Migeon, Carson, Petrucci, & Wisniewski, 2006; McGuire, Ryan, & Omenn, 1975; Ripa, Johannsen, Mortensen, & Muller, 2003). Studies of spatial ability in CAH males have obtained equally inconsistent results, with some finding worse spatial ability in CAH males relative to controls (Hampson et al., 1998; Hines et al., 2003) and others finding no significant difference (Baker & Ehrhardt, 1974; McGuire et al., 1975; Resnick et al., 1986).

Possible relationships between early androgens and human spatial ability have also motivated digit ratio studies. The ratio of the lengths of the second and fourth fingers (2D:4D), is a putative marker for early androgens. Males have a lower 2D:4D than do females (Manning, Scutt, Wilson, & Lewis-Jones, 1998), a sex difference present by the end of the first trimester of gestation (Malas, Dogan, Evcil, & Desdicioglu, in press). Because of its early emergence, sexual dimorphism in 2D:4D is thought to be influenced by prenatal sex hormones (Manning et al., 1998). In particular, 2D:4D appears to be influenced by androgens: a more masculine digit ratio has been associated with CAH (Brown, Hines, Fane, & Breedlove, 2002; Okten, Kalyoncu, & Yaris, 2002, but see Buck, Williams, Hughes., & Acerini, 2003), as well as genetic predictor of androgen sensitivity (Manning, Bundred, Newton, & Flanagan, 2003). Because 2D:4D may reflect prenatal androgens, multiple studies have utilized this morphological marker to examine a possible role of early androgens on spatial ability (Alexander, 2005; Austin, Manning, McInroy, & Mathews, 2002; Coolican & Peters, 2003; Csatho, Karadi, & Kallai., 2005; Csatho et al., 2003; Kempel, Burk, & Hennig, 2005; Kempel, Gohlke et al., 2005; Loehlin, Luciano, Medland, & Martin, 2005; Manning & Taylor, 2001; McFadden & Schubel, 2003; Peters & Manning, 2005; Poulin, O'Connell, & Freeman, 2004; Putz, Gaulin, Sporter, & McBurney, 2004; Rahman, Wilson, & Abrahams, 2004; Sanders, Bereckzei, Csatho, & Manning, 2005; Scarbrough & Johnston, 2005; van Anders & Hampson, 2005). The results of these studies have also been quite variable, with some finding positive relationships, others finding negative relationships, and still others finding no significant relationship, even within a single sex (see Putz et al., 2004 for a partial review).

The purpose of the present study is to investigate relationships between CAH and 2D:4D and spatial ability in men and women across studies using meta-analytic methods.

# METHODS

## Study Selection

All available published and unpublished studies that examined relationships between spatial ability and either CAH or 2D:4D were obtained. These studies were located via web-based searches using scientific internet search engines (e.g., PubMed, Scirus, Google Scholar), a query regarding such studies posted to an internet listserv (SEXNET) that reaches over 300 researchers of sex differences and sexual behavior, bibliographies of published papers, and personal communication with over 40 researchers in these areas. For studies in which the authors collected 2D:4D and spatial ability data but did not report the correlation between these measures, the correlations were requested from the authors.

## Decision Rules

Standardized mean differences were the effect size for CAH studies, and correlations were the effect size for 2D:4D studies. All measures of effect size contributing to the meta-analyses are from independent samples. Because it shows a large and reliable sex difference, performance on a three dimensional mental rotations test (3D MRT) was used as the measure of visuospatial ability with two exceptions. First, if a 3D MRT was not administered in a study, then the closest available measure that reliably exhibits a sex difference was used (e.g., 2D MRT). Second, if the seemingly closest available measure to 3D MRT did not exhibit a sex difference among controls (CAH studies), or if another visuospatial test exhibited a larger male advantage in a particular study, then the next closest test to 3D MRT was used. In one study (Hampson et al., 1998), results were presented both with and without an outlier that fell >4 SDs above the mean spatial performance of her group. The decision to use the effect size from the analysis with the outlier removed was made with a coin flip. For 2D:4D studies, correlations between spatial ability and right hand 2D:4D were used, because sex differences in 2D:4D and relationships between 2D:4D and behavioral traits have found to be greater in the right hand than in the left (Manning, 2002; McFadden & Schubel, 2003; T. J. Williams et al., 2000). If right 2D:4D was not reported or available from the authors, then mean 2D:4D was used (one male sample), and finally left 2D:4D was used (one male sample).

## Meta-analysis

All meta-analyses were performed using Comprehensive Meta-analysis Program V.2 (Borenstein, Hedges, Higgins, & Rothstein, 2005). Meta-analyses were conducted on effect sizes using both fixed and random effects models. The fixed effects model assumes that there are no moderators in the relationships between the predictor variable (CAH or 2D:4D) and spatial ability, while the random effects model considers the presence of moderators a possibility. Although we present both the fixed and random effects model results, the random model is the most appropriate for these data, and we limit our discussion to it. In addition to estimating the population mean (CAH studies) or population correlation (2D:4D studies) and confidence interval, we applied a “trim and fill” analysis (Duval & Tweedie, 2000) to the data in search of asymmetry that might be an indication of publication bias. Trim and fill determines where missing studies are likely to fall, adds them to the analysis, and then recomputes the combined effect. An “omit one study” analysis was also performed. This is a type of sensitivity analysis that determines if the results of the meta-analysis would change through the deletion of a study. The effect size to be analyzed for CAH studies was the standardized mean difference (*d*), which expresses the mean differences between a CAH group and a control group in standard deviation units. Thus, a *d* of 1 would indicate that the mean of the CAH group was one standard deviation higher than the mean of the control group. The effect size to be analyzed

for 2D:4D studies was the correlation coefficient between 2D:4D and spatial ability. Males and females were analyzed both separately and together.

# RESULTS

## CAH Studies

**Females—**Effect sizes for differences in spatial ability between CAH females and controls were obtained for nine samples from eight studies, involving a total of 128 CAH females and 108 controls (Baker & Ehrhardt, 1974; Hampson et al., 1998; Helleday et al., 1994; Hines et al., 2003; Malouf et al., 2006 [two samples]; McGuire et al., 1975; Perlman, 1973; Resnick et al., 1986, Table 1). CAH Females outperformed controls on spatial tasks. The population standardized mean difference in spatial ability between CAH females and controls was .465 for the random effects model and .336 for the fixed effects model (Figure 1). These results were robust with respect to the deletion of individual studies; "omit one study" analysis produced effect sizes ranging from .303 to .600 under the random effects model (Figure 2). Trim and fill analysis did not reveal any asymmetry in the data and did not change point estimates.

**Males—**Five studies compared the spatial performance of a total of 61 CAH males to 64 controls (Baker & Ehrhardt, 1974; Hampson et al., 1998; Hines et al., 2003; McGuire et al., 1975; Resnick et al., 1986, Table 1). Overall, CAH males performed worse on spatial tasks than did controls for both fixed and random effects models. For the random effects model, the effect size of the standardized mean difference between CAH males and controls was −.602, and the corresponding value for the fixed effects model was −.583 (Figure 1). The deletion of individual studies in the "omit one study" sensitivity analysis produced effect sizes under the random effects model ranging from −.822 to −.406 (Figure 2), and thus did not change the conclusion that CAH males exhibit poorer spatial performance. Trim and fill analysis suggested the presence of one missing study to the left of the mean effect. With this study imputed, trim and fill shifted the population standardized mean difference from −.602 to −.718 for the random effects model. To the extent that publication bias may be present in this literature, it does not alter the conclusion that CAH males exhibit poorer spatial ability.

## 2D:4D Studies

**Females—**Twenty-one correlations between 2D:4D and spatial ability were obtained from 11 published (Austin et al., 2002; Coolican & Peters, 2003; Csatho et al., 2003; Kempel, Gohlke et al., 2005 [3 samples]; McFadden & Schubel, 2003 [2 samples]; Poulin et al., 2004; Putz et al., 2004; Rahman et al., 2004 [2 samples]; Sanders et al., 2005; Scarbrough & Johnston, 2005; van Anders & Hampson, 2005) and five unpublished (Alexander, 2005 [2 samples]; Csatho et al., 2005; Kempel, Burk et al., 2005; Loehlin et al., 2005; Peters & Manning, 2005) studies, involving a total of 101,488 subjects (Table 2). The fixed effects model rendered an effect size estimate of −.028, and the random effects model produced a smaller effect size estimate in the opposite direction: .005 (Figure 3). Sensitivity analysis revealed that these near-zero results were minimally affected by the removal of any given study. When individual studies were deleted from the analysis, the population effect size estimate for the random effects model ranged from −.016 to .008 (Figure 4). Trim and fill analysis suggested that one study was missing to the left of the mean effect. Using the random effects model, the trim and fill point estimate was −.001.

**Males—**For relationships between 2D:4D and spatial ability in men, 18 effect sizes were obtained from nine published (Austin et al., 2002; Coolican & Peters, 2003; Kempel, Gohlke et al., 2005; Manning & Taylor, 2001; McFadden & Schubel, 2003 [2 samples]; Poulin et al., 2004; Putz et al., 2004; Rahman et al., 2004 [2 samples]; Sanders et al., 2005 [3 samples]) and

four unpublished (Alexander, 2005 [2 samples]; Kempel, Burk et al., 2005; Loehlin et al., 2005; Peters & Manning, 2005) studies, involving 117,353 total subjects (Table 2). The effect size estimate was −.030 using the fixed effects model, and −.068 using the random effects model (Figure 3). These near-zero point estimates were also robust with respect to removal of individual studies from the analysis; the "omit one study" analysis produced population correlation estimates ranging from −.073 to −.030 (Figure 4). Trim and fill analysis suggested that three studies were missing to the right of the mean correlation. With these studies imputed, the point estimate under the random effects model was −.015.

## DISCUSSION

Given these results, we offer the tentative conclusions that CAH females have an advantage in spatial ability, CAH males have a disadvantage in spatial ability, and spatial ability is very weakly, if at all, associated with 2D:4D.

### CAH Studies

We estimate the population standardized mean difference between CAH individuals and controls to be .465 for females and −.602 for males. According to Cohen (1988), these represent small- to medium-sized effects. Results were robust with respect to meta-analytical model (fixed vs. random effects) and sensitivity analyses. "Omit one study" analyses demonstrated minimal effects of deleting individual studies, indicating that these results do not rely on the inclusion of outlier studies or on the application of decision rules to idiosyncratic studies. In addition, trim and fill results suggested no evidence of publication bias in female studies, and, to the extent that publication bias exists in the male studies, it serves to underestimate the strength of the relationship.

One interpretation of these results is that the additional prenatal androgens provided by CAH increased spatial ability in females and decreased it in males. This interpretation accords with research on rats, in which males exhibit superior spatial performance to females (Jonasson, 2005), and testosterone treatment improves spatial ability in females (Dawson et al., 1975; Isgor & Sengelaub, 1998, 2003; Joseph et al., 1978; Roof, 1993; Roof & Havens, 1992; Stewart et al., 1975) but worsens it in males (Roof, 1993; Roof & Havens, 1992).

This interpretation is also consonant both with studies finding behavioral masculinization in CAH females (Berenbaum, 1999) and with studies suggesting that human spatial ability is related to prenatal androgens. For example, second trimester testosterone levels have been found to predict spatial ability positively in girls and negatively (but less clearly) in boys at age seven (Grimshaw, Sitarenios, & Finegan, 1995). Girls with male twins have also been found to exhibit superior spatial ability, possibly because of *in utero* exposure to androgens produced by their twins (Cole-Harding, Morstad, & Wilson, 1988). Additionally, females with Turner Syndrome, in which androgen and estrogen production are extremely low due to undifferentiated gonads (Hojbjerg Gravholt, Svenstrup, Bennett, & Sandahl Christiansen, 1999; Ross et al., 2002), exhibit specific cognitive deficits in spatial ability (Nijhuis-van der Sanden, Eling, & Otten, 2003). Complete androgen insensitivity syndrome (CAIS) individuals, who have a 46, XY karyotype, develop testes that remain undescended, and produce normal-to-high male levels of testosterone, are nonetheless phenotypically female because they lack functional androgen receptors (Imperato-McGinley et al., 1982). Females with CAIS performed worse on spatial tasks than both their male and non-CAIS female relatives (Imperato-McGinley, Pichardo, Gautier, Voyer, & Bryden, 1991). This finding is consistent with testosterone improving spatial ability in men and in women with functional androgen receptors, although ovarian hormone production in unaffected females may have caused them to differ from CAIS women.

Despite evidence that spatial ability is related to early androgens, and that CAH females are masculinized in other behavioral domains, the interpretation that elevated prenatal androgens produced the observed differences between CAH and unaffected individuals must be made cautiously. First, CAH individuals also differ from unaffected individuals in glucocorticoid levels, which may affect spatial abilities. However, if the relationship between glucocorticoids and spatial ability were simple, one would predict that the direction of the CAH effect on performance would be the same in males and females, since both see a profound lack of glucocorticoids. On the other hand, it is possible that the lack of glucocorticoids affects the two sexes differently. For example, glucocorticoid treatment impaired spatial ability more in female than in male rats (Vicedomini, Nonneman, DeKosky, & Scheff, 1986). On the other hand, stress increases glucocorticoid levels, and both prenatal and postnatal stress have been found to increase spatial ability in female rats and decrease it in males (Bowman et al., 2004; Kitraki, Kremmyda, Youlatos, Alexis, & Kittas, 2004). Second, although CAH is treated soon after birth with a synthetic glucocorticoid, improper management can lead to health complications and impaired cognitive performance (Berenbaum, 2001). This would appear to explain only why CAH males exhibit lower spatial abilities, however, and not why spatial abilities are elevated in CAH females. Of course, it is possible that imperfect glucocorticoid management decreases spatial ability in both males and females with CAH, but that the coincident increase in prenatal androgen masks this effect in females. Third, prenatal androgens may not consistently be elevated in CAH males, although evidence suggests that androgen levels are higher in CAH males during at least some stages of prenatal development. For example, androgen levels assayed via amniocentesis were higher in CAH males than in controls (Dorr & Sippell, 1993; Wudy, Dorr, Solleder, Djalali, & Homoki, 1999), and CAH males were found to have more masculine 2D:4D on both hands compared to their male relatives (Brown et al., 2002; Okten et al., 2002). However, negative feedback on testicular androgen production may normalize or even reduce androgen levels during the critical period for differentiation of spatial ability. Consequently, spatial deficits in CAH males may result from reduced androgens or even be unrelated to prenatal androgens, although only the former possibility explains elevated spatial ability in CAH females. It is also possible that a particular level of prenatal androgen exposure is optimal for adult spatial ability and that either lesser or greater exposure has less effect on this behavior. Finally, our CAH analyses were based on a relatively small amount of data. These analyses should be conducted again as more data cumulate.

### 2D:4D Studies

In contrast to the small- to medium-sized relationships observed between CAH and spatial ability, correlations between 2D:4D and spatial ability were negligible. Cohen (1988) suggests that a correlation of .1 represents a small effect, and in this meta-analysis, population correlations under the random effects model were .005 for females and −.068 for males. These effect sizes remained very small, regardless of which study was deleted in the “omit one study” sensitivity analysis. Trim and fill analysis suggested some publication bias, and after correcting for this bias by imputing hypothetical missing studies, the point estimates were shifted even closer to zero: −.001 for females, −.015 for males.

Assuming that both 2D:4D and spatial ability sexually differentiate under the influence of prenatal androgens, this essential lack of correlation may appear paradoxical. At least two possible explanations exist. First, the sex difference in 2D:4D accounts for only around 6–9% of the variation in 2D:4D (Coolican & Peters, 2003) and therefore probably only weakly reflects prenatal hormone regimes (van Anders & Hampson, 2005). In fact, this estimate represents the maximum variance in digit ratio that could be attributable to sex differences in prenatal hormones regimes. Because within-sex variation in sex hormones must be lower than between-sex variation, even less variance in digit ratio can be explained by within-sex variation in sex hormones. Males and females also overlap considerably in spatial ability (Maccoby & Jacklin,

1974), so the relationship between these two imperfect hypothetical correlates of prenatal androgens (2D:4D and spatial ability) would also tend to be weak.

2D:4D and spatial ability may also differ in the developmental timing of their putative sensitivity to androgens (Putz et al., 2004; van Anders & Hampson, 2005). 2D:4D should predict sexually dimorphic traits that differentiate under the influence of the same hormones during the same critical period. Sexual orientation appears to be one such trait; homosexual women have more masculine digit ratios on average than do heterosexual women (McFadden et al., 2005; T. J. Williams et al., 2000). However, if androgen levels during the critical periods for 2D:4D and spatial ability sexual differentiation are unrelated, then 2D:4D and spatial ability may also be uncorrelated.

### Implications for the Timing of Sexual Differentiation

Given that 2D:4D appears to have sexually differentiated by the ninth gestational week (Malas et al., in press), and testicular androgen production cannot begin until the fetal Leydig cell population arises at six weeks postconception (O'Shaughnessy, Baker, & Johnston, 2006), 2D:4D probably sexually differentiates during this interval, and spatial ability probably differentiates sometime thereafter. Hines et al. (2003) suggested that this period may occur as late as the first six months of postnatal life, but the fact that CAH is detected and treated soon after birth, especially in females, would seem to argue against differentiation occurring much after birth. In rats, spatial ability sexually differentiates during the first two of weeks after birth (Dawson et al., 1975; Joseph et al., 1978; Stewart et al., 1975). Because rats are born relatively underdeveloped, this corresponds approximately to the end of the third trimester of gestation in humans (Nunez & McCarthy, 2003), which would appear to be a likely time frame for the sexual differentiation of human spatial ability. If the hormonal abnormalities associated with CAH begin before the critical period for 2D:4D sexual differentiation and persist through the critical period for sexual differentiation of spatial ability, this would explain why both 2D:4D and spatial ability relate to CAH, even though they do not appear to be related to one another.

## CONCLUSIONS

These results, though tentative, can inform hypotheses regarding several aspects of human sexual differentiation. First, relationships between CAH and spatial ability support the hypothesis that early androgens affect the development of at least one cognitive sex difference, visuospatial cognition. However, decreased prenatal glucorticoid levels in CAH individuals may also affect spatial abilities. Second, these results suggest that the nature of a putative relationship between early androgens and human spatial ability is curvilinear, as in laboratory rats, with very low levels and very high levels of androgens associated with poorer spatial ability. This interpretation relies on higher androgen levels in CAH males than in controls, for which some evidence exists. Finally, moderate associations between CAH and spatial ability, and very small correlations between 2D:4D and spatial ability, provide evidence regarding the timing of sexual differentiation in the neural systems underlying spatial cognition. Specifically, spatial ability probably differentiates after 2D:4D, perhaps in the second or third trimester of gestation, or even in the early postnatal period.

Given the small number of CAH studies analyzed and some evidence for publication bias in studies of 2D:4D, we encourage replication of these results as more data accumulate. We also encourage improved reporting of results. For CAH studies, authors should report means and standard deviations by sex. For both 2D:4D studies and CAH studies, separate correlation matrices by sex should provide intercorrelations of all variables.

## References


Alexander, GM. Unpublished data. 2005. Correlations between 2D:4D and 3D mental rotation performance.

Astur RS, Ortiz ML, Sutherland RJ. A characterization of performance by men and women in a virtual Morris water task: a large and reliable sex difference. Behav Brain Res 1998;93(1–2):185–190. [PubMed: 9659999]

Austin EJ, Manning JT, McInroy K, Mathews E. A preliminary investigation of the associations between personality, cognitive ability and digit ratio. Personality and Individual Differences 2002;33:1115–1124.

Baker, SW.; Ehrhardt, AA. Prenatal androgen, intelligence, and cognitive sex differences. In: Friedman, RC.; Richart, RM.; Vande Wiele, RL., editors. Sex differences in behavior. New York: John Wiley & Sons; 1974. p. 53-76.

Berenbaum SA. Effects of early androgens on sex-typed activities and interests in adolescents with congenital adrenal hyperplasia. Horm Behav 1999;35(1):102–110. [PubMed: 10049608]

Berenbaum SA. Cognitive function in congenital adrenal hyperplasia. Endocrinol Metab Clin North Am 2001;30(1):173–192. [PubMed: 11344935]

Bodner GM, Guay RB. The Purdue visualization of rotations test. The Chemical Educator 1997;2:1–18.

Borenstein, M.; Hedges, L.; Higgins, J.; Rothstein, H. Comprehensive Meta-analysis Version 2. Englewood, NJ: Biostat; 2005.

Bowman RE, MacLusky NJ, Sarmiento Y, Frankfurt M, Gordon M, Luine VN. Sexually dimorphic effects of prenatal stress on cognition, hormonal responses, and central neurotransmitters. Endocrinology 2004;145(8):3778–3787. [PubMed: 15142991]

Brown WM, Hines M, Fane BA, Breedlove SM. Masculinized finger length patterns in human males and females with congenital adrenal hyperplasia. Horm Behav 2002;42(4):380–386. [PubMed: 12488105]

Buck JJ, Williams RM, Hughes IA, Acerini CL. In-utero androgen exposure and 2nd to 4th digit length ratio-conparisons between healthy control and females with classical congenital adrenal hyperplasia. Human Reproduction 2003;18:976–979. [PubMed: 12721171]

Cohen, J. Statistical power for the behavioral sciences. 2. Hillsdale, NJ: Erlbaum; 1988.

Cole-Harding S, Morstad AL, Wilson JR. Spatial ability in members of opposite-sex twin pairs. Behavior Genetics 1988;18:710.

Coolican J, Peters M. Sexual dimorphism in the 2D/4D ratio and its relation to mental rotation performance. Evolution and Human Behavior 2003;24:179–183.

Cooper, LA.; Shepard, RN. Chronometric studies of the rotation of mental images. In: Chase, WG., editor. Visual information processing. Oxford: Academic Press; 1973. p. 75-176.

Csatho, A.; Karadi, K.; Kallai, J. Unpublished data. 2005. Correlations between 2D:4D and 3D mental rotation performance.

Csatho A, Osvath A, Karadi K, Bicsak E, Manning JT, Kallai J. Spatial navigation related to the ratio of second to fourth digit length in women. Learning and Individual Differences 2003;13:239–249.

Dawson JL, Cheung YM, Lau RT. Developmental effects of neonatal sex hormones on spatial and activity skills in the white rat. Biol Psychol 1975;3(3):213–229. [PubMed: 1203405]

Dorr HG, Sippell WG. Prenatal dexamethasone treatment in pregnancies at risk for congenital adrenal hyperplasia due to 21-hydroxylase deficiency: effect on midgestational amniotic fluid steroid levels. J Clin Endocrinol Metab 1993;76(1):117–120. [PubMed: 8421074]

Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, et al. The aging hippocampus: cognitive, biochemical and structural findings. Cereb Cortex 2003;13(12):1344–1351. [PubMed: 14615299]

Driscoll I, Hamilton DA, Yeo RA, Brooks WM, Sutherland RJ. Virtual navigation in humans: the impact of age, sex, and hormones on place learning. Horm Behav 2005;47(3):326–335. [PubMed: 15708762]

Dureman, I.; Kebbon, L.; Osterberg, E. Manual till DS-batteriet. Stockholm: Psykologiforlaget; 1971.

Duval SJ, Tweedie RL. A non-parametric “Trim and Fill” method of accounting for publication bias in meta-analysis. Journal of the American Statistical Association 2000;95:89–98.

Ekstrom, RB.; French, JW.; Harman, HH.; Dermen, D. Manual for kit of factor-referenced cognitive tests. Princeton, NJ: Educational Testing Service; 1976.

Grimshaw GM, Sitarenios G, Finegan JA. Mental rotation at 7 years: relations with prenatal testosterone levels and spatial play experiences. Brain Cogn 1995;29(1):85–100. [PubMed: 8845125]

Hampson E, Rovet JF, Altmann D. Spatial reasoning in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Developmental Neuropsychology 1998;14(2):299–320.

Healy W. A pictorial completion test. Psychol Rev 1914;21(3):189–203.

Helleday J, Bartfai A, Ritzen EM, Forsman M. General intelligence and cognitive profile in women with congenital adrenal hyperplasia (CAH). Psychoneuroendocrinology 1994;19(4):343–356. [PubMed: 8047639]

Hines M, Fane BA, Pasterski VL, Mathews GA, Conway GS, Brook C. Spatial abilities following prenatal androgen abnormality: targeting and mental rotations performance in individuals with congenital adrenal hyperplasia. Psychoneuroendocrinology 2003;28(8):1010–1026. [PubMed: 14529705]

Hojbjerg Gravholt C, Svenstrup B, Bennett P, Sandahl Christiansen J. Reduced androgen levels in adult turner syndrome: influence of female sex steroids and growth hormone status. Clin Endocrinol (Oxf) 1999;50(6):791–800. [PubMed: 10468952]

Imperato-McGinley J, Peterson RE, Gautier T, Cooper G, Danner R, Arthur A, et al. Hormonal evaluation of a large kindred with complete androgen insensitivity: evidence for secondary 5 alpha-reductase deficiency. J Clin Endocrinol Metab 1982;54(5):931–941. [PubMed: 6801078]

Imperato-McGinley J, Pichardo M, Gautier T, Voyer D, Bryden MP. Cognitive abilities in androgen-insensitive subjects: comparison with control males and females from the same kindred. Clin Endocrinol (Oxf) 1991;34(5):341–347. [PubMed: 2060143]

Isgor C, Sengelaub DR. Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats. Horm Behav 1998;34(2):183–198. [PubMed: 9799628]

Isgor C, Sengelaub DR. Effects of neonatal gonadal steroids on adult CA3 pyramidal neuron dendritic morphology and spatial memory in rats. J Neurobiol 2003;55(2):179–190. [PubMed: 12672016]

Jackson DNI, Vernon PA, Jackson DN. Dynamic spatial performance and general intelligence. Intelligence 1993;17:451–460.

Jager, AO.; Althoff, K. WILDE-Intelligenz-Test. Gottingen: Hogrefe; 1983.

Jonasson Z. Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. Neurosci Biobehav Rev 2005;28(8):811–825. [PubMed: 15642623]

Joseph R, Hess S, Birecree E. Effects of hormone manipulations and exploration on sex differences in maze learning. Behav Biol 1978;24(3):364–377. [PubMed: 743070]

Kempel, P.; Burk, C.; Hennig, J. Unpublished data. 2005. Correlations between 2D:4D and 3D mental rotation performance.

Kempel P, Gohlke B, Klempau J, Zinsberger P, Reuter M, Hennig J. Second-to-fourth digit lengths, testosterone and spatial ability. Intelligence 2005;33:215–230.

Kitraki E, Kremmyda O, Youlatos D, Alexis MN, Kittas C. Gender-dependent alterations in corticosteroid receptor status and spatial performance following 21 days of restraint stress. Neuroscience 2004;125 (1):47–55. [PubMed: 15051144]

Loehlin, JC.; Luciano, M.; Medland, SE.; Martin, NG. Unpublished data. 2005. Correlations between 2D:4D and 3D mental rotation performance.

Maccoby, EE.; Jacklin, CN. The psychology of sex differences. Stanford, CA: Stanford University Press; 1974.

Malas MA, Dogan S, Evcil EH, Desdicioglu K. Fetal development of the hand, digits and digit ratio (2D: 4D). Early Human Development. (in press).

Malouf MA, Migeon CJ, Carson KA, Petrucci L, Wisniewski AB. Cognitive Outcome in Adult Women Affected by Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Horm Res 2006;65 (3):142–150. [PubMed: 16508325]

Mann VA, Sasanuma S, Sakuma N, Masaki S. Sex differences in cognitive abilities: a cross-cultural perspective. Neuropsychologia 1990;28:1063–1077. [PubMed: 2267058]

Manning, JT. Digit ratio: a pointer to fertility, behavior, and health. New Jersey: Rutgers University Press; 2002.

Manning JT, Bundred PE, Newton DJ, Flanagan BF. The second to fourth digit ratio and variation in the androgen receptor gene. Evolution and Human Behavior 2003;24:399–405.

Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of the 2nd and 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Human Reproduction 1998;13:3000–3004. [PubMed: 9853845]

Manning JT, Taylor RP. Second to fourth digit ratio and male ability in sport: implications for sexual selection in humans. Evolution and Human Behavior 2001;22:61–69. [PubMed: 11182575]

Mayes JT, Jahoda G. Patterns of visual-spatial performance and 'spatial ability': dissociation of ethnic and sex differences. British Journal of Psychology 1988;79:105–119. [PubMed: 3359116]

McFadden D, Loehlin JC, Breedlove SM, Lippa RA, Manning JT, Rahman Q. A reanalysis of five studies on sexual orientation and the relative length of the 2nd and 4th fingers (the 2D:4D ratio). Arch Sex Behav 2005;34(3):341–356. [PubMed: 15971017]

McFadden D, Schubel E. The relationships between otoacoustic emissions and relative lengths of fingers and toes in humans. Hormones and Behavior 2003;43:421–429. [PubMed: 12695116]

McGuire LS, Ryan KO, Omenn GS. Congenital adrenal hyperplasia. II. Cognitive and behavioral studies. Behav Genet 1975;5(2):175–188. [PubMed: 1131146]

Morris RGM. Spatial localization does not require the presence of local cues. Learning and Motivation 1981;12:239–260.

Nijhuis-van der Sanden MW, Eling PA, Otten BJ. A review of neuropsychological and motor studies in Turner Syndrome. Neurosci Biobehav Rev 2003;27(4):329–338. [PubMed: 12946685]

Nunez JL, McCarthy MM. Estradiol exacerbates hippocampal damage in a model of preterm infant brain injury. Endocrinology 2003;144(6):2350–2359. [PubMed: 12746295]

Okten A, Kalyoncu M, Yaris N. The ratio of second- and fourth-digit lengths and congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Early Human Development 2002;70:47–54. [PubMed: 12441204]

O'Shaughnessy PJ, Baker PJ, Johnston H. The foetal Leydig cell-- differentiation, function and regulation. Int J Androl 2006;29(1):90–95. [PubMed: 16466528]

Owen K, Lynn R. Sex differences in primary cognitive abilities among blacks, Indians and whites in South Africa. Journal of Biosocial Science 1993;25:557–560. [PubMed: 8227104]

Pang S, Levine LS, Cederqvist LL, Fuentes M, Riccardi VM, Holcombe JH, et al. Amniotic fluid concentrations of delta 5 and delta 4 steroids in fetuses with congenital adrenal hyperplasia due to 21 hydroxylase deficiency and in anencephalic fetuses. J Clin Endocrinol Metab 1980;51(2):223–229. [PubMed: 6447160]

Perlman SM. Cognitive abilities of children with hormone abnormalities: screening by psychoeducational tests. Journal of Learning Disabilities 1973;6(1):26–34.

Peters, M.; Manning, JT. Unpublished data. 2005. Correlations between 2D:4D and 3D mental rotation performance.

Poulin M, O'Connell RL, Freeman LM. Picture recall skills correlate with 2D:4D ratio in women but not in men. Evolution and Human Behavior 2004;25(3):174–181.

Puts, DA.; Gaulin, SJ.; Breedlove, SM. Sex differences in spatial ability: evolution, hormones, and the brain. In: Platek, SM.; Keenan, JP.; Shackelford, TK., editors. Evolutionary Cognitive Neuroscience. MIT Press; (in press)

Putz DA, Gaulin SJ, Sporter RJ, McBurney DH. Sex hormones and finger length: what does 2D:4D indicate? Evolution and Human Behavior 2004;25:182–199.

Rahman Q, Wilson GD, Abrahams S. Biosocial factors, sexual orientation and neurocognitive functioning. Psychoneuroendocrinology 2004;29(7):867–881. [PubMed: 15177702]

Resnick SM, Berenbaum SA, Gottesman II, Bouchard TJ. Early hormonal influences on cognitive functioning in congenital adrenal hyperplasia. Developmental Psychology 1986;22(2):191–198.

Ripa CPL, Johannsen TH, Mortensen EL, Muller J. General cognitive functions, mental rotations ability, and handedness in adult females with congenital adrenal hyperplasia. Horm Behav 2003;44:72.

Roof RL. Neonatal exogenous testosterone modifies sex difference in radial arm and Morris water maze performance in prepubescent and adult rats. Behav Brain Res 1993;53(1–2):1–10. [PubMed: 8466654]

Roof RL, Havens MD. Testosterone improves maze performance and induces development of a male hippocampus in females. Brain Res 1992;572(1–2):310–313. [PubMed: 1611529]

Ross JL, Stefanatos GA, Kushner H, Zinn A, Bondy C, Roeltgen D. Persistent cognitive deficits in adult women with Turner syndrome. Neurology 2002;58(2):218–225. [PubMed: 11805247]

Sanders G, Bereckzei T, Csatho A, Manning JT. The ratio of the 2nd to 4th finger length predicts spatial ability in men but not women. Cortex 2005;41(6):789–795. [PubMed: 16350659]

Scarbrough PS, Johnston VS. Individual differences in women's facial preferences as a function of digit ratio and mental rotation ability. Evolution and Human Behavior 2005;26(6):509–526.

Shepard RN, Metzler J. Mental rotation of three dimensional objects. Science 1971;171:701–703. [PubMed: 5540314]

Stewart J, Skvarenina A, Pottier J. Effects of neonatal androgens on open-field behavior and maze learning in the prepubescent and adult rat. Physiol Behav 1975;14(3):291–295. [PubMed: 1135305]

Thurstone, LL.; Thurstone, TG. Primary mental abilities (revised 1962). Chicago: Science Research Associates; 1963.

van Anders SM, Hampson E. Testing the prenatal androgen hypothesis: measuring digit ratios, sexual orientation, and spatial abilities in adults. Horm Behav 2005;47:92–98. [PubMed: 15579270]

Vandenberg SG, Kuse AR. Mental rotations: a group test of three-dimensional spatial visualization. Perceptual and Motor Skills 1978;47:599–604. [PubMed: 724398]

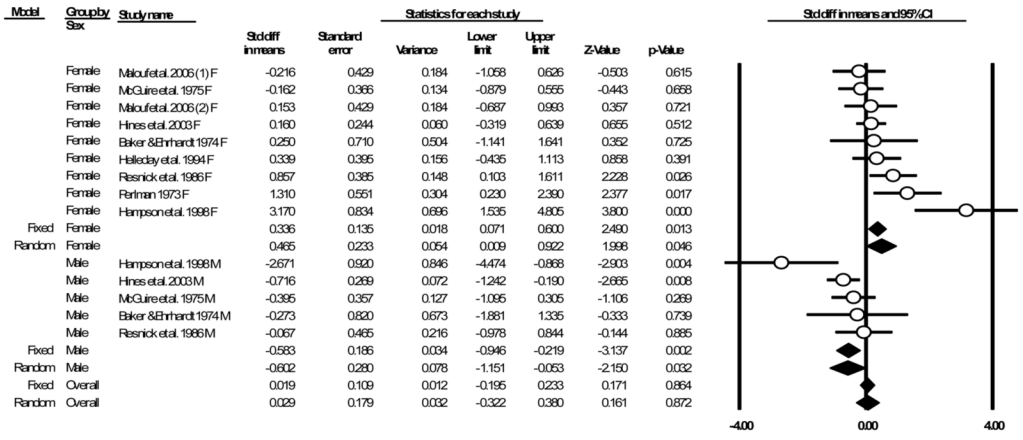
Vicedomini JP, Nonneman AJ, DeKosky ST, Scheff SW. Perinatal glucocorticoids disrupt learning: a sexually dimorphic response. Physiol Behav 1986;36(1):145–149. [PubMed: 3952174]

Voyer D, Voyer S, Bryden MP. Magnitude of sex differences in spatial abilities: a meta-analysis and consideration of critical variables. Psychol Bull 1995;117(2):250–270. [PubMed: 7724690]

Williams CL, Barnett AM, Meck WH. Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. Behav Neurosci 1990;104(1):84–97. [PubMed: 2317288]

Williams TJ, Pepitone ME, Christensen SE, Cooke BM, Huberman AD, Breedlove NJ, et al. Finger-length ratios and sexual orientation. Nature 2000;404(6777):455–456. [PubMed: 10761903]

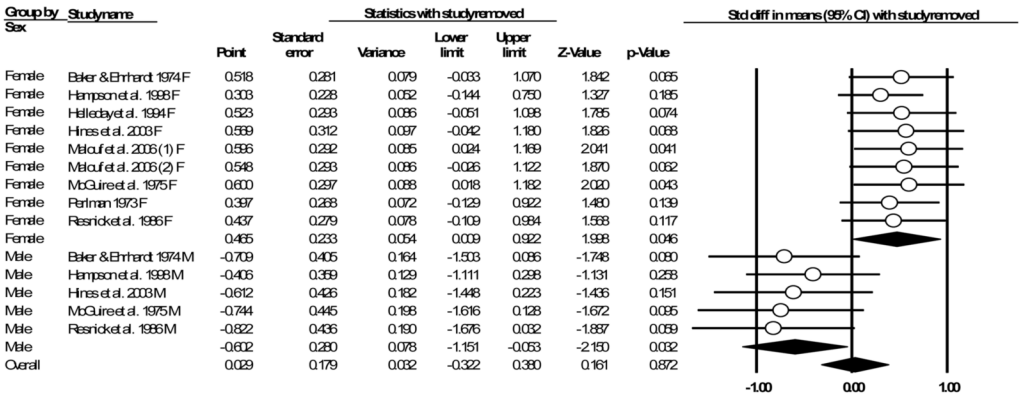
Wudy SA, Dorr HG, Solleder C, Djalali M, Homoki J. Profiling steroid hormones in amniotic fluid of midpregnancy by routine stable isotope dilution/gas chromatography-mass spectrometry: reference values and concentrations in fetuses at risk for 21-hydroxylase deficiency. J Clin Endocrinol Metab 1999;84(8):2724–2728. [PubMed: 10443667]



| Model | Group by Sex | Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|---|---|
| | Female | Malouf et al. 2006 (1) F | -0.216 | 0.429 | 0.184 | -1.058 | 0.626 | -0.503 | 0.615 |
| | Female | McGuire et al. 1975 F | -0.162 | 0.366 | 0.134 | -0.879 | 0.555 | -0.443 | 0.658 |
| | Female | Malouf et al. 2006 (2) F | 0.153 | 0.429 | 0.184 | -0.687 | 0.993 | 0.357 | 0.721 |
| | Female | Hines et al. 2003 F | 0.160 | 0.244 | 0.060 | -0.319 | 0.639 | 0.655 | 0.512 |
| | Female | Baker & Ehrhardt 1974 F | 0.250 | 0.710 | 0.504 | -1.141 | 1.641 | 0.352 | 0.725 |
| | Female | Halleday et al. 1994 F | 0.339 | 0.395 | 0.156 | -0.435 | 1.113 | 0.858 | 0.391 |
| | Female | Resnick et al. 1986 F | 0.857 | 0.385 | 0.148 | 0.103 | 1.611 | 2.228 | 0.026 |
| | Female | Perlman 1973 F | 1.310 | 0.551 | 0.304 | 0.230 | 2.390 | 2.377 | 0.017 |
| | Female | Hampson et al. 1998 F | 3.170 | 0.834 | 0.696 | 1.535 | 4.805 | 3.800 | 0.000 |
| Fixed | Female | | 0.336 | 0.135 | 0.018 | 0.071 | 0.600 | 2.490 | 0.013 |
| Random | Female | | 0.465 | 0.233 | 0.054 | 0.009 | 0.922 | 1.998 | 0.046 |
| | Male | Hampson et al. 1998 M | -2.671 | 0.920 | 0.846 | -4.474 | -0.868 | -2.903 | 0.004 |
| | Male | Hines et al. 2003 M | -0.716 | 0.269 | 0.072 | -1.242 | -0.190 | -2.665 | 0.008 |
| | Male | McGuire et al. 1975 M | -0.395 | 0.357 | 0.127 | -1.095 | 0.305 | -1.106 | 0.269 |
| | Male | Baker & Ehrhardt 1974 M | -0.273 | 0.820 | 0.673 | -1.881 | 1.335 | -0.333 | 0.739 |
| | Male | Resnick et al. 1986 M | -0.067 | 0.465 | 0.216 | -0.978 | 0.844 | -0.144 | 0.885 |
| Fixed | Male | | -0.583 | 0.186 | 0.034 | -0.946 | -0.219 | -3.137 | 0.002 |
| Random | Male | | -0.602 | 0.280 | 0.078 | -1.151 | -0.053 | -2.150 | 0.032 |
| Fixed | Overall | | 0.019 | 0.109 | 0.012 | -0.195 | 0.233 | 0.171 | 0.864 |
| Random | Overall | | 0.029 | 0.179 | 0.032 | -0.322 | 0.380 | 0.161 | 0.872 |



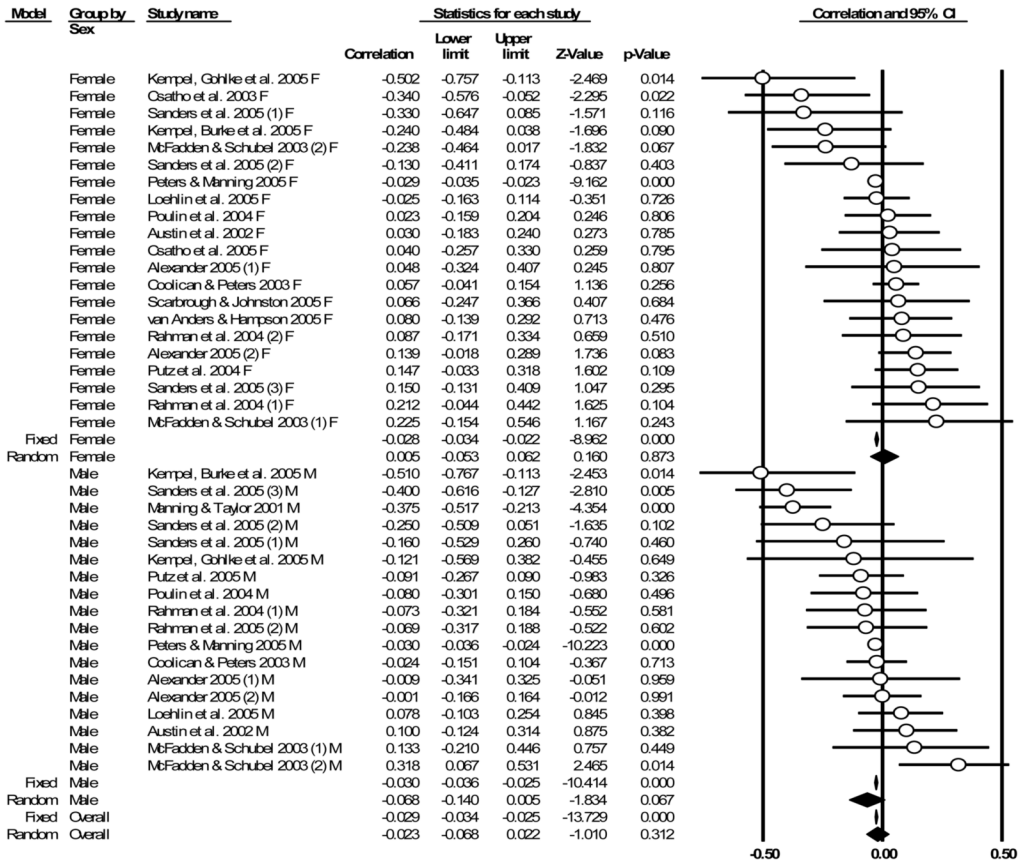
**Figure 1.**
CAH results overall and by sex.



| Group by Sex | Studyname | Point | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|---|
| Female | Baker & Ehrhardt 1974 F | 0.518 | 0.281 | 0.079 | -0.033 | 1.070 | 1.842 | 0.065 |
| Female | Hampson et al. 1998 F | 0.303 | 0.228 | 0.052 | -0.144 | 0.750 | 1.327 | 0.185 |
| Female | Helleday et al. 1994 F | 0.523 | 0.293 | 0.086 | -0.051 | 1.098 | 1.785 | 0.074 |
| Female | Hines et al. 2003 F | 0.599 | 0.312 | 0.097 | -0.042 | 1.180 | 1.826 | 0.068 |
| Female | Melcuf et al. 2006 (1) F | 0.596 | 0.292 | 0.085 | 0.024 | 1.169 | 2.041 | 0.041 |
| Female | Melcuf et al. 2006 (2) F | 0.548 | 0.293 | 0.086 | -0.026 | 1.122 | 1.870 | 0.062 |
| Female | McGuire et al. 1975 F | 0.600 | 0.297 | 0.088 | 0.018 | 1.182 | 2.020 | 0.043 |
| Female | Perlman 1973 F | 0.397 | 0.288 | 0.072 | -0.129 | 0.922 | 1.480 | 0.139 |
| Female | Resnick et al. 1986 F | 0.437 | 0.279 | 0.078 | -0.109 | 0.984 | 1.568 | 0.117 |
| Female | | 0.465 | 0.233 | 0.054 | 0.009 | 0.922 | 1.998 | 0.046 |
| Male | Baker & Ehrhardt 1974 M | -0.709 | 0.405 | 0.164 | -1.503 | 0.086 | -1.748 | 0.080 |
| Male | Hampson et al. 1998 M | -0.406 | 0.359 | 0.129 | -1.111 | 0.298 | -1.131 | 0.258 |
| Male | Hines et al. 2003 M | -0.612 | 0.426 | 0.182 | -1.448 | 0.223 | -1.436 | 0.151 |
| Male | McGuire et al. 1975 M | -0.744 | 0.445 | 0.198 | -1.616 | 0.128 | -1.672 | 0.095 |
| Male | Resnick et al. 1986 M | -0.822 | 0.436 | 0.190 | -1.676 | 0.032 | -1.887 | 0.059 |
| Male | | -0.602 | 0.280 | 0.078 | -1.151 | -0.053 | -2.150 | 0.032 |
| Overall | | 0.029 | 0.179 | 0.032 | -0.322 | 0.380 | 0.161 | 0.872 |



**Figure 2.**
Results of CAH "omit one study" analysis.



| Model | Group by Sex | Study name | Statistics for each study | | | | |
|---|---|---|---|---|---|---|---|
| | | | Correlation | Lower limit | Upper limit | Z-Value | p-Value |
| | Female | Kempel, Gohlke et al. 2005 F | -0.502 | -0.757 | -0.113 | -2.469 | 0.014 |
| | Female | Csatho et al. 2003 F | -0.340 | -0.576 | -0.052 | -2.295 | 0.022 |
| | Female | Sanders et al. 2005 (1) F | -0.330 | -0.647 | 0.085 | -1.571 | 0.116 |
| | Female | Kempel, Burke et al. 2005 F | -0.240 | -0.484 | 0.038 | -1.696 | 0.090 |
| | Female | McFadden & Schubel 2003 (2) F | -0.238 | -0.464 | 0.017 | -1.832 | 0.067 |
| | Female | Sanders et al. 2005 (2) F | -0.130 | -0.411 | 0.174 | -0.837 | 0.403 |
| | Female | Peters & Manning 2005 F | -0.029 | -0.035 | -0.023 | -9.162 | 0.000 |
| | Female | Loehlin et al. 2005 F | -0.025 | -0.163 | 0.114 | -0.351 | 0.726 |
| | Female | Poulin et al. 2004 F | 0.023 | -0.159 | 0.204 | 0.246 | 0.806 |
| | Female | Austin et al. 2002 F | 0.030 | -0.183 | 0.240 | 0.273 | 0.785 |
| | Female | Csatho et al. 2005 F | 0.040 | -0.257 | 0.330 | 0.259 | 0.795 |
| | Female | Alexander 2005 (1) F | 0.048 | -0.324 | 0.407 | 0.245 | 0.807 |
| | Female | Coolican & Peters 2003 F | 0.057 | -0.041 | 0.154 | 1.136 | 0.256 |
| | Female | Scarbrough & Johnston 2005 F | 0.066 | -0.247 | 0.366 | 0.407 | 0.684 |
| | Female | van Anders & Hampson 2005 F | 0.080 | -0.139 | 0.292 | 0.713 | 0.476 |
| | Female | Rahman et al. 2004 (2) F | 0.087 | -0.171 | 0.334 | 0.659 | 0.510 |
| | Female | Alexander 2005 (2) F | 0.139 | -0.018 | 0.289 | 1.736 | 0.083 |
| | Female | Putz et al. 2004 F | 0.147 | -0.033 | 0.318 | 1.602 | 0.109 |
| | Female | Sanders et al. 2005 (3) F | 0.150 | -0.131 | 0.409 | 1.047 | 0.295 |
| | Female | Rahman et al. 2004 (1) F | 0.212 | -0.044 | 0.442 | 1.625 | 0.104 |
| | Female | McFadden & Schubel 2003 (1) F | 0.225 | -0.154 | 0.546 | 1.167 | 0.243 |
| Fixed | Female | | -0.028 | -0.034 | -0.022 | -8.962 | 0.000 |
| Random | Female | | 0.005 | -0.053 | 0.062 | 0.160 | 0.873 |
| | Male | Kempel, Burke et al. 2005 M | -0.510 | -0.767 | -0.113 | -2.453 | 0.014 |
| | Male | Sanders et al. 2005 (3) M | -0.400 | -0.616 | -0.127 | -2.810 | 0.005 |
| | Male | Manning & Taylor 2001 M | -0.375 | -0.517 | -0.213 | -4.354 | 0.000 |
| | Male | Sanders et al. 2005 (2) M | -0.250 | -0.509 | 0.051 | -1.635 | 0.102 |
| | Male | Sanders et al. 2005 (1) M | -0.160 | -0.529 | 0.260 | -0.740 | 0.460 |
| | Male | Kempel, Gohlke et al. 2005 M | -0.121 | -0.569 | 0.382 | -0.455 | 0.649 |
| | Male | Putz et al. 2005 M | -0.091 | -0.267 | 0.090 | -0.983 | 0.326 |
| | Male | Poulin et al. 2004 M | -0.080 | -0.301 | 0.150 | -0.680 | 0.496 |
| | Male | Rahman et al. 2004 (1) M | -0.073 | -0.321 | 0.184 | -0.552 | 0.581 |
| | Male | Rahman et al. 2005 (2) M | -0.069 | -0.317 | 0.188 | -0.522 | 0.602 |
| | Male | Peters & Manning 2005 M | -0.030 | -0.036 | -0.024 | -10.223 | 0.000 |
| | Male | Coolican & Peters 2003 M | -0.024 | -0.151 | 0.104 | -0.367 | 0.713 |
| | Male | Alexander 2005 (1) M | -0.009 | -0.341 | 0.325 | -0.051 | 0.959 |
| | Male | Alexander 2005 (2) M | -0.001 | -0.166 | 0.164 | -0.012 | 0.991 |
| | Male | Loehlin et al. 2005 M | 0.078 | -0.103 | 0.254 | 0.845 | 0.398 |
| | Male | Austin et al. 2002 M | 0.100 | -0.124 | 0.314 | 0.875 | 0.382 |
| | Male | McFadden & Schubel 2003 (1) M | 0.133 | -0.210 | 0.446 | 0.757 | 0.449 |
| | Male | McFadden & Schubel 2003 (2) M | 0.318 | 0.067 | 0.531 | 2.465 | 0.014 |
| Fixed | Male | | -0.030 | -0.036 | -0.025 | -10.414 | 0.000 |
| Random | Male | | -0.068 | -0.140 | 0.005 | -1.834 | 0.067 |
| Fixed | Overall | | -0.029 | -0.034 | -0.025 | -13.729 | 0.000 |
| Random | Overall | | -0.023 | -0.068 | 0.022 | -1.010 | 0.312 |



**Figure 3.**
2D:4D results overall and by sex.

| Group by Sex | Study name | Statistics with study removed | | | | | Correlation (95% CI) with study removed |
|---|---|---|---|---|---|---|---|
| | | Point | Lower limit | Upper limit | Z-Value | p-Value | |
| Female | Kempel, Gohlke et al. 2005 F | -0.008 | -0.038 | 0.021 | -0.536 | 0.592 | |
| Female | Csatho et al. 2003 F | -0.007 | -0.037 | 0.023 | -0.455 | 0.649 | |
| Female | Sanders et al. 2005 (1) F | -0.008 | -0.038 | 0.022 | -0.514 | 0.607 | |
| Female | Kempel, Burke et al. 2005 F | -0.007 | -0.037 | 0.023 | -0.451 | 0.652 | |
| Female | McFadden & Schubel 2003 (2) F | -0.007 | -0.037 | 0.024 | -0.428 | 0.668 | |
| Female | Sanders et al. 2005 (2) F | -0.008 | -0.039 | 0.023 | -0.509 | 0.610 | |
| Female | Peters & Manning 2005 F | 0.008 | -0.059 | 0.074 | 0.231 | 0.817 | |
| Female | Loehlin et al. 2005 F | -0.008 | -0.040 | 0.023 | -0.520 | 0.603 | |
| Female | Poulin et al. 2004 F | -0.010 | -0.041 | 0.021 | -0.635 | 0.526 | |
| Female | Austin et al. 2002 F | -0.010 | -0.041 | 0.021 | -0.631 | 0.528 | |
| Female | Csatho et al. 2005 F | -0.010 | -0.041 | 0.021 | -0.614 | 0.539 | |
| Female | Alexander 2005 (1) F | -0.010 | -0.040 | 0.021 | -0.606 | 0.545 | |
| Female | Coolican & Peters 2003 F | -0.016 | -0.047 | 0.016 | -0.983 | 0.325 | |
| Female | Scarbrough & Johnston 2005 F | -0.010 | -0.041 | 0.021 | -0.630 | 0.529 | |
| Female | van Anders & Hampson 2005 F | -0.011 | -0.042 | 0.020 | -0.702 | 0.482 | |
| Female | Rahman et al. 2004 (2) F | -0.011 | -0.041 | 0.020 | -0.677 | 0.498 | |
| Female | Alexander 2005 (2) F | -0.015 | -0.046 | 0.015 | -1.002 | 0.317 | |
| Female | Putz et al. 2004 F | -0.014 | -0.045 | 0.016 | -0.924 | 0.355 | |
| Female | Sanders et al. 2005 (3) F | -0.011 | -0.042 | 0.019 | -0.728 | 0.467 | |
| Female | Rahman et al. 2004 (1) F | -0.013 | -0.043 | 0.017 | -0.842 | 0.400 | |
| Female | McFadden & Schubel 2003 (1) F | -0.011 | -0.042 | 0.019 | -0.710 | 0.478 | |
| Female | | 0.005 | -0.053 | 0.062 | 0.160 | 0.873 | |
| Male | Kempel, Burke et al. 2005 M | -0.039 | -0.070 | -0.008 | -2.458 | 0.014 | |
| Male | Sanders et al. 2005 (3) M | -0.037 | -0.067 | -0.006 | -2.364 | 0.018 | |
| Male | Manning & Taylor 2001 M | -0.030 | -0.058 | -0.003 | -2.159 | 0.031 | |
| Male | Sanders et al. 2005 (2) M | -0.040 | -0.071 | -0.008 | -2.431 | 0.015 | |
| Male | Sanders et al. 2005 (1) M | -0.041 | -0.074 | -0.009 | -2.521 | 0.012 | |
| Male | Kempel, Gohlke et al. 2005 M | -0.042 | -0.074 | -0.010 | -2.544 | 0.011 | |
| Male | Putz et al. 2005 M | -0.041 | -0.073 | -0.008 | -2.440 | 0.015 | |
| Male | Poulin et al. 2004 M | -0.041 | -0.074 | -0.009 | -2.498 | 0.012 | |
| Male | Rahman et al. 2004 (1) M | -0.042 | -0.074 | -0.009 | -2.518 | 0.012 | |
| Male | Rahman et al. 2005 (2) M | -0.042 | -0.074 | -0.009 | -2.522 | 0.012 | |
| Male | Peters & Manning 2005 M | -0.073 | -0.145 | 0.001 | -1.943 | 0.052 | |
| Male | Coolican & Peters 2003 M | -0.043 | -0.077 | -0.010 | -2.555 | 0.011 | |
| Male | Alexander 2005 (1) M | -0.042 | -0.075 | -0.010 | -2.572 | 0.010 | |
| Male | Alexander 2005 (2) M | -0.044 | -0.076 | -0.011 | -2.611 | 0.009 | |
| Male | Loehlin et al. 2005 M | -0.046 | -0.078 | -0.013 | -2.761 | 0.006 | |
| Male | Austin et al. 2002 M | -0.045 | -0.077 | -0.013 | -2.725 | 0.006 | |
| Male | McFadden & Schubel 2003 (1) M | -0.044 | -0.076 | -0.011 | -2.654 | 0.008 | |
| Male | McFadden & Schubel 2003 (2) M | -0.046 | -0.076 | -0.015 | -2.941 | 0.003 | |
| Male | | -0.068 | -0.140 | 0.005 | -1.834 | 0.067 | |
| Overall | | -0.023 | -0.068 | 0.022 | -1.010 | 0.312 | |

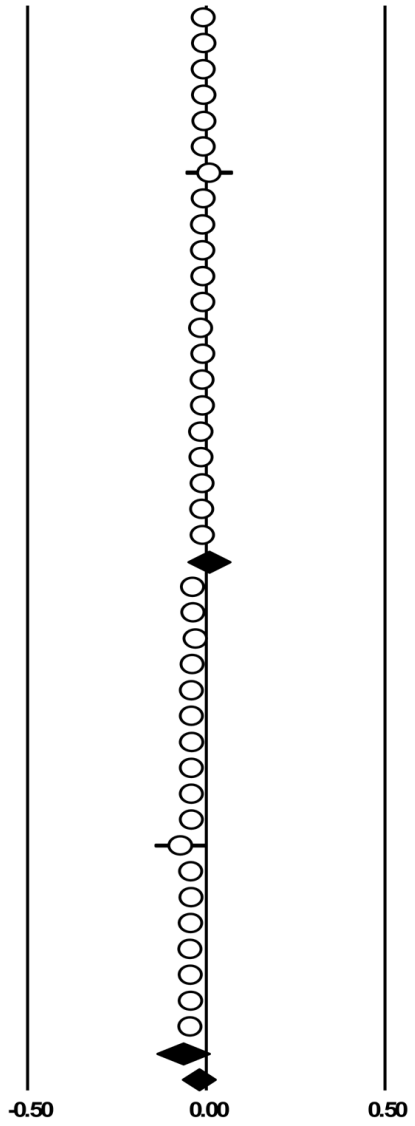



**Figure 4.**
Results of 2D:4D “omit one study” analysis.

**Table 1**

CAH sample characteristics.

| | Sample | Spatial Test | Age Range | CAH Type | CAH *N* | Ctrl *N* |
|---|---|---|---|---|---|---|
| **Female** | | | | | | |
| **Studies** | Baker & Ehrhardt 1974 | PMA | 4.3–19.9 | not reported | 4 | 4 |
| | Hampson et al. 1998 | PMA | 8–12 | SL & SV | 7 | 6 |
| | Helleday et al. 1994 | FR | 17–34 | 16 SL, 6 SV | 13 | 13 |
| | Hines et al. 2003 | PMA + V&K | 12–44 | mostly SL | 40 | 29 |
| | Malouf et al. 2006 (1) | CC | 20–73 | SL | 12 | 10 |
| | Malouf et al. 2006 (2) | CC | 21–73 | SV | 12 | 10 |
| | McGuire et al. 1975 | WBD | 7–20 | 5 SL, 10 SV | 15 | 15 |
| | Perlman 1973 | HPC | 3–15 | not reported | 8 | 8 |
| | Resnick et al. 1986 | V&K | 11.4–31.1 | SL & SV | 17 | 13 |
| **Male** | | | | | | |
| **Studies** | Baker & Ehrhardt 1974 | PMA | 4–26 | not reported | 3 | 3 |
| | Hampson et al. 1998 | PMA | 8–12 | SL & SV | 5 | 4 |
| | Hines et al. 2003 | PMA + V&K | 12–45 | mostly SL | 29 | 30 |
| | McGuire et al. 1975 | WBD | 5–32 | 4 SL, 12 SV | 16 | 16 |
| | Resnick et al. 1986 | V&K | 11–31 | SL & SV | 8 | 11 |

**Spatial Test**
CC Cube Comparisons (Ekstrom, French, Harman, & Dermen, 1976)
FR 2D figure rotation (Dureman, Kebbon, & Osterberg, 1971)
HPC Healy Pictorial Completion Test (Healy, 1914)
PMA Spatial test of Primary Mental Abilities (Thurstone & Thurstone, 1963)
PMA + V&K Average of PMA and Vandenberg & Kuse (1978) 3D MRT
V&K Vandenberg & Kuse (1978) 3D MRT
WBD Block design portion of Wechler Adult Intelligence Scale (WAIS) or Wechler Intelligence Scale for Children (WISC)

**CAH Type**
SL Salt losing
SV Simple virilizing

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**Table 2**

2D:4D sample characteristics.

| | Sample | Spatial Test | Age range, mean (SD), or estimate | 2D:4D Measure | *N* |
|---|---|---|---|---|---|
| **Female** | | | | | |
| **Studies** | Alexander 2005 (1) | V&K | 18–24 | right | 29 |
| | Alexander 2005 (2) | V&K | 18–25 | right | 157 |
| | Austin et al. 2002 | V&K | 20.6(2.5) | right | 86 |
| | Coolican & Peters 2003 | V&K | ~18–23 | right | 399 |
| | Csatho et al. 2003 | WM Analog | 19–26 | right | 45 |
| | Csatho et al. 2005 | S&M | 19–26 | right | 45 |
| | Kempel, Burke et al. 2005 | SIQ | 18–40 | right | 51 |
| | Kempel, Gohlke et al. 2005 | SIQ | 23.5(4.3) | right | 23 |
| | Loehlin et al. 2005 | MAB | ~16 | right | 200 |
| | McFadden & Schubel 2003 (1) | V&K | 20.7 | right | 29 |
| | McFadden & Schubel 2003 (2) | V&K | 19.2 | right | 60 |
| | Peters & Manning 2005 | V&K | 28.7(11.5) | right | 99765 |
| | Poulin et al. 2004 | B&G | ~18–25 | right | 117 |
| | Putz et al. 2004 | V&K | 18–30 | right | 120 |
| | Rahman et al. 2004 (1) | V&K | 18–40 | right | 60 |
| | Rahman et al. 2004 (2) | V&K | 18–40 | right | 60 |
| | Sanders et al. 2005 (1) | S&M | 27.0(4.7) | right | 24 |
| | Sanders et al. 2005 (2) | V&K | 22.2(1.9) | right | 44 |
| | Sanders et al. 2005 (3) | V&K | 30.3(10.1) | right | 51 |
| | Scarbrough & Johnston 2005 | C&S | 18–30 | right | 41 |
| | van Anders & Hampson 2005 | V&K | 18–42 | right | 82 |
| **Male** | | | | | |
| **Studies** | Alexander 2005 (1) | V&K | 18–24 | right | 35 |
| | Alexander 2005 (2) | V&K | 18–25 | right | 142 |
| | Austin et al. 2002 | V&K | 20.1(1.1) | right | 79 |
| | Coolican & Peters 2003 | V&K | 17–43 | right | 237 |
| | Kempel, Burke et al. 2005 | SIQ | 18–40 | right | 22 |
| | Kempel, Gohlke et al. 2005 | SIQ | 24.2(4.2) | left | 17 |

| Sample | Spatial Test | Age range, mean (SD), or estimate | 2D:4D Measure | *N* |
|---|---|---|---|---|
| Loehlin et al. 2005 | MAB | ~16 | right | 120 |
| Manning & Taylor 2001 | V&K | 25.4(8.2) | mean | 125 |
| McFadden & Schubel 2003 (1) | V&K | 22 | right | 35 |
| McFadden & Schubel 2003 (2) | V&K | 19 | right | 59 |
| Peters & Manning 2005 | V&K | 31.3(12.0) | right | 116053 |
| Poulin et al. 2004 | B&G | ~18–25 | right | 75 |
| Putz et al. 2005 | V&K | 18–30 | right | 119 |
| Rahman et al. 2004 (1) | V&K | 18–40 | right | 60 |
| Rahman et al. 2005 (2) | V&K | 18–40 | right | 60 |
| Sanders et al. 2005 (1) | S&M | 25.9(4.7) | right | 24 |
| Sanders et al. 2005 (2) | V&K | 22.5(3.0) | right | 44 |
| Sanders et al. 2005 (3) | V&K | 31.7(9.8) | right | 47 |

B&G Purdue visualization of rotations test 3D MRT (Bodner & Guay, 1997)
C&S Cooper & Shepard 3D MRT (1973)
MAB Multidimensional Aptitude Battery (Jackson, Vernon, & Jackson, 1993)
S&M Shepard & Metzler 3D MRT (1971)
SIQ Spatial IQ test (Jager & Althoff, 1983)
V&K Vandenburg & Kuse 3D MRT (1978)
WM Analog Analog of Morris (1981) water maze