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Spatial Ability and Prenatal Androgens: Meta-Analyses of Congenital Adrenal Hyperplasia and Digit Ratio (2D:4D) Studies

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Abstract Hormonal manipulations indicate that early androgens organize sex differences in spatial ability in laboratory rats. 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 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 androgens predict spatial ability, others have found no significant relationship, and yet others have obtained results in the opposite direction. In light of these mixed findings, we conducted meta-analyses of published literature and unpublished results to determine if, across studies, either of these indicators of prenatal androgens predicts performance on spatial tasks that show a male advantage. 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 indicated that females with CAH perform better on these spatial tasks, and CAH males perform worse, 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

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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).

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, 2005) and laboratory rats (Jonasson, 2005), rats are likely to represent useful models for possible hormonal contributions to sex differences in human spatial ability. In rats, spatial performance 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; 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 abilities (reviewed in Puts, Gaulin, & Breedlove, 2007). This evidence includes reported relationships between spatial abilities 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 physical signs of elevated prenatal androgen exposure (e.g., 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) (for a review, see Hines, 2004). Studies of spatial ability in CAH males have obtained equally inconsistent results, with some finding worse spatial abilities 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 abilities 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, Hilal Evcil, & Desdicioglu, 2006). 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 a 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 (G. M. Alexander, 2005, unpublished data; Austin, Manning, McInroy, & Mathews, 2002; Coolican & Peters, 2003; A. Csatho, K. Karadi, & J. Kallai, 2005, unpublished data; Csatho et al., 2003; P. Kempel, C. Burk, & J. Hennig, 2005, unpublished data; Kempel et al., 2005; J. C. Loehlin, M. Luciano, S. E. Medland, & N. G. Martin, 2005, unpublished data; Manning & Taylor, 2001; McFadden & Schubel, 2003; Peters, Manning, & Reimers, 2007; 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 (for a partial review, see Putz et al., 2004).

These discrepancies in CAH and 2D:4D studies may result partly from random sampling error due to small sample sizes and from methodological differences, including differences in the spatial abilities tested (Hines, 2004). On the other hand, apparent relationships between spatial ability and measures of prenatal androgens may simply reflect publication bias. Publication bias exists to the extent that studies available for summary are not representative of all studies (Rothstein, Sutton, & Borenstein, 2005) and may result when authors fail to submit studies with statistically non-significant or unexpected results, or when editors decline to accept such studies. Thus, the purpose of the present study was to investigate relationships between CAH and 2D:4D and spatial ability in men and women across studies using meta-analytic methods.

Method

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, and 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 were from independent samples. Ideally, all studies would have used the same measure of spatial ability. For 2D:4D studies this was largely true, but for CAH studies it was not. However, each study administered at least one spatial task showing a male advantage, thus representing a plausible candidate for the influence of androgens. 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 SD 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; 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), or 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 was 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 type of sensitivity analysis determines if the results of the meta-analysis would change through the deletion of a study. We chose not to include ratings of study quality as moderators in analyses because quality indicators are often not correlated, leaving a heterogeneous composite whose meaning is difficult to interpret. Further, partitioning our modest-size data sets by a quality factor would result in few data at each level.

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 SD units. Thus, a *d* of 1 would indicate that the mean of the CAH group was one SD 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 0.47 for the random effects model and 0.34 for the fixed effects model (Fig. 1). These results were robust with respect to the deletion of individual studies; "omit one study" analysis produced effect sizes ranging from 0.30 to 0.60 under the random effects model (Fig. 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

Table 1 CAH sample characteristics

	Sample	Spatial test	Age range	CAH type	CAH *N*	Control *N*
Female studies	Baker and Ehrhardt (1974)	PMA[a]	4.3–19.9	Not reported	4	4
	Hampson et al. (1998)	PMA[a]	8–12	SL[h] and SV[i]	7	6
	Helleday et al. (1994)	FR[b]	17–34	16 SL[h], 6 SV[i]	13	13
	Hines et al. (2003)	PMA + V and K[c]	12–44	Mostly SL[h]	40	29
	Malouf et al. (2006) (1)	CC[d]	20–73	SL[h]	12	10
	Malouf et al. (2006) (2)	CC[d]	21–73	SV[i]	12	10
	McGuire et al. (1975)	WBD[e]	7–20	5 SL[h], 10 SV[i]	15	15
	Perlman (1973)	HPC[f]	3–15	Not reported	8	8
	Resnick et al. (1986)	V and K[g]	11.4–31.1	SL[h] and SV[i]	17	13
Male studies	Baker and Ehrhardt (1974)	PMA[a]	4–26	Not reported	3	3
	Hampson et al. (1998)	PMA[a]	8–12	SL[h] and SV[i]	5	4
	Hines et al. (2003)	PMA + V and K[c]	12–45	Mostly SL[h]	29	30
	McGuire et al. (1975)	WBD[e]	5–32	4 SL[h], 12 SV[i]	16	16
	Resnick et al. (1986)	V and K[g]	11–31	SL[h] and SV[i]	8	11

[a] Spatial test of primary mental abilities (Thurstone & Thurstone, 1963)

[b] 2D figure rotation (Dureman, Kebbon, & Osterberg, 1971)

[c] Average of PMA and Vandenberg and Kuse (1978) 3D MRT

[d] Cube comparisons (Ekstrom, French, Harman, & Dermen, 1976)

[e] Block design portion of Wechsler Adult Intelligence Scale (WAIS) or Wechsler Intelligence Scale for Children (WISC)

[f] Healy pictorial completion test (Healy, 1914)

[g] Vandenberg and Kuse (1978) 3D MRT

[h] Salt losing

[i] Simple virilizing

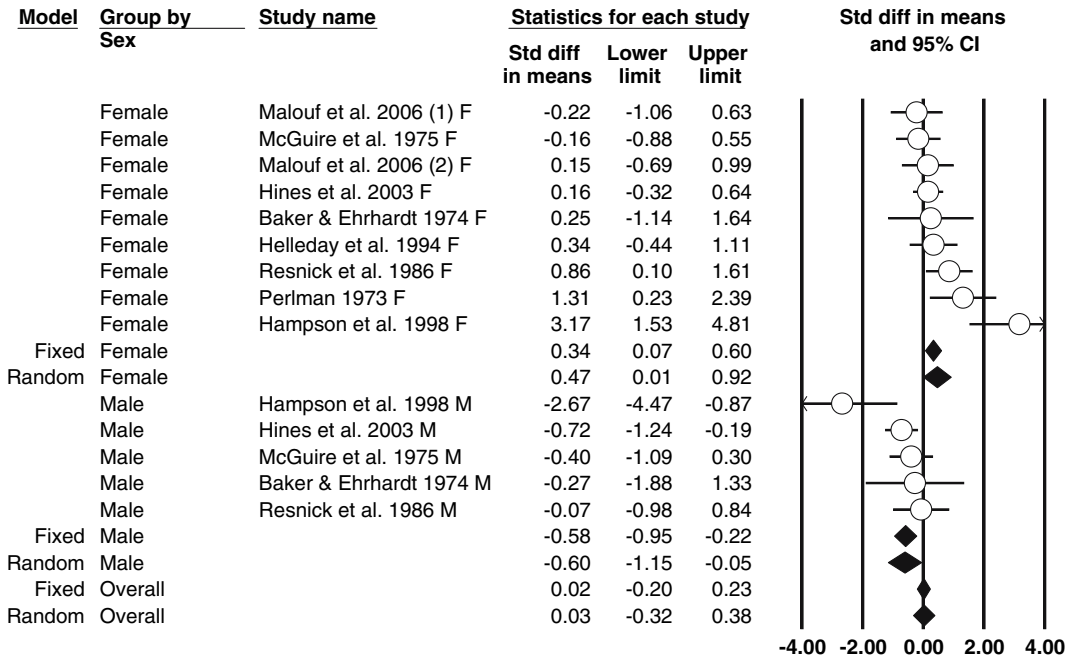

Fig. 1 CAH results overall and by sex

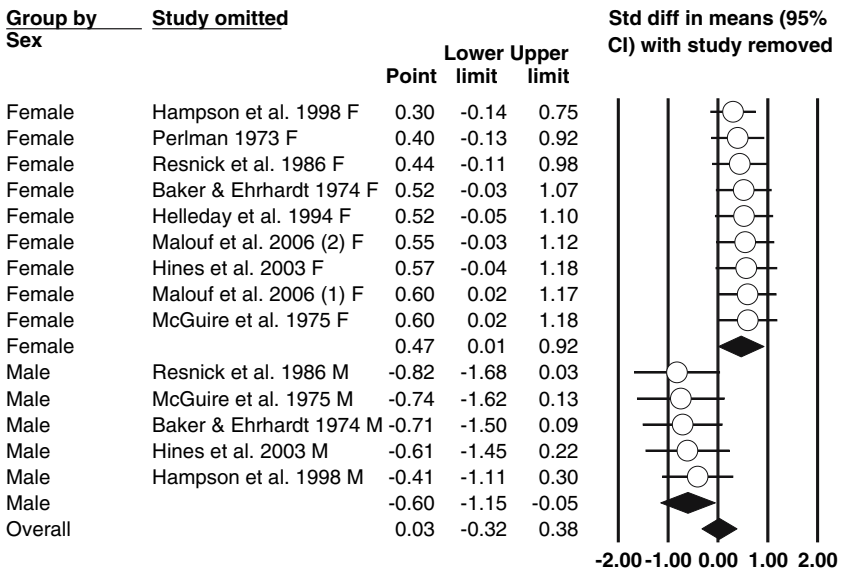

Fig. 2 Results of CAH "omit one study" analysis

effect size of the standardized mean difference between CAH males and controls was −0.60, and the corresponding value for the fixed effects model was −0.58 (Fig. 1). The deletion of individual studies in the "omit one study" sensitivity analysis produced effect sizes under the random effects model ranging from −0.82 to −0.41 (Fig. 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 −0.60 to −0.72 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 12 published (Austin et al., 2002; Coolican & Peters, 2003; Csatho et al., 2003; Kempel et al., 2005 [three samples]; McFadden & Schubel, 2003 [two samples]; Peters et al., 2007; Poulin et al., 2004; Putz et al., 2004; Rahman et al., 2004 [two samples]; Sanders et al., 2005; Scarbrough & Johnston, 2005; van Anders & Hampson, 2005) and four unpublished (G. M. Alexander, 2005, unpublished data [two samples]; A. Csatho et al., 2005, unpublished data; P. Kempel et al., 2005, unpublished data; J. C. Loehlin et al., 2005, unpublished data) studies, involving a total of 101,488 subjects (Table 2). The fixed effects model rendered an effect size estimate of −0.028, and the random effects model produced a smaller effect size estimate in the opposite direction: 0.005 (Fig. 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 −0.016 to 0.008 (Fig. 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 −0.001.

Males

For relationships between 2D:4D and spatial ability in men, 18 effect sizes were obtained from ten published (Austin et al., 2002; Coolican & Peters, 2003; Kempel et al., 2005; Manning & Taylor, 2001; McFadden & Schubel, 2003 [two samples]; Peters et al., 2007; Poulin et al., 2004; Putz et al., 2004; Rahman et al., 2004 [two samples]; Sanders et al., 2005 [three samples]) and three unpublished (G. M. Alexander, 2005, unpublished data [two samples]; P. Kempel et al., 2005, unpublished data; J. C. Loehlin et al., 2005, unpublished data) studies, involving 117,353 total subjects (Table 2). The effect size estimate was −0.030 using the fixed effects model and −0.068 using the random effects model (Fig. 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 −0.073 to −0.030 (Fig. 4). Trim and fill analysis suggested that three studies were missing to the right of the mean correlation. With these

Table 2 2D:4D sample characteristics

	Sample	Spatial test	Age range, mean (SD), or estimate	2D:4D Measure	*N*
Female studies	G. M. Alexander (2005, unpublished data) (1)	V and K[a]	18–24	Right	29
	G. M. Alexander (2005, unpublished data) (2)	V and K[a]	18–25	Right	157
	Austin et al. (2002)	V and K[a]	20.6(2.5)	Right	86
	Coolican and Peters (2003)	V and K[a]	~18–23	Right	399
	Csatho et al. (2003)	WM analog[b]	19–26	Right	45
	A. Csatho et al. (2005, unpublished data)	S and M[c]	19–26	Right	45
	P. Kempel et al. (2005, unpublished data)	SIQ[d]	18–40	Right	51
	Kempel et al. (2005)	SIQ[d]	23.5(4.3)	Right	23
	J. C. Loehlin et al. (2005, unpublished data)	MAB[e]	~16	Right	200
	McFadden and Schubel (2003) (1)	V and K[a]	20.7	Right	29
	McFadden and Schubel (2003) (2)	V and K[a]	19.2	Right	60
	Peters et al. (2007)	V and K[a]	28.7(11.5)	Right	99,765
	Poulin et al. (2004)	B and G[f]	~18–25	Right	117
	Putz et al. (2004)	V and K[a]	18–30	Right	120
	Rahman et al. (2004) (1)	V and K[a]	18–40	Right	60
	Rahman et al. (2004) (2)	V and K[a]	18–40	Right	60
	Sanders et al. (2005) (1)	S and M[c]	27.0(4.7)	Right	24
	Sanders et al. (2005) (2)	V and K[a]	22.2(1.9)	Right	44
	Sanders et al. (2005) (3)	V and K[a]	30.3(10.1)	Right	51
	Scarbrough and Johnston (2005)	C and S[g]	18–30	Right	41
	van Anders and Hampson (2005)	V and K[a]	18–42	Right	82
Male studies	G. M. Alexander (2005, unpublished data) (1)	V and K[a]	18–24	Right	35
	G. M. Alexander (2005, unpublished data) (2)	V and K[a]	18–25	Right	142
	Austin et al. (2002)	V and K[a]	20.1(1.1)	Right	79
	Coolican and Peters (2003)	V and K[a]	17–43	Right	237
	P. Kempel et al. (2005, unpublished data)	SIQ[d]	18–40	Right	22
	Kempel et al. (2005)	SIQ[d]	24.2(4.2)	Left	17
	J. C. Loehlin et al. (2005, unpublished data)	MAB[e]	~16	Right	120
	Manning and Taylor (2001)	V and K[a]	25.4(8.2)	Mean	125
	McFadden and Schubel (2003) (1)	V and K[a]	22	Right	35
	McFadden and Schubel (2003) (2)	V and K[a]	19	Right	59
	Peters et al. (2007)	V and K[a]	31.3(12.0)	Right	116,053
	Poulin et al. (2004)	B and G[f]	~18–25	Right	75
	Putz et al. (2005)	V and K[a]	18–30	Right	119
	Rahman et al. (2004) (1)	V and K[a]	18–40	Right	60
	Rahman et al. (2004) (2)	V and K[a]	18–40	Right	60
	Sanders et al. (2005) (1)	S and M[c]	25.9(4.7)	Right	24
	Sanders et al. (2005) (2)	V and K[a]	22.5(3.0)	Right	44
	Sanders et al. (2005) (3)	V and K[a]	31.7(9.8)	Right	47

[a] Vandenburg and Kuse (1978) 3D MRT

[b] Analog of Morris (1981) water maze

[c] Shepard and Metzler (1971) 3D MRT

[d] Spatial IQ test (Jager & Althoff, 1983)

[e] Multidimensional aptitude battery (Jackson, Vernon, & Jackson, 1993)

[f] Purdue visualization of rotations test 3D MRT (Bodner & Guay, 1997)

[g] Cooper and Shepard (1973) 3D MRT

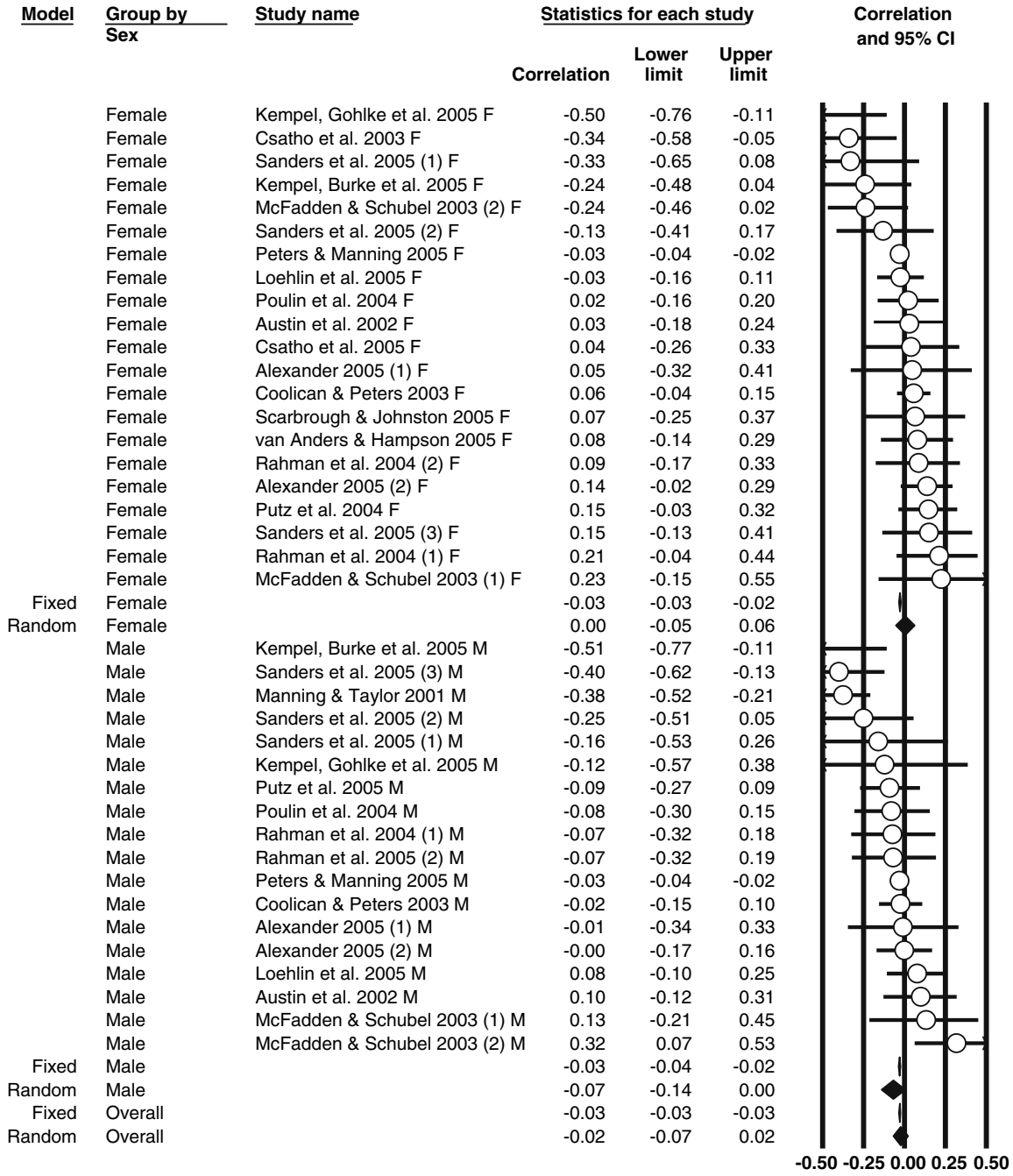

Fig. 3 2D:4D results overall and by sex

studies imputed, the point estimate under the random effects model was −0.015.

Discussion

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

CAH Studies

We estimated the population standardized mean difference between CAH individuals and controls to be 0.47 for females and −0.60 for males. According to Cohen (1988), these

Group by Sex	Study omitted	Point	Lower limit	Upper limit
Female	Coolican & Peters 2003 F	-0.02	-0.05	0.02
Female	Alexander 2005 (2) F	-0.02	-0.05	0.01
Female	Putz et al. 2004 F	-0.01	-0.04	0.02
Female	Rahman et al. 2004 (1) F	-0.01	-0.04	0.02
Female	Sanders et al. 2005 (3) F	-0.01	-0.04	0.02
Female	van Anders & Hampson 2005 F	-0.01	-0.04	0.02
Female	McFadden & Schubel 2003 (1) F	-0.01	-0.04	0.02
Female	Rahman et al. 2004 (2) F	-0.01	-0.04	0.02
Female	Poulin et al. 2004 F	-0.01	-0.04	0.02
Female	Austin et al. 2002 F	-0.01	-0.04	0.02
Female	Scarbrough & Johnston 2005 F	-0.01	-0.04	0.02
Female	Csatho et al. 2005 F	-0.01	-0.04	0.02
Female	Alexander 2005 (1) F	-0.01	-0.04	0.02
Female	Loehlin et al. 2005 F	-0.01	-0.04	0.02
Female	Kempel, Gohlke et al. 2005 F	-0.01	-0.04	0.02
Female	Sanders et al. 2005 (2) F	-0.01	-0.04	0.02
Female	Sanders et al. 2005 (1) F	-0.01	-0.04	0.02
Female	Kempel, Burke et al. 2005 F	-0.01	-0.04	0.02
Female	Csatho et al. 2003 F	-0.01	-0.04	0.02
Female	McFadden & Schubel 2003 (2) F	-0.01	-0.04	0.02
Female	Peters & Manning 2005 F	0.01	-0.06	0.07
Female		0.00	-0.05	0.06
Male	Peters & Manning 2005 M	-0.07	-0.14	0.00
Male	McFadden & Schubel 2003 (2) M	-0.05	-0.08	-0.02
Male	Loehlin et al. 2005 M	-0.05	-0.08	-0.01
Male	Austin et al. 2002 M	-0.04	-0.08	-0.01
Male	Alexander 2005 (2) M	-0.04	-0.08	-0.01
Male	McFadden & Schubel 2003 (1) M	-0.04	-0.08	-0.01
Male	Coolican & Peters 2003 M	-0.04	-0.08	-0.01
Male	Alexander 2005 (1) M	-0.04	-0.07	-0.01
Male	Kempel, Gohlke et al. 2005 M	-0.04	-0.07	-0.01
Male	Rahman et al. 2005 (2) M	-0.04	-0.07	-0.01
Male	Rahman et al. 2004 (1) M	-0.04	-0.07	-0.01
Male	Sanders et al. 2005 (1) M	-0.04	-0.07	-0.01
Male	Poulin et al. 2004 M	-0.04	-0.07	-0.01
Male	Putz et al. 2005 M	-0.04	-0.07	-0.01
Male	Sanders et al. 2005 (2) M	-0.04	-0.07	-0.01
Male	Kempel, Burke et al. 2005 M	-0.04	-0.07	-0.01
Male	Sanders et al. 2005 (3) M	-0.04	-0.07	-0.01
Male	Manning & Taylor 2001 M	-0.03	-0.06	-0.00
Male		-0.07	-0.14	0.00
Overall		-0.02	-0.07	0.02

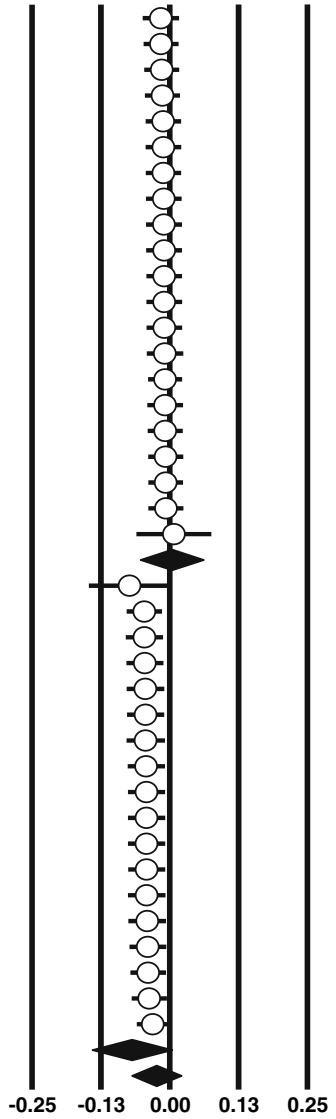

Fig. 4 Results of 2D:4D "omit one study" analysis

represent small- to medium-size effects. Results were robust with respect to meta-analytical model (fixed versus random effects) and sensitivity analyses. "Omit one study" analyses demonstrated minimal effects of deleting individual studies, indicating that these results did 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 served to underestimate the strength of the relationship.

One interpretation of these results is that the additional adrenal androgens provided by CAH elevate circulating androgens during a critical period for spatial ability, and that elevated androgens during this period increase spatial ability in females and decrease 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 gonadally intact 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 co-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 perform 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 cause them to differ from CAIS women.

Despite this evidence, 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, glucocorticoids may affect the two sexes differently. For example, glucocorticoid treatment impaired spatial ability more in female than in male rats (Vicedomini, Nonneman, DeKosky, & Scheff, 1986). However, 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 a critical period for differentiation of spatial ability. Consequently, spatial deficits in CAH males may result from a transient reduction of androgens, or even be unrelated to prenatal androgens, although only the former possibility explains increased spatial ability in CAH females.

Early androgens could influence spatial ability in CAH individuals by directly affecting the sensory or neurocognitive systems underlying spatial ability (e.g., the hippocampus), by affecting predispositions to engage in activities (e.g., play behaviors) that influence spatial ability, or by masculinizing appearance and thereby affecting treatment in a way that influences spatial ability. The last scenario is unlikely because, with the possible exception of virilized genitalia, which are often surgically repaired, CAH females are feminine in appearance. Moreover, rat studies suggest that androgens can influence spatial ability with minimal social input and with little opportunity for activities that enhance spatial ability.

If androgens affect spatial ability, these results are likely to apply specifically to spatial tasks that favor men. Women have been found to exhibit superior object location memory compared to men (McBurney, Gaulin, Devineni, & Adams, 1997; Silverman & Eals, 1992). Thus, this spatial ability is probably either unrelated to androgens or impaired by them, and it might therefore be unrelated to CAH, or perhaps impaired in both CAH males and females.

2D:4D Studies

In contrast to the small- to medium-size relationships observed between CAH and spatial ability, correlations between 2D:4D and spatial ability were negligible. Cohen (1988) suggests that a correlation of 0.1 represents a small effect, and in this meta-analysis, population correlations under the random effects model were 0.005 for females and −0.068 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: −0.001 for females, −0.015 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.

The 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 sexual dimorphisms 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; 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., 2006), and testicular androgen production cannot begin until the fetal Leydig cell population arises at 6-weeks post-conception (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 6 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.

Summary

These results, although 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 type of cognitive sex difference, visuospatial cognition. However, decreased prenatal glucocorticoid levels in CAH individuals may also affect spatial ability. 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 performance on spatial tasks favoring males. This interpretation relies on higher androgen levels in CAH males than in control males, for which some evidence exists. Third, the causal pathway linking early androgens to spatial ability is clarified. The CAH results presented here suggest that early androgen exposure directly affects the neural substrates for some spatial abilities, although it may also affect interest in pursuits that influence spatial ability. 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.

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