The contribution of the androgen receptor (AR) in human spatial learning and memory: a study in women with complete androgen insensitivity syndrome (CAIS)

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Abstract

Few studies have examined the impact of androgen insensitivity on human spatial learning and memory. In the present study, we tested 11 women with complete androgen insensitivity syndrome (CAIS), a rare genetic disorder characterized by complete absence of AR activity, and compared their performance against 20 comparison males and 19 comparison females on a virtual analog of the Morris Water Maze task. The results replicated a main sex effect showing that men relative to women were faster in finding the hidden platform and had reduced heading error. Furthermore, findings indicated that mean performance of women with CAIS was between control women and control men, though the differences were not statistically significant. Effect size estimates (and corresponding confidence intervals) of spatial learning trials showed little difference between women with CAIS and control women but CAIS women differed from men, but not women, on two variables, latency to find the platform and first-move latency. No differences between groups were present during visible platform trials or the probe trial, a measure of spatial memory. Moreover, groups did also not differ on estimates of IQ and variability of performance. The findings are discussed in relation to androgen insensitivity in human spatial learning and memory.

Keywords: testosterone; virtual maze; spatial navigation; water maze; androgen insensitivity; learning; memory

47 Sex differences in spatial abilities can be found across the entire life span (Moffat and
48 Resnick, 2002; Newhouse et al., 2007; Quinn and Liben, 2014; Voyer et al., 1995). Because
49 of converging lines of evidence from studies on hormonal variation during early development,
50 puberty or genetic conditions with excess or deficient levels of sex hormones, organizational
51 androgen effects on spatial abilities have been postulated (Berenbaum and Beltz, 2011).
52 However, other recent models also highlight the contributions of sex chromosomes to
53 sexually dimorphic behavior (Arnold, 2009). In rodents, the four core genotype model
54 (Arnold, 2009; Arnold and Chen, 2009) and the testicular feminization mutation (*tfm)* model
55 (Rizk et al., 2005; Yarbrough et al., 1990; Zuloaga et al., 2008) have been developed to assess
56 the influence of gonadal hormones and the androgen receptor (AR) as well as chromosomal
57 sex on behavior. While one study reported that androgen deficient *tfm* rats performed in-
58 between comparison male and female rats on the water maze task (Jones and Watson 2005),
59 such data should be interpreted with caution given some possible remaining maintenance of
60 androgen receptor function in the *tfm* rodent model. By comparison, findings from the four
61 core genotypes model indicate sex chromosomal effects on other behavior such as aggression,
62 social interaction or nociception (Arnold and Chen, 2009) although a recent study in this
63 model indicated an influence of sex hormones but not sex chromosomes on spatial learning
64 and memory (Corre et al., 2014).
65 As alluded to above, in humans, converging evidence supports a contribution of
66 androgens to spatial abilities (Berenbaum et al., 2012; Hampson and Rovet, 2015; Hines et
67 al., 2003b; Mueller et al., 2008b; Resnick et al., 1986). For example, prenatal exposure to
68 excess androgen in females with Congenital Adrenal Hyperplasia (CAH) reduced search
69 latencies and abolished the standard sex effect (faster performance for males relative to
70 females) on the human analog of the Morris Water Maze task thus equalizing performance
71 between men and women (Mueller et al., 2008b). Further, in male-limited conditions, recent

reports suggest that boys with early androgen excess (2-4 years of age, familial male precocious puberty, FMPP) have altered associations between spatial abilities and underlying structural morphology in spatial networks (Mueller et al., 2011). Such findings are not only consistent with other studies in CAH (e.g., Berenbaum etal., 2012; Hampson and Rovet, 2015) but also with previous reviews (Berenbaum and Beltz, 2011) that suggest that perinatal organizational effects by androgens on brain areas such as the hippocampus or striatum would lay the foundation for later spatial performance. By comparison, while studies in CAH and FMPP assess the influence of androgen excess, human studies specifically examining the role of testosterone depletion in spatial cognition are few but limited evidence is available from disparate conditions. In an important early illustration of pubertal hormones on spatial skills, men with idiopathic hypogonadotropic hypogonadism performed worse on paper and pencil tests of spatial abilities relative to unaffected comparison men (Hier and Crowley, 1982). Males with this condition carry an 46, XY karyotype, and are reared as 'normal' boys but fail to develop puberty (Hier and Crowley, 1982). In addition, some limited evidence for estrogen deficiency in girls and testosterone deficiency in boys due to aneuploidies also indicate a reduction in performance in spatial skills in girls with Turner Syndrome (45,X, Green et al., 2014), while the evidence for boys with Klinefelter Syndrome (47,XXY) has been mixed (Bender et al., 1989; Ross et al., 2009). Thus more evidence for the involvement of androgen deficiency in human spatial learning and memory is needed.

In another, rare condition, androgen insensitivity syndrome (AIS, 46,XY) is caused by mutations in the gene encoding the AR, and resulting in reduced (partial AIS, PAIS) or totally absent (complete AIS, CAIS) AR activity. 46,XY individuals with PAIS are characterized by varying degrees of virilization of the external genitalia (and presumably the brain) and can be raised either as males or females. Due to complete absence of T action, already prenatally, 46,XY individuals with CAIS (prevalence ranges from 20 400 to one in 99 100 genetic males,

97 (Hughes et al., 2012) are phenotypically female and have a female gender identity, in spite of
98 normal or even high serum testosterone levels. In many cases the diagnosis is made only
99 during late puberty, due to the absence of menses (Hughes et al., 2012). Given the rarity of
100 this disorder, in humans very few studies in CAIS have examined the effects of androgen
101 absence on cognitive function and psychological and sexual well-being. These studies in
102 women with CAIS have examined neuropsychological aspects (Imperato-McGinley et al.,
103 1991), mental rotation (van Hemmen et al., in press), otoacoustic emission (Wisniewski et al.,
104 2014), sexual well-being (Fliegner et al., 2013), psychosexual functioning (Callens et al.,
105 2012; Callens et al., 2014), sexual arousal (Hamann et al., 2014), gender identity and sexual
106 orientation (Brunner; Hines 2003), and quality of life (D'Alberton et al., 2015) as well as
107 psychological outcomes (Hines et al., 2003a). Findings with regards to spatial abilities have
108 been mixed, in our view. While one older study reports impaired performance of AIS
109 participants relative to both comparison males and females on IQ subtests probing perceptual
110 organization (e.g., block design)(Imperato-McGinley et al., 1991), a recent neuroimaging
111 study of mental rotation found a more female-typical pattern of responding in affected women
112 (van Hemmen et al., in press).
113 Because of absence of AR function but an XY karyotype, women with CAIS may
114 provide an excellent opportunity to examine the effects of sex chromosomes vs. prenatal
115 androgen action. In the present study we sought to assess spatial learning and memory in
116 women with CAIS on a previously validated task, the virtual analog of the Morris Water
117 Maze task (Hamilton et al., 2009; Mueller et al., 2008b). Given 1) the conflicting finding
118 noted above and 2) because of the unclear effects of gonadal vs. chromosomal effects on
119 spatial learning and memory in humans, we expected differences between CAIS women and
120 comparison men and women during performance of the Water Maze task but were unsure
121 about the directionality of effects.

Methods

Participants

Eleven women with CAIS (age = 29.00 years, SD = 9.24 years), 19 comparison women (CW)(age = 23.74 years, SD = 5.22 years) and 20 comparison men (CM)(age = 25.10 years, SD = 6.11 years) participated. Originally, a 20th comparison female was included in the study but had to be excluded due to experiencing a high and uncomfortable level of dizziness. This participant also showed an extremely high number of failed trials (>50%), possibly because of the dizziness. All remaining participants did not differ significantly in age ($F(2,47) = 2.53$, $p = .12$), or estimated IQ (block design: $F(2,47) = 0.41$, $p = .67$; vocabulary: $F(2,47) = 0.39$, $p = .68$)(Table 1). Patients were recruited by contacting them through the Department of Endocrinology of Ghent University Hospital. In addition, an advertisement was placed in a support group magazine. An official report of the original genetic testing could not be retrieved in two women, who were currently not seen by a doctor anymore (Table 2). Comparison participants were recruited by word-of-mouth by two experimenters (TV and AVB). The study was approved by the Ethical committee of Ghent University Hospital. Participants received 30 EUR for compensation. Prior to the study, all participants signed an informed consent. To secure homogeneity of our patient sample, only individuals with the complete but not the partial form of androgen insensitivity syndrome were invited to participate.

********** TABLE 1 ABOUT HERE PLEASE **********

********** TABLE 2 ABOUT HERE PLEASE **********

147 *Materials*

148 Prior to testing, participants completed an abbreviated estimate of IQ (Wechsler, Block design
149 and vocabulary, (Wechsler, 1999) as well as a previously used questionnaire (Mueller et al.,
150 2008a) regarding their experience with playing computer games and using a joystick. The
151 virtual Morris Water Maze (Hamilton et al., 2009) was used. In this virtual environment, a
152 square room contained a circular pool of water and displayed a different cue on each side of
153 the room: a door, a window, a bookshelf, and an abstract painting to aid orientation.
154 Participants navigated in the pool from a first-person perspective and moved around using a
155 commercially available joystick. Following previous suggestions (Skelton et al., 2000) to
156 closely model rodent behavior, the 'back' key on the joystick was disabled. Participants were
157 told they could not back up and if they wanted to spin around, they had to turn 180 degrees
158 around their left or right axis using the left or right arrow keys. The experiment was
159 completed in one session (about 20-25 min) without breaks on a laptop with a 17-inch
160 monitor. The maze consisted of 22 trials, including one familiarization/exploration trial of the
161 maze, 4 visible platform trials, 16 experimental trials and one probe trial. On the exploration
162 trial, participants had 4 minutes to explore the room and to learn to navigate comfortably in
163 this environment. No platform was present during this first trial. The platform was introduced
164 on the second trial. For this and the following 3 trials, participants were asked to simply
165 "swim" towards the visible platform. Over the next 16 experimental trials, the platform was
166 hidden but always located in the same position and participants were explicitly informed
167 about this feature. However, the platform location was different from the second visible
168 platform trial and participants were asked to 'hunt' for the platform on the first hidden trial.
169 Participants were dropped in a pseudo-randomized order, which was fixed for all participants,
170 across trials an equal number of times at four different locations on the side of the pool wall.
171 For each trial, the task consisted of "swimming" directly to the hidden platform. Once

participants successfully reached the platform, a neutral sound occurred. Participants remained on the platform for 5 s before the onset of the next trial. On each trial, participants were given 60 s to find the platform, after which the platform became visible and a written message appeared on the screen indicating the visibility of the platform and encouraging participants to move towards it. If such a trial occurred, it was counted as a failed trial. On the final, probe trial, the platform remained hidden for 60 seconds and participants were required to continue searching for the platform. After the experiment, participants were thanked and debriefed. Of note, participants also completed some questionnaires and a second cognitive task following this task (a rewarded Stroop task), the results of which will not be discussed here.

Statistical analysis

Because groups differed significantly in their experience of playing computer games during their youth and with 3D video games (Table 1), these two variables were used as a covariate of no interest in all analyses. Consequently, a 4 x 3 repeated measures ANCOVA was run for each variable during the hidden platform trials using a Block (1–4) by Group (CAIS, CW, CM) design. Based on previous studies (Mueller et al., 2009), we binned the 16 experimental trials into 4 blocks of 4 trials each, i.e., block 1: trials 1–4, block 2: trials 5–8, block 3: trials 9–12 and block 4: trials 13–16). The ANCOVA was repeated for the five performance variables: (1) latency, i.e., the time (s) spent to reach the platform; (2) path length, i.e., the distance (relative to the pool diameter) covered to reach the platform, (3) heading error (in deg), i.e., the angle between optimal heading direction and participant's heading direction; (4) first-move latency, an indicator of how long subjects remained at the wall edge at the beginning of a trial before they started moving towards the platform. In addition, (5) an

197 analysis was run on overall accuracy, i.e., number of failed attempts, in which the latency was
198 longer than 60 s. An additional 4 x 3 analysis on latency to reach the platform for the 4 visible
199 platform trials was also conducted to examine potential differences on basic motoric skills
200 with the task. Finally, for the probe trial, we conducted a simple one-way analysis of co-
201 variance on group differences on dwell time in the quadrant (North East) where the platform
202 was located. Greenhouse-Geisser correction was used in case of violation of sphericity. To
203 further exploit the data and to gain a more comprehensive picture of performance, effect sizes
204 were systematically explored using eta squared and Cohen's *d,* as appropriate. In addition, we
205 calculated 95% confidence intervals around *d* (Cumming, 2012). To assess the variability of
206 performance within and between groups, we calculated coefficients of variation
207 (CV)(standard deviation divided by its mean for a given dependent variable times 100). Then
208 we compared the variability using the ratio of squared coefficients of variation, which is
209 equivalent to an *f*-ratio (cf. Sokal and Braumann, 1980; Wallen and Lloyd, 2008). P-values
210 were then corrected for multiple comparisons using a step-down procedure (Finner, 1990,
211 1993).
212
213
214 **********FIGURE 1 ABOUT HERE PLEASE **********
215
216 **Results**
217 *Visible platform trial latency*
218 A significant main effect of trial ($F(1.98, 89.18) = 5.58$, $p = .005$, $\eta^2 = .10$) and a significant
219 linear effect ($F(1,45) = 8.51$, $p = .006$, $\eta^2 = .15$) indicated improvement over the course of
220 visible trials. No other effects were significant.
221

Hidden platform trials

In the latencies, the main effect of block was significant ($F(2.18, 98.02) = 3.22$, $p = .04$, $\eta^2 = .06$) alongside a significant linear effect showing improvement over the course of the trials ($F(1,45) = 4.26$, $p = .045$, $\eta^2 = .08$). Importantly, the main effect of group was significant ($F(2,45) = 5.87$, $p = .005$, $\eta^2 = .21$)(Figure1A). Post-hoc follow-up tests of this group effect revealed an expected sex effect showing that males were significantly faster in finding the hidden platform than females ($p = .001$). However, the performance of CAIS women was in-between that of comparison males and females and thus did not significantly differ from either group ($ps > .05$). As in the latencies, heading error also showed a significant learning effect over time ($F(2.36, 106.00) = 3.23$, $p = .036$, $\eta^2 = .06$) evidenced by a significant linear effect ($F(1,45) = 4.70$, $p = .04$, $\eta^2 = .09$). The main effect of group was also significant here ($F(2,45) = 3.76$, $p = .03$, $\eta^2 = .14$) and indicated a smaller heading error for CM relative to CW ($p = .03$), with no difference between CAIS and CW and CM ($ps > .05$)(Figure1B). In path length, the main effect of block ($F(1.98, 88.94) = 4.79$, $p = .011$, $\eta^2 = .09$) and the significant linear effect ($F(1,45) = 5.13$, $p = .03$, $\eta^2 = .10$) indicated learning across the trials. The main effect of group was not significant ($F(2,45) = 2.42$, $p = .10$) (Figure1C). There was a significant effect of block in first-move latency indicating that participants detached quicker from the maze wall as time progressed ($F(3,135) = 4.31$, $p = .006$, $\eta^2 = .08$) and as seen in a linear effect ($F(1,45) = 11.68$, $p = .001$, $\eta^2 = .17$). The main effect of group was not significant ($F(2,45) = 1.73$, $p = .19$). Finally, there were no significant effects on the number of failed trials (all $ps > .05$).

Probe trial

There was no significant main effect of group when looking for the platform ($F(2,45) = 0.21$, $p = .81$) as all participants searched in the correct quadrant most of the time (Figure 1D).

**********FIGURE 2 ABOUT HERE PLEASE **********

**********TABLE 3 ABOUT HERE PLEASE **********

Additional exploratory analyses of age, performance variability, and effect size

Although age did not differ significantly between groups, we examined the influence of this variable on the observed group effects. The main effects of group in latency ($F(2,46) = 7.51$, $p = .002$, $\eta^2 = 0.24$) and heading error ($F(2,46) = 5.71$, $p = .006$, $\eta^2 = 0.19$) remained significant. While the main effect of age was not significant for latency ($F(1,46) = 0.62$, $p = .44$), it approached significant for heading error ($F(1,46) = 3.93$, $p = .053$). To further characterize the effects from conventional testing reported above, effect sizes (Cohen's *d* and corresponding 95% CI) were calculated for all variables and groups (Figure 2, corresponding means and standard deviations are displayed in Table 3, left three columns). Examination of these results indicates that CAIS women and men differed on the dependent variables of latency and first move latency while there were no differences between CAIS women and comparison women. By comparison, differences between men and women emerged on latency, heading error, and path length. Finally, given the small sample size of the patient group and to assess the degree of variation and thus assess the heterogeneity of the study sample during performance, we calculated the ratio of squared coefficients of variation (Table 3, right three columns). After correction for multiple comparisons, no significant group differences in variability emerged.

Discussion

This study assessed spatial learning and memory in women with CAIS. Based on prior data, we had hypothesized that CAIS women would perform differently from comparison men and women leaving the exact directionality of effects open. The results revealed a standard sex effect showing improved performance in CM relative to CW on a spatial navigation task thus being consistent with previous work (Moffat et al., 1998; Mueller et al., 2008a; Newhouse et al., 2007; Voyer et al., 1995). Women with CAIS did not differ statistically from either men or women on any of the dependent variables. However, analyses of effect sizes (and corresponding confidence intervals) suggested a more female-like pattern in CAIS women on two performance variables, namely latency and first-move latency. Importantly, these findings were not driven by previous experience with computer games and groups did not differ on trials requiring basic motor control (visible platform trials) or measures of IQ.

Consistent with prior research (Moffat et al., 1998; Mueller et al., 2008a; Newhouse et al., 2007), men learned the spatial location of the hidden platform faster than women as shown in significantly faster latencies, smaller heading error, and shorter path length. Although this difference was abolished (statistically) in women with CAIS, affected women were closer in performance to comparison women relative to comparison men as indicated by smaller effect sizes and confidence intervals that overlapped with the performance of females (i.e., included 0) but that did not overlap with performance (i.e., excluded 0) of males on two performance measures, latency and first-move latency. These results have to be interpreted with caution given the absence of effects on other performance variables and the large CIs of the effect sizes. Previous authors (for reviews see Berenbaum and Beltz, 2011; Schulz et al., 2009) have suggested that performance differences between the sexes might arise out of early organizational effects of androgens during the perinatal period. This could also include brain structures supporting spatial abilities such as the hippocampus or the striatum. Such a

hypothesis is consistent with studies from disparate conditions as well as structural and functional MRI data. As mentioned in the introduction, boys with early (~ 2-4 years of life but likely earlier, Leschek, 2004) androgen excess show different associations between spatial performance variables on the virtual Morris Water Maze and grey matter volume in structures supporting spatial navigation when compared to healthy comparison boys (Mueller et al., 2011). Similarly, girls with Turner Syndrome exhibit reduced visuo-spatial processing and aberrant parietal cortical development (Green et al., 2014), an area involved such processing skills. Finally, van Hemmen and colleagues (in press) recently demonstrated in an fMRI study in women with CAIS that affected women showed a more female-typical response pattern in the parietal lobe during mental rotation, another critical spatial skill.

In comparison to the spatial learning parameters, the probe trial at the end of the experiment in the water maze task is usually taken to assess spatial memory. In our study, all three groups searched significantly longer in the correct quadrant relative to the other quadrants showing no indications of potential group differences. Such a finding is consistent with another, recent study in healthy participants, which did not report a significant impact of either serum testosterone levels or AR activity on probe trial measures in males, although an effect of T (but not of CAG repeats as a measure for AR activity) was present in women (Nowak et al., 2014). Although in her (Nowak et al., 2014) study the relative contributions of CAG repeats and T to performance is difficult to interpret, another recent study on the genetics of spatial abilities demonstrated an influence of the *MAO-A* gene, located on the X chromosome, on human spatial learning in males (Mueller et al., 2014). Moreover, consistent with findings in genetic conditions of sex chromosomal aneuploidies, i.e., 47 XXY or 45, X, reductions in spatial abilities have been observed (Green et al., 2014; Ross et al., 2009). Thus, taken together, while the present data might be more supportive of an influence of androgens

320 rather than chromosomal sex on spatial performance, it cannot be ruled out that genes located
321 on sex chromosomes, or other genes for that matter, might also play a role.
322 Given the scarcity of research in CAIS women, relatively little is known about the
323 consequences of AIS on cognitive-affective function. Although an earlier neuropsychological
324 study reported deficits in perceptual organization in AIS women (Imperato-McGinley et al.,
325 1991), our findings could not replicate such a deficit, as performance on block design, a
326 subtest of perceptual organization, was similar across the groups. In addition, participants also
327 performed similarly on vocabulary, a measure of verbal comprehension, again suggesting no
328 deficits. More recent investigations generally support a female-like response pattern in CAIS
329 including studies of mental rotation (van Hemmen et al., in press), the processing of sexual
330 stimuli (Hamann et al., 2014), or during otoacoustic emission (Wisniewski et al., 2014). In
331 our study, CAIS individuals did not differ statistically from either males or females. However,
332 on two measures CAIS women differed from men but not women when the effect sizes and
333 CIs were considered. Although such tentative data might indicate a more female-like pattern,
334 they have to be treated with great caution as the effect was only apparent on two variables and
335 based on effect sizes and CIs and in the absence of statistical differences.
336 Furthermore, some limitations require discussion. First, of course, we acknowledge
337 the small sample size of the patient group. However, small sample sizes present a common
338 problem when working with patients with rare conditions and our sample size of women with
339 CAIS is similar to those of other studies in this patient population (Fliegner et al., 2013;
340 Hamann et al., 2014) although some studies were able to recruit larger samples (see van
341 Hemmen et al., in press). In addition, no serum or saliva samples were obtained to assess
342 hormonal status at the time of investigation. Despite these shortcomings, additional analyses
343 of variability indicated no statistically significant differences in variability in performance or
344 IQ measures. Secondly, although prior experience with playing 3D virtual games differed

between CM and CW, sex differences in performance persisted even after taking this factor into consideration. The data are thus consistent with prior work that found little impact of gaming experience on spatial learning and memory processes (Mueller et al., 2008a; Nowak et al., 2014). Third, unfortunately, we did not obtain information on the menstrual cycle or contraception status of the control women, which might explain the relatively (non-significant) larger variability seen in Table 3 in performance relative to males or the patient group. Fourth, although the results of molecular genetic testing could not be retrieved in 2/11 women, we assumed they had indeed been diagnosed with CAIS based on the fact that they were well informed about their condition and that they have been a member of the AIS support group for many years.

In summary, in the present spatial learning and memory task, women with CAIS did not differ significantly from either comparison men or women, while men and women differed from each other. Moreover, we could also not find any differences in variability of performance or estimate measures of IQ. However, future work in larger samples may be necessary to further clarify the impact of prenatal androgens and/or chromosomal sex on specific sub-processes such as spatial learning and/or memory.

Figure Captions

Figure 1. Figure shows performance for CAIS women (thick dashed lines), comparison men (CM, solid lines), and comparison women (CW, thinly dotted lines) for spatial learning (A-C) and memory (D) variables. Error bars denote standard error of the mean (S.E.M.).

Figure 2. Effect sizes (ES, round circle, Cohen's *d* with 95% Confidence Intervals) of group differences for different performance variables. Solid black line = CAIS women vs. men (greater positive ES = improved performance for men), grey line = CAIS women vs. women (greater positive ES = improved performance for CAIS women), dashed black line = women vs. men (greater positive ES = improved performance for men).

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Table 1. Demographic information of the study sample for CAIS patients, control women (CW) and control men (CM)

	CAIS (N=11)	CW (N=19)	CM (N=20)	p-value	Effect size
Age	29.00 (9.24)	23.74 (5.22)	25.10 (6.11)	.12	.09
IQ block design[a]	11.36 (2.73)	11.05 (3.99)	10.30 (3.20)	.67	.02
IQ vocabulary[a]	11.55 (2.12)	10.63 (3.42)	11.15 (2.52)	.68	.02

Navigation questionnaire					
Dizziness	1.82 (0.87)	2.32 (1.06)	1.75 (0.79)	.14	.08
How often did you play during youth	2.00 (1.09)	2.67 (1.29)	4.00 (1.49)	**.001**	.28
How often last year	3.00 (1.79)	2.05 (0.85)	2.90 (1.62)	.11	.09
How often 3D games	1.18 (0.40)	1.05 (0.22)	2.35 (1.73)	**.001**	.24
How often 2D games	2.45 (1.57)	2.11 (1.33)	2.15 (1.09)	.76	.01
Experience with joystick	1.27 (0.47)	1.26 (0.56)	1.65 (0.98)	.22	.06

[a] Norm scores
Bold font indicates significant effect

Table 2. Characteristics of the CAIS women

Participant	Age	Hormonal replacement	Mutation	Gonadectomy
PTBU01	39	n	P893L	n
PTIE02	42	y	D767Y	y
PTDT03	19	n	N706S	y
PTKW04	25	y	complete deletion AR	y
PTBM05	24	stopped	V889M	y
PTLT06	32	y	NA[a]	
PTBW07	28	y	E804K	y
PTUO08	17	n	NA[a]	
PTKC09	44	y	R598X	y
PTOW10	21	y	A564D	y
PTOC11	28	n	R822X	

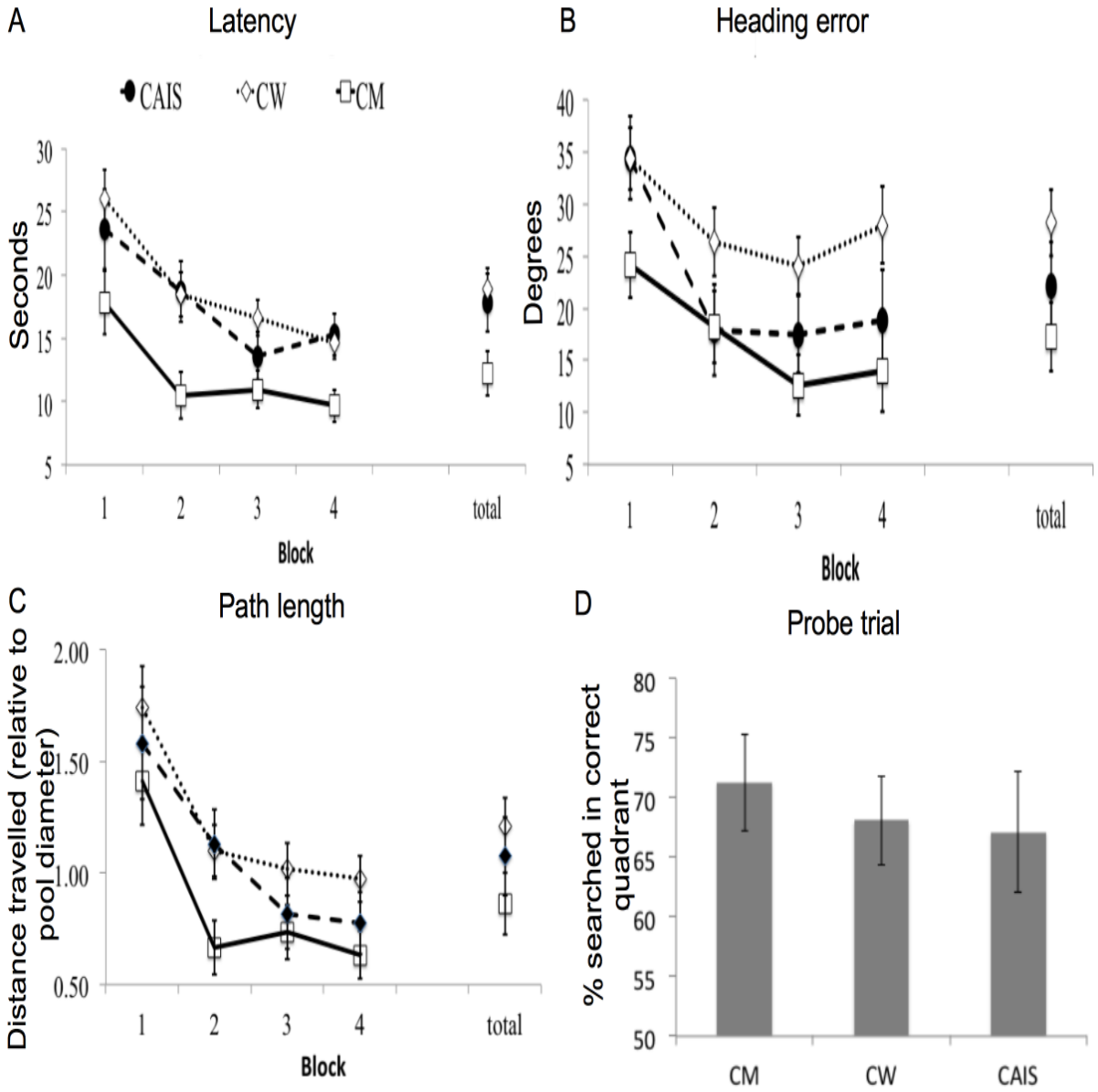
y = yes; n = no, NA: results of molecular genetic analyses (Sanger sequencing of the AR) were not available; [a] diagnosis confirmed by patient

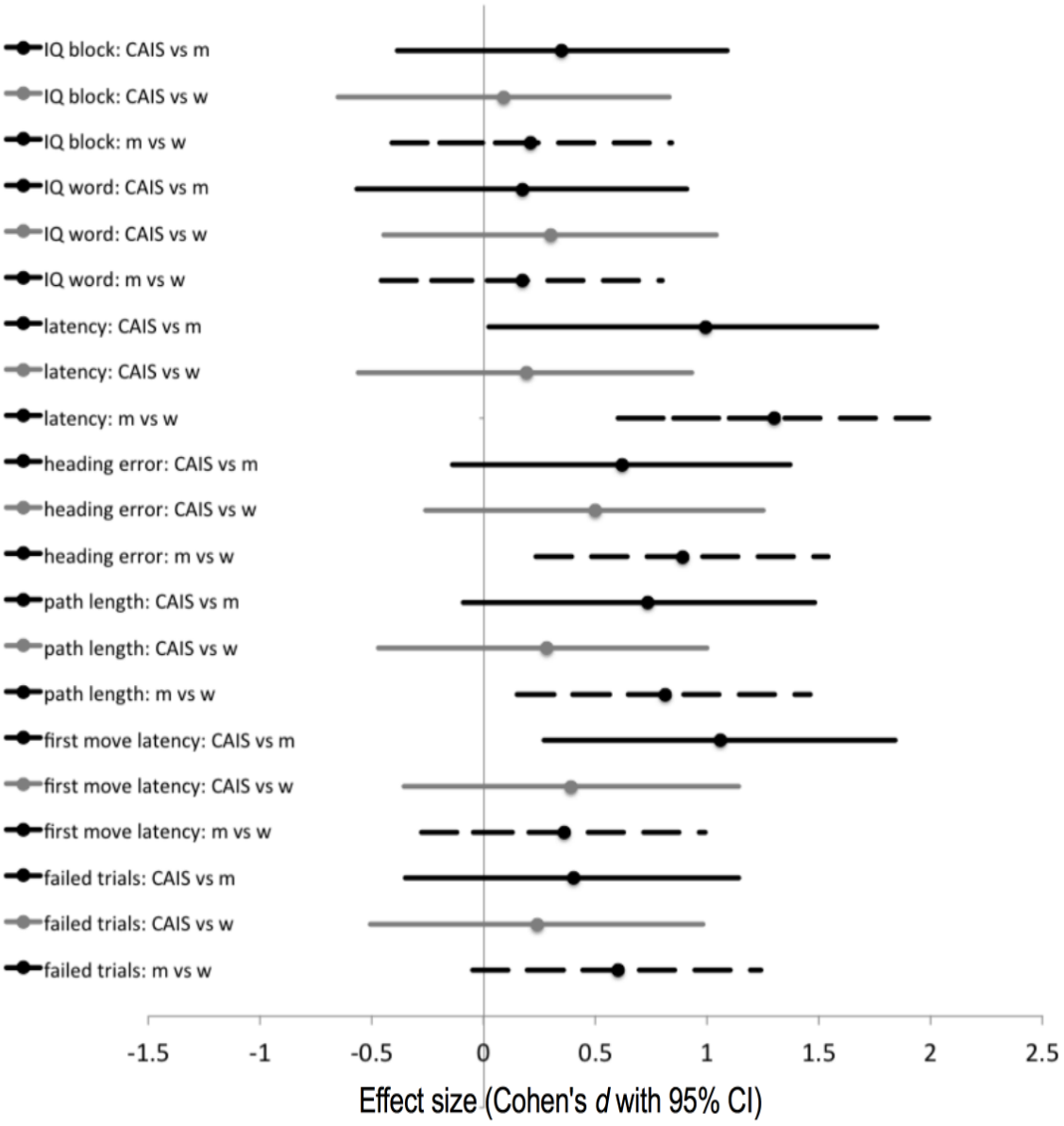
Table 3. Table displays the means and standard deviations for the measures of interest split by group (left 3 columns) as well as the ratio of squared CVs of one group divided by the squared CVs of another group for the possible group comparisons (right 3 columns) for comparison men (CM), comparison women (CW) and women with CAIS

	CAIS	CW	CM	Ratio CM CW (df = 37)	Ratio CM CAIS (df = 29)	Ratio CW CAI (df = 28
IQ block	49.82 (10.47)	46.42 (14.23)	44.85 (11.14)	0.66	1.40	2.13
IQ word	42.45 (8.41)	38.11 (10.90)	40.65 (8.62)	0.55	1.15	2.09

Latency (sec)	17.62 (6.68)	18.75 (5.39)	12.51 (4.15)	1.33	0.76	0.58
Heading error (deg)	21.59 (5.70)	28.08 (15.47)	17.61 (6.70)	0.48	2.08	4.36
Path length (units)	1.07 (0.34)	1.21 (0.56)	0.86 (0.26)	0.43	0.89	2.08
Fmove latency (sec)	4.65 (1.11)	4.04 (1.73)	3.53 (1.03)	0.47	1.50	3.21
Failed trials (number)	0.14 (0.17)	0.18 (0.22)	0.08 (0.14)	2.59	2.28	0.88

Fmove = first move latency
The ratio of each of the pairwise comparisons (3 rightmost columns) is the equivalent of an f-test




IQ block: CAIS vs m
IQ block: CAIS vs w
IQ block: m vs w
IQ word: CAIS vs m
IQ word: CAIS vs w
IQ word: m vs w
latency: CAIS vs m
latency: CAIS vs w
latency: m vs w
heading error: CAIS vs m
heading error: CAIS vs w
heading error: m vs w
path length: CAIS vs m
path length: CAIS vs w
path length: m vs w
first move latency: CAIS vs m
first move latency: CAIS vs w
first move latency: m vs w
failed trials: CAIS vs m
failed trials: CAIS vs w
failed trials: m vs w
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
Effect size (Cohen's d with 95% CI)