Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data

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Abstract

The existence of sex differences in the standard rat and mouse models of learning and memory is a controversial and contested topic in the literature. The present meta-analysis of radial maze and water maze experiments was conducted to assess the reliability and magnitude of sex effects in the standard rodent models of learning and memory. Data were culled from published and unpublished sources. Findings indicate large reliable male advantages for rats in radial maze and water maze protocols. Significant strain differences were also identified. In each paradigm, protocol variations were associated with differential sex effects. For the water maze, smaller male advantages were associated with pretraining regimens and for the radial maze, larger significant male advantages were observed in protocols that included unbaited arms (combined reference and working memory protocols). Mouse studies exhibited a different pattern of sex effects; small female advantages were evident in the water maze, but small male advantages were evident in the radial maze. Together these findings establish the reliability of male advantages in spatial working and reference memory for rats across strains, protocols, ages and rearing environments. The findings also support an important species dichotomy between rats and mice that should be considered when transitioning from rat to mouse models. In light of these results, the biological evidence supporting theoretical explanations of sex differences is reviewed and evaluated.

Keywords: Spatial learning and memory; Sex differences; Meta-analysis; Rats; Mice
The magnitude and reliability of sex differences in spatial cognition, particularly spatial learning capacities, have been of long standing debate in the literature [1,2]. Although sexual dimorphisms in neuroanatomy and neurophysiology believed to be important for spatial learning and memory processes have recently been verified [3–5], the cognitive implications of these differences are still contested. Much of the disagreement now centers on the apparent divergence of behavioral findings [6–11]. The following meta-analysis, the first systematic review of sex differences in the animal literature, was developed to provide a more consistent interpretation of behavioral findings and to resolve long-standing disagreements. Importantly, the analysis also considers the biological and procedural variations associated with disparate experimental findings in the literature.

In the psychology literature, human males have shown relatively consistent advantages in a variety of spatial tasks [2,12]. However, the validity of these studies continues to be challenged on the grounds that the tasks used are poorly characterized [2,13] and that task performance is necessarily confounded with socialization and gender-biased expectations [14–16].

Accordingly, animal models have been advocated for the study of cognitive sex-differences and their neurobiological bases [1]. However, even in the animal literature, reports of sex differences have been controversial. General male advantages were initially reported for rodents in early maze-learning paradigms, including the Lashley III, Hebb-Williams, Davenport closed-field and T-Mazes [17–19]. However, the validity of these tasks has also been challenged with several laboratories demonstrating influences of general nonmnemonic behavioral differences, primarily sex differences in locomotor and exploratory activity [18]. The radial maze and Morris water maze paradigms were later developed to counter such criticisms. Yet, further complicating the debate, many of the early radial and water maze studies frequently sited in support of male spatial learning advantages have relied on nonstandard protocols more consistent with current understandings of nondeclarative habit formation [3,20,21].

Over the past decade, modern rodent models employing standardized radial maze and water maze protocols have been widely adopted and are now used as routine behavioral-cognitive assays in a variety of study types, e.g. see [22–24]. Although rats were originally the model of choice for these tasks, mice have become increasingly important with the development of transgenic techniques, a trend that will likely continue following the recent sequencing of the mouse genome [25]. Moreover, even with the advent of more standardized protocols, important procedural variations still appear to influence learning performance in these paradigms. In the absence of a systematic meta-analytic synthesis, such confounds continue to cloud current understandings of sex differences in spatial learning capacities.

The radial-arm maze, developed by Olton and Samuelson [26], has been used primarily to assess working memory [27], but has also been adapted to assess working and reference memory conjointly [28,29]. Because choice accuracy is measured, the radial-arm maze is less sensitive to general sex and species behavioral differences in activity and exploratory levels [30]. In general, reports of sex-differences in the literature have been inconsistent in both the standard 8-arm version [10,28,31] and 17-arm version of the radial maze [11,32]. In the few protocols where both working and reference memory have been tested, reports of a male advantage have also been inconsistent [9,29]. Additionally, individual studies have suggested that performance in the radial maze is influenced by species and strain [25], age [33], diet [34], and procedural differences [31,35]. Rearing environment also reportedly can affect radial-arm maze performance in male species, but there is conflicting evidence about whether rearing environment influences females in the same manner [9,11,31].

In contrast, the Morris water maze, developed by Roger Morris [36] for rats and later adapted to mice, has been used to assess reference memory. Due to the simplicity of the paradigm, the water maze has become one of the most frequently used behavioral assays in neuroscience (for a review see [25]). Like the radial maze, the water maze is less susceptible to general sex and species behavioral differences in activity and exploratory levels, particularly when path-length measures are used to assess performance [37]. Reports of sex differences in the water maze have also been variable. Several studies have reported a male
advantage [8,38], but at least one study has reported a significant female advantage [6]. Moreover, the majority of studies have reported no advantage for either sex [1,7,39–42]. Additionally, a few studies have found evidence that, like radial maze performance, water maze performance may be influenced by species and strain [25], age [6], stress [43] and procedural variations [25,44].

Despite widespread adoption of the radial and water maze, few laboratories have tested female species [7,44] and fewer still have compared performance of female and male cohorts directly [25]. Moreover, studies that have used male and female control cohorts rarely fully report or discuss sex differences, making it difficult to evaluate the magnitude and reliability of innate sex differences in the literature, particularly with respect to other qualitative covariates. Of the few studies that have directly or indirectly compared male–female differences in these paradigms, results have apparently been mixed; given the variety of possible mediating factors, inconsistency and disagreement might be expected.

Importantly, no systematic meta-analysis of sex differences in the animal literature has yet been conducted. Such an analysis, which considers relevant biological and procedural variations, is needed to advance our current understanding of the animal models so heavily relied upon in contemporary neuroscience research. With advances in biological techniques, animal models, in so far as mechanistic homologues exist, will become increasingly important for basic research into the neurobiology of learning and memory, and for the study of neurocognitive disorders. A clearer understanding of sex differences in these models then will be crucial for more sophisticated understandings of neurocognitive diseases and for the development of effective therapeutics for such disorders.

The present study employs contemporary meta-analytic techniques to assess aggregate sex-differences in the standard rodent models of spatial working and reference memory. Data were culled from the body of published and unpublished studies, which have used standardized radial or water maze protocols. For several studies, published and unpublished, raw data were obtained and analyzed in order to incorporate unpublished sex effects (n = 6). The relevant qualitative variables from the literature, which may influence the magnitude of sex differences in these tasks, are also considered. Specifically, the influences of (i) species, (ii) strain, (iii) pretraining (water maze), (iv) rearing environment, (v) protocol complexity (radial maze) and (vi) age are assessed in the quantitative analysis that follows. Importantly, the analysis establishes the relative consistency of male advantages in both reference and working memory, but this result depends on the species and strain tested. Furthermore, important new evidence pertaining to the influences of pretraining (water maze) and combination reference-working memory protocols (radial maze) on sex effects is revealed.

2. Methods
2.1. Selection criteria

A PubMed literature search was performed using the key words, sex difference, water maze, radial maze, rat, mouse and spatial learning for the years 1960–2003. Within those studies identified as topical, reference searches were conducted to verify completeness of the initial literature search. As a final step, those laboratories known to use male and female cohorts as part of a standard experimental protocol were contacted in order to supplement the aforementioned literature searches and in order to locate unpublished data from any experiment utilizing unoperated male and female controls.

The following inclusion criteria were employed for the present study. First, only experiments using a standard protocol in either the water maze or radial arm maze were included. For water maze studies, an experiment was included if the protocol employed multiple acquisition trials administered over multiple days, a submerged escape platform located in a fixed location and variable start points. These inclusion criteria were formulated to ensure consistency across experiments and, specifically, to ensure that the protocol was designed to measured reference memory. In radial maze experiments, a standard protocol included multiple acquisition trials administered over multiple days in an open maze apparatus, which allowed for the effective use of visual cues. These criteria were formulated to ensure both consistency and that the protocol assessed either working memory or working and reference memory together. In the present study, no restriction was placed on the number of maze arms of the apparatus or the number of baited arms. Second, only those studies using male and female cohorts in the same protocol were included. Third, only experiments using rats or mice were included. Fourth, in order to avoid experimental confounds and variability biases, only sex-effects obtained from unoperated rodents were included. Fifth, only those experiments, which used rodents without previous experience in learning or memory tasks, excluding standard pretraining trials, were incorporated into the analysis.

Initially 432 studies were identified using this procedure. Thirty-nine experiments from 24 studies were retained for the analysis. Experiments were excluded primarily because they used nonstandard protocols or failed to report sufficient data (e.g. N, scores or significance tests, etc.). When insufficient data was reported, at least three attempts were made to contact the authors in order to obtain supplemental information. If no response was received or if additional data could not be located, only then was the experiment excluded from the meta-analysis. However, if figures containing sufficient supplemental information were available from a published article, measurements were taken directly from the appropriate graph or chart and combined to calculate an effect size and
Tables 1–3 show the experiments retained in the analysis, subdivided by task and type of memory tested. The potential bias associated with including primarily published experiments versus unpublished experiments, termed the “file drawer problem” [45], was addressed in two ways. Foremost, great effort was made to obtain unpublished data by contacting individual laboratories. Second, ‘fail-safe’ calculations were made to assess robustness of significant pooled effects following the method of Rosenthal [46]. Briefly, the fail-safe number refers to the number of experiments with average effect size of zero required to offset the significance level to 0.05. This calculation provides a measure of the resistance of the meta-analytic findings to the file drawer problem; the larger the fail-safe number, the less plausible a hypothetical file drawer problem accounts for the significance of the results. Although no clear statistical threshold has been established for the fail-safe number, Rosenthal [46] recommends that a fail-safe number exceeding $5K + 10$ (where $K$ refers to the number of sampled experiments) provides a conservative
indication that the meta-analytic results are sufficiently resistant.

2.2. Analytic procedure

For the current analysis, the unit of analysis was the experiment and the effect of interest was the overall standardized difference in learning between males and females (the main effect). Although learning in standard radial maze and water maze protocols is measured over multiple trials and days thereby yielding both main sex effects and sex by trial interactions, only main effects were used in this analysis, since interactions are less reliably reported and less accurately interpreted [47]. Moreover, main effects offer a more conservative estimate of sex differences versus effects calculated from intermediate or terminal acquisition trials, or from probe trials. Thus, although the present analysis may underestimate the magnitude of true sex differences in spatial learning, it offers the most comprehensive and consistent assessment possible.

Cohen’s $d$ was used as the initial measure of effect size [47,48] and was calculated according to Cohen [48] when means and standard deviations were given or according to Wolf [49] when $t$, $F$ or $p$ statistics were given. Adjustments were then made to $d$ according to the method of Hedges and Olkin [50] to obtain an unbiased estimate of the effect size, henceforth referred to as $d^*$. Separately, the methodology developed by Hedges and Becker [51] was used to assess the homogeneity of effect sizes (sex differences) across studies. This statistical assessment of homogeneity allows for the inference of whether or not individual effect sizes or subsets of effect sizes originate from samples drawn from the same population. Thus, an inference of homogeneity allows for the pooling of effect sizes to obtain a meaningful summary effect size. When heterogeneity is inferred, it is unlikely that study samples were drawn from the same population and therefore individual studies should not be treated as replicates, e.g. there may exist important intermediate variables.

The present meta-analysis followed a hierarchical procedure similar to that of Voyer, Voyer and Bryden [2]. The magnitude of the aggregate pooled effect size and homogeneity was first calculated for the entire sample of studies. Next, studies were partitioned into two groups according to the type of memory, working versus reference. Homogeneity and pooled effect sizes were assessed for each subset. Additional partitions were made according to the type of task paradigm, radial maze versus water maze, and species. Finally, as heterogeneity was further encountered, studies were again partitioned into subsets based on species and then on procedural variables, such as age, apparatus, etc.

3. Results

3.1. All paradigms

Initial analysis of the 39 experiments revealed an aggregate average $d^*$ of 0.60 ($z=9.14$, $p<0.01$) demonstrating a significant male advantage across spatial learning paradigms. The fail-safe calculation, $\psi=57.059$, indicated the robustness of the pooled effect. However, as expected, the test of homogeneity revealed that the full set of experiments likely originated from disparate subpopulations, $X^2(42)=131.70$, $p<0.01$. Thus, partitioning of experiments into homogeneous subsamples was initiated.

Initial partitioning was done according to the type of memory tested, reference versus working memory, the task paradigm, water maze versus radial maze, and the species, rat versus mouse (see Table 4). Not surprising, these broad partitions did not eliminate probable heterogeneity. It should be noted that robust effects in favor of a male advantage continued to be encountered, except from the set of mouse experiments. For example, reference memory experiments yielded a significant male advantage, $d^*_{\text{avg}}=0.52$, $z=5.83$, $p<0.01$, but heterogeneity was evident, $X^2(22)=82.08$, $p<0.01$. For the set of experiments assessing working memory, a larger male advantage was observed, $d^*_{\text{avg}}=0.69$, $z=7.15$, $p<0.01$, but so too was heterogeneity, $X^2(19)=48.03$, $p<0.01$. Analysis of the results of water maze experiments revealed a significant male advantage, $d^*_{\text{avg}}=0.49$, $z=4.72$, $p<0.01$, also with heterogeneity, $X^2(18)=65.47$, $p<0.01$. Similarly, analysis of the results of radial maze experiments showed a significant male advantage, $d^*_{\text{avg}}=0.67$, $z=7.94$, $p<0.01$, with heterogeneity again detected, $X^2(23)=64.48$, $p<0.01$. Partitioning by species revealed a small nonsignificant male advantage for mouse experiments, $d^*_{\text{avg}}=0.18$, $z=1.42$, $p=0.15$, but heterogeneity was detected, $X^2(7)=38.99$, $p<0.01$. Although both samples appeared heterogeneous, it is worth noting that the male advantage observed in the subset of experiments using rats, $d^*_{\text{avg}}=0.76$, $z=9.84$,
Different strains were used in each of the mouse studies.

Table 4
Partitions: all experiments

<table>
<thead>
<tr>
<th>Experiments</th>
<th>$d^{\text{avg}}$</th>
<th>Z</th>
<th>Homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All experiments</td>
<td>0.60</td>
<td>9.14</td>
<td>$Q(42)=131.70$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Reference memory</td>
<td>0.52</td>
<td>5.83</td>
<td>$Q(22)=82.08$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.69</td>
<td>7.15</td>
<td>$Q(19)=48.03$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Water maze</td>
<td>0.49</td>
<td>4.72</td>
<td>$Q(18)=65.47$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Radial maze</td>
<td>0.67</td>
<td>7.94</td>
<td>$Q(23)=64.48$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Species:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse*</td>
<td>0.18</td>
<td>1.42</td>
<td>$Q(7)=38.99$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Rat</td>
<td>0.76</td>
<td>9.84</td>
<td>$Q(34)=77.36$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Fisher</td>
<td>0.90</td>
<td>5.44</td>
<td>$Q(5)=4.59$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Long Evans</td>
<td>0.88</td>
<td>8.07</td>
<td>$Q(16)=44.12$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Sprague–Dawley</td>
<td>1.22</td>
<td>3.00</td>
<td>$Q(1)=0.09$, $p&lt;0.01$</td>
</tr>
<tr>
<td>Wistar</td>
<td>0.28</td>
<td>1.75</td>
<td>$Q(8)=15.82$, $p&lt;0.01$</td>
</tr>
</tbody>
</table>

*Different strains were used in each of the mouse studies.

$p<0.01$, was much larger than that of the subset of experiments using mice, $t(8.02)=12.47$, $p<0.01$.

Within each species, sex differences by strain were also assessed. This analysis, however, was only possible for rats, since the plurality of mouse strains did not allow for meta-analytic pooling. In rats, each strain showed a significant pooled male advantage. For example, experiments using Fisher rats yielded a highly significant male advantage, $d^{\text{avg}}=0.90$, $z=5.44$, $p<0.01$, and, moreover this set of experiments satisfied the homogeneity test, $X^2(5)=4.59$, $p=0.47$. The fail-safe calculation, $\psi=387$, indicated that the estimated male advantage was highly robust. A similar pooled effect size was obtained for those experiments using Long Evans rats, $d^{\text{avg}}=0.88$, $z=8.07$, $p<0.01$, but heterogeneity was apparent in this subset, $X^2(16)=44.12$, $p<0.01$. The two experiments that used Sprague–Dawley rats yielded the largest male advantage of any strain, $d^{\text{avg}}=1.22$, $z=3.00$, $p<0.01$, and appeared to originate from a homogeneous population, $X^2(1)=0.09$, $p=0.77$. However, due to the small number of such experiments, the fail-safe number was only 11, below the recommended confidence threshold. Alternatively, experiments using Wistar rats showed the smallest significant male advantage, $d^{\text{avg}}=0.28$, $z=1.75$, $p=0.08$; with the heterogeneity measure just reaching significance, $X^2(1)=15.82$, $p=0.04$. The average male advantages obtained from the Fisher and Long Evans experiments were each significantly larger than the average male advantage calculated for the Wistar experiments ($t(10.4)=7.32$, $p<0.01$; $t(12.2)=10.26$, $p<0.01$). Although the two experiments using Sprague–Dawley rats yielded the largest pooled male advantage, this effect was not significantly different from those derived from the other strains (versus Fisher rats, $t(1.11)=1.06$, $p=0.48$; versus Long Evans rats, $t(1.02)=1.17$, $p=0.45$; versus Wistar rats, $t(1.07)=3.22$, $p=0.19$). It should be noted, however, that the lack of significance for these comparisons stemmed from both the small number of Sprague–Dawley experiments ($n=2$) and the conservative methodology used to estimate the degrees of freedom for said comparisons. It should also be noted that the Fisher and Sprague–Dawley experiments, which yielded the largest male advantages of any rat strains, were confounded with rearing condition since all of these experiments used group-rearing protocols. Though, the influence of group rearing appeared statistically less relevant since this broader subgroup was associated with smaller male advantages in both water maze and radial maze protocols (see below).

3.2. Water maze

Hierarchical partitioning of the experiments according paradigm, to protocol and to species revealed more appropriate subgroupings. Table 5 presents the results for water maze experiments partitioned by pretraining protocol, rearing environment and species. Considering only those experiments that used pretraining trials, the average sex difference was again significantly in favor of males, $d^{\text{avg}}=0.28$, $z=4.09$, $p<0.01$, but the subset appeared to be heterogeneous, $X^2(5)=55.22$, $p<0.01$. Experiments that did not use pretraining exhibited a larger mean male advantage, $d^{\text{avg}}=0.54$, $z=2.36$, $p=0.02$, though not significantly so, $t(2.2)=0.42$, $p=0.72$; this subset also appeared to be heterogeneous, $X^2(3)=10.20$, $p<0.02$.

Experiments using group reared animals exhibited a significant pooled male advantage, $d^{\text{avg}}=0.39$, $z=3.21$, $p<0.01$.
p < 0.01, but the subgroup appeared to be heterogeneous, \( X^2(13) = 60.82, p < 0.01 \). Animals reared in isolation exhibited a significant male advantage, \( d^*_{\text{avg}} = 0.77, z = 3.81, p < 0.01 \), which was significantly larger than that of group-reared rats, \( t(3.6) = 3.58, p < 0.04 \). These five experiments appeared to constitute a homogeneous sample, \( X^2(4) = 2.05, p = 0.73 \) and the significance of the metaanalytic result appeared to be robust, \( \psi = 129 \).

Partitioning studies according to species revealed significant differences in the magnitude of sex differences in the water maze between rats and mice (see Table 5). In aggregate, experiments using rats showed a significant male advantage, \( d^*_{\text{avg}} = 0.71, z = 5.90, p < 0.01 \). Moreover, this set of 14 experiments appeared to originate from a homogeneous population, \( X^2(13) = 20.44, p = 0.08 \). The fail-safe number for this effect was calculated to be 2,505, indicating substantial resistance to a hypothetical file drawer problem. In contrast, the five experiments that assessed mice showed a female advantage, \( d^*_{\text{avg}} = -0.14, z = -0.69, p = 0.49 \). This pooled effect, however, was not significant and appeared to originate from a heterogeneous sample, \( X^2(4) = 32.02, p < 0.01 \). Still, the difference in sex effects between mice and rats was substantial, \( t(5.0) = 8.84, p < 0.01 \).

Further partitioning of the rat experiments within each species revealed important distinctions. For the set of 11 experiments that used rats in a water maze protocol, which included pretraining trials, a significant average male advantage was observed, \( d^*_{\text{avg}} = 0.63, z = 4.76, p < 0.01 \). Although variable, this set of experiments satisfied the homogeneity test, \( X^2(10) = 17.24, p = 0.07 \). Additionally, the fail-safe number, \( \psi = 1,003 \), illustrated substantial resistance to a file drawer problem. For the set of experiments using rats in a water maze protocol, which did not include pretraining trials, the male advantage was larger, \( d^*_{\text{avg}} = 1.19, z = 3.86, p < 0.01 \), though not significantly so, \( t(2.2) = 3.08, p = 0.09 \). This set of experiments \( (n = 3) \) appeared to satisfy the homogeneity criterion, \( X^2(2) = 0.40, p = 0.82 \), and the observed male advantage again appeared to be resistant to the file drawer problem, \( \psi = 47 \).

Experiments using group-reared rats appeared to constitute a heterogeneous sample, \( X^2(8) = 18.27, p = 0.02 \), and yielded a significant pooled male advantage, \( d^*_{\text{avg}} = 0.68, z = 4.51, p < 0.01 \). The five experiments using rats reared in isolation satisfied the homogeneity criterion, \( X^2(4) = 2.05, p = 0.73 \), and also yielded a significant average male advantage, \( d^*_{\text{avg}} = 0.77, z = 3.81, p < 0.01 \). This finding was also resistant to the file drawer problem, \( (fs = 129) \).

Further subdivision of water maze experiments according to the intersection of the aforementioned procedural variables did not uncover any clear synergistic relationships. For example, analysis of the eight rat experiments that included both pretraining and group rearing protocols revealed a significant average pooled advantage, \( d^*_{\text{avg}} = 0.63, z = 4.10, p < 0.01 \), though the subset did not appear to be homogeneous, \( X^2(7) = 16.82, p = 0.02 \). The three experiments that included both pretraining and isolated rearing protocols yielded a similar significant average male advantage, \( d^*_{\text{avg}} = 0.62, z = 2.57, p = 0.01 \), which did however, satisfy the homogeneity criterion, \( X^2(2) = 0.42, p = 0.81 \). Due to the small number of studies in this partition, the fail-safe number \( (fs = 19) \) was not highly robust. There were not enough experiments \( (n = 1) \) that used group-reared rats in a protocol, which did not include pretraining trials, to estimate a pooled effect size. The two experiments, which used rats reared in isolation and that did not include a pretraining protocol, yielded a large, significant male advantage, \( d^*_{\text{avg}} = 1.13, z = 3.04, p < 0.01 \). These two experiments appeared to constitute a homogeneous sample, \( X^2(1) = 0.31, p = 0.58 \). However, due to the small number of experiments, the effect was not highly robust versus a possible file drawer problem \( (fs = 12) \).

Although there were few experiments evaluating mice in the water maze, an attempt was made to further partition this set. Only one water maze experiment that used mice did not employ pretraining trials. This experiment showed a female learning advantage, \( d^*_{\text{avg}} = -0.23 \), that did not reach significance, \( z = -0.70, p = 0.49 \). The set of four mouse experiments that did use pretraining trials also yielded a nonsignificant female advantage, \( d^*_{\text{avg}} = -0.08, z = -0.33, p = 0.74 \). This set appeared, however, to originate from a heterogeneous population, \( X^2(3) = 31.90, p < 0.01 \). Since all of the water maze studies that used mice also housed the mice in groups, it was not possible to differentiate sex differences in this species associated with deprived rearing environments. Further partitioning of mouse studies was not feasible due to the paucity of experiments.

In order to evaluate the relationship between sex effects and the continuous covariates, age and number of pretraining trials, ordinary least squares (OLS) regressions were performed. Because previous partitioning had already shown differences between species, regressions were carried out separately for rat and mouse experiments. For rat experiments, a model was estimated with \( d^* \) as the dependent variable and age (in weeks), age-squared, number of pretraining trials and the interaction between age and number of pretraining trials as the independent variables. Results from this analysis are displayed in Table 6. Although the overall regression did not reach significance, \( F(4,13) = 2.04, p = 0.17 \), the four independent variables did explain a fair amount of the variance of sex differences, \( R^2 = 0.48 \). Moreover, a small but highly significant coefficient was estimated for the interaction between age and number of pretraining trials, \( \beta = 0.002, t(9) = 2.70, p = 0.02 \). Thus, an increase in both the age of the rats and the number of pretraining trials was associated with a small but reliable increase in the magnitude of a male advantage in the water maze. All other independent variables were nonsignificant predictors. A second regression model was estimated (output not shown) that did not include the quadratic age.
Table 6
OLS Regression output: water maze experiments with rats

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>B</th>
<th>t(9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.195</td>
<td>2.400</td>
<td>0.040</td>
</tr>
<tr>
<td>Age</td>
<td>−0.025</td>
<td>−0.973</td>
<td>0.356</td>
</tr>
<tr>
<td>Age2</td>
<td>0.000</td>
<td>0.337</td>
<td>0.744</td>
</tr>
<tr>
<td>Pretraining trials</td>
<td>−0.025</td>
<td>−1.527</td>
<td>0.161</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.002</td>
<td>2.703</td>
<td>0.024</td>
</tr>
</tbody>
</table>

predictor. While this model produced a more significant model \( F(4,13) = 2.95, p = 0.08 \) and the coefficients for age reached significance along with the interaction, this model was deemed a poorer fit based on the analysis of residual plots.

There were an insufficient number of experiments assessing mice to estimate a similar model. However, examination of plots of sex effect by age (Fig. 1) and sex effect by number of pretraining trials (Fig. 2) provided some support for the conclusion that mouse studies showed a similar relationship to these variables, but with an overall female advantage (e.g. a negative average intercept). One outlier indicating a large male advantage \( d^* = 3.16 \) was also evident in the mouse studies. Although no reported unusual procedural variations appeared to be associated with this result, the effect was clearly inconsistent with the other findings from mouse studies.

3.3. Radial maze

Table 7 presents the results from the hierarchical partitioning of radial maze experiments. Initial partitioning was performed according to the type of memory tested, rearing environment and species. The subset of experiments that assessed working memory only \( (n=16) \) yielded a significant pooled male advantage, \( d^*_{\text{avg}} = 0.62, z = 5.53, p < 0.01 \), and satisfied the homogeneity criterion, \( X^2(15) = 19.35, p = 0.20 \). Furthermore, the fail-safe calculation, \( \psi = 2.882 \), indicated the pooled effect was robust. Experiments that assessed working memory in conjunction with reference memory (i.e. experiments that included unbaited arms), also showed a larger significant pooled male advantage in working memory, \( d^*_{\text{avg}} = 0.85, z = 4.65, p < 0.01 \), and a similar male advantage in reference memory, \( d^*_{\text{avg}} = 0.61, z = 3.48, p < 0.01 \). However, these three experiments did not appear to originate from a homogeneous population with respect to either working \( (X^2(3) = 27.61, p < 0.01) \) or reference memory measures \( (X^2(3) = 16.29, p < 0.01) \).

Partitioning the set of radial maze experiments according to rearing environment also resulted in consistent male advantages. Sex differences in experiments using animals reared in groups (including enriched environments) favored males, generally, \( d^*_{\text{avg}} = 0.53, z = 4.79, p < 0.01 \) and, not surprisingly, this subset of eight experiments did not satisfy the homogeneity criterion, \( X^2(10) = 22.26, p < 0.01 \). Analysis of working memory measures \( (n=7) \), from the subset of working memory only experiments revealed a similar male advantage, \( d^*_{\text{avg}} = 0.52, z = 3.29, p < 0.01 \), and the subgroup was homogeneous, \( X^2(6) = 5.42, p = 0.49 \). Moreover, the pooled effect appeared to be robust, \( \psi = 178 \). Sex effects from those experiments testing working and reference memory together \( (n=2) \) yielded a larger pooled male advantage for working memory, \( d^*_{\text{avg}} = 0.71, z = 3.08, p < 0.01 \), but due to the small number of such experiments homogeneity was not satisfied, \( X^2(1) = 12.31, p < 0.01 \). Analysis of reference memory measures from this set of experiments showed a smaller male advantage that approached significance, \( d^*_{\text{avg}} = 0.41, z = 1.88, p = 0.06 \), and the subset appeared to originate from a homogeneous population, \( X^2(1) = 3.63, p = 0.06 \). The fail-safe calculation, \( \psi = 3 \), however indicated that the effect was not robust versus a hypothetical file drawer problem. Three studies in the dataset used enriched group rearing environments. Analysis of these experiments revealed a large significant male advantage, \( d^*_{\text{avg}} = 0.74, z = 2.62, p < 0.01 \), but the sample did not appear to be homogeneous, \( X^2(2) = 14.26, p < 0.01 \).

Fig. 1. Plot of sex effects in the water maze versus the average age of animal cohorts tested for each experiment.

Fig. 2. Plot of sex effects in the water maze versus the number of pretraining trials administered for each experiment.
but was not statistically larger than the effect observed in the smaller set of experiments that used enriched rearing environments ($t(2.3) = 1.47, p=0.28$). When the analysis was restricted to the subset of working memory only experiments, a similar, significant male advantage was evident, $d^*_{avg} = 0.74, z = 4.56, p < 0.01$. Moreover, this subset of experiments appeared to be homogeneous, $X^2(8) = 12.95, p < 0.11$. Analysis of the experiments testing working and reference memory together ($n=2$) yielded a larger significant pooled male advantage for working memory, $d^*_{avg} = 1.09, z = 3.62, p < 0.01$, but this set of experiments did not appear to be homogeneous, $X^2(1) = 17.67, p < 0.01$. Analysis of the reference memory measures from these experiments also yielded a significant male advantage, $d^*_{avg} = 0.95, z = 3.29, p < 0.01$, but the sample also appeared to be heterogeneous, $X^2(1) = 10.42, p < 0.01$.

Partitioning radial maze experiments by species revealed a less dramatic difference in sex effects than was observed in water maze experiments. For the set of 18 experiments that assessed rats, the pooled main effect significantly favored males, $d^*_{avg} = 0.78, z = 7.89, p < 0.01$, however, the sample did not satisfy the homogeneity criterion, $X^2(20) = 73.71, p < 0.01$. Considering only working memory measures from the set of experiments that did not include unbaited arms ($n=15$) yielded a similar significant pooled male advantage, $d^*_{avg} = 0.59, z = 4.94, p < 0.01$, and the sample appeared homogeneous, $X^2(14) = 18.76, p < 0.17$. For the set of rat experiments that included unbaited arms ($n=3$), analysis of working memory measures yielded a significant male advantage that was more than twice as large as that observed on working memory experiments, $d^*_{avg} = 1.40, z = 5.43, p < 0.01$, but this set did not appear to be homogeneous, $X^2(2) = 18.42, p < 0.01$. Similarly, analysis of the reference memory measures from this subset of experiments yielded a significant male advantage, $d^*_{avg} = 1.00, z = 4.18, p < 0.01$, but homogeneity was lacking, $X^2(2) = 11.71, p < 0.01$.

Next, the set of rat experiments was further partitioned according to procedural variables. For radial maze experiments that used group reared rats in a working memory only paradigm, a small male advantage was found, $d^*_{avg} = 0.42, z = 2.33, p = 0.02$, and the set of experiments was heterogeneous, $X^2(5) = 3.99, p = 0.55$. This result also appeared to be robust versus a hypothetical file drawer problem, $\psi = 66$. Experiments that assessed working and reference memory together ($n=2$), yielded a large significant pooled male advantage in working memory, $d^*_{avg} = 2.54, z = 6.80, p < 0.01$, and satisfied the homogeneity criterion, $X^2(1) = 6.60, p = 0.04$. This male advantage was robust, $\psi = 66$, and was considerably larger than that obtained from the set of working memory only experiments, $t(1.16) = 7.76, p = 0.08$. Analysis of sex effects in reference memory for this same subset of experiments also yielded a large significant pooled male advantage, $d^*_{avg} = 1.58,$

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Partitions: radial maze experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial maze experiments</td>
<td>$d^*_{avg}$</td>
</tr>
<tr>
<td>All experiments</td>
<td>0.67</td>
</tr>
<tr>
<td>Working memory only</td>
<td>0.62</td>
</tr>
<tr>
<td>Working memory (and RM)</td>
<td>0.85</td>
</tr>
<tr>
<td>Reference memory</td>
<td>0.81</td>
</tr>
<tr>
<td>Group rearing</td>
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</tr>
<tr>
<td>Working memory only</td>
<td>0.52</td>
</tr>
<tr>
<td>Working memory (and RM)</td>
<td>0.71</td>
</tr>
<tr>
<td>Reference memory</td>
<td>0.41</td>
</tr>
<tr>
<td>Enriched rearing (WM)</td>
<td>0.74</td>
</tr>
<tr>
<td>Isolated rearing</td>
<td>0.85</td>
</tr>
<tr>
<td>Working memory only</td>
<td>0.74</td>
</tr>
<tr>
<td>Working memory (and RM)</td>
<td>1.09</td>
</tr>
<tr>
<td>Reference memory</td>
<td>0.95</td>
</tr>
<tr>
<td>Rat</td>
<td>0.78</td>
</tr>
<tr>
<td>Working memory only</td>
<td>0.59</td>
</tr>
<tr>
<td>Working memory (and RM)</td>
<td>1.40</td>
</tr>
<tr>
<td>Reference memory</td>
<td>1.00</td>
</tr>
<tr>
<td>Group rearing × WM only</td>
<td>0.42</td>
</tr>
<tr>
<td>Group rearing × WM (and RM)</td>
<td>2.54</td>
</tr>
<tr>
<td>Group rearing × RM</td>
<td>1.58</td>
</tr>
<tr>
<td>Isolated Rearing × WM Only</td>
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</tr>
<tr>
<td>WM Only</td>
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<tr>
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</tr>
<tr>
<td>Mouse</td>
<td>0.51</td>
</tr>
<tr>
<td>Working memory only</td>
<td>NA</td>
</tr>
<tr>
<td>Reference memory</td>
<td>NA</td>
</tr>
</tbody>
</table>

For the set of 13 experiments, which used animals reared in isolation, sex differences also favored males, $d^*_{avg} = 0.85, z = 6.60, p < 0.01$, but this set did not satisfy the homogeneity criterion, $X^2(12) = 38.85, p < 0.01$. This effect was significantly larger than that observed from experiments using group reared animals ($t(15.6) = 6.28, p < 0.01$).
z = 4.90, p < 0.01, that was robust, ψ = 34. Again, the sample satisfied the homogeneity test, $X^2(1) = 3.28, p = 0.06$.

The subset of working memory only experiments that used rats reared in isolation yielded a larger significant male advantage than the subset that used group reared rats ($d^{*}_{\text{avg}} = 0.74, z = 4.56, p < 0.01; t(10.1) = 3.59, p < 0.01$). This set of experiments also appeared to originate from homogeneous population, $X^2(8) = 12.95, p < 0.16$, and the effect was highly robust, $\psi = 624$. Considering the subset of rat experiments, which used both an isolated rearing and a combination working-reference memory protocol ($n = 2$), yielded a significant pooled male advantage, $d^{*}_{\text{avg}} = 1.09, z = 3.62, p < 0.01$. This subset of experiments, however, appeared to be heterogeneous, $X^2(2) = 10.42, p < 0.01$.

Analysis of sex differences in reference memory for this subset experiments also produced a significant pooled male advantage, $d^{*}_{\text{avg}} = 0.95, z = 3.29, p < 0.01$, but heterogeneity was again encountered, $X^2(2) = 14.28, p < 0.01$.

There were very few ($n = 3$) experiments assessing mice in the radial maze. Aggregate analysis of these experiments also revealed a significant male advantage, $d^{*}_{\text{avg}} = 0.37, z = 2.35, p = 0.02$, that, however, was not entirely robust to a hypothetical file drawer problem ($fs = 15$). Nonetheless, this set of experiments constituted a homogeneous sample ($X^2(2) = 3.01, p = 0.22$). Also of note, the observed male advantage was significantly less than the male advantage observed in rats ($t(2.23) = -4.32, p < 0.05$). Considering only the working memory measures ($n = 2$) from the mouse experiments revealed a significant, yet smaller, male advantage, $d^{*}_{\text{avg}} = 0.51, z = 2.51, p = 0.01$. Again, the sample was homogeneous, $X^2(1) = 1.84, p = 0.17$, but the effect was not very robust, $\psi = 7$. Only one radial maze experiment assessed reference memory in mice. This study found a large and significant effect favoring males, $d^{*}_{\text{avg}} = 0.99, z = 2.24, p = 0.03$, however, because only on such experiment existed, an assessment of confidence was precluded.

To evaluate the relationship between sex effects and the age, an OLS regression was estimated for the set of experiments using rats (again too few mouse experiments existed to estimate a meaningful model). For the rat experiments, the model predicted the magnitude of sex difference, $d^*$, using the dependent variables age (in weeks) and age-squared. However, because there were very few experiments assessing memory in older rats of both sex, the model did not even approach significance, $F(2,15) = 0.16$, $p = 0.85$ and $R^2 = 0.02$, and neither predictor reached significance (for age, $t(15) = -3.10, p = 0.076$; for age-squared, $t(15) = 0.24, p = 0.81$). Fig. 3 plots the relationship between the magnitude of sex effect and the age of the animal cohort for each radial maze experiment. Consistent with the findings from the regression, no discernable pattern is evident for rat experiments. Although a negative correlation is suggested for mouse experiments, there are too few experiments for such a conclusion.

4. Discussion

4.1. All paradigms

The present analysis demonstrates the existence of reliable sex differences in standard water maze and radial maze protocols, respectively. Of primary interest, sizeable species and strain differences were evident, implying a need for closer attention to these variables when selecting appropriate animal models for in vivo biological experimentation. The analysis also finds support for the influence of a variety of protocol variations, which have heretofore contributed to the confusion over sex effects in the literature. Specifically, the pretraining regimen (for water maze experiments) and rearing environment were associated with differential sex effects.

The most striking findings from the present analysis were the differences in sex effects for individual rat strains, differences that were evident across paradigms. Sprague–Dawley rats, for example, showed substantially larger male advantages than any other strain. Fisher and Long Evans strains showed similar, large, robust male advantages, but Wistar rats exhibited significantly smaller male advantages. Although strain differences in mice tend to be more pronounced across several paradigms [25], meta-analytic assessment of studies using different mouse strains was infeasible since each mouse experiment utilized a variant strain. However, given previous evidence of strain differences in male mice [52–54], it is plausible that strain differences in sex effects are also prominent in the radial and water maze. Moreover, the present difficulty in obtaining homogeneous partitioning of mouse studies may be in part due to a significant degree of mouse strain differentiation. Further research will be necessary to delineate such differences.

4.2. Water maze

Analysis of reference memory measure from water maze experiments revealed significant species and procedural
influences. Most prominent, the set of experiments using rats (all classifications) showed large significant male advantages versus the heterogeneous set of experiments using mice (all classifications), which exhibited small female advantages. These species differences have likely contributed to the confusion over sex differences in the literature as studies routinely and selectively site experimentation across species when considering sex effects. Together these results point to the need for greater care in selection of species when constructing appropriate animal models, particularly as laboratories contemplate transitioning from rat to mouse models.

The present analysis also identified several procedural variations that were associated with accentuated or dampened sex effects in the water maze. Foremost, rat experiments with pretraining protocols tended to exhibit smaller male advantages than experiments without pretraining protocols—a comparison that nearly reached significance. This finding agrees with Perrot-Sinal et al.’s [43] direct comparison, which showed that a 12-trial pretraining protocol significantly reduced male advantages in the water maze. The biological support for pretraining influences centers on observed male–female differences in swim stress induced analgesia [55–57]. Although pretraining may be effective in reducing stress-related confounds, given the present results it does not appear to completely account for sex effects in the water maze. Importantly, rat experiments that used pretraining trials still show a significant, reliable pooled male advantage. Furthermore, the number of pretraining trials administered was not a reliable predictor of the magnitude of sex effects. The lack of strong correlation here was likely due to threshold effects and possibly to interactions with other variables, specifically interactions with age, as was demonstrated in the regression analysis.

Although contextual fear conditioning may depend on somewhat differentiable neural substrates, it is noteworthy that two studies examining sex effects in this model have reported the alleviation of male performance advantages for rats and mice, respectively, following preexposure trials [58,59]. Closer examination of these studies reveals that sizeable, although nonsignificant, male advantages persisted even with pretraining. Hence, these results may not be inconsistent with the present meta-analytic results for water maze experimentation. As more cross-sex contextual fear conditioning experiments are conducted it will be useful to more fully address the effects of pretraining in this model using meta-analytic techniques.

In the present analysis, rearing environment also appeared to influence sex differences, but to a lesser extent than pretraining regimen. For rats, isolated-rearing protocols were associated with slightly larger male advantages in the water maze than were group-rearing protocols, though this difference could not be reliably assessed due to heterogeneity in the later set of experiments. Together, these results indicate that a social rearing environment may be a less important protocol variant. Although enriched rearing may have greater influences, this hypothesis could not be addressed in the present study due to the paucity of water maze experiments using enriched rearing environments. Similarly, the interaction between rearing environment and pretraining appeared to have little influence on observed male advantages in the water maze, though, as expected, the few studies testing rats reared in isolation without pretraining reported the largest such male advantages.

The age of animals did not appear to be an important consideration with respect to sex effects. Similar male advantages were found for experiments using rats of a variety of ages. Consistent male advantages, specifically male advantages in rats exceeding 17 weeks of age, argue against the inference that sex effects in spatial learning stem from sex differences in the rate of hippocampal development [41]. The present findings also contrast two reports from experiments that found age by sex interactions. Markowska found a larger male advantage in middle-aged Fisher rats as compared to young and aged Fishers [8]. Similarly, in C57BL/6NIA mice, Frick, et al. reported a large female advantage in middle-aged cohorts only [6]. Although, such a quadratic trend was not evident in the present meta-analysis, interactions between sex and age should not be discounted. Possible confounds with strain, pretraining regimen and rearing environment may have obscured the detection of age influences. Further direct experimentation with individual strains and protocols will be necessary to confirm or disconfirm the generalizability of age-mediated influences.

Finally, because there were not enough mouse experiments to individuate pooled sex effects according to these subject and protocol variants, further research will be required to determine whether they affect mice similarly to rats.

4.3. Radial maze

For radial maze experiments, similar species and procedural influences were inferred. Most notably, experiments that assessed rats tended to yield larger male advantages in working memory than experiments using mice, though this difference was smaller and less reliable than the species difference observed in water maze experiments.

For experiments using rats, striking differences were confirmed between protocols that assessed working memory only and protocols that assessed working and reference memory together. Broadly, male advantages in combined protocols were more than twice as large as those observed in working memory only protocols. Importantly this effect did not appear to be driven by a more general enhancement of difficulty associated with combined paradigms; male advantages were slightly smaller in working memory only protocols that used 17-arms versus those that used 8-arms.
Instead, the striking difference between combined and singular paradigms implies that working memory across the two paradigms is not a unitary construct. The added reference memory demands in combined protocols may disrupt working memory process or interfere with them to a greater extent in female rats. At issue is the psychological characterization of what is meant by working memory errors in combined protocols. It appears that understanding of the interaction between working and reference memory will need to be revised and may require exacting parametric tests, which vary the number of baited versus unbaited arms. In the very least, the present finding points to the need for more careful consideration when selecting radial maze protocols and making comparisons across paradigms.

This relationship between sex effect and paradigm also appeared to interact with rearing environment. Experiments using group reared rats in combined working and reference memory protocols elicited male working memory advantages that were more than six times as large as those obtained from working memory only protocols. In contrast, isolated rearing environments were associated with smaller and less reliable differences in sex effects between combined and working memory only protocols. The fact that group rearing was associated with larger such differences bears further experimentation, but also points to an important procedural dimension that should be addressed in future research. Enriched rearing could not be addressed independently, but it should be noted that the two studies which tested the effects of enriched rearing on radial maze performance in male and female rats yielded mixed results [9,11].

There were insufficient radial maze experiments using old and middle-aged rats to adequately address the correlation between age and sex effect. Over the limited range of experiments, however, age did not appear to be associated with a reliable difference in sex effects. Further testing of aged cohorts will be required to address this issue. Finally, although sex differences in reference memory were of similar magnitude in radial maze (combined protocols) and water maze experiments using rats, further testing will be required to determine whether strain and rearing influences in the radial maze are similar to those in the water maze (see Section 4).

5. Causes of sex differences

Several theories have been advanced to explain reported male and female advantages in spatial learning, respectively, e.g. natural selection for male advantages [60]; natural selection for female advantages [61,62]; sexual selection for male advantages [63,64]. Differences in hippocampal size and physiology are typically sited as biological support of evolutionary explanations [4,3,65], though the characterization of more exact mechanistic causes is not yet available. Given the present results, evolutionary theories supporting female advantages appear implausible, particularly when considering rats. More generally, the strain and species diversity uncovered in this analysis is difficult to reconcile with any of these broad interpretations.

More recently, several laboratories have postulated that hormone fluctuations across the estrus cycle may account for apparent inconsistent male advantages [66–68]. Support for this explanation comes primarily from indirect evidence of the effects of hormone treatments in gonadectomized and developing animals [3,69,70]. This explanation has been further strengthened by several recent biological studies demonstrating that endogenous ovarian steroids modulate hippocampal dendritic spine density, synapse density and long-term potentiation across the estrus cycle, with the highest levels of each occurring during proestrus [4,71–75]. However, the functional-behavioral consequences of these cyclic morphological changes has not been forthcoming. For example, Warren and Juraska showed superior performance of female rats during the estrus rather than proestrus phase [68] and Daniel, Roberts and Dohanich showed a tendency for female ovariectomized rats to outperform intact females [76]. Moreover, recent evidence indicates that only large-scale, nonphysiological, manipulation of hormone levels is capable of eliciting reliable behavioral effects on spatial learning tasks [77,78]. Most disparaging to estrus cycle (endogenous hormone fluctuations) explanations are the results from studies explicitly measuring spatial learning across the estrus cycle. Warren and Juraska found superior performance during the estrus phase [69], but at least three other laboratories have failed to find performance differences across the estrus cycle [41,79,80]. Thus, although ovarian steroids exert measurable neurophysiological effects, their cognitive influence on spatial learning in physiologically relevant models has yet to be confirmed. The present results, in as much as they establish reliable male advantages in young and old rats, further challenge this explanation given its implication of differential performance between cycling and aged estrous females.

A final explanation contends that male spatial learning advantages observed in the radial and water maze are caused by male-female differences in strategy selection rather than spatial learning capacity per se [81]. A growing body of evidence suggests that females (rats and humans) navigate preferentially using landmarks versus males, which rely on a broader set of spatial representations [82–85]. Consistent with this view, in an early experiment Root and Stein [20] showed that female rats’ spatial learning was similar to that of male rats in a cued version of the water maze but was inferior to that of males in a standard non cued version of the water maze. The present meta-analytic findings, while not directly supportive, are consistent with such an interpretation. Further research will be required to characterize the biological mechanisms, which support such inherent differences.
6. Conclusion

Although reports in the literature initially appear to be inconsistent, with a majority of studies reporting null sex effects, the present meta-analysis clearly shows the existence of robust male advantages in working and reference memory for rats. In contrast, for mice, less reliable female advantages were found in reference memory (water maze only) and smaller reliable male advantages were observed in working memory. From the present analysis, it appears that many of the studies in the literature were underpowered and that the characterization of sex differences as inconsistent will need to be revised, particularly when considering rat models. Further experimentation in mice with particular attention to individual strains will be required to determine the reliability of sex effects and protocol variations in this species.

Finally, the present results for rats agree with recent findings in humans showing male advantages in spatial cognition [2,12] and spatial learning [82,86,87]. Thus, in this context, the rat model may be a behaviorally more appropriate model of human spatial learning. The present analysis also verifies the limited importance of rearing environment, pretraining (water maze) and combination protocols (radial maze), all of which should be considered when constructing and comparing the results of rodent models.

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