



## Sex effects on spatial learning but not on spatial memory retrieval in healthy young adults



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### ABSTRACT

**Objectives:** Sex differences have been found in spatial learning and spatial memory, with several studies indicating that males outperform females. We tested in the virtual Morris Water Maze (vMWM) task, whether sex differences in spatial cognitive processes are attributable to differences in spatial learning or spatial memory retrieval in a large student sample.

**Methods:** We tested 90 healthy students (45 women and 45 men) with a mean age of 23.5 years ( $SD = 3.5$ ). Spatial learning and spatial memory retrieval were measured by using the vMWM task, during which participants had to search a virtual pool for a hidden platform, facilitated by visual cues surrounding the pool. Several learning trials assessed spatial learning, while a separate probe trial assessed spatial memory retrieval.

**Results:** We found a significant sex effect during spatial learning, with males showing shorter latency and shorter path length, as compared to females (all  $p < 0.001$ ). Yet, there was no significant sex effect in spatial memory retrieval ( $p = 0.615$ ). Furthermore, *post-hoc* analyses revealed significant sex differences in spatial search strategies ( $p < 0.05$ ), but no difference in the number of platform crossings ( $p = 0.375$ ).

**Conclusion:** Our results indicate that in healthy young adults, males show faster spatial learning in a virtual environment, as compared to females. Interestingly, we found no significant sex differences during spatial memory retrieval. Our study raises the question, whether men and women use different learning strategies, which nevertheless result in equal performances of spatial memory retrieval.

### 1. Introduction

Spatial learning and spatial memory are ethologically relevant behavioral components that have evolved in almost all species to ensure survival. The hippocampus represents a key brain structure for spatial learning and spatial memory [1–3], which has been underlined by numerous studies, linking impaired spatial learning and spatial memory to hippocampal damage [4–7]. Moreover, a functional network of different brain regions, including the caudate nucleus, as well as inferior and medial parietal brain regions [8], support the hippocampus, depending on the specific task demands being involved.

To assess the behavioral components underlying this hippocampal-based network, Richard G. Morris developed a rodent paradigm in the early 1980ies – the Morris Water Maze (MWM) task [9]. It represents one of the most commonly used research tools in behavioral neuroscience to investigate spatial learning and spatial memory in rodents. In the MWM task, rodents have to search a round pool filled with opaque water for a hidden platform, facilitated by visual cues surrounding the pool. After a series of learning trials, the rodents undergo

a probe trial, which measures spatial memory retrieval. Throughout the last decades, the MWM task has progressed to a virtual research tool, applicable to the human model – the virtual Morris Water Maze (vMWM) task [10,11].

Examples from rodent studies have consistently shown that male rats perform better during *both phases* of the MWM task, the learning trials *and* the probe trial, as compared to females [12–14]. A recently published meta-analysis partially underlines these findings, showing a robust male advantage in rats, while reporting of mixed findings in mice. Specifically, the rat model, relative to the mouse model, has been suggested to be a behaviorally more appropriate model of human spatial learning [15]. The sex differences in the MWM task led to human studies that used the vMWM task to investigate spatial learning and spatial memory performance in healthy adults [10,16–20] and found comparable results, with males outperforming females. This sex effect has subsequently been underlined by a recently published meta-analysis, addressing sex differences in visual-spatial working memory [21].

Nevertheless, the published literature on sex differences in spatial learning and spatial memory has been partially equivocal. Studies that

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specifically used the vMWM task (and related paradigms) have repeatedly shown a male advantage during spatial memory retrieval [10,16,17,19,22,23], while the opposite effect has been shown in studies using radial mazes, with females outperforming males [24]. A few studies even report that there are no sex differences in spatial memory performance at all [25,26].

In healthy adults, sex differences in spatial learning and spatial memory processes have been linked to the interplay of neurobiological, behavioral and environmental factors. Data from fMRI studies suggest a link to sex differences in recruitment of specific brain regions, such as differences in hemispherical lateralization [27–29], functional connectivity in the mesocorticolimbic system [30], and brain volume [20]. Furthermore, the intake of oral contraceptives [31,32], as well as measured levels of sex hormones have shown to play a role in spatial memory performance [16,19,33–35]. Referring to this, a previous study of our research group has shown an association of hair testosterone with visuospatial memory in males [36]. In addition, sex differences in spatial learning and spatial memory have been linked to age [3,37–39], and differences in specific spatial search strategies [16,22,40].

The way humans (and also rodents) navigate, can generally be distinguished in a dichotomous manner, namely in an *allocentric* and an *egocentric* navigation type. The allocentric navigation type is characterized as a world-centered strategy using distal cues, such as landmarks outside and distant from the body, and has been described as hippocampus dependent [28,38]. The egocentric navigation type has been described as parietal lobe dependent [8] and is characterized as a body-centered strategy using internal cues, such as distances and directions to or from individual landmarks, as well as the perception of the own body movements. Nevertheless, it is important to note, that there is no absolute or exact way to dichotomize between these two navigational strategy types. Recently published data suggests that certain environmental factors can even induce a switch from one navigation strategy to another in order to solve a vMWM task [41]. On a behavioral level, specific navigation types manifest as specific spatial search patterns, such as direct, landmark-oriented, circle, or zigzag search patterns while performing in a vMWM task [42]. Previous research suggested that sex hormones play a crucial role in the use of a specific navigational strategy [19,33,43,44], and that males prefer allocentric strategies, while females favor egocentric strategies as a cognitive map [40,45–48]. However, these sex differences in spatial navigation have also been questioned by researchers based on their findings in animal studies. For instance, Blokland et al. found no sex differences in allocentric and egocentric search strategies [14], and Devan et al. made no definitive conclusions about sex differences in cognitive-spatial performance or memory consolidation [49]. Furthermore, there is also evidence that even if sex effects occur in spatial learning and memory performance, they might not be linked to sex differences in allocentric and egocentric search strategies [14]. There is also some evidence, that the preference of navigational search strategy is not influenced by the subject's sex [50–52], and even if sex differences occurs in the learning and memory outcome, females use allocentric strategies at least as often as males do [18].

Moreover, a few points have to be taken into account when reviewing the literature on sex effects in spatial learning and memory. On the one hand, there might be a publication bias with negative studies being under-represented in the literature. On the other hand, there is also a considerable number of studies showing the opposite of what has been generally discussed as the general male advantage in spatial learning and memory, specifically in mice [15]. Since the literature on spatial learning and spatial memory is somewhat ambiguous and previous studies [10,16,17,19,22,37,48] have mainly used smaller sample sizes, we aimed to investigate the described sex effects in a larger student sample using a dichotomized design, with separate foci on *spatial learning* and *spatial memory retrieval* performance. In addition, we aimed to address sex effects regarding the specific spatial search strategy. In line with the literature, we hypothesized that male participants show

better spatial learning performance and better spatial memory retrieval, as compared to female participants. Furthermore, we examined possible sex differences in spatial search strategies.

## 2. Experimental procedures

### 2.1. Participants

Ninety healthy university students (45 women, 45 men, age range 18–33 years, mean age  $23.5 \pm SD = 3.5$ ) participated in our study. All participants received a monetary compensation of €40. None of the participants reported physical diseases or psychiatric disorders. Further exclusion criteria were neurodegenerative or other CNS diseases, endocrine diseases, pregnancy and current breast-feeding in female participants. All participants had German as their first language or were fluent German speakers. No participant took any medication, except from oral contraceptives in some female participants. All participants underwent a screening for previous or current psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). All participants showed normal weight. Our study was approved by the Ethics Committee of Charité – Universitätsmedizin Berlin and was in line with the World Medical Association Declaration of Helsinki. Participants signed a written informed consent before participation.

### 2.2. Procedure

The experimental testing phase started at 3 p.m. in a quiet laboratory surrounding. Prior to the experiment phase, participants were screened for inclusion and exclusion criteria during a telephone interview and received an introduction of the study procedure. The vMWM task was part of a larger paradigm battery.

### 2.3. Assessment of spatial learning and spatial memory retrieval performance

To test for spatial learning and spatial memory retrieval performance, we used the vMWM task. This computerized paradigm is a validated analogue of the original animal research tool [10,11] and has been used in numerous human studies in various research domains. For our experiment, we used the vMWM task software version 1.2 of Derek Hamilton's lab [11], in an analogous manner to the previous work of our research group [53]. We used a 24-inch PC monitor, on which the virtual environment was presented from a first-person perspective. Following the methods of previous studies [4], the virtual environment of the vMWM task contained a square room with a round pool in its midst. Each wall of the square room showed a visual cue in the shape of an abstract painting to facilitate spatial learning and memory processes. These external cues resembled each other to a high extent with the intention of being hard to discriminate.

The behavioral experiment consisted of a total number of 22 trials. In detail, 1 exploration trial, 4 visible platform trials, 16 hidden platform trials, and 1 probe trial. During the exploration trial, participants were familiarized with the virtual environment and the handling of the joystick. During the 4 visible platform trials, the platform was introduced and participants had to swim towards the visible platform as fast as possible. The performance of the 4 visible platform trials represented a measure of motor control condition. Subsequently, participants underwent 16 hidden platform trials, during which the platform was being transferred to a new location, lowered underneath the pool's surface, and therefore invisible to the participants. The performance during the hidden platform trials represented a measure for spatial learning performance. Lastly, the platform was removed from the pool unbeknownst to the participants and a probe trial was performed for a total time of 60 s. During this probe trial the relative amount of search time spent in the correct quadrant of the pool was calculated, which

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