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Virtual navigation in humans: the impact of age, sex, and hormones on place learning

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Abstract

Certain cognitive processes, including spatial ability, decline with normal aging. Spatial ability is also a cognitive domain with robust sex differences typically favoring males. However, tests of spatial ability do not seem to measure a homogeneous class of processes. For many, mentally matching rotated three-dimensional images is the gold standard for measuring spatial cognition in humans, while the Morris water task (MWT) is a preferred method in the domain of nonhuman animal research. The MWT is sensitive to hippocampal damage, a structure critical for normal learning and memory and often implicated in age-related cognitive decline. A computerized (virtual) version of the MWT (VMWT) appears to require and engage human hippocampal circuitry, and has proven useful in studying sex differences and testing spatial learning theories. In Experiment 1, we tested participants (20–90 years of age) in the VMWT and compared their performance to that on the Vandenberg Mental Rotation Test. We report an age-related deficit in performance on both tasks. In Experiment 2, we tested young (age 20–39) and elderly (age >60) participants in the VMWT and correlated their performance to the circulating levels of testosterone and cortisol. Our findings indicate that the persistence of male spatial advantage may be related to circulating testosterone, but not cortisol levels, and independent of generalized age-related cognitive decline.

Keywords: Aging; Hippocampus; Testosterone; Cortisol; Virtual Morris water task

Introduction

Contemporary studies of cognitive aging attempt to understand the changing cognitive abilities as a normal developmental progression. Processes involving verbal skills, priming, implicit learning, and semantic memory seem to be largely spared. However, normal aging is associated with declines in numerous cognitive processes including episodic memory, attention, working memory, and spatial learning (Kausler, 1994). It is often assumed that the neural circuitry underlying different cognitive processes varies in terms of susceptibility to age-related degeneration. The hippocampal formation is often implicated in age-related cognitive decline and is critical for certain forms of learning and memory (O'Keefe and Nadel, 1978; Sutherland et al., 1982). Many cognitive deficits exhibited during normal aging are said to resemble impairments following bilateral damage to the hippocampus (Geinisman et al., 1995; Press et al., 1989; Zola-Morgan et al., 1986).

Nonhuman animal research provides a wealth of knowledge regarding tasks that are sensitive to hippocampal damage. The Morris water task (MWT; Morris, 1981; 1984) is dependent upon hippocampal integrity (Morris et al., 1982; Sutherland et al., 1982) and has been extensively employed in studying the relationship between hippocampal function, aging, and spatial learning and memory in rodents (for reviews, see Gallagher and Rapp, 1997; Geinisman et al., 1995; Rosenzweig and Barnes, 2003). In the MWT, animals are trained to locate an escape platform hidden in a featureless

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pool of opaque water based upon its fixed spatial relationship to a configuration of visual cues in the distal environment. Deficits similar to those seen in hippocampectomized animals have been previously reported in studies of aged animals (Geinisman et al., 1995; Pelleymounter et al., 1987; Rapp et al., 1987). Deficits in tasks requiring spatial information processing have also been reported in aged humans (Golomb et al., 1993; Kirasic and Allen, 1985; Perlmutter et al., 1981). It is not clear however whether spatial cognition documented in humans is homologous to that studied in nonhuman animals because the tasks used to assess spatial ability in respective species, while spatial in nature, are not analogous.

Recently, a computerized (virtual) version of the Morris water task (VMWT) has been developed for laboratory testing of human spatial ability (Astur et al., 1998; Hamilton and Sutherland, 1999; Hamilton et al., 2002). The research design was carried over from nonhuman work into a virtual domain, showing that many psychological functions engaged by the task in rats are similarly engaged in humans (Hamilton and Sutherland, 1999; Hamilton et al., 2002). In addition, the VMWT has proven useful in studying spatial learning theories (Hamilton and Sutherland, 1999; Hamilton et al., 2002), Fetal Alcohol Syndrome (Hamilton et al., 2003), aging (Driscoll et al., 2003), and sex differences in human spatial ability (Astur et al., 1998; Driscoll et al., 2003). The robust sex difference in spatial navigation reported in studies conducted in the virtual domain, where men are more successful than women (Astur et al., 1998; Driscoll et al., 2003; Hamilton and Sutherland, 1999; Moffat and Resnick, 2002; Moffat et al., 1998; Shore et al., 2001; Sandstrom et al., 1998), is of particular interest. Recently, we reported that sex differences persisted in a sample of healthy elderly compared to college-aged participants, such that males performed better than females despite deficits in the VMWT learning and memory, and despite age-related structural and biochemical changes in the hippocampus that may underlie observed cognitive deficits in performance (Driscoll et al., 2003). The male advantage in spatial ability has been reported in other mammalian species as well (Dawson, 1972; Williams and Meck, 1991; Williams et al., 1990). Despite numerous reports of male advantage in spatial performance of both rats and humans, the cause of sex differences in certain cognitive domains remains a matter of debate.

The inquiry into sex differences in spatial cognition has prompted questions regarding the biological bases of sexually dimorphic spatial behavior. Difference in the levels of circulating hormones represents one obvious possibility. Sex-specific patterns of relationships between circulating testosterone and spatial performance have been previously reported in both rodents (Gordon and Lee, 1986; Neave et al., 1999) and humans (Choi and Silverman, 2002; Christiansen and Knussmann, 1987; Silverman et al., 1999). Levels of total and bioavailable testosterone also gradually decrease with age and are associated with changes in cognition (Cherrier et al., 2001). There are emerging reports suggesting enhancement of cognitive function in healthy elderly men that received testosterone (Cherrier et al., 2001; Janowsky et al., 1994; Kenny et al., 2002; Yaffe et al., 2002), including improvements in spatial cognition (Cherrier, 1999). On a similar note, chronically elevated levels of glucocorticoids have deleterious effects on particular domains of cognition, and cognitive deficits due to elevated levels of cortisol are clearly apparent in Cushing's disease patients (Seeman et al., 1997; Starkman et al., 2001). Associations between cortisol and poor memory have been reported in both rodents (Shors and Dryver, 1992) and humans (Lupien et al., 1998) in response to increased stress.

As we previously alluded, a variety of tasks have been used to assess human spatial cognition showing superior male spatial ability. For example, mental rotation, spatial orientation, route learning, map learning, pointing to places, throwing to targets, intercepting projectiles, and measuring water levels have all been employed to measure spatial ability (see Kimura, 2002). For many, the mental rotation task originally described by Metzler and Sheperd (1974) is the gold standard for measuring spatial cognition in humans, and several studies have reported male advantage in mentally rotating images (Linn and Petersen, 1985; Masters and Sanders, 1993; Sanders et al., 1982; Wilson and Vandenberg, 1978). Men outperform women by as much as one standard deviation on this test, making this one of the largest cognitive sex differences, second only to that observed in the VMWT (Astur et al., 1998).

As it can be gathered from the literature, there have been numerous attempts to explain what underlies sex differences in certain domains of cognition, from hormonal factors (Silverman et al., 1999) to socialization practices (Maccoby and Jacklin, 1974). The recent development of virtual navigation tasks allows researchers to connect with the wealth of information concerning the neurobiology of spatial learning and memory in nonhuman animals, and facilitates comparison of human and nonhuman spatial behavior in analogous tasks. In the current study, we employ the VMWT to address two questions in Experiment 1: (1) does the sexual dimorphism previously reported in this task vary as a function of age, and (2) is there a relationship between behavior in the virtual Morris water task and a more traditional measure of spatial ability, the Vandenberg Mental Rotation Test. In Experiment 2, we attempt to relate the spatial ability to circulating salivary testosterone and cortisol levels.

Materials and methods

Experiment 1

Participants

A total of 70 volunteers participated in the study. Participants were divided into 3 groups: Young (age 20–

39), Middle (age 40–59), and Old (>60). The sex and age distribution of the sample is presented in Table 1. Young participants were University of New Mexico undergraduates who received research credit for a psychology course. Older and middle-aged participants were generally healthy, community-dwelling volunteers who responded to advertisements requesting participants and received no monetary compensation for their participation. All participants had normal or corrected to normal vision, no prior experience with the virtual Morris water task, and were screened for any history of neurological problems. All participants gave informed consent in accordance with the guidelines for human research at The University of New Mexico and were fully debriefed upon completion of the experiment.

Apparatus and training procedure

Each participant completed a Vandenberg Mental Rotation Test (Vandenberg and Kuse, 1978) and the virtual Morris water task. The order of presentation of the test type was counterbalanced across participants within each group. After completion of the two tasks, participants filled out a post-experiment questionnaire.

Vandenberg Mental Rotation Task (MRT)

The Vandenberg Mental Rotation Test (Vandenberg and Kuse, 1978) is a classic test for measuring spatial cognition in humans. This is a pen-and-paper test consisting of 12 target items. Target items are graphic representations of 3D objects. The task requires participants to identify two rotated images of the same target item out of four alternatives. Participants were given a point only when both choices were correct for a given target item and no points otherwise resulting in a possible score range from 0 to 12. We measured how many items were completed within the first 5 min, after which participants were allowed to complete the remaining items resulting in the total number of correct responses with no time limit. Participants were told: “You have 5 minutes to complete as many problems as possible, but it is just as important how many of them you can get correct in that amount of time. After 5 minutes, I will stop you and mark how many items you completed. You will be allowed then to go ahead and complete the remaining items.”

Virtual Morris water task (VMWT)

The virtual environment was presented on a computer screen and consisted of a circular pool located in the center of a square room (for a detailed description, see Driscoll et al., 2003; Hamilton et al., 2003). The distal room (extra-maze) environment consisted of 4 walls, which were visually identical and were located approximately twice the pool diameter from the center of the room. Four conspicuous distal visual cues, which were easily distinguishable, were placed flush with distal walls and off-center vertically by a fixed amount. These distal cues were of equal size and were the only visual features of the environment that disambiguated spatial locations. The location of cues was constrained so that participants could not take a straight trajectory toward a cue from any starting location and reliably find the platform.

Table 1
Number of male and female participants in each age group

	Young (20–39)	Middle (40–59)	Old (>60)	Total (Age)
Females	13	11	11	37 (48.9)
Males	11	12	12	33 (51.9)
Total (Age)	24 (28.6)	23 (49.6)	23 (73.7)	70 (50.3)

Mean age is shown in parentheses.

An IBM-compatible computer controlled the presentation of the environment, auditory feedback, and data collection. Participants viewed the virtual environment from a first person perspective with a field of view of approximately 45°. Visual aspects of the experiment were displayed on a color monitor and auditory feedback was delivered via headphones. The approximate distance between each participant’s nose and the monitor was 20 in. Navigation was controlled using the keyboard arrow keys. The UP arrow key was used to control forward movement and the LEFT and RIGHT arrow keys controlled rotation. Tapping the key initiated movement, but the key needed to be pressed continuously to maintain movement. Forward movement and turning could occur simultaneously. Backward navigation was not permitted. The fastest traversal of a virtual distance equal to the diameter of the pool took approximately 4 s to complete and a full rotation in the absence of forward movement took approximately 2.5 s.

All participants were tested individually. Participants were instructed that they would begin each trial facing the perimeter wall of the virtual pool and that their goal was to escape from the water by finding the submerged escape platform as quickly as possible. It was disclosed to our participants that the platform location would remain constant throughout the experiment and that the starting location would differ from trial to trial. However, the actual platform location was not revealed. Participants were told that once they found the platform and were standing on it, they will be ‘kept’ on the platform for 10 s, and that during that time they may look around from the platform but that the forward movement will not be permitted (i.e., they will not be able to jump of the platform back into the pool). They were also told that after those 10 s the screen will go black indicating that the new trial is about to begin, and shortly thereafter they will find themselves in the water again facing the wall of the pool. The instructions were presented on the screen and the participants were required to read them first, after which the instructions were repeated verbally by the experimenter and participants were allowed to ask questions before starting the experiment.

As soon as the platform was located, forward movement ceased, auditory confirmation was provided, and a verbal message appeared on the monitor stating that the platform had been found. A limit of 60 s was allotted to locate the platform, after which the platform became visible, a discordant tone sounded, and a verbal message appeared stating that the platform was now visible. Regardless of whether the platform was located when it was visible or hidden, participant remained on the platform for 10 s, after which the screen faded and a new trial began. Both hidden and visible platform stayed in the same location across trials. Each participant received 7 blocks of hidden platform training (4 trials each) followed by the 30 s no-platform probe trial and 2 blocks of visible platform training (4 trials each). A tone sounded and a verbal message stating that the platform was visible appeared at the beginning of each visible platform trial. The participant's position in x,y coordinates was recorded every 100 ms. Latency and path length to locate the platform were determined from this record. For analysis purposes, path length was expressed as the ratio of pixels traveled to the diameter of the pool. Upon completion of the VMWT, participants completed the post-experiment questionnaire.

A post-experiment questionnaire assessed the participant's age, experience playing video games, any strategies the participant may have employed, a subjective rating of task difficulty, and whether the participant believed the platform and starting location to be fixed or variable. Game-playing experience was assessed by asking participants: "How often do you play video games?" (0: Never, 1: Rarely, 2: Occasionally, 3: Often). Task difficulty was rated on a 10-point scale (1 = Easy, 10 = Very difficult).

Experiment 2

Participants

Recruitment, genetic testing, cognitive, and health status are described elsewhere (Driscoll et al., 2003). Briefly, we recruited normal elderly individuals from a larger ongoing study of aging, health, and nutrition (Garry et al., 1992). Elderly participants (N = 16) were healthy, free of neurological disorders, and not genetically predisposed to Alzheimer's disease (APOE genotyping). Again, their participation was completely voluntary and no monetary compensation was involved. Young participants (N = 16) were college-aged students that received research credits for participation. Each participant had normal or corrected-to-normal hearing and vision.

Procedure

All participants were tested at the approximately same time of a day (before noon). Each participant first completed behavioral testing on the VMWT as previously described (Driscoll et al., 2003, and the same as in Experiment 1), following which the saliva samples were obtained. The saliva samples were collected in a centrifuge tube via a 3-in. plastic straw. The samples were frozen and shipped for analysis to Salimetrics, Inc (www.salimetrics.com).

Values were obtained for circulating levels of both testosterone (pg/mL) and cortisol (μg/dL). The sensitivity of testosterone assay is <1.5 pg/mL, and cortisol assay is <0.007 μg/dL.

Results

Experiment 1

We report analyses of three performance measures on the VMWT: (1) latency to locate the platform, (2) percentage of time spent in correct quadrant of the pool on the no-platform probe trial, and (3) percentage of distance in correct quadrant of the pool on the no-platform probe trial. Performance on the MRT was assessed by the score for the timed portion of the task (5 min), as well as the total number of correct responses.

VMWT—training

Mean latency to navigate to the hidden platform was calculated for each trial block and subjected to the analysis of variance (ANOVA) with Age and Sex as independent variables. There was a significant Age effect ($F(2, 69)$ = 4.310, $P < 0.001$), where increasing age was associated with longer latencies to locate the platform (see Fig. 1A). We also found a significant effect of Sex ($F(1,69)$ = 4.995, P = 0.004), where males performed better than females. Overall, males had shorter latencies in locating the platform (see Fig. 1B). The largest discrepancy was observed on the last block

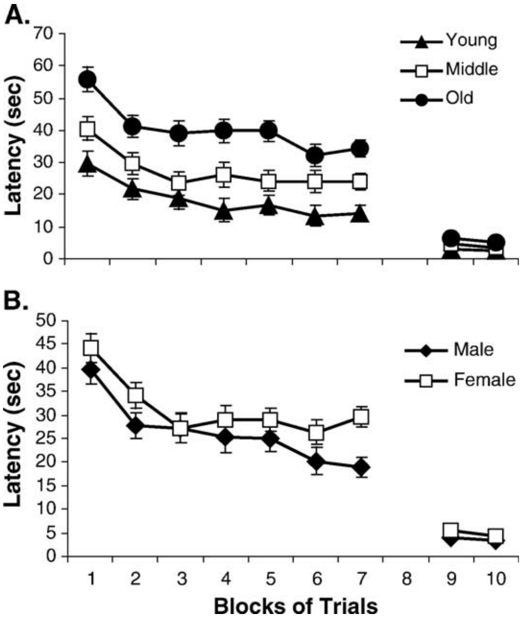

Fig. 1. Virtual Morris water task—training performance. Latency (Mean ± SEM) to locate the platform over the seven blocks of hidden platform training and two blocks of visible platform (blocks 9 and 10) by age (A; Young: N = 24; Middle: N = 23; Old: N = 23) and sex (B; Females: N = 37; Males: N = 33). Trial block 8 represents the probe trial and the results are presented in Fig. 2.

of training ($F(2,64) = 11.865$, $P = 0.001$), where females had significantly longer latencies in locating the platform than males. The Age by Sex interaction was not statistically significant, suggesting that the male superiority in navigation learning was similar for all age groups. The swimming speed did not significantly differ between age groups or between sexes.

VMWT—probe trial

Mean proportion for search time and path length was calculated for the quadrant where the platform had been located during training. Obtained values were subjected to an Age × Sex ANOVA. We found a significant effect of Age, where increasing age was associated with significantly lower percentage of time spent searching ($F(2,64) = 5.562$, $P = 0.006$; Fig. 2A); and with significantly lower percent path length traveled ($F(2,64) = 6.02$, $P = 0.004$; Fig. 2B) in the correct quadrant. The effect of Sex and the Age × Sex interaction were not significant.

VMWT—visible platform

Mean latency to locate the platform was calculated for each of the two visible platform trial blocks. MANCOVA with Age and Sex as independent variables and the mean latency to locate the platform on each of the 2 visible platform blocks of trials as a dependent variable was performed. We controlled for latency to locate the platform during training, as well as for the mean time to initiate movement. Our results revealed no significant Age or Sex differences in latency or path length to navigate to a visible platform (see Figs. 1A and B). The Age by Sex interaction also failed to reach statistical significance.

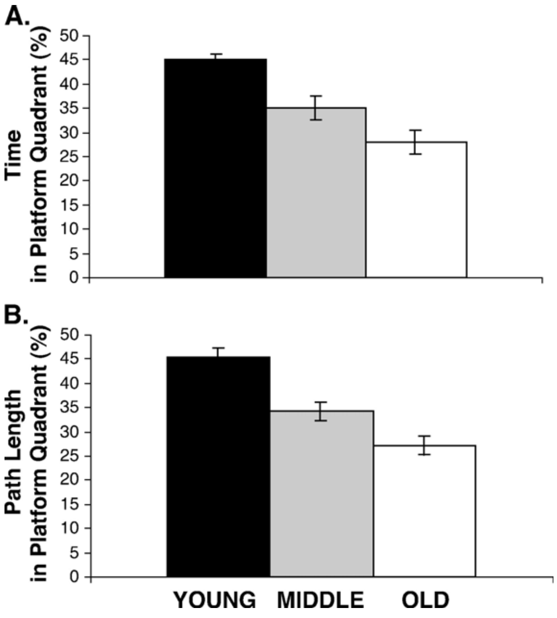

Fig. 2. Virtual Morris water task—probe trial performance. (A) Percent time (Mean ± SEM) spent and (B) percent path length (Mean ± SEM) traveled in the platform quadrant of the pool for each age group (Young: $N = 24$; Middle: $N = 23$; Old: $N = 23$).

VMWT—questionnaire

The number of participants reporting video game-playing experience differed significantly with respect to age group ($\chi^2(2, N = 70) = 8.217$; $P = 0.016$), but not sex. There were no differences in game-playing frequency with respect to both age and sex in this sample. The number of participants noting that the starting locations varied did not differ significantly with respect to age or sex. A significantly larger number of older participants failed to note that the platform location was fixed relative to the cues compared to the young and the middle-aged groups ($\chi^2(2, N = 70) = 9.496$, $P = 0.009$), but there was no difference between the sexes. The VMWT was rated as relatively easy ($M = 4.5$) on a scale from 1 to 10 and a one-way ANOVA on a difficulty rating revealed significant group differences ($F(2, 69) = 3.919$, $P = 0.025$), such that the difficulty rating went up a bit with age (mean difficulty rating: Young = 3.5; Middle = 4.8; Old = 5.2).

We obtained a self-report of strategies employed to find a platform and further coded them as either a place strategy or a random strategy. Any case where participants reported using distal cues as a means of disambiguating platform location was coded as a place strategy. A random strategy consisted of cases reporting a circuitous strategy or any other strategy inconsistent with a place strategy. There were two independent raters and a total of 92% of young, 65% of middle-aged, and 61% of elderly participants reported using a place strategy ($\chi^2(2, N = 70) = 6.644$, $P = 0.036$). There was no significant difference in the strategy employed between males and females, and most have employed the correct strategy.

Mental rotation task

In order to assess performance on the mental rotation task we performed separate two-way ANOVAs with Age and Sex as independent variables and scores for the timed portion of the test (5 min) and the total score as a dependent variable, respectively. Our results indicate a significant Age by Sex interaction for both the timed performance ($F(2,70) = 9.04$, $P < 0.001$; see Fig. 3A) and the total (not timed) number of correctly identified items ($F(2,70) = 5.71$, $P = 0.005$; see Fig. 3B). Although males performed better in the young and the elderly groups, females had higher scores in the middle-aged (40–59 years of age) group.

In order to examine the relationship between the VMWT and MRT performance, we computed zero-order correlations. For the VMWT, there were 3 summary variables used: (1) mean latency on the last block of training, (2) percentage of time in the correct quadrant of the pool on the probe trial, and (3) percentage of path length traveled in the correct quadrant of the pool on the

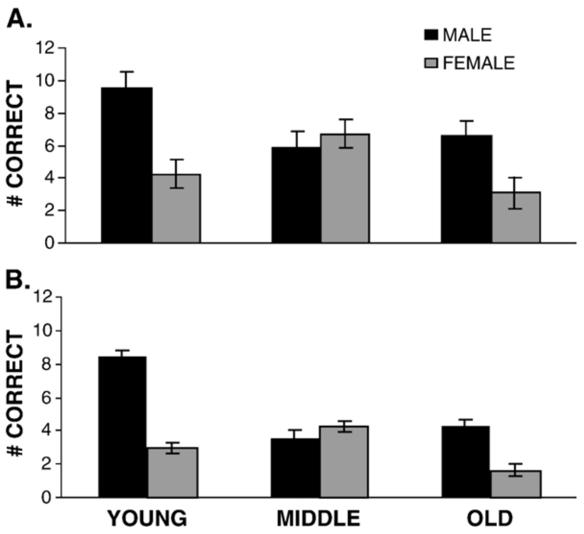

Fig. 3. Mental rotations (Mean ± SEM). Males (black bars) performed better in the young ($N = 11$) and the elderly ($N = 12$) groups, females (gray bars) had higher scores in the middle-aged ($N = 11$) group, on both (A) the non-timed and (B) the timed portion of the test.

probe trial. Variables used for the MRT were (1) the 5-min timed score and (2) the total score (not-timed). We found that Age significantly correlated with both VMWT (last training block: $r = 0.553$, $P < 0.001$; probe trial – percent latency: $r = -0.408$, $P < 0.001$; probe trial – percent path length: $r = -0.412$, $P < 0.001$) and MRT (timed score: $r = -0.370$, $P = 0.002$; total score: $r = -0.244$, $P = 0.042$) performance. We also found that the VMWT significantly correlated with both the timed score (last training block: $r = -0.483$, $P < 0.001$; probe trial – percent latency: $r = 0.380$, $P = 0.001$; probe trial – percent path length: $r = 0.342$, $P = 0.004$) and the total score (last training block: $r = -0.397$, $P = 0.001$; probe trial – percent latency: $r = 0.339$, $P = 0.004$; probe trial – percent path length: $r = 0.296$, $P = 0.013$) of the MRT. Also, the VMWT performance still significantly correlated with the timed MRT performance (last training block: $r = -0.359$, $P = 0.002$; probe trial – percent latency: $r = 0.269$, $P = 0.025$; probe trial – percent path length: $r = 0.224$, $P = 0.065$) and the total MRT performance (last training block: $r = -0.325$, $P = 0.007$; probe trial – percent latency: $r = 0.271$, $P = 0.024$; probe trial – percent path length: $r = 0.221$, $P = 0.068$) after we controlled for Age.

Experiment 2

VMWT

Performance of current participants on the VMWT has been previously analyzed and results, including the questionnaire data, have been reported elsewhere (Driscoll et al., 2003). In summary, we found a significant effect of Age ($F(10,17) = 3.669$, $P < 0.009$) and Sex ($F(10,17) = 5.203$, $P = 0.001$). Males, however, had shorter latencies regardless of age. There were no group differences on the visible platform trials or in the speed of swimming. The sex difference was not present with the probe trial performance measures.

VMWT—questionnaire

The number of participants reporting experience with video game-playing differed significantly with respect to group membership ($\chi^2(1, N = 32) = 9.0$; $P = 0.003$). The number of participants noting that the starting locations varied did not differ significantly between the groups, while a significantly larger number of older participants failed to note that the platform location was fixed relative to the cues ($\chi^2(1, N = 32) = 5.4$, $P = 0.02$). The VMWT was rated as relatively easy (Mean = 4.375, SD = 2.559) on a scale from 1 to 10 and a one-way ANOVA on a difficulty rating revealed no significant group differences. More of our younger participants adopted a place strategy compared to the elderly participants ($\chi^2(1, N = 32) = 9.0$, $P = 0.003$).

Testosterone

A two-way ANOVA with Age and Sex as independent variables revealed a significant Age × Sex interaction ($F(1,30) = 7.98$, $P = 0.009$; see Fig. 4A). Testosterone also significantly correlated with performance on the last block of the VMWT training ($r = -0.488$, $P = 0.005$), a measure that provided significant sex difference in spatial ability. Now, the same correlation between testosterone and the VMWT performance was not present in the young and the elderly group separately, but was present for males ($r = -0.585$, $P = 0.022$), but not females, suggesting that the

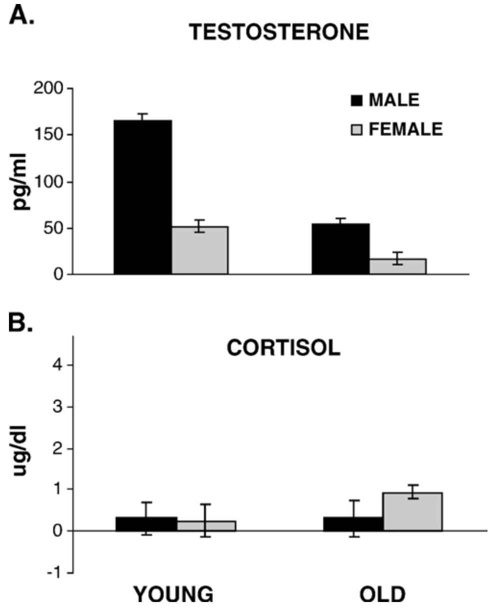

Fig. 4. (A) Testosterone (Mean ± SEM) and (B) cortisol (Mean ± SEM) concentrations for males (black bars; Young males: $N = 11$; Middle-aged males: $N = 12$; Old males: $N = 12$) and females (gray bars; Young females: $N = 13$; Middle-aged females: $N = 11$; Old females: $N = 11$) with respect to age.

observed relationship is not just due to age-related changes. Furthermore, testosterone, age, and sex were entered simultaneously into a regression equation. Testosterone explained a significant amount of variance in VMWT performance over and above age and sex (R^2 = 0.24, $F(1,29) = 9.09$, $P = 0.005$).

Cortisol

A two-way ANOVA with Age and Sex as independent variables revealed no significant interaction. The Age or Sex effects were not significant either (see Fig. 4B). Furthermore, we did not find a significant relationship between cortisol levels and VMWT performance.

General discussion

The broad aim of this study was to evaluate behavioral changes in human spatial cognition associated with normal aging. We employed the Vandenberg Mental Rotation Test in order to assess performance of our participants on this commonly used test of human spatial cognition and to allow comparison with the virtual Morris water task, a human analog of the test commonly used for measuring spatial ability in nonhuman animals. Our findings indicate a significant age-related deficit on both tests of spatial ability, which is consistent with previous reports. Despite the age-related deficits in performance, the robust sex difference favoring male participants did not diminish. Our findings suggest that persistence of male spatial advantage, despite the age-related deficits, may be independent of more generalized slowing of function associated with normal aging.

Notwithstanding the absence of significant differences in the speed of swimming or in performance on visible platform trials in the VMWT and the overall improvement in latency to locate the platform over consecutive trial blocks, elderly participants showed a deficit on general measures of place learning. The age-related deficit in place learning reported here cannot simply be accounted for by the lack of computer experience or generalized psychomotor slowing associated with age. We expected that our elderly participants would lack the computer and/or game-playing experience of our younger participants. In this experiment, to insure adequate training and familiarization with the virtual environment, we have allowed for two additional blocks of training compared to prior studies in our laboratory involving only younger subjects. Performance in all three age groups seemed to reach asymptote on the last three blocks of training (see Fig. 1A), suggesting that additional training would not necessarily be beneficial. Furthermore, our results show no significant differences in the speed of swimming or in performance on visible platform trials, which does not require place learning for successful performance. In fact, we find that the game-playing experience accounts for only a small portion of the variance (about 4%) in place learning performance of college-aged participants in our version of the VMWT (Hamilton, 2003), and no significant correlations were seen between game-playing frequency and any of the VMWT measures (latency or path length to the platform for hidden platform trials, percent time or path length in the correct quadrant of the pool on the no-platform probe trial, latency or path length to enter the correct quadrant on the probe trial, or heading error on the probe trial). Also, in a Fetal Alcohol Syndrome (FAS) study employing the VMWT (Hamilton et al., 2003), authors describe an impairment in place learning by male FAS children that reported playing video games frequently. We assert that computer or game-playing experience does not seem to be necessary or sufficient in facilitating place learning. A study by Moffat et al. (2001) also reports age-related deficits in virtual navigation of elderly compared to young volunteers, even though participants were pre-trained to navigate the virtual environment.

The lack of locomotor-based proprioceptive and vestibular cues intrinsic to virtual navigation and a narrower field of view may also be seen as methodological features limiting direct generalization to real-world navigation. However, all of our participants, males and females, young and old, were deprived of such information, suggesting that this alone cannot account for the observed age and sex differences in performance. Again, all groups performed comparably on the visible platform trials and there were no significant differences in swimming speed, suggesting that the observed differences in place learning were not sensorimotor or motivational in nature. Despite the inherent limitations of virtual environments, it has been demonstrated that humans can learn to navigate in virtual environments relying entirely on visual stimulation (Hamilton and Sutherland, 1999; Hamilton et al., 2002; Maguire et al., 1999; Moffat and Resnick, 2002; Moffat et al., 1998, 2001; Shore et al., 2001), that the neural basis for virtual navigation in humans has strong parallels to nonhuman animal findings (Maguire et al., 1999), and that rodents and humans perform in a similar manner under similar conditions in their respective versions of the MWT (Hamilton et al., 2002).

The nature of sex differences in cognition, however, remains a matter of debate. Other concurrent experiments address the strategies that females may prefer compared to males and how these strategies may be different (Sandstrom et al., 1998). Reported differences in strategies employed by males and females are, however, specific to the virtual navigation and do not directly explain the sex differences in performance on other tests of spatial ability.

We also report an age-related deficit in metal rotation performance. However, when it comes to mentally rotating images, the conclusions are not quite as clear as with place navigation. The significant interaction between age and sex indicates that male and female performance is different for different age groups. Specifically, males had higher scores (both timed and total) than females in the young and the elderly group, while the opposite pattern was observed for the middle-aged group. It is not possible, however, to delineate precisely from the data gathered here why females seem to perform better than males in this age group. One can speculate that perhaps females exhibit a different aging pattern from their male counterparts and that this task is particularly sensitive to such differences. Another, maybe more obvious, possibility could be related to the fact that middle-aged females may be undergoing menopause (i.e., hormonal changes), which may be at least partly responsible for the observed reversal in performance.

To the best of our knowledge, the studies of aging and mental rotations conducted thus far included participants over 60 years of age and omitted the middle-aged group. However, one of such studies (Maki et al., 2002) suggests a negative correlation between estradiol levels and mental rotation performance in the mid-luteal phase, holding estrogen responsible for changes in performance across the menstrual cycle. Also, it has been reported that females exhibit better performance on mental rotations during menstruation, which is also the time when the estrogen level is at its lowest (Moody, 1997; Silverman and Phillips, 1994). Another study by Hooven et al. (2004) reports that testosterone may facilitate male performance on mental rotations by affecting cognitive processes underlying the performance on this task. Additional research is needed in order to better characterize the nature of sex differences in mental rotation performance and the changes it undergoes with age.

To address the relationship between the virtual Morris water task and a more traditional measure of spatial ability, the Mental Rotation Test, we quantified the relationship between performance measures on the two tasks. Even after we controlled for age, the VMWT and MRT performance did correlate significantly. Recently, Astur et al. (2004) reported sex differences in performance on mental rotations and a virtual Morris water task. Similarly, according to Astur et al. (2004), participants who performed better on mental rotations found the hidden platform in shorter distances, with shorter latencies, and performed similarly during the probe trial.

The purpose of this study was to assess the place learning across life span and to provide information on the relationship between the virtual MWT and the mental rotations task, which has, until recently, been more commonly used as a test spatial ability in humans. Taken together, our results demonstrate the usefulness of the VMWT not only in assessing effects of age on place learning, but also in studying sex differences in spatial ability from young adulthood to senescence. Evidence from animal research suggests that age-related functional, structural, and neurochemical alterations in the hippocampus are related to inflexible use of information in memory (Gallagher and Rapp, 1997; Geinisman et al., 1995; Rosenzweig and Barnes, 2003). Learning deficits studied in aged animals are often assessed using the MWT. Animal behavioral studies demonstrating hippocampus-dependent deficits suggest a locus for cognitive impairments associated with normal and pathological aging in humans. In that sense, the VMWT may be more useful than the MRT not only because it makes contact with a vast amount of existing animal literature, but it also facilitates a need for a cross-species behavioral comparisons. Previous studies utilizing the VMWT suggest striking similarities in human and rodent performance on this task (Hamilton and Sutherland, 1999; Hamilton et al., 2002). However, the sex difference in water maze performance specifically appears more robust in humans, as it can be eliminated in rats by pre-training (e.g., Perrot-Sinal et al., 1996).

It has been suggested that the expression of sex differences in spatial cognition may be possibly influenced by genetic, biological, or hormonal factors, or a combination thereof. All are subject, of course, to modification by ones environment. Nonhuman animal literature strongly suggests a role of sex steroid hormones in modulating cognitive function, but not many address whether differences in such hormones are associated with differential spatial cognition, especially across different ages. Also, a high density of the glucocorticoid and androgen receptors in the hippocampus, the structure critical for spatial learning and memory, suggests a possibility for a relationship between these receptors and certain aspects of cognition that require hippocampus.

Previous reports concerning the role of hormones in spatial ability report deleterious effect of cortisol. However, a failure to detect a relationship between salivary cortisol levels and spatial performance has been previously noted in the literature (McCormick and Teillon, 2001). It is possible that we did not observe a significant relationship between VMWT performance and cortisol levels because none of our participants were under chronic stress at the time of testing. Often, subjects need to be chronically exposed to elevated glucocorticoid levels in order to observe related cognitive deficits (Bodnoff et al., 1995; Coburn-Litvak et al., 2003; Conrad et al., 1996; Luine et al., 1996), as acute stress has been shown to attenuate the ability to acquire new memories about associations between stimuli (Beylin and Shors, 2003).

It is well known, from the nonhuman animal literature, that the effects of testosterone mediated through androgen receptors, although complex, are also widespread and as such may have effects on place learning and memory. Testosterone is suggested to have a role in gender differences in performance on cognitive tasks in which men do better than women. However, studies of exogenous testosterone administration in men have provided equivocal results (Cherrier et al., 2001; Janowsky et al., 1994; Wolf and Kirschbaum, 2002; Wolf et al., 2000; Yaffe et al., 2002). Also, there have been relatively few studies examining the relationship between sex steroids and spatial cognition in older people. Here we find that circulating levels of testosterone predict spatial ability in men, even though testosterone levels significantly decreased with age. While our findings lend support to the body of data reporting a relationship between testosterone and spatial ability, the relationship between hormones and behavior is probably a rather complex one, especially when aging is taken into consideration.

Present findings have brought some light to changes in spatial ability that may occur with aging and how these changes may affect the human hippocampus-dependent cognition. Our findings suggest that spatial ability, as measured by VMWT, is markedly influenced by sex and sex steroid hormonal levels, namely testosterone. The aging process, however, may differentially modulate influence of testosterone on males and females. The use of virtual environments in future research, with normal and patient populations, may help further our understanding of cognitive sex differences, brain mechanisms involving aging, hippocampus, and learning and memory with greater clarity. In addition, the VMWT may further aid in the development of animal aging models as it continues to bridge the animal and human literature.

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