

Extrahippocampal Contributions to Age Differences in Human Spatial Navigation

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The hippocampus (HC) and associated neural structures are hypothesized to contribute to individual differences in human spatial navigation. However, functional imaging studies and theoretical models underscore the importance of extrahippocampal regions as well. The purpose of the present study was to examine age differences in virtual environment navigation and to assess possible relationships between navigation and structural integrity of hippocampal and extrahippocampal brain regions. Healthy adult volunteers completed a virtual navigation task and underwent magnetic resonance imaging to assess volumes of the caudate nucleus (CN), cerebellum, HC, prefrontal, and primary visual cortices. Results demonstrated robust age-related differences in place learning. Moreover, individual differences in regional brain volumes as well as performance on the tests of memory and executive functions contributed to age differences in human place learning. High performance in a virtual navigation task was associated with larger volume of the CN and prefrontal gray and white matter. Larger hippocampal volume was associated with improved performance in the young but not old participants. We conclude that human navigation requires both hippocampal and extrahippocampal brain systems and draws on executive resources for successful performance.

Keywords: aging, Alzheimer's disease, executive function, hippocampus, place learning, wandering

Introduction

Age-related deficits in spatial maze learning are evident in spatial navigation tasks across several mammalian species (Barnes 1979; Ingram 1988; McLay and others 1999). In particular, these deficits are observed in performance on the Morris water task (MWT) (Morris and others 1982) that has been used extensively in studying cognitive aging in animals. Briefly, in the MWT, an animal is required to search for a platform hidden beneath the surface of a circular pool. Because the platform cannot be seen directly, the animal must locate the platform position with reference to external cues throughout the environment and remember its location across a series of trials. Multiple studies of MWT performance have yielded a plethora of data, and age-related deficits on the MWT have been well characterized (Gallagher and Pellemounter 1988; Lindner 1997; Lukoyanov and others 1999; Begega and others 2001). One of the reasons for popularity of MWT in studies of cognitive aging is its sensitivity to hippocampal lesions and its functional dependence on the hippocampal formation (Morris and others 1982).

The investigation of age-related differences in human spatial navigation is a topic of considerable import. Nondemented elderly experience substantial deficits in spatial navigation (Kirasic 1991; Kirasic and others 1992; Burns 1999; Wilkniss

and others 1997; Newman and Kaszniak 2000), and impairment in navigational skills is often apparent in the early stages of dementia (Passini and others 1995; Klein and others 1999). Recently, virtual environment (VE) spatial learning tasks have been successfully applied to the study of age differences in spatial navigation among healthy elderly (Moffat and others 2001, 2006; Moffat and Resnick 2002; Driscoll and others 2005). In a virtual MWT, elderly individuals traveled a longer linear distance in locating the hidden goal, spent less time searching in the vicinity of the goal on a retention trial, and were impaired in constructing a cognitive map of the environment in comparison to their younger counterparts (Moffat and Resnick 2002).

Functional neuroimaging and lesion studies have identified a complex network of structures that are involved in spatial navigation. The proposed network includes the hippocampus (HC), parahippocampal gyrus, cerebellum (CB), parietal cortex, posterior cingulate gyrus, prefrontal cortex, retrosplenial cortex, and other cortical and subcortical regions (Aguirre and others 1996; Barrash 1998; Maguire and others 1998; Katayama and others 1999; Gron and others 2000). In a recent functional neuroimaging study, we found that in performing a virtual navigation task, elderly participants showed reduced activation in some of the same neural systems that young subjects use to navigate successfully. The cerebral regions identified in that study included the HC, parahippocampal gyrus, and retrosplenial cortex. Thus, reduced activation in the HC and extrahippocampal regions may underlie the observed age deficits in performance (Moffat and others 2006).

Most attention in research on human navigation has focused on the role of the HC and associated structures. This focus may be justified in light of the prominent place of the HC in models of human spatial and episodic memory and in animal models of spatial navigation. However, a closer examination of the executive and strategic demands of human navigation and their neural underpinnings is overdue. Successful navigation requires the selection of an appropriate search strategy and also depends on appropriate behavioral monitoring and alterations of searching behavior if the selected strategy proves unsuccessful. Such reliance on executive skills during acquisition is common in many tasks, including those that in their developed states are highly proceduralized. On other procedural tasks, shrinkage of the prefrontal cortex, neostriatum, and CB have been shown to contribute to age-related differences in these skills (Raz and others 2000; Kennedy and Raz 2005). Thus, it is plausible that age-related deficits in acquiring and maintaining navigational skills may reflect, at least in part, differential shrinkage of multiple regions rather than strictly hippocampal atrophy.

The age-related deficits observed in the virtual analog of MWT cannot be fully accounted for by models of performance

restricted to spatial memory. In particular, we have observed that healthy elderly perform more poorly than their younger counterparts even on the first trial, which does not depend on memory for platform location (Moffat and Resnick 2002; see Driscoll and others 2005, for similar results). According to strictly spatial memory models of performance, there should be no age difference on trial 1 performance because the search for the hidden platform on the first trial should be random. Importantly, our analyses indicated that this trial 1 deficit was not attributable to psychomotor impairment in the elderly. We hypothesize that the deficits observed among elderly participants in navigational behavior may be partially attributed to impaired executive and strategic functions that play a significant role in skill acquisition (Anderson 1983). In particular, our observations indicate that elderly individuals are reluctant to disengage from searching in locations that have been adequately explored, suggesting a perseverative component to their behavior or, more generally, the selection of inefficient spatial search strategies. This behavioral effect is illustrated in Figure 1. We therefore hypothesize that the deficits observed among elderly subjects in navigational behavior may be partially attributed to impaired executive and strategic functions and shrinkage of the neural systems that support executive control.

In the present study, we quantified navigational behavior in a sample of men and women whose regional brain volumes were assessed via structural magnetic resonance imaging (MRI). In addition to an extensive cognitive test battery, the individuals in the present study performed a VE place navigation task modeled after the MWT. The purpose of the study was 3-fold: 1) to investigate age differences on a virtual Morris water task (vMWT), regional brain volumes, and other cognitive tests; 2) to investigate associations between regional brain volumes and vMWT performance; and 3) to investigate associations between cognitive tasks and vMWT performance. We hypothesized age-related deficits in spatial navigation as assessed by the vMWT. We hypothesized that a significant portion of variance in vMWT performance would be explained by hippocampal, prefrontal, and striatal volume differences, whereas individual differences in the volume of a control region (primary visual cortex [VC]) would evidence no significant association with navigation performance. In addition, both hippocampal dependent measures of memory as well as frontal lobe executive measures would be positively associated with vMWT performance.

Materials and Methods

Participants

In this study, we examined cross-sectional differences in the normal aging brain using a sample of healthy volunteers who participate in an ongoing study of brain and cognitive aging. Participants in the present study (18 years and older) were recruited from a pool of more than 140 subjects who underwent MRI scanning and cognitive testing in our laboratory. These participants, who live in the Detroit metropolitan area, were contacted and agreed to return to complete the virtual MWT. Sixty-eight participants who had undergone MRI scanning agreed to participate in the study and met all study qualifications. These participants were divided into 2 groups, hereafter referred to as young and elderly. Persons who reported history of cardiovascular (except treated essential hypertension), neurological, or psychiatric illness, diabetes, head trauma with loss of consciousness for more than 5 min, thyroid problems, treatment for drug and alcohol problems, or a habit of taking 3 or more alcoholic drinks per day were excluded from the study as were participants who use antiepileptic medication, anxiolytics, or antidepressants. Persons who experience emotional distress that could interfere with cognitive performance were screened using a geriatric depression questionnaire (Radloff 1977). In addition, participants in our study were classified into those with current or history of hypertension. This was done to investigate the effects on performance of hypertension that is increasingly acknowledged as an important moderator of cognitive and brain aging (Raz and others 2003; Korf and others 2004; Wiseman and others 2004). General cognitive status was assessed by Mini Mental State Examination (Folstein and others 1975). All participants were strongly right handed as screened by the Edinburgh handedness questionnaire (Oldfield 1971). Table 1 presents demographic data for the subject sample. Mean delay between MRI and cognitive testing was 3.8 months (standard deviation [SD] = 2.7), and there were no differences in delay between the young and the old participants $t = 0.01$, not significant (NS). Before cognitive testing, all participants were interviewed to ensure that they had not experienced any health changes in the interim period. Because we performed a cross-sectional study comparing a group of older participants with a group of younger participants, any small cognitive or brain changes over the 3.8-month interval are unlikely to affect our cross sectional comparisons that average 44 years difference between old and young participants.

Procedures

Structural MRI and Regional Volumetry

Image acquisition and processing. Participants in the existing project underwent MRI scanning at Children's Hospital of Michigan on a GE Signa 1.5-T scanner. Regional brain volumes were measured on images acquired with T_1 -weighted 3-dimensional spoiled gradient recalled (SPGR) sequence with 124 contiguous axial slices, echo time = 5 ms,

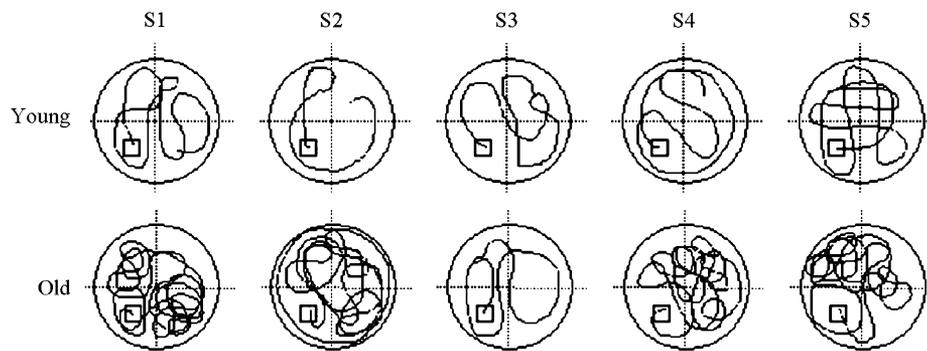


Figure 1. Top view of virtual MWT search paths (trial 1) in 5 representative young and old subjects in a previous study (Moffat and Resnick 2002). Older subjects took longer to find the platform and traveled a longer linear distance in their initial search. Inefficient search strategies and a reluctance to disengage from nongoal locations may contribute to this age difference on trial 1.

Table 1
Demographic characteristics of participants

	N	Percent female	Age (mean ± SE)	Education (mean ± SE)	Percent hypertensive
Young	32	75	24.5 (0.91)	15.16 (0.32)	0
Old	36	67	68.5 (0.92)	15.22 (0.52)	47.22

Note: SE, standard error.

time repetition = 24 ms, field of view = 22 cm, acquisition matrix 256 × 192, slice thickness = 1.3 mm, and flip angle = 30°. The images were reformatted to correct for undesirable effects of head tilt, pitch, and rotation with BrainImage 2.3.3 software. The procedure is described in detail elsewhere (Raz and others 2004).

Volumetry: region selection, demarcation, and tracing. The regions of interest (ROIs), selected on the basis of the hypotheses to be tested in this study, included HC, lateral prefrontal cortex gray matter (LPFC), prefrontal white matter (PFW), caudate nucleus (CN), and the CB. Each of these selected structures has been implicated as contributing to spatial navigation in human neuroimaging or animal studies. Primary VC was selected as a comparison (control) region for which no correlations were expected. To control statistically for individual differences in body size, especially for sexual dimorphism, we used intracranial volume (ICV). All regional brain volumes were corrected for total ICV using a regression analysis of covariance approach. Interrater reliability of all measures exceeded an intraclass correlation of 0.90.

The rules for demarcation and tracing of brain regions as well as the estimates of interrater reliability of volume estimates obtained with National Institutes of Health Image software (Version 1.62) are described in detail in previous publications (Raz and others 1997, 2004) and will be presented here in condensed form. Unless otherwise noted, we used the average of left and right hemisphere volumes in statistical analyses.

Caudate nucleus. The volume of the head and the body of the CN were estimated from 15 to 20 coronal slices. The most rostral slice was the one on which the CN first appeared, usually lateral to the lateral ventricles. The CN was traced on every other slice (interslice distance 3 mm) until no longer visible.

Cerebellum. The cerebellar hemispheres were measured on 32–40 coronal slices. The vermis, the cerebellar peduncles, and the fourth ventricle were excluded, whereas the hemispheric gray matter, the cerebellar tonsils, the vellum, and the corpus medullare were included in the tracing of each cerebellar hemisphere. The rostral border was defined as the first slice on which cerebellar gray matter became visible and distinguishable from the cerebellar peduncles, and the caudal border ended when the hemispheres were no longer distinguishable.

Hippocampus. HC volume was measured on continuous slices aligned perpendicular to the long axis of the right HC between the mammillary bodies and slice showing the fornices rising from the fimbria. The HC included sectors CA1–CA4, the dentate gyrus, and the subiculum.

Intracranial volume. The ICV was estimated from the coronal sections. The operator traced ICV on every eighth slice (a total of 11–12 slices) between the first slice following the orbits and last slice on which brain tissue was visible.

Lateral prefrontal cortex. Eight to 12 coronal slices located within 40% of the distance between the genu of the corpus callosum and the frontal pole are included in the prefrontal ROI.

Prefrontal cortex white matter. The range is identical to LPFC above and also includes orbitofrontal cortex. The volume includes all white matter on the coronal slice, excluding ventricles and other cerebrospinal fluid spaces.

Primary VC (calcarine). The volume of the VC is calculated as the volume of the cortical ribbon lining the calcarine sulcus on the anterior 50% of the coronal slices between the midvermis slice and the occipital pole.

Spatial Navigation Assessments: Virtual Water Maze

For the behavioral navigation testing, all subjects completed a vMWT that has been developed and validated previously (Moffat and Resnick 2002). Before beginning the navigation task, practice trials were allowed to familiarize subjects with movement through the environment and to be certain that participants were comfortable with the computer-administered task. The task environment was a circular arena surrounded by several cues, which could be used to guide navigation. Hidden beneath the surface of the arena was a platform, and the task required the participant to locate the platform as quickly as possible. Because the platform was not visible to the participant, it must be located with reference to its position relative to the external objects and cues. When the participant passed over the platform, the platform became visible, and a tone notified the participant that he or she had located the platform. Participants were informed that the platform remained in the same location on each trial and that they should try to remember its location. On each of 6 learning trials, participants were “placed” into one of the 3 quadrants of the pool, which did not contain the platform and facing a different orientation on each trial. The primary dependent measure was the distance traveled on each trial. Following the 6 learning trials, a “probe” trial was performed in which participants explored the same VE with the exception that the platform had been removed. Participants were given 1 min of search time in the probe trial. Individuals who have properly encoded platform location will spend a greater proportion of their time and distance searching in the vicinity of the platform. Thus, the dependent measures were the percentage of distance spent in the goal quadrant and the number of platform intersections (number of times a participant’s path would have passed over the platform had it been present).

Control Tests

Pretest training and assessment of joystick visuomotor control. Prior to virtual MWT testing, extensive pretraining was provided to familiarize participants with the VE and with the use of a joystick for movement. This was accomplished with an initial period of experimenter instruction, followed by a period of free exploration of a VE using the joystick. After participants were comfortable with the joystick and had satisfactorily demonstrated their ability to guide themselves to targets designated by the experimenter, the participants underwent a joystick control speed test. During the speed test, participants were required to navigate a long winding corridor as quickly and accurately as possible until they reached a trophy at the goal point. Participants were required to demonstrate their competency with the joystick by completing the corridor in less than 120 s.

Visible platform performance. As a further experimental control, a trial was performed in which the platform was visible on the surface of the pool. Subjects were instructed to move onto the platform from the starting location as quickly as possible. This served as an additional control for possible age differences in visual and motor skills. The magnitude of any age differences observed on this task should be considerably smaller than those observed in the vMWT trials and probe trials. The dependent measure was the total distance traveled to the platform.

Cognitive Tests

Cognitive tests were selected based on theoretical and empirical considerations. In particular, we selected tests that measure cognitive skills that have been empirically demonstrated to be related to spatial navigation in previous studies (Moffat and others 1998, 2001). In addition, we selected traditional neuropsychological measures that are sensitive to frontal lobe function to assess the contribution of prefrontal cortex to spatial navigation.

“Computation span” (Salthouse 1989) was obtained as a measure of verbal working memory, and the absolute span was used as the index of

performance, calculated by summing the number of correct items across all trials.

A modified "size-judgment span" (Cherry 1993) was administered as a measure of nonverbal working memory. In this task, participants are orally presented with a list of objects and animals and asked to repeat them in order of size from smallest to largest. Index of performance is total number of correct trials.

"Letter comparison" and "pattern comparison" tests (Salthouse and Meinz 1995) were indices of perceptual speed.

A computerized version of the "Wisconsin card sorting test" (WCST; Psychological Assessment Resources, Odessa, FL) was administered. Total number of perseverative errors was the index of perseveration.

"Vocabulary" (V-3) is a paper-and-pencil test from Educational Testing Service Factor-Referenced Test Kit (Ekstrom 1976) and was used as a measure of word knowledge.

"Spatial recall" test was modified from a task described previously (Salthouse 1994). In this task, participants were instructed to memorize the locations of a stimulus in 1 of 7 target locations within a 5 × 5 matrix and then asked to place an X in the location of the target in a blank matrix. Average number of correct items across the 25 trials was the index of performance.

"Buildings memory" test is a paper-and-pencil test from the Educational Testing Service Factor-Referenced Test Kit (Ekstrom 1976). After studying a fictitious map for 4 min, participants were shown a blank map and tested on their memory for the location of buildings on the map studied in a multiple-choice format. The index of performance was the number correct minus the number incorrect.

Data Reduction

To reduce the data, we analyzed cognitive performance by 4 construct domains: speed of processing, working memory, spatial memory and executive control. Each construct, except executive control, was measured by 2 tests; executive control was assessed by WCST. The working memory domain was assessed by computation span and size judgment span. The spatial memory construct was measured by spatial recall and the buildings memory test. The construct of perceptual speed was measured by letter and pattern comparison tests. Although the domains were determined on the basis of theoretical considerations, we performed principal component analysis on our data in order to verify the postulated factor structure. We conducted principal component analysis followed by varimax rotation on the young and older participants separately. For 32 young participants, the analysis yielded 3 factors that accounted for 78% of the score variance. The first factor was speed (letter comparison and pattern comparison loadings both 0.87, 29% of the variance accounted), the second factor was spatial memory (building memory 0.79, spatial recall 0.88, 25% of the variance), and the third factor was working memory (size judgment 0.87, computation span 0.86, 24% of the variance).

In the older age group, a different factor structure was obtained, with the first factor (letter and pattern comparison tests, spatial recall and building memory, loadings ranging between 0.74 and 0.91) accounting for 59% of the variance and the second factor (size judgment and computation span measures, loadings 0.87 and 0.88) accounting for additional 16%. The difference illustrates an often observed tendency for dedifferentiation of cognitive abilities with age (Ghisletta and Lindenberger 2004). For statistical analyses, we converted all raw scores from cognitive tests to standardized (*Z*) scores and computed composites consisting of the average of test performance in common cognitive domains as described above.

Statistical Approach and Analysis

As noted earlier, there were 3 overarching aims of the study: 1) to investigate basic age differences in vMWT performance, cognitive performance, and regional brain volumes; 2) to investigate correlations between vMWT performance and regional brain volumes; and 3) to investigate correlations between cognitive measures and vMWT performance. For all 3 aims, our hypotheses were tested within the framework of the general linear model with age and sex as independent variables and appropriate dependent variables. The primary dependent variable on the vMWT was the total distance traveled on each trial. Because the distribution of that index was positively skewed, a logarithmic transformation was applied. Following the evaluation of hypothesis 1, which

established basic age effects on vMWT, cognitive tests and ROI's, analyses were performed incorporating the regional brain volumes into the identical models, separately for each brain region with distance traveled on the 6 trials of vMWT as dependent variable. This allowed us to evaluate the contribution of each brain region to vMWT performance (hypothesis 2). Lastly, we deleted brain volumes from our statistical models and incorporated cognitive test scores allowing us to assess the correlation between performance on vMWT and other cognitive domains (hypothesis 3). To assess the specificity of possible associations between vMWT performance and specific cognitive domains, we also evaluated correlations with vocabulary scores as a control measure for which we expected no significant positive correlations.

Results

Age and Sex Effects on Brain, vMWT, and Cognitive Measures

Regional Brain Volumes

The effects of age and sex on regional brain volumes were evaluated in the framework of a general linear model with age group and sex as independent variables and regional volumes as a 6-level repeated measure. Before being entered into the equations, the volumes of all brain regions were adjusted for individual differences in ICV. Overall, there was a significant main effect of age ($F_{1,65} = 34.06, P < 0.001; \eta^2 = 0.34$) and no significant sex differences (all main effects and interactions *F* values < 1). The significant age × ROI interaction, $F_{5,325} = 10.09, P < 0.001, \eta^2 = 0.13$, indicated that the magnitude of the age differences varied across ROIs. There was a significant effect of hemisphere ($F_{1,65} = 6.19, P < 0.05, \eta^2 = 0.09$), with right hemisphere volumes, on average, larger than left but no interactions involving hemisphere were significant (but see below for the analysis of simple effects).

Analysis of simple effects with univariate *F*-tests indicated that the differences between the age groups were significant in LPFC ($F_{1,65} = 46.38, P < 0.001$), the HC ($F_{1,65} = 25.34, P < 0.001$), the caudate ($F_{1,65} = 21.07, P < 0.001$), the CB ($F = 11.37, P < 0.001$), and PFW ($F_{1,65} = 6.21, P < 0.05$) but not in the primary VC ($F_{1,65} = 2.82, P = 0.10$). Comparison of effect sizes revealed that the magnitude of age differences in the prefrontal volume was significantly greater than that for the pericalcarine volume. Other regional differences fell between the 2 values and did not differ significantly from each other (see Table 2).

No lateral differences were found in LPFC ($F < 1$), VC ($F < 1$), the caudate ($F_{1,65} = 1.71, NS$), or the CB ($F_{1,65} = 2.57, NS$). Right PFW was significantly larger than left, $F_{1,65} = 13.87, P < 0.001$. Left HC was larger than the right but only in the young ($F_{1,30} = 25.74, P < 0.001$) not in the older participants ($F < 1$).

We examined the possible influence of hypertension in the older age group on the observed volume differences. Only the older age group could be considered in these analyses as there

Table 2

Descriptive statistics (mean ± standard error of mean) and effect sizes for regional brain volumes (cm³) in the 2 age groups

	LPFC	PFW	HC	CB	CN	PVC
Young	20.94 (0.40)	43.51 (1.07)	7.39 (0.13)	133.06 (1.98)	10.15 (0.17)	5.36 (0.14)
Old	16.30 (0.38)	37.59 (1.01)	6.36 (0.12)	123.12 (1.87)	8.77 (0.16)	5.23 (0.13)
Effect size (<i>d</i>)	2.01	0.97	1.44	0.88	1.41	0.37
<i>P</i> value	<0.001	0.001	<0.001	0.001	<0.001	0.12

Note: Lateral prefrontal cortex white matter (PFW); Primary visual cortex (PVC).

were no young subjects with a diagnosis of hypertension. Separate analyses of the older participants revealed a trend for the diagnosis of hypertension to be associated with overall smaller regional brain volumes ($F_{1,32} = 3.53, P < 0.07, \eta^2 = 0.09$).

Virtual Water Maze: Learning

There was a significant main effect of age, $F_{1,65} = 84.34, P < 0.001, \eta^2 = 0.56$, with younger subjects outperforming older subjects and a main effect of trial, $F_{5,325} = 9.11, P < 0.001, \eta^2 = 0.12$, in which performance improved across trials. There was a nonsignificant trend for an age \times trial interaction: $F_{5,325} = 1.97, P < 0.09, \eta^2 = 0.03$. The linear component of the trial effect was significant, $F_{1,65} = 23.29, P < 0.001, \eta^2 = 0.26$, as was the quadratic component for an age \times trial interaction: $F_{1,65} = 5.99, P < 0.05, \eta^2 = 0.08$. Changes in performance across trials for both age groups are depicted in Figure 2. As seen in Figure 2, there was an unexpected increase in distance traveled on trial 4 in both the younger and older groups. This effect was an artifact of the random placement procedure across the 6 learning trials. On trial 4, participants were placed at the maximum possible distance and facing a direction opposite from the platform resulting in the increase in distance traveled. We performed all analyses again deleting trial 4 from our repeated measure and obtained virtually identical results. In particular, the task resulted in the same robust age and trial effects. In all remaining analyses, all 6 trials are used as dependent measure.

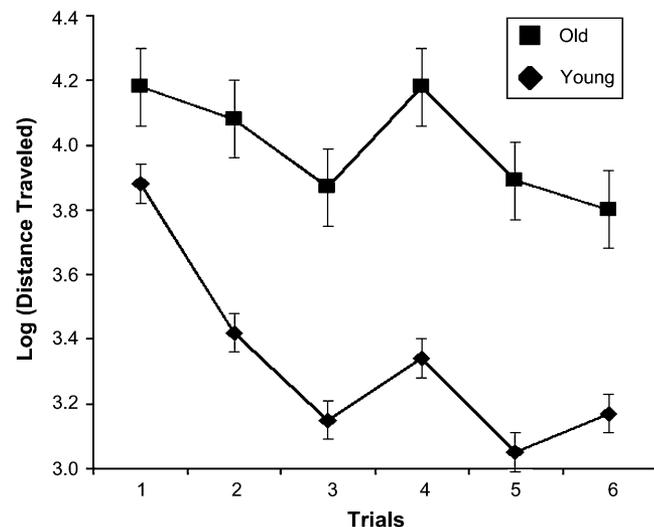


Figure 2. Total distance traveled in the vMWT as a function of age and trial. Performance improved across trials and older participants traversed a longer path in locating the hidden platform on all 6 trials.

The effects of hypertension on vMWT performance were investigated in the older participants. Within the older group, there was a trend for normotensive participants to perform better than hypertensive participants: $F_{1,32} = 3.94, P = 0.056, \eta^2 = 0.11$.

Virtual Water Maze: Probe Trial

In this analysis, the new dependent variable was the distance traveled in the quadrant of the pool that formerly contained the platform. The results indicated that younger (Mean = 52.50, SD = 22.16) individuals spent more of their distance searching in the goal quadrant than the older (Mean = 28.17, SD = 20.06) participants: main effect of age, $F_{1,64} = 6.49, P = 0.013$. Similarly, there was a trend for younger subjects (Mean = 2.94, SD = 1.56) to have more frequent platform intersections than their older (Mean = 1.97, SD = 1.34) counterparts: $F_{1,64} = 3.69, P = 0.059$. We observed neither a main effect of sex nor significant interactions.

Cognitive Tests

The descriptive statistics and the effect size indices (Cohen's d) for all cognitive tests by age group are presented in Table 3. The distribution of perseverative errors was skewed and was entered into the analysis after a logarithmic transformation.

The results of the analysis revealed a significant main effect of age ($F_{1,64} = 10.87, P < 0.01, \eta^2 = 0.15$) and no sex differences ($F_{1,64} = 1.56, NS, \eta^2 = 0.02$). However, the magnitude of age differences varied across the tested domains, as indicated by a significant age \times test interaction, $F_{7,448} = 15.35, P < 0.001$, with Hyunh-Feldt correction, $\eta^2 = 0.19$. Univariate analyses showed that the age differences (favoring the younger participants) were the smallest in the working memory domain ($F_{1,64} = 6.05, P < 0.05$ for computation span and $F_{1,64} = 9.49, P < 0.01$ for size judgment span) in comparison to the other domains: speed ($F_{1,64} = 33.64, P < 0.001$ for pattern comparison and $F_{1,64} = 32.92, P < 0.001$ for letter comparison); spatial memory ($F_{1,64} = 33.95, P < 0.001$ for spatial recall and $F_{1,64} = 20.64, P < 0.001$ for building memory); and perseveration: $F_{1,64} = 38.37, P < 0.001$. The effect of age on vocabulary was significant ($F_{1,64} = 23.70, P < 0.001$) but in the opposite direction (favoring the older participants).

Regional Brain Volumetry and Virtual MWT Performance

Because high correlations among the regional volumes would result in multicollinearity if all entered in the same model, we performed a separate analysis for each ROI. Before being entered into the equations, the volumes of all brain regions were adjusted for individual differences in ICV. In the interest of brevity, main effects of age and trial on vMWT performance that

Table 3

Descriptive statistics (mean \pm standard error of mean) and effect sizes (d) for cognitive test scores in the 2 age groups

	WCST ^a	Spatial	Vocab	Build	Size	CSPAN	Patcomp	Letcomp
Young	6.75 (0.64)	5.33 (0.10)	18.25 (1.14)	7.86 (0.52)	9.84 (0.31)	26.94 (3.07)	41.21 (1.26)	24.87 (0.72)
Old	19.23 (2.08)	4.22 (0.13)	26.52 (1.25)	4.26 (0.56)	8.50 (0.32)	18.06 (1.90)	32.19 (0.97)	18.26 (0.86)
Effect size (d)	1.31	1.41	-1.16	1.12	0.72	0.61	1.38	1.40
P value	<0.001	<0.001	<0.001	<0.001	0.004	0.014	<0.001	<0.001

Note: Wisconsin card sorting test (WCST) perseverative errors; spatial recall (Spatial); vocabulary (Vocab); buildings memory (Build.); size judgment (Size); computation span (CSPAN); pattern completion (Patcomp); letter completion (Letcomp). One older subject had missing data on Letcomp, making for that test the total $N = 67$.

^aScoring scale is reversed. Higher scores reflect poorer performance.

were reported above are not reported in these analyses. All zero-order correlations between ROI's and vMWT performance on each trial are presented in Table 4.

The inclusion of hippocampal volume as an independent variable revealed a complex pattern of differences in performance reflected in a significant interaction between age, trial, and HC volume: $F_{5,300} = 2.37$, $P = 0.04$, $\eta^2 = 0.04$, although the main effect of HC on vMWT performance was NS ($F_{1,60} = 1.18$, NS, $\eta^2 = 0.02$). Analysis of simple effects showed that the association between HC volume and maze performance was significant only among the younger participants and only on the first trial with young adults with larger HC accumulating shorter distances in their initial search for the virtual platform ($r = -0.38$, $P < 0.05$).

The analyses of the influence of other regional volumes revealed a less complex pattern of results. Larger volumes of prefrontal gray matter and PFW were linked to better vMWT performance: $F_{1,60} = 3.89$, $P = 0.05$, $\eta^2 = 0.06$ and $F_{1,60} = 7.28$, $P = 0.009$, $\eta^2 = 0.11$, respectively. A similar association between better vMWT performance and larger volumes was observed for the CN: $F_{1,60} = 11.07$, $P < 0.001$, $\eta^2 = 0.16$. A trend in the same direction was observed for the CB volume: $F_{1,60} = 2.89$, $P = 0.09$, $\eta^2 = 0.05$. Consistent with our hypothesis, VC, designated as a control region, showed no significant association with vMWT performance: main effect $F < 1$. In none of the models were there significant interactions between the regional volumes and age, sex, or trial.

In the models that included brain regional volumes, the effect of hypertension was significant only in conjunction with the caudate and HC volumes: $F_{1,31} = 7.43$, $P = 0.01$, $\eta^2 = 0.19$ and $F_{1,31} = 4.48$, $P < 0.05$, $\eta^2 = 0.13$, respectively. For all other ROI models, the trends for hypertension effect on performance were in the same direction but failed to reach the 0.05 level of significance. The probability levels of the trends ranged from $P = 0.056$ to $P = 0.20$, all NS.

Cognitive Test Performance and Virtual MWT Performance

All zero-order correlations between cognitive composites and vMWT performance on each trial are presented in Table 5. The analyses revealed that performance on executive function tests predicted vMWT performance: participants with better working memory ($F_{1,64} = 3.97$, $P = 0.05$) or fewer perseverative errors on WCST ($F_{1,64} = 7.98$, $P = 0.006$) attained higher vMWT scores. There were no significant interactions involving age, sex, or trial.

Better spatial memory was associated with better performance on vMWT as indicated by the significant main effect of spatial memory: $F_{1,64} = 17.68$, $P < 0.001$, $\eta^2 = 0.22$. A trend for trial by spatial memory interaction ($F_{5,320} = 2.17$, $P = 0.057$, $\eta^2 = 0.03$) suggested that spatial memory may be linked to performance on each trial except the first (see Table 5). A similar pattern of results was observed for perceptual speed: main effect $F_{1,63} = 7.15$, $P = 0.01$, $\eta^2 = 0.10$. Individuals who were faster on the perceptual speed tests performed better on the vMWT. Moreover, a significant interaction between perceptual speed and trial ($F_{5,315} = 2.52$, $P = 0.03$, $\eta^2 = 0.04$) indicated that perceptual speed was positively associated with performance on each trial but the first (see Table 5).

When vocabulary scores, intended as a measure of general crystallized abilities, were introduced into the model, we observed an unexpected significant main effect on vMWT

Table 4

Correlations between regional brain volumes and distance traveled on each trial of the vMWT

	Trial 1 ^a	Trial 2 ^a	Trial 3 ^a	Trial 4 ^a	Trial 5 ^a	Trial 6 ^a
LPFC	-0.28**	-0.47**	-0.43**	-0.40**	-0.40**	-0.37**
PFW	-0.25*	-0.40**	-0.41**	-0.31**	-0.23	-0.27*
HC	-0.17	-0.33**	-0.38**	-0.38**	-0.30**	-0.36**
CB	-0.10	-0.19	-0.34**	-0.34**	-0.31*	-0.27*
CN	-0.16	-0.43**	-0.39**	-0.50**	-0.47**	-0.46**
PVC	-0.11	-0.39**	-0.15	-0.10	0.03	-0.10

Note: Lateral prefrontal cortex white matter (PFW); Hippocampus (HC); Primary visual cortex (PVC). Correlations were essentially the same for right and left hemisphere volumes of each structure (data not shown).

^aScoring scale is reversed. Higher scores reflect poorer performance.

* $P < 0.05$; ** $P < 0.01$.

Table 5

Correlations between cognitive domains and distance traveled on each trial of the vMWT

	Trial 1 ^a	Trial 2 ^a	Trial 3 ^a	Trial 4 ^a	Trial 5 ^a	Trial 6 ^a
Working memory	0.00	-0.28*	-0.39**	-0.28*	-0.24*	-0.33**
Spatial memory	-0.11	-0.41**	-0.47**	-0.62**	-0.38**	-0.57**
Perseveration ^b	0.17	0.38**	0.42**	0.50**	0.34**	0.55**
Perceptual speed	-0.13	-0.46**	-0.48**	-0.52**	-0.25*	-0.53**
Vocabulary	0.09	0.16	0.12	0.33**	0.22	-0.09

^aScoring scale is reversed. Higher scores reflect poorer performance.

* $P < 0.05$, ** $P < 0.01$.

performance: $F_{1,64} = 5.77$, $P = 0.02$, $\eta^2 = 0.08$. Individuals with higher vocabulary scores performed more poorly on the vMWT. There were no significant interactions.

Discussion

The results of the present study replicate extant findings of age differences in spatial navigation (Moffat and others 2001; Moffat and Resnick 2002; Driscoll and others 2005) and contribute new evidence toward understanding of their neural substrates. We found that age effects on VE place learning are indeed substantial; older individuals traversed a longer linear distance in solving the learning trials of the vMWT. On a probe trial, a measure of retention of spatial location, younger individuals traveled a greater distance in the vicinity of the platform and had more frequent platform intersections relative to older subjects. These findings indicate that younger individuals learned and retained more accurate knowledge of platform location than their older counterparts. In search of neural correlates of the observed behavioral differences, we found that larger LPFC, PFW, and CN volumes were positively associated with navigational skill. However, individual differences in HC volume did not explain the age-related deficit in navigation performance. In addition, we found that success in spatial navigation was associated with superior executive skills, spatial memory, and speed of processing. Notably, the observed relationships between regional brain volumes, cognitive skills, and navigation performance were specific and dissociable from the control brain region (primary VC) and control cognitive variables (vocabulary).

In addition, our study replicated our earlier findings demonstrating that the age difference in vMWT performance emerges on the very first trial (see Figs 1 and 2) arguing against a strictly hippocampal/episodic memory explanation of the age difference. This behavioral difference may reflect planning, strategy selection or perseveration (i.e., persistence in searching of the

same region despite ample opportunity to determine that a particular pool location has been searched adequately), cognitive skills that are dependent on prefrontal executive resources. As well, it is important to note that within a trial, participants must remember preceding moves and locations and continually update this information to avoid returning to the same (incorrect) locations. Although clearly memory related, such within-trial immediate recall might best be characterized as requiring working memory, an age-sensitive ability (Salthouse and Meinz 1995) that has also been shown to be dependent on the prefrontal regions (Courtney and others 1998; Smith and Jonides 1999; D'Esposito and others 2000).

The most important evidence supporting our view that vMWT performance is influenced by frontal systems is the fact that both the gray and white matter volumes of the prefrontal cortex were positively associated with vMWT performance. In addition, 2 cognitive measures of executive/frontal function (the number of perseverative errors and working memory span) were both associated with performance on the vMWT. This strongly suggests that successful navigation in humans require substantial contribution from prefrontal circuits and associated cognitive systems. It should be noted that frontal lobe contributions to vMWT performance may not be restricted to the first trial but may extend across several trials, as evidenced by the significant correlations between frontal lobe volumes and vMWT performance across all 6 trials (see Table 4). However, it should also be acknowledged that our primary measure of frontal lobe executive resources (perseveration on the WCST) predicted performance on trials 2-6 but not trial 1 (see Table 5). Although this may be attributable to chance variation in a single study, it is also possible that other frontal lobe measures (or other cognitive domains) may better capture individual differences in trial 1 performance.

Studies in nonhuman species confirm important contributions from prefrontal systems in solving the MWT. The respective roles of the frontal cortex and hippocampal system have been delineated by adopting both the place and response versions of the MWT. In the former, the platform remains in the same position while the release site varies, thus requiring a place strategy for successful solution. In the latter, both the platform and release site vary from trial to trial with the spatial relationship between the release site and platform location held constant (e.g., a fixed distance to the right). Several studies have reported double dissociations with hippocampal and/or fimbria/fornix lesions impairing place learning in the place version of the MWT and frontal cortex lesions impairing response learning in the MWT (de Bruin and others 1997, 2001). It is noteworthy that we did not specifically assess response learning in our vMWT. However, as we outlined above, even in the place MWT, there are likely substantial executive demands required and at least one study observed impairments in the place version of the MWT following temporary inactivation of the orbital frontal cortex by tetrodotoxin (Vafaei and Rashidy-Pour 2004). Interestingly, consistent with the age differences observed in our study, this impairment was evident on the very first block of trials, suggesting that frontal dysfunction may impair MWT place learning early in the acquisition phase before there are significant mnemonic demands. Although separate tasks may be designed to investigate place and response strategies, respectively, animals (Packard and McGaugh 1996) and humans likely employ both strategies to some extent concurrently or successively across trials.

In addition to positive associations with frontal cortex measures, we also observed a positive correlation between CN volume and navigation performance. These findings are compatible with previous studies in humans and other mammals. The CN plays an important role in learning and spatial memory and is often activated in young subjects during virtual navigation tasks in functional imaging studies (Maguire and others 1998; Moffat and others 2006). Because of its extensive connections with the LPFC and HC (Alexander and others 1986), the CN is a part of distributed frontostriatal and striato-hippocampal systems, which are vulnerable to aging (Raz 2000; Raz 2003). Studies investigating contributions of the CN to human spatial navigation suggest that the CN may work in concert with hippocampal systems (Voermans and others 2004) and may play a role in nonspatial or procedural response components of spatial behavior (Hartley and others 2003; Iaria and others 2003). As the MRI methods used in this study were not geared to assessment of the integrity of corticocortical and cortico-subcortical connections, the intriguing question of the joint effects of multiple systems on navigation remains open.

Somewhat unexpectedly, we observed that hippocampal volume was associated with vMWT performance in the young but not in the elderly participants. The extant literature on HC memory relations in human aging consists primarily of studies that relied on verbal and visual memory tasks with positive associations between HC volume and episodic memory reported in some samples or specific groups of participants (Soininen and others 1994; Raz and others 1998; Jack and others 2000; Petersen and others 2000; but c.f. Van Petten 2004). A notable exception to that focus is a recent study that assessed the effects of age and HC volume and navigation performance in the framework of a virtual MWT similar to the one used in the current study (Driscoll and others 2003). In that investigation, HC volume was positively correlated with vMWT performance across all subjects. However, when these researchers incorporated age into their model as we did in this study, the relationship between HC volume and vMWT performance was reduced to nonsignificant. Thus, to our knowledge, the only studies to investigate the contributions of HC volume to age differences in navigation have produced similar results.

Although, the lack of a relationship between HC volume and vMWT performance in the elderly group should be interpreted with caution, a possible explanation for this finding may be found in the animal literature. It is known that animals have an initial preference for the use of a place strategy in the MWT (de Bruin and others 1997). Thus, when confronted with the response version of the MWT, animals first adopt a place strategy, which when unsuccessful is replaced by a response strategy. Importantly, Barnes has demonstrated that the preference for initial selection of a place strategy is age dependent with younger animals adopting a place (hippocampal) strategy, whereas older animals adopt a response (extrahippocampal) strategy. If a similar phenomenon is at work in humans, then it could be argued that our younger and elderly participants were adopting different solution strategies that were differentially dependent on the HC with younger participants adopting a place (hippocampal) strategy and older participants adopting a reference (extrahippocampal strategy), resulting in positive and null associations with hippocampal structure, respectively. Conceivably, after a reference strategy proved unsuccessful, elderly participants may switch to a place strategy. However, the number of trials employed in the present study was not

sufficient to test this hypothesis. In the future, the design of distinct place and response versions of the vMWT incorporating more learning trials may help to address this question.

It is also important to note that we assessed only the volume of the HC and not other important neurochemical and/or functional measures of HC integrity. An alternative conceptualization is that a variety of “functional” changes in the HC that were not reflected in our volume measurement may play a more important role in cognitive aging (Driscoll and others 2003; Grady and others 2003; Moffat and others 2006).

In the framework of a cross-sectional study, it is impossible to discern the influence of longstanding individual differences in brain and cognitive variables from true longitudinal declines. It is possible that smaller frontal and striatal volumes that predict poorer performance in the young and the elderly alike do so for age-specific reasons. For the younger participants, the frontal executive links may reflect developmental or even inborn differences in the size of the prefrontal cortex and white matter. In the older subgroup, better performance may be due to preservation of these age-vulnerable regions.

One of the factors that could have affected performance and the relationships between brain variables and navigation is hypertension, a commonly acknowledged negative modifier of age trajectories (Breteler and others 1994; Raz and Rodrigue 2006). An interesting trend was observed for the influence of hypertension on brain and cognitive performance. The diagnosis of hypertension is usually acquired in older age, and the current sample of older adults was relatively small to allow a powerful test of that hypothesis. However, our results indicated that hypertensive participants tended to show poorer navigation skills than their normotensive counterparts. Thus, hypertension and possibly other vascular risk factors need to be taken into account in future evaluation of age differences in cognitive performance.

In summary, the present study confirms robust age-related deficits in navigational skill. It indicates that successful navigation does not depend solely on the HC but is also associated with larger regional volumes of multiple cortical and subcortical structures and draws on age-sensitive executive abilities as well as task-specific spatial memory resources.

Notes

Conflict of Interest. None declared.

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