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Age differences in the neural systems supporting human allocentric spatial navigation

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Abstract

Age-related declines in spatial navigation are well-known in human and non-human species. Studies in non-human species suggest that alteration in hippocampal and other neural circuitry may underlie behavioral deficits associated with aging but little is known about the neural mechanisms of human age-related decline in spatial navigation. The purpose of the present study was to examine age differences in functional brain activation during virtual environment navigation. Voxel-based analysis of activation patterns in young subjects identified activation in the hippocampus and parahippocampal gyrus, retrosplenial cortex, right and left lateral parietal cortex, medial parietal lobe and cerebellum. In comparison to younger subjects, elderly participants showed reduced activation in the hippocampus and parahippocampal gyrus, medial parietal lobe and retrosplenial cortex. Relative to younger participants elderly subjects showed increased activation in anterior cingulate gyrus and medial frontal lobe. These results provide evidence of age specific neural networks supporting spatial navigation and identify a putative neural substrate for age-related differences in spatial memory and navigational skill.

Keywords: Cognitive aging; Navigation; Spatial memory; Human; fMRI; Alzheimer's disease; Hippocampus; Parahippocampal gyrus; Retro-splenial cortex

1. Introduction

Spatial navigation ability is crucially important for everyday functioning in a complex environment, yet its role in the difficulties experienced by older adults is grossly underestimated. Survey research indicates that elderly individuals have self-perceived deficits in navigation and develop behavioral patterns to avoid unfamiliar routes and places [5]. Furthermore, clinically-relevant impairments in navigational skills ("getting lost" and "wandering") are often apparent in the early stages of Alzheimer's disease. In many cases, reports of impaired spatial behavior, e.g. getting lost in familiar places, lead to the recognition of cognitive impairment and diagnosis of dementia [18].

In a series of studies, we have utilized virtual reality (VR) to study age differences in spatial navigation [21,22]. These studies demonstrate that elderly subjects commit more spatial memory errors in solving a virtual route learning task than their younger counterparts [22]. In a VR replication of the Morris Water Task [23], a task used extensively to study cognitive aging in non-human species, elderly subjects traveled a longer distance in locating the goal, spent less time searching the vicinity of the goal and were impaired in constructing a cognitive map of the environment. [21].

The cognitive and neural mechanisms underlying these age differences in humans remain unclear. Neuroimaging findings in young individuals and lesion studies have identified a network of structures that are involved in human navigation, including the hippocampus, parahippocampal gyrus, cerebellum, parietal cortex, and retrosplenial cortex [1,4,13,16,20]. Much of our knowledge of the neural substrates of navigation comes from studies of non-human species. Researchers examining spatial behavior in non-human species theorize that the hippocampus and related structures generate representations of an animal's position

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in space and continually update this position via the firing of networks of cells responsive to spatial location [9,24], head direction [8], optic flow [30] and other spatial and movement sensitive parameters.

It is likely that age-related alterations in hippocampal and other neural circuitry may manifest as deficiencies in spatial processing, consequently impairing spatial navigational skills. Place cells in the rodent hippocampus [19] change their response characteristics with age. These, and other cellular and extracellular modifications, may contribute to the well-characterized spatial deficits observed in aged mammals [2,3,27,28]. It is noteworthy that the medial temporal region, including the hippocampus, atrophies with human aging and is one of the first regions affected in Alzheimer's disease [15,29] suggesting a possible role for this region in mediating the age-related reduction in human spatial competence.

Although there is strong biological evidence supporting age-related alterations in the neural circuitry supporting spatial navigation, this has not been demonstrated in humans. In the present study, we tested the hypothesis that human aging is associated with alterations in the neural circuitry supporting allocentric navigation.

2. Methods

2.1. Participants

The sample included 51 individuals (30 young, 21 old) recruited from newspaper advertisements in the metropolitan Baltimore, MD area. To minimize the effects of age differences in health that could potentially influence the fMRI hemodynamic response, we excluded participants reporting histories of coronary artery disease, cerebrovascular disease, hyper/hypotension, liver, kidney or lung disease, thyroid disease, cancer, alcoholism, and neurological and psychiatric illness. No participants were taking medications that affect cognitive performance or cerebral blood flow. Mean age of the young participants was 27 years (range 21–39), and mean age of the elderly participants was 69 years (range 60–78).

2.2. Procedures

Prior to scanning, extensive pre-training 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. Participants were administered a complete practice run of the fMRI scanning task outside of the scanner to ensure that they were familiar with the tasks required of them during scanning. The VE used during practice training was of a different layout and configuration than the one used for scanning.

2.2.1. Experimental and control tasks

Employing functional MRI, we compared brain activation between healthy young and elderly volunteers (Table 1) during the encoding of a virtual environment. Younger and older volunteers were confronted with a virtual environment consisting of several rooms and interconnecting hallways (Fig. 1). Located throughout the environment were six common objects. Participants were instructed to move through the environment using an MR-compatible joystick (Medical College of Wisconsin) and to learn the locations of all the objects and how all the hallways interconnected with one another. Participants were instructed to learn the environment so that they could construct an accurate map following scanning. Participants also underwent a recall testing phase in which they were directed to locate a designated object by the shortest of several possible routes. Subjects were aware of both the upcoming mapping and directional tests. These procedures were adopted to encourage allocentric encoding of the environment. The control task consisted of following along a designated path through a VE that was visually similar to the navigation environment. The path was designated by a series of floor markers, over which the participant had to travel. This task required focused attention, the same joystick movements, visual stimulation, optic flow and other motion sensations as the navigation task but did not require learning of routes and object locations. The control and experimental tasks alternated every 60 s for a total of 600 s.

Table 1
Sample characteristics and behavioral performance

	Younger adults	Older adults
N	30	21
Sex (#male)	15	10
Mean age (S.D.)	27.07 (5.46)	68.43 (5.56)[a]
Speed (S.D.) (virtual units/s)	30.00 (3.08)	24.76 (3.89)[a]
Mean number errors (S.D.)	1.17 (1.97)	3.80 (2.84)[a]

[a] Comparison between older and younger adults significant at $p < 0.01$.

2.2.2. Image acquisition and statistical analysis

Images were acquired on a 1.5 Tesla Phillips Gyroscan NT Intera parallel to the plane containing the anterior and posterior commissures. Following high resolution anatomical images, functional images were obtained using echo-planar imaging (TR = 3000 ms; TE = 30 ms; field of view = 64 × 64; voxel size mm = 3.75 mm × 3.75 mm × 5.5 mm). The first eight preliminary volumes of a session were discarded to achieve equilibrium. Statistical analysis was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 5 on a Silicon Graphics workstation. A standard fMRI block design was used in which navigation and control conditions alternated every 60 s for a total of 600 s. All images were motion corrected by realigning to the first image of each subject. All images were spatially normalized to the standard template provided in SPM99 which is based on the reference brain provided by the Montreal Neurological Institute. Volumes were smoothed using an 8 mm full width half maximum height Gaussian filter.

For primary (first level) analysis, each imaging run was analyzed using a box car function convolved with the

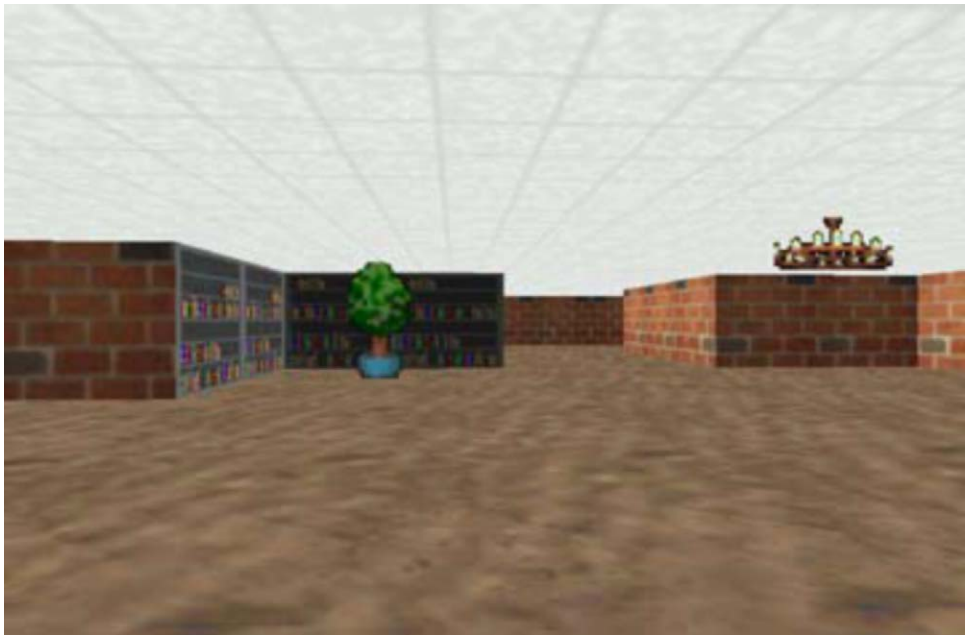

Fig. 1. Typical view from within the virtual environment. Participants viewed the environment from a first person perspective and guided their movements with the use of an MRI-compatible joystick. Participants were instructed to learn the layout of the environment including all object locations and interconnecting routes. To ensure that subjects were learning the environment, they were informed of an upcoming memory test. In addition, to encourage allocentric encoding of the environment subjects were advised that they would be required to reconstruct an overhead map of the environment upon completion of the learning trials.

hemodynamic response function. Contrast images producing t-statistics for each voxel were calculated for each subject based on the primary analysis. Voxels were thresholded at $p < 0.01$, corrected for multiple comparisons. These contrast images were then incorporated into second level group comparisons using a random effects model. To ensure replication of previous findings in young participants, the young subgroup was examined using a one-sample *t*-test comparing the navigation and control conditions (Table 1 and Fig. 1). For comparisons between old and young groups, analysis of covariance was performed with age group as a grouping variable and distance traveled and speed used as covariates in the model. These covariates were incorporated to control for behavioral differences in performance between old and young participants. For all random effects analyses, height threshold was set at $p < 0.01$, with an extent threshold set at 270 voxels ($p < 0.05$).

3. Results

3.1. Brain activation in young and elderly subjects

Several studies have been reported that investigated brain activation during allocentric navigation in young subjects. To ensure that our task replicated previous findings, we examined brain activation patterns in our younger participants. Our analysis replicates and extends previous findings. We observed highly significant clusters of activation in the right hippocampus, parahippocampal gyrus bilaterally (BA 30), cuneus (BA 19) and precuneus (BA 7), bilateral parietal lobe and the retrosplenial cortex (BA 30) of the posterior cingulate gyrus (Table 2 and Fig. 2). These posterior and medial temporal networks replicate previous studies and constitute what has been characterized as a human navigational network

Table 2
Activations in younger adults

Region	Side	BA	*X*	*Y*	*Z*	*T*-value
Cuneus	R	19	36	−76	36	12.09
Precuneus	L	7	10	−74	44	11.73
	R		−8	−76	40	10.10
Cuneus	L	19	−32	−90	22	10.21
Occipital gyrus	L	19	−28	−80	24	9.36
Superior occipital gyrus	L	19	−28	−74	32	9.16
Cerebellum	L		−28	−44	−18	8.81
	R		20	−32	−26	6.64
Medial frontal gyrus	R	6	4	18	48	8.32
	L	6	−6	12	50	8.23
Inferior parietal lobule	L	40	−36	−64	40	8.15
Retrosplenial cortex	L	30	14	−54	8	8.11
	R		6	−44	16	5.86
Superior frontal gyrus	R	8	26	24	50	6.97
	L	6	−28	−2	60	6.71
Middle occipital gyrus	R	19	28	−76	14	7.65
	L	19	−32	−92	8	6.17
Parahippocampal gyrus	R	30	10	−40	0	6.14
	L	30	−20	−36	−6	3.49
Inferior occipital gyrus	R	18	34	−84	−4	5.88
Lingual gyrus	L	19	−10	−52	2	5.47
Hippocampus	R		20	−32	−4	4.71
Fornix	R		20	−32	10	4.44
Fusiform gyrus	L	18	−26	−84	−16	4.13
Subthalamic nucleus	L		−22	−34	12	3.85

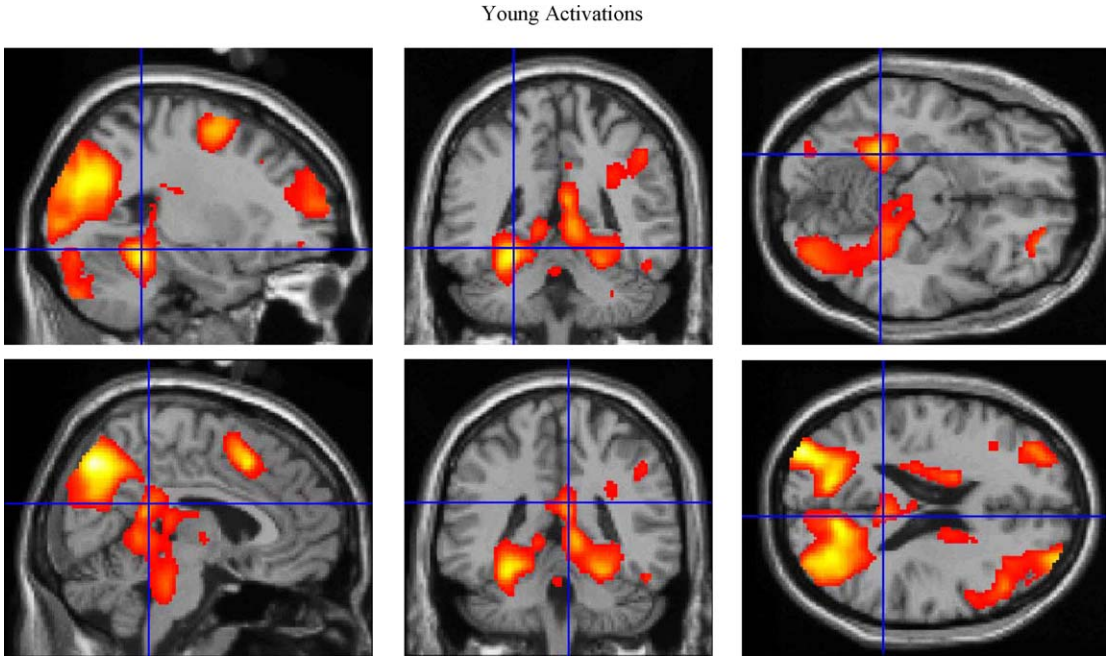

Fig. 2. Activations in young subjects during navigation compared to control condition. Activation images are superimposed on a single subject T1-weighted MRI in the sagittal, coronal and axial planes displayed in standardized space. These images show activation in the posterior parahippocampal gyrus, retrosplenial cortex, cerebellum, pre-frontal cortex, precuneus and widespread regions of the parietal lobe.

[20]. In addition to these posterior networks, our task also activated the middlle (BA 6) and superior frontal gyrus (BA 8, 6). This additional frontal activation is likely attributable to the fact that we employed an encoding task which allowed free movement of participants through the environment, was self-directed, and required planning, decision making, and response inhibition (Table 3).

Table 3
Activations in older adults

Region	Side	BA	*X*	*Y*	*Z*	*T*-value
Middle frontal gyrus	R	8	32	20	52	6.98
	L	8	−44	16	50	3.56
Superior frontal gyrus	R	6	28	10	58	6.40
	L	8	−30	24	52	5.04
Superior occipital gyrus	R	19	36	−72	32	6.13
	L	19	−26	−72	32	3.95
Precuneus	R	19	26	−82	42	5.39
	L	19	−2	−70	42	5.00
Occipital gyrus	R	19	28	−88	28	5.32
	L	19	−32	−86	24	5.96
Middle frontal gyrus	R	10	32	54	6	6.01
	L	10	−34	56	14	4.47
Middle frontal gyrus	R	46	38	38	18	5.07
Middle frontal gyrus	R	9	42	38	32	4.54
	L	9	−38	12	36	5.05
Inferior frontal gyrus	L	44	−40	14	26	3.90
	R	47	34	24	−8	5.00
Cerebellum	R		26	−30	−32	4.90
Cingulate gyrus	L	31	−16	−66	14	4.21
	R	31	14	−66	12	4.18
Inferior frontal gyrus	R	46	50	40	18	3.71

To analyze age-related differences in the neural networks that support human navigation, we conducted second level analyses contrasting activation between older and younger participants. Because younger and older participants differed in certain aspects of performance (see Table 1), we performed regression analysis both with and without covariates (speed of movement and distance traveled). These analyses produced similar results and thus we report only the more conservative analysis including covariates to control for behavioral differences between the young and older groups. Comparisons between younger and older individuals revealed an age-related shift in the neural systems supporting human navigation (Table 4 and Fig. 3). In particular, compared to their younger counterparts, older subjects showed reduced activation in the posterior hippocampus and posterior parahippocampal gyrus (BA 30) and reduced activity in the retrosplenial cortex (BA 30) of the posterior cingulate gyrus as well as reduced activation in circumscribed regions of the medial and lateral parietal lobe. In contrast, older participants showed increased activation in the frontal cortex, particularly in the medial frontal gyrus (BA 10) and the anterior cingulate gyrus (BA 32) (Table 4 and Fig. 3).

3.2. Relationship of brain activation to behavior

Additional analyses were performed to examine the influence of age differences in performance on neuroimaging outcomes. To assess the relationship between brain activation and navigational accuracy, regressions were performed between performance on the subsequent virtual environment

Table 4
Between group comparisons

Region	Side	BA	*X*	*Y*	*Z*	*T*-value
Young > Old						
Retrosplenial cortex	R	29	6	−42	18	4.21
Insula	R		30	−18	14	3.93
Parahippocampal gyrus	R	36	32	−42	−6	3.81
Inferior parietal lobule	R	40	42	−44	36	3.64
Angular gyrus	R	19	42	−78	36	3.55
Superior occipital gyrus	R	19	30	−72	30	3.35
Middle temporal gyrus	R	39	48	−80	14	3.24
Lingual gyrus?	R	18	8	−50	4	3.19
Thalamus-anterior nucleus	R		16	−6	14	3.13
Ventral posterolateral nucleus			18	−18	4	3.12
Putamen			18	−28	4	3.42
Hippocampus	R		34	−20	−12	2.98
cuneus	R	31	20	−66	14	2.89
	L	19	−30	−88	24	4.03
Precuneus	R	7	14	−64	58	4.91
	L	7	−10	−72	44	3.64
Fusiform gyrus	L	37	−28	−42	−14	4.45
Lingual gyrus	R	18	20	−58	4	3.09
	L	19	−26	−72	−4	3.52
Old > Young						
Medial frontal gyrus	R	10	2	56	6	4.03
	R	10	2	54	22	3.99
Anterior cingulate gyrus	L	32	−6	54	0	2.75

memory test and brain activation patterns. Height threshold was set at $p < 0.01$ for all correlational analsyses. When considering all subjects, higher navigational accuracy was associated with increased activation in the posterior parahippocampal gyrus, retrosplenial cortex and precuneus (see Fig. 4), consistent with the presence of age differences in accuracy and activation patterns. In addition, we performed regression analyses between navigational accuracy and brain activation within young and old groups, separately. Among the elderly participants, accurate navigation was associated with increased activation in the parahippocampal gyrus, cuneus, inferior occipital gyrus, fusiform gyrus and

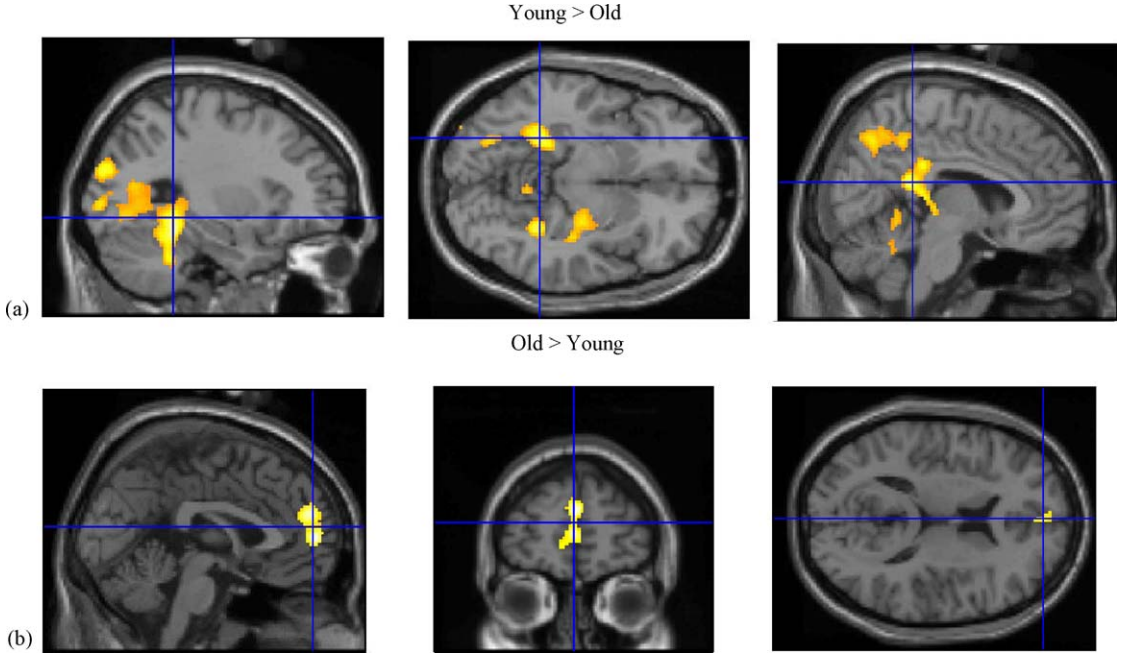

Fig. 3. Results from group comparisons of young and old subjects during navigation compared to control condition. Activation images are superimposed on a single subject T1-weighted MRI in the sagittal, coronal and axial planes displayed in standardized space. (a) Activations which were greater in younger compared to older individuals included the posterior hippocampus, posterior parahippocampal gyrus, retro-splenial cortex, medial inferior parietal lobe and cerebellum. (b) Activations which were greater in older compared to younger participants included the anterior cingulate gyrus and medial frontal gyrus.

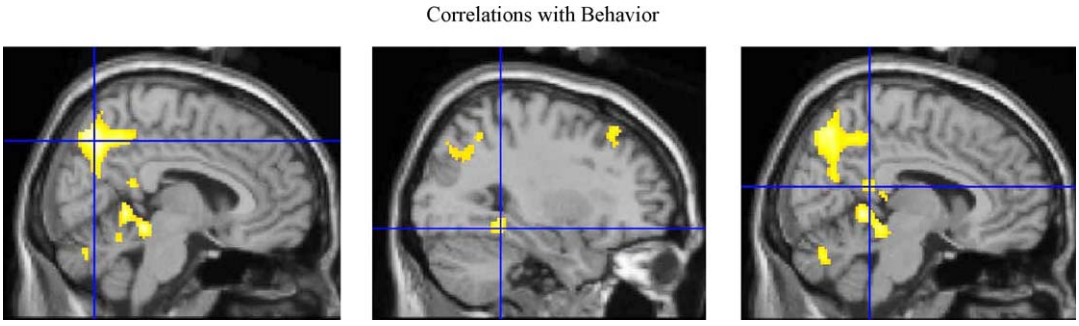

Fig. 4. Results from regression analysis correlating navigational accuracy and brain activation patterns in all participants. Higher navigational accuracy was associated with increased activation in the medial parietal lobe (left panel), the posterior parahippocampal gyrus (middle panel) and retrosplenial cortex (right panel).

inferior temporal gyrus (See Table 5). Among younger subjects, increased navigational accuracy was associated with increased activation in the superior frontal gyrus, parahippocampal gyrus and several other structures (See Table 5).

4. Discussion

The results of this study demonstrate substantial age-related alteration in the neural networks supporting

Table 5
Positive correlations with navigational accuracy

Region	Side	BA	*X*	*Y*	*Z*	*T*-value
All participants						
Precuneus	R	7	2	−66	42	4.25
	L	7	−10	−72	44	3.97
Cerebellum	R		18	−66	−36	3.77
	L		−18	−42	−14	2.96
Inferior frontal gyrus	L	47	−26	36	−2	3.41
Parahippocampal gyrus	R	37	30	−44	−10	3.30
Retrosplenial cortex	R	29	8	−42	18	3.14
	L	30	−8	−42	16	2.56
Cuneus	L	19	−26	−86	24	3.06
Fusiform gyrus	L	20	−30	−40	−18	3.06
Middle temporal gyrus	R	21	42	−4	−18	2.95
Inferior frontal gyrus	L	45	−52	40	6	2.94
Cingulate gyrus	L	35	−12	18	−10	2.89
Middle frontal gyrus	L	47	−36	44	−12	2.87
Middle occipital gyrus	L	18	−24	−84	4	2.87
Superior parietal lobule	R	7	34	−58	50	2.81
Young participants						
Superior frontal gyrus	L	11	−24	44	−14	3.93
	R	8	28	36	44	2.75
Superior temporal gyrus	R	22	60	−46	20	3.88
Cingulate gyrus	L	32	−10	44	0	3.00
Inferior frontal gyrus	L	46	−42	28	12	2.78
Precuneus	R	31	14	−64	20	2.71
	L	7	−4	−50	46	2.69
Middle temporal gyrus	R	21	40	−2	−28	2.69
Inferior temporal gyrus	L	37	−60	−44	−12	2.68
	R	20	56	4	−30	2.62
Cuneus	L	19	−14	−94	34	2.64
Parahippocampal gyrus	L	30	−6	−46	4	2.51
Old participants						
Parahippocampal gyrus	R	37	22	−26	−20	3.45
Cuneus	R	19	26	−88	36	3.16
Inferior occipital gyrus	R	17	20	−102	−8	2.97
Fusiform gyrus	R	18	24	−98	−14	2.76
Inferior temporal gyrus	R	21	64	−14	−16	2.81
Middle frontal gyrus	L	46	−52	36	18	2.66

allocentric navigation in humans. Compared to their younger counterparts, elderly adults showed reduced activation in the posterior hippocampus, parahippocampal gyrus, retrosplenial cortex and regions of the parietal lobe. Elderly subjects also showed greater frontal lobe activation during encoding than younger subjects. Age-related declines in navigational skills are well-documented in humans, as well as other species [3,17,21,22,28]. Reduced activation in elderly individuals in some of the same neural systems that support navigation in the young suggests that neural changes in these cortical regions may, in part, underlie the age-related behavioral impairments. This perspective is supported by our analyses showing that increased navigational accuracy is associated with increased activation in these same neural regions (see Fig. 4).

Of particular importance in the present study is the observation of reduced activation in the elderly in the hippocampal-parahippocampal complex and in the retrosplenial cortex of the posterior cingulate. These areas play a critical role in spatial navigation in both human and non-human species [2,3,27,28]. In particular the hippocampal/parahippocampal area has been hypothesized to act as a cognitive map [24], receiving egocentric and motion derived information from other cortical regions and converting this input into an allocentric representation of the environment. Our own work indicates that elderly subjects may show specific impairments in generating allocentric representations of their environment and that this deficit impacts their navigational competence [21]. As previously noted, several studies in non-human species have demonstrated substantial age-related changes in the properties of hippocampal place cells, suggesting a possible biologic basis for spatial learning deficits in older animals. This observation, combined with the recent demonstration of hippocampal place cells in humans [10], suggests that age-related changes in the cellular properties of the hippocampus/parahippocampal complex may play a role in age-related declines in navigational skill. Furthermore, both mesial temporal structures and the posterior cingulate region show early changes in Alzheimer's disease [31–34,36], and reduced temporal and posterior cingulate metabolism are associated with the Apolipoprotein E epsilon 4 risk factor for AD [35,37]. The fact that spatial navigation is dependent on these neural systems suggests that it may be a useful model for understanding wayfinding difficulties in AD and perhaps as a probe for establishing early risk for AD.

Our results are consistent with other studies that have shown reduced activation of posterior and medial temporal regions in older individuals during episodic memory tasks [7,11,14]. Although our experimental task clearly differs in important ways from other measures of memory, it does contain an explicit encoding dimension that may also involve neural circuitry similar to other encoding tasks. It is also important to note that older participants showed increased activation of some frontal systems, most notably in the anterior cingulate gyrus and medial frontal cortex. Our results are very similar to those of Gutchess et al. (2005), who observed that human aging was associated with both reduced medial temporal/parahippocampal activation and increased frontal lobe activation in a visual memory task. These findings may be attributed to a compensatory shift in memory performance away from medial temporal structures to frontal systems [12,14]. Similarly, one interpretation of our findings is that aging is associated a compensatory shift from more posterior and medial temporal systems supporting navigation to more anterior frontal systems.

Rather than a compensatory shift, it could also be argued that the age-differences reported here resulted from performance differences between groups rather than age-related alterations in neural networks per se. Older individuals moved more slowly through the environment and made more errors in a subsequent recall test. Increases in task difficulty have been associated with anterior cingulate activation [6,25]. If the task was more demanding or required increased error monitoring among the elderly, these factors could have contributed to increased activation of the anterior cingulate cortex. However, our primary analyses took these residual behavioral differences into account through analysis of covariance to examine age differences in neural activation after controlling statistically for behavioral age differences. The fact that there were robust activation differences between our old and young participants even after controlling for behavioral differences (see Fig. 3 and Table 4) argues against a strictly behavioral interpretation of our findings. Our secondary analyses indicated that increased activity in the parahippocampal gyrus and other structures may be associated with increased navigational accuracy among both young and older subjects.

However, measures of speed and accuracy may not fully account for other relevant behavioral factors. For example, previous behavioral studies indicate that older subjects may have altered navigational strategies including a shifted preference for the use of proximal landmarks as cues during navigation to the exclusion of more distal information [21]. Interestingly, hippocampal lesions in rats results in impaired use of distal but not proximal landmarks [26], raising the possibility that age differences in human hippocampal function may underlie the age-related shifts in cue-use strategies. We did not assess strategic differences between older and younger volunteers and cannot exclude the possibility that more subtle behavioral differences contribute to our findings. However, if older subjects do show some age-related shifting of cue use strategies (and concomitant neural activations), it is important to determine whether these alterations are adaptive and compensatory or sub-optimal strategies that result in reduced performance.

The outcome of the present study is important for several reasons. Firstly, our study elucidates age related shifts in the neural mechanisms of an important aspect of human behavior. The neural systems activated by spatial navigation are widespread and constitute some of the neural systems showing the earliest changes in both normal aging and in the neuropathology of Alzheimer's disease. The assessment of

spatial navigation in elderly at-risk populations may serve as a basis for early prediction of disease and may be a useful measure for assessment of outcomes of pharmacologic and/or behavioral intervention studies for cognitive impairment. Moreover, much of what we know about the neuroscience of cognitive aging comes from the use of animal models where behavioral assessments typically include measures of spatial navigation. Incorporation of navigational models into the evaluation of human cognitive aging provides a sound behavioral and neurological foundation to facilitate comparative research and ultimately aid in the development of advanced cross-species models of cognitive aging and cognitive impairment.

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