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Decreased Functional Magnetic Resonance Imaging Activity in the Hippocampus in favor of the Caudate Nucleus in Older Adults Tested in a Virtual Navigation Task

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ABSTRACT: The neuroimaging literature has shown consistent decreases in functional magnetic resonance imaging (fMRI) activity in the hippocampus of healthy older adults engaged in a navigation task. However, navigation in a virtual maze relies on spatial or response strategies known to depend on the hippocampus and caudate nucleus, respectively. Therefore, since the proportion of people using spatial strategies decreases with normal aging, we hypothesized that it was responsible for the observed decreases in fMRI activity in the hippocampus reported in the literature. The aim of this study was to examine the effects of aging on the hippocampus and caudate nucleus during navigation while taking into account individual navigational strategies. Young ($N = 23$) and older adults ($N = 29$) were tested using fMRI on the Concurrent Spatial Discrimination Learning Task, a radial task that dissociates between spatial and response strategies (in Stage 2) after participants reached criteria (in Stage 1). Success on Stage 2 requires that participants have encoded the spatial relationship between the target object and environmental landmarks, that is, the spatial strategy. While older adults required more trials, all participants reached criterion. fMRI results showed that, as a group, young adults had significant activity in the hippocampus as opposed to older adults who instead had significant activity in the caudate nucleus. Importantly, individual differences showed that the older participants who used a spatial strategy to solve the task had significant activity in the hippocampus. These findings suggest that the aging process involves a shift from using the hippocampus toward the caudate nucleus during navigation but that activity in the hippocampus is sustained in a subset of healthy older adults engaged in spatial strategies. © **2013 Wiley Periodicals, Inc.**

KEY WORDS: aging; radial maze; striatum; spatial memory; response learning

INTRODUCTION

The study of the effects of aging on different memory systems (Park et al., 1996) has important implications for the understanding of many neurodegenerative disorders such as Alzheimer's disease (Rusinek et al., 2003). Several studies have reported that spatial memory is affected by the aging process (Moffat et al., 2006, Antonova et al., 2009, Moffat, 2009) and is one of the first forms of memory to be affected by dementia (Klein et al., 1999; deIpolyi et al., 2007; Hort et al., 2007; Iachini et al., 2009).

Two separate strategies can be used to navigate within an environment (Packard et al., 1989; Packard and McGaugh, 1996; Iaria et al., 2003; Voermans et al., 2004). The "spatial" strategy is mediated by the hippocampus and involves the formation of relationships between different items (Davachi and Wagner, 2002; Naveh-Benjamin, 2000) or landmarks in the environment (O'Keefe and Nadel, 1978; Morris et al., 1982; Abrahams et al., 1997; Bohbot et al., 1998; Maguire et al., 2000; Naveh-Benjamin, 2000). Knowledge of these relationships is characterized with flexibility (O'Keefe and Nadel, 1978) in that it allows one to derive a direct path to a novel destination when navigating in a town. In contrast, the "response" strategy is mediated by the caudate nucleus which is also critically involved in habit formation and implicit learning (Packard et al., 1989; White and McDonald, 2002). The response strategy involves learning a series of stimulus-response associations such as a pattern of left and right turns from a given starting position. Unlike the spatial strategy, the response strategy is inflexible (O'Keefe and Nadel, 1978; White and McDonald, 2002) in that it does not allow deriving a direct path to a novel target location.

The deleterious effects of aging on spatial memory in favor of response strategies have been shown in both animals and humans (Marighetto et al., 1999; Driscoll et al., 2003; Wood and Dudchenko, 2003; Meulenbroek et al., 2004; Moffat et al., 2007; Iaria et al., 2009; Head and Isom, 2010). One study by Barnes et al. (1980) compared navigation strategies used by young and old rats in a T-maze. The study showed that older rats employed a response strategy to a greater extent than young rats. This finding was replicated in humans, showing that older adults predominantly use a caudate nucleus-dependent response strategy (Etchamendy et al., 2012). Furthermore, with

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a different task, the same group of researchers showed a decrease in spatial strategies across the life span (Bohbot et al., 2012). Neuroimaging research with older adults has also shown decreased activity in the hippocampus in a spatial task (Moffat et al., 2006; Antonova et al., 2009). However, it was unclear in these studies whether older adults shifted strategies and used another neural system that resulted in decreased hippocampal activation. The aim of this study was to examine the effects of aging on the hippocampus and caudate nucleus during navigation while taking into account individual navigational strategies. Thus, in the current study, we hypothesized that spatial memory impairments and decreased activity in the hippocampus observed in healthy older adults are associated with a shift toward using a caudate nucleus-based neural system to navigate. This will be in contrast to young adults who we expect to show greater functional magnetic resonance imaging (fMRI) activity in the hippocampus compared to the caudate nucleus. In addition, we expect that healthy older participants using a spatial strategy will show fMRI activity in the hippocampus.

METHODS

Subjects

Twenty-three healthy young adults (mean age = 23.8 ± 3.8; 14 women and 9 men) and 29 healthy older adult participants (mean age = 64.2 ± 4.7; 14 women and 15 men) participated in the study. All participants were right handed and had normal vision. None of the participants had any history of neurological or psychiatric illnesses, alcohol, or drug abuse assessed by a prescreening questionnaire. In addition, participants were screened for confounding factors that would affect cerebral blood flow during fMRI such as cardiovascular diseases, cholesterol, and diabetes. Older participants underwent neuropsychological assessment to control for dementia, depression, and mild cognitive impairment (Table 1). Young adult fMRI data were published elsewhere (Etchamendy et al., 2012). Informed consent was obtained from all participants in accordance to the guidelines of the local ethics committee. The study was approved by the institutional review boards at McGill University, the Douglas Mental Health University Institute, and the Montreal Neurological Institute.

TABLE 1.

Older Adult Participant Demographics and Test Means [SEM]

	Spatial	Response	p-value
Participant characteristrics			
N	14	15	
Women:Men	7:7	8:7	
Age (years)	62.9 ± 3.9	65.4 ± 5.12	p>0.05
IQ	113.5 ± 12.2	112.14 ± 13.5	p>0.05
Education	16 ± 2.04	16.2 ± 1.9	p>0.05
Handedness	Right	Right	
Neurop sychological test scores			
MMSE	29.4 ± 0.65	29.6 ± 0.65	p>0.05
MoCA	27.6 ± 1.7	27.1 ± 1.8	p>0.05

Training

Before the fMRI, both young and older adult participants were trained in a practice virtual environment both outside and inside the scanner. To navigate, they were given a four-key button-box, but were only asked to use the forward, left, and right keys. The practice virtual environment was a radial arm maze to ensure that all participants were equally comfortable with the procedural aspect of navigating.

Older adults underwent a mock scanner several days before the fMRI scan. The mock scan was given to the older adults to decrease dropout rates due to motion artifacts, failure to navigate using the keypad while lying in the scanner, and to ensure that they could be comfortable lying on their backs for a long period of time during the real scan. While in the mock scanner, participants performed a virtual radial maze task that took place in a completely different virtual environment with different task instructions from the one used in the fMRI scan. As the instructions and environment were different, information learned during the mock scan could not be used in the fMRI scan. In this task, participants were placed in a completely novel virtual environment and were presented with a single arm at a given time. Participants had to memorize whether each arm contained an object or not. These trials were interspersed with visuo-motor control trials in order to mimic the sequence of events presented during the fMRI scan. This mock scan was not given to the young adults as the dropout rates related to the aforementioned reasons were null in prior studies. A comparison of the scores obtained from older adults tested on the fMRI task, the Concurrent Spatial Discrimination Learning Task (CSDLT), with and without the mock training session indicated that the mock training did not affect performance on any of the measures. Scores obtained on all stages of the fMRI portion of the study were similar to those obtained by Etchamendy et al. (2012) where participants performed the task outside the scanner without a mock scan (With mock: Mean TTC = 9.2, Without mock: Mean TTC = 9.95, $t = 0.791$, $P = 0.$).

Functional Magnetic Resonance Imaging Experiment: Concurrent Spatial Discrimination Learning Task

All 23 young adults and 29 older adults participated in the fMRI portion of the experiment. The CSDLT was created using the editor program of a commercially available computer game (Unreal Tournament 2003; Epic Games, Raleigh, NC). The task was adapted from a two-stage mouse model radial maze involving concurrent spatial discrimination learning aimed at assessing memory flexibility in mice (Marighetto et al., 1999). The CSDLT takes place in a radial maze and consists of a center platform from which branch out 12 pathways. An enriched environment made up of mountains, trees,

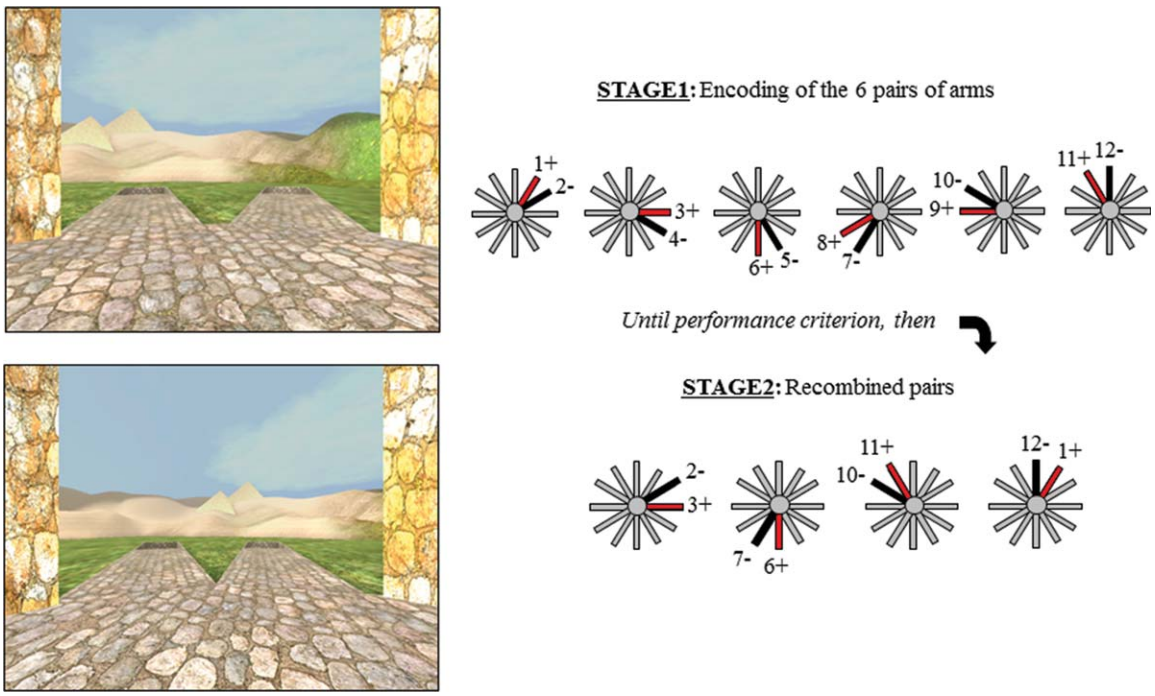

FIGURE 1. The two stages of the virtual radial maze with a schematic representation of the behavioral paradigm. Example of a pair of arms presented during encoding (Stage 1) and a recombined pair during Stage 2.

and landmarks surrounds the radial maze (Fig. 1). At the end of each arm, there is a set of stairs that leads to a small pit where, in some of the arms, an object is located. The 12 arms of the maze are divided up into six adjacent pairs of arms. Within each pair of arms, one arm, always the same one, contains an object and the other is always empty. During the experimental encoding phase (Stage 1), participants are repeatedly presented with the six pairs of arms in a pseudo-random order (Fig. 1). They are asked to learn within each pair of arms which one contains an object and to go down that arm to retrieve the object. Upon descending the stairs at the end of the pathway and entering the pit, participants are automatically transported back to the center platform and presented with the next pair of arms. The number of correct arms the participant visits within each trial is measured as choice accuracy. A trial consists of the presentation of all six pairs of arms. Participants are trained until a choice accuracy criterion of 11/12 is reached within two consecutive trials. A minimum of six trials was administered to all participants.

Upon reaching criterion, participants proceed to the probe phase (Stage 2) called the recombined pairs condition (Fig. 1). During this phase, the arms presented to the participants are rearranged into novel pairs; however, the reward contingency remains the same. Four pairs of recombined arms are presented twice in a pseudorandom order. Only four recombined pairs allowed for the presentation of adjacent arms with only one arm containing an object. This stage was designed so that only individuals who are flexible evidenced by the fact that they used a spatial strategy and learned the spatial relationship between the object and environmental landmarks, are able to find the objects within the recombined pairs with an 80% and above choice accuracy criterion. In other words, when the pairs of arms that are presented are recombined, participants who know the relationship between the target objects and landmarks are capable of discerning the target arm from the nontarget arm. Alternatively, people who used a response strategy, that is, when I see the pyramid, take the arm to the right, are unable to perform the task with the same flexibility. In this case, since the pairs of presented arms were rearranged, "the arm to the right when I see the pyramid" in this stage is not the same "arm to the right when I see the pyramid" as in the encoding stage. Thus, the recombined pairs' stage provides an objective method to distinguish between participants who are flexible at using the spatial relationships between the environmental landmarks and the target arm from a different point of view and those who are inflexible to do so. Given that the probe has eight trials and the probability of a success on an individual trial is 0.5, seven of eight successes (rounded to 80%) was used as the cutoff to obtain a binomial probability of $P < 0.05$. The probability that someone will get seven of eight trials correct by chance is less than 5%. Therefore, 80% accuracy was used as the cutoff to distinguish those that used a spatial strategy and those that used a response strategy.

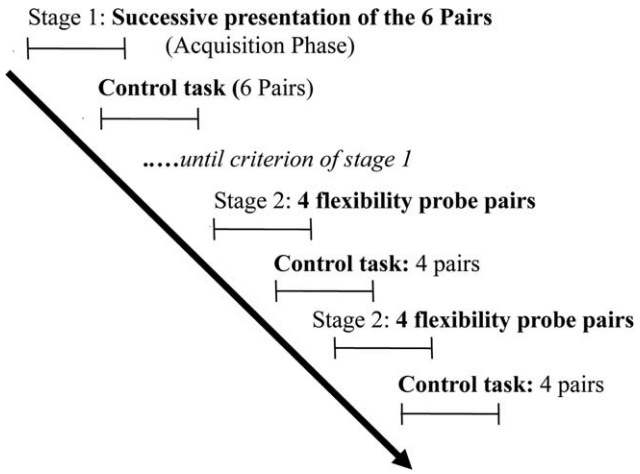

FIGURE 2. Overall design of the fMRI experiment.

Visuo-Motor Control Task

Interspersed between the experimental tasks was a visuo-motor control task. The control consists of a radial arm maze with no background environment. In addition, within each pair of arms, the location of the object is completely random. Participants are presented with six pairs of arms and asked to visit an arm at random. The experimenter explicitly states that there is nothing to learn during this task and that the location of the object is completely random with nothing to predict the location. Furthermore, to prevent participants from learning anything, they are distracted with a working memory counting task. During the entire duration of the control task, participants are required to count backward by 3 from 1,000. The aim of the control was to have a task identical to the experimental condition in terms of visuo-motor demands but with no learning involved. All experimental trials were contrasted against control trials to remove from our analysis the brain activity resulting from the visuo-motor aspects of virtual navigation. Furthermore, the control trials were interspersed with the experimental trials, allowing us to control for scanner drifts that could occur within each 10-min scanning session.

Functional Magnetic Resonance Imaging Acquisition Data

The scanning sessions consisted of multiple 10-min scans (average number of scans = 5.8 ± 1.5). The number of scans differed between participants depending on the number of experimental trials required to reach criteria. Each scanning session varied from 1 to 2 h. During the encoding phase (Stage 1), the 10-min scans included trials of ~90 s duration that alternated between experimental and control (Fig. 2). Before each trial, participants were prompted with a panel that reminded the participant of the task ahead. Once participants reached criteria, two probe trials were given, interleaved with control trials. The start and finish of each trial was marked with in-house "spy" software that records keystrokes and scanner frame times. The keystrokes made by the experimenter indicated the start and finish of experimental and control trials. They were used to select frame times that correspond to the experimental and control trials and exclude frames collected during the transition between trials.

Scanning was conducted at the Montreal Neurological Institute with a 1.5-Tesla Siemens Sonata scanner. Participants were comfortably placed in the scanner with their heads immobilized with an air cushion. They were provided with a mirror placed above the head coil in order to visualize the projection screen on which the virtual environments were displayed. After a 2-min localizer scan, an anatomical scan of ~15 min was first taken before the functional scan. A three-dimensional gradient echo acquisition was used to collect 160 contiguous 1-mm T_1-weighted images in the sagittal plane. Whole-brain functional scans were acquired using 32 contiguous 4-mm axial slices parallel to the hippocampus covering the entire brain (TR = 3000 ms; echo time (TE) = 50 ms; field of view = 256 mm^2; time between measurements = 3 s; matrix size = 64 × 64; 300 whole-brain acquisitions/run). Using in-house software (Collins et al., 1994), blood oxygen level–dependent (BOLD) signal images were spatially smoothed using a 6-mm Gaussian Kernel, motion corrected, and linearly transformed into standard stereotaxic Talairach space (Talairach and Tournoux, 1988). Statistical analysis of the fMRI data was conducted using in-house FMRISTAT software (Worsley et al., 2002). Statistical *t*-map images contrasting experimental trials to equal duration control trials, as well as group averaged statistical images, were generated. To view the analyses, statistical maps were overlaid on an average structural scan of the group. Based on our a priori hypothesis, an uncorrected *P* value of 0.001 was used for voxels in the predicted regions of interest, namely, the hippocampus and caudate nucleus. For the whole brain, a Bonferroni correction for multiple comparisons was used to calculate the *t*-statistical threshold ($N = 23$, $t = 5.42$; $N = 29$, $t = 5.07$).

Functional Magnetic Resonance Imaging Analysis

fMRI scans of young and older adults were directly contrasted as well as analyzed separately. It is necessary to apply caution when directly comparing fMRI scans of young and older adults. With age, changes in ultrastructure (Kalaria, 1996), resting cerebral blood flow (Schultz et al., 1999; Bentourkia et al., 2000; Restom et al., 2007), vascular reactivity (Niehaus et al., 2001), and cerebral metabolic rate of oxygen consumption (Yamaguchi et al., 1986; Takada et al., 1992) may lead to differences in BOLD responses that are unrelated to neuronal activity (D'Esposito et al., 2003). The experimental trials of the CSDLT were analyzed in the following way for both young and older adults: based on our a priori hypotheses from our previous research (Iaria et al., 2003) that found early hippocampal and late caudate activation during encoding, we examined the first experimental trial when participants are first presented with the environment and the last experimental trials

when participants reached criteria. We also examined the average of all experimental trials. A time by activity analysis was performed in both young and older adults to observe whether there is a correlation between time and activity in the hippocampus and caudate nucleus. Region of interest and whole-brain analysis was conducted for each resulting scan. The same analysis was performed for spatial and response older adults separately. fMRI scans for spatial and response older adults were contrasted directly. Detailed fMRI results of spatial and response young adults are reported in Etchamendy et al. (2012) showing that those using a spatial strategy had significant activation in the hippocampus while those using a response strategy had activation in the caudate nucleus.

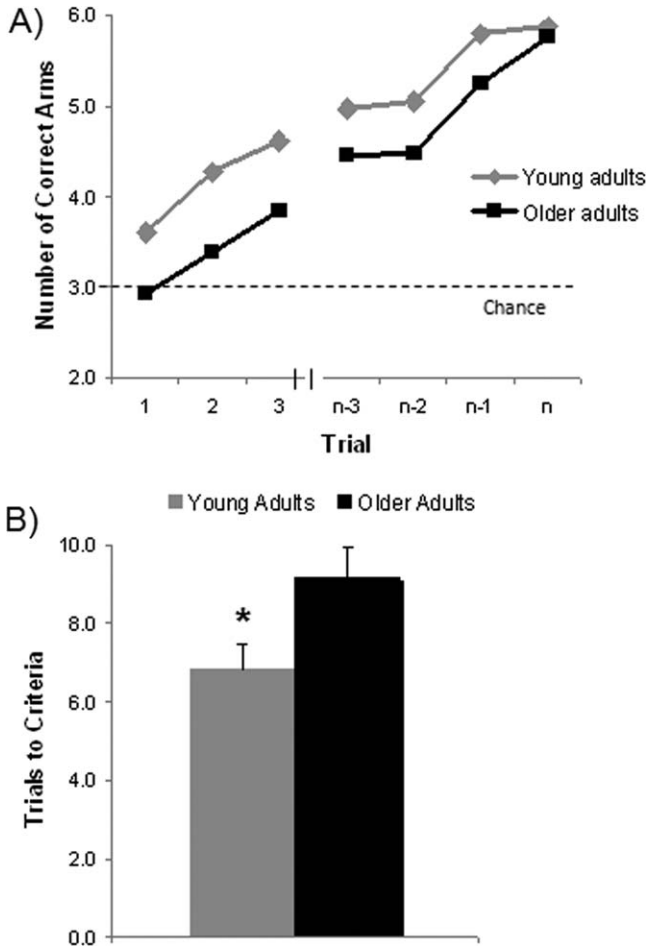

FIGURE 3. Behavioral data of young and older adults. (A) Mean number of correct choices over the first three and last four trials in the encoding phase (Stage 1) for both young and older participants. The young adults' mean performance at the end of the training was 98% correct (last trial) and older adults' mean performance was 97% correct. (B) Mean (± SEM) number of trials to criteria in the encoding phase (Stage 1) of young and older participants. *$P < 0.05$.

RESULTS

Behavioral

Both young and older adult participants learned the reward contingency of the arms during the encoding phase. There was no significant difference in performance between the young and older adults on the last experimental trial when criterion was reached ($t = 0.89$; $P = 0.38$). Although criterion was reached by both groups (Fig. 3a), older adults were significantly slower at learning than the younger adults and required more trials to reach criterion (Fig. 3b) (young adults mean = 6.9; older adults mean = 9.2; $t = -2.3$; $P < 0.05$). Performance on the probe trial (the two trials of four recombined pairs during Stage 2) did not significantly differ between the two groups (young adults mean = 4.7/8 (58.75%); older adults = 5.6/8 (70%); $t = -1.55$; $P = 0.13$). Spatial and response strategy users did not significantly differ in the number of trials to reach criteria in the young adult group or in the older adult group (young adults TTC: $t = 0.891$, $P > 0.05$; older adults TTC: $t = -0.243$, $P > 0.05$).

Functional Magnetic Resonance Imaging

We examined the brain activity patterns in young and older adults during the encoding phase of the task in contrast to the control trials. During the first experimental trial, when participants are exposed to the six pairs of arms for the first time, we observed significant activation in the right hippocampus (Fig. 4a) of the young adults ($x = 26.4$, $y = -8.0$, $z = -28.0$; $t = 4.41$, $P < 0.001$). When examining a similar region in the older adult group during the first experimental trial, no significant hippocampal activity could be found (Fig. 4b). A direct contrast between young and older adults showed that young adults had significantly more activation in the hippocampus compared to older adults at the beginning of learning when participants are presented with the environment for the first time ($x = 22.0$, $y = -8.0$, $z = -27.9$; $t = 4.54$, $P < 0.001$). As expected, no activity in the caudate nucleus was found in either the young or older adults in the early part of the encoding phase as the caudate nucleus-based learning system is a slow learning system (Packard and McGaugh, 1996). Significant activity in the hippocampus in the young adults is consistent with our hypothesis and is in line with previous studies (Parslow et al., 2004; Moffat et al., 2006; Antonova et al., 2009). Furthermore, in young adults, we observed a negative correlation between time and activity in the hippocampus ($x = 27.9$,$y = -8.0$, $z = -27.8$; $t = -2.97$, $P < 0.005$) indicating that over time there is a decrease in activity of the hippocampus.

With training and repetition, the last experimental trial of the encoding phase when criterion was reached revealed significant caudate nucleus activity (Fig. 5a) in the older group ($x = -19.0$, $y = 12.1$, $z = 18.2$; $t = 3.59$, $P < 0.001$). No significant caudate nucleus activity was found in the young adult group (Fig. 5b), and no activity in the hippocampus was found in either group during the last experimental trial. A direct contrast showed that older adults tended to have more activity in

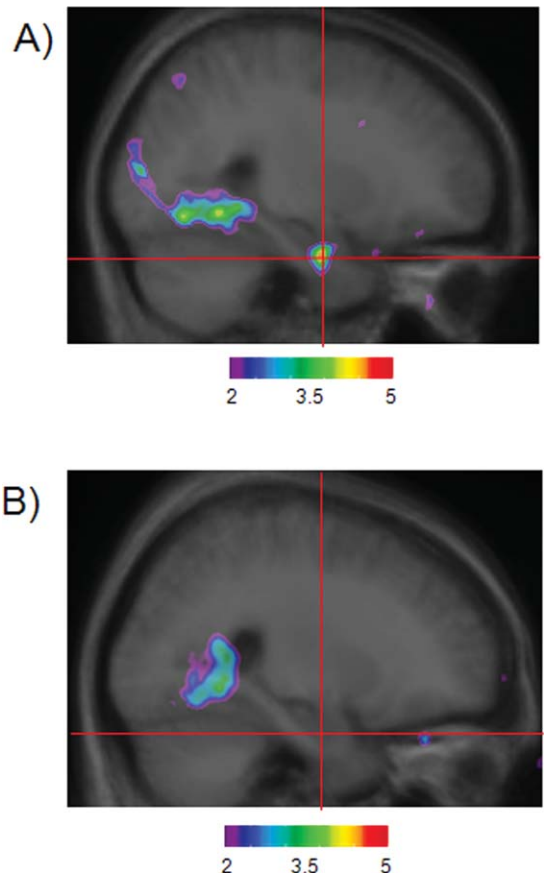

FIGURE 4. First experimental trial of the encoding phase (Stage 1) contrasted against control trials. (A) Significant activity in the right hippocampus of young adults ($x = 26.4$, $y = -8.0$, $z = -28.0$; $t = 4.41$, $P < 0.001$). (B) No activity in the right hippocampus of older adults ($x = 26.4$, $y = -8.0$, $z = -28.0$; $t = -0.89$, $P > 0.001$). The *t*-maps of the young participants are superimposed onto the anatomical average of all young participants ($N = 23$) and displayed in the sagittal plane. *t*-maps of older participants are superimposed onto the anatomical average of all older participants ($N = 29$).

the caudate nucleus compared to young adults during the last experimental trial ($x = -12.0$, $y = 0.3$, $z = 9.8$; $t = -2.7$, $P < 0.005$). At this phase, all participants learned the reward contingency of the six pairs of arms. In older adults, we observed a positive correlation between time and activity in the caudate nucleus ($x = -20$, $y = -11.9$, $z = -18.2$; $t = 3.18$, $P < 0.005$) indicating a trend in increased caudate nucleus activity over time.

During the probe phase of Stage 2, both young and older adults showed subthreshold activity in the caudate nucleus (young adults: $x = -16.0$, $y = 4.0$, $z = 13.7$; $t = 2.79$, $P < 0.01$; older adults: $x = -12.0$, $y = 4.5$, $z = 19.7$; $t = 3.36$, $P < 0.005$).

The older adult participants were divided into two groups based on their probe score (Table 1) to examine whether hippocampal and caudate nucleus activity during encoding was predictive of performance during retrieval. Brain activity throughout the encoding phase was examined and contrasted against activity during the control trials in the two older adult groups, those who scored 80% and above which is indicative of a flexible spatial strategy and those who scored below 80% which is indicative of an inflexible response strategy. Older adult participants who were inflexible and used a response strategy in Stage 2 showed significant activation in the left caudate nucleus (Fig. 6a) during the last experimental trial ($x = -12.0$, $y = 8.2$, $z = 0.0$; $t = 3.87$; $P < 0.001$) of the encoding phase, that is, Stage 1. In other words, healthy older participants who learned the task using a caudate nucleus-based neural system in Stage 1 were unable to use the information flexibly in Stage 2. Interestingly, the older participants who were flexible and used a spatial strategy to solve the probe trial in Stage 2 had activity in the hippocampus (Fig. 6b) during the first experimental trial of the encoding phase (Stage 1) that tended toward significance ($x = -18.1$, $y = -28.0$, $z = -13.8$; $t = 3.44$; $P < 0.005$). In other words, healthy older participants who learned the task with the hippocampus in Stage 1 were able to use the spatial information flexibly in Stage 2. Direct contrasts were performed between spatial and response older adults. Older adults using response strategies had significant activity in their caudate nucleus relative to those using spatial strategies during the last experimental trial ($x = -10$, $y = 10$, $z = -3.9$; $t = -3.6$; $P < 0.001$). In contrast, individuals using a spatial strategy tended to have more activity in the hippocampus compared to those using a response strategy during the first experimental trial ($x = -20$, $y = -27.8$, $z = -9.7$; $t = 2.40$; $P < 0.05$). These results demonstrate that healthy older adults who use a spatial strategy have activity in their hippocampus while those who use a response strategy have activity in the caudate nucleus. During the probe trial, there was no significant activity in either the caudate nucleus or hippocampus.

When examining all experimental trials together, two peaks crossed the whole-brain threshold after Bonferroni correction in the young adult sample. The peaks were observed in both the left and right fusiform gyrus extending into the parahippocampal cortex ($x = -30.0$, $y = -53.8$, $z = -15.5$; $t = 8.08$, $P < 0.05$ and $x = 30.0$, $y = -51.9$, $z = -11.6$; $t = 7.21$, $P < 0.05$). The same peak was observed in the left fusiform gyrus in older adults when again examining all the experimental trials together ($x = -34.0$, $y = -48.1$, $z = -19.5$; $t = 6.94$, $P < 0.05$). Again, the peak activation in the fusiform gyrus of older adults extended into the parahippocampal gyrus. No other peaks in any of the performed analyses crossed the threshold corrected for multiple comparisons across the whole brain in either the young or older adults.

DISCUSSION

The aim of the current study was to examine the effects of aging on the hippocampus and caudate nucleus during navigation while taking into account individual navigational strategies. fMRI results showed that, as a group, young adults had significant activity in the hippocampus as opposed to older

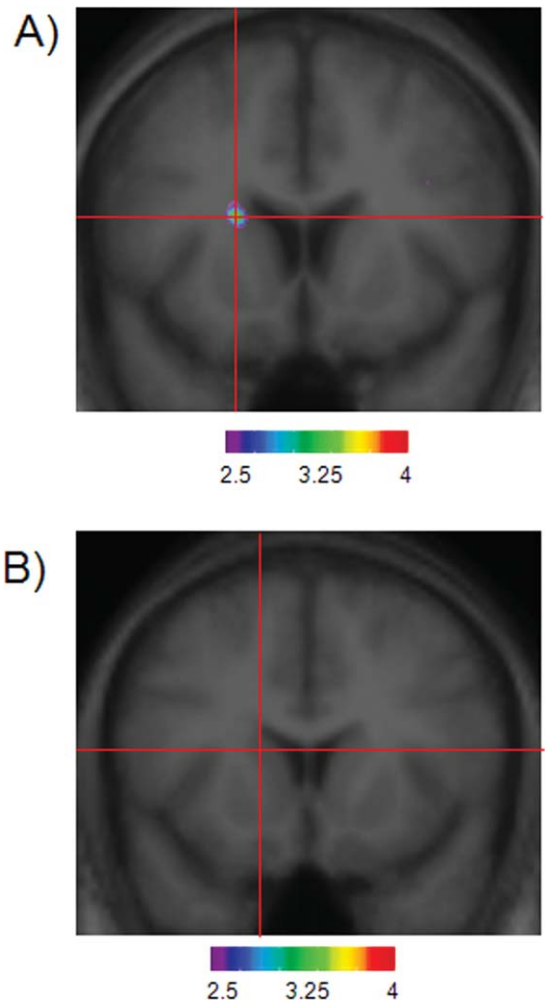

FIGURE 5. Last experimental trial of the encoding phase (Stage 1) contrasted against control trials. (A) Significant activity in the left caudate nucleus of older adults ($x = -19.0$, $y = 12.1$, $z = 18.2$; $t = 3.59$, $P < 0.001$). (B) No significant activity in the left caudate nucleus of young adults ($x = -19.0$, $y = 12.1$, $z = 18.2$; $t = -0.83$, $P > 0.001$).

adults who instead had activity in the caudate nucleus. Importantly, individual differences showed that the older participants who used a spatial strategy to solve the task had significant activity in the hippocampus.

It has been repeatedly shown that spatial memory is impaired in aging in both animals and humans (Marighetto et al., 1999; Moffat et al., 2001, 2006; Wood and Dudchenko, 2003; Meulenbroek et al., 2004; Iaria et al., 2009; Head and Isom, 2010). Numerous studies have shown that with age, there is an impairment in both the formation and the use of a cognitive map (Iaria et al., 2009). Consistent with the literature, older adults in our study took longer to learn the task, performing more trials to criteria than young adults.

Several studies have shown differences in activity in the hippocampus between young and older adults (Moffat et al., 2006; Antonova et al., 2009; Rodgers et al., 2010; Etchamendy et al., 2012). Moffat et al. (2006) tested both young and older participants in a virtual environment where they had to derive shortcuts between objects while undergoing fMRI scanning. Results showed that younger adults had increased activity in the hippocampus in comparison to older adults. Antonova et al. (2009) found similar results when testing young and older participants in a virtual human analog of the rat Morris Water Maze. During the encoding phase, young adults showed significant bilateral activity in the hippocampus relative to the control condition. Consistent with the literature, young adults in our study, showed significant activity in the hippocampus during navigation, while, as a group, older adults did not. This occurred despite the fact that navigational strategies in the two groups were matched. Therefore, our results demonstrate for the first time, an age-related reduction in fMRI activity in the hippocampus, even when strategies are taken into account.

The spatial memory impairment in older adults consistently reported in the literature may be the result of older adults using a different brain system to learn the navigation tasks (Rodgers et al., 2010; Etchamendy et al., 2012). In the present study, we examined the neurobiology of navigational strategies in aging using a validated human analog of a radial maze task traditionally used in mice (Marighetto et al., 1999; Rodgers et al., 2010; Etchamendy et al., 2012). The current fMRI findings showed that while young adults had activity in the hippocampus at the beginning of the encoding phase during the first experimental trial, older adults did not. Instead, older adults showed significant activity in the caudate nucleus at the end of the encoding phase when criterion was reached. Young adults did not show significant activity in the caudate nucleus during the last experimental trial. Navigation using a cognitive map requires the hippocampus, while navigation by way of stimulus-response learning requires the caudate nucleus (Iaria et al., 2003). These results support the hypothesis that young and older adults are using different brain systems to navigate.

Our results further showed equal performance between the young and older adults during Stage 2, which assesses navigational strategies. This is important because it shows that spatial and response strategies were balanced in young and older adults. This indicates that the different patterns in fMRI activity between the two groups can only be attributed to age-related alterations in the recruitment of neural networks, rather than differences in behavior. It is interesting that even though the overall performance of older adults is equal to young, they preferentially show activity of the caudate nucleus as opposed to the hippocampus as seen in young adults. Similar rationale was employed by Moffat et al. (2006) who found age differences between young and older adults. In order to determine whether differences were a result of performance differences or alterations in neural networks, the authors controlled for behavioral discrepancies in their analysis. Results showed activation differences between young and older adults and thus the authors concluded that, with aging, there are changes in the recruitment of neural networks. Earlier results from Etchamendy et al. (2012) showed an age-related impairment on the behavioral version of this task (no fMRI). Young adults tested on the CSDLT scored above 80% on Stage 2, which was significantly better than the older

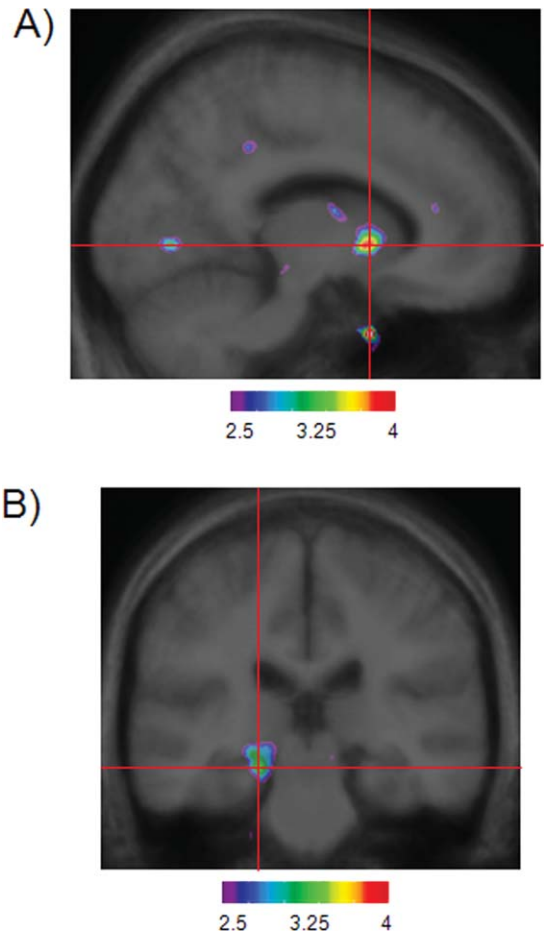

FIGURE 6. Older adults divided into two groups based on performance on probe trials (Stage 2) contrasted against control trials. The spatial group scored 80% and above on probe trials, and the response group scored below 80%. (A) Significant activity in the left caudate nucleus of the older adults during the last experimental trial of the Stage 1 encoding phase ($x = -12.0$, $y = 8.2$, $z = 0.0$; $t = 3.87$; $P < 0.001$) that predicts the use of a response strategy in Stage 2. (B) Significant activity in the left hippocampus of the older adults during the first experimental trial of the Stage 1 encoding phase ($x = -18.1$, $y = -28.0$, $z = -13.8$; $t = 3.44$; $P < 0.005$) that predicts the use of a spatial strategy in Stage 2.

adults. This discrepancy between the young adults in the fMRI and those who did the task behaviorally may be the result of stress experienced during scanning, which has been associated with elevated cortisol levels (Tessner et al., 2006). Previous studies in humans (Schwabe et al., 2007a) and in mice (Kim et al., 2001, 2007) show that stress before learning facilitates stimulus-response learning at the expense of a more cognitive spatial learning. However, even under mildly stressful conditions, young adults still had activation in the hippocampus during encoding in contrast to the control condition.

If the aging process can be measured as a general shift from using a hippocampal-based system to a caudate nucleus-based system rather than an impairment in hippocampal function and associated spatial memory deficits, we should be able to identify individual differences within the group of healthy older adults. Specifically, we should be able to show activity in the hippocampus of healthy older adults who use the spatial strategy and activity in the caudate nucleus in those who use the response strategy. To assess this, we divided the older adults based on their performance on the probe trial and examined their brain activity pattern during Stage 1. As per our hypothesis, in contrast to the control trials, older adults that scored equal or higher than 80% on the probe trial and were thus using a spatial strategy showed significant activity in the hippocampus during the first experimental trial of the Stage 1 encoding phase, as in young adults. Those that scored lower than 80% on the probe trial and were thus using a response strategy showed significant caudate nucleus activity in the last experimental trial of the Stage 1 encoding phase. In other words, brain activity during encoding was predictive of later performance during the Stage 2 probe trials. Similarly, Mingaud et al. (2007) showed that activity in the mouse hippocampus measured by c-fos mRNA expression predicted flexible spatial performance during retrieval and McIntyre et al. (2003) showed that increased extracellular acetylcholine in the hippocampus at baseline predicted spatial strategies as opposed to response strategies, which were predicted by increased baseline acetylcholine in the dorsal striatum/caudate. In sum, these results confirm that the response strategy observed in older adults is associated with activity of the caudate nucleus. Importantly, these results also suggest that the reduction of hippocampal function with aging does not occur in all individuals.

The fact that a portion of the older adult participants use their hippocampus and employ spatial strategies when navigating while others use their caudate nucleus and use stimulus-response strategies raises the question as to why some people shift with aging while others do not. Stress, habit formation, and reward are factors known to promote the shift from using spatial strategies to response strategies. Stress has been shown to have negative effects on the hippocampus and promote the use of a stimulus-response strategy (Schwabe et al., 2007b). Both habit formation and reward (Haruno et al., 2004; White and McDonald, 2002) are behaviors that have been shown to activate the caudate nucleus. As we age and as our lives include more routine behaviors, there is an increase in behaviors that can become automatized and become independent of the hippocampus, in favor of the caudate nucleus. Automatizing behavior with aging, by using response strategies, has the advantage of reducing cognitive demands (Iaria et al., 2003; Nadel and Hardt, 2004). Older adults previously reported that they are not comfortable driving unfamiliar routes or taking unexpected detours and feel more secure with a co-pilot in the car (Vrkljan and Polgar, 2007). Avoiding building cognitive maps and thus not using their hippocampus may lead to decreased hippocampal gray matter. In fact, Bohbot et al. (2007) and Lerch et al. (2011) both found a correlation between spatial memory and hippocampal gray matter in humans and in mice.

Studies have shown a link between decreased volume of the hippocampus and the risk of developing dementia (Convit et al., 1997; Rusinek et al., 2003; Tapiola et al., 2008). Consequently, individuals who are using a stimulus-response strategy early on and have reduced gray matter in the hippocampus (Bohbot et al.,

2007) may potentially be at risk of having cognitive deficits during normal aging. Valenzuela et al. (2008) has in fact shown that individuals who have higher levels of mental activity across their lifespan also have larger hippocampal volumes. Genes and experience have also been shown to play a role in modulating gray matter and functional changes in the hippocampus. Banner et al. (2011) demonstrated the importance of the brain-derived neurotrophic factor (BDNF) genotype in shaping spontaneous strategies. The authors showed that individuals who are methionine (met) carriers at codon 66 of the BDNF gene are more likely to spontaneously use a response strategy over those who are valine (val) homozygous at codon 66. In sum, both genetic and experience dependent modulators may be contributing to the shift toward stimulus-response strategies in normal aging.

In conclusion, the present findings are consistent with the literature reporting that healthy older adults show decreased activity in the hippocampus and further provides new evidence that the caudate nucleus becomes engaged instead (Della-Maggiore et al., 2000; Gron et al., 2006). Importantly, at an individual level, older adults using a spatial strategy demonstrated activity in the hippocampus during encoding, a pattern observed in young adults, suggesting that the aging process does not necessarily involve a reduction in hippocampal function in all individuals. Therefore, an intervention based on stimulation of the hippocampus with spatial memory training could prove to be beneficial to healthy cognition and successful aging.

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