Aging and KIBRA/WWC1 Genotype Affect Spatial Memory Processes in a Virtual Navigation Task

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ABSTRACT: Spatial navigation relies on multiple mnemonic mechanisms and previous work in younger adults has described two separate types of spatial memory. One type uses directional as well as boundary-related information for spatial memory and mainly implicates the hippocampal formation. The other type has been linked to directional and landmark-related information and primarily involves the striatum. Using a virtual reality navigation paradigm, we studied the impacts of aging and a single nucleotide polymorphism (SNP rs17070145) of the *KIBRA* gene (official name: *WWC1*) on these memory forms. Our data showed that older adult's spatial learning was preferentially related to processing of landmark information, whereas processing of boundary information played a more prominent role in younger adults. Moreover, among older adults T-allele carriers of the examined *KIBRA* polymorphism showed better spatial learning compared to C homozygotes. Together these findings provide the first evidence for an effect of the *KIBRA* rs17070145 polymorphism on spatial memory in humans and age differences in the reliance on landmark and boundary-related spatial information. © 2013 Wiley Periodicals, Inc.

KEY WORDS: spatial navigation; hippocampus; striatum; aging; *KIBRA*

INTRODUCTION

Spatial navigation is a complex ability that depends on multiple brain networks. It has been linked to the hippocampal formation, where place (O'Keefe and Dostrovsky, 1971) and grid cells (Hafting et al., 2005) provide the neuronal basis of a map-like spatial representation of the environment as shown by animal research (O'Keefe and Nadel, 1978). Importantly, the firing of both cell types is modulated by environmental boundaries (O'Keefe and Burgess, 1996; Barry et al., 2007). Furthermore, rodent studies showed that the striatum also plays an important role in spatial navigation, particularly when the spatial learning involves memory of relations between visual intra-maze cues and locations (Packard et al., 1989; Packard and McGaugh, 1992; McDonald and White, 1994). In line with these findings from animal studies, Doeller et al. (2008) showed that a similar distinction can be made in humans (see also Doeller and Burgess, 2008). Specifically Doeller et al. (2008) used a virtual reality (VR) task where locations of objects could be determined either based on (a) extra-maze directional cues together with the relative distance to an intra-maze landmark or (b) directional cues plus the relative distance to the environment boundary. In line with the operationalizations of the two memory forms in Doeller et al.'s (2008) VR navigation environment, here we use the terms boundary-related and landmark-related to differentiate between these two forms of spatial memory and learning. It should be noted that the use of these terms does not preclude that other navigationally relevant information also play important roles in determining object locations in space.

Of particular relevance, using functional magnetic resonance imaging (fMRI) Doeller et al. (2008) showed that boundary-related learning correlated with hippocampal activation, whereas landmark-related learning correlated with striatal activity. In addition, other experiments also indicated the behavioral relevance of boundary information in human navigation (Hartley et al., 2004). Specifically, Hartley et al. showed that humans in a VR task tended to match the proximities of locations to the walls of the environment (in addition to the use of extra maze visual information to determine orientation). A real world implementation of the Doeller et al. (2008) VR task with children (Bullens et al., 2010) also yielded results consistent with the original reports.

It is well established that aging affects the hippocampus and striatum both structurally (Raz et al., 2005; Walhovd et al., 2011) and neurochemically (Kaasinen et al., 2000; Bäckman et al., 2006 for a review; Li et al., 2001 for a theoretical account).

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However, the interactions between hippocampus and striatum during memory processes may change with age (et al., Rieckmann et al., 2010). Despite the extant literature indicating various effects of human aging on spatial navigation (e.g., Light and Zelinski, 1983; Moffat et al., 2001; Moffat and Resnick, 2002; Bohbot et al., 2004; Lövdén et al., 2005; Moffat et al., 2006; Iaria et al., 2009; Jansen et al., 2010; Etchamendy et al., 2011; Gazova et al., 2012; Harris and Wolbers, 2012; Harris et al., 2012; Wenger et al., 2012, for reviews, see Driscoll and Sutherland, 2005; Moffat, 2009), potential age differences in landmark- and boundary-related memory and learning during spatial navigation are unknown. In this respect, our approach differs from previous studies about the aging of spatial memory, which focused more on older adults' spatial memory errors (Moffat et al., 2001) or age differences in allocentric vs. egocentric strategies (Rodgers et al., 2012, see also Konishi and Bohbot, 2013).

The aim of this study was to investigate the impact of aging and genetic variations on striatal and hippocampal components of spatial memory and learning. In light of age-related impairments in the hippocampal memory system (Nilsson, 2003; Shing et al., 2011; Yassa et al., 2011), we expected negative age differences in boundary-related navigation memory. With respect to differences in boundary- and landmark-related learning, we take two major findings into account: First, studies showed that older adults' caudate nucleus but not hippocampus volume correlates with spatial memory and that they rely more on extrahippocampal navigation strategies (Moffat et al., 2007; Wiener et al., 2013). Second, milder age-related impairments in striatum-dependent implicit memory as compared to explicit memory (e.g., Howard and Howard, 1989) have been reported. Hence, we expected a greater reliance on landmark cues for spatial learning and less age-related impairment of landmark-related spatial memory. To gain further insights into the neurobiology of spatial navigation and its changes during aging, we also investigated the effects of the "gene encoding the kidney and brain expressed protein" (*KIBRA*; locus 5q34–q35.2; official name: WW and C2 domain containing 1 [*WWC1*]). *KIBRA* is mainly expressed in the hippocampus in humans and rats (Johannsen et al., 2008) and has been linked to hippocampal long-term potentiation in animals (LTP; Schneider et al., 2010). A common SNP (rs17070145) in *KIBRA* has been reported to be associated with episodic memory in humans (Papassotiropoulos et al., 2006; Preuschhof et al., 2010), with T allele carriers showing better memory performance than C homozygotes (see Milnik et al., 2012, for a recent review). Given the pivotal role of the hippocampus in spatial navigation and the role of the KIBRA protein in hippocampal LTP, we hypothesized an effect of SNP rs17070145 on hippocampus-dependent spatial navigation. Furthermore, based on evidence suggesting an age-related magnification of genetic effects on working memory (e.g., Nagel et al., 2008) and episodic memory (e.g., Li et al., 2010, 2012; Papenberg et al., 2013), we expected the possible effects of rs17070145 on spatial navigation to be stronger in older adults.

MATERIALS AND METHODS

Participants

One-hundred fifty-five participants of Caucasian origin participated in the study. Two participants whose genetic information could not be obtained (due to genotyping failure, overall genotype efficiency of the entire sample is greater than 0.98) and one younger participant whose performance exceeded 3.3 SDs from the mean of this age group were excluded from analyses. Thus, the effective sample included 77 older (mean age: 65.5 years, range: 60–70, 42 female) and 75 younger (mean age: 25.0 years, range: 19–30, 38 female) individuals. The local ethics committee at the Max Planck Institute for Human Development approved this study. All participants gave written consent to the experimental procedures and the collection of saliva samples for genotyping. The participants received 27 Euro as reimbursement for participation.

Before recruitment, participants were screened for neurologic, psychiatric, and other medical conditions via a telephone screening. Only participants without apparent health issues were recruited for the study. A demographic questionnaire assessed years of education and experience with computer games (i.e., more than 5 h of computer game playing per week, yes/no). The two age groups did not differ with respect to years of education (t-test, $P = 0.78$) or in the proportion of participants who played computer games more than 5 h per week (χ^2 -test, $P = 0.12$). Although both factors did not differ significantly between the age groups, we nonetheless included years of education and computer gaming experience as covariates. Table 1 shows statistics of the samples' demographic characteristics, including two marker tests of fluid (perceptual speed) and crystallized (verbal fluency) intelligence. In line with previous data from larger population-based lifespan samples (Li et al., 2004), younger adults performed better than older adults in perceptual speed as measured by the identical pictures test, $t(137.89) = -18.57$, $P < 0.0001$. In the spot-a-word test, a measure of crystallized intelligence, older adults showed superior performance, $t(139.95) = 5.03$, $P < 0.0001$. In light of potential effects of the brain-derived neurotrophic factor gene (*BDNF*, rs6265) on spatial memory (Banner et al., 2011) and episodic memory in general (Li et al., 2010), *BDNF* SNP rs6265 genotype was also used as a covariate in addition to sex, education, and computer gaming experience for all analyses.

Genotyping

Saliva samples were collected with Oragene OG-250 collection kits (DNA Genotek, Ontario, Canada), and DNA was extracted using standard methodology. Genotyping of the *KIBRA* (rs17070145; Assay ID: C__33286269_10) and the *BDNF* (rs6265; Assay ID: C__11592758_10) polymorphisms was carried out in a 384-well microtiter plate format using "TaqMan" 5'-exonuclease allelic discrimination assays. Sequences of primers and TaqMan probes for the genotyping were

TABLE 1.

Statistics of Sample of Current Study

Age Group	Age	Years of Education	KIBRA rs17070145 (n_{anyT}/ n_{CC})	PC Play (%)	Spot-a-Word*	Identical Pictures*
Older adults (n = 77)	65.4	14.16	39/38	5.3	25.23 (5.4)	22.53 (3.3)
Younger adults (n = 75)	25.0	14.44	38/37	13.5	20.17 (6.7)	34.07 (4.2)

Numbers in Spot-A-Word and Identical Pictures columns represent mean number of correct answers. Values in parentheses show SDs. Stars indicate a difference between the two age groups, see text.

designed and synthesized by Applied Biosystems (Foster City, CA) and experimental conditions followed the manufacturer's instructions. In line with previous studies, we grouped participants into "any T" and "C/C" carriers for the analyses of *KIBRA* SNP rs17070145 (Papassotiropoulos et al., 2006; Preuschhof et al., 2010), and into "any Met" and "Val/Val" carriers for *BDNF* SNP rs6265 (Li et al., 2010; Banner et al., 2011). The frequencies of the *KIBRA* SNP rs17070145 genotypes were 49.3% for C/C, 39.0% for C/T, and 11.7% for T/T in the older group. The corresponding percentages were 49.3%, 38.7%, and 12.0% in the younger group. The frequencies for the *BDNF* rs6265 genotypes were 64.9% for Val/Val, 32.5% for Val/Met and 2.5% for Met/Met for older participants. The younger participants' genotype distribution was 65.3%, 28.0%, and 6.5%, respectively. The observed frequencies of the *KIBRA* rs17070145 and *BDNF* rs6265 genotypes did not deviate from the Hardy–Weinberg equilibrium (all $\chi^2 < 1.7$; all $Ps > 0.05$) (Rodriguez et al., 2009).

Spatial Navigation Task

To assess spatial navigation performance, we used a virtual reality task where object locations can be learned relative to a single local landmark or to a boundary (Doeller and Burgess, 2008; Doeller et al., 2008). In this task, participants had a first-person view of a grassy plane surrounded by a circular boundary (a stone wall), with a diameter of ~180 virtual meters (vm; 1 vm = 62.5 Unreal Units). Virtual meter (vm) is a common unit in research using virtual reality tasks. This unit aims to translate the arbitrary units of the coordinate system within the virtual environment (Unreal Units) into a unit that mimics a meter in actual space (e.g., Maguire et al., 1998; Chai and Jacobs, 2009; for other research that used virtual meters). A traffic cone was used as an intra-maze landmark and had a fixed location during the learning trials. Landmark and boundary were not size-invariant. To provide distal orientation cues, the circular environment was embedded in a landscape of two mountains, clouds, and the sun. These distal cues were projected at infinity, which made it impossible to use these cues alone to determine a specific location, because their perceived distance was constant. At the same time, both the boundary and landmark were rotationally symmetric, leaving the distal cues as the only source of orientation for both boundary- and landmark-related learning. We acknowledge that spatial navigation related to processing of landmark or boundary information does also involve other navigationally relevant information, e.g. coming from extra-maze directional cues. The fact that the directional cues were rendered at infinity, however, might potentially limit the generalization of the present results to scenarios where orientation cues are indeed very distal (such as using the sun or distant mountains for directional information). In real life, such navigation based on distal direction cues probably occurs mostly in open spaces. The task was programmed using UnrealEngine2 Runtime software (Epic Games; http://udn.epicgames.com/). Participants could navigate through the virtual environment using a joystick. A forward tilt of the joystick resulted in a constant speed with a short period of acceleration. Given the virtual walking speed, the entire arena could be traversed in about 15 s. The height of the virtual player was about 1.92 vm, the height of the stone wall ~1.3 vm. Locations and direction of movement were recorded every 100 ms continuously throughout a trial.

Stimuli and Procedures

Before performing the task, participants received training with the joystick and the procedure in a different virtual environment. Before the experiment started, different trial types (see below for details) were explained and practiced.

Each run comprised three distinct trial types: In encoding trials, participants were instructed to pick up an object within the environment and remember the location of that object. In each trial one object was placed within the environment. Pictures of everyday items (e.g., a pear, a hat, etc.) were used as objects. When participants felt sufficiently confident about their knowledge of the location, they could complete the trial and proceed to the next trial by virtually walking over the object, mimicking the act of picking up (or collecting) the object. The maximum duration of each trial was two minutes; however, neither younger nor older adults exceeded this limit in the majority of trials ($mean_{older}$ 16.8 s; SD: 7.5 and $mean_{younger}$ 11.3 s; SD 3.9). In test trials, participants were asked to virtually walk to the pick-up location of a cued object and press a button once they reached the memorized target location. After the button press, the object appeared in its correct location (feedback) and participants again picked up the object by walking over it. In this manner, participants could further improve their knowledge of each object's location. The

test phase was followed by transfer trials in which the intra-maze landmark and the boundary were displaced relative to each other. The movement was 31.7 vm in size (22.4 vm in either direction, counterbalanced between runs and participants). Participants were not informed about this change and trials proceeded as before with the only difference that feedback was omitted.

Each run contained four unique objects. First, each object was shown once in the four encoding trials. Subsequently, each of the four objects was tested three times in 12 test trials. The 12 trials were grouped into three mini-blocks with four trials each. The order of objects was randomized within mini-blocks. Finally, each object was tested once in four transfer trials. The full procedure of one run (20 trials; four encoding, twelve test, and four transfer trials) was repeated three times for each participant. Between runs, participants could take a short break. In each new run, the environment was the same but new objects with different locations were used and the relative movement of the landmark and boundary was different. Between all trials a black fixation cross was displayed on a gray screen for 2 s. In the test and transfer trials the cue was presented after the fixation cross for 4 s.

At the start of each trial, participants were positioned close to the center of the environment. The start position was random but could not be closer than 29 vm to the current object or landmark position and was constrained to be within 76 vm of the center of the environment. Because of the variation in the start position, memory of a fixed route (Hartley et al., 2003) could not be used. Figure 1 illustrates the task and design.

Statistical Analyses

All data was analyzed and plotted using R (R Development Core Team, 2011) and SAS (SAS Institute Inc, Cary, USA). The data was analyzed with mixed effect ANOVAs using the SAS PROC MIXED procedure in combination with Kenward-Rodger estimation for the denominator of degrees of freedom (Kenward and Roger, 1997). *t*-tests were run within the same procedure and Bonferroni adjusted. Exact *p*-values are reported up to the level of 4 decimal points. The chosen critical significance level was $\alpha = 0.05$. Sex and *BDNF* rs6265 were used as a covariates in the statistical analyses to account for possible superiority of male subjects in spatial navigation and memory (e.g., Lövdén et al., 2007) and effects of *BDNF* rs6265 genotype (e.g., Li et al., 2010; Banner et al., 2011). Furthermore, potential age-effects in the ability to handle the PC/Joystick were accounted for by including a measure of regular computer gaming (>5 h per week) of each participant as a covariate. All reported effects in the results were also statistically reliable without the covariates.

RESULTS

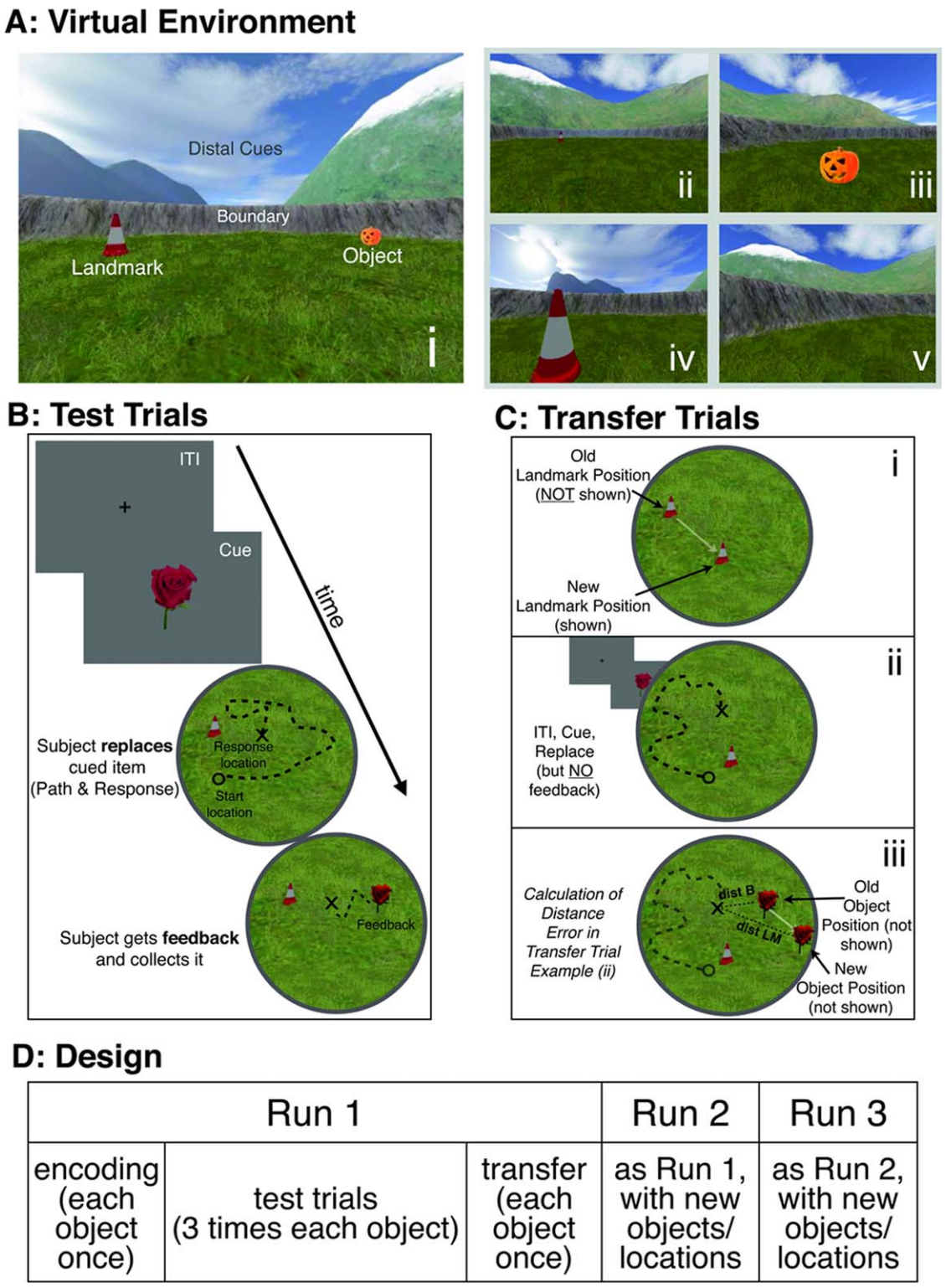
Age and Genetic Effects on Spatial Learning

For the test and transfer phase, we analyzed the cumulative distance to the correct target location (adjusted for the cumulative distance of a straight path at average speed, cf. Granon and Poucet, 1995). We chose this learning index because it is particularly suitable for age-related impairments in spatial memory (Gallagher et al., 1993). This learning index correlates highly with the distance between the participant's response location and the actual target location, $r = 0.73$, $P < 0.0001$ and the pattern of our main results is the same when the absolute distance is used (see below). For each of the three object repetitions (henceforth termed trial) within the test phase, we took the mean across runs for each participant (in each run a participant had to learn a set of novel object locations). A mixed effect ANOVA with one within-subject factor (trials) and two between-subject factors (age group and SNP 17070145 in *KIBRA*) revealed that older adults performed worse than younger adults as reflected in a significant main effect of age group $F(1, 88.6) = 133.84$, $P =< 0.0001$. Furthermore, a main effect of genotype showed that *KIBRA* T allele carriers had better performance, $F(1, 75.2) = 11.18$, $P = 0.0013$. This effect also interacted with age-group, $F(1, 72) = 9.75$, $P = 0.0026$. Post-hoc *t*-tests revealed that among the older adults the C homozygotes had larger mean distance error scores (mean: 3856 (cumulated) vm, SD 1561) than carriers of the beneficial T-allele (mean = 2995 vm, SD 1442), $t(57.9) = 3.46$, $P = 0.003$. In contrast, no such genotype effect was observed in younger adults, $t(58.4) = 0.23$, $P > 0.9999$. No triple interaction of age group, *KIBRA* SNP rs17070145 and trial was found, $F(2, 62.9) = 0.84$, $P = 0.4352$. Figure 2A shows the mean learning curves for both age by genotype groups. A similar pattern as seen in Figure 2A is also evident when the absolute distances are calculated. Specifically, in trials 1-3 older participants have distances of 33.5/37.9, 33.7/35.6, and 30.5/33.3 vm, for the carriers of the beneficial/nonbeneficial genotypes, respectively.

Finally, performing a median split based on mean cumulative distance separately for each age group revealed that among older adults there were significantly more carriers of the T-allele in the high performance group than in the low performance group, $\chi^2 = 10.63$, $P = 0.001$. This was not the case for the younger adults, $\chi^2 = 0.84$, $P = 0.3588$. There was no evidence of effects of *BDNF* SNP rs6265,$F(1, 57.1) = 0.01$, $P = 0.9037$, or sex $F(1, 73.7) < 0.07$, $P = 0.7871$. The binary variable indicating experience of PC gaming yielded an effect, $F(1,70.8) = 4.17$, $P = 0.0448$. In all analyses, we controlled for potential effects of computer gaming experience, sex, and *BDNF* rs6265. In summary, older adults performed worse than younger adults in our task. Moreover, older adults' performance was modulated by *KIBRA* rs17070145 genotype, even after controlling for the effects of BDNF rs6265, sex and game-playing.

Differential Age and Genetic Effects on Landmark- and Boundary-Related Learning

Next, we analyzed the data from the transfer phase. In line with earlier work (Doeller and Burgess, 2008; Doeller et al., 2008), we computed the (cumulative) distance of a response



Run 1			Run 2	Run 3
encoding (each object once)	test trials (3 times each object)	transfer (each object once)	as Run 1, with new objects/ locations	as Run 2, with new objects/ locations

FIGURE 1. **Continued**

location to (a) the location that would be predicted based on pure boundary learning (the same position relative to the boundaries) and (b) the location that would be predicted based on pure landmark learning (the same position relative to the landmark). In the following analyses, we considered the individual mean cumulative distances to the landmark and the boundary position (see Fig. 3). A corresponding ANOVA applying memory type (boundary vs. landmark) as a within-

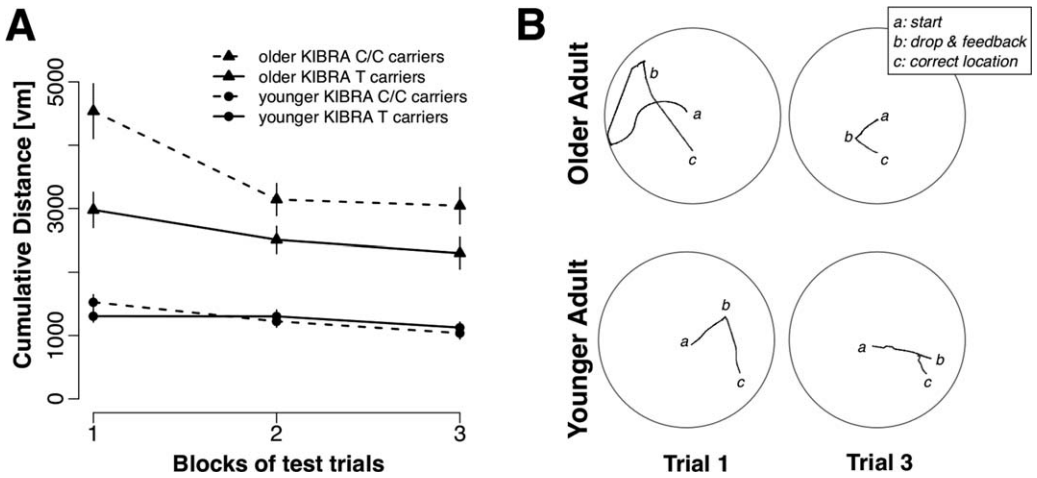


FIGURE 2. Mean cumulative distance to correct location. A: The figure shows mean cumulative distances (adjusted for covariates) as a function of repetition of the object location (test trials). Separate lines depict age groups and genotypes; see legend ("KIBRA" refers to SNP rs17070145). Error bars show standard errors of the mean. B: Exemplary paths of one older (upper two circles) and one younger adult (lower two circles) in the first and last test trial. Each circle shows the path as it would be seen from a bird's eye view (different from the participants' perspective). The path starts after the participant has seen the current cue at a start location (a). After the cue the participant walked to the memorized location (b). Once the participant had indicated his/her answer location, he/she received feedback (the object appeared at its actual location, c) and had to collect it.

subject factor and age group and *KIBRA* SNP rs17070145 as between subjects factors showed main effects of age group, $F(1, 99.7) = 39.00$, $P < 0.0001$ and memory type, $F(1,65.2) = 39.98$, $P < 0.0001$. These main effects indicate that older adults in general yielded larger distance errors than younger adults ($mean_{older}$ 3462 vm; $mean_{younger}$ 1879 vm) and that for all participants, landmark-distance errors were larger than boundary-distance errors (mean 2928 vm, vs. mean 2414 vm). The main effect of *KIBRA* SNP rs17070145 was marginally significant, $F(99.3) = 3.91$, $P = 0.0508$. Of specific interest, the ANOVA revealed an interaction of KIBRA polymorphism and memory type interaction, $F(1, 65.2) = 5.72$, $P = 0.0189$, and a triple interaction of these factors with age group, $F(1, 65.2) = 5.52$, $P = 0.0219$. Post-hoc analyses showed that the triple interaction is mainly driven by a significant difference between landmark- and boundary-related error, which was not present in any T carriers, $t(40) = 1.56$, $P = 0.2548$, but clearly existed among carriers of the C/C allele, $t(39) = 3.37$, $P = 0.0034$. In consequence, older any-T carriers and C/C-allele carriers showed a marginal difference in the landmark distances, $t(76.4) = 2.28$, $P = 0.0510$. None of corresponding differences for the younger adults or the boundary distances was significant (all Ps > 0.42). No effects of any of the covariates were observed. The same analysis with the absolute, not the cumulative, distance revealed a similar pattern, revealing main effects of age group, $F(1,166) = 148.36$, $P < 0.0001$ and memory type, $F(1,172) = 294.95$, $P < 0.0001$ as well as a significant triple interaction of *KIBRA* SNP rs17070145 x age group x memory type, $F(1, 151) = 4.41$, $P = 0.0372$. Of specific interest, this analysis also revealed an age group by memory type interaction, $F(1,151) = 27.30$, $P < 0.0001$, that indicated that the performance difference between age groups was smaller for the landmark relative to the boundary memory (12.0 vm vs 18.0 vm).

FIGURE 1. Virtual environment task. A: First person view of the environment, including grass plane surrounded by a circular boundary (stone wall) Picture i) shows a large view of the environment including the object and the landmark as the participants saw it. Pictures ii–v show additional views that illustrate how the environment was experienced from different positions close to the landmark or boundary. B,C: Trial structure for different conditions illustrated with bird's eye view of schematic environment and walking paths. B: Each test trial started with a fixation cross for 2 s, after which the current object was cued (4 s). After the cue, participants could walk freely in the environment until they reached the location where they remembered to have picked up the object in the encoding trials. Once they indicated their answer by a button press, the object appeared at its correct location and participants had to pick it up again. C: Upper panel: In transfer trials the landmark and boundary were shifted relative to each other, as indicated by the arrow. To the participant, neither the old landmark position nor the shift itself was visible. Middle panel: transfer trials proceeded as test trials (Fixation, Cue, Replacement of object) but without feedback. Lower Panel: For transfer trials, we calculated the distance of a given response to (a) the object location as defined by the boundaries ("dist B") as well as to (b) the object location as defined by the landmark (the location that would result if the same landmark/boundary movement would be applied to it, "dist LM"). D: The design of the experiment is illustrated. Each run consisted of one encoding trial per object, which were followed by 3 test trials per object. At the end of each run, 1 transfer trial was administered per object. The entire procedure was repeated three times in runs 1-3, where the objects and their locations were exchanged between runs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

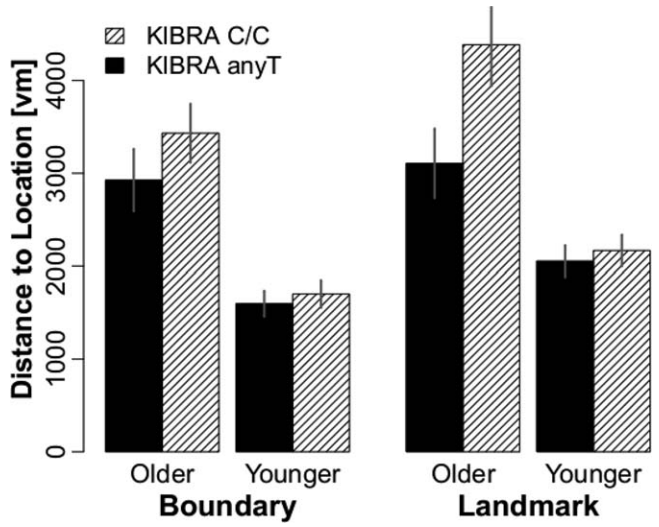


FIGURE 3. Mean cumulative distance to landmark and boundary locations. Only data (adjusted for covariates) from the transfer trials are shown after the relative movement of the landmark/boundary. Error bars show standard errors of the mean.

To further investigate the differential role of landmark and boundary-related spatial learning in younger and older adults, we examined the relation between learning success and behavior in the transfer trials. To this end, we calculated a regression for each age group with the cumulative distance to the target location at the end of learning as the dependent and the cumulative distance to the landmark and boundary locations as two independent variables. Among younger adults, the boundary distance error had a positive relation to the error at the end of learning, $\beta_B = 0.77$, $P < 0.0001$. This was not the case for the distance error to the landmark ($\beta_{LM} = -0.04$, $P = 0.783$). Furthermore, including intercept and interaction terms of *KIBRA* SNP rs17017145 genotype did still only indicate boundary as the sole meaningful independent variable, $\beta_B = 0.72$, $P < 0.0001$. These results indicate that among younger participants, responses closer to the boundary location in the transfer trials were associated with better performance during learning. The same analysis for older adults revealed an association of landmark distance error and error in the last test trial, $\beta_{LM} = 0.60$, $P = 0.0001$, but no association to boundary distance, $\beta_B = 0.16$, $P = 0.4373$. As for the younger adults, the inclusion of intercept and interaction terms for *KIBRA* rs17017145 polymorphism still indicated landmark distance as the only significant predictor, $\beta_{LM} = 0.45$, $P = 0.045$. Hence, among older participants transfer responses closer to the landmark location were associated with better performance during learning.

Age and Genetic Effects on Flexible Reactions to Environmental Change

Finally, we investigated how participants responded to changes in the environment that occurred with the transition from the test to the transfer phase (relative movement of landmark/boundary). This analysis is of interest for two reasons: first, to evaluate the performance during the transfer trials in light of the performance during test trials; it seems important to understand the behavioral consequences of a mismatch between two navigationally relevant cues in the transfer condition (as compared with a situation where both cues can be used, possibly in an integrated manner). Second, previous research has shown that aging and hippocampal damage results in specific impairments when an animal faces an environmental change (Tanila et al., 1997; Milani et al., 1998). Moreover it is known that neurogenesis decreases during aging (Kuhn et al., 1996; Leuner et al., 2007) and that decreased hippocampal neurogenesis results in an decreased ability to integrate novel information into existing spatial representations (Garthe et al., 2009, see also Kempermann, 2002, 2008, for a theoretical account). To characterize participants' behavior, we analyzed the time spent in the environment and the path length immediately before and after the landmark was moved. To this end, we computed the difference between time and path length in the last trial before and the first trial after the relative landmark to boundary movement. The difference in navigation time was submitted to an ANOVA with the same factors as above. In this analysis, only the main effect of age group and the age group by run interaction were significant, driven by the fact that younger adults had a larger increase in navigation time after environmental change than older adults, with $F(1, 142) = 8.87$, $P = 0.0034$, and $F(2, 112) = 4.71$, $P = 0.0108$ for the age main effect and the interaction, respectively (Fig. 4A). The same analysis with path length indicated a trend for an effect of age, $F(1, 80.2) = 3.24$, $P = 0.0757$. Moreover, we tested whether the increase in time has a functional implication by correlating individual mean increase in navigation time with the individual mean distance to the target during the testing phase. We took the distance because it is independent of the time (unlike the cumulative distance). This analysis showed that the better the older adults performed during the test trials (less mean distance to target), the more they increased the time spent after the change in the environment, $r = -0.23$, $P = 0.0402$, with younger adults showing a trend in the same direction, $r = -0.21$, $P = 0.0684$ (Fig. 4B).

DISCUSSION

Previous studies on younger adults have shown that spatial navigation can involve two distinct forms of memory (Doeller et al., 2008) and that genetic variations relevant for hippocampal functions (e.g., *BDNF* SNP rs6265) influence spatial (Banner et al., 2011) and episodic memory (Li et al., 2010). Moreover, earlier findings also revealed age-related declines in spatial navigation (cf. Moffat, 2009) and spatial memory (Lövdén et al., 2007, 2005). However, the effects of aging on different spatial navigation memory forms and its interactions with relevant genetic variations remain elusive. At the same

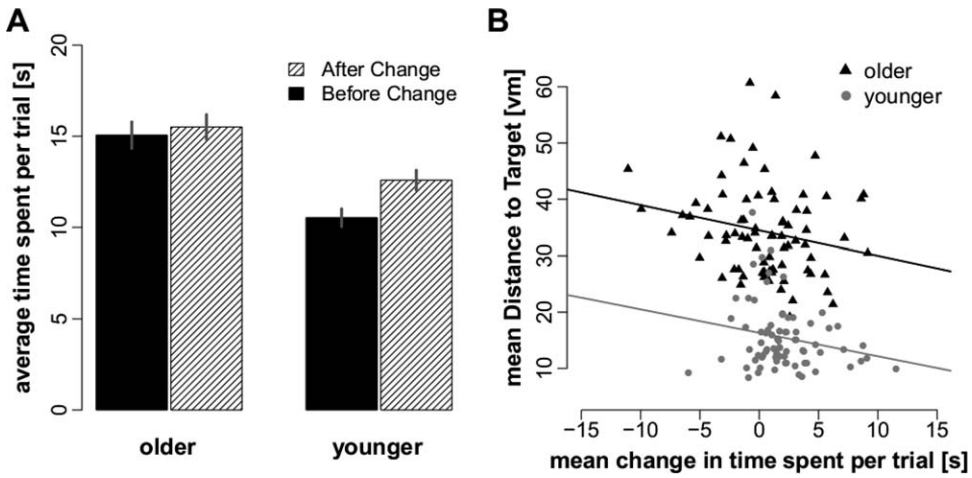


FIGURE 4. Change in time spent per trial after environmental change and its relation to performance. Plots show the last trials before and the first trials after we moved landmark relative to the boundary (one trial per object). Error bars show standard errors of the mean. A: Average time spent per trial before and after landmark/boundary movement (adjusted for covariates). B: Correlation between this change in time and the mean distance to target during the test trials separate for each age group. Each point represents one participant. The line shows the fitted linear regression.

time, previous research underlines the necessity of a better understanding of these effects. For instance, studies in other memory domains (such as implicit memory) have indicated that different types of memory may be impaired to different degrees during aging (e.g., Fleischman et al., 2004; Bennett et al., 2010) and that aging may magnify genetic effects on memory (e.g., Li et al., 2010, 2013; Papenberg et al., 2013). This study investigated these questions in the case of spatial navigation. In particular, we investigated the effect of the *KIBRA* SNP rs17070145 in the context of aging and boundary vs. landmark-related learning during spatial navigation in a VR task.

Our analysis revealed two major results: First, the SNP rs17070145 of *KIBRA* was related to spatial navigation performance in older but not younger participants. Second, our data indicated that among older adults spatial learning relied more on the processing of single intra-maze cues (a landmark) whereas in younger adults it was linked primarily to processing of boundary information. Moreover, younger adults showed larger behavioral effects when boundary and landmark information were put in conflict. Although direct evidence is lacking, the observed association between individual differences in the rs17070145 SNP and navigation performance may likely be enacted via KIBRA's effect on the protein-kinase Cζ (Büther et al., 2004; Schneider et al., 2010) which is involved in regulating hippocampal LTP (Serrano et al., 2008). Consistent with this link, it was previously reported that the *KIBRA* SNP rs17070145 is associated with episodic memory performance in younger (e.g., Papassotiropoulos et al., 2006; Preuschhof et al., 2010; Kauppi et al., 2011) as well as older (Almeida et al., 2008; Schaper et al., 2008) adults. Our finding of an effect of *KIBRA* SNP rs17070145 only in older adults is also in line with previous reports of age-magnified genetic effects, particularly of *BDNF* SNP rs6265 and genetic polymorphisms relevant for dopamine transmission (Nagel et al., 2008; Li et al., 2010; 2012; Papenberg et al., 2013; Störmer et al., 2012). Furthermore, it has also been shown that the association of *KIBRA* SNP rs17070145 with Alzheimer disease might be age-dependent (Rodríguez-Rodríguez et al., 2009). This study extends these findings by providing the first evidence of the same SNP's effect on spatial navigation in older but not younger adults. This genotype by age group interaction supports the conclusion that has been drawn from earlier studies that reported such an interaction; namely the notion that reduced brain resources in older adults in combination with a nonlinear cognition-resources relationship would result in stronger genotype-cognition associations in older as compared with younger adults (Lindenberger et al., 2008). Given the small sample size of our study, however, a replication of these results in a different study group is necessary. All analyses controlled for the influence of a number of covariates, including BDNF and sex. While the apparent lack of an effect of sex might be surprising (Lövdén et al., 2007), it is beyond the scope of the current investigation to evaluate possible explanations. Potential limitations that result from using a VR task come from the absence of proprioceptive and vestibular feedback. Because interactions between sensorimotor and cognitive functions might have an additional influence on effects of aging on spatial navigation (Lövdén et al., 2005), variants of the present task that employ real world navigation in older adults should be subject to further investigation. Despite the differences between virtual and real spatial navigation, results from VR experiments are well in line with the aforementioned previous results from animal studies and computational work (Packard et al., 1989; Burgess and O'Keefe, 1996; O'Keefe and Burgess, 1996; Pearce et al., 1998; Horne et al., 2010). Specifically, the validity of computer-based VR experiments for

studying the neural bases of spatial navigation as also been shown previously in animals (Dombeck et al., 2010; Chen et al., 2013; Domnisoru et al., 2013; Schmidt-Hieber and Häusser, 2013) and in humans (Moffat and Resnick, 2002; Doeller et al., 2010; Etchamendy et al., 2011).

Apart from our findings related to spatial learning in a stable virtual environment (test trials), our results from the transfer trials offer additional insights and could lead to future research. First, we found a greater reliance on landmark-related spatial information in older adults, a finding which was further supported by less age-related differences in landmark-related error as compared to boundary-related error. This seems unexpected in light of equivalent age-related decline of the striatum and the hippocampus (Raz et al., 2005). At the same time, however, this is in line with previous investigations that also studied striatum and hippocampus-dependent memory forms in different age groups. Specifically, it has been found that among older adults implicit memory, which relies on the striatum in younger adults, is relatively more intact as compared with explicit memory, which relies on the hippocampus in younger adults (e.g., Fleischman et al., 2004; Bennett et al., 2010). Moreover, other studies implied potential age differences in the use of navigation strategies, which might in part also have contributed to our finding. In particular, older adults appear to prefer a egocentric strategy that depends more on the striatum (Rodgers et al., 2012). Whether the egocentric strategy would translate into increased reliance on landmark information, however, needs to be a subject of future research.

Second, our finding that *KIBRA* SNP rs17070145 had a specific effect on landmark-related spatial memory in older adults, but no effect of boundary-related learning in either age group, seems to contradict some existing literature. Based on the known associations of the KIBRA protein with hippocampal processes and the link of boundary-related spatial navigation to hippocampal activity, one would expect a link between *KIBRA* SNP rs17017145 and boundary-related navigation. Similar to our argumentation above, however, it is important to take into account that the known links of spatial navigation processes to brain activity might be changed in older adults. Specifically, while the findings by Doeller et al. (2008) suggest that landmark-related spatial navigation is striatum but not hippocampus-dependent in younger adults, it does not necessarily imply that this is also the case in older adults. In contrast, the literature on implicit and explicit learning we mentioned above indeed suggests that memory processes that are striatum-dependent in younger adults (implicit learning) can involve the hippocampus in older adults (Dennis and Cabeza, 2011; Rieckmann et al., 2010). Rieckmann et al. (2010) provide a correlation between hippocampal activation and performance in the "striatal" implicit learning task, suggesting that hippocampal activation might be linked to the functional preservation of formerly striatum-dependent memory tasks. Similarly, it might be the case that landmark-related processes in older adults are also hippocampus-dependent, or are supported by a wider network of brain regions (e.g., Burgess, 2008; for all activation related to landmark processing see Doeller et al., 2008). In addition, Moffat et al. (2007) provide results that would not support the interpretation we offered above. The authors reported that volume of the caudate nucleus correlated with spatial navigation performance in younger and older adults, but hippocampal volume correlated only to younger adults performance, hence questioning a potential role of the hippocampus for spatial navigation in older adults (see also Moffat et al., 2006, where an increased activity of the frontal cortex and a reduced activity of the hippocampus is shown in older adults). Taken together, while the present findings seem contrary to some existing knowledge, they also seem consistent with previous investigations. These unresolved issues call for future studies that combine genetic variables with functional and structural brain measures which investigate interactions between molecular and brain mechanisms that affect age differences in spatial navigation.

A further behavioral finding was that younger adults reacted stronger to partial changes in an otherwise familiar environment. Compared with older participants, younger adults spend relatively more time in the environment when the landmark was changed. While the time participants spent is a rather broad characteristic of navigation behavior, correlations between changes in this measure and performance during learning suggested that it reflects something functional. One potential interpretation is that the increase in time reflects an integration of both cues in younger adults in the regular environment. The correlation between time increase and spatial learning might also suggest that the time increase observed to a larger extent in younger as compared to older adults might be linked to a general ability to flexibly use spatial cues present in a changed environment. The interpretation would be in line with a number of animal studies showing an increase in preservative behavior following hippocampal cell loss (Milani et al., 1998) and changed reactions of hippocampal place cells to changes in spatial cues in aged rats (Tanila and Shapiro, 1997), which are further characterized by a more rigid coding (Tanila et al., 1997), reduced selectivity in new environments (Tanila et al., 1997), increased remapping (Barnes et al., 1997), and less experience-dependent plasticity (Shen et al., 1997). In a wider context, our observed age-related difference in this ability would also be in line with previous research that has shown that decreased hippocampal neurogenesis resulted in an decreased ability to integrate novel information into existing spatial representations (Kempermann, 2002, 2008; Garthe et al., 2009, for a theoretical account), because neurogenesis is known to decrease during aging (Kuhn et al., 1996; Leuner et al., 2007).

In conclusion, this study showed that age-related differences in spatial navigation performance are modulated by *KIBRA* SNP rs17017145 genotype. Specifically, older T-allele carriers performed overall better than older C/C carriers, whereas we did not find such a difference among younger adults. Results from a transfer phase showed that among older adults more reliance on landmark information was associated with better performance, whereas among younger adults more reliance on boundary information was associated with better performance.

These findings suggest that younger and older adults differ with respect to the relative importance of the types of spatial cues that contribute to better spatial navigation performance, which might reflect age-related changes in spatial navigation strategies (Harris et al., 2012; Konishi and Bohbot, 2013; Wiener et al., 2013), or impaired hippocampal functioning (Moffat et al., 2006, 2007). Finally, from a broader perspective, the reported genotype by age group interactions substantiate the view that aging-related declines in brain integrity at multiple levels (neurochemical, structural, and functional) may contribute to age-related differences in genotype-phenotype relations (Lindenberger et al., 2008; Li et al., 2010, 2013; Papenberg et al., 2013).

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REFERENCES

Almeida OP, Schwab SG, Lautenschlager NT, Morar B, Greenop KR, Flicker L, Wildenauer D. 2008. KIBRA genetic polymorphism influences episodic memory in later life, but does not increase the risk of mild cognitive impairment. J Cell Mol Med 12:1672–6. doi:10.1111/j.1582-4934.2008.00229.x

Banner H, Bhat V, Etchamendy N, Joober R, Bohbot VD. 2011. The brain-derived neurotrophic factor Val66Met polymorphism is associated with reduced functional magnetic resonance imaging activity in the hippocampus and increased use of caudate nucleus-dependent strategies in a human virtual navigation task. Eur J Neurosci 33:968–977. doi:10.1111/j.1460-9568.2010.07550.x

Barnes CA, Suster MS, Shen J, McNaughton BL. 1997. Multistability of cognitive maps in the hippocampus of old rats. Nature 388:272–275. doi:10.1038/40859

Barry C, Hayman R, Burgess N, Jeffery KJ. 2007. Experience-dependent rescaling of entorhinal grids. Nat Neurosci 10:682–684. doi:10.1038/nn1905

Bennett IJ, Madden DJ, Vaidya CJ, Howard JH, Howard DV. 2011. White matter integrity correlates of implicit sequence learning in healthy aging. Neurobiol Aging 32:2317.e1–12. doi:10.1016/j.neurobiolaging.2010.03.017

Bohbot VD, Iaria G, Petrides M. 2004. Hippocampal function and spatial memory: Evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. Neuropsychology 18:418–425. doi:10.1037/0894-4105.18.3.418

Bohbot VD, Lerch J, Thorndycraft B, Iaria G, Zijdenbos AP. 2007. Gray matter differences correlate with spontaneous strategies in a human virtual navigation task. J Neurosci 27:10078–10083. doi:10.1523/JNEUROSCI.1763-07.2007

Bullens J, Nardini M, Doeller CF, Braddick O, Postma A, Burgess N. 2010. The role of landmarks and boundaries in the development of spatial memory. Dev Sci 13:170–180. doi:10.1111/j.1467-7687.2009.00870.x

Burgess N. 2008. Spatial cognition and the brain. Annals NY Acad Sci 1124:77–97. doi:10.1196/annals.1440.002

Burgess N, O'Keefe J. 1996. Neuronal computations underlying the firing of place cells and their role in navigation. Hippocampus 762:749–762.

Büther K, Plaas C, Barnekow A, Kremerskothen J. 2004. KIBRA is a novel substrate for protein kinase Czeta. Biochem Biophys Res Commun 317:703–707. doi:10.1016/j.bbrc.2004.03.107

Chai XJ, Jacobs LF. 2009. Sex differences in directional cue use in a virtual landscape. Behav Neurosci 123:276–283. doi:10.1037/a0014722

Chen G, King JA, Burgess N, O'Keefe J. 2013. How vision and movement combine in the hippocampal place code. Proc Natl Acad Sci USA 110:378–383. doi:10.1073/pnas.1215834110

Dennis NA, Cabeza R. 2011. Age-related dedifferentiation of learning systems: An fMRI study of implicit and explicit learning. Neurobiol Aging 32:2318.e17–30. doi:10.1016/j.neurobiolaging.2010.04.004

Doeller CF, Barry C, Burgess N. 2010. Evidence for grid cells in a human memory network. Nature 463:657–661. doi:10.1038/nature08704

Doeller CF, Burgess N. 2008. Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. Proc Natl Acad Sci USA 105:5909–5914. doi:10.1073/pnas.0711433105

Doeller CF, King JA, Burgess N. 2008. Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. Proc Natl Acad Sci USA 105:5915–5920. doi:10.1073/pnas.0801489105

Dombeck DA, Harvey CD, Tian L, Looger LL, Tank DW. 2010. Functional imaging of hippocampal place cells at cellular resolution during virtual navigation. Nat Neurosci 13:1433–1440. doi:10.1038/nn.2648

Domnisoru C, Kinkhabwala AA, Tank DW. 2013. Membrane potential dynamics of grid cells. Nature 495:199–204. doi:10.1038/nature11973

Driscoll I, Sutherland RJ. 2005. The aging hippocampus: Navigating between rat and human experiments. Rev Neurosci 16:87–121.

Etchamendy N, Konishi K, Pike GB, Marighetto A, Bohbot VD. 2011. Evidence for a virtual human analog of a rodent relational memory task: A study of aging and fMRI in young adults. Hippocampus 880:869–880. doi:10.1002/hipo.20948

Fleischman DA, Wilson RS, Gabrieli JDE, Bienias JL, Bennett DA. 2004. A longitudinal study of implicit and explicit memory in old persons. Psychol Aging 19:617–625. doi:10.1037/0882-7974.19.4.617

Gallagher M, Burwell R, Burchinal MR. 1993. Severity of spatial learning impairment in aging: development of a learning index for performance in the Morris water maze. Behav Neurosci 107:618.

Garthe A, Behr J, Kempermann G. 2009. Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. PLoS One 4:e5464. doi:10.1371/journal.pone.0005464

Gazova I, Vlcek K, Laczó J, Nedelska Z, Hyncicova E, Mokrisova I, Sheardova K, et al. 2012. Spatial navigation—A unique window into physiological and pathological aging. Frontiers Aging Neurosci 4:16. doi:10.3389/fnagi.2012.00016

Granon S, Poucet B. 1995. Medial prefrontal lesions in the rat and spatial navigation: evidence for impaired planning. Behav Neurosci 109:474–484.

Hafting T, Fyhn M, Molden S, Moser M-B, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. Nature 436:801–806. doi:10.1038/nature03721

Harris MA, Wiener JM, Wolbers T. 2012. Aging specifically impairs switching to an allocentric navigational strategy. Frontiers Aging Neurosci 4:29. doi:10.3389/fnagi.2012.00029

Harris MA, Wolbers T. 2012. Ageing effects on path integration and landmark navigation. Hippocampus 22:1770–1780. doi:10.1002/hipo.22011

Hartley T, Maguire EA, Spiers HJ, Burgess N. 2003. The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. Neuron 37:877–888.

Hartley T, Trinkler I, Burgess N. 2004. Geometric determinants of human spatial memory. Cognition 94:39–75. doi:10.1016/j.cognition.2003.12.001

Horne MR, Iordanova MD, Pearce JM. 2010. Spatial learning based on boundaries in rats is hippocampus-dependent and prone to overshadowing. Behav Neurosci 124:623–632. doi:10.1037/a0020824

Howard DV, Howard JH. 1989. Age differences in learning serial patterns: Direct versus indirect measures. Psychology Aging 4:357–364.

Iaria G, Palermo L, Committeri G, Barton JJS. 2009. Age differences in the formation and use of cognitive maps. Behav Brain Res 192:187–191. doi:10.1016/j.bbr.2008.08.040

Jansen P, Schmelter A, Heil M. 2010. Spatial knowledge acquisition in younger and elderly adults: A study in a virtual environment. Exp Psychol 57:54–60. doi:10.1027/1618-3169/a000007

Johannsen S, Duning K, Pavenstädt H, Kremerskothen J, Boeckers TM. 2008. Temporal-spatial expression and novel biochemical properties of the memory-related protein KIBRA. Neuroscience 155:1165–1173. doi:10.1016/j.neuroscience.2008.06.054

Kaasinen V, Vilkman H, Hietala J, Någren K, Helenius H, Olsson H, Farde L, et al. 2000. Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. Neurobiol Aging 21:683–688. doi:10.1016/S0197-4580(00)00149-4

Kauppi K, Nilsson L-G, Adolfsson R, Eriksson E, Nyberg L. 2011. KIBRA polymorphism is related to enhanced memory and elevated hippocampal processing. J Neurosci 31:14218–14222. doi:10.1523/JNEUROSCI.3292-11.2011

Kempermann G. 2002. Why new neurons? Possible functions for adult hippocampal neurogenesis. J Neurosci 22:635–638.

Kempermann G. 2008. The neurogenic reserve hypothesis: What is adult hippocampal neurogenesis good for? Trends Neurosci 31:163–169. doi:10.1016/j.tins.2008.01.002

Kenward MG, Roger JH. 1997. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 53:983–997.

Konishi K, Bohbot VD. 2013. Spatial navigational strategies correlate with gray matter in the hippocampus of healthy older adults tested in a virtual maze. Frontiers Aging Neurosci 5:1. doi:10.3389/fnagi.2013.00001

Kuhn HG, Dickinson-Anson H, Gage FH. 1996. Neurogenesis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. J Neurosci 16:2027–2033.

Leuner B, Kozorovitskiy Y, Gross CG, Gould E. 2007. Diminished adult neurogenesis in the marmoset brain precedes old age. Proc Natl Acad Sci USA 104:17169–17173. doi:10.1073/pnas.0708228104

Li S-C, Lindenberger U, Sikström S. 2001. Aging cognition: From neuromodulation to representation. Trends Cogn Sci 5:479–486.

Li S-C, Lindenberger U, Hommel B, Aschersleben G, Prinz W, Baltes PB. 2004. Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. Psychol Sci 15:155–163.

Li S-C, Chicherio C, Nyberg L, Von Oertzen T, Nagel IE, Papenberg G, Sander T, et al. 2010. Ebbinghaus revisited: Influences of the BDNF Val 66 Met polymorphism on backward serial recall are modulated by human aging. J Cogn Neurosci 22:2164–2173. doi:10.1162/jocn.2009.21374

Li S-C, Papenberg G, Nagel IE, Preuschhof C, Schröder J, Nietfeld W, Bertram L, et al. 2013. Aging magnifies the effects of dopamine transporter and D2 receptor genes on backward serial memory. Neurobiol Aging 34:358.e1–358.e10. doi:10.1016/j.neurobiolaging.2012.08.001

Light LL, Zelinski EM. 1983. Memory for spatial information in young and old adults. Developmental Psychology 19:901–906.

Lindenberger U, Nagel IE, Chicherio C, Li S-C, Heekeren HR, Bäckman L. 2008. Age-related decline in brain resources modulates genetic effects on cognitive functioning. Frontiers Neurosci 2:234–244. doi:10.3389/neuro.01.039.2008

Lövdén M, Schellenbach M, Grossman-Hutter B, Krüger A, Lindenberger U. 2005. Environmental topography and postural control demands shape aging-associated decrements in spatial navigation performance. Psychol Aging 20:683–694. doi:10.1037/0882-7974.20.4.683

Lövdén M, Herlitz A, Schellenbach M, Grossman-Hutter B, Krüger A, Lindenberger U. 2007. Quantitative and qualitative sex differences in spatial navigation. Scandinavian J Psychol 48:353–358. doi:10.1111/j.1467-9450.2007.00582.x

Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J. 1998. Knowing where and getting there: A human navigation network. Science 280:921–924. doi:10.1126/science.280.5365.921

McDonald RJ, White NM. 1994. Parallel information processing in the water maze: Evidence for independent memory systems involving dorsal striatum and hippocampus. Behav Neural Biol 61:260–270.

Milani H, Uemura U, Oliveira R. 1998. Loss of CA1 cells following global ischaemia correlates with spatial deficits in the circular platform task. J Neurosci 80:19–27.

Milnik A, Heck A, Vogler C, Heinze H-J, De Quervain DJ-F, Papassotiropoulos A. 2012. Association of KIBRA with episodic and working memory: A meta-analysis. Am J Med Gene Part B, Neuropsychiatric Gene 159B(8):958–969. doi:10.1002/ajmg.b.32101

Moffat SD. 2009. Aging and spatial navigation: What do we know and where do we go? Neuropsychol Rev 19:478–489. doi:10.1007/s11065-009-9120-3

Moffat SD, Resnick SM. 2002. Effects of age on virtual environment place navigation and allocentric cognitive mapping. Behav Neurosci 116:851–859. doi:10.1037/0735-7044.116.5.851

Moffat SD, Zonderman AB, Resnick SM. 2001. Age differences in spatial memory in a virtual environment navigation task. Neurobiol Aging 22:787–796.

Moffat SD, Elkins W, Resnick SM. 2006. Age differences in the neural systems supporting human allocentric spatial navigation. Neurobiol Aging 27:965–972. doi:10.1016/j.neurobiolaging.2005.05.011

Moffat SD, Kennedy KM, Rodrigue KM, Raz N. 2007. Extrahippocampal contributions to age differences in human spatial navigation. Cerebral Cortex 17:1274–1282. doi:10.1093/cercor/bhl036

Nagel IE, Chicherio C, Li S-C, Von Oertzen T, Sander T, Villringer A, Heekeren HR, et al. (2008). Human aging magnifies genetic effects on executive functioning and working memory. Frontiers Hum Neurosci 2:1. doi:10.3389/neuro.09.001.2008

Nilsson L-G. 2003. Memory function in normal aging. Acta Neurologica Scandinavica 179:7–13.

O'Keefe J, Burgess N. 1996. Geometric determinants of the place fields of hippocampal neurons. Nature 381:425–428. doi:10.1038/381425a0

O'Keefe J, Dostrovsky J. 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34:171–175. doi:10.1016/0006-8993(71)90358-1

O'Keefe J, Nadel L. 1978. The Hippocampus as a Cognitive Map. Oxford: Oxford University Press.

Packard MG, McGaugh JL. 1992. Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: Further evidence for multiple memory systems. Behav Neurosci 106:439–446.

Packard MG, Hirsh R, White NM. 1989. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. J Neurosci 9:1465–1472.

Papassotiropoulos A, Stephan DA, Huentelman MJ, Hoerndli FJ, Craig DW, Pearson JV, Huynh K-D, et al. (2006). Common Kibra alleles are associated with human memory performance. Science 314:475–478. doi:10.1126/science.1129837

Papenberg G, Bäckman L, Nagel IE, Nietfeld W, Schröder J, Bertram L, Heekeren HR, et al. (2013). Dopaminergic gene polymorphisms affect long-term forgetting in old age: Further support for the magnification hypothesis. J Cognitive Neurosci 25:571–579. doi: 10.1162/jocn_a_00359

Parslow D, Brammer M, Dawson GR, Jackson SHD, Morris RG, Hospital W. 2009. Age-related neural activity during allocentric spatial memory. Memory 17:125–134. doi:10.1080/09658210802077348

Pearce JJM, Roberts AADL, Good M. 1998. Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. Nature 62:1997–1999.

Preuschhof C, Heekeren HR, Li S-C, Sander T, Lindenberger U, Bäckman L. 2010. KIBRA and CLSTN2 polymorphisms exert interactive effects on human episodic memory. Neuropsychologia 48:402–408. doi:10.1016/j.neuropsychologia.2009.09.031

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, et al. 2005. Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. Cerebral Cortex 15:1676–1689. doi:10.1093/cercor/bhi044

Rieckmann A, Fischer H, Bäckman L. 2010. Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: Relations to performance. NeuroImage 50:1303–1312. doi:10.1016/j.neuroimage.2010.01.015

Rinne JO, Hietala J, Ruotsalainen U, Säkö E, Laihinen A, Någren K, Lehikoinen P, et al. 1993. Decrease in human striatal dopamine D2 receptor density with age: A PET study with [11C]raclopride. J Cerebral Blood Flow Metabolism? 13:310–314. doi:10.1038/jcbfm.1993.39

Rodgers MK, Sindone JA, Moffat SD. 2012. Effects of age on navigation strategy. Neurobiol Aging 33:202.e15–202.e22. doi:10.1016/j.neurobiolaging.2010.07.021

Rodriguez S, Gaunt TR, Day INM. 2009. Hardy-Weinberg equilibrium testing of biological ascertainment for mendelian randomization studies. Am J Epidemiol 169:505–514. doi:10.1093/aje/kwn359

Rodríguez-Rodríguez E, Infante J, Llorca J, Mateo I, Sánchez-Quintana C, García-Gorostiaga I, Sánchez-Juan P, et al. 2009. Age-dependent association of KIBRA genetic variation and Alzheimer's disease risk. Neurobiol Aging 30:322–324. doi:10.1016/j.neurobiolaging.2007.07.003

Schaper K, Kolsch H, Popp J, Wagner M, Jessen F. 2008. KIBRA gene variants are associated with episodic memory in healthy elderly. Neurobiol Aging 29:1123–1125. doi:10.1016/j.neurobiolaging.2007.02.001

Schmidt-Hieber C, Häusser M. 2013. Cellular mechanisms of spatial navigation in the medial entorhinal cortex. Nat Neurosci 16:325–331. doi:10.1038/nn.3340

Schneider A, Huentelman MJ, Kremerskothen J, Duning K, Spoelgen R, Nikolich K. 2010. KIBRA: A new gateway to learning and memory? Frontiers Aging Neurosci 2:4. doi:10.3389/neuro.24.004.2010

Serrano P, Friedman EL, Kenney J, Taubenfeld SM, Zimmerman JM, Hanna J, Alberini C, et al. 2008. PKMzeta maintains spatial, instrumental, and classically conditioned long-term memories. PLoS Biol 6:2698–2706. doi:10.1371/journal.pbio.0060318

Shen J, Barnes CA, McNaughton BL, Skaggs WE, Weaver KL. 1997. The effect of aging on experience-dependent plasticity of hippocampal place cells. J Neurosci 17:6769–6782.

Shing YL, Rodrigue KM, Kennedy KM, Fandakova Y, Bodammer N, Werkle-Bergner M, Lindenberger U, et al. 2011. Hippocampal subfield volumes: Age, vascular risk, and correlation with associative memory. Frontiers Aging Neurosci 3:2. doi:10.3389/fnagi.2011.00002

Störmer VS, Passow S, Biesenack J, Li S-C. 2012. Dopaminergic and cholinergic modulations of visual-spatial attention and working memory: Insights from molecular genetic research and implications for adult cognitive development. Dev Psychol 48:875–889. doi:10.1037/a0026198

Tanila H, Shapiro M, Gallagher M, Eichenbaum H. 1997. Brain aging: Changes in the nature of information coding by the hippocampus. J Neurosci 17:5155–5166.

Tanila H, Shapiro ML. 1997. Discordance of spatial representation in ensembles of hippocampal place cells. Hippocampus 3:613–623.

Tanila H, Sipila P, Shapiro M, Eichenbaum H. 1997. Brain aging?: Impaired coding of novel environmental cues. J Neurosci 17:5167–5174.

Taube JS. 2007. The head direction signal: Origins and sensory-motor integration. Ann Rev Neurosci 30:181–207. doi:10.1146/annurev.neuro.29.051605.112854

Walhovd KB, Westlye LT, Amlien I, Espeseth T, Reinvang I, Raz N, Agartz I, et al. 2011. Consistent neuroanatomical age-related volume differences across multiple samples. Neurobiol Aging 32:916–932. doi:10.1016/j.neurobiolaging.2009.05.013

Wenger E, Schaefer S, Noack H, Kühn S, Mårtensson J, Heinze H-J, Düzel E, et al. 2012. Cortical thickness changes following spatial navigation training in adulthood and aging. NeuroImage 59:3389–3397. doi:10.1016/j.neuroimage.2011.11.015

Wiener JM, De Condappa O, Harris MA, Wolbers T. 2013. Maladaptive bias for extrahippocampal navigation strategies in aging humans. J Neurosci 33:6012–6017. doi:10.1523/JNEUROSCI.0717-12.2013

Yassa MA, Mattfeld AT, Stark SM, Stark CEL. 2011. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. Proc Natl Acad Sci USA 108:8873–8878. doi:10.1073/pnas.1101567108