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Dissociating effects of aging and genetic risk of sporadic Alzheimer's disease on path integration

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ABSTRACT

Path integration is a spatial navigation ability that requires the integration of information derived from self-motion cues and stable landmarks, when available, to return to a previous location. Path integration declines with age and Alzheimer's disease (AD). Here, we sought to separate the effects of age and AD risk on path integration, with and without a landmark. Overall, 279 people participated, aged between 18 and 80 years old. Advanced age impaired the appropriate use of a landmark. Older participants furthermore remembered the location of the goal relative to their starting location and reproduced this initial view without considering that they had moved in the environment. This lack of adaptative behavior was not associated with AD risk. In contrast, participants at genetic risk of AD (apolipoprotein E ε4 carriers) exhibited a pure path integration deficit, corresponding to difficulty in performing path integration in the absence of a landmark. Our results show that advanced-age impacts landmark-supported path integration, and that this age effect is dissociable from the effects of AD risk impacting pure path integration.

1. Introduction

Spatial navigation in humans is a complex cognitive ability that allows individuals to orientate in space. Navigation is vulnerable to the aging process (Lester et al., 2017; Moffat, 2009), and disorientation is also an early symptom of Alzheimer's disease (AD) (Coughlan et al., 2018; Igarashi, 2023). Distinguishing impairment in spatial navigation due to aging from that related to early AD could help with detecting early AD pathology.

Navigation is guided by information derived from self-motion cues and stable landmarks (Wolbers and Hegarty, 2010). Various navigation strategies combine these 2 types of information to facilitate successful navigation. Path integration is a type of navigation that corresponds to the ability of keeping track of and returning to a previously visited location. It requires the integration of self-motion over time by using external landmarks, when available. In path integration, the current position is estimated continuously according to an initial location (Fukawa et al., 2020; McNaughton et al., 2006).

Path integration is assumed to rely on the entorhinal cortex (EC), particularly the postero-medial entorhinal cortex (pmEC), which contains grid cells. Grid cells have the property of firing according to a hexagonal pattern (Hafting et al., 2005). Grid cells are believed to contribute to path integration, estimating a particular location according to an initial location (Banino et al., 2018; Bush et al., 2015; Gil et al., 2018); however, errors accumulate over time (Hardcastle et al., 2015). Error accumulation can be corrected for with visual information from stable landmarks, objects, and boundaries (Hardcastle et al., 2015). This information is processed through the antero-lateral entorhinal cortex

Abbreviations: AD, alzheimer's disease; alEC, antero-lateral entorhinal cortex; APOE, apolipoprotein E; EC, entorhinal cortex; LPI, landamrk-supported path integration; MMSE, mini-mental state examination; PET, positron emission tomography; pmEC, postero-medial entorhinal cortex; PPI, pure path integration; SD, standard deviation; vkm, virtual kilometer; vm, virtual kilometer

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(alEC) and is projected to the hippocampus (Knierim et al., 2014). The hippocampus receives path integration information from the pmEC and visual information about objects from the alEC. These 2 sources of information are integrated in the hippocampus to improve self-localization estimates (Fukawa et al., 2020).

The entorhinal cortex and hippocampus are vulnerable to both normal aging and early AD pathology (Igarashi, 2023; Kunz et al., 2015; Segen et al., 2022). There is evidence that the alEC dysfunctions with healthy aging (Reagh et al., 2018) and in preclinical AD (Knierim et al., 2014). However, knowledge remains limited about how the presence of a landmark affects path integration across different age ranges (West et al., 2023) and to what extent the impairment of path integration is identical in normal aging versus preclinical AD. In AD, tauopathy, which is related to cognitive impairment (Hanseeuw et al., 2019), starts to accumulate in the transentorhinal cortex, which consists of the alEC and perirhinal cortex (Braak and Braak, 1991; Sanchez et al., 2021). Subsequently, tauopathy encompasses the entire EC (Braak stage II) and spreads to the medial temporal lobe, including the hippocampus (Braak stage III) (Braak and Braak, 1991). The spread of tauopathy in the entire EC, including the pmEC, could impair grid-cell functioning and lead to pure path integration (PPI) deficit in early stages of AD (Bierbrauer et al., 2020; Fu et al., 2017; Igarashi, 2023; Jun et al., 2020; Kunz et al., 2015; Ridler et al., 2020; Ying et al., 2022).

The main objective of this study was to distinguish path integration deficits relating to advanced age (up to 80 years old) from those related to an increased genetic risk of developing sporadic AD. Because the alEC is commonly affected by tau pathology due to aging, we hypothesized that older individuals would have greater difficulty in processing visual information from a proximal landmark. By contrast, because the pmEC is mainly affected by tau pathology due to preclinical AD stages, we hypothesized that PPI, without an external landmark, would be impaired in older carriers of the apolipoprotein E (*APOE*) ε4 allele (the main genetic risk factor for sporadic AD), as this process is considered to rely more strongly on grid cells localized in the pmEC. The second objective of this study was to investigate mechanisms used by older participants to navigate. Because we hypothesized that older adults would have difficulty in using an external landmark to navigate, we investigated whether older participants would have a bias toward an egocentric strategy.

2. Methods

2.1. Participants

We recruited 282 clinically normal volunteers with an age range of 18–80 years old in Belgium through local advertisements. These volunteers were asked to perform a visual path integration task, the "Apple Game" (Akan et al., 2023; Bierbrauer et al., 2020). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board. All participants gave their written informed consent. All participants reported normal or corrected-to-normal vision and no recent illness or change in medical treatment during the last 3 months.

We classified participants into four age groups: ≤50 years, 51–60 years, 61–70 years, and 71–80 years. The youngest group was considered to have no AD neuropathology, because AD is extremely rare before 50 years of age ("2022 Alzheimer's disease facts and figures," 2022). To ensure that participants older than 50 years old had no cognitive impairment, we evaluated their mini-mental state examination (MMSE) (Folstein et al., 1975). We excluded participants with an MMSE below 25/30 (n = 3). Furthermore, the genetic risk of developing AD was estimated by genotyping the *APOE* gene.

2.2. APOE genotyping

Participants were not genetically preselected. All participants were analyzed for *APOE* polymorphisms rs429358 (which is a [C/T] substitution on chromosome 19q13.32 of the sequence GCTGGGCG CGGACATGGAGGACGTG[C/T]GCGGCCGCCTGGTGCAGTACCG CGG) and rs7412 (which is a [C/T] substitution of the sequence CCGCGATGCCGATGACCTGCAGAAG[C/T]GCCTGGCAGTGTACCAGGCCG GGGC). Based on the 2 single-nucleotide polymorphisms, 1 of the 3 alleles was assigned ε2, ε3, or ε4 (see Supplement for detailed methods on *APOE* genotyping). The *APOE* ε4 allele represents a major risk factor of AD, whereas the ε2 allele confers a protective effect (Corder et al., 1993; Farrer, 1997; Roses, MD, 1996). We classified participants into 2 groups: "ε4 carriers–risk group" (ε3ε4 and ε4ε4) and "ε4 noncarrier–control group" (ε2ε2, ε2ε3 and ε3ε3); ε4 carriers had a higher risk of developing AD compared to ε4 noncarriers. We excluded participants with the genotypes ε2ε4, because their risk of developing AD was intermediate as they have 1 protective allele and 1 at risk allele.

2.3. Characteristics of the genetic subgroups

We recruited 282 participants, of which 279 had an MMSE higher or equal to 25/30. The 3 participants with an MMSE below 25/30 have been excluded from the analyses. Therefore, 279 participants were included in the study. The prevalence of ε4 carriers (risk group) was 26.16% (ε3ε4: 24.37%; ε4ε4: 1.79%). The prevalence of ε4 noncarriers (control group) was 70.97% (ε2ε3: 11.83%; ε3ε3: 58.78%, ε2ε2: 0.36%). The prevalence of excluded participants (n = 8) was 2.87% (ε2ε4: 2.87%). The MMSE, video game experience, education, and age did not differ between ε4 carriers and noncarriers using two-sample *t*-tests (Table 1). The video game experience corresponded to the number of hours during which participants played video games per week. Education corresponded to the number of years of study. A χ^2 test confirmed that gender repartition was not different between *APOE* groups (Table 1). Across age and *APOE* groups, we did not observe differences in terms of gender repartition using χ^2 tests, or education, MMSE, or video game experience, using a 1-way ANOVA.

2.4. Experimental task

Participants performed a visual path integration task, the Apple Game (Bierbrauer et al., 2020). The task was implemented via Unreal Engine (Epic Games, version 4.11). The game was displayed on a 15-inch full HD screen. During the game, players moved in a virtual

Table 1
Demographic data of included participants

	ε4 noncarriers	ε4 carriers	*p*-values
N (%)	198 (73%)	73 (27%)	
APOE genotype (n)	ε3ε3 (164), ε2ε3 (33), ε2ε2 (1)	ε3ε4 (68), ε4ε4 (5)	
Gender: male/female	70/128	28/45	0.75[a]
Education (years): mean (SD)	16.03 (2.38)	16.60 (2.33)	0.07[b]
MMSE*: mean (SD)	28.53 (1.19)	28.33 (1.29)	0.32[b]
Hours video game per week: mean (SD)	1.03 (2.70)	1.21 (3.00)	0.65[b]
Age: mean (SD)	57.29 (16.30)	58.61 (15.20)	0.53[b]
≤50 years: n	51	16	0.78[a]
51–60 years: n	41	16	
61–70 years: n	65	28	
71–80 years: n	41	13	

P-values refer to (a) χ^2-test and (b) two-sample *t*-test.
SD: standard deviation.
* For participants older than 50 years old.

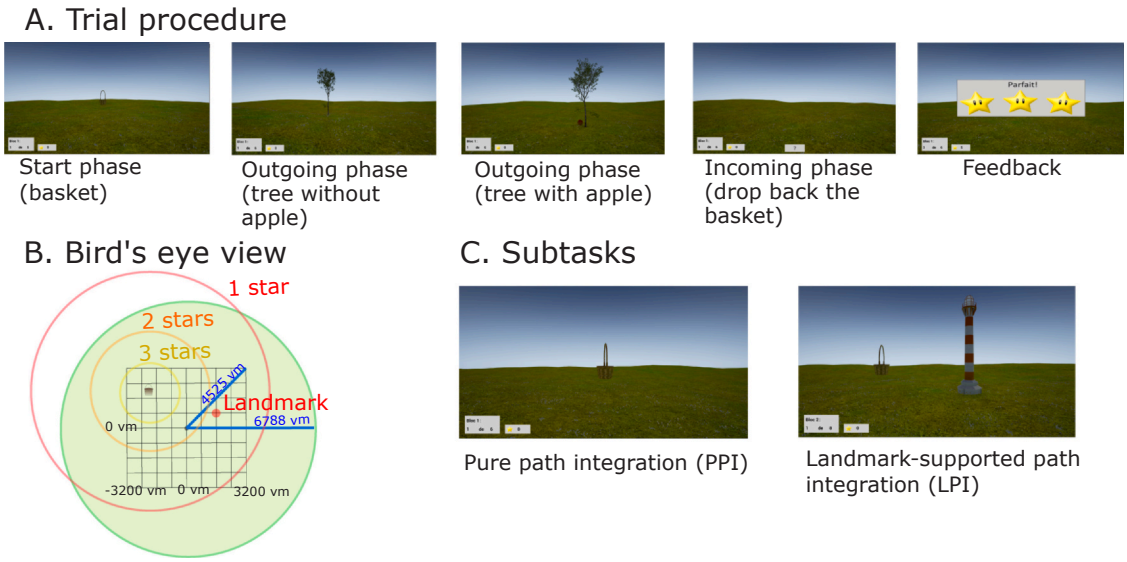

Fig. 1. Experimental paradigm. (A) Trial procedure: participants pick up an empty basket (start phase), find an apple under a tree (outgoing phase), and return the basket to its original location with the apple in it (incoming phase). They then received feedback as stars according to the distance between the correct basket location and the return location. (B) Bird's eye view of the virtual environment. Baskets and trees were randomly positioned in an 8 × 8 grid (3200 vm × 3200 vm). The landmark was located at x = 1600 vm and y = 800 vm in the LPI condition. (C) The task contained 2 subtasks depending on the presence or absence of supportive spatial cues. The PPI subtask contained no external cues, whereas the LPI subtask contained a landmark (lighthouse).

environment using a joystick (Trust GXT 555 Predator). The joystick allowed them to move forward, turn left, or turn right. Moving backward was not possible, such that movement direction was identical to heading direction. The position of participants was sampled at 5 Hz.

The game environment was an endless grassy field with a blue sky rendered at infinity. Players arrived on the field at a start location. First, they looked for an empty basket and collected it (start phase, Fig. 1A). Then, a tree appeared in the environment, with or without an apple at the bottom. In both cases, participants were asked to walk toward the tree. When they reached the tree, it disappeared, and a new tree appear if there was no apple at the bottom of the tree. Participants walked from tree to tree with the basket (outgoing phase, Fig. 1A) until reaching the tree with the apple. Once players collected the apple in the basket, they had to return, as directly as possible, to the remembered original location where the basket was collected from (incoming phase, Fig. 1A) and return it (drop it back). Then, the participants received feedback on performance via 0–3 stars. The number of stars depended on the Euclidean distance between the response location and the correct goal location (< 1600 vm [virtual meter] for 3 stars, < 3200 vm for 2 stars, < 6400 vm for 1 star, Fig. 1B). Virtual meters are the metric used to quantify distances in the virtual environment as given by Unreal Engine (Bierbrauer et al., 2020).

All phases were self-paced, except the incoming phase, which had a time limit of 30 seconds. The mean time to return the basket to the original location was 16.27 seconds. If participants did not return the basket within the time limit, their final position was used as the return (or drop) location. This happened in 3.3% of all trials.

The locations of baskets and trees were randomly distributed on an invisible grid of 8 × 8 squares (bin edge length 800 vm, Fig. 1B). The grid was surrounded by an invisible circular area with a radius of 1.5 * grid half diagonal (6788 vm). Participants could not move outside this circular area, and their speed decreased linearly to 0 when their distance from the center of the arena exceeded 5656 vm. In this speed reduction zone, participants could navigate at full speed when heading toward the center of the arena. This action was implemented to ensure that participants did not navigate too far away from the relevant part of the infinite environment.

The task was implemented as 2 environmental subtasks, which were defined by the absence or presence of supportive spatial cues (Fig. 1C). In the "PPI" subtask, the environment did not contain any landmarks. In the "landmark-supported path integration" (LPI) subtask, a landmark, represented by a lighthouse, which looked the same from every angle, was present in the virtual environment.

The paradigm was subdivided into 5 blocks. The first block was a training block and was not analyzed. Each block had 6 trials, with 3 trials for each subtask (PPI and LPI). For each subtask, there was 1 trial with 1, 2, and 3 trees. For trials with 1 tree, the apple was at the bottom of the first tree. For trials with 2 or 3 trees, the apple was at the bottom of the second or third tree. Thus, there were 1 or 2 distractor trees, respectively. A distractor tree was a tree that leads the participant to a particular location to increase the difficulty of path integration. In each block, trials were grouped by subtask in a pseudorandom order. The number of trees was also pseudorandomized. Participants could take breaks between blocks. Participants started the first trial for each block at the center of the virtual environment. In all other trials, their start location corresponded to the final location of the previous trial. Between each trial, a black screen was displayed for 5 seconds.

After the first analyses, we noticed that trials with 3 trees were very difficult for older participants. To increase the number of trials with 1 and 2 trees, without increasing the time for doing the task, we decided to remove trials with 3 trees from the task. Therefore, some participants (n = 64) conducted a paradigm of 5 blocks with 8 trials. The first block remained a training block. Each block had 4 trials in both subtasks (PPI and LPI), with 2 trials with 1 tree and 2 trials with 2 trees in a pseudorandom order.

A subsample of participants (n = 37) also performed a previous version of the Apple Game (Bierbrauer et al., 2020). This previous version was developed for younger participants (mean age: 38 years old) and included trials with 1–5 trees, in 3 subtasks (PPI, LPI, and boundary-based path integration). We decided to simplify the task by limiting the number of trees, and focusing on the PPI and LPI subtasks, to best test our hypotheses. For the subsample of participants having performed this previous version of the task, we only analyzed trials in the LPI and PPI subtasks, with 1, 2, or 3 trees (as was performed by the other participants). This setup corresponded

to 3 trials with 1 tree (corresponding to the tree with an apple), 3 trials with 2 trees, and 4 trials with 3 trees in PPI and LPI. The fact that not all participants conducted the same version of the paradigm was considered in our models by using a random effect. It was never significant indicating that the version of the task did not influence the performance of participants.

2.5. Data analysis

We extracted behavioral data from logfiles using MATLAB (2020a, The MathWorks Inc.). Statistical analyses were conducted with R (4.0.3) (R Core Team) using the lmerTest (3.1.3) (Bates et al., 2014) and emmeans (1.5.4) packages (Russell, 2019).

2.5.1. Performances analysis

We analyzed spatial navigation performances using linear mixed models. The participant and version of the paradigm were allocated as random factors in all models. All distance variables were divided by 1000 to be expressed as vkm (virtual kilometer). Gender, video game experience, and education were covariates in all models. We only reported the effects of the *APOE* and age groups here. We compared age groups differences, and *APOE* effects in each age group, using estimated marginal means (emmeans function) or estimated marginal means of linear trends (emtrends function) (Russell, 2019). We used the Kenward-Roger method to calculate the degrees of freedom. The level of significance was set to $\alpha = 0.05$. We corrected all *p*-values for multiple comparisons using Bonferroni-Holm methods.

Performance was quantified based on the drop error (Fig. 2A); in other words, the Euclidean distance between the correct original location of the basket and the final return (drop) location. Based on our hypothesis, we modeled the drop error with predictors for age groups, *APOE* status, and their interaction. As the effect of variables could vary according to subtask (PPI vs. LPI) and difficulty (number of trees), we constructed separate models for each subtask and difficulty level. Therefore, the subtask and difficulty level were not covariates in the models. The following linear mixed model was used to estimate the drop error:

$$error = \beta_0 + \beta_{0i} + \beta_{0j} + \beta_1 AgeGroup + \beta_2 APOE + \beta_3 Gender + \beta_4 Video\ Game + \beta_5 Education + \beta_{12} AgeGroup^{*} APOE \quad (1)$$

In the model, β_{0i} is a random intercept per participant, and β_{0j} is a random intercept per version. We analyzed whether drop errors differed between age groups and ε4 carriers and noncarriers in each age group using estimated marginal means, with covariates being set to the average (emmeans function) (Russell, 2019).

We also analyzed the 2 components of the drop error (distance and rotation errors) using analogous linear mixed models (Eq. 1). The distance error is the absolute value of the difference between the incoming distance (distance from the stop after the apple to the correct basket location) and the response distance (Fig. 2B). The response distance is the distance between the stop location after the apple and the drop location. The rotation error is the angle between the drop location, the stop after the apple, and the correct basket location (Fig. 2C). This angle could be any values between 0° and 180°. We used the stop location after the apple, not the exact apple location, as the reference point for the apple to compute metrics (response distance, angle error, incoming distance, and outgoing distance). In 7.1% of trials, the response distance was 0. In these trials, we used the angle between the gaze direction and the correct basket location (Fig. 2C) to determine the rotation error.

Next, we investigated the behavior of the participants. We hypothesized that the behavior of advanced-age participants could be affected by the initial view of the basket if they used an incorrect egocentric strategy. We focused on the response distance and studied parameters affected it. Ideally, the response distance should be equal to the incoming distance (Fig. 2A). We analyzed whether the response distance would be also affected by the start-basket distance. The start-basket distance is the distance between the start location of the participant in the trial and the basket (Fig. 2A) and corresponds to the distance at which participants initially saw the basket. This initial view distance of the basket should not affect the response distance but might disturb participants if they memorize the basket location relative to their initial starting location during a given trial. For each subtask and difficulty level, we computed a linear mixed model of the response distance according to the incoming distance (correct distance to travel), start-basket distance (initial view distance), age group, and *APOE* status. Because we were interested in the effects of aging, we added interactions between the incoming distance and age group and between the start-basket distance and age group. We fitted the following model:

$$Response\ distance = \beta_0 + \beta_{0i} + \beta_{0j} + \beta_1 Incoming\ distance + \beta_2 Start\ basket\ distance + \beta_3 AgeGroup + \beta_4 Gender + \beta_5 APOE + \beta_6 Video\ Game + \beta_7 Education + \beta_{13} Incoming\ distance^{*} AgeGroup + \beta_{23} Start\ basket\ distance^{*} AgeGroup \quad (2)$$

When participants performed the task perfectly, β_1 would be equal to 1 and all other regressors would be equal to 0, such that the response distance would be equal to the incoming distance. We first tested whether the response distance differed across age groups. We then compared the β estimates of the incoming distance and the start-basket distance according to age groups.

Then, to examine whether distance parameters were influenced by *APOE* status in addition to age, we fitted a second model by adding the triple interactions among *APOE* status, age group, and incoming distance and among *APOE* status, age group, and start-basket distance. We tested whether β estimates differed according to *APOE* status in each age group.

2.5.2. Landmark effect

We compared trials with and without a landmark. We estimated drop errors according to age groups, subtask (PPI vs. LPI), their interaction, and *APOE* status. The following linear mixed model was fitted for each difficulty level:

$$drop\ error = \beta_0 + \beta_{0i} + \beta_{0j} + \beta_1 AgeGroup + \beta_2 APOE + \beta_3 Gender + \beta_4 Video\ Game + \beta_5 Education + \beta_6 Subtask + \beta_{16} AgeGroup^{*} Subtask \quad (3)$$

The *p*-values of regressors were computed with Satterthwaite's method as implemented in the lmer function (Bates et al., 2014).

2.5.3. Angle relative to the landmark

We investigated whether the initial view of the basket relative to the landmark affected the drop location. During the task, participants first had to search for the empty basket. They initially viewed the basket at a certain location relative to the landmark. For example, players initially saw the basket to the right in front of the landmark (Fig. 2D). This initial view of the basket location relative to the landmark is represented by the initial view angle (start-landmark-basket angle). Then, participants walked toward the apple tree and had to return (drop back) the basket with the apple at the remembered original location. In the example (Fig. 2D), when participants were at the apple location, they had to return the basket to the left of the landmark (correct angle to drop the basket). We assessed how the apple-landmark-drop location angle was affected by the correct angle and the initial view angle for each age group. In the example (Fig. 2D), if participants were affected by the initial view of

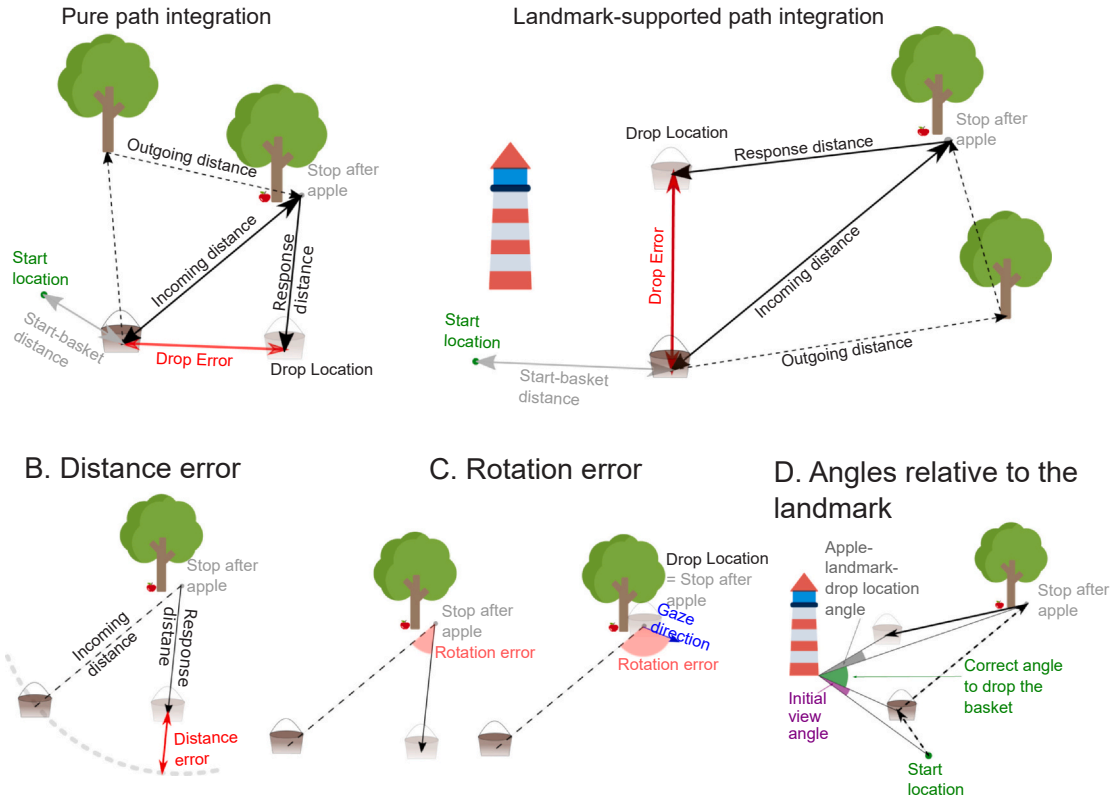

Fig. 2. (A) Task parameters. Participants started navigation at the start location, searched for an empty basket and collected it. The start-basket distance is the distance between the start location and the basket location. Participants then navigated from tree to tree until finding a tree with an apple (outgoing distance). Finally, they aimed to navigate back to the remembered original basket location. The drop error is the Euclidean distance between the correct basket location (basket in dark color) and the drop location (basket in bright color). The incoming distance is the distance between the apple tree (stop after apple) and the correct basket location. The response distance is the distance between the stop after apple and the drop location. (B) Distance error. The distance error is the absolute value of the difference between the incoming distance and the response distance. (C) Rotation error. The rotation error is the angle among the basket, apple (stop after the apple tree), and drop location. If the drop location is localized at the stop after apple (i.e., the response distance is 0), the rotation error is defined as the angle between the gaze direction when the player dropped the basket and the correct basket location. (D) Angles relative to the landmark. When players were at the start location, they saw the basket at a certain location relative to the landmark (initial view angle). Then, they collected the apple and had to drop the basket with the apple using an angle relative to the landmark called the correct angle to drop the basket. The angle relative to the landmark from the apple to the basket drop location is the apple-landmark-drop location angle.

the basket, they would drop the basket to the right in front of the landmark. Both angles (apple-landmark-drop location angle and correct angle to drop the basket) were computed with the stop after the apple as reference point. As parameters could change with age, we added the interaction between age group and angle regressors. We fitted the following model for each difficulty level:

$$\begin{aligned} \textit{angle apple landmark basket} = {} & \beta_0 + \beta_{0i} + \beta_{0j} + \beta_1 \textit{Correct angle} \\ & + \beta_2 \textit{Initial view angle} + \beta_3 \textit{Gender} \\ & + \beta_4 \textit{APOE} + \beta_5 \textit{Video Game} \\ & + \beta_6 \textit{Education} + \beta_7 \textit{AgeGroup} \\ & + \beta_{17}\, \textit{Correct angle*AgeGroup} \\ & + \beta_{27}\, \textit{Initial view angle*AgeGroup} \end{aligned} \quad (4)$$

Then, we assessed whether *APOE* status modified the effect of the correct angle and the initial view angle by adding the triple interactions among correct angle, age group, and *APOE* and among initial view angle, age group, and *APOE*.

2.5.4. Distractor trees

We evaluated the effect of distractor trees. We compared the drop error of trials with 1 and 2 distractor trees. We used Eq. (1) and added an interaction between the number of trees and age group.

2.6. Summary of hypotheses

Our hypotheses are summarized in Table 2. First, we hypothesized that, among older participants at risk of AD (ε4 carriers), tau pathology will spread to the entire EC, including the pmEC. This should lead to a deficit in PPI, due to the implication of grid cells localized in the pmEC. We therefore hypothesized that older ε4 carriers will make higher drop errors than noncarriers of the same age group in PPI (Hyp. 1.1). It is currently not clear how exactly grid cells support path integration. Some studies on rodents overt that grid cells support distance estimation for path integration (Evans et al., 2016; Stemmler et al., 2015). Other studies suggest that grid cells are more generally implied in path integration, including distance and direction estimation (McNaughton et al., 2006). Therefore, we decomposed the drop errors into distance and rotation errors. We hypothesized that higher drop errors among older ε4 carriers would be related to both higher distance errors and higher rotation errors. In contrast, in LPI, the landmark would help both ε4 carriers and noncarriers. Therefore, in the LPI subtask, we did not expect performance differences between ε4 carriers and noncarriers in any age group (Hyp. 1.2).

The second aim of our study was to investigate the effect of advanced age on LPI. We hypothesized that, with age, the alEC will dysfunction, which will affect landmark processing. Therefore, the drop error should increase with age in LPI (Hyp. 2.1) and the positive effect of the landmark should decrease with age (Hyp. 2.2).

Table 2
Summary of hypotheses on the *APOE* and aging effect on path integration

Effect of the risk of AD (older ε4 carriers) on path integration		
Hypothesis 1: With AD risk, tau accumulates in the entire EC, including the pmEC, leading to grid-cell dysfunction and a pure path integration (PPI) deficit		
	Hypotheses	Equations
Hyp. 1.1	Higher drop errors, distance errors, and rotation errors, in PPI in older ε4 carriers	Eq. (1) in PPI: errors according to age and *APOE* ε4 status
Hyp. 1.2	No deficit in landmark-supported path integration (LPI) in ε4 carriers versus noncarriers in any age group	Eq. (1) in LPI: errors according to age and *APOE* ε4 status
Effect of advanced age on path integration		
Hypothesis 2: Dysfunction of the alEC, leading to difficulty in using the landmark with age		
	Hypotheses	Equations
Hyp. 2.1	Decrease in the positive effect of the landmark with age	Eq. (3): Drop errors according to age and subtask (PPI vs. LPI)
Hyp. 2.2	Deficit in LPI performances with age, not with ε4 status	Eq. (1) in LPI: errors according to age and *APOE* ε4 status
Hypothesis 3: Bias toward an egocentric strategy with age		
	Hypotheses	Equations
Hyp. 3.1	Response distance influenced by the initial view distance with age	Eq. (2) in PPI and LPI: Response distance according to the correct distance and initial view distance for each age group
Hyp. 3.2	Drop location relative to the landmark influenced by the initial view angle of the goal relative to the landmark with age (Fig. 2D)	Eq. (4): Apple-landmark-drop location angle according to the correct angle and the initial view angle for each age group
Hyp. 3.3	The bias toward an egocentric strategy is not different in ε4 carriers versus noncarriers	No triple interaction among *APOE* group, age groups, and regressors of Eqs. (2) and (4)

Key: AD, Alzheimer's disease; pmEC, postero-medial entorhinal cortex; alEC, antero-lateral entorhinal cortex; *APOE*, apolipoprotein E; EC, entorhinal cortex.

Finally, we investigated the cognitive mechanisms behind age-related path integration deficits. We hypothesized that older participants use an incorrect egocentric strategy (Hyp. 3), resulting in an influence of the initial view of the goal on the response of the participants (Hyp. 3.1 and Hyp. 3.2.), while this initial view is not relevant for solving the task. We hypothesized that this bias toward the initial view of the goal increases with age, but not with AD risk (Hyp 3.3).

3. Results

3.1. Path integration performance without the distractor tree

We first investigated the effects of age and *APOE* status on path integration performance in trials with no distractor tree. In these trials, participants collected the apple at the first tree, then turned around, and returned to the remembered basket location.

3.1.1. Pure path integration—No landmark

In the PPI condition without a distractor tree, drop errors (Fig. 3A; Fig. S1A) and rotation errors (Fig. 3B; Fig. S1B) increased in the 71–80 age group compared to the ≤50 age group. In contrast, distance errors started to increase at the age of 51 years and increased between each consecutive age group (Fig. 3C; Fig. S1C). Thus, distance errors appeared to be more sensitive to aging. Furthermore, ε4 carriers in the 71–80 age group made higher drop errors than noncarriers of the same age (t_{197} = 2.12, p = 0.035), which confirmed our hypothesis 1.1. This deficit was not apparent in rotation errors (t_{203} = 1.51, p = 0.133) or distance errors (t_{195} = 1.39, p = 0.164), showing that the drop error, which combines rotation and distance errors, is most sensitive to AD risk-related deficits.

3.1.1.1. Response distance. Response distance decreased between each age group (Table 3), meaning that, from 50 years onwards, participants traveled shorter distances, an observation consistent with the increased distance error observed with age.

We investigated whether the response distance depended on the correct distance and/or the initial view distance according to the age group, in relation to hypothesis 3.1. Response distances depended well on the correct distance for participants younger than 71 years old whereas the initial view distance influenced participants older than 50 years old (Fig. 4). For participants in the ≤50 age group, the β estimate of the correct distance tended toward 1 (0.74), showing that the response distance was close to the correct distance. The effect of the correct distance on the response distance significantly decreased across age groups (Fig. 4; β incoming distance = 0.74, 0.42, 0.27, and 0.04 for ≤50, 51–60, 61–70, and 71–80 age groups, respectively). This β estimate value was not significantly different from 0 in the 71–80 age group. The ability to estimate distances decreased with age and was largely impaired in the 71–80 age group. In contrast, the β estimate of the start-basket distance was not significantly different from 0 in the ≤50 age group (β = 0.07), contrasting with those over 50 years old (β = 0.12, 0.19, and 0.26 for 51–60, 61–70, and 71–80 age groups, respectively, Fig. 4). The effect of the start-basket distance was higher in the 71–80 age group compared to the ≤50 age group (Fig. 4). In the 71–80 age group, the response distance depended on the initial view distance of the basket only, but not on the correct distance (i.e., they moved a greater distance if the basket was initially far away from them, independent of the distance between the basket and the apple tree). As suggested by hypothesis 3.1, we found that older participants tried to reproduce the distance of the initial view of the basket without considering their path from the basket to the apple tree.

To determine whether this effect of the initial view was related to *APOE* status (Hyp. 3.3), we next studied how *APOE* status affected the use of the correct distance or the initial view distance in each age group. The response distance depended less on the correct distance for ε4 carriers in the 61–70 age group as compared to noncarriers of the same age (t_{1123} = −2.42, p = 0.015). Thus, ε4 carriers in the 61–70 age group were less able to integrate distances, as were all participants in the 71–80 age group, which was not part of our hypotheses. This result highlights a subtle PPI deficit among participants in the 61–70 age group at risk of AD. There was no *APOE* effect on the initial view distance for any age group, as proposed in hypothesis 3.3.

3.1.2. Landmark-based path integration

The presence of the landmark was associated with lower drop errors (Eq. 3, t_{2303} = −7.23, p < 0.001). The interaction between age groups and subtasks was significant, such that the positive effect of the landmark was smaller for each age group above 50 years old compared to the ≤50 age group (t_{2303} = 3.39, p < 0.001 for 51–60; t_{2303} = 2.70, p = 0.007 for 61–70; t_{2303} = 3.73, p < 0.001 for 71–80), confirming hypothesis 2.1. Above 50 years old, participants had more difficulty in using the landmark to improve path integration.

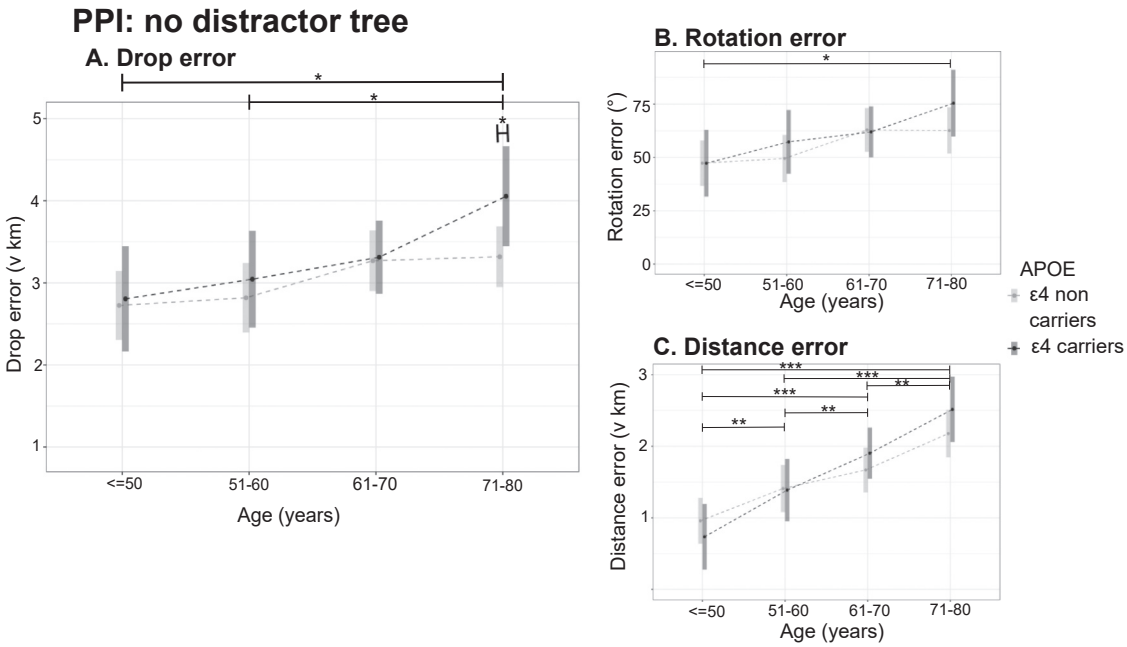

Fig. 3. Linear mixed models (Eq. 1): beta estimates and their confidence intervals according to age and *APOE* groups in pure path integration with no distractor tree (apple at the first tree). (A) Drop errors were higher in the 71–80 age group compared to groups younger than 61 years old. In the 71–80 age group, ε4 carriers had higher drop errors compared to ε4 noncarriers. (B) Rotation errors were higher in the 71–80 age group compared to the ≤50 age group. (C) Distance errors increased between each age group. *P*-values are corrected for multiple comparisons with Bonferroni-Holm method. *0.01 < p < 0.05; **0.001 < p < 0.01; ***p < 0.001. Abbreviations: *APOE*, apolipoprotein E; PPI, pure path integration.

Table 3
Comparison of the response distance between age groups, from Eq. (2), in pure path integration with no distractor tree, using estimated marginal means

Contrast	Degrees of freedom	*t*-ratio	*p*-value
≤50–51–60	212	2.96	0.007
≤50–61–70	157	5.14	< 0.001
≤50–71–80	98	6.91	< 0.001
51–60–61–70	257	2.12	0.035
51–60–71–80	231	4.59	< 0.001
61–70–71–80	231	3.18	0.005

P-values are corrected for multiple comparisons with the Bonferroni-Holm method.

Drop errors (Fig. 5A, Fig. S1D) and distance errors (Fig. 5C, Fig. S1F) were higher in all age groups above 50 years old compared to the ≤50 age group and further increased in the 71–80 age group. Rotation errors were also higher in all age groups above 50 years old (Fig. 5B, Fig. S1E). As stated in hypothesis 2.2, drop errors and rotation errors increased above 50 years old in LPI and increased only above 70 years old in PPI. Thus, the landmark-processing deficit appears earlier than the PPI deficit.

APOE did not affect the drop and rotation errors in any age group (Fig. 5A and B), as supposed by hypothesis 1.2. Interestingly, distance errors were greater for ε4 carriers compared to ε4 noncarriers in the

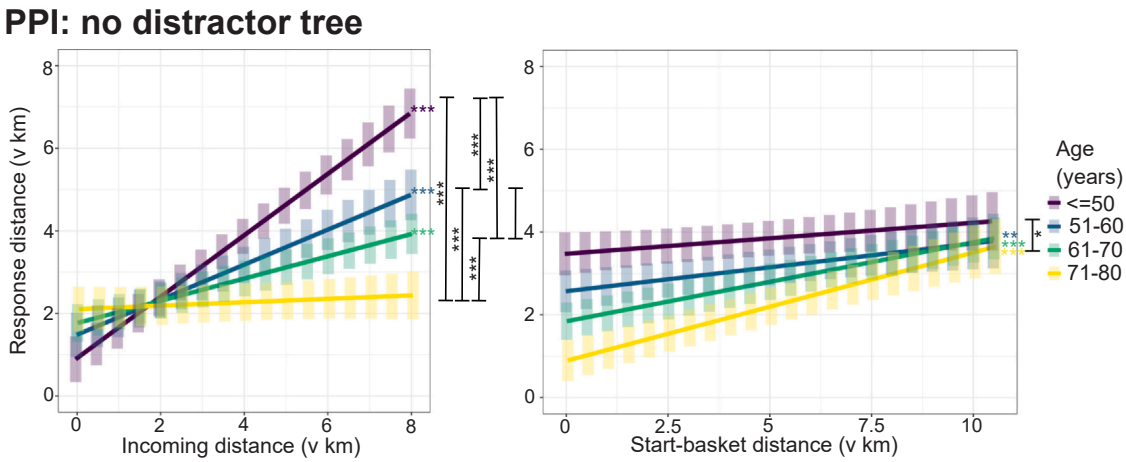

Fig. 4. Linear mixed models (Eq. 2): response distance according to the incoming distance (correct distance) and the start-basket distance (initial view distance of the basket) for each age group in pure path integration with no distractor tree. The effect of the incoming distance on the response distance decreased with age. The correct distance significantly affected the response distance for participants younger than 71 years old. The effect of the start-basket distance on the response distance was higher for the 71–80 age group compared to the ≤50 age group. Confidence intervals are plotted. *P*-values are corrected for multiple comparisons with the Bonferroni-Holm method. *0.01 < p < 0.05; **0.001 < p < 0.01; ***p < 0.001. Abbreviations: PPI, pure path integration.

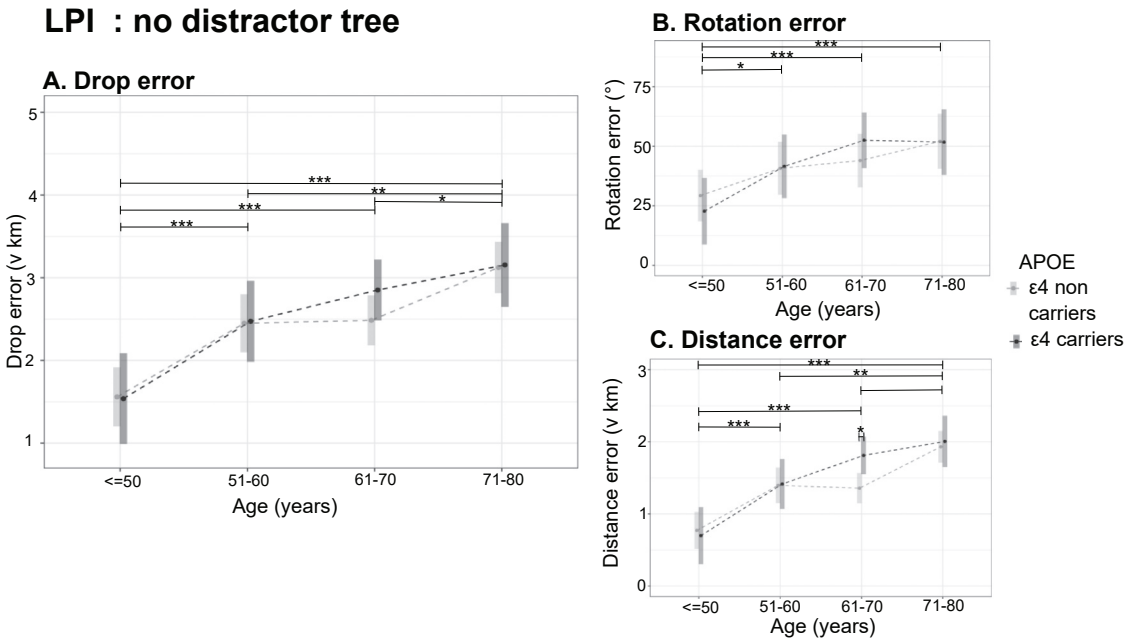

Fig. 5. Linear mixed models (Eq. 1): beta estimates and their confidences intervals according to the age and *APOE* groups in landmark-supported path integration with no distractor tree. (A) Drop errors increased above 50 years old and still increased in the 71–80 age group. (B) Rotation errors increased above 50 years old. (C) Distance errors increased above 50 years old and still increased in the 71–80 age group. In the 61–70 age group, ε4 carriers made greater distance errors compared to ε4 noncarriers. *P*-values are corrected for multiple comparisons by the Bonferroni-Holm method. *0.01 < p < 0.05; **0.001 < p < 0.01; ***p < 0.001. Abbreviations: *APOE*, apolipoprotein E; LPI, landmark-supported path integration.

61–70 age group (t_{220} = 2.98, p = 0.003, Fig. 5C), which was unexpected according to our hypotheses. Participants at risk of AD in the 61–70 age group had greater distance errors in LPI, just as they had difficulty in estimating the correct distance in PPI. Distance errors did not differ between carriers and noncarriers among participants in the 71–80 age group, possibly because older individuals had difficulty estimating distances in both *APOE* groups.

3.1.2.1. Response distance. The response distance was shorter for participants in the 61–70 (t_{133} = −2.97, p = 0.018) and 71–80 age groups (t_{54} = −3.29, p = 0.011) compared to participants in the ≤50 age group (Eq. 2). As in the PPI subtask, the effect of the correct distance on response distance decreased with age (Table 4; β correct distance = 0.74, 0.38, 0.29, and 0.17 for ≤50, 51–60, 61–70, and 71–80 age groups, respectively). In line with hypothesis 3.1, we found that the effect of the start-basket distance tended to increase with age (β start-basket distance = 0.09, 0.10, 0.16, and 0.25 for ≤50, 51–60, 61–70, and 71–80 age groups, respectively), but there were no significant differences across age groups.

We next added a triple interaction among *APOE*, age groups, and distance regressors to test whether the influence of the initial view distance was not affected by *APOE* status (Hyp. 3.3). As in the PPI subtask, the effect of the correct distance was smaller for ε4 carriers compared to noncarriers in the 61–70 age group (t_{1240} = −3.02, p = 0.003). Thus, participants with a higher risk of AD between 61 and 70 years old had more difficulty in estimating distances with and without a landmark. The effect of the start-basket distance was not correlated with *APOE* genotype.

3.1.2.2. Angle relative to the landmark. We furthermore investigated whether participants were affected by the initial view angle of the basket relative to the landmark with advanced age (Hyp. 3.2). The β estimate of the correct angle significantly decreased between each age group (Fig. 6, β correct angle = 0.61, 0.37, 0.20, and 0.07 for ≤50, 51–60, 61–70, and 71–80 age groups, respectively). Participants older than 50 years old were influenced by the initial view angle, whereas participants in the ≤50 age group were not (Fig. 6, β initial view angle = −0.02, 0.22, 0.22, and 0.29 for ≤50, 51–60, 61–70, and 71–80 age groups, respectively). For participants older than 50 years old, the angle depended more significantly on the initial view angle compared to participants in the ≤50 age group (Fig. 6). Thus, older participants were biased by the initial view of the basket and were less likely to take the correct angle into account, providing empirical evidence in support of hypothesis 3.2. For example, if older participants saw the basket initially to the right of the landmark, they would return the basket to the right of the landmark (Fig. 2D) even if they had to pass to the other side of the landmark to reach the apple tree.

We investigated whether the influence of the angle regressors differed between *APOE* groups. Our hypothesis 3.3 proposed that the influence of the initial view was not related to the *APOE* group. The ε4 carriers were less affected by the initial view angle compared to noncarriers in the 71–80 age group (t_{1230} = −2.20, p = 0.028). *APOE* did not affect the correct angle. Hence, participants at risk of AD, in the 71–80 age group, were less affected by the initial basket location

Table 4
Comparison of the effect of the correct distance on response distance across age groups, from Eq. (2), in landmark-supported path integration with no distractor tree, using estimated marginal means of linear trends

Contrast	Degrees of freedom	*t*-ratio	*p*-value
≤50–51–60	1277	4.25	< 0.001
≤50–61–70	1279	5.98	< 0.001
≤50–71–80	1276	7.12	< 0.001
51–60–61–70	1259	1.26	0.207
51–60–71–80	1250	2.68	0.022
61–70–71–80	1248	1.71	0.175

Key: *P*-values are corrected for multiple comparisons with the Bonferroni-Holm method.

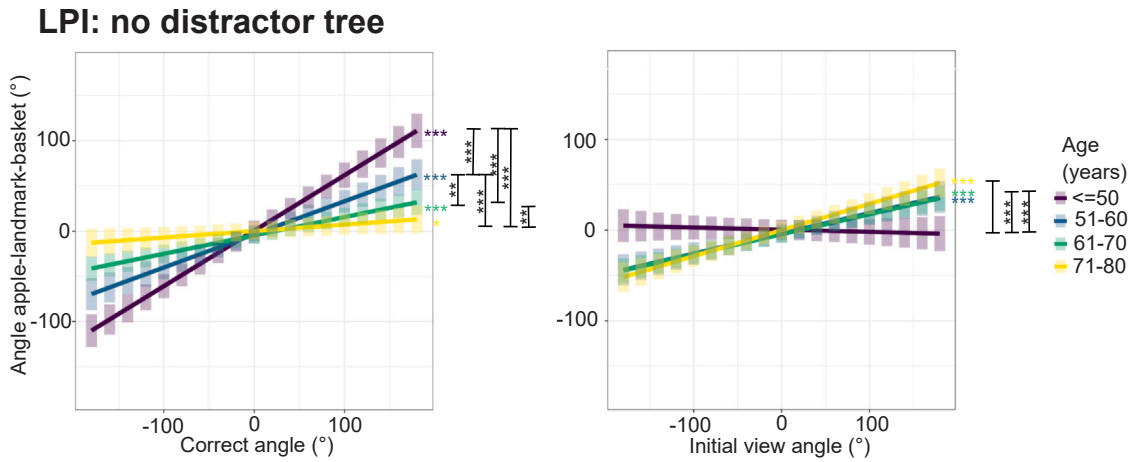

Fig. 6. Linear mixed models (Eq. 4): angle apple-landmark-basket according to the correct angle and initial view angle for each age group in landmark-supported path integration with no distractor tree (apple at the first tree). The effect of the correct angle decreased with increasing age groups. The initial view angle affected participants older than 50 years old more. Confidence intervals are plotted. *P*-values are corrected for multiple comparisons with the Bonferroni-Holm method. *0.01 < p < 0.05; **0.001 < p < 0.01; ***p < 0.001. Abbreviations: LPI, landmark-supported path integration.

relative to the landmark, which is a more correct behavior in principle. However, it could indicate that participants did not remember the initial location of the basket, as they did not drop the basket at a location depending more on the correct angle.

3.2. Path integration with distractor trees

The drop error was smaller with 1 distractor tree compared to 2 distractor trees only for participants younger than 50 years old in both subtasks (without landmark: t_{1861} = −2.01, p = 0.044; with landmark: t_{1864} = −3.43, p < 0.001). Above 50 years old, performance did not decline with the number of distractors, suggesting that the task with 1 distractor tree was already very difficult for these participants. Therefore, we restricted our analyses to trials with 1 distractor tree.

3.2.1. Pure path integration

We provided detailed results on trials with 1 distractor tree in the PPI subtask in Section S3. The drop error and its 2 components were higher above 50 years old compared to the ≤50 age group. The *APOE* group did not affect drop errors (Fig. S2A), rotation errors (Fig. S2B), and distance errors (Fig. S2C) in any age group. In contrast, in PPI with no distractor tree, ε4 carriers in the 71–80 age group had higher drop errors compared to noncarriers (see above). We did not observe any *APOE* effects when adding a distractor tree, probably because the task was too difficult for all older participants.

3.2.2. Landmark-supported path integration

Detailed results on trials with 1 distractor tree in the LPI subtask are provided in Section S4. As in the condition with no distractor tree, the positive effect of the landmark decreased with age. Drop errors (Fig. S3A), rotation errors (Fig. S3B), and distance errors (Fig. S3C) were significantly higher above 50 years old compared to the ≤50 age group. As in the condition without distractor tree, *APOE* did not affect drop errors in any age group; and distance errors were greater for ε4 carriers in the 61–70 age group compared to noncarriers (t_{214} = 2.27, p = 0.024). Interestingly, with a distractor tree, distance errors were also higher for ε4 carriers in the 51–60 age group (t_{232} = 2.03, p = 0.043) as well as rotation errors (Fig. S3B, t_{232} = 2.27, p = 0.024). Thus, adding a distractor tree allowed disclosing a deficit in distance and rotation errors in LPI among participants in the 51–60 age group, but decreased our ability to disclose differences in the participants older than 70 years old. Putatively, this is because the task was too difficult for all participants above a certain age, regardless of their risk status.

4. Discussion

This study provides evidence that aging is associated with a decline in LPI, whereas the risk of developing AD (older ε4 carriers) is related to impairment in PPI. Although both PPI and LPI deteriorated with age, in line with previous studies (Adamo et al., 2012; Allen et al., 2004; Harris and Wolbers, 2012; Lester et al., 2017; Mahmood et al., 2009; Segen et al., 2022; Stangl et al., 2018), we showed that the positive effect of the landmark decreased with age. Furthermore, higher drop errors in LPI appeared at a younger age (from 50 years old) compared to PPI (from 70 years old). We specifically showed that advanced-age participants used an unadaptative strategy, which could explain why they did not benefit as much from the landmark. Older participants were affected by the initial view of their goal (relative to their own start location and/or the external landmark) and reproduced this view without considering that they had moved during the trial. This effect of the initial view of the goal was not related to the participants' risk of developing AD. In contrast, we showed that participants in the 71–80 age group at risk of AD had a PPI deficit, supporting a previous study (Bierbrauer et al., 2020). We also showed that both aging and risk of AD are related to difficulty in estimating distances, and that participants at risk of AD in the 61–70 age group had more difficulty in estimating distances compared to non-at-risk participants.

The main observations were made based on a very simple task (returning after reaching a single tree). Using distractor trees allowed path integration deficits to be detected among younger participants at risk of AD (in the 51–60 age group) but made the task too difficult for advanced-age participants.

This study showed that LPI deteriorates with age, supporting previous studies, which showed that older adults have difficulty with landmark coding (Bécu et al., 2023, 2020; Hill, 2023). We hypothesized that the difficulty in using the landmark with advanced age was attributed to the initial view of the goal (a basket in our task). Older participants tended to return the basket at the same location relative to the landmark and to themselves, as in the initial view of the scene. For example, if participants initially saw the basket far from them at the right of the landmark, they would

remember the basket being far from them to the right of the landmark and would return without taking the fact that they had moved in the environment into account, and that their viewpoint had changed. Thus, older participants lost the ability to update their position and attempted to reproduce a remembered static image. This effect of the initial view shows that older participants remembered the initial view; thus, path integration deficits likely occurred in the absence of visual memory deficits. Of note, older ε4 carriers were less affected by the initial basket location relative to the landmark compared to ε4 noncarriers. Although this seems to be a beneficial behavior, it might indicate that older ε4 carriers had incipient impairment in visual memory, as they did not return the basket to a location depending more on the correct location either.

The current study was able to demonstrate the effect of the initial view of the goal because the task involved 2 important characteristics. First, the start locations differed from the goal locations. Standard path integration tasks tend to be triangle completion tasks (Allen et al., 2004; Harris and Wolbers, 2012; Mahmood et al., 2009); in contrast, here, participants had to reach the goal before starting path integration. During the start phase, participants saw the goal at a specific location relative to themselves and/or to the landmark. This initial view of the goal was not supposed to affect the behavior to return to the goal location at the end of the trial. Thus, participants were supposed to integrate the traveled path, starting at the goal location and not before, from the start location. Our results showed that the initial view of the goal biased the behavior of older participants, indicating that they performed path integration incorrectly.

The second important characteristic of our task was the proximal cue. This cue allowed participants to move around the landmark and change their view of it. Previous path integration studies mostly used distal cues, in which participant could not change their view relative to the cue (Harris and Wolbers, 2012). Our results support other studies showing that older adults have more difficulty with spatial memory tasks when the view point changes (Montefinese et al., 2015; Wiener et al., 2012).

The current study also highlighted that age mainly impaired distance estimation in the 2 subtasks. The response distance was shorter above 50 years old in PPI and above 60 years old in LPI, compared to the ≤50 age group. This result fits with previous studies, which demonstrated an underestimation of distances with age during path integration (Allen et al., 2004; Mahmood et al., 2009). The correct distance affected the response distance less with increasing age. In older adults, the response distance depended more on the distance at which participants initially saw the goal. This effect of the initial view distance was present in both subtasks, with and without the landmark, confirming the robustness of this result.

Our study demonstrated that ε4 carriers, in the 71–80 age group, had a PPI deficit compared to non-at-risk individuals of the same age. As aging and *APOE* ε4 allele are 2 main risk factors of AD, ε4 carriers in the 71–80 age group are more likely to have preclinical AD. Our finding supports studies showing the impairment of spatial navigation in preclinical and prodromal AD (Coughlan et al., 2018; Howett et al., 2019). The lower performance in path integration might be caused by tau pathology in the EC, particularly the pmEC, which contains grid cells. Previous studies showed that path integration performance is correlated with the volume or thickness of the EC (Bierbrauer et al., 2020; Mokrisova et al., 2016). Lower entorhinal grid-cell activity could explain path integration deficits in both normal aging (Stangl et al., 2018) and AD, as previously shown in mice (Fu et al., 2017; Igarashi, 2023; Jun et al., 2020; Ridler et al., 2020; Ying et al., 2022).

Moreover, we showed that ε4 carriers, in the 61–70 age group, had subtle path integration deficits. These participants at risk of AD had more difficulty in estimating distances compared to noncarriers of the same age. Their response distance depended less on the correct distance, in both subtasks (PPI and LPI), and they made higher distance errors with the landmark. This deficit could be related to tau pathology in the EC. Human studies point to a role of the pmEC in distance estimation (Chen et al., 2015; Evans et al., 2016). Previous studies with mice also showed that the medial entorhinal cortex, the mice homolog of human pmEC, contains neurons that encode the distance traveled in the dark, corresponding to grid cells (Campbell et al., 2021).

Age-related difficulty in using landmark information efficiently could be related to hippocampal dysfunction (Colombo et al., 2017) and/or an increasing deficiency of alEC with advanced age (Reagh et al., 2018). The alEC processes information about local landmarks (Chen et al., 2019; Knierim et al., 2014), and there is evidence of age-related dysfunction in the alEC (Reagh et al., 2018). Interestingly, the alEC is included in the transentorhinal cortex. Tau pathology starts accumulating with age in the alEC, which is called primary age-related tauopathy (Crary et al., 2014). Whether this condition is an early stage of AD is subject to debate (Duyckaerts et al., 2015). Tau pathology is observed in the alEC in many older individuals, whereas the entire EC is only affected in older adults with amyloid (Sanchez et al., 2021). Thus, landmark-based navigation might be affected with age independently of PPI. Tau imaging and longitudinal path integration data are needed to explore these subjects and establish a temporal sequence of path integration deficits.

In addition to the alEC and pmEC, hippocampal dysfunction also occurs in older individuals (Lester et al., 2017). Because the hippocampus integrates information from several brain regions, including the alEC and pmEC, it might dysfunction with any EC subregions. Several studies have shown that older adults use extrahippocampal strategies to solve spatial navigation tasks (Colombo et al., 2017; Moffat, 2009; Zhong and Moffat, 2018). We hypothesize that the unadaptative strategy used by older participants to solve our task (i.e., to reproduce the initial view of the basket location) is related to changes to hippocampal and/or alEC function.

This study has several limitations. First, we used genotype as a proxy for the risk of preclinical AD, but we did not measure AD pathology. Future work should evaluate the impact of AD neuropathology on path integration using positron emission tomography (PET) imaging, cerebrospinal fluid, or blood markers of amyloid and tau. Longitudinal studies could also be used to assess the predictive power of path integration measures on subsequent cognitive decline, and the sequence of navigational deficits in normal and pathological aging. Another limitation of this work is that we focused on recruiting older individuals and did not have the statistical power to investigate aging effects before 50 years old. Therefore, we grouped all our participants younger than 50 years old into a single group, which is an arbitrary age limit. Although some middle-age effects could be present before 50 years of age, Yu et al. found no differences in path integration between young and middle-aged participants (Yu et al., 2021). Deeper analyses of the initial view effects in middle-aged participants could help elucidate when and how path integration starts declining. Finally, as older adults displayed subtle deficits in using information about distance and self-motion from optic flow (Lich and Bremmer, 2014), using a purely visual flow task could interfere with performance. However, the function of other senses (proprioception, vestibular functions) also decreases with age. A visual path integration task allows body-based cues to be eliminated. Furthermore, previous studies confirmed that navigation performance in the real world is correlated with performances in virtual environments for healthy older individuals and for patients with neurodegenerative disease (Adamo et al., 2012; Cushman et al., 2008; Stangl et al., 2018).

5. Conclusion

This study showed that a simple path integration task (returning to an original location after reaching a single tree) is suitable for testing older participants, including detecting aging effects, and differences between older *APOE* ε4 carriers and noncarriers. Importantly, this study demonstrated that advanced age impairs the appropriate use of a landmark. Older adults kept in mind the initial view of their goal and reproduced this initial view, without considering their movement during the trial. This unadaptative behavior was not related to ε4 status. This study also confirmed that adults at risk of AD have a PPI deficit. This path integration task is promising to disclose AD pathology among clinically normal older individuals and allows to dissociate effects of age and *APOE*.

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CRediT authorship contribution statement

Lise Colmant: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Anne Bierbrauer**: Software, Writing – review & editing. **Youssef Bellaali**: Investigation. **Lukas Kunz**: Software, Writing – review & editing. **Jasper Van Dongen**: Formal analysis. **Kristel Sleegers**: Formal analysis. **Nikolai Axmacher**: Software, Writing – review & editing. **Philippe Lefèvre**: Writing – review & editing, Supervision. **Bernard Hanseeuw**: Writing – review & editing, Supervision.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2023.07.025.

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