

The Combined Effect of *APOE* and *BDNF* Val66Met Polymorphisms on Spatial Navigation in Older Adults

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Abstract.

Background: The apolipoprotein E (*APOE*) $\epsilon 4$ allele is associated with episodic memory and spatial navigation deficits. The brain-derived neurotrophic factor (*BDNF*) Met allele may further worsen memory impairment in *APOE* $\epsilon 4$ carriers but its role in *APOE* $\epsilon 4$ -related spatial navigation deficits has not been established.

Objective: We examined influence of *APOE* and *BDNF* Val66Met polymorphism combination on spatial navigation and volumes of selected navigation-related brain regions in cognitively unimpaired (CU) older adults and those with amnesic mild cognitive impairment (aMCI).

Methods: 187 participants (aMCI [$n = 116$] and CU [$n = 71$]) from the Czech Brain Aging Study were stratified based on *APOE* and *BDNF* Val66Met polymorphisms into four groups: $\epsilon 4^-/BDNF^{Val/Val}$, $\epsilon 4^-/BDNF^{Met}$, $\epsilon 4^+/BDNF^{Val/Val}$, and $\epsilon 4^+/BDNF^{Met}$. The participants underwent comprehensive neuropsychological examination, brain MRI, and spatial navigation testing of egocentric, allocentric, and allocentric delayed navigation in a real-space human analogue of the Morris water maze.

Results: Among the aMCI participants, the $\epsilon 4^+/BDNF^{Met}$ group had the least accurate egocentric navigation performance ($p < 0.05$) and lower verbal memory performance than the $\epsilon 4^-/BDNF^{Val/Val}$ group ($p = 0.007$). The $\epsilon 4^+/BDNF^{Met}$ group had smaller hippocampal and entorhinal cortical volumes than the $\epsilon 4^-/BDNF^{Val/Val}$ ($p \leq 0.019$) and $\epsilon 4^-/BDNF^{Met}$ ($p \leq 0.020$) groups. Among the CU participants, the $\epsilon 4^+/BDNF^{Met}$ group had less accurate allocentric and allocentric delayed navigation performance than the $\epsilon 4^-/BDNF^{Val/Val}$ group ($p < 0.05$).

Conclusion: The combination of *APOE* $\epsilon 4$ and *BDNF* Met polymorphisms is associated with more pronounced egocentric navigation impairment and atrophy of the medial temporal lobe regions in individuals with aMCI and less accurate allocentric navigation in CU older adults.

Keywords: Alzheimer's disease, apolipoproteins E, brain-derived neurotrophic factor, entorhinal cortex, episodic memory, gene polymorphism, magnetic resonance imaging, mild cognitive impairment, Morris water maze, spatial navigation

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INTRODUCTION

Spatial navigation is a complex and multi-modal cognitive process essential for everyday functioning. It encompasses two basic strategies, egocentric (self-centered) and allocentric (world-centered), using different types of spatial reference frames to develop internal representations of surrounding environment. Egocentric navigation is a navigation strategy, where spatial information about locations and objects is encoded from the viewpoint of the navigator to form a self-centered spatial reference frame (self-to-object representations). Allocentric navigation is a navigation strategy, where locations and objects are encoded in relation to one another independently of the position of the navigator to form a world-centered spatial reference frame (object-to-object representations). Previous research has shown that distinct brain regions underlie egocentric and allocentric navigation strategies. Egocentric navigation is associated with the level of function of the posterior parietal cortex [1] including the precuneus [2] and the posterior cingulate cortex [3]. Allocentric navigation is associated with the level of function of the hippocampus [1] and related medial temporal lobe structures including the entorhinal cortex [4]. Recently, more attention has been focused on spatial navigation impairment as a promising early cognitive marker of Alzheimer's disease (AD) [5, 6]. Allocentric navigation deficits have been observed in individuals with preclinical AD [7], while impairment of both navigation strategies (i.e., egocentric and allocentric) have been observed in individuals with mild cognitive impairment (MCI) [8], especially in those with amnesic MCI (aMCI) [2, 9–11], who are at higher risk of conversion to AD dementia [12]. Spatial navigation impairment observed in the early stages of AD can be explained by the fact that allocentric and egocentric spatial navigation is associated with the level of function of brain regions impaired very early in AD including the hippocampus and entorhinal cortex, and the posterior parietal cortex including precuneus and posterior cingulate cortex, respectively [13–15]. Recently, it has been shown that spatial navigation is a cognitive marker of early AD that shares only limited variance with other cognitive functions and is well distinguishable as a separate cognitive function [16].

Spatial navigation is influenced by genetic background, where the apolipoprotein E gene (*APOE*) is one of the most important indicators. The *APOE* $\epsilon 4$ allele is the strongest genetic risk factor for sporadic AD dementia [17] that lowers its age at onset

[18]. The *APOE* $\epsilon 4$ allele is associated with increased amyloid- β ($A\beta$) accumulation on positron emission tomography (PET) [19], increased tau load in the entorhinal cortex on PET [20], hippocampal atrophy on MRI [21], posterior cingulate and parietal hypometabolism on fluorodeoxyglucose (FDG) PET [22], and greater cognitive decline in older adults [23]. The *APOE* $\epsilon 4$ allele also increases the risk of progression from MCI to dementia [24] probably due to the fact that individuals with aMCI who are carriers of the *APOE* $\epsilon 4$ allele are more likely to have $A\beta$ pathology [25]. Studies found that the *APOE* $\epsilon 4$ allele is associated with worse allocentric navigation performance in cognitively normal older adults [26] and less accurate egocentric and allocentric navigation in individuals with MCI [27–29]. In addition to the *APOE* gene, other genetic polymorphisms associated with AD dementia and impairment of cognitive functions including spatial navigation have been identified. One of these polymorphisms is the very long poly-T variant at rs10524523 of the *TOMM40* gene that modulates risk and onset age of AD dementia [30]. This polymorphism has been associated with worse memory performance in late middle-aged and older adults [31, 32] and also less accurate allocentric navigation in individuals with aMCI [33]. The other polymorphism is the rs17070145 polymorphism of the *KIBRA* gene, where non-carriers of the T-allele have had increased risk of AD dementia [34], worse memory performance [35] and less accurate spatial navigation in a study of cognitively normal older adults [36].

Recent studies indicated that among other genetic polymorphisms the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism may also be associated with an increased risk of AD dementia [37] and more pronounced cognitive impairment [38, 39]. BDNF is a critical neurotrophic factor for synaptic plasticity [40], dendritic arborization [41], and facilitation of long-term potentiation [42], especially in the hippocampus and entorhinal cortex where the place cells and grid cells important for spatial navigation are located [43]. BDNF expression is profoundly reduced in the entorhinal cortex, hippocampus, and parietal cortex of individuals with AD dementia [44, 45], that is, in the regions where the earliest pathological changes of AD have been identified [46]. Lower BDNF levels have been found in *BDNF* Met carriers [47]. The *BDNF* Met allele has been associated with reduced entorhinal [48] and parietal cortical thickness [49] and smaller hippocampal volume on MRI [50], reduced hippocampal activation

on functional MRI [51], lower memory performance [52], and increased reliance on stimulus response rather than allocentric strategy in a human virtual navigation task [53] in cognitively normal younger adults. Next, the *BDNF* Met allele has been associated with accelerated memory decline and a greater rate of hippocampal volume reduction in cognitively normal older adults but only in those with high A β levels on PET [54]. The association between the *BDNF* Met allele and accelerated memory decline has also been reported in individuals with aMCI and high A β levels on PET [55]. The high risk combination of the *APOE* ϵ 4 and *BDNF* Met alleles has shown the most pronounced negative effect on memory in cognitively normal older adults [56]. The later study has found that the combination of the *APOE* ϵ 4 and *BDNF* Met alleles is associated with most accelerated memory decline in cognitively normal older adults but only in those with high A β levels on PET (i.e., those with preclinical AD) [57]. The combination of the *APOE* and *BDNF* Val66Met polymorphisms has also been associated with lowest memory performance in individuals with aMCI [58], prodromal AD and AD dementia [25]. The combined effect of the *APOE* and *BDNF* Val66Met polymorphisms on spatial navigation has not been studied.

Our group has demonstrated that egocentric and allocentric navigation is impaired in early clinical AD [11, 27] and can be influenced by genetic risk factors [33], especially by the *APOE* ϵ 4 allele [28, 29]. Next, the *BDNF* Met allele is associated with structural changes in the navigation-related brain regions (i.e., in the medial temporal lobe structures and parietal cortex [48–50]) and the recent study has indicated that the *BDNF* Val66Met polymorphism may influence spontaneous navigational strategies in younger adults [53]. Building on this research, we assessed the combined effects of the *APOE* and *BDNF* Val66Met polymorphisms on spatial navigation performance and atrophy of brain regions associated with spatial navigation in older adults.

First, we evaluated the effect of combination of the *APOE* and *BDNF* Val66Met polymorphisms on two spatial navigation strategies, egocentric and allocentric, in a real-space version of the human analogue of the Morris Water Maze task (hMWM) in cognitively unimpaired (CU) and aMCI individuals. The effect of combination of the polymorphisms on other cognitive functions was also assessed. Second, we assessed the influence of combination of the *APOE* and *BDNF* Val66Met polymorphisms on volumes of the selected brain regions associated with spatial navigation (the

hippocampus, entorhinal cortex, precuneus, inferior parietal cortex, and posterior cingulate cortex) in CU and aMCI individuals. The association between each spatial navigation strategy and volumes of the relevant brain regions was also tested.

We hypothesized that CU and aMCI participants with the high risk combination of the *APOE* ϵ 4 and *BDNF* Met alleles would exhibit the least accurate spatial navigation performance in the allocentric and both egocentric and allocentric navigation strategies, respectively. The high risk combination of both alleles would also be associated with the worst episodic memory performance, especially in the participants with aMCI. Further, we hypothesized that the high risk participants, especially those with aMCI, would have the most pronounced atrophy of the brain regions associated with spatial navigation and that less accurate spatial navigation performance would be associated with lower volumes of these brain regions, especially in the participants with aMCI.

METHODS

Participants

A total of 187 participants were recruited from the Czech Brain Aging Study (<http://cbas.cz/>) cohort at the Memory Clinic of the Charles University, Second Faculty of Medicine and Motol University Hospital in Prague, Czech Republic and signed an informed consent approved by the local ethics committee [59]. The participants were referred to the Memory Clinic by general practitioners, psychiatrists, and neurologists for memory complaints reported by themselves and/or by their informants. All participants underwent clinical and laboratory evaluations, *APOE* and *BDNF* Val66Met genotyping, comprehensive neuropsychological assessment, brain magnetic resonance imaging (MRI), and spatial navigation assessment in a real-space version of the hMWM. Data from various modalities were collected within 60 days of each other for every participant.

The participants with aMCI ($n = 116$) met the clinical criteria for aMCI outlined in recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD [60] including memory complaints, evidence of memory impairment (i.e., score lower than 1.5 standard deviations below the age- and education-adjusted norms in any memory test), generally intact activities of daily living (i.e., Clinical Dementia Rating [CDR] global score not greater than 0.5) and

absence of dementia. The aMCI group included participants with isolated memory impairment (single domain aMCI [aMCI_{sd}]; $n=31$) and those with memory impairment and additional impairment in any other non-memory cognitive domain (multiple domain aMCI [aMCI_{md}]; $n=85$). The CU participants ($n=71$) had cognitive performance within the normal range (i.e., score higher than 1.5 standard deviations below the age- and education-adjusted norms in any cognitive test). Participants with depressive symptoms (≥ 6 points on the 15-item Geriatric Depression Scale [GDS-15]) [61], moderate to severe white matter vascular lesions on MRI (Fazekas score > 2 points) [62] or other primary neurological or psychiatric disorders were not included in the study. The CU and aMCI participants were further stratified into 4 groups each based on the *APOE* and *BDNF* Val66Met polymorphisms: *APOE* $\epsilon 4$ and *BDNF* Met noncarriers ($\epsilon 4^-/BDNF^{Val/Val}$; aMCI [$n=29$], CU [$n=27$]), *APOE* $\epsilon 4$ noncarriers and *BDNF* Met carriers ($\epsilon 4^-/BDNF^{Met}$; aMCI [$n=11$], CU [$n=15$]), *APOE* $\epsilon 4$ carriers and *BDNF* Met noncarriers ($\epsilon 4^+/BDNF^{Val/Val}$; aMCI [$n=52$], CU [$n=18$]), and *APOE* $\epsilon 4$ and *BDNF* Met carriers ($\epsilon 4^+/BDNF^{Met}$; aMCI [$n=24$], CU [$n=11$]). We did not include the *APOE* $\epsilon 2$ carriers ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$ and $\epsilon 2/\epsilon 4$), as the $\epsilon 2$ allele is considered protective and its frequency among our participants was low. Group-wise characteristic are listed in Tables 1 and 2.

Neuropsychological assessment

The neuropsychological battery comprised the following tests for each cognitive domain: 1) verbal memory measured with the Logical Memory I – Immediate and 20-minute Delayed Recall conditions and the Rey Auditory Verbal Learning Test – trials 1–5 and 30-minute Delayed Recall trial; 2) non-verbal memory measured with the Rey-Osterrieth Complex Figure Test (ROCF) – the Recall condition after 3 minutes; 3) executive function measured with the Trail Making Test B, Prague Stroop Test – colors and Controlled Oral Word Association Test – Czech version with letters N, K, and P; 4) attention and working memory measured with the Forward and Backward Digit Spans and Trail Making Test A; 5) language measured with the Boston Naming Test – 60-item version and Category Fluency Test – animals and vegetables; and 6) visuospatial function measured with the ROCF – the Copy condition and the Clock Drawing Test. The Mini-Mental State

Examination (MMSE) was administered to measure global cognitive function. The GDS-15 was used to assess depressive symptoms among participants. Group-wise neuropsychological characteristics are listed in Tables 1 and 2.

APOE and *BDNF* Val66Met genotyping

To determine the *APOE* genotype, DNA was isolated from blood samples (ethylenediaminetetraacetic acid; Qiagen extraction) and genotyping was performed according to Idaho-tech protocol (Luna-Probes Genotyping Apolipoprotein [ApoE] Multiplexed Assay) for high-resolution melting (HRM) analysis [28, 63].

The *BDNF* rs6265 (Val66Met) polymorphism was analyzed with a novel HRM method using polymerase chain reaction (PCR). The PCR product of 59bp was amplified with primers. Subsequent HRM analysis of PCR product was performed on Light Scanner (IdahoTech, USA) [58].

MRI acquisition and analysis

Brain scans were performed on a 1.5 T scanner (Siemens AG, Erlangen, Germany) using the T1-weighted 3-dimensional high resolution magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: TR/TE/TI = 2000/3.08/1100 ms, flip angle 15° , 192 continuous partitions, slice thickness = 1.0 mm, and in-plane resolution = 1 mm. Scans were visually inspected by a neuroradiologist to ensure appropriate data quality and to exclude patients with a major brain pathology that could interfere with cognitive functioning such as cortical infarctions, tumor, subdural hematoma, and hydrocephalus.

FreeSurfer image analysis suite (version 5.3; <http://surfer.nmr.mgh.harvard.edu>) was used to compute regional brain volumes and estimated total intracranial volume (eTIV), the internal reference. The procedure was described in detail elsewhere [64–66]. We selected the regions that play a key role in spatial navigation [1, 4, 67] and are affected early in AD [68, 69] to limit the number of analyses to those that were aligned with our hypothesis. The selected regions included the hippocampus, entorhinal cortex, precuneus, inferior parietal cortex, and posterior cingulate cortex. Volumes were reported separately for the left and right hemisphere, since spatial navigation is thought to be lateralized to the right hemisphere

Table 1
 Characteristics of study participants with amnesic mild cognitive impairment

Variables	$\epsilon 4^-/BDNF^{Val/Val}$ ($n = 29$)	$\epsilon 4^-/BDNF^{Met}$ ($n = 11$)	$\epsilon 4^+/BDNF^{Val/Val}$ ($n = 52$)	$\epsilon 4^+/BDNF^{Met}$ ($n = 24$)	p	Effect size
<i>Demographic characteristics</i>						
Women/Men	10/19	5/6	24/28	16/8	0.13	0.22 ^d
aMCIsd/aMCImd	5/24	4/7	16/36	6/18	0.51	0.14 ^d
Age in years; range	72.14 (5.23); 59–85	71.91 (8.87); 51–86	70.10 (6.97); 52–84	72.67 (6.29); 62–85	0.356	0.03 ^e
Education in years	15.76 (3.80)	14.18 (2.96)	15.02 (3.09)	13.54 (3.36)	0.098	0.05 ^e
MMSE score	26.90 (2.30)	27.91 (1.22)	27.12 (2.24)	26.08 (2.04)	0.099	0.05 ^e
GDS-15 score	2.52 (1.95)	2.80 (1.55)	2.60 (1.94)	2.38 (1.41)	0.928	0.00 ^e
<i>Cognitive characteristics</i>						
Memory verbal ^a	0.20 (0.84)*	0.31 (0.55)	-0.01 (0.79)	-0.35 (0.52)	0.026	0.08 ^e
Memory nonverbal ^a	0.21 (1.11)	0.04 (0.90)	-0.03 (1.01)	-0.21 (0.89)	0.472	0.01 ^e
Executive function ^a	-0.22 (1.03)	0.07 (0.51)	0.04 (0.70)	0.16 (0.61)	0.300	0.05 ^e
Attention and working memory ^a	-0.19 (0.80)	0.20 (0.49)	-0.01 (0.75)	0.15 (0.70)	0.268	0.00 ^e
Language ^a	-0.12 (1.03)	-0.12 (0.43)	0.06 (0.77)	0.07 (0.62)	0.674	0.02 ^e
Visuospatial ^a	-0.23 (1.06)	0.25 (0.58)	0.06 (0.69)	0.03 (0.62)	0.270	0.04 ^e
<i>Navigational characteristics</i>						
Egocentric navigation	28.45 (17.41)*	24.65 (13.50)*	34.49 (26.54)*	56.63 (40.04)	0.037	0.13 ^f
Allocentric navigation	65.69 (27.43)	69.44 (34.56)	73.98 (36.65)	80.49 (40.51)	0.918	0.02 ^f
Delayed navigation	76.08 (42.97)	71.41 (43.66)	77.65 (52.14)	100.73 (60.35)	0.692	0.04 ^f
<i>MRI characteristics^b</i>						
Left hippocampal volume ^c (mm ³)	3504.42 (474.37)*	3755.13 (429.41)**	3224.87 (647.65)	2877.19 (421.63)	<0.001	0.24 ^g
Right hippocampal volume ^c (mm ³)	3419.31 (762.38)	3915.11 (592.66)*	3318.58 (635.68)	3151.07 (595.28)	0.020	0.14 ^g
Left entorhinal volume ^c (mm ³)	1401.27 (232.61)**	1365.48 (383.70)*	1044.38 (277.14)	1004.16 (158.99)	<0.001	0.29 ^g
Right entorhinal volume ^c (mm ³)	1053.15 (194.65)	1333.24 (392.48)*	1042.99 (266.38)	1036.85 (139.04)	0.002	0.19 ^g
Left inferior parietal volume ^c (mm ³)	9020.13 (1242.56)	10047.24 (1879.06)	9252.97 (1163.27)	8991.20 (873.12)	0.210	0.07 ^g
Right inferior parietal volume ^c (mm ³)	11550.19 (1380.26)	11297.88 (2921.69)	11226.68 (1295.92)	10337.68 (1198.49)	0.333	0.05 ^g
Left posterior cingulate volume ^c (mm ³)	2532.60 (498.63)	2399.50 (594.13)	2698.89 (348.26)	2500.84 (491.74)	0.167	0.07 ^g
Right posterior cingulate volume ^c (mm ³)	2646.09 (307.10)	2460.46 (642.13)	2739.80 (289.77)	2639.67 (398.46)	0.226	0.06 ^g
Left precuneus volume ^c (mm ³)	7067.74 (913.77)	7119.46 (1337.66)	7232.81 (750.66)	6852.11 (507.84)	0.684	0.02 ^g
Right precuneus volume ^c (mm ³)	7352.30 (846.09)	7455.15 (1501.38)	7695.30 (863.16)	7351.45 (669.35)	0.679	0.02 ^g

Values are mean (SD) except for gender and age range. For p indicating the level of significance compared with the $\epsilon 4^+/BDNF^{Met}$ group are * $p < 0.05$ and ** $p < 0.01$. ^aValues are presented in z-scores (SD). ^bBased on a sample restricted to those with brain imaging data ($n = 85$; $\epsilon 4^-/BDNF^{Val/Val}$ [$n = 23$], $\epsilon 4^-/BDNF^{Met}$ [$n = 11$], $\epsilon 4^+/BDNF^{Val/Val}$ [$n = 38$] and $\epsilon 4^+/BDNF^{Met}$ [$n = 13$]). ^cAdjusted for estimated total intracranial volume. ^dEffect size reported using Cramér's V (the χ^2 test). ^eEffect size reported using partial eta-squared (one-way ANOVA). ^fEffect size reported using partial eta-squared (linear mixed effects regression analyses). ^gEffect size reported using partial eta-squared (MANCOVA controlled for age, gender and education). $\epsilon 4^-/BDNF^{Val/Val}$, $APOE \epsilon 4$ and $BDNF$ Met noncarriers' group; $\epsilon 4^-/BDNF^{Met}$, $APOE \epsilon 4$ noncarriers and $BDNF$ Met carriers' group; $\epsilon 4^+/BDNF^{Val/Val}$, $APOE \epsilon 4$ carriers and $BDNF$ Met noncarriers' group; $\epsilon 4^+/BDNF^{Met}$, $APOE \epsilon 4$ and $BDNF$ Met carriers' group; aMCIsd, single domain amnesic mild cognitive impairment; aMCImd, multiple domain amnesic mild cognitive impairment; MMSE, Mini-Mental State Examination; GDS-15; 15-item Geriatric Depression Scale; MRI, magnetic resonance imaging.

Table 2
Characteristics of cognitively unimpaired study participants

Variables	$\epsilon 4^-/BDNF^{Val/Val}$ ($n = 27$)	$\epsilon 4^-/BDNF^{Met}$ ($n = 15$)	$\epsilon 4^+/BDNF^{Val/Val}$ ($n = 18$)	$\epsilon 4^+/BDNF^{Met}$ ($n = 11$)	p	Effect size
<i>Demographic characteristics</i>						
Women/Men	16/11	13/2	9/9	10/1	0.035	0.35 ^d
Age in years; range	68.44 (6.39); 54–86	64.87 (8.08); 52–82	65.61 (7.30); 52–82	66.55 (5.56); 55–74	0.364	0.05 ^e
Education in years	16.93 (2.62)	17.07 (2.87)	16.17 (2.26)	15.00 (2.83)	0.162	0.07 ^e
MMSE score	29.04 (1.09)	28.80 (1.37)	29.06 (0.97)	28.91 (1.38)	0.911	0.01 ^e
GDS-15 score	2.67 (3.28)	3.27 (3.61)	2.53 (2.32)	2.10 (1.51)	0.782	0.02 ^e
<i>Cognitive characteristics</i>						
Memory verbal ^a	0.08 (0.82)	0.01 (0.82)	-0.05 (0.80)	0.06 (0.83)	0.944	0.00 ^e
Memory nonverbal ^a	-0.07 (1.03)	-0.02 (1.18)	0.19 (0.85)	0.05 (1.03)	0.865	0.01 ^e
Executive function ^a	0.00 (0.78)	-0.11 (0.69)	0.06 (0.48)	0.22 (0.99)	0.693	0.02 ^e
Attention and working memory ^a	0.23 (0.77)	0.08 (0.57)	-0.25 (0.79)	-0.22 (0.57)	0.122	0.08 ^e
Language ^a	-0.10 (0.86)	-0.22 (0.85)	0.23 (0.58)	0.24 (0.88)	0.252	0.06 ^e
Visuospatial ^a	-0.08 (0.92)	-0.15 (0.61)	0.31 (0.60)	-0.10 (0.83)	0.279	0.06 ^e
<i>Navigational characteristics</i>						
Egocentric navigation	19.99 (6.57)	21.09 (6.33)	21.71 (7.40)	22.24 (10.10)	0.732	0.02 ^f
Allocentric navigation	19.00 (3.88)*	23.82 (5.50)	27.38 (8.22)	35.28 (16.67)	0.017	0.22 ^f
Delayed navigation	15.72 (6.04)*	21.25 (5.32)	21.77 (8.89)	25.99 (12.78)	0.028	0.19 ^f
<i>MRI characteristics^b</i>						
Left hippocampal volume ^c (mm ³)	3733.92 (657.66)	3941.28 (504.83)	3906.37 (339.6)	3862.18 (273.81)	0.206	0.09 ^g
Right hippocampal volume ^c (mm ³)	3697.89 (646.54)	4124.32 (418.13)	3888.16 (517.43)	4006.76 (378.62)	0.126	0.11 ^g
Left entorhinal volume ^c (mm ³)	1217.14 (195.58)	1375.90 (230.86)	1306.00 (275.89)	1404.36 (303.92)	0.112	0.12 ^g
Right entorhinal volume ^c (mm ³)	1139.21 (242.38)	1159.44 (179.72)	1193.61 (263.86)	1207.06 (344.16)	0.395	0.06 ^g
Left inferior parietal volume ^c (mm ³)	10193.91 (957.03)	10002.32 (1616.12)	9789.21 (1183.13)	10134.89 (1096.83)	0.702	0.03 ^g
Right inferior parietal volume ^c (mm ³)	11903.11 (1197.12)	11780.80 (1386.19)	11734.89 (995.51)	12038.19 (1533.04)	0.758	0.02 ^g
Left posterior cingulate volume ^c (mm ³)	2755.31 (320.93)	2798.20 (382.01)	2767.77 (215.05)	2767.62 (420.88)	0.544	0.04 ^g
Right posterior cingulate volume ^c (mm ³)	2729.43 (329.39)	2789.67 (383.44)	2849.55 (407.77)	2786.89 (293.95)	0.170	0.10 ^g
Left precuneus volume ^c (mm ³)	7733.91 (595.22)	8350.33 (895.09)	7673.38 (793.67)	7870.21 (576.64)	0.245	0.08 ^g
Right precuneus volume ^c (mm ³)	8225.50 (682.58)	8563.94 (816.38)	8068.20 (786.82)	8344.45 (477.81)	0.733	0.03 ^g

Values are mean (SD) except for gender and age range. For p indicating the level of significance compared with the $\epsilon 4^+/BDNF^{Met}$ group is $*p < 0.05$. ^aValues are presented in z-scores (SD). ^bBased on a sample restricted to those with brain imaging data ($n = 85$; $\epsilon 4^-/BDNF^{Val/Val}$ [$n = 18$], $\epsilon 4^-/BDNF^{Met}$ [$n = 12$], $\epsilon 4^+/BDNF^{Val/Val}$ [$n = 18$] and $\epsilon 4^+/BDNF^{Met}$ [$n = 9$]). ^cAdjusted for estimated total intracranial volume. ^dEffect size reported using Cramér's V (the χ^2 test). ^eEffect size reported using partial eta-squared (one-way ANOVA). ^fEffect size reported using partial eta-squared (linear mixed effects regression analyses). ^gEffect size reported using partial eta-squared (MANCOVA controlled for age, gender, and education). $\epsilon 4^-/BDNF^{Val/Val}$, $APOE \epsilon 4$ and $BDNF$ Met noncarriers' group; $\epsilon 4^-/BDNF^{Met}$, $APOE \epsilon 4$ noncarriers and $BDNF$ Met carriers' group; $\epsilon 4^+/BDNF^{Val/Val}$, $APOE \epsilon 4$ carriers and $BDNF$ Met noncarriers' group; $\epsilon 4^+/BDNF^{Met}$, $APOE \epsilon 4$ and $BDNF$ Met carriers' group; MMSE, Mini-Mental State Examination; GDS-15; 15-item Geriatric Depression Scale; MRI, magnetic resonance imaging.

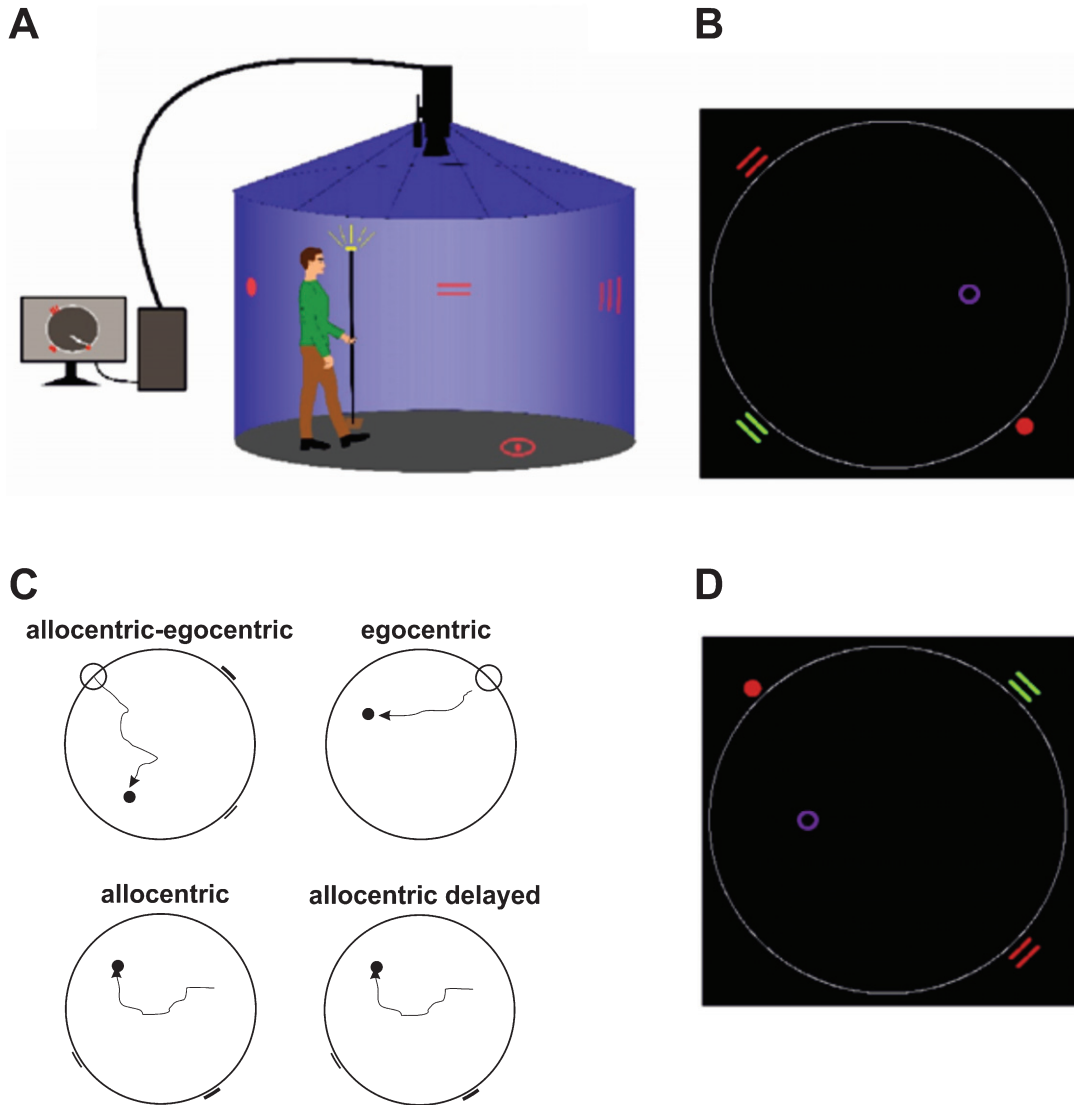


Fig. 1. Human analogue of the Morris Water Maze task. A) The real-space navigation setting. B) The scheme of the task showing an aerial view of the arena (large white circle) with starting point (red filled circle), orientation cues (red and green lines), and goal (purple circle). C) The scheme of 4 individual tasks: allocentric-egocentric (i.e., training; designed to use the starting point and 2 orientation cues for navigation), egocentric (designed to use the starting point for navigation), allocentric (designed to use 2 orientation cues for navigation) and allocentric delayed (identical to the allocentric task administered 30 minutes after its completion). D) An aerial view of the arena rotated 180 degrees from the previous trial shown in B.

[70]. Volumes were normalized to eTIV using the previously published regression formula [71]. MRI data were available for 85 participants with aMCI ($\epsilon 4^{-}/BDNF^{Val/Val}$ [$n=23$], $\epsilon 4^{-}/BDNF^{Met}$ [$n=11$], $\epsilon 4^{+}/BDNF^{Val/Val}$ [$n=38$], and $\epsilon 4^{+}/BDNF^{Met}$ [$n=13$]) and 57 CU participants ($\epsilon 4^{-}/BDNF^{Val/Val}$ [$n=18$], $\epsilon 4^{-}/BDNF^{Met}$ [$n=12$], $\epsilon 4^{+}/BDNF^{Val/Val}$ [$n=18$], and $\epsilon 4^{+}/BDNF^{Met}$ [$n=9$]). Group-wise MRI characteristics are listed in Tables 1 and 2.

Spatial navigation assessment

For spatial navigation assessment, we used the real-space version of the hMWM that was performed in a real-space navigational setting, a fully enclosed cylindrical arena 2.8 m in diameter surrounded by a 2.9 m high dark blue velvet curtain (Fig. 1A). The task and the real-space navigational setting were described in detail elsewhere [9, 10]. The participants

located an invisible goal on the arena floor in 4 different tasks using a start position (egocentric) or 2 distal orientation cues on the wall (allocentric), respectively (Fig. 1B, 1C). The first, allocentric–egocentric, task was a training task designed to familiarize participants with the testing procedure and involved locating the goal using both the start position and 2 distal orientation cues on the arena wall. The second, egocentric, task involved using the start position to locate the goal with no distal orientation cues displayed. The third, allocentric, task involved using 2 distal orientation cues at the arena wall for navigation to the goal from the start position that was unrelated to the goal position. The fourth, allocentric delayed, task was identical to the allocentric task and was administered 30 minutes after its completion. The training (egocentric–allocentric), egocentric, and allocentric tasks had 8 trials and the correct position of the goal was shown after each trial to provide the feedback. The delayed task had 2 trials and no feedback through showing the position of the goal was provided. The relative positions (distances and directions) of the goal to the start position or to both orientation cues were constant across all trials in all tasks. After each trial, the goal position along with the start position and the positions of 2 distal orientation cues were rotated in a pseudorandom sequence and the participants were instructed to go to the new start position at each consecutive trial in all tasks (Fig. 1D). The tasks had no time limit. Spatial navigation performance derived as distance error in centimeters from the correct goal position was automatically recorded by in-house developed software. A TV camera with a sampling frequency of 25 frames per second located above the center of the arena was used to capture the position of an infrared light-emitting diode placed on top of a hat that was worn by the participants during the testing and indicated their location.

Statistical analyses

Data standardization and analyses were performed separately for the CU and aMCI participants. Scores for neuropsychological and spatial navigation tests and MRI data were standardized to z-scores calculated from the overall mean and SD of the sample to enable comparison across the measurements scored on different scales. The values from the Prague Stroop Test, Trail Making Tests A and B (seconds to completion), and the Boston Naming Test (number of errors) were reversed before the z-scores were

generated. The scores for each cognitive domain were expressed as a unit-weighted composite z-score from the relevant neuropsychological tests. Higher z-scores reflected better neuropsychological performance, but less accurate spatial navigation performance (distance error in centimeters). All data were found to be adequate for parametric analysis. Spatial navigation data were log transformed prior to the standardization and analyses because of their right-skewed distribution. The transformation satisfactorily solved the skewness.

A one-way analysis of variance (ANOVA) with *post hoc* Sidak's test evaluated between-group differences in age, years of education, GDS and MMSE scores, and cognitive domains' composite scores. The χ^2 test evaluated differences in gender proportions. Differences in proportions of aMCI subtypes (aMCI_{sd} versus aMCI_{md}) were evaluated in the participants with aMCI.

In the spatial navigation analyses, scores from all trials in each spatial navigation task were entered into linear mixed effects regression models [72] that were used to properly account for the repeated measures structure of the spatial navigation data. The distance error in each spatial navigation task was the outcome and the polymorphism group was the independent variable. As in the one-way ANOVA, our primary interest was in the main effect for group and differences in spatial navigation performance across the individual polymorphism groups ($\epsilon 4^-/BDNF^{Val/Val}$ versus $\epsilon 4^-/BDNF^{Met}$ versus $\epsilon 4^+/BDNF^{Val/Val}$ versus $\epsilon 4^+/BDNF^{Met}$) that were evaluated by *post hoc* Sidak's test. We also report the main effect for trial (trials 1–8 for the egocentric and allocentric tasks and trials 1–2 for the allocentric delayed task) and the group-by-trial interaction, which reflect learning and differential learning by group, respectively. The intercept and trial were specified as random effects. Based on model fit, the final models used the unstructured covariance matrix. Gender distribution was not equal across the groups, so gender was added as a covariate to the analyses. This decreased the model fit and the main effects for gender and group-by-gender interactions were not significant. Therefore, gender was not used in the final analyses.

Next, we estimated a multivariate analysis of covariance (MANCOVA) to assess the between-group differences in volumes of the brain regions relevant for spatial navigation. Age, gender, and education were controlled in the analysis. Initially, we performed multivariate tests and when the Wilks' Lambda indicating overall differences across the four

groups in volumes of the brain regions was significant, we subsequently performed univariate tests with *post hoc* Sidak's test, where the polymorphism group was the independent variable and volumes of the relevant brain regions were separately entered as the outcome.

Finally, we calculated Pearson correlation coefficients to explore relationships between spatial navigation performance in the egocentric, allocentric, and allocentric delayed tasks and volumes of the selected brain regions. A Bonferroni correction for multiple comparisons was used, resulting in a p value of 0.005 (0.05/10 regions). The subsequent multivariate linear regression analysis was used to evaluate the associations between spatial navigation performance in each task and selected regional brain volumes controlling for age, gender, education, and polymorphism group membership. Volumes of the navigation-related brain regions that correlated with spatial navigation performance were separately entered as the independent variables. Spatial navigation performance was the dependent variable and was calculated as the distance error averaged across the trials for each spatial navigation task.

Statistical significance was set at 2-tailed (α) of 0.05. Effect sizes are reported using Cramér's V for the χ^2 test and partial eta-squared (η_p^2) for one-way ANOVA, MANCOVA, and linear mixed effects regression analyses [73]. Cramér's V of about 0.47 and partial eta-squared of 0.12 correspond to Cohen's d of about 1.0. All analyses were conducted with IBM SPSS 25.0 software.

RESULTS

Demographic and neuropsychological characteristics

The participants with aMCI

There were no significant differences in age, gender, years of education, aMCI subtypes, depressive symptoms (assessed by GDS-15), and global cognitive function (assessed by MMSE) between the polymorphism groups. The main effect of group on verbal memory performance was significant ($F[3,112]=5.18$, $p=0.026$, $\eta_p^2=0.08$). The *post hoc* analysis revealed that the $\epsilon 4^+/BDNF^{Met}$ group had lower verbal memory performance than the $\epsilon 4^-/BDNF^{Val/Val}$ ($p=0.007$) and similar performance to the $\epsilon 4^-/BDNF^{Met}$ ($p=0.071$) and $\epsilon 4^+/BDNF^{Val/Val}$ ($p=0.240$) groups. There were no

significant differences in other cognitive domains including attention and working memory, nonverbal memory, executive function, language and visuospatial function between the polymorphism groups. The results are presented in detail in Table 1.

The CU participants

There were no significant differences in age, years of education, depressive symptoms, and global cognitive function between the polymorphism groups but there were more women in the $\epsilon 4^-/BDNF^{Met}$ and $\epsilon 4^+/BDNF^{Met}$ groups than in the $\epsilon 4^-/BDNF^{Val/Val}$ and $\epsilon 4^+/BDNF^{Val/Val}$ groups (13/2 and 10/1 versus 16/11 and 9/9; $\chi^2[3]=3.09$, $p=0.035$, Cramér's $V=0.35$). There were no significant differences in cognitive performance in any cognitive domain including attention and working memory, verbal memory, nonverbal memory, executive function, language and visuospatial function between the polymorphism groups. The results are presented in detail in Table 2.

Spatial navigation performance

The participants with aMCI

Using the linear mixed models we found main effects for group on egocentric navigation performance ($F[3,110]=2.93$; $p=0.037$; $\eta_p^2=0.13$), where the $\epsilon 4^+/BDNF^{Met}$ group had less accurate egocentric navigation performance than the $\epsilon 4^-/BDNF^{Val/Val}$ ($p=0.028$), $\epsilon 4^-/BDNF^{Met}$ ($p=0.013$) and $\epsilon 4^+/BDNF^{Val/Val}$ ($p=0.045$) groups. The estimated pairwise differences were around 0.5 SD ($\epsilon 4^+/BDNF^{Met}$ versus $\epsilon 4^-/BDNF^{Val/Val}$ and $\epsilon 4^+/BDNF^{Met}$ versus $\epsilon 4^+/BDNF^{Val/Val}$) and approached 1 SD ($\epsilon 4^+/BDNF^{Met}$ versus $\epsilon 4^-/BDNF^{Met}$) for these comparisons. There were no significant differences in egocentric navigation performance between the $\epsilon 4^-/BDNF^{Val/Val}$, $\epsilon 4^-/BDNF^{Met}$ and $\epsilon 4^+/BDNF^{Val/Val}$ groups ($ps \geq 0.654$). There were no significant differences in allocentric ($F[3,107]=0.17$; $p=0.918$; $\eta_p^2=0.02$) and allocentric delayed ($F[3,105]=0.49$; $p=0.692$; $\eta_p^2=0.04$) navigation performance between the polymorphism groups. The between-group comparisons of spatial navigation performance in each task are listed in Tables 1 and 3. The main effects for trial were not significant in the egocentric ($F[1,110]=0.24$; $p=0.625$; $\eta_p^2=0.00$), allocentric ($F[1,106]=0.61$; $p=0.438$; $\eta_p^2=0.03$), and allocentric delayed ($F[1,105]=0.14$; $p=0.707$; $\eta_p^2=0.00$) tasks, indicating no signifi-

Table 3
Group-wise comparisons of adjusted mean error distances from the goal in spatial navigation tasks in the participants with amnesic mild cognitive impairment

(I) Groupcode	(J) Groupcode	Mean difference (I-J)	<i>p</i>	95% Confidence interval for difference	
				Lower bound	Upper bound
<i>Egocentric task</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.485	0.045	0.006	0.963
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.812	0.013	0.120	1.505
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.586	0.028	0.043	1.129
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.328	0.654	-0.296	0.951
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.101	0.992	-0.351	0.553
	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.226	0.938	-0.901	0.448
<i>Allocentric task</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.084	0.998	-0.415	0.582
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.240	0.935	-0.470	0.951
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.161	0.970	-0.401	0.723
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.157	0.986	-0.480	0.794
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.078	0.998	-0.388	0.543
	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.079	1.000	-0.768	0.609
<i>Delayed task</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.264	0.808	-0.335	0.864
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.450	0.651	-0.405	1.306
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.246	0.917	-0.441	0.933
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.186	0.987	-0.581	0.953
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.018	1.000	-0.591	0.555
	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.204	0.987	-1.041	0.632

Linear mixed models. Mean differences are in standard deviation units. Values in bold indicate significant between-group differences ($p < 0.05$). $\epsilon 4^+/\text{BDNF}^{\text{Met}}$, APOE $\epsilon 4$ and BDNF Met carriers' group; $\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$, APOE $\epsilon 4$ carriers and BDNF Met noncarriers' group; $\epsilon 4^-/\text{BDNF}^{\text{Met}}$, APOE $\epsilon 4$ noncarriers and BDNF Met carriers' group; $\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$, APOE $\epsilon 4$ and BDNF Met noncarriers' group.

cant learning effect across consecutive trials in the sample overall. Finally, there were no significant group-by-trial interactions, suggesting no significant differences in learning between the polymorphism groups in the egocentric ($F[3,110] = 0.38$; $p = 0.767$; $\eta_p^2 = 0.05$), allocentric ($F[3,106] = 1.48$; $p = 0.225$; $\eta_p^2 = 0.02$), and allocentric delayed ($F[3,105] = 0.09$; $p = 0.964$; $\eta_p^2 = 0.00$) tasks.

The CU participants

We found main effects for group on allocentric ($F[3,127] = 3.83$; $p = 0.017$; $\eta_p^2 = 0.22$) and allocentric delayed ($F[3,69] = 3.35$; $p = 0.028$; $\eta_p^2 = 0.19$) navigation performance where the $\epsilon 4^+/\text{BDNF}^{\text{Met}}$ group had less accurate performance than the $\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$ group ($p = 0.047$ and $p = 0.048$, respectively). The estimated pairwise differences were around 0.5 and 0.7 SD, respectively, for these comparisons. There were no significant differences in egocentric navigation performance between the polymorphism groups ($F[3,125] = 0.43$; $p = 0.732$; $\eta_p^2 = 0.02$). The between-group comparisons of spatial navigation performance in each task are listed in Tables 2 and 4. The main effects for trial were not sig-

nificant in the egocentric ($F[1,125] = 0.03$; $p = 0.999$; $\eta_p^2 = 0.00$), allocentric ($F[1,127] = 0.87$; $p = 0.534$; $\eta_p^2 = 0.02$), and allocentric delayed ($F[1,69] = 0.05$; $p = 0.826$; $\eta_p^2 = 0.00$) tasks. There were no significant group-by-trial interactions in the egocentric ($F[3,125] = 1.03$; $p = 0.423$; $\eta_p^2 = 0.05$), allocentric ($F[3,127] = 1.30$; $p = 0.173$; $\eta_p^2 = 0.09$), and allocentric delayed ($F[3,69] = 0.09$; $p = 0.968$; $\eta_p^2 = 0.01$) tasks.

Brain MRI characteristics and their association with spatial navigation

The participants with aMCI

Using the MANCOVA adjusted for age, gender, and education, the multivariate tests showed the between-group differences in volumes of the navigation-related brain regions (Wilks' Lambda = 2.33; $p \leq 0.001$; $\eta_p^2 = 0.29$). In the subsequent univariate tests analyzing each brain region separately, the between-group differences were found for left and right hippocampal volumes ($F[3,85] = 7.13$; $p < 0.001$; $\eta_p^2 = 0.24$ and $F[3,85] = 3.50$; $p = 0.020$; $\eta_p^2 = 0.14$, respectively) and left and

Table 4
Group-wise comparisons of adjusted mean error distances from the goal in spatial navigation tasks in the cognitively unimpaired participants

(I) Groupcode	(J) Groupcode	Mean difference (I-J)	<i>p</i>	95% Confidence interval for difference	
				Lower bound	Upper bound
<i>Egocentric task</i>					
$\epsilon 4^+ / BDNF^{Met}$	$\epsilon 4^+ / BDNF^{Val/Val}$	-0.014	1.000	-0.477	0.449
	$\epsilon 4^- / BDNF^{Met}$	0.002	1.000	-0.478	0.482
$\epsilon 4^+ / BDNF^{Val/Val}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.120	0.975	-0.315	0.555
	$\epsilon 4^- / BDNF^{Met}$	0.016	1.000	-0.407	0.439
$\epsilon 4^- / BDNF^{Met}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.134	0.911	-0.237	0.505
	$\epsilon 4^- / BDNF^{Val/Val}$	0.118	0.961	-0.274	0.510
<i>Allocentric task</i>					
$\epsilon 4^+ / BDNF^{Met}$	$\epsilon 4^+ / BDNF^{Val/Val}$	0.091	0.997	-0.412	0.594
	$\epsilon 4^- / BDNF^{Met}$	0.080	0.999	-0.451	0.611
$\epsilon 4^+ / BDNF^{Val/Val}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.501	0.047	0.005	0.997
	$\epsilon 4^- / BDNF^{Met}$	-0.011	1.000	-0.482	0.460
$\epsilon 4^- / BDNF^{Met}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.410	0.070	-0.021	0.841
	$\epsilon 4^- / BDNF^{Val/Val}$	0.421	0.093	-0.043	0.884
<i>Delayed task</i>					
$\epsilon 4^+ / BDNF^{Met}$	$\epsilon 4^+ / BDNF^{Val/Val}$	0.223	0.949	-0.488	0.934
	$\epsilon 4^- / BDNF^{Met}$	0.108	0.999	-0.645	0.862
$\epsilon 4^+ / BDNF^{Val/Val}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.705	0.048	0.004	1.406
	$\epsilon 4^- / BDNF^{Met}$	-0.115	0.998	-0.805	0.575
$\epsilon 4^- / BDNF^{Met}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.482	0.224	-0.150	1.114
	$\epsilon 4^- / BDNF^{Val/Val}$	0.596	0.113	-0.083	1.276

Linear mixed models. Mean differences are in standard deviation units. Values in bold indicate significant between-group differences ($p < 0.05$). $\epsilon 4^+ / BDNF^{Met}$, APOE $\epsilon 4$ and BDNF Met carriers' group; $\epsilon 4^+ / BDNF^{Val/Val}$, APOE $\epsilon 4$ carriers and BDNF Met noncarriers' group; $\epsilon 4^- / BDNF^{Met}$, APOE $\epsilon 4$ noncarriers and BDNF Met carriers' group; $\epsilon 4^- / BDNF^{Val/Val}$, APOE $\epsilon 4$ and BDNF Met noncarriers' group.

right entorhinal cortical volumes ($F[3,85] = 9.29$; $p < 0.001$; $\eta_p^2 = 0.29$ and $F[3,85] = 5.34$; $p = 0.002$; $\eta_p^2 = 0.19$, respectively). The between-group differences in volumes of other navigation-related brain regions were not significant ($F[3,85] \leq 1.74$; $p \geq 0.167$; $\eta_p^2 \leq 0.07$). The *post hoc* tests showed that the $\epsilon 4^+ / BDNF^{Met}$ group had smaller left hippocampal and left entorhinal cortical volumes compared to the $\epsilon 4^- / BDNF^{Val/Val}$ ($p = 0.019$ and $p = 0.004$) and $\epsilon 4^- / BDNF^{Met}$ ($p = 0.001$ and $p = 0.020$) groups and smaller right hippocampal and right entorhinal cortical volumes compared to the $\epsilon 4^- / BDNF^{Met}$ group ($p = 0.038$ and $p = 0.030$). The $\epsilon 4^+ / BDNF^{Val/Val}$ group had smaller left and right hippocampal and right entorhinal cortical volumes compared to the $\epsilon 4^- / BDNF^{Met}$ group ($p = 0.006$, $p = 0.020$ and $p = 0.001$) and left entorhinal cortical volume compared to the $\epsilon 4^- / BDNF^{Val/Val}$ ($p < 0.001$) and $\epsilon 4^- / BDNF^{Met}$ ($p = 0.007$) groups. The between-group comparisons of volumes of the navigation-related brain regions are listed in Tables 1 and 5.

In the correlational analyses (Supplementary Table 1), right hippocampal volume correlated

with allocentric navigation performance ($r = -0.39$; $p = 0.001$) indicating that smaller volume was associated with greater distance error in the navigational task. Right hippocampal volume correlated with allocentric delayed ($r = -0.33$; $p = 0.006$) and egocentric ($r = -0.32$; $p = 0.006$) navigation performance, left hippocampal volume correlated with allocentric ($r = -0.28$; $p = 0.020$), allocentric delayed ($r = -0.30$; $p = 0.014$), and egocentric ($r = -0.28$; $p = 0.017$) navigation performance, right entorhinal cortical volume correlated with allocentric delayed navigation performance ($r = -0.27$; $p = 0.028$) and left posterior cingulate volume correlated with allocentric delayed navigation performance ($r = -0.27$; $p = 0.028$); however, these relationships did not surpass the threshold of Bonferroni-corrected p -value.

In the multivariate linear regression analyses, right hippocampal volume was associated with allocentric navigation performance ($\beta = -0.41$; $p = 0.001$) indicating that smaller volume was associated with greater distance error in the navigational task above and beyond demographic characteristics. Right hippocampal volume was associated with allocentric delayed ($\beta = -0.30$; $p = 0.014$) and

Table 5
Group-wise comparisons of hippocampal and cortical volumes in the participants with amnesic mild cognitive impairment

(I) Groupcode	(J) Groupcode	Mean difference (I-J)	<i>p</i>	95% Confidence interval for difference	
				Lower bound	Upper bound
<i>Left hippocampal volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.376	0.655	-1.099	0.346
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.394	0.001	-2.345	-0.443
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.967	0.019	-1.823	-0.111
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.018	0.006	-1.825	-0.211
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.590	0.123	-1.270	0.090
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.428	0.767	-0.500	1.355
<i>Right hippocampal volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.093	1.000	-0.926	0.739
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.136	0.038	-2.232	-0.041
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.348	0.919	-1.334	0.638
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.043	0.020	-1.973	-0.113
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.255	0.944	-1.038	0.528
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.788	0.263	-0.280	1.856
<i>Left entorhinal volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.055	1.000	-0.825	0.715
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.135	0.020	-2.148	-0.122
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-1.202	0.004	-2.114	-0.290
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.079	0.007	-1.939	-0.219
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-1.147	0.000	-1.871	-0.422
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.067	1.000	-1.055	0.921
<i>Right entorhinal volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.166	0.989	-0.546	0.879
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.003	0.030	-1.940	-0.065
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.017	1.000	-0.827	0.861
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-1.169	0.001	-1.965	-0.373
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.149	0.991	-0.820	0.521
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	1.020	0.021	0.105	1.934
<i>Left inferior parietal volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.153	0.998	-1.041	0.735
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-0.818	0.319	-1.987	0.351
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.014	1.000	-1.066	1.038
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-0.665	0.368	-1.657	0.327
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.139	0.998	-0.697	0.974
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.804	0.311	-0.336	1.943
<i>Right inferior parietal volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.459	0.655	-1.339	0.422
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-0.600	0.661	-1.759	0.559
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.669	0.420	-1.713	0.374
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	-0.141	0.999	-1.125	0.843
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.211	0.983	-1.039	0.618
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	0.669	0.420	-0.374	1.713
<i>Left posterior cingulate volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.499	0.619	-1.424	0.426
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.240	0.996	-0.977	1.458
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.096	1.000	-1.192	1.000
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.739	0.296	-0.295	1.772
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.403	0.764	-0.468	1.274
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.336	0.971	-1.523	0.851
<i>Right posterior cingulate volume^a</i>					
$\epsilon 4^+/\text{BDNF}^{\text{Met}}$	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.293	0.950	-1.215	0.629
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.487	0.861	-0.726	1.701
$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	-0.025	1.000	-1.117	1.068
	$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	0.780	0.236	-0.250	1.811
$\epsilon 4^-/\text{BDNF}^{\text{Met}}$	$\epsilon 4^-/\text{BDNF}^{\text{Val/Val}}$	0.268	0.956	-0.600	1.136
	$\epsilon 4^+/\text{BDNF}^{\text{Val/Val}}$	-0.512	0.815	-1.696	0.671

Table 5
Continued

(I) Groupcode	(J) Groupcode	Mean difference (I-J)	<i>p</i>	95% Confidence interval for difference	
				Lower bound	Upper bound
<i>Left precuneus volume^a</i>					
$\epsilon 4^+ / BDNF^{Met}$	$\epsilon 4^+ / BDNF^{Val/Val}$	-0.400	0.809	-1.316	0.517
	$\epsilon 4^- / BDNF^{Met}$	-0.310	0.982	-1.517	0.896
	$\epsilon 4^- / BDNF^{Val/Val}$	-0.211	0.996	-1.297	0.875
$\epsilon 4^+ / BDNF^{Val/Val}$	$\epsilon 4^- / BDNF^{Met}$	0.089	1.000	-0.935	1.113
	$\epsilon 4^- / BDNF^{Val/Val}$	0.189	0.992	-0.674	1.052
$\epsilon 4^- / BDNF^{Met}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.100	1.000	-1.077	1.276
<i>Right precuneus volume^a</i>					
$\epsilon 4^+ / BDNF^{Met}$	$\epsilon 4^+ / BDNF^{Val/Val}$	-0.296	0.941	-1.199	0.606
	$\epsilon 4^- / BDNF^{Met}$	-0.120	1.000	-1.308	1.068
	$\epsilon 4^- / BDNF^{Val/Val}$	0.031	1.000	-1.038	1.101
$\epsilon 4^+ / BDNF^{Val/Val}$	$\epsilon 4^- / BDNF^{Met}$	0.176	0.998	-0.832	1.185
	$\epsilon 4^- / BDNF^{Val/Val}$	0.328	0.882	-0.522	1.177
$\epsilon 4^- / BDNF^{Met}$	$\epsilon 4^- / BDNF^{Val/Val}$	0.151	1.000	-1.007	1.310

Analysis of covariance adjusted for age, gender and education. Mean differences are in standard deviation units. Values in bold indicate significant between-group differences ($p < 0.05$). ^aAdjusted for estimated total intracranial volume. $\epsilon 4^+ / BDNF^{Met}$, APOE $\epsilon 4$ and BDNF Met carriers' group; $\epsilon 4^+ / BDNF^{Val/Val}$, APOE $\epsilon 4$ carriers and BDNF Met noncarriers' group; $\epsilon 4^- / BDNF^{Met}$, APOE $\epsilon 4$ noncarriers and BDNF Met carriers' group; $\epsilon 4^- / BDNF^{Val/Val}$, APOE $\epsilon 4$ and BDNF Met noncarriers' group.

egocentric ($\beta = -0.27$; $p = 0.022$) navigation performance, left hippocampal volume was associated with allocentric ($\beta = -0.37$; $p = 0.007$), allocentric delayed ($\beta = -0.32$; $p = 0.020$), and egocentric ($\beta = -0.26$; $p = 0.048$) navigation performance and left posterior cingulate volume was associated with allocentric delayed navigation performance ($\beta = -0.23$; $p = 0.042$); however, these associations did not surpass the threshold of Bonferroni-corrected p -value.

The CU participants

The multivariate tests did not show significant differences between the polymorphism groups in volumes of the navigation-related brain regions (Wilks' Lambda = 0.96; $p = 0.532$; $\eta_p^2 = 0.20$). There was no significant correlation between spatial navigation performance in the egocentric, allocentric, and allocentric delayed tasks and volumes of the selected brain regions. The results are presented in detail in Table 2 and Supplementary Tables 2 and 3.

DISCUSSION

In this study, we examined for the first time the combined effect of APOE and BDNF Val66Met polymorphisms on spatial navigation and volume of brain regions associated with spatial navigation in CU and

aMCI individuals. Our findings indicate that the combination of the APOE $\epsilon 4$ and BDNF Met alleles is associated with least accurate spatial navigation performance in individuals with aMCI. Specifically, we found that those with aMCI who carry both APOE $\epsilon 4$ and BDNF Met alleles, although similar to other polymorphism groups in demographic characteristics, aMCI subtypes, global cognitive function, or depressive symptoms, have the least accurate egocentric spatial navigation performance. Our findings further indicate that the combination of the APOE $\epsilon 4$ and BDNF Met alleles may influence spatial navigation in CU individuals. Specifically, we found that those CU individuals with the high risk combination of the APOE $\epsilon 4$ and BDNF Met alleles compared to those with the low risk combination of the APOE $\epsilon 3$ and BDNF Val/Val alleles have less accurate allocentric spatial navigation performance. Egocentric (self-centered) navigation, where spatial information about locations and objects is encoded from the viewpoint of the navigator, is associated with the level of function of the posterior parietal cortex including the precuneus [2]. The function of the parietal cortex is adversely affected by the APOE $\epsilon 4$ allele [74, 75], which is associated with less accurate egocentric navigation in individuals with aMCI [27–29]. In addition, levels of BDNF protein in this region are prominently decreased [45, 76] due to the presence of

the *BDNF* Met allele [52]. This may explain why the combination of the *APOE* ϵ 4 and *BDNF* Met alleles was negatively associated with egocentric navigation in our participants with aMCI. Allocentric (world-centered) navigation, where locations and objects are encoded in relation to one another and are independent of the position of the navigator, is associated with the level of function of the medial temporal lobe structures, especially of the hippocampus [1]. *BDNF* expression is profoundly reduced in the hippocampus and adjacent entorhinal cortex [44] that are affected by *APOE* ϵ 4-related changes [20, 21]. Next, the previous studies showed that the *APOE* ϵ 4 allele is associated with less accurate allocentric navigation performance in cognitively normal older adults [26] and that the *BDNF* Met allele is associated with decreased use of allocentric spatial strategy in cognitively normal younger adults [53]. This may explain why the combination of the *APOE* ϵ 4 and *BDNF* Met alleles was negatively associated with allocentric navigation in our CU participants. One would expect that the combination of the *APOE* ϵ 4 and *BDNF* Met alleles could also negatively influence allocentric navigation in individuals with aMCI. However, in the current study we did not find the differences in allocentric spatial navigation performance between the polymorphism groups of participants with aMCI. This finding may be explained by the severity of cognitive impairment in our participants who were in the late stage of aMCI (with a mean MMSE score of 26.9 and predominant multiple domain cognitive impairment) and whose results could thus be affected by the floor effect. Similar findings were reported in our previous study, where the results for allocentric unlike egocentric navigation as a function of *APOE* ϵ 4 categorization have not been significant in aMCI participants with a mean MMSE score of 26.4 [29]. Allocentric navigation is impaired in the course of aging [77, 78] and especially in preclinical AD and early aMCI [9, 79]. Impairment of egocentric navigation becomes increasingly more prominent later in the course of aMCI and in AD dementia [9, 10] and unlike impairment of allocentric navigation more accurately discriminates AD dementia from other types of dementia [80]. Therefore, aMCI participants with both *APOE* ϵ 4 and *BDNF* Met alleles who have more pronounced egocentric navigation impairment may represent the more advanced stage of the disease compared to other polymorphism groups and may be more likely to have steeper cognitive decline and progress to AD dementia. The CU participants with both *APOE* ϵ 4 and *BDNF* Met alleles who have

less accurate allocentric navigation performance may also be more prone to cognitive decline and progression to MCI. Since individuals with aMCI who are carriers of the *APOE* ϵ 4 allele are more likely to have A β pathology (i.e., prodromal AD) [81], it is plausible that the negative effect of the *BDNF* Met allele on spatial navigation has been influenced by abnormally high levels of A β in our aMCI cohort. Indeed, the *BDNF* Met allele enhances the brain vulnerability to A β toxicity [82] and therefore it may further worsen A β -related egocentric navigation impairment in individuals with aMCI and *APOE* ϵ 4 allele [27, 28]. In the current study, there was no evidence of a learning effect across the trials in individual spatial navigation tasks in the participants with aMCI, which is in line with previous studies showing impairment of spatial navigation learning in individuals with aMCI and early AD [9, 28, 29].

As expected, the combination of the *APOE* ϵ 4 and *BDNF* Met alleles was associated with more pronounced memory dysfunction in participants with aMCI. Specifically, the carriers of both *APOE* ϵ 4 and *BDNF* Met alleles had lower verbal memory performance compared to the non-carriers. These results are in agreement with previous findings in individuals with preclinical AD [57], aMCI [58], prodromal AD and AD dementia [25] and support the hypothesis that combination of the *APOE* ϵ 4 and *BDNF* Met alleles may specifically interfere with memory function. Again, as suggested previously [55, 57, 83], the negative effect of the *BDNF* Met allele on memory in our aMCI cohort may be influenced by abnormally high levels of A β that are more frequent in *APOE* ϵ 4 carriers [81]. However, neither the current nor the previous studies [25, 58] have found the differences in memory performance between the *BDNF* Met carriers and non-carriers within a group of individuals with aMCI and the *APOE* ϵ 4 allele, that is, within the group at increased risk of progressing to AD dementia [84]. The noteworthy finding in the current study was that the *APOE* ϵ 4/*BDNF* Met carriers with aMCI compared to all other polymorphism groups including those with *APOE* ϵ 4/*BDNF* Val/Val alleles have less accurate egocentric spatial navigation performance. This result may indicate that spatial navigation testing could more reliably reflect the deleterious effect of the *BDNF* Met allele on cognition than commonly used episodic memory tests. Given that spatial navigation is distinguishable from other cognitive functions [16] strongly influenced by genetic polymorphisms [29, 33] and impaired very early in AD [5, 6], its assessment along with exam-

ination of other cognitive functions could be highly beneficial when characterizing the cognitive profile of individuals with aMCI and their risk of progression to AD dementia.

The combination of the *APOE* $\epsilon 4$ and *BDNF* Met alleles was also associated with smaller volumes of the navigation-related brain regions in the participants with aMCI. Specifically, the carriers of both *APOE* $\epsilon 4$ and *BDNF* Met alleles had lower volumes of the hippocampus and the entorhinal cortex, that is, of the brain regions affected very early in AD and known to be important for allocentric navigation [1, 4]. The results are consistent with previous research demonstrating more pronounced hippocampal and entorhinal cortical atrophy in *APOE* $\epsilon 4$ [21, 85] and *BDNF* Met [48, 50] carriers and findings of the previous study showing lower right hippocampal volume in individuals with aMCI and combination of the *APOE* $\epsilon 4$ and *BDNF* Met alleles [58]. These *APOE* and *BDNF* Val66Met polymorphism-related structural changes in participants with aMCI could be explained by increased vulnerability of *APOE* $\epsilon 4$ carriers to AD-related pathological changes in this region [20] and by the fact that levels of BDNF protein that are decreased in *BDNF* Met carriers [47] are prominently reduced in the medial temporal lobe of individuals with AD [44]. This may negatively influence BDNF-induced neurogenesis [86] and dendritic arborization [41] and consequently lead to volumetric changes in this region. In our study, the *APOE* $\epsilon 4$ /*BDNF* Met carriers with aMCI had lower volumes of the hippocampus and the entorhinal cortex compared to the *APOE* $\epsilon 4$ non-carriers. However, lower volumes of these regions were also found in the *APOE* $\epsilon 4$ /*BDNF* Val/Val carriers. Therefore, it seems that structural differences in the medial temporal lobe between our aMCI polymorphism groups may be mainly driven by the presence of the *APOE* $\epsilon 4$ allele [21, 29]. Another noteworthy result was that right hippocampal volume was associated with allocentric navigation performance in participants with aMCI. This is in line with our previous findings in individuals with aMCI and AD dementia [16, 29, 70, 87] and underlines the important role of the right hippocampus in allocentric navigation. The combination of the *APOE* $\epsilon 4$ and *BDNF* Met alleles in individuals with aMCI was not associated with volume reduction of the inferior parietal cortex, precuneus, and posterior cingulate cortex, that is, of the brain regions known to be important for egocentric navigation [1, 2]. These brain regions have been associated with lower BDNF expression in AD dementia [45] and

hypometabolism on FDG-PET in *APOE* $\epsilon 4$ carriers [22, 88] but their structural changes related to the *APOE* and *BDNF* Val66Met polymorphisms have not been reported. This may be explained by the fact that AD-related pathological changes associated with tissue loss occur later in the parietal cortex than in the medial temporal lobe during the disease [89] and that functional changes in these areas associated with cognitive impairment precede structural abnormalities [90]. Therefore, more pronounced egocentric navigation impairment in individuals with aMCI and combination of the *APOE* $\epsilon 4$ and *BDNF* Met alleles may not be reflected in volumetric changes of these navigation-related brain regions.

One of the strengths of the current study is the fact that this is the first study to date to focus on the influence of combination of the *APOE* and *BDNF* Val66Met polymorphisms on spatial navigation in a well-defined cohort of CU and aMCI participants. In addition, we used the real-space version of the hMWM, a well-established method mimicking navigation in the real world, to examine spatial navigation, a specific and neglected cognitive function, whose impairment is observed and frequently reported by patients in the early stages of AD [5, 91]. The real-space version allows the use of vestibular and proprioceptive information that is missing in virtual reality and therefore may better reflect real-world navigation [15]. Finally, we assessed the influence of these polymorphisms on volumes of specific brain regions relevant for spatial navigation and being affected very early in the course of AD [13, 14].

This study also has some limitations. First, the number of participants was relatively small, which may increase the chances of bias towards the Type II error. Next, our hypotheses required many statistical comparisons, which may increase the chances of bias towards the Type I error, although the *post hoc* tests and corrections for multiple comparisons were used in all analyzes. Because of these limitations our results should be interpreted with caution. Further studies with larger study cohorts are required to validate our findings. In addition, specific AD biomarkers ($A\beta_{1-42}$ and p-tau₁₈₁ in cerebrospinal fluid and amyloid PET imaging) were assessed only in a subset of the participants and therefore we could not evaluate the presence of AD pathology in all CU and aMCI participants. Because of the relatively small number of participants in some groups we could not evaluate the differences between the polymorphism groups in associations between spatial navigation performance and volumes of the brain regions, which should be a

focus of future studies. Spatial navigation tasks were always performed in the same order and therefore we were not able to control for changes in participants' performance across the tasks. Future studies randomly varying order of egocentric and allocentric tasks between participants may be needed to control for the practice effect. Finally, the cross-sectional design did not allow evaluating the combined effect of *APOE* and *BDNF* Val66Met polymorphisms on spatial navigation changes over time but longitudinal follow-up is ongoing.

Conclusion

In conclusion, the current study demonstrated that the high risk combination of the *APOE* $\epsilon 4$ and *BDNF* Met alleles is associated with more pronounced egocentric spatial navigation impairment and smaller volumes of the medial temporal lobe structures in individuals with aMCI and allocentric spatial navigation deficits in CU individuals. This finding may indicate that aMCI individuals with both *APOE* $\epsilon 4$ and *BDNF* Met alleles may have more advanced AD pathology and higher risk of progression to AD dementia and CU individuals may be at greater risk of cognitive decline and progression to MCI. Further, our findings, in line with previous research [56–58], suggest that the combination of the *APOE* $\epsilon 4$ and *BDNF* Met alleles may interfere with memory function in individuals with aMCI. However, memory testing, unlike spatial navigation testing, did not distinguish *BDNF* Met carriers from non-carriers among the individuals with the *APOE* $\epsilon 4$ allele. These findings may indicate that spatial navigation testing could more reliably assess the deleterious effect of the *BDNF* Met allele on cognition than traditionally used episodic memory tests. The focus of future studies should be to evaluate the effect of combination of *APOE* and *BDNF* Val66Met polymorphisms on longitudinal spatial navigation changes in individuals with aMCI and those in the earlier stage of the disease, such as individuals with subjective cognitive decline.

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SUPPLEMENTARY MATERIAL

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