APOE ε4, but not polygenic AD risk, is related to longitudinal decrease in hippocampal brain activity in non-demented individuals

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Abstract

The hippocampus is early affected in Alzheimer's Disease (AD) and altered hippocampal functioning influences normal cognitive aging. Here, we used functional MRI to assess if the *APOE* ε4 allele or a polygenic risk score (PRS) for AD was linked to longitudinal changes in memory-related hippocampal activation also in normal aging (baseline age 50–95, n = 292; n = 182 at four-year follow-up, subsequently non-demented for at least two years). Mixed-models were used to predict level and change in hippocampal activation by *APOE* ε4 status and PRS based on gene variants previously linked to AD at $p \leq 1$, $p < 0.05$, or $p < 5e\text{-}8$ (excluding *APOE*). *APOE* ε4 and $PRS_{p<5e-8}$ significantly predicted AD risk in a larger sample from the same study population (n = 1,542), while $PRS_{p\leq1}$ predicted memory decline. *APOE* ε4 was linked to decreased hippocampal activation over time, with the most prominent effect in the posterior hippocampus, while PRS was unrelated to hippocampal activation at all p-thresholds. These results suggests a link for *APOE* ε4, but not for AD genetics in general, on functional changes of the hippocampus in normal aging. Among possible mechanisms are breakdown of the blood-brain barrier in *APOE* ε4 carriers, recently linked to cognitive aging independent from AD pathologies.

Introduction

During pre-clinical stages, Alzheimer's disease (AD) is difficult to discriminate from neurocognitive changes in the range of normal aging, with partly overlapping biological processes and genetic factors (1). Given that the strongest risk factor for AD is increased age (1), how individual variations in normal neurocognitive aging relates to the progression of AD needs to be elucidated. By studying how genetic risk factors of AD influence normal neurocognitive aging patterns, we can better understand the functional role of genetic risk factors of AD in disease development and bridge the gap between normal aging and AD.

AD is considered to have an oligogenetic heritability pattern, where the apolipoprotein E (*APOE*) ε4 allele constitutes the single strongest genetic risk factor for the disease (2). The role of *APOE* in the etiology of AD is not fully understood, but *APOE* ε4 has been linked to several AD-related mechanisms, including the accumulation of amyloid-β plaques, degeneration of tau neurofibrils, and neuroinflammation (2). Moreover, *APOE* ε4 is suggested to play a role in normal aging, where a link between *APOE* ε4 and cognitive aging via break-down of the blood-brain barrier (BBB) was recently demonstrated (3). Breakdown of the BBB may be induced by aging-related stiffening of arteries causing 'pulsatile stress' to blood vessels in the brain. This process is known to be linked to impaired cognition through neurovascular uncoupling, a failure to meet a brain regions higher energy demand with a sufficient increase in blood flow (4, 5).

Several other genetic variants have been associated with AD with weaker effect sizes, and linked to genes that are involved in lipid-, amyloid-β-, tau- and immune pathways (6, 7). Polygenic risk scores (PRS) for AD have been used to study the additive effect of multiple gene variants across the whole genome on endophenotypes and prediction of disease onset (8). A relation of *APOE* ε4-status and AD PRS with

variation in normal cognitive ability in elderly has been found (8). We recently showed that both *APOE* ε4 and PRS for AD predicted aging-related cognitive decline across 25 years in individuals that remained healthy at follow-up, where the effect of PRS was seen already 6-years prior to diagnostic follow-up (9).

The hippocampus is an important brain area for memory functioning that is structurally and functionally linked to both cognitive aging and development of AD. Atrophy of the hippocampus is observed already at preclinical stages of AD (10). Both *APOE* ε4 and AD PRS have been linked to hippocampal volume in healthy individuals (11, 12), although a larger study found the effect of AD PRS to be attenuated when removing the *APOE* locus (13). Longitudinal change in hippocampal volume was recently linked to episodic memory decline in *APOE* ε4 carriers but not in non-carriers (14). fMRI studies of hippocampal activation during memory tasks have shown both hypo- (15–17) and hyper-activation (18–23) in individuals with mild cognitive impairment (MCI) or AD compared to controls. Hippocampal hyper- (24–28) and hypo-activation (29) have also been reported in cross-sectional studies of healthy *APOE* ε4 allele carriers relative to non-carriers, and as a function of increased AD PRS (30, 31).

The goal of the present study was to examine the relation of *APOE* ε4 and AD PRS with both level and longitudinal change in hippocampal activation in participants who remained non-demented at diagnostic follow-up 2–4 years after their final fMRI session (32, 33). The rationale for investigating disease genetics in unaffect individuals is to study if hippocampal functioning in aging constitutes a genetic endophenotype of AD, rather than being a consequence of the disease. Given that 'biological AD' can be defined years before 'clinical AD' (34), we excluded individuals that subsequently developed AD within the study period. In a previous study using the same data, we observed longitudinal hypo-activation in the anterior hippocampus during memory encoding in aging (32). Our primary hypothesis here was that genetic risk factors for AD would magnify the decreases in hippocampus activity previously associated with normal aging. However, we cannot rule out the possibility of indirect effects from pathological processes in individuals at early pre-clinical stages of AD (i.e. >4 years before clinical AD). Thus, as fMRI studies have also reported hyper-activation of the hippocampus in preclinical AD (35, 36), another possible outcome would be increased hippocampal activation over time in elderly at genetic risk for AD.

Methods

Participants

Study participants belong to the longitudinal population-based prospective Betula cohort study on memory, health and aging (33). Exclusion criteria for the brain scanning sessions were contraindications to MRI or notable artifacts in the fMRI acquisition, history of known neurologic or psychiatric disease, and dementia diagnosis. Individuals who developed dementia up until the last diagnostic screening performed in Betula (2015–2017) were excluded from analysis of brain activation (n = 14). A total number of 292 subsequently healthy individuals (141 males and 151 females) aged 50-95 years at the first scanning session (2009-2010) were included, of which 182 returned for a second fMRI scan four years later (2013-2014). The study protocol of this project was approved by the local ethics board at

Umeå University (Regionala etikprövningsnämnden Umeå, Sweden) and the protocol was followed troughout the study period. All participants provided written informed consent and were compensated monetarily for their participation.The research was performed in accordance with the Declaration of Helsinki.

Dementia diagnosis procedure

Dementia diagnosis was made in 2015–2017 by a geropsychiatrist based on the DSM-IV criteria (37), using previous medical history and results from neuroradiological examination. Additional information was obtained from health examination and neuropsychological test assessments as follows: Mini-Mental State Examination (MMSE) score below 23 or a drop by 3 points compared to previous score, composite and memory test score ≥ 1.8 standard deviation below age-based norms with a decline in cognitive performance from previous test occasion, self-reported memory impairment or observed signs of neurocognitive dysfunction at test occasions by nurses and psychologist conducting the testing. Evaluation of medical records was done at baseline and follow-up to increase the diagnostic precision and the reliability of the assessments (38,39).

Episodic memory task

The task performed during fMRI acquisition at both baseline and follow-up was a face-name paired-associates task including encoding, retrieval, and a control task (40). In brief, this 10-min task was divided into six encoding blocks, six retrieval blocks, and eight blocks of an active control task, with randomized interstimulus intervals. During encoding, participants were asked to remember the name associated with an unfamiliar face, presented as a photograph (and press a button). During retrieval, the same faces were presented along with three letters, from which participants were asked to indicate by button press the letter that corresponds to the first letter of the previously encoded name. During the active control, participants indicated with a button press when a circle presented at the center of the screen changed to a cross (40).

fMRI acquisition

At both baseline and follow-up, the fMRI data were collected on a 3 T General Electric (GE) Discovery MR750 scanner with a 32-channel head coil. The functional images were acquired with a gradient-echo EPI sequence according to the following parameters: TR = 2.0 seconds, TE = 30 milliseconds, flip angle = 80°, 37 slices (3.9 mm thick), 96 x 96 matrix, FOV = 25 x 25 cm. To allow for saturation of the fMRI signal, ten dummy scans were collected and discarded prior to experimental image acquisition. Cushions inside the head coil were used to minimize subject head movement. E-Prime (Psychology Software Tools) was used for stimulus presentation and recording of responses from a MR-compatible response pad. In addition, structural T1-weighted images were acquired with a 3D fast spoiled gradient echo sequence (180 slices with a 1mm thickness, TR: 8.2 milliseconds, TE: 3.2 milliseconds, flip angle: 12°, FOV: 25 x 25 cm).

fMRI analyses

The fMRI data were preprocessed and analyzed using SPM12 (Statistical Parametric Mapping, Wellcome Centre for Human Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm), implemented in MATLAB R2014b (MathWorks). SPM was run through an in-house program (DataZ). Preprocessing of the fMRI data included slice-timing correction, head movement correction by unwarping and realignment to the first image of each volume. The realigned images were then spatially normalized by co-registering participants' functional images to their structural T1-weighted images. This was done separately for data from baseline and follow-up by segmenting each participants' structural T1-weighted image into gray matter, white matter and cerebrospinal fluid components. The DARTEL (41) toolbox was used to create a template image for each participant of the baseline and follow-up data, and also a group-level DARTEL template. The flow-field files that mapped the transformation from native space to DARTEL template and an affine transformation from DARTEL to Montreal Neurologic Institute (MNI) space was used for normalizing the fMRI data to MNI standard space with a 2-mm resolution, and smoothed with an 8-mm full width at half maximum Gaussian kernel. Left and right hippocampal volumes were measured using automatic subcortical segmentation (aseg) in FreeSurfer, and adjusted to head size by dividing the hippocampal volume with the total intracranial volume (ICV).

Genotyping and construction of polygenic risk scores

The DNA extraction for single-nucleotide polymorphism (SNP) genotyping was done at the Institute of Human Genetics, University of Bonn, Germany. All DNA samples were genotyped using two types of Illumina arrays: Illumina Omni Express and Omni 1S Bead chip kits. Imputation of the raw genotypes was done using the ENIGMA2 protocol of the ENIGMA Consortium (http://enigma.ini.usc.edu/) to the 1000 genomes reference panel (42) using minimac tools (version 2013.7.17) (43). Post-imputation quality control (QC) was performed based on genotype call rate < 10%, minor allele frequency (MAF) < 1%, SNP missingness < 5 %, and imputation info < 0.8. Before calculating the PRS, SNPs with ambiguous strand alignment were removed, as were SNPs within the *APOE* region (44.4 - 46.5 Mb on chromosome 19 on the hg19 assembly). Thereafter, PRS for AD were calculated using the summary statistics from a AD GWAS including 21,982 AD cases and 41,944 cognitively normal controls (6). Linkage disequilibrium (LD) clumping was performed by discarding SNPs within 250 kb of, and in $r^2 \geq 0.1$ with another more significant SNP. The European sample of the 1000 Genomes Project phase 3 (42) was used as LD reference panel for clumping, after removal of SNPs with genotype call rate < 1% and MAF < 1%. PRS were calculated for each individual by summing the alleles of the clumped SNPs weighted by the beta value from the GWAS (6). PRS were constructed at p-value thresholds of $p < 5e\text{-}8$, $p < 0.05$, and $p \leq 1$, including 18, 41,305, and 290,660 SNPs, respectively.

Statistical analyses

The data were high-pass filtered (128 seconds), and voxel-wise general linear models were set up for each participant using SPM12. In these models, block onsets and durations for each condition from the

scanner task were included as regressor, modeled as a boxcar and convolved with a canonical hemodynamic response function (HRF). To remove movement-related artifacts, six realignment parameters from the motion correction preprocessing steps were included as covariates of no interest. Subject-level contrast images were generated, comparing the experimental conditions of the scanner task (encoding vs. control, and retrieval vs. control), separately for baseline and follow-up data. To identify hippocampal regions more activated during encoding and retrieval relative to the control task, the contrast images were carried on to random-effects group analyses using one sample t-tests of all subjects at baseline. Peaks were labeled as either anterior or posterior hippocampus (32) depending on their location in MNI space relative to y = −21 mm (44,45), demonstrated in **Figure 1A**. Beta values from the hippocampus peak activations, identified from the whole-brain analysis of the baseline sample (32), were modeled separately for the left and right hippocampus. To examine the association of AD PRS and *APOE* 4 with level and change in brain activation in anterior and posterior hippocampus, we performed linear mixed-effect models that were fitted in R using the lmer function available through the lme4 and lmerTest packages, using the extracted beta values as dependent variables. These models included the AD PRS as well as *APOE* 4 carriage status (coded as 0/1 for non-carriers and carriers due to the low frequency of 4 homozygotes) as covariates of interest, and sex, baseline age, adjusted hippocampal volume, sample, education, scanner task performace (number of hits) and the first five genetic principal components (PCs) for genetic ancestry as covariates of no interest. Age at each scanning session was used to estimate the slope, representing individualized aging-related change in activation over five years. Slope of all covariates was included in the models as well as random subject-specific intercepts. To test for association between AD genetics and differences on level and slope of performance on the scanner task (number of hits and response time), a linear mixed-effect model was used, including sex and age at baseline as covariates and *APOE* 4 carriership or PRS as the independent variable and either hits or response time as the dependent variable. Again, age at each scanning session was used to estimate the slope. As an additional analysis, both behavioral and fMRI analyses of PRS were stratified into *APOE* 4 carriers and non-carriers. All analyses were performed in R version 4.0.3. All continuous variables were z-transformed using the scale function in R, i.e., scaled to zero-mean and standard deviation (SD) of one.

Prediction of AD risk

To evaluate whether *APOE* 4 and/or PRS predict the risk of AD, we employed a Cause-specific hazard regression accounting for other dementia types and death as competing risks events. Data come from the Betula project (33), of which the brain imaging sample in this study constitutes a subset. In this type of competing risk regression analysis, the Cause-specific hazard function denotes the instantaneous rate of occurrence of the event (i.e., AD), in participants who are curently event-free. PRS were available for n = 1,746 subjects. Subjects with missing data for age and sex (n = 33), unknown dementia diagnosis (n = 116) or with diagnosis at baseline or before baseline (n = 55) were excluded. Participants with the confounding *APOE* ε2/*APOE* ε4 genotype) (46) were not included (n = 40). The final sample included 1,542 individuals, of which 791 remained healthy, 145 were diagnosed with AD, 121 were diagnosed with other dementia types, and 485 individuals died non-demented. In a sensitivity Cause-specific hazard regression analysis, dementia types other than AD and vascular dementia were excluded due to the low

number of cases, such as dementia not-otherwise specified (n = 13), dementia due to Parkinson's disease (n = 8), Lewy body dementia (n = 6), frontotemporal dementia (n = 2), and progressive supranuclear paralysis (n = 1). The sensitivity analysis also excluded individuals with low risk to develop dementia during the studied period (participants younger than 45 years at baseline, n = 184). Thus, sensitivity analysis (n = 1,328) included 617 healthy individuals, 145 AD cases, 91 vascular dementia cases and 475 individuals who died non-demented. Cause-specific hazard regression analysis were performed with PRS excluding the *APOE* loci, based on p-thresholds of $p < 5e\text{-}8$, $p < 0.05$ and $p \leq 1$. Time from baseline (in years) was used as the time scale. Regressions were adjusted for the first five PCs, *APOE* ε4 carriage, sex, age, and age-squared, and a sensitivity analysis included years of education. Dementia status, carriers of the *APOE* ε4 allele, and sex were included in the models as binary indicator variables (coded as 0/1).

Results

Genetic predictors of AD risk

We tested the effect of *APOE* ε4 carriership, and PRS, calculated based on either all SNPs ($PRS_{p\leq1}$), SNPs that previously predicted AD at genome-wide significance ($PRS_{p<5e\text{-}8}$), or SNPs that previously predicted AD at uncorrected significance level ($PRS_{p<0.05}$).

Both *APOE* ε4 and higher $PRS_{p<5e\text{-}8}$ were significantly associated with increased risk of AD. *APOE* ε4 carriers had a 3.8 times higher risk of AD compared to non-carriers (hazard ratio [HR] = 3.84, CI 2.7 - 5.4, p = 6.8e-15), while an increase in $PRS_{p<5e\text{-}8}$ by one standard deviation from the mean was associated with a 1.2 times increase in the risk of AD (HR = 1.29, CI 1.080 - 1.549, p = 0.005). $PRS_{p<5e\text{-}8}$ was similarly associated with risk of AD after controlling for years of education (HR = 1.29, CI 1.08 - 1.547, p = 0.006). In a sensitivity analysis excluding rare dementia types and individuals with low risk of developing AD (younger than 45 years old), the PRS also remained predictive of AD (HR = 1.28, CI 1.073 - 1.531, p = 0.006). $PRS_{p<0.05}$ was marginally significantly associated with AD risk, while no effect was seen for $PRS_{p\leq1}$ (**Supplementary table 1**).

Effects of genetic risk on scanner task performance

Descriptives of the fMRI sample are presented in **Table 1**, divided by *APOE* ε4 status. At baseline, there was no relation of *APOE* ε4 or AD PRS at any p-value threshould with scanner task performance. Longitudinal analyses of scanner task performance revealed that AD $PRS_{p<1}$ was significantly associated with more negative slopes in hits across the two fMRI sessions (t = -3.37, p = 0.0008), whereas no effect was seen for *APOE* ε4 (t=-1.37, p =0.17). The AD PRS was not significant at more conservative PRS p-value thresholds ($PRS_{p<0.05}$, t = -1.65, p = 0.0997, $PRS_{p<5e\text{-}8}$, t = -0.969, p = 0.333). Post-hoc analyses stratified by *APOE* status revealed that the effect of AD $PRS_{p<1}$ on slope in task performance was strongest in *APOE* ε4 carriers (n = 78, t = -2.8, p = 0.0056) , with a trend-level effect in non-carriers (n = 213, t = -1.8, p = 0.067). A weak effect of $PRS_{p<5e\text{-}8}$ was seen on response time (t = -2.4, p=0.02, i.e.

shorter response time with higher risk), but no other genetic effects were observed for change in response time (all p's > 0.1).

Effect of genetic risk for AD on age-related change in hippocampal activation

During memory encoding, *APOE* ε4 carriers showed a more pronounced aging-related decrease in hippocampal activation relative to non-carriers, with the strongest effect in the right and left posterior hippocampus (**Table 2, Figure 1B**), and weaker effects in the same direction in the anterior hippocampus (**Table 2**). During memory retrieval, a trend-level effect of *APOE* ε4 was seen in the right posterior hippocampus only (**Table 2**). We found no effects of the AD PRS on level or slope in hippocampal activation, for any PRS p-value thresholds (all p's > 0.1, to exemplify the full model is presented in **Supplementary table 2** for the left posteror hippocampus during encoding). Post-hoc stratification based on *APOE* ε4 allele carriership or removing scanner task performance (hits and reaction time) from the model did not reveal any significant results of PRS on hippocampal activation (all p's > 0.1).

Discussion

We examined if the *APOE* ε4 allele and/or increased AD PRS influences aging-related change in hippocampal functioning across four years, using longitudinal fMRI from a large population-based study (33). Our primary hypothesis was that genetic risk for AD would magnify our previously observed effect on encoding-related decreases in anterior hippocampal activation with aging (32), or, alternatively, that hyper-activations over time in individuals with higher genetic risk for AD would be an indicator of pre-clinical AD processes in this group (35,36). We found that *APOE* ε4 carriers had decreased hippocampal activation with increasing age, whereas no difference over time was seen in non-carriers (**Figure 1)** or as a function of AD PRS. The effect of *APOE* ε4 was seen both during encoding and retrieval. The finding did not reflect a magnification of a general effect of age in the anterior hippocampus but was instead expressed most prominently in the posterior hippocampus. The associations are unlikely to be driven by AD-related processes since all included individuals remained non-demented for a minimum of two years after the second fMRI assessment, and *APOE* ε4 carriers did not differ from non-carriers in task performance or hippocampal volume. Also, no similar effect was seen for individuals at increased risk of subsequent development of AD based on non-*APOE* loci.

A plausible mechanism for an effect of *APOE* ε4 on age-related decreases in hippocampal functioning that is not secondary to pre-clinical AD pathologies, would be the role for *APOE* ε4 on breakdown of the BBB (47). The link between APOE and BBB breakdown was recently shown to be specific to the hippocampal region and linked to cognitive decline through neurovascular uncoupling independently of amyloid-b and tau pathologies (3). Similarly, our observation of a decrease in the BOLD signal in *APOE* ε4 carriers may represent an inability to increase blood flow sufficiently upon increased energy demand, rather than a decreased oxygen demand followed by reduced neuronal activity (5). Although reduced hippocampal activation in healthy elderly has previously been linked to reduced memory performance (32,48–50), lower activation in *APOE* ε4 was not linked to lower performance on the scanner task. One

explanation for this could be that we used a memory task at scanning that was optimized to elicit a strong hippocampal response, but not to reveal behavioral effects. In a previous publication on the same study population, we reported an *APOE* ε4 effect on age-related decreases in performance on more sensitive off-line cognitive tests (51).

By segmentation of the hippocampus along the long axis, we could further observe that the effect of *APOE* ε4 was most prominent in the posterior hippocampus. However, as a weaker effect of *APOE* ε4 was observed also in the anterior hippocampus, regional differences should be interpreted cautiously. APOE is expressed mainly in astrocytes and glia cells, but also in neurons of all hippocampal subunits (CA1-4 and DG) (52). Potential differences of the effect of *APOE* ε4 on the BBB in hippocampal subunits have not yet been explored.

Based on previous studies showing effects of AD PRS on cognitive decline (9) and level of hippocampal functioning in healthy aging (30,31), we hypothesized that AD PRS would also predict decline in hippocampal activation. However, we did not observe such an effect for any of our three selected PRS p-value thresholds. As our PRS sucessfully predicted both AD risk and scanner task performance, we believe it is unlikely that the lack of effect on brain activation is due to low power. Notably, only the $PRS_{p\leq1,}$ i.e. including all SNPs, predicted decline in task performance across age, in line with our previous work on cognitive task performance (9). This likely reflect a higher polygenicity of cognitive ability in general than of clinical AD (9,53,54). The mechanisms for variants with weaker association to AD could be mediated through a general effect on cognitive ability that impacts AD risk through educational attainment or other life-style factors. Thus, the genetic link to AD for $PRS_{p\leq1}$ is seemingly too distant to predict the disease in small independent studies, while a link to cognitive decline is more proximal. In contrast, $PRS_{p<5e\text{-}8}$ consisted of 18 SNPs excluding the *APOE* locus, from genes with roles in e.g. amyloid-β-, tau-, lipid transportations-, immune system-, and endocytosis pathways, with more direct link to AD-related processes (6). Our results suggests that those genes in general can predict AD risk in a small independent sample, but do not influence cognition or hippocampal functioning in healthy aging. However, one or a few of those genetic pathways might still play a role in normal neurocognitive aging individually.

Given that pathological AD processes can start ten years before clinical detection of AD (1), lack of longer diagnostic follow-up cannot rule out the possibility that some individuals who were assessed as cognitive healthy in fact were in a preclinical dementia stage. However, our two-year clinical follow-up was more extensive than most previous studies on aging in non-demented individuals. The number of individuals that underwent fMRI in this sample and have developed AD to date is too small to restrict analyses to this specific sub- group. It should be noted that we defined AD clinically, and that clinically healthy individuals can manifest with AD-related biomarkers in the cerebrospinal fluid that meet the criterias for a *biologically-defined* AD (34).

In conclusion, our findings suggest an effect of *APOE* 4, but not genetic risk for AD in general, on longitudinal change in hippocampal functioning in healthy aging.

Declarations

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Author contributions

E.K., S.H., and F.S.H. performed analyses and wrote parts of the manuscript. LN designed the fMRI paradigm, and advised on fMRI data analysis and interpretation of results. KK was responsible for idea, concept, and design of the study, performed analyses and wrote most the manuscript. All authors contributed with reviewing and editing of the final manuscript.

Data availability statement

The datasets generated and/or analysed during the current study are not publicly available due to lack of ethical permit for sharing sensitive person data, but are available from the corresponding author on reasonable request.

Competing interests statement

The authors declare no competing interests.

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References

1. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, *et al.* (2021): Alzheimer's disease. *Lancet* 397: 1577–1590.
2. Serrano-Pozo A, Das S, Hyman BT (2021): APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol* 20: 68–80.
3. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, *et al.* (2020): APOE4 leads to blood–brain barrier dysfunction predicting cognitive decline. *Nature* 581: 71–76.
4. Wåhlin A, Nyberg L (2019): At the Heart of Cognitive Functioning in Aging. *Trends Cogn Sci* 23: 717–720.
5. Iadecola C (2017): The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. *Neuron* 96: 17–42.

6. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, *et al.* (2019): Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet* 51: 414–430.
7. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, *et al.* (2019): Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet* 51: 404–413.
8. Bellou E, Stevenson-Hoare J, Escott-Price V (2020): Polygenic risk and pleiotropy in neurodegenerative diseases. *Neurobiol Dis* 142: 104953.
9. Kauppi K, Rönnlund M, Nordin Adolfsson A, Pudas S, Adolfsson R (2020): Effects of polygenic risk for Alzheimer's disease on rate of cognitive decline in normal aging. *Transl Psychiatry* 10. https://doi.org/10.1038/s41398-020-00934-y
10. Li J-Q, Tan L, Wang H-F, Tan M-S, Tan L, Xu W, *et al.* (2016): Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *J Neurol Neurosurg Psychiatry* 1–9.
11. Murray AN, Chandler HL, Lancaster TM (2021): Multimodal hippocampal and amygdala subfield volumetry in polygenic risk for Alzheimer's disease. *Neurobiol Aging* 98: 33–41.
12. Foley SF, Tansey KE, Caseras X, Lancaster T, Bracht T, Parker G, *et al.* (2017): Multimodal Brain Imaging Reveals Structural Differences in Alzheimer's Disease Polygenic Risk Carriers: A Study in Healthy Young Adults. *Biol Psychiatry* 81: 154–161.
13. Foo H, Thalamuthu A, Jiang J, Koch F, Mather KA, Wen W, Sachdev PS (2021): Associations between Alzheimer's disease polygenic risk scores and hippocampal subfield volumes in 17,161 UK Biobank participants. *Neurobiol Aging* 98: 108–115.
14. Gorbach T, Pudas S, Bartrés-Faz D, Brandmaier AM, Düzel S, Henson RN, *et al.* (2020): Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE ε4 carriers. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 12: 1–9.
15. Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O´Brien PC, *et al.* (2003): Comparison of memory fMRI response among Normal, MCI, and Alzheimer's patients. *Neurology* 61: 500–506.
16. Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, *et al.* (2006): Activation of brain regions vulnerable to Alzheimer's disease: The effect of mild cognitive impairment. *Neurobiol Aging* 27: 1604–1612.
17. Petrella JR, Krishnan S, Slavin MJ, Tran TTT, Murty L, Doraiswamy PM (2006): Mild cognitive impairment: Evaluation with 4-T functional MR imaging. *Radiology* 240: 177–186.
18. Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, *et al.* (2004): Medial temporal lobe function and structure in mild cognitive impairment. *Ann Neurol* 56: 27–35.
19. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, *et al.* (2005): Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* 65: 404–411.

20. Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, *et al.* (2006): Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: An independent component analysis. *J Neurosci* 26: 10222–10231.
21. Hämäläinen A, Pihlajamäki M, Tanila H, Hänninen T, Niskanen E, Tervo S, *et al.* (2007): Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol Aging* 28: 1889–1903.
22. Kircher TT, Weis S, Freymann K, Erb M, Jessen F, Grodd W, *et al.* (2007): Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry* 78: 812–818.
23. Yassa M a, Stark SM, Bakker A, Albert MS, Gallagher M, Stark CEL (2010): High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic Mild Cognitive Impairment. *Neuroimage* 51: 1242–52.
24. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, *et al.* (2009): Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proc Natl Acad Sci U S A* 106: 7209–7214.
25. Trachtenberg AJ, Filippini N, Mackay CE (2012, February): The effects of APOE-ε4 on the BOLD response. *Neurobiology of Aging*, vol. 33. Neurobiol Aging, pp 323–334.
26. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW (2000): Patterns of Brain Activation in People at Risk for Alzheimer's Disease. *N Engl J Med* 343: 450–456.
27. Trivedi MA, Schmitz TW, Ries ML, Hess TM, Fitzgerald ME, Atwood CS, *et al.* (2008): fMRI activation during episodic encoding and metacognitive appraisal across the lifespan: Risk factors for Alzheimer's disease. *Neuropsychologia* 46: 1667–1678.
28. Dennis NA, Browndyke JN, Stokes J, Need A, Burke JR, Welsh-Bohmer KA, Cabeza R (2010): Temporal lobe functional activity and connectivity in young adult APOE ε4 carriers. *Alzheimer's Dement* 6: 303–311.
29. Adamson MM, Hutchinson JB, Shelton AL, Wagner AD, Taylor JL (2011): Reduced hippocampal activity during encoding in cognitively normal adults carrying the APOE e{open}4 allele. *Neuropsychologia* 49: 2448–2455.
30. Chandler HL, Hodgetts CJ, Caseras X, Murphy K, Lancaster TM (2020): Polygenic risk for Alzheimer's disease shapes hippocampal scene-selectivity. *Neuropsychopharmacology* 45: 1171–1178.
31. Xiao E, Chen Q, Goldman AL, Tan HY, Healy K, Zoltick B, *et al.* (2017): Late-Onset Alzheimer's Disease Polygenic Risk Profile Score Predicts Hippocampal Function. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2: 673–679.
32. Nyberg L, Andersson M, Lundquist A, Salami A, Wåhlin A (2019): Frontal Contribution to Hippocampal Hyperactivity During Memory Encoding in Aging. *Front Mol Neurosci* 12: 1–11.
33. Nyberg L, Boraxbekk CJ, Sörman DE, Hansson P, Herlitz A, Kauppi K, *et al.* (2020): Biological and environmental predictors of heterogeneity in neurocognitive ageing: Evidence from Betula and other longitudinal studies. *Ageing Res Rev* 64. https://doi.org/10.1016/j.arr.2020.101184

34. Jack CR, Therneau TM, Weigand SD, Wiste HJ, Knopman DS, Vemuri P, *et al.* (2019): Prevalence of Biologically vs Clinically Defined Alzheimer Spectrum Entities Using the National Institute on Aging-Alzheimer's Association Research Framework. *JAMA Neurol* 55905: 1–10.
35. Talwar P, Kushwaha S, Chaturvedi M, Mahajan V (2021): Systematic Review of Different Neuroimaging Correlates in Mild Cognitive Impairment and Alzheimer's Disease. *Clin Neuroradiol* 953–967.
36. Li HJ, Hou XH, Liu HH, Yue CL, He Y, Zuo XN (2015): Toward systems neuroscience in mild cognitive impairment and Alzheimer's disease: A meta-analysis of 75 fMRI studies. *Hum Brain Mapp* 36: 1217–1232.
37. American Psychiatric Association (2000): Diagnostic and statistical manual of mental disorders (4th ed., Text Revision). *Washington*.
38. Rönnlund M, Sundström A, Adolfsson R, Nilsson LG (2015): Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: Evidence from the Betula prospective cohort study. *Alzheimer's Dement* 11: 1385–1392.
39. Nilsson L-G, Adolfsson R, Backman L, de Frias C, Molander B, Nyberg L (2004): Betula: A prospective cohort study on memory, health and aging. *Aging, Neuropsychol Cogn* 11: 134–148.
40. Nyberg L, Pudas S (2018): Successful Memory Aging. *Annu Rev Psychol* 70: 219–243.
41. Ashburner J (2007): A fast diffeomorphic image registration algorithm. *Neuroimage* 38: 95–113.
42. The 1000 Genomes Project Consortium (2016): A global reference for human genetic variation. *Nature* 526: 68–74.
43. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR (2013): Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nat Genet* 44: 955–959.
44. Poppenk J, Evensmoen HR, Moscovitch M, Nadel L (2013): Long-axis specialization of the human hippocampus. *Trends Cogn Sci* 17: 230–240.
45. Salami A, Wahlin A, Kaboodvand N, Lundquist A, Nyberg L (2016): Longitudinal Evidence for Dissociation of Anterior and Posterior MTL Resting-State Connectivity in Aging: Links to Perfusion and Memory. *Cereb Cortex* 26: 3953–3963.
46. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, Huentelman MJ, Beach TG, Caselli RJ, *et al.* (2020): Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. *Nat Commun* 11. https://doi.org/10.1038/s41467-019-14279-8
47. Halliday MR, Rege S V., Ma Q, Zhao Z, Miller CA, Winkler EA, Zlokovic B V. (2016): Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J Cereb Blood Flow Metab* 36: 216–227.
48. Nyberg L (2017): Functional brain imaging of episodic memory decline in ageing. *J Intern Med* 281: 65–74.
49. Tromp D, Dufour A, Lithfous S, Pebayle T, Després O (2015): Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies. *Ageing Res Rev* 24: 232–262.

50. Salami A, Eriksson J, Nyberg L (2012): Opposing effects of aging on large-scale brain systems for memory encoding and cognitive control. *J Neurosci* 32: 10749–10757.
51. Kauppi K, Rönnlund M, Nordin Adolfsson A, Pudas S, Adolfsson R (2020): Effects of polygenic risk for Alzheimer's disease on rate of cognitive decline in normal aging. *Transl Psychiatry* 10. https://doi.org/10.1038/s41398-020-00934-y
52. Pu-Ting X, Gilbert JR, Hui-Ling Q, Ervin J, Rothrock-Christian TR, Hulette C, Schmechel DE (1999): Specific regional transcription of apolipoprotein E in human brain neurons. *Am J Pathol* 154: 601–611.
53. Zhang Q, Sidorenko J, Couvy-duchesne B, Marioni RE, Wright MJ, Goate AM, *et al.* (2020): Risk prediction of late-onset Alzheimer ' s disease implies an oligogenic architecture. 1–11.
54. Hill WD, Marioni RE, Maghzian O, Ritchie SJ, Hagenaars SP, McIntosh AM, *et al.* (2018): A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence. *Mol Psychiatry* 1–13.

Tables

Table 1: Baseline characteristics of study sample for fMRI analyses

	***APOE* ε4 carriers (n = 77)**	***APOE* ε4 non-carriers (n = 215)**	**t/c^2 value**	**p-value**
Age, Mean (SD)	65.42 (7.96)	67.22 (8.02)	1.69	0.092[a]
Sex, n females (males)	38 (39)	113 (102)	0.12	0.73[b]
RT, Retrieval, Mean (SD)	2.653 (0.30)	2.673 (0.31)	0.50	0.62[a]
Hits, Retrieval, Mean (SD)	14.29 (3.95)	13.94 (4.24)	-0.65	0.52[a]
Adj. R Hippocampal volume	2.56e-3	2.52e-3	-0.89	0.38[a]
Adj. L Hippocampal volume	2.51e-3	2.47e-3	-0.88	0.38[a]

RT = mean response time (in seconds), SD = standard deviation, a: Welch Two Sample t-test, b: Chi-Square test. Adjusted hippocampal volume=Hippocampal volume/Intracranial volume.

Table 2: Effect of *APOE* ε4 on level and slope in hippocampal activation across four years.

Contrast, region		beta	SE	t	p-value
Encoding					
R posterior	Intercept	-4.739e-02	1.843e-02	-2.571	0.010743*
	Slope	-5.845e-02	1.886e-02	-3.098	0.002124**
L posterior	Intercept	-0.055278	0.020548	-2.690	0.007647**
	Slope	-0.080679	0.020946	-3.852	0.000142***
R anterior	Intercept	-2.501e-02	2.459e-02	-1.017	0.31010
	Slope	-4.535e-02	2.493e-02	-1.819	0.06982
L anterior	Intercept	-2.281e-02	2.645e-02	-0.862	0.38945
	Slope	-6.210e-02	2.682e-02	-2.315	0.02126*
Retrieval					
R posterior	Intercept	-5.904e-02	2.503e-02	-2.359	0.0192*
	Slope	-5.418e-02	2.521e-02	-2.149	0.0324*
L posterior	Intercept	-4.000e-02	2.707e-02	-1.478	0.1408
	Slope	-3.852e-02	2.725e-02	-1.413	0.1585
R anterior	Intercept	-7.809e-03	2.942e-02	-0.265	0.7909
	Slope	4.834e-02	3.026e-02	1.598	0.1111
L anterior	Intercept	-0.044201	0.029289	-1.509	0.13265
	Slope	0.023385	0.030076	0.778	0.43745

Linear mixed regression models were fitted using the lmer function in R. Sex, baseline age, sample, education, adjusted left or right hippocampus volume, hits, Response time, AD $PRS_{p<1}$, and the first 5 genetic principal components for genetic ancestry included in all models. Slope estimated between two time points with a four year interval, using age as time-varying covariate. * = p < 0.05, ** = p < 0.01, *** = p < 0.001. SE = standard error. L= left. R=right.

Figures

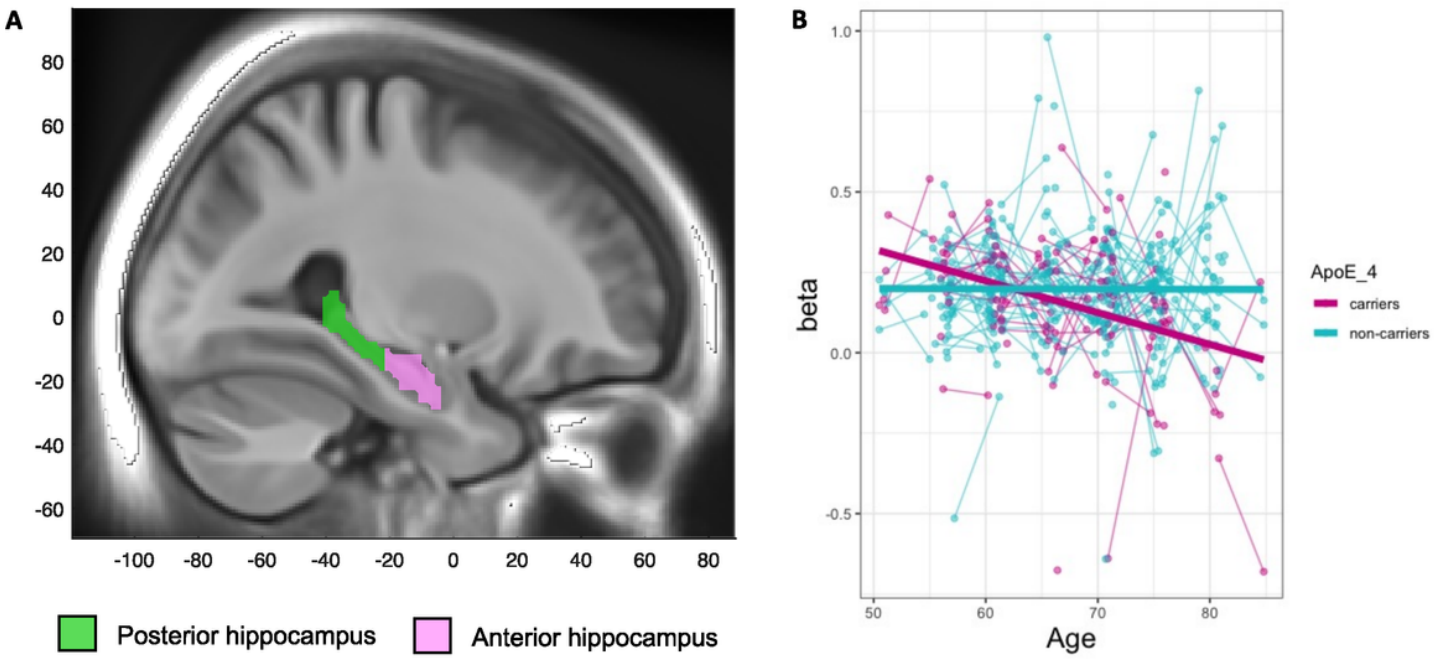

Figure 1

Representation of anterior and posterior hippocampi according to their location in MNI space relative to y = −21 mm (**A**). Age-related decrease in hippocampal activity in the left posterior hippocampus during memory encoding in *APOE* 4 carriers compared to non-carriers (**B**).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables.pdf