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**Vulnerability to memory decline in aging revealed by a mega-analysis of structural brain change**

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**Running title:** Coupled memory and brain decline.

**Abstract**

Brain atrophy is a key factor behind episodic memory loss in aging, but the nature and ubiquity of this relationship remains poorly understood. This study leverages 13 longitudinal datasets, including 3,737 cognitively healthy adults (10,343 MRI scans; 13,460 memory assessments), to determine whether brain change-memory change associations are more pronounced with age and genetic risk for Alzheimer's Disease. Both factors are associated with accelerated brain decline, yet it remains unclear whether memory loss is exacerbated beyond what atrophy alone would predict. Additionally, we assess whether memory decline aligns with a global pattern of atrophy or stems from distinct regional contributions. Our mega-analysis reveals a nonlinear relationship between memory decline and brain atrophy, primarily affecting individuals with above-average brain structural decline. The associations are stronger in the hippocampus but also spread across diverse cortical and subcortical regions. The associations strengthen with age, reaching moderate associations in participants in their eighties. While APOE  $\epsilon$ 4 carriers exhibit steeper brain and memory loss, genetic risk has no effect on the change-change associations. These findings support the presence of common biological macrostructural substrates underlying memory function in older age which are vulnerable to multiple age-related factors, even in the absence of overt pathological changes.

## Introduction

Episodic memory declines with age<sup>1,2</sup>, although individual trajectories vary significantly, with some experiencing marked cognitive decline and others maintaining relatively stable memory function over time<sup>3</sup>. Brain atrophy is considered a key contributor to these changes<sup>4,5</sup>. However, key questions remain poorly understood such as whether the change – change associations are dependent on age and genetic risk for Alzheimer's disease (AD) or if the patterns are driven exclusively by a subset of individuals with severe atrophy. Further, extant research remains inconclusive on whether the effects reflect global patterns of brain atrophy<sup>6,7</sup> or regional structural vulnerabilities, particularly in the hippocampus<sup>8,9</sup>. To examine these questions, we leveraged 13 datasets with more than 3,700 cognitively healthy adult participants who underwent repeated MRI scans and cognitive assessments, together with simulations to guide results interpretation.

Both episodic memory and medial temporal lobe (MTL) structures tend to show relative stability across early adulthood and middle age in longitudinal studies, with a more marked decline from about 60 years<sup>1,2,10–12</sup>. In contrast, trajectories of cortical thickness outside the MTL tend to follow largely monotonic declines across adulthood, likely with subtle acceleration in thinning late in life<sup>10,13–15</sup>, with a relatively large degree of heterogeneity for the remaining subcortical structures<sup>11,16,17</sup>. Aging is also associated with increased interindividual variability in cognition and biological measures, including memory performance and brain structure<sup>16,18</sup> and, even more importantly, the variability of brain and memory change also increases with age<sup>19–21</sup>.

Initial evidence for a relationship between memory function and brain structure in cognitively healthy aging came from cross-sectional research<sup>22,23</sup>, which indicated that differences in brain structure, particularly in the MTL, explained a modest amount of age-related variability in episodic memory function. Yet, it is now widely recognized that only longitudinal designs can effectively link co-occurring within-person changes in brain and cognition throughout the lifespan<sup>24</sup>. Indeed, longitudinal research has corroborated the association between memory decline and loss of grey matter in medial temporal features such as hippocampal atrophy<sup>25–29</sup> and entorhinal thinning<sup>8,30</sup>. The findings align with the key role of these structures in episodic

memory and their susceptibility to aging and AD<sup>31–33</sup>. Outside this region, associations have also been reported, albeit less consistently, in the frontal, parietal, and temporal lobes<sup>34,35</sup>, as well as in global grey matter<sup>6,27</sup>. These results are consistent with the complex cortico-subcortical circuitry supporting episodic memory function<sup>33,36–38</sup>. Debate remains on whether these change-change associations are driven by a main factor of brain decline or by one or more of these memory-sensitive structures<sup>6,26,29,34,39</sup>. Current research shows evidence of both domain-general dimensions of cortical and cognitive change<sup>6,40</sup> and domain-specific associations between MTL and episodic memory change<sup>39</sup>.

Since age affects both individual trajectories of brain structure and memory, and their variability across individuals, it is likely that age also moderates their relationship, such that the associations strengthen with increasing age. However, limited data exist on this topic, and when available, this data primarily concerns the hippocampus. Cross-sectional evidence suggests stronger associations between hippocampus volume and memory performance in late life<sup>41,42</sup>. Using longitudinal data, Gorbach and colleagues<sup>25</sup> found an association between hippocampal atrophy and memory decline that was significant in older (65 – 80 years) but not in middle-aged (55 – 60 years) individuals, and further suggested that steeper declines in memory and hippocampal volume facilitate detection of these associations.

The Apolipoprotein (APOE) ε4 allele represents the strongest known genetic risk factor for late-onset AD. In individuals with AD, ε4 carriers exhibit steeper brain atrophy, especially in limbic regions, and greater memory loss compared to non-carriers<sup>43,44</sup>. This pattern has also been observed in cognitively healthy older individuals<sup>45,46</sup>, although not universally<sup>47</sup>. Some theoretical models propose distinct AD subtypes based on the APOE ε4 allele<sup>48</sup>. In this account, the ε4 carrier subtype represents a more severe, limbic-dominant form of AD, characterized by steeper loss of memory and stronger links to amyloid pathophysiology. The non-carrier subtype is thought to represent a milder form, more heterogeneous, and more associated with environmental factors<sup>49</sup>. This model also predicts stronger associations between memory change and atrophy, particularly in the MTL, in ε4 carriers. Supporting this, some studies report a stronger brain-memory association amongst APOE ε4 carriers, in AD samples<sup>50</sup> and, crucially, in a longitudinal sample of cognitively healthy older adults<sup>9</sup>.

Not all observed changes in brain structure in older individuals reflect long-term changes, i.e., brain aging, but also short-term variations due to known, e.g., physical or cognitive training programs<sup>51,52</sup>, and unknown factors, i.e., noise<sup>20</sup>. Hence, only a fraction of the observed changes occurring in brain structure over time may relate to memory decline. Thus, it is possible that most variation in brain structure over time is not degenerative, and that only individuals with severe atrophy show memory loss, leading to non-linear change – change associations.

Given the inherent heterogeneity in brain and cognitive trajectories, study samples, and analytical approaches – along with partially conflicting findings and the need to sample diverse populations for broad conclusions –, large-scale mega-analyses across cohorts are essential to accurately investigate change - change relationships between episodic memory and structural brain decline<sup>5</sup>. Here, we conduct such a study to address key questions in the field: 1) Do brain change-memory change associations become more pronounced with increasing age? 2) Are these relationships consistent with a global factor of brain structural decline, MTL vulnerability, or multiple regional contributions? 3) Are change-change associations more pronounced in individuals with above-average brain decline and/or carriers of the APOE ε4 allele? We used a normative modeling framework to harmonize 13 datasets with longitudinal MRI scans and cognitive assessments, resulting in a final sample of 3,737 cognitively healthy adults (10,343 MRI scans; 13,460 memory assessments) (Table 1, Supplementary Figure 1). We estimated individual change in memory ( $\Delta$ memory) and 166 brain cortical and subcortical regions ( $\Delta$ brain), with a particular focus on the hippocampus. We focused on thickness as a measure of cortical change given its susceptibility to age<sup>53,54</sup>, used a mega-analytical approach to maximize statistical power<sup>55</sup>, and general additive mixed models (GAMMs) to enable greater analytical flexibility. Throughout the text, we refer to individuals with above- or below-average brain decline – relative to their age and sex peers – as brain decliners and maintainers. These labels do not reflect strict methodological criteria but are used solely for communicative clarity, as our analyses employ a dimensional approach throughout. Finally, we provide complete statistics, point estimates, and visualizations in a Supporting App ([https://vidalpineiro.shinyapps.io/brain\\_mem\\_change/](https://vidalpineiro.shinyapps.io/brain_mem_change/)) and simulate data to aid the interpretation of results.

## Results

### **Linking brain change and memory decline: main effects.**

We used GAMMs to assess the relationship between brain change ( $\Delta$ brain) (cortical thickness and subcortical volume) and memory change ( $\Delta$ memory) in 3,737 adults.  $\Delta$ brain was modelled as a smooth term and dataset as random intercept. Sex and age trends were regressed out during normative modelling-based preprocessing and thus not included in the higher-level model. Henceforth, change in brain and memory for a given individual is relative to their age and sex peers. Control analyses with age, sex, or intracranial volume (ICV) as covariates, or with random slopes per dataset, did not substantially affect the outcome of the main results ([Supporting App](#)). Data were weighted to account for differences in reliability of change, as longitudinal data with fewer observations and shorter follow-up time contain more uncertainty<sup>20</sup>. Regions were defined based on the Destrieux<sup>56</sup> cortical and aseg<sup>57</sup> subcortical atlas within FreeSurfer. Nineteen regions showed significant, False Discovery Rate (FDR) corrected ( $p_{FDR} < 0.05$ ) (Figure 1a), mostly subcortical structures and temporal regions. The relationship for all these regions was non-linear, generally showing an association between  $\Delta$ brain and  $\Delta$ memory only when  $\Delta$ brain was steeper than average (henceforth in *brain decliners*). When brain decline was milder than average (henceforth in *brain maintainers*), the association between  $\Delta$ brain and  $\Delta$ memory disappeared. Left and right hippocampus ( $\beta_{\text{weighted}[w][l]} = .165$ , effective degrees of freedom ( $edf$ ) = 3.2,  $p_{FDR} < 0.001$ ,  $\text{partial-}_{[p]}R^2 = 1.9\%$ );  $\beta_w[r] = .168$ ,  $edf = 3.3$ ,  $p_{FDR} < 0.001$ ,  $pR^2 = 1.6\%$ ), left amygdala ( $\beta_w = .155$ ,  $edf = 4.5$ ,  $p_{FDR} < 0.001$ ,  $pR^2 = 1.1\%$ ), left thalamus ( $\beta_w = .135$ ,  $edf = 3.7$ ,  $p_{FDR} = 0.03$ ,  $pR^2 = 0.8\%$ ), right long insular gyrus ( $\beta_w = .135$ ,  $edf = 2.8$ ,  $p_{FDR} = 0.02$ ,  $pR^2 = 0.8\%$ ) and left parahippocampal gyrus ( $\beta_w = .131$ ,  $p_{FDR} = 0.02$ ,  $edf = 4.4$ ,  $pR^2 = 0.8\%$ ) were amongst the regions showing strongest change – change associations in above-average brain decliners. See Figure 1b for visualization of selected regions. See Supplementary Table 1 for statistics in significant regions. See [Supporting App](#) for complete statistics and visualization in all regions. No strong evidence for left – right asymmetry in change – change associations was found (Supplementary Figure 2; SI). Education level did not significantly contribute either as a resilience factor, i.e., influencing the effect of education on brain and memory decline, or as a cognitive reserve factor, i.e., moderating the association between brain and memory, consistent with recent longitudinal studies on brain and memory decline<sup>58,59</sup> (SI).

***Age as a moderator of brain change - memory change associations.***

Next, we assessed whether the association between brain change and memory change varied with increasing age using tensor smooths (i.e., interactions between marginal smooth terms) as implemented in GAMM. For 7 regions, age significantly moderated the change - change associations ( $p_{FDR} < .05$ ) (Figure 2a) namely left ( $p_{FDR} = 0.02$ ,  $edf = 3.3$ ,  $pR^2 = 1.0\%$ ) and right hippocampus ( $p_{FDR} = 0.02$ ,  $edf = 4.2$ ,  $pR^2 = 1.0\%$ ), right inferior lateral ventricle ( $p_{FDR} < 0.001$ ,  $edf = 7.9$ ,  $pR^2 = 1.5\%$ ), left lateral ventricle ( $p_{FDR} = 0.05$ ,  $edf = 1.9$ ,  $pR^2 = 0.8\%$ ), right caudate ( $p_{FDR} = 0.03$ ,  $edf = 2.9$ ,  $pR^2 = 0.6\%$ ), right putamen ( $p_{FDR} = 0.03$ ,  $edf = 2.2$ ,  $pR^2 = 0.7\%$ ), and left short insular gyrus ( $p_{FDR} = 0.02$ ,  $edf = 2.8$ ,  $pR^2 = 0.7\%$ ). Combining the variance explained by the brain change and the brain change  $\times$  age interaction regressors for the left hippocampus explained up to 2.9% of the variance in memory change. In most of these regions, we found that change – change associations increased with higher age and progressively included brain maintainers. Change – change associations in some regions begin to be apparent between 50 and 60 years. These regions differ in the specific shape of the interaction. For example, change – change associations in brain decliners are first apparent at  $\approx 50$  years in the right hippocampus,  $\approx 60$  years for the left hippocampus and the right lateral inferior ventricle, and  $\approx 70$  years for the short insular gyrus and the right caudate. Similarly, associations between  $\Delta$ brain and  $\Delta$ memory in brain maintainers are apparent from  $\approx 70$  years in the left hippocampus and the right lateral inferior ventricle, but not in other regions such as the short insular gyrus or the right hippocampus. We use the left hippocampus to illustrate these effects: the relationship between  $\Delta$ brain and  $\Delta$ memory in brain decliners (i.e., point estimates) is  $\beta_w = -.04$  at age 40 years,  $\beta_w = .02$  at 50 years,  $\beta_w = .13$  at 60 years,  $\beta_w = .23$  at 70 years, and  $\beta_w = .29$  at 80 years. In contrast, the relationship between  $\Delta$ brain and  $-\Delta$ memory in brain maintainers is non-existent until age 70 ( $\beta_w = .13$ ), with a small increase at age 80 ( $\beta_w = .19$ ). See Figure 2b for visualization of selected regions. See Supplementary Table 2 for statistics in significant regions and complete statistical outcomes in the [Supporting App](#).

***Dimensionality of brain change.***

Next, we explored the dimensionality of those regional brain changes associated with memory decline. Is memory loss associated with a single global effect of brain decline, or does it reflect region-specific contributions? We computed the correlation of brain change across brain regions (Figure 3a, mean  $r = .14$  [0.10]; range =  $-.04$  -  $.58$ ) and carried out a PCA and a consensus

clustering analysis to investigate this question. On the one hand, the PCA revealed that the first principal component (PC1) accounted for a somewhat modest 20.7% of the total variance, with all its loadings pointing in the same direction, and a significant,  $\approx$ two-fold, fall in the variance explained by subsequent components (Figure 3b). This suggests a pattern of brain change that to some degree aligns with the presence of a global pattern of brain decline.

On the other hand, consensus clustering analysis was performed to explore whether the effects were regional. Importantly, we tested using Monte-Carlo simulations whether the clustering solution rejected the null hypothesis of  $K = 1$  cluster. Several clustering solutions rejected the null hypothesis, with 8 clusters being the best solution (Figure 3c; Supplementary Figure 3, Supplementary Table 3). Three clusters were subcortical (clusters #1 - #3) - one comprised of the left and right hippocampus and the left lateral ventricle - and 5 were cortical. Further, we assessed whether change in any of these clusters was associated with memory change, by respectively controlling for the hippocampus-based cluster, the main factor of brain decline, and by introducing all clusters together in a single model. Five clusters showed significant  $\Delta$ brain –  $\Delta$ memory associations controlling for the hippocampal-based cluster (cluster #1): cluster #3, the left and right amygdala ( $\beta_w = .11$ ,  $edf = 1.2$ ,  $p = 0.01$ ); cluster #5, left pericallosal sulcus, right straight gyrus, and right subcallosal gyrus ( $\beta_w = .16$ ,  $edf = 3.1$ ,  $p = 0.002$ ), cluster #6, right long insular gyrus and planum polare ( $\beta_w = .06$ ,  $edf = 1.0$ ,  $p = 0.012$ ); cluster #7, right transverse temporal sulcus ( $\beta_w = .05$ ,  $edf = 3.0$ ,  $p = 0.024$ ); and cluster #8, left parahippocampal gyrus ( $\beta_w = .05$ ,  $edf = 4.4$ ,  $p = .0301$ ). Similar results were found when using the main component of brain decline and when all clusters were added in a single model. The regional model, including brain change in the eight regional clusters, explained 1.3% more variance in memory decline than the model including only the global pattern of brain decline ( $partial-R^2 = 3.1\%$  and 1.9%, respectively). See SI and Supplementary Table 4 for detailed information. Altogether, the results suggest both global and regional factors influence the associations between brain and memory change.

#### ***Influence of APOE ε4 status on brain change - memory change associations***

A total of 3,149 subjects had APOE data available. Of these, 27.8 % were carriers of the APOE ε4 allele (carriers vs. non-carriers). First, we assessed whether carriers of the APOE ε4 allele showed a steeper decline in brain or memory and whether this relationship was associated

with age. For the main effects, we used linear mixed models with APOE ε4 allele as predictor and dataset as random intercept. For the interaction, we used GAMM with age as a smooth term by APOE ε4 allele as an ordered factor. APOE ε4 was not significantly related to memory decline ( $\beta_{[CI]} = -.035[-.10,.02]$ ,  $t(df) = -0.95(3296)$ ,  $p = 0.34$ ) (Figure 4a) but the relationship between APOE status and memory change increased with age ( $\beta_w = -0.008$ ,  $edf = 1$ ,  $p = 0.03$ ), that is, APOE ε4 carriers showed less memory decline until ≈60 years of age, and more memory decline thereafter (Figure 4b).

APOE ε4 was associated with steeper left and right hippocampal atrophy ( $\beta_l[CI] = -.135[-.20,-.07]$ ,  $t(df) = -4.2(3228.1)$ ,  $p_{FDR} = 0.004$ ;  $\beta_r[CI] = -.138[-.20,-.07]$ ,  $t(df) = -4.1(3261.1)$ ,  $p_{FDR} = 0.003$ ) as well as right amygdala atrophy ( $\beta[CI] = -.154[-.22,-.09]$ ,  $t(df) = -4.7(3249)$ ,  $p_{FDR} < 0.001$ ) (Figure 5a). Considering all regions together, no global effect of the APOE ε4 allele on brain decline was found ( $\beta[CI] = -.004[-.01,0.00]$ ,  $t(df) = -1.30(165)$ ,  $p = 0.20$ ) (Figure 5b). APOE ε4 was not significantly associated with steeper brain decline ( $p_{FDR} > .10$ ) with higher age. However, at an uncorrected level, APOE ε4 was associated with a higher degree of hippocampal atrophy with increasing age ( $\beta_{wl} = -.011$ ,  $edf = 1$ ,  $p_{unc} = 0.01$ ;  $\beta_{wr} = -.009$ ,  $edf = 1$ ,  $p_{unc} = 0.04$ , respectively) (Supplementary Figure 4).

Next, we assessed whether being an APOE ε4 carrier had any influence on the association between Δbrain and Δmemory. No region showed moderating effects of APOE ε4 on Δbrain – Δmemory associations ( $p_{FDR} > .50$ ). APOE ε4 did not significantly moderate the relationship between Δbrain and Δmemory in the left and right hippocampus ( $\beta_{wl} = -.011$ ,  $edf = 1$ ,  $p_{unc} = 0.44$ ;  $\beta_{wr} = -.001$ ,  $edf = 1$ ,  $p_{unc} = 0.61$ ) (Figure 6a). Finally, no regions showed a significant interaction between APOE ε4, age, and Δbrain on Δmemory ( $p_{FDR} > .15$ ). Left and right hippocampus showed comparable Δbrain - Δmemory associations with age regardless of APOE ε4 status ( $\beta_{wl} = .044$ ,  $edf = 1$ ,  $p_{unc} = 0.48$ ;  $\beta_{wr} = -.028$ ,  $edf = 1$ ,  $p_{unc} = 0.66$ ) (Figure 6b).

We conducted two sensitivity analyses: 1) In a subsample restricted to APOE ε4 non-carriers, where both the change–change effects and the moderator effects of age were comparable to those observed in the main sample (SI). 2) We reran the APOE ε4 analyses in a subsample of individuals aged 60 years or more at baseline ( $n = 2048$ ). As expected, the effect of APOE ε4 status on memory decline was found in a greater number of brain regions. However, due to

the restricted age range, APOE  $\epsilon 4 \times$  age interactions were not significant. Consistent with the main analyses, APOE  $\epsilon 4$  status did not moderate the relationship between brain change and memory change nor its interaction with age ( $p_{FDR} > .15$ ) (SI; Supplementary Figure 5). See complete statistics and additional visualization for all APOE  $\epsilon 4$  analyses in the [Supporting App](#). Altogether, the results show that cognitively healthy carriers of the APOE  $\epsilon 4$  allele have steeper rates of brain and memory decline, specifically in old adulthood, but no evidence of stronger  $\Delta$ brain –  $\Delta$ memory associations. The regional associations between brain change and memory change exist independently of an increased presence of pathological processes and cognitive changes associated with the genetic risk of AD.

#### ***Exploring mechanisms behind brain–cognitive relationships: A Post-hoc simulation study.***

Finally, we aimed to provide potential explanations for the empirical findings, focusing on the non-linear change–change associations, the moderating effect of age, and the absence of APOE  $\epsilon 4$  effects. We used a simplified schematic model using the *sn* v.2.1.1 package<sup>60</sup>, where observed brain data was the result of two underlying sources. The first source represented brain aging, characterized by a negatively skewed distribution with mean decline indicative of long-term, degenerative changes. This component is universal, as most individuals exhibited some degree of decline, with negative skewness arising from a subset of individuals undergoing accelerated brain aging<sup>16,20,22,32,61</sup>. The second source was modeled as a Gaussian distribution centered around zero, representing measurement error and other short-term influences<sup>20,51,52</sup>. Memory decline was modeled as linearly related to the brain aging component, plus random Gaussian noise. To explore the moderating effects (or lack thereof) of age and APOE  $\epsilon 4$ , we adjusted the parameters of the brain aging component, including mean, dispersion (e.g., variability), and skewness.

The simulation results revealed that observed brain decline was non-linearly associated with memory decline, with the relationship flattening among brain maintainers (Figure 7a) mimicking the empirical change–change associations. Increasing the variance of the brain aging component strengthened the change–change associations and affected brain maintainers, replicating the moderating effect of age (Figure 7c). Conversely, increasing mean decline and skewness did not alter the change–change associations despite leading to steeper mean decline in both observed brain and memory measures (Figure 7b, d). See details in SI.

## Discussion

By mega-analyzing data from over 3700 cognitively healthy adults and 13 independent longitudinal studies, we found that changes in brain structure are associated with changes in episodic memory across several cortical and subcortical areas, with the strongest associations in the MTL. These associations became more pronounced with increasing age, while no evidence was found for stronger relationships in APOE ε4 carriers. We argue for common macrostructural systems supporting memory function, where multiple factors converge to increase vulnerability in older age. The implications of these findings are discussed below.

**Brain decline - memory loss associations: a generalized phenomenon or constrained to above-average brain decliners?** Observed brain decline is non-linearly associated with memory decline, with stronger associations in brain decliners, i.e., individuals exhibiting above-average brain decline relative to their age and sex, compared to brain maintainers. This finding within the context of cognitively healthy aging differs from previous research, which may have over-relied on linear regression models and modest sample sizes. At first sight, it suggests change – change associations are constrained to a specific population of individuals with steeper brain decline, at-risk for pathological neurodegeneration. Yet, our simulations challenge this interpretation, rather suggesting the non-linear trends result from the presence of multiple sources contributing to noisy measures of brain change. Amongst these, one component, i.e., brain aging, has linear associations with memory decline and is characterized by a negative mean and skewness. These assumptions align well with current evidence, including, critically, the skewed distribution of brain aging<sup>16,20,22,32,61,62</sup>. The findings suggest that changes in brain aging are dimensional, skewed, and an inherent process, which is an important determinant of memory loss in cognitively unimpaired elderly. Rather than a categorical view, where a degenerative component of brain change is limited to vulnerable individuals, it is the combination of noise and a skewed distribution that limits our ability to observe empirical associations in individuals with less brain change. These results likely underpin other categorical distinctions in neurocognitive aging<sup>12</sup> and are closely aligned with brain maintenance theory predictions<sup>63</sup>.

**Brain change–Memory Change Associations in APOE  $\epsilon$ 4 Carriers: Distinct Decline, Shared Mechanisms?** APOE  $\epsilon$ 4 is associated with steeper brain decline and memory decline but does not affect the change – change associations between brain structure and memory. Carrying the APOE  $\epsilon$ 4 allele is the strongest genetic risk for sporadic AD, with dose-dependent effects<sup>64,65</sup>. Older carriers of the APOE  $\epsilon$ 4 allele exhibited steeper memory and brain decline, particularly in the hippocampi and the right amygdala, aligning with many other studies<sup>45,46</sup>. It is plausible that a higher proportion of APOE  $\epsilon$ 4 carriers are on a path to clinical disease manifestation of AD, putatively driven by the spreading of Tau deposition, which is strongly linked to steeper brain atrophy, memory decline, and short-term clinical diagnosis<sup>66</sup>. However, the change – change associations and the moderating effects of age were not influenced by APOE  $\epsilon$ 4 status, nor are they likely affected by preclinical AD. First, in some regions, the change – change associations were evident before age 60, when the prevalence of Tau deposition is generally very low<sup>67</sup>. A $\beta$  deposition before age 60 is slightly more common, but when controlling for Tau, the influence of A $\beta$  on brain and memory decline is modest at best<sup>66,68–70</sup>. Second, the associations are not constrained to the MTL, where earlier preclinical changes are observed in AD. Third, if preclinical AD were to influence the  $\Delta$ brain -  $\Delta$ memory associations, APOE  $\epsilon$ 4 non-carriers would display attenuated or age-delayed associations between brain and memory decline. One study using linear models reported stronger associations between hippocampal change and memory decline in cognitively healthy APOE  $\epsilon$ 4 carriers<sup>9</sup>, arguing that APOE  $\epsilon$ 4 carriers had a more hippocampal-centric pattern of atrophy in line with categorical aging and disease models. The current results align with a more hippocampal-centric pattern of atrophy but also fit well with a dimensional view of aging, where APOE  $\epsilon$ 4 contributes to accelerated brain aging, without changing the macrostructural mechanisms underlying the change – change associations. This is captured by the simulation analyses, which illustrate that a brain aging distribution with either steeper mean decline or higher skewness in APOE  $\epsilon$ 4 carriers would lead to both steeper brain and memory decline, but similar strength of the change – change associations. Altogether, these results fit with a dimensional view of aging, where APOE  $\epsilon$ 4 and early preclinical change in AD are one of many pathways affecting common biological substrates that determine memory function in older age, namely, regional and global macrostructural atrophy.

**Age is an important determinant of brain change – memory change associations.** Age strengthens the associations between brain decline and memory decline, gradually extending to brain maintainers across most significant regions. The hippocampi are among the earliest regions to exhibit these associations, emerging in the late fifties. This finding aligns with previous indirect evidence that the relationship between brain and memory decline strengthens with age<sup>25,41,42</sup>. Simulated data identified dispersion - greater variability in brain change across individuals - as the key factor driving stronger associations with age. This aligns with prior research indicating increased variability in both brain levels and brain change<sup>16,20</sup>, a pattern also observed in cognition, including episodic memory<sup>18,19</sup>. Interestingly, mean decline did not significantly affect the strength of the brain - cognition associations. The steeper memory and MTL declines from around 60 years of age<sup>10,11,15,16</sup> are therefore not direct causes of these associations but rather serve as indirect markers. Since brain aging follows a unidirectional trajectory - where everyone experiences some degree of decline over time - greater variability in brain aging gives rise to steeper rates of brain decline. Overall, age is the primary determinant of degenerative brain change, and henceforth of change – change associations. Below a certain age, brain aging – or better said, population-level variability – is minimal, making it unlikely to be a key factor behind episodic memory loss; if a meaningful decline in episodic memory occurs in young adulthood<sup>1,2,71</sup>. What makes age the prime risk factor for brain decline and which age-related factors may explain variations in brain (and memory) decline, remain amongst the most critical questions in the field. All points to a multidimensional view, where brain systems, even in the absence of overt pathological changes, are highly vulnerable to several aging factors<sup>32</sup>.

**Regional associations between brain change and memory change.** Hippocampal atrophy unsurprisingly showed the strongest associations with memory decline over time. This is consistent with earlier studies in the context of cognitively healthy elderly<sup>25–29</sup>, the key role of hippocampus in episodic memory<sup>33,37</sup>, and its vulnerability to aging<sup>32</sup>. In contrast, ventricular associations likely reflect global, non-specific patterns of brain atrophy and have also been reported elsewhere<sup>27,34</sup>. The mechanisms underlying observed caudate, thalamus, putamen, and amygdala change – change associations remain unclear and require experimental approaches to move beyond speculation. One possibility is altered coupling between these regions and the hippocampus, as they all exhibit connectivity changes with the hippocampi

during aging and episodic memory tasks<sup>72–75</sup>. Associations between cortical thinning and memory decline were weaker than those observed for subcortical structures<sup>29</sup>. Cortical thinning was chosen due to its high sensitivity to change; however, this sensitivity may render it more susceptible to influences unrelated to aging and long-term memory decline. Among the regions surviving multiple comparisons correction, the left parahippocampal gyrus stood out. Its anterior portion encompasses the entorhinal cortex, which serves as the main interface between the neocortex and the hippocampus, and is critically involved in memory<sup>37,76,77</sup>. Six additional regions in the temporal lobe were associated with memory decline, likely reflecting their roles in auditory, visual, or multimodal processing and integration. Most of the remaining regions, such as the pericallosal sulcus, the supramarginal gyrus, and the long insular gyrus, pertain to an action-mode network involved in task-positive, goal-directed behavior<sup>78</sup>. The overall pattern consists of relatively higher-order regions associated with both goal-directed and internal self-referential processing, which manifest the particular requirements that memory encoding and retrieval impose on the brain, that is, orchestrating dynamics amongst – often antagonistic – large-scale networks<sup>79</sup>.

**Dimensionality of brain change: Global decline or regional contributions?** Previous research has suggested the associations between brain atrophy and memory decline are driven either by a global factor of brain decline or are constrained to the MTL<sup>6,25,39</sup>. Our findings partially support both views, as we found evidence for a global factor of brain decline, while hippocampal atrophy showed the strongest regional associations with memory decline. However, the results reveal a more nuanced picture, with evidence for clustering observed. While the clustering solution made both topological and functional sense, caution is warranted regarding the specific solution obtained, as multiple solutions were plausible, and the input data were selected based on the somewhat arbitrary criterion of statistical significance. Nonetheless, several clustering solutions outperformed the one-factor solution, with some of these remaining associated with memory decline even after controlling for hippocampus or global decline. Most existing research, including this study, does not fully disentangle cross-regional correlations in brain aging from correlated errors. In any case, the current results indicate that a decline in regions critical to lower-order functions, such as attention, or indirectly related to memory via reward or executive control systems, contributes to memory loss independently of the integrity of medial lobe structures. Note also that the relationship

between some observed regions and memory decline may be explained by change in global cognition<sup>39</sup>.

**Technical considerations and limitations.** The study required considerable analytical flexibility, which may influence the outcome. A multiverse approach<sup>80</sup> was impractical due to constraints in data availability and computational resources. Applying iterative normative modeling and generating bootstrapped p-values across 166 regions would have rendered such an approach prohibitively time-consuming. Key considerations include: I) Normative modeling-based normalization using Hierarchical Bayesian Regression<sup>81,82</sup>, a flexible technique that often outperforms other harmonization methods<sup>83</sup>. It standardizes Z-scores based on age and sex, making data relative and somewhat challenging to interpret. However, it eliminates most age-related homoscedasticity and facilitates comparisons with other research, since data are aligned to an openly available norm. Assuming similar scanner harmonization performance, normative models should yield results comparable to other methods except in cases where interindividual variability strongly depends on age or sex. This is generally not the case for cortical thickness and subcortical volumes, except for ventricular features that show substantial age-related changes in variability. Consequently, we expect some attenuation in brain-memory change associations for ventricles when using normative modelling. In contrast, estimates for the age × brain atrophy interaction should be largely method-independent and reflect standardized associations. II) Bootstrapped p-values were estimated to better control the false positive rate in GAMMs<sup>84</sup>, leading to somewhat reduced power compared to linear models when the observed relationship is linear, although it can be argued that it hardly ever is. III) Estimation of change scores via linear changes over time per individual, with weighting applied to control for differences in longitudinal reliability as individuals with longer follow-up times and more observations contribute with more reliable data<sup>20,85</sup>. This represents a compromise choice, balancing data quality, flexibility, and interpretability; yet other approaches based, e.g., in standard equation modeling or use of random slopes as measures of individual change have also its strengths. IV) Inclusion of covariates representing other variables (e.g., neurochemical measurements) may account for unexplained variance and uncover further associations. V) Atlas choice was guided by practical considerations, particularly the availability of high-quality normative models<sup>82</sup>. While it is unclear which atlas would be optimal for our study, a multi-modal atlas may be a promising candidate<sup>86</sup>. In any

case, we conducted a series of control analyses that included additional covariates, analytical choices, and age-restricted subsamples. These analyses consistently produced similar patterns of association, supporting the robustness of our main findings.

Here, we combined datasets to increase sample size and statistical power. However, we also inherited the idiosyncrasies of these datasets, such as inclusion/exclusion criteria, sample unrepresentativeness, and recruitment methods. Also, analytical compromises were made to ensure compatibility across all datasets. Memory function was harmonized independently within each dataset, and thus reflects the specific tests used rather than a common construct; most of these tests primarily assessed verbal episodic learning and free recall. While modality or content-specific analyses could, in principle, reveal more precise specific anatomical relationships, the available data did not permit such detailed investigation. Also, an Item-response framework is theoretically a more robust approach for harmonisation, placing all individuals in the same space; yet unfeasible in practice, as some datasets lacked shared tests. Estimating non-linear trajectories within individuals was unadvisable given the relatively limited number of observations and follow-up durations per participant. Reliable estimation of non-linear change typically requires substantially more data than linear models. Moreover, our preprocessing pipeline explicitly accounts for and removes non-linear age trends at the group level, thereby addressing a major source of non-linearity in brain and cognitive measurements.

The two-source model proposed in the discussion remains speculative, while the specific mechanisms underlying brain aging remain elusive. Our post-hoc simulation requires external empirical validation using more precise estimates of change than those available in current legacy datasets<sup>87</sup>. Improved study design and advanced scanning protocols, such as cluster scanning<sup>88</sup>, offer a promising avenue to enable such validation. Young APOE ε4 carriers showed less memory change. We remain cautious of these results as the youngest segment of our sample had limited availability of APOE information, and thus emphasize the need for further research. For communication purposes, we used the terms brain maintainer and brain decliner despite employing a dimensional approach. This choice favors clarity over strict precision. For a more precise representation, readers are referred to the Supporting app, where point estimates are provided across varying levels of brain atrophy.

Overall, brain atrophy accounts for only a small proportion of the variance in memory decline, unsurprising given the substantial heterogeneity influencing interindividual differences in cognitive aging<sup>89,90</sup>. Other brain structure modalities, such as cortical area, are both associated with memory decline and independent from cortical thinning<sup>29,35</sup>. White matter integrity<sup>91</sup>, particularly within limbic pathways<sup>92</sup>, along with white matter hyperintensities<sup>93</sup> and other vascular factors, are also likely to contribute, at least partially independently. Additional potential contributors include brainstem, basal ganglia, and cortical neurochemistry<sup>94,95</sup> and indices of brain function<sup>96</sup>. Associations between memory decline and early pathological changes in limbic-predominant age-related TDP-43 encephalopathy (LATE-NC), primary age-related tauopathy (PART), or AD may be largely mediated by shared variance with temporal brain atrophy<sup>97–99</sup>. Even accounting for these factors, substantial variance in cognitive decline will remain unexplained due to measurement error, technological limitations, and resilience factors. The relationships among these factors, as well as our findings, are shaped by sample characteristics; accordingly, our results are most generalizable to other samples of clinically unimpaired individuals. Following up individuals after clinical conversion may produce modest quantitative shifts - such as stronger effects of brain atrophy, age × brain atrophy, and APOE ε4 on memory decline – consistent with established links among these measures and cognitive impairment. In contrast, qualitative changes, such as a reconfiguration of the regional pattern or its interaction with APOE ε4, are unlikely unless the sample is substantially clinically enriched. Only with significant pathology would a fundamental shift in the neurobiological basis of memory decline be expected. Multimodal integration of longitudinal neuroimaging and cognitive data with postmortem neuropathology offers a promising avenue for advancing our understanding<sup>100</sup>.

To conclude, regional brain decline over time, particularly, but not limited to, the hippocampus, was associated with memory loss with age, but APOE ε4 status was not a key factor behind these change-change associations. These associations strengthened with age from around 60 years. Methodologically, the findings underscore the necessity for methods and approaches that capture non-linear dynamics and put focus on the variability across individuals rather than mean change. Theoretically, the results support a multidimensional

view of memory, aging, and disease, where multiple factors converge to increase the vulnerability of common macrostructural systems supporting memory function in older age.

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## Methods

### Participants.

The research complies with all relevant ethical regulations, and all participants provided informed consent. The main project was approved by the Norwegian Regional Committee for Medical Research Ethics South (REK sør-øst, approval no. 8122), and each dataset was approved by the relevant ethical review board, as specified in Supplementary Table 7.

In this study, we combined 13 ongoing or retrospective datasets that included a) cognitively healthy adult individuals with longitudinal assessments of brain structure (T1-weighted [T1w] sequence) and of memory function. All the main analyses were carried out using only longitudinal information from both brain structure and memory function. Individuals with only 1 observation, or uncoupled memory – brain data, were used only in preprocessing stages: for calibration purposes in MRI preprocessing and for principal component extraction, and Z-scoring of memory scores (see below). Including these individuals alongside those with follow-up data allowed for a more robust and generalizable estimation of sex-specific age trajectories – less influenced by attrition bias – since participants with follow-up data tend to be healthier than their age peers. This approach also enabled more accurate estimation of test-retest effects in memory assessments. Sex was determined by self-report. See Supplementary Tables 5 and 6 for information on the initial MRI and memory samples. Unless otherwise stated, we focus on the longitudinal-coupled samples used in the main analyses.

3,737 cognitively healthy adults, with at least partially overlapping longitudinal follow-ups of brain structure and memory function, with a minimum total span of 1.5 years, were included in the analyses. In total, 10,343 MRI observations and 13,460 memory observations contributed to the analyses (Table 1, Supplementary Figure 1). The datasets include the LCBC<sup>101</sup>, Betula<sup>102</sup>, UB<sup>103,104</sup>, and BASE-II<sup>105,106</sup> datasets (from the Lifebrain Consortium)<sup>107</sup> as well as the COGNORM<sup>108</sup>, the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<https://adni.loni.usc.edu>)<sup>109</sup>, AIBL<sup>110</sup>, BBHI<sup>111</sup>, the Harvard Aging Brain Study (HABS)<sup>112</sup>, the UKB (<https://www.ukbiobank.ac.uk/>)<sup>113</sup>, PREVENT-AD<sup>114,115</sup>, OASIS3<sup>116</sup>, and VETSA<sup>117</sup> datasets. In addition to cohort-specific inclusion and exclusion criteria, observations concurrent with

cognitive impairment and Alzheimer's dementia were excluded. Individuals with baseline age <18 years, or with severe neurological or psychiatric disorders, were additionally excluded. Based on preprocessing requirements, MRI data from scanners with fewer than 25 observations were excluded, as well as individuals with less than 1.5 years of follow-up of either memory function or brain structure. Individuals without partially overlapping follow-up periods of brain and memory assessment were excluded, as well as those with non-overlapping periods >10 years. See Supplementary Table 7 for data availability, ethical standards, and contact information and SI for more sample details. A total of 3,149 subjects had APOE data available. Of these, 27.8 % were carriers of the APOE ε4 allele.

### Memory function

For each sample, we first z-normalized all measures based on the first time point and the different available memory tests. When multiple measures were available, we estimated a main component using Principal Component Analysis (PCA; *prcomp*) with all measures at the first time point as inputs. Missing values were imputed using *imputePCA* from the *missMDA* r-package<sup>118</sup>. Only for OASIS3, the imputed number of values was not negligible (> .5%). See Supplementary Table 8 for information on memory data for each sample. For each dataset, we regressed out age as a smoothing term, sex, and one or two dummy test-retest regressors using GAMMs (*mgcv R-package*)<sup>119</sup>. Individual identifiers were used as random intercepts, and the number of dummy test-retest regressors depended on whether the dataset had 2 or >=3 waves with memory function data. We retained individuals with at least 2 observations and a minimum follow-up of 1.5 years. For each individual, we then estimated yearly change by regressing memory observations on follow-up time, which were Z-standardized by site and fed to higher-level analyses.

### MRI preprocessing and brain structure

**MRI acquisition and preprocessing.** Structural T1w MPRAGE and FSPGR scans were collected using 1.5 and 3T MRI scanners. See information on scanner parameters and scanners across datasets in Supplementary Table 9. Data was converted to BIDS<sup>120</sup> and preprocessed using the longitudinal FreeSurfer v.7.1.0 stream<sup>121</sup> for cortical reconstruction and volumetric segmentation of the structural T1w scans<sup>122,123</sup>. See details in SI. Data was tabulated based on the Destrieux (cortical;  $N = 74$  regions per hemisphere)<sup>56</sup> and aseg (subcortical,  $N = 18$  regions)

atlases<sup>57</sup>. Atlas choice was guided by practical considerations, as high-quality normative models were readily available<sup>82</sup>.

**Data harmonization.** Brain regions were harmonized using a normative modelling framework resulting in site-agnostic deviation scores (z-scores) adjusted for age and sex<sup>61,82</sup> based on a Hierarchical Bayesian Regression technique<sup>81</sup> as implemented in the *PCNtoolkit* (v.0.30.post2), in *Python3* environment<sup>124</sup> (v.3.9.5). Calibration to the model was performed iteratively ( $N = 100$ ) to avoid losing longitudinal observations. This step was carried out with the initial MRI sample, i.e., regardless of availability of longitudinal MRI data or paired memory function assessments. Calibrated data, across iterations, showed high reliability. See SI for more normative modelling harmonization details. Next, we selected individuals with at least 2 observations and a minimum follow-up of 1.5 years. For each individual and region, we estimated yearly change by regressing normative MRI values on follow-up time, Z-standardized data by site, and fed the output into higher-level analyses. The correlation between individual change estimates derived from the normative-modelling approach and those obtained using a GAMM – with sex as fixed factor, age as smoothing term, and subject, scanner, and dataset as random intercepts<sup>58</sup> – was very high across most regions suggesting a null-to-modest impact of this analytical choice (mean  $r = .96$  across regions; see Supplementary Figure 6).

#### Higher-level analyses

All the analyses were carried out in the R environment (v.4.2.1)<sup>125</sup>. Visualizations were made with the *ggplot2* (v.4.0.0)<sup>126</sup> and the *ggseg* (brain images; v.1.6.5)<sup>127</sup> R-packages. Regions were selected among the statistically significant results to best illustrate the range of change-change associations. Visualization for all regions are available in the Supporting app. Analyses were mostly carried out using *gamm* models as implemented in the *mgcv* (v.1.9-3) R-package<sup>119</sup>. Derivatives were estimated based on finite differences as implemented in the *gratia* package (v.0.11-1)<sup>128</sup>. Linear mixed models as implemented in *lme4* (v.1.1-37), *lmerTest* (v.3.1-3)<sup>129,130</sup> were also used to assess the effect of APOE ε4 on brain and cognition.

To test the regional association between brain change and memory change, we carried out univariate weighted GAMMs, with a smooth term of Δbrain predicting Δmemory. An Δbrain × age tensor interaction term was added, as well as a smooth term of age, to assess the effect

of age on  $\Delta$ brain –  $\Delta$ memory associations. The effect of APOE  $\epsilon 4$  on memory and brain regions was tested using weighted linear mixed effects models, with APOE  $\epsilon 4$  status predicting either  $\Delta$ brain or  $\Delta$ memory. The age  $\times$  APOE  $\epsilon 4$  status interaction was tested using GAMMs with age as a smooth term by APOE  $\epsilon 4$  status as ordered factor, in addition to APOE  $\epsilon 4$  status as fixed effect, and age as smooth term. This effectively models the smooth term of age for APOE  $\epsilon 4$  non-carriers as reference, while the smoothed term for APOE  $\epsilon 4$  carriers models the difference with respect to the reference. Similarly, the  $\Delta$ brain  $\times$  APOE  $\epsilon 4$  status was used to assess the effect of APOE  $\epsilon 4$  on  $\Delta$ brain –  $\Delta$ memory associations. Finally, age  $\times$   $\Delta$ brain  $\times$  APOE  $\epsilon 4$  status with their simple effects) was used to test a triple interaction of age, APOE  $\epsilon 4$  status, and  $\Delta$ brain on  $\Delta$ memory. All models included dataset as random intercept.

We tested the dimensionality by performing PCA and clustering on the regions ( $N = 19$ ) showing significant  $\Delta$ brain –  $\Delta$ memory associations. To ensure the resulting global atrophy factor was aligned with the association of interest, we constrained it to regions linked to memory decline. As such, it may be more appropriate to interpret this factor as reflecting the common contribution of memory-sensitive areas. Therefore, the global factor identified here may not be fully generalizable to broader measures of global brain atrophy. This, along with the heterogeneity introduced by combining multiple cohorts, may explain the relatively modest variance explained by the global factor compared to those reported elsewhere<sup>6,29</sup>. The clustering was based on the M3C, Monte-Carlo Reference-based Consensus algorithm, implemented in the M3C (v.1.30.0) package<sup>131</sup>, which, critically, tests whether the desired solution is better than  $K = 1$ . We used a spectral clustering algorithm and PAC criteria, while the remaining parameters were set to the default. As post-hoc analyses, we tested whether the resulting clusters of brain change were related to memory change, controlling for the effect on memory of other brain regions such as the hippocampus or a general factor of brain decline using GAMMs as described above. See more details on SI along with pseudocode.

Note that in all analyses we have one observation per individual (e.g.,  $\Delta$ memory) as we are using change scores. Note also that age (and sex) trends are removed, and thus the model captures only interindividual associations - relative change - and age trends are uninterpretable. Prior to any analysis, outlier values, defined as values  $>4.5 SD$  from the mean, were removed from the analyses (based on a  $p < 0.05$  of observing at least one outlier value

given a normal distribution and our sample size). In GAMMs, we estimated p-values using a wild bootstrapping ( $n = 5000$ ) as the out-of-the-box p-values, as implemented in *mgcv*, are anticonservative<sup>84</sup>. Wild bootstrapping generates a null distribution of p-values by a) estimating a null model without the regressor of interest, b) extracting predicted values from the model and its residuals, c) adding the predicted value to the residuals multiplied by a random vector of 1 and -1s, and d) re-estimating a new model using this score as the predicted variable. When appropriate, p-values were corrected for multiple comparisons using FDR<sup>132</sup>. All models used weights to account for unequal reliability of longitudinal data. That is, individuals with short follow-up periods and fewer observations contribute with more unreliable, high-variance data and thus should produce an unequal spread of residuals. We used the square of reliability as weights, as estimated elsewhere<sup>20</sup>. Weights  $< .09$ , corresponding to longitudinal reliability  $< .3$ , were set at .09. For tensor interactions, we estimated the derivatives along  $\Delta\text{brain}$  at specific ages (40, 50, 60, 70, 80 years) using a finite differences approach. The degree of association between  $\Delta\text{brain}$  and  $\Delta\text{memory}$  is estimated only for  $\Delta\text{brain} < 0$  – as most associations are constrained in brain decliners, estimating the mean association across the  $\Delta\text{brain}$  weighted by the density of data-points. Note that the  $\beta$  coefficients are standardized and, therefore, somewhat comparable to an effect size measure. We estimated the partial variance explained by brain change and by brain change  $\times$  age interaction as the difference in variance explained between the full model and a null model without the regressors of interest. This approximation likely underestimates the variance explained by the regressors as i) *mgcv*'s default variance explained metric penalizes model complexity, ii) smooth terms are re-fitted in the null model, and iii) variance attributable to the regressors may be partially absorbed by re-fitting the random-effect components. Data from ventricles was sign-reversed. We slightly trimmed the x-axis in the figures – removing  $\approx 1\%$  of the observations – to exclude high uncertainty fittings from visualization.

**Data availability**

The raw data were gathered from 13 different datasets. Different agreements are required for each dataset. Most dataset are openly available with prespecified data usage agreements. For some datasets, such as UKB, fees may apply. Requests for Lifebrain cohorts (LCBC, Umeå, UB) and COGNORM, should be submitted to the corresponding principal investigator. See data availability and contact details for all datasets in Supplementary Table 7. Group-level estimates generated in this study are provided in the Supporting app ([https://vidalpineiro.shinyapps.io/brain\\_mem\\_change/](https://vidalpineiro.shinyapps.io/brain_mem_change/)). Source data to reproduce the figures is provided in a separate Source Data file.

**Code Availability**

Statistical analyses in this manuscript are available alongside the manuscript are available at <https://github.com/daidak/memory-brain-change><sup>133</sup>. All analyses were performed in R. The scripts were run on the Colossus processing cluster, University of Oslo. MRI preprocessing and feature generation scripts were performed with FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>) software.

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**Author Contributions**

D.V.P. Conceptualization, Methodology, Formal analysis, Writing - Original Draft; Ø.S. Methodology, Software, Formal analysis, Writing - Review & Editing; M.S. Resources, Data Curation, Writing - Review & Editing; I.K.A. Software, Writing - Review & Editing; W.B. Writing - Review & Editing; D.B-F. Resources, Writing - Review & Editing; A.B. Writing - Review & Editing; G.C. Resources, Writing - Review & Editing; S.D. Resources, Data Curation, Writing - Review & Editing; P.G. Methodology, Writing - Review & Editing; R.N.H. Conceptualization, Writing - Review & Editing; S.K. Writing - Review & Editing; U.L. Resources, Writing - Review & Editing; A.M.M. Software, Writing - Review & Editing; L.N. Conceptualization, Resources, Writing - Review & Editing; A.P.L. Conceptualization, Resources, Writing - Review & Editing; J.M.R. Data Curation, Writing - Review & Editing; J.S-S. Resources, Writing - Review & Editing; C.S.P. Resources, Writing - Review & Editing; L.O.W. Resources, Writing - Review & Editing; T.W. Methodology, Software, Formal analysis, Writing - Review & Editing; K.B.W. Conceptualization, Resources, Writing - Review & Editing; A.M.F. Conceptualization, Resources, Writing, Review & Editing.

**Declaration of Competing Interests**

A.P.-L. serves as a paid member of the scientific advisory boards for Neuroelectrics, Magstim Inc., TetraNeuron, Skin2Neuron, MedRhythms, and AscenZion. He is co-founder of TI solutions and co-founder and chief medical officer of Linus Health. A.P.-L. is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging, and applications of noninvasive brain stimulation in various neurological disorders; as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia. The remaining authors declare no conflict of interest.

**Tables**

Dataset	Subjects N (m)	Apoe ε4 NC:C	Age M (SD) range	Obs. Memory		Obs. Brain		Time Brain		Time Memory	
				N	M (SD)	N	M (SD)	range	M (SD)	range	M (SD)
adni	223 (92)	158:65	72.4 (6.3) 55.8 - 89.9	1118	5.0 (2.7) 2 - 13	984	4.4 (2.2) 2 - 12	3.9 (2.1) 1.6 - 9.6	4.6 (2.8) 2.0 - 13.5		
aibl	142 (70)	94:78	71.5 (6.4) 60.0 - 87.0	564	4.0 (1.1) 2 - 5	493	3.5 (1.1) 2 - 5	4.2 (1.6) 2.0 - 8.0	4.9 (1.6) 2.0 - 7.0		
base-ii	214 (127)	133:39	64.8 (15.0) 24.5 - 83.1	572	2.7 (0.5) 2 - 3	428	2.0 (0) 2 - 2	2.3 (0.4) 1.5 - 3.1	4.5 (1.5) 1.6 - 6.4		
bbhi	256 (141)	30:3	54.0 (7.2) 41.2 - 66.1	512	2.0 (0) 2 - 2	512	2.0 (0) 2 - 2	2.4 (0.2) 1.6 - 3.0	2.4 (0.2) 1.6 - 3.0		
betula	47 (27)	26:15	43.8 (12.8) 25.0 - 75.0	94	2.0 (0) 2 - 2	94	2.0 (0) 2 - 2	4.3 (0.4) 4.0 - 5.0	4.3 (0.4) 4.0 - 5.0		
cognorm	93 (42)	54:38	73.2 (6.0) 64.7 - 90.0	596	6.4 (1.0) 3 - 7	366	3.9 (1.3) 2 - 6	6.0 (2.6) 1.8 - 9.5	5.8 (0.9) 2.1 - 6.9		
habs	223 (94)	157:63	73.3 (6.1) 62.5 - 89.3	1180	5.3 (1.0) 3 - 6	615	2.8 (0.6) 2 - 4	4.4 (1.2) 2.0 - 8.5	4.5 (1.1) 2.0 - 8.5		
lcbc	304 (120)	100:72	47.9 (19.1) 20.0 - 85.5	781	2.6 (0.7) 2 - 4	799	2.6 (0.8) 2 - 7	6.2 (2.8) 2.4 - 11.5	6.0 (2.7) 2.4 - 11.5		
oasis3	431 (171)	287:137	67.2 (8.9) 43.5 - 95.6	3502	8.1 (4.0) 2 - 23	1458	3.4 (1.5) 2 - 8	6.4 (3.4) 1.5 - 15.8	9.9 (4.2) 2.0 - 24.0		
preventad	184 (53)	115:69	63.6 (5.0) 55.1 - 83.3	874	4.8 (1.0) 3 - 6	1061	5.8 (1.0) 4 - 7	3.3 (0.8) 1.9 - 4.7	3.2 (0.8) 1.6 - 4.5		
Ub	77 (28)	67:10	68.6 (5.0) 51.7 - 78.1	214	2.8 (0.4) 2 - 3	208	2.7 (0.5) 2 - 3	3.5 (1.0) 1.6 - 5.0	3.7 (1.0) 1.6 - 5.2		
Ukb	106 6 (525)	775:272	62.3 (7.0) 47.0 - 79.5	2132	2.0 (0) 2 - 2	2132	2.0 (0) 2 - 2	2.3 (0.1) 2.0 - 2.7	2.3 (0.1) 2.0 - 2.7		
vetsa	477 (477)	354:122	58.0 (3.9) 51.1 - 70.1	1321	2.8 (0.4) 2 - 3	1193	2.5 (0.5) 2 - 3	9.3 (2.7) 4.5 - 13.4	10.0 (2.4) 4.5 - 14.4		
All	3737 (1967)	2350:953	62.5 (11.6) 20.1 - 95.6	13460	3.6 (2.6) 2 - 23	10343	2.8 (1.3) 2 - 12	4.5 (3.0) 1.5 - 15.8	5.1 (3.6) 1.6 - 24.0		

**Table 1. Main Sample sociodemographics.** Main sociodemographic and observational detail of the main sample used in all main analyses. *N* = Total number of individuals or observations.

NC = Non-carriers. C = Carriers. *M* = mean. *SD* = Standard Deviation. *Obs.* = Observations.

**Figure Legends**

**Figure 1. Brain change – memory change associations.** a) Estimates ( $\beta_w$ ) for associations between  $\Delta$ brain and  $\Delta$ memory with orange color line representing  $p_{FDR} < 0.05$ .  $\Delta$ brain represents atrophy in subcortical and thinning in cortical regions and is operationalized as a smooth variable in GAMMs. P-values were obtained via wild bootstrapping. b) Change – change association for selected regions: left caudate ( $\beta_w = .074$ ,  $edf = 3.4$ ,  $p_{FDR} = 0.029$ ,  $pR^2 = 0.6\%$ ,  $n = 3730$ ), left hippocampus ( $\beta_w = .165$ ,  $edf = 3.2$ ,  $p_{FDR} < 0.001$ ,  $pR^2 = 1.9\%$ ,  $n = 3729$ ), left inferior lateral ventricle ( $\beta_w = .132$ ,  $edf = 3.2$ ,  $p_{FDR} < 0.001$ ,  $pR^2 = 1.1\%$ ,  $n = 3731$ ), and left parahippocampal gyrus ( $\beta_w = .131$ ,  $edf = 4.4$ ,  $p_{FDR} = 0.02$ ,  $pR^2 = 0.8\%$ ,  $n = 3731$ ). Upper plots display the smooth associations, while lower plots show their derivative (i.e. association between  $\Delta$ brain and  $\Delta$ memory for each  $\Delta$ brain value). Line and shaded ribbons represent mean and 95% CIs. See Supplementary Table 1 and [Supporting app](#) for more information.  $\beta_w$  = Density-weighted betas, using the derivative function.  $edf$  = estimated degrees of freedom.  $pR^2$  = partial variance explained.  $pFDR$  = False Discovered Rate-corrected p-values.

**Figure 2. Effect of age on Brain change – Memory change associations.** a)  $-\log_{10}(p_{FDR})$  values of the effect of age on  $\Delta$ brain –  $\Delta$ memory associations modeled as GAMM-based tensor interaction terms. Orange color line represents  $p_{FDR} < 0.05$ .  $\Delta$ brain represents atrophy in subcortical and thinning in cortical regions. P-values were obtained via wild bootstrapping. b) Change – change association for selected regions at specific ages: left hippocampus ( $edf = 3.3$ ,  $p_{FDR} < 0.02$ ,  $pR^2 = 1.0\%$ ,  $n = 3729$ ), left short insular gyri ( $edf = 2.8$ ,  $p_{FDR} = 0.02$ ,  $pR^2 = 0.7\%$ ,  $n = 3729$ ), and right inferior lateral ventricle ( $edf = 7.9$ ,  $p_{FDR} < 0.001$ ,  $pR^2 = 1.5\%$ ,  $n = 3725$ ). Black line - and colored 95% CIs ribbons - display mean  $\Delta$ brain -  $\Delta$ memory associations at a given age. The lightblue line represents their derivative (i.e., association between  $\Delta$ brain and  $\Delta$ memory for each  $\Delta$ brain value). See Supplementary Table 2 and [Supporting app](#) for more information. Note that  $\Delta$ brain is derived from normative data and thus does not necessarily reflect the same amount of decline at each age.  $edf$  = estimated degrees of freedom.  $pR^2$  = partial variance explained.  $pFDR$  = False Discovered Rate-corrected p-values.

**Figure 3. Dimensionality of brain change.** a) Pearson's r cross-correlation matrix of  $\Delta$ brain across regions with significant  $\Delta$ brain –  $\Delta$ memory associations ( $N = 19$ , see Figure 1). Below, a

density plot of the correlation coefficients. b) Variance explained by the principal PCA components and loading of the first component on the brain regions showing significant  $\Delta$ brain –  $\Delta$ memory associations. See ID to region name correspondence in Supplementary Table 3. c) Optimal consensus clustering solution ( $K = 8$  clusters). Ant. = anterior; inf. = inferior; lat. = lateral; col = collateral; l = left; r = right; vent = ventricle.

**Figure 4. APOE  $\epsilon$ 4 associations with memory change.** a) Association between APOE  $\epsilon$ 4 (carriers vs. non-carriers) and memory change ( $\beta[CI] = -.035[-.10,.02]$ ,  $t[p] = -0.95[0.34]$ ,  $n = 3298$ ) assessed using linear mixed models. Boxes represent the interquartile range ( $IQR$ ), and whiskers extend to  $1.5 \times IQR$ . Line represents the median. Distribution of values outside whiskers can be assessed in the contiguous density plots. b) Association between APOE  $\epsilon$ 4 (carriers, non-carriers) and memory change as a function of age ( $\beta_w = -0.008$ ,  $edf = 1$ ,  $p = 0.03$ ,  $n = 3298$ ). The interaction between APOE  $\epsilon$ 4 and age is operationalized as a smooth, factor interaction in a GAMM model. Line and ribbons represent mean and 95% CI.  $\beta_w$  = Density-weighted betas, using the derivative function.

**Figure 5. APOE  $\epsilon$ 4 associations with brain change.** a) Association between APOE  $\epsilon$ 4 (carriers vs. non-carriers) and brain change in the left and right hippocampus ( $\beta_l[CI] = -.135[-.20,-.07]$ ,  $t(df) = -4.2(3228.1)$ ,  $p_{FDR} = 0.004$ ,  $n = 3310$ ;  $\beta_r[CI] = -.138[-.20,-.07]$ ,  $t(df) = -4.1(3261.1)$ ,  $p_{FDR} = 0.003$ ,  $n = 3297$ ), and the right amygdala  $\beta[CI] = -.154[-.22,-.09]$ ,  $t(df) = -4.7(3249)$ ,  $p_{FDR} = .001$ ,  $n = 3302$ ) assessed with linear mixed model. b) Effect of APOE  $\epsilon$ 4 on brain change across all regions ( $h_0 = 0$ ;  $\beta = -.004$ ,  $t(df) = -1.30(165)$ ,  $p = .20$ ,  $n = 166$ ) assessed using a one-sample t-test. Each point represents a region. Note that the three regions with more negative effects of APOE  $\epsilon$ 4 correspond to those displayed in panel a). Boxes represent the interquartile range ( $IQR$ ), and whiskers extend to  $1.5 \times IQR$ . Line represents the median. Distribution of values outside whiskers can be assessed in the contiguous density plots.

**Figure 6. APOE  $\epsilon$ 4 effect on brain change – memory change associations.** a)  $\Delta$ brain -  $\Delta$ memory associations as a function of APOE  $\epsilon$ 4 (carriers vs. non-carriers) for the left and right hippocampus ( $\beta_{wl} = -.011$ ,  $edf = 1$ ,  $p_{unc} = .44$ ,  $n = 3296$ ;  $\beta_{wr} = -.001$ ,  $edf = 1$ ,  $p_{unc} = .61$ ,  $n = 3293$ ). b)  $\Delta$ brain -  $\Delta$ memory associations as a function of APOE  $\epsilon$ 4 (carriers vs. non-carriers) and age for the left and right hippocampus. None of the terms were significant ( $\beta_{wl} = .044$ ,  $edf = 1$ ,  $p_{unc}$

= .66,  $n = 3296$ ;  $\beta_{wr} = -.028$ , edf = 1,  $p_{unc} = .66$ ,  $n = 3293$ ). Black line and ribbons represent mean and 95% CIs. P-values were obtained via GAMM-bootstrapping. P-values were obtained via wild bootstrapping.  $\beta_w$  = Density-weighted betas, using the derivative function.

**Figure 7. Theoretical basis for brain change – memory change associations.** a) The main simulations demonstrate how a skewed true (latent) distribution of brain decline, which has a linear association with memory decline (red line), results in non-linear observed associations between observed (measured) brain decline and memory decline (green line) due to the measurement noise. Density plots illustrate different distributions: yellow represents true brain and memory decline, orange represents measurement error, and blue represents observed brain and memory. b-d) The impact of distribution moments on true brain distribution on observed  $\Delta$ brain –  $\Delta$ memory associations. Specifically, the effect of b) mean decline, c) dispersion, and d) negative skewness. Density plots correspond to the underlying distribution of true brain and memory decline. Black lines and ribbons indicate mean and 95% CIs across  $N = 1000$  simulations. GAMs were used to fit the associations. See SI for more details.

**Vietnam Era Twin Study of Aging (VETSA)**

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**Editor's Summary:** Across 13 longitudinal studies (3,737 adults), the authors show that brain atrophy parallels memory loss, with a stronger coupling in later life. APOE ε4 increases decline, yet genetic risk does not modify the brain–memory relationship.

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