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No moderating influence of education on the association between changes in hippocampus volume and memory performance in aging

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ABSTRACT

Contemporary accounts of factors that may modify the risk for age-related neurocognitive disorders highlight education and its contribution to a cognitive reserve. By this view, individuals with higher educational attainment should show weaker associations between changes in brain and cognition than individuals with lower educational attainment. We tested this prediction in longitudinal data on hippocampus volume and episodic memory from 708 middle-aged and older individuals using local structural equation modeling. This technique does not require categorization of years of education and does not constrain the shape of relationships, thereby maximizing the chances of revealing an effect of education on the hippocampus-memory association. The results showed that the data were plausible under the assumption that there was no influence of education on the association between change in episodic memory and change in hippocampus volume. Restricting the sample to individuals with elevated genetic risk for dementia (APOE ε4 carriers) did not change these

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results. We conclude that the influence of education on changes in episodic memory and hippocampus volume is inconsistent with predictions by the cognitive reserve theory.

Introduction

Cognitive performance declines in aging [1,2], but there are individual differences in these within-person changes [3–5]. Two complementary and broad theories of these differences have been much debated in recent years. The brain maintenance theory [6] holds that the changes in cognitive performance are proportional to changes in the brain, whereas the cognitive reserve theory [7] proposes that the cognitive performance of some people (i.e., those with higher cognitive reserve) are less affected than others (i.e., those with lower cognitive reserve) by the same aging-related brain alteration, brain injury, or disease [8,9].

Researchers have suggested that formal education may build cognitive reserve [7]. Educational attainment is associated with level of cognitive performance across the lifespan [10,11], partly because education can have a causal effect on performance in younger adulthood that is maintained into older age [12,13]. However, educational attainment is typically neither sizably associated with longitudinal changes in cognitive performance [14] nor with changes in brain volume [15,16] during the course of adult development and aging. Thus, so far there is little support for the notion that higher educational attainment renders individuals less vulnerable to neurocognitive aging. However, a central hypothesis of the cognitive reserve account of the role of education in neurocognitive aging is that educational attainment moderates the association between within-person (i.e., longitudinal) changes in brain and cognition. That is, groups of individuals with higher educational attainment should show smaller associations between changes in the brain and changes in cognition than groups of individuals with lower educational attainment [8,9]. The brain maintenance theory, in contrast, predicts that educational attainment does not moderate such associations. To our knowledge, only one study so far has addressed these differential predictions, finding that the association between changes in total brain volume and episodic memory performance did not significantly differ between groups of individuals with different education levels [16].

Here we address whether educational attainment influences the association between changes in hippocampus volume and changes in episodic memory performance in older age using local structural equation modeling [LSEM; 17, 18, 19]. This technique does not require categorization of years of education and does not constrain the shape of the relationship between years of education and the hippocampus-memory correlation, thereby maximizing the chances of revealing a statistical effect of education on the hippocampus-memory association. We use data from the European Lifebrain project [20; https://www.lifebrain.uio.no], which is a multi-center consortium of longitudinal studies of aging, brain, and cognition. Previous analyses [21] in this project have revealed a statistically significant correlation between changes in hippocampus volume and changes in episodic memory performance in a sample of older adults free from dementia diagnosis. The correlation was higher for APOE ε4 carriers than for non-carriers. We address our research question in the total sample as well as separately for APOE ε4 carriers and non-carriers because the cognitive reserve theory predicts that a moderating influence of education is most prominent in individuals with increased risk for dementia (e.g., APOE ε4 carriers) before advanced stages of disease are reached [22].

Methods

Following previous analyses in the Lifebrain project [21], we used data from six studies (BASE II, Betula, COBRA, LCBC, Cognorm, and WAHA) from four sites (Berlin, Germany; Umeå, Sweden; Oslo, Norway; Barcelona, Spain). Local ethics approvals for study participation and data sharing to the consortium were acquired at each participating site. Informed consent was obtained from all participants.

Participants

The supplementary materials include descriptions of the recruitment and inclusion criteria for each contributing study. In the present analyses, healthy participants [aged greater than 54 years at first assessment (time 1)] without a dementia diagnosis were included. Participants were required to have two or more measurements of hippocampus volume and memory performance acquired at least two years apart [as in 21]. For participants with more than two measurements, the first measurement acquired after a minimum of two years from time 1 was treated as the second measurement (time 2). This criterion resulted in that 19 subjects in the WAHA study contributed with their third measurement point to the time 2 data in the present study (whether first or second follow up was used was not significantly correlated with years of education, $r = -0.12$, $p = 0.441$). In addition to these inclusion and exclusion criteria, which were the same as in the analyses reported in [21], we also required data for years of education (resulting in the exclusion of 32 subjects). A few cases (n = 7) with extreme values on years of education (below 6 and above 22 years) were also excluded, as was one extreme outlier on change in hippocampus volume (the annual change was more than 5 standard deviations from the mean annual change). The final total sample size was 708. Table 1 reports the sample characteristics.

Table 1
Participant characteristics.

Study	n	Mean (SD) Age	n women	Mean (SD) years of education	APOE ε4 (carrier/non-carrier/NA)	Mean (min, max) follow-up time
BASE II	153	70.0 (3.8)	62	14.2 (3.0)	36/116/1	2.5 (2.0, 3.3)
Betula	134	64.4 (6.7)	61	12.9 (3.7)	32/97/5	4.7 (4.1, 5.1)
Cognorm	72	73.1 (5.8)	45	14.8 (3.1)	34/38/0	4.1 (2.0, 6.3)
COBRA	113	66.2 (1.2)	51	13.2 (3.2)	28/84/1	5.0 (5.0, 5.0)
LCBC	199	67.7 (7.9)	114	15.8 (2.8)	30/84/85	3.4 (2.4, 8.8)
WAHA	37	69.0 (2.9)	24	11.4 (3.5)	6/31/0	3.4 (2.0, 4.7)
Total	708	67.9 (6.3)	357	14.2 (3.4)	166/450/92	3.8 (2, 8.8)

Note: NA = Not available.

Procedures

Full details of the procedures can be found in cohort-profile publications describing each separate study [23–31]. Here we focus on the measurements used in the present analyses.

Episodic memory variables

Each separate study contributed at least one measure of episodic memory. In line with a long tradition of work on individual differences and age-related changes in memory performance [e.g., 1,32], we operationally defined episodic memory with supra-span and/or delayed recall or recognition tasks, but note that performance on these measures is also influenced by for example familiarity processes and semantic memory. The supplementary materials include a description of the tasks from each study. The COBRA and BASE II studies shared one measurement (an object-location memory task), but otherwise there were no overlap of tasks among the studies. For the main analyses including all six participating studies, we thus defined change in episodic memory performance with the same scaling approach that has been used previously in the Lifebrain project [21]. We first standardized the scores for each test, study, and measurement occasion by the test-scores' mean and standard deviation at time 1 (i.e., the first measurement considered). For studies with several memory test, we next averaged the scaled scores to form one score per study. We then computed a measure of annual change, calculated as: $(X_{time\ 2,i} - X_{time\ 1,i})/(age_{time\ 2,i} - age_{time\ 1,i})$, where $X_{time\ 1,i}$ and $X_{time\ 2,i}$ are the standardized memory score at time 1, respectively time 2, for subject i, and age is chronological age in years. Density plots of this measure, separately for each study, can be found in Supplementary Fig. 1. In follow-up control analyses, we restricted the data set to the BASE II and COBRA studies that shared one task. In these analyses, the scores at time 2 were rescaled to reflect one-year change from time 1, calculated as: adjusted $X_{time\ 2,i} = X_{time\ 1,i} + (X_{time\ 2,i} - X_{time\ 1,i})/(age_{time\ 2,i} - age_{time\ 1,i})$.

Magnetic resonance imaging (MRI) variables

The MRI data came from six different scanners. The supplementary materials include detailed description of the acquisition parameters for each study. The images were automatically processed in a harmonized way across studies with the longitudinal stream of Freesurfer 6.0 (https://surfer.nmr.mgh.harvard.edu). To minimize study-specific bias, no manual editing of the resulting segmentations was performed (only general quality control before a subject was included). We used the resulting estimates of intracranial and hippocampal (left and right) volumes. Note that whereas earlier versions of Freesurfer showed age-related differences in the overestimation of hippocampus volumes (relative to manual segmentation; [33]), this bias is much smaller in the present version of Freesurfer [34]. A previous study showed that there was a small main effect of scanner on the estimates of hippocampal volume, but that the rank order was virtually perfectly retained (mean r = 0.98) between scanners [35].

To prepare for the main analyses, we computed a measure of annual change in hippocampal volume, calculated as: $(Y_{time\ 2,i} - Y_{time\ 1,i})/(age_{time\ 2,i} - age_{time\ 1,i})$, where $Y_{time\ 1,i}$ and $Y_{time\ 2,i}$ are the averaged volume of the left and right hippocampi at time 1, respectively time 2, for subject i [21]. In the follow up control analyses restricted to the BASE II and COBRA studies, we used the estimates of left and right hippocampus volume at time 1 and time 2 adjusted for intracranial volume with an analysis of covariance approach [36]: adjusted $volume_{t,i}$ = raw $volume_{t,i}$ - b_t^* (intracranial $volume_i$ – mean intracranial volume), where b is the slope of the regression of the raw volume on intracranial volume at time point t and volume the estimates for subject i at time point t. Note that, with the longitudinal stream of Freesurfer, intracranial volume is assumed identical at both time points. In these latter analyses, the volumes at time 2 were rescaled to reflect one-year change from time 1, calculated in the same way as for the episodic memory measures.

APOE ε4 status

We defined a dichotomous variable coding for APOE ε4 carriers, with carriers defined as having the APOE alleles ε2/ε4, ε3/ε4, or ε4/ε4. APOE ε4/ε4 carriers were too few (n = 13) to be analyzed separately. Number of years between baseline and follow up assessment did not differ in a statistically significant way ($t(310) = 0.98$, $p = 0.325$) between carriers (mean = 3.9) and non-carriers (mean = 3.8). For details on genotyping methods, we refer to the cohort-profile publications listed above.

Statistical procedures

Data were analyzed with LSEM [17–19]. This approach can use the general advantages of SEM for longitudinal

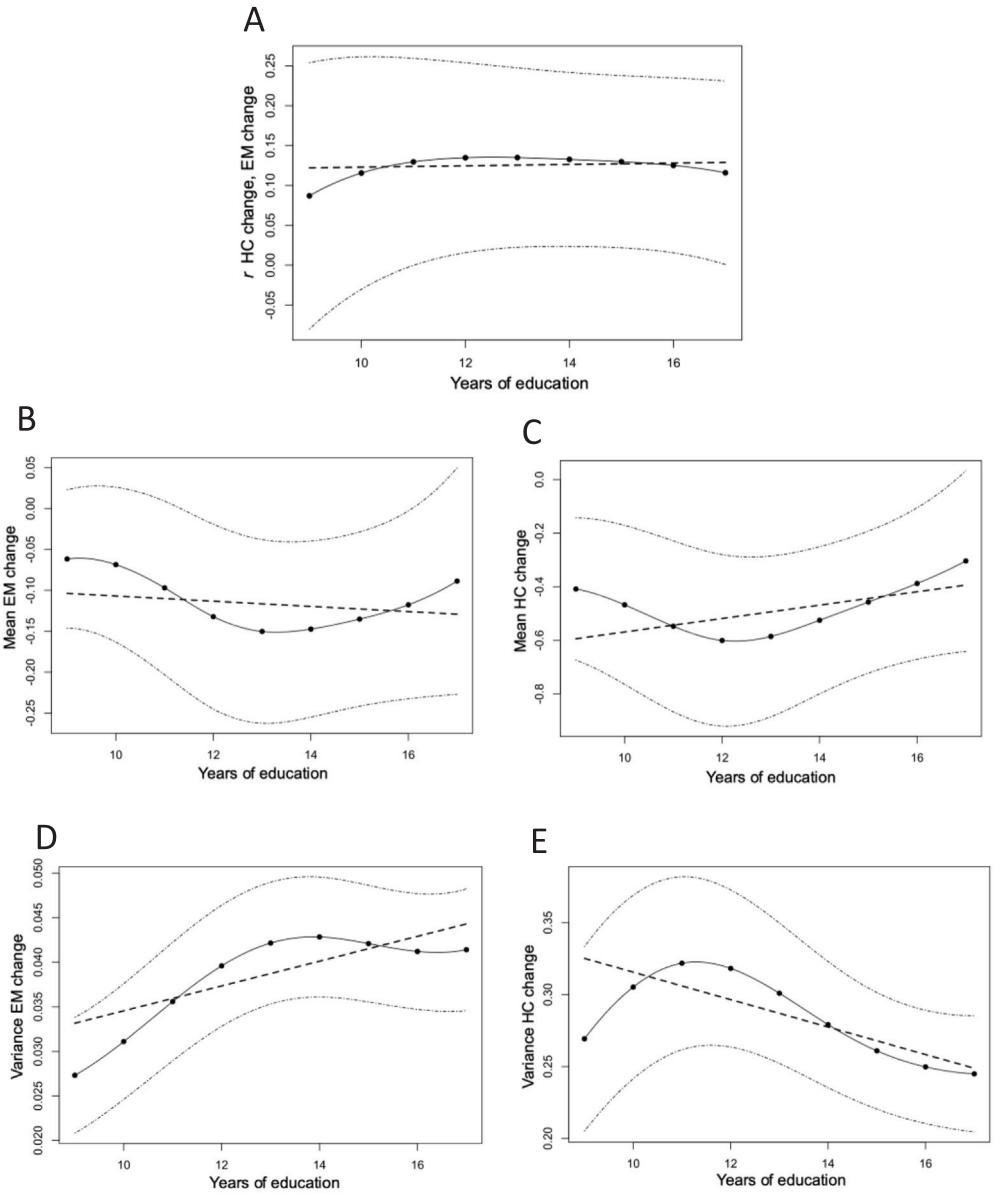

Fig. 1. Main results of the LSEM analyses, including (A) the association between changes in hippocampus (HC) volume and changes in episodic memory (EM) performance, (B) the mean change in EM performance, (C) mean changes in HC volume, (D) variance in change of EM performance, and (E) variance in change of HC volume as a function of years of education. Education ranges from 9 to 17 years, with one year interval. Black dots represent the point estimates at each focal point. Dashed grey lines represent the 95% confidence interval of the parameter estimation. The dashed black (linear) line represents a linear approximation of the difference pattern across focal points.

data but comes with the added feature of sequentially estimating separate models at defined focal values across a moderator (here, years of education). In this way, the technique provides the estimates in a model (e.g., correlation between changes in memory performance and hippocampus volume) for each of these focal points (e.g., 9 years of education, 10 years of education, etc.). The analyses accomplish this by implementing a sample-weighting function to partially include observations from the neighboring values of education. Data close to a focal moderator value are weighted more strongly than data farther away, along a Gaussian kernel function with a maximum of 1 at the focal point. Because the values of a Gaussian kernel function are always larger than zero, all observations will enter all models, but distant observations have negligible influence on the parameter estimation at a given focal model point (e.g., an observation that is 3 standard deviations away from the focal point counts only about 1/90 of

an observation at the focal point). The advantages of this approach are that categorization of years of education into groups of subjects is not needed, the shape of the relationship between years of education and the estimates does not need to be constrained (e.g., to linear), and the effects of years of education can be examined for all freely estimated parameters in the model. For these reasons, LSEM provides a powerful approach to examine whether years of education moderates the correlation between changes in memory performance and changes in hippocampus volume.

In the main analyses, we specified a simple model with the annual changes of memory performance and hippocampal volume as observed variables, and estimated their means, variances, and their covariance. These variables were regressed on age at baseline (centered) and study (dummy coded), which were allowed to covary. This is a model that is just identified and thus has perfect fit. The analyses were run on the entire sample as well as separately for the two groups differing in APOE ε4 status.

The follow up control analyses were restricted to the BASE II and COBRA samples that shared a measure of episodic memory performance. For these analyses, we specified a bivariate latent change score model [37,38]. Latent factors represent the shared variance among the observed variables used to identify the factor. The influence of measurement error is therefore attenuated (error is separately estimated), which helps to minimize the issues arising when analyzing raw change scores. We formed one such factor of episodic memory performance based on the observed test-scores from time 1 and one factor based on the variables from time 2. Five tests contributed data at each time point: The object-location test (administered in both studies), number-word memory (assessed in COBRA), word recall (assessed in COBRA), the verbal learning and memory test (administered in BASE II), and scene encoding (assessed in BASE II). This means that the subjects from the COBRA study have missing values on tests only administered in the BASE II study, and vice versa. The models were estimated with full information maximum likelihood, which assumes missingness at random. This assumption is acceptable in this situation because data are missing by design [e.g., 39]. To scale the latent factors, the loading and intercept of the object-location test on the latent factors were set to 1 and 0, respectively, and the loadings and intercepts of the other observed variables were freely estimated. All error variances at time 1 were allowed to covary with their corresponding error variance at time 2. A latent change factor, representing the within-person difference between time 1 and time 2, was specified. Specifically, the time-2 factor was regressed on the latent change factor (specifying the regression path to 1), the variance and intercept of the time-2 factors were set to 0, the time-2 was regressed on the time-1 factor (specifying the regression path to 1), and a covariance was specified between the time-1 and the latent change factors. Thus, all time-2 characteristics were specified as a function of the time-1 and the latent change factors. The time-1 factor and the latent change factor were regressed on age (centered) and study. The same latent change specification was set up for hippocampus volume, using the left and right hippocampus volumes as observed variables to identify the time-1 and time-2 latent factors [3]. To scale the latent factors, the loading and intercept of the left hippocampus on the latent factors were set to 1 and 0, respectively. In addition, the time 1 and latent change factors of episodic memory and hippocampus volume were all allowed to covary. We imposed strong measurement invariance over time by constraining the free loading and intercept of each of the observed variables to be equal across time.

The analyses were run in R 4.0.3 [40], using the lavaan 0.6–9 [41] and sirt 3.10–118 [42] packages. In all models, we restricted the focal education values for the analyses to range between 9 and 17 because the estimates at the focal points beyond this range had large confidence intervals (all subjects varying between 6 and 22 years of education still contribute to the reported estimates). Density plots of years of education, separately for each study, can be found in Supplementary Fig. 2. The bandwidth factor of the weighting function (i.e., the Gaussian kernel) was set to 2 (standard deviations of the normal density function around the focal value of education) in all models [17]. The permutation tests in sirt (1000 permutations) were used to test for linear trends in the estimates as a function of years of education. The threshold for statistical significance was set at $p < 0.05$. The code for the analyses is provided in the Supplementary Materials.

Results

The main model estimated on the entire sample resulted in a correlation between annual changes in memory performance and annual changes in hippocampal volume of r = 0.11, 95% Confidence Intervals (CI) [0.03, 0.18], p = 0.004. A scatter plot of the data behind this association can be found in Supplementary Figure 3. Based on the results from the LSEM, Figure 1A depicts this correlation and the associated CI as a function of years of education. Inspection of Figure 1A revealed no trend towards weaker memory-hippocampus correlation as a function of higher educational attainment, and the permutation test did not reveal a statistically significant (linear) moderation by years of education (b = 0.003, p = 0.908). Moreover, education did not moderate annual mean changes in memory performance (Figure 1B, b = -0.004, p = 0.794, for the linear trend) or hippocampus volume (Figure 1C, b = 0.017, p = 0.292, for the linear trend). The individual differences (i.e., variances) in annual memory changes (Fig. 1D) increased with years of education until 13 years and then remained stable. The permutation test of the linear trend relating education to variance in memory change was not statistically significant (b = 0.002, p = 0.138). The variances in annual volume changes (Fig. 1E) tended to be lower in individuals with more than 12 years of education. The linear trend related education to variance in volume change was not statistically significant (b = -0.006, p = 0.118). Including number of years between time 1 and time 2, which correlated weakly with education (r = 0.05, p = 0.021), change in hippocampus volume (r = 0.05, p = 0.025), and change in change in memory (r = -0.08,

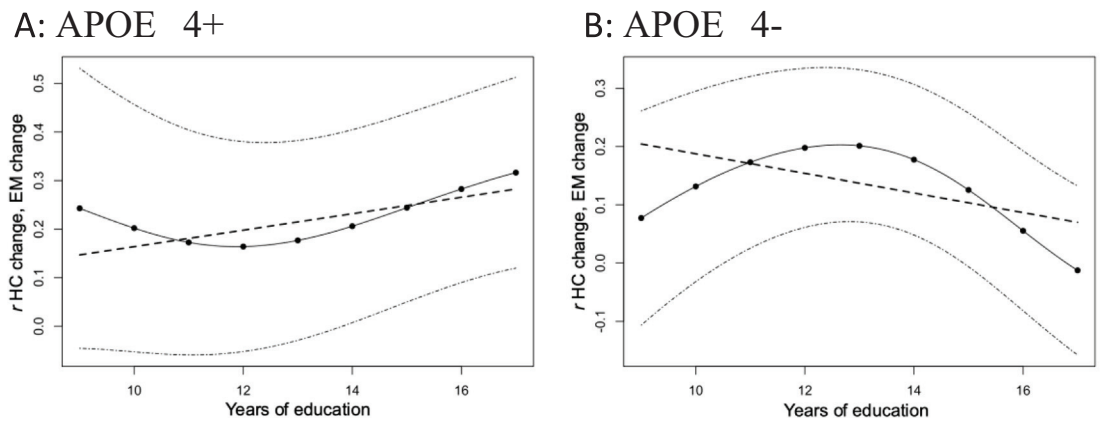

Fig. 2. The association between changes in hippocampus (HC) volume and changes in episodic memory (EM) performance as a function of years of education in (A) APOE ε4 carriers and (B) APOE ε4 non-carriers. Black dots represent the point estimates at each focal point. Dashed grey lines represent the 95% confidence interval of the parameter estimation. The dashed black (linear) lines represent a linear approximation of the difference pattern across focal points.

$p < 0.001$) after statistically controlling for study, as a predictor of annual changes in memory performance and hippocampus volume, did not affect the results substantially.

The model was next estimated separately for APOE ε4 carriers and non-carriers. In the sample of APOE ε4 carriers (n = 166), the correlation between annual changes in memory performance and annual changes in hippocampal volume was r = 0.24, 95% CI [0.10, 0.39], p = 0.001. In the sample of APOE ε4 non-carriers (n = 450), the correlation between annual changes in memory performance and annual changes in hippocampal volume was not statistically significant, r = 0.07, 95% CI [-0.02, 0.17], p = 0.115. The difference between the correlations observed in each of the two groups was statistically significant (z = 1.909; p = 0.028). Based on the results from the LSEM, Fig. 2 shows the correlation and the associated CIs as a function of years in education for APOE ε4 carriers (Fig. 2A) and non-carriers (Fig. 2B). In APOE ε4 carriers, there was no trend suggesting that education moderates the association between annual changes in hippocampus volume and memory performance (b = 0.017, p = 0.500, for the linear trend). For non-carriers, a non-linear trend is evident, with statistically significant associations (see the CIs in the figure) between 11 and 14 years of education, but not with lower or higher educational attainment (with linear trend not significant, b = -0.017, p = 0.258). For both groups, effects on means and variances were largely consistent with the results for the entire sample. However, in ε4 carriers the increase of variance in memory change continued also after 13 years of education, with a statistically significant linear trend (b = 0.003, p = 0.020). The results for the means and variances are reported in Supplementary Fig. 4. Note that number of years between time 1 and time 2 did not significantly differ between carriers (mean = 3.89 years) and non-carriers (mean = 3.80 years; $t(310) = 0.985$, p = 0.329).

The fit for the model used in the follow-up analyses restricted to the subsample of BASE II and COBRA participants was acceptable $\chi^2(94, N = 267) = 93.92$, p = 0.483, CFI = 1.000, and SRMR = 0.114. The point estimate of the correlation between changes in hippocampus volume and memory performance was estimated at unity (r = 1.0), but came with poor precision, 95% CI [-0.56, 2.67], p = 0.204. This was probably due to a small variance in change for episodic memory performance that was not statistically significant (0.014, p = 0.537). These analyses were limited to the participants of BASE II and COBRA studies and by design had many missing values, and most likely did not provide sufficient power to detect variance in change [43]. The results of the LSEM were consistent with the main analyses by revealing no trend for a moderation of the correlation by years of education, but the precision of the estimates was poor also across the range of education. We chose not to interpret these results further due to the ill-behaving latent factor of episodic memory, but the results of these follow-up analyses are reported in Supplementary Figure 5.

Discussion

The results did not provide support for an influence of educational attainment on the association between changes in hippocampus volume and changes in episodic memory performance in individuals with no dementia diagnosis. A similar pattern was found when the analyses were restricted to APOE ε4 carriers, with heightened risk for subsequent dementia. Furthermore, educational attainment was neither substantially associated with change in episodic-memory performance nor with change in hippocampus volume. The present results taken together with other recent results [14–16] paint a picture of the influence of education on neurocognitive aging that is inconsistent with a cognitive reserve account. The emerging picture is that educational attainment predicts late-life cognitive performance because education is associated with individual differences in cognitive skills in early life – individual

differences that then remain quite stable into older age [13].

A few other results are worth highlighting. Across all studies, the variance in change in memory performance increased with higher educational attainment (up until 13 years of education). This finding suggests more heterogeneity in cognitive aging among more highly educated individuals or that measures of memory performance are ill-suited to detect individual differences among individuals with lower education (e.g., due to floor effects). We also observed that, for APOE ε4 non-carriers, there was a trend for non-linear moderation of the association between change in memory performance and change in hippocampus volume by education, with statistically significant associations around the average education of the sample. Note that we restricted the reported results to focal education values between 9 and 17 because the confidence intervals beyond this range tended to be unreasonable large (all subjects still contribute to the estimates for the reported focal points). Therefore, we do not think this pattern of results is an artifact of the density of the data. The relatively similar confidence intervals across the range of focal values support this conclusion. On the other hand, whereas these results are potentially interesting, they result from exploratory analyses and require replication in other studies.

Some limitations of this study deserve discussion. We acknowledge that other brain measures and other cognitive measures could display different results than our reported data. However, changes in episodic-memory performance and hippocampus volume share unique variance among measures of change in brain and cognition [44], and both memory performance and the medial temporal lobe have been at the core of theoretical discussions related to cognitive reserve and maintenance [6,7]. Hippocampus volumes are also easier to estimate with high quality in the context of a large multi-center study than cortical volumes. Previous analyses in the Lifebrain samples also show that mean changes in hippocampal volume and total cortical volume are not differentially associated with educational attainment [15]. In addition, our focus on select measures served to maximize statistical power to detect associations that can be expected to be small [45]. Thus, we argue that the selection of the behavioral and brain measures served as an appropriate testbed for the considered theoretical perspectives.

Education may still operate in a way predicted by the cognitive reserve theory in other types of samples, such as samples including individuals with very low education [46]. However, there is so far little systematic evidence for non-linear associations between education and cognitive performance [13]. Findings may also be different in samples of individuals with neurodegenerative disease, but the absence of evidence for a moderating influence of education in APOE ε4 carriers is not supporting this perspective. We also note that our use of raw measures of standardized annual change is suboptimal from a psychometric perspective and relies on several assumptions. Estimating change at the latent level would have been beneficial from many perspectives [37,38], but the data used did not allow for a trustworthy estimation of a latent factor of episodic memory in our attempts for such a follow-up analysis. In this vein, we also note that other threats to validity of longitudinal studies, such as retest effect, may influence association between brain and cognition. Trends for floor and ceiling effects in some of the measures of episodic memory from some of the studies may also influence the studied association differently depending on educational attainment, but the summary measures used in the present study did show any clear trends for such effect (see Supplementary Fig. 1). We also note that the results are consistent with other recent studies using other measures of both brain structure and memory performance [16].

We cannot fully exclude that education has an undetected and small moderating influence on the association between changes in hippocampus volume and memory performance. However, our estimates of the association between changes in hippocampus volume and episodic memory performance were based on a large sample of more than 700 individuals and came with reasonable precision (as judged from the confidence intervals). We also note that we operationally defined episodic memory with a broad combination of supra-span, delayed recall, and recognition tasks, and that performance on these measures is influenced by a mix of memory-related processes that may differ in their association with education. We also acknowledge that years of formal education is a rough measure that fails to capture all learning-related experiences, such as qualitative differences in education and lifelong informal learning, that may be important in the context of neurocognitive aging. Finally, we note that associations among education, cognitive performance, and brain structure may differ across societies, time periods, and birth cohorts [47].

Taken together, whereas our results do not exclude the possibility that factors other than education contribute to a cognitive reserve and moderate associations between changes in brain and cognition, we conclude that the influence of education on changes in episodic memory and hippocampus volume is inconsistent with predictions by the cognitive reserve theory. These results are consistent with other recent findings [13–16]. Education is associated with individual differences in cognitive skills in early life and these individual differences remain remarkably stable into older age [13]. Future test of the cognitive-reserve theory may benefit from direct operational definitions of the concept of cognitive reserve [48,49].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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