



Educational attainment does not influence brain aging

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Education has been related to various advantageous lifetime outcomes. Here, using longitudinal structural MRI data (4,422 observations), we tested the influential hypothesis that higher education translates into slower rates of brain aging. Cross-sectionally, education was modestly associated with regional cortical volume. However, despite marked mean atrophy in the cortex and hippocampus, education did not influence rates of change. The results were replicated across two independent samples. Our findings challenge the view that higher education slows brain aging.

education | aging | cerebral cortex | hippocampus | reserve

Do higher levels of education attained in childhood and early adulthood slow the rate of brain and cognitive decline in later adulthood and old age? Prominent accounts of heterogeneity in neural and behavioral aging postulate that this is the case, arguing that education acts as a modifiable protective factor (1) or cognitive reserve (2, 3) of human neurocognitive aging. However, findings from cross-sectional studies provide only inconclusive support for an association between education and neurocognitive level in aging (4–7), and the longitudinal support for an influence of education on age-related neurocognitive change is even more elusive. In fact, a comprehensive review recently concluded that level of education does not reliably influence the rate of cognitive decline in aging (8). Also, associations between secular improvements in average education and historical changes in rates of cognitive change are generally weak (9). In relation to brain changes, longitudinal data are sparse and provide no support for an education–brain aging relation (6, 10). Therefore, we conducted a large-scale test of the hypothesis of a longitudinal relation between education and brain aging. Brain aging was operationalized as brain atrophy measured longitudinally by structural MRI. This metric does not capture the multitude of dimensions of brain aging, but is commonly used and very sensitive to normal and pathological aging.

Results

We considered MRI-based measures across the cortical mantle and the hippocampus from several regional samples within Lifebrain (LB) (11) and from the UK Biobank (UKB) (12). There were marked individual differences in education levels in LB ($n = 735$; age range = 29–91 y; Fig. 1A) and UKB ($n = 1,289$; age range = 47–79 y; 630 with college/university and 659 with nonuniversity education). The main analyses of longitudinal

brain aging were performed with mixed models, using age (at baseline), sex, and scanner as covariates, and the interaction term *education* \times *time* (*since first scan*) as the variable of interest. The longitudinal coverage was up to 11.2 y and three test waves. Models were run with and without intracranial volume (ICV) as an additional covariate.

Longitudinal analyses in LB (1,844 scans), revealed no significant relationship between education and vertex-wise volume change across the cortex. Similarly, when restricting the analysis to regions where volume loss was significantly larger with higher age (Fig. 1B), we found no support that higher education was related to less volume loss (Fig. 1C). Hippocampus atrophy in aging is well documented, and we found a marked age-related reduction in hippocampus volume with increasing age regardless of whether ICV was included as covariate ($F = 141.4$, $P < 2e^{-16}$, edf [effective degrees of freedom] = 8.51) or not ($F = 137.2$, $P < 2e^{-16}$, edf = 8.52). Crucially, rates of hippocampus volume change were not influenced by level of education ($F = 1.51$, $P = 0.22$; Fig. 1D).

Longitudinal analyses in UKB (2,578 scans) showed that regions in posterior association cortices and lateral and medial frontal and temporal cortex displayed more change with increasing age (Fig. 2A), but levels of education did not influence rate of change in these cortical regions (Fig. 2B). A vertex-wise mega-analysis of LB and UKB data pooled together confirmed the lack of an effect of education on cortical change (no vertices survived conventional criteria for multiple comparison corrections). Hippocampus volume loss was seen with ($F = 102.2$, $P < 2e^{-16}$) and without ($F = 98.74$, $P < 2e^{-16}$) covarying for ICV, but again level of education did not influence rate of hippocampal change (Fig. 2C; $t = -0.45$, $P = 0.65$) (Fig. 2C).

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The authors declare no competing interest.

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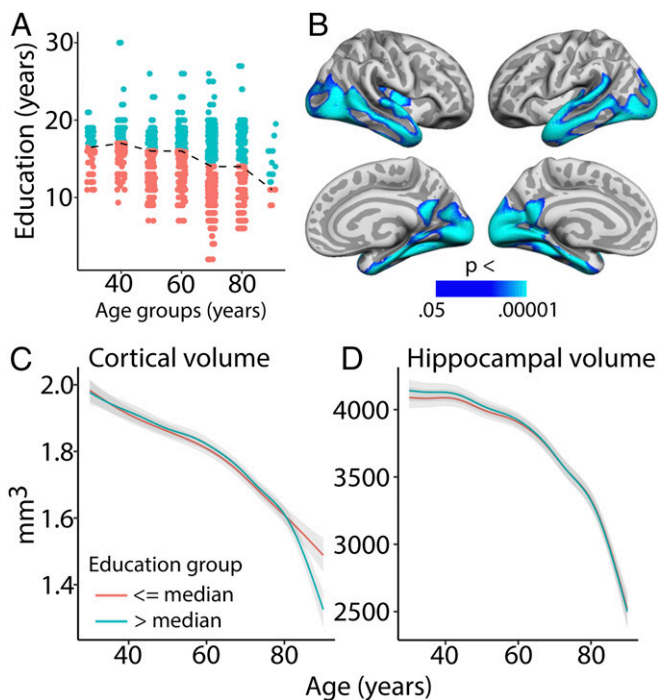


Fig. 1. Longitudinal education—brain-aging relations in LB. (A) Marked individual differences in education in all age groups. (B) Cortical regions showing more volume loss with increasing age, i.e., nonlinear age changes ($P < 0.05$, corrected for multiple comparisons; see *SI Appendix*). (C) Education was not related to rate of change in the atrophy-prone cortical regions in B. (D) There was significant hippocampus volume loss but no influence of education on rate of change. Education groups in C and D are based on a median split (indicated by the dashed line in A and used for illustrative purposes). The shaded areas around the lines denote 95% CI.

We used hypothesis testing with Bayes factors (BF) to quantify the evidence in favor of the null hypothesis of no relation of education with longitudinal brain aging. Given similar patterns of results for the cortex and hippocampus in both samples, the Bayesian analysis was restricted to the computationally less demanding hippocampal region in LB where education was coded as a continuous variable. We used mean-zero Gaussian priors with an uninformative prior followed by a sensitivity analysis with an informative prior. Based on previous studies of the effect of education on brain aging (5, 10), the informed prior stated that hippocampal volume loss (about 50 mm^3 per y, or 1%) would be slowed by around $0.5 \text{ mm}^3/\text{y}$ for each year of education. The uninformative prior's SD was set at 10 times the main effect ($\text{SD} = 500 \text{ mm}^3/\text{y}$), and yielded a BF corresponding to very strong evidence in favor of the null ($\text{BF}_{01} = 1,170$). The informative prior assigned a very large prior probability that the effect of interest was close to zero ($\text{SD} = 0.5 \text{ mm}^3/\text{y}$). The obtained $\text{BF}_{01} = 1.29$ implies that the posterior probability is even more concentrated around zero than the informative prior, thus favoring the null hypothesis.

Finally, in both LB and UKB, cross-sectional analyses revealed modest associations of education with regional cortical volume around left central sulcus (Fig. 2D; LB: cluster extension, $5,298 \text{ mm}^2$; cluster P values < 0.019 – 0.0002 ; UKB: $30,800 \text{ mm}^2$, $P < 0.013$ – 0.0002). Even in these cortical regions where education was related to intercept no relation was seen for slope (Fig. 2E). A large-scale ($n = 19,646$) cross-sectional UKB study reported a very small positive education–hippocampus volume association (12), but in the present smaller samples no significant cross-sectional associations were observed in LB or UKB between education and hippocampus volume.

Discussion

Taken together, the results from two large-scale datasets totaling almost 4,500 observations and over 2,000 individuals provided no support for the hypothesis that higher education translates into slower rates of brain aging. Instead, parallel rates of change were seen in cortical regions and in the hippocampus. It remains an open question whether other measures of brain aging than structural MRI are related to education levels.

Cross-sectionally, in both LB and UKB, education was modestly related to regional cortical volume, but even in the cortical regions where education was related to volume no relation was seen for rate of change. Thus, our brain-aging findings mimic those previously demonstrated for cognitive aging (8) by showing that education to some degree is related to level (intercept) but not rate of change (slope). A positive association between level of education and level of neurocognitive functioning has been reported in some past studies (5, 8, 12) (but see ref. 6), and is consistent with the notion of a “passive” reserve (13), which posits that individuals with higher education have an initial advantage over individuals with lower education that they may carry through their adult lives. It is this advantage, not attenuated longitudinal change, that reduces the risk among more educated individuals to be diagnosed with dementia and delays them reaching a threshold below which independent living is no longer possible. There is evidence for a genetic association of educational attainment with cortical surface area (14) and cognitive functions (15), indicating that shared genetic influences may account for cross-sectional relations of education with neurocognitive levels.

In conclusion, education is linked to many advantageous outcomes, but the present findings challenge theoretical and empirical claims that higher education slows brain aging.

Materials and Methods

MRIs were processed using FreeSurfer, version 7.1. All participants gave informed consent, subprojects were approved by the relevant ethical review board, and the Lifebrain project was approved by Regional Committees for Medical Research Ethics–South East Norway. Screening criteria were not identical across studies, but participants were recruited to be cognitively

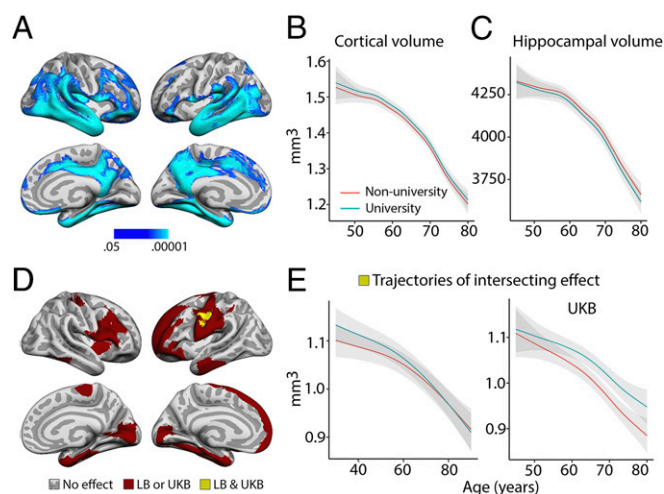


Fig. 2. Longitudinal education—brain-aging relations in UKB. (A) Cortical regions showing more volume loss with increasing age ($P < 0.05$, corrected). (B) Education was not related to rate of change in the atrophy-prone cortical regions in A. (C) There was significant hippocampus volume loss but no influence of education on rate of change. (D) Cross-sectional education—brain-volume relations in LB and UKB ($P < 0.05$, corrected). (E) In the regions in D where a cross-sectional effect of education was seen in both LB and UKB (yellow), no differences in longitudinal rate of change were seen in relation to education in LB or UKB (red, low education; blue, high education). The shaded areas around the lines denote 95% CI.

healthy and did not suffer from neurological conditions known to affect brain function, such as dementia. All samples consisted of community-dwelling participants, some were convenience samples, whereas others were contacted on the basis of population registry information. Details on samples, MRI acquisition and processing, statistical analyses, and data and code availability are presented in *SI Appendix*.

Data Availability. The LB data supporting the results of the current study are available from the Principal Investigator of each substudy on request, given appropriate ethical and data protection approvals. UK Biobank data requests can be submitted to <http://www.ukbiobank.ac.uk>.

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1. G. Livingston *et al.*, Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* **396**, 413–446 (2020).
2. Y. Stern *et al.*; The Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup, Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement.* **16**, 1305–1311 (2020).
3. R. Cabeza *et al.*, Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci.* **19**, 701–710 (2018).
4. Y. Chen *et al.*, The positive impacts of early-life education on cognition, leisure activity, and brain structure in healthy aging. *Aging (Albany NY)* **11**, 4923–4942 (2019).
5. K. B. Walhovd *et al.*, Education and income show heterogeneous relationships to lifespan brain and cognitive differences across European and US cohorts. *bioRxiv* [Preprint] (2020). <https://www.biorxiv.org/content/10.1101/2020.10.12.335687v1> (Accessed 1 December 2020).
6. J. A. Pillai *et al.*; Alzheimer’s Disease Neuroimaging Initiative, Higher education is not associated with greater cortical thickness in brain areas related to literacy or intelligence in normal aging or mild cognitive impairment. *J. Clin. Exp. Neuropsychol.* **34**, 925–935 (2012).
7. C. Habeck, Y. Gazes, Q. Razlighi, Y. Stern, Cortical thickness and its associations with age, total cognition and education across the adult lifespan. *PLoS One* **15**, e0230298 (2020).
8. M. Lövdén, L. Fratiglioni, M. M. Glymour, U. Lindenberger, E. M. Tucker-Drob, Education and cognitive functioning across the life span. *Psychol. Sci. Public Interest* **21**, 6–41 (2020).
9. D. Finkel, C. A. Reynolds, J. J. McArdle, N. L. Pedersen, Cohort differences in trajectories of cognitive aging. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **62**, 286–294 (2007).
10. N. Raz *et al.*, Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cereb. Cortex* **15**, 1676–1689 (2005).
11. K. B. Walhovd *et al.*, Lifebrain Consortium, healthy minds 0-100 years: Optimising the use of European brain imaging cohorts (‘Lifebrain’). *Eur. Psychiatry* **50**, 47–56 (2018).
12. L. Nobis *et al.*, Hippocampal volume across age: Nomograms derived from over 19,700 people in UK Biobank. *Neuroimage Clin.* **23**, 101904 (2019).
13. D. Barulli, Y. Stern, Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends Cogn. Sci.* **17**, 502–509 (2013).
14. K. L. Grasby *et al.*, The genetic architecture of the human cerebral cortex. *Science* **367**, eaay6690 (2020).
15. G. Davies *et al.*, Genome-wide association study of cognitive functions and educational attainment in UK Biobank ($N=112\,151$). *Mol. Psychiatry* **21**, 758–767 (2016).