Education as a Moderator of the Relationship Between Episodic Memory and Amyloid Load in Normal Aging

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Abstract

The current study explored whether education, a proxy of cognitive reserve, modifies the association between episodic memory (EM) performance and βeta-amyloid load (Aβ), a biomarker of Alzheimer's disease, in a cohort of cognitively normal older adults. One hundred and four participants (mean age 73.3 years) evenly spread out in three bands of education were recruited. Participants underwent neuropsychological assessment, structural MRI as well as PET imaging to quantify Aβ load. Moderation analyses and the Johnson–Neyman technique were carried out to examine the interaction of education with Aβ load to predict EM performance. Linear regressions were then performed within each group of education to better illustrate the interaction effect (all analyses were controlled for age and sex). The interaction between education and Aβ load was significant ($p < .05$) for years of education, reaching a cutoff point of 13.5 years, above which the relationship between Aβ load and EM was no longer significant. Similarly, significant associations were found between Aβ and EM among participants with secondary ($p < .01$) and preuniversity education ($p < .01$), but not with a university degree ($p = .253$). EM performance is associated with Aβ load in cognitively normal older individuals, and this relationship is moderated by educational attainment.

Keywords: Biomarkers, Brain aging, Cognition, Cognitive reserve

The current state of the literature tends to demonstrate a subtle but significant impact of amyloid load (Aβ), one of the main Alzheimer's disease (AD) changes, on neuropsychological performances of older adults in a period of life where cognition is still clinically normal (1, 2). More specifically, a greater effect of Aβ is found in regard to episodic memory (EM) (3). AD is also characterized by a large and progressive deficit in verbal learning, which remains predominant throughout the disease course (4). EM decline is recognized as one of the first clinical signs of AD and thus the best cognitive predictor of future conversion to the disease (5, 6).

Aβ begins to accumulate before the first clinical signs of AD and is associated with an increased risk for future cognitive decline (7, 8). Although some older individuals have a significant amount of Aβ pathology, their cognitive performances are still within normal limits (9). The concept of cognitive reserve (CR) has thereby been proposed to account for the discrepancy between the level of brain pathologies, such as Aβ load, and expected clinical manifestations generally associated with it (10). Education is one of the most studied proxies of CR and has been widely recognized as a moderator of cognitive changes associated with an underlying pathology, such as AD (11, 12). Indeed, this capacity to withstand brain damage is largely studied in cases of patients with AD to account for the fact that at equal level of cognitive performance, higher-educated patients present more aggregation of Aβ than less-educated patients (13). CR, as measured by level of education, is also known to moderate cognitive changes observed in normal aging (10, 14). Older adults who benefits from a higher education tend to show a slower rate of cognitive decline over time compare to those with lower level of education (15).

Nevertheless, whether educational attainment may help withstand the effect of Aβ deposition on cognitive functioning among cognitively intact older adults is still unclear, more specifically regarding EM. For instance, in postmortem studies, EM performance was reported to be associated to the count of neuritic plaques in nondemented older participants, but this association

was found to be weaker in higher-educated than in lower-educated individuals (16). In contrast, in vivo studies showed that education interacted with Aβ to predict global cognitive functioning (17) but not EM (17-19). However, these previous studies were conducted, for the most part, with highly educated older individuals. This more restrictive sample regarding educational level of the general population may have masked the potential moderating effect of this latter proxy of CR. The nature of the relationship between EM, Aβ load and education in normal aging remains a question of great interest since this cognitive function seems particularly vulnerable to Aβ accumulation (2, 3).

The present study takes place in the ongoing efforts to better characterize the preclinical phase of AD by examining potential reserve factors, such as educational attainment, that may contribute to differential neuropsychological performances associated with the underlying Aβ changes. Thus, the aim of the study was to determine whether education, a surrogate of CR, can moderate the effect of Aβ, as measured using in vivo PET imaging with ^{11}C-Pittsburgh Compound B (PiB) (20), on EM in normal aging. Furthermore, this question was investigated through the recruitment of an equivalent number of participants in three bands of education. Our main hypothesis was that the association between Aβ load and EM would be weaker among cognitively intact older individuals with higher education compared to their peers with lower education.

Methods

Participants

In this cross-sectional study, 104 cognitively normal older individuals (aged 65 and older; mean age 73.3 years), without significant memory complaints nor significant cognitive impairment, that is, mild cognitive impairment (MCI) or dementia, were recruited in this study. Exclusion criteria included a history of neurological and/or traumatic brain injury, psychiatric disorders including untreated past or current severe depression and anxiety, untreated illnesses that may cause cognitive

impairment (eg, diabetes, metabolic or endocrine condition, etc.), alcohol or drug abuse during life, anesthesia in the last 6 months and uncorrected visual or hearing problems. Participants were recruited from a pool of participants at the Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM) and through advertising. Cognitive testing and MRI imaging were performed at the CRIUGM and PET imaging at the Montreal Neurological Institute (MNI). This study protocol was reviewed and approved by local research ethic boards. All participants provided written informed consent prior to their participation in the study.

Neuropsychological Tests

The following screening procedure allowed to confirm the absence of significant memory complaints as well as cognitive impairment (MCI or dementia). The Conversations and Movies/Books subtests of the Self-Evaluation Questionnaire (21), which are associated with objective memory deficits in MCI (22), were administered (inclusion score> –2 *SD*). A visual recognition memory test (DMS-48, 2 minutes delay (23)) and a verbal memory test (Logical Memory (24)) were used to screen for objective memory deficits (inclusion score> –1.5 *SD* on at least one of these tests). The Montreal Cognitive Assessment (MoCA) (25) was also administered to all participants, in which a score of >23/30 is considered as an inclusion criterion (26). To exclude significant depressive symptomatology, participants had to score <11/30 on the Geriatric Depression Scale (GDS) (27).

A large body of evidence shows that delayed recall scores in EM tests are among the earliest cognitive changes observed in preclinical AD and are predictive of future conversion to AD (6). Thus, delayed recall scores were used to compute an EM measure. To ensure internal validity of our EM composite score, we performed a correlational matrix between our measures of delayed recall. This analysis allowed to determine which of these measures best intercorrelated. Delayed

recalls of the Rey Auditory Verbal Learning Test (RAVLT) (28) and Logical Memory (24) were selected based on a medium effect size correlation of $r = .31$ ($p < .001$) (29). The EM composite score was then computed by converting raw scores into z-scores based on the mean and standard deviations of the whole sample and averaging the z-scores of those two memory tests. The RAVLT was initially chosen over other word-list learning tests because it is free of a semantic learning context (ie, semantic categories). Indeed, the latter often results in ceiling effects in more educated individuals (30). Similarly, the sensitivity of the Logical Memory test shows a high level of accuracy in discriminating between cognitively healthy older individuals and those with very mild AD (31).

In addition, all participants underwent neuropsychological testing assessing a range of cognitive functions including processing speed, attention, working memory, executive functions, language/semantics and visuospatial abilities. Global intellectual ability (IQ) was also assessed as part of the cognitive assessment (32).

Measure of CR

Educational achievement was selected as a proxy of CR. Participants were evenly distributed into three groups based on their level of education: secondary school, CEGEP or its equivalent (a preuniversity program in Quebec) and university, each level leading to a specific diploma in Quebec educational system. Participants with secondary school education had between 9 and 11 years of education, participants with preuniversity education had between 12 and 13 years of education, whereas participants with a university background had more than 13 years of education. Participants had to have a minimal number of 9 years of education, in order to exclude potential confounding factors such as a history of neurodevelopmental disorder. There was no maximum number of years of education. In each group, however, a diploma did not necessarily have to be

obtained for participants to be included. In addition to classifying participants into three bands of education, the number of years of formal education was also considered and examined as a continuous variable. The level of educational attainment and number of years of education were obtained via self-reported information.

PiB-PET Imaging

All Positron Emission Tomography (PET) imaging occurred, on average, 85.12 days (SD = 73.26) following neuropsychological assessment. PET data were acquired with an ECAT HR+ scanner (Siemens/CTI) in 3D imaging mode at the McConnell Brain Imaging Center of the MNI. The scanning session began 50 minutes prior to start of the actual scan during which time the PiB bolus was injected. After 50 minutes, during which time the participant rested comfortably, the participant was positioned in the scanner, and data acquisition was started, resulting in the acquisition of seven frames: 6 × 300 seconds, and 1 × 600 seconds. Each frame was comprised of 63 axial slices with an in-plane resolution of 2.06 × 2.06 mm. Total time required for the entire scanning session was 90 minutes. PET data were reconstructed using filtered back projection and were corrected for photon attenuation, scattering and radioactive decay. The standardized uptake value ratio (SUVR) was computed to quantitatively characterize the binding of the radioactive tracer PiB to amyloid during PET scanning. This ratio provides a quantifiable measure of Aβ accumulation in each participant's brain, which was used as a continuous variable in all subsequent statistical analyses. The SUVR was determined by normalizing the radioactivity concentration of the whole cortex using average gray matter of the cerebellum as the reference tissue, since this region is known to be unaffected by Aβ deposition (20).

Structural MRI Imaging

The MR images were acquired at the Unité de Neuroimagerie Fonctionnelle (UNF) located at the CRIUGM on a 3T Trio Siemens Magnetic Resonance Imaging (MRI). High resolution anatomical images included T1-weighted magnetization and were obtained using an optimized MPRAGE protocol (TR = 2.3 seconds, TE = 2.94 ms, TI = 900 ms, flip angle = 9°, FOV = 256 × 240, voxel 1 × 1 × 1.2 mm) using an eight-channel coil. This optimized MPRAGE protocol allowed the coregistration of PET to the MR image for each participant. The total acquisition time was approximately 30 minutes.

Statistical Analysis

One-tailed bivariate correlations were performed to examine associations between age on the one hand, and Aβ load and EM performance on the other hand. Education and its associations with Aβ load, EM performance and IQ were also explored. Similarly, a one-tailed bivariate correlation was carried out to verify the association between years of education and IQ. As for EM and education, a one-tailed partial correlation (controlled for age) was conducted. A partial correlation while controlling for age was used in order to assess the relationship between Aβ load and number of years of education. In fact, there are conflicting findings in the literature regarding the association between education and Aβ load. While some studies did not find a significant relationship between education and Aβ deposition (16, 33, 34), others have reported that greater cognitive engagement based on lifestyle factors, such as a higher level of education, is associated with a reduced level of Aβ load (35, 36).

A stepwise multiple regression was performed to examine the independent associations of age, sex and Aβ with EM composite score. This descriptive model was used to better understand

the relationship between these variables and determine which one is most strongly associated with EM performance.

Then, we performed a moderation analysis in which an interaction term was included (education × Aβ load) to assess whether Aβ load interacts differently with EM as a function of years of education. EM performance was introduced in the model as the dependent variable, Aβ load as the independent variable and the moderator was the number of years of education. Age and sex were included in the statistical model as covariates. This analysis allowed us to assess the effect of education when considered as a continuous variable (ie, number of years of education) and was performed using Model 1 in PROCESS macro 3.1 for SPSS (37). The Johnson–Neyman technique (37) was then applied in order to determine the regions of significance. This latter analysis identifies the values of the moderator (ie, number of years of education) for which the effect of Aβ load on EM transitions between being nonsignificant to statistically significant by probing the relationship between these two variables for all the possible values of the education variable.

In addition, in order to examine whether the moderation effect is solely due to education, IQ was added as a covariate in the moderation model. In a secondary set of analysis, we explored whether IQ could also moderate the relationship between performance in EM and Aβ load. Moderation analysis was carried out here as well with age and sex added to the model as covariates.

Then, to better illustrate the interaction effect, multiple regression analyses (stepwise) were performed for each group of education with age, sex and Aβ load included in the models to determine which had an impact on EM performance. This analysis permitted the visualization of the relationship between Aβ load and EM performance as a function of educational attainment.

Effect sizes were computed for each main analysis using SPSS 25. For all tests, $p < .05$ was considered significant. Assumption criteria were met for all analysis performed in this study.

Results

Participants Characteristics

A total of 104 cognitively normal older adults composed the whole sample of this study. Clinical and demographic characteristics are presented in Table 1. Aβ load was found to be positively correlated with age (r = .388, p < .001) within the entire group, indicating higher Aβ deposition at older ages, which is consistent with literature. Unsurprisingly, age was negatively correlated to EM performance (r = –.223, p < .05). As for the relation between education and IQ, a significant correlation was found (r = .440, p < .001). No association was found between years of education and EM performance (p = .118) which is a surprising result since higher education is generally associated with better memory performance (38). The association between education and Aβ load was also examined and the analysis revealed a marginal and negative correlation between years of education and Aβ load in our sample (r = –.186, p = .059).

TABLE 1. Demographic Characteristics and General Cognitive Performance of all Participants

Characteristics	Range	Mean (*SD*)
Age (y)	65 - 93	73.30 (6.2)
Women (no.)	-	77 (74%)
Education (y)	9 - 24	13.70 (3.2)
Aβ load (SUVR)	1.04 - 2.03	1.24 (0.17)
MoCA score	23 - 30	27.30 (2.0)
IQ	78 - 138	104.90 (11.9)

Note: N = 104; Aβ = βeta-amyloid; SUVR = Standardized uptake value ratio; MoCA = Montreal Cognitive Assessment.

Association Between EM and Aβ Load

EM performance was found to be associated solely with Aβ load, and not age or sex. The analysis revealed a significant regression equation (F (1, 102) = 20.51, p < .001, R^2 = .167). This result

indicates that age and sex are not associated with EM performance when Aβ load is taken into account.

Effect of the Number of Years of Education on the Association of EM and Aβ Load

There was an interaction between the number of years of education and Aβ load to predict EM performance indicating the presence of a moderation effect; F (1, 98) = 4.3995, $p < .05$, $R^2 = .0344$ (Figure 1). More specifically, with each additional year of education, the effect of Aβ load on EM changed by 0.469 units. This result suggests that the association between Abeta and EM is stronger among those with lower education. This interaction was further explored in order to determine the specific threshold (years of education) above which Aβ load does not influence EM anymore. Results show that the relationship between Aβ load and EM ceases to be significant at 13.5 years of education and above (Figure 2). Furthermore, since IQ is related to educational attainment, we further controlled for IQ in the model. IQ did not influence the moderation effect of education on the relationship between Aβ burden and EM described above. The interaction remained statistically significant when IQ was included in the model as a covariate and the effect size remained similar (F (1, 97) = 4.7619, $p < .05$, $R^2 = .0340$). When a moderation analysis was carried out with IQ, and not education, as a moderator of the relationship between EM performance and Aβ load (age and sex included as covariates), the interaction did not reach significance ($p = .648$).

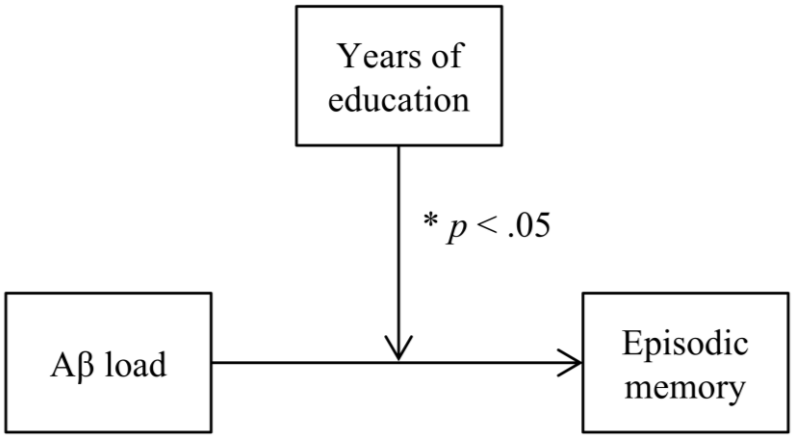

Figure 1. Model of a significant moderation effect of education on the relationship between Aβ load and episodic memory. Illustration of the moderation model with the horizontal arrow indicating that Aβ load is significantly associated with episodic memory in cognitively normal older adults ($p < .05$). This association is significantly moderated by number of years of education ($p < .05$) indicated by the vertical arrow.

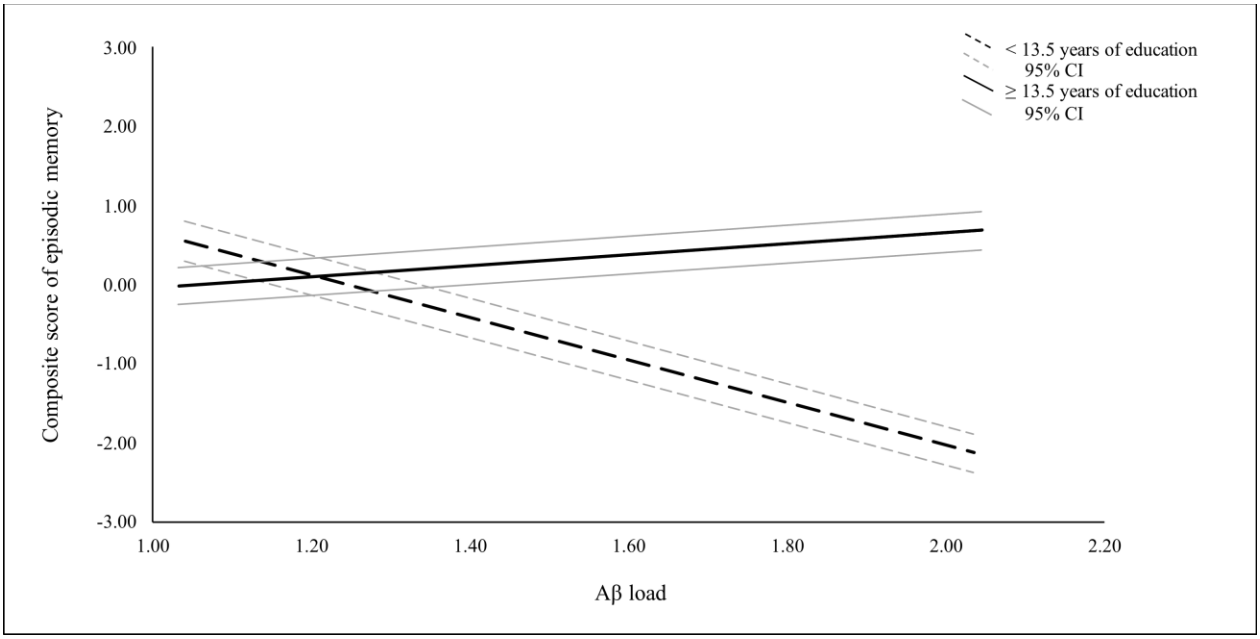

Figure 2. Relationship between composite episodic memory z-scores (y-axis) and Aβ load scores (x-axis) among cognitively normal older adults with < or ≥ 13.5 years of education.

Association Between EM and Aβ Load by Groups of Education

Relationships between Aβ load and EM performance as a function of educational attainment are illustrated in Figure 3. Performance in EM was significantly and uniquely associated with the level of Aβ load in participants with secondary education (F (1, 32) = 10.59, p < .01, R^2 = .249, β = - 0.499) and in participants with preuniversity education (F (1, 33) = 12.68, p < .01, R^2 = .278, β = -0.527). As for the group of participants with university education, no association was found between EM and all three variables, ie, Aβ deposition, age and sex (p > .05, β = 0.116).

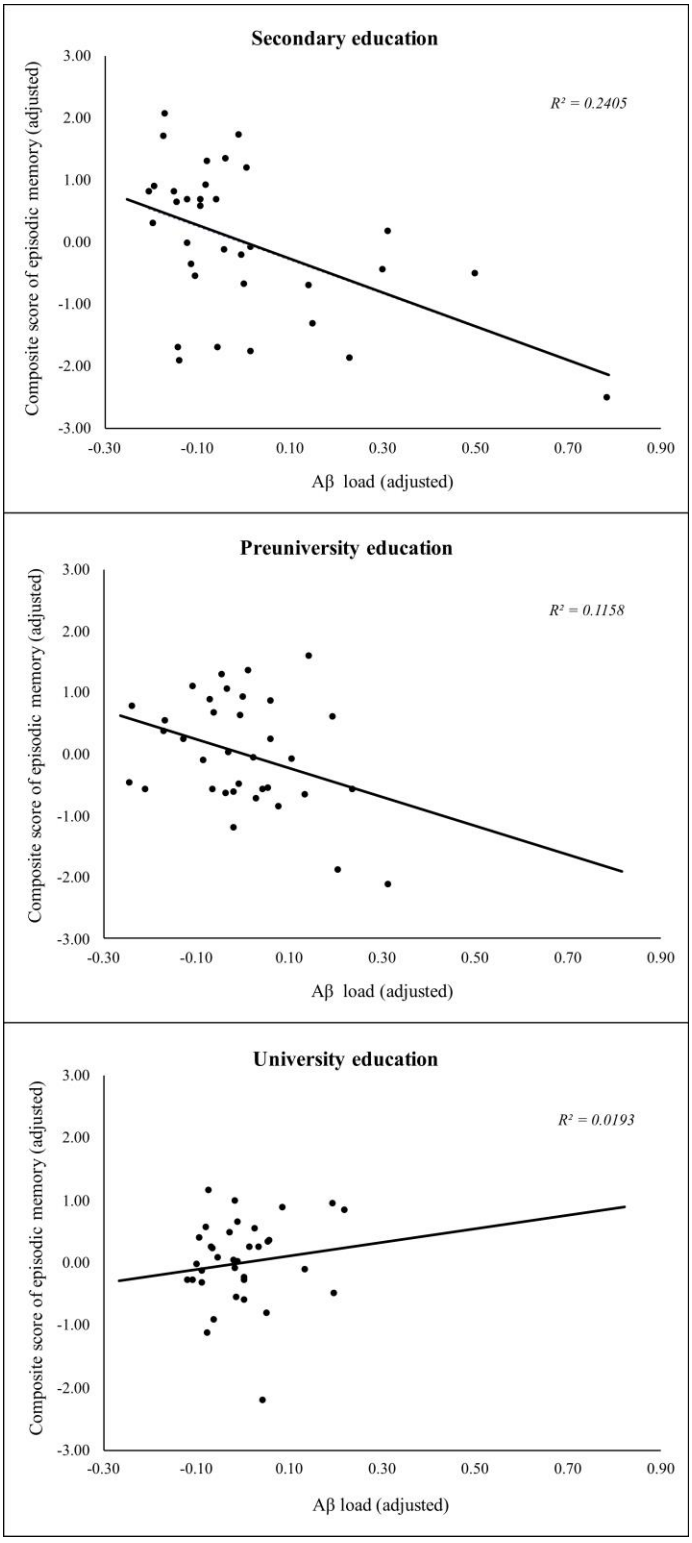

Figure 3. Moderation effect of education on the relationship between episodic memory (y-axis) and Aβ load (x-axis). Episodic memory scores and Aβ load are expressed as unstandardized residuals. Data points are thus adjusted for age and sex.

Discussion

In this study, we examined the relationship between CR, EM and Aβ pathology among a group of cognitively normal older adults (without SMI, MCI or dementia). We aimed to determine whether educational attainment could modify the negative association between EM performance and Aβ load, which reflects an Alzheimer change in the brain. First, our results corroborate a growing body of evidence showing that Aβ load has a significant deleterious impact on EM in cognitively normal older adults (2, 3, 18). This is in keeping with the fact that EM decline is the hallmark of AD (5).

Education was found to moderate the relationship between Aβ load and EM performance, a result which has been found in previous postmortem studies (16, 39). In our study, Aβ load only had an impact on EM performance in cognitively intact older participants in the secondary and preuniversity groups, but not in the university group. Furthermore, the adverse effect of Aβ load on EM performance was shown to become nonsignificant at or above 13.5 years of education, a value which corresponds to the transition between preuniversity programs and university. In summary, these results suggest that education has a protective effect on EM against pathophysiological mechanisms associated with amyloid load present in healthy older adults. Thus, individuals with higher educational attainment, that is, a university degree, are better able to compensate for the accumulation of Aβ deposition by maintaining a more stable memory performance. This is consistent with the notion of CR, which is based mainly on evidence showing that there can be a marked discrepancy between clinical symptoms and brain disease severity in patients with AD as a function of education. In other words, individuals with higher education can better compensate the effects of advancing AD brain pathology (10, 13). The current study now extends these findings to an asymptomatic, cognitively healthy older population. It suggests that education can moderate the effect of accumulating Aβ load, reflecting AD changes, even in older individuals who do not present with MCI or full-blown dementia.

Thus, the tempering effect of education on the relationship between brain Aβ pathology and EM can be interpreted in terms of CR. Indeed, it can be viewed as an active process characterized by a reduced vulnerability to cognitive impairment due to the use of alternative strategies (40). This capacity to cope with pathology to maintain normal cognitive performances is now described in terms of a greater resilience in face of neuropathological processes (41). In other words, differences in cognitive processes, more precisely, in cognitive capacity, efficiency and flexibility, would explain this heightened ability in highly educated older individuals to withstand the adverse effects of neuropathological processes observed in AD and maintain optimal cognitive functioning. These cognitive processes are thought to be modified through life experiences (40). As such, education is considered to be an early and midlife experience-based cognitive enrichment which promotes lifelong brain health (42) and is thought to enable a more efficient way of processing information (43). Consequently, education is one of the most well-documented proxies of CR and has been shown to play an important role in reducing the risk of developing AD as well as in delaying the onset of clinical symptoms (11, 44). Accordingly, education is associated with greater cognitive efficiency both in normal aging and in the presence of brain pathology, such as AD pathology (45). Moreover, it has been shown that intellectual learning throughout life, including education and occupation, had a bigger contribution on cognitive functioning later in life, than current ongoing intellectual activity in older individuals (46).

Even though education is acquired, it may also rely on preexisting intrinsic characteristics, such as innate intellectual capacity. It is thus conceivable that the moderating effect of education on the relation between Aβ load and EM may be explained by underlying intellectual abilities (ie, IQ). Our results, however, do not support this claim. In fact, results showed that although IQ was significantly correlated with education in our group, it did not moderate the relation between Aβ load and EM performance. In addition, the moderating effect of education on the relation between

Aβ load and EM performance remained significant even when IQ was controlled for in the analysis. Overall, these results indicate that rather than intellectual ability, acquired experience acts as a protective factor against AD pathology in normal aging. Therefore, cognitive enrichment based on life experiences appears to be the determining factor in increasing CR within the context of normal aging.

As mentioned previously, a postmortem study did find a moderating effect of education on the association between EM and Aβ deposition in nondemented individuals (16). Other groups, however, did not find this association in normal aging (17-19). In our view, this may be due to the fact that the vast majority of studies recruited highly educated participants. For instance, in the above-mentioned articles which studied the role of education on the relation between Aβ deposition and EM performance, mean education was, respectively, 15.5 (2.7) years (17) and 18.29 (3.59) years (19). As suggested by our own results, recruiting only highly educated participants may mask the relation between brain pathology and memory ability. Indeed, the relation between Aβ load and EM performance was not significant in the university group while it was in the secondary and preuniversity groups. One of the strengths of our study is that we recruited an equivalent number of participants across different education bands, providing a more accurate picture of the general population. Therefore, particularly within the context of studying CR, but more generally in the context of studying the relation between brain biomarkers and cognition in cognitively intact populations, we highlight the importance of avoiding the pitfall of not recruiting only highly educated participants.

Moreover, other proxies of CR have also been found to moderate the impact of Aβ load on cognition. For instance, in a group of older individuals with intact cognition, a weaker association between cognitive functioning and level of Aβ load was found in participants with higher CR, measured with the estimated verbal IQ from the American National Adult Reading Test, compared

to a group with lower CR (33, 47). Similar results have also been found using the Extended Range Vocabulary Test (ERVT) as a surrogate of CR (19), in a cognitively normal older population. These findings further support the concept of CR, whereby certain individuals are able to maintain optimal cognitive functioning despite accumulating brain pathology. These results as a whole suggest a protective effect of CR against the subtle cognitive decline associated with elevated Aβ in normal aging. There are some discrepancies, however, between the above-mentioned studies which found that estimated verbal IQ had a protective effect against Aβ, and our own study which found that IQ did not moderate the relationship between Aβ load and memory performance. Further studies will need to investigate the relation between intellectual abilities and cognitive decline in aging.

There are some limitations which need to be pointed out in this study. First, education is a self-reported measure, and it has been suggested that in order to better operationalize this variable, the degree of literacy may represent a better surrogate of CR (48). Nevertheless, education remains the most widely reported surrogate of CR. Second, the group size remains relatively small compared to other studies. This is compensated by the fact that we recruited participants across a broader spectrum of educational achievement and by using more specific and sensitive neuropsychological tests. Finally, the results are cross-sectional in nature, so the current results do not have any prognostic value regarding the future risk of developing AD. However, a longitudinal follow-up will allow monitoring cognitive changes amongst older individuals with significant amyloid burden recruited in this cohort.

Future work should investigate other proxies of CR in relation to Aβ deposition among older individuals with normal cognition. For instance, measures of occupational attainment, engagement in cognitively demanding activities and bilingualism are also recognized to impart CR (45, 49). Investigating the tripartite relationship between Aβ, cognitive function and other proxies

of CR could further shed light on how these factors differ from education and how they interact to predict cognitive performance in the presence of Aβ deposition. It will also be interesting to investigate more dynamic measures of CR such as engagement in cognitively demanding lifestyle activities, as opposed to education which is described as a static measure. Indeed, education is typically acquired in a fixed period of early and middle life, while dynamic measures of CR may be acquired during the course of life (19). Lastly, in order to gain more insights on the reserve concept, another interesting avenue of research would be to examine the deleterious effects of factors such as history of affective disorder, vascular burden, stress or sleep disorders on the interaction between CR and Aβ.

This study as a whole provides novel evidence concerning the protective role of education against Aβ deposition in cognitively normal older adults. It is critical at this stage to identify modifiable protective factors in the preclinical stage of AD, which may help reducing the risk or delaying the onset of AD. Reducing cognitive inactivity throughout life, including low educational attainment, could have significant impact on the prevalence of AD (50). Previous research has highlighted the role of CR in autopsy studies or in patients with full-blown dementia, but the current study contributes to a new endeavor aimed at studying CR in healthy asymptomatic older individuals with AD pathology using in vivo biomarkers.

Funding

This work was supported by a grant from the Canadian Institutes of Health Research (MOP123376) and the Institute of Aging (IA0120269). S.J. was supported by a Chercheur boursier senior award from the Fonds de recherche du Québec – Santé (FRQ-S). M.J. was supported by a doctoral award from the FRQ-S.

Acknowledgments

We thank Emma Campbell, PhD candidate, for her thorough revision of this manuscript and assistance with English language. We also thank Cristina McHenry and Constant Rainville for their assistance in this project.

Author Contributions

M.J., S.J., C.B., and H.C. were responsible for conception and design of the study. M.J., S.J., P.S.D., M.M.L. and G.T.V. contributed to acquisition and statistical analysis of data, and J.N., H.C., and C.B. were responsible for MRI/PET preprocessing and interpretation. M.J. and S.J. contributed to drafting the manuscript and M.J. was responsible for drafting the figures. All authors reviewed the manuscript and approved the final version of the manuscript.

Conflict of Interest

M.J., P.S.D., M.M.L., J.N., G.T.V., and S.J. have no conflicts of interest to declare. C.B. discloses investments at Imeka. H.C. is supported by operating grants from the Canadian Institutes for Health Research (CIHR) and the Weston Foundation. Pharmaceutical activities in the past 5 years in which he took part include Bristol Myers Squib (adjudication board for clinical trials), Hoffmann-La Roche Limited, TauRx, and Immunocal (site investigator for trials). H.C. is also Scientific Director for the Canadian Consortium on Neurodegeneration in Aging (CCNA), which receives partner support from a set of 15 partners including Pfizer Inc., Lilly, Sanofi, and the Alzheimer Society of Canada.

References

1. Duke Han S, Nguyen CP, Stricker NH, Nation DA. Detectable neuropsychological differences in early preclinical Alzheimer's disease: a meta-analysis. *Neuropsychol Rev*. 2017;27 :305–325. doi:10.1007/s11065-017-9345-5
2. Dupont PS, Bocti C, Joannette M, et al. Amyloid burden and white matter hyperintensities mediate age-related cognitive differences. *Neurobiol Aging*. 2019. In press. pii: S0197-4580(19)30304-5. doi:10.1016/j.neurobiolaging.2019.08.025
3. Hedden T, Oh H, Younger AP, Patel TA. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*. 2013;80:1341–1348. doi:10.1212/WNL.0b013e31828ab35d
4. Hodges JR. Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain*. 2006;129(Pt 11):2811–2822. doi:10.1093/brain/awl275
5. Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *J Int Neuropsychol Soc*. 2008;14:266–278. doi:10.1017/S1355617708080302
6. Small BJ, Fratiglioni L, Viitanen M, Winblad B, Bäckman L. The course of cognitive impairment in preclinical alzheimer disease: Three- and 6-year follow-up of a population-based sample. *Arch Neurology*. 2000;57:839–844. doi:10.1001/archneur.57.6.839
7. Vos SJ, Xiong C, Visser PJ, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013;12:957–965. doi:10.1016/S1474-4422(13)70194-7

8. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313:1924–1938. doi:10.1001/jama.2015.4668
9. Ince PG. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Lancet (London, England)*. 2001;357(9251):169–75. doi:10.1016/S0140-6736(00)03589-3
10. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11:1006–1012. doi:10.1016/S1474-4422(12)70191-6
11. Opdebeeck C, Martyr A, Clare L. Cognitive reserve and cognitive function in healthy older people: a meta-analysis. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2016;2:40–60. doi:10.1080/13825585.2015.1041450
12. Stern Y. Cognitive reserve. *Neuropsychologia*. 2009;47:2015–2028. doi:10.1016/j.neuropsychologia.2009.03.004
13. Kemppainen NM, Aalto S, Karrasch M, et al. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. *Ann Neurol*. 2008;63:112–118. doi:10.1002/ana.21212
14. Tucker AM, Stern Y. Cognitive reserve in aging. *Curr Alzheimer Res*. 2011;8:354–360. doi:10.2174/156720511795745320
15. Albert MS, Jones K, Savage CR, et al. Predictors of cognitive change in older persons: MacArthur studies of successful aging. *Psychol Aging*. 1995;10:578–589. doi:10.1037/0882-7974.10.4.578

16. Bennett DA, Wilson R, Schneider J, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*. 2003;60:1909–1915. doi:10.1212/01.WNL.0000069923.64550.9F
17. Roe CM, Mintun MA, D'Angelo G, Xiong C, Grant EA, Morris JC. Alzheimer disease and cognitive reserve: variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake. *Arch Neurol*. 2008;65:1467–1471. doi:10.1001/archneur.65.11.1467
18. Pike KE, Ellis KA, Villemagne VL, et al. Cognition and beta-amyloid in preclinical Alzheimer's disease: data from the AIBL study. *Neuropsychologia*. 2011;49:2384–2390. doi:10.1016/j.neuropsychologia.2011.04.012
19. Malek-Ahmadi M, Lu S, Chan Y, Perez SE, Chen K, Mufson EJ. Static and dynamic cognitive reserve proxy measures: interactions with Alzheimer's disease neuropathology and cognition. *J Alzheimer's Dis Parkinson*. 2017;7:390. doi:10.4172/2161-0460.1000390
20. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55:306–319. doi:10.1002/ana.20009
21. Van der Linden M, Wyns C, Coyette F, Von Frankell R, Seron X. *Le Q.A.M., Questionnaire d'auto-évaluation de la mémoire*. Bruxelles: Editest; 1989.
22. Clement F, Belleville S, Gauthier S. Cognitive complaint in mild cognitive impairment and Alzheimer's disease. *J Int Neuropsychol Soc*. 2008;14:222–232. doi:10.1017/S1355617708080260
23. Barbeau E, Didic M, Tramoni E, et al. Evaluation of visual recognition memory in MCI patients. *Neurology*. 2004;62:1317–1322. doi:10.1212/01.WNL.0000120548.24298.DB
24. Tulsky DS, Chiaravalloti ND, Palmer BW, Chelune GJ. Chapter 3 - The wechsler memory scale, third edition: a new perspective. *Clinical Interpretation of the WAIS-III and WMS-III*. San Diego: Academic Press; 2003:93–139. doi:10.1016/B978-012703570-3/50007-9

25. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695–699. doi:10.1111/j.1532-5415.2005.53221.x
26. Carson N, Leach L, Murphy KJ. A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. *Int J Geriatr Psychiatry*. 2018;33:379–388. doi:10.1002/gps.4756
27. Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24:709–711.
28. Schmidt M. Rey Auditory Verbal Learning Test: A Handbook. Los Angeles, CA: Western Psychological Services; 1996.
29. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
30. Drolet V, Vallet GT, Imbeault H, et al. A comparison of the performances between healthy older adults and persons with Alzheimer's disease on the Rey auditory verbal learning test and the Test de rappel libre/rappel indicé 16 items. *Geriatr Psychol Neuropsychiatr Vieil*. 2014;12:218–226.
31. Storandt M, Hill RD. Very mild senile dementia of the Alzheimer type: Ii. psychometric test performance. *Arch Neurology*. 1989;46:383–386. doi:10.1001/archneur.1989.00520400037017
32. Wechsler D. *Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV).* San Antonio, Texas: Psychological Corporation; 2014.
33. Rentz DM, Mormino EC, Papp KV, Betensky RA, Sperling RA, Johnson KA. Cognitive resilience in clinical and preclinical Alzheimer's disease: the Association of Amyloid and Tau Burden on cognitive performance. *Brain Imaging Behav*. 2017;11:383–390. doi:10.1007/s11682-016-9640-4

34. Brayne C, Ince PG, Keage HA, et al. Education, the brain and dementia: neuroprotection or compensation? EClipSE Collaborative Members. *Brain*. 2010;133:2210–2216. doi:10.1093/brain/awq185

35. Arenaza-Urquijo EM, Bejanin A, Gonneaud J, et al. Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: neuroimaging evidence for protection and compensation. *Neurobiol Aging*. 2017;59:72–79. doi:10.1016/j.neurobiolaging.2017.06.016

36. Landau SM, Marks SM, Mormino EC, et al. Association of lifetime cognitive engagement and low beta-amyloid deposition. *Arch Neurol*. 2012;69:623–629. doi:10.1001/archneurol.2011.2748

37. Hayes AF. PROCESS: a versatile computational tool for observed variable mediation, moderation, and conditional process modeling. 2012. *Acesso em*. 2016;2.

38. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, 3rd ed. New York, NY: Oxford University Press; 2006:xvii, 1216-xvii.

39. Roe CM, Xiong C, Miller JP, Cairns NJ, Morris JC. Interaction of neuritic plaques and education predicts dementia. *Alzheimer Dis Assoc Disord*. 2008;22:188–193. doi:10.1097/WAD.0b013e3181610fff

40. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn Sci*. 2013;17:502–509. doi:10.1016/j.tics.2013.08.012

41. Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer disease: Clarifying terminology for preclinical studies. *Neurology*. 2018;90:695–703. doi:10.1212/WNL.0000000000005303

42. Kramer AF, Bherer L, Colcombe SJ, Dong W, Greenough WT. Environmental influences on cognitive and brain plasticity during aging. *J Gerontol A Biol Sci Med Sci*. 2004;59:M940–M957. doi:10.1093/gerona/59.9.M940
43. Jagust WJ, Mormino EC. Lifespan brain activity, beta-amyloid, and Alzheimer's disease. *Trends Cogn Sci*. 2011;15:520–526. doi:10.1016/j.tics.2011.09.004
44. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*. 1994;271:1004–1010. doi:10.1001/jama.1994.03510370056032
45. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc*. 2002;8:448–460. doi:10.1017/S1355617702813248
46. Vemuri P, Lesnick TG, Przybelski SA, et al. Effect of lifestyle activities on Alzheimer disease biomarkers and cognition. *Ann Neurol*. 2012;72:730–738. doi:10.1002/ana.23665
47. Rentz DM, Locascio JJ, Becker JA, et al. Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol*. 2010;67:353–364. doi:10.1002/ana.21904
48. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20 (3 Suppl 2):S69–S74. doi:10.1097/01.wad.0000213815.20177.19
49. Craik FI, Bialystok E, Freedman M. Delaying the onset of Alzheimer disease: bilingualism as a form of cognitive reserve. *Neurology*. 2010;75:1726–1729. doi:10.1212/WNL.0b013e3181fc2a1c
50. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10:819–828. doi:10.1016/S1474-4422(11)70072-2