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Education is associated with sub-regions of the hippocampus and the amygdala vulnerable to neuropathologies of Alzheimer's disease

Xiaoying Tang^{a,b,*}, Vijay R. Varma^{c,d}, Michael I. Miller^{e,f,g}, and Michelle C. Carlson^{c,d,*}

^aSun Yat-sen University-Carnegie Mellon University (SYSU-CMU) Joint Institute of Engineering, Sun Yat-sen University, Guangzhou, Guangdong, China

^bSun Yat-sen University-Carnegie Mellon University (SYSU-CMU) Shunde International Joint Research Institute, Shunde, Guangdong, China

^cDepartment of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

^dCenter on Aging and Health, Johns Hopkins University, Baltimore, MD, USA

^eCenter for Imaging Science, Johns Hopkins University, Baltimore, MD, USA

^fInstitute for Computational Medicine, Johns Hopkins University, Baltimore, MD, USA

^gDepartment of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA

Abstract

We evaluated the correlation of educational attainment with structural volume and shape morphometry of the bilateral hippocampi and amygdalae in a sample of 110 non-demented, older adults at elevated sociodemographic risk for cognitive and functional declines. In both men and women, no significant education-volume correlation was detected for either structure. However, when performing shape analysis, we observed regionally specific associations with education after adjusting for age, intracranial volume, and race. By sub-dividing the hippocampus and the amygdala into compatible subregions, we found that education was positively associated with size variations in the CA1 and subiculum subregions of the hippocampus and the basolateral subregion of the amygdala ($p < 0.05$). In addition, we detected a greater left versus right asymmetric pattern in the shape-education correlation for the hippocampus but not the amygdala. This asymmetric association was largely observed in men versus women. These findings suggest that education in youth may exert direct and indirect influences on brain reserve in regions that are most vulnerable to the neuropathologies of aging, dementia, and specifically, Alzheimer disease.

Keywords

Brain reserve; cognitive reserve; education; hippocampus; amygdala; shape

*Corresponding author: Xiaoying Tang, tangxiaoy@mail.sysu.edu.cn, Phone: (+1) 410-949-0497, Fax: (+1) 412-268-2860, Address: 250 Roberts Engineering Hall, 5000 Forbes Avenue, Pittsburgh, 15213, PA, USA. Michelle C. Carlson, mcarlso2@jhu.edu, Phone: (+1) 410-790-8205, Fax: (+1) 410-614-9625, Address: Department of Mental Health, Hampton House 805, 624 N. Broadway St., Baltimore, 21205, MD, USA.

1 Introduction

Cognitive reserve, or resilience (CR) refers to differences in cognitive processes, as a function of lifetime intellectual activities and environmental factors, that explain differential susceptibility to functional impairment (Stern 2002; Stern 2009; Barulli and Stern 2013). CR compensates for the eroding effect of brain pathology, allowing people with the same clinical status to cope differently in the face of the same degree of pathology, especially in the context of aging and Alzheimer disease (AD) (Stern et al. 1992; Stern et al. 1994; Letenneur et al. 1999; Fritsch et al. 2002). As one of the most influential aspects of life experience, educational attainment has been proposed by Stern to contribute to increased cognitive flexibility and efficiency over the life course (subsequently including occupation and leisure-time activity), and can be considered an index or proxy of CR (Scarmeas and Stern 2003). A number of studies have shown that an individual's level of education is tightly linked to their cognitive ability (Evans et al. 1993; Farmer et al. 1995; Stern et al. 1999; Bennett et al. 2003; Zahodne et al. 2014).

A second type of reserve, also suggested to help buffer between brain pathology and cognitive performance, is brain reserve (BR) (Satz 1993) where a larger brain volume contributes to a preservation of cognitive function and an accommodation of a greater degree of pathology. In addition to whole brain based quantities (Graves et al. 1996; Schofield et al. 1997; Jenkins et al. 2000; Mortimer et al. 2003; Wolf et al. 2003; Perneczky et al. 2010), measures of medial temporal lobe structures, such as the hippocampus and the amygdala, emerge as potentially important markers of BR (Chelune 1995; Erten-Lyons et al. 2009; Ali et al. 2009; Cavado et al. 2012). The hippocampus has been shown to be critical to memory formation (Squire 1992; Burgess et al. 2002; Fortin et al. 2002). The amygdala, because of its neural connections to the hippocampus, has also been identified as being intimately associated with emotion-related memory cognitive function (Mishkin 1978; McDonald and White 1993; LeDoux 1993; McGaugh 2004; Phelps 2004). Extensive evidence, obtained from both cross-sectional and longitudinal studies, has shown that hippocampal and amygdalar atrophies serve as important anatomical precursors of AD (Cuénod et al. 1993; Basso et al. 2006; Horinek et al. 2007; Tang et al. 2014; Miller et al. 2015; Tang et al. 2015c), and these two structures are also plastic in response to chronic stressors (McEwen and Gianaros 2010) and environmental enrichment (Kempermann et al. 1997; Draganski et al. 2006).

CR and BR are complementary concepts. BR can be considered a passive model of reserve related to physiological capacity while CR can be considered as an active model of reserve related to compensatory processes that are influenced by education and other behavioral factors (e.g., physical activity) (Stern 2009). These two reserve components are inter-related; in particular, certain life experiences and behaviors associated with CR (e.g., education) can have direct effects on the brain and influence how one can make use of BR (Tucker and Stern 2011).

Given the intimate association between education and CR, the compatible and complementary relationship between CR and BR, and the evidence that the hippocampal and

the amygdalar volumetric measures (the volume size of the entire structure) are important indices of BR, it is natural to hypothesize that educational attainment in early life is associated with quantitative measures of those structures in later life. Such associations are relatively unexplored; the study by (Piras et al. 2011) was the only previous work of which we are aware that has specifically analyzed the association between education and the hippocampal volumetric measures, with no significant correlation detected. Furthermore, another study observed that neither hippocampal nor amygdalar volumes showed a significant correlation to education (Soininen et al. 1994). The lack of associations observed between these structural volumes and education may be due to the use of global volumetric measures rather than specific measures of subregions related to plasticity and memory formation, such as the CA1 subregion of the hippocampus. As a result, these global measures may mask significant and informative regionally specific correlations with education. In addition, while volumetric measures have generally been proven valuable when measuring BR, more granular and specific metrics related to the function of specific subregions of the hippocampus merit consideration.

To explore the local properties of a structure without predefining morphologic properties, we modeled its surface as a triangulated 2-D mesh and performed statistical shape analysis. In older adults, shape analysis has been widely employed to examine the correlation between localized structural surface morphometrics and AD's progression as well as brain behavior and function (Thompson et al. 2004; Chou et al. 2009; Tondelli et al. 2012; Carmichael et al. 2012; Tang et al. 2015b; Tang et al. 2015c).

In this paper, we will test the hypothesis that higher educational attainment in youth is associated with larger surface areas of certain regions of the bilateral hippocampi and amygdalae in a cohort of nondemented older adults enrolled in the Brain Health Study (BHS) of the Baltimore Experience Corps Trial. It is important to note that while educational attainment itself may be impacted by individual differences in cognitive capacity, based on our cognitive exclusion criteria (described below) we considered all individuals in the study as having equivalent cognitive capacity for educational attainment. This approach is consistent with that used by Stern and colleagues in prior work on CR (Stern et al. 1992; Stern et al. 1994; Stern 2009; Stern 2012). The BHS was designed to extend upon results observed in our Experience Corps® (Carlson et al. 2015) pilot studies of primarily (Carlson et al. 2008) and solely (Carlson et al. 2009), female volunteer samples by recruiting a sufficient number of men to allow for a formal evaluation of mechanistic benefits of volunteer service to men and women (Chuang et al. 2014; Carlson et al. 2015). Sex-stratification was included in the design of the BHS given reported sex differences in brain morphometry and risk for age-related neuropathologies, including AD (Lessov-Schlaggar et al. 2005; Mielke et al. 2014) and vascular dementia (Cherbuin et al. 2015). Therefore, in this study, our primary interest will be the investigation of sex-dependent correlations, in terms of both spatial patterns and correlation magnitudes.

2 Materials and Method

2.1 Participants

Participants were from the Brain Health Study (Carlson et al. 2015), a trial nested within the larger Baltimore Experience Corps Trial (BECT). The BECT was a sex-stratified, randomized, controlled effectiveness trial aiming to evaluate the health benefits for older adults participating in Experience Corps® Baltimore, a high-intensity volunteer service program, versus a control group offered other low-intensity volunteer opportunities. Details on sex-stratification, randomization, study design, sampling methodology, and recruitment have been described elsewhere (Fried et al. 2013). BHS enrollment criteria have been described elsewhere (Chuang et al. 2014; Carlson et al. 2015) and included being 60 years of age or older; having a score of 24 or higher on the MMSE; minimum sixth grade reading level on the Wide Range Achievement Test (Wilkinson 1993); right-hand dominance; free of a pacemaker or other ferrous metals in the body; no history of brain cancer or brain aneurism/stroke in the past year. Participants were not screened for mental disorders or medication use. Self-reported educational attainment was measured by asking participants how many total years of formal education they had completed prior to randomization into the BECT. Depressive symptoms were measured using the short form of the Geriatric Depression Scale (GDS) (Yesavage et al. 1983; Yesavage et al. 2000).

From 2006–2009, 702 participants were randomized into the BECT. Of those, 123 participants agreed to participate and were simultaneously randomized into the BHS. BHS participants did not differ from the remaining BECT participants on any socio-demographic or health characteristic at baseline other than sex; by design the BHS over-sampled for men (Fried et al. 2013; Carlson et al. 2015). Among the 123 participants enrolled in BHS, 10 did not complete the magnetic resonance imaging (MRI) evaluation because of excessive head movement or claustrophobia, and one participant did not provide education data. Among the remaining 112 participants, two MRI scans were of poor quality resulting in their exclusion from our analyses.

The final sample used in our analysis thus comprised 110 participants. This study was approved by the Johns Hopkins School of Medicine Institutional Review Board, and each participant provided written informed consent. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2 Verbal memory

Verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) (Rey 1941). The RAVLT is widely used to measure memory in older adults (Lezak et al. 2012) with good validity and reliability (Strauss et al. 2006). The RAVLT is comprised of a list-learning test, and an interference test followed by short and delayed tests. Participants were presented with a 15-word list and asked to recall words for five learning trials, followed by an interference trial with words not included in the original list. A total learning score was calculated by summing the first five trials in the list-learning test.

2.3 MRI dataset and volumetric segmentation

High-resolution T1-weighted 3D-volume MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) brain images were acquired from a 3.0 T Phillips scanner (Best, the Netherlands) with the following parameters: repetition time = 8.037 ms; echo time = 3.7 ms; flip angle = 8°; 200 contiguous 1 mm sagittal slices; field of view = 200 mm × 256 mm × 200 mm; matrix size = 256 mm × 256 mm; and voxel size = 1 mm × 1 mm × 1 mm. The imaging protocol has been described previously (Carlson et al. 2015).

For each T1-weighted image, volumetric segmentations of the bilateral hippocampi and amygdalae were automatically obtained from a hierarchical segmentation pipeline (Tang et al. 2015a) consisting of two steps; skull-stripping and brain structure segmentation. This hierarchical segmentation pipeline is built upon a two-level multi-atlas likelihood-fusion algorithm in the framework of the random deformable template model (Tang et al. 2013). In this study, we used 16 atlases (a subset of the BHS sample) with the four structures of interest (bilateral hippocampi and amygdalae) manually delineated by a neuroanatomist with more than 15 years of experience in manual tracing. The accuracy of this hierarchical pipeline in segmenting the bilateral hippocampi and amygdalae of our BHS scans was evaluated using a leave-one-out strategy; one atlas image was treated as the to-be-segmented image and the remainder served as the atlas set to segment that excluded image. The segmentation accuracy was quantified using the Dice overlap (Dice 1945) by comparing the automated segmentations with the corresponding manual ones. From this leave-one-out experiment, we obtained Dice overlaps of 0.91 ± 0.03 for the left hippocampus, 0.92 ± 0.04 for the right hippocampus, 0.84 ± 0.03 for the left amygdala, and 0.85 ± 0.04 for the right amygdala, computed across the 16 atlases. The mean volumetric measurements and the corresponding standard deviations for each of the four structures of interest, for the sex-stratified sample, are listed in Table 1. In addition to the quantitative evaluation, we also visually examined the segmentation results. No participant was excluded due to volumetric segmentation failure.

2.4 Shape processing

After obtaining the volumetric segmentations of the bilateral hippocampi and amygdalae for each of the 110 T1-weighted images, we created a 2-D triangulated surface contouring the boundary of each 3-D volumetric segmentation based on an approach similar to the one that has been validated and detailed elsewhere (Tang et al. 2014). Briefly, for each 3-D volumetric segmentation corresponding to each structure of interest, its bounding surface was obtained by applying an optimized diffeomorphism to a template surface of that specific structure. The template surface for each of the structures of interest was created manually, ensuring sufficient smoothness and correct anatomical topology. The optimized diffeomorphism was obtained using a Large Deformation Diffeomorphic Metric Mapping (LDDMM) image registration (Beg et al. 2005), mapping the template segmentation to the scan-specific segmentation of the same structure. This surface-generation methodology was used to create the target shapes whose localized surface areas were then analyzed.

The vertex-wise surface areas of each target shape were quantified by a diffeomorphism that connected a common template shape to that target shape. To create the common template

shape, we generated a “population-averaged” template surface, for each structure of interest, using all of the 110 target surfaces based on the template estimation algorithm (Ma et al. 2010). Using an averaged template surface lying in the center of the population allows for more accurate mappings between the template surface and each target surface compared to using an arbitrary single template surface (Qiu et al. 2010).

After generating the structure-specific common template surface, we used the LDDMM-surface mapping algorithm (Vaillant and Glaunès 2005) to map the common template surface to each individual target surface. From each template-to-target LDDMM-surface mapping, a scalar field was subsequently calculated as the log-determinant of the Jacobian of the diffeomorphism. This scalar field is indexed at each vertex of the common template surface, quantifying the factor by which the diffeomorphism expands or shrinks the vertex-based localized surface area in the target relative to the template in a logarithmic scale; i.e. a positive value corresponds to a localized surface area expansion of the subject relative to the template while a negative value suggests a localized surface area contraction. This scalar field is referred to as the deformation marker. This deformation marker, indexed at each vertex of the template surface, was correlated with educational attainment. Specific details on the methodology and validation of each step of the shape processing pipeline can be found in (Tang et al. 2014), (Ma et al. 2010), and (Vaillant and Glaunès 2005).

2.5 Correlation analysis

We were interested in exploring associations between education and RAVLT as a behavioral correlate to strengthen the biological plausibility of our finding for the association between education and hippocampal shape, and particularly for the plausible left-versus-right asymmetry. Therefore, we first correlated educational attainment (in years) and the sum of the five RAVLT trial scores. We further correlated education and morphometry for both global volumes and localized shape measures in the bilateral hippocampi and amygdalae. The Pearson product-moment correlation coefficient (PCC) was employed to quantify the correlation strength. In all of our correlation analyses, we included the following covariates; age, intracranial volume (ICV), which was automatically obtained from FreeSurfer (version 5.1.0) (Buckner et al. 2004), and race (African American vs. none Africa American). The statistical significance of a correlation is measured by a p -value obtained from non-parametric permutation tests with a total of 40,000 permutations employed. To correct for multiple correlation tests being performed simultaneously at all vertices of the template surface, we adjusted the p -values to control for familywise error rate (FWER) at a level of 0.05 based on the “maximum statistic” method (Nichols and Hayasaka 2003; Groppe et al. 2011). All correlation analyses were performed separately for men and women.

2.6 Template surface sub-division

To identify the anatomical subregions on the hippocampus and the amygdala, we divided our template surface for each of the four structures into multiple anatomical subregions using the approach detailed in (Tang et al. 2014). This sub-division was accomplished by manually sub-dividing surfaces of high-field segmentations (obtained from a 7 Tesla scanner with an image voxel resolution of 0.8 mm) and transferring the boundary definitions of those subregions to our population template surfaces. Both the left and right amygdala were sub-

divided into four subregions; the basolateral, the basomedial, the centromedial, and the lateral nucleus. Both of the bilateral hippocampi were sub-divided into four subregions; CA1, CA2, CA3 combined with the dentate gyrus, and the subiculum.

3 Results

3.1 Characteristics of study participants

The demographic characteristics of the scans used in this analysis are presented in Table 1. Women averaged 67.4 years of age, had an average of 13.6 years of education, and 93.6% were African American. Men averaged 66.7 years of age, had an average of 14.3 years of education, and 87.5% were African American. On average, women had a marginally lower level of education compared to men (p -value = 0.17). There were no statistically significant sex differences in age (p -value = 0.54) or MMSE (p -value = 0.60). Participants had very low GDS scores, with an average of 1.25 out of 15 total points; GDS scores did not vary significantly by sex (p -value = 0.55). For each of the four structures of interest, women exhibited significantly smaller volume than men (p -value $< 1e^{-7}$) after adjusting for ICV. Sex differences in the demographic characteristics were tested using the Student's t -test.

3.2 Correlation analysis

As expected, a greater number of years in education was positively correlated with verbal memory, in terms of the RAVLT total learning score, in both men and women, with a stronger correlation in men (PCC = 0.4104, p -value = 0.0178) than in women (PCC = 0.1324, p -value = 0.0561).

There were no statistically significant correlations between education and the global volumetric measures of the bilateral hippocampi and amygdalae in men or women.

3.3 Localized shape correlation analysis

The maps of correlation between educational attainment and the vertex-wise surface areas of the bilateral hippocampi and the bilateral amygdalae are displayed in Figure 1 and Figure 2 respectively; PCCs are charted only for vertices whose surface areas correlated statistically significantly with educational attainment after performing multiple comparison correction by controlling the FWER at a level of 0.05. In each figure, panel (a) denotes the vertex-wise PCC values obtained in correlating the localized surface area and educational attainment in women, panel (b) denotes the vertex-wise PCC values of the correlation analysis in men, and panel (c) denotes the anatomical sub-divisions of the template surfaces into the four compatible subregions. In addition to the spatial correlation maps, in Table 2 we give both the amount of surface area and the corresponding percentage thereof, relative to the structure's total surface area, that are represented by vertices whose surface areas correlated significantly with educational attainment after multiple comparison correction. Values tabulated in Table 2 were obtained by 1) measuring the significance of the correlation between localized surface area and educational attainment at each vertex of a structure of interest; 2) performing multiple comparison correction by controlling the FWER at a level of 0.05; and 3) measuring the total area (in mm²) of the subset of vertices that survive

correction as well as the corresponding percentage relative to the total surface area of the entire structure.

The hippocampal shape correlation results, presented in Figure 1 and Table 2, show a left-lateralized pattern, with a stronger shape-education correlation in the left hippocampus compared to that in the right hippocampus, and much stronger correlations in men compared to women as indicated by both the correlation strength and the amount of surface vertices that were significantly correlated (men (left hippocampus, right hippocampus): 18.4 %, 2.1%; women: 0.2%, 4.6%). Spatial correlation patterns were also sex-dependent. As indicated in Figure 1, in men vertices belonging to the CA1, CA2, and subiculum sub-regions of the left hippocampus were significantly positively correlated to education. A few vertices in the subiculum sub-region of the left hippocampus were negatively correlated with education in men. In women, the education-shape associations were weaker. In the left hippocampus, a very few vertices belonging to part of the CA1 sub-region were positively correlated with education. Similar to men, vertices belonging to parts of the CA1 and CA2 sub-regions of the right hippocampus were also positively correlated to education in women.

The amygdalar shape correlations, as presented in Figure 2 and Table 2, show much weaker shape-education correlation patterns compared to the hippocampal results, yet similar sex-dependent correlations. In women, none of the bilateral amygdalar vertices were significantly correlated with education. In men, 2.3% and 5.6% of the left and right amygdalar surface vertices, respectively, correlated significantly with education, indicating a modest right-lateralized pattern. Vertices with significant shape-education correlations in men were mainly found in the basolateral amygdala sub-region (see panel (b) of Figure 2).

4 Discussion

In this study, we used a novel shape diffeomorphometry-based analysis method to explore the associations between educational attainment and both memory and structural morphometry (global volumetric measures and localized surface areas) of the bilateral hippocampi and amygdalae in an educationally diverse sample of community-dwelling men and women. In line with prior studies, we found significant correlations between education and memory in men and women (Schmand et al. 1997; Stern et al. 1999). Using our novel shape analysis method, we additionally observed significant region-specific correlations between sub-regions of the hippocampus and amygdala that were not detectable using global volumetric measures, especially in men. These shape-based spatial correlations in men improve our understanding of the potentially specific relationships between brain reserve that are intended to inform our understanding of the biological pathways through which intellectual enrichment influences cognitive health and risk for Alzheimer's disease.

Our finding of a significant positive correlation between education and verbal memory corresponds well with prior evidence suggesting that education contributes to cognitive resilience (Evans et al. 1993; Stern et al. 1994; Farmer et al. 1995; Stern et al. 1999; Fritsch et al. 2002; Bennett et al. 2003; Hall et al. 2007; Roe et al. 2007; Bruandet et al. 2008; Garibotto et al. 2012; Sattler et al. 2012) and has motivated our exploration of correlations between education and volumetric measures of brain structures relevant to brain reserve.

In sex-stratified analyses, we did not observe significant correlations between education and global volumes for the bilateral hippocampi and amygdalae. This finding is generally consistent with the results from other studies (Soininen et al. 1994; Piras et al. 2011). However, a more refined education-morphometry analysis, considering the correlation between educational attainment and vertex-based surface areas, suggests that education affects the morphometry of the hippocampus and the amygdala in a more localized manner.

As revealed by the spatial correlation maps in Figure 1, we observed a left asymmetric pattern in the hippocampal shape-educational correlation primarily in men. Elsewhere, it has been suggested that the left hippocampus is more vulnerable to the pathology of AD than the right hippocampus (Müller et al. 2005). This may suggest that educational attainment is more likely to exert beneficial influences (greater resistance to pathology) in brain regions that are most vulnerable to AD pathology. Additionally, in the left hippocampus, vertices with significant correlations to education were found to be part of the CA1 and subiculum subregions, the two subregions that are generally recognized as being affected earliest and most substantially by the pathology of AD (Braak and Braak 1995; Rossler et al. 2002; Schonheit et al. 2004; Wang et al. 2006; Tang et al. 2014). Another mutually plausible explanation for this asymmetric hippocampal correlation is that education increases the hippocampal reserve in a more lateralized manner. It has been suggested that education can generally increase intellectual ability and literacy skills and such increases may affect the left hippocampus more than the right given that the left hippocampus is more associated with the retrieval of verbal material (Locascio et al. 1995) whereas the right hippocampus is more associated with visuo-spatial memory (de Toledo-Morrell et al. 2000) which may be less affected by education.

Significant regionally specific shape-education correlations were also detected in the amygdala in men. Similar to our finding in the hippocampal shape analysis, educational attainment correlated to the amygdalar surface areas more so in men than in women (see Figure 2). As shown in panel (b) of Figure 2, for both the left and the right amygdala for men, the vertices with significant correlation to education were mainly observed in the basolateral subregion, the subregion of the amygdala that has been shown to be the most affected and the earliest affected in mild cognitive impairment (MCI) and AD (Tang et al. 2014; Tang et al. 2015c). This finding bolsters our conclusion that education positively affects brain regions that are vulnerable to AD pathology. The weaker correlations and asymmetric patterns observed in the amygdala, as compared to the hippocampus, suggest that other lifestyle factors may affect age-related changes in the amygdala, including chronic stress and environmental enrichment (McEwen and Gianaros 2010).

For both the hippocampus and the amygdala, we found a clear sex difference in their surface area correlation with educational attainment. Overall, the surface areas of each of these four structures are more strongly correlated with education in men than in women. This may be because men are more susceptible to age-related brain changes than women (Gur et al. 1991; Murphy DM, DeCarli C, McIntosh AR, et al 1996) so that, at the same level of pathology, early educational attainment provides greater brain reserve in men than in women. Multiple hypotheses regarding the reasons for sex differences in brain aging have been considered, including more active female immune functioning, the protective effect of estrogen,

compensatory effects of the second X chromosome, and reduction in the activity of growth hormone (Austad 2006; Oksuzyan et al. 2008). There may also be indirect effects of education over the life course through its influence on occupation, socioeconomic status (Carlson et al. 2012) and other risk exposures (Nordahl et al. 2014) that may make it more likely that associations would be detected in men, however as presented in Table 1, variability in brain volume (as indicated by the standard deviations) was similar between men and women. Another possible explanation for sex differences in our study may be related to evidence suggesting that men, in the mid-20th century may have had more educational opportunities and higher quality of education compared to women (Manly et al. 2002; Stern et al. 2005). While the mean total years of education did not vary between men and women in this study, differences in quality of education may contribute to a lower correlation between education and shape morphometry in women compared to men.

Broadly, our observation of sex differences is consistent with existing evidence that men have higher overall brain reserve than women (Perneczky et al. 2007). This sex difference was mirrored in our education-to-memory correlations where the association between education and verbal memory was much stronger in men than it was in women (PCCs being 0.4104 versus 0.1324 for men versus women). The stronger associations in men than in women between education and measures of cognitive resilience and brain reserve were highly consistent in this study.

Given that education is a key component of socioeconomic status (SES) obtained early on in the course of life, a natural continuation of this work is to explore the association between brain reserve and other components of SES obtained later in life, such as literacy (Manly et al. 2003) and income (Richards and Sacker 2003). It would also be of great importance to investigate the interactive effects of various aspects of SES on brain reserve; for example, whether early education's associations with brain reserve may be independent of income in midlife or interact with income to exert combined effects on brain reserve. Such an interaction between education and income has already been demonstrated to actively affect cognitive resilience (Zahodne et al. 2014). Additionally, recent studies have suggested that the effects of cognitive and social activities on cognitive resilience differ based on one's educational attainment. Participants included in this study were part of a longitudinal trial testing the effects of a multimodal intervention, including cognitive and social activity components (Fried et al. 2013; Parisi et al. 2015). Future work on this sample will be able to provide insight into whether activity interventions exert a greater impact on cognitive and brain health among those with lower educational attainment.

This study has a number of limitations. First, one needs to be cautious when drawing strong conclusions regarding the effects of education on brain anatomy from cross-sectional studies. To overcome this limitation, we have collected longitudinal data that will allow us to examine the effect of education and other forms of environmental enrichment on the morphometry of the hippocampus and the amygdala. Second, this study included a relatively small sample, with a limited age range, and it was not designed to disentangle the possible effects of education on brain development nor its association with SES.

To our knowledge, this study is the first to explore the associations between educational attainment and sub-regions of the hippocampus and the amygdala in a nondemented, community-dwelling cohort. Use of this shape analysis method allowed us to explore with greater regional specificity the associations between education and brain reserve and can be extended to inform our understanding of how the brain benefits from intellectual and environmental enrichment to reduce the risk for AD in a group at elevated sociodemographic risk for cognitive and functional declines.

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Fig. 1.

Panel (a) and panel (b) represent the spatial hippocampal surface maps in correlating educational attainment with vertex-based surface areas in women and men respectively. The color bar denotes the PCC values, which were plotted only for vertices whose correlations were statistically significant after a multiple comparison correction. Panel (c) represents subdivisions of the template surfaces into four compatible subregions: CA1, CA2, CA3 combined with the dentate gyrus, and the subiculum

Fig. 2.

Panel (a) and panel (b) represent the amygdalar surface maps in correlating educational attainment with vertex-based surface areas in women and men respectively, wherein the color bar denotes the PCC values that were plotted only for vertices whose correlations were statistically significant after a multiple comparison correction. Panel (c) represents sub-divisions of the template surfaces into four compatible subregions: the basolateral, basomedial, centromedial, and the lateral nucleus

Table 1

Baseline characteristics of the Brain Healthy Study subjects used in this study (N = 110).

	Female (N = 78)	Male (N = 32)
Age (years)	67.4 ± 6.0	66.7 ± 6.4
Race (African American)	73 (93.6%)	28 (87.5%)
Education (years)	13.6 ± 2.7	14.3 ± 3.0
MMSE	28.4 ± 1.4	28.2 ± 1.5
GDS	1.1 ± 1.6	1.7 ± 2.7
Structure Volume		
left amygdala	1074.3 ± 117.7	1230.3 ± 139.5
right amygdala	1083.1 ± 140.0	1266.5 ± 128.5
left hippocampus	2752.2 ± 241.4	3056.7 ± 235.9
right hippocampus	2941.8 ± 238.8	3250.0 ± 250.2

^a Adjusted for intracranial volume (ICV).

MMSE – Mini Mental State Exam; GDS – Geriatric Depression Scale.

Table 2

The amount (percentage and raw value) of surface area of each structure showing statistically significant correlation with educational attainment after multiple comparison correction at a level of 0.05.

	Female	Male
Left amygdala	0.0% (0.0 mm ²)	2.3% (14.1 mm ²)
Right amygdala	0.0% (0.0 mm ²)	5.6% (34.2 mm ²)
Left hippocampus	0.2% (2.5 mm ²)	18.4% (285.2 mm ²)
Right hippocampus	4.6% (75.0 mm ²)	2.1% (33.6 mm ²)