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RESEARCH ARTICLE

Health literacy, but not memory, is associated with hippocampal connectivity in adults with low levels of formal education

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Abstract

INTRODUCTION: The influence of hippocampal connectivity on memory performance is well established in individuals with high educational attainment. However, the role of hippocampal connectivity in illiterate populations remains poorly understood.

METHODS: Thirty-five illiterate adults were administered a literacy assessment (Test of Functional Health Literacy in Adults [TOFHLA]), structural and resting state functional magnetic resonance imaging, and an episodic memory test (Free and Cued Selective Reminding Test). Illiteracy was defined as a TOFHLA score < 53. We evaluated the correlation between hippocampal connectivity at rest and both free recall and literacy scores.

RESULTS: Participants were mostly female (57.1%) and self-declared as being Black individuals (84.8%), with a median age of 50 years. The median TOFHLA literacy score was 28.0 [21.0; 42.5] out of 100 points and the median free recall score was 30.0 [26.2; 35] out of 48 points. The median gray matter volume of both the left and right hippocampi was 2.3 [2.1; 2.4] cm^3. We observed a significant connectivity between both hippocampi and the precuneus and the ventral medial prefrontal cortex. The right hippocampal connectivity positively correlated with the literacy scores ($\beta = 0.58$, $P = 0.008$). There was no significant association between episodic memory and hippocampal connectivity. Neither memory nor literacy scores correlated with hippocampal gray matter volume.

DISCUSSION: Low literacy levels correlated with hippocampal connectivity in illiterate adults. The lack of association with memory scores might be associated with low brain reserve in this sample.

KEYWORDS
cognitive reserve, episodic memory, hippocampal connectivity, illiteracy

Highlights

- A significant link was found between health literacy and hippocampal connectivity.
- Enhanced hippocampus– ventromedial prefrontal cortex connectivity suggests potential cognitive reserve improvement.
- Higher cognitive reserve may protect against hippocampal atrophy and neurodegeneration.
- Health literacy improvements could help prevent cognitive impairment in illiterate populations.
- Study highlights importance of considering structural racism in brain connectivity research.

1 | INTRODUCTION

Life expectancy is increasing in low- and middle-income countries (LMIC) with the prevalence of dementia rapidly rising.[1] Preventing dementia is a powerful strategy to mitigate the high burden of the disease because dementia has no curative treatments and the disease-modifying drugs for Alzheimer's disease (AD) have a high cost and are only suitable to a limited group of patients.

In LMIC 48% of dementia cases could be prevented by controlling 12 modifiable dementia risk factors[2] with low educational level accounting for an important proportion of risk. Dementia prevalence and incidence are significantly higher in illiterate older adults.[3,4] Low educational attainment accounts for up to 19% of dementia cases in high-income countries (HIC) and up to 30% in LMIC.[2] An increase in educational attainment in HIC is believed to have contributed to the recently observed decline in dementia incidence.[5] In the Framingham Heart Study, the incidence of dementia is declining only among persons who have at least a high-school degree.[6] However, in Brazil, a LMIC, low educational level is typically defined as having $<$ 8 years of formal education.[7] Although other socioeconomic determinants of health associated with high education may play a role in the apparent protective trends, evidence supports education as an independent factor leading to lower risk of dementia.[8,9]

Literacy and formal education are tightly interconnected. Literacy is defined by the United Nations Educational, Scientific and Cultural Organization (UNESCO) as the abilities to read, write, and make simple arithmetic calculations as well as to use these abilities to communicate, understand, interpret, create, and be independent.[10] Individuals with low limited formal education tend to have low literacy levels. For this paper, we will use the term "literacy" as defined by UNESCO and the term "health literacy" as the applied knowledge about health conditions. Health literacy and literacy are closely related[11] because a person needs to have writing, reading, and numeracy abilities to understand and appropriately manage health conditions. Health illiteracy is associated with poor health outcomes.[12,13]

To capture the broader complexity of cognitive determinants of health conditions such as dementia, it is essential to consider some concepts like cognitive reserve, language skills, and emotion recognition. Cognitive reserve refers to distinct cognitive mechanisms, developed across the lifespan that make a person more resilient or resistant to cognitive decline caused by brain damage.[14] One aspect of this is hippocampal efficiency, which can be defined as the hippocampus's capacity to form and maintain effective neural connections with other brain regions, thereby supporting optimal cognitive performance, particularly in memory-related tasks. A higher level of cognitive reserve equips the brain to compensate through more efficient brain activation patterns that are more resilient to brain injury.[14] Higher levels of formal education and literacy are associated with better cognitive reserve.[15] Furthermore, language abilities like reading and writing are tied to formal education and literacy and should be explored in studies examining the role of health literacy in brain health. Emotion recognition is another ability linked to formal education and language skills,[16] though its association with health literacy has been less explored. Additionally, ethnicity plays a significant role in these complex relationships. For instance, Black individuals in the United States exhibit a faster cognitive decline[17] and higher incidence of dementia[18] compared to White individuals, which is likely related to lower socioeconomic levels, limited formal education, and stressful events experienced by many Black Americans in the United States.[19] By considering these factors, we can better understand the diverse influences on brain health and develop more targeted interventions to mitigate the risk of dementia across different populations.

AD is the leading cause of dementia.[20] One of the first areas of the brain affected by AD pathology is the hippocampus.[21] Research conducted on individuals with predominantly high levels of education indicate that the hippocampal structures and its connections are crucial for episodic memory performance.[22] However, the role of hippocampal connectivity in episodic memory performance remains a subject of debate, particularly in populations with lower educational attainment. Contributing to this debate are the fact that most studies have primarily focused on educated populations, leaving a gap in understanding how hippocampal connectivity functions in those with limited formal education. Individuals with lower education might have different neural strategies for memory processing, potentially relying less on hippocampal connectivity and more on other brain networks.[23,24] Different exposures to environmental factors such as lifelong learning experiences, occupational complexity, and engagement in cognitively stimulating activities in individuals with low education levels can modulate hippocampal connectivity and its relationship with memory performance.[25,26] For instance, less educated individuals may not develop the same level of hippocampal connectivity due to fewer opportunities for cognitive engagement, thus influencing how memory processes are supported neurologically.

Moreover, the default mode network (DMN), which includes the hippocampus and its connections with the medial prefrontal cortex, is crucial for memory processing.[27] The DMN's role in episodic memory has been well documented in educated individuals, but its functionality might differ in those with lower educational attainment. The DMN is known to be affected in patients with dementia of the amnestic type,[28] and understanding its role in less educated populations could provide insights into early detection and intervention strategies for cognitive decline. Therefore, we hypothesized that episodic memory would positively correlate with hippocampal connectivity in a sample of low-literate individuals.

Considering the previously described different patterns of brain activation and connectivity in literate and illiterate individuals,[29,30] we also aimed to investigate the association between hippocampal connectivity and literacy, specifically focusing on health literacy. We hypothesized that better health literacy would positively correlate with hippocampal connectivity.

By addressing these factors our study aims to contribute to a more nuanced understanding of how literacy, more specifically, health literacy, plays a role in hippocampal connectivity and memory. Understanding the brain mechanisms involved in episodic memory processing in low-literate individuals can help identify possible markers for successful interventions to enhance cognitive reserve and mitigate the risk of dementia. Examples of such interventions could be implementing cognitive training programs focused on memory exercises, problem-solving tasks, and learning new skills, as well as community education initiatives that offer opportunities for learning, such as adult literacy classes.

RESEARCH IN CONTEXT

1. Systematic Review: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts. Much is known about the role of hippocampal connectivity in episodic memory processing in individuals with high levels of education, but less is known in persons with barely any formal education, or illiterates.
2. Interpretation: Our results suggest that hippocampal connectivity seems to play a minor role in episodic memory performance in illiterate individuals, while health literacy scores correlated with hippocampal connectivity. The correlation between hippocampal connectivity and health literacy levels suggests that there may be room for improvement in hippocampal connectivity if literacy training is provided to illiterate adults.
3. Future Directions: Although preliminary because of the limited sample size, our study sheds light on possible targets such as hippocampal connectivity for clinical trials aiming to improve episodic memory in adults with low levels of education.

2 | METHODS

2.1 | Population

We used a community-based participatory research approach to collaborate with a basic-literacy training program for adults that is sponsored by the Brazilian government. This program, called EJA: *Educação para Jovens e Adultos* (Young and Adult Education) targets adults that did not have the opportunity to go to school when they were young and consists of 3-hour daily classes held four times a week, taught by experienced adult education teachers. Adults aged 40 to 80 years that spontaneously enrolled in EJA in the city of Belo Horizonte, Brazil, from February to July 2019, were invited to participate. Upon screening, participants underwent the Mini-Mental State Examination (MMSE)[31] and the Brief Cognitive Battery.[32] Participants who scored < 1.5 standard deviations below the normative data for these two tests[33] were considered to have cognitive impairment and were not recruited. A total of 43 cognitively unimpaired individuals agreed to participate in the research. Sociodemographic and smoking habits were collected through a structured questionnaire. Physical activity was assessed with the Baecke scale.[34] Depression, anxiety, and alcohol abuse were investigated using the Mini International Neuropsychiatric Interview.[35] All evaluations were conducted upon entry in EJA before any education training. The socioeconomic levels were determined using the ABEPE (Brazilian Association of Research Companies) framework that categorizes households into different socioeconomic levels. The level A category represents the highest socioeconomic level with high income levels, advanced education, and ownership of multiple properties and luxury goods. The level B includes households with a relatively high socioeconomic status, good incomes, tertiary education, and ownership of properties and durable goods. The level C encompasses households with a middle socioeconomic status with moderate income, secondary education, and ownership of a house or an apartment. The levels D and E represent households with a lower socioeconomic status that often have low incomes, limited education, and may live in rented accommodations or informal settlements. They may face significant economic challenges and lack of access to basic services. They often live in poverty, struggling to meet their basic needs and relying on government assistance programs.

2.2 | Literacy and cognitive assessment

Participants that enroll in EJA have various degrees of reading and writing skills. Some never attended formal school while others attended for few years. Their reading abilities vary from inability to recognize letters to some reading capacity, without comprehending the meaning of the text. Because of this diversity in reading and writing skills, we used the Test of Functional Health Literacy in Adults (TOFHLA) to evaluate the participant's literacy skills across different levels. This test was chosen because it has been validated for Brazilian Portuguese,[36] it assesses reading and numeracy skills, and it has proven to be a good predictor of health outcomes.[12] It ranges from 0 to 100, and a score $\leq$ 53 defines health illiteracy, meaning a person has poor reading and numeracy skills and cannot understand written health instructions, such as a medical prescription.[36]

Global cognition was assessed by the MMSE.[31] Episodic memory was assessed with the visual form (pictures) of the Free and Cued Selective Reminding Test (FCSRT).[37,38] The FCSRT Free Recall sum-of-attempts was considered the proxy for episodic memory. Nonverbal intelligence was assessed by the Beta-3 test,[39] attention with the Digit Span Test,[40] reading abilities with the Human Frontier Science Program reading test,[41] words and sentence repetition with the Boston Diagnostic Aphasia Examination,[42] and verbal comprehension with the Token Test.[40] Finally, participants performed the rapid naming of colors, letters, numbers, and objects[43] and the Ekman facial emotion recognition test.[44] A comprehensive assessment of cognitive abilities beyond episodic memory is essential to ensure participants do not have other impairments that could affect episodic memory.

Global cognitive reserve was assessed with a structured questionnaire available in Portuguese that includes years of education, leisure activities, and occupational attainment, the Cognitive Reserve Index questionnaire (CRIq).[45]

2.3 | Neuroimaging

2.3.1 | Neuroimaging acquisition

Brain magnetic resonance imaging (MRI) was acquired in a 3 Tesla Siemens Verio scanner with 3D-T1 and resting-state functional MRI (rsfMRI) acquisitions. The acquisition parameters are described in the supporting information. All T1-weighted images were visually inspected for quality control. One image was excluded because of a large artifact.

2.3.2 | Neuroimaging preprocessing

Details of imaging preprocessing are described in the supporting information. In summary, the T1-weighted images were segmented, a group template was generated from the segmented gray and white matter tissues and cerebrospinal fluid (CSF), then normalized, modulated, and smoothed in the group template using a Gaussian kernel with an 8~mm full width half maximum (FWHM). The Harvard–Oxford atlas[46] was used to calculate the hippocampal volumes for each participant. Preprocessing was done with SPM12.[47]

The rsfMRI analyses were done using the CONN[48] release 20.b toolbox. Functional and anatomical data were preprocessed using a pipeline[49] that included realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and Montreal Neurological Institute space normalization, smoothing, and band-pass filtering. Details of further rsfMRI analyses are described in the supporting information.

2.3.3 | Neuroimaging analyses

Seed-based connectivity maps and region of interest (ROI)-to-ROI connectivity matrices were estimated characterizing the patterns of functional connectivity with 164 HPC-ICA networks[48] and Harvard–Oxford atlas ROIs.[46] Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a weighted general linear model (GLM), defined separately for each pair of seed and target areas, modeling the association between their blood-oxygen-level dependent signal time series. Individual scans were adjusted for transient magnetization using a step function convolved with an SPM canonical hemodynamic response function and rectified. Seed-based connectivity analyses were conducted using the Harvard–Oxford automated atlas[46] with seeds placed in each hippocampus. The analyzed ROI-to-ROI connectivity matrices included connections between each hippocampus and the ventromedial prefrontal cortex (VMPFC), each hippocampus (HC), and the precuneus cingulate cortex (PCC) and between the VMPFC and PCC.

Group-level analyses were conducted using a GLM, estimating separate GLMs for each voxel. First-level connectivity measures served as dependent variables with groups as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects and sample covariance estimation. Inferences were made at the level of individual voxel clusters. Cluster-level inferences were based on parametric statistics from Gaussian random field theory.[50] Results were thresholded using a combination of a cluster-forming $P < 0.001$ voxel-level threshold, and a familywise corrected P-false discovery rate < 0.05 cluster-size threshold.[51]

Demeaned age was used as a covariate in all neuroimaging analyses.

Hippocampal efficiency was operationally defined and measured by assessing the strength of connectivity between the HC and the VMPFC. Stronger connectivity indicates higher hippocampal efficiency.

2.4 | Statistical analyses

Continuous variables were depicted in median and interquartile intervals; categorical variables were depicted in frequencies. GLM considering age, sex, and total intracranial volume as covariates were used to calculate the correlations among episodic memory, literacy levels, brain connectivity, and hippocampal volumes. In the first model, the FCSRT free recall sum-of-attempts was the dependent variable, and the predictors were the functional connectivity between each HC separately and the VMPFC, between each HC and PCC, and between the VMPFC and PCC, as well as with each hippocampal volume. In the second model, the health literacy level measured by the TOFHLA total score was the dependent variable and the predictors were the same as depicted above. The Pearson correlation test examined relationships between TOFLHA and reading fluency, cognitive reserve (CRIq total), episodic memory, and emotion recognition (Ekman total), adjusting for years of formal education.

Based on an effect size (δ) of 0.5, our sample size of 35 provides an 85.9% chance of finding a significant result at an alpha level of 0.05 for one-sample *t* tests of correlation.[52]

3 | RESULTS

The final sample had 35 participants. We excluded three participants that had claustrophobia and did not tolerate the brain MRI, one participant whose scan had artifacts that precluded the analysis, three that were left-handed; and one that scored 98 on the TOFLHA and was therefore considered health literate. The median age was 50 years, 57.1% (n = 20) of participants were women, and 84.8% (n = 28) self-declared themselves as Black individuals. Most participants were from a low socioeconomic level of C or D–E (Table 1). Depression and anxiety were present in 17.1% and 14.3% of participants, respectively. The median TOFHLA score was 28 with an interquartile interval of 21.0 to 42.5. Overall, participants had low reading fluency with a median of 40 words, but 25% of individuals were unable to read any words.

The seed-based connectivity analysis showed a significant connectivity between both HC and the VMPFC and PCC, and other brain regions (Figure 1). However, we failed to find a significant association between the HC–VMPFC connectivity and episodic memory (Table 2).

On the other hand, we found a significant association between the TOFHLA scores and the right HC–VMPFC connectivity ($\beta = 0.58$, P = 0.008; Table 3). The association was not significant for left HC–VMPFC connectivity ($\beta = -0.35$, $P = 0.145$).

There was no significant association between hippocampal gray matter volumes and either episodic memory or health literacy (Tables 2 and 3).

Age and sex did not significantly correlate with the association between HC connectivity and memory or health literacy scores.

The TOFHLA scores significantly correlated with the reading fluency (Pearson R = 0.68, P < 0.001) and emotion recognition (Ekman total; Pearson $R = 0.36$, $p = 0.038$), but not with cognitive reserve (CRIq; Pearson $R = -0.07$, $P = 0.676$). Last, cognitive reserve did not correlate with episodic memory (Pearson $R = -0.06$, $P = 0.732$).

TABLE 1 Participant characteristics.

Characteristics $n = 35$	
Age (years)	50.0 [42.5; 58.0]
Sex female n (%)	20 (57.1 %)
Self-reported ethnicity	
Black	28 (84.8 %)
White	3 (9.1 %)
Indigenous	2 (6.1 %)
Unknown	2 (5.4 %)
Socioeconomic level	
B	6 (17.1 %)
C	11 (32.4 %)
D–E	17 (50.0 %)
Current anxiety	5 (14.3 %)
Current depression	6 (17.1 %)
Baecke physical exercise scale	3.0 [2.2; 5.8]
Cognitive Reserve Index	73.0 [70.0; 79.0]
MMSE	22.0 [21.0; 25.5]
Animal fluency/minute	14.0 [12.0; 16.5]
Brief Cognitive Battery Delayed Recall	8.0 [7.5; 9.0]
TOFHLA total	28.0 [21; 42.5]
FCSRT free recall sum of attempts	30.0 [26.2; 35.0]
FCSRT cue efficiency	0.98 [0.96; 1.0]
FCSRT delayed free recall	11.0 [9.0; 13.0]
Word reading test	40.0 [0.0; 66.5]
Token verbal comprehension	27.0 [21.5; 29.0]
Rapid naming colors (seg)	45.5 [42.2; 57.7]
Rapid naming letters (seg)	41.5 [32.2; 54.2]
Rapid naming numbers (seg)	35.5 [31.2; 42.0]
Rapid naming objects (seg)	55.0 [47.2; 62.0]
Non-verbal intelligence Beta III test	6.0 [5.0; 7.7]
Ekman facial recognition (total)	22.0 [16.5; 24.5]
Right hippocampal volume (mm^3)	2.3 [2.1; 2.5]
Left hippocampal volume (mm^3)	2.3 [2.2; 2.4]

Note: Values depicted in median and Interquartile interval. See the text for more details about the socioeconomic levels.
Abbreviations: FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; TOFHLA, Test of Functional Health Literacy in Adults.

4 | DISCUSSION

Our study investigated the relationships among hippocampal connectivity, episodic memory, and health literacy in adults with low levels of formal education. Contrary to our expectations, we did not find a

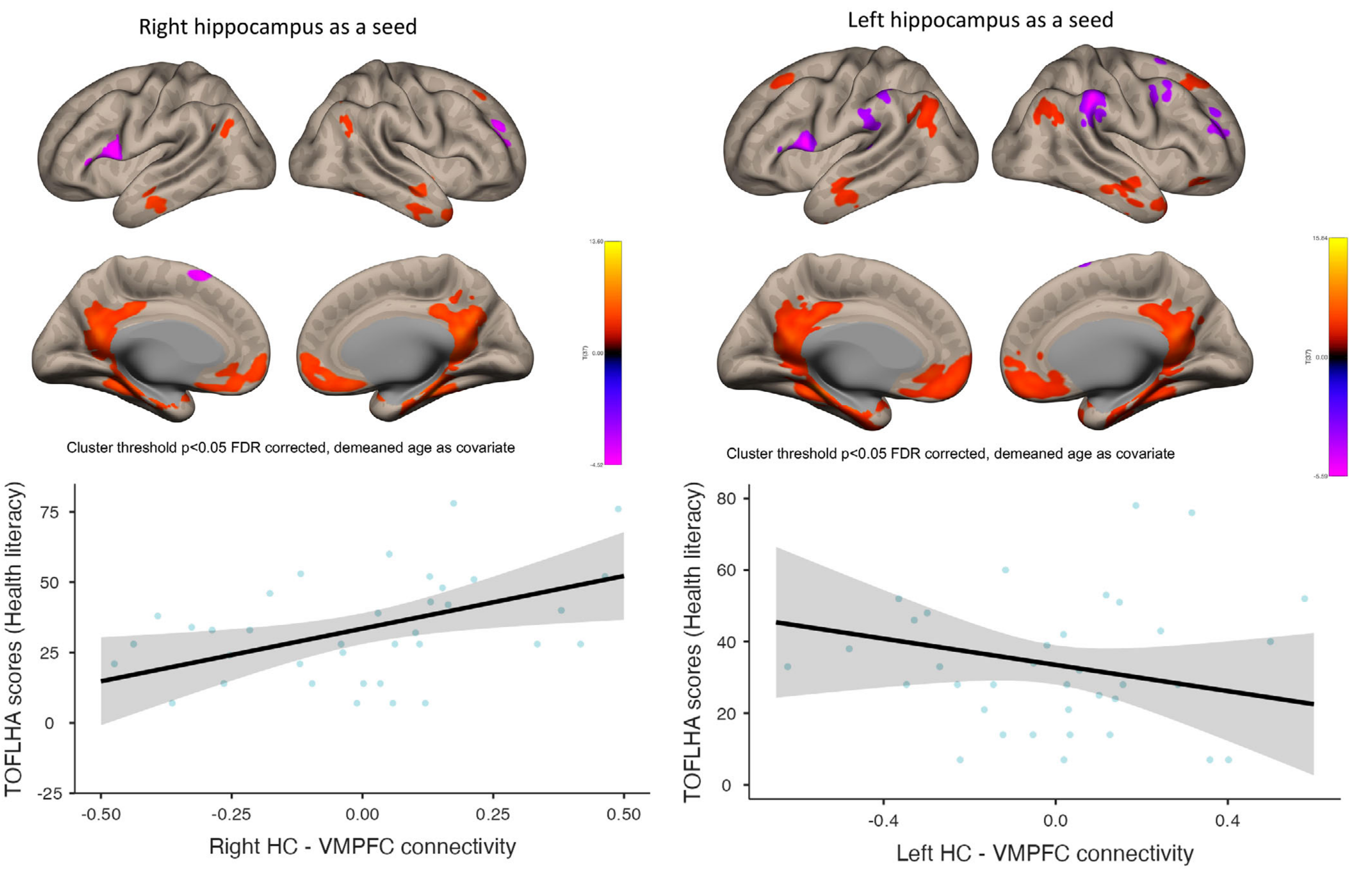

FIGURE 1 Correlation between hippocampal connectivity and low literacy levels. The statistical map is displayed on an inflated brain image. The heat maps represent the *t* statistical value for the connectivity between the right and left hippocampal seed and the other clusters. Blue means anticorrelation and red means positive correlation. The graph depicts the correlation between literacy levels measured by the Test of Functional Health Literacy Assessment (TOFHLA) and the HC-VMPFC connectivity. FDR, false discovery rate; HC, hippocampus; VMPFC, ventromedial prefrontal cortex.

significant association between hippocampal connectivity and episodic memory performance. This finding diverges from previous studies that primarily included individuals with higher educational attainment, highlighting the need to explore different neural mechanisms in populations with limited education.

We did, however, find a significant positive association between health literacy, as measured by the TOFHLA, and right HC–VMPFC connectivity. This suggests that higher health literacy is linked to stronger connectivity in this brain region. Our finding may substantiate the theory that improved hippocampal efficiency, reflected in stronger connections between the hippocampus and critical areas for memory processing such as the prefrontal cortex, may impact cognitive reserve. Right hippocampal connectivity is more sensitive to interventions,[53] less affected by neurodegeneration,[54] and the right hippocampus is more activated during visual tasks, while the left is more involved in verbal tasks.[55] Also, the right hemisphere is crucial for holistic processing and context integration, which are essential components of functional health literacy.[56] Therefore, the absence of significant association with left hippocampal connectivity in our study might be due to the TOFHLA's focus on broader cognitive processes beyond verbal memory.

The TOFHLA test has been widely used to measure health literacy[57] and low health literacy measured by the TOFHLA was associated with poor health outcomes.[36] Although reading and writing literacy has been associated with different patterns of brain activation and connectivity,[58] the neural correlates of health literacy have been less studied, especially in the context of limited education. A previous study showed that higher academic literacy measured by the Rapid Estimate of Adult Literacy in Medicine–Short Form test, a reading exam, correlated with brain structural connectivity, but not with hippocampal volumes.[59] Previous studies have suggested neurobiological differences between literate and illiterate individuals regarding patterns of brain activation and structural connectivity.[30,60] Despite evidence of the neurobiological correlates of literacy concerning language processing, less is known about episodic memory function and its neurobiological correlates such as the hippocampal structure and its connectivity in individuals with low levels of formal education. Now, we found an association between health literacy and brain functional connectivity, suggesting the role of health literacy in brain connectivity as another possible mechanism of cognitive reserve, although the cognitive reserve measured in our sample was not related to health literacy. The positive association we found between health literacy and

TABLE 2 General linear models showing the association between FCSRT free recall sum-of-attempts scores and functional connectivity and hippocampal volume.

	B	t	P
Sex (Male)	0.09	0.23	0.822
Age	−0.38	−1.34	0.193
Right HC—VMPFC connectivity	0.15	0.63	0.535
Left HC—VMPFC connectivity	0.24	0.86	0.400
Right HC—PCC connectivity	−0.39	−1.67	0.109
Left HC—PCC connectivity	0.23	0.97	0.343
VMPFC—PCC connectivity	0.25	1.22	0.235
Left HC volume	0.11	0.31	0.762
Right HC volume	−0.37	−0.98	0.336
TIV	0.04	0.23	0.822

Abbreviations: FCSRT, Free and Cued Selective Reminding Test; HC, hippocampus; PCC, precuneus cingulate cortex; TIV, total intracranial volume; VMPFC, ventromedial prefrontal cortex.

TABLE 3 General linear models showing the association between TOFHLA scores (health literacy) and functional connectivity and hippocampal volume.

Names	B	T	P
Sex (Male)	0.25	0.65	0.522
Age	−0.16	−0.76	0.456
Right HC—VMPFC connectivity	0.58	2.90	**0.008**
Left HC—VMPFC connectivity	−0.35	−1.5	0.145
Right HC—PCC connectivity	0.10	0.51	0.616
Left HC—PCC connectivity	0.16	0.82	0.419
VMPFC—PCC connectivity	0.18	1.0	0.320
Left HC volume	0.39	1.26	0.219
Right HC volume	−0.35	−1.08	0.288
TIV	0.22	1.3	0.208

Abbreviations: FCSRT, Free and Cued Selective Reminding Test; HC, hippocampus; PCC, precuneus cingulate cortex; TIV, total intracranial volume; TOFHLA, Test of Functional Health Literacy in Adults; VMPFC, ventromedial prefrontal cortex.

reading abilities underscores the close relationship between these two abilities, but probably other aspects play a role in cognitive reserve itself.

Regarding episodic memory and hippocampal connectivity, there is still a debate in the literature. Although the neural correlates of the verbal version of the FCSRT are more explored than the visual, we preferred the visual version in our sample due to the low education level. The visual FCSRT test has been linked to activations in the left superior temporal gyrus, left prefrontal cortex,[61] inferior parietal lobe, precuneus, hippocampus, parahippocampal gyrus,[62] and the PCC[63] in task-based fMRI studies conducted in highly educated adults. However, in our study, we used rsfMRI, which is one possible reason we did not find an association between episodic memory and hippocampal connectivity, because task-based fMRI is more sensitive to detecting cognitive-brain correlations than resting state.[64] Additionally, individuals with low education might rely less on their hippocampal connectivity for memory processing, potentially indicating a lower cognitive reserve in this group. This theory is supported by our finding of a significant positive link between health literacy and right HC–VMPFC connectivity.

Regarding structural neural correlates of the visual version of the FCSRT, previous studies have implicated hippocampal volumes[65] and brain areas involving visual processing.[66] For the verbal version of FCSRT, hippocampal gray matter volume, particularly in the left side, has been consistently associated with memory performance[67–69] in individuals with high education levels. This association is more evident in patients with AD[70–72] and behavioral variant frontotemporal dementia.[73,74] The low education level of our sample combined with the absence of participants with dementia may explain why we did not find an association between episodic memory and hippocampal gray matter volumes. Indeed, the relationship between episodic memory and hippocampal volumes is moderated by education level.[23,24] Understanding these nuances highlights the importance of considering educational background, the type of fMRI (resting state vs. task based) and memory test used (visual vs. verbal), when interpreting the relationship between hippocampal connectivity and episodic memory performance. Future research should aim to include diverse education backgrounds and use both resting-state and task-based fMRI to provide a more comprehensive understanding of these associations.

Our study has strengths and limitations. It is one of the first studies to look at the associations between the FCSRT visual version and hippocampal functional connectivity and gray matter volumes in an underserved and hard-to-reach population of illiterate adults. However, because the study is cross-sectional, it cannot demonstrate causality. A significant limitation of the study is the absence of a control group composed of individuals with higher education and literacy levels making it difficult to ascertain if the patterns of hippocampal connectivity identified are specific to the illiterate group. Furthermore, there is a potential selection bias because the participants were self-selected from the literacy program and recruitment was based entirely on individuals who were willing and able to volunteer their time to research.

While much research has focused on samples predominantly consisting of White individuals, our study uniquely fills a gap by presenting data from a sample with most Black participants. This is significant as it reflects the low socioeconomic level associated with being Black in Brazil, a consequence of structural racism perpetuated since the era of slavery. Given the scarcity of studies in adults with no formal education, our research takes an important first step in demonstrating the potential impact of late-life literacy on cognitive reserve in this vulnerable population underscoring the importance of gathering data on minorities who are often underrepresented in research.

Future studies should explore the effects of adult-literacy training in brain structural and functional connectivity and in cognitive abilities, to determine whether adult-literacy acquisition has a beneficial effect on dementia prevention. We also need to include nutrition, health status, and socio-economic factors that might influence cognitive outcomes in further analysis and expand this work in larger populations to be able to inform public policies to increase educational attainment in adulthood as a potential way to reduce dementia burden.

AUTHOR CONTRIBUTIONS

Elisa de Paula França Resende: conceived the study, contributed to the study design, supervised data collection and analysis, interpreted the results, and wrote the manuscript; Vivian P. Lara, Ana Luisa C. Santiago: participated in data collection and contributed to data analysis; Clarisse V. Friedlaender: contributed to the study design and assisted in data collection; Howard J. Rosen: contributed to the study design and critically revised the manuscript; Jesse A. Brown: assisted in neuroimaging data analysis, contributed to the interpretation of results, and provided critical feedback on the manuscript; Yann Cobigo: assisted in neuroimaging data preprocessing, analysis, and interpretation; Lênio L. G. Silva: assisted with neuroimaging acquisition and preprocessing the data; Leonardo Cruz de Souza: assisted in data interpretation and contributed to the critical discussion of results, and reviewed the manuscript; Luciana Rincon: assisted in data collection and interpretation; Lea T. Grinberg: contributed to the study design, supervised data collection and analysis, interpreted the results, and critically revised the manuscript; Francisca I.P. Maciel: assisted in data collection, contributed to the literature review, and provided critical revisions to the manuscript; Paulo Caramelli: conceived and designed the study, provided overall supervision, contributed to data interpretation, and critically revised the manuscript. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest that could have influenced the design, conduct, or reporting of the study. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent prior to data collection. The purpose, procedures, potential risks, and benefits of the study were clearly explained, ensuring that participants understood their rights and had the opportunity to ask questions. All personal information and data collected from participants were treated with confidentiality. Identifying information was anonymized and stored securely, limiting access to authorized researchers only. Any data presented in the manuscript has been de-identified to ensure the privacy and confidentiality of participants. The study protocol was reviewed and approved by the relevant institutional or independent ethics committee, ensuring that it complied with ethical guidelines and safeguarded the welfare and rights of participants.

DATA AVAILABILITY STATEMENT

The data that support the findings are available upon reasonable request. Aggregated and anonymized data, as well as additional information related to the study methodology, can be made available to interested researchers. Requests for data access should be addressed to the corresponding author, Dr. Elisa de Paula França Resende (email: elisaresende@gbhi.org), who will assess each request on a case-by-case basis in consultation with the research team and in compliance with applicable data protection regulations and institutional policies.

ETHICAL APPROVAL

The present study adheres to the ethical standards and guidelines in research, and it was approved by the Institutional Ethical Review Board – Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais. Approval number 2.955.960, CAAE number: 89764918.2.0000.5149.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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