Received: 24 June 2020 | Revised: 9 September 2020 | Accepted: 16 September 2020 | Published online: 9 November 2020

DOI: 10.1002/dad2.12122

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

In vivo imaging evidence of poor cognitive resilience to Alzheimer's disease pathology in subjects with very low cognitive reserve from a low-middle income environment

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Funding information
Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant/Award Numbers: 12/50329-6, 14/50873-3, 2018/15167-1

Abstract

INTRODUCTION: Reduced cognitive reserve (CR) due to very low educational (VLE) levels may influence high dementia rates in low-middle income environments, leading to decreased cognitive resilience (RES) to Alzheimert's disease (AD) pathology. However, *in vivo* findings in VLE groups confirming this prediction are lacking.

METHODS: Cognitively impaired patients (with clinically defined AD dementia or amnestic mild cognitive impairment) and cognitively unimpaired older adults (n = 126) were recruited for a positron emission tomography (PET) and magnetic resonance imaging (MRI) investigation in Brazil, including 37 VLE individuals (≤5 years of education). A CR score was generated combining educational attainment and vocabulary knowledge. RES indices to AD pathology were calculated using standardized residuals from linear regression models relating current cognitive performance (episodic memory or overall cognition) to amyloid beta (Aβ) burden Pittsburgh compound-B ([11C]PiB-PET).

RESULTS: Aβ burden was lower in VLE relative to highly-educated subjects (controlling for age, sex, and Mini-Mental Status Exam [MMSE] scores) in the overall cognitively impaired sample, and in dementia subjects when the three clinically defined groups were evaluated separately. In bivariate regression analyses for the overall sample, the RES index based on a composite cognitive score was predicted by CR, socioeconomic

status, and hippocampal volume (but not white matter hyperintensities or intracranial volume [ICV]); in the multivariate model, only CR retained significance (and similar results were obtained in the Aβ-positive subsample). In the multivariate model for the overall sample using the RES index based on memory performance, CR, hippocampal volume, and ICV were significant predictors, whereas only CR retained significance in Aβ-positive subjects.

DISCUSSION: Lower CR consistently predicted less resilience to AD pathology in older adults from a low-middle income environment.

KEYWORDS
Alzheimer's disease, biomarkers, cognitive reserve, cognitive resilience, dementia, low education

1 | INTRODUCTION

In samples of subjects at the symptomatic or preclinical stages of Alzheimer's disease (AD), there are large variations in the degree of neuropathologic burden among individuals presenting comparable levels of cognitive performance at similar ages.[1,2] Such a high level of inter-subject variability has raised interest in the notion of resilience to AD, conceptualized as one's capacity to sustain better-than-expected cognitive performance in relation to the degree of AD pathology.[3,4] Brain reserve, commonly estimated by intracranial volume (ICV),[5] is thought to play a role in resilience to AD, referring to the greater degree of brain structure that allows some individuals to cope with larger amounts of damage before reaching the threshold for the emergence of clinical AD.[1,4] Cognitive reserve (CR) (most commonly estimated by educational attainment) is one other concept usually invoked to explain inter-individual differences in resilience to AD, referring to the capacity to maintain cognitive functioning by one's adaptability to recruit alternate neural networks or utilize existing networks more efficiently to compensate for the burden of AD pathology.[1] Findings from both post-mortem investigations and *in vivo* studies using cerebrospinal fluid (CSF) or neuroimaging techniques have suggested that variations in educational attainment (or other CR proxies) influence differences in the degree of cognitive resilience to AD pathology, as measured by indices of cortical amyloid beta (Aβ) burden or tau accumulation.[3,6–11]

Variations in dementia prevalence are present across separate populations,[12,13] and such differences are likely to be at least partially driven by health and socioeconomic disparities.[12] Low educational attainment, related to poor socioeconomic status (SES), is thought to influence increased rates of cognitive decline and earlier emergence of dementia in low/middle-income countries.[12,13] One possible explanation, based on the concept of CR, is that elderly individuals with very low educational attainment (VLE) are at a higher risk of presenting dementia symptoms even in the face of a low degree of AD pathology. However, this prediction has not yet been tested *in vivo;* previous studies evaluating CR proxies and markers of AD pathology have been most often carried out in high-income environments, enrolling elderly subjects with a minimum of 6 years of educational attainment or recruiting smaller numbers of VLE subjects relative to the number of individuals with higher educational attainment.[3,6–11] Moreover, given the association of lower SES with higher cerebrovascular disease risk,[14] one other possibility is that the emergence of AD dementia or amnestic mild cognitive impairment (aMCI) in VLE individuals may be influenced by the presence of microvascular lesions, in interaction or not with AD pathology.[15]

We conducted a multimodal neuroimaging investigation involving both cognitively impaired patients (with dementia compatible with AD or aMCI) and cognitively unimpaired elderly individuals from a low/middle-income environment, with VLE subjects (≤5 years of education) comprising approximately 30% of the sample. Subjects underwent positron emission tomography (PET) imaging with Pittsburgh compound-B ([^{11}C]PiB-PET) to detect cortical Aβ deposition and [^{18}F]-labeled fluorodeoxyglucose ([^{18}F]FDG-PET) to assess brain glucose metabolism,[16] as well as structural magnetic resonance imaging (MRI) to quantify ICV, hippocampal volumes, and white matter hyperintensities (WMHs) (assessing cerebral microvascular pathology).[15] We tested herein the prediction that VLE subjects would present clinically relevant cognitive decline at a milder level of Aβ burden relative to subjects with higher CR. In addition, we calculated indices of cognitive resilience relating current cognitive performance to the degree of Aβ burden,[3,4] and used such indices to investigate whether CR levels would be significantly associated with resilience to AD pathology in the overall sample and the subsample belonging to the "Alzheimert's continuum" (ie, subjects classified as displaying anomalous Aβ deposition).[17] Finally, we investigated the presence of associations between cognitive resilience and variables other than CR, including SES, ICV, hippocampal volumes, and WMH volume.

2 | MATERIAL AND METHODS

2.1 | Study population and assessment schedules

We enrolled 135 elderly individuals, including 93 cognitively impaired subjects (with dementia compatible with AD or aMCI) recruited at the

Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP), and 42 cognitively unimpaired individuals. São Paulo is a megacity with high inequality levels, and HC-FMUSP is its largest government-funded medical facility, intensely used by the population within Brazil's unified health system. Subjects were allocated to either of three categories according to their educational attainment,[18] including a VLE subgroup, a highly educated subgroup (HIE; ≥12 years of education), and an intermediate education (IE) subgroup.

Details for clinical/cognitive assessments and inclusion/exclusion criteria, as well as psychiatric comorbidities and medication use (supplementary file) have been described elsewhere.[16]

Three cognitive performance measures were used: the Delayed-Recall score of the Rey Auditory-Verbal Learning Test (RAVLT),[19] chosen as an episodic memory index known to be sensitive to Aβ-burden variations both in cognitively impaired and unimpaired samples;[20] a larger cognitive composite score[3] combining tests evaluating executive functioning, language, and visuoconstructional ability, and verbal/nonverbal episodic memory (supplementary file); and Mini-Mental Status Examination (MMSE) scores.

Subjects were classified according to their SES using a five-category scale validated for use in Brazil, including several items to assess current family income.[21] The Hachinski ischemic score (HIS) estimated the contribution of cerebrovascular pathology to the development of dementia.[22]

The institutional review board of HC-FMUSP approved the investigation (CAPPesq_368.037), and written informed consent was obtained from participants prior to study procedures according to the Declaration of Helsinki, or caregivers in the case of patients with dementia.

RESEARCH IN CONTEXT

1. Systematic review: A PubMed-based search indicated that elderly individuals with very low educational attainment (VLE) may be prone to cognitive decline in the face of a low degree of Alzheimer's disease (AD) pathology, based on the cognitive reserve (CR) concept. Our systematic perusal of *in vivo* studies in the field showed a complete lack of AD-biomarker investigations in subgroups with ≤5 years of education.
2. Interpretation: We confirmed the prediction that very low CR is related to lesser cognitive resilience to amyloid beta (Aβ) burden. Moreover, the identification of several VLE dementia subjects displaying only mild Aβ burden demonstrates that education must be accounted for when biomarker-based AD staging systems are applied to low CR subgroups, to avoid the risk of misplacing cases with true AD pathology outside the disease continuum.
3. Future directions: Similar studies on VLE samples are needed using resilience indices based on tau biomarkers, given the key relevance of tau pathology to the emergence of cognitive deficits.

2.2 | Neuroimaging data

Fluid-attenuation inversion recovery (FLAIR) and T1-weighted MRI sequences were acquired using a Philips-Achieva 3T-scanner. [^{11}C]PiB was produced using an on-site cyclotron (PETtrace-880, GE-Healthcare) and PET/computerized tomography (CT) images were acquired using a Discovery-710 PET/CT-scanner (GE-Healthcare). PET data were also collected using [^{18}F]-labeled fluorodeoxyglucose ([^{18}F]FDG-PET). Details regarding acquisition protocols and exclusions due to incidental brain lesions (n = 9) or artifacts during acquisition of PET (n = 1) or MRI (n = 2) data are provided as supplementary material.

WMH assessments were conducted with the Lesion Segmentation Tool version-2.0.15[23] applied on FLAIR data, whereas brain volumetric measurements including ICV and hippocampal volumes were obtained by applying the FreeSurfer software package on T1-weighted data.[5] Processing details, quality-control protocols, and information on exclusions from specific analyses due to MRI scanner upgrade (n = 11) or MRI-data processing errors (n = 7) are provided in the as supplementary file.

Standardized uptake value ratios of [^{11}C]PiB uptake ([^{11}C]PIB-SUVRs) were calculated to generate quantitative indices of cortical Aβ deposition for each subject, normalized to whole-cerebellar uptake. In addition, two individual Aβ classifications were conducted using a conventional [^{11}C]PiB-SUVR = 1.42 cut-off and a more sensitive [^{11}C]PIB-SUVR = 1.21 cut-off[24] (supplementary file).

Individual [^{18}F]FDG-PET patterns were rated as normal or abnormal based on blinded visual inspection by two experienced nuclear medicine physicians, as reported previously[16] (supplementary file). This aimed to document signs of overt neurodegeneration, and to investigate patterns of regional metabolic abnormalities that might be suggestive of brain disorders other than AD.[25]

2.3 | Statistical analysis

All analyses were conducted using SPSS-v.20.0.

Measures of CR included years of educational attainment, vocabulary knowledge (as measured by Wechsler Adult Intelligence Scale, 3rd edition [WAIS-III] vocabulary subscores), and a CR score combining the two variables[9] (supplementary file).

Using an analysis of covariance (ANCOVA) design (covaried for age, sex, and MMSE scores), between-group [^{11}C]PIB-SUVR comparisons were conducted between the three subgroups of educational attainment (VLE, IE, and HIE) in the cognitively impaired subsample (dementia plus aMCI subjects), and the separate dementia, aMCI, and cognitively unimpaired groups. A $P < 0.05$ level of statistical significance was employed, whereas findings significant at the $P < 0.10$ level were reported as trends considering this

TABLE 1 Demographic, clinical, cognitive, and biomarker characteristics of the sample

	Overall sample (n = 126)	Cognitively unimpaired subjects (n = 40)	Overall cognitively impaired subsample (n = 86)	Dementia group (n = 39)	Amnestic cognitive impairment group (n = 47)
Mean age in years (SD)	72.41 (6.33)	70.75 (5.63)	73.19 (6.52)[a]	73.90 (7.29)[a]	72.60 (5.82)
Female-to-male ratio	92 : 34	30 : 10	62 : 24	25 : 14	37 : 10
Mean years of education (SD)	10.16 (5.15)	11.38 (5.38)	9.59 (4.98)[b]	9.49 (5.07)	9.68 (4.95)
Range of values	2 - 20	3 - 20	2 - 20	2 - 20	2 - 17
Mean vocabulary subtest (WAIS-III) scores (SD)[n]	36.07 (11.53)	40.72 (10.18)	33.85 (11.53)[c]	32.19 (12.17)[c]	35.15 (10.97)[a]
SES (A : B : C : D : E)	28 : 66 : 26 : 6 : 0	11 : 21 : 8 : 0 : 0	17 : 45 : 18 : 6 : 0	8 : 21 : 7 : 3 : 0	9 : 24 : 11 : 3 : 0
Handedness (Right : Left : Mixed)	119 : 4 : 3	38 : 1 : 1	81 : 3 : 2	36 : 3 : 0	45 : 0 : 2
Mean MMSE scores (SD)[o]	25.51 (3.79)	27.95 (1.60)	24.35 (3.98)[d]	21.92 (4.08)[e]	26.35 (2.56)[d]
Mean delayed episodic memory recall (RAVLT) scores (SD)[p]	6.81 (4.49)	10.43 (2.72)	5.11 (4.14)[d]	2.53 (3.61)[e]	7.19 (3.31)[d]
Mean cognitive composite scores (SD)[q]	0.3816 (5.99)	4.987 (3.85)	−1.921 (5.53)[d]	−5.538 (5.78)[e]	0.710 (3.52)[d]
Mean HIS (SD)[r]	1.64 (1.34)	1.45 (1.01)	1.73 (1.47)	1.97 (1.51)	1.52 (1.41)
Mean Blessed scale scores (SD)[s]				6.07 (3.80)	
Mean IQ-CODE scores (SD)[s]				3.94 (0.44)	
Mean [^{11}C]PiB-SUVR (SD)[t]	1.31 (0.32)	1.14 (0.19)	1.38 (0.34)[f]	1.52 (0.34)[g]	1.26 (0.30)[l]
% A+ / A-[t]					
1.42 SUVR cut-off	67.0 / 33.0	8.8 / 91.2	43.2 / 56.8[h]	63.2 / 36.8[i]	25.6 / 74.4[j]
1.21 SUVR cut-off	43.5 / 56.5	17.6 / 82.4	54.3 / 45.7[h]	73.7 / 26.3[i]	37.2 / 62.8[j]
% Abnormal / normal [^{18}F]FDG-PET[t]	36.5 / 63.5	5.9 / 94.1	49.4 / 50.6[i]	76.3 / 23.7[i]	25.6 / 74.4[k]
Mean intracranial volume (ICV)[u]	1401964.34	1418039.37	1395613.70	1381683.61	1406757.78
(SD)	(136956.83)	(143391.74)	(134715.94)	(133273.92)	(136317.53)
Mean hippocampal volume corrected for ICV (SD)[v]	2.084 (0.418)	2.270 (0.370)	2.008 (0.414)[f]	1.925 (0.415)[l]	2.078 (0.405)[m]

(Continues)

90% confidence interval as a reasonable balance between the significance and the power balance of the statistical test.[26] Effect sizes for ANCOVA comparisons were given by partial eta squared (η_p^2), and significant results were followed-up with post hoc two-group comparisons (with findings reported at the $P < 0.05$ level of significance).

With the purpose of further examining the extent to which CR accounted for variance in cerebral Aβ burden, we also conducted linear regression analyses between SUVR measures (dependent variable) and the CR score, entering age, gender, and MMSE scores as covariates. These analyses were conducted for the overall sample and the cognitively impaired subsample, and also separately for dementia, aMCI, and the cognitively impaired groups.

The same ANCOVA design above was used for group comparisons of ICV, volume of WMH, and hippocampal volumes.

To obtain scores of cognitive resilience (RES) to AD pathology (1), we saved the standardized residuals from bivariate linear regression analyses between [^{11}C]PiB-SUVR and current cognitive scores; two RES indices were calculated, respectively, using RAVLT scores (RES_{RAVLT}), the larger cognitive composite ($RES_{COMPOSITE}$), and MMSE scores (RES_{MMSE}) (further details in supplementary file). Both bivariate and stepwise multivariate regression analyses were then conducted using each RES index as a dependent variable, and CR, SES, ICV, right and left hippocampal volumes, and WMH volume as independent variables, with age and gender forced as additional predictors (enter-method) (supplementary file). Finally, the same methods were applied to generate RES indices that were used in multivariate regression analyses specifically for the Aβ-positive subsample.

In all regression analyses, effect sizes were calculated using Cohen f^2.

3 | RESULTS

3.1 | Sociodemographic, cognitive, and biomarker data in the clinically defined groups

Table 1 provides sociodemographic, cognitive, and biomarker data for the overall sample and the clinically defined groups. Mean age was significantly higher both in the overall cognitively impaired subsample and

TABLE 1 (Continued)

	Overall sample (n = 126)	Cognitively unimpaired subjects (n = 40)	Overall cognitively impaired subsample (n = 86)	Dementia group (n = 39)	Amnestic cognitive impairment group (n = 47)
Mean volume of WMH as percentage of total WM volume (SD)[w]	0.538 (1.231)	0.445 (1.054)	0.577 (1.303)	0.696 (1.777)	0.476 (0.690)
Mean number of WMH lesions (SD)[w]	7.19 (5.49)	5.69 (6.69)	7.83 (4.80)	7.26 (4.25)	8.31 (5.23)

Abbreviations: [11C]PiB-SUVR, [11C]PiB standardized uptake value ratio in a composite region-of-interest encompassing the frontal, temporo-parietal, and cingulate cortices and the precuneus; [18F]FDG, brain glucose metabolism as assessed with [18F]FDG-PET; A-, amyloid negativity; A+, amyloid positivity; HIS, Hachinski ischemic score; ICV, intracranial volume (in mm^3); IQ-CODE, Informant Questionnaire on Cognitive Decline in the Elderly; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Memory Test; SD, standard deviation; SES, socio-economic status measured in accordance with a standardized five-category scale evaluating family income in Brazil, from "A" (upper income socioeconomic class) to "E" (lowest-income class) (reference 21); WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition; WMH, white matter hyperintensity.

[a]Significantly different from controls ($P < 0.05$, independent sample *t* test).
[b]Trend toward significant difference from controls ($P < 0.10$, independent sample *t* test).
[c]Significantly different from controls ($P < 0.005$, independent sample *t* test).
[d]Significantly different from controls ($P \leq 0.001$, independent sample *t* test).
[e]Significantly different from both controls and MCI patients ($P < 0.001$, independent sample *t* test).
[f]Significantly different from controls ($P \leq 0.001$, ANCOVA taking into account the influence of age and gender).
[g]Significantly different from both controls and MCI patients ($P < 0.001$, ANCOVA taking into account the influence of age and gender).
[h]Significant difference between cognitively impaired and unimpaired subjects ($P < 0.005$, chi-square test).
[i]Significantly different from controls ($P < 0.001$, chi-square test).
[j]Trend toward significant difference from controls ($P < 0.10$, chi-square test).
[k]Significantly different from controls ($P < 0.05$, chi-square test).
[l]Significantly different from controls ($P \leq 0.005$, ANCOVA taking into account the influence of age and gender).
[m]Significantly different from controls ($P < 0.05$, ANCOVA taking into account the influence of age and gender).
[n]Missing values in three dementia subjects, one amnestic MCI subject and one cognitively intact subject.
[o]Missing values in one dementia subject and one amnestic MCI subject.
[p]Missing value in one dementia subject.
[q]Sum of Z-transformed scores from nine neuropsychological items evaluating executive functioning, visuoconstructive ability, language, and verbal and non-verbal episodic memory. Missing values in seven dementia, three amnestic MCI, and two control subjects.
[r]Missing values in one subject with amnestic MCI and one dementia subject.
[s]Missing values in four subjects.
[t]Missing values in one subject with dementia, four MCI subjects, and six cognitively unimpaired subject.
[u]Missing values in three dementia subjects, two MCI subjects, and eight cognitively impaired subjects.
[v]Missing values in three dementia subjects, four MCI subjects, and eight cognitively impaired subjects.
[w]Missing values in four subjects with dementia, six MCI subjects, and eight cognitively intact subjects.

the dementia group relative to cognitively unimpaired controls. There was a trend toward a lower number of years of education in the cognitively impaired subsample relative to controls ($P < 0.10$), whereas vocabulary scores were significantly lower in the overall cognitively impaired subsample, the dementia group, and the aMCI group relative to controls (Table 1).

Across separate SES categories, there were significant differences regarding CR-related variables, MMSE and cognitive composite scores, but not episodic memory scores (supplementary_Table_1).

Differences between the clinically defined groups regarding biomarker data are reported in the supplementary file.

3.2 | Sociodemographic, clinical, and cognitive data in subgroups of educational attainment

The VLE (n = 37), IE (n = 42), and HIE (n = 47) subgroups had a similar proportion of cognitively impaired and cognitively intact subjects (14 dementia/13 aMCI /10 cognitively unimpaired, 13 dementia/17 aMCI /12 cognitively unimpaired, and 12 dementia/17 aMCI /18 cognitively unimpaired, respectively) ($\chi^2 = 2.22$, $P = 0.696$).

Sociodemographic, cognitive, and biomarker data for three subgroups of educational attainment in the cognitively impaired subsample are provided in supplementary_Table_2. Significant differences between VLE and HIE subjects were detected regarding MMSE and the cognitive composite score both in the overall cognitively impaired sample and the aMCI group, with trend differences detected in the dementia group (supplementary Table 2). The cognitive composite score was also significantly lower in subjects with intermediate levels of education relative to the HIE category in the cognitively impaired subsample and the aMCI group (supplementary Table 2). In the dementia sample, subjects in the three subgroups of educational attainment had HIS ≤4 , except for one VLE individual with HIS = 5 and one HIE subject with HIS = 6. Levels of functional impairment were similar between the three subgroups of educational attainment (supplementary_Table_2).

TABLE 2 Cognitive reserve, socioeconomic status, and imaging variables associated with cognitive resilience to Alzheimer's disease pathological change

	Resilience index calculated using delayed episodic memory scores[a]		Resilience index calculated using composite cognitive test scores[b]	
Variable	***Standardized ß***	***P value***	***Standardized ß***	***P value***
Overall sample				
Bivariate models (age- and sex-corrected)				
Cognitive reserve score	0.340	<**0.001**	0.563	<**0.001**
Socioeconomic status	−0.172	0.067	−0.414	<**0.001**
Intracranial volume	0.186	0.078	0.117	0.307
Left hippocampal volume	0.323	**0.002**	0.218	0.051
Right hippocampal volume	0.289	**0.006**	0.229	**0.040**
Volume of WMH	0.049	0.647	−0.024	0.832
Multivariate models				
Number of subjects	94		88	
Age	−0.053	0.583	−0.013	0.884
Sex	−0.182	0.072	−0.013	0.881
Cognitive reserve score	0.361	<**0.001**	0.601	<**0.001**
Socio-economic status	0.005	0.962	−0.190	0.057
Intracranial volume	0.234	**0.020**	0.103	0.281
Left hippocampal volume	0.334	**0.001**	0.134	0.147
Right hippocampal volume	0.270	0.266	0.148	0.112
Volume of WMH	0.000	0.998	−0.048	0.603
Effect size (f^{b})	0.37		0.56	
Aß-positive subsample				
Bivariate models (age- and sex-corrected)				
Cognitive reserve score	0.286	0.053	0.576	<**0.001**
Socio-economic status	−0.221	0.145	−0.413	**0.010**
Intracranial volume	0.177	0.273	0.059	0.752
Left hippocampal volume	0.228	0.151	0.203	0.234
Right hippocampal volume	0.202	0.189	0.155	0.358
Volume of WMH	−0.049	0.778	−0.146	0.449
Multivariate models				
Number of subjects	42		38	
Age	−0.113	0.455	0.023	0.873
Sex	−0.209	0.176	−0.104	0.471
Cognitive reserve score	0.342	**0.030**	0.554	<**0.001**
Socio-economic status	−0.135	0.445	−0.217	0.176
Intracranial volume	0.106	0.510	0.013	0.937
Left hippocampal volume	0.216	0.168	0.145	0.327
Right hippocampal volume	0.200	0.188	0.113	0.440
Volume of WMH	−0.140	0.417	−0.247	0.129
Effect size (f^{2})	0.18		0.45	

Abbreviations: Aß, amyloid-beta deposition; MMSE, Mini-Mental State Exam; WMH, white matter hyperintensity.

[a]Delayed-recall score of the Rey Auditory-Verbal Learning Test (RAVLT).

[b]Sum of Z-transformed scores from nine neuropsychological items evaluating executive functioning, visuoconstructive ability, language, and verbal and non-verbal episodic memory.

3.3 | PET imaging findings in subjects with very low levels of education

Between-group [^{11}C]PiB-SUVR comparisons showed significant differences across the three subgroups of educational attainment in the cognitively impaired subsample (F = 3.61, P = 0.006; η_p^2 = 0.198); post hoc two-group comparisons indicated significantly lower SUVR in VLE relative to HIE subjects (F = 4.31, P = 0.005; η_p^2 = 0.277) (supplementary Table 2). There was also a trend difference between the three educational categories in the dementia group (F = 2.43, P = 0.057; η_p^2 = 0.282), and post hoc two-group comparisons indicated significantly lower SUVR in VLE relative to HIE subjects (F = 5.48, P = 0.004; η_p^2 = 0.523) (supplementary Table 2). Between-group comparisons showed non-significant findings either for the aMCI (F = 1.11, P = 0.363) or cognitively unimpaired groups (F = 0.283, P = 0.919).

All three educational attainment categories within the dementia group presented higher mean [^{11}C]PiB-SUVR when compared separately against cognitively unimpaired individuals (adjusted for age, gender, and education), but with substantially lesser statistical significance for the VLE subgroup (F = 4.56, P = 0.039) than for the HIE (F = 51.45, P < 0.001) and IE (F = 22.89, P < 0.001) subgroups.

Individual [^{11}C]PiB-SUVR inspection in HIE and VLE dementia patients (Figure 1, supplementary Table 2) showed that all HIE subjects were Aβ positive (at the 1.21 [^{11}C]PIB-SUVR threshold), whereas eight VLE dementia patients (57.1%) were Aβ positive. Inspections of [^{11}C]PiB-SUVR across separate regions of interest (ROIs) in the remaining VLE dementia patients are detailed as supplementary material (supplementary file).

As the above-reported Aβ-burden differences were most salient in dementia patients, individual ratings of [^{18}F]FDG-PET were inspected, together with clinical and cognitive information, in order to investigate whether [^{11}C]PiB-PET findings might have been influenced by the inclusion of VLE dementia patients with brain disorders other than AD. A summary of those individual [^{18}F]FDG-PET reports is provided as supplementary material (supplementary file).

3.4 | Relationship between cognitive reserve as a continuous variable and level of cerebral amyloid-beta burden

Linear regression analyses investigating the relationship between SUVR and the CR score (with age, gender, and MMSE scores as covariates) were significant for the following: the overall sample (standardized β [stβ] = 0.211, P = 0.038; f ^{2} = 0.21); the cognitively impaired subsample (stβ = 0.288, P = 0.023; f ^{2} = 0.18); and the dementia group (stβ = 0.450, P = 0.046; f ^{2} = 0.23). Findings were non-significant for the aMCI group (stβ = 0.067, P = 0.697) and the cognitively unimpaired group (stβ = −0.138, P = 0.522).

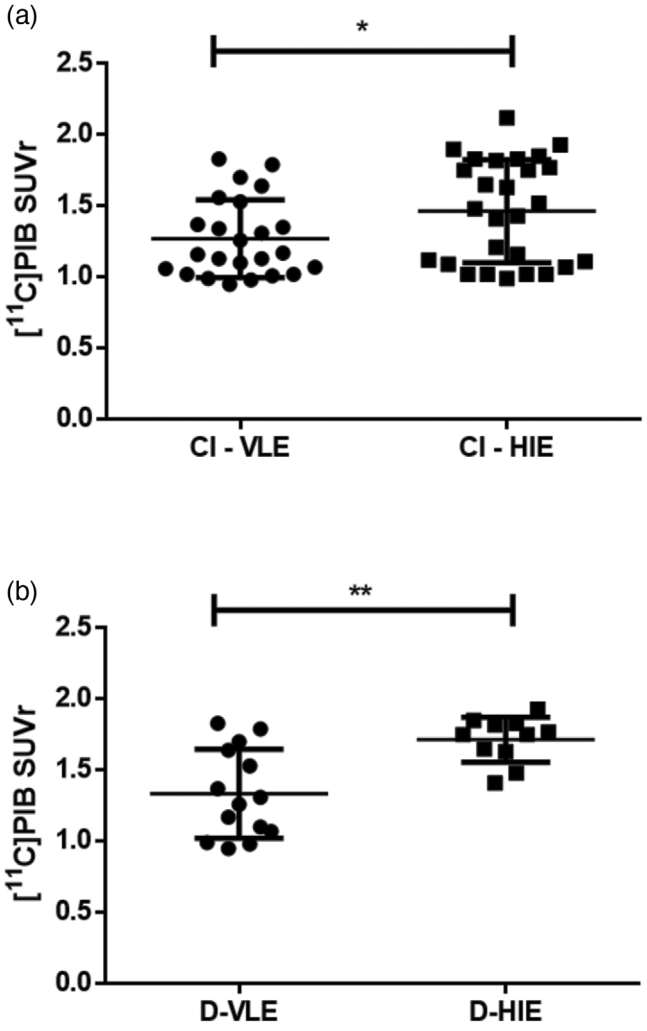

FIGURE 1 (a) Scatter plots showing results of the sensitivity analyses assessing differences in [^{11}C]PiB standardized uptake value ratios (SUVRs, shown on the y-axis) between cognitively impaired (CI) subgroups at the extremes of educational level: 5 years or less (very low education, VLE); and 12 years or more (high education, HIE). SUVRs were obtained using [^{11}C]PiB uptake measurements in a meta-region of interest encompassing the prefrontal, orbitofrontal, parietal, temporal, cingulate cortices, and the precuneus, normalized to the tracer uptake in the whole cerebellum. Statistical testing was carried out by one-way ANCOVA adjusted for age, sex, and current cognitive status as assessed using scores on the Mini-Mental State Examination. In (b), the same statistical comparison is shown for the dementia subsample (D). $^{*}P \leq 0.005$; $^{**}P \leq 0.001$

3.5 | Relationship between MRI-based measurements and cognitive reserve

There were no significant differences between the three subgroups of educational attainment regarding to ICV or WMH measurements (supplementary Table 2). In the aMCI group only, there were significant differences across the three education categories regarding the combined volumes of right and left hippocampi (F = 2.71, P = 0.035; η_p^2 = 0.341), with post hoc two-group comparisons indicating larger

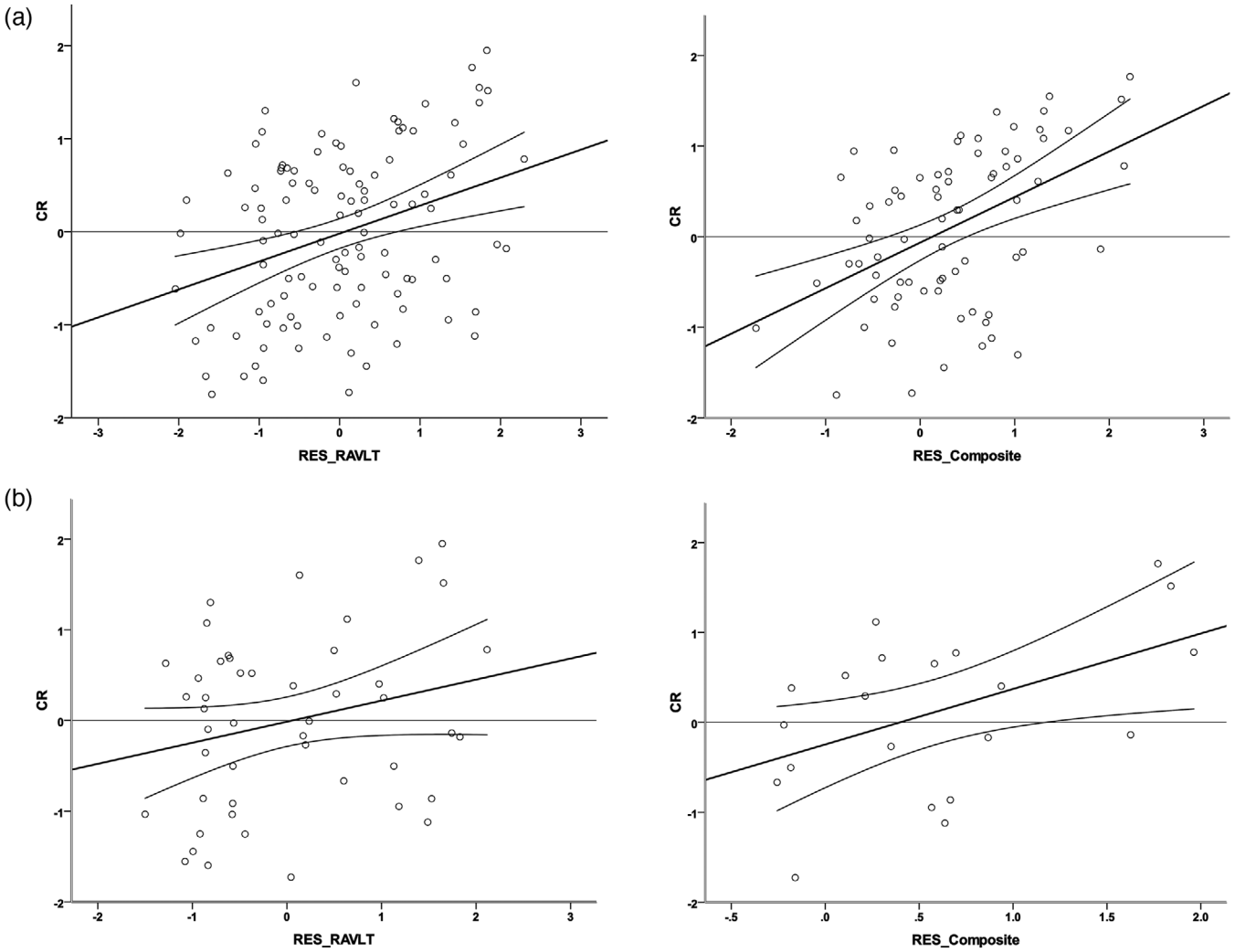

FIGURE 2 (a) Associations between cognitive resilience (RES; x-axis) and level of cognitive reserve (CR; y-axis) in cognitively impaired *plus* cognitively unimpaired elderly subjects. The RES indices were calculated using standardized residuals from linear regression models between [^{11}C]PiB standardized uptake value ratios (SUVRs) normalized to cerebellar uptake ([^{11}C]PiB-SUVRs) and either the delayed-recall score of the Rey Auditory-Verbal Learning Test (RES_RAVLT, on the left side) (n = 114) or a cognitive composite based on the sum of Z-transformed scores from nine neuropsychological items evaluating executive functioning, visuoconstructive ability, language, and verbal and non-verbal episodic memory (RES_Composite, on the right side) (n = 104). The CR score was calculated averaging individual z-scores of two measures: years of education and vocabulary sub-scores of the Wechsler Adult Intelligence Scale, 3rd revision (WAIS-III). Statistical values were as follows: standardized β [stβ] = 0.340, $P < 0.001$ for the relationship of the RES-RAVLT index with CR; and stβ = 0.563, $P < 0.001$ for the RES_composite index. (b) The same associations between resilience and CR are shown for the subgroup of subjects rated as amyloid beta (Aβ) positive using a [^{11}C]PiB-SUVR threshold of 1.21, respectively, for the RES-RAVLT index (n = 47; stβ = 0.286, $P = 0.053$) (left side) and the RES-Composite index (n = 43; stβ = 0.576, $P < 0.001$) (right side)

volumes in the IE subgroup relative to the two other subgroups ($F > 2.84$, $P < 0.05$; $\eta_p^2 > 0.34$) (supplementary Table 2).

When linear regression analyses were conducted to investigate relationships between MRI-based measurements and the CR score as a continuous variable (with age, gender, and MMSE scores as covariates), no significant findings were detected either in the overall sample, the cognitively impaired subsample, or the three clinically defined groups with regard to ICV ($P > 0.28$); left hippocampal volume ($P > 0.49$); right hippocampal volume ($P > 0.44$); or WMH volume ($P > 0.55$).

3.6 | Cognitive resilience to AD pathology: regression analyses

In the overall sample, bivariate regression analyses showed that the RES_{RAVLT} index was predicted significantly by CR ($P < 0.001$) (Figure 2a) and hippocampal volumes on the left ($P = 0.002$) and right ($P = 0.006$) hemispheres, with trend significance for both ICV and SES ($P < 0.10$) (Table 2). The $RES_{COMPOSITE}$ index was predicted significantly by CR (Figure 2a), SES ($P < 0.001$), and hippocampal volumes on the right side ($P = 0.040$), and as a trend on the left side ($P = 0.051$) (Table 2).

In the multivariate models for the overall sample using the RES_{RAVLT} index, associations were significant with CR ($P < 0.001$); left hippocampal volume ($P = 0.001$); and ICV ($P = 0.020$). When the $RES_{COMPOSITE}$ index was used, only CR retained significance ($P < 0.001$), with a trend for SES ($P < 0.10$) (Table 2).

Effect sizes were large in both multivariate analyses above (Cohen $f^2 > 0.35$) (Table 2).

We repeated the above analyses including only Aβ-positive individuals (at the 1.21 [^{11}C]PiB-SUVR threshold) (Table 2, Figure 2b); in multivariate models, CR was the only significant predictor for both the RES_{RAVLT} index to Aβ burden ($P = 0.030$; Cohen f^2 between 0.15 and 0.35) and the $RES_{COMPOSITE}$ index ($P < 0.001$; Cohen $f^2 > 0.35$) (Table 2).

Finally, multivariate models using the RES_{MMSE} index indicated associations with CR ($P < 0.001$), left hippocampal volume ($P = 0.001$), and ICV ($P = 0.033$) in the overall sample; and only CR ($P < 0.001$) in the Aβ-positive subsample.

4 | DISCUSSION

In the present cross-sectional study, we confirmed the prediction that very low CR would be associated with milder levels of Aβ deposition in elderly subjects displaying clinically meaningful cognitive deficits, in a sample including individuals from an environment that differs substantially from those of previous *in vivo* studies that evaluated relationships between CR and AD pathology. When treated as a continuous variable, lower CR was significantly related to lesser Aβ burden, with the largest effect size in the dementia group. In addition, there were significant findings when the sample was divided in three subgroups according to educational attainment cut-offs, with post hoc comparisons showing significantly lower Aβ burden in VLE relative to HIE subjects, both in the overall cognitively impaired sample and the dementia group (but not in the aMCI and cognitively unimpaired groups). Such differences emerged despite the fact that VLE subjects displayed, relative to the other subgroups, a similar proportion of individuals fulfilling criteria for aMCI or dementia and similar episodic memory scores, as well as lower overall cognitive performance relative to HIE subjects (supplementary_Table_2).

In contrast with our findings, which indicated that the relationship between CR and Aβ burden was driven by the clinically defined dementia group, there are previous studies that reported associations between educational attainment and Aβ deposition in aMCI but not dementia samples.[10] Such discrepancy may be related to the known heterogeneity of aMCI; only one-third of our aMCI subjects showed signs of Aβ positivity (Table 1), similar to the findings of recent population-based Aβ-PET investigations.[27] Significant CR-related findings in aMCI but not dementia samples in previous studies[10] were interpreted as reflecting that cortical Aβ deposition is already stabilized at a plateau by the time AD patients reach the clinical dementia stage.[28] Our finding of mild levels of Aβ burden in VLE dementia subjects relative to HIE patients is not consistent with such an explanation, instead suggesting that the difference between our results and those of previous Aβ-PET imaging investigations is because VLE dementia patients were only infrequently enrolled in those studies.

Despite their lower Aβ-burden levels relative to non-VLE patients, our VLE dementia patients still displayed significantly higher mean [^{11}C]PiB-SUVR relative to cognitively unimpaired subjects, with 57.1% of them being rated as Aβ positive based on a sensitive Aβ-burden threshold. Previous studies of preclinical and clinical AD samples showed that lower CR levels shift to the left the curve of incremental cognitive decline over time, bringing it closer to the ascending curve of biomarker abnormalities that precede the emergence of symptoms.[8] Our findings are consistent with such a proposition and provide direct evidence that VLE may drive some susceptible elderly individuals to the development of cognitive deficits compatible with AD dementia (with impairments in activities of daily living and need of care) in the face of mild levels of Aβ deposition, before the cortical saturation typically associated with the emergence of dementia in studies conducted in other environments.[28] The findings reported herein extend the results of previous blinded visual inspections of individual PET images from our overall cognitively impaired sample,[16] which highlighted a small proportion of dementia patients displaying no overt Aβ burden or brain hypometabolism and who were found to be in the VLE range. Our findings have implications regarding the use of the 2018 National Institute on Aging/Alzheimer's Association research framework for AD[17] across separate populations, indicating that CR levels must be taken into account when applying Aβ-tau-neurodegeneration staging systems. Our results indicate that a proportion of VLE dementia subjects presenting mild (but true) AD pathology may be misplaced outside the AD continuum.

The second prediction of our study was also confirmed, that is, that lower CR would be a significant predictor of reduced cognitive resilience to AD pathology. Cognitive tests such as the MMSE and RAVLT are known to be biased regarding low education.[29] However, as our indices of cognitive resilience depended also on the degree of Aβ deposition, the results reported herein cannot be taken to simply reflect disease-independent relationships between CR proxies and current cognitive performance. Moreover, the association between CR and cognitive resilience remained significant in our sample when an RES index based on a larger cognitive composite comprising several neuropsychological task items was employed. In the overall sample and in the Aβ-positive subsample, relationships between CR and quantitative measures of cognitive resilience to Aβ deposition were significant not only in bivariate regression models, but also when multivariate models accounted for the effects of other variables. It is notable that although SES also predicted cognitive resilience in bivariate regression analyses using the $RES_{COMPOSITE}$ index, such contribution was no longer significant in multivariate models including the CR score, suggesting a stronger influence of formative CR proxies than current SES on cognitive resilience to AD pathology in our sample.

In contrast with the above results implicating CR as a relevant predictor of cognitive resilience to AD pathology, there was only modest evidence of brain reserve influencing cognitive resilience in the present study, and no evidence of WMH either affecting cognitive resilience or influencing the emergence of dementia in VLE subjects. The latter

negative results may be due to the modest presence of cerebrovascular pathology in our overall sample, as attested by their low mean HIS scores and the exclusion of subjects with cortical or lacunar infarcts. Conversely, hippocampal volume deficits were present in cognitively impaired subjects as expected,[16] and these volume decrements significantly predicted lesser cognitive resilience to AD pathology independent of the influence of CR, particularly when the RES_{RAVLT} index was used. In early AD stages, key brain regions such as the hippocampus have been shown to undergo neuroplastic changes against a background of cortical Aβ deposition;[30] it may be the case that interindividual variations in such neuroplastic capacity of the hippocampus reflected variations in hippocampal volumes in our subjects, and influenced their degree of cognitive resilience.

Indices of cognitive resilience to AD pathology based on quantitative measures of Aβ burden have also been used in previous investigations.[3,4] The validity of such a choice is supported by findings of studies conducted with large samples of aMCI and/or cognitively unimpaired subjects, indicating that even mild levels of Aβ deposition may be significantly associated with cognitive functioning.[20,31] As in previous investigations,[3] we evaluated RES indices to Aβ burden in the overall sample regardless of inter-individual differences in Aβ classification, and one could argue that the results of such analyses might have been confounded by the inclusion of aMCI and cognitively unimpaired subjects classified as Aβ negative. However, it should be noted that we obtained highly similar results when regression analyses were restricted to Aβ-positive subjects, using indices of cognitive resilience to Aβ burden built specifically for those individuals classified as belonging to the "AD continuum."[17]

Along the "AD continuum," tau pathology is seen as more strongly linked to the emergence of neurodegeneration and clinically relevant cognitive decline than Aβ burden,[17,25] and it should be acknowledged that CSF- or PET-based tau measurements were not available in the present study. Therefore, we cannot ascertain the degree to which the cognitive resilience findings of the above regression analyses (and/or the emergence of dementia in the face of low Aβ burden in our VLE subjects) were influenced by inter-subject variations in the level of resilience to cope with combined effects of Aβ and tau pathologies;[4,11] the inclusion of AD individuals presenting an atypically earlier emergence of tau pathology;[32] or the inclusion of subjects presenting tau pathology with no Aβ deposition.[33] It should also be noted that overt signs of neurodegeneration were present in ≈50% of our cognitively impaired subjects (as ascertained by visual inspection of FDG-PET data sets), and it is most likely that inter-subject variations in the degree of Aβ- and tau-driven neurodegenerative changes influenced the results of the analyses using RES indices in the present study.

In addition to the above-mentioned absence of tau pathology measurements, other limitations of the present investigation should be acknowledged. Although effect sizes were not small either for the comparisons of VLE subjects against non-VLE subjects or the multivariate regression analyses reported herein, the size of our single-site sample was relatively modest in comparison to multi-center initiatives conducted elsewhere.[11] Therefore, replication of the current findings in samples including a large proportion of VLE subjects is warranted. In addition, subjects were allocated to education categories according to arbitrary cut-offs aimed to provide an even distribution of the sample in three subgroups approximating the first stage of elementary school, the second stage of elementary school plus high-school, and the stage of higher education in Brazil.[18] Finally, we did not add information on lifelong enriching exposures to build a more comprehensive CR score.[6]

In conclusion, this study provided direct *in vivo* support to the notion that very low CR is associated with limited cognitive resilience to AD pathology. Our results expand on findings of similar investigations conducted in other environments, and shed light on the brain mechanisms that may underlie the high rates and earlier emergence of dementia in low/middle-income countries. The demonstration that VLE subjects may develop dementia when presenting only mild levels of Aβ burden indicates that education must be accounted for when contemporary biological AD staging systems are applied across separate populations.

ACKNOWLEDGMENTS

This work was supported by grants from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (12/50329-6, 14/50873-3, and 2018/15167-1). We thank Maira O. de Oliveira and Eduardo S. Trés for assistance with the recruitment of subjects for the study, Patricia Rzezak Tenser for her input with the initial design and data collection for the study, and Sharon Sanz Simon for assistance in the definition of composite cognitive indices.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

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How to cite this article: Busatto GF, Porto FHdG, Faria DdP, et al. *In vivo* imaging evidence of poor cognitive resilience to Alzheimert's disease pathology in subjects with very low cognitive reserve from a low-middle income environment. *Alzheimer's Dement*. 2020;12:e12122.
https://doi.org/10.1002/dad2.12122