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Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease

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Neurology® 2018;90:e149-156. doi:10.1212/WNL.0000000000004802

Abstract

Objective

To examine cross-sectional effects of cognitive reserve (CR) and brain reserve (BR) on cognition across the spectrum of Alzheimer disease (AD).

Methods

We included 663 AD biomarker–positive participants with dementia (probable AD, n = 462) or in the predementia stages (preclinical/prodromal AD, n = 201). Education was used as a proxy of CR and intracranial volume as a proxy of BR. Cognition was assessed across 5 domains (memory, attention, language, visuospatial, and executive functions). We performed multiple linear regression models to examine effects of CR and BR on cognitive domain *Z* scores, adjusted for cerebral atrophy. Furthermore, we assessed differences in effects according to disease stage and across degrees of total reserve using a 4-level variable (high CR/high BR, high CR/low BR, low CR/high BR, and low CR/low BR).

Results

We found positive, independent effects of both CR and BR across multiple cognitive domains. Stratification for disease stage showed that effects of CR on attention and executive functioning were greater in predementia than in dementia ($\beta = 0.39$ vs $\beta = 0.21$ [Welch $t = 2.40$, $p < 0.01$] and $\beta = 0.46$ vs $\beta = 0.26$ [$t = 2.83$, $p < 0.01$]). Furthermore, we found a linear trend for better cognitive performance in all domains in the high CR/high BR group, followed by high CR/low BR, low CR/high BR, and then low CR/low BR (p for trend <0.05).

Conclusions

CR and BR both independently mitigate cognitive symptoms in AD. The positive effect of CR is most strongly expressed in the predementia stages and the additive effects of high CR and BR are most beneficial.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **BR** = brain reserve; **CR** = cognitive reserve; **ICV** = intracranial volume; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NIA-AA** = National Institute on Aging and Alzheimer's Association; **SCD** = subjective cognitive decline.

Neuropathologic and biomarker studies in patients with Alzheimer disease (AD) have revealed remarkable interindividual differences in the level of cognitive function at a comparable neuropathologic burden.[1–3] To account for these clinicopathologic discrepancies, the concept of reserve has been proposed.[4–6] Reserve describes the capacity to preserve cognitive function in the presence of neuropathology and can be divided into 2 components: cognitive reserve (CR) and brain reserve (BR).[4] CR is thought to act by recruiting alternate neural networks or utilizing existing networks more efficiently to cope with neuropathologic changes, and is often estimated using educational attainment.[4–6] When matched for clinical disease severity, patients with AD with higher education have more advanced levels of neuropathology,[7,8] indicating that individuals with greater CR can tolerate greater neuropathologic burden. BR represents a higher quantity of neural resources acting as a buffer that enables the brain to better tolerate emerging neuropathology, and is typically operationalized by intracranial volume (ICV) in human neuroimaging studies.[9–11] ICV increases during development[12] but remains largely stable with neurodegeneration due to chronologic aging or AD,[13] and has been shown to act as a resilience factor against clinical deterioration in the presence of AD pathology.[9–11] In the present study of AD biomarker–positive (preclinical, prodromal, and dementia) participants, we examine the independent and additive effects of CR and BR on memory, attention, visuospatial, language, and executive functions, while controlling for the degree of neurodegeneration as measured by cerebral atrophy.

Methods

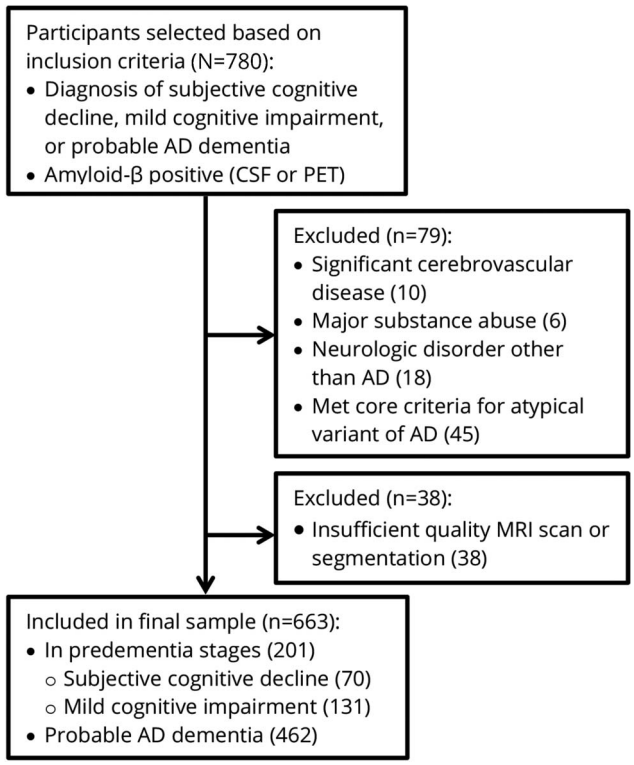
Participants

In this cross-sectional study, we included 663 participants with positive AD biomarkers. The sample was selected from the Amsterdam Dementia Cohort[14] and consisted of patients who visited the memory clinic of the VU University Medical Center in Amsterdam between January 2008 and December 2015 who consented to have their data used for research. All participants underwent standardized dementia screening including medical history, informant-based history, physical and neurologic examinations, lumbar puncture, brain MRI, and neuropsychological testing. Clinical diagnosis of probable AD or mild cognitive impairment (MCI) due to AD was established by consensus in a multidisciplinary team according to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria.[15,16] A diagnosis of subjective cognitive decline (SCD) was established when a patient presented with cognitive complaints in the absence of objective cognitive, neurologic, or psychiatric impairment.[17] Due to positive AD biomarkers and according to NIA-AA nomenclature,[18] these participants were classified as preclinical AD. Participants were included based on (1) diagnosis of probable AD,[15] MCI due to AD,[16] or SCD[17]; (2) positive CSF biomarkers for AD (i.e., β-amyloid $[A\beta]_{42}$ <638 ng/L or tau/$A\beta_{42}$ fraction >0.52[19]) or a positive Aβ (^{18}F-flutemetamol, ^{18}F-florbetaben, ^{18}F-florbetapir, or [^{11}C] Pittsburgh compound B) PET scan by visual assessment[20]; (3) availability of a 3T T1-weighted structural MRI scan; and (4) Mini-Mental State Examination (MMSE) ≥10. Exclusion criteria were (1) significant cerebrovascular disease on MRI, (2) a history of substance abuse, (3) major traumatic brain injury, (4) major psychiatric or neurologic disorders (other than AD), and (5) meeting core clinical criteria for an atypical variant of AD (e.g., posterior cortical atrophy; figure 1).

Standard protocol approvals, registrations, and patient consents

Informed consent was obtained from all participants and the medical ethics review committee of the VU University Medical Center approved the study.

Figure 1 Flowchart of the sample selection



AD = Alzheimer disease.

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MRI

All participants underwent MRI scans on a 3T MRI scanner, according to standardized acquisition protocols including a T1 sequence. Three different scanner types were used: SignaHDxt 3T (n = 493, GE Healthcare [Cleveland, OH], voxel size 0.94 × 0.94 × 1 mm, echo time 3 milliseconds, repetition time 7.8 milliseconds, flip angle 12°, field of view 240 mm), Vantage Titan 3T (n = 105, Toshiba Medical Systems [Glen Mills, PA], voxel size 1 × 1 × 1 mm, echo time 3.2 milliseconds, repetition time 9.5 milliseconds, flip angle 7°, field of view 256 mm), or Ingenuity TF PET-MRI 3T (n = 65, Philips Medical Systems [Best, the Netherlands], voxel size 0.87 × 0.87 × 1 mm, echo time 3 milliseconds, repetition time 7 milliseconds, flip angle 12°, field of view 250 mm). All statistical models included scanner type as a covariate.

CR and BR

As a proxy of CR, we used the Verhage system[21] to measure education. This is a standardized index (range 1–7), with a score of 1 indicating that primary school was not completed, while a score of 7 corresponds to an academic degree. ICV was used as a proxy measure of BR and was obtained by segmenting T1-weighted MRI using Statistical Parametric Mapping 12 software (SPM12; Wellcome Trust Centre for Neuroimaging, Institute of Neurology at University College, London, UK). This yields volumetric measures of gray matter, white matter, and CSF, which were summed to provide ICV.

Neurodegeneration

The concepts of CR and BR posit to explain discrepancies between observed and expected performance based on the level of underlying neuropathology. Therefore, operationalizations of CR and BR should include a measure of neuropathology.[22] In the present study, we used whole brain gray matter volume relative to ICV (reflecting cerebral atrophy) as a surrogate measure of neuropathology.

Cognition

A standardized neuropsychological test battery was used to assess performance in 5 cognitive domains: memory (visual association test; Rey Auditory Verbal Learning Test immediate and delayed recall), attention (digit span forward; Trail-Making Test part A; Stroop test form I and II), executive functioning (frontal assessment battery; Stroop test form III; digit span backward), language (category fluency [animal naming]; naming condition of the visual association test), and visuospatial ability (number location; dot counting; fragmented letters).[23,24] To obtain cognitive domain scores, all raw test scores were first converted into *Z* scores using the mean and SD of equivalent neuropsychological test scores from an independent reference group of healthy controls (n = 533, age = 59.7 ± 9.8 years, 46% male, MMSE = 28.9 ± 1.0) of AD biomarker–negative participants with SCD. *Z* scores for Trail-Making Test and Stroop test were inverted as higher scores indicate worse performance. *Z* scores were combined into cognitive domain scores by averaging scores across tests within each domain. Composite scores for each cognitive domain were only calculated if there were data available on ≥2 tests within that specific domain; otherwise that domain score was classified as missing (n for missing domain scores: memory = 7, attention = 7, executive functioning = 10, language = 25, visuospatial ability = 26). In addition, MMSE scores (available for all participants) were used as an index of global cognitive functioning.

Statistical analysis

We used multiple linear regression models, adjusted for cerebral atrophy, age, sex, and scanner type, to examine the effects of education and ICV on cognition. Cognitive domain *Z* scores and MMSE scores were the dependent variables in the models and cases with missing cognitive domain scores were excluded from the analyses. First, we assessed the predictive effects of education and ICV separately (model 1), followed by a model including both predictors (model 2) to examine their independent effects. Next, we examined whether the effects of education and ICV on cognition differed according to disease stage, by performing regression models in predementia participants (SCD or MCI, n = 201) and in participants with dementia (probable AD, n = 462). Differences in effects across disease stages were assessed by Welch *t* tests,[25] using the regression slopes (β) and corresponding standard error.[26,27] To test the assumptions of the regression analyses, we plotted and checked residuals of all models. Residuals were normally distributed, heteroscedasticity was in conformance with test assumptions, and Durbin-Watson test statistics indicated independence of observations. Furthermore, variance inflation factor values, tolerance values, and correlations between variables did not indicate multicollinearity between predictors. Next, we dichotomized the total sample according to low vs high CR using a median split for education (Verhage 1–5 = low education, 6–7 = high education) and according to low vs high BR using a mean split for ICV (1.12–1.51 = low ICV, 1.52–2.01 = high ICV). Using these dichotomized groups, we computed a 4-level variable representing degree of total reserve; low CR and BR (CR−/BR−, n = 220), low CR and high BR (CR−/BR+, n = 180), high CR and low BR (CR+/BR−, n = 121), high CR and BR (CR+/BR+, n = 142). To assess differences in cognition across these 4 levels, we fitted general linear models, adjusted for cerebral atrophy, age, sex, and scanner type, and examined post hoc linear trends across levels. All statistical analyses were performed in SPSS version 20 (released 2011, IBM SPSS Statistics for Windows, Armonk, NY) and statistical significance in all models was set at $\alpha = 0.05$ (2-tailed), uncorrected for multiple comparisons. GraphPad Prism (GraphPad Software, La Jolla, CA) version 6.0 was used for the figures.

Results

Demographic and clinical characteristics of the total sample and according to disease stage are presented in table 1. There were no differences according to disease stage in sex ($p = 0.17$), age ($p = 0.41$), or ICV ($p = 0.18$), while education

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was lower in participants with dementia than in predementia participants ($p < 0.05$). As expected, participants with dementia had lower cognitive scores ($p < 0.05$) and reduced ICV-corrected gray matter volumes (i.e., more cerebral atrophy, $p < 0.05$) compared to predementia participants. Pearson correlation analysis revealed a modest association between education and ICV in the total sample ($r = 0.17$, $p < 0.01$). Furthermore, ICV-corrected gray matter volume was moderately associated with cognition (memory: $r = 0.31$, attention: $r = 0.36$, executive functioning: $r = 0.41$, language: $r = 0.31$, visuospatial ability: $r = 0.39$, and MMSE: $r = 0.45$, all $p < 0.01$), adjusted for age, sex, and scanner type.

Effects of CR and BR on cognition

Multiple regression analyses with adjustment for cerebral atrophy, age, sex, and scanner type (model 1) revealed positive effects of both education and ICV on all cognitive domains (all $p < 0.05$; table 2). When combining education and ICV in a single model (model 2), all effects survived, except for the effect of ICV on language ($p = 0.11$; table 2). These results indicate that, while controlling for the degree of cerebral atrophy, both CR and BR have a positive effect on cognition in participants with positive AD biomarkers.

Effects of CR and BR on cognition according to disease stage

Next, we stratified the sample according to disease stage (dementia vs predementia) and performed model 1 and 2 in both patient groups. Model 1 showed positive effects of education on attention, executive functioning, and MMSE scores in predementia participants, and on memory, attention, executive functioning, visuospatial ability, and MMSE in participants with dementia (all $p < 0.05$). Furthermore, there were positive effects of ICV on executive functioning and MMSE in predementia participants ($p < 0.05$) and on memory, attention, executive functioning, visuospatial ability, and MMSE in participants with dementia (all $p < 0.05$; table 2). When combining education and ICV in one model (model 2), we found that all effects of education and ICV survived ($p < 0.05$), with the exception of the effects on memory in participants with dementia ($p = 0.08$ for education, $p = 0.11$ for ICV; table 2) and the effect of ICV on MMSE in predementia participants ($p = 0.07$; table 2). The effect sizes of education on attention ($\beta = 0.39$, $p < 0.01$ vs $\beta = 0.21$, $p < 0.01$) and executive functioning ($\beta = 0.46$, $p < 0.05$ vs $\beta = 0.26$, $p < 0.01$) were 46% and 43% larger in predementia participants than in participants with dementia (Welch $t = 2.40$, $p < 0.01$ and $t = 2.83$, $p < 0.01$; figure 2A). This indicates that high CR is especially beneficial for cognition in early stages of AD. There were no differences for the effects of ICV (i.e., BR) according to disease stage (figure 2B).

Differences in cognitive functioning across levels of reserve

Subsequently, we constructed a 4-level variable (i.e., CR−/BR−, CR−/BR+, CR+/BR−, and CR+/BR+) and fitted general linear models, adjusted for cerebral atrophy, age, sex, and scanner type, to assess cognitive performance across

Table 1 Demographic and clinical characteristics of the total sample and according to disease stage

	Total (n = 663)	Predementia (n = 201)	Dementia (n = 462)
Diagnosis		SCD (70); MCI (131)	Probable AD (462)
Sex, % male	49	53	47
Age, y	66.2 (7.4)	66.6 (7.5)	66.1 (7.4)
Education, Verhage, median (range)	5 (2–7)	5 (2–7)[a]	5 (2–7)
ICV	1.51 (0.16)	1.52 (0.16)	1.50 (0.16)
MMSE	22.7 (4.8)	27.0 (2.2)[a]	20.8 (4.3)
Cerebral atrophy[b]	0.39 (0.04)	0.41 (0.04)[a]	0.38 (0.04)
Cognitive function *Z* scores[c]			
Memory	−3.78 (3.27)	−1.39 (1.56)[a]	−4.83 (3.36)
Attention	−1.87 (2.58)	−0.39 (0.81)[a]	−2.53 (2.81)
Executive functioning	−1.84 (1.81)	−0.50 (0.91)[a]	−2.43 (1.80)
Language	−1.09 (1.33)	−0.29 (0.58)[a]	−1.45 (1.41)
Visuospatial ability	−1.69 (2.67)	−0.21 (0.87)[a]	−2.35 (2.93)

Abbreviations: AD = Alzheimer disease; ICV = intracranial volume in dm^3; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SCD = subjective cognitive decline.
Values are depicted as mean (SD) unless otherwise indicated. Group comparisons were performed using χ^2, Mann-Whitney *U*, or independent samples *t* tests, where appropriate.
[a] Predementia > dementia.
[b] Gray matter volumes relative to ICV; lower values indicate more cerebral atrophy.
[c] *Z* scores calculated using the mean and SD of independent reference group.

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Table 2 Effects of education and intracranial volume (ICV) in the total sample and according to disease stage

	Education		ICV	
Domain	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[c]**
Memory	0.12[d]	0.10[d]	0.18[d]	0.16[d]
Attention	0.24[d]	0.22[d]	0.21[d]	0.15[d]
Executive function	0.31[d]	0.28[d]	0.26[d]	0.19[d]
Language	0.11[d]	0.10[d]	0.11[d]	0.08
Visuospatial ability	0.16[d]	0.14[d]	0.18[d]	0.15[d]
MMSE	0.28[d]	0.25[d]	0.26[d]	0.19[d]

	Education				ICV			
	Predementia (n = 201)		Dementia (n = 462)		Predementia (n = 201)		Dementia (n = 462)	
Domain	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[b]**	**Model 1[a]**	**Model 2[c]**	**Model 1[a]**	**Model 2[c]**
Memory	0.04	0.02	0.10[d]	0.08	0.12	0.12	0.13[d]	0.10
Attention	0.40[d]	0.39[d]	0.23[d]	0.21[d]	0.12	0.06	0.21[d]	0.14[d]
Executive function	0.48[d]	0.46[d]	0.28[d]	0.26[d]	0.26[d]	0.18[d]	0.23[d]	0.15[d]
Language	0.13	0.13	0.06	0.06	−0.01	−0.03	0.08	0.05
Visuospatial ability	0.10	0.08	0.16[d]	0.14[d]	0.15	0.14	0.17[d]	0.13[d]
MMSE	0.34[d]	0.32[d]	0.27[d]	0.25[d]	0.21[d]	0.16	0.23[d]	0.15[d]

Abbreviations: ICV = intracranial volume; MMSE = Mini-Mental State Examination.
Values depicted are partial regression coefficients (β).
[a] Effects adjusted for cerebral atrophy, age, sex, and scanner type.
[b] Effects adjusted for cerebral atrophy, age, sex, scanner type, and intracranial volume.
[c] Effects adjusted for cerebral atrophy, age, sex, scanner type, and education.
[d] Significant effect at $p < 0.05$.

levels. We observed a linear trend across all cognitive domains and MMSE with highest estimated marginal means for CR+/BR+, followed by CR+/BR−, CR−/BR+, and then CR−/BR− (p for trend <0.05, figure 3). Sensitivity analysis (switching the CR−/BR+ and CR+/BR− groups) confirmed the linear trend ($p < 0.05$).

Discussion

The main findings of our study are (1) CR and BR both have independent positive effects on cognition in participants with biomarker evidence of AD, adjusted for cerebral atrophy, (2) the effects of CR on attention and executive functioning were greater in predementia participants than in participants with dementia, (3) the effects of CR were generally greater than those of BR, and (4) there was a linear trend for better cognitive performance in all domains (adjusted for cerebral atrophy) in the CR+/BR+ group, followed by CR+/BR−, CR−/BR+, and then CR−/BR−.

The positive effects of CR and BR (as indicated by education and ICV) on cognitive functioning in this study are in line with most literature, suggesting that higher education and greater ICV positively influence the cognitive trajectory of patients with AD.[7–11] We extend on these findings by demonstrating that CR and BR differentially mitigate cognitive symptoms in AD, as CR was most beneficial in predementia stages (there was no disease stage–specific effect for BR) and the effects of CR were overall stronger than those of BR. Although CR and BR are related to similar underlying factors, our results thus indicate that they are at least partially separate components of a larger concept (i.e., reserve) rather than interchangeable terms describing a single entity. This is further highlighted by the small correlation ($r = 0.17$) between education and ICV in our sample.

Physiologic mechanisms underlying the protective effect of CR may include facilitating the development of new cognitive strategies,[4] modulation of functional connectivity in hub regions such as the posterior cingulate cortex,[28,29] and strengthened network reliability,[30] which are all associated with higher education. These mechanisms actively support the brain to cope with neuropathology. The mechanism underlying BR is to increase resilience to neuropathology through greater quantities of premorbid brain parenchyma. In the event of neurodegeneration, the necessary structural integrity to maintain normal cognitive functioning will be retained for a longer period in individuals with high BR than in individuals with low BR.[4–6] More detailed examinations into

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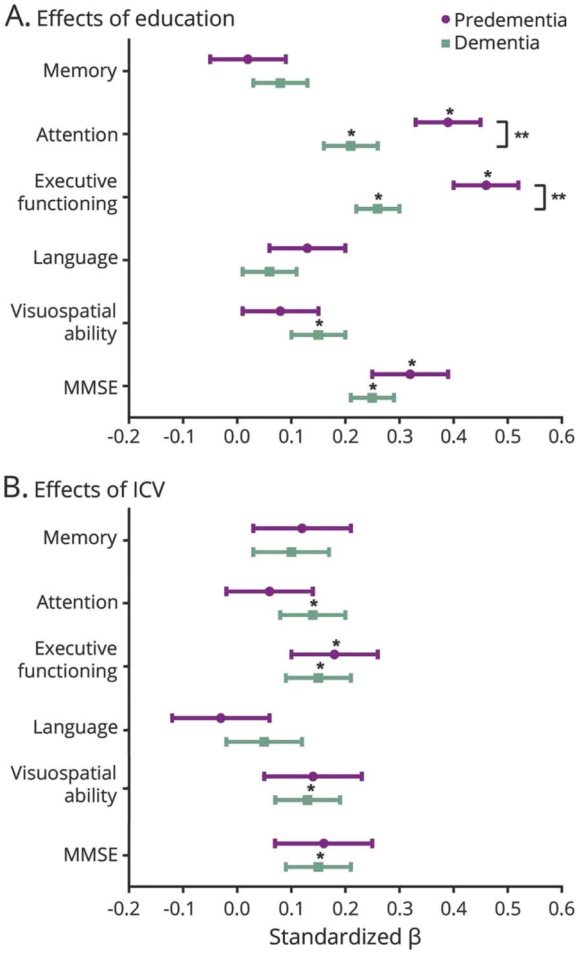
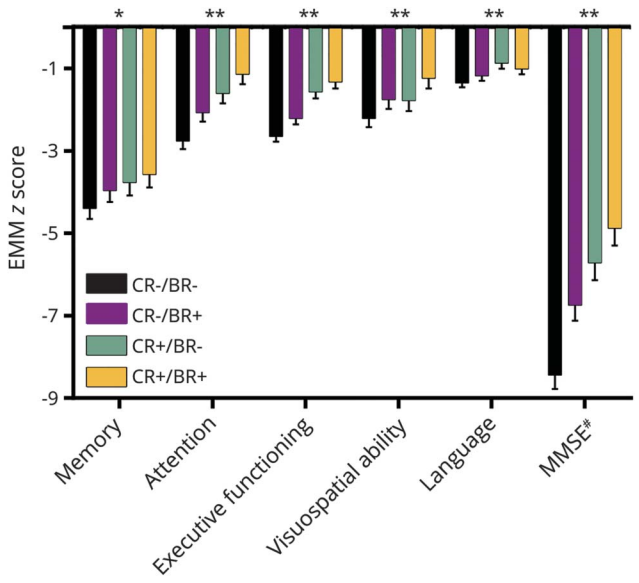
Figure 2 Effect sizes of education and intracranial volume (ICV) on cognition according to disease stage



(A) Effect size of education. (B) Effect size of ICV. Effect sizes are partial regression coefficients (β), adjusted for cerebral atrophy, age, sex, and scanner type. Error bars indicate the standard error. *Significant effect at $p < 0.05$. **Difference of effect sizes between groups (Welch t test, $p < 0.05$). MMSE = Mini-Mental State Examination.

Figure 3 Standardized cognitive domain and Mini-Mental State Examination (MMSE) scores (adjusted for cerebral atrophy) across degrees of total reserve



Data are estimated marginal means (EMM) (plus standard error) for cognitive domain Z scores, adjusted for cerebral atrophy, age, sex, and scanner type. BR = brain reserve; CR = cognitive reserve. *p for trend <0.05. **p for trend <0.01. #MMSE scores were converted to Z scores for visualization purposes; we used raw scores in the statistical analyses.

the effects of BR, for instance focused on microstructural integrity of the brain (e.g., synaptic density measured with PET[31]), could provide a more comprehensive depiction of the mechanisms behind the protective effect of BR in AD.

A considerable body of literature has described positive effects of education and ICV on cognition, but these effects—especially for ICV—have not been replicated in all studies.[32,33] Strengths of the present study, such as the large sample size, inclusion of AD biomarker–positive participants ranging from preclinical to dementia stages, availability of 3T MRI, SPM12-based tissue segmentation,[34] and detailed neuropsychological testing, likely increased sensitivity for detecting effects of education and ICV compared to some previous studies. Some limitations of the present study also need to be addressed. First, there are inherent limitations related to cross-sectional designs and longitudinal follow-up studies are needed to confirm whether reserve has a direct effect on the progression of cognitive decline. Second, the difference in sample size between the predementia group (n = 201) and dementia group (n = 462) may have resulted in more significant effects being observed in the dementia group with similar effect sizes. However, power analyses revealed that both sample sizes were sufficient to detect effects and interpretation of results was focused on (differences in) effect sizes rather than levels of significance. Possible associations between predictors, especially between ICV and cerebral atrophy, may have resulted in multicollinearity in the regression models. However, we conducted thorough assessment of multicollinearity by examining tolerance values and variance inflation factors, and these assessments revealed no indication for significant multicollinearity in the regression models. Furthermore, the modest correlations between predictors ($r = 0.32$ between ICV and cerebral atrophy in the total sample) fall well below the assumption that a correlation higher than $r = 0.70$ indicates multicollinearity.[35] Third, our relatively young cohort (mean age 66.2 ± 7.4 years) may be characterized by an overrepresentation of hippocampal-sparing AD[36] and relative paucity of comorbidities. This should be taken into account when generalizing or replicating our findings to cohorts with a higher average age. Finally, reserve is a hypothetical construct that is often measured using proxies, which come with inherent limitations and imperfections. For instance, there may be geographical differences related to access and level of education and there exists a range of methods to measure education, from total years of school to categorical scales such

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as the Verhage scale.[21] Also, education is associated with other socioeconomic characteristics (e.g., occupation, access to general health care), which in turn may affect CR. Furthermore, ICV serves as an easily obtainable proxy of BR but may reflect early childhood brain development to a higher extent than later childhood and adolescent influences.

Our results indicate that CR, as measured by education, has the greatest potential to delay or slow down cognitive decline in AD. This highlights the importance of education in early life. However, our findings regarding the differential effects of CR between disease stages may also serve tailoring clinical interventions in late life. We have shown that the effects of CR are especially beneficial in the earlier phases of the disease, which indicates that interventions (e.g., physical activity interventions[37] or cognitive training) would preferentially be offered early on in the disease course. BR as measured by ICV is in itself a nonmodifiable factor. However, our results regarding the additive effects of CR and BR suggest that interventions tailored to increasing CR would show maximized treatment effects in individuals with high BR. These insights may help to tailor interventions and to reduce the rate of cognitive decline in neurodegenerative diseases and promote successful aging.

Author contributions

Colin Groot contributed to study design; acquisition, analysis, and interpretation of data; writing and revising the manuscript; and performed statistical analysis. Anna C. van Loenhoud contributed to study design and statistical analysis and helped with interpretation of data and revising the manuscript. Bart N.M. van Berckel was involved in the acquisition of PET data and revised the manuscript. Philip Scheltens and Frederik Barkhof helped with critical revision of manuscript for intellectual content and interpretation of data. Teddy Koene was involved in the acquisition of neuropsychology data. Charlotte C. Teunissen was involved in acquisition of CSF biomarker data and helped with critical revision of manuscript for intellectual content and interpretation of data. Wiesje M. van der Flier contributed to acquisition of patient data from the Amsterdam Dementia Cohort, performed statistical analysis, and helped with interpretation of results and critical revision of manuscript for intellectual content. Rik Ossenkoppele contributed to study concept and design and critical revision of manuscript for intellectual content; helped in writing and revising the manuscript, statistical analysis, acquisition and analysis of MRI data, and revising the manuscript; and supervised the study.

Study funding

Research of the VUMC Alzheimer Center is part of the Neurodegeneration Research Program of the Neuroscience Campus Amsterdam. The VUMC Alzheimer Center is supported by Alzheimer Nederland and Stichting VUMC funds. The clinical database structure was developed with funding from Stichting Dioraphte. This research was funded by the Internationale Stichting Alzheimer Onderzoek (ISAO) (to R.O.); Marie Curie FP7 International Outgoing Fellowship (628812) (to R.O.); and the donors of Alzheimer's Disease Research, a program of BrightFocus Foundation (to R.O.). F.B. is supported by the NIHR UCLH biomedical research center.

Disclosure

C. Groot and A. van Loenhoud report no disclosures relevant to the manuscript. F. Barkhof is editorial board member of *Brain*, *European Radiology*, *Neurology®*, *Multiple Sclerosis Journal*, and *Radiology*; performed consultancy and received personal compensation and honoraria from Bayer-Schering Pharma and Genzyme; received compensation (personal and to institution) and honoraria from Biogen-IDEC, TEVA, Merck-Serono, Novartis, Roche, Synthon BV, and Jansen Research; received payment for development of educational presentations from IXICO and Biogen-IDEC (to institution); is funded by a Dutch MS Society grant, EU-FP7/H2020; and is supported by the NIH Research Biomedical Research Center at University College London Hospital. B. van Berckel, T. Koene, C. Teunissen, P. Scheltens, W. van der Flier, and R. Ossenkoppele report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received June 16, 2017. Accepted in final form September 27, 2017.

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SOURCE ARTICLE NPub.org/yfs0tr

Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease

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Neurology® 2018;90:64. doi:10.1212/WNL.0000000000004802

Study question

What are the cross-sectional effects of cognitive reserve (CR) and brain reserve (BR) on cognition across the spectrum of Alzheimer disease (AD)?

Summary answer

CR and BR both independently and additively mitigate cognitive symptom severities in AD, with the benefits of CR being strongest in predementia stages.

What is known and what this article adds

CR and BR both mitigate the cognitive symptoms of AD by helping patients cope with neuropathologic changes. This study elucidates how CR and BR independently and additively affect various cognitive domains in different AD stages.

Participants and setting

The study included 462 persons with dementia-stage AD and 201 persons with predementia AD. They were selected from the Amsterdam Dementia Cohort and had visited the VU University Medical Center Amsterdam between January 2008 and December 2015.

Design, size, and duration

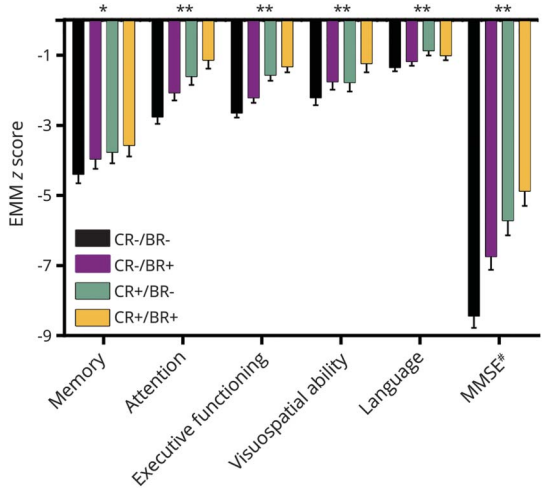
The study used education levels, as measured with the Verhage system, as a proxy for CR and intracranial volume (ICV), as measured with MRI, as a proxy for BR. The ratio of whole-brain gray matter volume to ICV was used as a proxy for cerebral atrophy.

Primary outcomes

The primary outcomes were scores in 5 cognition domains: memory, attention, visuospatial, language, and executive functions.

Main results and the role of chance

Compared to patients in predementia stages, those with dementia had lower education, lower cognitive scores, and greater cerebral atrophy ($p < 0.05$ for all). Multiple regression analyses showed that, controlling for the effects of cerebral atrophy, greater education and ICV had independent positive effects on all cognitive domains except for the absence of an effect of ICV on language ($p < 0.05$). General linear models confirmed the additively beneficial effects of education and ICV on all domains ($p < 0.05$ for trend). Analyses by disease stage showed that the effects of CR were especially beneficial in predementia cases and were generally larger than the effects of BR, but there was no benefit for education in patients with dementia.



Bias, confounding, and other reasons for caution

The cross-sectional design of this study precluded any determination of whether CR and BR directly affect the progression of cognitive decline. CR and BR were measured via proxies.

Generalizability to other populations

The participants were relatively young (mean age 66.2 ± 7.4 years), so there is limited generalization to older patients.

Study funding/potential competing interests

This study was funded by various medical research foundations. Dr. Barkhof has received personal compensation from various pharmaceutical companies and serves on several journals' editorial boards. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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