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Research Article

Psychometric Characteristics of Cognitive Reserve: How High Education Might Improve Certain Cognitive Abilities in Aging

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Aging Brain: Vasculature, Ischemia, and Behavior Study

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Keywords
Cognitive impairment · Cognitive aging · Education · Psychometrics · Symptomatology

Abstract
Background: The capacity to mitigate dementia symptomology despite the prevailing brain pathology has been attributed to cognitive reserve. ***Objectives:*** This study aimed to investigate how psychometric performance differs between individuals with a high school versus college education (surrogate measures for medium and high cognitive reserves) given the same level of brain pathology assessed using quantitative structural MRI. ***Methods:*** We used data from the Aging Brain: Vasculature, Ischemia, and Behavior Study (ABVIB). Cognition was assessed using a neuropsychological battery that included those contained in the National Alzheimer's Coordinating Center (NACC) uniform data set. Participants with a medium and high cognitive reserve were matched by level of structural MRI changes, gender, and age. ***Results:*** Matched-pair regression analyses indicated that individuals with a higher education had a significantly better performance in recognition and verbal fluency animals, working

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memory, and processing speed in complex tasks. Moreover, they had a better performance in interference trails compared to individuals with a high school education (medium cognitive reserve). ***Conclusions:*** Our findings suggest that, given the same level of brain pathology, individuals with a higher education (cognitive reserve) benefit from a superior performance in semantic memory and executive functioning. Differences in these cognitive domains may be key pathways explaining how individuals with a high cognitive reserve are able to diminish dementia symptomatology despite physical changes in the brain.

Introduction

Cognitive reserve can be viewed as an active capacity to mitigate dementia symptomatology despite the prevailing brain pathology. It is seen as "the ability to optimize or maximize performance through differential recruitment of brain networks, which perhaps reflect the use of alternate cognitive strategies" [1]. This capacity is formed by exposure to high mental demands throughout the life course, such as attaining a high level of education [2]. Engaging in intellectually stimulating activities also seems to foster a higher cognitive reserve [3], yet it is unclear what exactly cognitive reserve is and what cognitive mechanisms (e.g., synaptic density and neuronal circuitry) are involved.

To arrive at a better understanding of cognitive reserve, a great number of research papers have investigated the neurobiological differences in the brains of individuals with high and low cognitive reserves. Individuals with a higher cognitive reserve seem to have a greater brain volume, increased cortical thickness [4], diminished age-related alterations in CSF biomarkers of Alzheimer's disease [5, 6], and better functional connectivity between brain areas [4, 7], and they seem to recruit alternate networks to compensate for the pathological disruption [8, 9]. However, the structural state of the brain only partially explains how some individuals obviate clinical symptoms of dementia despite brain pathology.

Studies investigating functional processes of the brain have shown that cognitive reserve draws on the ventral and dorsal attention systems [10–12]. Compensating for brain pathology seems to be accomplished by recruiting the contralateral dorsolateral prefrontal cortex and by shifting brain networks from posterior to anterior [4, 13], which suggests that cognitive processes in this brain area, such as executive functioning and mental representations, might play a role [14]. However, the cognitive processes that enable individuals with a high cognitive reserve to withhold dementia symptomatology have not been established using psychometric data.

The cognitive or neuropsychological characteristics of cognitive reserve are rarely described in scientific literature. There seems to be only one construct that has been investigated so far, i.e., "residual memory variance," which is the discrepancy between an individual's predicted and actual memory performance [15] that correlates with resilience to dementia incidence [16] but not with indicators of brain pathology [17]. However, "residual memory performance" cannot explain the entire effect of cognitive reserve [18] and evidence from longitudinal studies comparing cognitive decline in individuals with high and low education indicates that besides memory also executive functioning could play a role [19–22].

The aim of our study was to investigate the psychometric characteristics of cognitive processes associated with cognitive reserve. By matching participants with 2 levels of education (a proxy for cognitive reserve) on severity of brain pathology, we investigated differences in psychometric performance hypothesizing that individuals with a higher education (mean greater than 19 years) have a better performance in memory and executive functioning compared to individuals with a lesser education (mean less than 13 years).

Table 1. Sample characteristics

Characteristic		High education (cases)	Low education (controls)	p^a
Age, years		75.1±5.3	75.1±5.6	0.99
Education, years		20.2±1.2	11.7±0.8	<0.0001
MMSE score		28.6±1.9	27.9±2.2	<0.0001
HCV		37.5±2.7	37±3.1	0.049
White-matter lesions, *n*		0.4±0.1	0.4±0.1	0.61
Gender	male	82.5	63.1	<0.0001
	female	17.5	36.9	
Marital status	married/living together	68.3	63.9	0.30
	single/widowed/divorced	31.7	36.1	
APOE e4 allele	yes	25.0	33.7	0.03
	no	75.0	66.3	
Race	white	82.5	73.4	0.001
	African-American	7.5	9.5	
	Hispanic	2.8	11.5	
	Asian	7.2	5.6	
Study site	USC	19.0	12.7	<0.0001
	UCSF	50.0	2.0	
	UCD-S	14.3	54.0	
	UCD-M	16.7	31.3	

Values are presented as means ± SD or percents. There were 252 matched pairs. HCV, hippocampal volume as a percentage of the total intracranial volume; UCSF, University of California, San Francisco; UCD, University of California, Davis; USC-M, University of Southern California Martinez; USC-S, University of Southern California Sacramento. [a] Estimated via a χ^2 test (for categorical variables) or the Mann-Whitney U test or the Kruskal-Wallis test (for continuous variables).

Materials and Methods

Study Population

This study is based on a prospective, longitudinal cohort study started in 2008 known as the Aging Brain: Vasculature, Ischemia, and Behavior Study (ABVIB; https://ida.loni.usc.edu/login.jsp?project = ABVIB). The primary goal of ABVIB was to assess the contributions of cardiovascular risk factors (laboratory studies) and cerebrovascular disease (carotid intima media thickness and retinal vessels) to brain structure and function, alone or in combination with Alzheimer's disease. Measures of brain structure and function included serial MRI and neuropsychological testing. Exclusion criteria were: age younger than 55 years, non-English-speaking, cortical strokes, severe illnesses other than cardiovascular or dementia, and use of medications that affect cognition. A total of 280 participants completed the neuropsychological assessments as well as the brain imaging. For the purpose of this study, we used only data from those participants who had valid psychometric testing and brain data. Further, the sample size was restricted to individuals matched into pairs of lesser and high cognitive reserve based on brain pathology (details in the following section) who did not have dementia.

Cognitive Reserve

There is currently no standardized measure of cognitive reserve. However, there is a consensus that individuals with a higher education have a high cognitive reserve and individuals with a low education have a low cognitive reserve [1]. The mean level of education in our sample was 16.09 years, with an SD of 2.79 years. Accordingly, individuals with less than 13 years of education were considered to have a lesser education (i.e., lesser cognitive reserve; Table 1). Individuals with more than 19 years of education were considered to have a higher education (i.e., higher cognitive reserve; Table 1).

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Matching of Pairs with High and Low Cognitive Reserves by Age, Gender, and Imaging

The matching procedure followed the matched case-control design where the "cases" are those individuals with a higher education, and thus a higher cognitive reserve, and the "controls" are those with a low education, and thus a lower cognitive reserve. Participants were matched individually by pairing one individual with a high education to one individual with a low education of the same gender. Further matching criteria were: an age difference of no more than 6 years and a hippocampal volume as a percentage of the entire intracranial volume of ±0.08 between cases and controls. The brain scans of 495 potential pairs were compared visually with respect to atrophy and white-matter lesions. We identified 252 matched pairs that had a comparable level of brain pathology. One participant was paired with several different other participants if the criteria matched. We chose this approach to maximize the number of pairs available for analysis. For sensitivity analysis, we also identified pairs in which one participant was uniquely matched to another participant. Application of an algorithm with the restriction that every participant be used only once resulted in the identification of 29 matched pairs for analysis.

Psychometric Testing

This study employed the standardized psychometric tests, including those contained in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) neuropsychological battery. The NACC neurological battery was developed by a task force constituted by the National Institute on Aging (NIA) to have standardized methods for collecting longitudinal data across all Alzheimer's disease centers in the USA [23]. It comprises 10 tests that focus on early detection of cognitive impairment and is available online (https://www.alz.washington.edu/WEB/forms_uds.html). Executive functioning was assessed via the Trail Making Test B (category switching) and the Stroop test (inhibitory control). Long-term memory was assessed via psychometric tests that require the use of semantic knowledge/long-term memories, i.e., the Boston Naming Test and the Semantic Verbal Fluency Test (animals and vegetables). The use of semantic networks within which long-term memories are embedded was assessed via the number of intrusions in the Verbal Fluency Test and the semantic relatedness of the answers in the MAS. Further, working memory was assessed using the Digit Span Test, processing speed was assessed using the Trail Making Test A and the Digit Substitution Test, and learning was assessed using the Biber Visual Learning Test (delayed recall) and the MAS Verbal Learning Test (delayed recall).

Statistical Analyses

All statistical analyses employed an α level for a statistical significance of 0.05 (two-tailed) and were performed using Stata 14.2.

Descriptive comparison of the characteristics of individuals with higher and lower cognitive reserves were obtained using a χ^2 test (for the categorical variables gender, marital status, APOE e4 allele, race, and study site) and the Mann-Whitney U or Kruskal-Wallis test (for the continuous variables age, years of education, Mini-Mental State Examination [MMSE], hippocampal volume, white-matter lesions, and performance on the psychometric test).

The hypothesis that individuals with a higher cognitive reserve have a significantly better performance on tests involving memories and executive functioning compared to individuals with a lower cognitive reserve, while taking into account brain pathology, was analyzed in a matched case-control design. Using pairs of individuals with low and high cognitive reserves matched by brain pathology, we conducted conditional regression analyses on the impact of cognitive reserve (lower/higher education) on performance in cognitive testing adjusted for study site and MMSE (significant differences between cases and controls) separately for each psychometric test.

In a sensitivity analyses, we repeated the same analyses but with the 29 pairs in which every participant was used only once.

Results

The characteristics of the study sample are shown in Table 1. Individuals with a higher education were significantly more likely to have more years of education, to be male, non-Hispanic white, or Asian, to come from the San Francisco (University of California, San Francisco; UCSF) study site, and to not have an APOE e4 allele. Moreover, individuals with a higher

Table 2. Mean performance on psychometric tests

Cognitive domain	Test	Higher education (cases)	Lower education (controls)	p^a
Executive cognitive abilities				
Switching	Trail Making Test B	84.5±36.9	159.5±66.7	<0.0001
	Stroop words	124.1±20.2	110.6±19.2	<0.0001
	Stroop colors	89.7±15.2	84.3±17	0.0002
Inhibition	Stroop interference	42.1±9.8	32.6±13	<0.0001
	Stroop errors (words)	0.2±0.6	0.3±0.7	0.72
	Stroop errors (colors)	0.6±0.9	0.7±0.8	0.43
	Stroop errors (interference)	0.7±1.4	1.8±2.5	<0.0001
Memories				
Verbal knowledge	verbal fluency (animals)	19.8±5.5	15.9±4	<0.0001
	verbal fluency (vegetables)	11.6±3.5	12.1±3.6	0.18
Visual confrontation naming	Boston naming (uncued)	56.2±3.6	46.4±10.8	<0.0001
	Boston naming (total)	56.4±3.4	46.8±10.7	<0.0001
Speed	Trail Making Test A	36±16.1	39.9±11.9	0.002
	digit symbol substitution	45.2±7.7	34.4±10.6	<0.0001
Working memory	digit span (forward)	6.6±1.1	5.7±1.3	<0.0001
	digit span (backward)	5±1.4	3.8±1.1	<0.0001
Learning	Biber visual learning delayed recall	4.1±1.7	3.2±1.5	<0.0001
	MAS verbal learning delayed recall	9.3±2.5	8.4±3	0.0002
Semantic networks	verbal fluency animals (intrusions)	0.1±0.4	0.1±0.2	0.28
	verbal fluency vegetables (intrusions)	0.6±1.1	1±2.2	0.023
	MAS semantically related	0.4±0.7	2±3.5	<0.0001
	MAS semi-related	0.1±0.3	1.5±3.6	<0.0001
	MAS unrelated	0.1±0.3	0.9±2	<0.0001

Values are presented as means ± SD. [a] Estimated via the Mann-Whitney U test or the Kruskal-Wallis test.

education were more likely to have higher MMSE scores (28.6 vs. 27.9) and a greater hippocampal volume (37.5 vs. 37.0; Table 1).

Comparison of mean scores on the psychometric tests between those with a higher education and those with a lower education indicated that individuals with a higher education had a significantly different performance with respect to almost all psychometric aspects tested, except for word and color errors in the Stroop test, the number of vegetables named in the verbal fluency test, and the number of intrusions in the verbal fluency test with animals (Table 2).

As the performance on psychometric tests is subject to the level of brain pathology, we matched individuals with lower and higher education levels by brain pathology and estimated the difference in performance on psychometric tests via conditional regression analysis adjusted for study site, and MMSE. Results confirmed the observation from the comparison of the means: a higher education was a significant predictor of performance with respect to almost all psychometric aspects tested except for color errors in the Stroop test and the number of vegetables named in the verbal fluency test (Table 3). In addition, results suggested that the performance on the Stroop color trails and the Trail Making Test A was not significantly different between individuals with high and lower education levels.

To see whether the fact that we "reused" participants in different pairs affected the results, we conducted sensitivity analyses. Repeating the previous analyses but with the 29 pairs in which every participant was used only once reduced the statistically significant

Table 3. Conditional regression analysis estimates of the effect of high cognitive reserve (being a case) on performance in psychometric tests, adjusted for study site and MMSE

Cognitive domain	Test	OR (95% CI)	*p*
Executive cognitive abilities			
Switching	Trail Making Test B	0.97 (0.96–0.98)	<0.0001
	Stroop words	1.02 (1.01–1.04)	0.004
	Stroop colors	1.01 (1–1.03)	0.14
Inhibition	Stroop interference	1.05 (1.02–1.08)	0.0004
	Stroop errors (words)	1.06 (0.66–1.69)	0.81
	Stroop errors (colors)	1.84 (1.26–2.69)	0.002
	Stroop errors (interference)	0.75 (0.61–0.92)	0.005
Mental representations			
Verbal knowledge	verbal fluency (animals)	1.09 (1.03–1.16)	0.004
	verbal fluency (vegetables)	0.95 (0.88–1.02)	0.17
Visual confrontation naming	Boston naming (uncued)	1.26 (1.15–1.39)	<0.0001
	Boston naming (total)	1.28 (1.16–1.42)	<0.0001
Speed	Trail Making Test A	0.99 (0.97–1.02)	0.62
	digit symbol substitution	1.14 (1.09–1.2)	<0.0001
Working memory	digit span (forward)	2.1 (1.47–2.98)	<0.0001
	digit span (backward)	1.79 (1.38–2.32)	<0.0001
Learning	Biber visual learning delayed recall	1.21 (0.97–1.5)	0.08
	MAS verbal learning delayed recall	0.82 (0.71–0.94)	0.005
Semantic networks	verbal fluency animals (intrusions)	2.62 (1.25–5.53)	0.011
	verbal fluency vegetables (intrusions)	0.7 (0.57–0.87)	0.001
	MAS semantically related	0.81 (0.68–0.97)	0.02
	MAS semi-related	0.78 (0.62–0.97)	0.024
	MAS unrelated	0.67 (0.49–0.93)	0.015

There were 252 matched pairs.

differences between individuals with higher and lower education levels (Table 4). Results from these analyses indicated that individuals with a higher education had a higher score in recognition (total and uncued), visual confrontation naming (Boston naming test), and verbal fluency animals (not vegetables), a better working memory (digit span forward and backward), and a faster processing speed as measured with the digit symbol substitution test and the Trail Making Test B (but not the Trail Making test A; Table 4). Individuals with a higher education also performed better when having to resolve interference; they had a better performance on the Stroop interference trails, including fewer errors compared to individuals with a lower education (Table 4).

Discussion

This study aimed to investigate the psychometric characteristics of cognitive reserve. We hypothesized that individuals with a high cognitive reserve have a better performance in memory and executive functioning. Analysis of matched pairs of individuals with lower and higher education levels (a proxy for cognitive reserve) revealed that a high cognitive reserve was associated with a better performance in memory as measured by recognition but not necessarily as measured by learning. This finding is not consistent with results reported on residual memory variance because residual memory variance refers to performance on word learning tasks [16, 24]. There are 2 possible explanations for this inconsis-

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Table 4. Conditional regression analysis estimates of the effect of high cognitive reserve (being a case) on performance in psychometric tests, adjusted for study site and MMSE

Cognitive domain	Test	OR (95% CI)	*p*
Executive cognitive abilities			
Switching	Trail Making Test B	0.97 (0.95–0.99)	0.009
	Stroop words	1.07 (1.02–1.12)	0.009
	Stroop colors	1.03 (0.98–1.07)	0.22
Inhibition	Stroop interference	1.05 (1–1.11)	0.045
	Stroop errors (words)	0.68 (0.32–1.45)	0.32
	Stroop errors (colors)	0.69 (0.37–1.3)	0.25
	Stroop errors (interference)	0.51 (0.27–0.95)	0.033
Mental representations			
Verbal knowledge	verbal fluency (animals)	1.16 (1.02–1.32)	0.023
	verbal fluency (vegetables)	0.92 (0.8–1.05)	0.2
Visual confrontation naming	Boston naming (uncued)	1.50 (1.04–2.16)	0.031
	Boston naming (total)	1.59 (1.02–2.48)	0.04
Speed	Trail Making Test A	0.99 (0.95–1.02)	0.39
	digit symbol substitution	1.11 (1.02–1.21)	0.014
Working memory	digit span (forward)	2.04 (1.09–3.81)	0.026
	digit span (backward)	5.88 (1.57–21.94)	0.008
Learning	Biber visual learning delayed recall	1.34 (0.95–1.89)	0.09
	MAS verbal learning delayed recall	1.04 (0.85–1.27)	0.69
Semantic networks	verbal fluency animals (intrusions)	1.52 (0.23–10.01)	0.66
	verbal fluency vegetables (intrusions)	0.91 (0.61–1.35)	0.63
	MAS semantically related	0.76 (0.53–1.08)	0.12
	MAS semi-related	0.66 (0.32–1.37)	0.27
	MAS unrelated	0.56 (0.25–1.26)	0.16

There were 29 uniquely matched pairs.

tency. First, impaired learning is a clinical marker of Alzheimer's disease [25] and our cohort did not include severe Alzheimer's disease cases. Second, differences in study design wherein residual memory variance predicted future cognitive decline whereas our study demonstrated cross-sectional psychometric differences given similar volumetric measures of brain pathology. Since cognitive reserve is the capacity to withhold dementia symptomology in the face of a prevailing brain pathology [1], our results relate to the extant cognitive abilities involved in cognitive reserve. According to our results, recall as measured by recognition may be more closely linked to mechanisms of cognitive reserve than recall measured by learning.

Our results confirm the second part of our hypothesis that individuals with a higher education (i.e., high cognitive reserve) have a better performance on tests involving executive functioning given that we did not find any differences in simple reaction time tasks but in performance with more complex demands. For instance, significant differences were found for the Trail Making Test B and the digit symbol substitution test, which require higher executive abilities, but not for the Trail Making Test A, a measure of psychomotor speed [26]. Even though all 3 tests are timed and reflect processing speed, the Trail Making Test B also requires set switching [27] and cognitive flexibility [28], and the digit symbol substitution test also requires working memory [29]. Our findings suggest that cognitive reserve may be linked to superior executive cognitive abilities like inhibition and switching. These abilities may contribute an important component of cognitive reserve that helps an individual to compensate for brain pathology [30].

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Our results are similar to those of studies. A study from Australia and a study using the Alzheimer's Disease Neuroimaging Initiative database both observed that cognitive reserve was associated with attention, executive functions, and semantic memory but not with processing speed [31, 32]. Semantic memories may represent crystallized intelligence, while executive functions may provide the active capacity to mitigate dementia symptomatology. In a recent study, Stern et al. [33] identified a task-invariant cognitive reserve network – spanning brain regions that are involved in decision making [34, 35], inhibitory control [36], and the processing of semantic memories [37, 38] and language [39, 40]. The finding suggests that the mechanisms of cognitive reserve may involve the proficient processing of memories.

Education may enhance the cognitive reserve by strengthening knowledge [41, 42] and executive cognitive abilities [43]. Associations between cognitive reserve and education could be consistent with either reverse or forward causality. Individuals with an innately higher executive ability may be more likely to obtain a higher education and are just naturally less prone to dementia symptomatology. Alternatively, executive cognitive abilities are a result of sociocultural factors [44], can be trained [45] through education, and result in a higher cognitive reserve.

A major strength of our study is the ability to match pairs based on the severity of neurodegenerative and cerebrovascular brain pathology based on neuroimaging measures. Limitations of our study include the convenience sample and the cross-sectional nature of the analysis. Other limitations were related to power. In our first set of analyses, our matched pairs included subjects who were matched multiple times and, in our second set of analyses, we uniquely matched participants so that every participant was used only once but the sample was rather small. Due to the smaller number of uniquely matched pairs, the confidence intervals became larger and the level of significance dropped. The matching for several brain parameters (e.g., hippocampal volume and white-matter lesions) in addition to demographic characteristics resulted in some small discrepancies between cases and controls. However, we expect that these were averaged out over the several pairs in the sample. A further limitation is that we used education as the sole surrogate marker for cognitive reserve, while occupational demands and leisure activities also build up the cognitive reserve. It is unclear to what extent this may have biased our analysis. Our sample was highly educated so that even the lower-education group had 12 years of education. Thus, our study focused essentially on differences between high school education and college/graduate level education. Further studies will have to validate whether our findings can be generalized to individuals with lower levels of educational attainment.

With the objective of learning about protective mechanisms against cognitive decline and dementia symptomatology in old age, we investigated the psychometric characteristics of a high education as a proxy for cognitive reserve. The challenge with studying cognitive reserve is that it is a cognitive capacity in the face of a brain pathology that differs between groups. To be able to gain more insight into this cognitive capacity, we decided to take a case-control approach in which the "cases" were those with a high cognitive reserve. Our findings do not predict the cognitive status itself. Instead, they indicate differences in cognitive capacities between individuals with higher and lower education levels. Accordingly, our observations suggest that long-term memories acquired over the life course together with proficient executive cognitive functions may constitute a cognitive reserve that helps people to maintain cognitive functioning in the face of prevailing brain damage. The training of executive cognitive abilities throughout life and the acquisition of knowledge may be instrumental for maintaining cognitive functioning in old age, not because they protect the brain against damage but because they provide a functional capacity that is resilient to brain damage.

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Statement of Ethics

Subjects gave their written informed consent. The study protocol was approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflict of interests to declare.

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