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Cognitive Reserve, Age, and Neuropsychological Performance in Healthy Participants

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The first aim of this study was to explore the relation between cognitive reserve, age, and neuropsychological functioning in a healthy sample; and second, to determine the risk of showing cognitive deficits as a function of cognitive reserve. One hundred forty-six healthy participants between the ages of 20 and 79 were submitted to neuropsychological assessment, focusing on attention, memory, visuo-construction, conceptualization and reasoning. Premorbid IQ as measured with the Wechsler Adult Intelligence Scale Vocabulary subtest was used as a proxy of cognitive reserve. Multivariate regression analysis with age and premorbid IQ as explanatory factors revealed a significant effect in all neuropsychological tests. Logistic regression revealed that participants with low cognitive reserve were more likely to obtain deficient scores (≤ 1.5 *SD* below the mean) in the cognitive domains of attention (odds ratio [OR], 3.13; 95% confidence interval [CI], 1.05–9.29), memory (OR, 6.17; 95% CI, 1.69–22.61) and global functioning (OR, 6.44; 95% CI, 2.56–16.22) than participants with high cognitive reserve. Results suggest that cognitive reserve acts as a protective factor against the expression of cognitive decline related to age in healthy individuals.

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The reserve hypothesis was initially proposed to account for the repeated observation that there is no direct relationship between the severity of brain damage and its clinical expression (Katzman, 1993; Satz, 1993; Y. Stern, 2002). This discrepancy was initially explained by passive models such as Satz's *threshold effect* (1993). Its assumption is that there is a critical threshold of brain reserve capacity that, after becoming depleted, leads to the appearance of clinical and functional deficits. This brain reserve capacity is defined in terms of the synapse count or brain volume. The model has been supported by studies showing a positive relationship between brain size and cognitive functioning in pathological and healthy samples. Katzman et al. (1988) were the first to observe a relationship between the clinical expression of dementia and brain volume in a sample of 137 nursing home residents. They found that 10 participants with brain pathologies confirmed in postmortem examination demonstrated an equal performance to that of residents without any brain pathologies. These participants had higher brain weights and a higher quantity of neurons as compared to age-matched control residents. The authors attributed the absence of clinical manifestations by these participants to their greater brain "reserve."

The relationship between brain size and cognitive functioning was later observed in healthy young adult and older individuals. Reynolds, Johnston, Dodge, DeKosky, and Ganguli (1999) reported that smaller head size was associated with low Mini-Mental State Examination (MMSE) scores in 825 older participants without dementia participating in a community-based survey. MacLullich et al. (2002) reported positive correlations between brain volume and general intelligence in 97 healthy older individuals examined with magnetic resonance imaging. Meguro et al. (2001) also found a significant effect of education on brain atrophy and neuropsychological performance in 99 healthy older participants. The results only revealed a positive correlation between age and frontal lobe atrophy in participants with a lower level of education.

A complementary explanation to the passive models is offered by active models such as that proposed by Y. Stern (2002), who considered two other types of reserve—cognitive reserve and compensation—that may be operating in healthy individuals and individuals with brain damage. Cognitive reserve is understood as the ability to optimize performance by 'recruiting' alternative brain networks, reflecting the use of different cognitive strategies. The compensation refers to the use of structures or brain networks that are not normally used in a nondamaged brain to compensate for the deficit. And so, whereas the passive models consider the reserve in terms of "hardware," or how much damage it is possible to withstand before reaching the threshold of clinical expression, the active models define it in terms of "software," or individual task processing differences. Evidence supporting the active models has been provided by positron-emission tomography studies on Alzheimer's disease and with healthy individuals (Scarmeas et al., 2003, 2004). These studies show brain networks in which the amount of increased activation from low to high demands of a visual recognition task is correlated with cognitive reserve.

Whereas the passive models use anatomical variables as an index of reserve, the active models consider that it is mediated by factors such as education (calculated according to years of school or higher degrees obtained), premorbid IQ estimated using the Wechsler Adult Intelligence Scale (WAIS) Vocabulary subtest or the National Adult Reading Test, and profession or occupational experience. Recently, leisure activities have also been proposed as indexes of cognitive reserve (Scarmeas & Stern, 2003). However, at present there is no consensus on what is the best measure of cognitive reserve.

The role of cognitive reserve has been studied in relation to neuropsychological manifestations of several cerebral pathologies, particularly dementia, but also HIV, epilepsy, Parkinson's disease, and traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003; Sánchez, Rodríguez, & Carro, 2002b; Satz et al., 1993; Sawrie et al., 2000; R. A. Stern, Silva, Chaisson, & Evans, 1996). From the studies on populations with pathology, the most numerous are those that focus on Alzheimer's disease. It seems to be agreed that a larger brain, higher educational level, and other related factors reduce the incidence and prevalence of the disease and protect against associated clinical cognitive manifestations (for a review, see Scarmeas & Stern, 2004). However, to date, few studies have specifically tested the relationship between cognitive reserve and cognitive functioning in healthy participants.

In a previous study, we analyzed the role of cognitive reserve on the clinical manifestations of sporadic-type Alzheimer's disease (Sánchez, Rodríguez, & Carro, 2002a). We observed a significant effect of cognitive reserve on the neuropsychological performance of 43 healthy participants between the ages of 60 and 83 who were selected as controls. This result prompted us to increase the size of the sample with the aim of studying the effect of cognitive reserve in individuals without dementia in greater detail. The present study was aimed, first, at exploring the relationship between cognitive reserve, age, and neuropsychological functioning in a healthy sample and, second, at determining the risk of presenting neuropsychological deficits as a function of cognitive reserve.

MATERIALS AND METHODS

Participants

The study sample comprised 146 men and women ages 20 to 70 years living in the community. The participants were carefully screened to exclude those with dementia or any medical conditions that would affect their neuropsychological performance. The following exclusion criteria were considered: (a) a history of neurological disorders; (b) visual and auditory noncorrected deficits; (c) a history of abuse of or dependence on alcohol or other drugs; and (d) a score lower than 28 on the Spanish MMSE (Lobo, Ezquerra, Gomez Burgada, Sala, & Seva Diaz, 1979). Information about the variables considered was gathered from the participants and their relatives during a semistructured interview. Because of the limitations ob-

served in previous studies, we included participants from a wide range of educational levels, from elementary to university studies. We also increased the minimum score on the MMSE to participate in the study to exclude participants possibly having dementia or cognitive impairment.

According to previous studies (Scarmeas et al., 2004; Y. Stern et al., 2004), premorbid IQ as estimated using the WAIS Vocabulary score was used as proxy of cognitive reserve. When necessary, the participants were distributed into high cognitive reserve (HCR) and low cognitive reserve (LCR) groups according the Vocabulary median. Also, the following age groups were defined: 20 to 35, 36 to 50, 51 to 65, and 66 to 80 years. Table 1 shows the demographic characteristics and the neuropsychological performance of the participants by cognitive reserve.

Materials

The neuropsychological battery was composed of standardized tests in order to assess specific cognitive domains. Attention was assessed using the WAIS Digit Span subtest (Wechsler, 1998), which provides information about focused attention, short-term storage capacity, and mental tracking. The longest sequence of Digits Forward and Digits Backward were recorded. The WAIS Digit Symbol subtest, considered as being highly sensitive to brain damage, was included in order to assess visuomotor abilities and complex attention. Episodic verbal memory was assessed using the Rey Auditory–Verbal Learning Test (RAVLT; Rey, 1964). Total score (the sum of the five trials) was registered as an index of verbal learning capacity. The Benton Visual Retention Test (BVRT; Benton, Sivan, Hamsher, Varney, & Spreen, 1983) was chosen to assess visual memory. We used Form C, Administration A and recorded the number of correct designs. Visuo-construction abilities were assessed with the WAIS Block Design subtest, according to the standard procedure. Another two WAIS subtests, Similarities and Comprehension, were used to assess conceptualization and abstract reasoning capacities, respectively. The neuropsychological battery also included the WAIS Vocabulary subtest and the Edinburgh Inventory (Oldfield, 1971).

The neuropsychological battery was administered by psychologists experienced in neuropsychological assessment and took place in a comfortable room. The tasks were administered in the same order for all participants, and the administration time did not exceed 50 min. All participants signed a consent form and were given a neuropsychological report of their performance.

RESULTS

Data Analysis

Multiple linear regression adjustment by age was used to evaluate the relationship between cognitive reserve and neuropsychological performance. In this model,

TABLE 1
Demographics Characteristics and Neuropsychological Performance of the Sample

	Low Cognitive Reserve (Age)					*High Cognitive Reserve (Age)*					*Total Sample (Age)*				
Variable	*20–35*	*36–50*	*51–65*	*66–79*	*Total*	*20–35*	*36–50*	*51–65*	*66–79*	*Total*	*20–35*	*36–50*	*51–65*	*66–79*	*Total*
N	19	16	16	27	78	24	12	10	22	68	43	28	26	49	146
Gender (male/female)	13/6	8/8	6/10	10/17	37/41	20/4	9/3	7/31	1/11	47/21	33/10	17/11	13/13	21/28	84/62
Age															
M	26.16	40.81	60.94	73.00	52.51	27.08	40.17	60.80	73.00	49.21	26.67	40.54	60.88	73.00	50.97
SD	3.35	4.00	3.53	3.54	19.34	3.88	3.74	4.49	3.83	20.26	3.64	3.83	3.84	3.63	19.78
Years of education															
M	10.32	6.69	5.69	4.85	6.73	13.21	10.50	11.50	8.82	11.06	11.93	8.32	7.92	6.63	8.75
SD	4.10	1.92	4.91	2.98	4.12	3.53	2.68	4.88	4.08	4.15	4.01	2.94	5.60	4.00	4.66
Neuropsychological tests															
Comprehension															
M					16.66					20.41					18.37
SD					3.89					3.41					4.12

(*continued*)

TABLE 1 (*Continued*)

	Low Cognitive Reserve (Age)					*High Cognitive Reserve (Age)*					*Total Sample (Age)*				
Variable	*20–35*	*36–50*	*51–65*	*66–79*	*Total*	*20–35*	*36–50*	*51–65*	*66–79*	*Total*	*20–35*	*36–50*	*51–65*	*66–79*	*Total*
Similarities															
M					12.75					19.36					15.77
SD					4.39					2.97					5.03
Digits forward															
M					5.60					6.21					5.88
SD					1.22					1.46					1.37
Digits backward															
M					3.92					4.78					4.32
SD					1.11					1.26					1.25
Symbol digit															
M					33.24					52.78					42.17
SD					18.22					16.33					19.89
Block design															
M					27.58					35.37					31.23
SD					8.59					8.38					9.32
BVRT															
M					5.42					6.75					6.04
SD					2.10					2.00					2.15
RAVLT															
M					42.17					47.82					44.80
SD					11.67					10.07					11.28

Note. BVRT = Benton Visual Retention; RAVLT = Rey Auditory–Verbal Learning Test.

age was categorized as a dummy variable with the following categories: 20 to 35, 36 to 50, 51 to 65, and 66 to 80 years.

To analyze the relationship between cognitive reserve and neuropsychological deficits, the scores from each test were converted to age-based *z* scores. Scores ≤ 1.5 *SD* below the mean were defined as impaired. This cutoff score was selected to increase specificity. The individual tests were also grouped according to the following cognitive domains: attention (Digits Forward, Digits Backward, and Digit symbol), memory (RAVLT and BVRT), and global functioning (the sum of the individual impaired tests scores in the battery). Multiple logistic regression was used to calculate the odds ratios (ORs) to obtain deficit scores in the tests considered.

Age, Cognitive Reserve, and Neuropsychological Performance

Table 2 shows the multivariate model for the neuropsychological tests performance. Results of analyses of variance were significant for all tests considered: Comprehesion, $F(4, 135) = 26.918$, $p < .001$, adjusted $R^2 = .427$; Similarities, $F(4, 135) = 57.822$, $p < .001$, adjusted $R^2 = .621$; Digits Forward, $F(4, 141) = 18.897$, $p < .001$, adjusted $R^2 = .331$; Digits Backward, $F(4, 141) = 13.647$, $p < .001$, adjusted $R^2 = .259$; Digit Symbol, $F(4, 135) = 45.848$, $p < .001$, adjusted $R^2 = .563$; Block Design, $F(4, 140) = 41.732$, $p < .001$, adjusted $R^2 = .531$; BVRT, $F(4, 131) = 28.506$, $p < .001$, adjusted $R^2 = .449$; and RAVLT, $F(4, 139) = 25.830$, $p < .001$, adjusted $R^2 = .410$. In relation to age, our results revealed that performance declines with age on all tests, but the decrements were evident at different ages. We found significant changes on Comprehension, Digits Backward, Digit Symbol, and Block Design between the first and second range of age, whereas the decrements on Similarities, Digit Forward, RAVLT, and BVRT were initially evident between the second and third interval of age. Table 2 also shows the association between Vocabulary scores and neuropsychological performance adjusted by age. The multiple regression revealed that higher vocabulary is associated with better performance in each test considered.

Cognitive Reserve and the Risk of Neuropsychological Deficits

Logistical regression (see Table 3) revealed that the Vocabulary scores predicted neuropsychological "impairment", whereby those with higher Vocabulary scores were more likely to obtain scores ≤ 1.5 standard deviations below the mean on the Comprehension subtest (OR = 9.75, 95% confidence interval [CI]: 1.21–78.71), Digits Backward (OR = 8.62, 95% CI: 1.06–70.12), and Block Design (OR = 11.70, 95% CI: 1.46–93.82). On the contrary, for Digits Forward, Digit Symbol, and BVRT tests, our results did not reveal any significant association between Vo-

TABLE 2
Multiple Linear Regression of the Effect of Age and Vocabulary on the Raw Scores of the Neuropsychological Tests

Variable	*Comprehesion*	*Similarities*	*Digits Forward*	*Digits Backward*	*Digit Symbol*	*Block Design*	*BVRT*	*RAVLT*
Age[a]								
d1	0.240 (.001)	–0.025 (.672)	–0.138 (.083)	–0.165 (.049)	–0.184 (.005)	–0.208 (.002)	–0.079 (.282)	–0.080 (.285)
d2	0.280 (<.001)	–0.136 (.027)	–0.321 (<.001)	–0.297 (.001)	–0.365 (<.001)	–0.331 (<.001)	–0.427 (<.001)	–0.356 (<.001)
d3	0.067 (.381)	–0.237 (<.001)	–0.593 (<.001)	–0.438 (<.001)	–0.548 (<.001)	–0.589 (<.001)	–0.605 (<.001)	–0.612 (<.001)
Vocabulary	0.650 (<.001)	0.73 (<.001)	0.216 (.002)	0.302 (<.001)	0.510 (<.001)	0.469 (<.001)	0.310 (<.001)	0.265 (<.001)

Note. Multiple linear regression coefficients are shown, with p values in parentheses. BVRT = Benton Visual Retention; RAVLT = Rey Auditory–Verbal Learning Test.

[a]Age was included as a dummy variable with the following categories: <35, 36 to 50, 51 to 65, >66 years.

TABLE 3
Logistic Regression Analysis of the Effect of Vocabulary on the Age-Standardized *z* Scores of the Neuropsychological Tests

Measure of Risk	*Comprehesion*	*Digits Forward*	*Digits Backward*	*Digit Symbol*	*Block Design*	*RAVLT*	*Attention*	*Memory*	*Global*
OR[a,b]	9.75	1.71	8.62	2.85	11.70	3.19	3.13	6.17	6.44
CI 95%	1.20–78.71	0.47–6.20	1.06–70.12	0.51–16.05	1.46–93.80	0.84–12.15	1.05–9.29	1.69–22.61	2.56–16.22

Note. RAVLT = Rey Auditory–Verbal Learning Test; OR = odds ratio; CI = confidence interval.

[a]Adjustment by age. [b]Case was defined as a score ≤ 1.5 *SD* below the median for logistic regression analyses. Reference category is high cognitive reserve (vocabulary above median). Similarities and Benton Visual Retention were not included because there was no cases for the high cognitive reserve group.

cabulary and neuropsychological deficits. When performance was grouped by cognitive domain, participants with lower Vocabulary were significantly more likely to have impaired scores for attention (OR = 3.13, 95% CI: 1.05–9.29), memory (OR = 6.17, 95% CI: 1.69–22.61) and global functioning (OR = 6.43, 95% CI: 2.56–16.22).

DISCUSSION

The first aim of this study was to explore the relationship between age, cognitive reserve, and neuropsychological performance in healthy participants. With regard to age, as was expected, our results revealed that advancing age is associated with lower performance in all of the measures considered. The wide age range of our sample made it possible for us to detect differences in the period in which a performance decrement is observed. The earliest decline was found in Digit Span, Digit Symbol and Block Design tests, with changes between the 3rd and 4th decades, whereas performance decrements in BVRT, RAVLT, and Similarities were evident over the age of 40. Our results therefore show a significant cognitive decline with age independent of the participants' cognitive reserve in all of the cognitive domains considered: attention, visual and verbal memory, visuo-constructive abilities, and conceptualization.

We also found a significant effect of cognitive reserve on all neuropsychological measures after adjusting for age. This result replicates those obtained in other studies exploring the role of cognitive reserve in healthy participants. Le Carret, Lafont, Mayo, and Fabrigoule (2003) carried out a study on 1,022 healthy individuals age 66 and older in order to evaluate the impact of education—as a proxy of cognitive reserve—on cognitive functioning. Their neuropsychological battery was composed of tests for attention, verbal and visual memory, verbal fluency, and conceptualization. The multivariate analysis included age, gender, educational level, occupational activity, and depressive symptomatology as explanatory variables. They reported a significant effect of education on most neuropsychological performance, particularly in the high-attention-demanding tests, also suggesting that the effect of education on cognitive reserve may be explained by an increase in controlled processes and conceptualization abilities. Meguro et al. (2001) also found a significant effect of educational level on the neuropsychological performance of 99 healthy older individuals age 65 and over. This effect was more evident on tasks related to frontal lobe functioning (fluency, working memory, shifting attention, and abstract reasoning). The authors also observed a positive relationship between frontal cortical atrophy and age that was only significant for the participants with a lower level of education. However, none of the studies reported any clinical relevance of the effect.

Our second question referred to the risk of obtaining deficient scores as a function of cognitive reserve in healthy people. The cognitive reserve model hypothe-

sizes that participants with HCR will show fewer deficits than LCR participants with similar brain damage, or in this case, with similar age. Our results confirmed this hypothesis, as we observed that participants with LCR have a higher risk of altered performance in the cognitive domains of attention, memory, and global functioning. Specifically, participants with LCR were 6 times more likely to obtain a deficient score in the neuropsychological assessment than were HCR participants. As a point of reference, for the participants over 66 years the corresponding ≤ 1.5 standard deviation scores were as follows: for the WAIS subtests, scaled scores lower 8; for Digits Forward and Digits Backward, 4 and 3 digits respectively; for BVRT, 2 or fewer correct designs; and for the RAVLT, total score below 21. This means that among people with healthy aging, those with LCR would more frequently show cognitive deficits, with their potential implications in the activities of daily life. We should not forget that two of the tasks in which differences in cognitive reserve were evident involve attention and working memory.

Our results are consistent with the findings of other studies that suggested that cognitive reserve acts a protective factor against the clinical manifestation of cognitive decline related to age. On the whole, these results show that cognitive reserve protects against the clinical expression of impairment in certain cognitive domains, particularly complex attention and conceptualization.

How may these results be explained using the cognitive reserve hypothesis? At present, the neural mechanism that cognitive reserve uses to protect cognitive functioning is not clear. Using active models, Y. Stern (2002) defined *cognitive reserve* operating in healthy individuals as the effective use of brain networks or the ability to recruit alternative brain structures or networks whenever necessary. This explanation has been supported by neuroimaging studies of healthy young and older participants, showing significant correlations between proxies of cognitive reserve and neural activity in a visual memory task (Y. Stern et al., 2003, 2004). Further detailed studies are necessary into the relationship between cognitive reserve and age in healthy participants. One approximation is using neuroimaging, but qualitative analysis of neuropsychological performance may also provide information about cognitive paradigms used in solving tasks. This also will allow examination of an alternative explanation to the cognitive reserve hypothesis: Individuals who score well on one cognitive test will likely score well on another, reflecting a general cognitive ability factor.

This study presents at least two limitations that must be considered. First, although we included young and older participants across a wide range of ages, a cross-sectional study reveals only the effect of age and not the effect of aging. Therefore, it was not possible to conclude that cognitive reserve protects against cognitive decline associated with aging. Second, we explored the cognitive domains of attention, visual and verbal episodic memory, visuoconstruction, conceptualization, and abstract reasoning, but, because of time limitations, measures to assess executive function in depth were not included in the neuropsychological

battery. This is an area of particular interest, as it has been associated with the functional status of healthy older people (Cahn-Weiner, Boyle, & Malloy, 2002).

In summary, our results show that cognitive reserve acts a protective factor against the expression of neuropsychological deficits with age in healthy participants. Further studies are necessary in order to clarify this relationship and its implications for day-to-day activities.

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