**ARTICLE**

# Cognitive reserve and the severity of Alzheimer's disease

## Reserva cognitiva e a severidade da doença de Alzheimer

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**ABSTRACT**

Alzheimer´s disease (AD) is a clinical syndrome caused by neurodegeneration and characterized by a progressive deterioration in cognitive ability and capacity for independent living. Cognitive reserve (CR) describes the capacity of the adult brain to cope with the effects of the neurodegenerative process and to minimize the clinical manifestation of pathology of dementia. The aim of this study was to evaluate the association of CR and the severity of AD. **Method:** This study was cross-sectional. Functional and neuropsychological abilities of 75 outpatients with probable AD diagnosis were evaluated. Patients completed two questionnaires, "Participation in leisure activities throughout life" and CR Questionnaire. **Result:** The relationship between Clinical Dementia Rating (CDR) and the level of CR was statistically significant (likelihood ratio (LR), p = 0.015). **Conclusion:** The level of CR influenced the severity of dementia. This study suggests that AD patients with higher CR may benefit against cognitive decline after diagnosis of AD.

Keywords: Alzheimer´s disease, cognitive reserve, education, leisure activities, lifelong occupation.

**RESUMO**

Doença de Alzheimer (DA) é uma síndrome neurodegenerativa caracterizada por uma deterioração progressiva das capacidades cognitivas e das competências para uma vida independente. A reserva cognitiva (RC) descreve a capacidade do cérebro adulto em lidar com os efeitos deste processo neurodegenerativo e minimizar a manifestação clínica da patologia de demência. O objetivo deste trabalho foi avaliar a associação entre RC e a severidade da DA. **Método:** Este estudo foi transversal. Foram avaliadas as competências funcionais e neuropsicológicas de 75 pacientes com diagnóstico provável de DA. Os pacientes completaram dois questionários, "Participação em atividades de lazer ao longo da vida" e o Questionário de RC. **Resultados:** A relação entre o nível de Clinical Dementia Rating (CDR) e de RC foi estatisticamente significativa (likelihood ratio (LR), p = 0,015). **Conclusão:** O nível de RC influenciou a severidade da demência. Este estudo sugere que os doentes com DA com um maior nível de RC podem beneficiar de proteção relativamente ao declínio cognitivo após o diagnóstico de DA.

Palavras-chave: doença de Alzheimer, reserva cognitiva, educação, atividades de lazer, ocupação ao longo da vida.

Alzheimer's disease (AD) is the most common form of dementia in the elderly[1] and a clinical syndrome caused by neurodegeneration and characterized by a progressive deterioration in cognitive ability and capacity for independent living. The course of AD is not the same in every person, but symptoms seem to develop over the same general stages. Cognitive reserve (CR) is a hypothetical construct that has been used to inform of cognitive aging and describes the capacity of the adult brain to deal with the effects of the neurodegenerative process and to minimize the clinical manifestation of pathology of dementia that is probably the result of innate intelligence or life experience[2]. The CR hypothesis suggests that individual differences in the ability to cope with AD pathology[2,3] are consistent with the prediction that people with more reserve can cope with advancing AD pathology longer before it is expressed clinically[3,4,5]. CR is not fixed, but continues to evolve across the lifespan[5]. Variables pertaining to lifetime experience (education, occupation attainment and leisure activities)[4,5] are the most commonly used proxies for CR and help retain cognitive function in old age. Epidemiological studies suggest that lifelong experiences, including educational, occupational attainment and leisure activities (LA) in later life, can increase reserve[4]. Greater understanding of the concept of CR could lead to

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interventions to slow cognitive aging[4,6]. Sobral and Paúl[7] demonstrated that AD patients with higher levels of education achieved better results on cognitive tests and the participants with higher participation in leisure activities (PLA) exhibited better results on cognitive and functional tests than those with lower participation.

Tschanz et al.[8] found that a significant proportion of persons with AD progresses slowly and suggest ongoing need to identify factors that may slow the progression of AD. Other studies have noted faster rates of progression in high CR patients after the diagnosis of AD[3,9,10]. A research has indicated that high PLA is associated with more rapid cognitive decline than in those with lower PLA[9] and some studies have shown that AD patients with higher education have a more rapid cognitive decline[3,10] than those with lower education, because at any level of clinical severity, the underlying progression is more advanced in patients with higher education, which has been attributed to harbouring a higher pathological burden at the time of clinical dementia for subjects with higher education[3]. Other authors[7,11] concluded that education slows the rate of cognitive decline in person with AD and Treiber and colleagues[12] proved that the increased engagement in cognitive LA through late life was associated with slower deterioration in general cognitive ability in mild dementia. Sobral and Paúl[7] found that AD patients with high education and high PLA may benefit from a slower cognitive and functional decline after diagnosis of AD. Other studies have found no relationship between education and cognitive decline in the clinical course of AD[13] and between occupation and cognitive decline in the clinical course of AD[11].

We wanted to know the association between CR and disease progression and the aim of this study was to evaluate the association of CR and the severity of AD.

## METHODS

### Participants

This study includes 75 outpatients (mean age: 80.20 years; range 61-92 years) diagnosed with probable AD, recruited at a psychiatric hospital, psychogeriatrics service. This Psychogeriatrics Service is designed to follow-up patients with dementia, using an integrated multidisciplinary approach to diagnosing and managing dementia. Physical, neurological, neuropsychological and psychiatric examinations, neuroimaging and additional tests, including blood tests were used to triage the various types of dementia. Diagnosis of AD among the individuals selected was obtained according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition[14] and the National Institute on Aging and the Alzheimer's Association workgroup for probable AD[15]. We excluded participants with mild cognitive impairment and psychiatric disorders. All participants were free of severe medical conditions other than those pertinent to the study, including no history of alcohol abuse or recurrent substance abuse or dependence and no history of heart disease or diabetes. The patients (or his/her legal representative) included in the study have provided written consent to participate in this study.

### Instruments

In order to quantify CR, the Cognitive Reserve Questionnaire (CRQ)[16] was administered. The CRQ includes the participation in as activities (reading, intellectual games), years of education, years of parents' education, occupation, training courses, musical training and languages carried out by participants during their adult lifetime. The CRQ has been validated for the Portuguese population and CRQ has high reliability and suitable content validity[17]. CRQ consists of eight items and the Portuguese version of CRQ proved to be a valuable CR instrument for testing in research and clinical setting[17]. Regarding reliability the internal consistency of CRQ was 0.795 (Cronbach's Alpha). The factorial analysis of principal components with varimax rotation shows good indicators of the quality of the adjustment obtained either by Goodness of fit index = 0.99 and by Root Mean Square Residual = 0.048, which were based on the residual matrix correlation assuring the validity of the construct. The existence of eigenvalues > 1 (Kaiser Criterion) and the steepening of the scree plot indicate the existence of a single dimension in CR. The responses were consistent, because there was a good correlation between the items, according to the measure of sampling adequacy Kaiser-Meyer-Olkin = 0.761 and Bartlett's Sphericity Test = 204.159; df = 28; p < 0.01.

Data on PLA was obtained from a questionnaire, "PLA throughout life"[7], answered by the participants or/and the caregiver. We begin by discriminating current and past activities. The caregivers were asked to confirm the information about the PLA throughout life of patients as current low PLA of patients may be a consequence of cognitive decline. This tool includes mental activities (reading books/newspapers, jigsaw puzzles), physical activities (walking or other sport), social activities (playing cards/board games, visiting friends or relatives), productive activities (housekeeping, babysitting, gardening, crocheting) and recreational activities (listening to the radio, watching television). Participants were asked it they regularly engaged in other particular activities, to specify which types of activities they were engaged in and to report the frequency of PLA throughout life. The instrument presents a global score and classifies people in three categories (low, medium and high PLA throughout life). The questionnaire "PLA throughout life", has 17 questions and for each question, subjects received 5 points for "daily", 4 points for "several days per week", 3 points for "once a weekly", 2 points for "two or three days per month", 1 points for "monthly" and 0 points for "never or less than a once a month". Its quotation

can vary from 0 points up to 85 points. The factor structure of an instrument can also be used to assess the structural validity of the observe scores. We conducted an exploratory factor analysis using varimax rotation. Through the analysis of major components 5 factors were extracted. The total variance explained by the questionnaire is of 55.3% and the KMO value of sample adequacy is 0.6. The variance explained by each factor was 1º factor (cognitive LA) = 19.5% (Cronbach's Alpha = 0.7), 2º factor (productive and social LA) = 11.6% (Cronbach's Alpha = 0.6) and other factors (unnamed because they have a Cronbach's Alpha < 0.5): 3º factor = 9.2%, 4º factor = 7.7% and 5º factor = 7.3%.

All participants were given the Mini-Mental State Examination (MMSE)[18] for cognitive screening, as well as the Clinical Dementia Rating (CDR) which classifies dementia along 3 stages of severity as a function of overall cognitive and functional impairment. We applied the Portuguese version of the MMSE from Guerreiro et al.[19]. The MMSE includes questions on orientation, registration, attention and calculation, recall, language and visual construction. The normative cut-off values adjusted to the education for Portuguese population were used. The cut-off points for the diagnosis of dementia are above 27 if they had > 11 years of education, ≤ 22 if they had 1-11 years of education or ≤ 15 if they were illiterate. Despite some limitations, MMSE score is a good indicator of severity of the disease. CDR[20] classifies dementia along 3 stages of severity as a function of overall cognitive and functional impairment. We used the translation and adaptation of Garret et al.[21]. The CDR determines the impairment associated with dementia, through parameters such as memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. The overall CDR score is obtained by a standard algorithm to stage the patient's level of impairment: 0 (no impairment), 0.5 (very mild impairment), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).

Addenbrooke's Cognitive Examination Revised (ACE-R)[22] is a brief cognitive test that assesses five cognitive domains, namely attention/orientation, memory, verbal fluency, language and visuospatial abilities. Total score is 100, higher scores indicates better cognitive functioning. The ACE-R has been validated for the Portuguese population[23].

Functional abilities were assessed with two activities of daily living scales: the Barthel's Index[24] (BI), addressing basic activities of daily living such as grooming, eating, bathing, dressing, mobility, and the Lawton and Brody's Index[25] (LBI), targeting instrumental activities (e.g. managing money, using the telephone). The BI have a possible total scores range from 0 to 100 ( fully independent) and the LBI have a possible total scores range from 8 (independent) to 30 (completely dependent). Socioeconomic status was evaluated according to Graffar Index[26]. This index has five categories from I (the highest) to V (the lowest). The lifelong occupation was assessed with "National Classification of Occupations"[27].

## Procedure and statistical design

This study was cross-sectional and used data from the database of a research project designed to investigate CR and AD among patients recruited at a mental health hospital. The research protocol was approved by the Review Board (ethic committee) of the institution where the study was conducted. Data collected included socio-demographic and clinical variables including age, gender, marital status and retirement status and variables that usually inform CR (education level, lifelong occupation and frequency of PLA). Each participant underwent a standard evaluation, including medical history, physical examination, laboratory tests and a neuro-imaging (computed axial tomography). AD patients were evaluated with MMSE and CDR for recruitment at the first consultation of multidisciplinary assessment. Patients were submitted to a functional and neuropsychological evaluation. We have examined specific neuropsychological domains such as memory, language, attention, visuospatial ability and executive functioning. We have rated the severity of dementia according to the CDR.

In this study variables hypothesized to represent the CR construct were: CRQ (level of CR), education (as defined in terms of level of educational attainment), frequency of PLA (scores of LA) and lifelong occupation. General exploratory analyses were conducted to determine sample characteristics. For statistical analysis we computed descriptive statistics with percentages, mean, trends, standard deviations and percentiles. In order to inferential relationship between the metric and categorical variables with two or more categories we used the Student t-test and F test and Brown-Forsythe's One-Way ANOVA; to check the relationship between categorical variables we used whenever there were no interactive effects, models of contingency tables, using the Chi-square test Pearson, Fisher and likelihood ratio (LR), depending on the number of categories for analysis; the relationship between categorical variables was analyzed by using the interactive effects logistic regression models and relative risk to quantify the effects, the degree of association between variables was evaluated using metrics R Pearson[28]. The analyses were conducted using the IBM Statistical Package for Social Sciences 21.

## RESULTS

Table shows the sociodemographic and clinical characteristics of AD participants.

There was a significant majority of women compared to men, according to the binomial test (p < 0.001). The age difference between the sexes was not statistically significant. It was more likely to find married men (80.5%) than married women (30.9%), likelihood ratio test (p < 0.001), while in other marital status differences were not relevant. Women had very different levels of education. The mean 5.75 years

**Table.** Demographic and clinical characteristics.

| Demographic and clinical characteristics | AD patients (n = 75) | Tests (p) |
|---|---|---|
| Men (%) (n) < Women (%) (n) | 26.7 (20) < 73.3 (55) | Binomial (p < 0.001) |
| Age (mean) (SD) (Min/Max) | 80.20 (5.64) (61/92) | t-test (p = 0.3) |
| Married (%) (n) | 45.3 (34) | |
| Widower (%) (n) | 38.7 (29) | LR (p = 0.6) |
| Single (%) (n) | 10.7 (8) | LR (p = 0.6) |
| Divorced (%) (n) | 5.3 (4) | LR (p = 0.6) |
| Educacional level (5% trimmed mean) (IR) (Min/Max) | 5.45 (3/9) (0/17) | |
| Men > Women | 7.39 (4/10) (2/17) > | |
| | 4.76 (3/4.5) (0/16) | t-test (p = 0.025) |
| Iliterate (%) (n) | 6.7 (5) | |
| Reading and writing (%) (n) | 22.7 (17) | |
| 4 years (%) (n) | 41.3 (31) | |
| > 4 - 9 years (%) (n) | 16.0 (12) | |
| ≥ 11 years (%) (n) | 13.4 (10) | |
| Portuguese nationality (%) (n) | 100 (75) | |
| Work Retired (%) (n) | 96 (72) | |
| Unskilled workers | 57.3 (43) | |
| Men < Women | 20% < 70.9% | LR (p < 0.001) |
| Skilled workers | 10.7 (8) | LR (p = 0.4) |
| Service workers, safety, vendors and administrative staff | 24.0 (18) | LR (p = 0.4) |
| Intermediate level professions, intellectual and scientific activity | 8.0 (6) | LR (p = 0.4) |
| Years of disease (mean) (SD) (Min/Max) | 5.17 (3.31) (1/13) | t-test (p = 0.223) |
| MMSE (mean) (SD) | 17.15 (4.57) | t-test (p = 0.000) |
| ACE- R | 86.66 (18.64) | t-test (p = 0.000) |
| Barthel Index | 23.36 (5.18) | t-test (p = 0.000) |
| Lawton Index | 41.53 (15.60) | t-test (p = 0.000) |
| Social Class (Graffar) (%) (n) | | LR (p = 0.241) |
| II (medium/high) | 10.7 (8) | |
| III (medium) | 42.7 (32) | |
| IV (medium/low) and V (low) | 46.7 (35) | |
| CDR = 1 (%) (n) | 46.7 (35) | LR (p = 0.463) |
| CDR = 2 (%) (n) | 36.0 (27) | |
| CDR = 3 (%) (n) | 17.3 (13) | |

AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; ACE-R: Addenbrooke´s Cognitive Examination Revised; CDR: Clinical Dementia Rating; IR: interquartile range; LR: chi-square likelihood ratio test; SD: standard deviation.

of education was replaced by a trimmed mean of 5% (5% trimmed mean = 5.45), while the standard deviation was replaced by the interquartile range Tukeys Hinges where 50% of men had between 4 and 10 years instruction, whereas 50% of women had between 3 and 4.5 years. The men had on average 2.63 more years of education than women. For each increase of one category of education, it was 13% more likely to be male than female, as binary logistic regression model, with good sampling adequacy (Hosmer and Lemeshow test = 1.73, df = 4, p = 0.79) and Exp (sex) = 1.13. It was more likely to find women with no qualifications (70.9%) than men (20%), according the likelihood ratio test (LR) (p < 0.001), whereas in the other categories the differences were not significant. The difference of years of disease between the sexes was not statistically significant. The difference of social classes between the sexes was not statistically significant.

The patients with "> 4 years of education" obtained a mean of 19.21 points on the MMSE, while the illiterate obtained a mean of 9.60 points. The mean of ACE-R in elderly with "> 4 years of education" was 49.83, whereas the mean of ACE-R in older persons without any educational level was 15.60. The BI mean of the participants with "> 4 years of education" was 86.46, whereas the BI mean of illiterate AD patients was 70.00. The LBI mean of illiterate patients was 27.80 and with "> 4 years of education" group was 22.38. The patients with "≥ 36 scores" on "PLA throughout life" questionnaire obtained on 19.62 of mean in the MMSE, while the patients with "≤ 25 scores" obtained 17.00. The mean in ACE-R of elderly with "≥ 36 scores" on "PLA throughout life" questionnaire was 52.95, while in the "≤ 25 scores" group obtained 37.38. The MMSE mean of "Intermediate level professions, intellectual and scientific activity" group was 19.83, while the MMSE mean of "Unskilled workers" group was 15.98. The mean in ACE-R of "Professions intermediate level, intellectual and scientific activity" group was 49.00, while in the "Unskilled workers" group was 37.35.

## Association of cognitive reserve and the severity of Alzheimer's disease

Regarding the association of cognitive measures and the severity of AD, there was a statistically significant decreasing linear trend between MMSE and CDR, ANOVA ($p < 0.001$).

The Figure 1A shows the patterns of MMSE obtained for different CR levels by CDR and the Figure 1B shows the patterns of ACE-R obtained for different CR levels by CDR. The "medium/high level of CR" group (more or equal than 7 points on CRQ) obtained the higher scores on MMSE and ACE-R (see Figures 1A and 1B). The participants with higher CR levels had higher scores on cognitive tests than elderly with lower CR levels. The Figure 1C show patterns of BI obtained for different CR levels by CDR. The "low level of CR" group obtained the higher scores on BI. AD patients with higher levels of CR showed worse results with a BI than those with lower levels of CR.
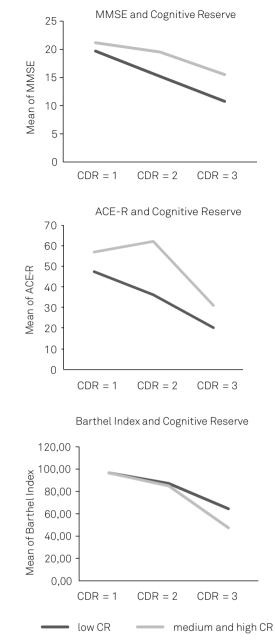
The Figure 2A shows the patterns of PLA for different CR levels by CDR. The participants with "medium/high level of CR" group had the higher scores on PLA. The Figure 2B shows the patterns of MMSE obtained for different education levels by CDR. This study showed that AD patients with higher levels of education achieved better results on MMSE.

As standardized adjusted residual = 2.1, only elderly with more than five years of education were more likely to have mild dementia than moderate or severe dementia (45.7% vs 33.3%). Up to 4 years of education the CDR patients do not differ from each other. As standardized adjusted residual = 2.0, only "Service workers, safety, vendors and administrative staff" are more likely (34.3% vs 24%) to have had mild stage dementia than in moderate or severe dementia.

The relationship between the CR (evaluated with the CRQ) and the years of evolution of dementia along the CDR, showed no statistically significant differences, according to Chi-Square Test ($p = 0.946$). The results showed that the level of CR did not influence the number of years of disease evolution. We crossed the disease stage (assessed with the CDR) and the years of the disease and we found statistically significant differences only in the category of the mild dementia, according to Chi-Square Test ($p < 0.001$). The years of the disease were associated with the severity of the disease. The relationship between CDR and the level of CR (assessed with the CRQ) was statistically significant (LR, $p = 0.015$). Decomposition of this test shows that mild dementia presents values statistically lower than those with moderate or severe dementia (LR, $p = 0.027$). The CDR moderate and severe does not distinguish from each other in the CRQ. The level of CR influenced the severity of dementia (severity of dementia assessed with CDR).
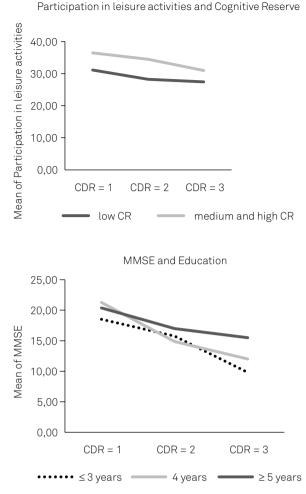
## DISCUSSION

According the current literature, AD is characterized by inexorably progressive deterioration in cognitive ability and



CR: Cognitive Reserve; MMSE: Mini-Mental State Examination; ACE-R: Addenbrooke´s Cognitive Examination Revised; CDR: Clinical Dementia Rating; CDR = 1: mild dementia; CDR = 2: moderate dementia; CDR = 3: severe dementia.

**Figure 1.** Patterns of MMSE, ACE-R and Barthel Index obtained for different CR levels. (A) Patterns of MMSE obtained for different CR levels (Cognitive Reserve Questionnaire); (B) Patterns of ACE-R obtained for different CR levels (Cognitive Reserve Questionnaire); (C) Patterns of Barthel Index for different CR levels.

capacity for independent living[29] and, in this study we evaluated the association of CR and the severity of AD in an outpatient sample. We noticed a relationship between the level of CR and the level of staging of dementia (severity of dementia assessed with CDR). So, the level of CR influenced the severity of dementia. Education, occupation attainment and LA are the most commonly used proxies for CR and our study was consistent with other studies which showed that high

## Participation in leisure activities and Cognitive Reserve



## MMSE and Education



CR: Cognitive Reserve; MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating; CDR = 1: mild dementia; CDR = 2: moderate dementia; CDR = 3: severe dementia; "≤ 3 years" : Three years or less than three years of education; "4 years": 4 years of education; "≥ 5 years": Five years or more than five years of education.

**Figure 2.** Participation in leisure activities and CR; MMSE and education. **(A)** Patterns of participation in leisure activities for different CR levels by CDR. **(B)** MMSE and Education.

levels of CR, education, high PLA and substantively complex work (eg, "Intermediate level professions, intellectual and scientific activity") influenced the rate of cognitive decline in persons with AD[7,11,12].

The results of this study confirm other studies' results have shown that higher levels of education are associated with better performance on cognitive tests[7,30]. The group "> 4 years" got better results on functional tests than the group of illiterates. This study showed that the patients with higher PLA levels had higher scores on cognitive tests than the participants with lower PLA levels. We found that participants who belonged to the "Intermediate level professions, intellectual and scientific activity" group achieved higher results on cognitive tests than those that belonged to the "Unskilled workers" group, corroborating the findings of other studies[31] that showed that substantively complex work significantly increased the level of intellectual functioning. The participants with higher CR levels had higher scores on cognitive tests than elderly with lower CR levels.

The main limitation of this study was the small sample size, the small variability of education level, the fact that some tests are not validated for the Portuguese population and particularly the study design was a cross-sectional observation. Future studies with larger sample sizes will be needed to address these limitations and we must design prospective long-term follow-up observations.

In conclusion, we must highlight that the level of CR influenced the severity of AD. According to Tucker and Stern[5], CR explains why those with higher IQ, education, occupational attainment, or PLA, evidence less severe clinical or cognitive changes in the presence of age-related or AD pathology.

CR is not fixed and continues to evolve across the lifespan. We agree that there are advantages in achieving high levels of CR and we think that healthy life styles should be promoted to improve the health of older adults, helping them to make healthy choices, such as lifelong cognitive stimulation, maintaining an active life or getting regular physical activity. Community preventive approaches for dementia should focus on the improvement of education, changes in lifestyles and the promotion of PLA.

This study suggests that AD patients with a higher CR may benefit against cognitive decline after diagnosis of AD. However, will be needed longitudinal studies to clarify the course of AD along different stages of the disease and its relationship with CR.

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