American Psychological Association

Neuropsychology

ISSN: 0894-4105

https://doi.org/10.1037/neu0000770

Heterogeneity of Effects of Cognitive Reserve on Performance in Probable Alzheimer's Disease and in Subjective Cognitive Decline

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Objective: Cognitive reserve (CR) is a term used to describe the adaptability of cognitive processes to brain changes. It helps to explain the different cognitive adaptation to daily functioning in aging individuals and in individuals with brain pathology: a higher CR is associated with a delay in the manifestation of cognitive symptoms. CR is estimated using different proxies, such as education, cognitively stimulating life experiences, premorbid intelligence quotient (IQ), and vocabulary size. Despite the complexity of CR, little research to date has systematically focused on the heterogeneity of its effects. ***Method:*** We investigated this issue in individuals with probable Alzheimer's Disease (AD) and in individuals with subjective cognitive decline (SCD) by focusing on two variables: (a) the type of CR proxy (i.e., Education and Life experience) and (b) the type of test used to assess cognitive performance (i.e., the Mini-Mental State Examination [MMSE] screening test and the extensive Brief Neuropsychological Examination-2 [ENB-2] test battery). ***Results:*** Our results suggest that effects on CR varied: in individuals with probable AD, we found a positive relationship of Education with performance on both the MMSE and the ENB-2 tests; in contrast, individuals with SCD showed a positive relationship of a Life experience proxy selectively with the ENB-2 global score. ***Conclusions***: Different proxies may reflect different compensatory mechanisms of CR depending on task demand and on an individual's global cognitive condition. In particular, while the Education proxy can capture CR-related cognitive compensation in a pathological condition such as probable AD, the more complex Life experience proxy might be useful for capturing CR-related effects when signs of deterioration are subtle, like in SCD.

Key Points

Question: Cognitive reserve (CR) can be estimated through different proxies, but little is known about the heterogeneity of CR-related effects. ***Findings:*** CR-related effects were found to vary across proxies (Education and Life experience) and neuropsychological tests (MMSE and the extensive ENB-2 battery) in two different clinical conditions (probable Alzheimer's Disease and subjective cognitive decline). ***Importance:*** We used generalized additive models (GAMs) to investigate the joint effects of Age with the CR proxies and their association with the neuropsychological test scores. ***Next Steps:*** Future research should take into account the heterogeneity of CR-related effects by studying different proxies and different neuropsychological tests in relation to individuals' cognitive condition.

Keywords: cognitive reserve proxies, education, life experience, Alzheimer's Disease, subjective cognitive decline

Supplemental materials: https://doi.org/10.1037/neu0000770.supp

Studies on Cognitive Reserve

The construct of *cognitive reserve* (CR) allows to understand interindividual differences in susceptibility to manifest cognitive symptoms due to age- or disease-related neurological changes. CR refers to cognitive resources that are accumulated through exposure to learning experiences across the lifespan (Chan et al., 2018; Stern, 2002; Stern et al., 2020; Tucker & Stern, 2011) and provides a scaffolding to the cognitive system (Arenaza-Urquijo & Vemuri, 2018). Individuals with very high CR and an age-related brain impairment may remain asymptomatic until the very late stages of deterioration (Snowdon, 1997) or until the collapse of compensatory mechanisms (Mortimer et al., 2005). In contrast, individuals with low CR and brain pathology may show symptoms of age-related decline from the early stages of the disease (Arenaza-Urquijo et al., 2015). Interestingly, many demographic and lifestyle factors dynamically combine to build up CR across the early, mid, and late stages of life (Livingston et al., 2017).

A relevant distinction has been made in the past between "brain reserve" (BR) and CR, in an attempt to distinguish a "passive" from an "active" model of reserve, respectively. The "passive" BR model

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Sonia Montemurro played equal role in conceptualization, formal analysis, and writing of original draft. Sara Mondini played equal role in methodology and writing of review and editing. Giorgio Arcara played equal role in conceptualization, supervision, and writing of original draft.

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assumes that differences in susceptibility to age- or disease-related brain damage can be estimated by purely quantitative measures of brain capacity, which can be obtained using neuroimaging techniques. This model is considered "passive" since it posits that "once a certain ratio of pathological quantity to brain quantity is reached, functional impairment is inevitable" (Barulli & Stern, 2013; Stern, 2009). However, the threshold for clinical manifestation of degeneration is not merely associated with brain measures and can be modulated by life experiences (Scarmeas & Stern, 2003; Snowdon, 1997; Snowdon et al., 1996). The "active" CR model considers cognitive efficiency to be shaped by exposure to learning experiences across the lifespan. It is able to explain differences between individuals who are functionally impaired and those who are not, despite an equal level of brain deterioration. To date, the sharp distinction between CR and BR has been considered somewhat artificial (e.g., Cabeza et al., 2018). Unless a Cartesian perspective with a clear-cut separation between brain and mind is adopted, CR should be associated with underlying compensatory mechanisms in the brain. It is important to stress that the concept of CR is still under debate (Cabeza et al., 2018, 2019; Stern et al., 2019), and that developing fully integrated models to operationalize CR-related effects remains a challenge (Ansado et al., 2013; Arenaza-Urquijo et al., 2013; Cole et al., 2014; Perneczky et al., 2019).

The literature on CR has mainly focused on resilience to neurodegeneration that derives from education and life experiences, often irrespective of brain measures (Harrison et al., 2015). In this context, it is often assumed that education, working activities, or leisure activities contribute to the accumulation of CR (Delgado-Losada et al., 2019; Fratiglioni et al., 2004; White et al., 1994). An important aspect to consider is that a compensatory effect of CR can only be observed in longitudinal studies, which show that individuals with high CR maintain a healthy cognitive functioning for longer compared to those with lower premorbid resources (Scarmeas et al., 2001; Snowdon, 2003). However, the large majority of studies of CR to date have adopted a more feasible cross-sectional approach, which compare individuals with different clinical conditions that are associated with different levels of neurodegeneration and/or different amount of accumulated CR. Typically in these studies, the assumption is that both groups have suffered analogous brain damage, but that, depending on their levels of accumulated CR, they compensate differently for the brain deterioration (e.g., Clare et al., 2017).

Proxies of Cognitive Reserve

As CR itself is something that cannot be directly measured (see Stern et al., 2019 for recent considerations), most of the time *socio-behavioral factors* are used to provide a quantitative estimate of CR (Stern et al., 2018). Importantly, socio-behavioral and other factors are better considered as "proxies" (e.g., Chan et al., 2018; Valenzuela & Sachdev, 2007) that *contribute* to CR, rather than as representing CR itself.

One of the most commonly used socio-behavioral factors is education. From the late 1980s, studies in this field have explained the relationship between low education and cognitive performance as resulting from an early life deprivation of stimuli that affects the accumulation of resources for later life (e.g., Katzman et al., 1988, 1989; Zhang et al., 1990). Stern et al. (1992) showed how education can mask the manifestation of brain disease by delaying the onset of cognitive symptoms. Many other studies have reported that different trends in cognitive decline are modulated by level of education (e.g., Chan et al., 2018; Le Carret et al., 2003, 2005), with highly educated patients maintaining their cognitive functioning for longer time in the case of brain deterioration. The concept of education as the sole proxy of CR, however, has been overcome by evidence that CR is built up through a much wider range of activities carried out over the lifespan, that is, experiences encountered after the formal years of schooling, such as occupational attainments and leisure activities (Snowdon, 1997; Snowdon et al., 1996; Stern et al., 1994, 1995). White et al. (1994) demonstrated how occupational attainment plays a crucial role in contributing to CR. They classified the degrees of effort required for different working activities and showed that occupation and education were independent predictors of age-related trajectories of cognitive decline, controlling for demographic variables. In another study, leisure activities were used as CR proxy: 1,772 healthy older adults were assessed in terms of their hobbies (e.g., knitting or music), physical activities (e.g., walking, excursions, or sports), social activities (e.g., visiting friends or being visited by relatives or friends), reading (e.g., newspapers, magazines, or books), volunteering, playing games, or attending religious community events (Scarmeas et al., 2001). The authors found a significant contribution of leisure activities to preventing the manifestation of symptoms of Alzheimer's Disease (AD).

Studies have used a range of different CR proxies and found various relationships between these proxies and cognitive performance. For example, Arcara et al. (2017) evaluated the different effects of education and a CR proxy based on lifelong education, occupational attainment, and significant leisure experiences on mathematical skills in healthy older adults. The authors found that the CR proxy based on life experiences did not significantly predict math performance, while education did.

Another important proxy often used in studies on CR is the intelligence quotient (IQ), which is a measure of crystallized intelligence that can moderate cognitive decline (e.g., Allegri et al., 2010; Sumowski et al., 2009). It is important to underline that not all the IQ measures have the same meaning as proxies of CR. In particular, while some IQ proxies are not strongly influenced by the current cognitive status of an individual (e.g., premorbid measurement of IQ via the National Adult Reading Test [NART]; Nelson & O'Connell, 1978), other IQ measures are influenced by their performance, and hence by their current status of cognitive functioning (e.g., measures of fluid intelligence as the Raven's Progressive Matrices tests; Alchanatis et al., 2005; Campanella et al., 2021; Whalley et al., 2016). Thus, the latter measures may fail to capture the resources that compensate for deterioration, instead providing a picture of the current deterioration. Moreover, IQ measures and proxies based on life activities may be uncorrelated with each other (Nucci et al., 2012), indicating that they should be considered as investigating complementary, rather than analogous, aspects of CR.

For the sake of clarity, in the remainder of this study, we will use the term "CR" to refer to the concept of "accumulation" of resources that allow an individual to cope with age-related or pathological cognitive decline, and the term "CR proxy" to define any quantitative measure (e.g., years of education or scores deriving from a Life experience Questionnaire) used to estimate the accumulated CR.

Heterogeneity of Cognitive Reserve During Healthy and Pathological Aging

In recent times, although the concept of CR has been used in relation to several neurological diseases (e.g., Montemurro, Mondini, Nucci, et al., 2019; Montemurro, Mondini, Signorini, et al., 2019; Rosenich et al., 2020), the large majority of studies on this topic have referred to the compensatory effects of CR in the context of healthy and pathological aging (Lesuis et al., 2018; Stern, 2012; Stern et al., 2020). Several studies suggest that CR may have a protective effect against cognitive decline (see Chapko et al., 2018 for a systematic literature review). However, a close inspection of the literature shows inconsistencies and heterogeneous results. For example, in a qualitative review, Chapko et al. (2018) found that only education was a reliable CR proxy for explaining compensatory mechanisms in cognitive aging and dementia, while proxies based on life experiences showed inconsistent results. Other longitudinal studies have reported that education may not show continuity in its protective effects along trajectories from premorbid to pathological aging (Christensen et al., 2001; Wilson et al., 2019). A longitudinal community-based study conducted in China (Wang et al., 2017) demonstrated the relevance of CR estimated through life experiences, which predicted a reduced risk of developing age-related pathology.

Although there are many possible explanations for the inconsistencies in the literature, at least part of the reason for the discrepancies between the studies listed so far seems to depend on the CR proxy used, for example, between an education proxy and proxies based on life experiences.

From another perspective, the inconsistency associated with the effects of CR might relate to the type of test or cognitive domain assessed. In healthy aging, for example, our research group found that math abilities are not strongly associated with CR based on life experiences but are associated with an education proxy (Arcara et al., 2017). A larger study on healthy aging that assessed several cognitive domains (Lavrencic et al., 2018) proposed that the compensatory effect of CR is associated with orientation, attention, verbal and working memory, and executive function, but not with emotion perception, processing speed, and motor performance. In another study on healthy aging, a significant relationship of CR with global cognitive status and executive functions was shown, but not with language comprehension (Delgado-Losada et al., 2019). With respect to dementia, CR (estimated through education) has been shown to be strongly associated with semantic memory and executive function, as compared to short-term memory performance (Darby et al., 2017).

A third source of heterogeneity related to CR may involve different effects depending on the stage of the cognitive disease or decline. For example, Groot et al. (2018) showed that, especially in preclinical AD, there is a stronger effect of CR (estimated through education) on attention and executive functions, compared to its effect on tests of memory and language function. During the stages that precede the clinical manifestation of dementia, CR has been shown to be strongly associated with better cognitive performance (Bessi et al., 2018; Mazzeo et al., 2019), especially in tasks assessing (higher level) working memory compared with episodic memory (Lojo-Seoane et al., 2018).

In summary, many studies show a potential compensatory effect of CR on cognitive functioning related to normal or pathological aging; however, these effects may be very heterogeneous due to different variables (i.e., proxies used, cognitive tests, and cognitive condition).

The Present Study

The aim of the present retrospective study was to clarify the potential heterogeneity of the effects of CR on cognitive performance in individuals with probable AD and with subjective cognitive decline (SCD). There are several reasons why SCD may be of particular interest for studying the effects of CR: Despite being less investigated than AD or mild cognitive impairment (MCI), SCD represents a condition that could be seen as being midway along the continuum between healthy and pathological aging (Slot et al., 2019). Individuals with SCD have a high risk of developing MCI or AD (Jessen et al., 2014; Rabin et al., 2017), but their global cognitive performance is largely unimpaired. In this context, some standardized screens and batteries are potentially useful for obtaining a global picture about the individuals' profiles. Finally, and in contrast to healthy individuals, those with SCD represent a better group for controlling for cognitive performance in a retrospective study, as both SCD and AD individuals are typically assessed in a clinical context. In (suspected) cases of SCD, individuals are admitted to the clinic after some initial signs of cognitive decline and undergo a clinical assessment to clarify their cognitive status for a potential diagnosis.

We investigated the potential effect of CR in individuals with probable AD and in those with SCD by focusing on two variables: the proxy used to estimate CR and the test used to assess global cognitive performance. To estimate CR, we analyzed two CR proxies related to socio-behavioral factors: Education and Life experiences.

Based on previous studies in the literature showing unclear effects of CR on cognition, our hypothesis was that these effects might depend systematically on the characteristics of CR proxies (i.e., education at school vs. cognitively stimulating life experiences) or on the characteristics of the cognitive tests used (i.e., requiring different degrees of cognitive demand). Furthermore, we hypothesized that these effects may be different for individuals with distinct levels of cognitive resources available (i.e., probable AD vs. SCD).

We tested this hypothesis using an advanced analytical method, *generalized additive models* (GAMs), to provide a comprehensive picture of the interplay among cognitive, demographic, and socio-behavioral variables that contributes to CR.

Method

Participants

Two groups were retrospectively selected from a larger database of individuals referred to the clinical service of the University of Padova, Italy. First, data from 514 individuals were selected based on the availability of the predictors of interest for this study, namely: Age, Education (i.e., number of years of school attended), and the composite Life experience CR proxy, which was the cognitive reserve index (CRI) derived from the Cognitive Reserve Index questionnaire (CRIq; Nucci et al., 2012). We excluded those who presented comorbidity with: (a) motor neurodegenerative disorders (i.e., Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis); (b) focal neurological injuries; (c) psychiatric diseases; and (d) toxic, inflammatory, and metabolic disorders. After

this initial screening, we selected all individuals who fulfilled the criteria either of probable AD or of SCD, as defined below.

The group of individuals with probable AD comprised those diagnosed using neurological criteria (Bennett et al., 2006; Dubois et al., 2007), which always included neuropsychological testing (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [*DSM-5*]; American Psychiatric Association, 2013) and, if available, brain scans (magnetic resonance imaging [MRI] and/or positron emission tomography [PET]). According to the diagnostic criteria, this group of individuals presented evidence of significant cognitive deficits that did not occur exclusively with delirium and that interfered with the daily activities or independence. We also excluded other forms of dementia (e.g., fronto-temporal dementia and Lewy body dementia) from this group. As no systematic collection of fluid and imaging biomarkers was performed (i.e., while these biomarkers strongly contributed to the diagnosis of probable AD, they were collected using a variety of different techniques), we were unable to use these data in this study. In total, there were 104 individuals who fulfilled these criteria, comprising 54 females and 50 males.

The SCD group included individuals fulfilling the classification criteria for SCD (Studart Neto & Nitrini, 2016), who were admitted for a neuropsychological assessment after reporting experiences of cognitive decline in everyday activities. However, they did not meet the criteria either for MCI or for probable AD (see Jessen et al., 2020; Slot et al., 2019 for more details regarding the characterization of SCD). In total, there were 111 individuals, comprising 66 females and 45 males, who fulfilled the criteria for SCD.

Individuals either with probable AD or with SCD were referred to the clinical service based on the advice of the family doctor or on the concerns of a family member about the possible pathological decline of the individual.

All individuals gave their written consent for the anonymous use of their data at the time of the neuropsychological evaluation. The study was conducted in accordance with the Declaration of Helsinki.

Materials and Procedure

To measure cognitive performance, we used the global neuropsychological test scores from two tools that are widely used for neuropsychological evaluations during clinical routine: (a) the Mini-Mental State Examination (MMSE), a brief screening test (Folstein et al., 1975), and (b) the Brief Neuropsychological Examination-2 (ENB-2, tr. Esame Neuropsicologico Breve-2), a more extensive battery of traditional neuropsychological tests available for the Italian population (Mondini et al., 2011). Details of the two tests are provided below.

The MMSE (Folstein et al., 1975) is a screening test that returns a global score. It is a widely used tool that allows a brief screening of cognitive function to be performed by assessing the following domains in 5–10 min: orientation to time and place, immediate and short-delayed recall of three words, attention, calculation, language, and visual construction. The maximum value for the global score of the MMSE is 30.

The ENB-2 (Mondini et al., 2011) is a neuropsychological battery consisting of 16 subtests, which are administered in a fixed order. It lasts for 40–45 min and allows a deeper picture of the cognitive profile of the individual to be obtained compared to the MMSE. ENB-2 scores can be compared to the normative sample of 702 Italian individuals of different levels of age and education. The ENB-2 includes the following tests: Digit Span Test; Story Recall Test Immediate and Delayed for 5 min; Interference Memory Test (interference of either 10 or 30 s); Trail Making Test part A (TMT-A) and part B (TMT-B); Token Test; Phonemic Fluency Test; Abstract Reasoning Test; Cognitive Estimation Test; Overlapping Figure Test; Spontaneous Drawing Test; Copy Drawing Test; Clock Drawing Test; and the Test for Apraxia. In the present study, analyses were based on the global scores resulting from administering the aforementioned cognitive tests. For an overview of the scores on the neuropsychological tests included in the ENB-2 by individuals with probable AD or with SCD, see Table 1. In the ENB-2, the maximum value for the global score is 100: This score is obtained by summing the weighted score of each test included in the ENB-2 battery. Figure 1 shows the *z*-score distribution of MMSE and ENB-2 test scores from all individuals in the study.

The CRIq (Nucci et al., 2012) is a semistructured interview comprising 20 questions that assess formal educational experience (CRI-Education), working activity (CRI-WorkingActivity), and leisure time activity (CRI-LeisureTime). CRI-Education refers to the number of years of formal education achieved plus those of any courses studied during adulthood over a period of at least 6 months. CRI-WorkingActivity refers to number of years spent in work occupations over the lifespan. CRI-LeisureTime refers to the total number of social, intellectual, and physical activities pursued in adulthood and their duration in time (e.g., reading books, painting, volunteering, or playing sport). For CRI-Education, one point is assigned for every year of school attended and 0.5 points is assigned for every 6 months of a vocational course attended during adulthood. For CRI-WorkingActivity, the score is assigned to at least 5 years of time spent working, with jobs weighted differently based on five levels each for the cognitive load, responsibility, and mental resources required for the work. For CRI-LeisureTime, the score is assigned to at least 5 years of time spent carrying out a stimulating activity, at a weekly (e.g., reading newspapers, playing sport, or using computer-based devices), monthly (e.g., voluntary work or playing music), or annual frequency (e.g., traveling or attending concerts and/or conferences). "CRI" is the term used to define the total score of the CRIq questionnaire and is calculated as the average of CRI-Education, CRI-WorkingActivity, and CRI-LeisureTime (Nucci et al., 2012), which is then standardized to have a *M* of 100 and *SD* of 50. In cases in which it was impossible for the participant to directly respond to the questionnaire, it was answered by the caregiver (i.e., his/her close family member see also Bertoni et al., 2020; Mondini et al., 2016). The frequencies of certain leisure activities had possibly changed in some participants with probable AD due to their clinical condition; thus, the period during their lifespan in which they engaged in those activities with the highest frequency was used in the calculation of CRI. Administration of the CRIq lasted between 15-20 min.

Statistical Analyses

In our analysis, we considered the group of individuals with probable AD and the group of individuals with SCD, categorized according with clinical diagnostic criteria as reported above.

Table 1

Neuropsychological Test Scores of Individuals With Probable Alzheimer's Disease (AD) or With Subjective Cognitive Decline (SCD) on the ENB-2 Subtests

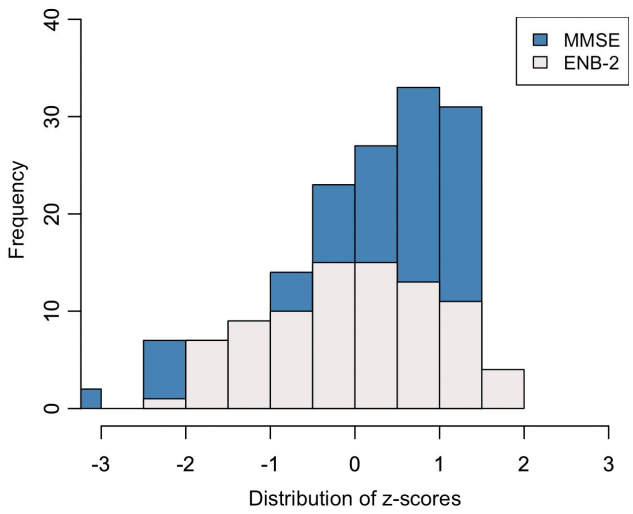
Tests	Individuals with probable AD		Individuals with SCD			
	M	*SD*	*M*	*SD*	*p* value	Adj. *p* value
Digit Span (max = 8)	4.78	0.95	5.17	0.81	.015	.240
Immediate Story Recall (max = 28)	3.85	2.95	11.00	4.43	<.001	<.001
Delayed Story Recall (max = 28)	4.38	4.23	13.52	5.45	<.001	<.001
Interference Memory (10 s; max = 9)	2.79	2.28	5.90	2.19	<.001	<.001
Interference Memory (30 s; max = 9)	2.26	2.07	5.05	2.34	<.001	<.001
TMT-A	101.15	58.92	59.24	30.69	<.001	<.001
TMT-B	212.80	87.99	133.21	52.54	<.001	.009
Token Test (max = 5)	4.39	0.76	4.95	0.21	<.001	.006
Phonemic Fluency	6.47	4.10	10.29	3.56	<.001	<.001
Abstract Reasoning (max = 6)	2.87	2.16	5.06	2.05	<.001	<.001
Cognitive Estimation (max = 5)	3.66	1.19	4.44	0.88	<.001	.007
Overlapping Figures (max = 50)	16.52	6.93	23.99	6.32	<.001	<.001
Copy Drawing (max = 2)	0.96	0.88	1.78	0.51	<.001	<.001
Spontaneous Drawing (max = 2)	1.09	0.86	1.79	0.49	<.001	<.001
Clock Drawing (max = 10)	3.79	3.52	8.70	2.34	<.001	<.001
Test for Apraxia (max = 6)	5.37	0.84	5.85	0.49	.003	.059

Note. TMT-A = trail making test part A (expressed in seconds); TMT-B = trail making test part B (expressed in seconds); ENB-2 = brief neuropsychological Examination-2; Adj. = Adjusted. The first column reports the name of the tests and the respective maximum scores, while the second and third columns report the mean and standard deviation of the neuropsychological test scores obtained by individuals in each of the two groups. The maximum scores indicated for the Phonemic Fluency and the Overlapping Figures tests are not considered clinically to be the maximum score that an individual can achieve, but as the maximum score that the test is validated to record (max = 34 in the Phonemic Fluency test and max = 50 in the Overlapping Figures test). Reported *p* values are corrected using the Bonferroni method according to the total number of tests performed (i.e., 16 comparisons).

We first obtained a general picture about the demographic characteristics of participants (Age, Education, and CRI) and neuropsychological test scores (MMSE and ENB-2). We ran a series of independent *t* tests, with Cohen's *d* as the measure of effect size. To provide a more complete picture, we calculated both uncorrected *p* values and Bonferroni corrected *p* values, considering all of the scores included in the analysis (i.e., five variables in total comprising three for demographic characteristics and two for neuropsychological test scores). Note that although the performance at neuropsychological tests contributed to the diagnosis, the focus of the study was not to investigate this difference, rather to investigate the complex interactions among performance on neuropsychological tests and CR proxies.

Figure 1

Frequencies of Scores Obtained on the MMSE and ENB-2 Tests



Note. MMSE = Mini-Mental State Examination; ENB-2 = Brief Neuropsychological Examination-2. Histogram showing the distribution of scores on the MMSE and the ENB-2 tests. Raw test scores were transformed into *z*-scores to enable comparisons to be made. The blue bars of the histogram refer to the scores obtained on the MMSE, while the gray bars refer to the scores obtained on the ENB-2. The distribution of ENB-2 scores is approximately normal, but the MMSE score distribution is skewed and shows a ceiling effect. See the online article for the color version of this figure.

To investigate the effects of the two different CR proxies on the test scores, we used GAMs (Hastie & Tibshirani, 1986), which are an extension of general linear models (GLMs). The main advantage of GAMs over GLMs is their ability to efficiently model, based on smooth functions, nonlinear relationships between the predictors and the dependent variable. Although this is also possible with GLMs, in GLMs nonlinearity must be specified explicitly, a priori. In contrast, the modeling procedure in a GAM uses a bottom-up approach to estimate if a nonlinear relationship improves the fit. In GAMs, the relationship between the predictor and the expected value of the dependent variable is modeled through a smooth function, which in turn may follow any exponential family distribution or simply have a known mean–variance relationship, allowing the use of a quasi-likelihood approach (Wood, 2017).

To investigate the effect of CR, Education and CRI were included in GAM analyses as continuous variables. The proxy Education was calculated as the number of years that the individual spent at school: this type of proxy has been widely used to estimate CR. Meanwhile, the Life experience CR proxy (i.e., CRI) quantified a range of cognitively stimulating life experiences. With regard to CRI, we focused on the total score and not on the three separate composite

scores, as we did not have specific predictions for the different parts of the CRIq.

We expected Age to be a relevant predictor of test performance, as it is able to capture the ongoing age-related deterioration in cognition. CR, however, may be able to compensate for the effect of Age. Within the GAM framework, this influence can be easily incorporated by modeling the interaction between two continuous variables as a tensor surface. Education and CRI were entered as the two continuous variables of the tensor surface along with Age, which was centered over the two-level categorical variable GROUP (individuals with probable AD or individuals with SCD).

While information about Age, Education, and CRI was available for every participant, not all individuals responded to both the MMSE and the ENB-2. Thus, to achieve the aims of the study, we built two distinct GAM models, one for MMSE and one for ENB-2. The model with MMSE as a dependent variable included 85 individuals with probable AD and 68 individuals with SCD, while the model with ENB-2 as a dependent variable included 32 individuals with probable AD and 53 individuals with SCD.

The GAM model with Education and CRI as predictors of the MMSE score had the following R (R Core Team, 2018) syntax:

(1) MMSE_mod <- gam (MMSE ~ GROUP + te(Age, Education, k = c(3,3), by = GROUP) + te (Age, CRI, k = c(3,3), by = GROUP), data = dataset)

The GAM model with Education and CRI as predictors of the ENB-2 score had the following R syntax:

(2) ENB_2_mod <- gam (ENB2 ~ GROUP + te (Age, Education, k = c(3,3), by = GROUP) + te (Age, CRI, k = c(3,3), by = GROUP), data = dataset)

The parameter $k = c(3, 3)$ specifies the number of "basis functions" used to define the smothing function, where a lower value of k leads to smoother functions, reducing the risk of overfitting. In the context of the present work, we opted for a conservative approach by using a low value of k.

We used the R package *itsadug* (van Rij et al., 2016) to inspect areas of significant interactions: In the data visualization, we overlaid a gray area where the 95% confidence interval included zero. We reported Bonferroni corrected p values, considering all of the terms included within each model: The group term; the interaction term between Age and Education in the probable AD group; the interaction term between Age and Education in the SCD group; the interaction term between Age and CRI in the probable AD group; and the interaction term between Age and CRI in the SCD group. Statistical analyses were performed in R Version 4.0.1 (2020-06-06; R Core Team, 2018), using the package *mgcv* Version 1.8-24 (Wood, 2017) to implement the GAMs.

Results

Mini-Mental State examination

In the t-test analysis, the two groups performed significantly differently in terms of MMSE scores: individuals with probable AD obtained significantly lower scores than those with SCD (see Table 2 and Figure 2).

The GAM model with MMSE as the dependent variable showed a significant main effect of the variable GROUP ($B = 8.14$, $t = 12.88$, corrected $p < .001$), showing that overall, individuals with probable AD had lower scores than those with SCD. Moreover, the results showed a significant interaction between Education and Age in the probable AD group (estimated degrees of freedom; $edf = 5.23$, $F = 4.03$, corrected $p = .011$), but not in the SCD group ($edf = 3$, $F = 0.06$, corrected $p = 1$). In contrast, the interaction of CRI and Age was not significant in predicting the MMSE either in the probable AD group ($edf = 2.51$, $F = 1.84$, corrected $p = .421$) or in the SCD group ($edf = 1$, $F = 0.01$, corrected $p = 1$).

To interpret the significant interactions identified by the GAM analysis, a visual inspection of topographic plots offers the best approach. For a more detailed explanation about how to interpret contour plots, see the Supplemental Materials. The left panels of Figure 3 show the graphical representation of the interactions between Age and CR proxies for the MMSE. In the topographic plots, darker shades of blue indicate lower predicted values on the neuropsychological tests and deeper shades of yellow indicate higher predicted values. The grayed out parts of the plots indicate surfaces whose confidence interval included zero (and hence are not significant). The MMSE model of the probable AD group selectively showed an effect in which MMSE was significantly lower in the case of higher Age and lower Education, and significantly higher in the case of lower Age and higher Education. In contrast, no

Table 2

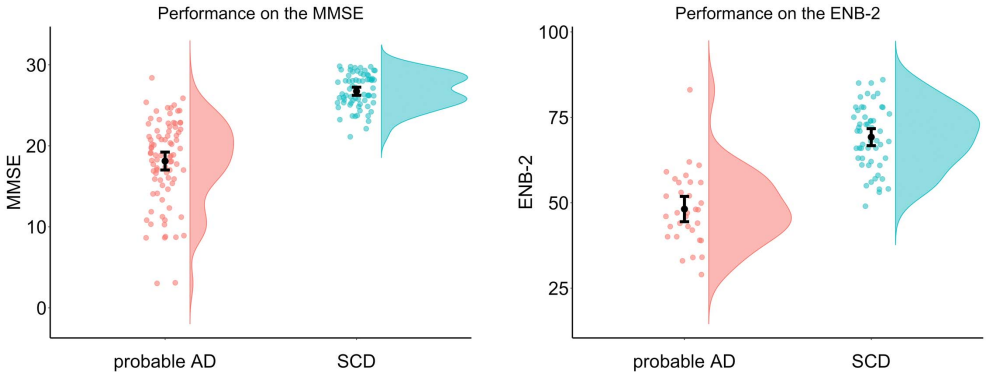
Group Comparison of Demographic Variables and Neuropsychological Test Scores Obtained by Individuals With Probable Alzheimer's Disease (AD) and Individuals With Subjective Cognitive Decline (SCD)

	Individuals with probable AD ($N = 104$)		Individuals with SCD ($N = 111$)		Group differences				
Variable	*M* (*SD*)	Range	*M* (*SD*)	Range	*df*	*t*	*p* value	Adj. *p* value	Effect size (Cohen's *d*)
Age	77.17 (6.01)	61–88	76.29 (5.91)	65–92	213	1.07	.280	1	0.15
Education	8.16 (4)	2–22	9.83 (4.65)	4–24	213	-2.87	.006	.032	0.38
CRI	98.98 (19.72)	76–159	103.95 (19.95)	74–150	213	-1.83	.068	.337	0.25
MMSE	18.11 (5.19)	3–28	26.73 (2.11)	21–30	151	-12.85	<.001	<.001	2.09
ENB-2	48.15 (10.69)	29–83	69.21 (9.25)	49–86	83	-9.58	<.001	<.001	2.15

Note. ENB-2 = Brief Neuropsychological Examination-2; MMSE = Mini-Mental State Examination; Adj. = Adjusted. The demographic and sociobehavioral variables such as Age, Education, and cognitive reserve index (CRI) were examined. Education is a cognitive reserve (CR) proxy expressed in terms of the number of years of schooling, while CRI is a CR proxy based on life experiences. In addition, neuropsychological test scores on the MMSE and the ENB-2 were also examined. The mean, standard deviation, range, and degrees of freedom associated with the t test comparing the two groups (individuals with probable AD and individuals with SCD) are reported. Both uncorrected and Bonferroni corrected p values are reported.

Figure 2

Performance of Individuals With Probable Alzheimer's Disease (AD) and Subjective Cognitive Decline (SCD) on the Mini-Mental State Examination (MMSE) and on the Brief Neuropsychological Examination-2 (ENB-2)



Note. Density plots and individual data points showing the performance of the two groups on the neuropsychological tests. Along the *x*-axis, the probable AD group is shown on the left-hand side of both panels, while the SCD group is shown on the right-hand side. The *y*-axis shows the MMSE (left plot) and ENB-2 (right panel) scores (maximum obtainable scores: MMSE, 30; ENB-2, 100), both as density plots and as individual data points. Each point represents a single observation (i.e., one participant) and the error bars show the variability of the data. Individuals with probable AD performed significantly worse than those with SCD on both the MMSE and the ENB-2. See the online article for the color version of this figure.

significant interaction was found for the SCD group (graphically represented on the plots with grayed out surfaces).

Brief Neuropsychological Examination-2

In the *t*-test analysis, the two groups showed significantly different performance on the ENB-2: the AD group obtained significantly lower scores than the SCD group (see Table 2 and Figure 2). The GAM model with ENB-2 test scores as the dependent variable showed a significant main effect of the variable GROUP ($B = 20.71$, $t = 11.81$, corrected $p < .001$), confirming that, individuals with probable AD obtained lower scores than individuals with SCD. While the probable AD group showed a significant interaction between Education and Age ($edf = 5.2$, $F = 3.7$, corrected $p = .011$), this was not the case of the SCD group ($edf = 4.69$, $F = 1.1$, corrected $p = 1$). In contrast, we found that CRI and Age showed a significant interaction in the SCD group ($edf = 2.41$, $F = 3.93$, corrected $p = .035$), but this effect was absent in the probable AD group ($edf = 1$, $F = 0.14$, corrected $p = 1$); see Figure 3.

The tensor surfaces in the right-hand panel of Figure 3 indicate that in the probable AD group, the cognitive performance measured by the ENB-2 was significantly lower for higher Age and lower Education, and significantly higher for lower Age and higher Education. In the SCD group, ENB-2 scores were significantly lower for higher Age and lower CRI, and significantly higher for lower Age and higher CRI.

To better characterize the effects identified by the GAM models, the partial effects on MMSE and ENB-2 scores are reported using the specific predictor values. Figure 4 shows that individuals with probable AD showed better cognitive performance with higher values of Education across different Age values (i.e., the three quartiles). Interestingly, at the higher Education values, individuals in both the SCD and probable AD groups performed similarly on the MMSE (i.e., they both achieved very high scores on this brief screening test).

Figure 5 illustrates the relationship between the CRI on the ENB-2 for different values of Age. It shows that in individuals with SCD, cognitive performance was better in the case of higher CRI for different values of Age.

Discussion

The aim of the present study was to systematically investigate the heterogeneity of the potential effects of CR in individuals with probable AD and with SCD. We explored this issue using two CR proxies: Years of Education and CRI, a composite measure obtained from the CRIq (Nucci et al., 2012) that quantifies a wide range of life experiences (Bertoni et al., 2020; Franzmeier et al., 2017; Lee et al., 2020).

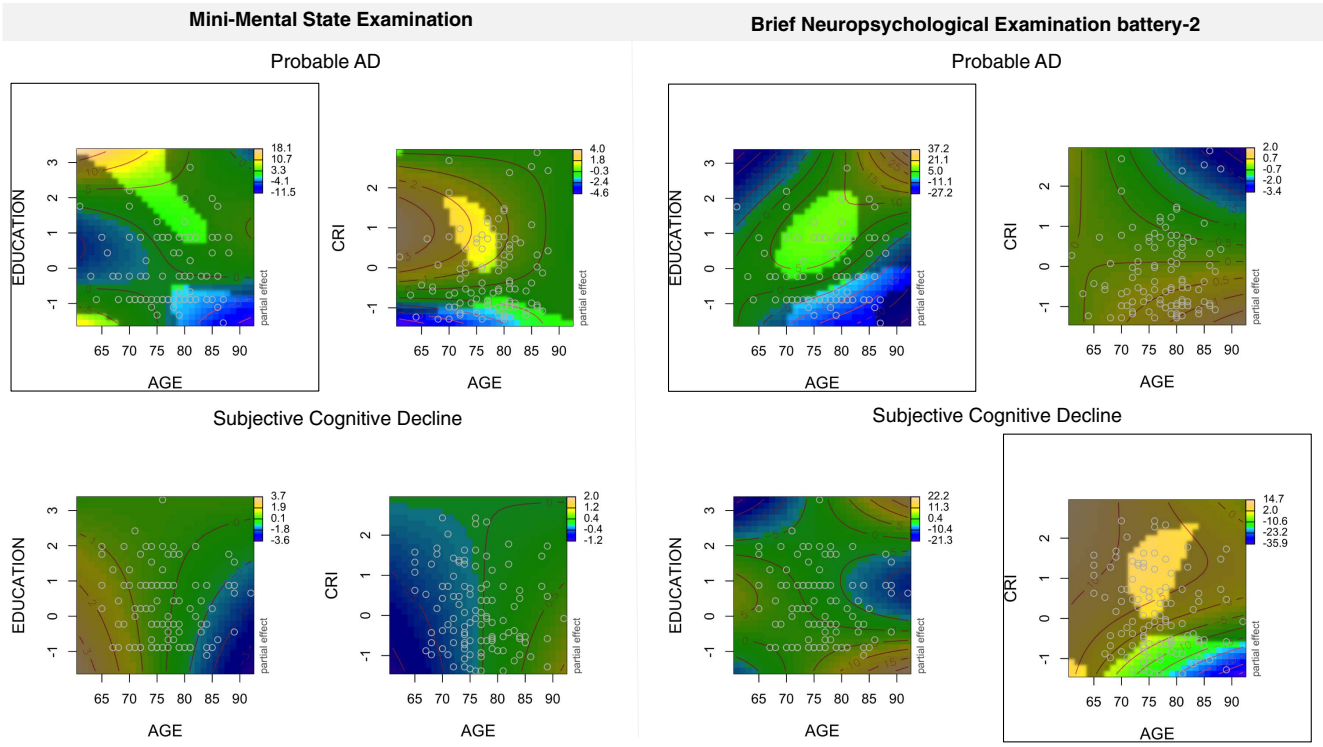
We used two tests of global cognitive performance: global scores on the MMSE and global scores on the ENB-2: a more extensive battery of traditional neuropsychological tests. To investigate the potential complexity of CR effects, we used an analytical method, the GAM, which allows to examine the complex interactions between continuous variables.

As expected, an initial comparison of group performances by means of *t*-tests showed a significantly lower level of performance in individuals with probable AD than those with SCD in both of the neuropsychological tests.

The GAM analyses showed different patterns of results. In the probable AD group, the GAM models showed an interaction between the effects of Age and Education on both MMSE and ENB-2 scores. In particular, in both tests, individuals with probable AD and with higher Age and lower Education performed significantly worse than those with lower Age and higher Education. In the SCD group, we did not find any significant effect of Education, but

Figure 3

Heterogeneity of Interaction Effects Between CR and Age on Global Cognitive Performance



Note. CR = cognitive reserve; CRI = cognitive reserve index; AD = Alzheimer's Disease; SCD = subjective cognitive decline; ENB-2 = Brief Neuropsychological Examination-2; MMSE = Mini-Mental State Examination; GAM = generalized additive models. Interaction effects were assessed in individuals with probable AD and those with SCD using the MMSE and the ENB-2 battery. The figure shows the tensor surfaces associated with the interactions between Age and two CR proxies, Education and Life experience (i.e., CRI). Age is always placed on the *x*-axis (in years), while the two CR proxies (Education and CRI) are placed on the *y*-axis, separately for each group. The CR proxies were transformed into *z*-scores to enable them to be compared. The upper panels show the results for individuals with probable AD, while the lower panels show the results for those with SCD. The left-hand panels show the results of the model with MMSE score as the dependent variable, while the right-hand panels show those of the model with ENB-2 score as the dependent variable. Darker shades of blue in the contour plots indicate lower predicted neuropsychological test scores on the MMSE and on the ENB-2, while deeper shades of yellow indicate higher neuropsychological test scores. The panels drawn with black lines highlight the contour plots in which the interaction between Age and the CR proxies of the GAM model had $p < .05$. Within each contour plot, areas in which the colors are covered with darker shades indicate predicted values in which the confidence interval at 95% included the value zero. See the online article for the color version of this figure.

there was a significant effect of CRI. In particular, individuals with SCD who had with higher Age and lower CRI performed significantly worse than those with lower Age and higher CRI.

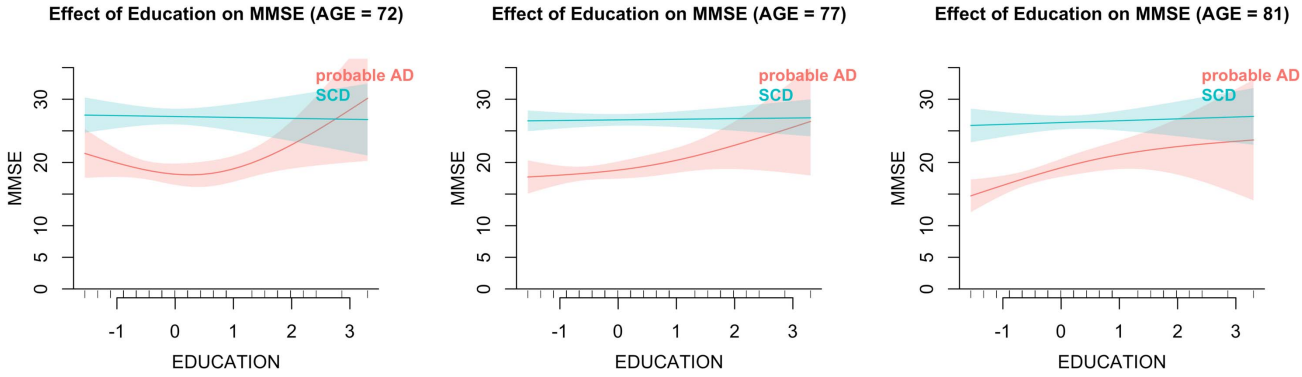
A first important consideration that can be drawn from these results is that, depending on the proxies considered, the effect of CR can show a different association with performance depending on the degree of cognitive decline. In particular, in the probable AD group, the results showed a potential positive relationship of Education, but not of a Life experience CR proxy (i.e., CRI), to cognitive performance. A different pattern was found in the SCD group, only for the ENB-2, that is, CR effects were evident for CRI and not for Education. This result is in line with previous studies, which have indicated that, although high CR is potentially beneficial for global cognition in older adults (Opdebeeck et al., 2018), such an effect is not clear-cut (Arcara et al., 2017; Montemurro, Mondini, Nucci, et al., 2019).

Prior studies corroborate the lack of an effect of Education on the performance of individuals with SCD. Christensen et al. (2001) and Van Dijk et al. (2008) found that when Education was used as the sole proxy of CR, this was not sufficient to predict trajectories of cognitive decline. Similar results were reported more recently by Wilson et al. (2019), who found no indication that Education is an effective proxy of CR during the early stages of cognitive decline. This suggests that, in some cases, the effect of socio-behavioral proxies of CR on cognitive functioning vary over time. In contrast, a number of other studies have reported a strong association between higher Education and cognitive functioning over time, that is along with the different stages of cognitive decline (Bennett et al., 2003; Perneczky et al., 2009).

Our results and those of previous studies indicate that, although Education is an important and widely used proxy of CR, it could not be suitable for making clinical evaluations about compensatory effects, in individuals with subtle cognitive impairment, like SCD. However, we found that a Life experience proxy of CR did potentially contribute to a compensation of cognitive performance

Figure 4

Effect of Education on MMSE Score in Individuals With Probable Alzheimer's Disease (AD) and With Subjective Cognitive Decline (SCD) at Different Years of Age



Note. CRI = cognitive reserve index; MMSE = Mini-Mental State Examination; GAM = generalized additive models. Analysis of the partial effects of the GAM model with MMSE score as the dependent variable showed a significant interaction effect between Age and Education in the probable AD group. In the three plots shown, MMSE scores are reported on the *y*-axis, while Education level is reported on the x-axis as a *z*-score. The left-hand, center, and right-hand plots, respectively, show data for the first quartile (72 years), median (77 years), and third quartile (81 years) of the variable Age. The three plots are set on the median value of CRI = −0.228 (in *z*-points). The small vertical segments on the *x*-axis indicate the observed values in the data set for the variable reported in the *x*-axis. Individuals in the probable AD group with higher Education performed better on the MMSE than those with lower Education at all of the three Age values shown. See the online article for the color version of this figure.

in individuals with SCD. This is in line with recent studies reporting that the effect of CR is stronger for CR measures that quantify learning experiences occurring along with the lifespan (Bertoni et al., 2020; Lee et al., 2020).

A potential explanation of the difference we found between Education and the Life experience CR proxy (i.e., CRI) can be found in the distinctive characteristics of these two proxies: (a) Education is acquired during a developmental period of high plasticity, and involves systematic and intensive learning (Ramey et al., 1984); while (b) the Life experience CR proxy represents the accumulation of cognitively stimulating experiences during adulthood in a less structured and diversely assorted way.

Although both Education and Life experience CR proxies may be overall affected by many latent factors (Jones et al., 2011), such as family cultural background and economic context, the fact that Education is acquired in a structured way suggests that it may represent more consolidated aspects contributing to CR. Thus, the prominent effect of Education we found even during the advanced stages of decline might indicate that the contribution that Education makes to CR can be more resilient to brain damage. A similar conclusion was drawn by our research group (Arcara et al., 2017) in a study of healthy older individuals, in which we found a significant effect of Education and a nonsignificant effect of CRI on early acquired mathematical abilities.

The results of this study indicate that a Life experience proxy of CR may play a role in predicting global cognitive performance during the stages of age-related neural deterioration in which an objective decline has not been manifested, such as in SCD. This is in line with previous research highlighting how potentially modifiable lifestyle activities can continuously shape the cognitive system and potentially reduce the risk of cognitive decline (Clare et al., 2017).

The results of this study showed, in both the groups, an effect of CR on the ENB-2 test. In contrast, only the probable AD group showed a CR effect on the MMSE test.

To clarify this difference, we propose two main explanations that are intrinsically related and that only future studies will be able to tease apart. The first explanation is related to the different nature of the two tests. While the MMSE is a brief cognitive screening test, the ENB-2 is a wider battery involving more tasks, many of which tap into executive functions. Our results therefore suggest that a brief screening test may not be helpful for detecting the possible compensatory role of CR in groups with differing degrees of cognitive decline.

The second explanation is related to the distributions of neuropsychological test scores from these tests. For the SCD group, the performance on the MMSE was almost at ceiling and this may have prevented modulatory effects of the CR proxies from being found. Moreover, at high levels of Education, individuals with probable AD or with SCD performed similarly on the MMSE. This highlights the limited capacity of the MMSE to differentiate between individuals at different stages of cognitive decline when Education is considered as proxy of CR. In contrast, ENB-2 is a more complex test that requires more resources and better preserved cognition.

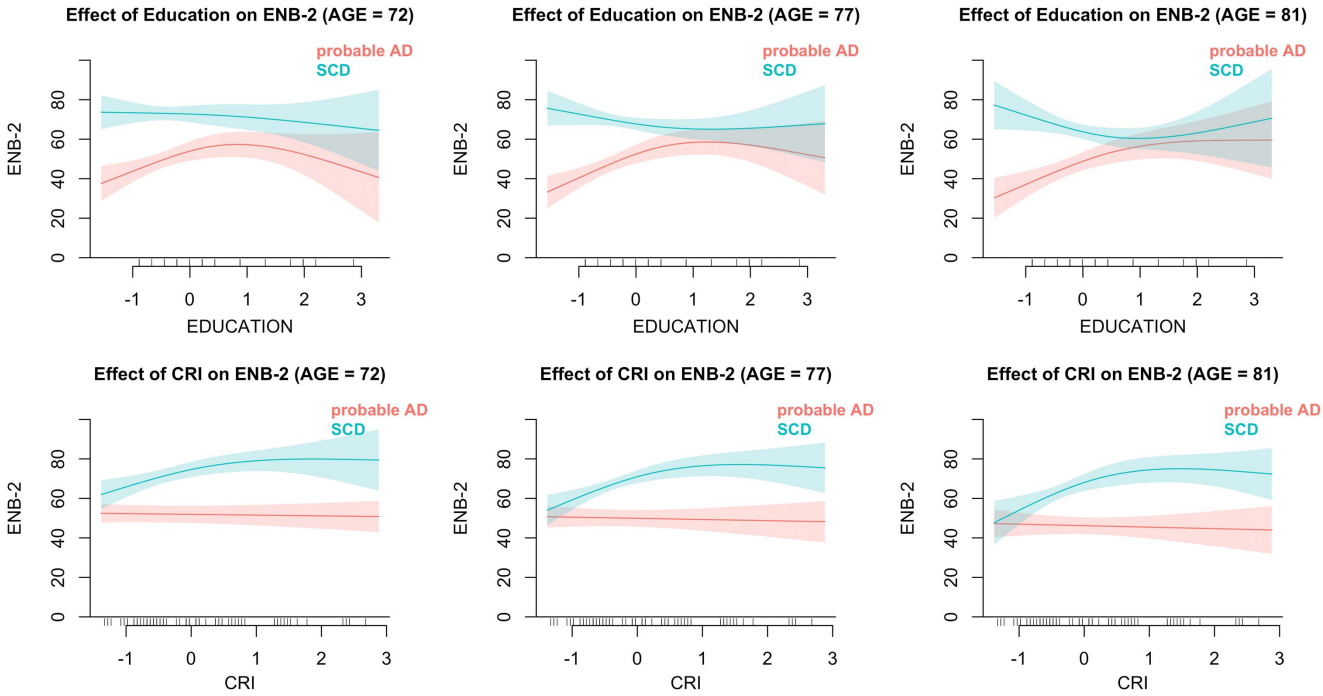
Thus, CR proxies could be capable of predicting neuropsychological test scores when the test used is *within* the ability of individuals with probable AD (i.e., the MMSE) and *difficult enough* for those with SCD (i.e., the ENB-2).

Limitations and Future Directions

This study has a number of limitations that are important to mention here. The first relates to the missing data from the participants. Based on the selection criteria for this retrospective study, not

Figure 5

Effect of Education and CRI on ENB-2 Score in Individuals With Probable Alzheimer's Disease (AD) or Subjective Cognitive Decline (SCD) at Different Years of Age



Note. CRI = cognitive reserve index; ENB-2 = Brief Neuropsychological Examination-2; MMSE = Mini-Mental State Examination; GAM = generalized additive models. Analysis of the partial effects of the GAM model with ENB-2 score as the dependent variable showed a significant interaction effect between Age and Education in the probable AD group. In the six plots shown, ENB-2 scores are reported on the *y*-axis. In the three upper panels, Education is reported on the *x*-axis, while the three lower panels report the CRI on the *x*-axis. Both Education and CRI are reported in the form of *z*-scores to allow the results to be compared. The left-hand, center, and right-hand panels, respectively, show data for the first quartile (72 years), median (77 years), and third quartile (81 years) of the variable Age. The three panels on the upper side are set on the median value of CRI = −0.228, and the panels on the lower side are set on the median value of education = −0.0226 (in *z*-points). The small vertical segments on the *x*-axis indicate the observed values in the data set for the variable reported in the *x*-axis. Individuals with probable AD who were able to perform the ENB-2 despite their clinical condition, especially those advanced in Age, significantly benefitted from a higher level of Education. Individuals with SCD who had a higher CRI maintained a better level of cognitive performance compared with those with lower CRI. See the online article for the color version of this figure.

all participants completed both the MMSE and the ENB-2, meaning that the two GAM model analyses were not run on identical samples. Although the number of observations analyzed was relatively high, further studies with larger sample sizes are necessary to corroborate our conclusions.

Additionally, our analyses were based on only two outcome tests (MMSE and ENB-2 global scores). However, different conclusions might be drawn using other tests, in particular tests of memory and executive function. Future studies should take into greater consideration the potential heterogeneity and multifaceted nature of CR used to predict performance in cognitive tests having different characteristics.

Conclusions

We showed the heterogeneity of CR effects across proxies and tests in two clinical conditions: probable AD and SCD. The results suggest that Education and Life experience CR proxies may tap on different aspects of CR depending on the stage of cognitive decline, as well as on the test used to assess cognitive performance. We wanted to investigate the complex interactions among cognitive performance and other variables as proxies of CR. As the interactions and relationships here assessed were not taken into account (and known) to the clinicians for the diagnostic categorization, there are no issues of circularity in the analysis.

Advanced analytical methods, namely GAMs, were used to provide a global picture of the interplay among cognitive, demographic, and socio-behavioral variables. From a clinical perspective, we analyzed potential age-related CR effects by comparing the performance of individuals with probable AD with those of a population that is potentially at risk of manifesting symptoms of AD. Finally, this study provides new insights into the heterogeneity of CR effects, which may deepen our understanding of the implications of estimating CR with different proxies.

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Received February 11, 2021
Revision received July 21, 2021
Accepted July 24, 2021 ■