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RESEARCH ARTICLE

The indirect effect of cognitive reserve on the relationship between age and cognition in pathological ageing: A cross-sectional retrospective study in an unselected and consecutively enrolled sample

Francesco Giaquinto[1] | **Giorgia Tosi**[1,2] | **Chiara Abbatantuono**[3] | **Ilaria Pepe**[3] | **Marika Iaia**[1] | **Luigi Macchitella**[1,4] | **Ezia Rizzi**[1,2] | **Maria Fara De Caro**[3] | **Daniele Romano**[2] | **Paolo Taurisano**[3] | **Paola Angelelli**[1]

[1]Laboratory of Applied Psychology and Intervention, Department of Human and Social Sciences, University of Salento, Lecce, Italy

[2]Psychology Department, University of Milano-Bicocca, Milan, Italy

[3]Department of Translational Biomedicine and Neuroscience "DiBraiN", University of Bari "Aldo Moro", Bari, Italy

[4]Scientific Institute I.R.C.C.S. "E. Medea"- Unit for Severe Disabilities in Developmental Age and Young Adults (Developmental Neurology and Neurorehabilitation), Brindisi, Italy

Correspondence
Paolo Taurisano, Department of Translational Biomedicine and Neuroscience "DiBraiN", University of Bari "Aldo Moro", Policlinico di Bari, Piazza Giulio Cesare 11, 70124 Bari (BA), Italy.
Email: paolo.taurisano@uniba.it

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Abstract

Cognitive reserve (CR) allows individuals to maintain cognitive functionality even in the presence of pathologies. The compensation hypothesis suggests that CR plays an indirect role between age and cognitive decline, contrasting the negative effect of ageing on cognition. We test this hypothesis in an unselected and consecutively enrolled sample of memory clinic attendees ($n = 134$) who completed the CR Index questionnaire and three neuropsychological tests assessing global cognition (MMSE, FAB, CDT). Participants were divided into two groups based on standard diagnostic criteria (DSM-5): those who were cognitively impaired ($n = 92$) and those who were preserved ($n = 42$). A principal component analysis was used to extract a composite measure of global cognitive functioning from the three neuropsychological tests, and mediation analysis was used to examine the relationship between CR, age and global cognitive functioning in the two groups. Results revealed that: (i) age had a significant direct negative effect on the global cognitive score in both groups; (ii) the three socio-behavioural proxies of CR together suppress the direct negative relationship

Paolo Taurisano and Paola Angelelli contributed equally as senior author.

between age and global cognitive score in cognitively impaired patients but not in cognitively preserved participants. This study confirms the association between CR, age and cognition and allows us to validate its role in a population with cognitive impairment and extend findings to a low-to-middle educated population. These results hold important implications for public health and wellness promotion, emphasising the beneficial role of maintaining healthy and active physical, cognitive and social lifestyles.

KEYWORDS

ageing, cognition, cognitive reserve, principal component analysis

INTRODUCTION

Ageing is characterised by heterogeneity in cognitive functioning trajectories (Bettcher et al., 2019), and there are individual differences in the effects of physiological or neuropathological changes on cognitive performance and speed of decline (Cholerton et al., 2016). It has been hypothesised that certain life course experiences enrich neural resources and significantly contribute to brain compensation processes, mitigating the effects of ageing and neural damage (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). Stern et al. (1999) introduced the concepts of brain reserve (BR), brain maintenance (BM) and cognitive reserve (CR) to account for 'resilience' against age- and disease-related changes. BR refers to neurological characteristics of the brain, such as brain size and the number of synapses, and can be directly measured using *in vivo* or post-mortem techniques (Stern et al., 2019). BM expresses the notion of modifiability of the brain, and it is defined as reduced development over time of age-related brain changes and pathology based on genetics or lifestyle (Stern et al., 2020). CR concerns the adaptability (i.e. efficiency, capacity, flexibility) of cognitive processes in facing difficulties due to brain ageing and neuropathology (Stern et al., 2020). It is a multidimensional construct that is influenced by the interaction of individual innate features and lifetime experiences, such as education, occupation, leisure activities and social engagement, explaining individual differences (Stern et al., 1999). Higher CR reduces the prevalence of dementia, bringing down public costs related to care (Zissimopoulos et al., 2015). At the individual level, this corresponds to fewer years of disability and patient dependence (Li et al., 2022) and yields important practical implications for prevention and cure policies for neurodegenerative diseases (Wu et al., 2016). CR can only be indirectly measured, using socio-behavioural proxies (Stern et al., 2020), which share an underlying process and each adds a unique contribution to CR (Opdebeeck et al., 2016). The construct of CR is broader than education alone, as it also considers the influence of work activity and leisure time (Nucci et al., 2012; Stern et al., 1999). Examples of CR proxies include level of education (Arce Rentería et al., 2019), complexity and commitment of work activity (Lane et al., 2017) and participation in leisure and social activities, depending on their specific content (Park et al., 2019). Less commonly, CR has been operationalised using global measures of premorbid intelligence or solely the level of education (e.g. Alchanatis et al., 2005; Berry et al., 2019; Olaithe et al., 2015). Moreover, although vocabulary and reading ability allow for the consideration of educational quality, years of formal education are the most commonly used proxy variable for CR (Pettigrew & Soldan, 2019). In normal ageing, more years of formal education are associated with better cognitive performance in later life (Valenzuela & Sachdev, 2006; Zahodne et al., 2015). In the presence of neuropathology, higher education does not affect the age of onset of dementia or the age of death but is associated with a delayed manifestation of clinical cognitive symptoms together with accelerated cognitive decline (Clouston et al., 2020; Ko et al., 2022). Post-mortem and imaging studies have revealed greater brain pathology among people with dementia (Meng & D'arcy, 2012).

Many studies on CR have focused on samples with more than 13 years of education (e.g. Lee et al., 2022; Soldan et al., 2017). As mentioned earlier, a high CR is associated with better cognitive functioning before the onset of dementia, delayed manifestation of cognitive decline and faster rate of decline (Soldan et al., 2017). These findings suggest that CR plays a compensatory role in mitigating the effects of neuropathology on cognitive performance (Barulli & Stern, 2013). Conversely, people with low literacy levels have a higher incidence of dementia and related disorders (Meng & D'arcy, 2012; Roe et al., 2007), and low education is considered a risk factor for the development of neurodegenerative disorders (Livingston et al., 2020).

However, the generalisation of these results remains limited due to sample selection, and there has already been an emphasis on the need to test research hypotheses in consecutive samples of the unselected population, such as older adults referring to a memory clinic for a consultation (e.g. Staekenborg et al., 2020). There are few ecological studies, which are often limited by the use of education as a sole proxy for CR evaluation and conducted with highly educated samples (Persson et al., 2017; Ramakrishnan et al., 2017; Staekenborg et al., 2020). Indeed, little is known about how CR affects the cognitive performance of people with low-to-middle education. It could be hypothesised that even in a group of people with fewer years of education, a high overall CR could compensate and counteract the negative effects of ageing on cognitive performance under pathological conditions.

On the assumption that CR can be enhanced through the whole life course (even when the brain is already affected by neuropathology), increasing CR by promoting lifelong education, social participation and physical activity may on the one hand help to reduce several dementia-related risks (Livingston et al., 2020), on the other provide greater resilience in facing the neuropathology, improving patients' global functioning and cognition (e.g. Liberati et al., 2012).

The present study aims to investigate the relationship between CR, age and global cognitive functioning in a large, unselected sample of adults and elderly individuals attending memory clinics. To accomplish this, we utilised a comprehensive measure of CR that included education, work activity and leisure time. Additionally, we recognised the limitations of using single tools to assess different cognitive functions, as well as the importance of considering differences in the diagnostic accuracy of screening tests for cognitive impairment in the elderly population (Lenehan et al., 2015). Therefore, we calculated a single 'general factor' as a measure of global cognitive functioning that captures information from the three neuropsychological tests, allowing us to better assess overall cognitive functioning among participants.

This approach has been used in previous works (i.e. Proust-Lima et al., 2008). Finally, we used a statistical analysis, namely mediation analysis, which is a useful method for revealing different indirect effects, including mediation and suppression. Mediation occurs when direct and indirect effects go in the same direction, showing the different paths followed by the total effect of one variable with respect to another (e.g. loneliness mediated the relationship between social isolation and cognitive functioning, accentuating the negative effects of social isolation, Yang et al., 2020). Suppression, on the other hand, occurs when an indirect effect reduces or even completely cancels the influence of one variable on another because its indirect influence goes in the opposite direction of the direct effect. For instance, if CR suppressed the negative effects of age on cognitive performance in a sample of older adults, it would attenuate the negative effect of age on cognitive performance. According to previous findings, we hypothesise that CR plays an indirect role between age and cognitive decline (Soldan et al., 2020), and we expect a suppression effect in accordance with the compensation hypothesis (Barulli & Stern, 2013). Furthermore, we were interested to study if this suppression effect occurs in both pathological and normal aging participants.

METHODS

Sample

We considered all patients ($n = 557$) who were consecutively admitted to the Simple Operative Unit (U.O.S.) of Psychology and Clinical Neuropsychology, which is part of the Complex Operative Unit (U.O.C.) of Neurology 'L. Amaducci' at Bari Polyclinic and University of Bari 'Aldo Moro' (Apulia, Italy), from 19 May 2021 to 14 April 2022. The sample comprised both inpatients admitted to the Department of Neurology at Bari Polyclinic or Day-Hospital with a specific request for neuropsychological counselling, as well as outpatients referred by general practitioners or specialists for an initial neuropsychological evaluation due to memory or cognitive problems. The assessment was conducted in a single 90-min session using a standardised methodology by psychologists who were specially trained in neuropsychology and belonged to the U.O.S. Department of Psychology and Clinical Neuropsychology. The evaluations took place face to face between the examiner and the examinee in dedicated testing rooms. After a preliminary interview, a triple multilevel screening was conducted, followed by a domain-specific assessment based on the DSM-5 (American Psychiatric Association, 2013) criteria and domains. The tests used for analysis are described in detail in the 'Measures' section. All patients who completed the CR Index questionnaire (CRIq, Nucci et al., 2012) and the three neuropsychological screening instruments (Mini Mental State Examination, MMSE, Folstein et al., 1975; Frontal Assessment Battery, FAB, Dubois et al., 2000; Clock Drawing Test, CDT, Sunderland et al., 1989) were included in this study ($n = 134$). The majority of the participants included in the studies (78%) reported memory difficulties. Seven per cent of them already had a diagnosis of a neurodegenerative disorder (e.g. Alzheimer's disease, Parkinson's disease, frontotemporal dementia), while others came for diagnostic investigations due to other neurological disorders (8%), psychiatric disorders (1.5%), depressive symptoms (1.5%) or other unspecified causes (4%). Based on the results of the neuropsychological tests, and evaluations by expert neuropsychologists (MFDC, PT) of medical history and other clinical data, the sample was divided into two groups: (i) a cognitively preserved group ($n = 42$), comprising participants without cognitive decline; (ii) and a cognitively impaired group ($n = 92$), which included patients with a diagnosis of mild cognitive impairment (MCI, 11.2%), major neurocognitive disorder (22.4%), memory impairment (3.1%) and cognitive dysfunctions not otherwise specified (64.3%). Patterns of cognitive impairment or dysfunction not otherwise specified were defined by the presence of at least one deficit in the neuropsychological performance of each subject examined on domain-specific cognitive tests, in accordance with the multidomain evaluation criteria proposed by the DSM-5 (American Psychiatric Association, 2013). The clinical judgement was made by an experienced neuropsychologist (i.e. MFDC). Qualitative information and data on the participants' functional autonomies (i.e. ADLs/IADLs) were collected to complement the assessment procedures.

Measures

Cognitive reserve

The CRIq (Nucci et al., 2012) provides a standardised measure of CR accumulated by individuals throughout their lifespan through the computation of three socio-behavioural proxies that return a total score and a specific score for each proxy: CRI-Education (CRI-E), which considers years of formal education and extra training courses; CRI-Working activity (CRI-W), which considers years of adulthood professional activity classified into five levels of job complexity, dealing with the degree of intellectual involvement and personal responsibility; and CRI-Leisure time (CRI-L), which refers to cognitively stimulating occupations carried out during leisure time, including intellectual, social and physical activities. The CRIq is one of the most used measures of CR based on Stern's theory, with supported construct validity, especially in the diseased population (Kartschmit et al., 2019).

Cognitive screening tests

The MMSE (Folstein et al., 1975; Italian norms: Magni et al., 1996) assesses nine cognitive domains: orientation, learning, delayed recall, naming, visuospatial function, comprehension, language, reading and writing. In memory clinic settings, the pooled sensitivity is 79.8% and specificity is 81.3% for the detection of dementia compared to healthy participants (Mitchell, 2009).

The FAB (Dubois et al., 2000; Italian norms: Apollonio et al., 2005) is a widely used first-level test for executive deficits (Hurtado-Pomares et al., 2018) and it assesses concept formation, cognitive flexibility, motor planning, interference control, response inhibition and environmental autonomy. Studies in the Italian population have shown sensitivity levels ranging from 61.1% to 77.8% and specificities ranging from 64.4% to 80.3% for first-level assessments of dysexecutive-related global cognitive inefficiency (Aiello et al., 2022).

The CDT (Sunderland et al., 1989; Italian norms: Mondini, 2011) is a cognitive screening tool that assesses various cognitive functions, including selective and sustained attention, auditory comprehension, verbal memory, numerical knowledge, visual memory and reconstruction, visuospatial organisation and praxis (Shulman et al., 2006). It is highly correlated with global cognitive functioning (Amodeo et al., 2015). The pooled sensitivity and specificity of the CDT, among the different scoring systems, range from 72.6% to 82% and from 75.7% to 87.9% respectively (Park et al., 2018).

Statistical analysis

Chi-squared tests were used to analyse the qualitative variables, while *t*-tests were used for quantitative variables to test for any differences between the two groups. We conducted a principal component analysis (PCA) on the cognitive screening test data (MMSE, FAB and CDT) to extract a single 'general factor' as a measure of global cognitive functioning for each group. This method encapsulates the information from all the neuropsychological tests in a sound methodological approach. Similar procedures have been used in previous studies (e.g. Kudlicka et al., 2013; Paulsen et al., 2020). The factorial scores were used as the dependent measure in the mediation analysis.

To investigate the potential indirect effect of CR on the association between age and cognitive functioning, we used a mediation analysis. In particular, we considered the age of the participants as the independent variable, the global cognitive score as the dependent variable and the CR proxies as the mediating variables. The analysis returns these effects: direct effects (reporting the relationship between age and the cognitive functioning composite score without considering the CR proxies); indirect effects (reporting the mediation role of each CR proxy); total indirect effects (reporting the mediation role of the CR proxies as considered together); and total effects (reporting both the direct and mediated effects). Direct, indirect and total effects were estimated separately for cognitively preserved and impaired participants.

The mediation effect for each CR proxy was calculated using the products of coefficient approach. The total indirect effect was calculated by summing up the indirect effects mediated by each CR proxy.

The level of statistical significance was set at $p < .05$. All statistical analyses were conducted using the JASP 0.16.3 software (JASP Team, 2021).

Data used in this study are publicly available at: https://osf.io/bx96u/?view_only=fa26d0872d42487083986eef95f17ec0.

Ethical approvement

The study protocol was approved by the Ethical Committee of Bari General Hospital (study code: 7450).

RESULTS

Sample characteristics

The final sample consisted of 134 participants, 52.59% were females. The mean age was 69.47 years. In particular, 39 participants were less than 65 years old, 56 were aged between 65 and 75 years and 40 were more than 75 years old. The sample was mostly low educated, since 61.5% of people had less than 9 years of formal education, while only 23.7% had between 9 and 13 years, and 14.8% had more than 13 years. Regarding employment, the sample consisted of 6.8% self-employed, 15.2% employed, 3.8% unemployed or first-time job seekers, 17.5% housewives, 43.6% retired, 1.3% other and 11.8% missing values. The cognitively impaired group consisted of 93 patients (45 females), while 42 people (26 females) constituted the cognitively preserved group. Healthy participants were significantly younger than patients ($t(133) = 2.49$, $p < .05$, $d = .46$), while there was not any significant difference between groups in gender ($\chi(1) = 2.12$, $p = .15$, $\phi = .14$) and education ($t(133) = -.23$, $p = .82$, $d = .04$). As expected, patients performed worse than the healthy participants on MMSE ($t(133) = -6.43$, $p < .001$, $d = -1.20$), FAB ($t(133) = -8.35$, $p < .001$, $d = -1.55$) and CDT ($t(133) = -3.68$, $p < .001$, $d = -.68$). No significant differences between groups were found for the CRIq total score ($t(132) = -.63$, $p = .53$, $d = .12$), the CRIq-E ($t(133) = .52$, $p = .61$, $d = .10$) and the CRIq-W ($t(133) = -.29$, $p = .78$, $d = .05$). Conversely, patients reported lower scores than the healthy group on the CRIq-L ($t(133) = -2.01$, $p < .05$, $d = -.37$). Demographic information and comparisons are summarised in Table 1.

Relationship between CR, age and global cognitive functioning

In both groups, a single component was extracted using PCA. This single component solution is supported by quantitative indices such as the scree plot, eigenvalues greater than one and parallel analysis, as well as the theoretical need for a single score to represent cognitive functioning. In the cognitively impaired group (Figure 1), the single component (Eigenvalue = 2.04) accounted for 68.1% of the variance

TABLE 1 Demographic information, mean raw scores on CR and cognitive tests.

	Total ($n = 135$)	Cognitively preserved group ($n = 42$)	Cognitively impaired group ($n = 93$)
Demographic data			
Sex, *n* (%) female	71 (52.59%)	26 (62%)	45 (48.39%)
Age (SD)	69.47 (9.65)	66.45 (10.45)	70.83 (9.00)*
Years of education (SD)	9.41 (4.79)	9.55 (3.95)	9.34 (5.15)
Cognitive reserve			
CRIq total (SD)	98.43 (22.48)	100.24 (19.49)	97.61 (23.78)
CRIq education (SD)	99.78 (17.82)	98.60 (15.70)	100.31 (18.76)
CRIq working activity (SD)	98.04 (22.71)	98.88 (20.75)	97.67 (23.65)
CRIq leisure time (SD)	96.79 (20.87)	102.09 (17.89)	94.39 (21.75)*
Cognitive functioning			
MMSE (SD)	24.79 (4.62)	28.12 (2.01)	23.28 (4.68)***
FAB (SD)	12.99 (3.41)	15.95 (1.46)	11.65 (3.19)***
CDT (SD)	6.39 (3.66)	8.04 (2.89)	5.64 (3.75)***

Note: Data are presented as mean and standard deviation (SD) in parenthesis, unless otherwise specified. Significant differences between unimpaired and impaired groups (ANOVA). Significant relationships are highlighted as follows: *$p < .05$, ***$p < .001$.

Abbreviations: CDT, clock drawing test; CRIq, cognitive reserve index questionnaire; FAB, frontal assessment battery; MMSE, Mini Mental State Examination.

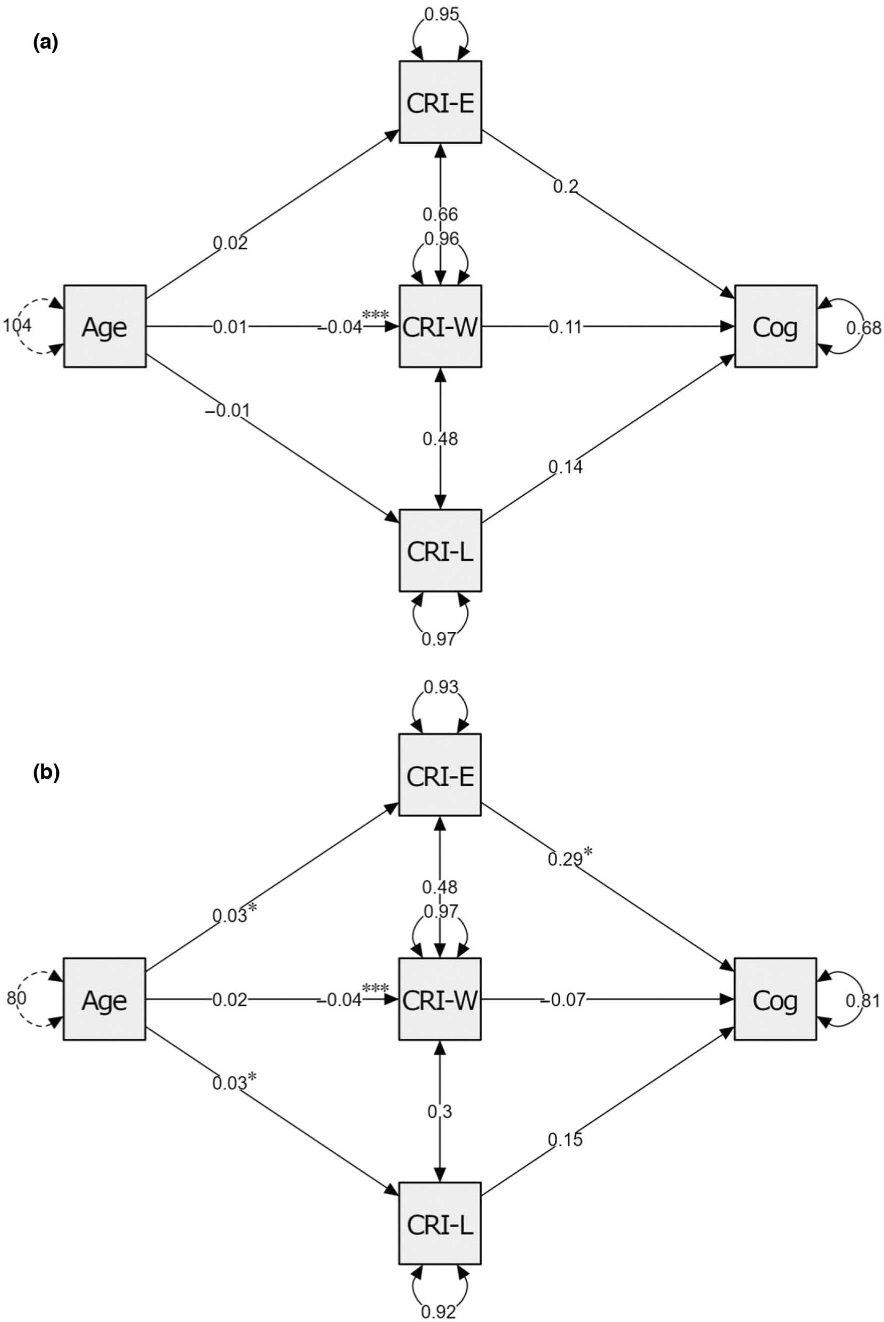

FIGURE 1 Path diagrams. Panel (a) shows the cognitively preserved group results; Panel (b) shows the cognitively impaired group results. CRI-E, CRI-Education; CRI-W, CRI-Working activity; CRI-L, CRI-Leisure time; Cog, global cognitive score. Path coefficients represent b estimates. Significant relationships are highlighted as follows: * <.05; ** <.01; *** <.001.

and demonstrated an internal consistency of $\alpha = .755$. In the cognitively preserved group, the component (Eigenvalue = 2.09) accounted for 69.6% of the variance and demonstrated an internal consistency of $\alpha = .737$. The loadings for the components are provided in Table 2.

TABLE 2 Summary of PCA of cognitive screening test scores.

	Cognitively preserved group		Cognitively impaired group	
	Component 1	Uniqueness	Component 1	Uniqueness
MMSE	.874	.236	.856	.268
FAB	.830	.311	.854	.271
CDT	.797	.365	.762	.419

Note: The table shows the component loading of PCA for each group.

Abbreviations: CDT, clock drawing test; FAB, frontal assessment battery; MMSE, mini-mental state examination.

In the cognitively preserved group, the mediation analysis revealed that age had a significant direct negative effect on the global cognitive score ($z = -3.35$; $p < .001$). Additionally, the CR proxies did not impact this relationship (all p values for indirect effects >.425). Crucially, in cognitively impaired patients, the CR proxies impacted the relationship between age and the global cognitive score, showing a significant total indirect effect (z-value = 2.21; $p < .05$). Together, age and CR proxies explained 17.4% of the variance in the global cognitive score. When we considered the indirect effects driven by each component of the CR, we did not find any significant influence (all p values >.09). The CRIq-E showed a positive effect near statistical significance (z-value = 1.69; $p = .09$). Age confirmed its significant direct negative effect on cognitive functioning (z-value = −3.44; $p < .001$). Results are reported in Table 3.

DISCUSSION

The goal of this study was to investigate the relationship between CR, age and global cognitive functioning in a consecutive and unselected sample of older adults with or without cognitive impairment. Results revealed that: (i) age had a significant direct negative effect on the global cognitive score in both groups; (ii) CR, measured by three coded socio-behavioural proxies (education, work activity and leisure time), suppressed the relationship between age and global cognitive score in cognitively impaired patients but not in cognitively preserved participants. The results therefore suggest a relationship between CR, age and cognitive functioning, but also highlight a differential impact of CR in the two groups, pointing out the specific role of CR in countering the negative effects of ageing and pathology on cognition.

From a theoretical point of view, the understanding of these findings encompasses two complementary lines of research. On the one hand, in line with the Scaffolding Theory of Aging and Cognition model (STAC; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014), life experiences such as intellectual engagement, education, physical fitness, multilingualism and higher ability contribute to the brain's compensatory structure that counteracts the pathological damage of ageing. Observing the socio-behavioural proxies that suppress the relationship between age and cognition in a pathological sample means observing the indirect effects of scaffolding activation. On the other hand, there is the perspective introduced by Stern et al. (1999), who argues that CR improves or maximises performance by recruiting different brain networks. Indeed, a recent review on CR (Soldan et al., 2020) illustrates possible pathways by which CR may influence cognitive decline and the risk of dementia in later life. One hypothesis suggests that CR changes the relationship between age and cognitive outcomes, resulting in a mediating effect. In individuals with cognitive impairment, the neural structure underpinning CR is efficient and sustains the neurocognitive scaffold, relatively preserving cognitive functions (Fairjones et al., 2011). In the presence of neuropathology, the reduced efficiency on neuropsychological tasks can be mitigated by higher CR (Steffener et al., 2016), leading to the consideration of a compensatory role of CR in partially attenuating cognitive decline (Barulli & Stern, 2013). Differences in cognitive performance between individuals could be due to different levels of CR and, consequently, different compensatory abilities. The results of the mediation analysis, which indicate a suppressive effect of CR on the negative effects of age on global cognitive functioning, are consistent with this perspective. In

TABLE 3 Mediation analyses results.

	Estimate	95% CI lower	95% CI upper	*z*-value	*p*
Cognitively preserved group					
Direct effects					
age → Cog	−.043	−.068	−.018	−3.347	<.001***
Indirect effects					
age → CRIq-E → Cog	.003	−.005	.011	.798	.425
age → CRIq-W → Cog	.002	−.005	.008	.504	.614
age → CRIq-L → Cog	.001	−.005	.004	−.411	.681
Total indirect effects					
age → CR proxies → Cog	.004	−.008	.016	.634	.526
Total effects					
age → Cog	−.039	−.065	−.012	−2.884	.004**
Cognitively impaired group					
Direct effects					
age → Cog	−.038	−.059	−.016	−3.442	<.001***
Indirect effects					
age → CRIq-E → Cog	.008	−.001	.017	1.692	.091
age → CRIq-W → Cog	−.001	−.005	.003	−.600	.548
age → CRIq-L → Cog	.005	−.003	.012	1.202	.229
Total indirect effects					
age → CR proxies → Cog	.011	.001	.021	2.205	.027*
Total effects					
age → Cog	−.027	−.049	−.005	−2.392	.017*

Note: Direct effects report the relationship between age and the screening test composite score not considering the CRIq proxies. Indirect effects report the mediation role of each CR proxy. Total indirect effects report the mediation role of the CR proxies as considered together. Total effects report both the direct and mediated effect. Path coefficients represent b estimates. Significant relationships are highlighted as follows: * <.05; ** <.01; *** <.001.

Abbreviations: Cog, global cognitive score; CRI-E, CRI-Education; CRI-L, CRI-Leisure time; CRI-W, CRI-Working activity.

particular, only the three CR proxies considered together produced a significant mediating effect, while isolated CR dimensions/proxies (related to education, work experiences and leisure time) did not. This result highlights the importance of considering various aspects of CR rather than a single proxy. In the absence of neuropathology, our results reveal no significant impact of CR in suppressing the negative effect of age on global cognitive functioning. This finding differs from the outcomes of samples consisting of highly educated individuals (Lee et al., 2022; Soldan et al., 2017). This could suggest that in individuals with lower to middle education, higher CR only compensates for cognitive performance in the presence of neuropathology. However, this hypothesis should be further explored using longitudinal studies.

Although the percentage of variance in the global cognitive score explained by age and CR proxies (17.4%) was consistent with previous findings (e.g. Ihle et al., 2016), a more comprehensive view of CR can be proposed by considering qualitative aspects of education, such as vocabulary or reading skills (Pettigrew & Soldan, 2019), and harmful life experiences that also deplete neural resources, such as stress, head trauma or depression, as suggested by the STAC model (Reuter-Lorenz & Park, 2014). Future research should evaluate the impact of these additional factors.

In spite of methodological differences, the results are in line with cross-sectional studies that revealed an attenuation of the association between age and Alzheimer's disease progression (Almeida et al., 2015) or age-related structural brain changes (Steffener et al., 2016) among individuals with higher

CR. Moreover, the results are also consistent with neuroimaging data showing that different brain areas were associated with CR proxies in healthy and pathological ageing, indicating CR-related neural changes in the presence of pathology (Colangeli et al., 2016).

Otherwise, the evidence suggests that participating in activities that enrich CR early in life may benefit cognitive health in later life (Wu et al., 2016). Promoting an active lifestyle that begins with education, acquiring complex work skills, cultivating good socialisation habits and engaging in stimulating hobbies during leisure time has significant positive effects on healthy ageing and helps to cope with the difficulties associated with advancing age. Planning healthcare policies that promote CR is a crucial step in preventing dementia and other neurodegenerative pathologies.

One of the advantages of this study is that the sample characteristics allow us to generalise the beneficial effect of CR to a low- to middle-educated population, emphasising the importance of a multidimensional assessment of this construct (Proust-Lima et al., 2008; Staekenborg et al., 2020). The sample used in this study, in terms of years of education, is representative of the Italian population of the same age and of other European countries (e.g. Greece, Dardiotis et al., 2014; Spain, Contador et al., 2017). Our groups are indeed derived from an ecological sample drawn from a memory clinic in Southern Italy, with CR and education characteristics similar to those reported in previous studies (Caffò et al., 2016). However, due to the limited sample size, the group of patients with cognitive impairment consists of individuals with different pathologies. Studying the impact of CR on specific diagnostic categories would be unreliable with our sample size.

The assessment of CR through the CRIq (Nucci et al., 2012) allowed us to consider the interaction between three socio-behavioural proxies, which produced a significant total effect that did not emerge when considering the single CR dimensions alone. This finding reinforces the idea of considering CR in a more complex way, without referring to education alone, as it is often done in the literature (Soldan et al., 2020). It is also consistent with studies that show how these proxies contribute to CR both independently and by sharing a common underlying process (Farina et al., 2018; Opdebeeck et al., 2016). Moreover, the computation of a 'general cognitive factor' derived from the three screening tests allowed us to overcome the limitation in the cognitive-domains assessment of the single tools and provides a reliable measure of global cognition.

The cross-sectional design of this study does not allow us to investigate symptom progression over time, and we cannot determine how many of the undiagnosed patients will progress to dementia. Additionally, we cannot explore predictive hypotheses regarding the role of CR, as recommended by Nelson et al. (2021). However, this study represents the first step in longitudinal studies and provides important confirmations of the hypothesis of mediating CR by considering age as an independent variable, as suggested by Soldan et al. (2020). Future studies should consider investigating the indirect role of CR by examining not only global cognitive functioning but also domain-specific performance to determine whether there are differences in the influence of CR on specific cognitive functions.

CR is a construct that enables the identification of an action plan on protective factors, reducing the risk of dementia. This concept opens up important scenarios in terms of public health and wellness promotion, emphasising healthy and active physical, cognitive and social lifestyles. The extension of these findings to low-to-middle educated, non-selectively recruited populations increases the strength of these results and suggests social and health actions to prevent and/or postpone the effect of neurodegenerative diseases in the elderly population.

AUTHOR CONTRIBUTIONS

Francesco Giaquinto: Conceptualization; writing – original draft; writing – review and editing. **Giorgia Tosi:** Data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Chiara Abbatantuono:** Data curation; investigation; writing – original draft; writing – review and editing. **Marika Iaia:** Writing – original draft; writing – review and editing. **Ilaria Pepe:** Data curation; investigation; writing – original draft. **Luigi Macchitella:** Writing – original draft; writing – review and editing. **Ezia Rizzi:** Writing – original draft; writing – review and editing. **Maria Fara De Caro:** Investigation; project administration; resources; supervision;

writing – original draft. **Daniele Romano:** Conceptualization; data curation; formal analysis; funding acquisition; project administration; resources; supervision; writing – original draft; writing – review and editing. **Paolo Taurisano:** Data curation; investigation; project administration; resources; supervision; writing – original draft; writing – review and editing. **Paola Angelelli:** Funding acquisition; project administration; resources; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

OPEN RESEARCH BADGES

This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available at https://osf.io/bx96u/?view_only=fa26d0872d42487083986eef95f17ec0.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/bx96u/?view_only=fa26d0872d42487083986eef95f17ec0.

ORCID

Francesco Giaquinto https://orcid.org/0000-0002-0967-6256
Paolo Taurisano https://orcid.org/0000-0001-6140-9326

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