

Cognitive reserve in young-onset cognitive impairment

Chiara Carbone^{a,*} , Riccardo Maramotti^{a,b}, Erica Balboni^c, Daniela Beltrami^d, Daniela Ballotta^a, Roberta Bedin^a, Chiara Galligani^{a,e}, Manuela Tondelli^{a,e}, Simone Salemm^{a,e}, Federico Gasparini^d, Giulia Vinceti^e, Alessandro Marti^d, Annalisa Chiari^e, Luca Nocetti^c, Giuseppe Pagnoni^a, Giovanna Zamboni^{a,e}

^a Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, via Giuseppe Campi 287, 41125 Modena, Italy

^b Department of Physics, Informatics and Mathematics, University of Modena and Reggio Emilia, via Giuseppe Campi 213/a, 41125 Modena, Italy

^c Medical Physics Unit, Azienda Ospedaliero-Universitaria of Modena, via Giardini 1355, 41126 Modena, Italy

^d Clinical Neuropsychology Unit, Azienda Unità Sanitaria Locale of Reggio Emilia-IRCCS, viale Risorgimento 80, 42123 Reggio Emilia, Italy

^e Neurology Unit, Azienda Ospedaliero-Universitaria of Modena, via Giardini 1355, 41126 Modena, Italy

ARTICLE INFO

Keywords:

Cognitive reserve
Cognitive Reserve Index questionnaire
Cognition
Neurofilaments light-chain
MRI

ABSTRACT

Cognitive reserve (CR) reflects brain's resilience to pathology, enabling to maintain function despite structural damage. This study investigates its role in young-onset cognitive impairment (<65 years) beyond brain integrity and neurodegeneration. Participants underwent neuropsychological assessment – including the Cognitive Reserve Index questionnaire (CRIq) –, magnetic resonance imaging (MRI), and blood neurofilaments light-chain (NfLs) measurement. Scores of *global cognition* and domain-specific cognition were derived from Principal Component Analyses of neuropsychological results. Linear regression models estimated CR's contribution to *global* and domain-specific cognition, alongside age, sex, MRI measures, and NfLs as predictors. Among the 115 participants, *global cognition* was significantly explained by CR [effect size (ES) = 0.229], grey matter volume (ES = 0.348), and NfLs (ES = -0.302). The effect of CR was prominent on *language* and *attentional-executive functions*: while the CRIq subscore related to education predicted performance in both these domains, the subscore related to leisure activities was positively associated with the *language* domain only. These findings highlight CR's protective role in young-onset cognitive impairment, particularly for non-amnesic cognitive domains. Since a high CR can mask or compensate for neurological cognitive disorders delaying its diagnosis, our results suggest that measures of CR, including time spent on leisure activities, should be considered when interpreting neuropsychological tests.

1. Introduction

In clinical settings, individuals with subtle cognitive deficits identified by a neuropsychological assessment, and not interfering with everyday functioning, are diagnosed with Mild Cognitive Impairment (MCI) (Petersen et al., 2014) regardless of the underlying cause. However, several factors such as anxiety, depression, alcohol or substance abuse, and comorbid health conditions can contribute to abnormal scores on neuropsychological assessment, even if there are no neurological diseases, while high levels of education and time spent on

physical, intellectual, and social activities – or anything that enhances cognitive engagement in everyday life – can improve the performance on cognitive testing (Alvares Pereira et al., 2021), masking or compensating for the clinical manifestation of an underlying neurological condition. The concept of cognitive reserve (CR) captures such a discrepancy and implies that a brain that has been engaged and stimulated during life will better cope with damage by using pre-existing skills and abilities (Reserve and Resilience, 2025; Stern et al., 2020, 2023; Stern, 2002). A positive association between CR and cognitive performance across adulthood has been demonstrated, as well as the fact that

* Corresponding author at: Via Giardini 1355, 41126 Modena, Italy.

E-mail addresses: chiara.carbone@unimore.it (C. Carbone), riccardo.maramotti@unimore.it (R. Maramotti), erica.balboni@unimore.it (E. Balboni), daniela.beltrami@ausl.re.it (D. Beltrami), daniela.ballotta@unimore.it (D. Ballotta), roberta.bedin@unimore.it (R. Bedin), galliganichiar@gmail.com (C. Galligani), manuela.tondelli@unimore.it (M. Tondelli), simone.salemm@unimore.it (S. Salemm), federico.gasparini@ausl.re.it (F. Gasparini), gvinceti@gmail.com (G. Vinceti), alessandro.marti@ausl.re.it (A. Marti), chiari.annalisa@aou.mo.it (A. Chiari), nocetti.luca@aou.mo.it (L. Nocetti), giuseppe.pagnoni@unimore.it (G. Pagnoni), giovanna.zamboni@unimore.it (G. Zamboni).

<https://doi.org/10.1016/j.bandc.2025.106297>

Received 25 February 2025; Received in revised form 5 April 2025; Accepted 5 April 2025

Available online 11 April 2025

0278-2626/© 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

high CR has a protective role against the risk of developing MCI and dementia in older age groups, both cognitively healthy (Weaver & Jaeggi, 2021) and cognitively impaired (Corbo et al., 2023). However, there is still limited knowledge regarding the impact of CR when cognitive symptoms manifest at an early age, specifically prior to 65 years (i.e., in individuals experiencing young-onset cognitive impairment). While the prevalence of neurodegenerative diseases increases with age, these conditions also affect younger individuals (Chiari et al., 2021). Although CR is a fluid construct that continues to change across the whole life, understanding its impact on cognitive performance at any time, even in people with young-onset mild cognitive symptoms, may reveal to be crucial in guiding clinical decision-making on whether a diagnosis of cognitive impairment should be given or not, and whether second-level investigations should be performed.

Several proxies such as education, premorbid intelligence quotient, or occupational attainment have been used to estimate CR (Jones et al., 2011). Specific questionnaires have also been developed, including – among others – the Cognitive Reserve Index questionnaire (CRIq) (Nogueira et al., 2022; Nucci et al., 2012). Another way to estimate CR indicated as *residual method* (Reed et al., 2010) assumes that CR can be measured as the residual variance in cognition not explained by known measures of brain integrity [e.g., grey matter (GM) volume, hippocampal volume, perivascular spaces] or by demographical variables. Across the literature, studies measuring CR with questionnaires such as the CRIq have only marginally considered the effect of such other variables in explaining cognitive performance (Lee et al., 2020; Ye et al., 2022). The aim of the present study was to estimate the role of CR, directly measured with the CRIq, in relation to cognitive performance in people with young-onset cognitive impairment, above and beyond variables measuring cerebral neurodegeneration [i.e., neurofilaments light-chain (NfLs), GM atrophy, and white matter (WM) microstructural characteristics]. We hypothesized that CR would significantly modulate cognitive performance and explored in which cognitive domains its effect would be most prominent in this young-onset population.

2. Materials and methods

2.1. Participants

Individuals with a clinical diagnosis of MCI (Petersen et al., 2014) and symptoms onset before the age of 65 seen in the Cognitive Neurology Clinics of Modena University Hospital and Arcispedale Santa Maria Nuova in Reggio Emilia (Italy) between 2019 and 2023 were considered eligible. We excluded patients with a medical history suggestive of a vascular, traumatic, or other focal brain lesion as the aetiology of the cognitive impairment, Parkinson's disease, Huntington's disease, inflammatory diseases of the central nervous system or major psychiatric disorders (e.g., schizophrenia, bipolar mood disorder). Participants underwent neurological examination, extensive neuropsychological assessment, blood exams, and magnetic resonance imaging (MRI) scan, as detailed below. The study was approved by the Local Ethics committees (832/2018/SPER/AOUMO and AUSLRE n. 2019/0009686) and conducted in accordance with local clinical research regulations and conformed to the Declaration of Helsinki. Participants gave written informed consent to participate in the study before taking part.

2.2. Neuropsychological assessment

The neuropsychological battery explored the following cognitive domains: *language, memory, visuospatial abilities, and attentional-executive functions*. The specific tests and questionnaires included are detailed in [Supplementary Material](#).

CR was evaluated using the CRIq (Nucci et al., 2012), aimed at measuring lifetime CR accumulated from the age of 18 onward. The questionnaire returns four scores: CRIq-Education, derived by years of education and training; CRIq-WorkingActivity, resulting from the type

of adulthood profession based on five different possible levels of intellectual involvement and personal responsibility; CRIq-LeisureTime, from the all types of activities carried out during leisure time (e.g., intellectual, social, and physical activities); and CRIq-Total, which combines all the previous measures. Due to the presence of cognitive complaints, the questionnaire was administered by addressing questions to both participant and caregiver together. However, since participants had only very subtle deficits, they were usually the primary respondents. Caregivers intervened only when needed, helping to clarify or confirm responses for greater accuracy.

2.3. Blood testing

Patients underwent the measurement of serum NfLs, a biomarker of axonal degeneration considered non-specific and informative across diseases (Gaetani et al., 2019). Serum NfLs concentration was determined via immune-enzymatic test on Simple Plex NfLs Assay on Ella microfluidic platform (ProteinSimple® Bio-Techne), according to the manufacturer's instructions. Calibration was performed using in-cartridge factory standard curves. Blood samples were centrifuged upon arrival, and the serum was stored in aliquots at -80°C . Before testing, samples were thawed and centrifuged at $2500 \times g$ for 5 min in strict accordance with the manufacturer's protocols. The quantification method has been explained in detail elsewhere (Urbano et al., 2024).

2.4. Image acquisition and analysis

Images of patients were acquired on a 3T GE Signa Architect scanner in Ospedale Civile di Baggiovara, Modena, equipped with a 48-channel-array head coil. The multimodal MRI protocol included, among other sequences, high-resolution T1-weighted 3D MP-RAGE structural images (TR 2 sec; TE 3.1 msec; FOV $172 \times 256 \times 256 \text{ mm}^3$; voxel size 1 mm isotropic) and diffusion tensor imaging (DTI) (TR 7 sec; TE 108.7 msec; slice thickness 2.5 mm; voxel size 2.5 mm isotropic; 64 diffusion directions; b 1000 sec/mm^2). Images were analysed using FSL (FMRIB Software Library) v6.0 software (<https://fsl.fmrib.ox.ac.uk/fsl>) and Freesurfer v7.3.2 software (Fischl et al., 2002).

The processing of structural T1-weighted volumes consisted of brain extraction and calculation of total intracranial (TIV) and grey matter (GM) volumes. Brain extraction and TIV computation were performed with the "mri_synstrip" routine from Freesurfer (Hoopes et al., 2022). GM segmentation was computed from the brain extracted images using the GM probability map obtained with the "fast" routine of FSL (Zhang et al., 2001), with a threshold of 0.25. GM volume was calculated with the FSL tool "fslstats" and divided by the TIV, to give a GM volume normalized by TIV (and thus more comparable across subjects).

DTI images were processed with the FSL tools "bet" (brain extraction) and "eddy", which corrects for eddy currents and patient motion (Smith et al., 2004). Then, the "dtifit" tool of FSL was used to obtain fractional anisotropy (FA) maps, which were registered to the $1 \times 1 \times 1 \text{ mm}$ FMRIB58_FA standard template, using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). Finally, the FA mean value inside the skeleton mask in standard space was computed for each subject with "fslstats".

2.5. Statistical analysis

2.5.1. Descriptive statistics and multiple imputation of missing data

Descriptive statistics of demographic, cognitive, NfLs, and neuroimaging variables were performed with Stata version 15 and reported as median score and interquartile range. Missing data in cognitive tests were estimated with a Multiple Imputation model (Rubin, 1987), using Predictive Mean Matching (PMM) (Little, 1988). Analyses were performed in R using the "mice" package (van Buuren & Groothuis-Oudshoorn, 2011). For more details, see [Supplementary Material](#).

2.5.2. The effect of CR on cognition: Regression models

The dataset was standardized so that all variables had zero mean and the same variance. A Principal Component Analysis (PCA) was then performed on the cognitive test scores. As the first principal component represents the direction of maximum inter-subject variance, we have considered it as a measure of global cognitive performance (hereafter, *global cognition*); thus, it was used as the outcome variable in a linear regression model that included, as predictors, the CRIq-Total score, age, sex, serum NfLs, FA mean value, total GM volume and TIV.

To examine if there was a cognitive domain more affected by CR, analyses were repeated after grouping the cognitive tests in four sub-categories, each representing a specific domain: (I) *Language* – Boston Naming Test, phonemic fluency, and semantic fluency; (II) *Memory* – forward Digit and Corsi span, immediate and delayed free recall and index of sensitivity of cueing of Free and Cued Selective Reminding Test, immediate and delayed recall of Babcock Short Tale, Corsi Supraspan, and delayed recall of Rey-Osterrieth Complex Figure (ROCF); (III) *Visuospatial abilities* – copy of ROCF, Judgment of Line Orientation, and Clock Drawing Test; (IV) *Attentional-executive functions* – backward Digit and Corsi span, Stroop test – time, Trail Making Test, Raven's Coloured Progressive Matrices, Cancellation Test, Cognitive Estimation Task (form A), and phonemic/semantic alternate fluency. PCA was performed on each group of neuropsychological tests (i.e., examining *language*, *memory*, *visuospatial abilities*, and *attentional-executive functions*) and each first component was used as the comprehensive score for the considered cognitive domain instead of the *global cognition* score in separate regression models.

Then, for each cognitive domain, three further regression analyses were conducted by replacing CRIq-Total score separately with each of its subscores (CRIq-Education, CRIq-WorkingActivity, and CRIq-LeisureTime).

For all regression models applied to investigate CRIq-Total and CRIq subscores effects on both *global cognition* and specific cognitive domains, we checked regressors collinearity using Variance Inflation Factor (VIF), considering a VIF score < 5 acceptable (Kim, 2019). Furthermore, we applied Bonferroni correction to all regression models to account for multiple comparisons, and corrected p -values (p_{corr}) were considered statistically significant if $p_{\text{corr}} < 0.050$.

3. Results

One hundred thirty-five individuals with young-onset cognitive impairment (56 male and 79 female) were recruited. Among them, three were excluded for missing more than 25 % of the neuropsychological tests and 17 because of meeting exclusion criteria for the MRI procedure. Analyses were performed on the remaining 115 participants, for whom all regressors were available, except for the few neuropsychological scores imputed (see [Supplementary Material](#)). Their characteristics are shown in [Table 1](#).

3.1. The effect of CR on cognition

In all the linear regression models, the regressors showed a VIF score lower than 2.3, indicating low multicollinearity. The relationships among variables included in the models are illustrated with a scatterplot matrix in [Supplementary Material](#) ([Supplementary Fig. 2](#)). The first principal component of the PCA (*global cognition*) captured 41.6 % of cognitive variability. The regression model with *global cognition* as the outcome variable explained 42.1 % of its variance ($R^2 = 0.421$, adjusted $R^2 = 0.383$). The strongest predictors were the CRIq-Total score [standardized effect size (ES) = 0.229, $p_{\text{corr}} = 0.016$], total GM volume (ES = 0.348, $p_{\text{corr}} = 0.011$), and serum NfLs (ES = -0.302, $p_{\text{corr}} = 0.016$) ([Table 2](#), [Fig. 1](#)).

Among the cognitive domain-specific regression models, the one featuring *attentional-executive function* as the outcome variable explained 46.3 % of its variance ($R^2 = 0.463$, adjusted $R^2 = 0.427$). Significant

Table 1

Descriptive statistics of demographic, cognitive, and imaging variables of the 115 included participants. Data are reported as median score and IQR. Stroop test and TMT scores are reported in seconds.

	Median (IQR)
Age (years)	61 (55–65)
Education (years)	11 (8–13)
MMSE	28 (26–29)
CRIq-Total	107 (99–123)
CRIq-Education	101 (93–109)
CRIq-WorkingActivity	107 (97–114)
CRIq-LeisureTime	112 (100–128)
BNT	73 (64–78)
Phonemic fluency	30 (22–36)
Semantic fluency	40 (34–47)
Phonemic/semantic alternate fluency	28 (18–36)
ROCF – copy	32 (29–34)
JLO	21 (18–24)
Digit span forward	5 (5–6)
Digit span backward	4 (3–4)
Corsi span forward	5 (4–5)
Corsi span backward	4 (4–5)
Babcock – IR	5 (3.1–5.8)
Babcock – DR	4.4 (2–5.5)
FCSRT – IFR	24 (18–28.5)
FCSRT – DFR	8.5 (6–11)
FCSRT – ISC	0.8 (0.7–0.9)
ROCF – DR	13 (8.5–16)
Corsi Supraspan	17.9 (11.4–23.8)
RCPM	27 (23–32)
Stroop – time	25.5 (18–34)
TMT – A	40 (30–62)
TMT – B	101 (78–166)
Cancellation Test	39 (33–45)
FAB	17 (15–18)
CDT	9.5 (7–10)
CET – A (errors)	8 (5–10)
BDI-II	9 (6–17)
Ham-A	13 (7–21)
NPI	5 (2–12)
Serum NfLs (pg/mL)	16.9 (11.7–24.1)
Mean FA	0.40 (0.39–0.42)
Total GM [§]	0.46 (0.45–0.48)
TIV (mm ³)	1.5 × 10 ⁶ (1.4 × 10 ⁶ – 1.6 × 10 ⁶)

[§] TIV adjusted. BDI, Beck Depression Inventory; BNT, Boston Naming Test; CDT, Clock Drawing Test; CET, Cognitive Estimation Task; CRIq, Cognitive Reserve Index questionnaire; DFR, delayed free recall; DR, delayed recall; FA, fractional anisotropy; FAB, Frontal Assessment Battery; GM, grey matter; Ham-A, Hamilton Anxiety Rating Scale; IFR, immediate free recall; IR, immediate recall; ISC, index of sensitivity of cueing; IQR, interquartile range; JLO, Judgment of Line Orientation; MMSE, Mini-Mental State Examination; NfLs, neurofilaments light-chain; NPI, Neuropsychiatric Inventory; RCPM, Raven's Coloured Progressive Matrices; ROCF, Rey-Osterrieth Complex Figure; TIV, total intracranial volume; TMT, Trail Making Test.

predictors were the CRIq-Total score (ES = 0.255, $p_{\text{corr}} = 0.011$), total GM volume (ES = 0.366, $p_{\text{corr}} = 0.004$), and serum NfLs (ES = -0.317, $p_{\text{corr}} = 0.011$). In the *language* model ($R^2 = 0.395$, adjusted $R^2 = 0.356$), the *language* component resulted significantly dependent on the CRIq-Total score (ES = 0.361, $p_{\text{corr}} < 0.001$) and serum NfLs (ES = -0.388, $p_{\text{corr}} = 0.002$). The impact of the CRIq-Total scores on models with *memory* and *visuospatial abilities* components as outcome variables was, instead, not significant: both *memory* and *visuospatial abilities* components were not significantly predicted by any regressor ([Table 2](#)).

When considering the influence of individual CRIq subscores, the CRIq-Education subscore significantly impacted both the *language* and *attentional-executive functions* domains (*language*: ES = 0.329, $p_{\text{corr}} < 0.001$; *attentional-executive functions*: ES = 0.257, $p_{\text{corr}} = 0.008$). The CRIq-LeisureTime subscore significantly impacted the *language* domain (ES = 0.278, $p_{\text{corr}} = 0.013$, [Fig. 1](#)).

Table 2
Estimated coefficients of the regression models. First column refers to the *global cognition* model, while the other columns refer to the cognitive domains' models.

	Global cognition	Language	Memory	Visuospatial abilities	Attentional-executive functions
CRIq-Total	0.229 ($p = 0.044$)*	0.361 ($p < 0.001$)*	0.104 ($p = 0.999$)	0.123 ($p = 0.999$)	0.255 ($p = 0.011$)*
Age	-0.123 ($p = 0.999$)	-0.253 ($p = 0.050$)	-0.032 ($p = 0.999$)	-0.223 ($p = 0.999$)	-0.095 ($p = 0.999$)
Male sex	0.123 ($p = 0.999$)	0.133 ($p = 0.999$)	0.083 ($p = 0.999$)	0.114 ($p = 0.999$)	0.126 ($p = 0.999$)
FA	0.019 ($p = 0.999$)	-0.043 ($p = 0.999$)	-0.015 ($p = 0.999$)	0.029 ($p = 0.999$)	0.057 ($p = 0.999$)
Total GM volume [§]	0.348 ($p = 0.011$)*	0.049 ($p = 0.999$)	0.355 ($p = 0.136$)	0.237 ($p = 0.999$)	0.366 ($p = 0.004$)*
TIV	0.224 ($p = 0.487$)	-0.009 ($p = 0.999$)	0.178 ($p = 0.999$)	0.266 ($p = 0.999$)	0.256 ($p = 0.196$)
Serum NfLs	-0.302 ($p = 0.016$)*	-0.388 ($p = 0.002$)*	-0.260 ($p = 0.948$)	-0.042 ($p = 0.999$)	-0.317 ($p = 0.011$)*

P_{corr} are reported as p . Significant p_{corr} -values are denoted with (*).

[§]TIV adjusted.

CRIq, Cognitive Reserve Index questionnaire; FA, fractional anisotropy; GM, grey matter; NfLs, neurofilaments light-chain; TIV, total intracranial volume.

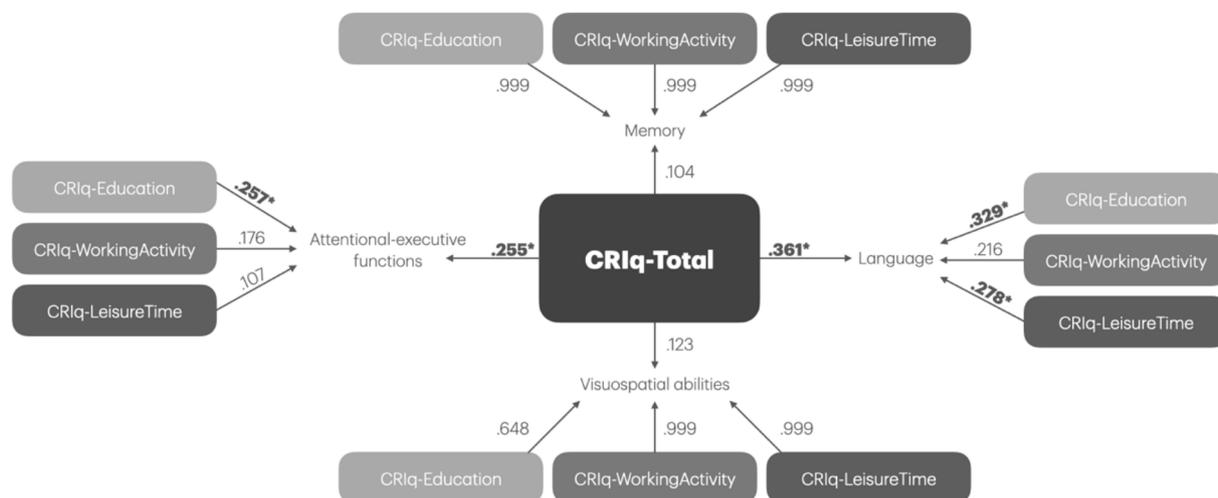


Fig. 1. Impact of CR on cognition. Numbers on directional arrows represent the standardized effect sizes of CRIq-Total score and subscores in the regression models. Bold numbers and asterisks indicate significant p_{corr} -values.

4. Discussion

We investigated if CR measured with a questionnaire considering education, engagement in leisure activities, and type of work (the CRIq) affects cognitive performance in people with young-onset cognitive impairment, over and above the effect of variables related to the brain's structural integrity.

CR measured with the CRIq-Total score significantly affected *global cognition*, alongside total GM volume and serum NfLs. The finding that higher CR is related to better global cognitive performance is in line with recent studies, which found associations between measures of global functioning (i.e., Mini-Mental State Examination and Montreal Cognitive Assessment) and the CRIq score (Lee et al., 2020; Ye et al., 2022; Quattropani et al., 2021).

When we investigated single cognitive domains, only performance in *language* and *attentional-executive functions*, but not in *memory* and *visuospatial abilities*, were influenced by the CRIq-Total score. This supports the hypothesis that higher CR mainly compensates for non-amnesic cognitive deficits (Andrejeva et al., 2016; Damian et al., 2013).

When exploring individual CRIq subscores, we found that the CRIq subscore related to years of education (CRIq-Education) had a significant impact on *language* and *attentional-executive functions* domains. To illustrate the results of our regression models with an example, if we consider a 61-year-old person, one extra cycle of school (i.e., having completed high school rather than middle school) increases by more than 0.5 standard deviations the performance on *language* and *attentional-executive functions* tests. This aligns with previous works highlighting associations between CRIq measuring education and better cognitive performances in MCI patients (Berezuk et al., 2021; Feldberg et al., 2016), specifically in naming ability and divided attention (Allegr

et al., 2010; Ciccarelli et al., 2018; Roldán-Tapia et al., 2012). In addition, Groot et al. (Groot et al., 2018) found that education, used as a proxy of CR, had an impact on *language* and *attentional-executive functions* in MCI due to Alzheimer's Disease (AD) patients, whereas they found an effect also on *visuospatial abilities* and *memory* only in more advanced dementia phases.

The CRIq subscore related to engagement in leisure activities (CRIq-LeisureTime) positively impacted the *language* domain: many questions of this subdomain focused on activities that foster language development and social interaction, suggesting that being involved in activities such as reading books or newspapers, going to the cinema or theatre, doing crosswords, attending conferences, and being socially active in general improves *language* performances specifically. Whereas education is usually considered in correction grids of neuropsychological tests – and is therefore already taken into account when evaluating cognitive performance – the present findings emphasize the importance of also enquiring about the level of engagement in leisure activities as these seem to improve particularly the *language* function in young-onset cognitive impairment, in line with literature in older patients (Lee et al., 2024). This is even more important in younger population at risk of developing dementia, where atypical presentation of AD or Frontotemporal dementia involving language deficits (i.e., Primary Progressive Aphasia) are more frequent (Zamboni et al., 2024).

We included in our regression models measures of brain integrity and blood-based measures of neurodegeneration to also consider variables related to synaptic density and brain size. These variables are thought to capture the so-called brain reserve (BR), which represents the structural and biological aspect of reserve; together with CR, they constitute the two complementary aspects of the broader reserve concept, offering a holistic view of the brain's resilience to damage (Stern et al., 2019,

2023). More specifically, we included TIV and whole-brain GM volume which are the brain's measures most frequently included in models of BR, FA as an index of WM microstructural characteristics (Zamboni, 2016), and blood NfLs, an early-stage, non-specific biomarker of neurodegeneration. We did not include the volume of white matter hyperintensities (WMHs) as they were almost undetectable in our participants. Whereas we did not find an effect of FA on cognition, we found that total GM volume significantly affected *global cognition* and *attentional-executive functions*, in line with previous studies (Broadhouse et al., 2019; Carbone et al., 2023; Grundman et al., 2003).

Previous studies using the *residual method* that did therefore include, instead, measures of BR have usually variably considered the volume of WMHs, whole-brain GM volume, hippocampal volume, lateral ventricular volume, and number of lacunae or enlarged perivascular spaces (Gallo et al., 2021; Zahodne et al., 2015). No previous studies on CR have considered serum NfLs as a measure of neurodegeneration, a non-invasive and easy to obtain biomarker which is rapidly gaining importance, being especially helpful in screening patients with MCI to identify those with underlying neurodegenerative conditions (Gallingani, Carbone, Tondelli, & Zamboni, 2024; Kern et al., 2019; Preische et al., 2019). In our cohort, serum NfLs were found to have a significant effect on *global cognition*, *language*, and *attentional-executive functions*. This result emphasizes how measuring CR with the *residual method* in models that did not include this variable certainly overestimated CR, loading it with the weight of a hidden factor that should not be considered a proxy of CR but rather attributable to an underlying neurodegenerative disease (Elman et al., 2022).

The present study has limitations. First, it was cross-sectional; therefore, we provided a depiction of the relationship between CR and cognitive abilities at a specific point in time. Longitudinal studies will offer a more comprehensive understanding of how CR is associated with cognitive changes overtime. Second, we are aware that the choice of variables considered in the regression models influences results. However, we did not use a *residual* but a *direct* method to measure CR and also verified the non-collinearity of the predicting variables. Thus, our results can be considered stable and provide new information on factors affecting cognition in young-onset cognitive impairment. Lastly, we investigated the role of CR on cognition in MCI patients irrespective of their status on AD biomarkers as this information was not available for all the subjects. However, in the present manuscript we purposefully focussed on the role that CR should have on the diagnostic pathway of patients with subtle cognitive impairment and MCI (intended as clinical syndrome) before the measurement of biomarkers. Our results suggest, indeed, that CR should be always considered, even at the very beginning of the cognitive evaluation, as its effect on cognition may then inform and guide the clinical decision on whether further investigations such as AD biomarker testing should or should not be performed.

CRedit authorship contribution statement

Chiara Carbone: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Riccardo Maramotti:** Writing – original draft, Methodology, Formal analysis. **Erica Balboni:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Daniela Beltrami:** Writing – review & editing, Investigation. **Daniela Ballotta:** Writing – review & editing, Methodology. **Roberta Bedin:** Writing – review & editing, Investigation. **Chiara Gallingani:** Writing – review & editing, Investigation. **Manuela Tondelli:** Writing – review & editing, Methodology, Investigation. **Simone Saleme:** Writing – review & editing, Investigation. **Federico Gasparini:** Writing – review & editing, Investigation. **Giulia Vinceti:** Writing – review & editing, Investigation. **Alessandro Marti:** Writing – review & editing, Investigation. **Annalisa Chiari:** Writing – review & editing, Investigation. **Luca Nocetti:** Writing – review & editing, Methodology. **Giuseppe Pagnoni:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Giovanna Zamboni:** Writing – review & editing,

Supervision, Investigation, Funding acquisition, Conceptualization.

Funding sources

This work was supported by the grant “Dipartimenti di eccellenza 2018–2022”, MIUR, Italy, to the Department of Biomedical, Metabolic, and Neural Sciences, University of Modena. C. Carbone, R. Maramotti, D. Ballotta, M. Tondelli, A. Chiari, and G. Zamboni are funded by the European Union ERC, UnaWireD, project number 101042625. Views and opinions expressed are however those of the authors only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful to all the patients and their families, and to the general practices that referred patients to our service and collaborated with the study. We thank Dr Marcella Malagoli (neuroradiologist) and Dr Najara Iacovino (neuropsychologists) who supported data acquisition and patients' diagnosis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bandc.2025.106297>.

Data availability

Anonymized data will be made available upon request and permission granted by our Local Ethical committee.

References

- Allegri, R. F., Taragano, F. E., Krupitzki, H., Serrano, C. M., Dillon, C., Sarasola, D., Feldman, M., Tufró, G., Martelli, M., & Sanchez, V. (2010). Role of cognitive reserve in progression from mild cognitive impairment to dementia. *Dementia Neuropsychology*, 4, 28–34. <https://doi.org/10.1590/S1980-57642010DN40100005>
- Alvares Pereira, G., Silva Nunes, M. V., Alzola, P., & Contador, I. (2021). Cognitive reserve and brain maintenance in aging and dementia: An integrative review. *Applied Neuropsychology: Adult*, 1–11. <https://doi.org/10.1080/23279095.2021.1872079>
- Andrejeva, N., Knebel, M., Santos, V. D., Schmidt, J., Herold, C. J., Tudoran, R., Wetzel, P., Wendelstein, B., Meyer-Kühling, I., Navratil, S. D., Gorenc-Mahmutaj, L., Rosenbaum, G., Pantel, J., & Schröder, J. (2016). Neurocognitive deficits and effects of cognitive reserve in mild cognitive impairment. *DEM*, 41, 199–209. <https://doi.org/10.1159/000443791>
- Berezuk, C., Scott, S. C., Black, S. E., & Zakzanis, K. K. (2021). Cognitive reserve, cognition, and real-world functioning in MCI: A systematic review and meta-analysis. *Journal of Clinical and Experimental Neuropsychology*, 43, 991–1005. <https://doi.org/10.1080/13803395.2022.2047160>
- Broadhouse, K. M., Mowszowski, L., Duffy, S., Leung, I., Cross, N., Valenzuela, M. J., & Naismith, S. L. (2019). Memory performance correlates of hippocampal subfield volume in mild cognitive impairment subtype. *Frontiers in Behavioral Neuroscience*, 13, 259. <https://doi.org/10.3389/fnbeh.2019.00259>
- Carbone, C., Balboni, E., Beltrami, D., Gasparini, F., Vinceti, G., Gallingani, C., Salvatori, D., Saleme, S., Molinari, M. A., Tondelli, M., Marti, A., Chiari, A., & Zamboni, G. (2023). Neuroanatomical correlates of cognitive tests in young-onset MCI. *JIN*, 22, 152. <https://doi.org/10.31083/j.jin2206152>
- Chiari, A., Vinceti, G., Adani, G., Tondelli, M., Galli, C., Fiondella, L., Costa, M., Molinari, M. A., Filippini, T., Zamboni, G., & Vinceti, M. (2021). Epidemiology of early onset dementia and its clinical presentations in the province of Modena, Italy. *Alzheimer's & Dementia*, 17, 81–88. <https://doi.org/10.1002/alz.12177>
- Ciccarelli, N., Monaco, M. R. L., Fusco, D., Vetrano, D. L., Zuccalà, G., Bernabei, R., Brandi, V., Pisciotto, M. S., & Silveri, M. C. (2018). The role of cognitive reserve in cognitive aging: What we can learn from Parkinson's disease. *Aging Clinical and Experimental Research*, 30, 877–880. <https://doi.org/10.1007/s40520-017-0838-0>
- Corbo, I., Marselli, G., Di Ciero, V., & Casagrande, M. (2023). The protective role of cognitive reserve in mild cognitive impairment: a systematic review. *Journal of Clinical Medicine*, 12, 1759. <https://doi.org/10.3390/jcm12051759>

- Damian, M., Hausner, L., Jekel, K., Richter, M., Froelich, L., Almkvist, O., Boada, M., Bullock, R., De Deyn, P. P., Frisoni, G. B., Hampel, H., Jones, R. W., Kehoe, P., Lenoir, H., Minthon, L., Olde Rikkert, M. G. M., Rodriguez, G., Scheltens, P., Sooinen, H., Spuru, L., Touchon, J., Tsolaki, M., Vellas, B., Verhey, F. R. J., Winblad, B., Wahlund, L.-O., Wilcock, G., & Visser, P. J. (2013). Single-domain amnesic mild cognitive impairment identified by cluster analysis predicts Alzheimer's disease in the European prospective DESCRIPA study. *Dementia and Geriatric Cognitive Disorders*, *36*, 1–19. <https://doi.org/10.1159/000348354>
- Elman, J. A., Vogel, J. W., Bocancea, D. I., Ossenkoppele, R., van Loenhoud, A. C., Tu, X. M., & Kremen, W. S. (2022). Issues and recommendations for the residual approach to quantifying cognitive resilience and reserve. *Alzheimer's Research & Therapy*, *14*, 102. <https://doi.org/10.1186/s13195-022-01049-w>
- C. Feldberg, P.D. Hermida, M.F. Tartaglino, D. Stefani, V. Somale, A.R.F. F. Carolina, H.P. D. M.F. Tartaglino, S. Dorina, S. Verónica, A.R. F. Cognitive reserve in patients with mild cognitive impairment: the importance of occupational complexity as a buffer of declining cognition in older adults, *AIMSMEDS* 3 (2016) 77–95. Doi: 10.3934/medsci.2016.1.77.
- Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*, 341–355. [https://doi.org/10.1016/s0896-6273\(02\)00569-x](https://doi.org/10.1016/s0896-6273(02)00569-x)
- Gaetani, L., Blennow, K., Calabresi, P., Di Filippo, M., Parnetti, L., & Zetterberg, H. (2019). Neurofilament light chain as a biomarker in neurological disorders. *Journal of Neurology, Neurosurgery, and Psychiatry*, *90*, 870–881. <https://doi.org/10.1136/jnnp-2018-320106>
- Gallingani, C., Carbone, C., Tondelli, M., & Zamboni, G. (2024). Neurofilaments light chain in neurodegenerative dementias: a review of imaging correlates. *Brain Sciences*, *14*, 272. <https://doi.org/10.3390/brainsci14030272>
- Gallo, F., Kalpouzos, G., Laukka, E. J., Wang, R., Qiu, C., Bäckman, L., Marseglia, A., Fratiglioni, L., & Dekhtyar, S. (2021). Cognitive trajectories and dementia risk: a comparison of two cognitive reserve measures. *Frontiers in Aging Neuroscience*, *13*, Article 737736. <https://doi.org/10.3389/fnagi.2021.737736>
- Groot, C., van Loenhoud, A. C., Barkhof, F., van Berckel, B. N. M., Koene, T., Teunissen, C. C., Scheltens, P., van der Flier, W. M., & Ossenkoppele, R. (2018). Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. *Neurology*, *90*, e149–e156. <https://doi.org/10.1212/WNL.0000000000004802>
- Grundman, M., Jack, C. R., Petersen, R. C., Kim, H. T., Taylor, C., Datvian, M., Weiner, M. F., DeCarli, C., DeKosky, S. T., van Dyck, C., Darvesh, S., Yaffe, K., Kaye, J., Ferris, S. H., Thomas, R. G., & Thal, L. J. (2003). Alzheimer's Disease Cooperative Study, Hippocampal volume is associated with memory but not nonmemory cognitive performance in patients with mild cognitive impairment. *Journal of Molecular Neuroscience*, *20*, 241–248. <https://doi.org/10.1385/jmn:20:3:241>
- Hoopes, A., Mora, J. S., Dalca, A. V., Fischl, B., & Hoffmann, M. (2022). SynthStrip: Skull-stripping for any brain image. *NeuroImage*, *260*, Article 119474. <https://doi.org/10.1016/j.neuroimage.2022.119474>
- Jones, R. N., Manly, J., Glymour, M. M., Rentz, D. M., Jefferson, A. L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society*, *17*, 593–601. <https://doi.org/10.1017/S1355617710001748>
- Kern, S., Syrjänen, J. A., Blennow, K., Zetterberg, H., Skoog, I., Waern, M., Hagen, C. E., van Harten, A. C., Knopman, D. S., Jack, C. R., Petersen, R. C., & Mielke, M. M. (2019). Association of cerebrospinal fluid neurofilament light protein with risk of mild cognitive impairment among individuals without cognitive impairment. *JAMA Neurology*, *76*, 187–193. <https://doi.org/10.1001/jamaneurol.2018.3459>
- Kim, J. H. (2019). Multicollinearity and misleading statistical results. *Korean Journal of Anesthesiology*, *72*, 558–569. <https://doi.org/10.4097/kja.19087>
- Lee, S. Y., Kang, J. M., Kim, D. J., Woo, S. K., Lee, J.-Y., & Cho, S.-J. (2020). Cognitive reserve, leisure activity, and neuropsychological profile in the early stage of cognitive decline. *Frontiers in Aging Neuroscience*, *12*, Article 590607. <https://doi.org/10.3389/fnagi.2020.590607>
- Lee, J., Kim, J., & Valdivia, D. S. (2024). A longitudinal analysis of the relationship between different levels of cognitively stimulating leisure activity and cognitive function among older adults with MCI. *Journal of Cognitive Enhancement*, *8*, 257–270. <https://doi.org/10.1007/s41465-024-00293-2>
- Little, R. J. A. (1988). Missing-data adjustments in large surveys. *Journal of Business & Economic Statistics*, *6*, 287–296. <https://doi.org/10.2307/1391878>
- Nogueira, J., Gerardo, B., Santana, I., Simões, M. R., & Freitas, S. (2022). The assessment of cognitive reserve: a systematic review of the most used quantitative measurement methods of cognitive reserve for aging. *Frontiers in Psychology*, *13*, Article 847186. <https://doi.org/10.3389/fpsyg.2022.847186>
- Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): A new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research*, *24*, 218–226. <https://doi.org/10.3275/7800>
- Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., & Fratiglioni, L. (2014). Mild cognitive impairment: A concept in evolution. *Journal of Internal Medicine*, *275*, 214–228. <https://doi.org/10.1111/joim.12190>
- Preischo, O., Schultz, S. A., Apel, A., Kuhle, J., Kaeser, S. A., Barro, C., Gräber, S., Kuder-Buletta, E., LaFougere, C., Laske, C., Vögler, J., Levin, J., Masters, C. L., Martins, R., Schofield, P. R., Rossor, M. N., Graff-Radford, N. R., Salloway, S., Ghetti, B., Ringman, J. M., Noble, J. M., Chhatwal, J., Goate, A. M., Benzinger, T. L. S., Morris, J. C., Bateman, R. J., Wang, G., Fagan, A. M., McDade, E. M., Gordon, B. A., & Jucker, M. (2019). Dominantly Inherited Alzheimer Network, Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nature Medicine*, *25*, 277–283. <https://doi.org/10.1038/s41591-018-0304-3>
- Quattropiani, M. C., Sardella, A., Morgante, F., Ricciardi, L., Alibrandi, A., Lenzo, V., Catalano, A., Squadrito, G., & Basile, G. (2021). Impact of cognitive reserve and premorbid IQ on cognitive and functional status in older outpatients. *Brain Sciences*, *11*, 824. <https://doi.org/10.3390/brainsci11070824>
- Reed, B. R., Mungas, D., Farias, S. T., Harvey, D., Beckett, L., Widaman, K., Hinton, L., & DeCarli, C. (2010). Measuring cognitive reserve based on the decomposition of episodic memory variance. *Brain*, *133*, 2196–2209. <https://doi.org/10.1093/brain/awq154>
- Reserve and Resilience | Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia. <https://reserveandresilience.com/> (accessed April 3, 2025).
- Roldán-Tapia, L., García, J., Cánovas, R., & León, I. (2012). Cognitive reserve, age, and their relation to attentional and executive functions. *Cognited Neuropsychology. Adult*, *19*, 2–8. <https://doi.org/10.1080/09084282.2011.595458>
- Rubin, D. B. (1987). In *Multiple imputation for nonresponse in surveys* (first ed.). Wiley. <https://doi.org/10.1002/9780470316696>
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*, 1487–1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>
- Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niaz, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Suppl 1), S208–S219. <https://doi.org/10.1016/j.neuroimage.2004.07.051>
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*, 448–460. <https://doi.org/10.1017/S1355617702813248>
- Stern, Y., Albert, M., Barnes, C. A., Cabeza, R., Pascual-Leone, A., & Rapp, P. R. (2023). A framework for concepts of reserve and resilience in aging. *Neurobiology of Aging*, *124*, 100–103. <https://doi.org/10.1016/j.neurobiolaging.2022.10.015>
- Stern, Y., Arenaza-Urquijo, E. M., Barrés-Faz, D., Belleville, S., Cantillon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., & Vuoksimaa, E. (2020). The Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup, Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, *16*, 1305–1311. <https://doi.org/10.1016/j.jalz.2018.07.219>
- Stern, Y., Barnes, C. A., Grady, C., Jones, R. N., & Raz, N. (2019). Brain reserve, cognitive reserve, compensation, and maintenance: Operationalization, validity, and mechanisms of cognitive resilience. *Neurobiology of Aging*, *83*, 124–129. <https://doi.org/10.1016/j.neurobiolaging.2019.03.022>
- Urbano, T., Maramotti, R., Tondelli, M., Gallingani, C., Carbone, C., Iacovino, N., Vinceti, G., Zamboni, G., Chiari, A., & Bedin, R. (2024). Comparison of serum and cerebrospinal fluid neurofilament light chain concentrations measured by Ella™ and Lumipulse™ in patients with cognitive impairment. *Diagnostics (Basel)*, *14*, 2408. <https://doi.org/10.3390/diagnostics14212408>
- van Buuren, S., & Groothuis-Oudshoorn, K. (2011). Mice: multivariate imputation by chained equations in R. *J. Stat. Soft.*, *45*, 1–67. <https://doi.org/10.18637/jss.v045.i03>
- Weaver, A. N., & Jaeggi, S. M. (2021). Activity engagement and cognitive performance amongst older adults. *Frontiers in Psychology*, *12*, Article 620867. <https://doi.org/10.3389/fpsyg.2021.620867>
- Ye, Q., Zhu, H., Chen, H., Liu, R., Huang, L., Chen, H., Cheng, Y., Qin, R., Shao, P., Xu, H., Ma, J., & Xu, Y. (2022). Effects of cognitive reserve proxies on cognitive function and frontoparietal control network in subjects with white matter hyperintensities: A cross-sectional functional magnetic resonance imaging study. *CNS Neuroscience & Therapeutics*, *28*, 932–941. <https://doi.org/10.1111/cns.13824>
- Zahodne, L. B., Manly, J. J., Brickman, A. M., Narkhede, A., Griffith, E. Y., Guzman, V. A., Schupf, N., & Stern, Y. (2015). Is residual memory variance a valid method for quantifying cognitive reserve? A longitudinal application. *Neuropsychologia*, *77*, 260–266. <https://doi.org/10.1016/j.neuropsychologia.2015.09.009>
- Zamboni, G. (2016). *Functional specialization and network connectivity in brain function*. Oxford University Press.
- Zamboni, G., Maramotti, R., Saleme, S., Tondelli, M., Adani, G., Vinceti, G., Carbone, C., Filippini, T., Vinceti, M., Pagnoni, G., & Chiari, A. (2024). Age-specific prevalence of the different clinical presentations of AD and FTD in young-onset dementia. *Journal of Neurology*, *271*, 4326–4335. <https://doi.org/10.1007/s00415-024-12364-7>
- Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*, 45–57. <https://doi.org/10.1109/42.906424>