scientific reports

OPEN

Moderating effect of the domains of the cognitive reserve index questionnaire (CRIq) on longitudinal change slopes in episodic memory across the cognitive aging continuum

Sonali Arora[1,2,3], Cristina Lojo-Seoane[1,2,3], David Leiva[4], Lucía Pérez Blanco[1,2,3], Sabela C. Mallo[1,2,3], Ana Nieto-Vieites[1,2] & Arturo X. Pereiro[1,2,3]✉

Cognitive reserve (CR) hypothesis predicts reduced impact of aging and neurodegeneration on cognition in adults who have lived in cognitively stimulating environments. Our study tested the moderating role of socio-behavioral CR proxies on longitudinal episodic memory (EM) decline, one of the cognitive domains that has been suggested to be most sensitive to early deterioration in presymptomatic stages of dementia. 323 participants (≥ 50 years old) from CompAS study were classified into four groups based on baseline diagnosis and progression at 18–24 (T1) and 48–70 months (T2): Subjective cognitive complaints (SCC) who remain stable (SCC-stable), Mild cognitive impairment (MCI) who remain stable (MCI-stable), SCC who progressed to MCI (Prog-to-MCI), and SCC or MCI who progressed to dementia (Prog-to-Dem). Mixed models analyzed changes across EM measures of immediate and long delay with and without cued recall from the Spanish CVLT to account for the EM processes of encoding and consolidation in the short and long term. Domains from Cognitive Reserve Index Questionnaire (School, Work and Leisure) were tested as moderators of longitudinal EM trends in progression groups across two nested models. Our results confirm the CR hypothesis:1) steeper memory decline observed in all progression groups compared to SCC-stable, especially at T2 relative to baseline; 2) Higher CRIq-School and CRIq-Work scores moderated changes in EM measures in participants who progress to MCI and who progress to dementia compared to SCC-stable group; 3) CR moderation effect was stronger at T2. Our findings support the validity of CR proxies of Education and Occupation in attenuating memory decline along the continuum of subjective and objective cognitive decline.

Keywords Socio-behavioral CR proxies, Cognitive reserve index questionnaire, Longitudinal design, Older adults, Episodic memory, Cognitive complaints, MCI

Cognitive Reserve (CR) refers to the brain's adaptive ability to maintain or improve cognitive performance despite age-related brain changes, injuries, insults, neurological diseases, or risk factors that can impair cognitive skills[1]. Thus, it is expected that older adults with higher CR significantly reduces the risk of the appearance of objective cognitive symptoms[2], presumably due to the positive effect of brain-stimulating experiences and/or favourable biophysical conditions, such as genetics, physical activity, nutrition, or cardiovascular health in

[1]Department of Developmental Psychology, Universidade de Santiago de Compostela, Xosé María Suárez Núñez Street, Campus Sur, Santiago de Compostela, Santiago de Compostela, Galicia 15782, Spain. [2]Applied Cognitive Neuroscience and Psychogerontology group, Health Research Institute of Santiago (IDIS), Universidade de Santiago de Compostela, Rúa Xosé María Suárez Núñez, s/n, Campus Vida, Santiago de Compostela 15782, Spain. [3]Institute of Psychology (IPsiUS), Universidade de Santiago de Compostela, Santiago de Compostela, Spain. [4]Department of Social Psychology and Quantitative Psychology, Universitat de Barcelona, Edifici de Ponent, 4rth floor, Vall d'Hebron, 171, Barcelona 08035, Spain. ✉email: arturoxose.pereiro@usc.gal; arturoxose.pereiro@usc.es

counteracting gradual, whether normative or pathological brain changes[3], and potentially delaying the onset of the disease or reducing the severity of its symptoms[4]. The mechanisms underlying the compensation effect of CR are still not well understood[5] but possibly both neural compensatory neural networks[3] and dynamic cognitive and functional (e.g., compensatory mental strategies[6] are involved. Neuroimaging studies based on structural and functional MRI data have shown that sufficient brain-stimulating experiences over the lifetime can improve the ability to efficiently use as well as recruit additional compensatory CR networks to compensate for pathological brain changes[7,8].

In practice, CR has been considered as a latent construct that cannot be measured directly[1]. Traditionally, assessing the CR construct relies on indirect socio-behavioral proxy indicators such as education, occupation, premorbid intelligence, social engagement, physical activity, and leisure activity[7], which poses a major challenge to its objective measurement[9]. Standardized questionnaires offer a method for measuring CR that addresses some of these limitations[10] including more systematic information collection about several domains, overcoming possible CR underestimation or overestimation by ignoring the contribution of other relevant cognitively stimulating activities in addition to education[4,9]. Among the most commonly used CR questionnaires, the Cognitive Reserve Index Questionnaire (CRIq) stands out due to its extensive usage in clinical and research settings[11], extensive adaptation to several linguistic and cultural contexts[11–13]. Several studies[14–16] have shown that the CRIq questionnaire measures behave as expected from the CR hypothesis, that is, the extent to which CRIq scores reflect the theoretical concept of CR as defined by Stern et al.[3], thus supporting good or excellent levels of construct validity. For example, a study found that higher CRIq scores predicted better performance on word fluency and working memory tasks in patients with Parkinson's disease without dementia[16], another showed that higher CRIq total, education, and leisure time scores were associated with lower regional cerebral blood flow in frontal and temporal cortices in patients with frontotemporal dementia and primary progressive aphasia[15]. CRIq synthesizes various proxies to represent CR based on a formative measurement model, in which the construct is "built" from its indicators which may differ from each other and are not necessarily strongly correlated, but collectively predict reserve. Additionally, recent studies on neurological and structural MRI biomarker data have found evidence that high CRIq scores are associated with the maintenance of cognitive function, with correlates in flexible neural compensatory networks such as increased functional connectivity within the frontoparietal control network (supporting efficient cognitive control and resource allocation) and reduced connectivity in the dorsal attention network(providing more efficient recruitment of attentional processes), as a marker of greater neural efficiency which is a central concept in CR[8], as well as in the presence of indicators of neurodegeneration (e.g., atrophy in the right middle cingulate and parahippocampal regions, and greater CSF volumes)[17]. These neurophysiological measures are relevant to CR from a cognitive and functional standpoint because they show how efficiently existing brain networks perform a particular task (neural reserve) or how flexibly different brain regions communicate to maintain a normal cognitive status (neural compensation) despite age-related or pathological changes[3,5]. Patterns of efficient and flexible functional connectivity are considered neural expressions of compensatory processes (adaptive reorganization of neural resources) underlying CR, which are inferred when individuals with higher CR show better cognitive functioning or performance than those with lower CR despite similar brain damage or pathology[7,8].

Previous meta-analyses including longitudinal studies provided a robust evidence that several proxies of CR[9] such as educational attainment[18], occupational engagement[19], and involvement in leisure activities[20] at any point of time in life is significantly linked to a lower risk of developing dementia[21,22]. Similarly, some studies suggested that CR may help reduce the risk of Mild Cognitive Impairment (MCI)[23,24] but there is not enough evidence to confirm its role in the early preclinical stages[25]. According to the revised NIA–AA criteria, different stages have been identified within a continuum of progressively increasing risk of developing dementia, particularly the most prevalent form, Alzheimer's Disease (AD), and this continuum is accompanied by growing evidence of neurostructural, neurofunctional, and pathophysiological alterations[26].

Recent findings seem to support the differential role of the socio-behavioural proxies on cognitive decline[23,27]. Meta-analytical evidence including MCI participants[23] showed that education established a more consistent cross-sectional association with cognitive measures, but only moderate relationships were observed between occupation and cognitive performance. However, leisure activities were not associated with any cognitive domain although they showed stronger associations with activities of daily functioning[23]. Complementary meta-analytical evidence including longitudinal studies agrees in pointing out that education could have a stronger predictive effect in attenuating cognitive decline and the incidence of dementia compared to other CR indicators such as occupation and leisure activities[27,28].

Some studies have suggested a stage-dependent effect of CR on the trajectory of cognitive functioning, where high CR was found to be associated with greater cognitive decline after the onset of objective cognitive impairment (i.e., MCI)[29], also in individuals who were more likely to progress to dementia[30]. A recent meta-analysis of cross-sectional studies considering the association between CR indicators in MCI found that, although higher educational attainment was significantly associated with better cognitive functioning on several cognitive measures, it had a weaker impact on memory which was interpreted as being due to more rapid memory decline in MCI in those with higher CR[21]. Thus, the delaying effect of CR may reverse due to a critical overflow of the compensatory capacity, when the brain can no longer offset accumulating neuropathology. At this stage, individuals with higher CR who have maintained normal performance despite underlying pathology, may experience a faster rate of decline once clinical symptoms appear, as compensatory capacity becomes exhausted, especially after the onset of dementia[18,29].

Episodic memory (EM), which refers to the ability to remember specific events and experiences stored according to spatiotemporal parameters, is one of the most vulnerable cognitive functions affected by age associated cognitive decline and pathological processes of dementias[31] and the MCI prodromic stage[31,32]. EM measures are sensitive predictors in discriminating cognitive decline progression in Subjective Cognitive Decline

(SCD) participants[33,34]. Although the basic criteria for identifying participants in the presymptomatic stage are the presence of persistent subjective cognitive complaints (SCCs) in the absence of a known cause and objective cognitive impairment, high baseline memory scores are associated with a more accelerated decline in immediate and delayed verbal recall on EM tests over an 8-year follow-up period in earliest clinical stage of dementia[35]. Longitudinal studies have shown that delayed recall EM measures, immediate and short delay cued recall[36,37], and memory recognition discriminability index are strong predictors of progression from MCI to AD[32,38] and can successfully distinguish between participants in presymptomatic and preclinical participants who remain stable or progress to dementia[36–38].

Several studies showed strong cross-sectional[39–42], and longitudinal[43,44] associations between EM and CR. Again, education was the most valid CR proxy in predicting longitudinal changes in EM and dementia risk[27,36,44–47] but other CR proxies as occupational complexity have also been shown to be able to improve EM performance over time[46].

Therefore, though existing cross-sectional studies strongly supports the protective role of CR and its proxies to attenuate age-related cognitive and EM decline[45,47–51], research on their impact on longitudinal trajectories, particularly in early preclinical stages, is limited[29,50]. Our aim was to test the moderation effect of some socio-behavioral CRIq domains in longitudinal change slopes observed in EM measures considering the stability or progression of participants in preclinical and prodromic stages of dementia. First, we compared the slopes of change of measures of EM in participants who progress to objective impairment or convert to dementia from the preclinical and prodromal stages of dementia, respectively (Model 1). Based on longitudinal findings on cognitive decline across age-associated aging continuum[35,40,51], it is expected EM steeper slope trends: (a) in participants in prodromic than in preclinical stages; (b) in participants who progress or convert than in those who remain stable; and (c) when comparing the baseline assessment to the second follow-up than to the first follow-up. Finally, we explored the moderating role of the socio-behavioral CRIq domains (i.e., education, leisure, professional attainment) in the eventual longitudinal memory decline across the continuum of subjective and objective cognitive decline (Model 2). Considering the CR hypothesis, it is expected that the moderator effect of CRIq domains (i.e., education, professional attainment, leisure) : (a) will reduce the memory decline slopes in participants with higher CR who progress mainly in preclinical but also prodromic stages regarding those with lower CR; and (b) the moderating effect of the levels of CR in memory decline will be considerably lower or neglected in stable groups both in preclinical and prodromic stages. This expectation is consistent with the CR theory that says that the protective effect will be visible in the presence of accumulated neuropathology where it can actively compensate the harmful effects of early pathology especially in the earlier stages of the dementia continuum[3,50].

Results

Descriptive statistics (proportions, Mean, SD) of sociodemographic, neuropsychological, and CRIq items, by progression groups, are included in Table 1.

	Total	SCC-Stable	MCI-Stable	Prog-to-MCI	Prog-to-Dem
N	251	148	44	34	19
Age *M*(*SD*)	66.24 (8.81)	64.01 (8.52)	69.95 (8.29)	66.41 (8.97)	74.21 (4.85)
Sex (% women)	71.3%	75%	59.1%	73.53%	68.4%
Schooling *M*(*SD*)	10.8 (5.57)	12.4 (5.76)	7.75 (3.99)	10.44 (5.05)	6.95 (3.39)
CCI *M*(*SD*)	0.33 (0.59)	0.25 (0.49)	0.64 (0.81)	0.32 (0.59)	0.37 (0.6)
QAM *M*(*SD*)	16.35 (3.54))	16.51 (3.55)	16.1 (3.32)	17.15 (3.08)	15.16 (4.34)
MMSE *M*(*SD*)	27.74 (2.28)	28.66 (1.46)	25.89 (2.72)	27.88 (1.59)	25 (2.91)
CAMCOG-R *M*(*SD*)	90.16 (9.72)	94.26 (7.46)	82.41 (8.63)	90.91 (6.24)	76.89 (10.73)
CRIq School *M*(*SD*)	105.85 (18.32)	110.52 (18.9)	97.43 (14.19)	103.59 (18.25)	96.47 (12.08)
CRIq Work *M*(*SD*)	99.84 (19.39)	103.25 (19.48)	92.81 (17.51)	95.97 (19.8)	97.47 (15.59)
CRIq Leisure *M*(*SD*)	107.9 (20.37)	112.76 (20.41)	99.34 (18.86)	107.35 (16.11)	93.53 (19.44)
IFR *M*(*SD*)	47.67 (12.61)	53,37 (10.22)	35.5 (9.36)	46.18 (8.8)	35.32 (14.05)
SDCR *M*(*SD*)	10.47 (3.46)	11.99 (2)	6.95 (2.56)	10.59 (2.12)	6.74 (4.15)
LDFR *M*(*SD*)	9.98 (4.07)	11.9 (2.92)	5.73 (3.12)	10.06 (2.2)	5.26 (5.09)
LDCR *M*(*SD*)	10.63 (3.73)	12.37 (2.73)	6.59 (2.95)	10.56 (2.22)	6.95 (4.67)

Table 1. Descriptive statistics for sociodemographic, health, and neuropsychological, measures at baseline by SCC and MCI stable-progressing groups. SCC = Subjective Cognitive Complaints; MCI = Mild Cognitive Impairment; SCC-Stable = SCC who remain stable; MCI-Stable = MCI who remain stable; Prog-to-MCI = SCC who progress to MCI; Prog-to-Dem = SCC/MCI who progress to dementia; CCI = Charlson Comorbidity Index; IFR = Immediate Free Recall; SDCR = Short-Delay Cued Recall; LDFR = Long-Delay Free Recall; LDCR = Long-Delay Cued Recall; QAM = Questionnaire d'Auto-évaluation de la Mémoire; MMSE = Mini-Mental State Examination; CAMCOG-R = Cambridge Cognitive Examination-Revised; CRIq = Cognitive Reserve Index Questionnaire.

Longitudinal patterns of memory change considering time to recall (i.e., immediate vs. delayed), and with or without cued recall measures from the TAVEC (i.e., IFR, SDCR LDFR, LDCR) were analyzed using Mixed Models (MMs). Model 1 assessed the interaction effects of different measurement time points (BL, T1, T2) with diagnostic groups (SCC-Stable, MCI-Stable, Prog-to-MCI, and Prog-to-Dem) as factors. Model 2 included all main and interaction effects among time, diagnostic groups, and CRIq domains (school, work, and leisure) to assess how CR moderates the relationship between diagnosis and memory performance over time. The goodness of fit of the two models was done using the Akaike Information Criterion (AIC) and Bayesian Information Criterion indices (BIC). Only those tables with significant chi-square tests are shown in the Results section (see the Supplementary file Tables S1–S8 online for complete results of the analyzed contrasts).

Immediate free recall (IFR)

A significant Time × Group interaction was observed in Model 1 (χ^2 = 28.18; df = 6; $p < .001$) showing (see Table 2): (a) a significant decline in IFR in the Prog-to-MCI group compared to the SCC-stable group at T2 relative to BL ($\beta = -6.899$, $p < .001$); and (b) a significant decline in IFR in the Prog-to-Dem group compared to the SCC-stable group at both T1 ($\beta = -7.916$, $p < .05$) and T2 ($\beta = -16.381$, $p < .001$) relative to BL.

A significant Time × Group × CRIq-school (χ^2 = 16.83; df = 6; $p < .001$) interaction was observed in Model 2 (χ^2 = 16.83; df = 6; $p < .001$) while model fit values slightly improved or remain almost unchanged (see Table 2). The interaction pointed-out a significantly smaller decline in IFR measure at T2 relative to BL ($\beta = 21.205$, $p < .01$) in the Prog-to-Dem group compared to the SCC-stable group as CRIq-School values increase (see Chart A in Fig. 1).

Short delay cued recall (SDCR)

A significant Time × Group interaction was observed in Model 1 (χ^2 = 21.40; df = 6; $p < .01$) indicating a differential association between levels of time and progression groups in SDCR (see Table 3). This interaction showed: (a) a significant decline in SDCR in the Prog-to-MCI group compared to the SCC-stable group at both T1 ($\beta = -1.237$, $p < .05$) and T2 ($\beta = -1.573$, $p < .05$) relative to BL; and (b) a significant decline in SDCR in the Prog-to-Dem group compared to the SCC-stable group at both T1 ($\beta = -2.563$, $p < .05$) and T2 ($\beta = -4.060$, $p < .001$) relative to BL.

A significant Time × Group × CRIq-school (χ^2 = 28.29; df = 6; $p < .001$) and Time × Group × CRIq-Work (χ^2=19.00; df = 6; $p < .001$) interactions were observed in Model 2 with model fit values slightly improving or remaining almost unchanged comparing to those obtained for the Model 1 (see Table 3). These interactions pointed-out (see Charts B1 and B2 in Fig. 1): (a) a significantly smaller decline in SDCR measure at T2 relative to BL in the Prog-to-Dem group ($\beta = 7.490$, $p < .001$) compared to the SCC-Stable group as CRIq-School values increase; and (b) a significantly smaller decline in SDCR measure at T2 relative to BL in the Prog-to-MCI group ($\beta = 1.752$, $p < .01$) compared to the SCC-Stable group as CRIq-Work values increase.

Long delay free recall (LDFR)

A significant Time × Group interaction was observed in Model 1 (χ^2 = 28.72; df = 6; $p < .001$) indicating a differential association between levels of time and progression groups in LDFR (see Table 4).This interaction showed a significant decline in LDFR in both the Prog-to-MCI ($\beta = -2.903$, $p < .001$) and Prog-to-Dem ($\beta = -2.327$, $p < .05$) groups compared to the SCC-Stable group at T2 and relative to BL.

A significant Time × Group × CRIq-Work (χ^2 = 12.97; df = 6; $p < .05$) interaction was observed in Model 2 with model fit values remaining almost unchanged regarding to those obtained for the Model 1 (see Table 4). These interactions pointed-out (see Charts C1 and C2 in Fig. 1): (a) A significant moderation of the decline as CRIq-Work values increase in LDFR measure at T2 (β = 1.503, $p < .05$) relative to BL in the Prog-to-MCI group

	Estimated models	
	Model 1[(1)]	**Model 2[(2)]**
MCI-Stable	− 21.031*** (2.682)	− 17.924*** (2.987)
Prog-to-MCI	− 9.238*** (2.263)	− 7.889 *** (2.240)
Prog-to-Dem	− 16.174*** (4.184)	
T2 × Prog-to-MCI	− 6.899*** (1.931)	− 6.322** (1.997)
T1 × Prog-to-Dem	− 7.916* (3.571)	− 10.600* (4.519)
T2 × Prog-to-Dem	− 16.381*** (3.571)	− 17.070***(4.519)
T2 × Prog-to-Dem × CRIq-School		21.205** (6.666)
Intercept	55.031*** (1.086)	12.600*** (0.280)
Nakagawa's R2C	0.7937	0.8061
Observations	456	456
Log Likelihood	− 1,612.503	− 1,520.387
Akaike Information Criterion	3,253.006	3,140.774
Bayesian Information Criterion	3,310.721	3,346.899

Table 2. MMs for IFR in stable and progressing groups across follow-ups. *$p < .05$; **$p < .01$; ***$p < .001$; [(1)] SCC-Stable is the reference group; [(2)] SCC-Stable at baseline is the reference group.

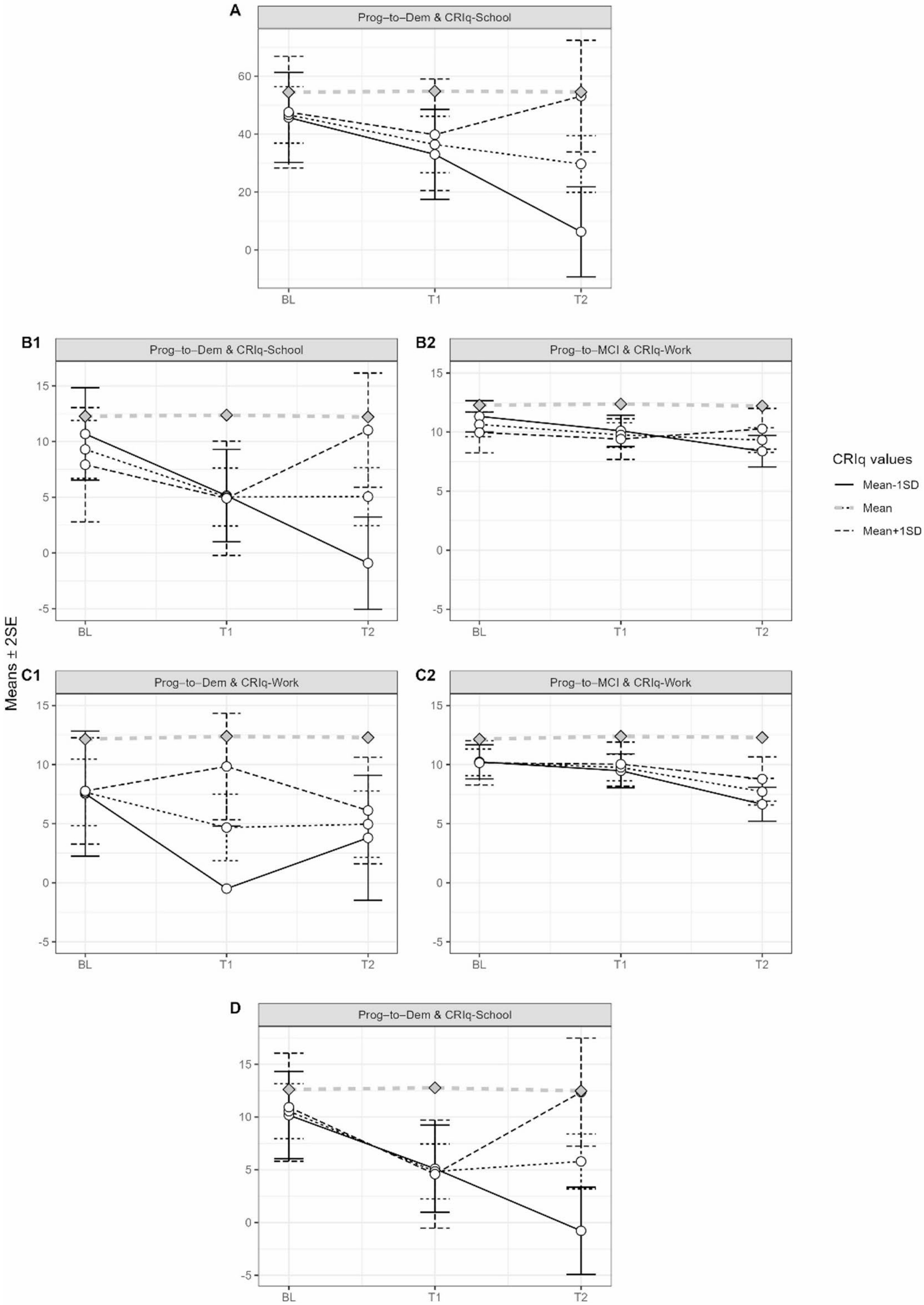

Fig. 1. Estimated marginal means and error bars (± 2SE) across follow-ups for IFR (Chart A), SDCR (Charts B1 and B2), LDFR (Charts C1 and C2), and LDCR (Chart D) considering CR levels (average mean, -1 SD and + 1 SD) in CRIq domains and progression groups when CR significantly moderate change slopes. SE = Standard Error; BL = baseline; T1 = 1st follow-up (18–24 months after BL); T2 = 2nd follow-up (48–70 months after BL); SCC-Stable = SCC who remain stable; MCI-Stable = MCI who remain stable; Prog-to-MCI = SCC who progress to MCI; Prog-to-Dem = SCC/MCI who progress to Dementia. Grey line and diamonds represent marginal means for the reference group (i.e., SCC-Stable).

	Estimated models	
	Modjlel 1^(1)^	Model 2^(2)^
MCI-Stable	− 6.244*** (0.699)	− 6.303*** (0.796)
Prog-to-MCI	− 1.643** (0.589)	− 1.628** (0.597)
Prog-to-Dem	− 4.545*** (1.090)	− 2.972* (1.351)
CRIq-School		0.769* (0.324)
T1 × Prog-to-MCI	− 1.237* (0.592)	
T2 × Prog-to-MCI	− 1.573** (0.592)	− 1.252* (0.592)
T1 × Prog-to-Dem	− 2.563* (1.096)	− 4.372** (1.339)
T2 × Prog-to-Dem	− 4.060*** (1.096)	− 4.182** (1.339)
T2 × Prog-to-Dem × CRIq-School		7.490*** (1.974)
T2 × Prog-to-MCI × CRIq-Work		1.752** (0.654)
Intercept	12.402*** (0.283)	12.273*** (0.281)
Nakagawa's R2C	0.7203	0.7554
Observations	456	456
Log Likelihood	− 1,053.905	− 1,003.595
Akaike Information Criterion	2,135.809	2,107.189
Bayesian Information Criterion	2,193.524	2,313.314

Table 3. MMs for SDCR in stable and progressing groups across follow-ups. *$p < .05$; **$p < .01$; ***$p < .001$; (1)SCC-Stable is the reference group; (2) SCC-Stable at baseline is the reference group.

	Estimated models	
	Model 1(1)	Model 2(2)
MCI-Stable	− 7.035*** (0.773)	− 6.526*** (0.861)
Prog-to-MCI	− 2.247*** (0.652)	− 1.960** (0.646)
Prog-to-Dem	− 7.208*** (1.205)	− 4.494** (1.461)
CRIq-School		0.762* (0.350)
T2 × Prog-to-MCI	− 2.903*** (0.631)	− 2.622*** (0.650)
T1 × Prog-to-Dem		− 3.225* (1.471)
T2 × Prog-to-Dem	-2.327* (1.166)	
T2 × Prog-to-MCI × CRIq-Work		1.503* (0.719)
T1 × Prog-to-Dem × CRIq-Work		4.719* (2.086)
Intercept	12.351*** (0.313)	12.150*** (0.304)
Nakagawa's R2C	0.7586	0.7741
Observations	456	456
Log Likelihood	− 1,089.969	− 1,038.831
Akaike Information Criterion	2,207.937	2,177.663
Bayesian Information Criterion	2,265.652	2,383.788

Table 4. MMs for LDFR comparing stable and progressing groups across follow-ups. *$p < .05$; **$p < .01$; ***$p < .001$; (1) SCC-Stable is the reference group; (2) SCC-Stable at baseline is the reference group.

compared to the SCC-Stable group; (b) A significant moderation of the decline as CRIq-Work values increase in LDFR measure at T1 (β = 4.719, $p < .05$), relative to BL, in the Prog-to-Dem group compared to the SCC-Stable group.

Long delay cued recall (LDCR)

A significant Time × Group interaction was observed in Model 1 (χ^2 = 33.87; df = 6; $p < .001$) indicating a differential association between levels of time and progression groups in LDCR (see Table 5). This interaction showed: (a) a significant decline in LDCR in the Prog-to-MCI group compared to the SCC-Stable group at both T1 (β = −1.265, $p < .05$) and T2 (β = −2.466, $p < .001$) relative to BL; and (b) a significant decline in LDCR in the Prog-to-Dem group compared to the SCC-Stable group at T1 (β = − 3.767, $p < .001$) and T2 (β = −3.988, $p < .001$) relative to BL.

A significant Time × Group × CRIq-School (χ^2 = 17.00; df = 6; $p < .01$) interaction was observed in Model 2 with model fit values slightly improving or remaining almost unchanged comparing to those obtained for the Model 1 (see Table 5). These interactions pointed-out a significant moderation of the decline as CRIq-School

	Estimated models	
	Model 1$^{(1)}$	Model 2$^{(2)}$
MCI-Stable	− 7.279*** (0.703)	− 6.874*** (0.795)
Prog-to-MCI	− 2.063*** (0.593)	− 1.937** (0.596)
Prog-to-Dem	− 4.610*** (1.096)	
CRIq-School		0.721* (0.323)
T1 × Prog-to-MCI	− 1.265* (0.607)	
T2 × Prog-to-MCI	− 2.466*** (0.607)	− 2.300*** (0.622)
T1 × Prog-to-Dem	− 3.767*** (1.122)	− 5.870*** (1.407)
T2 × Prog-to-Dem	− 3.988*** (1.122)	− 4.631*** (1.407)
T2 × Prog-to-Dem × CRIq-School		6.216** (2.075)
Intercept	12.753*** (0.284)	12.600***(0.280)
Nakagawa's R2C	0.7356	0.7556
Observations	456	456
Log Likelihood	− 1,1060.343	− 1,013.176
Akaike Information Criterion	2,148.685	2,126.352
Bayesian Information Criterion	2,206.400	2,332.477

Table 5. MMs 2 for LDCR in stable and progressing groups across follow-ups. $*p<.05$; $**p<.01$; $***p<.001$; $^{(1)}$ SCC-Stable is the reference group; $^{(2)}$ SCC-Stable at baseline is the reference group.

values increase in LDCR measure at T2 ($\beta=6.216$, $p<.01$) relative to BL in the Prog-to-Dem group compared to the SCC-Stable group (see Chart D in Fig. 1).

Discussion

The main objective of our study was to investigate the moderation effect of the CR socio-behavioural proxies to longitudinally moderate memory decline across EM measures differentiating between participants who progress and those who remain stable along the continuum of subjective and objective cognitive decline. To our knowledge, a considerable amount of literature has been published on the cross-sectional as well as longitudinal influence of the moderating role of CR and its proxies to attenuate age-related cognitive and EM decline in MCI and dementia[45,47]. Yet, no study has studied the moderating effect of socio behavioural CR proxies on longitudinal change slopes in measures of EM recall in SCC participants who progress to objective impairment or convert to dementia[29,50].

As expected, the results of our study showed steeper EM slope trends in worsening participants comparing to SCCs participants who remain stable both when prodromic and preclinical stages were jointly considered (i.e., Prog-to-Dem) and also when only SCC participants in preclinical stages were considered (Prog-to-MCI), particularly when comparing the baseline assessment to the second follow-up than to the first follow-up (Model 1). This is congruent with results from longitudinal studies showing a non-linear trajectory of memory decline, where EM measures initially exhibited slower, stable decline during preclinical stages, followed by steeper and more accelerated decline slopes after a change point over the follow-ups as participants progressed to MCI or dementia[38,51,40].

Regarding the role of CR in moderating EM slopes, our results (Model 2) support the idea that participants with high scores in CRIq domains of School and Work reduce the memory decline slopes compared to those with lower CR. These results are in line with previous findings by a longitudinal study that measured CR through a composite score based on education and occupational complexity, which demonstrated that, older adults with high education and occupational complexity showed slower cognitive decline compared to those with lower CR levels[19]. Specifically, higher School CR scores were associated with reduced memory decline across IFR, SDCR, and LDCR measures. This is consistent with previous research showing that educational attainment has a moderating effect on EM measures such as immediate free recall[37] and short and long delay-free recall[41,42]. Another study found that higher educational attainment was linked to better verbal EM performance in immediate and short delay cued recall tasks[36]. Higher CR Work scores were also found to be associated with a lesser decline in SDCR and LDFR measures of EM. Similarly, studies have shown that higher occupational complexity is associated with improved immediate free recall and immediate category cued recall[44], better long-delay free recall[48], and a slower rate of memory decline over time[52]. Conversely, in our study, Leisure domain of CR showed no significant impact in moderating trajectories of cognitive decline. This is consistent with findings from previous meta-analysis of longitudinal and cross-sectional studies showing that education is the most important CR measure, followed by occupation, and to a lesser extent, leisure in moderating the progression of cognitive decline[23,27,28,49]. An alternative explanation to the lack of a significant effect of the CRIq Leisure domain on memory trajectories is that this subscale weighs too heavily on the frequency of engagement in cognitively stimulating activities rather than different types of leisure activities. Research suggests that variety, rather than frequency, is more strongly associated with cognitive function as engaging in less activities frequently can be less cognitively stimulating[53]. Moreover, research shows that early-life education, midlife occupational complexity, and late-life leisure activities each contribute to moderating the risk of cognitive decline and dementia progression[27]. However, the CRIq does not differentiate between earlier and later life leisure experiences, instead combining them into a single score. This conflation could partly explain why the Leisure domain of CRIq was not significantly associated with memory trajectories in the present study.

Also, in line with our hypothesis, the moderating effect of CRIq domains on memory decline was evident in participants in preclinical and prodromic stages who progressed (i.e., Prog-to-MCI and Prog-to-Dem groups) compared to those who remained stable. Similarly, a longitudinal study showed that CR measured through Test di Intelligenza Breve (TIB, i.e., Brief Intelligence Test) protected against cognitive decline in SCC and MCI participants who converted to AD, but this effect was not significantly different from the SCC-Stable group and in those with MCI who did not convert[2]. The moderator effect of CR was observed at both follow-ups, but they were more significant at the second one than at the first follow-up (i.e., closer, or coincident with the onset) in both SCC participants who progressed to MCI or SCC/MCI participants who convert to dementia. Our results are congruent with the findings from a recent longitudinal study that measures cognitive status as global cognitive performance using the MMSE and CR through a composite score combining years of education with occupation, which found that the differences in cognitive status between participants with high CR and low CR were more noticeable in the second follow up than at the first follow up, especially in the SCC/MCI participants who progress to dementia[50]. These results suggest that participants with high CR who are closer to progression to dementia show a stronger protective effect compared to those with low CR[50].

The protective effect of CR was observed when both SCC and MCI were analyzed together (Prog-to-Dem) and when SCC was analyzed alone (Prog-to-MCI), and this effect was more evident in those who converted to dementia than in those who progressed only to MCI. This is consistent with previous studies suggesting that in both preclinical and prodromal stages, CR effects are simultaneously maintained and consumed which delays the risk of progression or conversion[3,5].

Additionally, our results, according to the best-fitting model, show that CRIq domains of School and Work had a differential effect on EM in moderating progression trajectories of slopes of cognitive decline. While previous research has shown that composite CR measures can explain more variance than education alone, our findings align with the notion of a growing amount of literature on the domain-specific effect of CR, where different socio-behavioral proxies of CR may assume more responsibility in moderating the negative impact of AD pathology on cognition[49]. In line with this, a recent study found that when participants were distinguished based on education and occupation, they showed different rates of cognitive decline trajectories, but this differential effect disappeared when considering them together[50].

The novelty of our study is that it confirms the sensitivity of different EM measures in predicting cognitive decline progression also in SCC participants[33,34] and highlight the importance of considering moderating effect of CR in EM measures to discriminate between SCC or MCI participants who remain stable as well as participants who progress to MCI or who convert to dementia[39].

Future studies should include cognitively unimpaired participants as well as other common CR proxies such as premorbid IQ can be used to better know the differences in moderating effect of CR across the cognitive continuum. An important direction is to disentangle CR from intelligence, as prior work shows childhood IQ partly explains links between occupational complexity and cognition[44] thereby adjusting for general intelligence (g) in future studies will clarify whether education or work history in preclinic and prodromic stages can moderate EM decline independently of intelligence[54] comparing stable and worsening groups. Additionally, inclusion of neuroanatomical measures and/or biomarkers of CRIq domains and their links to compensatory neural networks for a better determination of participants in prodromic stages is also desirable. Accumulative selective attrition rate observed in the sample size (47%) over time could introduce bias in our findings. One limitation is that we could not differentiate individuals progressing to MCI from those conversing to dementia. New cohort study follow-ups will allow us to increase the size of the groups that progress or convert to include them in differentiated analyses. Future work will extend these analyses to cognitive domains other than episodic memory and investigate the moderating effect of CR along the cognitive aging continuum.

Conclusions

In conclusion, our results confirm the CR hypothesis, showing that participants who progress or convert than in those who remain stable showed steeper memory decline particularly in prodromic stages, but also in preclinical stages in second follow-up compared to the baseline. High scores in the School and Work domains of the CR reduce memory decline slopes in immediate and delayed memory, with and without cues in SCC participants who progress to MCI and SCC/MCI participants who convert to dementia compared to stable participants. The moderating effect of CRIq domains was significant both in preclinical and prodromal stages, and was stronger at the second follow-up, suggesting that CR shows greater protective effect closer to the cognitive impairment onset. Our findings support the validity of socio-behavioural CR proxies of Education and Occupation in attenuating memory decline from preclinical to prodromal stages of dementia. Future research should build on these initial findings and explore how neurodegeneration or amyloid burden moderates the trajectories of cognitive decline in participants with high and low CR across the continuum of both subjective and objective cognitive decline.

Methods

Data source

A total of 251 participants over 50 years of age, who completed at least one follow-up, were selected from an initial sample of 323 individuals who met the inclusion and exclusion criteria in the Compostela Aging Study (CompAS)[55]. This longitudinal study is focused on early detection and progression of cognitive impairment in individuals who present subjective cognitive complaints (SCCs) at primary care centres in Galicia, an autonomous region in north-western Spain. These participants were assessed longitudinally at 3 time points: Baseline (BL), Time 1 (T1; 18–24 months after baseline) and Time 2 (T2; 48–70 months after BL assessment).

Participants with prior diagnosis of MCI or dementia, clinical stroke, traumatic brain injury, motor-sensory defects, previous chemotherapy treatment, prior diagnosis of diabetes type II, alcohol, or drug abuse/dependence, or any neurological or psychiatric disease at BL were excluded.

Participants were evaluated at BL and re-diagnosed at first (T1) and second (T2) follow-ups. At BL, participants were classified with SCC and MCI using respectively, Qi and Petersen criterion for the SCC and MCI identification[31,56,57]. Of the total 251 participants who completed the first follow-up, 153 also completed the second follow-up. Participants were grouped considering diagnoses at baseline and their stability or progression in the diagnostic status across follow-ups: (1) Stable groups: SCC participants who remain stable (SCC-Stable: 148 participants) and MCI participants who remain stable (MCI-Stable: 44 participants); and (2) Worsening groups: SCC participants who progressed to MCI (Prog-to-MCI: 34 participants); and SCC or MCI participants who progressed to dementia (Prog-to-Dem: 19 participants). Reversals of diagnosis from MCI (6 participants) were not included in the analysis.

All participants gave their written informed consent prior to participation in the study. The research project was approved by the Galician Clinical Research Ethics Committee (Xunta de Galicia, Spain), and the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki as revised in Fortaleza, Brazil in 2013.

Instruments

The participants underwent clinical, neuropsychological, and neurological evaluations, conducted by cognitive psychologists and neurologists who are experts in aging and dementia. SCCs were assessed using a short version of the Questionnaire d' auto-évaluation de la Mémoire (QAM)[58,59].

CRIq[11] was administered to participants to evaluate socio-behavioral domains of CR. It was designed for the adult population from 18 years up to the date of assessment and consists of 24 items that provide a total score and subscale scores for three domains: Education, Working activity, and Leisure time evaluated through a 15-minute semi-structured interview. The Education domain is assessed by summing total years of formal schooling and years of vocational training, rounded to one year and six months period, respectively. The Working Activity domain consists five levels of occupational complexity ranging from unskilled manual labour (e.g., farmer, driver, babysitter), skilled manual labour (e.g., cook, hairdresser), skilled non manual labour (e.g. real estate agent, musician), professional work (e.g., director of a small firm, professor, doctor), and highly intellectual jobs (e.g., politician, surgeon, researchers). For each participant, years spent in all jobs are recorded, summed, rounded to the nearest five-year interval, and multiplied by the cognitive complexity level (1–5) associated with each job to calculate the domain score. The Leisure Time domain covers cognitively stimulating, social, and physical leisure activities over the adult life categorised into four frequency categories: weekly (e.g., dancing, playing chess), monthly (e.g., attending cultural events, theatre visit), annual (e.g., concerts, reading books), and fixed (e.g., caring for pets, managing finances). For fixed-frequency activities, participants provide a yes/no response, with years of participation recorded if "yes." For the other categories, frequency is rated as "Never/Rarely" or "Often/Always," with definition changing depending on the frequency (e.g., for monthly activities, Never/Rarely = ≤ 2 times/month; Often/Always = ≥ 3 times/month). Only activities rated as "Often/Always" are included and rounded to the nearest five-year interval. For each domain, linear regression analyses in an independent Spanish sample were conducted to adjust for age effects, treating raw scores as dependent variables with age as the independent variable, the residual from this model is used as the age-adjusted subscale score[11]. The residuals scores were standardized (M = 100, SD = 15), and then averaged to produce the CRI total score. The CRIq questionnaire along with instructions and calculation is available online at https://www.cognitivereserveindex.org/.

Good test-retest reliability (r = .85, p < .001) was found for CRIq-School, and excellent and acceptable convergent validity were observed, respectively, with years of schooling (r = .86, p < .001) and professional attainment (r = .57, p < .001). Adequate values in divergent validity were also observed for CRIq-School and functionality[60] (r = .09; p = .16) and comorbidity (Charlson Comorbidity Index)[61] (r = − .089; p = .16).

CRIq-Work also showed good test-retest reliability (r = .80, p < .001), and acceptable and excellent concurrent validity, respectively, with schooling (r = .52, p < .001) and professional attainment (r = .70, p < .001). Adequate values in divergent validity were also observed for CRIq-Work with functionality (− 0.08; p = .22) and comorbidity (0.21; p = .74).

Moderate test-retest consistency was found for CRIq-Leisure (r = .69, p < .001), and acceptable concurrent validity with schooling (r = .55, p < .001) and professional attainment (0.41, p < .001). Adequate values in divergent validity were observed for CRIq-Leisure with functionality (0.22; p < .001) and comorbidity (− 0.11; p = .08).

Regarding the divergent validity of the CRIq domains, the three domains (Schooling, Work, and Leisure) were moderately intercorrelated, with correlations ranging from r = .35 (CRIq-Leisure and CRIq-Work, p < .01) to r = .46 (CRIq-School and CRIq-Work, p < .01). Similarly, each domain showed strong correlations with the total CRIq score (CRIq-School r = .80, CRIq-Work r = .78, CRIq-Leisure r = .77; all p < .01), consistent with the multifactorial nature of CRIq as a CR construct[4] (see Supplementary Table S1).

Verbal EM was included as the target outcome in the study because it is highly vulnerable to both normative aging and early pathological processes of dementia, as well the MCI stage and has been identified as a sensitive early marker of progression from the preclinical to prodromal stages of dementia[31,32].Verbal EM was assessed by TAVEC[62], the Spanish adaptation of the California Verbal Learning Test (CVLT)[63]. Immediate and delay TAVEC measures in free and cued recall modalities were used in this study: Immediate Free Recall (IFR), which measures the total number of correct words recalled across the 5 immediate recall trials of List A (an original list of 16 words, four words from each of four different semantic categories presented in a pseudo-random order); Short-Delay Cued Recall (SDCR), which assesses the ability to correctly recall words from List A after Short Delay Free Recall, in the trial immediately following the presentation of semantic category cues (with the four semantic categories from List A as cues); Long-Delay Free Recall (LDFR), which measures the ability to correctly remember words from List A after a longer delay (20 min); and Long-Delay Cued Recall (LDCR), which assesses the ability to correctly recall words from List A after LDFR, in the trial following the subsequent presentation of semantic category cues (using the four semantic categories from List A as cues). TAVEC scores show an adequate reliability (odd pair correlation, 0.94; split half correlation, 0.82) and validity (factorial structure explains 67% of the variance[62]; pp. 27–31).

Diagnostic procedure

At each follow-up assessment, participants were reclassified according to stability of their condition (i.e., diagnosis remains unchanged from BL to T2), or a change in diagnosis at some point between the BL and T2 (i.e., negative changes due to progression to MCI or Dementia). Reversals in diagnostic status in MCI participants (2.39%) were excluded from analyses.

Diagnosis of MCI followed the consensus criteria recommended by the National Institute on Aging-Alzheimer's Association workgroups[31,56]: (1) participant-reported cognitive changes confirmed by an informant, assessed by a short version of the QAM[58,59]; (2) evidence of poorer performance in one or more cognitive domains that is greater than expected for the patient's age and educational background; this criterion was considered fulfilled when the scores lied in the 1–2 standard deviation (SD) range (between the 3rd and 16th percentiles) below the norm by age and education[64]. MCI was diagnosed when participants were impaired on at least two of the three measures for each of the following cognitive domains: (1) Attention (TMT-A[65,66], Attention and Calculation subscale of CAMCOG-R[67]); (2) Executive functions (TMT-B[65,66], Phonological verbal fluency test for the letter "p"[65,68], Executive Function subscale of CAMCOG-R[67]); (3) Memory (Verbal EM using TAVEC[62], Memory subscale of CAMCOG-R[67]); and (4) Language (BNT[66,69], Semantic verbal fluency test for animals[66,68], Language subscale of CAMCOG-R[67]).

Dementia was diagnosed following the NINCDS-ADRDA[70] and DSM-IV-TR criteria[71]: (1) objective evidence of impairment in memory and other cognitive domains that exceeds what is expected for the patient's age and educational background, with scores below 2 SDs based on age and education norms; (2) a gradual onset and continued cognitive decline; (3) cognitive deficits not attributed to other neurological or systemic diseases, nor are they induced by substances; (4) deficits not occurring exclusively during the course of delirium; (5) cognitive changes not primarily due to other affective disorders; and (6) significant impairment in instrumental activities of daily living assessed using the Lawton and Brody Index[60]. Progression to dementia was confirmed by consultation of the medical history and recording the date of neurological diagnosis.

Statistical analysis

Longitudinal change slope estimates obtained using MMs allowed us to assess change patterns in the IFR, SDCR, LDFR, and LDCR scores, measures of the TAVEC[62]. TAVEC measure scores served as dependent variables at the different measurement times (BL, T1, T2). MMs included two factors as main predictors of EM measures: (1) diagnostic group, a factor including four progression groups (i.e., SCC-stable, MCI-stable, Prog-to-MCI, Prog-to-Dem) to analyze between-group differences (SCC-stable as reference group); and (2) Time, a factor including 3 evaluations (i.e., LB, T1, T2) to analyze intra-group differences (BL measure as reference time). Two nested models were estimated allowing thus to assess the relative importance of the added factors in the predictive model: (a) In the first model (Model 1), interaction effects of the diagnostic groups and the different measurement times were explored to examine changes over time across progression groups (SCC-stable group and BL evaluation were established as comparative reference levels); and (b) In the second model (Model 2), CRIq domains covariates with interaction effects for time and diagnostic groups (first and second order interaction) were analyzed to test the moderating role of CR proxies in longitudinal slopes for EM measures.

Model 1 should report EM decreases (negative sign) or increases (positive sign) in T1 and/or T2 relative to the reference time (i.e., BL) in any of the diagnostic groups (MCI-stable, Prog-to-MCI, Prog-to-Dem) relative to the reference group (i.e., SCC-stable). Model 2 should report EM decreases (positive sign) or increases (negative sign) associated with, respectively higher, or lower scores in CRIq domains in T1 and/or T2 relative to the reference time (i.e., BL) in any of the diagnostic groups (MCI-stable, Prog-to-MCI, Prog-to-Dem) relative to the reference group (i.e., SCC-stable). Thus, a significant decrease in IFR scores in Prog-to-MCI in T2 or T1 relative to the IFR scores in SCC-stable at BL can be inferred when negative sign in β value and $p < .05$ is observed in Model 1. A positive moderation effect of higher CR scores (i.e., difference in IFR scores between T2 or T1 compared to BL for Prog-to-MCI relative to SCC-stable decrease as CR scores increase) could be expected if in Model 2, positive sign in β value and $p < .05$ is obtained.

The goodness of fit of the two models was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion indices (BIC). Additionally, Nakagawa's R2c index and Log Likelihood index were used to quantify the relative improvement of the nested models in terms of their predictive capacity[72]. Similar or lower values in Akaike and Bayesian information criteria for the model that includes CR measures are desirable to support the CR hypothesis, as these fit indices penalize more complex models in favour of simpler ones to prevent overfitting.

Data availability

The data presented in this study are available on request from the first and corresponding author.

Received: 13 June 2025; Accepted: 17 November 2025
Published online: 19 January 2026

References

1. Stern, Y. et al. A framework for concepts of reserve and resilience in aging. *Neurobiol. Aging*. https://doi.org/10.1016/j.neurobiolaging.2022.10.015 (2023).
2. Mazzeo, S. et al. The dual role of cognitive reserve in subjective cognitive decline and mild cognitive impairment: A 7-year follow-up study. *J. Neurol.* **266**, 487–497. https://doi.org/10.1007/s00415-018-9164-5 (2019).
3. Stern, Y. Cognitive reserve. *Neuropsychologia* **47**, 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004 (2009).
4. Stern, Y. et al. Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement. J.* **16**, 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.219 (2020)
5. Cabeza, R. et al. Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci.* **19**, 701–710. https://doi.org/10.1038/s41583-018-0068-2 (2018).
6. Frankenmolen, N. L., Fasotti, L., Kessels, R. P. C. & Oosterman, J. M. The influence of cognitive reserve and age on the use of memory strategies. *Exp. Aging Res.* **44**, 117–134. https://doi.org/10.1017/S1355617718000619 (2018).
7. Stern, Y., Gazes, Y., Razlighi, Q., Steffener, J. & Habeck, C. A task-invariant cognitive reserve network. *NeuroImage* **178**, 36–45. https://doi.org/10.1016/j.neuroimage.2018.05.033 (2018).
8. Varela-López, B. et al. Cognitive reserve, neurocognitive performance, and high-order resting-state networks in cognitively unimpaired aging. *Neurobiol. Aging*. **117**, 151–164. https://doi.org/10.1016/j.neurobiolaging.2022.05.012 (2022).
9. Jones, R. N. et al. Conceptual and measurement challenges in research on cognitive reserve. *J. Int. Neuropsychol. Soc.* **17**, 593–601. https://doi.org/10.1017/S1355617710001748 (2011).
10. Grotz, C., Seron, X., Van Wissen, M. & Adam, S. How should proxies of cognitive reserve be evaluated in a population of healthy older adults? *Int. Psychogeriatr.* **29**, 123–136. https://doi.org/10.1017/S1041610216001745 (2017).
11. Nucci, M., Mapelli, D. & Mondini, S. Cognitive reserve index questionnaire (CRIq): A new instrument for measuring cognitive reserve. *Aging Clin. Exp. Res.* **24**, 218–226. https://doi.org/10.3275/7800 (2012).
12. Nogueira, J., Gerardo, B., Santana, I., Simões, M. R. & Freitas, S. The assessment of cognitive reserve: A systematic review of the most used quantitative measurement methods of cognitive reserve for aging. *Front. Psychol.* **13**, 847186. https://doi.org/10.3389/fpsyg.2022.847186 (2022).
13. Ozakbas, S. et al. Validity and reliability of cognitive reserve index questionnaire for the Turkish population. *Mult Scler. Relat. Disord*. **50**, 102817. https://doi.org/10.1016/j.msard.2021.102817 (2021).
14. Kartschmit, N., Mikolajczyk, R., Schubert, T. & Lacruz, M. E. Measuring cognitive reserve (CR): A systematic review of measurement properties of CR questionnaires for the adult population. *PloS One*. **14**, e0219851. https://doi.org/10.1371/journal.pone.0219851 (2019).
15. Maiovis, P. et al. Cognitive reserve hypothesis in frontotemporal dementia: Evidence from a brain SPECT study in a series of Greek frontotemporal dementia patients. *Neurodegenerative Dis.* **18**, 69–73. https://doi.org/10.1159/000486621 (2018).
16. Ciccarelli, N. et al. The role of cognitive reserve in cognitive aging: What we can learn from parkinson's disease. *Aging Clin. Exp. Res.* **30**, 877–880. https://doi.org/10.1007/s40520-017-0838-0 (2018).
17. Zhou, L. et al. Correlations between cognitive reserve, Gray matter, and cerebrospinal fluid volume in healthy elders and mild cognitive impairment patients. *Front. Neurol.* **15** https://doi.org/10.3389/fneur.2024.1355546 (2024).
18. Mungas, D. et al. Education amplifies brain atrophy effect on cognitive decline: Implications for cognitive reserve. *Neurobiol. Aging*. **68**, 142–150. https://doi.org/10.1016/j.neurobiolaging.2018.04.002 (2018).
19. Mondini, S., Pucci, V., Montemurro, S. & Rumiati, R. I. Protective factors for subjective cognitive decline individuals: Trajectories and changes in a longitudinal study with Italian elderly. *Eur. J. Neurol.* **29**, 691–697. https://doi.org/10.1111/ene.15183 (2022).
20. Yang, X. et al. Effect of leisure activities on cognitive aging in older adults: A systematic review and meta-analysis. *Front. Psychol.* **13**, 1080740. https://doi.org/10.3389/fpsyg.2022.1080740 (2022).
21. Liu, Y., Lu, G., Liu, L., He, Y. & Gong, W. Cognitive reserve over the life course and risk of dementia: A systematic review and meta-analysis. *Front. Aging Neurosci.* **16**, 1358992. https://doi.org/10.3389/fnagi.2024.1358992 (2024).
22. Nelson, M. E. et al. Alzheimer's neuropathology, and risk of dementia: A systematic review and meta-analysis. *Neuropsychol. Rev.* **31**, 233–250. https://doi.org/10.1007/s11065-021-09478-4 (2021).
23. Berezuk, C., Scott, S. C., Black, S. E. & Zakzanis, K. K. Cognitive reserve, cognition, and real-world functioning in MCI: A systematic review and meta-analysis. *J. Clin. Exp. Neuropsychol.* **43**, 991–1005. https://doi.org/10.1080/13803395.2022.2047160 (2021).
24. Corbo, I., Marselli, G., Di Ciero, V. & Casagrande, M. The protective role of cognitive reserve in mild cognitive impairment: A systematic review. *J. Clin. Med.* **12**, 1759. https://doi.org/10.3390/jcm12051759 (2023).
25. Arora, S. et al. The influence of education in predicting conversion from subjective cognitive decline (SCD) to objective cognitive impairment: A systematic review and meta-analysis. *Ageing Res. Rev.* **101**, 102487. https://doi.org/10.1016/j.arr.2024.102487 (2024).
26. Jack, C. R. et al. Revised criteria for diagnosis and staging of alzheimer's disease: Alzheimer's association workgroup. *Alzheimer S Dement.* **20**, 5143–5169. https://doi.org/10.1002/alz.13859 (2024).
27. Opdebeeck, C., Martyr, A. & Clare, L. Cognitive reserve and cognitive function in healthy older people: A meta-analysis. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* **23**, 40–60. https://doi.org/10.1080/13825585.2015.1041450 (2016).
28. Valenzuela, M. J. & Sachdev, P. Brain reserve and dementia: A systematic review. *Psychol. Med.* **36**, 441–454. https://doi.org/10.1017/S0033291705006264 (2006).
29. Soldan, A. et al. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. *Neurobiol. Aging*. **60**, 164–172. https://doi.org/10.1016/j.neurobiolaging.2017.09.002 (2017).
30. Zahodne, L. B. et al. The role of education in a vascular pathway to episodic memory: Brain maintenance or cognitive reserve? *Neurobiol. Aging*. **84**, 109–118. https://doi.org/10.1017/S1355617711001044 (2019).
31. Albert, M. S. et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimers Dement. J.* **7**, 270–279. https://doi.org/10.1016/j.jalz.2011.03.008 (2011).
32. Rabin, L. A. et al. Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to alzheimer's disease. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* **16**, 357–376. https://doi.org/10.1080/13825580902825220 (2009).
33. Campos-Magdaleno, M., Facal, D., Juncos-Rabadán, O., Braña, T. & Pereiro, A. X. Cluster subtypes of the Spanish version of the California verbal learning test in a sample of adults with subjective memory complaints. *J. Clin. Exp. Neuropsychol.* **36**, 317–333. https://doi.org/10.1080/13803395.2014.890698 (2014).
34. Studart, A. & Nitrini, R. Subjective cognitive decline: The first clinical manifestation of Alzheimer's disease? *Dement. Neuropsychol.* **10**, 170–177. https://doi.org/10.1590/S1980-5764-2016DN1003002 (2016).
35. Koppara, A. et al. Cognitive performance before and after the onset of subjective cognitive decline in old age. *Alzheimers Dement.* **1**, 194–205. https://doi.org/10.1016/j.dadm.2015.02.005 (2015).
36. Linden, M. V. D., Wyns, C., Bruyer, R., Ansay, C. & Seron, X. Effect of educational level on cued recall in young and elderly subjects. *Psychol. Belg.* **33** https://doi.org/10.5334/pb.837 (1993).
37. Kang, W. Associations between big five personality traits and episodic memory performance in young, middle-aged, and older people: Evidence from the immediate and delayed word recall tasks. *Personal Individ Differ.* **202**, 111967. https://doi.org/10.1016/j.paid.2022.111967 (2023).

38. Cloutier, S., Chertkow, H., Kergoat, M. J., Gauthier, S. & Belleville, S. Patterns of cognitive decline prior to dementia in persons with mild cognitive impairment. *J. Alzheimers Dis.* **47**, 901–913. https://doi.org/10.3233/JAD-142910 (2015).
39. Pereiro, A. X. et al. Relevance of complaint severity in predicting the progression of subjective cognitive decline and mild cognitive impairment: A machine learning approach. *J. Alzheimers Dis.* **82**, 1229–1242. https://doi.org/10.3233/JAD-210334 (2021).
40. Hamel, R. et al. The trajectory of cognitive decline in the pre-dementia phase in memory clinic visitors: Findings from the 4 C-MCI study. *Psychol. Med.* **45**, 1509–1519. https://doi.org/10.1017/S0033291714002645 (2015).
41. Gyllenhammar, M. et al. The association between Temporal atrophy and episodic memory is moderated by education in a Multi-Center memory clinic sample. *J. Alzheimers Dis.* **92** https://doi.org/10.3233/JAD-220741 (2023).
42. Kwak, S. et al. Moderating effect of cognitive reserve on the association between grey matter atrophy and memory varies with age in older adults. *Psychogeriatr. Off J. Jpn Psychogeriatr. Soc.* **20**, 87–95. https://doi.org/10.1111/psyg.12460 (2020).
43. Schwarz, C., Franz, C. E., Kremen, W. S. & Vuoksimaa, E. Reserve, resilience and maintenance of episodic memory and other cognitive functions in aging. *Neurobiol. Aging*. **140**, 60–69. https://doi.org/10.1016/j.neurobiolaging.2024.04.011 (2024).
44. Sörman, D. E. et al. Occupational cognitive complexity and episodic memory in old age. *Intelligence* **89**, 101598. https://doi.org/10.1016/j.intell.2021.101598 (2021).
45. Ersoezlue, E. et al. Lifelong experiences as a proxy of cognitive reserve moderate the association between connectivity and cognition in Alzheimer's disease. *Neurobiol. Aging*. **122**, 33–44. https://doi.org/10.1016/j.neurobiolaging.2022.05.015 (2023).
46. Coleman, M. E. et al. Social enrichment on the job: Complex work with people improves episodic memory, promotes brain reserve, and reduces the risk of dementia. *Alzheimers Dement. J. Alzheimers Assoc.* **19**, 2655–2665. https://doi.org/10.1002/alz.13035 (2023).
47. Franzmeier, N. et al. Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI. *Neurobiol. Aging*. **50**, 152–162. https://doi.org/10.1016/j.neurobiolaging.2016.11.013 (2017).
48. Jokinen, H. et al. Cognitive reserve moderates long-term cognitive and functional outcome in cerebral small vessel disease. *J. Neurol. Neurosurg. Psychiatry*. **87**, 1296–1302. https://doi.org/10.1136/jnnp-2016-313914 (2016).
49. Ko, K. et al. Cognitive reserve proxies, alzheimer pathologies, and cognition. *Neurobiol. Aging*. **110**, 88–95. https://doi.org/10.1016/j.neurobiolaging.2021.10.005 (2022).
50. Montemurro, S., Rumiati, R. I., Pucci, V., Nucci, M. & Mondini, S. Cognitive reserve can impact trajectories in ageing: A longitudinal study. *Aging Clin. Exp. Res.* **37**, 93. https://doi.org/10.1007/s40520-025-03000-z (2025).
51. Pietrzak, R. H. et al. Trajectories of memory decline in preclinical Alzheimer's disease: Results from the Australian Imaging, biomarkers and lifestyle flagship study of ageing. *Neurobiol. Aging*. **36**, 1231–1238. https://doi.org/10.1016/j.neurobiolaging.2014.12.015 (2015).
52. Farina, M., Paloski, L., Oliveira, C., Argimon, I. & Irigaray, T. Cognitive reserve in elderly and its connection with cognitive performance: A systematic review. *Ageing Int.* **43**. https://doi.org/10.1007/s12126-017-9295-5 (2018).
53. Bransby, L. et al. The relationship between cognitive engagement and better memory in midlife. *Dement. Diagnosis Assess. Disease Monit.* https://doi.org/10.1002/dad2.12278 (2022).
54. Clouston, S. et al. Benefits of educational attainment on adult fluid cognition: international evidence from three birth cohorts. *Int. J. Epidemiol.* **41**, 1729–1736. https://doi.org/10.1093/ije/dys148 (2012).
55. Juncos-Rabadán, O. et al. Prevalence and correlates of mild cognitive impairment in adults aged over 50 years with subjective cognitive complaints in primary care centers. *Geriatr. Gerontol. Int.* **14**, 667–673. https://doi.org/10.1111/ggi.12157 (2014).
56. Petersen, R. C. Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* **256**, 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x (2004).
57. Qi, X. M., Gu, L., Tang, H. D., Chen, S. D. & Ma, J. F. Association of Source of Memory Complaints and Increased Risk of Cognitive Impairment and Cognitive Decline: A Community-Based Study. *Chin. Med. J. (Engl.)* **131**, (2018). https://doi.org/10.4103/0366-6999.229904
58. Benedet, M. J. & Seisdedos Cubero, N. *Evaluación clínica de las quejas de memoria en la vida cotidiana*. (1996). https://dialnet.unirioja.es/servlet/libro?codigo=225589
59. Van der Linden, M., Wyns, C., Coyette, F., Frenkell, R. & Seron, X. *Un Questionnaire d'auto-évaluation De La mémoire (QAM)* (Editest, 1989).
60. Lawton, M. P. & Brody, E. M. Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist* **9**(Part 1), 179–186 (1969). https://doi.org/10.1093/geront/9.3_Part_1.179
61. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–383. https://doi.org/10.1016/0021-9681(87)90171-8 (1987).
62. Benedet, M. J. & Alejandre, M. A. Test de Aprendizaje Verbal España-Complutense (TAVEC). Spain: TEA Ediciones. (1998). https://web.teaediciones.com/tavec-test-de-aprendizaje-verbal-espa%C3%B1a-complutense.aspx
63. Delis, D. C., Freeland, J., Kramer, J. H. & Kaplan, E. *California Verbal Learning Test* (Psychological Corporation, 1987). https://doi.org/10.1037/t48844-000
64. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (5th Ed). Washington, DC: American Psychiatric Association. (2013). https://doi.org/10.1176/appi.books.9780890425596
65. Reitan, R. M. Validity of the trail making test as an indicator of organic brain damage. *Percept. Mot Skills*. https://doi.org/10.2466/PMS.8.7.271-276 (1958).
66. Peña-Casanova, J. et al. Spanish multicenter normative studies (NEURONORMA Project): Norms for verbal span, visuospatial span, letter and number sequencing, trail making test, and symbol digit modalities test. *Arch. Clin. Neuropsychol.* **24**, 321–341. https://doi.org/10.1093/arclin/acp038 (2009).
67. Roth, M. et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br. J. Psychiatry.* **149** (1986). https://doi.org/10.1192/bjp.149.6.698
68. Lezak, M. D. *Neuropsychological Assessment* (Oxford University Press, 2004).
69. García-Albea, J. E., Sánchez-Bernardos, M. L. & del Viso-Pabón in *La evaluación de la afasia y de trastornos relacionados*. Vol. 3 (eds En Goodglass, H. & Kaplan, E.) (Editorial Medica Panamericana, 2005). S. Test de Boston para el diagnóstico de la afasia: adaptación española.
70. Dubois, B. et al. Research criteria for the diagnosis of alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* https://doi.org/10.1016/S1474-4422(07)70178-3 (2007).
71. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edn, Text Revision (DSM-IV-TR). American Psychiatric Association, (2000).
72. Nakagawa, S. & Schielzeth, H. A general and simple method for obtaining R^2 from generalized linear mixed-effects models. *Methods Ecol. Evol.* **4**, 133–142. https://doi.org/10.1111/j.2041-210x.2012.00261.x (2013).

Acknowledgements
The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was financially supported through FEDER founds ('A way to make Europe') by the Spanish AEI (Doi: 10.13039/501100011033; Refs. PID2020-114521RB-C21 and PID2023-151659OB-C21) and by the Galician Government (Consellería de Cultura, Educación e Ordenación Universitaria; axudas para a consolidación

e estruturación de unidades de investigación competitivas do Sistema Universitario de Galicia ED431C 2021/04; GI-1807-USC: Ref. 2021-PG011).

Author contributions

SA: Data curation, Methodology, Writing—original draft, Investigation. CL-S: Data curation, Methodology, Statistical analysis, Writing—review & editing. DL: Statistical analysis, Writing—review & editing. LP-B: Data curation, Methodology. SC-M: Data curation, Methodology. AN-V: Methodology, AX-P: Methodology, Data curation, Writing—review & editing.

Funding

This work was financially supported through FEDER founds ('A way to make Europe') by the Spanish AEI (Doi: https://doi.org/10.13039/501100011033; Refs. PID2020-114521RB-C21 and PID2023-151659OB-C21) and by the Galician Government (Consellería de Cultura, Educación e Ordenación Universitaria; axudas para a consolidación e estruturación de unidades de investigación competitivas do Sistema Universitario de Galicia ED431C 2021/04; GI-1807-USC: Ref. 2021-PG011).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-29374-8.

Correspondence and requests for materials should be addressed to A.X.P.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.