Protective factors for cognitive decline: Trajectories and changes in a longitudinal study with Italian elderly

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Protective factors for Subjective Cognitive Decline Individuals: Trajectories and changes in a longitudinal study with Italian elderly

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Abstract (226 words)

Background: Many different factors have been hypothesized to modulate cognition in an aging population according to their functioning at baseline.

Methods: This retrospective study quantifies the relative contribution of age and sex as demographic factors, comorbidity, education, and occupation (classified with the International Standard Classification of Occupation, ISCO-08) as cognitive reserve (CR) proxies in accounting for cognitive aging. All participants (3,081) were evaluated at baseline with a complete neuropsychological test battery (T1) and those with unimpaired profiles were classified as Subjective Cognitive Decline, those mildly impaired as Mild Neurocognitive Decline, and those severely impaired as Major Neurocognitive Decline. From the first assessment 543 individuals were assessed a second time (T2), and 125 a third time (T3). Depending on whether they maintained or worsened their profile, based on their initial performance, participants were then classified as resistant or declining.

Results: At baseline, all individuals showed education and occupation as the best predictors of performance, in addition to age. Furthermore, across assessments, the resistant had higher levels of education and occupation than the declining. In particular, the Subjective Cognitive Decline, and all other groups included the most severely impaired, education and occupation predicted cognitive performance.

Conclusions: This study highlights the role of working activity in protecting from cognitive decline across all fragile elderly groups and even more so the individuals who are at very high risk of decline.

1. Introduction

Cognitive reserve (CR) is a construct that has been operationalized using several proxies such as education, occupation, indexes of quality of life and physical activity. High values of such proxies have been found to have a positive influence on cognitive health and to significantly discriminate between healthy and pathological aging. Education has been repeatedly associated with lower risk of developing dementia and with improved cognitive functioning[1,2]. Indeed, individual differences in cognitive decline have often been observed in association with educational level[3], with highly educated patients maintaining their functioning longer. In line with previous longitudinal cohort studies[4], a recent longitudinal study involving 28,417 individuals confirmed the association between education and cognitive performance at baseline and between education and delayed onset of cognitive decline[1].

As mentioned above, other factors, such as occupation or leisure activities[5–7], have been hypothesized to contribute to CR in addition to formal education. Social, mental, and physical activities have beneficial effects on cognition in the elderly and have a protective role against dementia (see a review of longitudinal studies published between 1996 and 2004 by Fratiglioni, Paillard-Borg, & Winblad, 2004[8]). A satisfactory social life is considered of great importance in decreasing the risk of morbidity and death in old age[9], as well as in dementia[10]. An active daily social life involves a series of tasks that rely on cognition, and indeed older adults who have taken part in leisure activities show a lower risk of dementia than those with lesser involvement[11].

The cognitive processes required for job duties may also contribute to CR[12]. Early evidence suggested that occupation, together with education, plays a crucial role against the development of dementia[13]. This has been replicated in subsequent studies with large groups[12,14]. One critical aspect that has been poorly investigated in previous studies is when and how the different CR proxies have an effect. In fact, most studies adopted a cross-sectional approach[15], which does not allow to clearly verify how cognitive profiles change over time.

In this retrospective study, we investigated the effect of demographic factors (age and sex), presence of comorbidities, and CR proxies (education and occupation) on a continuum from healthy to pathological aging and their persistence over time. In the Baseline Study, 3,018 individuals underwent a first neuropsychological assessment (T1) for suspected pathological aging. We predicted that the younger the age and the higher the cognitive reserve proxies, the better the cognitive outcomes. In follow-up Studies, 543 participants underwent a second (T2), and 125 a third (T3) neuropsychological assessment. In addition, to replicate the same pattern found in the Baseline Study, we expected a slower cognitive decline over time in participants with higher levels of CR.

The novelty of the present study consists in the inclusion of individuals with an unimpaired cognitive profile (e.g., SCD). There are several reasons why individuals with SCD may be of particular interest for studying the effects of CR. They have been less investigated than Major Neurocognitive Disorder or Mild Neurocognitive Disorder, although they represent a midway condition along the continuum between healthy and pathological aging (Slot et al., 2019). Individuals with SCD have a high risk of developing dementia (Jessen et al., 2014; Rabin et al., 2017), although their global cognitive performance is largely unimpaired.

2. Methods and Results

2.1 Baseline study

From a cohort of 4,638 individuals, 3,081 (2,010 females) entered the study (mean age = 78.2 yrs, SD = 7.79, range = 45-99; mean education = 6.99 yrs, SD = 3.85, range = 0-25 yrs). Predictors of cognitive outcomes were age and sex as socio-demographic variables, comorbidity (number of concomitant relevant pathologies) as the clinical variable, and education and occupation as proxies of CR. The occupation was classified using the ISCO-08 code (International Standard Classification of Occupations, 2008[16]) which is fully supported by the international community as an accepted standard for international labour statistics. This system classifies each working activity along a continuous numeric value where the higher is the numerical code and the lower is the complexity of the occupation in terms of skills and cognitive resources involved (e.g., 9629 corresponds to “elementary workers not elsewhere classified”, while 0110 corresponds to “commissioned armed forces officers”).

At each assessment, participants underwent a complete neuropsychological evaluation, but only six tests routinely used in our clinical unit, and known to be sensitive to detecting cognitive decline in the elderly, were selected for the present analysis: 1) MMSE (Mini-Mental State Examination[17], Italian version[18]) for a global measure of cognition; 2) Famous Face naming test, to measure proper name retrieval[19]; 3) Memory test, to measure episodic memory; 4) Fluency test, to measure lexical access and executive function; 5) Trail Making Test-A (TMT), to assess selective and spatial attention and psychomotor speed; and 6) Clock test, to measure visuo-spatial abilities, planning and praxis. The last three tests are all taken from the ENB-2 battery[20]. Three diagnostic groups were identified based on psychometric data and anamnestic and clinical information: 1) Subjective Cognitive Decline[21] (SCD) with 507 participants (17%); 2) Mild Neurocognitive Disorder (MildND) with 584 participants (19%); and 3) Major Neurocognitive Disorder due to Alzheimer's disease (MajorND) with 1980 participants (64%). The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethical Committee of the School of Psychology of the University of Padua.

Results

Generalized Linear Model (GLM) analyses were carried out to verify whether and how age, sex, education, occupation and comorbidities could predict participants' cognitive performance in the six tests. Models with best fit (after entering one predictor at a time, based on R-squared) were those with all five predictors and all these models were significant (see Model fit measure on Table 1). A consistent effect of age and education was expected but, interestingly, occupation was also found predictive on all tests except for Clock and TMT. Sex and comorbidity played a minor role and predicted only two tests each. In particular, females outperformed males in naming faces, while males outperformed females in the Clock. A similar verbal/visuo-spatial gender difference had been observed in a previous study on the effect of CR on aging and found this verbal/visuo-spatial gender difference3, while Tappen et al.24 found that in an older adult population men were better than women at the Clock test.

Table 1

About here

The effect of age and education persisted within each of the three diagnostic groups (SCD, MildND, MajorND) and, although occupation did not play a role within each group, it differed significantly among them (F(2, 900)31.0, *p*<.001): SCD had the lowest score (i.e., more complex jobs), while MajorND had the highest score (i.e., less complex jobs) (see Figure 1).

Figure 1

About here

2.2 Follow-up Studies

Five hundred and forty-three individuals from Baseline Study underwent a second assessment (T2), and 125 underwent a third assessment (T3). In a series of GLM analyses, age, sex, education, occupation and comorbidity were introduced as predictors, and participants' performance in the six cognitive tests as the dependent variable. At T2 all GLM were significant in predicting the outcomes in the cognitive tests. Education confirmed its effect on all six tests, and age had an effect only on two. No other effect was found. At T3, education was the only significant predictor in the three tests. Participants were then sorted into two groups based on clinical evidence and on their cognitive performance in the tests. At T2 and T3, individuals who performed worse than in the previous assessment were put in a single group and named *declining.* This group also included MajorND participants who maintained the same clinical diagnosis but worsened their cognitive performance (no MajorND patient improved on cognitive tests). Participants who at T2 (or T3) did not worsen their profile were put in a single group and named *resistant* (see Table S1 for more details about participants' changing cognitive profiles). At each assessment, the *declining* group showed lower average scores at T2 than at T1 and at T3 than at T2 on 4 out of 6 tests. Instead, the average scores on all six tests of the *resistant* did not change at either T2 or T3 (see Table 2).

Table 2
About here

Results

The time interval between assessments (from T1 to T2) was different among participants: Short (1 year; 242 participants), Medium (2-3 years; 207 participants) and Long (more than 3 years; 94 participants). Assuming that the longer the time, the higher the possible cognitive decline, the aim of this analysis was to verify if the effect of CR proxies changed depending on the time elapsed between assessments.

At T2, as expected, the *resistant* had higher education than the *declining* (t = 8.04, df = 1064, mean difference = 2.43, p < .001) at all time intervals: Short (t = 5.67, df = 480, mean difference = 2.77, p < .001), Medium (t = 3.02, df = 398, mean difference = 1.34, p = .003), Long (t = 5.43, df = 182, mean difference = 3.77, p < .001), but more interestingly,
the *resistant showed* higher occupation than the *declining* (t = -4.80, df = 924, mean difference = -979, p < .001) across the three time intervals: Short (t = -2.69, df = 424, mean difference = -819, p =.007); Medium (t = -2.60, df= 342, mean difference = -858, p = .01); Long (t = -3.30, df = 154, mean difference = -1565, p = .001). Noteworthy, the *resistant* had the highest education and also more complex occupations when the interval was the longest (see Figure 2).

Figure 2
About here

Of the 125 who underwent a third assessment (T3),104 participants were *declining* (83.9%) and only 21 (16.1%) were *resistant*. Once again, the *resistant* were not only more educated (t = 3.86, df = 361, mean difference = 2.49, p <.001) but held a more complex occupation than the *declining* (t = 2.25, df = 319, mean difference = -941, p =

0.025), (see Figure 3). The time intervals among assessments were not considered in this analysis.

Figure 3

About here

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3. Discussion

This study aimed at identifying which factors may have a modulating effect on cognition in aging and how such an effect may change across time. In the Baseline Study, the higher the education, the better the performance, an effect already well known and reported in the literature. However, with this study we have also made a new contribution to the field by demonstrating the role of occupation as a good predictor of participants' performance. The younger participants, the more educated ones, and those with more complex jobs showed better cognitive performance. While it is known that cognition deteriorates with aging and in particular in less educated people3,22, the clear-cut effect of occupation found in this study point to the relevance of occupation in operationalizing CR. Different from education, which is mostly although not exclusively acquired during the first part of life, occupation is built on activities carried out during adulthood and demonstrates the benefits of life-long learning mechanisms. Adult learning seems to be quite effective in preserving cognition in the elderly[15,23].

Age and education were confirmed as predictors of performance in all tests for all three diagnostic groups (SCD, MildND, and MajorND). We found that education does protect people potentially at risk of developing cognitive decline (SCD group), but more interestingly, these same individuals also held more complex jobs than the other two groups. Thus, it seems that less impaired individuals had CR proxies at the highest degree.

Across assessments, the explanatory power of predictors seems progressively attenuated. In fact, as age increases, there are a multitude of factors that affect the elderly's cognition and give rise to huge heterogeneity[25]. Education was the only variable that continued to predict performance over time, although its effect decreased at T2 and T3.

When considering all participants, progressive worsening was found from one assessment to the next in most tests. However, when they were sorted into *resistant* (i.e., those who maintained their profile) or *declining* (i.e, those who worsened their profile), the former showed significantly higher education and more complex occupation than the latter at both T2 and T3. This result suggests a critical role of CR proxies in characterizing the evolution of dementia.

We are aware of a number of limitations of this retrospective study. First of all, the lack of precise biomarkers in our sample could have misdiagnosed the patients. However, structural and functional neuroimaging information was used to obtain the clinical diagnosis at baseline. We are aware that the number of participants between assessments decreased significantly, as is usual in the majority of studies that consider an elderly population with a percentage of pathological individuals. Another limitation may be that the concept of CR in this study was confined to education and occupation, even though CR is likely to be more than that. As this is a retrospective study, we cannot obtain further useful data and information (e.g., lifestyle, place of residence, etc.) to better understand how our participants aged. Although we consider SCD individuals within the continuum between normal and pathological aging, in future studies it would be appropriate to include non-clinical participants. To our knowledge, this is one of the few studies including the category of Subjective Cognitive Decline individuals when CR is used as a potential modulator of age-related trajectories. Moreover, we demonstrated the importance of working activities carried out during adulthood as a critical factor of CR and cognitive performance in SCD individuals [26,27].

In conclusion, our longitudinal study on healthy and pathological participants maintains that, together with social connectedness, ongoing sense of purpose, and ability to function independently, higher levels of cognitive reserve contribute to mental health and general wellbeing along the trajectories of aging.

Data sharing and data accessibility

The datasets generated during and/or analyzed during the current study are not publicly available due to information that could compromise participant privacy but are available from the corresponding author on reasonable request.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethical Committee of the School of Psychology of the University of Padua.

Consent to participate

All patients gave their written informed consent for the use of their data for research purposes at the moment of their consultation.

Consent for publication

Patients signed informed consent regarding publishing their data under the guarantee of anonymity.

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Tables and Figures Captions

Table 1. **GLM significance for each test.** The Table shows the contribution of each predictor to the model. Model fit measures indicate the significance of models with all covaried predictors.

Table 2. Resistant and declining. Paired sample T-tests which show the mean difference of the 6 tests between T1 and T2 and between T2 and T3 in the two groups separately (*declining* and *resistant*).

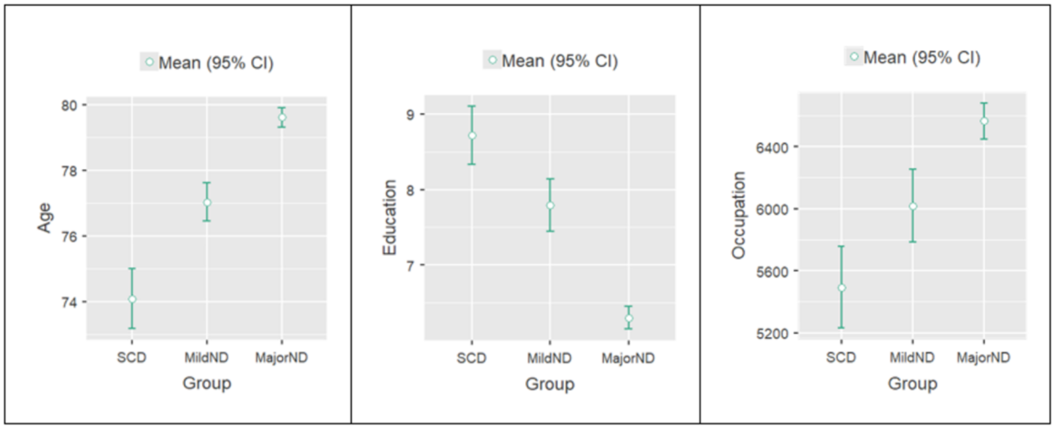
Figure 1. Predictors in the groups. The graphs show the mean differences in age (years), education (years) and occupation (ISCO-08 codes: lower scores indicate more complex occupations) resulting from one-way ANOVA among the three groups (SCD, MildND and MajorND).

Figure 2. Education and occupation effects on resistant and declining individuals at the second assessment, on different time intervals. The two graphs on the left-hand side show the mean difference of education and occupation between *resistant* and *declining*, while the two graphs on the right-hand side show the mean difference of education and occupation between *resistant* and *declining* on the three time intervals.

Figure 3. Education and occupation effects on resistant and declining individuals at the third assessment. The graphs represent the mean difference of education (on the left-hand side) and occupation (on the right-hand side) between *resistant* and *declining* at the third assessment (T3).

	Predictors (Beta and *p*)											
	Age		Sex		Education		Occupation		Comorb		Model fit measure	
Models	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	R^2	*p*
MMSE	-0.250	**<.001**	0.030	.135	0.259	**<.001**	-0.048	**.037**	-0.030	.111	.164	**<.001**
Memory	-0.312	**<.001**	0.003	.952	0.246	**<.001**	-0.067	**.017**	-0.020	.367	.201	**<.001**
Faces	-0.300	**<.001**	-0.140	**.013**	0.212	**<.001**	-0.066	**.042**	-0.039	.141	.175	**<.001**
Fluency	-0.213	**<.001**	0.021	.065	0.268	**<.001**	-0.067	**.016**	-0.077	**<.001**	.166	**<.001**
TMT	0.250	**<.001**	-0.035	.497	-0.271	**<.001**	0.052	.083	0.083	**<.001**	.192	**<.001**
Clock	-0.193	**<.001**	0.187	**<.001**	0.247	**<.001**	-0.017	.568	-0.006	.803	.134	**<.001**

	declining					
	From T1 to T2			From T2 to T3		
	t (df)	*mean diff.*	*p-value*	*t (df)*	*mean diff.*	*p-value*
MMSE	11.4 (399)	2.80	**<.001**	5.92 (92)	2.47	**<.001**
Memory	4.15 (220)	0.64	**.005**	5.35 (51)	4.75	**<.001**
Faces	3.92 (83)	0.99	**<.001**	3.17 (17)	1.33	**.006**
Fluency	1.18 (176)	0.24	.240	1.62 (52)	0.63	.111
TMT	-3.08 (182)	-14.25	**.002**	-1.97 (54)	-15.38	.054
Clock	1.75 (225)	0.37	.082	2.26 (64)	0.79	**.027**
	resistant					
	From T1 to T2			From T2 to T3		
	t (df)	*mean diff.*	*p-value*	*t (df)*	*mean diff.*	*p*
MMSE	0.32 (81)	0.11	.710	1.20 (15)	1.00	.248
Memory	1.29 (87)	1.06	.200	0.87 (17)	1.28	.398
Faces	1.58 (29)	0.73	.125	2.61 (3)	1.25	.080
Fluency	0.32 (83)	0.13	.751	-1.99 (17)	-1.52	.066
TMT	-0.42 (29)	-1.56	.672	-1.46 (15)	-6.63	.165
Clock	-1.04 (60)	-0.34	.301	0-38 (13)	0.18	.707



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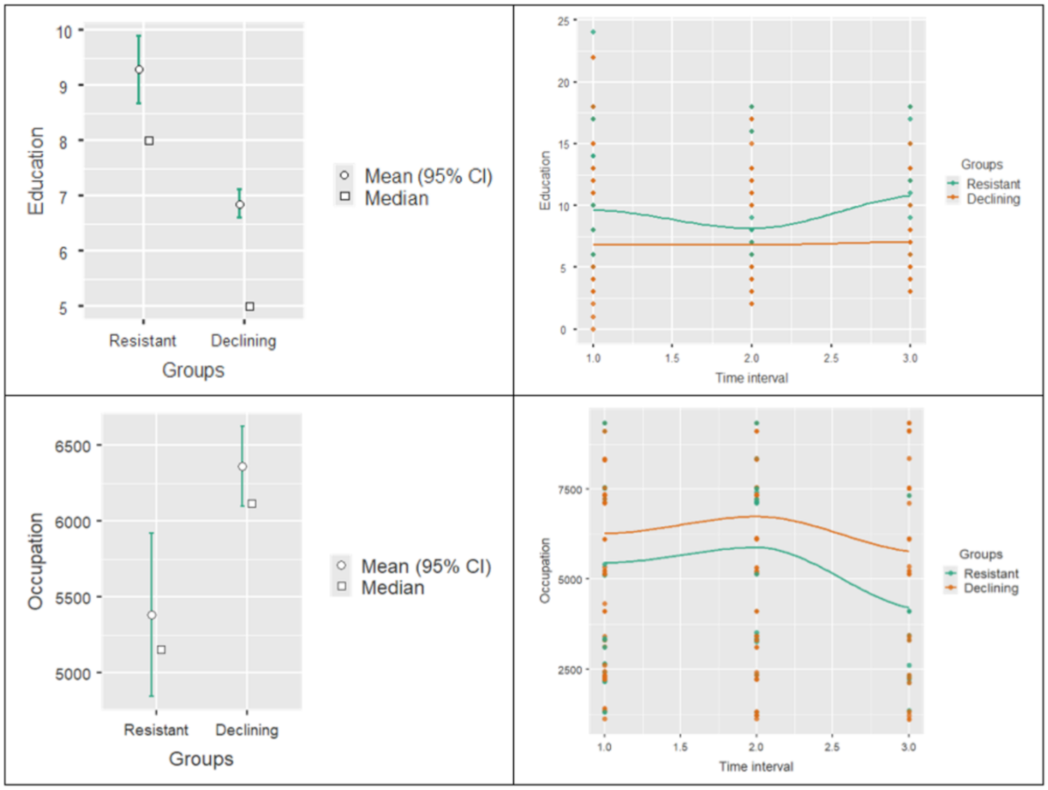

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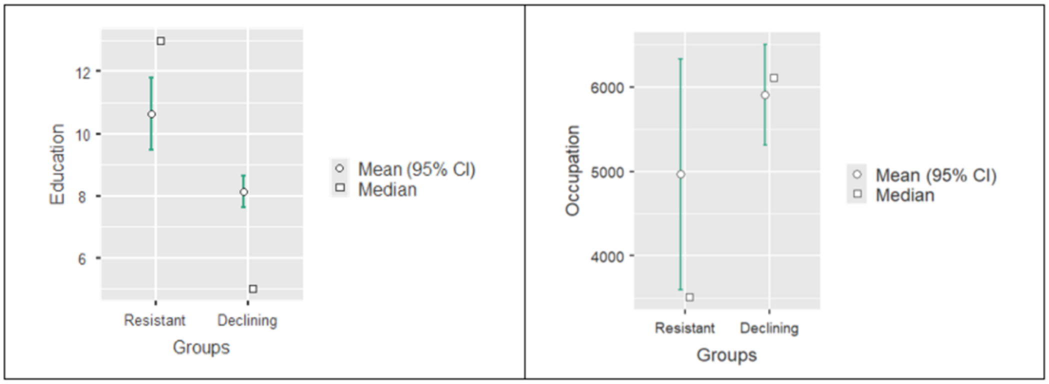

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