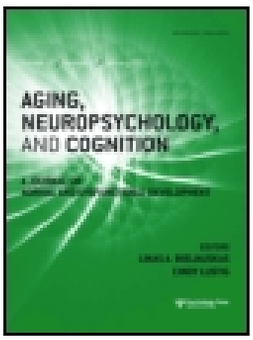

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Cognitive reserve: a multidimensional protective factor in Parkinson's disease related cognitive impairment

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ABSTRACT

We explored the association between cognitive reserve (CR) and Parkinson' s disease (PD) related cognitive deterioration.

Forty PD patients and 12 matchedhealthy controls (HC) were enrolled. The PD group was balanced for the presence/absence of cognitive impairment All participants underwent MOCA. CR was measured by the Brief Intelligence Test, and a new comprehensive tool, named Cognitive Reserve Test (CoRe-T), including sections on leisure activities and creativity.

Participants with higher CR obtained a better MOCA score irrespective of the group they belonged to. At the same time, irrespective of the CR level, the performance of the HC group was always better in comparison to the PD group. Within the PD group, a higher frequency of leisure activities was associated to be cognitively unimpaired, independently by the severity of motor symptoms and age . CR could help to cope with PD-related cognitive decline. Its multidimensional nature could have important applications in prevention and rehabilitation interventions.

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Parkinson's disease; cognitive reserve; cognitive impairment; neuropsychology evaluation; creativity

Introduction

Although Parkinson's disease (PD) is best known as a movement disorder, cognitive impairments (typically dominated by dysexecutive disorders) are frequent at the time of diagnosis, and a significant fraction of patients evolve toward dementia during the late stages (Hely et al., 2008; Leverenz et al., 2009). Different factors have been proposed to explain different PD cognitive evolution, principally phenotype, and age at the onset (Muslimović et al., 2007). Also, factors such as education, premorbid intelligence, and brain volume could explain individual tolerance and response to cognitive difficulties due to age or brain pathologies as Alzheimer's disease (AD) or PD (Andel et al., 2006; Colombo, Piromalli et al., 2019; Hindle et al., 2014; Richards & Deary, 2005; Stern, 2012). These effects are usually explained by referring to the brain reserve (mainly related to brain size and neuroplasticity and assumed to have genetic components) and cognitive reserve (CR) (defined as the efficiency and flexibility of neural networks and highly influenced by life experiences) models (Medaglia et al., 2017; Stern, 2002, 2009). Research suggests that two

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mechanisms are most likely involved in the CR's effects: recruitment of brain networks and compensation by alternative cognitive strategies (Nucci et al., 2012; Steffener & Stern, 2012).

This paper focuses on the concept of CR and its possible role in the cognitive evolution of people with PD. However, evidence of CR as a protective factor for dementia, by raising the tolerance threshold to cognitive impairment and delaying the clinical manifestation of decline, originates from studies conducted mainly on patients affected by AD (Stern, 2012; Stern et al., 1999; Valenzuela & Sachdev, 2006). As regards PD, it is yet unclear whether CR might have a similar protective effect on cognition. Two studies conducted on patients with PD found a positive association between CR and cognitive performance mainly in tests sensitive to frontal lobe dysfunction (Ciccarelli et al., 2018; Cohen et al., 2007): CR compensation mechanism could rely on general semantic knowledge, problem-solving abilities, and executive functions, therefore its effects may be more significant on tasks with high executive demand (Barulli & Stern, 2013).

Furthermore, a higher level of CR has found to be associated to a lower severity of PD motor impairment, especially after several years from the diagnosis (Guzzetti et al., 2019), possibly mediated through an extranigral protective effect on white matter integrity (Kotagal et al., 2015). A prospective 5-years study (Herman et al., 2018) highlighted another possible protective effect of CR on PD pathology: reducing the development of postural instability/gait difficulty phenotype, which generally shows a worse cognitive and motor progression compared to tremor-dominant subtype (Hariz & Forsgren, 2011).

However, literature still reports limited longitudinal evidence of a specific effect of CR in delaying the evolution toward cognitive impairment and dementia in PD (Hindle et al., 2016, 2014; Lee et al., 2019; Muslimović et al., 2007), and most of the studies reported the effect of only one CR proxy, most commonly education (Rouillard et al., 2017), with no consistent results (Pai & Chan, 2001). A problematic aspect appears the lack of a standardized and shared method for the CR measurement. Education, which is still one of the most widely used proxies for CR, if taken alone could be too simplistic or even misleading (Guzzetti et al., 2019; Jones et al., 2011). Recently, new assessment tools have been proposed, which consider CR as a multidimensional construct and consider not only education but also the complexity of work activity (Garibotto et al., 2008), the engagement in cognitively stimulating leisure activities (Colombo et al., 2018), and the cohesion of social networks (Colombo, Balzarotti et al., 2019; Nucci et al., 2012). Among cognitively stimulating hobbies also physical activities are included: fitness might be another protective factor against both normal and pathological cognitive decline (Kramer et al., 2005).

By examining these new tools, it is clear that many of the proxies used to assess CR refer (more or less directly) to the flexibility of thought and the ability to use alternative cognitive strategies, namely skills that characterize creativity. This means that there are similarities between the hypothesized mechanisms at the basis of CR and the ones that are supposed to support the creative processes, as the ability to keep an open mind, to establish new and unusual relationships, and to change the perspective when required (Antonietti & Colombo, 2013, 2016). In other words, creativity could be a unique aspect of CR. Data reported in recent literature showed a clear positive relationship between both creative verbal tasks (i.e., alternative uses and generation of acronyms) and creative vs. routine job activities and CR (Colombo et al., 2018; Palmiero et al., 2016). Thus, creativity tasks can be considered useful to improve and refine CR measurement.

Starting from the above assumptions, we aimed to better explore the association between CR and PD-related cognitive deterioration, by using a comprehensive tool to measure CR including also the creativity. Our study design involved the comparison between a group of patients with PD (balanced for the presence/absence of cognitive impairment) and a matched healthy control sample. We hypothesized that CR was positively associated with a better cognitive performance both in patients and controls. In the PD group, higher CR was expected to be associated with the cognitively unimpaired subgroup. We were also interested in evaluating whether different CR indices showed different findings in the protective role on cognition. The possible role of CR as a moderator of motor disability was also explored.

Materials and methods

Subjects

Forty patients (24 males and 16 females) with a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank for at least 1 year and a sample of 12 healthy controls (HC) (MOCA≥ 23, according to Italian normative data from Conti et al., 2015) matched for age, education, and gender were enrolled in the study (see Table 1 for groups' characteristics).

Between August 2018 and February 2019, patients with PD were enrolled during routine outpatient visits at the Neurology Unit. During routine clinical follow-up, patients underwent the Unified Parkinson's Disease Rating Scale (UPDRS), one of the most commonly used scales to evaluate both impairment and disability in PD (Ramaker et al., 2002). The UPDRS includes many sections and in this study we analyzed the Part I (clinical evaluation of cognition, behavior, and mood) and the Part III (clinical evaluation of motor state).

Table 1. Groups' characteristics and neuropsychological evaluation.

Variables	PD (N = 40)	HC (N = 12)	P	PD (N = 20) Cognitively Unimpaired	PD (N = 20) Cognitively Impaired	P
Age (years)	74.3 (6.8)	71.2 (4.9)	.080	71.7 (6.7)	76.9 (5.9)	.007
Education (years)	8.2 (4.1)	8.5 (4.2)	.525	8.7 (4.5)	7.6 (3.9)	.602
Gender (male)	24 (60%)	6 (50%)	.740	12 (60%)	12 (60%)	1.00
PD history (years)	8.3 (5.5)			7.6 (4.8)	8.8 (7.7)	.718
Age at time of diagnosis (years)	66.0 (7.8)			64.1 (7.8)	67.9 (7.4)	.121
Left side motor onset	17 (42.5%)			7 (35%)	10 (50%)	.587
Tremor dominant subtype	18 (45%)			8 (40%)	10 (50%)	.376
ADL (range 0–6)	5.03 (1.73)			5.89 (0.47)	4.25 (2.07)	.003
IADL (range 0–8)	5.69 (2.74)			7.47 (1.26)	4.00 (2.71)	<.001
UPDRS I item 3 > 0 (depression)	10 (25%)			4 (20%)	6 (30%)	.716
UPDRS – III (motor disability)	35.50 (12.56)			26.35 (9.06)	40.65 (11.58)	<.001
MOCA (range 1–30)	18.90 (6.78)	24.75 (2.49)	.010	22.30 (4.56)	15.31 (6.98)	.002
Babcock test (range 0–52)	13.88 (9.15)			17.76 (7.74)	10.00 (8.96)	.004
Stroop test (errors)	8.32 (7.50)			7.97 (7.53)	8.76 (7.70)	.891
Stroop test (time)	42.53 (23.00)			34.70 (14.61)	52.44 (28.01)	.043

Notes: Continuous variables are presented as mean (standard deviation) and categorical variables are presented as number (%).

PD: Parkinson disease; HC: Healthy controls; ADL: Basic activities of daily living; IADL: Instrumental activities of daily living; UPDRS: Unified Parkinson's Disease Rating Scale.

Exclusion criteria were: early onset of motor symptoms (age <45 years), education <5 years, presence of other psychiatric/neurological disorders, deep brain stimulation, not defining Italian as their native language, and the presence of documented cognitive impairment at the time of PD diagnosis based on the score at the UPDRS I–item 1 (that clinically evaluates cognitive dysfunctions and their impact on activities of daily living as perceived by the patient and/or caregiver), that ranges from 0 (no cognitive impairment) to 4 (severe dementia). According to the same item, the sample was balanced for the presence (all patients with a score ≥1) or absence of cognitive impairment at the time of enrollment, obtaining two subgroups (cognitively unimpaired vs. cognitively impaired). Left or right dominance of motor symptoms and the severity of motor impairment were identified using the UPDRS III. All participants with PD were on daily dopamine replacement therapy and/or dopamine receptor agonists, and they were tested during the on phase.

HC participants had no history of neurologic/psychiatric disorders and were not taking any medication that could affect cognitive abilities. HC participants were predominantly recruited among patients' caregivers or relatives. All participants were volunteers. They did not receive any financial remuneration for participating.

All participants provided written informed consent before enrollment.

Neuropsychological examination

We administered the MOCA to all participants to assess their cognitive profiles. The PD group also underwent the Babcock test (De Renzi. et al., 1977) and the brief version of the Stroop test (Caffarra et al., 2002) (see Table 1) to better evaluate memory and attention abilities, respectively. Clinicians estimated depression through the UPDRS I–item 3 that ranges from 0 (normal) to 4 (severe depression), and we also computed a dichotomous score of 0 (no depression) or 1 (depression; for all patients with a score >0). Instrumental activities of daily living (IADL) and basic activities of daily living (ADL) self-report questionnaires were also administered (Lawton & Brody, 1969) (for patients affected by cognitive impairment they were administered to caregivers).

Cognitive reserve evaluation

During the same session, all participants received also the CR evaluation by:

(i) The Brief Intelligence Test (TIB), an Italian version (L. Colombo et al., 2002) of the National Adult Reading Test (NART) (Blair & Spreen, 1989; Nelson & Willison, 1991). It provides a good estimate of premorbid intelligence, and a score <93.1 is considered under the normal curve.

(ii) The CoRe-T (Cognitive Reserve Test) (Colombo et al., 2018), a tool including two main sections (self-report and creative tasks). Self-report data include education (years of completed education, including vocational training), occupation history, and leisure activities (a total of 17 activities). These activities are classified as creative (i.e., playing music, making art, attending arts events, etc.), cognitive (i.e., crosswords, using technology to look up information, taking care of the family budget, etc.), physical (i.e., exercising, gardening, practicing a sport, etc.), and

social (i.e., being part of a club, taking care of family members, attending social events, etc.). For each activity, participants were asked to rate the lifetime (before PD onset) frequency [based on an average week by a Likert-like scale from 1 (rarely/never) to 5 (often/every day)], and the highest consecutive number of years of performing that activity [on a Likert-like scale from 1 (1 year or less) to 3 (5 years or more)]. For patients affected by cognitive impairment, the self-report section was administered to caregivers. The mean score of the reported frequencies for all leisure activities listed in the CoRe-T was computed to get a total index. The mean frequency score for each leisure activities category was also calculated.

(iii) Two tasks commonly used to assess verbal creative abilities are included in the CoRe-T and constitute the second section of the test:

a. Acronyms (Guilford, 1967): Participants are given 5 minutes to list all the terms that can fit into the three given acronyms (SOS – OMG – TGIF). The words have to make sense together and did not have to correspond to any actual acronym. Only completely original answers (e.g., Sunny Optimistic Sisters or Operatic Musical Groups) were accepted as valid. The number of valid answers was computed to obtain a total fluidity score.

b. Alternative uses (Guilford, 1967; Torrance, 1990): Participants are given 5 minutes to list as many different, interesting, or unusual usages for an empty plastic bottle as they could. Two scores are computed: the number of valid answers (fluidity score) and an originality score. To compute the total originality score, each response was coded as original (1) or not original (0) according to the guidelines derived from the Torrance Test of Creative Thinking (Torrance, 1990). A final score was computed by adding the number of original answers.

c. An evaluation of how creative participants' main occupation was (creative job vs. non-creative job) was carried out for each participant considering the prevalent type of employment. Jobs were coded as creative if they were not routine tasks, required constant flexibility of thoughts, changes of perspective, and creation of innovative ideas/solutions (for example, lawyer vs. post office employer). Two independent raters (with previous experience in scoring results from the CoRe-T) were provided with a coding grid where the key variables to identify the job as creative (constant flexibility of thoughts, changes of perspective, and creation of innovative ideas/solutions) were listed. Each rater evaluated each job by assigning a score of 0 (this job does not require this, or it requires it to a minimum extent) or 1 (this is needed for this job, regularly). Jobs who scored 3 were classified as creative. The rare cases of disagreement were discussed between raters and resolved case by case. Inter-rater reliability, measured using Cohen's kappa coefficient, was good ($\kappa = .80$).

The Italian version of the CoRe-T was obtained from the English one using backward translation performed by two independent researchers.

Statistical analyses

Comparisons between groups were based on the Mann–Whitney *U* test for continuous variables, and the chi-squared test or, when appropriate, the Fisher exact test for categorical variables.

The impact of CR indices on cognitive performance or cognitive impairment (within the PD group) was explored through multivariate linear or logistic regression models, adjusting for those demographic and clinical variables showing a significant association at univariate analysis. CR indices were investigated in separate multivariate models. A power analysis was conducted a priori: in a regression analysis with three predictors and assuming a medium effect size (0.30), the power is >80% with a sample of 40 participants. All these analyses were performed using SPSS statistical software.

Furthermore, a series of explorative regressions were run to identify the variable that had the most substantial influence on the severity of motor disability in the PD group. Then, we explored the moderating role of CR in the relationship between the identified variable and motor impairment (UPDRS III score) using moderation models, performed through Jamovi statistical software.

A two-tailed p-value of <.05 was considered statistically significant.

Results

Study population's characteristics

Overall, the mean interval from diagnosis to enrollment was of 8.3 (SD = 5.5) years; the mean age at onset was 66.0 years (SD 7.8) (see Table 1 for clinical and neuropsychological characteristics). Seventeen patients (42.5%) had a left side motor onset and 18 (45%) a tremor dominant symptomatology. The majority of PD participants showed no limitations in functional activities, according to ADL and IADL scores.

PD and HC groups were not matched at MOCA performance (p = .010). When comparing the two subgroups of patients (cognitively unimpaired vs. impaired), participants with cognitive impairment showed: Higher age (p = .007), lower ADL (p = .003), and IADL scores (p < .001), more severe motor disability (higher UPDRS III score, p < .001), and worse neuropsychological performance not only at MOCA (p = .002) but also at Babcock (p = .004) and Stroop test (time) (p = .043). To be more specific, 21 patients (52.5%) obtained a pathological performance at the Babcock test (cut off = 15.76), 8 (20%) and 18 (45%) scored below the normative cutoff at Stroop test time (cut off = 36.91) and errors (cut off = 4.23), respectively.

Cognitive reserve and cognition in study groups

The comparison between PD and HC groups across all CR indices is shown in Table 2. They were comparable in all Core-T measures, except for a higher frequency of cognitive activities (p = .041) and a better alternative use fluidity (p = .004) and originality (p = .015) in the controls. PD group obtained a mean TIB score of 103.52 (SD 12.75) vs. 107.98 (SD 9.12) (p = .362) in the HC group.

Analyzing the effects of CR on MOCA performance (raw score) in the total study population, we found that many CR indices were significantly associated with the MOCA score, adjusting for group belonging and age (Table 3). In other words, participants with higher CR obtained a better MOCA score irrespective of the group they belonged to. At the same time, regardless of the CR level, the performance of the HC group was always better in comparison to the PD group. In particular, we found a significant association

Table 2. Cognitive reserve comparison between PD and HC groups.

CR measures	PD (N = 40) mean (sd)	HC (N = 12) mean (sd)	P
CoRe-T			
Cognitive activities	2.49 (0.96)	3.11 (0.69)	.041
Creative activities	2.41 (1.05)	2.77 (0.69)	.135
Physical activities	2.71 (0.94)	2.64 (0.80)	.869
Social activities	2.80 (0.85)	3.14 (0.91)	.231
Total leisure activities	2.60 (0.67)	2.95 (0.52)	.145
Alternative use originality	1.15 (1.61)	2.00 (1.35)	.015
Alternative use fluidity	1.72 (2.11)	3.33 (1.67)	.004
Acronym fluidity	2.30 (3.07)	3.67 (2.57)	.101
Creative job*	13 (32.5%)	4 (33.3%)	1.00
TIB	103.52 (12.75)	107.98 (9.12)	.362

Notes: * Number (%).
PD: Parkinson disease; HC: Healthy controls; TIB: Brief Intelligence Test;
CR: Cognitive reserve; sd: standard deviation; CoRe-T: Cognitive Reserve Test.

Table 3. Impact of each cognitive reserve index on MOCA performance in the total study population.

Variables	B	95% CI	P
Education	.40	.39; .76	.031
Group	4.53	.99; 8.07	.013
Age	−4.01	−6.13; −1.17	.001
Cognitive activities	2.27	.57; 3.98	.010
Group	3.21	−.38; 6.81	.079
Age	−.37	−.60; −.13	.003
Creative activities	2.29	.40; 4.19	.019
Group	4.12	.60; 7.64	.023
Age	−.26	−.53; .02	.067
Physical activities	1.06	−.73; 2.85	.240
Group	4.70	1.02; 8.39	.013
Age	−.41	−.66; −.17	.001
Social activities	1.21	−.90; 3.32	.255
Group	4.36	.67; 8.04	.021
Age	−.36	−.64; −.08	.014
Total leisure activities	4.04	1.4; 6.65	.003
Group	3.66	.23; 7.09	.037
Age	−.23	−.49; −.03	.026
Use originality	.90	−.22; 2.02	.114
Group	4.08	.42; 7.74	.030
Age	−.34	−.61; −.07	.016
Alternative use fluidity	.81	−.08; 1.71	.074
Group	3.65	−.06; 7.36	.054
Age	−.30	−.58; −.02	.036
Acronym fluidity	.99	.46; 1.05	<.001
Group	3.82	.57; 7.08	.022
Age	−.24	−.48; −.02	.048
Creative job	2.05	−1.23; 5.32	.215
Group	4.45	.79; 8.11	.018
Age	−.44	−.68; −.20	.001
TIB	.20	.08; .32	.002
Group	3.48	.01; 6.94	.049
Age	−.36	−.58; −.13	.002

Notes: Group was a dichotomous variable: 1 (PD group) vs. 2 (HC group).
Each cognitive reserve index was investigated in a separate regression model. Cognitive reserve indices and significant p values are in bold.
CI: Confidence interval; TIB: Brief Intelligence Test.

between MOCA and all CR indices, except for social and physical activities frequency, alternative use (both fluidity and originality), and job creativity (Table 3).

Focusing on the PD group, we also analyzed the associations between CR indices and the performance obtained at Babcock and Stroop tests (raw scores). To be more specific, we observed that a better performance at Babcock test was associated to higher education (B = 0.66, 95% CI .47–1.28, p = .036), creative activity frequency (B = 5.00, 95% CI 1.39–8.61, p = .008) and creative job (B = 6.71, 95% CI 1.03–12.40, p = .022), after adjusting for age and UPDRS III; a better performance at Stroop test (time) was associated with total (B = −13.65, 95% CI −26.22; −1.07, p = .034) and cognitive (B = −7.94, 95% CI −15.62; −.25, p = .043) leisure activity frequency, after adjusting for age, UPDRS III, and tremor dominant subtype. Fewer errors in the Stroop test were associated to TIB score (B = −2.11, 95% −3.99; −.023, p = .029), acronym fluidity (B = −1.21, 95% −1.95; −.46, p = .002), alternative use fluidity (B = −1.49, 95% CI −2.61; −.28, p = .017), and alternative use originality (B = −1.75, 95% CI −3.37; −.13, p = .035).

Cognitive reserve impact on cognitive impairment in the PD group

The associations between CR indices and cognitive impairment (according to UPDRS I–item 1) in the PD group are shown in Table 4. Each CR measure was analyzed in a separate multivariate logistic regression model, including also age and UPDRS III score (motor disability), two variables showing a significant association at univariate analysis. Given the high number of independent regressions, we used the Holm-Bonferroni formula HB = Target α/(n − rank + 1) to test the validity of our hypotheses and their associated p-values at an alpha level of .05, considering the 33 independent regressions we run. All the significant p values up to p = .04 allowed us to reject the null hypothesis safely.

We found that a higher frequency of the total leisure activities was independently associated with being cognitively unimpaired (OR .13; p = .040). A near significant negative association with cognitive impairment was also found for creative (OR .30; p = .058) and social (OR .32; p = .079) activities frequency. No association was observed with education. Notably, the severity of motor disability confirmed in all regression models the association with a higher risk of cognitive impairment.

Cognitive reserve and motor impairment

Age at diagnosis was the factor that showed the most substantial influence on the severity of motor disability in the PD group. Then, we explored if CR-related variables could moderate the relation between age at diagnosis and motor impairment. For simplicity, only the analyses of CR-related variables revealing significant effects of interest are listed below:

Frequency of performing creative activities

Age at diagnosis and the severity of motor disability were entered in the first step of the regression analysis. The interaction term (frequency of performing creative activities) was entered the second step of the regression analysis: It explained a significant increase in variance in the severity of the motor disability, $\Delta R^2 = .09$, $F(1, 37) = 3.91$, $p = .04$. Thus, the

Table 4. Effects of each cognitive reserve index on cognitive impairment in PD group.

Variables	OR	95% CI	P
Education	.93	.75; 1.16	.521
UPDRS III	1.17	1.04; 1.33	.008
Age	1.07	.94; 1.21	.305
Cognitive activities	.48	.17; 1.37	.171
UPDRS III	1.19	1.05; 1.36	.007
Age	1.04	.92; 1.19	.520
Creative activities	.30	.09; 1.04	.058
UPDRS III	1.25	1.06; 1.48	.008
Age	.94	.79; 1.13	.543
Physical activities	.74	.27; 2.03	.558
UPDRS III	1.16	1.03; 1.30	.012
Age	1.08	.95; 1.23	.243
Social activities	.32	.09; 1.14	.079
UPDRS III	1.19	1.05; 1.34	.012
Age	1.01	.87; 1.17	.872
Total leisure activities	.13	.02; .91	.040
UPDRS III	1.23	1.06; 1.42	.008
Age	.97	.82; 1.13	.678
Alternative use originality	.67	.33; 1.34	.256
UPDRS III	1.20	1.05; 1.37	.007
Age	1.02	.87; 1.20	.787
Alternative use fluidity	.75	.43; 1.33	.333
UPDRS III	1.18	1.05; 1.34	.007
Age	1.02	.87; 1.20	.787
Acronym fluidity	.80	.58; 1.09	.159
UPDRS III	1.19	1.05; 1.36	.007
Age	1.03	.89; 1.18	.723
Creative job	.89	.15; 5.37	.904
UPDRS III	1.17	1.04; 1.32	.009
Age	1.08	.95; 1.22	.246
TIB	1.01	.95; 1.08	.668
UPDRS III	1.17	1.04; 1.31	.008
Age	1.08	.95; 1.23	.247

Notes: Each cognitive reserve index was investigated in a separate regression model.
Cognitive reserve indices and significant p values are in bold.
OR: Odds ratio; CI: Confidence interval; UPDRS: Unified Parkinson's Disease Rating Scale;
TIB: Brief Intelligence Test.

frequency of performing creative activities was a significant moderator of the relationship between age at diagnosis and the severity of the motor disability. The unstandardized simple slope for patients 1 SD below the mean of frequency of performing creative activities was .08 (p = .01), the unstandardized simple slope for patients with a mean level of frequency of performing creative activities was .51 (p = .03). The unstandardized simple slope for patients 1 SD above the mean of frequency of performing creative activities was .19 (p = .50) (see Figure 1a).

Frequency of performing physical activities

Age at diagnosis and the severity of motor disability were entered in the first step of the regression analysis. The interaction term (frequency of performing physical activities) was entered in the second step of the regression analysis: It explained a significant increase in variance in the severity of the motor disability, $\Delta R^2 = .13$, $F(1, 37) = 5.57$, $p = .02$. The frequency of performing physical activities was a significant moderator of the relationship

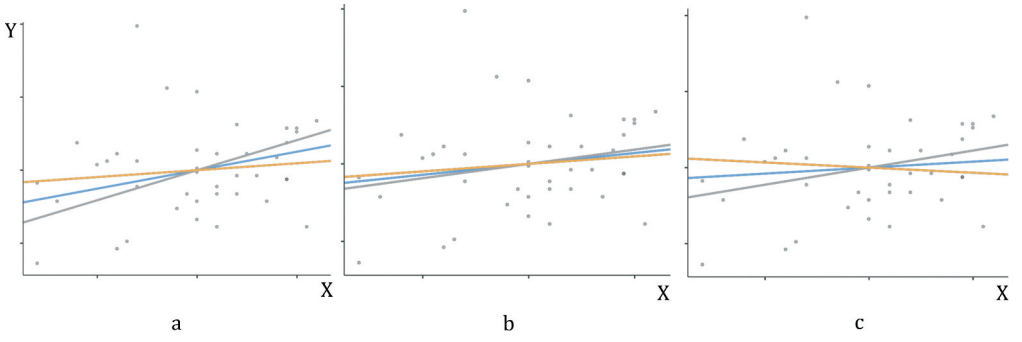

Figure 1. Cognitive reserve moderation of severity of motor impairment. Simple slope analyses model. X = Age at diagnosis; Y = UPDRS III score; Blue line: average; Grey line: low (- 1 SD); Yellow line: high (+ 1 SD). (a) Interaction term: frequency of performing creative activities; (b) interaction term: frequency of performing physical activities; (c) interaction term: frequency of performing social activities.

between age at diagnosis and the severity of the motor disability. The unstandardized simple slope for patients 1 SD below the mean of frequency of performing physical activities was .37 (p = .22), the unstandardized simple slope for patients with a mean level of frequency of performing physical activities was .28 (p = .24). The unstandardized simple slope for patients 1 SD above the mean of frequency of performing physical activities was .19 (p = .54) (see Figure 1b).

Frequency of performing social activities

Age at diagnosis and the severity of motor disability were entered in the first step of the regression analysis. The interaction term (frequency of performing social activities) was entered in the second step of the regression analysis: It explained a significant increase in variance in the severity of the motor disability, ΔR^2 = .11, F(1,37) = 4.95, p = .03. The frequency of performing social activities was a significant moderator of the relationship between age at diagnosis and the severity of the motor disability. The unstandardized simple slope for patients 1 SD below the mean of frequency of performing physical activities was .45 (p = .53), the unstandardized simple slope for patients with a mean level of frequency of performing physical activities was .16 (p = .26). The unstandardized simple slope for patients 1 SD above the mean of frequency of performing physical activities was −.13 (p = .64) (see Figure 1 c).

Discussion

The present study aimed to explore CR as a protective factor in PD-related cognitive impairment. As could be expected based on results from previous studies (Ciccarelli et al., 2018; Cohen et al., 2007; Guzzetti et al., 2019), we found a significant positive association between CR and global cognitive performance, both in patients with PD and in comparable healthy controls. The same prior studies also highlighted an effect of CR especially on neuropsychological tests sensitive to frontal lobe dysfunction. We did not administer a comprehensive neuropsychological battery. Still, a significant correlation was observed

between CR and MOCA, a screening test that has shown to be more sensitive than the Mini-Mental State Examination (MMSE) in detecting PD-related cognitive impairment for a greater emphasis on frontal executive functions and attention (Zadikoff et al., 2008).

Thus, our main results support previous evidence that CR might help to cope with PD cognitive deterioration. However, at the same level of CR, PD participants also showed a worse performance compared to healthy controls, suggesting that CR could only in part protect from cognitive decline and, most likely, it has a noticeable effect only on a slight or moderate level of brain atrophy (Rouillard et al., 2017).

A strength of our investigation, in comparison with the majority of previous studies on patients with PD, was to consider CR as a multidimensional construct. To do so, we used a new comprehensive tool, the CoRe-T (Colombo et al., 2018). On top of recording education and occupational history, the CoRe-T collects information about the type and frequency of leisure activities (with the possibility of a global score) that participants practice. This kind of information can also be collected by using another recent comprehensive tool – the Cognitive Reserve Index (CRI) questionnaire (Nucci et al., 2012). The unique feature of the CoRe-T is the addition of two creative tasks (generation of acronyms and alternative uses task). We also used information about occupational history differently by computing an index of how creative participants' main occupation was. This is relevant since a positive association between CR and creativity has been previously reported in the literature (Antonietti & Colombo, 2013; Palmiero et al., 2016). In our study, we found a positive association between global cognitive performance and both performing creative activities and the generation of acronyms in all of our participants. When focusing exclusively on the PD group, we also found a positive association between learning and job creativity, and between attention and alternative uses fluidity and originality. These results confirm that also creativity is a multidimensional construct.

Notably, both in PD and HC groups, the general cognitive profile was associated not only with education and premorbid intelligence but also with performing creative and cognitive leisure activities. At the same time, no association was observed with social and physical activities. These results are partially consistent with a previous study (Rouillard et al., 2017) reporting no association between cognition and performing physical activities. A possible explanation proposed by the authors is that the positive effects of physical activity would not persist if subjects stopped practicing it. Our data suggest another possible reason. By exploring the data at a deeper level, we found that performing physical activities, in addition to social and creative ones, had a moderating effect on the association between age at PD diagnosis and severity of motor impairment. Thus, different activities might be involved in the protection of different brain networks. Further evidence of the role of CR as protection on both motor and cognitive dysfunctions in PD is reported by Guzzetti et al. (2019). The authors claimed that, although motor functions subtend peripheral components, they also involve distributed brain networks that support movement planning and control, which might be influenced by cognitively stimulating activities.

In contrast with Rouillard et al. (2017), we found no association between global cognitive performance and work activity in healthy participants, but only a positive association between memory and occupation in the PD group. However, this difference could be explained by the use of different criteria to evaluate occupation. In particular, in the previous study, the authors considered the decisional latitude (autonomy) and

the psychological job demand (i.e., the quantity of work, stress), while we measured another occupation dimension as the job creativity. These data seem to suggest that the relation between job activities and cognition could be related to different and conflicting job-defining properties. Furthermore, analysis on data from the British 1946 birth cohort to model lifetime antecedents of CR showed independent paths from childhood cognition, educational attainment, and adult occupation to CR, with evidence that childhood cognition is the most substantial factor, while adult occupation the weakest (Richards & Sacker, 2003); also, the direct influence of paternal occupation on CR appeared negligible, and mediated by childhood cognitive ability and educational attainment.

Due to few available longitudinal data, the effects of CR in delaying cognitive impairment and dementia are still not clear (Hindle et al., 2016, 2014; Lee et al., 2019; Muslimović et al., 2007; Poletti et al., 2011). Most likely, high CR does not protect individuals from developing neurodegenerative and vascular neuropathologies, but it could mitigate the impact of the pathology on the clinical expression of dementia before death (EClipSE et al., 2010; Roe et al., 2007). Our study is cross-sectional, but a critical strength was to select only patients with no documented cognitive complaints at the time of PD diagnosis. A remarkable result was to find that a higher frequency of performing leisure activities was associated with being cognitively unimpaired after a mean PD history of 8 years, while no correlation was found with education. Consistently with our data, in a longitudinal survey on PD, the development of dementia resulted correlated to older age, more severe motor impairment, and low levels of social engagement, but not to education (Hindle et al., 2016). However, a reduction in social activities could be the consequence of cognitive decline, rather than an index of social lifestyle. For this reason, in our study we assessed the frequency of leisure activities before PD onset.

This study presents some limitations. First of all, our population was recruited only from one clinical center accessed by people from the same socio-cultural background. Data from different cultural and socio-economical backgrounds should be collected. A second limitation is that the CoRe-T is a not standardized tool; however, across CR studies, the use of not standardized measures as CR proxy is common. Moreover, we also collected a small matched control group as an additional reference to data collected from our clinical sample. Another methodological limitation was that our database included only a brief screening method, the UPDRS I–item 1, as routine cognitive evaluation. Finally, although we selected only patients affected by PD with no cognitive impairment at the onset and balanced the final group according to developing or not cognitive impairment, our study design is cross-sectional, and further longitudinal studies are needed.

Conclusions

Available data suggest that it is challenging to try to disentangle the specific implication of each CR index in cognitive protection, due to several reasons. The main reasons are the high inter-correlation between CR factors and the possible different approaches in their assessing that could generate different results across studies. Probably, different CR proxies share an underlying process but each additionally provides a unique contribution to CR (Opdebeeck et al., 2013). Our study confirmed the multidimensional nature of CR,

particularly the importance of considering the engagement in cognitively stimulating leisure activities and its association with both normal and pathological cognitive decline. Moreover, our data corroborate previous evidence that a higher level of CR might help to cope also with PD motor impairment. For this reason, considering all its possible lifetime antecedents could help to implement specific and efficient prevention and rehabilitation strategies in PD or other neurodegenerative pathologies.

Creativity appears another critical factor worth being better explored as one of CR components and could also inspire potential neurorehabilitation approaches.

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