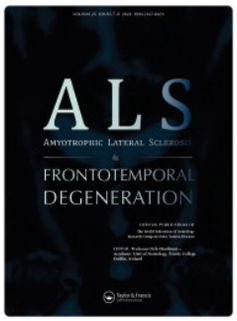

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iafd20

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To cite this article: Andrea Rosano, Manuel Bicaj, Marta Cillerai, Marta Ponzano, Corrado Cabona, Chiara Gemelli, Claudia Caponnetto, Matteo Pardini, Alessio Signori, Antonio Uccelli, Angelo Schenone & Pilar M. Ferraro (2024) Psychological resilience is protective against cognitive deterioration in motor neuron diseases, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 25:7-8, 717-725, DOI: 10.1080/21678421.2024.2385690

To link to this article: https://doi.org/10.1080/21678421.2024.2385690

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2024; 25: 717–725

RESEARCH ARTICLE

Psychological resilience is protective against cognitive deterioration in motor neuron diseases

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Abstract

Objectives: Recent studies suggest that psychological resilience (PR) is associated with more well-preserved cognition in healthy subjects (HS), but an investigation of such phenomenon in patients with motor neuron diseases (MNDs) is still lacking. The aim of our study was therefore to evaluate PR and its relationship with baseline cognitive/behavioral and mood symptoms, as well as longitudinal cognitive functioning, in MNDs. *Methods*: 94 MND patients and 87 demographically matched HS were enrolled. PR was assessed using the Connor-Davidson Resilience Scale (CD-RISC). Patients were further evaluated both at baseline and every 6 months for cognitive/behavioral disturbances using the Edinburgh Cognitive and Behavioral ALS Screen (ECAS), and for mood symptoms using the Hospital Anxiety and Depression Scale (HADS). CD-RISC scores were compared between patients and HS using the Mann–Whitney *U* test, and regression models were applied to evaluate the role of CD-RISC scores in predicting baseline cognitive/behavioral and mood measures, as well as longitudinal cognitive performances, in MND patients. *Results*: MND cases showed significantly greater PR compared to HS (p from <0.001 to 0.02). In MNDs, higher PR levels were significant predictors of both greater cognitive performance (p from 0.01 to 0.05) and milder mood symptoms (p from <0.001 to 0.04) at baseline, as well as less severe memory decline (p from 0.001 to 0.04) longitudinally. *Conclusions*: PR is an important protective factor against the onset and evolution of cognitive/mood disturbances in MNDs, suggesting the usefulness of resilience enhancement psychological interventions to prevent or delay cognitive and mood disorders in these neurodegenerative conditions.

Keywords: *Motor neuron diseases, psychological resilience, cognitive/behavioral impairment, longitudinal study*

Introduction

Psychological resilience (PR) is defined as the human capacity to overcome adverse events using individual and social resources, and to use crises as an incentive for personal growth.

PR can therefore be viewed as a measure of stress coping ability (1) which is thought to arise from a combination of personality-related, genetic, biological as well as environmental factors (2) and, most notably, this multidimensional feature can be improved with treatment (1).

Given the well-known association between neuropsychiatric diseases, depression in particular, and progressive cognitive deterioration (3), an increasing number of studies are now focusing on factors which may prevent the emergence of mental illnesses after adverse events, PR in particular.

The most recent investigations have observed that PR is significantly associated with more well-

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21678421.2024.2385690.

(Received 24 January 2024; revised 14 July 2024; accepted 22 July 2024)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2024.2385690

preserved cognitive functioning in middle-aged and old cognitively normal adults (4,5).

Additionally, a recent work from Son and colleagues (6) has demonstrated that PR is further associated with enhanced functional connectivity of the orbitofrontal network in mild cognitive impairment, suggesting that PR focused interventions during the presymptomatic period may be promising tools to promote the efficient arrangement of functional network connections, and therefore contribute to prevent cognitive deterioration in this neurodegenerative condition.

Despite these considerations, similar works exploring the association between PR and cognitive status in amyotrophic lateral sclerosis (ALS) and other motor neuron diseases (MNDs) are still lacking, even if it is well-known that up to 50% of patients manifest cognitive and/or behavioral changes (7) reaching overt frontotemporal dementia (FTD) in 5 to 22% of cases (8).

The vast majority of studies investigating PR in MNDs have indeed rather focused on coping strategies and resilience factors. As regards coping strategies, it has been shown that these are various and may change over time. Jakobsson Larsson and colleagues observed that support and independence were the most used coping strategies in patients with ALS, while information seeking was more rarely used and decreased over time (9), a finding in line with other works reporting progressive behavioral disengagement (10).

Further studies have identified additional coping strategies in ALS patients, such as rumination and religiosity (11), seeking support from families and technological devices (12), acceptance, active coping, planning, positive re-interpretation and growth (13).

Concerning resilience factors, diverse mechanisms to promote positive adjustment to the disease have been identified, including hope, optimism, social problem solving, spirituality, social support, and relationship satisfaction (14).

However, it is noteworthy mentioning that the use of construct-specific validated measures to evaluate PR, such as the Connor-Davidson resilience scale (CD-RISC), has been scarce in ALS and other MNDs.

To our knowledge, indeed, only two studies have specifically investigated resilience in these pathologies using such instruments (15,16). The work by Kullmann and colleagues reported higher PR levels in ALS patients compared to a large group of healthy controls, but a subsequent investigation of possible associations between PR and non-motor symptoms was absent. The work by Demuru and colleagues examined the association between PR and mood symptoms, evidencing a significant negative correlation, but did not investigate the relationship between PR and cognitive/behavioral symptoms.

In this context, the aims of the present study were therefore to: a) apply a validated instrument, the CD-RISC, to compare PR levels between patients with MNDs and healthy subjects (HS), b) investigate possible associations, in MND cases, between PR levels, cognitive/behavioral and mood features at symptoms onset, and c) test whether greater PR levels may also have a protective role against longitudinal cognitive deterioration in MNDs.

Materials and methods

Participants

A total of 94 MND patients (47 patients with classic ALS, 17 patients with a clinical pure/predominant upper motor neuron (pUMN) phenotype, and 30 patients with a clinical pure/predominant lower motor neuron (pLMN) LMN phenotype) were consecutively recruited at our referral MND Clinic.

Inclusion criteria for MND patients were: a) absence of overt frontotemporal dementia according to current diagnostic criteria (17), and b) absence of comorbid psychiatric conditions (as ascertained from clinical interview and anamnesis evaluation).

Diagnosis of classic ALS was made according to the revised Escorial criteria (18). PUMN (including primary lateral sclerosis and pyramidal phenotypes) and pLMN (including pure LMN, flail arm and flail leg phenotypes) cases were defined according to current classifications (19).

At study entry, all patients underwent a comprehensive evaluation including neurological history, neurophysiological assessment, clinical, cognitive/behavioral and mood examinations.

Experienced neurologists performed all the clinical examinations. The site of disease onset and disease duration were recorded. Disease severity was assessed using the ALS Functional Rating Scale-revised (ALSFRS-r) (20), and the rate of baseline disease progression was calculated as follows: (48 - ALSFRS-r score at the time of examination)/months from symptoms onset to examination.

Experienced neuropsychologists performed all the cognitive/behavioral and mood examinations.

Cognitive and behavioral symptoms were evaluated using the Italian version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) (21,22). Anxiety and depression were assessed using the Italian version of the Hospital Anxiety and Depression Scale (23), with the following modifications in our study to adjust for motor impairment: HADS Depression item 8 "I feel as if I am slowed down" was reformulated as: "I feel as if I am mentally fatigued" and HADS Anxiety item 11 "I feel restless as I have to be on the move" was reformulated as: "I feel restless as I have difficulties in concentrating and I am not able to relax."

Patients were then followed longitudinally with cognitive/behavioral and mood examinations

approximately every 6 months, for up to 46 months.

An additional sample of 87 demographically matched HS was recruited among spouses of patients and by word of mouth. The inclusion criterion for HS was the absence of any psychiatric and/or neurological disorder (as ascertained from clinical interview, neurological assessment, and absence of any impairment in daily life activities).

Resilience was evaluated both in MND patients and HS using the 10-items Italian version of the Connor-Davidson Resilience Scale (CD-RISC 10) (1, 24). This unifactorial scale consists of 10 statements which respondent rate on a 5-point scale from "strongly disagree" to "strongly agree."

Each item describes different components of resilience, respectively: 1) the ability to adapt to change, 2) the ability to deal with obstacles, 3) the ability to see the humorous side of problems, 4) the ability to feel strengthened after coping with stress, 5) the ability to recover quickly after hardships, 6) the ability to achieve goals despite difficulties, 7) the ability to stay focused under pressure, 8) the ability to not get easily discouraged by failure, 9) the ability to consider itself as a strong person, and 10) the ability to handle unpleasant feelings.

Answers are scored from 0 to 4 to reach a total score ranging from 0 to 40, with higher numbers denoting greater resilience. MND patients were asked to provide responses they would have given to the statements *before* their diagnosis.

Approval of the institutional review board (Comitato Etico Regionale della Liguria) and written informed consent from all participants were obtained. The study was conducted in agreement with the Declaration of Helsinki.

Statistical analyses

All data were analyzed using CRAN R Version 3.4.1. Cronbach's alpha was used to evaluate the internal consistency of the CD-RISC 10 and HADS questionnaires in our MND sample. According to current references (25), Cronbach's alpha values ≥ 0.9 were considered "excellent"; between < 0.9 and ≥ 0.8 "good"; between < 0.8 and ≥ 0.7 "acceptable"; between < 0.7 and ≥ 0.6 "questionable"; between < 0.6 and ≥ 0.5 "poor"; < 0.5 "unacceptable."

Normal distribution assumption was checked by means of Shapiro–Wilk test and graphically. Accordingly, demographic/clinical features and CD-RISC 10 scores were compared between MND patients and HS using Mann–Whitney *U* test (for not normally distributed numeric data), *T* test (for normally distributed numeric data) and Chi-squared test (for categorical data), as appropriate.

Correlations between item/subscale-based and total scores for the CD-RISC 10 and were evaluated using the Spearman correlation coefficient.

Linear regression models were then used to evaluate the role of CD-RISC 10 scores in predicting baseline cognitive/behavioral and mood measures in MND patients.

In exploratory analyses, using as a cutoff the median CD-RISC 10 score, MND patients were further classified as MND with low CD-RISC 10 scores, referred to as "MND low resilience," and MND with high CD-RISC 10 scores, referred to as "MND high resilience," and differences in demographic and clinical features between the two groups were analyzed using Mann–Whitney *U* test (for not normally distributed numeric data), *T* test (for normally distributed numeric data) and Chi-squared test (for categorical data), as appropriate.

Based on longitudinal data, relative deltas of variations (adjusted for the time interval between examinations) were generated for each ECAS-derived cognitive measure (calculated as: score on last available follow-up—baseline score/baseline score)/months between last available follow-up and baseline evaluation. Linear regression models were then used to test the role of CD-RISC 10 scores in predicting longitudinal rates of cognitive decline.

To account for multiple comparisons, an additional adjustment for false discovery rate (FDR) using the Benjamini & Hochberg method (26) was applied to assess which baseline and longitudinal associations remained significant after correction.

Results

Internal consistency of the CD-RISC 10 and HADS questionnaires

In our MND sample, the CD-RISC 10 questionnaire showed an internal consistency classifiable as "good," with a Cronbach's alpha of 0.85 and confidence intervals **(CI)** ranging from 0.75 to 0.90, and the HADS scale showed an internal consistency classifiable as "acceptable," with a Cronbach's alpha of 0.77 and CI ranging from 0.64 to 0.85 (HADS depression subscale Cronbach's alpha = 0.71, CI from 0.58 to 0.79; HADS anxiety subscale Cronbach's alpha = 0.71, CI from 0.59 to 0.78).

Cross-sectional findings

PR levels in MNDs. Demographic features of MND patients and HS, as well as clinical features of MND patients, are reported in Table 1. MND cases and HS were matched in terms of age ($p = 0.27$), gender ($p = 0.13$) and education ($p = 0.62$).

MND patients exhibited significantly higher CD-RISC 10 scores compared to HS (CD-RISC 10 total median score: 31.00 *vs* 25.00, $p < 0.0001$; CD-RISC 3 median score 3.00 *vs* 2.00, $p = 0.0008$; CD-RISC 5 median score 4.00 *vs* 3.00, $p = 0.001$; CD-RISC 6 median score 4.00 *vs* 3.00, $p = 0.001$; CD-RISC 7 median score 3.00 *vs* 2.00, $p = 0.001$; CD-RISC 8

Table 1. Demographic and clinical features of HS and MND patients.

	HS	All MND patients	p^*	MND low resilience	MND high resilience	p^{**}
N	87	94	–	51	43	–
Age (years)	65.23 ± 7.40	66.82 ± 11.50	0.27	65.92 ± 11.96	67.95 ± 10.94	0.40
Gender (M/F)	44/43	59/35	0.13	29/22	30/13	0.28
Education (years)	11.00 (5.00)	11.50 (5.00)	0.62	11.00 (5.00)	13.00(5.00)	0.73
Site of onset (spinal/bulbar/respiratory)	–	76/15/3	–	42/8/1	34/7/2	0.75
Disease duration (months)	–	24.00(33.00)	–	28.00(35.75)	16.50(23.00)	0.08
Clinical phenotype (ALS/pLMN/pUMN)	–	47/30/17	–	24/15/12	23/15/5	0.36
ALSFRS-r score (0–48) ⇑	–	39.50(9.25)	–	38.50(10.50)	40.50(8.75)	0.89
ALSFRS-r rate of progression (points/month) ⇓	–	0.36(0.39)	–	0.34 (0.34)	0.36(0.60)	0.22
Cognitive phenotype (motor/ALS-CBI)	–	72/22	–	39/12	33/10	1.00
ECAS language functions (0–28) ⇑	–	25.97 (3.74)	–	25.40(4.35)	26.05(2.61)	0.23
ECAS verbal fluency (0–24) ⇑	–	19.99(6.31)	–	19.99(6.19)	21.09(6.53)	0.40
ECAS executive functions (0–48) ⇑	–	38.97(7.05)	–	38.31(6.13)	39.76 (7.27)	**0.02**
ECAS ALS specific functions (0–100) ⇑	–	83.68(14.00)	–	82.24(13.40)	85.71 (13.56)	**0.04**
ECAS memory functions (0–24) ⇑	–	16.46(4.25)	–	15.25(4.87)	16.93 (4.47)	**0.01**
ECAS visuospatial functions (0–12) ⇑	–	11.90 (0.75)	–	11.87 (0.64)	12.14 (0.87)	0.06
ECAS ALS nonspecific functions (0–36) ⇑	–	28.21(4.22)	–	27.25(4.50)	29.21(3.05)	**0.002**
ECAS total (0–136) ⇑	–	111.32(15.23)	–	109.15(12.86)	114.33(15.95)	**0.008**
ECAS Carer behavior screen (0–10) ⇓	–	0.00(0.00)	–	0.00(0.00)	0.00(0.00)	0.99
HADS total (0–42) ⇓	–	7.00(8.50)	–	9.00 (8.25)	5.00 (6.50)	**0.001**
HADS depression (0–21) ⇓	–	3.00 (4.00)	–	3.00(4.00)	3.00(4.00)	**0.03**
HADS anxiety (0–21) ⇓	–	4.00 (5.00)	–	5.00 (5.25)	2.00 (3.50)	**0.0007**

Note: Values are given as mean ± standard deviations for normally distributed numeric variables; median (interquartile range) for not normally distributed numeric variables; and absolute frequencies for categorical variables. *P* values refer to Mann–Whitney U/*t*-test or chi-squared test, as appropriate. p^* all MND patients vs HS; p^{**} MND low resilience vs MND high resilience. Significant *p* values (≤0.05) are reported in bold. ⇑: greater score: milder symptoms; ⇓ greater score: more severe symptoms.

ALS: amyotrophic lateral sclerosis; ALSFRS-r: Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; CBI: either cognitive or behavioral impairment or both; ECAS: Edinburgh Cognitive and Behavioral ALS Screen; F: female; HADS: Hospital Anxiety and Depression Scale; HS: healthy subjects; M: male; MND: motor neuron disease; pLMN: pure/predominant lower motor neuron; pUMN: pure/predominant upper motor neuron.

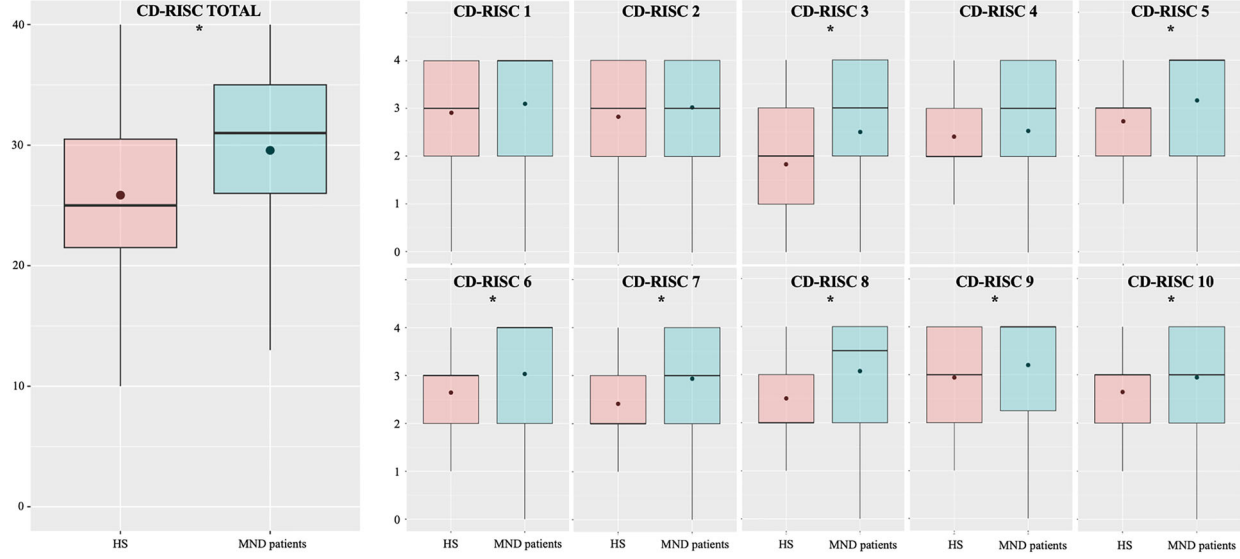

Figure 1. Boxplots showing median (bold black lines) and mean (black dots) values of CD-RISC 10 scores in HS (light red) and MND patients (light blue). *Note*: Significant *p* values (≤0.05) are signed with an asterisk. CD-RISC: Connor-Davidson Resilience Scale; HS: healthy subjects; MND: motor neuron disease.

median score 3.50 *vs* 2.00, $p < 0.0001$; CD-RISC 9 median score 4.00 *vs* 3.00, $p = 0.02$; CD-RISC 10 median score 3.00 *vs* 3.00, $p = 0.02$) (Figure 1). No significant differences were observed between the two groups for the CD-RISC 1, CD-RISC 2 and CD-RISC 4 items (Figure 1).

Associations between item/subscale-based and total scores and between subscales scores. Results of the correlation analyses between item/subscale-based and total scores for the CD-RISC 10 and HADS scales, and between HADS anxiety and depression subscales scores are shown in

Supplementary Table 1. Spearman correlation coefficients ranged from 0.54 to 0.83 ($p < 0.0001$) for the association between CD-RISC 10 item-based and total scores, and from 0.86 to 0.89 ($p < 0.0001$) for the association between HADS anxiety/depression subscale-based and total scores. HADS anxiety and depression subscales scores showed a Spearman correlation coefficient of 0.57 ($p < 0.0001$).

Relationship between PR levels and baseline cognitive/behavioral and mood symptoms in MNDs. As regards the associations between PR levels and baseline cognitive measures, greater CD-RISC 10 total, CD-RISC 4, CD-RISC 5, CD-RISC 8, and CD-RISC 9 scores were associated with higher ECAS memory, and therefore also higher ECAS ALS nonspecific functions, scores (p from 0.01 to 0.05), while greater CD-RISC 5 scores were associated with higher ECAS executive functions scores ($p = 0.03$) (Table 2).

Concerning the associations between PR levels and baseline mood symptoms measures, greater CD-RISC 10 total, CD-RISC 3, CD-RISC 5, CD-RISC 7, CD-RISC 8, CD-RISC 9 and CD-RISC 10 scores were associated with lower HADS total as well as HADS anxiety and depression scores (p from <0.0001 to 0.03) (Table 2). Almost all these associations remained significant after FDR correction for multiple comparisons (Table 2).

No significant associations were observed between PR levels and baseline behavioral symptoms (Table 2).

Comparison between "MND low resilience" and "MND high resilience" groups. Demographic and clinical features of the whole MND sample stratified by the CD-RISC 10 score are reported in Table 1. Using the median split, fifty-one patients were categorized as "MND low resilience", and 43 as "MND high resilience" (Table 1).

In exploratory analyses comparing the two groups, we found that MND high resilience patients exhibited greater performances on the ECAS Total ($p = 0.008$) as well as ECAS Executive functions ($p = 0.02$), ECAS ALS Specific functions ($p = 0.04$), ECAS Memory functions ($p = 0.01$), and ECAS ALS Nonspecific functions ($p = 0.002$) domains. Additionally, MND high resilience cases manifested significantly lower HADS Total ($p = 0.001$), HADS Depression ($p = 0.03$) and HADS Anxiety ($p = 0.0007$) scores (Table 1). No significant differences emerged between the two groups in terms of behavioral symptoms severity.

Longitudinal findings. Of the whole sample, 9 cases (9.56%) were deceased before the first longitudinal examination, 12 cases (12.77%) dropped out from the study due to increasing disability, and 31 cases (32.97%) were not yet in the 6-

Table 2. Results of the regression analyses linking CD-RISC scores to baseline cognitive, behavioral and mood features in MND patients.

	CD-RISC TOT	CD-RISC 1	CD-RISC 2	CD-RISC 3	CD-RISC 4	CD-RISC 5	CD-RISC 6	CD-RISC 7	CD-RISC 8	CD-RISC 9	CD-RISC 10
ECAS Language functions	0.04 (0.303)	0.24 (0.398)	0.32 (0.277)	−0.05 (0.812)	0.10 (0.653)	0.32 (0.324)	−0.19 (0.423)	0.27 (0.367)	0.37 (0.194)	0.55 (0.056)	0.28 (0.321)
ECAS Verbal fluency	−0.007 (0.911)	0.40 (0.419)	0.16 (0.739)	0.30 (0.448)	−0.11 (0.774)	−0.20 (0.704)	−0.45 (0.262)	−0.39 (0.442)	−0.0001 (0.999)	0.20 (0.679)	−0.23 (0.628)
ECAS Executive functions	0.14 (0.082)	0.60 (0.308)	1.13 (0.052)	0.05 (0.906)	0.67 (0.167)	**1.40 (0.032)**	0.32 (0.503)	0.45 (0.466)	0.81 (0.159)	0.95 (0.103)	0.50 (0.391)
ECAS ALS Specific functions	0.18(0.243)	1.34 (0.233)	1.69 (0.132)	0.21 (0.819)	0.73 (0.429)	1.59 (0.204)	−0.30 (0.741)	0.37 (0.756)	1.18 (0.285)	1.76 (0.114)	0.59 (0.591)
ECAS Memory functions	**0.12 (0.016)**	0.45 (0.208)	0.68 (0.057)	0.19 (0.493)	**0.67 (0.022)**	**0.81 (0.042)**	0.49 (0.095)	0.72 (0.054)	**0.80 (0.023)**	**0.74 (0.035)**	−0.06 (0.847)
ECAS Visuospatial functions	0.006 (0.561)	0.04 (0.631)	0.04 (0.593)	0.02 (0.741)	0.004 (0.951)	0.10 (0.275)	−0.07 (0.271)	0.01 (0.879)	0.03 (0.680)	0.05 (0.481)	0.13 (0.105)
ECAS ALS Nonspecific functions	**0.13 (0.014)**	0.49 (0.192)	**0.74 (0.049)**	0.22 (0.463)	**0.67 (0.029)**	**0.94 (0.023)**	0.42 (0.169)	**0.76 (0.050)**	**0.83 (0.024)**	**0.80 (0.030)**	0.06 (0.862)
ECAS TOT	0.34 (0.088)	2.40 (0.088)	**2.95 (0.035)**	0.58 (0.611)	1.68 (0.148)	2.29 (0.145)	−0.05 (0.965)	1.38 (0.357)	2.03 (0.142)	2.59 (0.063)	0.36 (0.793)
ECAS Carer behavior screen	0.001 (0.889)	−0.09 (0.230)	0.05(0.425)	0.006(0.899)	0.06(0.299)	−0.01 (0.898)	0.06(0.268)	0.07(0.312)	−0.04(0.537)	−0.08(0.275)	−0.04(0.500)
HADS TOT	**−0.36(<0.0001)***	**−1.21 (0.048)**	−1.03(0.105)	**−1.47 (0.001)***	**−1.15 (0.019)***	**−2.88 (<0.0001)***	−0.47 (0.335)	**−1.66 (0.013)***	**−1.39 (0.025)***	**−2.22 (0.0002)***	**−2.37 (<0.0001)***
HADS Depression	**−0.17 (0.0001)***	−0.45 (0.179)	−0.43 (0.215)	**−0.74 (0.002)***	**−0.53 (0.049)***	**−1.27 (0.0004)***	−0.28 (0.292)	**−0.87 (0.018)***	−0.58 (0.087)	**−1.25 (0.0001)***	**−1.25 (<0.0001)***
HADS Anxiety	**−0.18 (0.0001)***	**−0.75 (0.028)***	−0.60 (0.096)	**−0.72 (0.004)***	**−0.62 (0.026)***	**−1.60 (<0.0001)***	−0.19 (0.492)	**−0.79 (0.037)***	**−0.81 (0.021)***	**−0.96 (0.006)***	**−1.12 (0.0007)***

Note: Values are given as β coefficient (p value). Significant p values (≤ 0.05) are reported in bold. *p values remaining significant after FDR correction for multiple comparisons.
CD-RISC: Connor-Davidson Resilience Scale; ECAS: Edinburgh Cognitive and Behavioral ALS Screen; HADS: Hospital Anxiety and Depression Scale; TOT: total.

months' time window to execute the first longitudinal examination by the time of study closure.

The remaining 42 cases (44.70%) underwent at least one longitudinal examination (minimum at 6 months and maximum at 46 months from baseline evaluation) and, therefore, constituted the final longitudinal sample.

Demographic and clinical features of the longitudinal and cross-sectional cohorts are reported in Supplementary Table 2. The longitudinal sample was broadly comparable to the cross-sectional one across all the investigated measures, except for a younger age ($p = 0.006$), longer disease duration ($p = 0.0001$) and lower ALSFRS-r rate of progression ($p = 0.0003$) at the time of first examination.

Relationship between PR levels and longitudinal cognitive decline in MNDs. Higher CD-RISC 5, CD-RISC 6, CD-RISC 9 and CD-RISC 10 scores were significant predictors of milder decline in memory functions (p from 0.001 to 0.04), and CD-RISC 10 scores were significant predictors of milder decline in ALS Nonspecific functions ($p = 0.04$) (Table 3). The association between CD-RISC 6 and memory functions further remained significant after FDR correction for multiple comparisons (Table 3). No other significant associations were observed between CD-RISC 10 scores and longitudinal decline in ECAS derived measures.

Table 3. Results of the regression analyses linking CD-RISC scores to longitudinal deltas of variation of cognitive measures in MND patients.

	CD-RISC TOT	CD-RISC 1	CD-RISC 2	CD-RISC 3	CD-RISC 4	CD-RISC 5	CD-RISC 6	CD-RISC 7	CD-RISC 8	CD-RISC 9	CD-RISC 10
ECAS Language functions	−0.0001 (0.946)	−0.003 (0.485)	−0.001 (0.696)	0.001 (0.761)	0.004 (0.172)	0.0007 (0.870)	0.0004 (0.881)	−0.002 (0.569)	−0.001 (0.643)	−0.001 (0.639)	−0.0005 (0.897)
ECAS Verbal fluency	−0.0001 (0.928)	0.002 (0.781)	0.002 (0.771)	−0.003 (0.699)	0.001 (0.899)	−0.006 (0.492)	0.004 (0.485)	0.007 (0.455)	−0.007 (0.344)	−0.0008 (0.921)	−0.006 (0.476)
ECAS Executive functions	0.001 (0.278)	−0.006 (0.418)	0.0007 (0.922)	0.005 (0.342)	0.007 (0.195)	0.007 (0.330)	0.0009 (0.856)	0.004 (0.549)	0.007 (0.229)	0.01 (0.125)	0.006 (0.386)
ECAS ALS Specific functions	0.0007 (0.209)	−0.001 (0.776)	0.004 (0.342)	0.005 (0.164)	0.004 (0.185)	0.003 (0.409)	0.003 (0.325)	0.003 (0.486)	0.002 (0.472)	0.003 (0.328)	0.001 (0.757)
ECAS Memory functions	0.001 (0.373)	−0.005 (0.731)	−0.009 (0.577)	0.01 (0.232)	0.02 (0.107)	**0.03 (0.042)**	**0.03 (0.001)***	0.01 (0.441)	0.01 (0.425)	**0.02 (0.035)**	**0.03 (0.032)**
ECAS Visuospatial functions	0.0001 (0.795)	0.004 (0.095)	0.0006 (0.834)	0.0006 (0.786)	0.0002 (0.920)	−0.002 (0.471)	−0.001 (0.444)	0.001 (0.524)	0.003 (0.137)	−0.0001 (0.961)	−0.002 (0.355)
ECAS ALS Nonspecific functions	0.0008 (0.161)	0.001 (0.667)	0.002 (0.553)	0.006 (0.070)	0.002 (0.461)	0.004 (0.317)	0.0002 (0.946)	0.003 (0.358)	0.003 (0.306)	0.002 (0.548)	**0.008 (0.045)**
ECAS Total	−0.0001 (0.999)	−0.001 (0.483)	0.0007 (0.665)	0.001 (0.374)	0.0003 (0.835)	−0.0002 (0.883)	0.0001 (0.885)	−0.0004 (0.809)	−0.0001 (0.931)	−0.0002 (0.894)	−0.001 (0.548)

Note: Values are given as β coefficient (p value). Significant p values (≤ 0.05) are reported in bold. *p values remaining significant after FDR correction for multiple comparisons.
CD-RISC: Connor-Davidson Resilience Scale; ECAS: Edinburgh Cognitive and Behavioral ALS Screen; TOT: Total.

Discussion

To our knowledge, this is the first study investigating the association between PR and cognitive/behavioral as well as mood symptoms in MNDs both at disease onset and over disease course.

Our finding of greater resilience levels in patients with MNDs is in line with the previous work from Kullmann and colleagues (15). As outlined by the authors, indeed, resilient people show a peculiar personality profile characterized by increased conscientiousness and openness and lower neuroticism (15,27), all features matching the personality traits often described in MND patients (28).

Notably, such features are important mediators of stress responses, so that people with higher conscientiousness and extraversion report their life stressors to be less stressful than others (29). PR indeed moderates the negative effects of adversities on mental well-being in contexts of depression, anxiety, and other disorders induced by chronic conditions (30).

In line with these observations, we indeed observed that greater PR levels were significant predictors of less severe depressive and anxiety symptoms in the MND sample.

Notably, in our study PR not only predicted milder mood symptoms, but also greater cognitive

performances both at disease onset and longitudinally.

Significant associations between resilience levels and cognitive functioning have already been described in healthy older adults (4,5), but the temporal sequence of these two constructs is still a matter of debate.

On one hand, some theories propose high cognitive functioning as a driver of greater resilience. In particular, the situationally appropriate application of cognitive flexibility would be a key element in promoting resilient responses. In this conceptual framework, the ability to combine information from a variety of sources, including the current situation and prior experience, as well as more conscious and goal-driven processes, would represent the cognitive bases of PR (31).

On the other hand, PR has been conversely identified as a significant driver of cognitive functioning through different putative mechanisms.

One of these is psychological well-being, with recent studies suggesting that resilience might lessen the deleterious effects of depression and anxiety on cognitive performances, therefore promoting cognitive health (32).

Another one is cognitive reserve, as more recent theories propose that PR could be a socio-cultural index of cognitive reserve and, as such, would act as a protective factor against cognitive decline (33).

As regards the ECAS longitudinal findings, it is noteworthy mentioning that in our sample we only observed either stable or worsening performances. Data regarding practice effects on the ECAS have been conflicting, with some studies reporting the presence of such phenomenon in patients with ALS (34) and others the absence (35).

Concerning the Italian version of the ECAS, the original work from Poletti and colleagues (34) observed a significant improvement on the ECAS Total/ALS-Non-specific scores, which in turn was driven by a significant improvement of the Memory score. However, this effect was selectively observed for the 18 patients evaluated through three different timepoints who were further showing lower baseline ECAS scores on those domains compared to the ones observed in our sample. The discrepancy observed between our findings and those by Poletti and colleagues might therefore be due to the features and size of the investigated samples.

On the other hand, it is not possible to completely rule out that the stable longitudinal ECAS performance observed in our sample might have been due to actual practice effects masking progressing cognitive deterioration. In this context, future studies applying the parallel Italian versions of the ECAS are warranted to disentangle this aspect.

Notably, the longitudinal design of our study has enabled to demonstrate that, in MNDs, PR not only predicts better cognitive performances at baseline, but also less severe cognitive deterioration over time.

As regards cognitive domains, both the comparison between "MND low resilience" and "MND high resilience" patients, as well as the regression analysis linking CD-RISC scores to baseline cognitive performances, evidenced a significant impact of resilience both on ALS Specific (executive) and Nonspecific (memory) functions at disease onset. Conversely, in the longitudinal analyses, resilience had a significant impact only on the progression of memory performances.

This finding might be explained by the temporal sequence of cognitive domains involvement in ALS. It is indeed increasingly recognized that the longitudinal pattern of cognitive domains decline mirrors the sequential involvement of underlying brain regions due to pathological spread (from frontal regions related to executive functions to temporal regions related to memory functions) (36,37).

In this context, it is plausible to hypothesize that the initially generalized protective effect of PR on cognitive functioning tends to lessen earlier on the primarily involved cognitive domains (such as executive functions), and later on the more well-preserved cognitive domains (such as memory).

The milder neuropsychological decline observed in patients with greater PR needs further investigation. On one hand, our baseline findings seem to suggest that this phenomenon might be due to the better initial cognitive status, so patients with higher resilience levels are those showing better neuropsychological performances at disease onset and therefore less severe longitudinal decline.

On the other hand, given that the longitudinal rates of cognitive decline were measured using relative deltas of variation (therefore keeping into account the baseline cognitive status), it is more plausible to hypothesize that, as a socio-cultural index of cognitive reserve, PR further slows down cognitive deterioration independently from the baseline cognitive status. In this context, future studies in larger and more homogeneous samples are warranted to further elucidate this aspect.

An unexpected finding of our study was the absence of significant associations between PR and behavioral symptoms, especially considering the well-known relationship between the latter and mood disturbances (depression in particular) (38).

In this context, it is plausible to hypothesize that no significant correlations could be detected since, differently from the ECAS cognitive and HADS scales, the ECAS carer behavior screen

simply evaluates the presence or absence, not the severity, of specific behavioral symptoms.

Notably, the protective role of PR against cognitive and mood disturbances evidenced in our work has important translational applications in the context of MNDs. Resilience can indeed be improved with treatments such as mindfulness and cognitive behavioral therapy (39). Taken together, these observations suggest that psychological interventions might represent an important instrument to prevent or delay the onset of cognitive and mood disturbances in MNDs.

The present study is not without limitations. The first shortcoming deals with the longitudinal sample size, as only 44.70% of cases were able to perform at least one follow-up examination.

Second, while our study specifically focused on resilience, future works further investigating which premorbid life events may act as stressors are needed to better understand and frame the concept of PR in MNDs.

Third, while the evaluation of mood symptoms in our study was adjusted for motor impairment, we are aware that language-specific, validated versions of more tailored instruments such as the HADS scale adapted for patients with MND (40) are increasingly needed to better examine mood alterations in these neurodegenerative motor syndromes.

Despite these shortcomings, our study provides the first evidence that PR is an important protective factor against the onset and evolution of extramotor disturbances in MNDs.

In this context, future studies are warranted to explore other potential protective factors, such as brain structural and cognitive reserves, even if more recent observations suggest that the latest one may moderate the effect of brain damage rather than modulate cognitive decline itself (41).

In summary, our observations suggest the usefulness of resilience enhancement psychological interventions as a future strategy to prevent or delay cognitive deterioration and mood disorders in MNDs.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

Work supported by: #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – (DN. 1553 11.10.2022); #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project RAISE (ECS00000035) – (DN. 1053 del 23.06.2022); Italian Ministry of Research, under the complementary actions to the NRRP "Fit4MedRob - Fit for Medical Robotics" Grant (# PNC0000007); Italian Ministry of Health "Fondi per la Ricerca Corrente 2022-2024" to IRCCS Ospedale Policlinico San Martino; grant number NET-2018-12366666 NeuroArtP3 (as in the paper from Malaguti et al 2024 "Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine for Parkinson Disease: The NeuroArtP3 protocol for a multicenter research study").

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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