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ORIGINAL ARTICLE

Premorbid functional reserve modulates the effect of rehabilitation in multiple sclerosis

Letizia Castelli[1] · Laura De Giglio[2,3] · Shalom Haggiag[4] · Arianna Traini[5] · Francesca De Luca[6] · Serena Ruggieri[4] · Luca Prosperini[4]

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Abstract

Background Premorbid physically and intellectually enriching lifestyles have increasingly been recognized as able to mitigate the risk of disease-related disability in patients with multiple sclerosis (MS).

Objective To explore if premorbid physical activity, cognitive reserve and trait personality act as proxies for functional reserve that contributes to rehabilitation outcome.

Methods We recruited all patients previously enrolled in two pilot trials investigating the effect of home-based video game training in improving balance (Study 1) and attention (Study 2) for additional assessments with the Historical Leisure Activity Questionnaire (HLAQ; a proxy for premorbid physical activity), Cognitive Reserve Index Questionnaire (CRIQ), and Temperament and Character Inventory (TCI). Hierarchical logistic regression (HLR) analyses tested the association of HLAQ, CRIQ, and TCI with training effect on balance (static posturography) and on attention (Symbol Digit Modalities Test).

Results We identified 94% (34/36) and 74% (26/35) of patients participating at the original Study 1 and Study 2, respectively. HLR analyses showed an exclusive "intra-modal" modulation of rehabilitation outcome by functional reserve, given that (1) larger training effect on balance was associated with higher HLAQ (OR = 2.03, $p = 0.031$); (2) larger training effect on attention was associated with higher CRIQ (OR = 1.27, $p = 0.033$). Furthermore, we found specific personality traits associated with (1) greater training effect on balance (self-directedness; OR = 1.40, $p = 0.051$) and lower training effect on attention (harm avoidance; OR = 0.66, $p = 0.075$).

Conclusion We hypothesize that premorbid physical and intellectual activities not only act as a buffer for limiting the MS-related damage but also as functional reserve that can be retrieved by task-oriented training to promote recovery through rehabilitation.

Keywords Multiple sclerosis · Reserve · Rehabilitation

✉ Luca Prosperini
luca.prosperini@gmail.com

Letizia Castelli
letizia.castelli@gmail.com

Laura De Giglio
lauradegiglio@gmail.com

Shalom Haggiag
lvshalom@hotmail.com

Arianna Traini
arianna_traini@yahoo.com

Francesca De Luca
francideluca84@libero.it

Serena Ruggieri
serena.ruggieri@gmail.com

1 IRCCS Don Carlo Gnocchi Foundation, Piazzale Morandi 6, 20121 Milan, Italy

2 S. Filippo Neri Hospital, Via G. Martinotti 20, 00135 Roma, Italy

3 Department of Human Neuroscience, Sapienza University, viale dell'Università 30, 00185 Rome, Italy

4 S. Camillo-Forlanini Hospital, C.ne Gianicolense 87, 00152 Rome, Italy

5 Physical Therapy Unit, S. Andrea Hospital, Via di Grottarossa 1035, 00189 Rome, Italy

6 Department of Psychology, Sapienza University, Viale dell'Università 30, 00185 Rome, Italy

Introduction

Neural plasticity is the intrinsic property of the central nervous system (CNS) to adapt to the ever-changing conditions of the environment encountered during development, learning and even injuries, by reorganizing its structure, function, and connections [1]. Neural plasticity also represents the substrate by which the damaged brain relearns lost behaviors through rehabilitation in persons with neurological diseases [2], including multiple sclerosis (MS) [3]. There is indeed growing evidence that the accumulation of disability in MS may be not driven by plasticity exhaustion, but rather by pathological disease processes involving critical neural pathways and by disability-related deconditioning [3]. However, the clinical course of MS, as well as the functional recovery after a rehabilitative intervention, is unpredictable and largely heterogeneous even among persons with similar patterns of disease burden. Such mismatch between brain pathology and its clinical expression is known as the clinico-radiological paradox [4] that, in turn, draws attention to the concept of functional reserve, i.e., the adaptability of CNS that allows someone to cope better than others with the MS-related damage [5]. Functional reserve seems to be mainly influenced by premorbid individual's education, intellect, mental stimulation, participation in leisure activities, social engagement, physical activity, and even dietary factors [6]. While premorbid physically and intellectually enriching lifestyles have increasingly been recognized as able to mitigate the risk of MS-related disability, factors associated with improved functional recovery through rehabilitation in MS are largely unknown.

Based on the postulate that "functional improvement after brain injury is a relearning process" mediated by neural plasticity [2], our working hypothesis is that a greater premorbid functional reserve may contribute – at least partially – to improve the rehabilitation outcome in people with MS. Premorbid personality traits may also predicts functional outcomes, as shown in other neurological conditions [7, 8].

To test this hypothesis, we explored whether the outcome of rehabilitation could be predicted by premorbid physical activity, cognitive reserve, and personality traits in two independent samples of persons with MS who underwent rehabilitative intervention aimed to improve balance and sustained attention.

Methods

Study design and participants

In this ancillary study, we sought to include all patients previously enrolled in two pilot randomized controlled clinical trials conducted at the Dept. of Neurology and Psychiatry of Sapienza University, Rome, Italy:

(i) Study 1: a 24-week, randomized, crossover pilot study aimed at exploring the effect of exergames delivered by the Nintendo Wii balance board on balance and gait impairment [9];
(ii) Study 2: an 8-week, randomized, wait-list control pilot study aimed at exploring the effect of video games on sustained attention and information processing speed [10].

Both studies showed a significant effect of home-based training, with a medium effect size both on balance (Cohen's f-squared: 0.20) and attention (Cohen's f-squared 0.18). Furthermore, in both study samples, rehabilitation-induced structural and functional changes were also detected in brain areas subserving the trained domains through advanced magnetic resonance (MRI) techniques [11, 12].

Ethical standards

The present study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The ethical committee board of our University provided exemption of approval for non-interventional studies. We obtained an informed consent from each participant prior to any study procedure.

Procedures

In early 2018, all patients identified from the two aforementioned pilot studies [9, 10] underwent the following assessments: premorbid Historical Leisure Activity Questionnaire (HLAQ) [13], Cognitive Reserve Index questionnaire (CRIQ) [14], and Temperament and Character Inventory (TCI) [15].

The HLAQ is an interviewer-administered assessment of leisure time physical activities for adults in different periods of life [13]. We have exclusively collected information on leisure time physical activities conducted by participants ≥ 10 times in the period between 12 and 18 years of age-time period, i.e., prior the diagnosis of MS. Average attendance in weekly hours was calculated for each single activity according to the following formula: number of years participated in activity multiplied by months per year multiplied by 4 weeks per month multiplied by hours per week divided by 52 weeks per year. The final score was obtained by adding the average weekly hours for all reported activities.

The CRIQ is a 20-item semi-structured interview that, in addiction with collecting demographic data, is aimed at collecting data on the following aspects: (1) education, that refers to both formal and nonformal education and training years; (2) working activity, that includes five occupational categories with different degrees of responsibility and cognitive demands, quantifying years spent in each occupation; (3)

leisure activity, with information regarding free time activities (sporting activities, reading, watching television, attending concerts, etc.). The total score is calculated by combining the three sub-scores of each section and after adjusting for age.

The TCI is a self-administered 240-item inventory for seven dimensions of personality traits: four temperaments, namely, novelty seeking (NS), harm avoidance (HA), reward dependence (RD), persistence (PS); and three characters, namely, self-directedness (SD), cooperativeness (CO), and self-transcendence (ST) [15]. The TCI is based on a psychobiological model that attempts to explain the underlying causes of individual differences in personality traits, by correlating specific temperaments with neurotransmitters activity. NS refers to exploratory activity in response to novel stimulation, impulsive decision-making, extravagance in approach to reward cues, quick loss of temper, and avoidance of frustration. HA refers to excessive worrying, pessimism, shyness, and being fearful, doubtful, and easily fatigued. RD refers to respond markedly to signals of reward, particularly to verbal signals of social approval, social support, and sentiment. PS refers to perseverance in spite of fatigue or frustration. SD refers to regulate and adapt behavior to the demands of a situation in order to achieve personally chosen goals and values. CO refers to the degree to which a person is generally agreeable in their relations with other people as opposed to aggressively self-centered and hostile. ST refers to the expansion of personal boundaries, including, potentially, experiencing spiritual ideas. Participants were given a revised Italian validated version [16].

Outcome definition

For each study, we estimated the magnitude of performance change in the main study endpoint, measured as post-training value minus baseline value divided by baseline value.

We also estimated the number of patients who achieved a clinically relevant improvement in the main study endpoint after the training, as follows:

(i) For postural sway measurements (main endpoint for the Study 1), the minimal detectable change – i.e., the smallest amount of change which not results from a measurement error – was 31%, according to literature data [17];

(ii) For the SDMT (main endpoint for the Study 2), a raw score change of 4 points or a 10% change is considered clinically meaningful, according to literature data [18].

Statistical analysis

Data are presented as count (proportion) for categorical variables and mean (standard deviation) (SD) or median [interval] for continuous variables.

The association between sex and the magnitude of performance change (postural sway for Study 1 and SDMT for Study 2) was explored by the Mann-Whitney U test. Spearman rank-order correlations (unadjusted and adjusted by baseline value) were performed to explore relationships between the magnitude of performance change (postural sway for Study 1 and SDMT for Study 2) and age, years of formal education, disease duration, EDSS score, HLAQ score, CRIQ score, and TCI subscores.

We also ran two hierarchical logistic regression analyses (forward stepwise fashion) to ascertain the effects of some independent variables such as sex, age, years of formal education, disease duration, EDSS score (first step), HLAQ score, CRIQ score (second step), and TCI subscores (third step) on the likelihood of achieving a clinically relevant improvement (dependent variable) in postural sway (for Study 1) and SDMT (for Study 2) after the two types of training. In each subsequent step, the regression equation comprised those independent variables reaching specific thresholds of F- and *p*-values (for inclusion: $F \geq 1$ and $p \leq 0.05$; for exclusion: $F < 1$ and $p > 0.05$). Both logistic models were adjusted by baseline value of postural sway (Study 1) and SDMT (Study 2). Odds ratios (ORs), their corresponding 95% confidence intervals (CIs), and p values were provided for any significant independent variables associated with a clinically relevant improvement in postural sway (for Study 1) and SDMT (for Study 2) (dependent variables).

Lastly, we conducted two sensitivity analyses estimating the magnitude of a hypothetical unmeasured confounder that would be needed to erase the observed association between the dependent and independent variables. For each model, we plotted the relative odds between a hypothetical unmeasured confounder and the dependent variable (on the x axis) and between a hypothetical unmeasured confounder and the significant predictors (on the y axis), assuming an arbitrary 20% prevalence of a hypothetical unmeasured confounder.

Two-tailed *p*-values less than 0.05 were considered as significant. Given its exploratory nature, no correction for multiple comparisons was applied.

Results

Patients' ascertainment

We achieved 94% ascertainment (34/36) for the Study 1 and 74% (26/35) ascertainment for Study 2. There was no difference in baseline characteristics (i.e., at the original study start) of patients who were identified and those who did not (data not shown).

Table 1 shows the main baseline characteristics of patients included in this ancillary analysis, as well as the magnitude of score change from baseline and proportion of patients achieving a clinically relevant change after the training period.

Table 1 Demographic and clinical features at baseline (i.e., at the beginning of the original pilot study), magnitude of performance change, and proportions achieving a clinically relevant change in the main study endpoints

Variable	Study 1	Study 2
Baseline		
Sex female:male, *n* (%)	23:11	16:10
Age in years	42.4 (8.3)	47.7 (8.2)
Formal education in years	14.8 (3.5)	13.6 (2.9)
Disease duration in years	16.3 (6.1)	18.5 (8.5)
EDSS score, median	3.5 [1.5–5.0]	3.5 [1.5–6.0]
After the training		
Magnitude of performance change *	15 (28)	18 (19)
Clinically relevant change, *n* (%)	14 (41)	15 (58)

All values are mean (standard deviation), unless indicated otherwise

*postural sway for Study 1 and SDMT for Study 2

We found no association between baseline patients' characteristics (sex, age, disease duration, disability level) and premorbid HLAQ and CRIQ and TCI subscores in both studies (data not shown), except for an expected association between formal education and CRIQ (Study 1: rho = 0.671, $p <$ 0.001; Study 2: rho = 0.470, $p = 0.015$).

Study 1

Larger training effect on balance and gait, estimated as magnitude of performance change from baseline in postural sway, was associated only with higher HLAQ values (rho = 0.375, $p = 0.029$), but not with demographic and clinical features, CRIQ, or TCI subscores. This finding was confirmed even after controlling for the baseline value of postural sway (rho = 0.385, $p = 0.027$) (see also Table 2).

Fourteen (41%) patients achieved a clinically relevant improvement in postural sway after the training. The logistic regression model was statistically significant, $\chi^2(2) = 10.359$, $p = 0.006$. The model explained 34% (Nagelkerke R^2) of the variance and correctly classified 73.5% of cases. Higher HLAQ values (OR = 2.03, $p = 0.031$) and higher SD scores (OR = 1.40, $p = 0.051$) were associated with an increased likelihood of achieving a clinically relevant improvement in postural sway (see also Table 3).

Sensitivity analysis showed that, assuming a 20% prevalence of an hypothetical unmeasured confounder, its association with either the dependent variable or the independent variables should lead to ORs of 5 to 6 or 3 to 4 to erase the predictive value of HLAQ and SD, respectively, on achieving a clinically relevant improvement in postural sway after the training (Fig. 1/**A**).

Table 2 Spearman rank-order correlations for magnitude of score change after the training; in bold are reported significant p-values <0.05 (two-tailed)

		Study 1		Study 2	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Age	rho	− 0.086	0.042	0.107	0.092
	p	0.628	0.816	0.604	0.663
Formal education	rho	0.110	0.121	− 0.100	− 0.055
	p	0.534	0.501	0.628	− 0.795
Disease duration	rho	0.026	0.024	0.006	− 0.057
	p	0.886	0.896	0.978	0.787
EDSS score	rho	0.062	0.004	− 0.117	− 0.143
	p	0.726	0.980	0.569	0.496
CRIQ	rho	0.187	0.195	**0.408**	**0.406**
	p	0.288	0.277	**0.039**	**0.044**
HLAQ	rho	**0.375**	**0.385**	− 0.116	− 0.089
	p	**0.029**	**0.027**	0.572	0.673
NS	rho	0.030	0.051	− 0.262	− 0.257
	p	0.866	0.779	0.196	0.215
HA	rho	0.006	− 0.038	− 0.099	− 0.090
	p	0.972	0.835	0.631	0.670
RD	rho	− 0.070	− 0.082	− 0.106	− 0.129
	p	0.696	0.649	0.607	0.539
PS	rho	0.080	0.114	0.039	0.021
	p	0.652	0.527	0.849	0.921
SD	rho	0.235	0.241	− 0.030	− 0.065
	p	0.181	0.177	0.883	0.757
CO	rho	0.017	0.174	− 0.145	− 0.168
	p	0.923	0.334	0.481	0.423
ST	rho	0.297	0.254	0.322	0.339
	p	0.088	0.154	0.109	0.098

CO, Cooperation; *CRIQ*, Cognitive Reserve Index Questionnaire; *EDSS*, Expanded Disability Status Scale; *HA*, Harm Avoidance; *HLAQ*, Historical Leisure Activity Questionnaire; *NS*, Novelty Seeking; *PS*, Persistence; *RD*, Reward Dependence; *SD*, Self-Directedness; *ST*, Self-Transcendence

Study 2

Larger training effect on sustained attention and information processing speed, estimated as magnitude of SDMT performance change from baseline, was associated only with higher CRIQ values (rho = 0.408, $p = 0.039$), but not with demographic and clinical features, HLAQ, or TCI subscores. This finding remained unaltered even after controlling for the baseline value of postural sway (rho = 0.406, $p = 0.044$).

Table 3 Predictors of achieving a clinically relevant improvement by hierarchical forward stepwise logistic regression models

	Nagelkerke R-squared	Predictor(s)	OR	95% CIs	*p* value
Study 1	0.34	HLAQ	2.03	1.07–3.87	0.031
		SD	1.40	1.00–1.98	0.051
Study 2	0.41	CRIQ	1.27	1.02–1.57	0.033
		HA	0.66	0.42–1.04	0.075

CRIQ, Cognitive Reserve Index Questionnaire; *HA*, Harm Avoidance; *HLAQ*, Historical Leisure Activity; *SD*, Self-Directedness

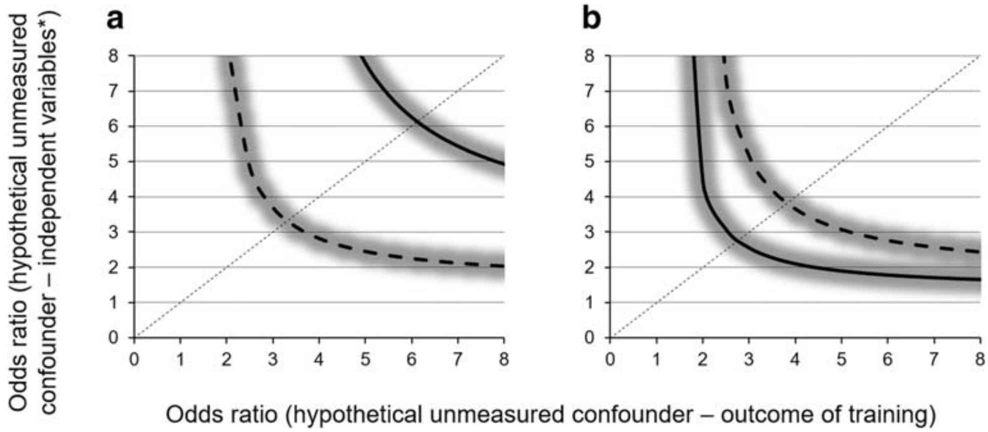

Fig. 1 Sensitivity analyses to define the strength of the association of an hypothetical unmeasured confounder with either the outcome of rehabilitation (dependent variable) and proxies for functional reserves (independent variables) to erase the results of hierarchical logistic regressions predicting the outcome of training to improve balance (A; Study 1) and cognition (B; Study 2). ***A**: Historical Leisure Activity Questionnaire (continuous line), and Self-Directedness (dotted line); **B**: Cognitive Reserve Index Questionnaire (continuous line), and Harm Avoidance (dotted line).

Fifteen (58%) achieved a clinically relevant improvement in SDMT. The logistic regression model was statistically significant, $\chi^2(2) = 9.466$, $p = 0.009$. The model explained 41% (Nagelkerke R^2) of the variance and correctly classified 76.8% of cases. Higher CRIQ scores (OR = 1.27, $p = 0.033$) and lower HA scores (OR = 0.66, $p = 0.075$) were associated with an increased likelihood of achieved a clinically relevant improvement in SDMT (see also Table 3).

Sensitivity analysis showed that, assuming a 20% prevalence of an hypothetical unmeasured confounder, its association with either the dependent or independent variables should lead to ORs of 3 to 3 or 3 to 4 to erase the predictive value of CRIQ and HA, respectively, on achieving a clinically relevant improvement in SDMT after the training (Fig. 1/**B**).

Discussion

In this study, we tested the hypothesis of an association between improved outcome after rehabilitation and premorbid physical activity, cognitive reserve, and personality traits as proxies for functional reserve. To our knowledge, this issue has so far never been specifically investigated in persons with MS. We found better outcome (i.e., reduced postural sway) after balance rehabilitation as associated with higher level of premorbid physical activities (HLAQ) and SD character (TCI). We also found better outcome (i.e., improved SDMT scores) after rehabilitation of attention as associated with greater cognitive reserve (CRIQ), whereas the HA temperament (TCI) was associated with worse outcome. Our findings suggest an exclusive "intra-modal" modulation rather than a "cross-modal" modulation of rehabilitation outcome by the individual functional reserve, with premorbid physical activity predicting the improvement in the motor domain and premorbid intellectual enrichment predicting the improvement in cognitive domain.

While premorbid physically and intellectually enriching lifestyles have increasingly been recognized as able to mitigate the risk of MS-related disability and brain damage detected at MRI [6, 13, 19], studies on personality traits in persons with MS are less conclusive. Some Authors have suggested a possible relationship between personality characteristics and disease stage [20], the degree of damage [21], memory function [22], and quality of life [23]. In particular, higher values in HA temperament and neuroticism trait were found associated with worse clinical outcomes; however, these findings should be interpreted with caution given that some of these relationships are not confirmed after controlling for depression [20] and given that the MS-related cognitive decline may also induce longitudinal personality change [24]. Consequently, it is not possible to conclude whether the personality trait of persons with MS is a predictor for better or worse outcomes or rather another aspect of the disease-related damage.

Despite of the marked success of disease modifying therapy research, rehabilitation is a key therapy option for many persons with MS, since it promotes the recovery of impaired functions by exploiting neural plasticity [3, 25]. Nevertheless, factors associated with improved functional recovery through rehabilitation in MS are largely unknown. Studies investigating similar topics in other neurological disabilities provided mixed results. Engagement in premorbid physical activities was proven as a proxy for functional reserve of the motor domain in patients with Parkinson's disease (PD) [26] and post-stroke survivors [27], although not confirmed in other studies [28].

Educational attainment is reported to be an independent predictor of better outcomes in traumatic brain injury (TBI) [29] and cerebral small vessel disease [30]. Longitudinal studies showed a reduced risk of dementia in persons who engaged leisure-time activities and less age-related gray and white matter loss associated with higher levels of physical activity, particularly aerobic exercise [31]. By contrast, other authors found that higher premorbid CRIQ is not associated with a rapid adaptation and recovery from TBI [32], and one study showed even greater improvement in balance associated with lower CRIQ score in patients with PD who underwent a specific rehabilitation program [33].

We propose at least two (not mutually exclusive) explanations for the aforementioned discrepancies: (1) the effect of functional reserve in mediating recovery after CNS damage is only modest, thus suggesting that other key factors, such as the extent of injury and age-related processes, are involved; (2) different study designs and methodologies across studies do not allow to draw unequivocal conclusions, thus claiming the need for a framework to investigate this topic [34].

Our study should be considered merely hypothesis-generating and bears several limitations, mainly due to the small sample sizes and the collection of premorbid proxies for motor reserve, cognitive reserve, and personality traits only after the completion of the interventions (possibly leading to recall bias). While we are confident that this is only a minor concern for HLAQ and CRIQ, we cannot rather exclude that TCI scores may correlate not only with premorbid personality traits but also with disease-induced longitudinal changes [24]. Furthermore, we cannot explore if other life periods may have greater effect on functional reserve, therefore failing to provide suggestions on when to promote at maximum physical and/or intellectual activities. Similarly, we cannot confirm whether the promotion of these activities in the early stages of the disease, when the disability level is minimal, can buffer the MS-related disability progression over time, as previously proposed [35].

Conclusions

Our study raises the hypothesis that rehabilitation outcome is modulated by premorbid level of physical and intellectual enriched activities, as well as by specific temperament and character traits. These preliminary findings have potentially a twofold implication for future research: (i) further efforts should be made to better define when and how to promote physical activity and intellectual enrichment in order to strengthen functional reserve; (ii) assessment of patients' character traits and temperaments may help neurologists to tailor rehabilitation strategies.

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Compliance with ethical standards

Conflict of interest None related to this article.

Ethical standards The present study was conducted after approval of the Local Ethics Committee. All data were gathered after informed consent was obtained from each participant, in accordance with specific national laws and the ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments. In no way this study did interfere in the care received by patients. Anonymized data will be shared upon request by the corresponding author (LP).

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