The Cognitive Reserve May Influence Fatigue after Rehabilitation in Progressive Multiple Sclerosis: A Secondary Analysis of the RAGTIME Trial

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Abstract: Cognitive reserve (CR) seems to be an ability to adapt cognitive processes in response to brain disease and may influence rehabilitation outcomes. This is a secondary analysis of the “Robot-Assisted Gait Training versus conventional therapy on mobility in severely disabled progressive MultiplE sclerosis patients” (RAGTIME) trial to investigate the influence of CR on the outcomes after gait rehabilitation in people with multiple sclerosis (PwMS). We included 53 PwMS and severe gait disability (EDSS 6–7). The participants were randomized into two groups to receive either robot-assisted gait training or overground walking (three times/week over four weeks). CR was evaluated by the Cognitive Reserve Index questionnaire (CRIq), which encompasses three sections (CRI Education, CRI Working Activity, and CRI Leisure Time). We stratified the patients using the 115 cut-off CRIq total score of at least a medium-high CR. The outcome measures were Timed 25-Foot Walk, 6 min walking test, Berg Balance Scale, Multiple Sclerosis Impact Scale—29, Multiple Sclerosis Walking Scale—12, Patient Health Questionnaire—9, and Fatigue Severity Scale (FSS). After gait rehabilitation, the FSS was significantly improved in those patients with higher CR compared with the others ($F = 4.757$, $p = 0.015$). In our study, CR did not affect the gait, balance, disability perception, and depression. Conversely, it positively influenced the fatigue after gait rehabilitation.

Keywords: cognitive reserve; multiple sclerosis; gait rehabilitation; rehabilitation outcomes; fatigue

1. Introduction

Cognitive reserve is a personal factor that can positively influence the rehabilitation adherence and outcomes in people with multiple sclerosis (PwMS) that typically present inflammatory demyelination, axonal loss, and neurodegeneration with grey matter atrophy within the central nervous system. In PwMS, sensory–motor impairments, such as impaired mobility and balance, weakness, spasticity, and sensory loss, are commonly reported [1]. Moreover, fatigue may have a negative impact on mobility, cognition, and quality of life (QoL) [1]. Central nervous system damage tends to increase over time and leads to the progression of disability [2]. Gait rehabilitation can reduce the accrual of a disability, effectively improving the mobility, with positive repercussions on QoL [3]. Various interventions have been proposed, including conventional or robot-assisted gait rehabilitation, positively affecting gait speed, endurance, fatigue, and disability [4–6]. Moreover, identifying personal prognostic factors is essential in defining responders, tailoring rehabilitation, and increasing effectiveness.

Cognitive reserve (CR) may play a role in preventing disability and shaping rehabilitative outcomes [7–10]. Indeed, differences in the cognitive processes related to personal...
lifetime intellectual activities or other environmental factors can explain the variability in the functional impairments after neurological conditions [11,12] and increase the ability to cope with neurodegenerative diseases. It is well-recognized how a discrepancy between the severity of the neurological condition and the clinical manifestation of impairment or disability may occur. Specifically, CR is associated with lifetime intellectual and cognitive use in different ways, such as leisure time, study, work, and physical activity [13], and it implies anatomic brain network variability [11].

The measurement of cognitive reserve is not associated with the homogeneity of the methods and tools in the various scientific studies. Several authors have recently used single proxy parameters to quantify cognitive reserve (e.g., years of education), but they are not precisely representative of the definition of CR. One of the most prominent solutions to comprehensively assess this cognitive function is using the Cognitive Reserve Index questionnaire (CRIq) [14]. It is an Italian instrument available in several languages, has good construct validity, and seems suitable even for disabled populations to measure the different domains of CR, such as education, working activities, and leisure time [12].

So far, several studies underline the role of cognitive reserve in PwMS, especially in preserving some cognitive functions’ efficiency and enabling better performance in different cognitive tasks [15]. Patients with higher CR showed greater cognitive processing speed [16,17] and better memory functioning [15,18]. Cognitive reserve also modulates the relationship between disability and depression; specifically, physical disability does not appear to influence depression in PwMS with high cognitive reserve [19]. On the contrary, little evidence is available on the role of CR in motor function and referring to other neurodegenerative conditions, such as Parkinson’s disease (PD). In this population, patients with higher CR show reduced motor impairment and better global cognitive performance than those with lower CR [20].

Considering the motor rehabilitation outcomes, mixed results are available thus far. Padua et al. reported how cognitive reserve was related to better motor outcomes in stroke survivors after robot-assisted upper limb training [21]; similarly, Imbimbo et al. found a correlation between the CR and rehabilitation outcome in PD patients after walking and balance virtual reality treatment [10]. Conversely, this beneficial effect was not found in PD after conventional therapy by Piccinini et al. [22]. Moreover, Castelli et al. highlighted significantly improved attention rather than motor function after home-based video game balance training in PwMS and higher CR [23].

Recently, we conducted a randomized controlled trial in PwMS, named RAGTIME, with severe gait disability [6,24]. This trial examined the effectiveness of robot-assisted gait training (RAGT) compared to conventional treatment (CT). The result showed beneficial effects on mobility and disability with no significant differences among the treatment types after twelve 2 h gait rehabilitation sessions. This ancillary study aimed to verify if PwMS with a higher cognitive reserve enrolled in the RAGTIME trial [6,25] would have more significant benefits on the motor function, fatigue, and depression after gait training. Specifically, we hypothesized that cognitive reserve might be a favourable personal cognitive factor in determining the effects of motor rehabilitation in PwMS and severe gait disability.

2. Materials and Methods

This is a secondary analysis of the RAGTIME trial (ClinicalTrials.gov, identifier: NCT02421731) [6] in which we investigated the role of cognitive reserve on rehabilitation outcomes. We included men and women aged between 18 and 65 years and with a diagnosis of primary or secondary progressive MS with severe gait disability, defined by the Expanded Disability Status Scale (EDSS) score between 6 and 7.

The exclusion criteria were the following: (i) inability to perform the Timed 25-Foot-Walk test (T25FW); (ii) MS worsening in the three months before the enrolment; (iii) impaired cognitive functions at Mini-Mental Examination Test screening (<24); (iv) lower limb modified Ashworth scale score > 3; (v) clinical conditions other than MS that could interfere with the ability to complete the protocol study safely (i.e., heart disease or respiratory
infections); (vi) changes in drug therapy during the study; and (vii) rehabilitation treatment or botulinum toxin injections in the three months before enrolment. All these criteria were defined for safely performing gait rehabilitation and reducing potential confounding factors (i.e., drugs and other rehabilitation).

The local ethics committee of Ferrara University Hospital approved the present study (ethical protocol code: 101-2012). The research was carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all participants.

The Cognitive Reserve Index questionnaire (CRIq) quantified the cognitive reserve. The CRIq considers especially the years of education, attendance of training courses, intellectual involvement in job tasks, and participation in cognitively stimulating activities during leisure time [14]. It comprises 20 items grouped into three sections (CRI Education, CRI Working Activity, and CRI Leisure Time). The authors identify five ordered levels of CRI total score: low (<70), medium-low (70–84), medium (85–114), medium-high (115–130), and high (>130). In this study, we grouped our sample into two groups: low, medium-low, and medium (CRI < 115), and medium-high and high (CRI ≥ 115). We used 115 as a cut-off given that it marked the transition from a cognitive reserve considered “medium” to “medium-high”, as previously reported by Nucci et al. [14].

Participants received a gait rehabilitation based on twelve 2 h sessions three times a week over four weeks. In the first hour, specific gait training was carried out (robot-assisted or overground gait training); the second-hour program was based on stretching the lower limbs, increasing muscle flexibility. In the RAGT group, patients were trained with a gait exoskeleton on a treadmill for approximately 40 min (Lokomat, Hocoma, Volketswil, Switzerland). Training parameters, including gait speed, bodyweight support, guidance force, and torque of the knee and hip drives, were individually set up and progressively adjusted for each patient by expert physiotherapists. In the conventional treatment group, patients underwent individual physiotherapy sessions. The sessions included assisted overground walking for 40 min on an 80 m internal flat corridor, inserted between 10 min of warm-up and cool-down periods. The gait speed was set to patient tolerance. Rest breaks were allowed as needed. The complete protocol has been reported elsewhere [25]. The outcome measures considered in this study were collected at baseline (T0) and the end of rehabilitation (T1).

The primary outcome measure was walking speed, as assessed by the Timed 25-Foot Walk (T25FW). The patient was instructed to walk 25 ft (7.62 m) as quickly as possible but safely. Immediately after, they walk back the same distance. The mean time from the two trials was calculated. Secondary outcomes included functional and patient-reported measures. To verify walking endurance, we used the 6 min walking test (6MWT), which measures walking endurance in 6 min with the option to rest if necessary. The Berg Balance Scale (BBS) assessed static and dynamic balance.

Self-reported fatigue was verified with the Fatigue Severity Scale (FSS), a short questionnaire in which patients read a statement and rate their level of fatigue from 1 to 7 regarding the preceding week. The possible presence of recent depression was investigated with the Patient Health Questionnaire (PHQ-9). The impact of MS symptoms, both psychological and motor, on everyday life was assessed using the Multiple Sclerosis Impact Scale (MSIS-29). In contrast, a self-report measure of the impact of MS on the individual’s walking ability was evaluated with the 12-Item Multiple Sclerosis Walking Scale (MSWS-12).

Statistical Analysis

Data distribution was verified through the Shapiro–Wilk test. The baseline characteristics of the two groups (CRI < 115 and CRI ≥ 115) were compared through chi-squared test for categorical variables and Student’s t-test or Mann–Whitney U test as appropriate. The variations in the outcomes at the end of rehabilitation were performed through Analysis of Covariance, applying age, sex, disease vintage, and severity as covariates. The
p-values were Bonferroni-corrected. The within-group analyses (end of treatment versus baseline) have been performed with paired-sample t-tests or Wilcoxon tests as appropriate. A p-value < 0.05 was considered statistically significant. Data analysis was performed using MedCalc Statistical Software version 20.110 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

A sample of 53 out of 72 PwMS (35 females and 18 males) with a severe walking disability was included in this analysis. They were grouped according to their CRIq score (CRI < 115: n = 36; CRI ≥ 115: n = 17). See Figure 1.

Figure 1. Cognitive reserve allocation flow diagram.

There was a significant difference (p < 0.001) between the two groups in the CRI total score and the three subscales (CRI Education, CRI Working Activity, and CRI Leisure Time). The demographic and baseline characteristics are summarized in Tables 1 and 2.

Table 1. Demographic sample characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CRI &lt; 115 (n = 36)</th>
<th>CRI ≥ 115 (n = 17)</th>
<th>Total (n = 53)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (M/F) (a)</td>
<td>10/26</td>
<td>8/9</td>
<td>18/35</td>
<td>0.16</td>
</tr>
<tr>
<td>MS type (PP/SP) (a)</td>
<td>19/17</td>
<td>7/10</td>
<td>26/27</td>
<td>0.43</td>
</tr>
<tr>
<td>treatment (CT/RAGT) (b)</td>
<td>16/20</td>
<td>10/7</td>
<td>26/27</td>
<td>0.33</td>
</tr>
<tr>
<td>age (years) (b)</td>
<td>54.0 [46–60.3]</td>
<td>60 [56–63]</td>
<td>56 [48–63]</td>
<td>0.02</td>
</tr>
<tr>
<td>MS years (b)</td>
<td>12 [7.50–20.5]</td>
<td>19 [12–25]</td>
<td>13.5 [8–21.3]</td>
<td>0.13</td>
</tr>
<tr>
<td>EDSS (b)</td>
<td>6.50 [6–6.50]</td>
<td>6.50 [6–6.5]</td>
<td>6.50 [6–6.5]</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Values are presented as median [25–75 percentile]. CRI, Cognitive Reserve Index; CRI < 115, from low to medium cognitive reserve; CRI ≥ 115 medium-high/high cognitive reserve; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; PP, primary progressive; SP, secondary progressive; (a) Chi-squared for categorical variables (sex, MS Type). (b) T-test or Mann–Whitney test for the others.
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Table 2. Baseline clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CRI &lt; 115 (n = 36)</th>
<th>CRI ≥ 115 (n = 17)</th>
<th>Total (n = 53)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT T0 (m)</td>
<td>147 [68.3–260]</td>
<td>106 [32–157]</td>
<td>130 [60–237]</td>
<td>0.05</td>
</tr>
<tr>
<td>Speed25FW T0 (speed, m s(^{-1}))</td>
<td>0.558 [0.328–0.748]</td>
<td>0.427 [0.121–0.566]</td>
<td>0.495 [0.288–0.731]</td>
<td>0.06</td>
</tr>
<tr>
<td>Berg T0</td>
<td>40.0 [26.8–49.5]</td>
<td>30 [18–49]</td>
<td>39 [25–49]</td>
<td>0.24</td>
</tr>
<tr>
<td>FSS T0</td>
<td>0.558 [0.328–0.748]</td>
<td>0.427 [0.121–0.566]</td>
<td>0.495 [0.288–0.731]</td>
<td>0.06</td>
</tr>
<tr>
<td>MSWS12 T0</td>
<td>47.5 [42.5–55]</td>
<td>49 [43–55]</td>
<td>49 [43–55]</td>
<td>0.98</td>
</tr>
<tr>
<td>MSIS29mot T0</td>
<td>62.5 [50.5–75]</td>
<td>56 [53–75]</td>
<td>61 [51–75]</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Values are presented as median [25–75 percentile]. T0, baseline performance; 6MWT, Six-Minute Walk Test; Berg, Berg Balance Scale; PHQ-9, Patient Health Questionnaire; FSS, Fatigue Severity Scale; MSWS12, Multiple Sclerosis Walking Scale; MSIS29mot, multiple sclerosis impact (motor) scale; MSIS29psyc, multiple sclerosis impact (psychological) scale.

All the baseline demographic and clinical characteristics except for age were similar in the two groups (Tables 1 and 2). PwMS with a higher cognitive reserve were significantly older than the other group (60 vs. 54; \(F\(1,53\); p = 0.028; see Table 1). Considering the baseline imbalances, the analysis of covariance was performed, applying age, sex, disease duration, and severity (EDSS) as potential covariates.

After that, the two groups did not show significant differences in gait speed, endurance, or balance recovery after rehabilitation (Table 3).

Conversely, the patients with a CRI ≥ 115 obtained a statistically significant decrease in fatigue perception after motor rehabilitation (\(F = 4.757, p = 0.015\)) (Figure 2 and Table 3).

Figure 2. Fatigue recovery (FSS, Fatigue Severity Scale) after rehabilitation treatment—comparison between the two groups. Legend: grey: CRI < 115 and black: CRI ≥ 115. The averages obtained on the FSS scale for each group at the start of treatment (T0) and the end of treatment (T1) and the highest and lowest 95% confidence intervals, respectively.
Table 3. Functional and patient-reported outcomes according to the Cognitive Reserve Index.

|                      | T0                 | CRI < 115 (n = 36) | CRI ≥ 115 (n = 17) | CRI < 115 (n = 36) | CRI ≥ 115 (n = 17) | p-Value ANCOVA
<table>
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<tr>
<td></td>
<td>T1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ΔT1-T0</td>
</tr>
<tr>
<td>Speed (speed, m s(^{-1}))</td>
<td>0.558 [0.328–0.748]</td>
<td>0.427 [0.121–0.566]</td>
<td>0.552 [0.344–0.967]</td>
<td>0.420 [0.192–0.661]</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>147 [68.3–260]</td>
<td>106 [32–157]</td>
<td>160 [78.0–288]</td>
<td>128 [41.2–202]</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Berg</td>
<td>40.0 [26.8–49.5]</td>
<td>30 [18–49]</td>
<td>43.0 [30.3–52.0]</td>
<td>33 [26.0–46.0]</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>MSWS12</td>
<td>47.5 [42.5–55]</td>
<td>49 [43–55]</td>
<td>42.5 [31.8–51.0]</td>
<td>42 [33.0–51.0]</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>MSIS29mot</td>
<td>62.5 [50.5–75]</td>
<td>56 [53–75]</td>
<td>59.5 [45.0–67.5]</td>
<td>55 [38.0–66.0]</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median [25–75 percentile]. CRI, Cognitive Reserve Index; CRI < 115, from low to medium cognitive reserve; CRI ≥ 115, medium-high/high cognitive reserve; T0, variables at entry; T1, variables at the end of treatment; 6MWT, 6-Minute Walking Test; Berg, Berg Balance Scale; PHQ-9, Patient Health Questionnaire; FSS, Fatigue Severity Scale; MSWS12, Multiple Sclerosis Walking Scale; MSIS29mot, multiple sclerosis impact (motor) scale; MSIS29psyc, multiple sclerosis impact (psychological) scale. ANCOVA: Analysis of Covariance, applying age, sex, disease vintage, and severity as covariates.

4. Discussion

This study suggested that cognitive reserve can influence the perceived fatigue reduction after motor rehabilitation in PwMS and severe gait disability. According to the International Classification of Functioning Disability and Health (ICF), cognitive reserve is a critical factor between the personal and environmental factors influencing rehabilitation outcomes. This study is a secondary analysis of the RAGTIME trial [6] that failed to prove the superiority of RAGT on CT in progressive PwMS and severe gait disability. So far, only one study has investigated the possible CR influence on the motor treatment in PwMS, revealing how it can increase the attention instead of motor domains after home-based video game training [23]. Our findings are consistent with Castelli et al.’s hypothesis [23], suggesting an intramodal modulation of rehabilitation outcomes by cognitive reserve. Indeed, fatigue may be considered the outcome most related to the cognitive domain given its dual nature, both motor and cognitive.

Fatigue is a subjective feeling defined as “a reversible motor and cognitive impairment with reduced motivation and desire to rest. It could appear spontaneously or be brought on by mental or physical activity, humidity, acute infection and food ingestion” [26]. It can manifest in any life activity, such as work, family, social events, planning, and motivation. The gait rehabilitation in our study may have contributed favourably to reducing the fatigue in subjects without cognitive impairment and with high cognitive reserve. Therefore, CR could be considered a beneficial factor in motor rehabilitation. The role of motor training on fatigue has been controversial. Recent studies and a Cochrane review [27,28] showed a significant beneficial effect of exercise on the fatigue outcomes in this population.

Moreover, task-oriented practice, such as gait rehabilitation, may promote cortical functional reorganization in PwMS [29] and act upon maladaptive network recruitment, usually reported as one of the pathophysiology mechanisms of fatigue [30]. However, other studies should be conducted to find evidence of this effect on patients with severe disabilities [31]. Multidisciplinary treatments (physical and psychological approaches) showed excellent results on fatigue when applied in clinical practice, confirming the complexity of this symptom and its management [32].

The neural mechanisms that explain CR and fatigue have similarities. Fatigue in MS is associated with a malfunction mainly of the prefrontal cortex and frontoparietal pathways [33,34] and other subcortical regions [35]. At the same time, a high CR seems to be associated with greater efficiency in brain functioning in PwMS, mainly in terms of the functional connectivity preserved despite the atrophy of the grey matter [17] and lower intensity of the activation of some areas, including the dorsolateral prefrontal cortex [8]. Therefore,
the fatigue in MS could partially be explained by demyelination, axonal loss, functional cortical reorganization [36], increased cortical activation, impaired cortico-subcortical interaction, and deep grey matter involvement, such as the thalamus [37]. Instead, CR has a protective role in some of these potential consequences. Similarly, increased brain activation was found in PwMS, with fatigue during the execution of motor tasks [30], which was reduced in healthy subjects with higher cognitive reserve [38]. These elements could partially explain the possible relationship between CR and fatigue. Moreover, even if, in our sample, there was no difference in fatigue, depression, or disability at the baseline between the patients according to cognitive reserve, several modifiable factors, such as depression, self-efficacy, and years of education, can influence fatigue. Specifically, higher education is linked with lower fatigue, as perceived by PwMS [39]. Moreover, given the small sample size, differences can be masked. In our sample, PwMS with higher CR that perceived a more significant decrease in fatigue may probably have more resources, such as greater coping strategies, motivation, and functional network compensation, to reduce the fatigue perception after motor rehabilitation.

This study has several limitations. Firstly, the sample size was small, and the statistical design was not balanced: 17 people demonstrated higher cognitive reserve, and the remaining 36 had lower CR. However, this is not surprising considering that this is a secondary analysis of an RCT study. Moreover, considering that CRiq was administered in 53/72 PwMS enrolled in the RAGTIME trial, a selection bias must be considered. Secondly, the FSS was not the proper tool to assess the MS-related fatigue given that it does not capture the cognitive aspects of fatigue [40]. In future studies, the Modified Fatigue Impact Scale (MFIS) should be selected to understand the relationship between CR and fatigue considering that it encompasses psychosocial, motor, and cognitive components [41]. Thirdly, it would be interesting to study the effect of CR on PwMS with less gait disability, assuming a possibly more significant beneficial role on the motor treatment outcomes. At the same time, it would be interesting to study the effect of CR in different types of treatment to confirm or deny a more significant positive impact on the motor treatments.

Moreover, we can hypothesize that CR can impact the rehabilitation interventions that rely on cognitive engagement, such as virtual reality. Finally, the lack of neurophysiological (TMS or EEG) and neuroimaging (fNIRS or fMRI) data prevent us from providing insight into the relationship between cognitive reserve, fatigue, and gait rehabilitation.

5. Conclusions

This study suggests a potential influence of cognitive reserve in reducing fatigue after the motor rehabilitation in progressive multiple sclerosis with severe gait disability and without cognitive impairment. These preliminary findings may contribute to the definition of clinical practice and research recommendations. From a clinical perspective, the assessment of cognitive reserve through the Cognitive Reserve Index Questionnaire can be useful in detecting a meaningful contextual factor for motor rehabilitation outcomes, especially for fatigue. Our recommendation for research is to design clinical studies where PwMS are stratified for cognitive reserve to confirm our results. Moreover, the additional use of neurophysiological metrics will help to define the mechanisms underlying cognitive reserve’s effects in motor rehabilitation in PwMS.

Author Contributions: Conceptualization, A.B. (Ambra Balzeri) and S.S.; methodology, A.B. (Ambra Balzeri) and F.S.; formal analysis, A.B. (Ambra Balzeri) and N.L.; investigation, A.B. (Ambra Balzeri) and A.B. (Andrea Baroni); data curation, A.B. (Ambra Balzeri), N.L. and A.B. (Andrea Baroni); writing—original draft preparation, A.B. (Ambra Balzeri) and S.S.; writing—review and editing, F.S. and N.L.; supervision, A.B. (Antonella Bergonzoni); funding acquisition, F.M. and N.B. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ferrara University Hospital (number 101-2012).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data supporting this study’s findings are available from the corresponding author upon reasonable request.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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