*Journal of the International Neuropsychological Society* (2025), 1–9
doi:10.1017/S1355617725000086

## Research Article

# The relationship between biological sex, cognitive reserve, and cognition in multiple sclerosis

Manuela Altieri[1,2], Alvino Bisecco[1], Alessandro d'Ambrosio[1], Valentina Rippa[1], Mario Risi[1], Riccardo Maria Borgo[1], Daniela Buonanno[1], Teresa Cuomo[3], Alessandro Tessitore[1], Gabriella Santangelo[2] and Antonio Gallo[1]

[1]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy, [2]Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy and [3]Department of Neurology, Umberto I Hospital, Nocera Inferiore, Italy

### Abstract

**Objective:** Cognitive impairment is a common feature of multiple sclerosis (MS), and its severity may be influenced by several factors, such as biological sex and levels of cognitive reserve (CR). The relationship between sex, CR, and cognition has not yet been fully investigated. Therefore, the present study aimed to explore sex differences in CR building and the effect of sex and CR on cognitive performance in MS. **Method:** 233 participants underwent the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), the Stroop test, and the Cognitive Reserve Scale. The *t*-test was performed to compare sociodemographic variables, Italian adaptation of the Cognitive Reserve Scale, and cognitive test scores between sexes. To evaluate the effect of CR and sex and their interaction on cognitive performance several models of multivariate analyses of covariance were performed (dependent variables: all subtests of Brief Repeatable Battery of Neuropsychological Tests and Stroop scores; independent variables: sex and CR). Covariates included age, Expanded Disability Status Scale, and BDI-II scores. **Results:** Women showed higher levels of CR, particularly in daily activities ($t = -5.848$, $p<.001$), hobbies ($t = -2.591$, $p = .010$), and social life ($t = -2.362$, $p = .011$). Sex differences were noted in verbal memory and fluency (with women outperforming men) and processing speed (with men performing better than women). Multivariate analyses revealed a nonsignificant interaction between CR and sex on cognition ($\Lambda$=.950, $F_{(10,260)=}$.813, $p = .617$, $\eta_p^2 = .050$). **Conclusions:** CR and sex seemed to affect cognitive performance independently in pwMS. This highlights the importance of considering both factors in cognitive assessment, and that both sexes may benefit from specific psychoeducational training aimed at increasing CR levels.

**Keywords:** Sex; cognitive reserve; cognition; multiple sclerosis; cognitive performance; sex differences

(Received 7 August 2024; final revision 7 January 2025; accepted 28 February 2025)

### Statement of research significance

Cognitive impairment significantly impacts the quality of life in people with multiple sclerosis (pwMS), yet the potential combined effects of biological sex and cognitive reserve (CR) on cognitive outcomes remain underexplored. This study provides critical insights into how sex and CR independently influence cognitive performance in pwMS, highlighting that women generally exhibit higher CR levels, particularly in daily activities, hobbies, and social life. Despite observed sex differences in specific cognitive domains —verbal memory and fluency favoring women, and processing speed favoring men—the interaction between sex and CR on cognition was not statistically significant. These findings emphasize the need for tailored psychoeducational interventions to enhance CR, potentially mitigating/reducing the risk of cognitive deficits in MS. By addressing CR in both sexes, clinicians can develop more effective strategies for cognitive preservation and rehabilitation.

### Introduction

Cognitive dysfunctions in multiple sclerosis (MS) are one of the most common features of the disease (Grzegorski & Losy, 2017; Sumowski et al., 2018). People with MS (pwMS) experience more difficulties, compared with their healthy peers, in several cognitive domains, particularly in information processing speed, memory, and executive functions, with repercussions on quality of life and activities of daily living. The scientific literature on MS found that several factors may influence cognitive abilities, and most studies focused on the role of central nervous system (CNS) burden, evaluated by means of Magnetic Resonance Imaging (MRI) measures such as brain atrophy, lesion burden, or functional connectivity. For example, in a recent meta-analysis of 21 studies and more than 3000 MS patients, T1 and T2 weighted lesions strongly correlated with cognitive functions, particularly with task assessing processing speed and attention (Nabizadeh et al., 2024). Longitudinal changes in T2 lesions and atrophy were also

**Corresponding author:** Manuela Altieri; Email: manuela.altieri@unicampania.it
**Cite this article:** Altieri M., Bisecco A., d'Ambrosio A., Rippa V., Risi M., Borgo R.M., Buonanno D., Cuomo T., Tessitore A., Santangelo G., & Gallo A. The relationship between biological sex, cognitive reserve, and cognition in multiple sclerosis. *Journal of the International Neuropsychological Society*, 1–9, https://doi.org/10.1017/S1355617725000086

associated with changes in cognition, particularly in processing speed, attention, and verbal fluency domains (Simani et al., 2024). Subcortical volumetry (i.e., hippocampal and thalamic volumes) and white matter integrity were also correlated to cognitive performance in MS (Bisecco et al., 2021; Hulst et al., 2015; Schoonheim et al., 2012, 2014; Tóth et al., 2019), highlighting these metrics' critical role in predicting cognitive outcomes. Furthermore, several resting-state functional connectivity studies found a correlation between cognitive impairment and disruption of several networks, such as the default mode network and the frontoparietal network, as pointed out in a recent review (Mahmoudi et al., 2025). However, a recent study (Motyl et al., 2024), when further examining the relationship between CNS burden and cognitive performance, found that MRI measures only partially explain interindividual differences in cognitive outcomes, suggesting the need to explore additional factors.

As for sociodemographic factors linked to cognitive performance in MS, it has been found that biological sex may cause differences in cognition between men and women with MS, as also noted in healthy people and other neurological diseases (Cerri et al., 2019; Gibson & Galea, 2023; Li & Singh, 2014). Some studies on the prevalence and severity of cognitive impairment in MS reported sex differences: for example, one early study on this topic (Savettieri et al., 2004) found that cognitive impairment was more frequent in men with MS and it was associated with disease duration and physical disability; however, in women, no association between cognition and clinical variables was found. Similarly, another study pointed out that men tended to exhibit a more severe cognitive dysfunction (Schoonheim et al., 2012). However, other studies have found no significant sex differences in the prevalence of cognitive deficits in MS (Amato et al., 2006; Beatty & Aupperle, 2002) and suggested that biological sex may influence specific cognitive domains, but not overall prevalence.

As regards differences in specific cognitive domains, scores on verbal memory were consistently and significantly higher in women with MS (when compared with their male counterparts) in several studies (Altieri et al., 2021; Beatty & Aupperle, 2002; Donaldson et al., 2019; Motyl et al., 2024). However, there have also been other studies that have found no differences (Amato et al., 2006). However, the analysis of sex differences in other cognitive domains provided more discordant results, which may be ascribed to different study designs and study populations, and to the use of neuropsychological batteries in some studies that were not validated specifically for MS (Altieri et al., 2021; Amato et al., 2006; Beatty & Aupperle, 2002; Donaldson et al., 2019; Motyl et al., 2024).

There is evidence of other contributing factors to cognitive impairment in MS population, namely levels of depression, anxiety and/or fatigue. It has been found that higher depressive levels may exacerbate cognitive deficits through reduced motivation, impaired attention, and slower processing speed; moreover, longitudinal studies suggested that depression can also predict cognitive decline independent of disease burden, particularly in memory and executive functions (Feinstein et al., 2014; Rao et al., 1991). On the other hand, higher anxiety levels have been correlated with lower performance on tasks assessing attentional control, processing speed, and memory (Marrie et al., 2019, 2021; Ribbons et al., 2017), although there are also studies that do not confirm this correlation (Gill et al., 2019; Sandroff et al., 2019; Wallis et al., 2020). Regarding fatigue, one of the most debilitating symptoms of MS, trait, and cognitive fatigue were associated with poorer performance in sustained attention and information processing speed, working memory and executive functions (Guillemin et al., 2022). This association may be explained by overlapping pathophysiological mechanisms underlying fatigue and cognitive impairment, suggesting shared inflammatory and neurodegenerative processes (Chitnis et al., 2022).

Another factor linked to cognition in MS is disease duration (DD); indeed, longer DD has been associated with a higher prevalence of cognitive impairment, reflecting the cumulative impact of neurodegeneration and neuroinflammation of the CNS. Early in the disease course cognitive deficits may limited to specific domains such as processing speed and attention (Rao et al., 1991); as the disease progresses, cognitive deficits tend to be more pronounced and widespread, encompassing memory, executive function, and visuospatial abilities (Chiaravalloti & DeLuca, 2008). However, the trajectory of cognitive decline does not follow a uniform pattern across all patients, and it was theorized that CNS burden, along with levels of cognitive reserve (CR) may be responsible for these different clinical outcomes (Eijlers et al., 2018; Sumowski et al., 2013).

CR is a set of cognitively enriching life experiences (formal education, work, speaking multiple languages, leisure, and social activities) that allow coping with brain damage (Stern, 2009, 2012). The role of CR on cognitive performance in pwMS has been explored in several studies and meta-analyses (Artemiadis et al., 2020; Estrada-López et al., 2021; Santangelo, Altieri, Enzinger, et al., 2019; Santangelo, Altieri, Gallo, et al., 2019), revealing an association between higher levels of CR and better cognitive performance on tests evaluating several cognitive abilities, such as memory, processing speed, attention, and some executive functions. However, most studies employed educational attainment as a proxy of CR (Luerding et al., 2016; Machado et al., 2021; Scarpazza et al., 2013), whereas only a small portion of studies used other proxies limited to specific sets of abilities or activities (i.e., premorbid IQ, leisure activities, vocabulary knowledge) (Ifantopoulou et al., 2019; Maggi, Altieri, Risi, Rippa, Borgo, Lavorgna et al., 2024; Maggi, Altieri, Risi, Rippa, Borgo, Sacco, et al., 2024; Sumowski et al., 2010). These single indexes may not be able to fully explore engagement in a wide range of cognitively enhancing activities across several life stages; therefore, in recent years, researchers tried to produce questionnaires to evaluate a multitude of stimulating activities in adulthood, such as the Cognitive Reserve Scale (CRS) (Leon-Estrada et al., 2017), that explores the engagement of the individual on several sets of activities in various stages of adult life.

Several studies have highlighted the relationship between CR and the other abovementioned variables associated with cognitive performance in MS. For example, individuals with higher CR reported higher cognitive performance despite significant grey matter atrophy (Sumowski et al., 2013); moreover, there is evidence that CR may moderate the impact of subcortical grey matter atrophy on cognitive status (Machado et al., 2021). Regarding the association between CR and functional connectivity, CR was associated with preserving brain network efficiency, providing a compensatory mechanism that buffers the effects of CNS burden on cognitive performance (Fuchs et al., 2019; Leavitt et al., 2024; Lopez-Soley et al., 2020). Resting-state functional MRI studies revealed that pwMS with high CR had reduced intrinsic functional connectivity within the dorsal anterior insula, a key hub of the salience network (Bizzo et al., 2021).

CR has also been examined in relation to psychological factors. For example, higher CR was linked to lower levels of depression (Artemiadis et al., 2020); moreover, it may moderate the

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

relationship between physical disability and depressive symptoms, suggesting that individuals with higher CR are less likely to experience depression even when they have a significant disability (Cadden et al., 2019). Similarly, Bradson and colleagues (Bradson et al., 2023) reported that CR seems to moderate the relationship between fatigue and depressive symptomatology, suggesting that CR may play a protective role against the psychological burden of MS.

Despite these advancements, the relationship between sex, CR and cognition (i.e., sex differences on the level of engaging in several sets of cognitively stimulating activities linked to CR), or how sex and the CR have an impact on cognition were not fully investigated. Considering the above-mentioned studies and the evidence in other conditions (e.g., subjective cognitive decline, Alzheimer's disease) that show sex differences in CR (Giacomucci et al., 2021; Letenneur et al., 2000), there is a need to fill the abovementioned gaps in literature.

Therefore, in a sample of pwMS, the present study aimed to explore sex differences in engaging in cognitively stimulating activities associated with CR, and to investigate the possible effect of sex and CR on performance on several cognitive domains.

## Materials and methods

### *Participants*

pwMS were enrolled at the MS Center of the I Division of Neurology, University of Campania "Luigi Vanvitelli", Naples, Italy. We performed a consecutive sampling, in which every eligible participant who met the inclusion and exclusion criteria was enrolled in the study without omission, provided they were available during the recruitment period. To be included in the study, all participants had to meet the following inclusion criteria: a) diagnosis of MS according to the latest McDonald diagnostic criteria (Thompson et al., 2018) and relapsing-remitting MS phenotype; b) age above 18 years old; c) no relapses or corticosteroids therapy within 1 month from the evaluation; d) no neurological comorbidities; e) no assumption of psychotropic drugs that could interfere with the neuropsychological examination. All participants were informed about the purposes of the study and signed an informed consent form before proceeding to the clinical and neuropsychological evaluation. The research was approved by the Local Ethics Committee and performed following the Declaration of Helsinki.

### *Clinical and neuropsychological evaluation*

Each participant was evaluated by a trained neurologist with expertise in MS, who collected clinical data (i.e., disease duration, disability, disease modifying therapies); moreover, the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) was administered to evaluate the degree of physical disability. The Beck Depression Inventory, second edition (BDI-II) was completed by each participant to evaluate levels of depressive symptomatology. Moreover, a trained psychologist collected sociodemographic data (i.e., age, educational status, work activity based on the International Standard Classification of Occupations) and administered Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N) to assess cognitive performance (Amato et al., 2006; Rao et al., 1991; Tedone et al., 2024). BRB-N is a neuropsychological battery that includes several cognitive tests evaluating different cognitive domains:

*The Selective Reminding Test (SRT)* measures verbal learning and long-term verbal memory through a list-learning procedure over six trials. The participant is required to immediately recall as many words as possible from a list of 12 words that is pronounced in full only on trial 1. In trials 2–6 only the words that are immediately recalled by the participant are presented. Two scores are produced: Long term storage (SRT-LTS), which indicates the sum of words that are recalled without reminding in each trial, and the Consistent long term retrieval (SRT-CLTR) which indicates how much the retrieval of the words is organized and consistent. Moreover, after ~ 10 minutes, the administrator asks the participant to recall das many words of the list as possible, without any cue. The score of the delayed recall of SRT (SRT-D) is the total number of recalled words. Higher scores of the SRT-LTS, SRT-CLTR and SRT-D are associated to better performance.

*The Spatial Recall Test (SPART)* is a measure of visuospatial learning and long-term visuospatial memory. The psychologist presents a visual stimulus (a grid with 10 painted black tokens) for ten seconds; after that, the participant is asked to place 10 tokens on an empty grid in the exact pattern that was shown to them. The stimulus is presented for 3 trials. The SPART score is calculated by summing up the number of the tokens placed in the correct position in each trial. As for the SRT, the SPART has also a delayed recall task (SPART-D), that it is administered after ~ 10 minutes. The number of tokens put in the correct position is the raw score of SPART-D. Higher scores of the SPART and SPART-D are associated to better performance.

*The Symbol Digit Modalities Test (SDMT)* assesses attention and information processing speed, and it is considered one of the most sensitive tests to detect cognitive disorders in MS (Benedict et al., 2017). The administrator presents a page headed with a key that associates numbers from 1 to 9 to nine different symbols. Below the key, there are several rows of symbols, and the patient is asked to orally report the correct number associated to each symbol. Only the first 10 items are completed with the guidance of the psychologist. The score of the SDMT is calculated by reporting the number of correct responses in 90 s; the higher the score, the better is the performance.

*The Paced Auditory Serial Addition Test* is employed to assess levels of auditory information processing speed, cognitive flexibility, and calculation ability. The participant listens to a tape recording of digits, and it is asked to add each number to the one that immediately precedes it. The task is presented twice: for the PASAT 3" task, each number is presented every 3 s, whereas in the PASAT 2" the presentation rate is every 2 s. The scores of PASAT 3" and 2" are the total number of correct responses for the two tasks; higher scores are indicative of a better performance.

*The Word List Generation (WLG)* is a task that evaluates semantic verbal fluency. The patient is asked to report all word that fall within the category "fruit and vegetables". Score is calculated by summing up the correct words pronounced in 90 s. Higher scores of the WLG are associated to a better performance.

In addition to the BRB-N, *the Stroop test (STROOP)* was administered to measure sustained attention and some executive functions, such as inhibitory control. The STROOP presents 3 trials: in trial 1, the participant is asked to read some words enlisting different colors; in trial 2, the participant needs to report the name of the color of several rows of squares; in trial 3, called the interference task, there are several rows of words indicating different colors, but the meaning of the word and the ink employed to write the word does not match. The patient is asked to pronounce the colors that the words are printed in. The

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

psychologist reports the time needed to reach half of the task (STROOP T ½; Amato et. al, 2006). For the STROOP 30", higher scores reflect a better performance; as for the STROOP T ½, higher scores indicate a worse performance. For this study, we employed the STROOP T ½ score.

CR was assessed through the Italian adaptation of the Cognitive Reserve Scale (I-CRS) (Altieri et al., 2018). The I-CRS is a 24-item self-administered questionnaire that evaluates how much a person is involved in several cognitively stimulating activities. Based on the operational definition of CR provided by León-Estrada and colleagues (Leon-Estrada et al., 2017), the items of the I-CRS reflect 4 groups of activities that, taken together, form the CR construct. These factors are: a) daily activities (I-CRS_DA): activities linked to functional autonomy, such as the ability to manage engagements and appointments in everyday life, to do chores and to be able to use widespread technology; b) training-information (I-CRS_TI): activities related to the acquisition of formal and informal knowledge; c) hobbies (I-CRS_H): engagement in leisure activities; d) social life (I-CRS_SL): the ability to create and maintain social relationship.

I-CRS is based on a 5-point Likert scale; scores range from 0 to 4, with higher scores indicating a higher engagement in that specific activity. The level of cognitive stimulation is assessed in three life stages: young adulthood (18–35 years), adulthood (36–64 years), and late adulthood ( ≥65 years). Participants are required to complete the questionnaire once, twice, or three times, according to their age: adults and older adults need to complete the I-CRS for their current life stage and the previous ones. The total I-CRS score is obtained by producing the mean score on each item in every life stage. Moreover, scores of I-CRS subscales can be calculated by summing up the scores of the items of the single subscale.

### Statistical analysis

Statistical analysis was performed with SPSS (SPSS Statistics, version 25.0). Means and standard deviations, or medians and minimum-maximum ranges were calculated as appropriate. The Chi square test was performed to examine the relationship between sex and overall cognitive impairment. pwMS defined as cognitively impaired had at least two tests failed with a Z score ≤ 1.5 according to the latest normative data (Tedone et al., 2024). The *t*-test for independent samples (or the Chi square test, as appropriate) were performed to compare sociodemographic variables, I-CRS and cognitive test scores between men and women with MS. To evaluate the effect of CR and sex, and a possible interaction between these factors on cognitive performance several models of multivariate analyses of covariance (MANCOVAs) were performed. Dependent variables were SRT-LTS, SRT-CLTR, SRT-D, SPART, SPART-D, SDMT, PASAT 3", PASAT 2", WLG, and STROOP scores; the independent variables were sex (men vs women) and CR (high vs low CR; each MANCOVA included one of the following: I-CRS total score, I-CRS_DA, I-CRS_TI, I-CRS_H, and I-CRS_SL). In each model, CR dichotomous level was calculated by computing the median score of I-CRS on the whole sample: pwMS with a CR score under or above the median value were allocated to the low CR or high CR group, respectively. Covariates included: age, EDSS, and BDI-II scores. A *p*-value of .05 was considered the cut-off for statistical significance. Bonferroni correction for multiple comparisons was applied to reduce the probability of incurring in type I error.

## Results

The whole sample included 233 participants (95 men, 138 women) with MS, with age ranging from 18 to 64 years old, education ranging from 5 to 24 years and disease duration ranging from 0 to 32 years. Men and women with MS did not differ significantly for sociodemographic variables, except for frequencies in specific work activities: when compared to men with MS, women with MS were more likely to be unemployed or to be working as "Professionals"; on the other hand, men were more likely to be craft and related trades workers. As regards clinical variables, women reported higher scores at BDI-II compared to men. Demographic, clinical, and neuropsychological characteristics of the sample are shown in Table 1.

### Sex differences in cognition and CR levels

Cognitive impairment was present in 45.26% of men with MS and 39.85% of women with MS. The proportion of participants who showed cognitive impairment did not differ by biological sex ($\chi 2 = .675$, $p = 4.11$). The independent samples *t*-test revealed that women performed significantly better on WLG ($t = -4.091$, $p < .001$) and SRT-D ($t = -2.145$, $p = .033$), whereas men with MS showed higher scores on PASAT 3" ($t = 2.326$, $p = .021$). Women with MS reported higher scores on I-CRS than men with MS ($t = -2.372$, $p = .019$). As regards I-CRS subscales (see Figure 1), women reported higher scores on I-CRS_DA ($t = -5.848$, $p < .001$), I-CRS_H ($t = -2.591$, $p = .010$), and I-CRS_SL ($t = -2.362$, $p = .011$), whereas the comparison of scores of I-CRS_TI ($t = 1.791$, $p = .075$) revealed no difference between sexes.

### Multivariate analyses of sex and CR effects on cognitive performance

#### Interaction between CR (I-CRS) and sex

After the correction for multiple comparisons, the MANOVA (see Table 2) revealed a significant main effect of CR level ($\Lambda = .876$, $F_{(10,154)=} 2.185$, $p = .021$, $\eta_p^2 = .124$) and sex ($\Lambda = .836$, $F_{(10,260)=} 3.017$, $p = .002$, $\eta_p^2 = .164$) on cognitive performance, but the interaction between CR and sex did not reach statistical significance ($\Lambda = .950$, $F_{(10,154)=} .813$, $p = .617$, $\eta_p^2 = .050$).

Univariate analyses revealed a significant main effect of CR on SRT-LTS ($F_{(1,195)} = 6.551$, $p = .011$, $\eta_p^2 = .039$), SRT-CLTR ($F_{(2,195)} = 12.252$, $p = .011$, $\eta_p^2 = .039$), SPART ($F_{(2,195)} = 5.482$, $p = .020$, $\eta_p^2 = .033$), SDMT ($F_{(2,195)} = 9.582$, $p = .002$, $\eta_p^2 = .056$), SRT-D ($F_{(1,195)} = 11.829$, $p = .001$, $\eta_p^2 = .068$), SPART-D ($F_{(1,195)} = 4.503$, $p = .035$, $\eta_p^2 = .027$), and WLG ($F_{(1,195)} = 5.724$, $p = .018$, $\eta_p^2 = .034$) scores. Moreover, a significant main effect of sex was found on PASAT 3" ($F_{(1,195)} = 4.819$, $p = .030$, $\eta_p^2 = .029$; men>women), and WLG ($F_{(1,195)} = 6.837$, $p = .010$, $\eta_p^2 = .040$; women>men) scores.

#### Interaction between daily activities (I-CRS_DA) and sex

*Daily activities (I-CRS_DA) and sex.* A significant main effect of sex on cognitive performance ($\Lambda = .858$, $F_{(10,154)=} 2.549$, $p = .007$, $\eta_p^2 = .142$) was found. I-CRS_DA subscale ($\Lambda = .938$, $F_{(10,154)=} 1.010$, $p = .438$, $\eta_p^2 = .062$) and the interaction between I-CRS_DA and sex ($\Lambda = .946$, $F_{(10,154)=} .878$, $p = .555$, $\eta_p^2 = .054$) were not significant. Univariate analyses revealed a significant main effect of sex on PASAT 3" ($F_{(1,195)} = 5.620$, $p = .019$, $\eta_p^2 = .033$; men > women), and WLG ($F_{(1,195)} = 4.664$, $p = .032$, $\eta_p^2 = .028$; women > men) scores.

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

**Table 1.** Demographic, clinical and neuropsychological characteristics of the sample

| | | Whole Sample ($N = 233$) | Men with MS ($N = 95$) | Women with MS ($N = 138$) | $t$ ($p$) |
|---|---|---|---|---|---|
| **Age (years)** | | 37.48 (11.23) | 37.12 (11.18) | 37.73 (11.31) | −.411 (.682) |
| **Education (years)** | | 13.89 (3.49) | 13.37 (3.17) | 14.25 (3.66) | −1.913 (.057) |
| **Disease duration (months)** | | 59.76 (87.61) | 58.31 (84.57) | 60.77 (89.99) | −.207 (.836) |
| **EDSS (median – min, max)** | | 2 (0–6.5) | 2 (0–6.5) | 2 (0–6.5) | −.742 (.459) |
| **DMTs (n, %)** | **None** | 73 (31.3%) | 28 (29.5%) | 45 (32.6%) | 2.007 (0.157) [a] |
| | **Alemtuzumab** | 4 (1.7%) | 2 (2.1%) | 2 (1.4%) | 0 (1) [a] |
| | **Azatioprine** | 3 (1.3%) | 2 (2.1%) | 1 (0.7%) | 0.171 (0.679) [a] |
| | **Cladribine** | 6 (2.6%) | 3 (3.3%) | 3 (2.2%) | 0 (1) [a] |
| | **Dimethyl fumarate** | 35 (15%) | 11 (11.6%) | 24 (17.4%) | 2.501 (0.114) [a] |
| | **Fingolimod** | 27 (11.6%) | 16 (16.8%) | 11 (8%) | 0.467 (0.494) [a] |
| | **Glatiramer acetate** | 5 (2.1%) | 2 (2.1%) | 3 (2.2%) | 0.101 (0.751) [a] |
| | **Interferon beta 1a** | 13 (5.6%) | 5 (5.3%) | 8 (5.8%) | 0.351 (0.554) [a] |
| | **Natalizumab** | 23 (9.9%) | 6 (6.3%) | 17 (12.3%) | 2.790 (0.095) [a] |
| | **Ocrelizumab** | 23 (9.9%) | 8 (8.4%) | 15 (10.9%) | 1.090 (0.296) [a] |
| | **Ozanimod** | 5 (2.1%) | 2 (2.1%) | 3 (2.2%) | .101 (0.751) [a] |
| | **Ponesimod** | 3 (1.3%) | 2 (2.1%) | 1 (0.7%) | 0.171 (0.679) [a] |
| | **Siponimod** | 6 (2.6%) | 2 (2.1%) | 4 (2.9%) | 0.343 (0.558) [a] |
| | **Teriflunomide** | 7 (3%) | 6 (6.3%) | 1 (0.7%) | 2.047 (0.153) [a] |
| **Work activity** | **Not working** | 86 (36.9%) | 24 (25.3%) | 62 (44.9%) | 13.19 (**<0.001**) |
| | **Managers and Legislators** | 9 (3.9%) | 6 (6.3%) | 3 (2.2%) | 1.22 (0.269) [a] |
| | **Professionals** | 28 (12%) | 6 (6.3%) | 22 (15.9%) | 8.36 (**0.004**) [a] |
| | **Technicians and associate professionals** | 14 (6%) | 4 (4.2%) | 10 (7.2%) | 2.160 (0.142) [a] |
| | **Clerical support workers** | 33 (14.2%) | 16 (16.8%) | 17 (12.3%) | 0.03 (0.864) [a] |
| | **Service and sales workers** | 34 (14.6%) | 15 (15.8%) | 19 (13.8%) | 0.45 (0.503) [a] |
| | **Skilled agricultural, forestry and fishery workers** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (1) [a] |
| | **Craft and related trades workers** | 8 (3.4%) | 7 (7.4%) | 1 (0.7%) | 4.5 (**0.034**) [a] |
| | **Plant and machine operators and assemblers** | 1 (0.4) | 1 (1.1%) | 0 (0%) | 1 (0.317) [a] |
| | **Elementary occupations** | 16 (6.9%) | 12 (12.6%) | 4 (2.9%) | 5.33 (**0.021**) [a] |
| | **Armed forces occupations** | 4 (1.7%) | 4 (4.2%) | 0 (0%) | 4 (0.046) [a] |
| **SRT-LTS** | | 40.82 (14.37) | 39.36 (14.94) | 41.83 (13.94) | −1.294 (.197) |
| **SRT-CLTR** | | 31.34 (14.67) | 29.40 (15.60) | 32.67 (13.89) | −1.680 (.094) |
| **SRT-D** | | 7.74 (2.60) | 7.30 (2.79) | 8.04 (2.42) | −2.145 (**.033**) |
| **SPART** | | 19.71 (4.85) | 19.64 (4.98) | 19.76 (4.78) | −.183 (.855) |
| **SPART-D** | | 6.71 (2.24) | 6.84 (2.24) | 6.63 (5.26) | .708 (.479) |
| **SDMT** | | 49.64 (13.27) | 47.99 (13.34) | 50.78 (13.15) | −1.584 (.115) |
| **PASAT 3''** | | 38.72 (12.18) | 40.94 (12.29) | 37.20 (11.91) | 2.326 (**.021**) |
| **PASAT 2''** | | 29.03 (9.73) | 30.49 (10.45) | 28.02 (9.09) | 1.918 (.056) |
| **WLG** | | 21.75 (5.52) | 20.02 (5.45) | 22.93 (5.26) | −4.091 (**<.001**) |
| **STROOP** | | 67.77 (32.54) | 71.78 (40.71) | 65.01 (25.23) | 1.564 (.119) |
| **I-CRS** | | 50.95 (12.78) | 48.56 (13.04) | 52.58 (12.39) | −2.372 (**.019**) |
| **BDI-II** | | 10.91 (9.39) | 9.0 (8.07) | 12.2 (10.02) | −2.528 (**.012**) |

*Note:* [a] = chi-square test was performed. Unless otherwise specified, all values are reported as mean (standard deviation). Statistically significant values are reported in bold. EDSS = Expanded Disability Status Scale, SRT-LTS = Selective reminding test long term storage, SRT-CLTR = Selective reminding test consistent long term retrieval, SRT-D = Selective reminding test delayed recall, SPART = Spatial recall test, SPART-D = Spatial recall test Delayed Recall, SDMT = Symbol Digit Modalities Test, PASAT 3'' and 2'' = Paced Auditory Serial Addition Test, 3 secondss and 2 secondss, WLG = Word List Generation, STROOP = Stroop Test, I-CRS = Cognitive Reserve Scale Italian version, BDI-II = Beck Depression Inventory, second edition.

*Training-information (I-CRS_TI) and sex.* The MANOVA revealed a significant main effect of sex on cognition ($\Lambda = .798$, $F_{(10,154)=} 3.902$, $p < .001$, $\eta_p^2 = .202$); nor I-CRS_TI ($\Lambda = .932$, $F_{(10,154)=} .1.124$, $p = .348$, $\eta_p^2 = .068$), nor the interaction between sex and I-CRS_TI ($\Lambda = .915$, $F_{(10,154)=} .1.422$, $p = .175$, $\eta_p^2 = .085$) were significant. At the univariate level, sex had a significant impact on SRT-D ($F_{(1,195)} = 5.510$, $p = .020$, $\eta_p^2 = .033$; women>men) and WLG ($F_{(1,195)} = 10.945$, $p = .001$, $\eta_p^2 = .063$; women>men).

*Hobbies (I-CRS_H) and sex.* The results revealed a significant main effect of sex ($\Lambda = .835$, $F_{(10,154)=} 3.023$, $p = .002$, $\eta_p^2 = .165$) and I-CRS_H ($\Lambda = .791$, $F_{(10,154)=} 4.042$, $p < .001$, $\eta_p^2 = .209$) on cognitive performance; on the other hand, the interaction between sex and I-CRS_H was not significant ($\Lambda = .969$, $F_{(10,154)=} 487$, $p = .897$, $\eta_p^2 = .031$). Univariate analyses were performed, and a main effect of sex was found on PASAT 3'' ($F_{(1,195)} = 6.719$, $p = .010$, $\eta_p^2 = .040$; men>women), PASAT 2'' ($F_{(1,195)} = 3.987$, $p = .048$, $\eta_p^2 = .024$; men>women) and WLG ($F_{(1,195)} = 5.380$, $p = .022$, $\eta_p^2 = .032$; women>men) scores, whereas a main effect of I-CRS_H was found on SRT-LTS ($F_{(1,195)} = 24.840$, $p < .001$, $\eta_p^2 = .133$; high I-CRS_H > low I-CRS_H), SRT-CLTR ($F_{(1,195)} = 29.116$, $p < .001$, $\eta_p^2 = .152$; high I-CRS_H > low I-CRS_H), SPART ($F_{(1,195)} = 7.011$, $p = .009$, $\eta_p^2 = .041$; high I-CRS_H > low I-CRS_H), SDMT ($F_{(1,195)} = 11.925$, $p = .001$, $\eta_p^2 = .069$; high I-CRS_H > low I-CRS_H), SRT-D ($F_{(1,195)} = 28.280$, $p < .001$, $\eta_p^2 = .149$; high I-CRS_H > low I-CRS_H), SPART-D ($F_{(1,195)} = 5.281$, $p = .023$, $\eta_p^2 = .032$; high I-CRS_H > low I-CRS_H), WLG ($F_{(1,195)} = 19.826$, $p < .001$, $\eta_p^2 = .109$; high I-CRS_H > low I-CRS_H), and STROOP ($F_{(1,195)} = 4.083$, $p = .045$, $\eta_p^2 = .025$; high I-CRS_H > low I-CRS_H).

*Social life (I-CRS_SL) and sex.* A significant main effect of sex on cognitive performance ($\Lambda = .861$, $F_{(10,154)=} 2.472$, $p = .009$, $\eta_p^2 = .139$) was found. I-CRS_SL subscale ($\Lambda = .895$, $F_{(10,154)=} 1.787$, $p = .067$, $\eta_p^2 = .105$) and the interaction between I-CRS_DA and sex ($\Lambda = .907$, $F_{(10,154)=} .1.569$, $p = .121$, $\eta_p^2 = .093$) were not significant. Univariate analyses revealed a significant main effect of sex on PASAT 3'' ($F_{(1,195)} = 4.208$, $p = .042$, $\eta_p^2 = .025$;

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

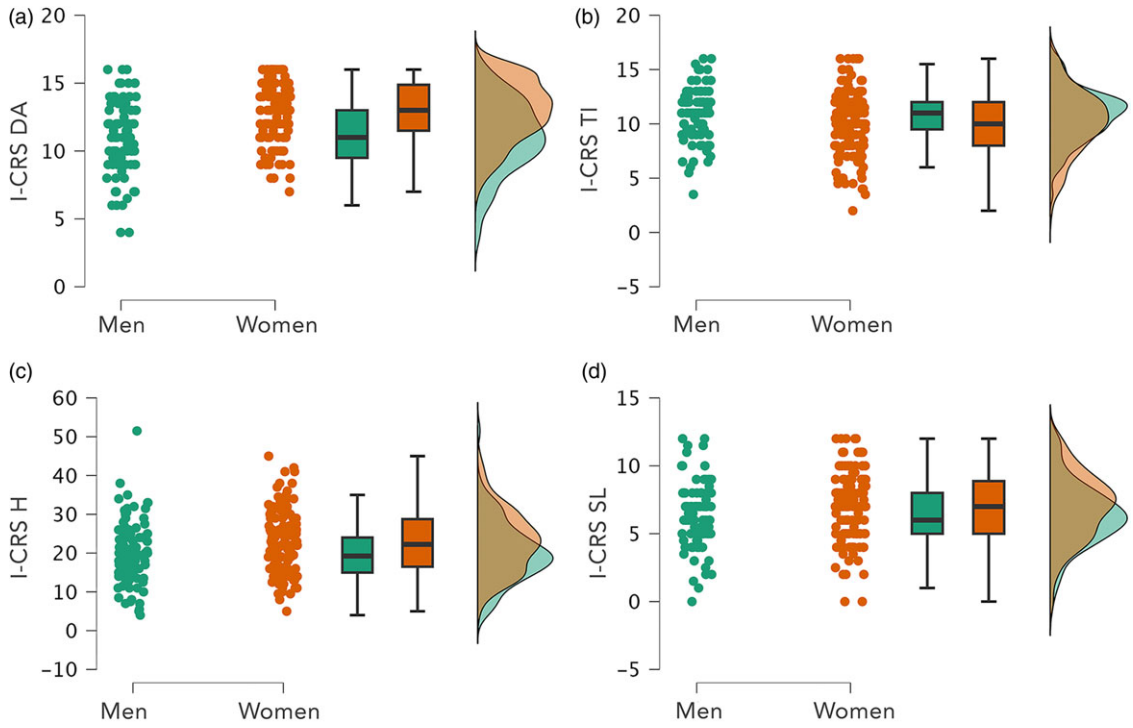


**Figure 1.** Raincloud plots of independent samples t-tests regarding the comparison between men and women with MS on: a) scores of the daily activities subscale of I-CRS (I-CRS_DA); b) scores of the training-information subscale of I-CRS (I-CRS_TI); c) scores of the hobbies subscale of I-CRS (I-CRS_H); d) scores of the social life subscale of I-CRS (I-CRS_SL).

**Table 2.** Multivariate analysis of sex, CR, and their interaction effect on cognitive performance in people with MS

| MANOVA | Df | Λ | *F* | *p* | $\eta_p^2$ |
|---|---|---|---|---|---|
| **CR** | 10,154 | .876 | 2.185 | **.021** | .124 |
| **Sex** | 10,154 | .836 | 3.017 | **0.002** | .164 |
| **CR*Sex** | 10,154 | .950 | .813 | .617 | .050 |

*Note:* Df = degrees of freedom, Λ = Wilks lambda, FF = Fischer test, p*p* = probability value, $\eta_p^2$ = partial eta squared. Significant values are reported in bold.

men > women), and WLG ($F_{(1,195)} = 4.289$, $p = .040$, $\eta_p^2 = .026$; women > men) scores.

## Discussion

Our study aimed at evaluating, in a sample of pwMS, the relationship between biological sex, CR, and cognition; in particular, we analyzed possible sex differences in levels of engagement in cognitively enhancing activities (which reflect the construct of CR) and explored the possible effect of sex and CR on performance in several cognitive domains. In this study, CR was measured with a specific questionnaire, the CRS, that evaluates how much a person engages in activities related to functional autonomy, formal and informal knowledge, leisure and social activities.

As regards the possible sex differences in levels of engagement in cognitively enhancing activities, the comparison of levels of CR in women and men with MS revealed that women with MS showed significantly higher levels of CR when compared with their male peers. The comparison of groups of activities related to CR (by comparing single I-CRS subscales) revealed that women reported higher levels of engagement in daily, leisure, and social activities. In contrast, mean scores of the engagement in activities related to the acquisition of knowledge were comparable between the two sexes. As noted in previous studies on CR in other neurological diseases (i.e., Alzheimer's disease) some proxies of CR were highly gendered (Subramaniapillai et al., 2021): for example, until a few decades ago men had easier access to formal education and acquisition of knowledge; on the other hand, women were more prone to engage in daily activities, mostly related to housekeeping. Modernization and evolution of gender norms may have had an impact on the engagement of specific cognitively stimulating activities (such as the acquisition of knowledge) thus reducing sex differences to a negligible level; on the other hand, the other sets of activities linked to CR would not have to be affected yet by the abovementioned factors, and therefore they remain highly gendered. Hence, CR activities, especially those related to functional autonomy, leisure, and social activities should be carefully assessed in pwMS, particularly in men, who may benefit from specific training to increase engagement in these activities.

Moreover, our results corroborated the hypothesis of sex differences in cognitive performance in pwMS. For example, women showed an advantage in the semantic verbal fluency task. This is in line with the literature on healthy participants (Capitani et al., 1999, 2005; Filippetti & Allegri, 2011; Munro et al., 2012) and in other studies on MS patients (Altieri et al., 2021; Amato et al., 2006). However, it should be noted that a recent meta-analysis revealed that sex differences in semantic fluency tasks may be category-dependent (Hirnstein et al., 2023): since our study employed the WLG from BRB-N, in which participants were required to list names of only one category (fruits and vegetables), future studies should employ tools that allow evaluating multiple categories to verify if differences between sexes are category-dependent in MS, too.

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

Furthermore, in our study women with MS showed higher scores on recall of verbal material when compared to men with MS, a finding that confirms previous MS studies (Altieri et al., 2021; Beatty & Aupperle, 2002; Donaldson et al., 2019). A recent meta-analysis of 617 studies with more than 1 million participants (without neurological diseases or pathologies that could affect neuropsychological performance) found a female advantage for several verbal memory tasks, such as the ability to remember words, sentences and prose, and nameable images; on the other hand, men were more capable in spatial memory tasks, such as remembering routes and abstract images (Asperholm et al., 2019). In neurological diseases, there is evidence that women outperform men in verbal memory in amnestic mild cognitive impairment, independently from levels of hippocampal volume loss, temporal lobe hypometabolism and cortical amyloid-β deposition; however, in patients with clinically defined Alzheimer's disease, sex differences were attenuated (Sundermann et al., 2017). The authors explained this finding by postulating a form of sex-specific CR that protects from the effects of brain burden up to some point of the disease; however, when the threshold of protection is surpassed, cognitive decline in women with AD is more accelerated than in men, as previously demonstrated (Stern, 2002). Since the cognitive profile of pwMS rarely evolves in frank dementia, our results may suggest a mechanism comparable to what is found in people with mild cognitive impairment. However, future studies are needed to further expand this aspect by employing neuroimaging techniques to evaluate lesion load in the MS population and a longitudinal study design to evaluate if sex difference in delayed verbal memory is reduced when the disease progresses.

Sex differences were also noted in auditory information processing speed and sustained attention, with men reporting higher scores than women. Studies on sex differences in PASAT scores reported a similar performance between men and women in healthy participants and pwMS (Amato et al., 2006; Wiens et al., 1997; Wingenfeld et al., 1999). However, other studies found an advantage in men in pwMS (Altieri et al., 2021). This discrepancy in our results may be due to different study designs and differences in the sociodemographic and clinical variables of the samples. Given that the PASAT is one of the most employed tests in MS, the possible sex difference in performance in this task deserves further investigation in future studies.

Our multivariate analyses revealed a significant effect of CR in cognition only in models with the I-CRS total scale and the I-CRS_H subscale: higher CR, and in particular higher engagement in leisure activities, was associated with a better performance in verbal and spatial memory, processing speed, verbal fluency and inhibitory control tests. Several leisure activities, such as reading and engaging in hobbies, have been related to increased performance in several cognitive domains, including verbal memory and processing speed (Sumowski et al., 2010, 2016). These results particularly emphasize the possibility for individuals to actively increase their levels of CR throughout life by engaging in a specific set of cognitively stimulating activities. The first (and most) studies on CR have focused on the role of formal education as a protective variable on cognitive performance. However, most adults acquire knowledge in formal settings (school, university) only in early adulthood. In this case, our results would confirm how even activities that can be easily performed at any stage of adult life can play a role in preserving cognitive performance. Therefore, clinicians should evaluate CR levels at the time of diagnosis of MS to more precisely indicate which activities should be most strengthened in the individual; moreover, during routine visits, they should encourage patients to engage in these activities and check their progress.

The possible interaction effect between sex and CR was revealed to be nonsignificant on neuropsychological tests administered in our study; that could mean that the impact of CR on cognitive performance did not depend on being a man or a woman with MS, but this finding must be taken with caution due to unavailability of other data (e.g, CNS burden metrics). However, due to the significant association between specific cognitively stimulating activities and cognitive performance in MS, our findings may prompt clinicians to address MS patients with cognitive impairment to specific tailored neuropsychological rehabilitation programs or to enable cognitive stimulation programs focusing on CR-building activities regardless of the sex of the MS patient.

Our study, however, is not exempt from limitations. Due to the cross-sectional nature of this study, it was not possible to verify if, and to what extent, CR protects from cognitive decline over time, and if an interaction between CR levels and sex can emerge in follow-up evaluations. Secondly, this study lacks a control group, so future studies may include a group of healthy peers to evaluate if the interaction effect between CR and sex on cognitive performance is present in healthy participants. Moreover, the impact of CR and sex differences on cognition in participants with progressive forms of MS was not evaluated in the present study. This could be an area of investigation for future studies. Finally, MRI data were unavailable, so we did not control for lesion load, cerebral volumes or CNS burden metrics. Studies focusing on the effect of CNS burden metrics and biological sex on cognition were discordant, with some studies revealing that sex differences in cognitive performance in pwMS were independent of CNS burden (Motyl et al., 2024), and some other studies that demonstrated a better neurocognitive functioning and brain resilience (evaluated by using MRI metrics) in women (Leavitt et al., 2024); nonetheless, this is an area of paramount importance that deserves to be further investigated in future studies.

Taken together, our results highlight the association between CR and specific cognitive domains, and that this association is independent of the sex of the MS patient.

**Acknowledgements.** The authors thank Taysia del Pozzo, Genoveffa Maddaloni, and Arianna Mazzella for their support in acquiring neuropsychological data.

**Funding statement.** None.

**Competing interests.** None.

**Ethical approval statement.** The present study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (Naples, Italy).

## References

Altieri, M., Santangelo, G., Bisecco, A., D'Ambrosio, A., Rippa, V., Capuano, R., Giuliano, F., Matrone, F., Bonavita, S., Tedeschi, G., & Gallo, A. (2021). The influence of biological sex on cognitive performance in people with multiple sclerosis. *Journal of the Neurological Sciences*, *429*, 118175.

Altieri, M., Siciliano, M., Pappacena, S., Roldán-Tapia, M. D., Trojano, L., & Santangelo, G. (2018). Psychometric properties of the Italian version of the Cognitive Reserve Scale (I-CRS). *Neurological Sciences*, *39*(8), 1383–1390.

Amato, M. P., Portaccio, E., Goretti, B., Zipoli, V., Ricchiuti, L., De Caro, M. F., Patti, F., Vecchio, R., Sorbi, S., & Trojano, M. (2006). The Rao's brief repeatable battery and Stroop test: Normative values with age, education and gender corrections in an Italian population. *Multiple Sclerosis Journal*, *12*(6), 787–793.

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

Artemiadis, A., Bakirtzis, C., Ifantopoulou, P., Zis, P., Bargiotas, P., Grigoriadis, N., & Hadjigeorgiou, G. (2020). The role of cognitive reserve in multiple sclerosis: A cross-sectional study in 526 patients. *Multiple Sclerosis and Related Disorders*, *41*, 102047.

Asperholm, M., Högman, N., Rafi, J., & Herlitz, A. (2019). What did you do yesterday? A meta-analysis of sex differences in episodic memory. *Psychological Bulletin*, *145*(8), 785–821.

Beatty, W. W., & Aupperle, R. L. (2002). Sex differences in cognitive impairment in Multiple Sclerosis. *The Clinical Neuropsychologist*, *16*(4), 472–480, APA PsycInfo®.

Benedict, R. H., DeLuca, J., Phillips, G., LaRocca, N., Hudson, L. D., Rudick, R., & Multiple Sclerosis Outcome Assessments Consortium (2017). Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England)*, *23*(5), 721–733. https://doi.org/10.1177/1352458517690821

Bisecco, A., Capuano, R., Caiazzo, G., d'Ambrosio, A., Docimo, R., Cirillo, M., Russo, A., Altieri, M., Bonavita, S., Rocca, M. A., Filippi, M., Tedeschi, G., & Gallo, A. (2021). Regional changes in thalamic shape and volume are related to cognitive performance in multiple sclerosis. *Multiple Sclerosis Journal*, *27*(1), 134–138.(Houndmills, Basingstoke, England)

Bizzo, B. C., Arruda-Sanchez, T., Tobyne, S. M., Bireley, J. D., Lev, M. H., Gasparetto, E. L., & Klawiter, E. C. (2021). Anterior insular resting-state functional connectivity is related to cognitive reserve in Multiple Sclerosis. *Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging*, *31*(1), 98–102.

Bradson, M. L., Cadden, M. H., Riegler, K. E., Thomas, G. A., Randolph, J. J., & Arnett, P. A. (2023). Cognitive reserve moderates the effects of fatigue and depressive symptoms in Multiple Sclerosis. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *38*(8), 1597–1609.

Cadden, M. H., Guty, E. T., & Arnett, P. A. (2019). Cognitive reserve attenuates the effect of disability on depression in Multiple Sclerosis. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *34*(4), 495–502.

Capitani, E., Barbarotto, R., & Laiacona, M. (2005). Gender differences and the brain representation of semantic knowledge. *Brain and Language*, *95*(1), 56–57.

Capitani, E., Laiacona, M., & Barbarotto, R. (1999). Gender affects word retrieval of certain categories in semantic fluency tasks. *Cortex*, *35*(2), 273–278.a Journal Devoted to the Study of the Nervous System and Behavior

Cerri, S., Mus, L., & Blandini, F. (2019). Parkinson's Disease in women and men: What's the difference? *Journal of Parkinson's Disease*, *9*(3), 501–515.

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in Multiple Sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151.

Chitnis, T., Vandercappellen, J., King, M., & Brichetto, G. (2022). Symptom interconnectivity in Multiple Sclerosis: A narrative review of potential underlying biological disease processes. *Neurology and Therapy*, *11*(3), 1043–1070.

Donaldson, E., Patel, V. P., Shammi, P., & Feinstein, A. (2019). Why sex matters: A cognitive study of people with multiple sclerosis. *Cognitive and Behavioral Neurology*, *32*(1), 39–45, APA PsycInfo®.https://doi.org/10.1097/WNN.0000000000000188,

Eijlers, A. J. C., van Geest, Q., Dekker, I., Steenwijk, M. D., Meijer, K. A., Hulst, H. E., Barkhof, F., Uitdehaag, B. M. J., Schoonheim, M. M., & Geurts, J. J. G. (2018). Predicting cognitive decline in Multiple Sclerosis: A 5-year follow-up study. *Brain: A Journal of Neurology*, *141*(9), 2605–2618.

Estrada-López, M., García-Martín, S., & Cantón-Mayo, I. (2021). Cognitive dysfunction in Multiple Sclerosis: Educational level as a protective factor. *Neurology International*, *13*(3), 335–342.

Feinstein, A., Magalhaes, S., Richard, J.-F., Audet, B., & Moore, C. (2014). The link between Multiple Sclerosis and depression. *Nature Reviews Neurology*, *10*(9), 507–517.

Filippetti, V. A., & Allegri, R. F. (2011). [image omitted] Verbal fluency in Spanish-speaking children: Analysis model according to task type, clustering, and switching strategies and performance over time. *The Clinical Neuropsychologist*, *25*(3), 413–436.

Fuchs, T. A., Benedict, R. H. B., Bartnik, A., Choudhery, S., Li, X., Mallory, M., Oship, D., Yasin, F., Ashton, K., Jakimovski, D., Bergsland, N., Ramasamy, D. P., Weinstock-Guttman, B., Zivadinov, R., & Dwyer, M. G. (2019). Preserved network functional connectivity underlies cognitive reserve in multiple sclerosis. *Human Brain Mapping*, *40*(18), 5231–5241.

Giacomucci, G., Mazzeo, S., Padiglioni, S., Bagnoli, S., Ferrari, C., Bracco, L., Nacmias, B., Sorbi, S., & Bessi, V. (2021). Gender differences in cognitive reserve: Implication for subjective cognitive decline in women. *Journal of the Neurological Sciences*, *429*, 117827.

Gibson, C., & Galea, L. A. M. (2023). *Sex differences in brain function and dysfunction*. Springer Cham, Switzerland. https://doi.org/10.1007/978-3-031-26723-9.

Gill, S., Santo, J., Blair, M., & Morrow, S. A. (2019). Depressive symptoms are associated with more negative functional outcomes than anxiety symptoms in persons with Multiple Sclerosis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *31*(1), 37–42, APA PsycInfo®.

Grzegorski, T., & Losy, J. (2017). Cognitive impairment in multiple sclerosis—A review of current knowledge and recent research. *Reviews in the Neurosciences*, *28*(8), 845–860.

Guillemin, C., Lommers, E., Delrue, G., Gester, E., Maquet, P., & Collette, F. (2022). The complex interplay between trait fatigue and cognition in Multiple Sclerosis. *Psychologica Belgica*, *62*(1), 108–122.

Hirnstein, M., Stuebs, J., Moè, A., & Hausmann, M. (2023). Sex/Gender differences in verbal fluency and verbal-episodic memory: A meta-analysis. *Perspectives on Psychological Science*, *18*(1), 67–90.

Hulst, H. E., Schoonheim, M. M., Van Geest, Q., Uitdehaag, B. M. J., Barkhof, F., & Geurts, J. J. G. (2015). Memory impairment in multiple sclerosis: Relevance of hippocampal activation and hippocampal connectivity. *Multiple Sclerosis Journal*, *21*(13), 1705–1712.(Houndmills, Basingstoke, England)

Ifantopoulou, P., Artemiadis, A. K., Bakirtzis, C., Zekiou, K., Papadopoulos, T.-S., Diakogiannis, I., Hadjigeorgiou, G., Grigoriadis, N., & Orologas, A. (2019). Cognitive and brain reserve in multiple sclerosis—A cross-sectional study. *Multiple Sclerosis and Related Disorders*, *35*, 128–134.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444–1452.

Leavitt, V. M., Dworkin, J. D., Kalina, T., & Ratzan, A. S. (2024). Sex differences in brain resilience of individuals with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *87*, 105646.

Leon-Estrada, I., Garcia-Garcia, J., & Roldan-Tapia, L. (2017). [Cognitive reserve scale: Testing the theoretical model and norms]. *Revista De Neurologia*, *64*(1), 7–16.

Letenneur, L., Launer, L. J., Andersen, K., Dewey, M. E., Ott, A., Copeland, J. R., Dartigues, J. F., Kragh-Sorensen, P., Baldereschi, M., Brayne, C., Lobo, A., Martinez-Lage, J. M., Stijnen, T., & Hofman, A. (2000). Education and Risk for Alzheimer's Disease: Sex Makes a Difference EURODEM Pooled Analyses. EURODEM Incidence Research Group. *American Journal of Epidemiology*, *151*(11), 1064–1071.

Li, R., & Singh, M. (2014). Sex differences in cognitive impairment and Alzheimer's disease. *Frontiers in Neuroendocrinology*, *35*(3), 385–403.

Lopez-Soley, E., Solana, E., Martínez-Heras, E., Andorra, M., Radua, J., Prats-Uribe, A., Montejo, C., Sola-Valls, N., Sepulveda, M., Pulido-Valdeolivas, I., Blanco, Y., Martinez-Lapiscina, E. H., Saiz, A., & Llufriu, S. (2020). Impact of cognitive reserve and structural connectivity on cognitive performance in Multiple Sclerosis. *Frontiers in Neurology*, *11*, 581700, https://doi.org/10.3389/fneur.2020.581700

Luerding, R., Gebel, S., Gebel, E.-M., Schwab-Malek, S., & Weissert, R. (2016). Influence of formal education on cognitive reserve in patients with Multiple Sclerosis. *Frontiers in Neurology*, *7*, 46.

Machado, R., Lima, C., d'Almeida, O. C., Afonso, A., Macário, C., Castelo-Branco, M., Sousa, L., Santana, I., & Batista, S. (2021). Protective effects of cognitive and brain reserve in multiple sclerosis: Differential roles on social cognition and 2018;classic cognition2019. *Multiple Sclerosis and Related Disorders*, *48*, 102716.

Maggi, G., Altieri, M., Risi, M., Rippa, V., Borgo, R. M., Lavorgna, L., Bonavita, S., Buonanno, D., D'Ambrosio, A., Bisecco, A., Santangelo, G., Tessitore, A., & Gallo, A. (2024). Cognitive reserve predicts long-term cognitive trajectories in relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal*, *31*(1), 107–116.(Houndmills, Basingstoke, England), 13524585241302167

Maggi, G., Altieri, M., Risi, M., Rippa, V., Borgo, R. M., Sacco, R., Buonanno, D., D'Ambrosio, A., Bisecco, A., Santangelo, G., & Gallo, A. (2024). Vocabulary knowledge as a reliable proxy of cognitive reserve in multiple sclerosis: A validation study. *Neurological Sciences: Official Journal of the Italian*

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press

*Neurological Society and of the Italian Society of Clinical Neurophysiology*, *45*(8), 3931–3938.

Mahmoudi, F., McCarthy, M., & Nelson, F. (2025). Functional MRI and cognition in multiple sclerosis—Where are we now? *Journal of Neuroimaging*, *35*(1), e13252.

Marrie, R. A., Patel, R., Bernstein, C. N., Bolton, J. M., Graff, L. A., Marriott, J. J., Hitchon, C. A., Figley, C. R., Kornelsen, J., & Fisk, J. D. (2021). Anxiety and depression affect performance on the symbol digit modalities test over time in MS and other immune disorders. *Multiple Sclerosis Journal*, *27*(8), 1284–1292.(Houndmills, Basingstoke, England)

Marrie, R. A., Patel, R., Figley, C. R., Kornelsen, J., Bolton, J. M., Graff, L., Mazerolle, E. L., Marriott, J. J., Bernstein, C. N., & Fisk, J. D. (2019). Diabetes and anxiety adversely affect cognition in Multiple Sclerosis. *Multiple Sclerosis and Related Disorders*, *27*, 164–170.

Motyl, J., Friedova, L., Ganapathy Subramanian, R., Vaneckova, M., Fuchs, T. A., Krasensky, J., Blahova Dusankova, J., Kubala Havrdova, E., Horakova, D., & Uher, T. (2024). Brain MRI disease burden and sex differences in cognitive performance of patients with Multiple Sclerosis. *Acta Neurologica Belgica*, *124*(1), 109–118.

Munro, C. A., Winicki, J. M., Schretlen, D. J., Gower, E. W., Turano, K. A., Muñoz, B., Keay, L., Bandeen-Roche, K., & West, S. K. (2012). Sex differences in cognition in healthy elderly individuals. *Aging, Neuropsychology, and Cognition*, *19*(6), 759–768.

Nabizadeh, F., Pirahesh, K., Azami, M., Moradkhani, A., Sardaripour, A., & Ramezannezhad, E. (2024). T1 and T2 weighted lesions and cognition in Multiple Sclerosis: A systematic review and meta-analysis. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia*, *119*, 1–7.

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in Multiple Sclerosis. *Neurology*, *41*(5), 685–691.

Ribbons, K., Lea, R., Schofield, P. W., & Lechner-Scott, J. (2017). Anxiety levels are independently associated with cognitive performance in an Australian Multiple Sclerosis patient cohort. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(2), 128–134, APA PsycInfo®.

Sandroff, B. M., Pilutti, L. A., & Motl, R. W. (2019). Cardiorespiratory fitness and cognitive processing speed in Multiple Sclerosis: The possible roles of psychological symptoms. *Multiple Sclerosis and Related Disorders*, *27*, 23–29.

Santangelo, G., Altieri, M., Enzinger, C., Gallo, A., & Trojano, L. (2019). Cognitive reserve and neuropsychological performance in Multiple Sclerosis: A meta-analysis. *Neuropsychology*, *33*(3), 379–390.

Santangelo, G., Altieri, M., Gallo, A., & Trojano, L. (2019). Does cognitive reserve play any role in Multiple Sclerosis? A meta-analytic study. *Multiple Sclerosis and Related Disorders*, *30*, 265–276.

Savettieri, G., Messina, D., Andreoli, V., Bonavita, S., Caltagirone, C., Cittadella, R., Farina, D., Fazio, M. C., Girlanda, P., Le Pira, F., Liguori, M., Lugaresi, A., Nocentini, U., Reggio, A., Salemi, G., Tedeschi, G., Trojano, M., Valentino, P., & Quattrone, A. (2004). Gender-related effect of clinical and genetic variables on the cognitive impairment in Multiple Sclerosis. *Journal of Neurology*, *251*(10), 1208–1214.

Scarpazza, C., Braghittoni, D., Casale, B., Malagú, S., Mattioli, F., di Pellegrino, G., & Ladavas, E. (2013). Education protects against cognitive changes associated with Multiple Sclerosis. *Restorative Neurology and Neuroscience*, *31*(5), 619–631.

Schoonheim, M. M., Popescu, V., Rueda Lopes, F. C., Wiebenga, O. T., Vrenken, H., Douw, L., Polman, C. H., Geurts, J. J. G., & Barkhof, F. (2012). Subcortical atrophy and cognition: Sex effects in Multiple Sclerosis. *Neurology*, *79*(17), 1754–1761.

Schoonheim, M. M., Vigeveno, R. M., Rueda Lopes, F. C., Pouwels, P. J. W., Polman, C. H., Barkhof, F., & Geurts, J. J. G. (2014). Sex-specific extent and severity of white matter damage in Multiple Sclerosis: Implications for cognitive decline. *Human Brain Mapping*, *35*(5), 2348–2358.

Simani, L., Molaeipour, L., Kian, S., & Leavitt, V. M. (2024). Correlation between cognitive changes and neuroradiological changes over time in Multiple Sclerosis: A systematic review and meta-analysis. *Journal of Neurology*, *271*(8), 5498–5518.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 448–460.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006–1012.

Subramaniapillai, S., Almey, A., Natasha Rajah, M., & Einstein, G. (2021). Sex and gender differences in cognitive and brain reserve: Implications for Alzheimer's disease in women. *Frontiers in Neuroendocrinology*, *60*, 100879.

Sumowski, J. F., Benedict, R., Enzinger, C., Filippi, M., Geurts, J. J., Hamalainen, P., Hulst, H., Inglese, M., Leavitt, V. M., Rocca, M. A., Rosti-Otajarvi, E. M., & Rao, S. (2018). Cognition in Multiple Sclerosis: State of the field and priorities for the future. *Neurology*, *90*(6), 278–288.

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Riccitelli, G., Comi, G., DeLuca, J., & Filippi, M. (2013). Brain reserve and cognitive reserve in Multiple Sclerosis: What you've got and how you use it. *Neurology*, *80*(24), 2186–2193.

Sumowski, J. F., Rocca, M. A., Leavitt, V. M., Riccitelli, G., Meani, A., Comi, G., & Filippi, M. (2016). Reading, writing, and reserve: Literacy activities are linked to hippocampal volume and memory in Multiple Sclerosis. *Multiple Sclerosis Journal*, *22*(12), 1621–1625.

Sumowski, J. F., Wylie, G. R., Gonnella, A., Chiaravalloti, N., & Deluca, J. (2010). Premorbid cognitive leisure independently contributes to cognitive reserve in Multiple Sclerosis. *Neurology*, *75*(16), 1428–1431.

Sundermann, E. E., Biegon, A., Rubin, L. H., Lipton, R. B., Landau, S., & Maki, P. M. (2017). Does the female advantage in verbal memory contribute to underestimating Alzheimer's Disease pathology in women versus men? *Journal of Alzheimer's disease : JAD*, *56*(3), 947–957.

Tedone, Nò, Vizzino, C., Meani, A., Gallo, A., Altieri, M., D'Ambrosio, A., Pantano, P., Piervincenzi, C., Tommasin, S., De Stefano, N., Cortese, R., Stromillo, M. L., Rocca, M. A., Sala, S., Valsasina, P., Pagani, E., Preziosa, P., Giannì, C., Petsas, N. . . . Filippi, M. (2024). The brief repeatable battery of neuropsychological tests (BRB-N) version a: Update of Italian normative data from the Italian Neuroimaging Network Initiative (INNI). *Journal of Neurology*, *271*(4), 1813–1823.

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X. . . . Cohen, J. A. (2018). Diagnosis of Multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, *17*(2), 162–173.

Tóth, E., Faragó, P., Király, A., Szabó, N., Veréb, D., Kocsis, K., Kincses, B., Sandi, D., Bencsik, K., Vécsei, L., & Kincses, Z. T. (2019). The contribution of various MRI parameters to clinical and cognitive disability in Multiple Sclerosis. *Frontiers in Neurology*, *9*, 1–11.

Wallis, O., Bol, Y., Köhler, S., & van Heugten, C. (2020). Anxiety in Multiple Sclerosis is related to depressive symptoms and cognitive complaints. *Acta Neurologica Scandinavica*, *141*(3), 212–218.

Wiens, A. N., Fuller, K. H., & Crossen, J. R. (1997). Paced auditory serial addition test: Adult norms and moderator variables. *Journal of Clinical and Experimental Neuropsychology*, *19*(4), 473–483.

Wingenfeld, S. A., Holdwick, D. J., Davis, J. L., & Hunter, B. B. (1999). Normative data on computerized paced auditory serial addition task performance. *The Clinical Neuropsychologist*, *13*(3), 268–273.

https://doi.org/10.1017/S1355617725000086 Published online by Cambridge University Press