DOI: 10.21554/hrr.042510

The Effect of Cognitive Reserve on the Cognitive Status of Persons With Multiple Sclerosis

Review scientific paper

Jovana Pavlovic, Ivana Sretenovic and Goran Nedovic

University of Belgrade, Faculty of Special Education and Rehabilitation, Serbia

Received: 2024/09/04
Accepted: 2024/12/04

Abstract

This literature review examined publications on cognitive reserve and multiple sclerosis cognitive function. Educational attainment proxied cognitive reserve. Google Scholar and KoBSON were used for the literature review. Twelve publications were examined. Cognitive reserve improves multiple sclerosis patients' cognitive functions, according to selected literature. Higher education, as a measure of cognitive reserve, protects the population under investigation against cognitive decline and disability. Cognitive performance is also linked to education quality, cognitive enrichment, and years of education. Regular exercise, reading, and hard work can help low-educated people protect their cognitive reserve. As more research demonstrates that cognitively stimulating activities outside of formal education can improve cognitive function in people with multiple sclerosis, the reviewed studies underscore the need for additional research into parameters influencing cognitive reserve.

Keywords: *Cognitive Deficits, Education, Protective Role*

Multiple sclerosis (MS) is a progressive inflammatory disease of the central nervous system (CNS) that causes grey and white matter lesions, axonal terminal damage, and brain atrophy (Calabrese et al., 2010; Weissert, 2013). MS has a distinct clinical and pathological spectrum that results in a wide range of motor, sensory, cognitive, and psychosocial effects. In terms of cognitive abnormalities, it is believed that 40-60% of patients with MS exhibit cognitive impairment or decline at some time throughout the disease's progression (Amato et al., 2001, as cited in Lovera & Kovner, 2012, p. 619). Attention, information processing efficiency, executive functioning, information processing speed, and long-term memory are among the most frequent cognitive abnormalities in MS (Chiaravalloti & DeLuca, 2008). The variability of cognitive profiles in MS cannot be entirely explained by clinical variables such as disease duration or physical handicap, or by brain magnetic resonance

Correspondence to: Ivana Sretenovic, University of Belgrade – Faculty of Special Education and Rehabilitation, Serbia.
Email: ivanasretenovic@fasper.bg.ac.rs

imaging findings, which demonstrate brain tissue damage (Benedict et al., 2004; Filippi et al., 2010). Other disorders, such as Alzheimer's disease, natural ageing (Stern, 2012), and Parkinson's disease (Ciccarelli et al., 2017; Guzzetti et al., 2019), have revealed an incomplete relationship between cognitive status and structural findings.

As a possible response to the previous observations, the theory of cognitive reserve (CR) emerged, attempting to explain the individual differences that allow some people to cope with the same level of brain pathology without developing cognitive deficits, whereas others develop deficits associated with the disease (Stern, 2009). CR's role is to modify the relationship between brain pathology and clinical manifestation; that is, high CR acts as a protective factor in the development of various neurological diseases, whereas low CR acts as a vulnerability factor in the manifestation of the disease's clinical picture (Barnett et al., 2006). The immediacy with which cognitive reserve is measured reflects its unique characteristics (Jones et al., 2011). Specifically, the characteristics involved in the assessment of CR include education, occupation, and leisure activities, implying that they rely on life experience elements that can influence CR and its function in brain illness (Grotz et al., 2016). It should be noted that years of education are the most commonly used parameter in measuring CR (Avila et al., 2020), which is especially important in the study of CR in MS, given that the disease typically begins between the ages of 20 and 30, usually after formal education has been completed (Martins Da Silva et al., 2015). An growing number of research have led to MS being seen through the lens of the CR theory, demonstrating that a higher CR reduces the deleterious impact of disease load on the cognitive status of patients with MS (Sumowski & Leavitt, 2013).

The aim of this study was to assess the existing literature in order to select and analyse articles that investigated the impact of CR on the cognitive status of patients with MS. One of CR's parameters was education.

Method

This literature research was conducted using the Google Scholar and the service of the Serbian Library Consortium for Coordinated Acquisition (KoBSON). The research was conducted in July 2024, using the following keywords: multiple sclerosis, cognitive reserve, education, proxy. Articles were included based on the following criteria: they had to be available in their whole, published in English between 2010. and 2024, have a title or abstract including a key word, focus on the impact of CR on cognitive status of individuals with MS, and use education as a parameter of CR. Upon inputting the specified keywords into the Google Scholar search engine, a total of 10.500 articles were found. Subsequently, after modifying the publication range of articles to include data from 2010. to 2024, a further 8.210 articles were detected. The titles and abstracts of review articles, master's and graduate theses, books, and publications that were not available in their whole and not written in English were excluded from the analysis. Thus, a total of 10 articles were identified that correspond to the search criteria defined on the Google Scholar search engine. The KoBSON search identified two other articles that match the specified criteria.

Results with Discussion

The next section will provide a description and analysis of research that examined the effects of CR on the cognitive function of individuals with MS. The studies under analysis are displayed in Table 1.

Table 1.
Review of the Literature on the Impact of CR on the Cognitive Status of People with MS

Authors and year	Aim	Sample	Instruments	The most important results
Scarpazza et al., 2013	To investigate the influence of CR and the experienced fatigue on cognitive function.	Experimental group: 50 subjects with relapsing-remitting MS Control group: 157 healthy subjects.	Paced Auditory Serial Addition Task (PASAT); Modified Fatigue Impact Scale (MFIS).	Subjects with MS who have attained a high level of education exhibit less cognitive impairment on neuropsychological tests in comparison to subjects with a lower level of education.
Modica et al., 2015	To examine how CR and brain reserve affect subcortical gray matter atrophy and cognitive decline in people with MS over a three-year period.	Experimental group: 71 subjects with relapsing-remitting and secondary progressive MS Control group: 23 healthy subjects.	Symbol Digit Modalities Test (SDMT); California Verbal Learning Test (CVLT2); Brief Visouspatial Memory Test revised (BVMTR); Magnetic resonance imaging (MRI).	High CR has been shown to be a protective factor in cognitive decline associated with subcortical gray matter atrophy.
Conway et al., 2022	To examine the longitudinal influence of educational attainment on the speed of data processing and on the work status of persons with MS over a period of three years.	13.732 subjects with different types of MS.	Processing speed test; Employment status; Patient Determined Disease Steps.	Increased educational attainment enhances data processing speed and provides protection against unstable employment status, while its effect over the three-year period is minimal.
Benedict et al., 2010	To examine whether differences in CR have a protective role in cognitive dysfunction in people with MS, over a period of five years.	91 subjects with relapsing-remitting, secondary progressive and primary progressive MS.	Paced Auditory Serial Addition Task (PASAT); Symbol Digit Modalities Test (SDMT); North American Adult Reading Test (NAART).	A higher CR has a protective role in the progression of cognitive dysfunction in people with MS.
Luerding et al., 2016	To examine the influence of formal education on the state of CR in people with MS.	128 subjects with relapsing-remitting, secondary progressive and primary progressive MS.	27 tests that assessed basic cognitive functions, attention, executive functions, visual perception and construction, memory and learning, problem solving and language; Occupation; Physical activity; Reading habits.	Stronger correlation exists between longer formal education and superior neurocognitive performance. The benefit of a lengthier formal education in comparison to a shorter one can be counterbalanced by more regular engagement in physical exercise, reading, and demanding professional pursuits.

Table 1 (continued).
Review of the Literature on the Impact of CR on the Cognitive Status of People with MS

Grant et al., 2023	To examine how three sociobehavioral parameters of CR (years of education, quality of education, and cognitive enrichment) differ in predicting the cognitive performance of people with MS.	82 subjects with relapsing-remitting, secondary progressive and primary progressive MS.	Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS); Complete neurological examination; Expanded Disability Status Scale (EDSS); Wechsler Test of Adult Reading (WTAR); Cognitive Reserve Scale (CRS).	Quality of education and cognitive enrichment are more strongly related to cognitive performance than years of education.
Martins Da Silva et al., 2015	To examine education as an indicator of CR, while controlling for demographic, clinical, and genetic characteristics of subjects.	Experimental group: 419 subjects with relapsing-remitting, secondary progressive and primary progressive MS Control group: 159 healthy subjects.	Complete neurological examination; Expanded Disability Status Scale (EDSS); Multiple Sclerosis Severity Scale (MSSS); Mini-Mental Exemination (MMSE); Attentive Matrices (AM); Digit Span; Corsi Block-Tapping Test; Auditory Verbal Learning Test (AVLT); 30-minute recall and 30-minute recognition; Sentence Repetition; Letter Word Fluency; Wisconsin Card Sorting Test (WCST); Hospital Anxiety and Depression Scale (HADS); Genetic parameters of HLA-DRB1 and apolipoprotein E.	The protective effect of education and the justification of using education as a parameter of CR were confirmed. The robust association with education was independent of other clinical and demographic variables.

Table 1 (continued).
Review of the Literature on the Impact of CR on the Cognitive Status of People with MS

Della Corte et al., 2018	To examine the relationship between two parameters of CR and cognition in MS.	147 subjects with relapsing-remitting and secondary progressive MS.	Complete neurological examination; Expanded Disability Status Scale (EDSS); Rao's brief repeatable battery - version A (BRB); Stroop Color-Word Interference Test (SCWIT); The Wechsler Adult Intelligence Scale (WAIS VOC); Chicago Multiscale Depression Inventory (CMDI); Fatigue Severity Scale (FSS).	Empirical evidence demonstrated a significant correlation between VOC, rather than years of education, and the outcomes of applied neuropsychological tests. The level of education attained a positive link with the executive functions of the participants.
Rimkus et al., 2018	To examine the frequency and characteristics of cognitive impairment in subjects with MS of different educational status. To examine the correlation between T2 lesions (disease burden variable) and cognitive performance in different stages of MS.	Experimental group: 136 subjects with MS Control group: 65 healthy subjects.	Complete neurological examination; Expanded Disability Status Scale (EDSS); Wechsler Adult Intelligence Scale (WAIS III); Hopkins Verbal Learning Test - revised (HVLTR); Brief Visuospatial Memory Test - revised (BVMT-R); Controlled Oral Association Test (COWAT); Modified Wisconsin Card Sorting Test (MWCST); Symbol Digit Modality Test (SDMT); Stroop test; Magnetic resonance imaging (MRI).	A higher frequency of cognitive impairment was found among respondents with lower educational levels. The protective effects of higher education are stronger in the early stages of the disease (less than five years).
Nunnari et al., 2016	To examine the influence of certain demographic and clinical variables on the cognitive outcome of subjects with MS, assuming that CR has a protective role against cognitive impairment due to disease burden.	66 subjects with relapsing-remitting, secondary progressive and primary progressive MS.	Rao Brief Repeatable Battery of Neuropsychological Tests (BRB-N); Cognitive Reserve Index Questionnaire (CRIq); Magnetic resonance imaging (MRI).	The CRIq score proved to be a significant predictor of attention, information processing speed, working memory and verbal learning. Education and occupation subscores are significantly related to the cognitive performance of the participants.

Table 1 (continued).
Review of the Literature on the Impact of CR on the Cognitive Status of People with MS

Sumowski et al., 2012	To examine whether intellectual enrichment protects individuals with secondary progressive MS from cognitive decline in the domains of memory and cognitive efficiency.	Experimental group: 25 subjects with secondary progressive MS Control group: 25 healthy subjects.	Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Task (PASAT); Logical Wechsler Memory Scale Revised - Memory tasks; Open-trial Selective Reminding Test - total learnig and delayed recall scores; Wechsler Abbreviated Scale of Intelligence (WASI) - Subtest Vocabulary; Wide Range Achievement Test - Reading subtest.	MS subjects with lower CR had worse cognitive performance compared to the control group in both examined domains, but this difference disappeared at higher reserve levels, both in the domain of cognitive efficiency and in the domain of memory.
Machado et al., 2021	To examine the effects of cognitive and brain reserve on social cognition and compare these effects with the effects of the same on "classical cognition".	Experimental group: 60 subjects with relapsing-remitting and secondary progressive MS Control group: 60 healthy subjects.	Complete neurological examination; Expanded Disability Status Scale (EDSS); Theory of Mind (ToM) testing: Revised “Reading the Mind in the Eyes” Test; ToM videos test; Rao adaptation of Symbol Digit Modalities Test - oral version (SDMT); Rao adaptation of Paced Auditory Serial Addition Test (PASAT); Brief Visuospatial Memory Test-Revised (BVMT); California Verbal Learning Test (CVLT); Judgment of Line Orientation Test (JLOT); Controlled Oral Word Association Test (COWAT); Wisconsin Card Sorting Test (WCST); Magnetic resonance imaging (MRI).	CR and brain reserve have a different protective role in MS, brain reserve showed a positive effect on social cognition, while CR had a positive effect on "classical" cognitive domains.

A study undertook in Italy, sought to investigate the influence of CR (as evaluated by years of education and occupation) and the occurrence of fatigue on the cognitive function of individuals with MS. Fifty relapsing-remitting MS patients were included in the study; their average age was 39.65, their average educational attainment was 12.88 years, their average illness duration was 105.22 months, and their age at disease beginning was 30.60 years. All participants had not experienced exacerbations in the month prior to the study. The control group comprised of 157 healthy participants who were matched on age, education, and gender. Cognitive performance was assessed using the Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977, as cited in Scarpazza et al., 2013), a tool that evaluates working memory and speed of information processing. Participants were categorized based on their educational attainment, distinguished as low educational level (less than 13 years of education) and high educational level (greater than 13 years of education). The findings

indicated that adults with MS with a lower level of education had inferior performance on the PASAT test compared to healthy individuals with the same level of education. However, there was no significant difference found between the control group and the experimental group with a higher level of education. Furthermore, compared to MS participants with high levels of education, it was demonstrated that MS subjects with low levels of education performed worse on the PASAT test. This was not the case in the control group, where people with higher and lower levels of education displayed comparable performance. This finding indicates that higher education acts as a safeguard against cognitive impairments induced by multiple sclerosis. Higher education, on the other hand, will have less of an impact on healthy people's cognitive performance.

A three-year longitudinal study examined the impact of brain reserve (BR) and CR on subcortical grey matter (SGM) atrophy and cognitive decline in MS patients. The study sample comprised of 71 individuals diagnosed with MS, with 48 identified as relapsing-remitting MS and 23 as secondary-progressive MS. The average age of the participants was 46.1 years, and the average duration of the condition was 11.5 years. Control group comprised of 23 healthy people. Participants underwent thorough neuropsychological testing to assess cognitive processing speed and memory, as well as magnetic resonance imaging (MRI) of the brain to acquire data on SGM atrophy and BR. Years of education (M = 14.6 years for the experimental group and 15.3 years for the control group) were utilised as a CR parameter. The findings indicated that SGM atrophy is present in the control group as well, but it is notably more pronounced in the group of individuals with MS. Moreover, the cognitive processing speed remained constant throughout this time frame in the control group, but individuals with MS showed a decline in cognitive processing speed where lower CR was linked. The authors' conclusion is that a high levels of CR serve as a protective factor against cognitive deterioration associated with SGM atrophy (Modica et al., 2015).

A further longitudinal study was undertaken to investigate the impact of educational achievement on the speed of data processing, as well as on the employment characteristics of individuals with MS. The research conducted by Conway et al. (2022) utilised a multi-institutional registry known as The Multiple Sclerosis Partners Advancing Technology and Health Solutions - MS PATHS. MS PATHS participants do the processing speed test (PST) at each clinical visit, which is an electronic measure of information processing speed based on the Symbol-Digit Modalities Test (SDMT, Smith, 1968, as cited in Conway et al., 2022). Among the individuals in this registry, 13.732 individuals with MS were found to possess all the necessary data for research purposes. This includes at least one PST result, information on educational accomplishments, and employment status. Educational achievement is categorised as follows: ≥ 12 years - high school diploma; ≥ 16 years - university degree; ≥ 18 years - master's degree. The results indicated a robust association between academic success and the first PST. Nevertheless, the long-term advantage of education was minimal. Individuals with a university degree did not have a lower likelihood of experiencing declines in PST scores during the first, second, or third year compared to those with a high school diploma. Individuals holding a master's degree exhibited a reduced likelihood of experiencing a decline in these outcomes compared to those with a high school diploma, although this benefit was specific to the first and second year, and was absent in the third year. The authors believe that these findings may be a function of CR, emphasising that highly educated people may compensate for neurological damage up to a certain point, but once that point is reached, education loses its advantage.

Similar to the previous study, Benedict et al. (2010) conducted a five-year study to determine whether individual differences in CR have a protective role in cognitive deterioration in persons with MS. Out of 91 MS patients, 71 had relapsing-remitting MS, 17 had secondary progressive MS, and three had primary progressive MS. The mean duration of the chronic condition was 11.0 years, whereas the mean age of the individuals affected was 44.8 years. CR was evaluated based on academic years of study (M = 14.3) and performance on the North American Adult Reading Test (NAART, Blair & Spreen, 1989, as cited in

Benedict et al., 2010). The cognitive status of data processing speed was evaluated using the SDMT, a visual modality form of assessment, and the PASAT to measure auditory processing speed and working memory. This study demonstrates that the established parameters of CR influenced the extent of decrease in neuropsychological tests evaluating the speed of information processing. Subjects with low CR were more likely to reduce information processing speed, particularly on the SDMT, as compared to subjects with high CR.

Unlike earlier studies, the German authors were interested in the influence of formal education on the status of CR in a sample of 128 MS patients, with an average age of 48.0 and a disease duration of 6.75 years. The study included 66 individuals with relapsing-remitting MS, 34 with secondary progressive MS, and 21 with primary progressive MS. To assess cognitive status, 27 neuropsychological tests were administered, including basic cognitive skills, attention, executive functions, visual perception and construction, memory and learning, problem solving, and language. The participants were categorised into three groups based on the duration of their formal education in Germany: those with education up to nine years, those with education up to ten years, and those with education of at least 13 years. Furthermore, information was gathered regarding the occupational status, level of physical activity, and reading habits of the participants. While there is a correlation between longer formal education and improved neurocognitive performance among the participants, the most noteworthy finding is that the group with the least formal education exhibited the most significant improvements in cognitive functioning through activities such as reading, physical exercise, and engaging in demanding occupational tasks. According to the authors, persons with a shorter formal education may gain more from the CR factor than those with a longer education (Luerding et al., 2016).

Consistent with the earlier study, Grant et al. (2023) sought to investigate the variations in predicting the cognitive performance of individuals with MS based on three sociobehavioral factors of CR (years of schooling, quality of education, and cognitive enrichment). The sample comprised of 82 participants diagnosed with MS, with an average age of 50.0 years. The average length of the disease was 11.2 years, and the average years of schooling were 14.8. 75.6% of the participants had relapsing-remitting MS, while 12.2% had both primary and secondary progressive MS. The participants in the study had neurological and neuropsychological assessments, which included word recognition tests, verbal memory, visuospatial memory, and information processing speed. CR data included information on years of education, education quality assessed using the Wechsler Test of Adult Reading (WTAR, Holdnack, 2001, as cited in Grant et al., 2023), and cognitive enrichment evaluated using the Cognitive Reserves Scale (CRS, Leon et al., 2014, as cited in Grant et al., 2023). Furthermore, the participants provided their information of their level of engagement in several cognitive enrichment activities (training-information; daily activities; hobby; social life) during three different time periods (18-35 years; 36-64 years; over 64 years). Empirical evidence indicated that the correlation between cognitive performance and the quality of education and cognitive enrichment was more robust than the correlation between years of education. Nevertheless, there was no correlation between cognitive enrichment and cognitive function among participants who had received a high standard of education. Conversely, among those with poor educational quality, there was a significant correlation between cognitive enrichment and cognitive function. This suggests that active participation in cognitively stimulating activities offers comparable measures of protection as educational quality.

Furthermore, a study conducted by Martins Da Silva et al. (2015) sought to examine education as a predictor of CR, while controlling for demographic, clinical, and genetic profile of the participants. The sample comprised of 419 individuals diagnosed with MS, with 79.2% identified as having relapsing-remitting MS, 10.5% as secondary progressive MS, and 10.3% as primary progressive MS. A median age of 39 (16-71) and an illness duration of 8 (1-47) were observed. Educational status was determined based on the number of years of formal education completed successfully (3-19 years). The control group included 159 individuals who were classified as

healthy and free from neurological or psychiatric disorders. The participants had comprehensive neurological and cognitive assessments, together with the Hospital Anxiety and Depression Scale (HADS, Menses et al., 2009, as cited in Martins Da Silva et al., 2015), and genetic factors including HLA-DRB1 and apolipoprotein E. The study findings validated the protective impact of education and offered a rationale for including education as a determinant of CR. A correlation between the level of education and cognitive impairment was observed in several neuropsychological tests, such as psychomotor speed, visual search, verbal memory, and executive functional abilities. An empirical correlation with education was demonstrated to be unaffected by other clinical and demographic factors.

The two CR parameters and cognition in MS were the focus of the Italian study (Della Corte et al., 2018), in contrast to the prior one. In addition to years of education, CR was also measured using the Wechsler Adult Intelligence Scale - the Vocabulary subtest (WAIS - VOC). Concurrently with CR, neurological and neuropsychological testing were performed, including with an evaluation of depressed symptoms and exhaustion. In the sample of 147 MS patients, 128 had relapsing-remitting MS, 19 had secondary progressive MS, and the average age was 37.76, education 12.46, and disease duration 10.06 years. This study demonstrates that WAIS - VOC, rather than years of education, has a significant correlation with the outcomes of all ten applied neuropsychological tests, which contradicts earlier findings. Conversely, the number of years of education shown a negative link with the executive functions of these participants.

To explore the impact of education on cognition, a study conducted by Rimkus et al. (2018) analysed the occurrence and features of cognitive impairment in individuals with MS who had varying educational backgrounds. The study aimed to determine if the number of years of education serves as a predictor of cognitive impairment. Researchers also looked at the link between T2 lesions (as a measure of disease load) and cognitive function in people with different stages of MS. They studied 136 people with MS and 65 healthy people as a control group. The median age of those diagnosed with MS was 34 years (17-65 years), and the usual duration of the condition was 6 years (0.3-32.6 years). Based on the number of years of education, participants were split into two groups: low educational level (≤ 12 years) and high educational level (> 12 years). Comprehensive neuropsychological testing was performed on all participants, including assessments of IQ and six cognitive domains (verbal memory, visuospatial memory, executive functioning, speed of information processing, working memory, and selective attention). Additionally, MRI testing was completed. Furthermore, individuals diagnosed with MS had neurological examinations. The findings indicated a greater prevalence of cognitive impairment among participants with lower levels of education, in comparison to those with higher levels of education. Two probable education-cognition interactions in MS were observed. During the initial phases of the disease, there is a positive correlation between a greater degree of education and a higher CR. This correlation is seen to have a protective effect against cognitive decline in individuals with MS. Following a period of five years of illness progression, there is a noticeable increase in the influence of T2 lesions, as shown by the association between the size of the lesions and cognitive function. Furthermore, those with a limited level of education exhibit a higher prevalence of lesions, suggesting a heightened vulnerability to brain damage caused by the disease, which in turn leads to advanced cognitive impairment in the latter phases of the illness.

The Cognitive Reserve Index Questionnaire (CRIq, Nucci et al., 2012, as cited in Nunnari et al., 2016) was used as a standardised instrument to measure CR in the research conducted by Nunnari and colleagues (2016). The CRIq is a trustworthy instrument that includes the three most commonly evaluated CR parameters: education, occupation, and leisure activities. Investigators were intrigued by the potential differential impact of these characteristics on cognitive performance. Thus, the primary objective of this study was to assess the impact of specific demographic and clinical factors on the cognitive profile of individuals with MS, under the assumption that CR plays a protective function against cognitive deterioration caused by the burden of the disease. Of the 66 MS patients in

this study, 86.4% had relapsing-remitting, 3.0% primary progressive, and 10.6% secondary progressive MS. The mean age of the participants was 39.5 years, the mean educational attainment was 13.7 years, and the mean long-term duration of the illness was 6.3 years. Further to the CRIq, the Rao Brief Repeatable Battery of Neuropsychological Tests (BRB-N, Rao, 1990, as cited in Nunnari et al., 2016) was used for neuropsychological assessment, together with MRI brain imaging, to determine the overall brain volume and cortical volume. The findings indicate that the CRIq score is a strong indicator of attention, speed of information processing, working memory, and verbal learning comprehension. Furthermore, there was no correlation between the CRIq score and the scale used to assess the severity of the disease, as well as between the CRIq and the duration of the disease. This suggests that the measurements of CR are not influenced by the severity of the disease. In relation to the examined parameters of CR, it has been demonstrated that education and occupation are subscores of CRIq that exhibit a substantial correlation with the cognitive performance of these individuals. The researchers' conclusion is that CR, as assessed by a specialised standardised questionnaire, serves as a protective element against cognitive impairments in individuals with MS. However, they did not find any substantial evidence to suggest that CR acts as a mediator between brain damage and cognitive performance.

A group of American authors was interested in whether the notion of CR was applicable to the population of people with secondary progressive MS (Sumowski et al., 2012). Particularly, the authors aimed to investigate if intellectual enrichment serves as a protective factor against cognitive impairment in individuals with secondary progressive MS. For this, 25 secondary progressive MS patients and 25 healthy controls were recruited. Participants with MS averaged 49.2 years old, 15.3 years of education, and 13.2 years of disease. Through education and vocabulary, intellectual enrichment was examined. Assessment of vocabulary was conducted using the Wechsler Abbreviated Scale of Intelligence (WASI) and the Reading subtest of the Wide Range Achievement Test (Wilkinson, 1993, as cited in Sumowski et al., 2012). An evaluation of cognitive functioning was conducted by measuring memory and cognitive efficiency (speed of information processing) using appropriate instruments. The results indicated that individuals with MS who had lower CR had inferior cognitive performance in both examined areas compared to the control group. However, this disparity was no longer evident at higher reserve levels, both in the domain of cognitive efficiency and to memory. More precisely, a greater CR value mitigated the adverse impact of the condition on memory and cognitive performance. The findings indicate that higher levels of intellectual enrichment do not impact the cognitive abilities of a mentally sound adult. However, it does play a safeguarding function in mitigating cognitive deterioration that occurs as a result of neurological disorders.

A research conducted by Portuguese scientists (Machado et al., 2021) sought to investigate the impact of cognitive and brain reserve on social cognition and to compare these effects with those on what the authors refer to as "classical cognition". This study included 60 MS patients and 60 healthy controls. In MS, 50 participants had relapsing-remitting MS and 10 had secondary progressive MS. The average age was 37.2 years and the average duration of disease was 10.6 years. The parameter of CR in both groups was established based on years of education, whereas the parameter of BR was determined by intracranial volume. A neuropsychological evaluation was conducted on the participants, including tests measuring visual and auditory information processing speed, working memory, visuospatial learning and memory, verbal episodic learning and memory, spatial perception, verbal fluency, and executive functioning. Additionally, Theory of Mind testing and MRI brain imaging were performed to record the volumes of cortical and subcortical grey matter. The results indicated that education and intracranial volume had beneficial impacts on both overall cognitive status and social cognition. The impact of subcortical grey matter atrophy on "classical" cognitive status was mitigated by a sufficient amount of education. Larger intracranial volume, on the other hand, mitigated the effect of cortical grey matter atrophy on social cognition.

Furthermore, it has been demonstrated that the major protective effect of education and cerebral volume is most pronounced during the initial phases of the disease. Therefore, the authors deduce that CR and brain reserve play distinct protective roles in MS. Brain reserve was found to have a beneficial impact on social cognition, whereas CR displayed a positive influence on "classic" cognitive domains.

Conclusion

Analysing the chosen literature revealed a beneficial effect of CR on the cognitive function of individuals with MS. A higher degree of education, as a measure of CR, has a protective function in preventing cognitive decline and the advancement of cognitive impairments in the population under study. Furthermore, cognitive performance is significantly linked to not just the number of years of education, but also the quality of education and cognitive enrichment. For those with a lower level of education, the protective function of CR can be attained by adopting more regular practices of physical exercise, reading, and engagement in demanding jobs. While the cognitive performance of individuals with secondary progressive MS is lower than that of healthy individuals, this disparity still disappears at higher reserve levels. The protective effects of education are more pronounced in the early stages of the illness. Nevertheless, when drawing broad generalisations, it is important to exercise caution primarily because of the methodological variations among the examined research, including the sample size and structure, the inclusion of a control group, disparities in the choice of measuring procedures, and so on. The literature that has been analyzed suggests that it is necessary to conduct further research in order to identify additional parameters that influence the CR and can be used in the assessment. This is because an increasing number of studies demonstrate that participating in intellectually stimulating activities outside of formal education can also serve as a safeguard against cognitive deterioration in individuals with MS. In the end, a limited number of researchers in our region are working on the topic of cognitive reserve. Therefore, it is important to analyze the existing literature that can highlight the importance of studying cognitive reserve and its influence on the cognitive state of individuals with multiple sclerosis.

Funding

This research was funded by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia - Contracts No. 451-03-66/2024-03.

References

Avila, J.F., Rentería, M.A., Jones, R.N., Vonk, J.M.J., Turney, I., Sol, K., Seblova, D., Arias, F., Hill-Jarrett, T., Levy, S.A., Meyer, O., Racine, A.M., Tom, S.E., Melrose, R. J., Deters, K., Medina, L.D., Carrion, C.I., Díaz-Santos, M., Byrd, D.R., ... Manly, J.J. (2020). Education differentially contributes to cognitive reserve across racial/ethnic groups. *Alzheimer's & Dementia, 17*(1), 1-11. https://doi.org/10.1002/alz.12176

Barnett, J., Salmond, C., Jones, P., & Sahakian, B. (2006). Cognitive reserve in neuropsychiatry. *Psychological Medicine, 36*(8), 1053-1064. https://doi.org/10.1017/S0033291706007501

Benedict, R. H., Morrow, S. A., Guttman, B. W., Cookfair, D., & Schretlen, D. J. (2010). Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients. *Journal of the International Neuropsychological Society, 16*(5), 829-835. https://doi.org/10.1017/S1355617710000688

Benedict, R. H., Weinstock-Guttman, B., Fishman, I., Sharma, J., Tjoa, C. W., & Bakshi, R. (2004). Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Archives of Neurology, 61*(2), 226-230. https://doi.org/10.1001/archneur.61.2.226

Calabrese, M., Filippi, M., & Gallo, P. (2010). Cortical lesions in multiple sclerosis. *Nature Reviews Neurology, 6*(8), 438–444. https://doi.org/10.1038/nrneurol.2010.93

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology, 7*(12), 1139-1151. https://doi.org/10.1016/S1474-4422(08)70259-X

Ciccarelli, N., Monaco, M. R. L., Fusco, D., Vetrano, D. L., Zuccalà, G., Bernabei, R., Brandi, V., Stella Pisciotta, M., & Silveri, M. C. (2017). The role of cognitive reserve in cognitive aging: what we can learn from Parkinson's disease. *Aging Clinical and Experimental*

Research, 30(7), 877–880. https://doi.org/10.1007/s40520-017-0838-0

Conway, D. S., Bermel, R. A., & Planchon, S. M. (2022). The relationship between cognition, education, and employment in multiple sclerosis patients. *Multiple Sclerosis Journal–Experimental, Translational and Clinical, 8*(3). https://doi.org/10.1177/20552173221118309

Della Corte, M., Santangelo, G., Bisecco, A., Sacco, R., Siciliano, M., d'Ambrosio, A., Docimo, R., Cuomo, T., Lavorgna, L., Bonavita, S., Tedeschi, G., & Gallo, A. (2018). A simple measure of cognitive reserve is relevant for cognitive performance in MS patients. *Neurological Sciences, 39*, 1267-1273. https://doi.org/10.1007/s10072-018-3422-2

Filippi, M., Rocca, M. A., Benedict, R. H. B., DeLuca, J., Geurts, J. J. G., Rombouts, S. A. R. B., Ron, M., & Comi, G. (2010). The contribution of MRI in assessing cognitive impairment in multiple sclerosis. *Neurology, 75*(23), 2121-2128. https://doi.org/10.1212/WNL.0b013e318200d768

Grant, J. G., Rapport, L. J., Darling, R., Waldron-Perrine, B., Lumley, M. A., Whitfield, K. E., & Bernitsas, E. (2023). Cognitive enrichment and education quality moderate cognitive dysfunction in black and white adults with multiple sclerosis. *Multiple Sclerosis and Related Disorders, 78*, 1-11. https://doi.org/10.1016/j.msard.2023.104916

Grotz, C., Seron, X., Van Wissen, M., & Adam, S. (2016). How should proxies of cognitive reserve be evaluated in a population of healthy older adults? *International Psychogeriatrics, 29*(01), 123–136. https://doi.org/10.1017/S1041610216001745

Guzzetti, S., Mancini, F., Caporali, A., Manfredi, L., & Daini, R. (2019). The association of cognitive reserve with motor and cognitive functions for different stages of Parkinson's disease. *Experimental Gerontology, 115*, 79–87. https://doi.org/10.1016/j.exger.2018.11.020

Jones, R., Manly, J., Glymour, M., Rentz, D., Jefferson, A., & Stern, Y. (2011). Conceptual and Measurement Challenges in Research on Cognitive Reserve. *Journal of the International Neuropsychological Society, 17*(4), 593-601. https://doi.org/10.1017/S1355617710001748

Lovera, J., & Kovner, B. (2012). Cognitive Impairment in Multiple Sclerosis. *Current Neurology and Neuroscience Reports, 12*(5), 1-10. https://doi.org/10.1007/s11910-012-0294-3

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*, 1-9. https://doi.org/10.3389/fneur.2016.00046

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 'classic cognition'. *Multiple Sclerosis and Related Disorders, 48*, 1-7. https://doi.org/10.1016/j.msard.2020.102716

Martins Da Silva, A., Cavaco, S., Moreira, I., Bettencourt, A., Santos, E., Pinto, C., Gonçalves, A., Coutinho, E., Samões, R., Dias, C. C., Teixeira-Pinto, A., Martins Da Silva, B., & Montalban, X. (2015). Cognitive reserve in multiple sclerosis: Protective effects of education. *Multiple Sclerosis Journal, 21*(10), 1-10. https://doi.org/10.1177/1352458515581874

Modica, C. M., Bergsland, N., Dwyer, M. G., Ramasamy, D. P., Carl, E., Zivadinov, R., & Benedict, R. H. (2015). Cognitive reserve moderates the impact of subcortical gray matter atrophy on neuropsychological status in multiple sclerosis. *Multiple Sclerosis Journal, 22*(1), 1-7. https://doi.org/10.1177/1352458515579443

Nunnari, D., De Cola, M. C., Costa, A., Rifici, C., Bramanti, P., & Marino, S. (2016). Exploring cognitive reserve in multiple sclerosis: new findings from a cross-sectional study. *Journal of Clinical and Experimental Neuropsychology, 38*(10), 1158-1167. https://doi.org/10.1080/13803395.2016.1200538

Rimkus, C. M., Avolio, I. M. B., Miotto, E. C., Pereira, S. A., Mendes, M. F., Callegaro, D., & Leite, C. D. C. (2018). The protective effects of high-education levels on cognition in different stages of multiple sclerosis. *Multiple sclerosis and related disorders, 22*, 41–48. https://doi.org/10.1016/j.msard.2018.03.001

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. https://doi.org/10.3233/RNN-120261

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006-1012. https://doi.org/10.1016/S1474-4422(12)70191-6

Sumowski, J. F., & Leavitt, V. M. (2013). Cognitive reserve in multiple sclerosis. *Multiple Sclerosis Journal, 19*(9), 1122–1127. https://doi.org/10.1177/1352458513498834

Sumowski, J. F., Chiaravalloti, N., Leavitt, V. M., & DeLuca, J. (2012). Cognitive reserve in secondary progressive multiple sclerosis. *Multiple Sclerosis Journal, 18*(10), 1454-1458. https://doi.org/10.1177/1352458512440205

Weissert, R. (2013). The Immune Pathogenesis of Multiple Sclerosis. *Journal of Neuroimmune Pharmacology, 8*(4), 1-10. https://doi.org/10.1007/s11481-013-9467-3