Research Paper

# The Relationship Between Chronic Fatigue Syndrome and Depression: Mediating Roles of Executive Functions in Patients With Relapsing-Remitting Multiple Sclerosis

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## ABSTRACT

**Objective:** This study aimed to investigate the relationship between chronic fatigue syndrome (CFS) and depression with the mediating role of executive functions (EFs) in patients with relapsing-remitting multiple sclerosis (RRMS).

**Methods:** The statistical population of this descriptive correlational study included all patients with RRMS who were referred to Tehran neurologists in the summer of 2021 and among them, 208 samples who were eligible to enter the study, were selected via available sampling methods. To collect data, Krupp et al.'s (1988) fatigue severity scale (FSS), Nejati's cognitive abilities (NCA), and Beck depression inventory (II-BDI) were used. Pearson correlation method and structural equation modeling (SEM) were used to analyze the data.

**Results:** Of seven subscales of EFs, the subscales of working memory, inhibitory control, selective attention, planning, and cognitive flexibility, which are called "cold" processes of EFs, were approved as mediators at the level ($P<0.001$), but the subscales of cognitive functioning, decision-making, and controlled attention, which are hot functions and require emotional awareness and regulation of personal social behaviors and decision-making with emotional and personal interpretation and empathy, were not approved as mediating roles. The results also showed that in patients with RRMS, there was a significant relationship between CFS and depression, between CFS and EFs, and between EFs and depression ($P<0.001$).

**Conclusion:** The results of the present study can be used in cognitive rehabilitation to improve EFs and consequently improve depression in patients with MS.

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## Highlights

- The subscales of working memory, inhibitory control, selective attention, planning, and cognitive flexibility, were approved as mediators.
- The subscales of cognitive functioning, decision-making, and controlled attention, were not approved as mediators.
- There was a significant relationship between CFS and depression, between CFS and EFs, and between EFs and depression in patients with RRMS.
- The results can be used in cognitive rehabilitation to improve EFs and consequently improve depression.


## Plain Language Summary

Multiple sclerosis (MS) is the most common neurological disorder in people aged 20-50 years, with a clinical diagnosis occurring after observing two lesions (damaged areas of neurons) separated by time and place in the central nervous system. Among patients with MS, chronic fatigue syndrome is the most commonly reported symptom and one of the most debilitating. The statistical population of this descriptive correlational study included all patients with RRMS who were referred to Tehran neurologists in the summer of 2021 and among them, 208 samples who were eligible to enter the study, were selected via available sampling methods. To collect data, Krupp et al.'s (1988) Fatigue Severity Scale (FSS), Nejati's Cognitive Abilities (NCA), and Beck Depression Inventory (II-BDI) were used. Pearson correlation method and structural equation modeling (SEM) were used to analyze the data. Of the seven subscales of EFs, the subscales of working memory, inhibitory control, selective attention, planning, and cognitive flexibility, which are called "cold" processes of EFs, were approved as mediators at the level ($P<0.001$), but the subscales of cognitive functioning, decision-making and controlled attention, which are hot functions and require emotional awareness and regulation of personal social behaviors and decision-making with emotional and personal interpretation and empathy, were not approved as mediating roles. The results also showed that in patients with RRMS, there was a significant relationship between CFS and depression, between CFS and EFs, and between EFs and depression ($P<0.001$). The results of the present study can be used in cognitive rehabilitation to improve EFs and consequently improve depression in patients with MS.


## 1. Introduction

Multiple sclerosis (MS) is the most common neurological disorder in people in the age range of 20 to 50 years, with a clinical diagnosis occurring after observing two lesions (damaged areas of neurons) separated by time and place in the central nervous system (Calabresi, 2004). The age of onset of MS is declining and the majority of patients are young people, most of whom are diagnosed between the ages of 20 and 30, and are diagnosed with relapsing-remitting multiple sclerosis (RRMS) (Broch et al., 2021; Sorensen et al., 2021). Uncertainty in the treatment options and unknown prognosis of this disease leads people to the point of suicidal ideation and attempts (Knowles et al., 2021). Iran is among the top 10 countries in the world in terms of MS (Amini et al., 2021). Although there are no exact statistics on the prevalence of MS in Iran, the prevalence is estimated at 57 per 100 000 (Salehi et al., 2020). These disorders are rarely reversible if they occur. Preliminary studies conducted in Iran indicate that there are approximately 50 000 patients with MS. Studies of a group of people with MS show that about 60% of them are women and 78% of them are married, of which 81.5% are landed (Tavakol & Yusefi, 2013). MS affects the economic, social, and emotional aspects of the individual, family, and community. Therefore, preventing depression and the inability to perform daily activities promotes the health of the individual and society (Rodriguez-Rincon et al., 2019).

Depression is one of the most important debilitating diseases that affect many people worldwide and affects their ability to function, think, and feel. It is a clinically important issue in MS (Wang et al., 2000) and hurts the quality of life of a person with MS. It is even a risk factor for suicide (Lee & Giuliani, 2019; Feinstein et al., 2015) and may also hurt the patient's adherence to the treatment process (Mohr et al., 2003). There is a consensus in all studies that the prevalence of depression in MS has increased compared to normal people (Patten et al., 2003).

Beck & Steer (1991) defined clinical depression as a pathological disorder that involves changes in 5 major behavioral domains and the symptoms of these changes may be all or any of the manifestations of negative emotions, negative cognitions, negative motivation, behavioral changes, and include plant changes (appetite and sex). Depression is one of the key factors in reducing the quality of life in patients with chronic diseases (Lee & Giuliani, 2019).

Research has shown that pain, fatigue, and depression occur together in a variety of diseases, including cancer and MS (Powell et al., 2021). Among these symptoms, chronic fatigue syndrome (CFS) and depression are closely related in a 2-way manner and more complex. CFS, also called myalgic encephalomyelitis, is one of the most distressing conditions that MS patients may experience in their lifetime and is present as a physical or mental deficiency in 35% to 97% of people with MS (Tarasiuk et al., 2022). Despite its high prevalence, the physiological etiology of MS and CFS is not entirely clear and several mechanisms appear to be involved (Ayache & Chalah, 2017; Kalfas et al., 2022). People with CFS experience long-term fatigue, joint pain, headaches, sleep problems, poor concentration, and short-term memory (Grech et al., 2021). These symptoms cause significant disability and distress (Larun et al., 2020). Studies by Kale et al., (2013) report a statistically significant relationship between CFS and depression in people with MS. Voss et al. (2002) showed in their study that CFS has a direct effect on mood, but also emphasized its complexity and the need to examine the mediating variables involved in the relationship between these two variables. Executive functions (EFs) are one of the variables that according to research, such as Rock et al. (2014), Amani (2021), Warren et al. (2021) can play a mediating role between CFS and depression.

EFs as neuropsychological processes are cognitive abilities that enable individuals to manage their attention effectively (Chan et al., 2021). They are also responsible for self-regulation and goal-oriented behaviors and enable the individual to create new behavioral patterns, ways of thinking, and reviewing thoughts (Pfeffer & Strobach, 2021). These capabilities are much needed in unfamiliar situations (Gurd et al.. 2003; Soltani Kouhbanani & Arabi, 2021).

EFs refer to a set of cognitive processes that enable purposeful behavior by regulating different types of cognitive processes (Ashori, 2022). Because EFs influence behavior, they influence daily activities as well as social and personal growth, including job success (Diamond, 2013; Amunts et al., 2020; Chan et al., 2021) or better feelings in life (Tofighian et al., 2021). Deficiency in this area causes several neurological and psychiatric diseases, such as attention-deficit hyperactivity disorder, Parkinson disease, depression, schizophrenia, MS, and so on (Migliore et al., 2017; Amunts et al., 2020; Schiavolin et al., 2016). In addition, it poses a significant risk to reduced quality of life (Crouch et al., 2021). On this basis, the importance and comprehensiveness of EFs in different fields of study have led to examining the different domains of EFs (Thuaire et al., 2020).

Of the 7 subscales of EFs, the subscales of working memory, inhibitory control, selective attention, planning, and cognitive flexibility are called "cold" processes of EFs, and the subscales of cognitive functioning, decision-making, and controlled attention are "hot" EFs (Memisevic & Sinanovic, 2013). A conceptual distinction is usually made between cold and hot EFs. Cold EFs refer to higher-order mechanical cognitive operations (such as working memory) and are based on

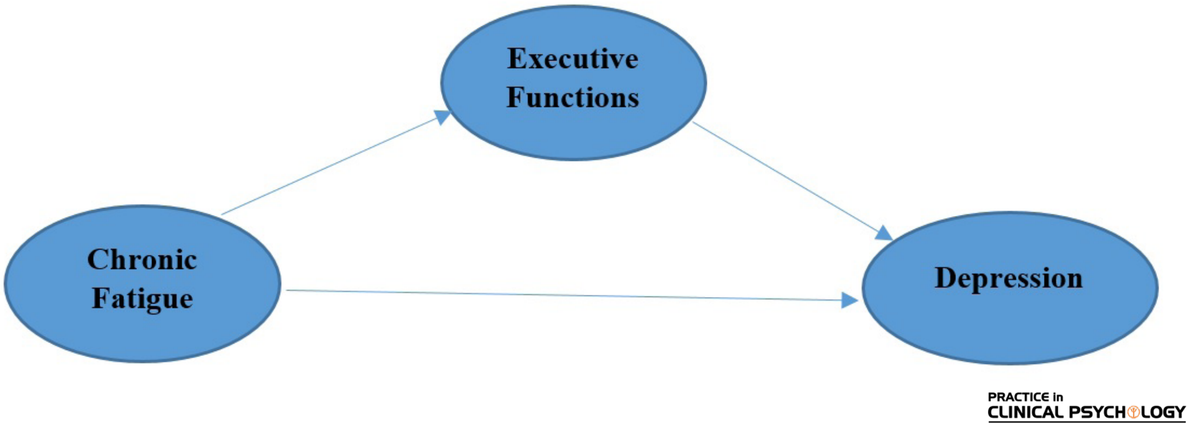


**Figure 1.** Hypothetical model of the relationship between chronic fatigue syndrome and depression mediated by executive functions

the law that regulates and controls one's thinking and actions. On the other hand, hot EFs require cognitive abilities that are supported by emotional awareness and social perception and include illegal functions based on emotions, desires, social cognition, and situational influencing factors (Zimmerman et al., 2016).

Among patients with MS, CFS is the most commonly reported symptom and one of the most debilitating (Ramari et al., 2018; Silveira et al., 2019). Despite its high prevalence and significant impact, CFS is still not well understood given its complexity and mental nature, and is often less emphasized (Takeda et al., 2021). In recent years, many scientific sources from sleep medicine, neurology, psychiatry, psychology, physical medicine and rehabilitation, and radiology have clarified the potential causes, effects, and treatment of MS fatigue. Although such a variety of contributions has benefits, several recent articles that attempted to integrate this literature and existing studies have focused more on the possible causes of CFS rather than the clinical evaluation or treatment (Braley & Chervin, 2010).

To date, no independent study has examined the mediating role of EFs in the relationship between depression and CFS in patients with RRMS. Previous research has largely examined the relationship between CFS and depression separately. Unlike previous studies that examined the effect of depression on EFs, new studies emphasize the importance of the effects of EFs on depression (Barkley, 2012). Figure 1 shows a hypothetical model of the relationship between CFS and depression mediated by EFs. Therefore, according to previous research, the hypothetical model of causal relationships between CFS and depression with the mediating role of EFs in patients with RRMS is fitting the data. Accordingly, this study aims to investigate the relationship between CFS and depression with the mediating role of EFs in patients with RRMS. In the proposed model, each of the designed paths is assumed to be a direct relation. It has also been suggested that EFs mediate CFS and depression in patients with RRMS.

## 2. Participants and Methods

### Participants

This is a descriptive-correlational study. To answer the general hypothesis of the research, we utilized structural equation modeling (SEM), and to examine the specific hypotheses, the Pearson correlation method was employed. After the confirmatory factor analysis in the measurement model section in the SEM section, the causal relationships between latent variables were examined. In the SEM, the intensity of causal relationships (direct, indirect, and total) between latent variables in the whole model was specified.

### Study participants

The statistical population of this descriptive-correlational study included all patients with RRMS who were referred to neurologists in Tehran City, Iran, in the summer of 2021. A total of 208 samples of this population who were eligible to enter the study were selected via available sampling methods. A review of the research literature shows that in using the statistical method of SEM, there is no precise strategy for determining the sample size. Hoyle (1995) and Schumacker and Lomax (2004) emphasized that the minimum sample size of 100 people and the sample size of 200 people are desirable for using this statistical technique. Garson (2016) maintained that since SEM is the most common method of estimating the maximum probability, the sample size of 200 has acceptable results. Using this statistical method, Kline (2005) suggested another solution for determining the sample size. Kline emphasized that the minimum sample size ratio for each estimated parameter is 5, a ratio of 10 to 1 is more appropriate, and a ratio of 20 to 1 is considered desirable. In the hypothetical model of the present study, according to Kline's view, 208 people were selected considering the possibility of falling. According to Kline (2005), a ratio of 22 to 1 is observed with the possibility of a 5% drop.

### Inclusion and exclusion criteria

The inclusion criteria were diagnosis of RRMS by a specialist and being in the age range of 19 to 50 years. The exclusion criteria were failure to complete the questionnaire and previous diagnosis by a psychiatrist of mental disorders.

### Study measurements

To collect the data, we used Krupp et al. (1989) fatigue severity scale (FSS), Nejati's cognitive abilities (NCA), and Beck depression inventory (BDI-II).

### Beck depression inventory-II

The 21-item long form of BDI is a type of self-assessment test that subjects must answer on a 4-point scale from 0-3. These substances are in areas, such as sadness, pessimism, feelings of helplessness and failure, guilt, sleep disturbance, loss of appetite, and self-loathing. The minimum and maximum scores in this test are 0 and 63, respectively. By summing a person's scores in each of the items, their score is obtained directly. Arnau et al. (2001), showed that with a cut-off score of 18, up to 92% of patients with major depressive disorder can be correctly diagnosed. The following scores can be used to indicate the overall magnitude of depression: none or minimal depression (0 to 13), mild depression (14 to 19), moderate depression (20 to 28), and severe depression (29 to 63).

## Reliability and validity

The BDI has been used in many countries and cultures and its validity and reliability have been accepted (Grothe et al., 2005; Kapci et al., 2008; Asiamah & Mensah, 2017). Beck et al. (1996) obtained a retest reliability of 0.93 for the BDI, and Arnau et al. (2001), reported internal consistency of 0.89 to 0.94. In Iran, BDI has been used extensively and its psychometric properties have been confirmed. For example, Dobson and Mohammad Khani (2007) reported retest reliability of 0.93 and showed its convergent validity in the correlation between BDI scores and Beck hopelessness scale scores, the Beck scale for suicide ideation (Beck & Steer, 1991), and the Hamilton rating scale for depression (Hamilton, 1960). In this study, the validity of the questionnaire was obtained through the α coefficient of 0.915, which reports the internal consistency of the questionnaire. Also, in exploratory factor analysis (EFA), the factor structure of the questionnaire was examined using the principal component analysis method. The adequacy of the sample size was 0.912, which indicates that the data were suitable for EFA. The result of the Bartlett test of sphericity (with degrees of freedom [DF]=153 and P<0.001) was obtained equal to 1602.057. Therefore, there is a significant relationship between the variables (P<0.05). Accordingly, it is possible to perform the EFA of the BDI. To determine the most appropriate factors, oblique rotation was performed in EFA assuming the variables were correlated. Finally, according to the special values, the depression factor was extracted.

## Fatigue severity scale

The FSS questionnaire was designed by Krupp et al. (1989) to measure the severity of fatigue in people with MS and lupus and was examined by psychometrics (psychometric). This questionnaire consists of 9 items that have been extracted from the 28 Items fatigue questionnaire. The scoring is based on the Likert scale and from 1 (completely opposite) to 7 (completely successful). Scores of 9 phrases are added together. The minimum and maximum scores in this test are 9 and 63, respectively. The following scores can be used to indicate the overall magnitude of fatigue severity: low fatigue (9 to 18), moderate fatigue (18 to 45), and severe fatigue (more than 45).

## Reliability and validity

Krupp et al. (1989) examined the construct validity and reliability of FSS in people with MS and lupus. The Cronbach α of the FSS was 0.88 in healthy individuals, 0.81 in people with MS, and 0.89 in people with lupus, and finally, the FSS had a high internal consistency. They concluded that FSS has good validity and reliability. In Shahvaroughi-Farahani's study et al. (2010), the data obtained from two patient assessments were analyzed using the FSS questionnaire, via statistical methods. In this way, a descriptive analysis was performed for each item to show the distributive characteristics of each item, and the Mean±SD were calculated. The internal structure and reliability of the questionnaire were assessed through internal consistency at the level of items, calculation of the Cronbach α coefficient, and repeatability in the number of tests. On the other hand, in the present study, the α coefficient in this study was equal to 0.936, which demonstrates the internal consistency of the FSS.

In EFA, the factor structure of the FSS was examined using the principal component analysis method. The adequacy of the sample size was 0.93, which indicates that the data are suitable for EFA. The result of the Bartlett test of sphericity (with DF=36 and P<0.001) was obtained at 1441. Therefore, there is a significant relationship between the variables (P<0.05). Accordingly, it is possible to perform the EFA of the BDI. To determine the most appropriate factors, oblique rotation was performed in EFA assuming the variables were correlated. Finally, according to the special values, the fatigue severity factor was extracted.

## Nejati cognitive abilities

Considering the peak of the COVID-19 period during the data collection process and the vulnerability of MS patients, Ashori and Tajvar-Rostami (2019) used this questionnaire to assess EFs; hence, this questionnaire was selected. The questions are in the Likert spectrum and include 7 distinct factors (working memory: questions 1 to 6; inhibitory control and selective attention: questions 7 to 12; decision-making: questions 13 to 17; planning: questions 18 to 20; controlled attention: questions 21 to 23; cognitive functioning: questions 24 to 26;

and cognitive flexibility: questions 27 to 30). Values for numbers range from 1 (almost never) to 5 (almost always). The scoring method is negative for other scales except for the cognitive functioning scale.

## Reliability and validity

The Cronbach α of the questionnaire was obtained at 0.83 and the Pearson correlation of the two tests was significant at 0.01. All scales (except social cognition) were correlated with a grade point average of 0.01. The t-test showed a significant difference between all test indicators (except for the planning and cognitive functioning). This questionnaire has been used in domestic research (Nejati et al., 2016) and has acceptable validity and reliability. In the present study, the α coefficient in this study was equal to 0.927, which indicates the internal consistency of the NCA. In EFA, the factor structure of the NCA was examined using the principal component analysis method. The adequacy of the sample size was 0.886, which indicates that the data are suitable for EFA. The result of the Bartlett test of sphericity (with DF=36 and P<0.001) was obtained at 3158.83. Therefore, there is a significant relationship between the variables (P<0.05). Accordingly, it is possible to perform the EFA of the NCA. To determine the most appropriate factors, oblique rotation was performed in EFA assuming that the variables were correlated. Finally, according to the special values, factors of working memory, inhibitory control, selective attention, decision-making, planning, controlled attention, cognitive functioning, and cognitive flexibility were extracted.

## Study procedure

Given the COVID-19 pandemic, the questionnaires were designed online, and in their initial explanations, issues such as privacy, confidentiality, personal consent, the importance of the research findings, and the participant's role in the study were clearly stated. The final version of these questionnaires was shared in the Telegram group created by a neurologist, and all members of the group were patients with MS. Finally, the results were collected on the website and analyzed by the Pearson correlation method and SEM.

## Statistical analysis

Descriptive statistics (Mean, SD, variance, and frequency) and inferential statistics (Pearson correlation coefficient and SEM) were used to analyze the data and identify the variables. Then by performing confirmatory factor analysis and using model fit indices, such as the Chi-square ($\chi^2$), Chi-square/$d_f$ ratio ($\chi^2/df'$), comparative fit index, incremental fit index, and the root mean square error of approximation of the obtained factor structure was confirmed. To evaluate how the model fits the data, SPSS and PLS software were used. EFA was analyzed using the SPSS software, v. 22. Confirmatory factor analysis was performed using the partial least square (PLS) analyses.

## Ethical considerations

This plan was approved in the working meeting of the research Ethics Committee of Shahid Beheshti University and was announced with the code IR.SBU.REC.1400.102. Given the COVID-19 pandemic, the questionnaires were designed online and then referred to MS patients by a neurologist. The goals and procedures of the research were explained to all participants. They were confident of the confidentiality and that they could withdraw from the study at any time. Each participant initially wrote an informed consent and then completed the instrument. Completed instruments were stored securely.

# 3. Results

## Study sample

The subjects of this study included 208 (165 women and 43 men) who were identified as having RRMS and the inclusion criteria (being in the given age range and having RRMS). Mean±SD of the variables were obtained for CFS (41.60±14.51), depression (19.70±12.46) and EFs (76.62 ±21.12), respectively.

**Table 1.** Descriptive indicators of variables of chronic fatigue syndrome, depression, and executive functions

| Variables | Lowest Possible Score | Highest Possible Score | Mean±SD | Skewness | Kurtosis |
|---|---|---|---|---|---|
| Chronic fatigue syndrome | 9 | 63 | 41.60±14.51 | -0.37 | -0.87 |
| Executive functions | 30 | 150 | 76.62±21.12 | 0.49 | 0.24 |
| Depression | 0 | 63 | 19.70±12.46 | 0.61 | -0.12 |

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**Table 2.** Goodness of fit indicators of the tested research model

| Indices | Acceptable Range | Ideal Range | Values |
|---|---|---|---|
| Chi Square ($\chi^2$) | $2df \leq \chi^2 \leq 3df$ | $0 \leq \chi^2 \leq 2df$ | 111.98 |
| $\chi^2$ P (Chi-squared P) | 0.05<P≤1 | 0.1<P≤0.05 | 0.001 |
| Goodness of Fit (GoF) | 0.05≤GFI<0.95 | 0.95≤GFI≤1 | 0.54 |
| Root mean square residual (RMR) | 0<RMR≤0.1 | 0≤RMR≤0.05 | 0.07 |
| Normed fit index (NFI) | 0.05≤PNFI<0.6 | 0.6≤PNFI≤1 | 0.88 |

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**Table 3.** Direct effect of chronic fatigue syndrome on depression mediated by executive functions

| Paths | β | SE | t | Sig. | Result |
|---|---|---|---|---|---|
| EFs and depression | 0.55 | 0.05 | 10.84 | 0.001 | Confirmed |
| CFS and depression | 0.28 | 0.05 | 5.30 | 0.001 | Confirmed |
| CFS and EFs | 0.44 | 0.05 | 7.7 | 0.001 | Confirmed |
| CFS and EFs and depression | 0.24 | 0.04 | 6.03 | 0.001 | Confirmed |

EF: executive functions; CFS: chronic fatigue syndrome.

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**Table 4.** Direct effects of chronic fatigue syndrome on the subscales of executive functions and the indirect effect of chronic fatigue syndrome on depression mediated by each subscale

| Row | Subscales of EFs | Paths | β | SE | t | Sig. | Results |
|---|---|---|---|---|---|---|---|
| 1 | Working memory | CFS-memory | 0.39 | 0.06 | 6.83 | 0.001 | Accepted |
| | | Memory-depression | 0.20 | 0.07 | 3.01 | 0.001 | Accepted |
| | | CFS-memory-depression | 0.08 | 0.03 | 2.62 | 0.001 | Accepted |
| 2 | Inhibitory control and selective attention | CFS-inhibitory control | 0.48 | 0.06 | 8.57 | 0.001 | Accepted |
| | | Inhibitory control – depression | 0.3 | 0.07 | 4.09 | 0.001 | Accepted |
| | | CFS-inhibitory control-depression | -0.09 | 0.04 | 2.39 | 0.02 | Accepted |
| 3 | Decision-making | CFS-Decision-making | 0.27 | 0.07 | 3.72 | 0.00 | Accepted |
| | | Decision-making-depression | -0.04 | 0.07 | 0.65 | 0.51 | Rejected |
| | | CFS-Decision-making-depression | -0.01 | 0.02 | 0.66 | 0.51 | Rejected |
| 4 | Planning | CFS-Planning | 0.34 | 0.06 | 5.61 | 0.001 | Accepted |
| | | Planning-depression | 0.19 | 0.06 | 2.91 | 0.001 | Accepted |
| | | CFS-Planning-depression | 0.06 | 0.03 | 2.39 | 0.02 | Accepted |
| 5 | Controlled attention | CFS-Controlled attention | 0.21 | 0.07 | 2.95 | 0.00 | Accepted |
| | | Controlled attention-depression | 0.02 | 0.07 | 0.29 | 0.77 | Rejected |
| | | CFS-controlled attention-depression | 0.00 | 0.02 | 0.27 | 0.79 | Rejected |
| 6 | Cognitive functioning | CFS-cognitive functioning | 0.23 | 0.08 | 2.99 | 0.00 | Accepted |
| | | Cognitive functioning-depression | 0.06 | 0.06 | 0.98 | 0.33 | Rejected |
| | | CFS-cognitive functioning- depression | 0.01 | 0.02 | 0.83 | 0.41 | Rejected |
| 7 | Cognitive flexibility | CFS-cognitive flexibility | 0.31 | 0.06 | 5.02 | 0.001 | Accepted |
| | | Cognitive flexibility-depression | 0.16 | 0.08 | 1.99 | 0.05 | Accepted |
| | | CFS-cognitive flexibility- depression | 0.05 | 0.03 | 1.68 | 0.09 | Accepted |

CFS: chronic fatigue syndrome.

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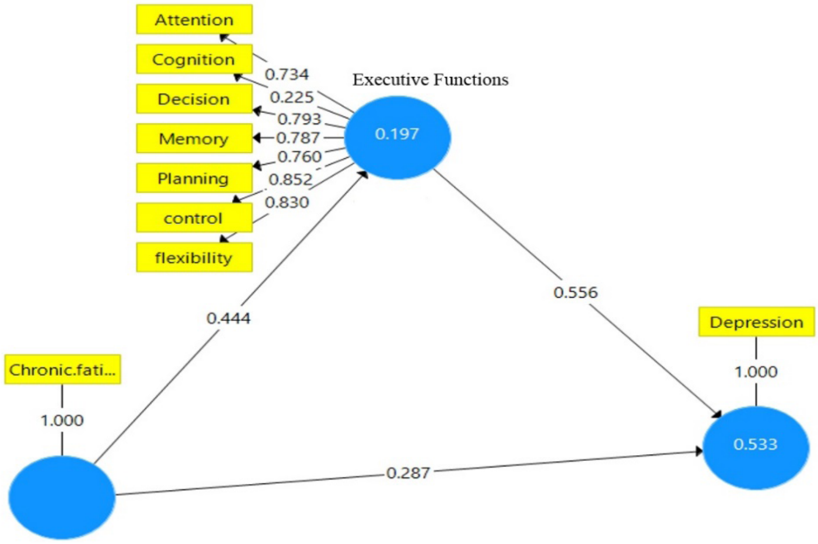


**Figure 2.** Path coefficients of the tested model for the research hypothesis

Table 1 shows the descriptive indicators of variables of CFS, depression, and EFs.

## Psychometric properties

In this study, to test the fitness of the tested model, the goodness of fit (GoF), the normed fit index, and the root mean square residual were considered the fit indices. In Table 2, these indicators are reported separately.

The results of Table 2 demonstrate that the goodness indicators of the test model of the research. The GoF index is one of the adaptive indices for which a value greater than 0.50 indicates a good fit of the model by the data. The GoF value for the model was 0.54, which indicates a good fit for the model. The root mean square residual is one of the common matrices that can be used to evaluate both the overall fit (the developed model) and the partial fit (the parameters defined between the two variables). The root mean square residual for the model is 0.08,

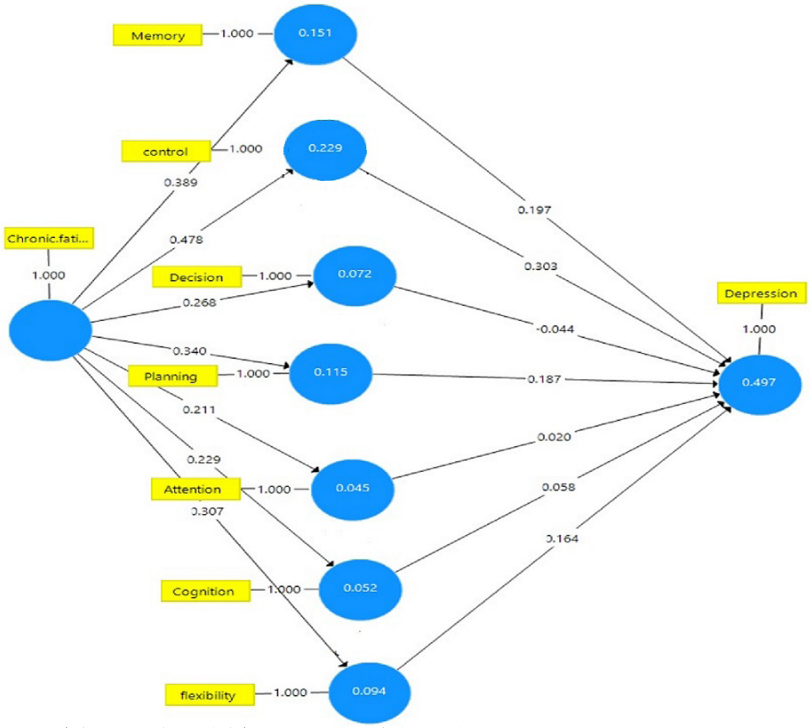


**Figure 3.** Path coefficients of the tested model for research sub-hypotheses

which is a good fit for the model. One of the comparative indicators is the NFI standardized fit index, in which values between 0.50 and 0.60 are acceptable, and values above 0.60 are interpreted as a very good fit of the data to the model. The NFI value for this model is 0.88, which is a good value for the model. Figure 2 shows the path coefficients of the tested model for the research hypothesis. The results showed that in patients with RRMS, there was a significant relationship between CFS and depression, CFS and EFs, and EFs and depression ($P<0.001$).

According to the results of Table 3, CFS has a direct and positive effect on EFs, and EFs and CFS have a direct negative effect on depression. Because the critical value of the test is higher than 1.96, the significance level of the test is less than 0.05, and the indirect effect of CFS on depression is significant, it can be concluded that EFs have a mediating role in the relationship between CFS and depression of patients with RRMS.

The EFs include 7 subscales, which are then examined using the SEM, the mediating role of each in the relationship between CFS and depression (Figure 3). Table 4 presents the direct effect of CFS on the subscales of EFs and also the indirect effect of CFS on depression mediated by each subscale.

According to the results of Table 4, CFS has a direct and positive effect on the subscales of working memory, inhibitory control, selective attention, planning, and cognitive flexibility, and these subscales have a direct positive effect on depression. Because the critical value of the test is higher than 1.96, the significance level of the test is less than 0.05, and the indirect effect of CFS on depression is significant, it can be concluded that these subscales have a mediating role in the relationship between CFS and the depression of patients with RRMS.

Also, according to the results of Table 4, CFS has a direct and positive effect on subscales of decision-making, controlled attention, and cognitive functioning. However, since the critical value of the test is less than 1.96 and also the significance level of the test is higher than 0.05, the indirect effect of CFS on depression is not significant. Therefore, it can be concluded that these subscales (decision-making, controlled attention, and cognitive functioning) do not mediate the relationship between CFS and depression in patients with RRMS.

## 4. Discussion

The purpose of this study was to investigate the relationship between CFS and depression with the mediating role of EFs in patients with RRMS. The results of the present study showed that some subscales of EFs have a mediating role in the relationship between CFS and depression in patients with RRMS. According to the results, CFS has a direct positive effect on EFs. However, in the relationship between CFS and depression in people with RRMS, subscales of working memory, inhibitory control and selective attention, planning, and cognitive flexibility play a mediating role, and subscales of decision-making, controlled attention, and cognitive functioning do not play a mediating role. The findings of the present study are in line with the results of Joyce et al. (1996) and Golan et al. (2018).

In explaining the above findings, according to industrial theory, CFS has been identified with cognitive dysfunction, including increased reaction time, decreased alertness, perceptual and cognitive distortions, decreased skill effectiveness, impaired information processing, and decreased concentration, motivation, and activity. This relationship disrupts the sense of agency and leads to dysfunction in hard work. Impairment of information processing and reduced focus are effective on working memory, inhibitory control, selective attention, planning, and controlled attention. Decision-making requires basic cognitive processes, such as working memory, controlled attention, and inhibitory control. Also, the disruption of human agency and cognitive-perceptual distortions can affect social resilience and reduce performance in recognizing facial emotion; therefore, it can have a relationship with depressive symptoms. Also, according to the theory of cold and hot EFs, planning, cognitive flexibility, working memory, behavior monitoring, and inhibitory control belong to the "cold" processes of EFs that were accepted as mediating roles in this study. In explaining this finding, the cognitive processes related to cold EFs do not tend to have a lot of emotional stimulation and are relatively logical.

In explaining the mediating role of subscales of working memory, inhibitory control, selective attention, planning, and cognitive flexibility, according to Ghaemi et al.'s research (2021), working memory with 14% has the highest share and other cases (inhibitory control and selective attention, planning and cognitive flexibility) have 10%, 12%, and 12%, respectively. This is one of the most important components of the executive functions of the brain.

But the subscales of cognitive functioning, decision-making, and controlled attention belong to hot EFs. As hot EFs support behaviors that require emotional awareness and regulation of a person's social behaviors and decisions with emotional and personal interpretation and empathy, they can be expected not to act as mediators.

In explaining the non-confirmation of the mediating role of the cognitive functioning subscale, the selected sample in this study were members of the Telegram social network. Some of these individuals interacted during the COVID-19 pandemic, and the effect of CFS had a direct and positive effect on cognitive functioning. Therefore, in this study, they neutralized each other and did not play a mediatory role.

In explaining the non-confirmation of the mediating role of the decision-making subscale, social and creative dimensions can influence decision-making and decision-making usually takes place in changing, dynamic, social, and other contexts. On the other hand, the effect of CFS on decision-making was direct and positive; therefore, in this study, they neutralized each other. Also, the most correlation between decision-making and controlled attention is that, in this study, the mediatory role of controlled attention was not confirmed.

In explaining the non-confirmation of the mediating role of the subscale of controlled attention, we can refer to the issue of imagination and positive imagery, which is expressed in several sessions of patients with RRMS, and is consistent with them and reduces depression. On the other hand, the effect of CFS has a direct positive effect on controlled attention. Therefore, in this study, these variables neutralize the effect of each other, hence, controlled attention does not play a mediating role in this hypothesis.

## 5. Conclusion

The present study has investigated the relationship between CFS and depression from a different perspective, emphasizing the mediating role of EFs in MS patients. Based on the findings of the present study, it can be concluded that CFS is related to depression and EFs play a mediating role in this relationship. EFs consist of seven subscales of memory, inhibitory control and selective attention, planning, cognitive flexibility, social cognition, decision-making, and sustained attention, which cold EFs refer to mechanical higher-order cognitive operations and are based on a law that regulates and controls the thinking and performance of the individual, in this research the findings indicated the mediating role of cold EFs. The sense is that hot EFs require cognitive abilities that are supported by emotional awareness and social perception and non-legal functions are based on emotions, desires, social cognition, and situational influencing factors. In this research, the mediating role of hot EFs was not confirmed. The meaning that they need to be emotionally aware and adjust their social behaviors and make decisions with emotional and personal interpretation and empathy was not included as a mediator role. Also, the results indicated that there is a significant relationship between CFS and depression, there is a significant relationship between CFS and EFs, and there is a significant relationship between EFs and depression in people with RRMS. There is a relationship. The results of the following research can be used in cognitive rehabilitation to improve EFs and consequently improve depression in patients with MS.

### Study limitations

One of the limitations of this study is that the sampling of patients in a medical clinic has been done at a specific time and place. Also, the communication limitations that prevail in the COVID-19 period along with the experience of the quarantine may affect the participants in the form of psychological challenges.

### Direction for future research

The results of this study make it possible to understand the nature of the relationship between CFS and depression in a more comprehensive and integrative way. In addition, the existing contradictions in the relationship between the variables of this study, especially depression and CFS, require further research in this field. The results of this study, based on the mediating effect of cold EFs, can be used in clinical treatment applications and measures to strengthen the EFs of patients with RRMS. Given the effectiveness of the present study in prioritizing cognitive rehabilitation, it can be expected to prevent the occurrence of defects in the EFs of people with RRMS, thereby increasing their self-efficacy and, as far as possible reducing their physical and mental problems.

One of the practical suggestions of this research is to design and teach fatigue management interventions for patients to the extent that they feel in control of the environment and reduce depression. It is also suggested that the evidence-based Cogmed program, whose main goal is to improve attention and working memory training, be included in treatment programs to decrease depression by increasing the level of cognitive functions.

## Ethical Considerations

### Compliance with ethical guidelines

All procedures performed in studies involving human participants were by the ethical standards of the institutional and or national Research Committee, following the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the present study. All data generated or analyzed during this study are included in this published article along with its supplementary information files.

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### Authors' contributions

Investigation, Data collection, Data analysis: Maziar Saffariantoosi; Writing-original draft, Methodology: Vahid Sadeghi-Firoozabadi; Conceptualization and Supervision: Jalil Fathabadi; Writing–review & editing: Abdorreza Naser Moghadasi.

### Conflict of interest

The authors declared no conflict of interest.

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