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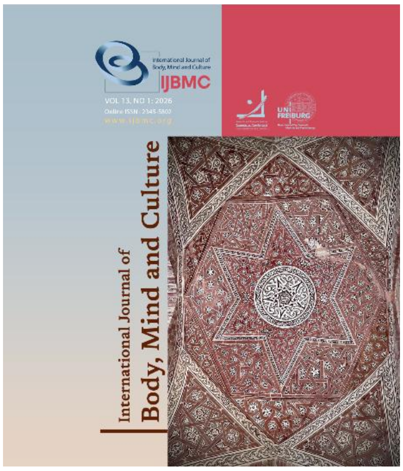
1 Department of Psychology, Ra.C., Islamic Azad University, Rasht, Iran.
2 Department of Nursing and Midwifery, Ra.C., Islamic Azad University, Rasht, Iran.
3 Professor, Department of Psychology, Faculty of Literature and Humanities, University of Guilan, Rasht, Iran.

Brain–Behavioral Systems and Executive Functions in Women with Multiple Sclerosis: The Mediating Role of Cognitive Emotion Regulation

Corresponding author email address:
mm.mousavi@iau.ac.ir

Sharareh. Haddadi[1], Seyedeh Maryam. Mousavi[2*], Abbas Ali. Hosseinkhanzadeh[3]



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ABSTRACT

Objective: This study examined a structural model predicting executive functions in women with multiple sclerosis based on brain–behavioral systems, with cognitive emotion regulation as a mediating variable.

Methods and Materials: This descriptive-correlational study used structural equation modeling. The study population included women with relapsing–remitting multiple sclerosis who were members of the Iran MS Society in Tehran during 2024–2025. A total of 306 women were selected through purposive sampling. Data were collected using the Executive Functions Questionnaire, Cognitive Emotion Regulation Questionnaire, and Behavioral Inhibition/Behavioral Activation Systems Questionnaire. Data were analyzed using SPSS-26 and AMOS-24 with bootstrap testing.

Findings: The final model showed good fit: $\chi^2 = 92.14$, $\chi^2/df = 1.66$, GFI = 0.99, AGFI = 0.96, CFI = 0.99, IFI = 0.99, TLI = 0.98, and RMSEA = 0.05. Executive functions were significantly correlated with behavioral inhibition ($r = 0.49$, $p < 0.01$), behavioral activation ($r = -0.50$, $p < 0.01$), positive cognitive emotion regulation ($r = -0.54$, $p < 0.01$), and negative cognitive emotion regulation ($r = 0.55$, $p < 0.01$). Bootstrap results showed significant indirect effects through positive cognitive emotion regulation for behavioral activation ($\beta = 0.22$, $p = 0.001$) and behavioral inhibition ($\beta = -0.20$, $p = 0.001$), and through negative cognitive emotion regulation for behavioral activation ($\beta = 0.24$, $p = 0.001$) and behavioral inhibition ($\beta = -0.23$, $p = 0.001$).

Conclusion: Cognitive emotion regulation mediated the relationship between brain–behavioral systems and executive functions in women with multiple sclerosis. Emotion regulation–focused interventions may help improve cognitive functioning in this population.

Keywords: Executive functions, multiple sclerosis, behavioral brain systems, cognitive regulation of emotion.

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, and neurodegenerative disorder of the central nervous system that affects more than 2.8 million people worldwide (Woo et al., 2024). MS is an autoimmune disease that leads to the gradual loss of the myelin sheath surrounding neuronal axons (Portaccio et al., 2024). The onset of the disease typically occurs in early to mid-adulthood (20–40 years), it is more prevalent in women than in men, and individuals of Northern European ancestry and White populations are at greater risk. Moreover, its prevalence decreases with increasing distance from the equator (Haki et al., 2024). Based on the initial clinical course, MS has traditionally been classified as either relapsing–remitting (RRMS) or primary progressive (PPMS). RRMS is the more common phenotype, affecting approximately 85–90% of patients, whereas PPMS occurs in about 10–15% and is typically characterized by an insidious, continuous progression without distinct relapses (Portaccio et al., 2024).

Research on MS has often emphasized patients' physical problems, whereas it is cognitive impairment that imposes the greatest limitations on patients' daily functioning (Chiaravalloti & DeLuca, 2008). In addition, studies by Megías et al. (2017) and Schmeichel & Tang (2015) have shown that cognitive processes are closely related to emotions and play a role in their formation. Among cognitive processes, investigations by Lantrip & Huang (2017) and Rueda & Paz-Alonzo (2018) have highlighted the role of executive functions in emotion control. Therefore, examining executive functions as a key cognitive domain appears essential.

The brain is thought to encompass two broad types of cognitive functioning: rule-based functions, namely executive functions, and non–rule-based functions that are grounded in emotions, motives, social cognition, and situational influences (Ardila, 2017). One conceptualization of executive functions includes five components: response inhibition, planning, cognitive flexibility, attentional shifting, and working memory. A useful way to define executive functions more precisely is to focus on the set of operations involved in problem solving Koudys & Ruocco (2022), given that executive functioning is crucial for goal setting and problem resolution (Narmashiri & Akbari, 2025). Executive functions constitute a set of higher-order cognitive processes responsible for self-regulation and goal-directed behavior. They refer to capacities that enable individuals to generate new behavioral patterns, adopt new ways of thinking, and revise thoughts (Perkins et al., 1993). These capacities are particularly needed in unfamiliar situations in which individuals do not know what to do, or in situations where previously established behavioral strategies are no longer useful or appropriate (Cantor, 1990).

Recent research suggests that structural and functional brain abnormalities, along with genetic and immunological factors, may influence executive functioning (Katz et al., 2020; Sullivan et al., 2025). One variable that prior research has identified as contributing to deficits in executive functions is the brain/behavioral systems (Solomonov et al., 2025; Yazdani & Mirzaian, 2024). In relation to executive dysfunction in individuals with MS, attention has also been directed toward these systems (Abedzadeh et al., 2023). According to Gray's neuropsychological theory, the brain includes two fundamental systems—the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS)—that regulate emotion and behavior. This theory explains how brain-related personality traits can predispose individuals to psychopathological disorders (YAMAGATA et al., 2012). The BIS is sensitive to cues of punishment and threat, leading to avoidance and behavioral inhibition, and is associated with fear- and passivity-related tendencies such as introversion, depression, and anxiety. In contrast, the BAS is sensitive to reward cues and underlies reward-seeking behavior, impulsivity, and extraversion; it also predicts positive affect and happiness and promotes approach behavior (Gray, 1990).

Another variable that, in addition to the sensitivity and activity of the brain–behavioral systems, may affect executive functions in individuals with MS is cognitive emotion regulation (Duraney et al., 2022; Prakash et al., 2019). Cognitive emotion regulation refers to conscious, cognitive ways of managing the processing of emotionally arousing information (Garnefski et al., 2001). In other words, cognitive emotion regulation strategies are the approaches individuals use to cope with adverse conditions, and they are typically classified as adaptive or maladaptive (Garnefski & Kraaij, 2006). The predictive role of cognitive emotion regulation in executive functioning, along with its susceptibility to influence from brain–behavioral systems, suggests that cognitive emotion regulation may mediate the relationship between brain–behavioral systems and executive functions. That is, dysregulation in brain–behavioral systems may lead to impairments in cognitive emotion regulation and a greater reliance on maladaptive rather than adaptive strategies, which may in turn contribute to executive dysfunction in women with MS. In separate studies, Sam et al. (2025) and Vasheghani Farahani & Safari (2025) reported that BAS/BIS functioning is associated with difficulties and disruptions in emotion regulation among depressed adolescents.

Given the progressive nature of MS and the widespread involvement of the central nervous system, executive functions represent a particularly vulnerable cognitive domain in these patients. At the same time, evidence indicates that brain–behavioral systems play a central role in organizing emotional and behavioral responses and may therefore influence cognitive performance. Cognitive emotion regulation, as a key process, may further shape the extent to which these systems affect executive functioning. Examining these variables simultaneously can facilitate the development of a more comprehensive explanatory model of executive functions in women with MS. Despite a substantial body of research on cognitive impairments in MS, relatively few studies have investigated emotional–cognitive mechanisms within mediation frameworks. In particular, the mediating role of cognitive emotion regulation in the association between brain–behavioral systems and executive functions has received limited attention. Moreover, the scarcity of research focusing specifically on women with MS—as a group with distinct biological and psychological characteristics—constitutes a notable gap in the literature. Accordingly, the present study may help address this gap, contribute to the development of targeted psychological interventions, and ultimately improve the quality of life of these patients.

Methods and Materials

Study Design

The present study employed a descriptive–correlational design using structural equation modeling (SEM). In this model, brain–behavioral systems served as the exogenous variable, executive functions as the endogenous variable, and cognitive emotion regulation as the mediating variable. The statistical population consisted of women with multiple sclerosis who were members of the Iran MS Society in Tehran in 2024-25. Using purposive sampling, 306 participants were selected and studied. With regard to sample size, a minimum of 200 participants is considered defensible for SEM Kline (2015); however, due to anticipated attrition, the possibility of incomplete questionnaires, and the number of volunteers, 500 questionnaires were distributed.

Inclusion criteria were: basic literacy (at least completion of primary school), age between 20 and 45 years, informed consent, and a diagnosis of relapsing–remitting MS. Exclusion criteria were: incomplete or invalid questionnaires, acute physical or psychiatric disorders such as psychosis, bipolar disorder, or borderline personality disorder (self-reported), and high consumption of antipsychotic medications or other agents that depress the nervous system.

Procedure

After the research proposal was approved, the necessary permissions to conduct the study were obtained. The researchers then visited the Iran MS Society in Tehran in person, contacted members, and provided an explanation of the study aims. Subsequently, during June to December 2024, an online demographic form, an ethics/informed consent form, and the questionnaires related to the study variables were made available to volunteers (N = 500). Of these, 354 individuals who met the inclusion criteria were initially considered eligible participants. Following data collection and final screening, 48 questionnaires were excluded due to incomplete responses, and ultimately 306 questionnaires were included in the analyses. Ethical principles were observed throughout the study. All analyses were conducted using SPSS version 26 and AMOS version 24, employing SEM and the bootstrap method.

Intruments

Brain/Behavioral Systems Questionnaire (BIS/BAS)

The Behavioral Inhibition/Behavioral Activation Systems (BIS/BAS) questionnaire was developed by Carver & White (1994). It includes 24 self-report items and two main subscales: the Behavioral Inhibition System (BIS) and the Behavioral Activation System

(BAS). The BIS subscale comprises 7 items assessing sensitivity to behavioral inhibition (i.e., responsiveness to threat and anxiety when facing threat cues). The BAS subscale contains 13 items assessing sensitivity to behavioral activation and includes three additional subscales: Drive (4 items), Reward Responsiveness (5 items), and Fun Seeking (4 items). Items are rated on a 4-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). It should be noted that items 1, 6, 11, and 17 do not contribute to scoring. Item scores are summed to yield a total score. Total scores from 24 to 40 indicate low system sensitivity; 40 to 60 indicate moderate sensitivity; and scores above 60 indicate high sensitivity. Carver & White (1994) identified four factors in the initial factor analysis, but in a second-order exploratory factor analysis found that three factors—Reward Responsiveness, Drive (goal-directed striving), and Fun Seeking—loaded on a general BAS factor. They reported internal consistency coefficients ranging from 0.66 to 0.76. Cronbach's alpha was reported as 0.74 for BIS and 0.71 for BAS. In the present study, Cronbach's alpha was 0.77 for BIS and 0.75 for BAS.

Cognitive Emotion Regulation Questionnaire (CERQ)

The Cognitive Emotion Regulation Questionnaire was developed by Garnefski and colleagues in the Netherlands in 2001 to identify cognitive emotion regulation strategies after experiencing negative events or situations (Garnefski et al., 2001). It assesses nine subscales: Self-blame, Other-blame, Rumination, Catastrophizing, Positive Refocusing, Refocus on Planning, Positive Reappraisal, Putting into Perspective (Broader Perspective), and Acceptance. Higher scores indicate greater use of the corresponding cognitive strategy. Responses are provided on a 5-point Likert continuum from 1 (never) to 5 (always). In this study description, the questionnaire is also reported as measuring emotion regulation patterns across six subscales: Nonacceptance of emotional responses (items 11, 12, 21, 23, 25, 29), Difficulties engaging in goal-directed behavior (items 13, 18, 20, 26, 33), Impulse control difficulties (items 3, 14, 19, 24, 27, 33), Lack of emotional awareness (items 2, 6, 8, 10, 17, 34), Limited access to emotion regulation strategies (items 15, 16, 22, 28, 30, 31, 35, 36), and Lack of emotional clarity (items 1, 4, 5, 7, 9). Items 1, 2, 6, 7, 8, 10, 17, 20, 22, 24, and 34 are reverse scored. Total scores range from 36 to 180, with 108 considered the cut-off score. Notably, in the present study, only the total score was used for reporting the analyses.

In Garnefski et al., (2001) study, criterion validity (concurrent validity) was supported in a sample of 547 Dutch secondary school students through correlations with depression, anxiety, and stress scales (r = 0.41). Internal consistency (Cronbach's alpha) for adaptive and maladaptive strategy dimensions was reported as 0.91 and 0.87, respectively Garnefski & Kraaij (2006). In an Iranian study by Besharat et al., (2015) with 478 adults in Tehran, Kendall's coefficient of concordance based on judgments from 10 psychology experts was reported as 0.86 for adaptive strategies and 0.72 for maladaptive strategies. They also reported Cronbach's alpha values of 0.83 (adaptive strategies) and 0.92 (maladaptive strategies).

Executive Functions Questionnaire (EFQ)

The Executive Functions Questionnaire (EFQ) was developed by Nejati (2013). It contains 30 items and seven subscales. Items are rated on a 5-point Likert scale ranging from 5 (almost never) to 1 (always). The seven subscales include: Memory (items 1–6), Selective Attention (items 7–12), Decision Making (items 13–17), Planning (items 18–20), Sustained Attention (items 21–23), Social Cognition (items 24–26), and Cognitive Flexibility (items 27–30). Social cognition items are reverse scored. The total score ranges from 30 to 150. Scores of 30–70 indicate weak executive functioning, 70–110 indicate moderate executive functioning, and 110–150 indicate high executive functioning. The overall reliability of the questionnaire has been reported as 0.84 using Cronbach's alpha. Internal consistency coefficients for subscales were reported as follows: Memory (0.75), inhibitory control/selective attention (0.62), decision making (0.61), planning (0.57), sustained attention (0.53), social cognition (0.43), and cognitive flexibility (0.45) (Nejati, 2013). For concurrent validity, correlations between academic grade point average and questionnaire subscales were examined; with the exception of social cognition, all subscales were significantly correlated with GPA at the 0.001 level (Nejati, 2013). In the present study, the overall Cronbach's alpha coefficient was 0.81.

Findings and Results

A total of 306 women with multiple sclerosis participated in the present study. The mean age of the sample was 34.63 years (SD = 6.46), ranging from 20 to 45 years. With respect to marital status, 140 participants (45.8%) were single and 166 (54.2%) were married. Regarding educational level, the majority (n = 138; 45.1%) held a bachelor's degree, whereas the smallest proportion (n = 3; 1.02%) had less than a high-school diploma. In terms of disease duration, 104 participants (34.0%) had been diagnosed for less than 5 years, 102 (33.3%) for 5–10 years, and 100 (32.7%) for more than 10 years. Table 1 presents the correlation matrix, means, and standard deviations of the study variables.

Table 1

Correlation matrix, means, and standard deviations of study variables

Variable	1	2	3	4	5	6	7	8	Mean	SD
1. Executive functions	1								67.90	7.95
2. Behavioral inhibition	0.49	1							54.12	4.03
3. Behavioral activation	−0.50	−0.52	1						23.46	5.61
4. Drive	−0.47	−0.43	0.82	1					7.48	2.29
5. Fun seeking	−0.34	−0.38	0.80	0.47	1				8.37	2.38
6. Reward responsiveness	−0.40	−0.44	0.81	0.52	0.45	1			7.61	2.26
7. Positive cognitive emotion regulation	−0.54	−0.51	0.56	0.48	0.39	0.49	1		52.77	10.42
8. Negative cognitive emotion regulation	0.55	0.57	−0.61	−0.53	−0.49	−0.47	−0.58	1	51.85	12.52

As shown in Table 1, executive functions were positively and significantly correlated with behavioral inhibition ($r = 0.49$, $p < .01$) and with negative cognitive emotion regulation ($r = 0.55$, $p < .01$). Executive functions were negatively and significantly correlated with behavioral activation ($r = −0.50$, $p < .01$) and its components, as well as with positive cognitive emotion regulation ($r = −0.54$, $p < .01$). Behavioral inhibition was negatively and significantly correlated with positive cognitive emotion regulation ($r = −0.51$, $p < .01$), and positively and significantly correlated with negative cognitive emotion regulation ($r = 0.57$, $p < .01$). Behavioral activation showed a positive and significant correlation with positive cognitive emotion regulation ($r = 0.56$, $p < .01$), and a negative and significant correlation with negative cognitive emotion regulation ($r = −0.61$, $p < .01$). Overall, the findings indicated significant linear relationships among the study variables. To evaluate the proposed model, path analysis was conducted using AMOS. Prior to testing the model, assumptions were examined. Skewness and kurtosis values for the study variables were within the range of −2 to +2, indicating acceptable normality. Figure 1 presents the fitted (final) model. Table 2 presents the indirect path coefficients of the final model estimated using the bootstrap method.

Table 2

Indirect effects in the final model using bootstrapping

Path	Standardized estimate	Lower CI	Upper CI	p
Behavioral activation → Positive cognitive emotion regulation → Executive functions	0.22	0.13	0.32	.001
Behavioral inhibition → Positive cognitive emotion regulation → Executive functions	−0.20	−0.28	−0.14	.001
Behavioral activation → Negative cognitive emotion regulation → Executive functions	0.24	0.13	0.36	.001
Behavioral inhibition → Negative cognitive emotion regulation → Executive functions	−0.23	−0.31	−0.16	.001

To test indirect effects, bootstrapping—a resampling technique that estimates population parameters via sampling with replacement and is commonly used to compute confidence intervals—was applied. In the present study, bootstrap estimates were based on 2,000 resamples. Results indicated that the indirect effect of positive cognitive emotion regulation in the relationship between behavioral activation and executive functions was significant (standardized effect = 0.22, $p = .001$). The indirect effect of positive cognitive emotion regulation in the relationship between behavioral inhibition and executive functions was also significant (standardized effect = −0.20, $p = .001$). Likewise, the indirect effect of negative cognitive emotion regulation in the relationship between behavioral activation and executive functions was significant (standardized effect = 0.24, p = .001), and the indirect effect of negative cognitive emotion regulation in the relationship between behavioral inhibition and executive functions was significant (standardized effect = −0.23, p = .001). Overall, these findings suggest that brain–behavioral systems exert an indirect effect on executive functions through the mediating role of cognitive emotion regulation in women with multiple sclerosis.

Table 3

Model fit indices

Model	χ^2	χ^2/df	GFI	AGFI	CFI	IFI	TLI	RMSEA
Study model	92.14	1.66	0.99	0.96	0.99	0.99	0.98	0.05
Acceptable criteria	—	1–5	> 0.90	> 0.90	> 0.90	> 0.90	> 0.90	< 0.08

Table 3 indicates that the χ^2/df ratio was 1.66, which falls within the acceptable range of 1 to 5 and supports adequate model fit. In addition, the Goodness-of-Fit Index (GFI), Adjusted Goodness-of-Fit Index (AGFI), Comparative Fit Index (CFI), Incremental Fit Index MamSharifi et al., and Tucker–Lewis Index (TLI) were all above 0.90, indicating satisfactory fit. The Root Mean Square Error of Approximation (RMSEA) was 0.05, which is below 0.08 and suggests a good fit of the model.

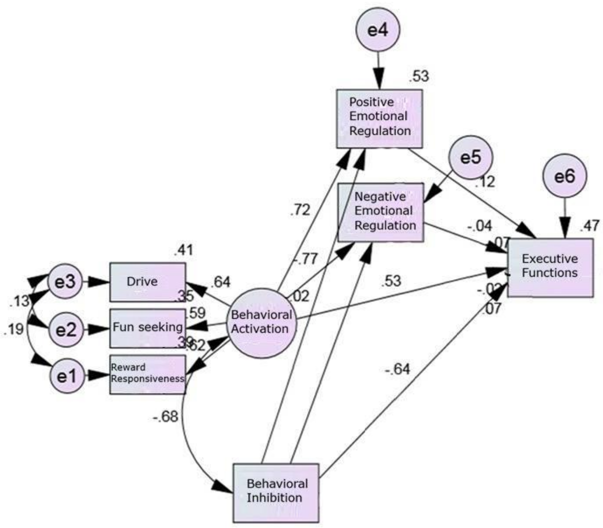

Figure 1

Final model with standardized path coefficients.

Discussion and Conclusion

The aim of the present study was to predict executive functions in women with multiple sclerosis (MS) based on brain–behavioral systems, with the mediating role of cognitive emotion regulation. The first finding indicated that the Behavioral Inhibition System (BIS) had a significant negative direct effect on executive functioning; however, the Behavioral Activation System (BAS) did not have a significant direct effect on executive functions. These results are consistent with part of the findings reported by Abdi et al. (2017) and Pahlavanpour et al. (2024).

To interpret this finding, the significant negative effect of BIS on executive functions may be attributed to excessive threat focus, heightened anticipatory anxiety, and overactive cognitive inhibition. Individuals with a highly reactive BIS tend to experience greater hesitation and slower processing in decision-making situations, because their cognitive resources are allocated to evaluating potential risks and preventing errors. In contrast, the absence of a positive BAS effect on executive functions may reflect a weakened linkage between positive motivation and cognitive control networks due to neurological damage and dopaminergic dysregulation in MS. Taken together, these results portray a psychological profile in which avoidance and inhibition override motivational, goal-directed engagement, thereby substantially undermining executive functioning.

In addition, the results showed that the indirect pathway through positive cognitive emotion regulation in the relationship between BAS and executive functions was significant, and the indirect pathway through positive cognitive emotion regulation in the relationship between BIS and executive functions was also significant. Likewise, the indirect pathway through negative cognitive emotion regulation in the relationship between BAS and executive functions was significant, and the indirect pathway through negative cognitive emotion regulation in the relationship between BIS and executive functions was significant. Accordingly, the eighth (partial) hypothesis of the study was supported, indicating that brain–behavioral systems exert an indirect effect on executive functions through the mediating role of cognitive emotion regulation in women with MS. These findings are broadly consistent (at least indirectly) with the results reported by Abdi et al. (2017), Eshaghzadeh et al. (2023), Haddadi et al. (2025); Pahlavanpour et al. (2024), Pennington et al. (2024); Phillips et al. (2014), and Saffariantoosi et al. (2022).

With respect to interpretation, the indirect pathways between brain–behavioral systems (BAS/BIS), cognitive emotion regulation, and executive functions suggest that the association between basic motivational tendencies and higher-order cognitive capacities cannot be fully explained by direct effects alone. Rather, cognitive emotion regulation appears to function as a central mediating mechanism, and the observed indirect effects reflect a multistage neuropsychological process. In practice, BAS and BIS do not merely generate raw motivational signals; they also shape individuals' preferred patterns of employing cognitive emotion regulation strategies (e.g., cognitive reappraisal versus rumination), thereby altering the cognitive resources available for executive functioning. This is precisely what the modeled indirect pathways demonstrated: BAS and BIS each exerted meaningful and significant effects on executive functions through two routes—positive and negative cognitive emotion regulation. Recent studies have similarly suggested that BIS/BAS sensitivities predict the use of adaptive versus maladaptive emotion regulation strategies, which in turn modify the intensity and impact of emotional states. Therefore, the mediating role of cognitive emotion regulation is theoretically and empirically plausible.

From a cognitive-mechanistic perspective, the positive and negative indirect pathways can be explained through the common classification of emotion regulation strategies. Positive cognitive emotion regulation strategies (e.g., cognitive reappraisal and positive refocusing) are typically associated with reductions in negative emotional load and the freeing of working memory and attentional control resources. Thus, when an individual's BAS is higher and they preferentially use positive strategies, fewer executive resources are consumed by threat processing and rumination, and executive functions may improve. Conversely, heightened BIS is associated with greater reliance on avoidance-based or ruminative strategies, which increase cognitive load and reduce the resources required for inhibitory control and updating processes. This "shared resource consumption" mechanism—where emotion regulation draws on the same limited resources needed for executive control—has been repeatedly discussed in research on emotion–executive control interactions (Löffler, 2025).

From a neurobiological perspective, BAS-related networks (including mesolimbic reward circuitry and orbitofrontal regions) are implicated in motivation reinforcement and the experience of positive affect, whereas BIS is linked to amygdala–hippocampal circuitry and regions involved in threat detection. Effective cognitive emotion regulation (e.g., cognitive reappraisal) requires the engagement of prefrontal cortical control, which exerts inhibitory influence over limbic responses. Such prefrontal engagement not only reduces emotional reactivity but may also preserve or strengthen executive capacities. Accordingly, when BAS increases the use of positive regulation strategies and recruits prefrontal control pathways, it may facilitate executive functioning; in contrast, when BIS promotes heightened limbic activity and reduced prefrontal efficiency, it may indirectly impair executive functioning through a preference for maladaptive strategies.

Neuroimaging and psychophysiological evidence has also pointed to this interaction among motivational circuits, emotion regulation processes, and executive networks.

This study had several limitations. First, the use of self-report questionnaires constitutes an important limitation. Second, the nonrandom sampling method limits the generalizability of the findings. Third, many socioeconomic and demographic variables that could influence psychological outcomes in individuals with MS were not considered in the present study. Future studies are therefore recommended to use interviews and additional psychological assessment tools to collect data. Additionally, where possible, probabilistic sampling methods are recommended. It is also advisable to include socioeconomic variables such as employment status and income in future research.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants. Ethical considerations in this study were that participation was entirely optional.

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

All authors equally contribute to this study.

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