

# Relationship between Brain-Behavioral System and Perceived Stress: Control of Biomarker among of Multiple Sclerosis Patients

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## Abstract

**Background:** Multiple sclerosis (MS) is a chronic, often disabling disease in which the immune system attacks the myelin sheath of neurons in the central nervous system. The purpose of this study was to explore the correlation between the Behavioral Inhibition/Approach System (BIS-BAS) and Perceived Stress (PS), while controlling for White Blood Cell (WBC) count.

**Methods:** 120 MS patients (36.7% male, 63.3% female; aged 15-65 years) participated in this study. They completed a demographic questionnaire, underwent a Complete Blood Cell (CBC) test, filled out the Behavioral Activation and Behavioral Inhibition Scale (BIS-BAS) and responded to the Perceived Stress Questionnaire (PSS-14).

**Results and conclusion:** The results indicated a significant relationship between the BAS-Reward Responsiveness (BAS-RR) subscale and PS, particularly in a subset of MS patients with increased WBC counts.

**Keywords:** Behavioral inhibition/approach system • Multiple sclerosis • Perceived stress • White blood cell

## Introduction

MS is an autoimmune condition characterized by the migration of immune cells into the central nervous system, production of proinflammatory cytokines, demyelination and neuronal damage. A neurodegenerative process may contribute to loss of neurologic function during later secondary progressive MS [1]. People with MS have long reported that psychological stress can worsen their symptoms and studies show that chronic exposure to a wide range of challenging life events is correlated with worsening neurological symptoms in MS [1-5]. This process is highly personalized and influenced by inherent personality traits, early life experiences and learned responses to stressful events [6]. Moreover, studies show that alterations in stress physiology may affect the stress response in MS [7,8]. Given that the function of the body's major stress response system may be altered in MS, it is particularly important to understand specific factors that influence vulnerability to stress in people with MS [9-11].

According to data from the third edition of Atlas reports, it is estimated that there are over 2.8 million individuals living with MS worldwide, equating to approximately 35.9 cases per 100,000 populations. The majority of MS diagnoses occur in individuals aged between 20 and 40 years. Pediatric MS is considered rare, constituting around 2%-10% of the total MS patient population. Furthermore, MS disproportionately affects women, with a prevalence two to three times higher in females compared to males [12-17].

On the other hand, it seems that many genetic, psychosocial and epigenetic factors are also effective in MS and its severity and the interaction of these factors can create a system that causes failure in the one-dimensional treatment of autoimmune diseases. Therefore, due to the complexity in the etiology of MS disease, the importance of multiple factors of the disease should be considered in the treatment. It seems that patients with MS have differences with healthy people in terms of personality, genetics, psychology, coping styles and brain-

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behavioral system. The manifestations of the illness exhibit diversity and are contingent upon the specific regions of the brain or spinal cord that are impacted. When an area of the brain is under more stress due to developmental development, the possibility of damage and Oxidative Stress (OS) in that area increases, and since the damaged and stressed cells of that area face the reaction of the immune system and its manifestations, including cytokines. Therefore, it stimulates the demyelination and opening of chromatin and creates the expression of certain genes and these epigenetic effects will increase with time. Previous studies have established connections between fatigue and inflammatory markers such as interleukin-6, Tumor Necrosis Factor-alpha (TNF $\alpha$ ) and C-reactive protein, which is an acute phase protein, across a range of medical conditions like cancer, chronic inflammatory disease, autoimmunity, neurological diseases and mood disorders.

Inflammatory mechanisms have been demonstrated to impact the operation of the basal ganglia, leading to the hypothesis that impairment in this subcortical region may be responsible for diminished motivation and modified reward mechanisms in chronic populations, as suggested by previous studies. The basal ganglia, in conjunction with cortico-frontal brain structures, oversee the reward system which regulates motivational disposition mechanisms influencing the activation or inhibition of actions. Consequently, it has been suggested that dysfunction in motivation and reward processes may contribute to the experience of fatigue in individuals with chronic conditions. Previous research has indicated the importance of taking into account gender-specific traits in order to enhance the comprehension of the common factors that impact BIS/BAS functioning and associated behavioral consequences. The research indicates that females exhibit higher rates of affective disturbances, including anxiety, depression and dysthymia, compared to males, as evidenced by the Behavioral Inhibition System (BIS) and prevalence rates. The prevalence of substance abuse, impulsive behaviors, compulsive behaviors and aggression is reported to be higher in males compared to females, as indicated by BAS and incidence rates. Prior research has indicated a potential link between behavioral inhibition and activation systems, which represent motivational tendencies, perceptions of stress levels, and varying patient experiences with chronic conditions, akin to the management

of chronic diseases. Collectively, these pieces of evidence have led us to consider that the BIS/BAS theoretical framework and its associated measurement scale may offer a valuable means of assessing motivational tendencies in individuals with multiple sclerosis. Furthermore, this measure could potentially be utilized to explore variations in levels of fatigue and in continue stress perception levels among this patient population. So, the present study aims to investigate the relationship between the behavioral inhibition/ approach system, perceived stress and WBC count in MS patients.

## Materials and Methods

### Patients

This was a cross-sectional study of a sample of the general population of Iranian MS patients. As part of this study, 120 MS patients were randomly recruited from the MS treatment clinic of Emamreza in Shiraz, Iran, between February and November 2023. These patients were selected based on specific criteria, including literacy, early diagnosis of MS, consent to participate in the research and an age range of 15 to 65 years. A correlation study was conducted, employing the Pearson correlation coefficient for data analysis. The group of relapsing-remitting MS patients consisted of 44 males and 76 females, with a mean age of 33.53 (SD=1.18). Among them, 56 had completed either a diploma or under diploma education, 86 were married, 42 were engaged in homemaker jobs, and most experienced MS onset between the ages of 27-32 years. The average disease duration was more than 6 months and the age range of the participants was between 15 and 65 years (Table 1). All diagnostic criteria were determined by a sub-specialist of neurology (Dr. S.I.). The MS patients included in the study had no prior or current history of psychiatric or mental retardation. Additionally, they had no previous or current history of psychiatric and neurological disorders, which was determined using the structured clinical interview for DSM-V disorder, non-patient version (SCID-I/NP). Written informed consent was obtained from each subject and the study was conducted in accordance with the 1989 revision of the Helsinki Declaration, as approved by the code of ethics of the MS treatment clinic of Dr. S.I.

Variable	N (%)
Gender, males-females	(22-38) (63.3%-36.7%)
<b>Age-age of begin, no.</b>	
15-20	1 (1.7%)-5 (8.3%)
21-26	9 (15.0%)-12 (20.0%)
27-32	22 (36.7%)-19 (31.7%)
33-38	14 (23.3%)-14 (23.3%)
39-44	10 (16.7%)-9 (15.0%)
45+	4 (6.7%)-1 (1.7%)

Level of education, no.	
Under diploma and diploma	56 (46.7%)
Associate degree and bachelor	50 (41.7%)
MA and PHD	14 (11.7%)
Marital status, no.	
Single	32 (26.7%)
Married	86 (71.7%)
Divorced	2 (1.7%)
Duration of the disease, no.	
Under 6 months	68 (56.7%)
6 month-under 2 years	12 (10.0%)
2-5 years	32 (26.7%)
6-9 years	2 (1.7%)
10+ years	6 (5.0%)
Job, no.	
Homemaker	42 (35.0%)
Student	6 (5.0%)
Self employed	22 (18.3%)
Employee	20 (16.7%)
University professor	6 (5.0%)
Unemployed	24 (20.0%)

**Table 1.** Participants' characteristics (N=120).

## Instruments

**Demographic questionnaire:** Participant's demographic characteristics (gender, age, education, age at onset of MS and duration of illness) were collected.

**Count Blood Cell (CBC) test:** The WBC count of participants was measured.

**Behavioral Activation and Behavioral Inhibition Scale (BIS-BAS):** The BIS/BAS scale is a self-report measure consisting of 20 questions, with responses ranging from "Very True=1" to "Very False=4".

Traditionally, this scale comprises four separate subscales: BIS, BAS-Drive (reflecting goal-directed motivation), BAS-reward responsiveness (related to response upon receiving rewards) and BAS-fun seeking (associated with the desire for novel rewards). The convergent and discriminant validity of the BIS/BAS scales has been previously supported. In this study, we used Persian version of the BIS/BAS scale. In Iran, Mohammadi confirmed the psychometric properties of the Persian version of BIS/BAS scale using test-retest reliability, Cronbach's alpha and exploratory factor analysis. Table 2 for the Cronbach's alpha coefficient of BIS/BAS in the present study.

	Variables	1	2	3	4	5	6
1	WBC	-					
2	BIS	-0.27*	-				
3	BAS-reward responsiveness	0.1	0.28*	-			
4	BAS-drive	-0.24	0.48**	0.39**	-		
5	BAS-fun seeking	-0.2	0.35**	0.29*	0.46**	-	
6	PS	0.14	-0.02	0.33*	-0.02	-0.15	-
7	Cronbach's a	-	0.21	0.3	0.45	0.46	0.41

8	M	-	20.16	10.31	17.41	11.48	43
9	SD	-	0.38	0.3	0.31	0.31	0.67

**Note:** DAS: Depression Anxiety Stress; BIS: Behavioral Inhibition System; BAS: Behavioral Approach System-Reward; PS: Perceived Stress; \*P<0.05 (two tailed); \*\*P<0.01 (two tailed).

**Table 2.** Mean, SD, Cronbach's alpha; zero-order correlations for the BIS, BAS-DR, BAS-Rr, bas-fs subscale and PS and WBC (N=120).

**Perceived Stress Questionnaire (PSS-14):** Perceived stress was measured using the Perceived Stress Scale (PSS), which comprised of 14 questions with responses varying from 0 to 4 for each item and ranging from never, almost never, sometimes, fairly often and very often, respectively, on the basis of their occurrence during one month prior to the survey. The PSS has an internal consistency of 0.85 (Cronbach's alpha co-efficient) and test-retest reliability during a short retest interval (several days) of 0.85. It assesses the degree to which participants evaluate their lives as being stressful during the past month. It does not tie to a particular situation; the scale is sensitive to the non-occurrence of events as well as ongoing life circumstance. PSS-14 scores are obtained by reversing the scores on four positive items, for example 0=4, 1=3, 2=2, etc., and then summing across all 14 items. Items 4, 5, 6, 7 and 10 are the positively stated items. Table 2 for the Cronbach's alpha coefficient of SPSS-16 in the present study.

### Statistical analysis

Demographic and research variables are presented as mean± standard deviation or as percentages within a specific range. The relationship between the BAS-DR subscale and PS, as well as the BIS subscale with control WBC, was analyzed using zero-order correlation. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using SPSS@ version 16.0 for Windows (IBM Corporation, Armonk, NY, USA). The reliability of the applied scales was assessed using Cronbach's alpha coefficient. The result of the Kolmogorov-Smirnov test revealed that the data were normal. Also, there were no missing values.

## Results

The demographic and clinical characteristics are presented in Table 1. There were 120 MS patients in the study, consisting of 44 males and 76 females. The mean age was 3.53 years with a standard deviation of 1.18. Among the patients, 56 (46.7%) had an education level under diploma or diploma, 86 (71.7%) were married and 42 (35.0%) had homemaker jobs. The majority of patients (31.7%) experienced MS onset between the ages of 27 and 32 years and 68 (56.7%) had a disease duration of more than 6 months.

The means, standard deviations, Cronbach's alpha and correlations among the studied variables are reported in Table 2. The results showed a positive relationship between the BAS-DR subscale and PS ( $r=0.332$ ,  $p<0.05$ ), indicating that higher scores on the BAS-DR subscale were associated with higher levels of perceived stress in MS patients. Additionally, there was a negative relationship between the BIS sub-scale and WBC ( $r=-0.271$ ,  $p<0.05$ ), suggesting that higher scores on the BIS subscale were associated with lower WBC in MS patients. Please refer to Table 2 for more details.

## Discussion

The main objective of this study was to investigate the relationship between behavioral brain functions, perceived stress and psychological symptoms with control WBC count in MS patients. The data revealed a positive relationship between the BAS-DR subscale and Perceived Stress (PS) and a negative relationship between the BIS subscale and WBC count in MS patients. These results suggest that certain behavioral tendencies and stress levels may be associated with variations in WBC counts among individuals with MS and were in accordance with previous findings. Herbert and Cohen demonstrated substantial evidence supporting a relationship between stress and decreases in functional immune measures, such as the proliferative response to mitogens and natural killer cell activity. Stress is also associated with the numbers and percentages of circulating WBCs, immunoglobulin levels and antibody titers to herpes viruses. Subsequent analyses suggest that objective stressful events are related to larger immune changes than subjective self-reports of stress and that immune response varies with stressor duration. Therefore, when emotions are not expressed, environmental stressors are more severe and can be exacerbated by behavioral inhibition. This, in turn, affects blood cells and neurons, which are identified as visible signs of fear and worry. Pathways in the brain that are activated or deactivated by stress are identified as antigens by the immune system and are attacked, in other words, epigenetics acts as a two-way role in the relationship between stress and disease, which it requires detailed laboratory research.

## Conclusion

In conclusion, it can be inferred that a higher BIS subscale score is predictive of more WBCs in MS patients. This suggests that the BIS might amplify the count of WBC through the perception of stress, particularly catastrophizing, in MS patients. Thus, when emotions are not expressed, environmental stress is perceived more acutely, behavioral inhibition is reduced and WBC are increased to counter the visible signs of fear and anxiety, such as highly active and stress-sensitive neurons, to the point that the immune system recognizes neurons with high perceived stress as invaders and attacks them. It seems that by performing coping skills that play a role in stopping the progress of psychosomatic disorders, it is possible to activate the neuropsychological system of the prefrontal lobe, which plays a role in controlling behavioral inhibition from top to bottom, in order to reduce the severe perception of stress and to express it was appropriate for the emotions to stop the progression of MS.

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