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ARAŞTIRMA / RESEARCH

Temperament and character in relapsing-remitting multiple sclerosis: association with clinical factors and psychiatric disorders

Tekrarlayan ve düzelen multipl sklerozda mizaç ve karakter: klinik faktörler ve psikiyatrik bozukluklarla ilişkisi

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Abstract

Purpose: Despite its implications for quality of life, temperament, and character in multiple sclerosis are underexplored. We aimed to explore temperament and character traits, their association with clinical characteristics, and explore the factors that impact depression in patients with relapsing-remitting multiple sclerosis (RRMS).

Materials and Methods: This cross-sectional study enrolled 67 patients (male/female=12/55) (median age=30 (18-53)) and 50 age-and gender-matched healthy controls (HCs) (male/female=16/34) (median age= 26.5 (18-60)) using a convenience sampling method. Temperament and Character Inventory, Beck Depression and Beck Anxiety Inventories, and Structured Clinical Interview for DSM-Axis I Disorders-SCID-I were applied.

Results: In the patient group there were 45 MS patients with no psychiatric comorbidity (MSN) and 22 MS patients with psychiatric comorbidity (MSP). Higher self-forgetfulness was observed in the MSP group compared with MSN and HC groups. MSP and MSN demonstrated higher total harm avoidance than HCs. MSP group showed lower total self-directedness compared with HCs. While EDSS, duration of disease, or the number of relapses did not impact depression scores; higher anxiety (B=0.416) and lower purposefulness (B=-1.565) significantly impacted them (R2=.50, F=32.459).

Conclusion: Temperament and character differences were observed in patients with and without psychiatric

Öz

Amaç: Yaşam kalitesi üzerindeki etkilerine rağmen, multipl sklerozda mizaç ve karakter yeterince araştırılmamıştır. Mizaç ve karakter boyutlarını, i, bunların klinik özelliklerle ilişkisini ve depresyon şiddetini etkileyen faktörleri tekrarlayan ve düzelen multiple skleroz (TDMS) hastalarında incelemeyi amaçladık.

Gereç ve Yöntem: Bu kesitsel çalışmaya, elverişli örnekleme yöntemiyle 67 hasta (erkek/kadın=12/55) (medyan yaş=30 (18-53)) ve yaş ve cinsiyet açısından eşleştirilmiş 50 sağlıklı kontrol (SK) (erkek/kadın=16/34) (medyan yaş= 26.5 (18-60)) alındı. Mizaç ve Karakter Envanteri, Beck Depresyon ve Beck Anksiyete Envanterleri, DSM-Eksen I Bozuklukları için Yapılandırılmış Klinik Görüşme uygulandı.

Bulgular: Hasta grubu içinde, psikiyatrik komorbiditesi olan 45 (MSP), psikiyatrik komorbiditesi olmayan (MSO) 22 hasta bulunuyordu. MSP grubu, MSO grubuna ve SK'lere göre daha yüksek kendilik kaybı gösterdi. MSP grubu ve MSO grubu toplam zarardan kaçınma puanları SK'lere kıyasla yüksekti. Toplam kendini yönetme puanları MSP grubunda SK'lerden düşüktü. EDSS, hastalık süresi, toplam nüks sayısı depresyon şiddetini etkilemezken; yüksek anksiyete (B=0,416) ve düşük amaçlılık düzeyleri (B=-1,565) depresyon düzeyini anlamlı derecede etkilemekteydi (R2=0.50, F=32.459).

Sonuç: Komorbid psikiyatrik bozukluğu olan ve olmayan hastalar arasında mizaç ve karakter özellikleri açısından farklılıklar gözlendi. Artmış anksiyete düzeyleri; anlamlı

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comorbidity. Higher anxiety levels and the difficulty to establish and attain meaningful goals may relate to higher depression levels. Future studies with larger samples examining coping, health behaviors, and resilience as potential mediators or moderators between self-forgetfulness and psychiatric disorders may aid in defining interventions for psychiatric disorders. Adequate treatment of anxiety symptoms and addressing purposefulness are potential targets for planning behavioral interventions.
Keywords: Multiple sclerosis, temperament and character, depression, anxiety, personality

hedefler belirleme ve bunlara ulaşmada güçlük, artmış depresyon düzeyleriyle ilişkili olabilir. Gelecek çalışmalar, daha geniş örneklemlerde, baş etme, sağlık davranışları ve dayanıklılığın kendilik kaybı ve psikiyatrik bozukluklar arasındaki aracı ve düzenleyici rolünü inceleyerek, psikiyatrik bozukluklara yönelik müdahalelerin tanımlanmasına yardımcı olabilir. Anksiyete belirtilerinin etkin tedavisi ve yaşam amaçlarının ele alınması, davranışsal müdahalelerin planlanması için olası hedeflerdir.
Anahtar kelimeler: Multiple skleroz, mizaç ve karakter, depresyon, anksiyete, kişilik

INTRODUCTION

Multiple sclerosis (MS) leads to permanent neurological impairment in young and middle-aged adults[1]. Due to increased awareness of the disease and earlier diagnosis resulting from recent advances, the incidence of MS is increasing. The primary phenotypes of MS are relapsing-remitting multiple sclerosis (RRMS) and progressive disease. RRMS is identified by a clearly defined pattern of relapses with either full or incomplete recovery. This type represents roughly 85 to 90 percent of cases at the time of onset. Progressive disease is defined by increased neurologic disability independently quantified from relapses and is age-dependent but not an inevitable outcome of RRMS[2].

Psychiatric disorders are often diagnosed in the early stages of MS[3]. They may arise even before the onset of MS[4]. Depression is the most common comorbidity, has the greatest impact on quality of life[5] and has not been extensively studied in the global literature[6]. Anxiety is also a common symptom with a weighted prevalence of 22%[7].

Personality refers to an individual's pattern of adapting thoughts, emotions, and behaviors by learning from experiences. Certain personality characteristics can either make living with MS easier or more complicated[8] and affect the quality of life[9]. In MS patients, discrete temperament profiles may predict different health and disease-related features[10] and may affect self-management[11]. Studies that have previously examined temperament and character profiles in MS[12-14] have shown higher harm avoidance[12-14], lower self-directedness[12,13], and lower persistence[13,14]. However, these studies did not segregate progressive and relapsing-remitting types and included patients with a high level of disability and longer duration of illness. In the current study, we have addressed this gap by recruiting early-stage patients with the most common subtype of RRMS, who have mild or no disability and do not show substantial cognitive impairment. We aimed to explore temperament and character and the association between temperament and character and clinical characteristics and explore the predictors of depression.

MATERIALS AND METHODS

The study was approved by Istanbul University Cerrahpasa Medical Faculty Research Ethics Board with the decision dated 4.10.2011 and numbered 36371. It conforms to the principles of the declaration of Helsinki. Patient anonymity was preserved, and informed consent was obtained from each participant after the procedure(s) had been fully explained.

Setting and participants

This cross-sectional study recruited patients consecutively from the specialized MS outpatient clinic in the Department of Neurology of Istanbul University Cerrahpasa Medical Faculty. Inclusion criteria were ages between 18 and 60, being capable of reading and writing without assistance, and being diagnosed based on the 2010 revised McDonald criteria[15]. The exclusion criteria included a history of schizophrenia, bipolar disorder, substance use disorder, eating disorder, intellectual disability, history of seizures, stroke, head trauma, a recent exacerbation of MS, a standardized mini-mental test (SMMT) score of less than 23 and having been prescribed corticosteroids or benzodiazepines in the last month. The neurological examinations and EDSS scoring for each patient were carried out by expert neurologists (S.S., A.A., A.S., G.G.Ç.). SCID-I interviews were performed by (O.K).SMMTs were performed by upon suspicion of substantial cognitive

impairment by (O.K). To provide a more homogenous group of patients, only patients with RRMS type were included.

Ninety patients were identified. Seven of them refused to participate in the study, 1 of them had a mini-mental test score of 23, 8 of them could not adapt to completing TCI, 1 of them had a history of head trauma, 1 of them was suspected of acute MS attack, 1 of them received steroid treatment one week ago, 1 patient was diagnosed with bipolar disorder, 2 because of missing data in the scales, and 1 patient had the progressive type of MS. Totally, 23 patients were excluded and around ¾ of the approached were interviewed. Access to the participants' personal and biomedical data was provided only to the authors of this manuscript. The personal information was kept coded and electronic medical data were kept confidential with the use of a password.

Measures

Demographic form

A structured form was used to gather sociodemographic and clinical information.

Temperament and Character Inventory

Personality was assessed with the revised Temperament and Character Inventory (TCI), a 240-item, self-report, true/false questionnaire[16]. Among temperament traits, (1) novelty seeking (NS) represents behavioral activation in response to novelty and cues indicating reward or relief of punishment, (2) harm avoidance (HA) refers to behavioral inhibition in response to punishment or non-reward cues, (3) reward dependence (RD) describes the maintenance of socially rewarded behavior, and (4) persistence (P) indicates the preservation of behavior with only occasional reinforcement. In terms of the character dimensions, (1) self-directedness (SD) is the capacity to control and adjust behavior based on the needs of a situation to accomplish an individual's objectives, and (2) cooperativeness (C) represents the extent to which a person is usually supportive and agreeable with others in their relationships, and (3) self-transcendence (ST) refers to individual differences in selflessness or self-forgetfulness, patience, spirituality, and identification with something greater than the self that gives meaning to one's existence. NS has four subscales: Exploratory excitability (NS1) impulsiveness (NS2), extravagance (NS3) disorderliness (NS4). HA has four subscales: anticipatory worry (HA1), fear of uncertainty (HA2), shyness (HA3), and fatigability (HA4). SD has five subscales: responsibility (SD1) purposefulness (SD2) resourcefulness (SD3) self-acceptance (SD4) enlightened second nature (SD5). C has five subscales: social acceptance (C1), empathy (C2) helpfulness (C3) compassion (C4) pure-hearted conscience (C5). RD and ST have three subscales: sentimentality (RD1), attachment (RD3) dependence (RD4); self-forgetfulness (ST1) transpersonal identification (ST2) spiritual acceptance (ST3) respectively. P is measured by a single scale. The validity and reliability of Turkish version of TCI have been demonstrated by Kose and colleagues. Cronbach's alpha values of the TCI scales were found between .60 and .85 in the temperament dimension and between .82 and .83 in the character dimension. The lowest Cronbach alpha coefficients were found as reward dependence (.60) and persistence (.62) [17].

Beck Depression Inventory

The severity of emotional, cognitive, psychomotor, vegetative, and motivational symptoms of depression was measured using the 21-item self-report Beck Depression Inventory (BDI). Each item is scored from 0 (null) to 3 (severe), and their sum provides a total score of 0-63[18]. The psychometric properties of the instrument were investigated in the context of Turkish culture. It was found to be reliable with a split-half reliability of r=.80, and Cronbach's alpha of .74. On student and psychiatric samples, its concurrent validity with the Turkish adapted MMPI-depression ranged between .63 and .50, respectively. The cut-off score in the Turkish validity and reliability study is stated as 17[19].

Beck Anxiety Inventory

The self-report Beck Anxiety Inventory (BAI) consists of 21 items, rated according to how much has been bothered by the particular symptom over the past week. The 4-point Likert scale ranges from 0 (not at all) to 3 (severe-I could barely stand it) with a total score between 0-63. It is primarily concerned with the physiological aspects of anxiety. Four of the 21 items are phrases for anxious mood, three items are for specific fears, and the remaining 14 are symptoms of autonomic arousal, motor tension, panic, and generalized anxiety. The original study reported excellent internal consistency (Cronbach alpha= .92) and a 1-week retest reliability coefficient of r= .75[20]. The results of the Turkish validity and reliability study demonstrated a high internal

consistency (Cronbach alpha= .92) with item-total correlations ranging from .45 to .72. A total score of 0-14 is considered normal, 16-25 indicates mild-medium anxiety and 26-63 indicates severe anxiety[21].

The Standardized Mini-Mental Test

The standardized Mini-Mental Test (SMMT) is a clinician-administered test that screens for cognitive impairment. It assesses orientation, registration, attention and calculation, recall, and language. Items under language are naming, repetition, 3-stage command, reading, writing, and copying[22]. In the Turkish validity and reliability study, the interrater reliability resulted in r=0.99. The cut-off scores of 23/24 have .91 sensitivity, .91 specificity, .90 positive predictive, .95 negative predictive, and .86 kappa values[23]. SMMT in this study was used to screen cognitive impairment in cases when there was clinical suspicion of its presence[24]. Patients that scored 23 or less were excluded.

Structured Clinical Interview For DSM-Axis I Disorders

The structured clinical interview for DSM-axis I disorders (SCID-I) is used to investigate the existence of Axis I diagnoses according to the DSM-IV by taking into account "the characteristics of "the current situation" and "the lifetime" in healthy as well as the sick. The presence of diagnostic criteria is dependent on symptoms that exceed the severity threshold[25]. It was translated into Turkish and validated by Öztürkçügil and colleagues[26].

Kurtzke Expanded Disability Status Scale

The Kurtzke Expanded Disability Status Scale (EDSS) is a widely accepted clinical disability scale for monitoring patients with MS. It assigns a severity score that ranges from 0-10 in increments of 0.5. Zero indicates normal neurological examination and 10 indicates death. The scoring between 1.0-4.0 is based on these functional systems, while 4.0-8.0 indicates patient ambulation[27].

Statistical analysis

The statistical power analysis revealed that a minimum sample size of n=47 would reach 80% power (β=0.2) with a 5% significance level (a =0.05) in a two-tailed test under the assumption of linear multiple regression[28]. The data was analyzed using SPSS 26.0 for Windows. The distribution pattern of the variables was investigated using the Shapiro-Wilk test. Descriptive statistics were presented as numbers and proportions for categorical variables, and "median (min-max)." for non-normal distributed continuous variables. The Chi-Square test was used to compare categorical variables. Nonparametric statistical methods were used as the data were not normally distributed. Kruskal Wallis test was used to compare multiple non-parametric variables across three groups. When an overall significance level lower than 0.05 was obtained, pairwise post-hoc tests were performed using the Mann-Whitney U test. To explore the associations between non-normally distributed variables, correlation coefficients and significance levels were calculated using the two-tailed Spearman's rank correlation. Three separate linear regression analyses were conducted with the following independent variables: (1) disease characteristics, (2) temperament and character traits, and (3) anxiety. Multiple linear regression with a forward method was applied to analyze factors significantly affecting depression. To infer statistical significance, an alpha significance level of $p<0.05$ (two-tailed) was used.

RESULTS

Sixty-seven patients (12 male, 55 female) with 30 (18-53) ages and 50 (16 male, 34 female) healthy controls (HCs) with (26.5 (18-60) ages were recruited. The number of females was higher than the number of males in both groups as MS is more prevalent in women. The patients and the HCs did not differ with respect to age (p=0.96) and gender (p=0.08, X^2=3.122, df=1). Clinical characteristics are summarized in Table 1. For those patients that were on immunomodulatory treatment (n=46) duration was 24 (2-144) months. In the patient group, there were 45 patients with multiple sclerosis with no psychiatric comorbidity (MSN) and 22 patients with psychiatric comorbidity (MSP). Depression levels were higher in MSP than HCs (p<0.001) and higher in MSP than MSN (p<0.001). Anxiety levels were higher in MSP than HCs (p<0.001) and in MSN than HCs (p<0.001) (Table 2).

MS patients with a psychiatric disorder (MSP), MS patients without a psychiatric disorder (MSN), and HCs were compared, findings were summarized in Table 2. The three groups did not differ in gender. Years of education were higher in HCs (15 (5-19), than MSN (12 (5-17) and MSP (13 (5-18) (p<.0001). Pairwise comparisons with the Mann-Whitney U test revealed that anticipatory worry (HA1) in MSP, was higher than HCs (p<.0001). Fear of uncertainty

(HA2) was higher in MSP (p=0.018) and MSN groups (p=0.012) than HCs. Fatigability (HA4) (p<.0001) was higher in MSP (p<.0001) and MSN (p=0.007) than HCs. HA total score was higher in MSP (p<.0001) and MSN (p=0.014) than HCs. Self-forgetfulness was higher in MSP (p=0.030) and MSN (p=0.017) compared with HCs but it did not differ between MSN and HCs. MSP rated lower in responsibility (SD1) than MSN (p=0.033) and HCs (p<.0001). Purposefulness (SD2) was lower in MSP than HCs (p=0.002) but not in MSN (p=0.185). Resourcefulness (SD3) was lower in MSP (p=0.012) and MSN (p=0.011) than HCs. The total SD score was lower in MSP than HCs (p=0.003). The severity of depression and anxiety were not associated with disease duration (Table 3). Analyses revealed a negative correlation between disease duration and total HA (p= 0.036) and a positive correlation between disease duration and total SD (p =0.022) and total C (p=0.016). The total SD score was negatively correlated with depression (p<0.0001) and anxiety (p<0.0001). The total C score was negatively correlated with depression (p=0.026) and anxiety (p=0.005). Total ST score was positively correlated with depression (p=0.020) and anxiety (p=0.009). The self-forgetfulness score was positively correlated with anxiety (p=0.018) and depression (p=0.09). Total RD score and total NS score were neither associated with depression nor anxiety. HA score was positively associated with depression (p<0.0001) and anxiety (p=0.017).

Table 1. Clinical characteristics of patients (n=67)

	Median	**Minimum-maximum**
Disease duration (months)	36	2-180
Total number of relapses	2	1-8
EDSS score	1	0-3.5
	n	%
Immunomodulatory medications	21	31.3
IFN- β-1a	37	55.2
IFN-β-1b	7	10.5
Fingolimod	1	1.5
Glatiramer acetate	1	1.5
Psychiatric diagnoses		
No diagnosis	45	67.1
Depression	12	17.9
Adjustment disorder	4	6
Unspecified anxiety disorder	2	3
Generalized anxiety disorder	2	3
Depression + unspecified anxiety disorder	1	1.5
Obsessive-compulsive disorder	1	1.5
Psychiatric medications		
None	56	83.6
SSRI	9	13.4
SNRI	1	1.5
SSRI + serotonin-dopamine antagonists	1	1.5

EDSS: Expanded disability status scale; IFN- β-1a: Interferon beta-1a; IFN- β-1b: Interferon beta-1b; SSRI: selective serotonin reuptake inhibitor; SNRI: selective noradrenaline reuptake inhibitor

Table 2. Comparisons of temperament and character traits between patients with a psychiatric disorder, patients without a psychiatric disorder and healthy controls

	HCs (n=50)	**MSN (n=45)**	**MSP (n=22)**		
TCI scores	Med.(min.-max.)	Med.(min.-max.)	Med.(min.-max.)	*p*	Pairwise comparisons †
Exploratory excitability (NS1)	6 (1-10)	6 (3-10)	5.5 (2-10)	0.082	
Impulsiveness (NS2)	4 (0-7)	4 (0-10)	4.5 (1-8)	0.25	
Extravagance (NS3)	5 (1-9)	4 (0-9)	4.5 (2-9)	0.288	
Disorderliness (NS4)	4 (1-8)	4 (1-9)	4 (1-8)	0.719	
Novelty-seeking (NS) total	19 (13-31)	18 (7-29)	17 (10-33)	0.057	
Anticipatory worry (HA1)	4 (0-10)	5 (1-9)	7 (1-10)	<0.0001*	HC < MSN, MSP; MSN < MSP
Fear of uncertainty (HA2)	3.75 (0-7)	5 (0-7)	5 (1-7)	0.003*	HC < MSN, MSP
Shyness (HA3)	3 (0-8)	3 (0-8)	4 (0-7)	0.183	
Fatigability (HA4)	3 (0-8)	4 (1-9)	6 (2-9)	<0.0001*	HC < MSN, MSP
Harm avoidance (HA) total	14 (2-28)	17 (5-28)	20.5 (7-31)	<0.0001*	HC < MSN, MSP
Sentimentality (RD1)	7 (2-10)	7 (3-10)	8 (4-10)	0.37	
Attachment (RD3)	4 (2-8)	5 (1-7)	4 (1-8)	0.412	
Dependence (RD4)	3 (1-6)	3 (0-6)	2 (1-5)	0.699	
Reward dependence (RD) total	14 (6-21)	14 (8-21)	14 (8-19)	0.579	
Persistence (P)	6 (1-8)	4 (0-8)	5 (0-8)	0.077	
Responsibility (SD1)	7 (2-8)	6 (2-8)	3 (0-8)	<0.0001*	HC>MSN>MSP
Purposefulness (SD2)	7 (2-8)	6 (1-8)	5 (1-7)	0.003*	HC > MSP
Resourcefulness (SD3)	4 (0-5)	3 (0-5)	3 (0-5)	0.002*	HC > MSN, MSP
Self-acceptance (SD4)	6.5 (1-11)	6 (0-11)	6 (3-10)	0.535	
Enlightened second nature (SD5)	9.5 (6-12)	9 (1-12)	9 (6-12)	0.259	
Self-directedness (SD) total	33 (18-44)	31 (11-44)	25.5 (16-38)	0.003*	HC > MSP
Social acceptance (C1)	7 (2-8)	6 (1-8)	5 (3-8)	0.045*‡	
Empathy (C2)	5 (1-7)	5 (2-7)	4 (2-7)	0.061	
Helpfulness (C3)	5 (3-8)	5 (2-8)	5 (1-8)	0.416	
Compassion (C4)	8 (1-10)	8 (1-10)	7.5 (1-10)	0.815	
Pure-hearted conscience (C5)	7 (3-9)	8 (3-9)	7 (4-9)	0.932	
Self-forgetfulness (ST1)	5 (0-11)	5 (0-11)	7.5 (1-11)	0.014*	HC < MSP; MSN < MSP
Transpersonal identification (ST2)	5 (0-8)	5 (0-9)	5 (1-8)	0.634	
Spiritual acceptance (ST3)	7.5 (0-13)	6 (1-11)	7 (2-13)	0.504	
Self-transcendence (ST) total	18 (2-27)	17 (6-27)	20 (5-28)	0.298	
Beck depression	3 (0-17)	6 (0-23)	15.5 (5-35)	<0.0001*	HC < MSP; MSN < MSP
Beck anxiety	3 (0-21)	10 (0-33)	15.5 (4-43)	<0.0001*	HC < MSP, MSN

TCI: temperament and character; HCs: healthy controls; MSN: multiple sclerosis with no psychiatric disorder.
MSP: multiple sclerosis with a psychiatric disorder; Med.(min.-max.): Median (minimum-maximum)
"<"and ">" shows that there is statistical significance between groups ($p < 0.05$).
†Pairwise comparisons were carried out with the Mann-Whitney U test
‡Significant difference in Kruskal Wallis test between three groups, but no significant difference in any of the pairwise comparisons with Mann-Whitney U test.

Table 3. Correlations between patient characteristics and temperament and character traits

	Age	Ed (yr)	Dis. dur.	BDI	BAI	NS1	NS2	NS3	NS4	NS total	HA1	HA2	HA3	HA4	HA total	RD1	RD3	RD4	RD total	P	SD1	SD2	SD3	SD4	SD5	SD total	C1	C2	C3	C4	C5	C total	ST1	ST2	ST3	ST total
Age	1																																		
Ed. (yr)	-.24**	1																																	
Dis. dur.	.46**	.16	1																																
BDI	-.14	-.14	-.18	1																															
BAI	-.14	-.14	-.13	.63**	1																														
NS1	.13	.11	.02	-.11	.02	1																													
NS2	-.13	.04	.08	.22	.08	-.05	1																												
NS3	-.21	-.02	-.06	.14	.09	.06	.31*	1																											
NS4	-.14	.03	-.10	-.04	.14	.06	.42**	.14	1																										
NS total	-.21	.12	-.05	.09	.11	.42**	.66**	.68**	.59**	1																									
HA1	-.12	-.13	-.34**	.41**	.18	-.14	-.07	-.07	-.05	-.10	1																								
HA2	.08	-.06	-.06	.12	.07	-.31*	-.08	-.01	-.25*	-.21	.34**	1																							
HA3	-.07	-.27*	-.22	.42**	.29*	-.32**	-.13	.05	-.24	-.19	.45**	.44**	1																						
HA4	-.22	.13	-.10	.40**	.36**	-.42**	-.04	-.08	.01	-.22	.47**	.37**	.39**	1																					
HA total	-.12	-.11	-.26*	.46**	.29*	-.38**	-.13	-.02	-.17	-.24	.77**	.68**	.77**	.73**	1																				
RD1	-.01	.14	.09	-.02	-.06	.05	.03	-.14	.20	.02	.26*	.11	-.04	.18	.19	1																			
RD3	-.16	.00	-.16	-.03	.02	.24	.02	.05	.10	.12	.14	.09	.04	.00	.11	-.03	1																		
RD4	-.16	.14	-.10	.09	.09	-.03	.08	.03	.06	.03	.34**	.29*	.35**	.16	.39**	.23	.35**	1																	
RD total	-.17	.14	-.08	.03	-.03	.11	-.01	-.04	.20	.07	.37**	.24*	.14	.18	.33**	.60**	.65**	.72**	1																
P	.03	.20	.13	-.12	.03	.33**	-.07	-.21	.14	.02	-.06	-.16	-.19	-.02	-.14	.30*	.04	-.18	.10	1															
SD1	.16	.22	.13	-.48**	-.37**	-.02	-.27*	-.05	-.13	-.15	-.26*	-.04	-.17	-.13	-.19	-.30*	.08	.10	-.13	.16	1														
SD2	.26*	.30*	.25*	-.60**	-.44**	.17	-.18	-.14	-.19	-.11	-.34**	.09	-.29*	-.26*	-.27*	.01	-.05	-.12	-.05	.12	.49**	1													
SD3	.26*	.24*	.25*	-.45**	-.25*	.41**	-.01	.10	.00	.20	-.49**	-.22	-.49**	-.38**	-.53**	-.12	-.03	-.33**	-.21	.16	.46**	.48**	1												
SD4	.35**	.05	.18	-.25*	-.16	.16	-.17	-.21	-.18	-.20	-.22	.04	-.12	-.22	-.17	-.14	.06	-.22	-.11	.04	.39**	.50**	.40**	1										
SD5	.24	.27*	.26*	-.30*	-.34**	.01	.03	-.07	-.22	-.11	-.25*	.12	-.24*	-.05	-.14	.03	-.05	-.09	-.06	.01	.36**	.58**	.30*	.40**	1									
SD total	.35**	.27*	.28*	-.55**	-.41**	.13	-.16	-.11	-.23	-.14	-.39**	.06	-.30*	-.24	-.29*	-.15	.00	-.26*	-.17	.03	.72**	.82**	.65**	.74**	.73**	1								
C1	.12	0.10	.31*	-.24	-.24	.16	.05	.05	.01	.10	-.14	.06	-.08	-.19	-.10	.12	.11	.08	.17	.03	.20	.23	.27*	.29*	.20	.31**	1							
C2	.00	.44**	.01	-.24	-.24	.18	.12	.11	.29*	.29*	-.08	-.02	-.27*	-.11	-.16	.17	.01	.25*	.20	.07	.16	.18	.21	-.02	.20	.16	.30*	1						
C3	.10	.27*	.18	-.18	-.23	.12	.17	-.10	.22	.11	-.08	.01	-.26*	.08	-.08	.11	.07	.08	.15	.02	.13	.24*	.21	.09	.16	.21	.23	.44**	1					
C4	.18	0.07	.16	-.07	-.21	.15	.07	.16	.04	.03	-.01	.00	.17	-.03	-.03	.33**	-.02	.04	.17	.24*	.08	.21	.07	.12	.21	.17	.46**	.13	.12	1				
C5	.06	.25*	.29*	-.13	-.11	.20	.08	-.18	-.13	.01	-.01	.11	-.06	.01	.02	.18	.08	.05	.15	.17	.07	.44**	.11	.49**	.50**	.43**	.32**	.15	.17	.35**	1			
C total	.17	.31*	.29*	-.27*	-.34**	.25*	.10	-.09	.11	.13	-.11	.04	-.23	-.07	-.09	.29*	.10	.14	.23*	.21	.15	.38**	.26*	.30*	.40**	.40**	.71**	.56**	.52**	.70**	.62**	1		
ST1	.11	.13	.02	.32**	.29*	.17	.03	.05	-.03	.08	.09	.14	.04	-.03	-.01	.41**	-.20	-.17	.03	-.05	-.45**	-.13	-.22	.10	.11	.21*	-.15	-.15	.10	.02	-.01	.13	1	
ST2	.16	-.01	.22	.14	.16	.08	-.02	-.12	.12	.02	-.13	-.26*	-.13	-.11	.18	.32**	.17	.17	.00	.22	-.29*	.04	-.13	-.09	.03	-.11	.02	.01	-.06	.42**	.17	.19	.51**	1	
ST3	.00	.05	.16	.20	.28*	.23	.13	.30*	-.10	.28*	-.26*	-.04	.00	-.09	-.14	.05	.17	.17	.15	.07	-.27*	.03	.00	-.07	.06	-.06	.13	.08	-.06	.03	.12	.08	.50**	.38**	1
ST total	.10	-.05	.16	.28*	.32**	.22	.10	.14	-.01	.20	-.13	-.17	-.08	-.10	-.14	.31**	-.24	-.22	-.05	.03	-.43**	-.03	-.13	-.12	-.03	-.19	.00	-.03	-.08	.18	.11	.04	.83**	.75**	.81**	1

Ed (yr): Education in years; Dis (dur): Disease duration; BDI: Beck depression inventory; BAI: Beck anxiety inventory; NS1: Exploratory excitability; NS2: Impulsiveness NS3: Extravagance; NS4: Disorderliness; NS: Novelty-seeking; HA1: Anticipatory worry; HA2: Fear of uncertainty; HA3: Shyness; HA4: Fatigability; HA: Harm avoidance; RD1: Sentimentality; RD3: Attachment; RD4: Dependence; RD: Reward dependence; P: Persistence; SD1: Responsibility; SD2: Purposefulness; SD3: Resourcefulness; SD4: Self-acceptance; SD5: Enlightened second nature, SD: Self-directedness; C1: Social acceptance; C2: Empathy; C3: Helpfulness; C4: Compassion; C5: Pure-hearted conscience; C: cooperativeness total; ST1: Self-forgetfulness; ST2: Transpersonal identification; ST3: Spiritual acceptance; ST: Self-transcendence

Table 4. Correlation matrix of scores of depression and temperament and character subscales

	rho†	***p***
Anxiety	.647**	<0.0001
Anticipatory worry (HA1)	.405**	0.001
Fear of uncertainty (HA2)	.402**	0.001
Shyness (HA3)	.418**	<0.0001
Harm avoidance (HA) total	.455**	<0.0001
Responsibility (SD1)	-.478**	<0.0001
Purposefulness (SD2)	-.603**	<0.0001
Resourcefulness (SD3)	-.449**	<0.0001
Self-acceptance (SD4)	-.254*	0.038
Enlightened second nature (SD5)	-.302*	0.013
Self-directedness (SD) total	-.546**	<0.0001
Cooperativeness (C) total	-.272*	0.026
Self-forgetfulness (ST1)	.316**	0.009
Self-transcendence (ST) total	.284*	0.020

*=p< 0.05 level; **p< 0.01 level; †=Spearman correlation

Three linear regression analyses were performed to evaluate the most salient factors affecting depression in patients. None of the disease characteristics, including EDSS, duration of disease, or the number of relapses, affected depression scores. Anxiety was confirmed as a significant factor affecting depression. From TCI, anticipatory worry (HA1), fear of uncertainty (HA2), shyness (HA3), harm avoidance total (HA), responsibility (SD1) purposefulness (SD2), resourcefulness (SD3) self-acceptance (SD4), enlightened second nature (SD5) total SD, total C, total ST, and self-forgetfulness retained in the model (*p* to enter .05) (Table 4). These variables were assessed for collinearity and were found to have a variance inflation factor (VIF) of 1.00-1.48 which means variables did not have a significant correlation. Higher anxiety (*B* = 0.416) and lower purposefulness (SD2) affected higher depression scores (*B* =-1.565) (R^2= 0.50, *F* =32.459, p<0.001). The most salient factors affecting depression were anxiety and purposefulness (SD2), accounting for 50 % of the variation in depression scores (Table 5).

Table 5. Forward (Wald) stepwise linear regression of depression

					95% *CI*	
	B	***SE***	***p***	***t***	**Lower**	**Upper**
Step 1						
Anxiety	0.538	0.085	*p*<0.001	6.328	0.368	0.708
Step 2						
Anxiety	0.416	0.083	*p*<0.001	5.033	0.251	0.581
Purposefulness	-1.565	0.394	*p*<0.001	-3.972	-2.352	-0.778

R^2 = 0.50, Model *F* = 32.459, *p*<0.001; *CI*=Confidence interval; *SE*: standard error; *B:* unstandardized beta

DISCUSSION

We observed higher self-forgetfulness in MSP compared with HCs and in MSP compared with MSN. The other main differences were that MSP showed higher total HA and lower total SD than HCs. While EDSS, duration of disease, or the number of relapses did not impact depression scores, higher anxiety levels, and lower purposefulness positively affected depression scores in patients.

Few previous studies in MS reported findings on self-forgetfulness. It is a facet of self-transcendence characterized by a tendency to experience altered states of consciousness. High scorers in self-forgetfulness tend to forget where they are for a while and lose awareness of the passing of time. They may appear to be distracted or 'in another world'[29] and become so engrossed in experiences, that they may lack somatic awareness[30]. It could be hypothesized that self-forgetfulness may be associated with a propensity to psychiatric disorders, especially when individuals have low scores in self-directedness (SD) and cooperativeness (C) and high scores in HA. This path from high self-forgetfulness to psychiatric disorders could be through inadequate self-monitoring, and self-recognition -not related to healthy coping- and through lower reaction to disease and psychiatric symptoms. As such, a study that recruited patients who have comorbid psychiatric disorders and low SD scores suggested that self-forgetfulness may represent an unhealthy defense mechanism[31].

Two studies demonstrated no significant difference between MS and HCs in terms of self-forgetfulness. Our study differs from these two[12,13] because of recruiting a homogeneous group of patients with a lower duration of disease and establishing psychiatric diagnoses through structured clinical interviews. Generally, in patients with mood disorders high HA and low SD were found to be trait markers for mood in general, high ST may be specific to bipolar disorder[32] According to the most recent studies, bipolar disorder, depressive and anxiety disorders are more prevalent in MS population compared to healthy matched controls[33]. Another possible explanation is that some temperament and character traits in MS may imply subclinical manifestations of mood problems

Our findings regarding abnormal TC traits in MS are consistent with previous research that reported lower self-directedness (SD) [12,14,34]and higher harm avoidance (HA) [12,14] compared with HCs. The negative correlation between disease duration and total HA in our study was demonstrated as positive in Gazioglu's study[12]. This difference may be explained by their recruiting different types of MS

with a higher median duration of disease (8.6 years) than ours (3 years). Higher HA scores in early phases decreasing in the middle phases, then becoming profound again in the advanced phases may be one hypothesis for this. The positive correlation between disease duration and self-directedness (SD) and cooperativeness (C) suggests that in the early phases of MS where there is little cognitive impairment, patients may be adjusting to the disease by improving their self-directedness (SD) and cooperativeness (C). The observed variability in temperament and character findings in MS in the literature is likely to be explained by recruiting patients from different phases of the disease[35].

We did not find a relationship between disease duration and TC traits. As such, Fazekas and colleagues demonstrated no temperament trait significantly contributing to differences in clinical variability in early-stage patients[36]. Since the patients in this study had low EDSS scores, these findings should be confirmed by examining patient samples with higher disability levels[13].

We found elevated scores of depression and anxiety in MS patients consistent with the previous research[4,7] also in line with a study in early phase MS. Symptoms of anxiety are comparable or even marginally higher in early stages relative to later stages of MS[37]. Our findings suggest that, in the early phase of cognitively preserved MS patients, higher anxiety and lower purposefulness (SD2) significantly impacted depression symptoms.

An uncertain future is one of the major themes expressed by patients with MS[38]. However, the suggested underlying cause of MS-related depression as a psychological reaction to having an unpredictable and progressively disabling disease[39] does not explain the whole picture. Large-scale community survey data suggest that the 12-month prevalence of depression in MS exceeds the rate of depression in other long-term medical conditions[4]. Siblings of MS patients did not have an elevated incidence of depression and bipolar disorder[40]. There is support for the presence of pathology in the HPA axis in MS. A study demonstrated that increased levels of cortisol in depressed MS subjects were not reduced when the exogenous steroid dexamethasone was administered. On a different note, this study has indicated that drug-based disease-modifying treatments (DMT) do not induce depression[41].

Interestingly, MS patients with depression were 13% more likely than those without depression to start DMT at the index date whereas anxiety comorbidity correlated with a decrease in the probability of future initiation of DMT[42]. Despite significantly predicting quality of life in MS, anxiety disorders and their subtypes are both overlooked and under-treated[43]. Further understanding of the anxiety disorders in MS is warranted.

The limitations of this study include the small sample size with a cross-sectional design, which reduces the ability to draw causal relationships between personality, depression, and disease characteristics. Secondly, recruiting patients from a specialty outpatient clinic reduces the generalizability of the findings. Thirdly, another control group of patients with solely a psychiatric disorder would give a better idea of the association of self-forgetfulness with MS and psychiatric disorders. A more robust tool for cognitive evaluation would have provided further information. However, the strengths of this study included using structured clinical interviews for the diagnostic evaluation and robust comprehensive tools to assess temperament and character, studying a well-described homogeneous sample, and providing data on psychiatric disorder diagnoses, psychiatric, and neurological treatments.

In conclusion, our findings suggest MSP exhibited greater self-forgetfulness compared with MSN and HCs. Patients demonstrated increased harm avoidance, and lower self-directedness compared with HCs. Depression has significant consequences including exacerbation of MS, decreased health-related quality of life, and increased suicide risk. Recognizing a depressive disorder in MS and the factors that impact depression is of vital importance. Our paper contributes to scientific knowledge by showing specific contributors to depression in MS which are anxiety and purposefulness. Exploring the effect of early intervention, adequate treatment of anxiety symptoms, and addressing purposefulness may reduce the risk of depression, prevent its adverse outcomes, and would expand knowledge in this area. Future longitudinal studies with larger samples utilizing neuroimaging and cognitive evaluations should investigate the effects of interventions on anxiety and purposefulness to prevent depression in MS.

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