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Alexithymia and temperament and character model of personality in patients with major depressive disorder

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Abstract

Alexithymia is thought to be a stable personality trait and a predisposing risk factor for depression. In this study, we aimed to identify the prevalence of alexithymia in a depressed and nondepressed sample and examined the relationship between Cloninger's psychobiological model of personality with alexithymia. The Turkish version of the 20-item Toronto Alexithymia Scale (TAS-20), the Turkish version of the Temperament and Character Inventory, and the 21-item Beck Depression Inventory (BDI) were administered to 81 depressed patients and 51 controls. The mean age of the groups was 30.5 ± 7.7 and 32.75 ± 8.73, respectively. Depression severity was evaluated with the BDI. In the depressed group, 33.3% were alexithymic, and alexithymic subjects had significantly higher BDI scores. Depressed individuals were significantly more alexithymic than the controls on the total and all the 3 subscales of TAS-20. The TAS-20 total score was negatively correlated with the temperament dimension of Reward Dependence (RD) and the character dimension of Self-Directedness (SD). In the TAS-20 subscale, difficulties in identifying feelings was positively correlated with Self-Transcendence and negatively correlated with SD. The difficulties in expressing feelings subscale was negatively correlated with RD and SD. In the depressed patient group, the temperament dimension of RD was significantly lower in the alexithymic group. The rate of alexithymia is found high among this sample of Turkish depressed patients, and the results suggested a strong connection between alexithymia and depression. Alexithymia is explained by specific dimensions and subscale within Cloninger's psychobiological model of personality in this sample of depressed Turkish patients.

1. Introduction

The alexithymia construct refers to a cognitive-affective disturbance manifesting itself with markedly reduced symbolic thinking, impoverished fantasy life, and limited ability to identify and verbally express emotions. Alexithymic individuals are characterized by reduced ability to recognize and describe feelings and elaborate fantasies and a concrete cognitive style [1,2]. Alexithymia researchers have debated for many years whether alexithymia is a stable personality trait or a state-dependent phenomenon. This applies to personality traits, as well. They are both thought to play a role in the onset of psychiatric disorders. Although some longitudinal studies have shown no significant change in alexithymia scores even when levels of emotional distress change [2], others have found significant reductions in alexithymia scores especially when levels of depression decrease [3]. During the past decade, several studies have shown that alexithymia is associated strongly with depression in both general and clinical populations [4,5].

Salient features of alexithymia are the inability to distinguish one's feelings from the accompanying bodily sensations, the inability to communicate feelings to others, and an externally orientated cognitive style reflecting an absence of inner thoughts and fantasies. These 3 concepts reflect separate, yet empirically related, facets of the alexithymia construct [6].

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Several studies have explored the relationship between alexithymia and personality traits. Bagby et al [7] found a positive correlation between alexithymia and neuroticism and a negative correlation with extraversion and openness and found no relationship to the conceptually unrelated traits of agreeableness and conscientiousness. Luminet et al [8] concluded that alexithymia represents a unique cluster of traits across the dimensions and facets of the 5-factor model of personality. Grabe et al [9], in their study of 254 psychiatric inpatients and outpatients, the temperament and character inventory (TCI) dimensions harm avoidance, low self-directedness, and low reward dependence were found to be independent predictors for alexithymia. These personality traits may contribute to the characterization of high alexithymic patients as experiencing predominantly poorly differentiated emotional distress because they lack the necessary psychological capacities for modulating emotions [10]. Picardi et al [11] studied a healthy student sample and found that TAS-20 was correlated with both temperament and character dimensions of personality indicating that both genetics and environmental factors might contribute to alexithymia development. In the biosocial model of temperament and character by Cloninger et al [12,13], relationships between the biogenetic structure of personality and psychiatric disorders are described. This model postulates that personality is comprehensively developed with respect to genetic traits, learning, and insight into the self-concept. The personality model consists of 4 temperament and 3 character dimensions, all of which are viewed as being the results of continuous interactions during the life span [14].

Cloninger's concepts of personality elaborates 4 dimensions of temperament—Novelty Seeking (NS), Harm Avoidance (HA), Rewards Dependence (RD), and Persistence (P). They are thought to be genetically independent traits and are moderately inheritable and stable throughout life. *Novelty Seeking* is thought to be derived by the behavioral activation system. It reflects the tendency of an individual toward exhiliration in response to novel stimuli and cues. *Harm Avoidance* is related to the behavioral inhibition system. It reflects the tendency of an individual to inhibit or interrupt behaviors. *Reward Dependence* involves maintaining or continuing behaviors that have been previously associated with reinforcement and is manifested as sensitivity, sentimentality, and dependency on others' approval. *Persistence* reflects perseverance in behavior despite frustration, fatigue, and lack of reward [12-14]. Character reflects individual differences in self-concepts about goals and values in relation to experience which is predominantly determined by socialization. Cloninger's model includes 3 dimensions of character which are Self-directedness (SD), Cooperativeness (C), and Self-transcendence (ST). The 3 dimensions of Character mature over time, through learning about self-concepts, and they influence personal and social effectiveness into adulthood. They are believed to be more culturally inherited than the temperament traits. *Self-directedness* expresses individual's competence toward autonomy, reliability, and maturity, *Cooperativeness* is related to social skills, such as support, collaboration, and partnership, and *Self-transcendence* denotes aptitude toward spirituality and idealism [12-14].

Frequent comorbidity of alexithymia and depression has been consistently reported [5,15,16]; such comorbidity suggests that depression and alexithymia share a common construct. Studies have indicated relatively high prevalence rates of alexithymia in depression, ranging from 11% to 48% in several studies [5,17]. The prevalence of alexithymia was not different in Turkish depressive patient groups [18,19]. In the present study, we aimed to identify the prevalence of alexithymia in a depressed and nondepressed sample and examined the relationship of Cloninger's psychobiological model of personality with alexithymia in a sample of depressed outpatients. Among the TCI dimensions, we expected to find that SD and reward dependence would negatively and HA positively be correlated with alexithymia; NS, P, C, and ST would be unrelated to alexithymia.

2. Methods

2.1. Participants and procedures

The study was conducted in depressive outpatients admitted to the Psychiatric Unit of the Gaziosmanpasa University School of Medicine, Tokat, Turkey. The sample was composed of 81 outpatients—67 women and 14 men—with a mean age of 30.54 ± 7.72, who met *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (*DSM-IV*) [20] criteria for major depressive disorder. The control group was composed of 51 healthy subjects, 35 women, 16 men, with a mean age of 32.75 ± 8.73. All the subjects gave written informed consent before participation.

2.2. Measures

For psychiatric assessment, Structured Clinical Interview for *DSM-IV*-Clinical Version [21], Turkish version Axis I Disorders [22] was used. Depression severity was evaluated with the 21-item Beck Depression Inventory [23,24]. Alexithymia was assessed by using the Turkish version of the 20-item Toronto Alexithymia Scale (TAS-20) [7,25]. The TAS-20 is a self-report scale composed of 20 items. Each item was rated on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree), with total scores of 20 to 100. Items 4, 5, 10, 18, and 19 are negatively keyed. The first factor (F1) in the 3-factor model for the TAS-20 consists of 7 items (items 1, 3, 6, 7, 9, 13, and 14) assessing the ability to identify feelings and to distinguish them from the somatic sensations that accompany emotional arousal. Factor 2 (F2) consists of 5 items (items 2, 4, 11, 12, and 17) assessing the ability to describe feelings to other people. Factor 3 (F3) consists of 8 items (items 5, 8, 10, 15, 16, 18, 19, and 20) assessing externally oriented thinking. The total scores of the TAS-20 were dichotomized as follows: a score

of 61 or greater indicated alexithymia and a score below 61 indicated no alexithymia. The Turkish version of TAS-20 has been developed by Sayar et al [26] and Kose et al [27] and approved by Bagby et al [7]. The approved form has been validated in a Turkish population study.

The depressed patients completed the Turkish version of the TCI at the end of the psychiatric interview and the control group had received the instruction to complete the questionnaire at home. The TCI [13] is a 240-item self-administered questionnaire that measures the 7 personality, 4 temperament (NS, HA, Reward Dependence, and P), and 3 character dimensions (SD, C, and ST). The Turkish version of the TCI has been developed by Kose et al [28] and approved by Cloninger and validated in a Turkish population study.

2.3. Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 13.0) statistical program. The variables in the present study were examined by the Kolmogorov-Smirnov test of normality. All variables were normally distributed. Two independent sample t tests were used for comparison between the patient and the control groups. χ^2 Tests were used for categorical data. Unpaired Student t test was used for group comparisons of continuous variables. Within-group correlations between TCI scores were performed using the Pearson's correlation coefficient. Multivariate analysis was used for the comparisons as age-adjusted between the control and the depression groups. $P < .05$ was considered significant.

3. Results

The mean values for the TAS-20 total and the 3 subscale scores are presented in Table 1. Depressed individuals were significantly more alexithymic than the controls on the total and all the 3 subscales (Table 1).

In the patient sample (n = 81), 33.3% (n = 27) of patients had a score greater than 60 on the TAS-20 and were therefore considered as alexithymic. There were no statistical differences between the alexithymic and the nonalexithymic groups in terms of age ($t = -0.192$, $P = .848$), sex ($\chi^2 = -$, $P = .212$), marital status ($\chi^2 = 0.113$, $P = .805$), education level ($t = 1.471$, $P = .145$), profession ($\chi^2 = 4.253$, $P = .119$), and residence ($\chi^2 = -$, $P = .522$). The family types differed significantly between the alexithymic and the nonalexithymic subjects in the depressed patient group. There was significantly higher alexithymia among depressive individuals in nuclear families ($\chi^2 = 8.134$, $P = .017$). Alexithymic subjects had significantly higher Beck Depression Inventory scores ($t = -2.664$, $P = .009$). Patients with recurrent depressions were not significantly more alexithymic than those having the first depressive episode ($\chi^2 = 2.613$, $P = .106$). In the depressive group, the alexithymic and the nonalexithymic patients did not differ significantly in the duration of the current depressive episode ($t = -0.528$, $P = .599$) and the depression onset age ($t = -0.019$, $P = .985$). Table 2 shows the correlations between TAS-20 and TCI scores in the depressed group. Total score for TAS-20 was negatively correlated with the temperament dimension of RD and character dimension of SD. As for the subscales, a positive correlation was found between TAS-20 total score and NS4 and a negative correlation between RD3, SD1, SD2, SD5, and C5. The alexithymia subscale, difficulties in identifying feelings (F1), was positively correlated with NS4 and ST and negatively correlated with RD3, SD, SD1, SD2, SD4, and SD5. The subscales, difficulties in expressing feelings (F2) was negatively correlated with RD, RD3, SD, SD1, SD5, and C5, whereas externally oriented thinking (F3) was negatively correlated with HA1 and ST2, and positively correlated with SD3 and C1 (Table 2). In the depressed patient group, the temperament dimension RD was significantly lower in the alexithymic group than the nonalexithymic group. None of the character dimensions showed significant differences between alexithymic and nonalexithymic patients (Table 3). Taking TAS-20 total score as a dependent variable in multiple linear regression analysis and including 7 TCI dimensions into the model as independent variables did not reveal a significant predictive power of any of the dimensions for the total alexithymia scores in both groups (Table 4).

In the depressed patient group, taking TAS F1 (difficulties in identifying feelings) score as a dependent variable in multiple linear regression analysis and including 7 TCI dimensions into the model as independent variables revealed a significant predictive power of SD for the TAS F1 scores. In the control group, taking TAS F2 (difficulties in expressing feelings) score as a dependent variable in multiple linear regression analysis and including 7 TCI dimensions into the model as independent variables revealed a significant predictive power of NS and SD for the TAS F2 (Table 4).

Table 1
Scores for TAS-20 for the depressed patients and the controls

	Depressed group (n = 81)	Control group (n = 51)	t	P	P^a
	Mean ± SD	Mean ± SD			
TAS-20 Total	55.67 ± 9.44	42.26 ± 6.38	9.319	<.001	<.001
TAS-20 F1	20.44 ± 5.35	11.36 ± 3.96	10.659	<.001	<.001
TAS-20 F2	14.37 ± 3.85	11.55 ± 2.31	5.070	<.001	<.001
TAS-20 F3	21.41 ± 4.67	19.36 ± 2.90	2.989	.003	.008

[a] Age-adjusted P value.

4. Discussion

More than 33% of the patients with a *DSM-IV* depressive disorder were found to be alexithymic in this study. This is consistent with the prevalences reported in the Western

Table 2
Correlation coefficients (r) between TAS and TCI scores in the depressed group

	Difficulties in identifying feelings (TAS-20 F1)	Difficulties in expressing feelings (TAS-20 F2)	Externally oriented thinking (TAS-20 F3)	TAS-20 total score
Temperament				
NS	0.102	0.063	−0.028	0.019
Exploratory excitability (NS1)	−0.110	−0.049	−0.001	−0.131
Impulsiveness (NS2)	0.133	−0.013	−0.063	0.036
Extravagance (NS3)	0.038	0.050	−0.029	−0.050
Disorderliness (NS4)	0.219*	0.203	0.042	0.253*
HA	0.181	0.152	−0.062	0.165
Worry/pessimism (HA1)	0.184	0.054	−0.233*	0.076
Fear of uncertainty	−0.005	0.058	0.108	0.060
Shyness with strangers	0.070	0.186	−0.008	0.102
Fatigability and asthenia (HA4)	0.199	0.101	0.002	0.189
RD	−0.085	−0.229*	−0.097	−0.222*
Sentimentality vs insensitivity (RD1)	0.115	−0.130	−0.177	−0.001
Attachment vs detachment (RD3)	−0.320*	−0.307*	0.034	−0.356*
Dependence vs independence (RD4)	0.085	0.061	−0.033	−0.018
P	−0.098	−0.212	−0.200	−0.211
Character				
SD	−0.422*	−0.228*	0.106	−0.327*
Responsibility vs Blaming (SD1)	−0.393*	−0.213*	0.065	−0.321*
Purposefulness (SD2)	−0.352*	−0.138	0.070	−0.241*
Resourcefulness (SD3)	−0.145	−0.049	0.238*	−0.031
Self-acceptancevs Self-striving (SD4)	−0.224*	−0.114	0.055	−0.187
Congruent second nature (SD5)	−0.361*	−0.276*	−0.001	−0.337*
C	−0.184	−0.185	0.032	−0.214
Social acceptance vs social intolerance (C1)	−0.128	−0.111	0.243*	−0.045
Empathy (C2)	−0.168	−0.162	−0.055	−0.205
Helpfulness (C3)	−0.142	−0.047	0.024	−0.177
Compassion vs revengefulness (C4)	−0.047	−0.108	−0.002	−0.077
Pure-hearted principles (C5)	−0.210	−0.219*	−0.188	−0.325*
ST	0.231*	−0.026	−0.150	0.162
Self-forgetfulness vs self-conscious (ST1)	0.213	0.024	0.054	0.210
Transpersonal identification vs self-differentiation (ST2)	0.121	−0.014	−0.257*	0.008
Spiritual acceptance vs rational materialism (ST3)	0.161	−0.067	−0.141	0.120
Age	−0.037	−0.062	0.021	−0.032

* $P < .05$.

populations [5,17,29,30] and in samples of Turkish depressive outpatients [18,19]. Significantly high alexithymia rate supports previous studies suggesting a strong connection between alexithymia and depression [3-6].

The alexithymic depressed patients in our study differed from the nonalexithymic patients, in their depression severities, as measured by the BDI. Alexithymic patients more often showed severe depression than did their

Table 3
TCI scores in alexithymic and nonalexithymic groups

	Depressed group (n = 81)				Control group (n = 51)			
	Nonalexithymic (n = 54)	Alexithymic (n = 27)	*t*	*P*	Nonalexitymic (n = 42)	Alexitymic (n = 9)	*t*	*P*
	Mean ± SD	Mean ± SD			Mean ± SD	Mean ± SD		
NS	17.17 ± 5.10	16.89 ± 3.65	.252	.801	17.50 ± 5.40	19.22 ± 4.47	−0.891	.377
HA	24.17 ± 4.99	25.33 ± 6.44	−.899	.371	17.98 ± 7.66	14.56 ± 7.58	1.218	.229
RD	16.26 ± 2.64	14.44 ± 3.20	2.545	.015	14.64 ± 2.44	14.89 ± 3.30	−.258	.798
P	5.54 ± 2.16	5.19 ± 1.64	.745	.459	5.24 ± 1.85	6.00 ± 1.58	−1.149	.256
SD	24.33 ± 7.60	21.96 ± 6.81	1.368	.175	28.74 ± 7.22	29.00 ± 8.05	−.097	.923
C	29.80 ± 5.66	27.85 ± 4.37	1.567	.121	28.98 ± 5.55	28.67 ± 5.52	.152	.880
ST	18.24 ± 4.69	19.44 ± 5.69	−1.013	.314	17.93 ± 5.73	16.56 ± 5.29	.661	.512

Table 4
Multiple regression analyses between TAS-20 and TCI dimensions in both groups

	Depressed group				Control group			
	TAS-20 F1	TAS-20 F2	TAS-20 F3	TAS-20 total score	TAS-20 F1	TAS-20 F2	TAS-20 F3	TAS-20 total score
Analysis of variance	F = 2.524, P = .022	F = 1.599, P = .149	F = 0.948, P = .476	F = 2.142, P = .050	F = 0.974, P = .466	F = 0.115, P = .377	F = 0.882, P = .531	F = 0.818, P = .579
Adjusted R^2	0.118	0.050	−0.005	0.091	−0.004	0.019	−0.020	−0.032
NS	0.004	0.015	−0.042	−0.064	0.159	0.542*	0.097	0.339
HA	−0.121	0.091	0.012	−0.037	0.071	0.292	0.207	0.244
RD	−0.064	−0.221	−0.099	−0.199	−0.075	−0.008	0.237	0.059
P	−0.006	−0.094	−0.257	−0.142	0.350	0.454	0.069	0.413
SD	−0.470*	−0.213	0.089	−0.312	0.010	0.465*	0.255	0.291
C	0.012	0.023	0.134	0.042	0.274	−0.087	−0.111	0.088
ST	0.060	−0.132	−0.054	0.065	−0.074	0.154	0.283	0.139

* P< .05.

nonalexithymic counterparts, thus confirming previous findings [31,32]. However, alexithymia was not affected by the duration of the current depressive episode or whether it is the first or a recurrent episode. These findings, overall, might support the argument that alexithymia is a trait rather than state-dependent feature. Longitudinal studies were needed to further support this argument. Studies have shown that alexithymia predicted poor outcome in depressive outpatients. In our sample, the alexithymic traits of individuals might have lead to a lack of verbal and emotional contacts and eventually lead to the development of more severe depression.

There were more women than men in our sample, which is in accordance with earlier figures showing that women suffer from depression more often than men [33,34]. The effect of sex on alexithymia might be speculated because of our small sample size.

Specific types of family disfunction were reported to have unique relationships with specific alexithymia characteristics. Family emotional dysfunction, specifically either over- or underinvolvement in other members' concerns, was found to be related to young adults' difficulty identifying feelings. A lack of family rules or guidelines for members' behavior was found to be related to increased preference for externally oriented thinking. Poor family problem solving skills were also found to be related to deficits in imagination and symbolic functioning [35]. In our study; we found that alexithymia scores were significantly higher among depressive individuals living in nuclear families. This is an interesting finding in a cultural setting where living in extended families is a social norm. Individuals' abilities to recognize and verbally express their emotions might be expected to reduce in large families rather than in a family of parents and children only. This finding might be explained by overinvolvement in other members' concerns and lack of privacy that might be potentially related to young adults' difficulty identifying feelings.

Our second aim was to identify the relationship between alexithymia and Cloninger's temperament and character model of personality among Turkish depressed outpatients. We found alexithymia negatively correlated with temperament dimension of RD and character dimension of SD. Thus, our first hypothesis that alexithymia was negatively correlated with RD and SD was confirmed. Besides, in the depressed patient group, the temperament dimension RD was significantly lower in the alexithymic group than the nonalexithymic group; RD, referred to a heritable bias for maintenance of ongoing behavior, might more often be expected in individuals described as sentimental, socially attached, and dependent on the approval of others. This is in accordance with the Grabe et al [9] study, in which low RD was found as an independent predictor for alexithymia. We found alexithymia negatively correlated with the character dimension of SD. Self-directedness includes acceptance of responsibility for one's own choices, identification of individually valued goals and purposes, development of skills and confidence in solving problems, and self-acceptance. Self-directedness expresses individual's competence toward autonomy, reliability, and maturity; therefore, it is expected for those individuals to have lower alexithymia scores. Interestingly, HA was not found to be correlated with TAS-20 total scores, which was contrary to our initial hypothesis. On the contrary, worry/pessimism (HA1) subscale of HA was found to be negatively correlated with externally oriented thinking (TAS F3). Harm Avoidance is a hereditary tendency to inhibition or cessation of behavior, such as pessimistic worry in anticipation of future problems, passive avoidant behaviors such as fear of uncertainty and shyness of strangers, and fatigue. This is not in accordance with previous studies [9,11], in which HA was found positively correlated with alexithymia. This difference might be attributed to sampling differences, different treatment settings (our sample had only outpatients) or simply because of cultural differences. As expected, NS, P, C, and ST were essentially unrelated to alexithymia. To our knowledge, this study is the first to investigate this relationship of alexithymia and personality in a sample of

Turkish depressed patients. Our results supported the findings of the Grabe et al [9] study, which was carried out with a more heterogenous sample of psychiatric in-and outpatients. Our results are consistent with the general view that alexithymia is not represented by one single personality dimension but is best explained by a mixture across different traits within Cloninger's temperament and character model of personality. The findings of this study support the idea that alexithymia is a dimensional personality construct which is associated with distinct personality dimensions [7,8,36]. Previous studies have shown that alexithymia is multidimensional rather than unidimensional, made up of emotional and cognitive components [6,37]. Cognitive component is characterized by the deficit of daydreaming and the externally oriented thinking whereas emotional component is characterized by an incapacity to describe and identify feelings. In the present study, the incapacity to identify feelings was positively correlated with ST and negatively correlated with SD, and difficulties in expressing feelings was negatively correlated with RD and SD. This suggests that the emotional component of alexithymia, that is, difficulties in identifying feelings, is the most important factor that determines the relationship with the temperament and character dimensions of personalty in depressive patients. The regression analysis identified none of the TCI dimensions as independent predictors for TAS-20 total scores in the depressed group. However, taking the subscale, difficulties in identifying feelings, score as a dependent variable in multiple linear regression analysis, and including 7 TCI dimensions into the model as independent variables revealed a significant predictive power of SD. In the control group, taking the subscale, difficulties in expressing feelings, score as a dependent variable in multiple linear regression analysis, and including 7 TCI dimensions into the model as independent variables revealed a significant predictive power of NS and SD. This supports the conclusions of Grabe et al [9] and Picardi et al [11] that both genetic (temperament) and environmental (character) dimensions of personalty contribute to the alexithymia construct. Alexiythmic deficits in emotion regulation are related to the reduced ability to control, regulate, and adapt behavior according to chosen goals and values that characterizes individuals in low SD.

There are advantages of this study over previous work in this field. One is the sample selection. Most the previous studies in this area have used heterogeneous populations in terms of depressive subtype, age, sex, and ethnicity. In this study, all participants are selected from a socially, economically, and educationally homogenous population. Another possible confounding factor is that antidepressant therapy contributes to the differences in mean personality scores between patients and controls. There are very little data currently available in this area, although one study has suggested that selective serotonin reuptake inhibitors can exert effects on personality characteristics that are independent of clinical treatment response. In this study; in an attempt to control this confound, all depressed patients were evaluated and scales were administered at baseline before the initiation of a treatment.

Our study is subject to certain limitations. First, all evaluations were based on self-report measures. Alexithymic subjects are perhaps unable to express themselves correctly because of their difficulties in cognitive processing of emotions. Second, alexithymia, personality, and depression were measured at a single time. To understand the state/trait dependency of personality and the course of recovery from depression, longitudinal studies are required. Third, it should be acknowledged that the study was carried out with a relatively small sample. Therefore, the conclusions should be not considered as definitive, and further studies with larger sample of patients should be conducted.

In conclusion, the rate of alexithymia is high among this sample of Turkish depressed outpatients and results suggested a strong connection between alexithymia and depression. These findings, overall, support the argument that alexithymia is a trait rather than a state-dependent feature. We found alexithymia negatively correlated with the temperament dimension of RD and the character dimension of SD. Alexithymia is explained by specific dimensions and subscale within Cloninger's psychobiological model of personality in this sample of depressed Turkish patients. Further studies are needed for a better understanding of the link between alexithymia and personality in depressive patients.

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