Cloninger'in Mizaç ve Karakter Boyutları'nın Depresyon Tedavisi ile İlişkisi

The Relationship between Cloninger's Temperament and Character Dimensions, and Depression Treatment Outcome

[1]Meltem GURU, [2]Gül Ferda CENGİZ, [3]Sibel ÖRSEL

[1]Gazi University Health Care Center, Department of Psychiatry, Ankara, Türkiye
[2]Bozok University Faculty of Medicine, Department of Psychiatry, Yozgat, Türkiye
[3]Diskapi Yildirim Beyazit Training and Research Hospital, Department of Psychiatry, Ankara, Türkiye

Meltem Gürü: https://orcid.org/0000-0001-8751-6453
Gül Ferda Cengiz: https://orcid.org/0000-0003-0919-5708
Sibel Örsel: https://orcid.org/0000-0003-0184-7038

ÖZ

Amaç: Bu çalışmada Majör Depresif Bozukluk hastalarında mizaç ve karakter özelliklerinin, 8 haftalık süreçte tedavi yanıtı üzerine etkileri araştırılması, tedaviye yanıt veren ve vermeyen hasta gruplarında mizaç ve karakter özelliklerinin karşılaştırılması amaçlanmıştır.

Materyal ve Metot: Çalışmaya Majör Depresif Bozukluk tanısı konmuş 88 hasta alınmıştır. Hastalara tedaviye başlamadan önce Sosyodemografik Veri Formu, Mizaç ve Karakter Envanteri ve Beck Depresyon Envanteri uygulanmıştır. Tedavinin başlangıcından 8 hafta sonra uygulanan Beck Depresyon Envanteri'ne göre hastalar tedaviye yanıt veren ve vermeyen hastalar şeklinde iki gruba ayrılarak bu iki grubun mizaç ve karakter özellikleri karşılaştırılmıştır.

Bulgular: Hastaların eğitim düzeyi tedaviye yanıt veren grupta daha yüksektir. 2. gruptaki işsiz ve ev hanımı (92,3) hasta sayısı tedaviye yanıt veren gruptaki işsiz ve ev hanımı (%41,3) hasta sayısından daha fazla bulunmuştur. Şiddetli depresyonu olan hasta sayısı tedaviye yanıt vermeyen grupta istatistiksel olarak anlamlı düzeyde daha yüksektir. Tedaviye yanıt vermeyen gruptaki hastaların zarardan kaçınma puanı ortalaması tedaviye yanıt veren gruba göre istatistiksel olarak daha yüksek bulunmuştur. Tedaviye yanıt veren gruptaki hastaların sebat etme puanı ortalaması tedaviye yanıt vermeyen gruba göre istatistiksel olarak daha yüksek bulunmuştur.

Sonuç: Çalışmamız Majör Depresif Bozukluk hastalarında bazı sosyodemografik özelliklerin ve mizaç ve karakter özelliklerinin erken tedavi yanıtı ile ilişkili olabileceğini göstermektedir.

Anahtar Kelimeler: Depresyon, kişilik, mizaç ve karakter

ABSTRACT

Objective: The aim of our study is to investigate the relationship between Temperament and Character Inventory (TCI) dimensions and treatment response in Major Depressive Disorder (MDD) patients.

Materials and Methods: 88 patients diagnosed with MDD were included in the study. Patients were given Sociodemographic Data Form, Beck Depression Inventory (BDI) and TCI before the treatment. According to the BDI, which was applied 8 weeks after the treatment, the patients were divided into two groups as those who responded to the treatment and those who did not (responders and non-responders).

Results: The education level of the patients was statistically higher in the responders. The number of unemployed (92.3%) patients in the non-responders was statistically higher than the number of unemployed (41.3%) patients in the responders. The number of patients with severe depression was statistically significantly higher in the non-responders. The mean harm avoidance score of the patients in the non-responders were found to be statistically higher than in the responders. The mean persistence score of the patients in the responders was found to be statistically higher than the non-responders.

Conclusion: Our study shows that some sociodemographic characteristics and TCI dimensions may be associated with early treatment response in MDD patients.

Keywords: Depression, personality, temperament and character

Sorumlu Yazar / Corresponding Author:
Meltem Gürü
Gazi University Health Care Center, Department of Psychiatry
Ankara (zip-code:06500), Türkiye.
Tel: +90 542 6421708 +90 312 2022732
E-mail: meltemguru@gmail.com

INTRODUCTION

The lifetime prevalence of major depressive disorder (MDD) is between 17% and 21% . According to the World Health Organization (WHO) data, it is the first mental illness among the causes of disability.[1,2] Although it is so common and causes disability, only 30-40% of patients respond completely to treatment.[3]

There have been many studies investigating factors predicting response and remission to MDD treatment. One of the most important of these factors is personality traits. The Temperament and Character Inventory (TCI) was developed by Cloninger et al.[4] It is a dimensional model for the conceptualization and classification of personality that includes both normal personality traits and personality disorders.[4,5] It evaluates four temperament and three character traits: Novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P) are temperament components. Self-directedness (SD), cooperation (C), and self-transcendence (ST) are character components.[4,5]

Researchers suggest a bio-psychological perspective focused on personality traits in order to create diagnosis and treatment protocols suitable for individual differences observed in the course of mental disorders.[6] In this context, TCI is important because it considers biological and genetic evidence. It is known that some specific personality traits determined by TCI are associated with susceptibility to MDD and play an important role in the course of treatment and prognosis.[7,8] In a recent comprehensive study by Balestri et al.,[9] it was concluded that personality traits determined by TCI can predict MDD treatment response. There are remarkable results showing that many temperament and character dimensions, especially HA, affect the response to antidepressant treatment.[7,10,11]

Although the effect of personality traits on MDD in clinical practice is known, these traits are not included in treatment algorithms. It is necessary to identify these factors that predict response to treatment, to increase treatment efficacy in treatment-resistant patients. Considering these studies, determination of temperament and character traits is important in the MDD treatment process. The aim of our study is to investigate sociodemographic and clinical factors that may affect the early treatment response in MDD patients, and to evaluate the relationship between personality traits measured by TCI and treatment response.

MATERIALS AND METHODS

Ethical Status: Permission was obtained from Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee for the research (Date: 21.04.2014, decision no: 15/01). The study was designed on the basis of the Declaration of Helsinki rules.

Studying Group: Among the patients who applied to the psychiatry outpatient clinic of our hospital, 215 patients with MDD were evaluated for the study. Patients between the ages of 18-65, with at least primary school education, and who have not received antidepressant treatment for at least 2 weeks were included in the study. Patients with psychiatric disorders other than MDD, and using any other psychotropic medication were not included in the study. The study was conducted with the remaining 88 patients. On the 4th and 8th weeks, face-to-face interviews were conducted with the patients in order to regulate the control and treatment. The patients were informed about the purpose and method of the study and their consent was obtained. Sociodemographic Data Form, TCI and Beck Depression Inventory (BDI) were applied to the patients at the first admission. Appropriate dose and duration of antidepressant treatment was administered to the patients, based on the Turkish Psychiatric Association Depression Treatment Guidebook.[12] Whether the patients responded to the treatment was determined according to the clinical diagnostic criteria and BDI scores at the 8th week control. A decrease of 50% or more in the total score obtained from the depression symptom severity assessment scales compared to the baseline is considered as a response to treatment.[13,14] Based on this, the patients were divided into 2 groups considering the scores they got from BDI at the 8th week control. Patients whose BDI scores decreased by 50% or more compared to the beginning of treatment constituted the group that responded to treatment, responders, and patients whose BDI scores decreased less than 50% or did not change compared to the beginning of treatment constituted the group that did not respond to treatment, nonresponders.

Scales For Assessments: Sociodemographic data form was composed of questions regarding characteristics such as age, sex, education level, occupation, and other demographic variables.

Cloninger's TCI is one widely used measure of personality.[4] It is a 240-item self-report inventory. The scale measures four dimensions of personality and three dimensions of character and the seven dimensions have totally 29 subscales. Novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P) are temperament components. Self-directedness (SD), cooperation (C), and self-transcendence (ST) are character components.

TCI has been adapted into Turkish and the reliability and validity has been examined by Köse et al.[15] and Arkar et al.[16]

BDI is a self-report scale composed of 21 items and measures somatic, emotional, cognitive, and impulsive symptoms of depression.[17] Each item takes a point between 0 and 3. Total scores of 0–12 indicated minimal, 13–18 mild, 19–28 moderate, and 29–63 severe depression. BDI has been adapted into Turkish and the reliability and validity has been examined by Hisli.[18]

Statistical Analysis: All data were analyzed using the Statistical Package for the Social Sciences (SPSS) Ver. 15 software package. Categorical data are presented as percentages and numbers, and as mean and standard deviation values for continuous data. Whether the variables showed normal distribution was evaluated using the Kolmogorov-Smirnov test. Whether the two groups differ in terms of continuous variables; Student's t test was evaluated when parametric assumptions were met, and Mann Whitney U test when parametric assumptions were not met. Fisher Exact test, Yates Chi-square test and Pearson Chi-square test were used to determine whether there was a difference between the distributions of categorical variables in the groups. $p < 0.05$ was accepted for the significance level.

RESULTS

Mean age and marital status distribution of the patients are presented in Table 1. The mean age of the responders was 45.12 ± 11.71 years, and the mean age of the non-responders was 40.92 ± 9.76 years. There was no statistically significant difference between the groups in terms of mean age. (p=0.584) Among the patients in the responders, 17 (22.7%) were single, 53 (70.7%) were married, and 5 (6.6%) were divorced. Among the patients in the non-responders, 2 (15.4%) were single, 8 (61.5%) were married, and 3 (23.1%) were divorced. There was no statistically significant difference between the groups in terms of marital status distribution (x^2=4.964, p=0.174).

Table 1. Mean age and marital status distribution of the patients.

		Responders	Non-responders	p
Mean age		45.12 ± 11.71	40.92 ± 9.76	0.584*
Marital status Distribution (n)	**Single**	17	2	0.174*
	Married	53	8	
	Divorced	5	3	

*: Yate's Ki-kare Test

Gender, education level and occupational distribution of the patients are presented in Table 2. Among the patients in the responders, 42.7% was male and 57.3% was female. Among the patients in the non-responders %23.1 was male and %76.9 was female. There was no statistically significant difference between the groups in terms of gender (p=0.0230). 52% of the responders were primary school graduated, 32% were high school graduated, and 16% were university graduated. 69.2% of the non-responders were primary school graduated and %30.8 were high school graduated. The education level of the patients was statistically significantly higher in the responders (p=0.010). 41.3% of the responders and 92.3% of the non-responders were unemployed. Unemployed patients in the non-responders were statistically significantly higher than in the responders (p=0.010).

Table 2. Gender, education level and occupational distribution of the pati-

		Responders	Non-responders	
		%	%	p
Gender	Male	42.7	23.1	0.230*
	Female	57.3	76.9	
Education level	Primary school	52	69.2	0.010*
	High school	32.0	30.8	
	University	16.0	0	
Occupation	Unemployed	41.3	92.3	0.010*
	Other occupations	24.0	7.7	
	Official	24.0	0	
	Student	10.7	0	

*: Yate's Ki-kare Test

The distribution of the previous psychiatric disorder histories, history of psychiatric diorder in first degree relatives, suicide attempts and the patients with severe depression are presented in Table 3. 16% of the responders and 38.5% of the non-responders had a previous psychiatric disorder There was no statistically significant difference between the groups in terms of having a previous psychiatric disorder (p=0.071). 28% of the responders and 30.8% of the non-responders had a history of psychiatric disorder in first degree relatives. There was no statistically significant difference between the groups in terms of having a history of psychiatric disorder in first degree relatives (p=0.537). Patients with active suicidal ideation and psychiatric comorbidity were excluded from the study. The remaining patients in the study had not been hospitalized in the psychiatry service before. There was no statistically significant difference between the groups in terms of having a history of suicide attempt (p=0.060). When evaluated in terms of having previously been diagnosed with MDD, there was no statistically significant difference between the groups (responders %16, non-responders %38.5, p=0.071). The severity of depression was determined according to the BDI scores. The number of patients with severe depression in the non-responders was statistically significant higher (p=0.004).

Table 3. The distribution of the previous psychiatric disorder histories, history of psychiatric diorder in first degree relatives, and suicide attempts of the patient.

		Responders	Non-responders	
		(%)	(%)	**p**
Previous psychiatric disorder	Yes	16.0	38.5	0.071*
	No	84.0	61.5	
History of psychiatric diorder in first degree relatives	Yes	28.0	30.8	0.537*
	No	72.0	69.2	
Suicide attempt	Yes	49.3	76.9	0.060*
	No	50.7	23.1	
Severe depression		15	54	0.004*

*: Yate's Ki-kare Test

The comparison of temperament and character dimensions of the groups are given in Table 4. The mean HA scores of the non-responders were statistically significant higher than the responders (p=0.034). The mean P scores of the responders were statistically significant higher than the non-responders (p=0.010).

Table 4. The comparison of temperament and character dimensions of the groups.

		Responders	Non-responders	
		(%)	(%)	**p**
Temperament	NS	57.3	46.2	0.326*
	HA	45.3	76.9	0.034*
	RD	62.7	53.8	0.379*
	P	69.3	30.8	0.010*
Character	SD	56.0	30.8	0.083*
	C	53.3	30.8	0.114*
	ST	56.0	53.8	0.559*

*: Pearson Ki-kare Test; NS: Novelty seeking, HA: Harm avoidance; RD: Reward dependence; P: Persistence; SD: Self-directedness; C: cooperation; ST: self-transcendence.

DISCUSSION AND CONCLUSION

Our study results revealed that sociodemographic characteristics, clinical factors and TCI dimensions may affect early treatment response in MDD patients.

In clinical studies, MDD treatment response has been shown to be related to demographic and psychosocial factors as well as biological factors. Factors such as female gender, 65-84 years of age, low education level, being single, unemployment, low economic level, severe and recurrent depression, familial depression can both facilitate the onset of MDD and worsen the treatment response.[19-21] In our study, no difference was found between the groups in terms of mean age, gender, marital status and income level. The education level of the patients was higher in the responders. The number of unemployed (92.3%) patients in the non-responders was higher than the number of unemployed (41.3%) patients in the responders. When evaluated in terms of the presence of a family history of MDD, there was no difference between the groups in our study. Consis-

tent with the literature, the number of patients with severe depression was higher in the non-responders. Since patients with comorbid psychiatric disorders were excluded from the study, this factor was not evaluated in our study. It is known that having history of suicide attempt and suicidal ideation may affect the MDD treatment response.[22,23] Patients with active suicidal thoughts were excluded from our study. When evaluated in terms of having a previous suicide attempt, no difference was found between the groups. This result might be related to the exclusion of patients with active suicidal ideation. It is known that recurrent depression and other previous psychiatric disorder are associated with low response to antidepressant treatment.[24] When evaluated in terms of previous psychiatric disorder, no difference was found between the groups in our study. This result might be related to the low number of non-responder patients .

Although there are studies showing the relationship between TCI dimensions and susceptibility to MDD, the approach to predicting response to antidepressant treatment with TCI dimensions is new. It is thought that some specific TCI components may predict antidepressant treatment response in MDD.[25] In these studies, the most emphasized temperament component is harm avoidance. Harm avoidance refers to temperament features such as pessimistic worries about future problems, fear of uncertainty, shyness and fatigue.[4] Although individuals who score high on this item seem to be advantageous to be ready for possible dangers, they may be considered to be high-risk for MDD at other times. It has been emphasized in many studies that harm avoidance has a negative correlation with MDD treatment response.[9] It is known that harm avoidance is a risk factor for both the onset of MDD and MDD treatment resistance.[26,27] Consistent with the literature, in our study, the harm avoidance scores of the patients in the non-responders were found to be higher than in the responders.

Another significant result in our study is related to persistence of temperament components. The persistence score of the patients in the responders was found to be higher than the non-responders. Likewise, in their study investigating the effects of TCI components on MDD treatment response, Ballestri et al.[9] found low persistence scores to be associated with treatment resistance. Persistence is associated with positive personality traits of hardworking, determined, perfectionist and enthusiastic temperament. [4,5] People with this temperament tend to continue the behavior despite frustration and fatigue. In this regard, the result of our study seems to be compatible with the literature.

Results related to reward dependence, self-directedness and cooperation from other TCI com-

ponents are significant.[28,29] Takahashi et al.[29] found that reward dependence and self-directedness scores in treatment-resistant MDD patients were lower than in patients in remission and healthy controls. In a comprehensive study evaluating 455 patients with MDD, low reward dependence and cooperation scores were associated with treatment resistance.[9] In our study, however, no difference was found between the groups for TCI components except harm avoidance and persistence. Although the self-directedness score of the patients in the responders was found to be higher than the non-responders, this finding was not statistically significant. It can be thought that the difference in the results may be due to the distribution of MDD severity among the groups, variables such as the number of samples and the treatment method.

According to our research, there are a limited number of studies examining the effect of TCI components on the treatment of MDD. All patients were evaluated by a psychiatrist in face-to-face interviews. Exclusion of patients with comorbid anxiety disorder increased the effectiveness of our study. There are some limitations of our study. The patients participating in the study consisted of outpatients. Since the severity of depression may be higher in inpatient MDD patients, the effect of TCI components on the treatment response can be evaluated more clearly in this group of patients. The sample size is smaller than similar studies in the literature. Also, self-report scales may affect the results of patients with personality disorders. It would be appropriate to evaluate these findings with larger patient groups in future studies.

In conclusion, our study shows that some sociodemographic characteristics and TCI dimensions are associated with treatment response in MDD patients. We think that these findings will play an important role in predicting the MDD treatment response and course, and therefore in determining appropriate treatment options for the patient.

REFERENCES

1. World Health Organization WHO. Depression

and Other Common Mental Disorders, Global Health Estimates 2017. http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2-eng.pdf. Accessed March 3,2022.

2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, WalterS EE. Lifetime prevalence and age-of-onset distributions of DSM-IVdisorders in the Natioanal Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593-602. doi:10.1001/archpsyc.62.6.593

3. Dilbaz N, Çavuş SY. Depresyon tedavisinde yetersiz yanıt durumunda güçlendirme tedavileri. Klinik Psikofarmakoloji Bülteni. 2010;20(Suppl. 1):4-14.

4. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry. 1993;50(12):975-990. doi:10.1001/archpsyc.1993.01820240059008

5. Kose S, Yalcin M, Akin E, Turkcapar H. Normative data and factorial structure of the Turkish version of the temperament and character inventory-revised (Turkish TCI-R). Psychiatr Clin Psychopharmacol. 2019;29(2):189-196. doi:10.1080/24750573.2019.1610144

6. Noll R. Styles of Psychiatric Practice, 1906-1925: Clinical evaluations of the same patient by James Jackson Putnam, Adolph Meyer, August Hoch, Emil Kraepelin and Smith Ely Jelliffe. Hist Psychiatry. 1999;10(38Pt2):145-189. doi:10.1177/0957154X9901003801

7. Kampman O, Poutanen O. Can onset and recovery indepression be predicted by temperament? A systematic review and meta-analysis. J Affect Disord. 2011;135(1-3):20-27. doi:10.1016/j.jad.2010.12.021

8. de Winter RFP, Wolterbeek RS, Philip ZFG, Goekoop JG. Character and temperament in major depressive disorder and highly anxious-retarded subtype derived from melancholia. Compr Psychiatry. 2007;48(5):426-435. doi:10.1016/j.comppsych.2007.04.002

9. Balestri M, Porcelli S, Souery D, et al. Temperament and character influence on depression treatment outcome. J Affect Disord. 2019; 252:464-474. doi:10.1016/j.jad.2019.04.031

10. Kampman O, Poutanen O, Illi A, et al. Temperament profiles, major depression, and response to treatment with SSRIs in psychiatric outpatients. Eur Psychiatry. 2012;27(4):245-249. doi:10.1016/j.eurpsy.2010.07.006

11. Paavonen V, Luoto K, Koivukangas A, Lassila A, Leinonen E, Kampman O. Temperament and character profiles associated with depression and treatment response in patients with or without comorbid substance abuse. Psychiatry Res. 2016;245:250-258. doi:10.1016/j.psychres.2016.08.043

12. Akdeniz F. Depresyonda optimal ilaç kullanımı. In: Yazıcı O, Oral ET, Vahip S, Özer Ş, ed. Türkiye Psikiyatri Derneği Depresyon Sağaltım Kılavuzu Kaynak Kitabı. 1st edition. Inc; 2008:71-79.

13. Frank E, Prien R, Jarrett B, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Arch Gen Psychiatry,1991;48(9):851-855. doi:10.1001/archpsyc.1991.01810330075011

14. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: Remission and beyond. JAMA. 2003;289(23):3152-3160. doi:10.1001/jama.289.23.3152

15. Köse S, Sayar K, Ak İ, et al. Mizaç ve karakter envanteri (Türkçe TCI): Geçerlik, güvenirliği ve faktör yapısı. Klinik Psikofarmakoloji Bulteni. 2004;14(3):107-131.

16. Arkar H, Sorias O, Tunca Z, et al. Mizaç ve karakter envanteri'nin Türkçe formunun faktör yapısı, geçerlik ve güvenirliği. Türk Psikiyatri Dergisi. 2015;16(3):190-204.

17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-571. doi:10.1001/archpsyc.1961.01710120031004

18. Hisli N. Beck Depresyon Envanterinin geçerliliği üzerine bir çalışma. Psikoloji Dergisi. 1988;6:118-121.

19. Prasko J, Ociskova M, Grambal A, et al. Personality features, dissociation, self-stigma, hope, and the complex treatment of depressive disorder. Neuropsychiatr Dis Treat. 2016;12:2539–2552. doi:10.2147/NDT.S117037

20. Gronemann FH, Jorgensen MB, Nordentoft M, Andersen PK, Osler M. Socio-demographic and clinical risk factors of treatment-resistant depression: A Danish population-based cohort study. J Affect Disord. 2020;261:221-229. doi:10.1016/j.jad.2019.10.005

21. Tüfekçi B, Karaca S. Examining loneliness, depression and burnout among employees at a factory. Online Turkish Journal of Health Sciences. 2021;6(4):514-520. doi:10.26453/otjhs.882828

22. Kraus C, Kadriu B, Lanzenberger R. Zarate Jr CA, Kasper S. Prognosis and improved outcomes in major depression: A review. Transl Psychiatry. 2019;9(1):127. doi:10.1038/s41398-019-0460-3

23. De Carlo V, Calati R, Serretti A. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: A systematic review. Psychiatry Res. 2016;240:421-430. doi:10.1016/j.psychres.2016.04.034

24. Perlman K, Benrimoh D, Israel S, et al. A systematic meta-review of predictors of antidepressant

treatment outcome in major depressive disorder. J Affect Disord. 2019;243:503-515. doi:10.1016/j.jad.2018.09.067

25. Paavonen V, Kampan O, Illi A, Viikki M, Setala-Soikkeli E, Leinonen E. A cluster model of temperament as an indicator of antidepressant response and symptom severity in major depression. Psychiatry Investig. 2014;11(1):18-23. doi:10.4306/pi.2014.11.1.18

26. Bajraktarov S, Novotni A, Arsova S, Gudeva-Nikovska D, Vujovik V. Character and temperament dimensions in subjects with depressive disorder: Impact of the affective state on their expression. Open Access Maced J Med Sci. 2017;5(1):64–67. doi:10.3889/oamjms.2017.012

27. Zaninotto L, Solmi M, Toffanin T, Veronese N, Cloninger CR, Correll CU. A meta-analysis of temperament and character dimensions in patients with mood disorders: Comparison to healthy controls and unaffected siblings. J Affect Disord. 2016;194:84-97. doi:10.1016/j.jad.2015.12.077

28. Murphy JA, Sarris J, Byrne GJ. A Review of the conceptualisation and risk factors associated with treatment-resistant depression. Depress Res Treat. 2017;2017:4176825. doi:10.1155/2017/4176825

29. Takahashi M, Shirayama Y, Muneoka K, Suzuki M, Sato K, Hashimoto K. Personality traits as risk factors for treatment-resistant depression. PLoS One. 2013;8(5):e63756. doi:10.1371/journal.pone.0063756