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ICP 2021 Outstanding Research Award Nominees Brief Reports

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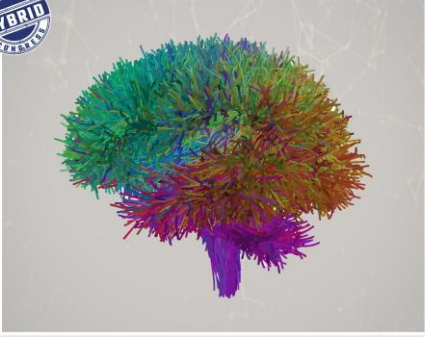
It is our great pleasure to announce that the Turkish Association for Psychopharmacology (TAP)'s 12th International Congress on Psychopharmacology & 8th International Symposium on Child and Adolescent Psychopharmacology will be held on November 17-20, 2021 in Antalya, Turkey.

12th ICP & 8th ISCAP Organizing Committee

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Outstanding Research Award Nominees Brief Reports

12th International Congress on Psychopharmacology &
8th International Symposium on Child and Adolescent Psychopharmacology

Brief Reports of Oral Research Presentations

[Abstract:0043]

0043 - Group emdr for female adolescents with complex posttraumatic stress disorder: a pilot study

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ABSTRACT

INTRODUCTION: Complex PTSD is a condition that can be seen in children and adults who experience trauma such as violence, neglect, and abuse in early childhood and for a prolonged time [1]. Complex PTSD is a common condition accompanied by comorbid psychiatric diagnoses such as Depressive Disorders, Anxiety Disorders, Substance Use Disorders and even metabolic disorders. EMDR is a therapy method that has been used for more than 30 years in people with traumatic experiences. This method, developed by Shapiro, is based on the principle of desensitizing traumatic events with eye movements and developing adaptive beliefs [2]. Studies have shown that EMDR is effective in improving PTSD symptoms in children and adolescents as well as adults [3]. In recent years, controlled studies have been shown that. EMDR Integrative Group Treatment Protocol (EMDR-IGTP) is a relatively new treatment model compared to individual EMDR. With this method bilateral stimulation is added to standard group therapy methods. Previously used only in the early stages of social traumas such as natural disasters, and war, EMDR-IGTP has been revised over time and has been brought into the literature by Artigas et al. [4, 5]. It is also suggested that this method can be used for early intervention of natural disasters such as earthquakes[6].

According to our information, there have not been any studies on EMDR-IGTP for girls with Complex PTSD. Therefore, in this study, we aim to evaluate whether adolescent girls diagnosed with Complex PTSD who had been sexually abused would benefit from the EMDR-IGPT and whether their depressive symptoms would decrease.

METHODS: *Study Design and Participants,* The study was conducted in Mardin, a city in southeastern in Turkey, at a Child Support Center, in May 2019. The initial sample included 17 girls from the institution who were victims of sexual abuse, and 13 of them completed all treatment steps and were included in the analysis. Out of 4 girls who were excluded from the study one had need psychiatric inpatient treatment, and one did not volunteer to attend further sessions. Approval for the study was obtained from the institution authorities and local ethics committee. All the participants had been followed by a child and adolescent psychiatrist for at least 6 months, had received appropriate doses of medical treatment, and had regularly attended supportive interviews with institutional psychologists. PTSD diagnoses were determined acoording to DSM-V diagnostic criteria by a child and adolescent psychiatrist. Socio-demographic information was obtained before the study and adolescents were asked to fill the Child Post-Traumatic Stress Reaction Index (CPTS-RI) and Children's Depression Inventory (CDI). Then, the clients were divided into two groups of 9 and 8, and then received 3 sessions of EMDR-IGTP. 13 girls completed all 3 therapy sessions. At the end of the study, 1 month after the last therapy session, the 13 participants were asked to fill the CPTS-RI and CDI again.

EMDR Integrative Group Treatment Protocol (EMDR-IGTP) for Children [4]

EMDR-IGTP was developed by the Mexican Association for Mental Health Support in Crisis in 1997 after Hurricane Pauline. This model was created by combining the standard EMDR protocol developed by Francine Shapiro [7] and group therapy protocols [5]. It was shown in a study by Jajero et al. that group EMDR sessions could benefit clients when the time and cost of individual EMDR sessions could not be met [8]. In the same study, it was also stated that group therapy combined with EMDR may be more effective than standard group therapies. As a result, EMDR-IGTP has been used and found effective for thousands of trauma survivors in many field studies [9]. In this study, EMDR-IGTP was applied in 8 steps for children, as in the original protocol.

Data analysis

Statistical analyses were performed using the SPSS software version 22. The variables were investigated using histograms, probability plots and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk's test) to determine whether they are normally distributed. Since Child Post-Traumatic Stress Reaction Index Scores and Children's Depression Inventory Scores were not normally distributed; non-parametric tests were conducted to compare these parameters, as well as to compare the ordinal variables. The Wilcoxon test was used to compare the change in these parameters between pre-treatment and 1-month follow-up. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS: In total, 13 female adolescents with Complex PTSD completed the study. The patients had a mean age of 16 (SD= 1.08). The mean age of first sexual trauma experience of the patients was 12.2. Most of them had more than one traumatic experience according to the List of Traumatic Events (n:11, 84.6%). The pre-treatment CPTS-RI scores of all the adolescents ranged from 42 to 68 with the average CPTS-RI score being 53.5 (SD= 7.5). All girls were above the threshold before treatment according to this cutoff value. Pretreatment mean CDI was 19 (SD= 6.9) and ranged from 11 to 36. 6 out of 13 patients had depressive disorder according to cutoff value of the questionnaire. After 2 session of EMDR-IGTP, patients were re-evaluated at the end of first month. CPTS-RI and CDI Scales were reapplied. Mean CPTS-RI and CDI scores were 39.4 and 11.4 respectively. On the other hand, there were significant differences between the mean pre-test scores and follow-up scores for both questionnaires (p<0.05). The number of patients with over-threshold PTSD decreased to 7 in 13. In addition, CDI scores of all patients decreased to sub-threshold values (Table 1).

DISCUSSION: This field study at a Children Support Center in Turkey investigated whether EMDR-IGTP might be an efficient instrument in alleviating symptoms of adolescent females who had been exposed to sexual abuse. Studies have reported individual EMDR sessions to be more effective than group EMDR sessions, however group EMDR has been shown is a strong option in cases of limited time and opportunity [10]. In a study by Allon, individual EMDR sessions were compared to EMDR-IGTP in victims of sexual assault and other trauma. At the end of the study, Impact of Event Scale Scores decreased from 52 to 33. While the mean pre-treatment SUD value was 9, post-treatment mean SUD values decreased to 4.8 in group therapy and to 2.8 in individual therapy. The author was only able to evaluate the post-treatment scores, due to time constraints. One of the reasons why group therapy less effective was discussed to be that the processing has not been completed due to lack of follow-up evaluations [11]. A stronger therapeutic relationship and the chance of cognitive interventions may have played a role in the rapidity and effectiveness of individual therapy [12]. In our study, statistically significant improvement has occurred between pre-treatment and 1-month follow-up in complex PTSD patients who have been treated with standard treatment models for at least 6 months. However, the presence of 7 patients who still had over-threshold scores may be an indication that some patients require additional individual interventions. In a study conducted by Jajero et al. in 2014, Group EMDR was shown to be effective in children and adolescents with interpersonal trauma in line with our research [13]. Group EMDR frequently focused on PTSD symptoms, and there is a lack of studies evaluating depressive symptoms in the literature. However, recent publications report that EMDR can reduce depressive symptoms in addition to PTSD symptoms [14, 15]. In our study, a significant improvement in depressive symptoms was observed, and all patients received sub-threshold scores after follow-up. Due to time and staff limitations we could only conduct the study with a small number of clients and without a control group. Also, the absence of a long-time follow-up was another limitation of the study. However, the participants were treated as usual for at least six months before therapy, so it can be assumed that their symptom severity was mostly stable for a long period. Thus, long-term follow-up of patients can be considered as the strength of the study. In addition, evaluating the change of depressive symptoms in addition to PTSD symptoms with therapy can be considered among the strengths of the study.

As a result, EMDR-IGTP can be considered as a method for the therapy of girls who are sexually abused, especially in cases of time and specialist limitations. Although the effects are moderated, EMDR-IGTP may be a promising tool due to its novel approach to trauma in Complex PTSD. However, long-term follow-up, randomized controlled and large-sample studies are needed to determine the strength and continuity of the treatment effect.

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Table 1: Group EMDR intervention results according to CPTS-RI and CDI scales

	Before treatment	After follow-up	p value
Child Post-Traumatic Stress Reaction Index Scores	53.5 (SD 7.5)	39.4 (SD 8.6)	P=0,002
Presence of PTSD (cut-off score :40)	13 (100%)	7 (53.8%)	P=0,014
Children's Depression Inventory Scores	19 (SD 6.9)	11,4 (SD 5.5)	P=0,007
Presence of Depression (cut-off score :20)	6 (46.2%)	0 (0%)	P=0,014

[Abstract:0055]

0055 - Inflammation-neopterin-tetrahydrobiopterin pathway and nitric oxide (no) levels in adolescents with obsessive compulsive disorder

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ABSTRACT

INTRODUCTION: Obsessive compulsive disorder (OCD) is a common neuropsychiatric disorder with the presence of either obsessions or compulsions that cause significant distress and interfere with normal functioning at work, home, social activities, or personal relationships. The biological mechanisms underlying obsessive compulsive disorder (OCD) are not yet sufficiently understood. Neuroinflammation-mediated changes in the brain caused by stress, changes in the immune system may also play a role in the etiology of OCD. Recent reports have indicated the presence of immune system alterations in OCD patients. Despite the strong recent interest in immunologic abnormalities in OCD, few studies have examined cytokines in this disorder [1]. Cytokines, which increased as a result of chronic inflammation, increased neopterin levels and decreased tetrahydrobiopterin levels by activating the neopterin-tetrahydrobiopterin pathway. Neopterin, a biopterin precursor that is released by macrophages, is accepted as a biochemical marker of cell-mediated immune response. In addition, studies have shown that it can be an important biomarker especially for major depressive disorder (MDD) in psychiatric disorders. Tetrahidrobiopterin (BH4) is the main cofactor for speed limiting steps in the conversion of phenylalanine to tyrosine, hydroxylation of tyrosine and tryptophan and the formation of serotonin, neuradrenaline and dopamine. And, also BH4 plays an important role in regulating presynaptic release of neurotransmitters from nerve terminals [2]. Nitric oxide levels are associated with increased oxidative stress. Cytokines (especially IFN- γ) and neopterin increase nitric oxide (NO) levels by increasing reactive oxygen species such as NADPH-oxidase (NOX) and superoxide anion (O_2^-) (Figure 1). Nitric oxide (NO) participates in the regulation of neurotransmission in the central nervous system. The importance of monoaminergic systems in the function of the brain is clearly shown by the number of severe neuropsychiatric diseases caused by the impairment of monoaminergic neurotransmission. NO has been implicated in a number of physiological functions such as noradrenaline and dopamine releases, memory and learning and certain pathologies such as schizophrenia, bipolar disorder and major depression [3]. In this study, we aimed to compare levels of serum TGF-1β, TNF-α, IL-1β, IL-2, IL-6, IL-10, IL-17 and neopterin, tetrahydrobiopterin, nitric oxide (NO) levels in patients with obsessive compulsive disorder and healthy controls.

METHODS: This study was conducted between December 2018 and November 2019 at the Manisa Celal Bayar University, Faculty of Medicine (MCBUFM), Department of Child and Adolescent Psychiatry, Outpatient Clinic. In the semi-structured psychiatric interview conducted by the researcher, patients diagnosed with OCD were included in the study by reviewing the inclusion and exclusion criteria. For the healthy control group, young patients aged 11–18 years who were admitted to the MCBUFM Pediatric Outpatient Clinic for any reason, did not have a chronic disease, and were not previously diagnosed with a psychiatric disorder were referred to the researcher. In the semi-structured psychiatric interview conducted by the researcher, the subjects who did not meet the diagnostic criteria of psychiatric disorder were included in the study as controls after taking into consideration the inclusion and exclusion criteria.
Inclusion and Exclusion Criteria of the Study
Exclusion criteria for all participants were as follows: using of drugs affecting the immune system in the last 6 months; having any immunological, hematological,or infectious disease in the last month; having a significant medical or neurological disease or substance abuse in the last 3 months. Inclusion criteria for the patient group were as follows: being in the age range of 11–18 years; being diagnosed with active OCD according to DSM-5; persistence of OCD episode for at least 6 weeks. Patients with psychotropic medication use in the last 6 weeks and patients who were diagnosed with comorbidity of psychiatric disorder and substance abuse during their life time were excluded from the study. Exclusion criteria for the healthy control group were as follows: having a history of major psychiatric illness and psychotropic drug use.
Clinical Evaluation: Schedule for Affective Disorders and Schizophrenia for School Aged Children Kiddie-SADS-lifetime Version, DSM-5 (K-SADS-PL-DSM-5) and Children Yale-Brown Obsessive Compulsive Scale- (C-Y-BOCS) were applied, and a sociodemographic data form was completed.
Biochemical Analyses: For the measurement of neurobiological markers, blood samples were collected in 10 mL anticoagulant tubes between 9 and 10 a.m. on an empty stomach. The venous blood samples were centrifuged at 3000 rpm for 15 min to be separated from serum and stored

at −80°C until analyzed. Serum samples were analyzed for TGF-1β, TNF-α, IL-1β, IL-2, IL-6, IL-10, IL-17 and neopterin, tetrahydrobiopterin, nitric oxide (NO) levels using enzyme-linked immunosorbent assay.

Statistical Evaluation

The data obtained from the study were evaluated using the Statistical Package for Social Sciences 21.0 program. Continuous variables obtained by measurement were expressed as mean ± standard deviation,and categorical variables were expressed as percentage and number. Student's t-test was used to compare means between two independent groups with normal distribution,and the non-parametric Mann–Whitney U test was used for groups that did not show normal distribution. One-way analysis of variance was used for the comparison of three or more groups with normal distribution, and the non-parametric Kruskal–Wallis analysis was used for those that did not show normal distribution. Chi-square analysis and Fisher's exact test were used to compare the categorical data. In order to determine the direction and level of the relationship between numerical variables, Pearson's test was used for those with normal distribution, and Spearman's rank-order correlation was used for those that did not show normal distribution. In all analyses, $p<0.05$ was considered statistically significant.

RESULTS: Demographic and Clinical Features: The study included 29 (%50,9) adolescent patients with OCD and 28 (%49,1) adolescent healthy controls. No significant difference was found between the groups in terms of age (p=0.179) and gender (p=0.198).

C-YOCBS Features and Scores of Patient Group: All of our patients had both obsessions and compulsions. While washing-cleaning (%82,8) and controlling (%79,3) compulsions were the most common compulsions, contamination (%89,7) and magical thought-superstition (%44,8) obsessions were the most common obsessions. While the least seen compulsions were hoarding-picking compulsions (%17,2), the least seen obsessions were sexual (%3,4) and religious (%20,7) obsessions. According to the total score of C-YBOCS, 6 patients (%20,7) were evaluated as intermediate, 17 patients (%58,6) were evaluated as severe and 6 patients (%20,7) were evaluated as advanced.

Cytokines Levels: No significant difference was found between the groups when the levels of TNF-α (p=0.983), IL-1β (p=0.357), IL-2 (p=0.135), IL-6 (p=0.458), IL-10 (p=0.877), IL-17 (p=0.391) were compared. A significant difference was found between the patient and control groups in terms of TGF-1β (p=0.002) levels (Table 1). There was a negative correlation between TGF-1β level and C-YOCBS total score in the patient group (r=-0,124 / p=0,032).

Neopterin-Tetrahydrobiopterin and Nitric Oxide Levels: Neopterin (p=0.021), Tetrahydrobiopterin (p=0.001), Nitric Oxide (p=0.013) levels were significantly different between the groups (Table 1). In the patient group, there was a negative correlation between Tetrahydrobiopterin levels (r=-0,218 / p=0,001) and C-YBOCS total score; there was a positive correlation between Neopterin levels (r=0,352 / p=0,002) and C-YBOCS total score; there was a positive correlation between Nitric Oxide levels (r=0,198 / p=0,005) and C-YBOCS total score.

DISCUSSION: In accordance with our hypothesis, neopterin and nitric oxide levels were found to be significantly higher and tetrahydrobiopterin level was found to be statistically low in children with OCD compared to the healthy control group. Incompatible with our hypothesis, all proinflammatory cytokine levels were found to be low, but this decrease was statistically significant only in TGF-1β levels. The reasons for this are thought to be the exclusion of psychiatric comorbidities in the literature and the effect of OCD on the stress level and consequently the decrease in immune system cell levels and cytokine levels due to increased cortisol levels [4]. However, cortisol levels were not examined in our study. Although the proinflammatory cytokine levels did not increase in our study, the reasons for activation of the neopterin-tetrahydrobiopterin pathway could be elevated IFN-γ levels and decreased 6-pyruvyl-tetrahydropterinsynthase (PTPS) enzyme levels [5]. In addition, it was thought that increased neopterin levels and possible increased IFN-gamma levels may cause reactive oxygen species to increase and thus increase NO levels. However, IFN- ɣ cytokine and PTPS enzyme levels were not examined in our study. It was determined that the activity of the neopterin-tetrahydrobiopterin pathway and the changes of inflammatory and oxidative in patients with OCD. In addition, the correlation of between neopterin, tetrahydrobiopterin, nitric oxide, TGF-1β levels and C-YBOCS total scores suggested that this pathway is involved in the etiology of OCD. Consequently, the results of our study suggest that the levels of proinflammatory cytokines and nitric oxide and the activation of neopterin-tetrahydrobiopterin pathway may be implicated in the pathophysiology of obsessive compulsive disorder.

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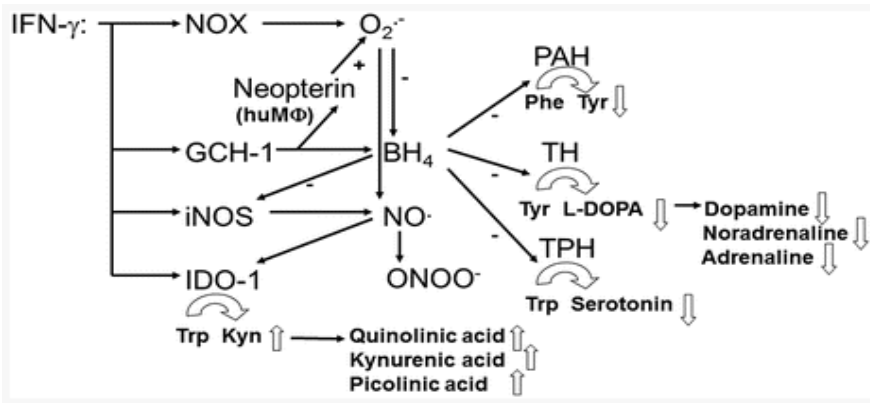
Figure 1. Cytokines (especially IFN- γ) and neopterin increase nitric oxide (NO) levels by increasing reactive oxygen species such as NADPH-oxidase (NOX) and superoxide anion ($O_2^{.-}$).

Table 1. Biochemical analysis of patient and control groups.

	OCD Group	Healthy Control Group	p value (Mann-Whitney U Test)
TGF-ß (pg/ml)	167.20±82.98	216.75±201.78	p=0.002
TNF-α (pg/ml)	6.56±2.80	8.13±7.12	p=0.983
IL-1ß (pg/ml)	47.93±16.95	70.12±21,89	p=0.357
IL-2 (pg/ml)	86,13±23.87	113,26±34.98	p=0.135
IL-6 (pg/ml)	34.67±58.97	67.08±75.32	p=0.458
IL-10 (pg/ml)	14,67±2.45	13,49±5.13	p=0.877
IL-17 (pg/ml)	180,66±46.93	364,06±97.19	p=0.391
Neopterin (nmol/L)	9,72±5,57	7,14±6.78	p=0.021
Tetrahidrobiopterin (pg/ml)	148.35±29.13	177.67±35.87	p=0.001
Nitrik Oksit (NO) (Umol/L)	246,28±54.79	217.89±39.76	p=0.013

[Abstract:0065]

0065 - Relationship between irritability and psychopathology and parental temperament in child and adolescent

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OBJECTIVE: Irritability is one of the most common reasons why children and adolescents are referred for psychiatric evaluation [1]. In addition to being associated with psychopathologies such as anxiety disorder and depression, irritability in children and adolescents was significantly associated with impaired functioning in adulthood, academic problems, poverty and suicidal behavior [2]–[8]

Irritability is seen as a continuous feature in the youth period [9]. This has caused irritability to fall within the Research Domain Criteria (RDoC) of the US National Institute of Mental Health (NIMH) [10].

Genetics and family history of psychopathology in the presence of the topics is investigated on the pathophysiology of irritability. The heritability of irritability is approximately 30-40%, similar to unipolar depression and anxiety disorder [11]–[13]

Behavior patterns that children learn from their parents are one of the environmental factors for irritability. Irritable children often live in inconsistent rewards and punishments that can reward disruptive behavior. Inconsistent parental behaviors have been associated with anger, aggression and externalized problems in children [14]–[16].

Research has shown that parental temperament and personality traits have a role in parenting attitudes, beliefs and practices, and also in children's behavior, and that both variables affect the family system [17]–[19]. Parental temperament characteristics affect parents' behavior towards their children. Thus, parental temperament can be an important factor that has an impact on irritability in children.

In the light of these findings, this study desingned to investigate;

1-) The relationship between irritability and parental affective temperament characteristics

2-) The relationship between irritability and symptoms of common disorders (attention deficit, hyperactivity-impulsivity, oppositional defiant disorder, conduct disorder, depression, anxiety disorders, obsessive-compulsive disorder) in children and adolescents in 6-18 age group children and adolescents who applied to Cerrahpasa Child and Adolescent Psychiatry outpatient clinic

METHODS: This is a cross-sectional study. The study sample consist of 329 children and adolescents with their parents who applied to Cerrahpaşa Child and Adolescent Psychiatry outpatient clinic. Sociodemographic data form, Turgay DSM-IV Based Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S), Revised Child Anxiety and Depression Scale (RCADS) Parent and Child version, Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A), Affective Reactivity Index (ARI) child and parent forms were used. Data were evaluated using kolmogorov simirnov, wilcoxon, chi-square test, fischer test, spearman correlation analysis. SPSS 22.0 program was used in the analyzes.

RESULTS: A significant positive correlation was found between the irritability scores reported in the Affective Reactivity Index-parent scale and parental anxious, depressive, irritable and cyclothymic temperament scores (p<.001). There was a significant positive correlation between irritability scores in adolescent scale and parental anxious temperament scores only (p=0.02). There was no correlation between irritability score and parental hyperthymic temperament scores in both scales (See Table 1). Also a statistically significant positive correlation was found between the total score of parent affective reactivity index and the total score of child affective reactivity index (p <.001) (See Table 2). A significant correlation was found between total irritability score in Affective Reactivity Index and attention deficit, hyperactivity-impulsivity, total attention deficit and hyperactivity, oppositional defiant and conduct disorder score (See Table 3). In addition, there was a significant relationship between anxiety and depression scores and irritability levels in children and adolescents reported by both parents and children and adolescents (See Table 4)..

DISCUSSION: To date there are no cross-sectional and longitudinal studies investigating the relationship between parent temperament and child irritability. This is the first study to investigate the relationship between irritability and parental temperament characteristics in children and adolescents.

In the present study, a statistically significant relationship was found between the anxiety scores of the parents and the irritability scores reported by both the parent and the child. In a study by Whaley et al., it was shown that anxious mothers had less warm relationships in their mother-child interactions, gave their children less autonomy, and were more critical and destructive than healthy mothers even after controlling depressive symptoms [20]. Another study revealed the negative impact of parental anxiety on parenting practices[21]

Considering the relationship between anxiety and depression in parents and the negative effects on parental behavior styles, it can be considered that these parents may have high levels of irritability in their children. Parental anxious temperament characteristics should be considered in children who identify themselves as irritable. On the contrary, it should be taken into consideration that cyclothymic, depressive, anxious and irritable temperament states generally affect irritability assessment in parents who see their children as irritable.

Parental management training for inconsistent parental behavior, which has an important role in pathophysiology, is effective in the management of irritability in children and adolescents. Temperament is seen as one of the important factors determining parental behavior style. Parents may also exaggerate or, on the contrary, evaluate their children more precisely in line with their temperament and psychopathology. Considering parental temperament factors will help clinicians to manage irritability in children

Affective Reactivity Index showed a significant positive correlation between total irritability score and attention deficit, hyperactivity, impulsivity, total attention deficit and hyperactivity, oppositional defiant and conduct disorder scores in both children and parent questionnaires. Severe and non-episodic irritability is a descriptive symptom of distruptive mood disregulation disorder [22] In addition, irritability is frequently seen in ADHD and ODD [23]. In this study, in accordance with the literature, ADHD, ODD and CD scores were significantly correlated with irritability.

Previously Stringaris et al. suggested that irritability, measured by ARI, positively correlated with the Strength and Difficulties Questionniare subscale scores (behavioral problems, attention deficit and hyperactivity, social behavior, emotional problems)[24]. In a meta-analysis study, chronic irritability was found to be an important predictor of future diagnosis Oppositional defiant disorder [25].

In the literature, irritability is associated with anxiety disorder, depressive disorder and behavior disorder in children and adolescents[26]–[28]

The levels of irritability in both self-report and parental reporting of adolescents with severe mood disregulation disorder (SMDD) and anxiety disorder were compared with those without psychopathology[29]. The level of irritability reported by the adolescents without psychopathology and their parents was lower than the level of irritability reported by the adolescents diagnosed with anxiety disorder and their parents. Young people with SMDD reported lower levels of irritability in their self-report than their parents. In terms of irritability assessment, there was no difference between adolescents with anxiety disorder and their parents [29].

Similarly, in this study, a significant correlation was found between both parent and child and adolescent anxiety and depression scores, and the levels of irritability reported by the parent and child. It has been shown in previous studies that chronic irritability causes a high level of dysfunction in young people and is an important risk factor for suicide [2], [6], [7], [30].

Considering all these effects, it is thought that clinicians will investigate the effects of irritability on functionality and psychopathology in young people with depression and anxiety disorders in terms of treatment and clinical course. In addition, it is important to investigate the presence of anxiety and depression among adolescents presenting with irritability.

Table 1. Relationship Between Affective Reactivity Index Child Scale and Parent Scale and TEMPS-A

Temperament		*TEMSP-A* Depressive	Cyclothymic	Hyperthymic	Irritable	Anxious
Affective Reactivity Index						
Child Scale	r	0,111	0,111	-0,084	0,098	0,213
	p	0,117	0,115	0,232	0,166	0,002
Parent Scale	r	0,260	0,237	0,033	0,230	0,289
	p	<.001	<.001	0,556	<.001	<.001
Spearman Correlation						

Table 2. Relationship Between Affective Reactivity Index Parent Scale and Child Scale

		Affective Reactivity Index Child Scale
Affective Reactivity Index Parent Scale	r	0,497
	p	<.001

Spearman Correlation

Table 3. The Relationship Between Affective Reactivity Index and Turgay DSM-IV Based Disruptive Behavioral Disorders Screening and Rating Scale

		T-DSM-IV-Ö Attention Deficit	Hyperactivity and İmpulsivity	Total Attention deficit and Hyperactivity-İmpulsivity	Oppositional Defiant Disorder	Conduct Disorder
AFFECTİVE REACTİVİTY INDEX						
CHİLD SCALE	r	0,270	0,304	0,312	0,439	0,334
	p	<.001	<.001	<.001	<.001	<.001
PARENT SCALE	r	0,456	0,529	0,543	0,752	0,499
	p	<.001	<.001	<.001	<.001	<.001
SPEARMAN CORRELATİON						

Table 4. Relationship Between Affective Reactivity Index (ARI) and Revised Child Anxiety and Depression Scale (RCADS)

		Affective Reactivity Index (ARI) Child Scale	Affective Reactivity Index (ARI) Parent Scale
RCADS-Child Depresyon T Score	r	0,322	0,529
	p	<.001	<.001
RCADS- Child Total Anksiyete T Score	r	0,267	0,413
	p	<.001	<.001
RCADS- Child Total Anxiety-Depression T Score	r	0,292	0,458
	p	<.001	<.001
RCADS- Parent Depression T Score	r	0,460	0,460
	p	<.001	<.001
RCADS- Parent Total Anxiety T Score	r	0,464	0,464
	p	<.001	<.001
RCADS- Parent Total Anxiety - Depression T Score	r	0,495	0,495
	p	<.001	<.001
Spearman Correlation			

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[Abstract:0087]

0087 - Clinical and genetic factors predicting the development of psychotic disorders in patients with cannabis or synthetic cannabinoid use disorder

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ABSTRACT

OBJECTIVE: Cannabis is globally the most widely used illicit drug. Recently, synthetic cannabinoids (SCs) represent the largest, most diversified and fastest growing substance group. Cannabinoids can modulate the release of a number of neurotransmitters by activating Cannabinoid Binding 1 Receptors (CB_1Rs). Delta-9-tetrahidrokannabinol (Δ9-THC) is a partial agonist at CB_1Rs. SCs desired and adverse effects are considered to be more intense than those observed with cannabis, which is partly explained by the full agonist activity and higher affinity for CB_1Rs.

The endocannabinoid system plays an important role in the maintenance and modulation of synaptic plasticity in a period of adolescence. During frequent cannabis use, a series of poorly understood neuroplastic changes occur which can lead to the development of dependence. As such, early cannabinoids exposure may increase the risk of psychosis by disrupting the endocannabinoid system and interfere with neurodevelopmental processes.

In some individuals, cannabis or SCs use is associated with immediate psychosis that lasts longer than the period of acute intoxication and warrants clinical intervention. A biologically plausible mechanism whereby exposure to cannabis can increase the risk for a psychotic disorder has not yet been established. The association between cannabis and permanent psychotic disorders may be significantly stronger in individuals with genetic vulnerability than in the general population. The COMT(Val108/158Met) gene is involved in the metabolism of dopamine and is thought to play a role in the pathogenesis of schizophrenia and related disorders. In addition, the COMT(Val108/158Met) polymorphism was found to mediate vulnerability to the effect of Δ9-THC on psychotic symptoms. In one of the first study that drew attention to gene-environment interactions, by Caspi et al. reported the COMT(Val108/158Met) genotype may moderate the risk of psychotic disorder outcomes following exposure to cannabis (1).

The aim of this study was to examine the relationship between the COMT(Val108/158Met) polymorphism and cannabis or SCs use disorder. In this present study, we also aimed to examine the clinical and genetic nature of association between continued cannabis or SCs use and risk of psychosis among the patient group.

METHODS: This cross-sectional study was conducted between December 2017 and June 2018. Data were collected from 150 help-seeking male subjects who met the diagnostic criteria of cannabis or SCs use disorder from the inpatient clinic of Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery and 56 healthy male controls. People were eligible for the study when they were aged between 18 and 65 years and when they met the inclusion and exclusion criteria. Exclusion criteria for inpatients were to be free of any psychotic disorder due to general medical condition or organic mental disorders. Inclusion criteria for healthy controls were to be free of any substance use, psychiatric disorders and family history of psychosis. DNA was isolated from blood and 3 variants of COMT (Val108/158Met) genotype were analyzed by polymerase chain reaction (PCR and/or PCR-RFLP) method. Kolmogorov-Smirnov test was used to examine the distributions of parameters. Student t test and Mann-Whitney U test used to compare of accounts of parameters in multiple groups. Logistic regression analysis was used to determine the independent variables predicting psychotic disorders. $P < 0.05$ was considered statistically significant.

RESULTS: The median age of patients and control groups were 28/18-51 (median/min-max) years and 29/18-53 (median/min-max) years respectively. There was no significant difference in terms of age between two groups. However it was found that patients have significantly lower education level and higher rate of unemployed participants compared to controls (p<0,001). The sociodemographic data of the study groups is in Table 1.

The median age of onset for substance use was 16/10-30 (median/min-max) years and the median duration of substance use was 7/2-30 (median/min-max) years.

57.4% (86) of the participants in the patient group were diagnosed with psychotic disorder in addition to cannabis or SCs use disorder.

The average age of onset for psychotic disorder was 24.2 ± 5.2 (mean ± standart deviation) years and the time between onset of cannabis or SCs use and psychotic disorder was 7,0 ⊠ 4,16 (mean ± standart deviation) years.

There was significant difference between patient with comorbid psychotic disorder and without psychotic disorder when compared in terms of family history of psychosis (p<0,001).

The median numbers of re-hospitalization of patients with and without psychotic disorder were 2/0-26 (median/min-max) and 0/0-10 (median/min-max) respectively. The median duration of hospitalization of patients with and without psychotic disorder were 16/4-210 (median/min-max) days and 11.5/2-34 (median/min-max) days respectively. There was significant difference between two patient groups in terms of re-hospitalization and duration of hospitalization (p<0.001).

The median duration of substance use of patients with and without psychotic disorder were 8/2-30 years (median/min-max) and 7/2-15 (median/min-max) years respectively. There was significant difference between two patient groups in terms of duration of substance use (p<0.039).

The patient and control groups were compared in terms of COMT (Val108/158Met) gene polymorphism in our study. There was significant difference between patient and control groups in terms of COMT (Val108/158Met) gene polymorphism (p<0.042). When patients with and without psychotic disorder compared in terms of COMT (Val108/150Met) polymorphism, there was significant difference between these two patient groups (p<0.001). Results were outlined at Table 2.

The logistic regression analysis was used to determine the predictors of psychotic disorder. Patients with comorbid psychotic disorder (86) and patients without any comorbid psychiatric disorder (50) were included in the logistic regression analysis. The study model was obtained from candidate independent variables by using forward likelihood ratio method. As a result, Val/Met variant of COMT, duration of substance use and family history of psychosis have been found as the strongest predictors of psychotic disorder. Val/Met carriers were 54 times and Met/Met carriers were 5 times more likely to develop psychotic disorder than those with the Val/Val carriers (Table 3).

DISCUSSION: Researches support our findings about the notion that adults diagnosed with a psychotic disorder, having used cannabis is predictive of a poorer prognosis for their psychotic illness, including more frequent psychotic relapses, poorer treatment adherence and increased hospitalization (2).

As a result of a meta-analysis by Myles et al., interval between initiation of regular cannabis use and age at onset of psychotic disorder was 6.3 years, similar to our findings (3). These findings illustrate the importance of providing timely and appropriate treatment and intervention efforts for adolescents who have a substance use disorder because of increasing risk for psychotic disorders.

According to the results of our study, duration of substance use and family history of psychosis were statistically significant in the prediction of psychotic disorder in addition to cannabis or SCs use disorder. There are several case control, epidemiological and experimental laboratory studies supporting the relationship between cannabis use and psychosis. Mcguire et al. reported that morbid risk of psychosis was 10 times higher for the patients with cannabinoid use disorder who have history of schizophrenia in their family (4).

As a result of our study, carrying Val/Met genotype was statistically significant in the both prediction of psychotic disorder and cannabis or SCs use disorder. These findings suggest that susceptibility to both cannabinoid use disorder and psychotic disorder may be higher in the individuals with carrying Val/Met genotype. Baransel et al. reported a significant association between COMT(Val158Met) polymorphism and susceptibility to cannabis dependence. There was a significant difference in genotype frequencies between patients with cannabis use disorder and controls, including the distribution of Val/Val and Val/Met genotype variants (5).

Although, Caspi et al. reported that adolescent-onset cannabinoid use was associated with increased risk of schizophreniform disorder in adulthood among Val/Val carriers and to a lesser extent among Val/Met carriers, but not among Met/Met carriers (1).

When the literature is reviewed, existence of diverse results related to COMT(Val108/158Met) polymorphism may be due to the confounding effect of genetic variations of various neurotransmitters and enzymes responsible for the development of the mesolimbic dopaminergic system other than COMT. Furthermore, one possible interpretation of this is that the research samples include different ethnic groups. Genetic variations between ethnic groups based on geography may lead to these different study results.

There are several limitataions in our study. The data is collected from a single clinic retrospectively and the patients have had prodromal psychotic symptoms could not be excluded before the onset of cannabis or SCs use in the cross-sectional design of our study. Furthermore, it is impossible to determine the exclusive effect of SCs on the causal relationship between COMT(Val108/158Met) polymorphism and psychosis because of the mixed use of cannabis and SCs in this study sample. This can be stated as another limitations in generalizing the results.

As far as we know, this is the first study that evaluates the relation of COMT(Val108/158Met) and cannabis and SCs use in subjects with psychotic disorder in Turkish population. Further larger scale studies are required to elucidate relationship between COMT variations and SCs use with psychosis.

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TABLE 1: SOCIODEMOGRAPHIC DATA OF THE STUDY GROUPS

		Patient group (n=150)		Control Group (n=56)			
		n	%	n	%	x^2	P
EMPLOYMENT STATUS	Student	3	2,0	18	32,1	87,346	**<0,001[1]**
	Working	32	21,3	29	51,8		
	Retired	0	0	3	5,4		
	Unemployed	115	76,7	6	10,7		
		Median Min – Max		Median Min – Max		Z	P
AGE		28 18 – 51		29 18 – 53		-0,598	**0,550[2]**
YEARS OF EDUCATION		**8 5 – 16**		**16 1 – 16**		**-7,743**	**<0,001[2]**

TABLE 2: COMPARISON OF PATIENT AND CONTROL GROUPS IN TERMS OF COMT (VAL108/158MET) POLYMORPHISM

	n	%	N	%	x^2	P
	Patient group (n = 150)		Control group (n= 56)			
VAL/VAL	36	24,0	22	39,3	6,340	**0,042[1]**
VAL/MET	78	52,0	19	33,9		
MET/MET	36	24,0	15	26,8		
	Patients with psychotic disorder (n = 86)		Patients without psychotic disorder (n=50)			
VAL/VAL	7	8,1	21	42,0	32,653	**<0,001[1]**
VAL/MET	63	73,3	13	26,0		
MET/MET	16	18,6	16	32.0		

[1]CHİ-SQUARE TEST WAS USED.

Table 3: Variables predicting psychotic disorder: Univariate and Multivariate Logistic Regression Analysis[1]

Variable	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	Odds Ratio	95 % CI	p	Odds Ratio	95 % CI	p
Age	1,041	0,987 – 1,099	0,136			
Employment Status						
Working	Reference					
Unemployed	1,143	0,866 – 1,509	0,346			
COMT Polymorphism						
Val/Val	Reference			Reference		
Val/Met	14,538	5,122 – 41,263	<0,001	54,225	10,184 – 289,053	<0,001
Met/Met	3,000	0,998 – 9,020	0,051	5,163	0,994 – 26,815	0,051
Family History						
Other	Reference					
Psychosis	22,424	2,940 – 171,003	0,003	40,088	4,452 – 360,957	0,001
First initiating substance						
Cannabinoid	Reference					
SCs	0,949	0,378 – 2,380	0,911			
Volatile substances	0,854	0,226 – 3,222	0,816			
Age of onset of substance use						
16 years and over	Reference					
15 years and under	1,383	0,565 – 2,917	0,395			
Duration of substance use	1,130	1,028 – 1,242	0,011	1,266	1,070 – 1,499	0,006
Primary substance used in last year						
Cannabinoid	Reference					
SCs	2,257	0,719 – 7,087	0,163			
Polysubstance	1,057	0,335 – 3,338	0,924			
Frequency of cannabis use						
Never	Reference			Reference		
Rare	0,818	0,182 – 3,680	0,794	0,267	0,024 – 2,912	0,279
Occasionally	1,309	0,460 – 3,723	0,614	2,093	0,386 – 11,354	0,392
Frequent	0,351	0,138 – 0,891	0,028	0,186	0,045 – 0,770	0,020
Frequency of SCs use						
Never	Reference					
Rare	2,444	0,473 – 12,629	0,286			
Occasionally	6,519	1,432 – 29,669	0,015			
Frequent	2,037	0,764 – 5,433	0,155			
Frequency of polysubstance use						
Never	Reference					
Rare	1,088	0,095 – 12,479	0,946			
Occasionally	0,293	0,113 – 0,764	0,012			
Frequent	0,821	0,333 – 2,022	0,668			

[1]Regression analysis was performed in a sample of 136 patient; 86 patients with additional psychotic disorder and 50 patients without psychotic disorder.

[Abstract:0136]

0136 - The course of bipolar affective disorder and related factors in a university clinic, 30-year retrospective study

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ABSTRACT

OBJECTIVE: Bipolar affective disorder (BAD) is a serious, often chronic and recurrent disorder. It negatively affects the lives of the patients and their caregivers and causes disability due to reasons such as impaired social and professional functionality, high risk of suicide, and frequent recurrence [1]. The long-term course of BAB is extremely destructive if not treated. Each episode increases the risk of recurrence and worsens the course. Treatment of bipolar disorder conventionally focuses on acute stabilisation and on maintenance. The goals of acute stabilisation are to bring a patient with mania or depression to a symptomatic recovery with euthymic mood, to control risky behaviors, to ensure the safety of the patient and to relief symptoms. The goals of maintenance treatment are relapse prevention, reduction of subthreshold symptoms and enhance social and occupational functioning [2]. Commonly used medications for treatment of bipolar disorder are mood stabilisers including lithium and anticonvulsants (valproate, carbamazepine, lamotrigine). First generation antipsychotics , second generation antipsychotics and benzodiazepines are used for acute stabilisation [3]. The mood stabilizer lithium has been the standard pharmacological treatment for individuals with bipolar disorder and it remains an agent of first choice in the preventative treatment of bipolar disorder. Valproate can be used in mixed mania, late-onset mania and mania accompanied by organic diseases. Pharmacological treatment of bipolar depression is a complex and controversial issue. Lithium is usually the first option in the treatment of bipolar depression. Lamotrigine has been reported to be a promising agent in the treatment of bipolar depression. In depression with marked suicidality or severe psychosis, ECT should be considered first option in the treatment. It is inadvisable to use antidepressants without mood stabilizers in bipolar depression. Over time, there have been changes in the treatment trends in the direction of new generation drugs in the treatment of BAD [4-5]. This situation may also cause changes in the clinical features associated with the disorder.

In our study, we aimed to investigate the sociodemographic and clinical features of the BAB and changes in the treatment strategies in the long-term course of the disease, by examining the files of patients who were hospitalized in the psychiatry clinic of Atatürk University Medical Faculty between 1985 and 2015.

METHODS: In order to perform the study, files of 1267 patients who were treated with the diagnosis of BAD in the inpatient psychiatry clinic of Atatürk University Medical Faculty between 1985 and 2015 were analyzed retrospectively.

Data were presented as mean, standard deviation, median, minimum, maximum, percentage and number. The normal distribution of continuous variables was analyzed by Shapiro Wilk test. In the comparison between the two groups, the Independent Samples T test was used when the normal distribution condition was satisfied, and Mann Whitney U test was used when the condition was not provided. In the comparison of continuous variables with more than two groups, ANOVA test was used in case of normal distribution condition and Kruskal Wallis test was used in case of not providing. The comparison between the categorical variables was made using the Chi-square test and Fisher's Exact test. Pearson's correlation test was used for normal distribution and Spearman's correlation test was used for comparison of two continuous variables. IBM SPSS 20 version was used for statistical analysis. Statistical significance level was taken as $p < 0.05$.

RESULTS: Sample characteristics and general results: We identified 1267 patients' files diagnosed with bipolar disorder during the study period. 528 (41%) of the examined files were female and 739 (58%) were male. The mean age of onset of the disorder was 24.18 ± 8.9 years. The most common comorbid psychiatric disorders were personality disorders. The most common concomitant medical disease was hypothyroidism. Manic episode is most often triggered by nonadherence to treatment and lack of treatment efficiency was the most important factor in triggering a new depressive episode. Psychotic manifestations were present in 62.4% of the episodes. Suicide attempts were present in 5.8% of the disorder episodes and mostly seen in manic and depressive periods. The most common suicide methods were drug poisoning and jumping from heights (Table 1). The rate of suicide attempt was significantly lower in patients treated with atypical antipsychotics and lithium and higher in patients with comorbid personality disorder and female patients.

Overall trends in treatment pattern: During the observation period between 1985 and 2015 there was any significant change in the proportion of patients treated with Mood stabilizer (lithium and anticonvulsants). The proportion of patients treated with lithium decreased significantly from 93.1% between 1985-1995 to 53.5% between 2005-2015 and carbamazepine decreased singificantly from 6,9% to 3,0%. The proportion of patients using valproate increased significantly from 0,0% between 1985-1995 to 44.2% between 2005-2015. There was an increase in the proportion of patients treated with lamotrigine but it was not significant (Figure 1). The proportion of patients treated with typical antipsychotics decreased significantly from 92% between 1985-1995 to 9.7% between 2005-2015 and the proportion treated with combined antipsychotic decreased significantly from 46.1% between 1985-1995 to 5.1% between 2005-2015 (Figure 2). The most commonly used typical antipsychotics used for bipolar disorder in study period were haloperidol (33.9%) and chlorpromazine (18.6%). The proportion of patients treated with atypical antipsychotics and long-acting antipsychotic increased significantly (respectively from 0% between 1985-1995 to 91.4% between 2005-2015 and from 0.5% between 1985-1995 to 6.4% between 2005-2015).The most popular atypical antipsychotics were olanzapine (26.2%), risperidone (17.8%) and quetiapine (14.1%). The proportion of patients treated with antidepressant decreased from 13.8% between 1985-1995 to 5% between 2005-2015. Between 1985-1995, noradrenaline specific serotonergic antidepressants (30.8%), and tricyclic antidepressants (23.1%) were used more frequently. Between 2005-2015, the most preferred antidepressant classes were SSRI (56.7%) and SNRI (13.3%).

DISCUSSION: We observed marked changes in the psychopharmacological treatment of bipolar disorder in the period from 1985 to 2015 for inpatients. Most importantly, a larger proportion of patients received treatment with valproate and atypical antipsychotics, while fewer patients received treatment with lithium and typical antipsychotics in the last decade of study period. Supporting this situation, Carney and Goodwin reported that lithium use decreased in North America, but this decrease was due to physician ideas rather than scientific evidence. According to the literature, it has been reported as a repeated result in studies that the use of typical antipsychotic decreases in the treatment of bipolar disorder, while the use of atypical antipsychotic increases. The use of atypical antipsychotics in bipolar disorder increased substantially, probably due to less extrapyramidal side effects of these agents, which often lead to more compliance. Another reason may be that some atypical antipsychotics have mood stabilizing properties. Adherence to pharmacological treatment is crucial for effective control of depressive and manic symptoms and essential for patients with bipolar disorder to respond satisfactorily to the treatment. However, adherence to pharmacotherapy is often poor in chronic psychiatric illnesses, including bipolar disorder. Nonadherence increases the risk of relapse and suicide as well as risk of rehospitalization. Long-acting injectable antipsychotics are considered to possess several benefits compared with oral antipsychotics including predictable medication adherence. All these causes may have led to increased use of long-acting injectable antipsychotics in the treatment of bipolar disorder. Antidepressants have been used in 50% of patients with bipolar depression, despite concerns about limited efficacy and potential to induce mania. Similar to the literature the rate of antidepressant use in bipolar depression was 58.5% in our study during the entire study period. In some studies investigating the treatment trend in bipolar disorder, it is seen that the proportion of patients treated with antidepressants increased or not changed over time. As mentioned before the proportion of patients treated with antidepressant decreased from 13.8% between 1985-1995 to 5% between 2005-2015 in our study. Recent evidence suggests that antidepressants, particularly if used as monotherapy, may have mood destabilizing properties and trigger manic episodes. These evidences may be the main reason for decreasing use of antidepressants. Between 1985-1995, noradrenaline specific serotonergic antidepressants (30,8%), and tricyclic antidepressants (23,1%) were used more frequently. Between 2005-2015, the most preferred antidepressant classes were SSRI (56,7%) and SNRI (13,3%). It has been reported that the risk of manic shift is higher with tricyclic antidepressants and to use a selective serotonin reuptake inhibitor may be prudent. It has been reported that the risk of manic switch is higher with SNRIs such as venlafaxine. Thus SNRIs may be used less than SSRIs.

CONCLUSIONS: Our findings suggest a number of important trends in the psychopharmacological treatment of bipolar disorder. Investigating possible changes in factors affecting the course of the disorder over a period of 30 years can be useful in understanding BAD. A number of questions remain unanswered about the long-term management of bipolar disorder. Because bipolar disorder is heterogeneous, there is unlikely to be one ideal treatment for all patients with bipolar disorder. Further studies with long follow-up times are necessary to clarify the benefits and risks of different psychotropic medications, especially antipsychotics.

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Table 1. Methods of suicide

		METHODS OF SUICIDE				
		Drug intoxication	Jumping from a height	Hanging	Cutting or piercing	Firearms
SUICIDAL ATTEMPTS (N)	n	36	24	4	14	1
SUICIDAL ATTEMPTS (%)	%	49,3	32,9	5,5	19,2	1,4
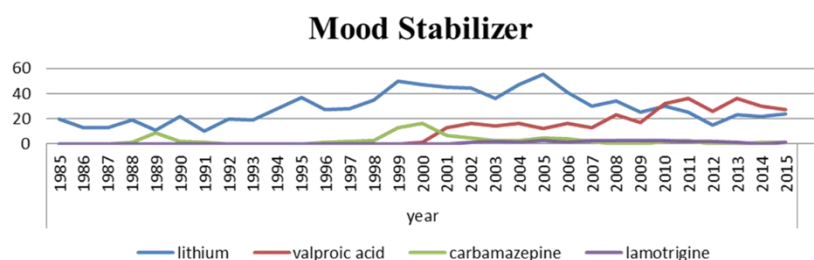
Figüre 1.
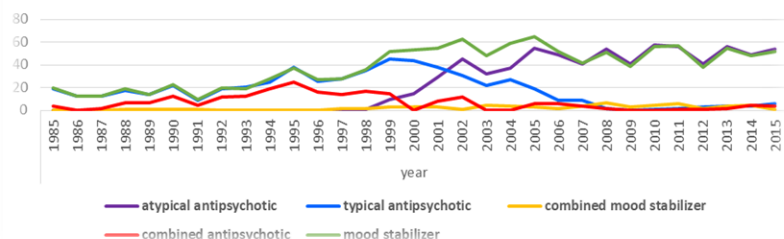
Figüre 2.

[Abstract:0148]

0148 - Evaluation of inflammatory cytokines and response to treatment in drug-naive-female patients with obsessive-compulsive disorder

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ABSTRACT

OBJECTIVE: Obsessive-compulsive disorder (OCD) is a chronic disease that affects approximately 2% of the population and has serious negative effects on the individual's social and professional functioning. Although the etiopathogenesis of OCD is still not fully understood, there are strong hypotheses that the immune system and cytokines play a role in the development and triggering of OCD [1].

It has been suggested that OCD and autoimmunity might share common immune responses regarding the certain type of childhood-onset OCD which is directly linked with immune processes after streptococcal infection. Therefore, it would be important to evaluate the levels of Th17/T reg derived cytokines from the autoimmune axis. Despite the strong inflammatory hypothesis in the etiology of OCD, in the literature, the studies have shown contradictory results [1]. Additionally, no follow-up studies have been conducted to evaluate treatment effect on the levels of cytokines.

The aim of our study was to compare the level of cytokines in patients with OCD than healthy controls and to investigate the changes in the level of cytokines after treatment and relationship with clinical severity in patients with OCD. Specifically, we measured (a) the levels of IL-1 beta (IL-1β), IL-6, IL-17A which are proinflammatory cytokines and the levels of IL-10, TGF-beta (TGF- β) which are anti-inflammatory cytokines in patients with OCD at the baseline, after 4 weeks treatment and 8-week treatment and compared with the healthy controls (b) the relationship between the cytokine response and clinical symptom severity after treatment in patients with OCD. Accumulating evidence suggested that inflammatory responses can be affected by confounder variables such as age, gender and body mass index (BMI). Hence, we conducted our research with only female patients and matched healthy controls regarding to age and BMI.

METHODS: This study was conducted with 22 drug-naive-female patients who were diagnosed with OCD according to DSM-V criteria and 20 healthy controls (HC) in Bezmialem Vakif University Hospital.

We excluded the patients and HC from study based on having stroke and head trauma in the last 6 months, low mental capacity, learning disabilities, neurodegenaritive diseases, active infection or allergy, a history of seizure, alcohol and psychoactive substance use, autoimmune diseases. The participants who were using anti-inflammatory agents (including nonsteroidal and steroidal), antidepressants and antipsychotics within last 6 months excluded from to the study. Additionally, the exclusion criteria for the HC were a personal and family history of having schizophrenia, bipolar disorder, severe major depressive episode and OCD.

Inclusion criteria for the patient group and HC were determined as follows: To be diagnosed with OCD according to DSM-V criteria, to be between 18-65 years of age, to have willingness to participitate the study and to understand clinical guidelines.

All participitants evaluated through the use of the Yale brown obsessive compulsive scale (Y-BOCS), Beck Depression (BD) and Beck Anxiety (BA) scales. These scales were administered to the patients three times before starting to use the drug, 4 and 8 weeks following the drug use. In this way, the disease severity and follow-up processes of the patients were evaluated.

We collected serum samples for the 3-time point (baseline, after 4 weeks, after 8 weeks) in the OCD group to investigate the efect of the treatment. Blood samples were taken into dry tubes during the diagnosis and follow-up processes, precipitated by centrifugation at 4500 rpm for 5 minutes, plasma collected and kept at -80 degrees Celsius. Levels of cytokines TGF-β were measured by using ELISA kit; IL1β, IL-6, IL-10, IL-17A were measured by using Luminex Human Magnetic Assay Kit.SPSS 22 for Macintosh program was used for statistical analysis. All data are expressed as mean±standart deviation, while numerical data are expressed as percentages. Kolmogorov-Smirnov test was used to determine whether the obtained data show normal distribution. Descriptive statistics were calculated by Chi-square tests for categorical variables and t-test for continous variables. Comparisons of normally distributed numerical variables between two independent groups were performed using t-test,while non-normally distributed variables were compared using the Mann-Whitney U test. Kruskall-Wallis test was used to compare for

clinical test between 3 timepoints(baseline, after4 weeks, after 8 weeks) and post-hoc analysis was made by Friedman test. A paired t-test was run on a sample of 22 patients with OCD to determine wheter there was a statistically significant mean difference of cytokine levels between 3 timepoints. Spearman correlation analyses were performed in order to test between clinical findings (Y-BOCS, BD, BA. scores) and cytokine levels. Statistical analyzes were evaluated according to 5% significance level.

RESULTS: Our study group consisted of 22 drug naive female OCD patients and 20 female healthy controls aged between 18-65 years. The mean age of the 22 OCD patients included in the study was 39.05 ± 12.90 years. The mean age of the control group was 39.05 ± 10.23 years. The mean BMI of the OCD group was 25.56 ± 4.82 and the mean BMI of the control group was 24.84 ± 4.22. 27.27% (n = 6) of the patients and 30% (n = 6) of the control group were smoking.

All participitants evaluated through the use of the Y-BOCS, BD and BA scales. When the YBOCS, BD and BA scores of the drug-naïve patient and HC were compared, a statistically significant difference was found ($p<0,001$). When the scales of the patients without medication and at the 4th and 8th weeks following the drug use are compared, their clinical improvements are clearly seen (Friedman $p<0,001$). Compared with HC, the levels of IL-6 were higher (P = 0.016) and the levels of TGF-β were lower (P = 0.005) in drug-naive patients with OCD (Figure 1). In the paired test analysis, YBOCS were decreased (P <0.001) and the level of IL-10 (P = 0.042) and TGF-β (P = 0.033) were higher after 8-week treatment in the patients with OCD (Figure 2). IL-10 also correlated with the last YBOC score (Rho= -494, P= 0.19) after 8 weeks of treatment and TGF-β correlated with baseline BA score after 4 weeks treatment (Rho= .614, P= 0.002) and 8-week treatment (Rho= .484, P= 0.022). In our study, no significant difference was found between IL-1β, IL-10, IL-17A levels of patients and healthy controls.

DISCUSSION: The primary finding of our study were that patients with OCD had increased levels of IL-6 and decreased levels of TGF-β at the baseline compared with HC. Importantly, we found the increased levels of IL-10 and TGF-β after 8 weeks treatment and increased levels of IL-10 were correlated with the last YBOCS score.

Our results might support hypothesis that there is an increased proinflammatory response as well as a decreased anti-inflammatory response in OCD patients. Similar to our study, there are studies that found IL-6 levels higher in OCD patients compared to healthy controls [2,3]. In contrast to our research, some previous studies have reported lower IL-6 levels in OCD patients than in healthy controls [4]. There are still studies in which there is no significant difference in IL-6 levels in OCD patients [1].

Only one study has examined the levels of TGF-β and found no difference compared to the healthy controls [5]. In the literature, the increased level of IL-17A and no significant difference in the levels of IL-17A were found in OCD patients compared to the control group [1,5]. The level of IL-17A/ TGF-β was held accountable as a main immune axis underlying in autoimmune disorders via Th17 and regulatory T cell responses.

In the literature, few studies have investigated anti-inflammatory cytokines in OCD patients. In our study, no significant difference was found between IL-10 levels of patients and healthy controls. Similar to our study, the Denys et al. study found no significant difference between IL-10 levels of the patient and control groups. [1]. On the other hand, Rao et al. examined IL-10 levels in naïve OCD patients and healthy controls and found IL-10 levels higher in OCD patients than healthy controls [3]. To our knowledge, our study is the first follow-up study of OCD and cytokines. IL-10 and TGF- β levels of our patients increased after 8 weeks of treatment. There are few studies in the literature exploring the relationship between anti-inflammatory cytokines and OCD. In addition, IL-10 levels correlated with the YBOCS scores of our patients. The clinical improvement observed in OCD patients after treatment was also might be indicated in biochemical values points out that antidepressant drugs may have anti-inflammatory effect in patients with OCD. The contradiction of the studies in the literature makes the generalization of results difficult. The heterogeneity of the patient group (child, adolescent or adult), no age-gender and BMI matched patients and control groups, the story of anti-inflammatory drug treatment or having autoimmune and neuropsychiatric disorders, which may affect cytokine parameters can cause the discrepancies of the results. Therefore, we studied with only drug-naïve female patients and age, BMI matched healthy controls and excluded having following-up autoimmune and neurodegenerative disorders. Our study showed an increased proinflammatory response, and a decreased anti-inflammatory response in OCD patients. It also suggests that treatment might cause a high level of anti-inflammatory immune response in OCD patients. Further follow-up studies need to investigate with the large sample sizes.

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[Abstract:0299]

0299 - Comparing the structural brains changes in the schizophrena patients with and without the deficit syndrome: a five-year follow-up study

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ABSTRACT

OBJECTIVE: Schizophrenia is a psychiatric disorder which effects 1% of the population and results in a significant loss of functionality. The symptoms start at early ages and its chronic course increases economic and social burden. While the chronic disability primarily results from negative and cognitive symptoms, acute exacerbations of positive symptoms such as delusions and hallucinations lead to significant morbidity. Many researchers, including Crow et al. stated the importance of negative symptoms on the functionality of the patients. Furthermore, they showed evidence that patients with primary negative symptoms might have alterations in their brain structures different from other schizophrenia patients. In 1988, Carpenter et al. defined a group comprising permanent, primary and negative symptoms, and named as deficit syndrome of schizophrenia. In 2009, Galderisi et al. proposed that deficit schizophrenia is a different illness than non-deficit schizophrenia based on the fact that these two groups show some differences in terms of the factors used to distinguish between the illnesses. Despite the extensive studies, the diagnostic accuracy and certainty of the deficit syndrome of schizophrenia and its pathophysiology is yet to be fully known. It has been long shown that schizophrenia patients altered brain structures. However, the heterogenous findings of structural studies suggest that possible subgroups of schizophrenia might present. To clarify the trajectories of schizophrenia brain structures, we designed the current study. This study aims to find out the structural changes in the brains of the patients who have and who do not have the deficit syndrome in their long-term observation (5 years), and aims to evaluate if the gray matter changes in the patients who have the deficit syndrome is more than in the patients who do not have the deficit syndrome, and its relations to the clinical differences.

METHODS: Thirty-nine of forty-five schizophrenia patients who had previous structural brain MR scan 5 years ago accepted to involve in the current study. One of the researcher give a detailed explanation to patients and their families. Only those who gave their written consent was included in further steps of the study. In addition to psychiatric examination, we evaluated the patients via Structured Clinical Interview for DSM IV (SCID-I), Positive and Negative Symptoms Scale (PANSS), Negative Symptoms Assessment Scale (SANS), The Schedule for The Deficit Syndrome (SDS), Brief Negative Symptoms Scale (BNSS), Calgary Depression Scale (CDRS), Extrapyramidal Symptoms Assessment Scale (ESRS) for evaluate symptom severity. Subsequently MR images were obtained by using 3 Tesla MR devices and images obtained with 3D T1 weighted MP-RAGE sequences have been used for the region of interest analysis. Volumes of brain subsections have been measured with FreeSurfer software package. Scale scores and the illness features of the participants have been calculated separately in baseline and current scans. Baseline and current scores have been compared by Mann Whitney U test, and nominal data have been calculated by Chi square test to check if they have a meaningful difference in them. Wilcoxon signed rank test has been used to determine if there was a difference between the basal and current scores of scale points and illness features of the participants in the groups. Volumes of the parts of the brain have been measured for the right and left hemispheres in the basal and current years for each group, and after calculating TIV average, effect of the factors such as age, gender and TIV which may have an effect on the volumes of brain parts has been evaluated using Multiple Linear Regression Analysis-Repeated Measures ANOVA. Post-hoc analysis has been carried out for the parts which show differences to determine which factors cause the difference. Spearmen correlation test has been applied including independent variables for the factors in which there is a meaningful difference.

RESULTS: During the recruitment, six patients (5 DS, 1 ND) did not accept the second scan. Five of A final 13 DS and 26 NDS were included in the study. There was no difference among the groups the parameters of age, gender, education, employment status, marital status, duration of the disorder, familial clustering, current antipsychotic doses (chlorpromazine equivalents, mg/d), PANSS positive subscale, PANSS general psychopathology subscale (basal), ESRS (basal), and Calgary Depression Scale. As expected, in the group with the deficit syndrome, the scores of the basal and current PANSS negative subscale, SANS and BNSS scale were higher compared to the group without the deficit syndrome (p<0,001). While the extrapyramidal symptom scale scores of the patients in DS group was high, their affective symptom (depression) scores were lower. Compared to those of ND group, DS group had larger GM volume while smaller WM volume, despite neither of them were significant (z=-1,71 p=0,09; z=-1,9 p=0,06; respectively). We observed that LV volume showed a significant interaction and only those of DS showed increased in volume. (respectively average difference =-1360,84 p=0,01; average difference=-1400,9 p=0,01). In addition, it is found out that there is a negative correlation between the current volumes of the left lateral ventricle in the group with the deficit syndrome and PANNS negative subscale score (kk=-,84 p=0,001) and that this negative correlation with the SANS scores tend to be meaningful (kk=-,6 0=0,06). It was also found out that the tendency towards decreasing by years in the volume of right hemisphere caudate area and the increase by years in the left lateral orbitofrontal cortex was tended to be statistically meaningful (respectively F(1)=3,44 p=0,07; (F(1)=3,7 p=0,06)).

DISCUSSION: Our findings showed that in patients with DS, where negative symptoms were prominent during the 5-year follow-up, had more enlargement in lateral ventricular volumes compared to ND patients. This finding of our study supported the finding that "structural changes and especially LV width is clear in patient groups where negative symptoms are predominant". Greater enlargement of LV in DS might reflect tissue loss in the brain, which echoes severe negative symptoms in clinical presentation. On the other hand, negative symptoms of the patients were present in the baseline, and LV enlargement became more prominent in the follow-up. Thus, the ongoing changes in the brain of DS might be present before the LV enlargement becomes severe. We propose that larger LV might not be the reason for negative symptoms but the

result of the pathophysiology of DS and associated with negative symptoms. There is a need for further multicentral research which includes the healthy controls, which has a wider sample and which has longer observation period to obtain more accurate information and to explain cause effect relationship.

KEYWORDS: Schizophrenia, Deficit Syndrome, Lateral Ventricle, Gray Matter, Magnetic Resonance Imaging

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Table 1: Clinical and Demographic Characteristics of Deficit and Nondeficit Schizophrenic Patients			
		DEFICIT SYNDROME (n=13)	NONDEFICIT SYNDROME (n=26)	
Gender	Female	3 (%23,1)	6 (%23,1)	χ^2= ,0, df=1 p=1
	Male	10 (%76,9)	20 (%76,9)	
Age	Basal (2014)	32,08±7,61	34,08±6,94	z=0,9 u=197 p=0,4
	Current (2019)	37,08±7,61	39,08±6,94	
Education(years)		11±3,15	10,7±3	z=-0,4 u=156 p=0,7
Marital status	Married	1 (%7,7)	6 (%23,1)	χ^2= 5,3, df=2 p=0,07
	Single	11 (%84,6)	20 (%76,9)	
	Divorced	1 (%7,7)	0	
Employment status	Unemployed	5 (%38,5)	8 (%30,8)	χ^2= 0,6, df=2 p=0,7
	Employed	4 (%30,8)	11 (%42,3)	
	Retired	4 (%30,8)	7 (%26,9)	

Table 2: Comparison of the participants' basal and current scale scores between the groups by year				
		DEFICIT SYNDROME (n=13) mean±sd	**NONDEFICIT SYNDROME (n=26) mean±sd**	
PANSS				
Positive	**Basal (2014)**	13,1±6,34	10,84±5,63	z=-1,3 u=121 p=0,21
	Current (2019)	14±7,22	11,6±6,06	z=-4,8 u=110 p=0,52
	Basal (2014)	26,08±6	16,6±6,11	z=-0,4 u=46 **p<0,001**
	Current (2019)	27,33±4	16,8±3,7	z=-4,8 u=3 **p<0,001**
Negative	**Basal (2014)**	30,54±4,4	28,04±4,6	z=-1,5 u=115 p=0,15
	Current (2019)	33,8±5	28,4±7,5	z=-2,4 u=7 **p=0,02**
General psychopathology				
SANS	**Basal (2014)**	60,15±14,34	31,92±19,7	z=-3,71 u=42 **p<0,001**
	Current (2019)	61,83±14,6	30,2±10,64	z=-4,62 u=7,5 **p<0,001**
ESRS	**Basal (2014)**	6,8±5,5	4,17±5,24	z=-1,52 u=108 p=0,13
	Current (2019)	11,83±4,42	5,9±3,71	z=-3,5 u=41 **p<0,001**
Calgary Depression Scale	**Basal (2014)**	2,31±3,7	2,04±3,3	z=-0,4 u=144 p=0,71
	Current (2019)	2,33±2,74	2,12±3,11	z=-0,6 u=134 p=0,62
BNSS	**Basal (2014)**	50,6±13,34	24,4±16,13	z=-3,5 u=32 **p<0,001**
	Current (2019)	48,3±12,3	21,24±10,2	z=-4,6 u=8,5 **p<0,001**

Table 4: Right and left lateral ventricle post-hoc analysis					
Group	Basal	Current	Average Difference (Basal-Current)	Standard error	P
Right lateral ventricle					
DS	1	2	-1360,84*	500,51	0,01
	2	1	1360,84*	500,51	0,01
NDS	1	2	-100	850,4	0,71
	2	1	100	850,4	0,71
Left lateral ventricle					
DS	1	2	-1400,9*	542,5	0,01
	2	1	1400,9*	542,5	0,01
NDS	1	2	-129,62	382,3	0,74
	2	1	129,62	382,3	0,74

Table 3: Comparison of the right and left hemisphere lateral ventricle volumes among the groups by years							
Right Hemisphere							
Regions		**DS**	**NDS**	**Comparisons**			
		mean±sd	mean±sd	**F**	**df**	**p**	**η2**
Lateral ventricle	**2014**	9372,7±5198,3	9197,3±3928,2	4,2	1	**0,05**	0,11
	2019	10589,7±6681,4	9370,1±4300,6				
Left Hemisphere							
Regions				**F**	**df**	**p**	**η2**
Lateral ventricle	**2014**	11338,5±6746,8	10638,5±4837,2	3,64	1	**0,07**	0,09
	2019	12568,3±8731,2	10853,6±5059,1				

Sağ Lateral Ventrikül Hacim Değişimi Grafiği

Covariates appearing in the model are evaluated at the following values: Yaş = 38,41, Cinsiyet = 1,23, lheTIV_2014 = 1540228,5185842
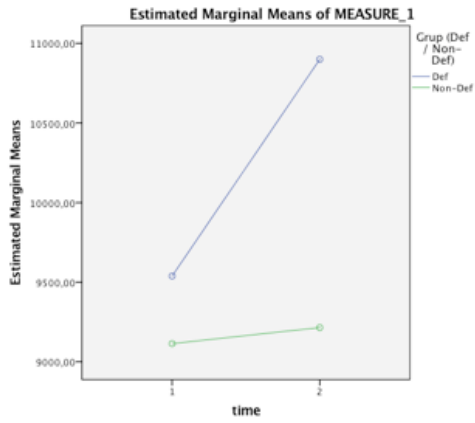
Sol Lateral Ventrikül Hacim Değişim Grafiği

Covariates appearing in the model are evaluated at the following values: Cinsiyet = 1,23, Yaş = 38,41, lheTIV_2014 = 1540228,5185842
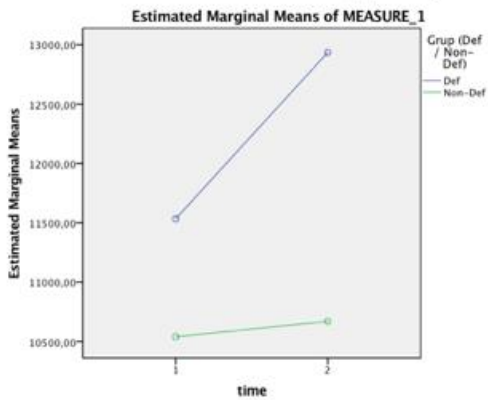
[Abstract:0369]

0369 - Effects of metformin on learning and memory functions of young and aged rats

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BRIEF REPORT

OBJECTIVE: Aging is a multifactorial and progressive phenomenon, exclusively leading to loss of cellular, molecular and physiological functionality. It is well established that overproduction of free radicals such as reactive oxygen species (ROS) leads to oxidative stress which results in senescence and aging-related disorders. Moreover, the brain neurons are more susceptible to oxidative stress due to the presence of high lipid content and higher oxygen consumption.

The aim of this study was to investigate the effects of Metformin (Met), an antidiabetic biguanide, on learning and memory functions of young and aged rats using different behavioral tasks and combining with the PCR gene expression method as well as additional histological evidence, we were able to achieve a very unique result.

METHODS: Wistar-Albino male rats were separated into four groups: young mice (<12months-old), young mice +metformin, aged mice (24 months old), aged mice+ metformin. Metformin (100mg/kg) was supplemented into drinking water for 8 weeks. Morris water maze (MWM) and passive avoidance (PA) tests were used to determine learning and memory functions. Locomotor activity (locomotor activity cabinet system) was measured with a computerized system.

Locomotor activity test

Because old age and compounds altering locomotor activity may give false-positive/negative effects in behavioral tests, an additional test was carried out with the specific aim of monitoring motor activity. The spontaneous locomotor activity of the animals was assessed by monitoring their activity in a locomotor activity cage. Locomotor activity was measured with a computerized system (40×40×35 cm box; May Commat, Ankara, Turkey). Total number of movements was measured for a 5-min period before the behavioral tests and is expressed as the sum of stereotypic, ambulatory, and vertical activity. In this study, the 24-month-old naturally aged rats were chosen, which do not have impaired locomotor activity or any neurological deficit, in order avoid false-positive/negative effects in behavioral tests.

Passive avoidance test

In this type of avoidance learning test, the animals were refraining from making measured response. A step-down variant passive avoidance apparatus was used (Ugo Basile model 7551, Italy). The apparatus (measuring 22×21×22 cm) consisted of 2 compartments: a light and dark compartment separated by a guillotine door. On Day 1 (training trial), the rats were placed individually into light compartment and allowed to explore the boxes to become aware of environment.
1. Pre-acquisition trial: After 30 s, the door between the 2 boxes was opened, and animal moved into dark compartment freely.
2. The acquisition (training) trial was conducted 15 min after pre-acquisition trial. Rats were placed in light compartment, after 30-s adaptation period, door between the compartments were opened. Having completely entered dark compartment, door was automatically closed, and an electric foot-shock (0.5 mA) of 3-s duration was delivered to animal via grid floor. The time taken to reenter dark compartment was recorded (training latency). Any animal failing to cross from the light to dark compartment within 300 s was discarded from the experiment. Animals were then removed from dark compartment and returned to their home cages. Between each training session, both chamber compartments were cleaned to remove any confounding olfactory cues.
3. Retention trial: Recall of inhibitory stimulus was evaluated at 24-h post-training by returning animals to light compartment and recording their latency to enter dark compartment (4 paws in). No foot-shock was applied in this trial. If animal did not enter dark compartment within 300-s, it was returned to its cage and a maximum latency of 300-s was recorded. This latency served as a measure of retention performance of step-down avoidance responses (retention latency).

Morris water maze test

The Morris water maze consisted of a circular pool (150-cm diameter) was filled with water (25°C) and rendered opaque by addition of small white pieces of plastic. The pool was located in a dimly lit and soundproof test room with a camera and the experimenter. The maze was divided into 4 quadrants. Three equally-spaced points around the edge of pool were used as release positions. Order of release positions was varied systematically throughout the experiment. An escape platform (6-cm in diameter and 12-cm high) was located in 1 quadrant, 1 cm above water surface during familiarization session and 1 cm below water surface during other sessions. Video tracking was conducted with a video camera (Sony Dcr-Hc40e) focused on full diameter of pool. The rats were trained in Morris water maze during 5 daily sessions (familiarization session, S1, S2, S3, and S4). The 5 sessions were performed on consecutive days between 9:00 and 12:00. During acquisition phase of experiments, each rat participated in 3 trials per day. For each daily trial, the rat was taken from home cage and placed into the water maze at 1 of 3 randomly

determined locations with its head facing the center of water maze. A trial was started when rat was released from 1 of 3 randomly chosen start positions. After rat found and climbed onto platform, trial was stopped and escape latency was recorded. Maximum trial length was 60 s. If rat had not climbed onto platform within 60 s, the experimenter guided rat by hand to platform and an escape latency of 60 s was recorded. Inter-trial time was 60 s. During this time, rat was kept on escape platform before starting next trial. Rat was then placed in pool again, but at a different location, and next trial began upon its release. Normally, escape latency declines during acquisition as animal learns the location of hidden platform. At the end of third trial, rat was returned to its cage. Twenty-four hours after last acquisition session, a 'probe trial' was used to assess rats' spatial retention of location of hidden platform. During this trial, platform was removed from the maze, and each rat was allowed to search pool for 60 s before being removed. During this trial, animals should spend more time swimming in quadrant that previously contained the hidden platform than in other 3 quadrants.

After these tests, according to the guidelines of animal ethics committees, the hippocampus and the cortex of brain tissues was excised after the rats were sacrificed. The effect of senescence related inflammation on the tissues in aging rats was evaluated by PCR gene expression analysis. Histological study was performed for cortex and hippocampus tissues.

Statistics

All results are expressed as the mean ±S.E. Acquisition (1–4 days) latency scores in MWM test were measured by 2-way analysis of variance (ANOVA), following post hoc Bonferroni test. Scores of time spent in escape platform's quadrant in MWM test, first day and retention latencies in PA test, total locomotor activity, and foot shock sensitivity scores were measured by 1-way ANOVA. Criteria for statistical significance was $P<0.05$. In PCR gene expression analyses, One way ANOVA, Post hoc / Tukey HSD were used and Kruskal Wallis analysis of variance was performed for data that did not fit the normal distribution.

RESULTS: In MWM test, there's a significant increase in acquisition latency (1-4 days) of 24-month-old rats. In acquisition session of MWM test, in **day 1**, there's a significant difference between aged vs young rats. In **day 2**, there's a significant difference between aged vs young rats and aged vs (young +met) group. In **day 3**, there's a significant difference between aged vs young rats; aged vs (young +met) group and also (aged+met) group vs aged rats. In **day 4**, there's a significant difference between **(1)** aged vs young rats and **(2)** aged vs (young+Met) and **(3)** (aged +Met) vs aged rats.

In *probe trial of MWM test*, there's a significant difference between young vs aged rats. There's a significant difference between (young+Met) vs aged rats and there's a significant difference between aged vs (aged+met) group. In probe trial of MWM test, there's a significant reduction in "*time spent in the escape platform's quadrant*" in aged rats compared to young rats. Metformin treatment reversed reduction of "*time spent in escape platform's quadrant*" of aged rats.

In *PA test*, there was no significant difference in 1st-day latency of rats in all groups. There's a significant difference between young vs aged rats and there's a significant difference between aged vs (aged+Met) group. The *locomotor activity* of rats was not affected.

A regular cerebral cortex was seen with neurons of normal morphology in the young control and young metformin groups. Degenerated neurons, intercellular and perivascular edema were observed in the aged control group. Regenerated neurons were observed with decreased edema in the aged metformin group. Hippocampus (CA2) with regular morphology was observed in the young control and young metformin groups. Degenerated neurons and severe pericellular and perivascular edema were observed in the aged control group, whereas neurons in the aged metformin group showed regeneration close to normal morphology.

By PCR gene expression analyses there was very significant results in all metformin groups **p<0,001;**

Ki67 & NF-κB & TNF-α ➔ hippocampus and cortex

PDGFR- β & i-NOS ➔ hippocampus

TGF-β & IL-6 ➔ cortex

DISCUSSION: This study demonstrates that chronic metformin treatment affects learning and memory performance in different learning and memory tasks in aged animals. Memory function may be defined as the ability to acquire, process, store, and retrieve information. We investigated the effects of long-term administration of metformin in passive avoidance and Morris water maze test, finding that metformin improved spatial and emotional learning and memory in distinct behavioral tasks involving different brain structures including hippocampus and amygdala.

In our study, we used metformin which beyond its impact on glycemic control, it may have pleotropic effects targeting multiple age-related mechanisms. Previous studies have found that metformin decreases inflammatory markers, NF-κB, ROS and mTOR pathways, thus decreasing DNA damage. Our findings suggest that aging itself, negatively affects spatial and emotional memory functions in rats. Metformin administration might have an affirmative effect on age-related learning and memory dysfunctions. In response to age-related increased inflammatory and oxidative stress, the neuroprotective effects seen in metformin groups *correlate with learning and memory functions.* The statistically significant decrease in inflammatory cytokine levels in hippocampus and cortex tissues with metformin and the increase in the levels of proliferation markers with cell-protective properties *support the neuroprotective effects of metformin*, and these results are consistent with histological findings.

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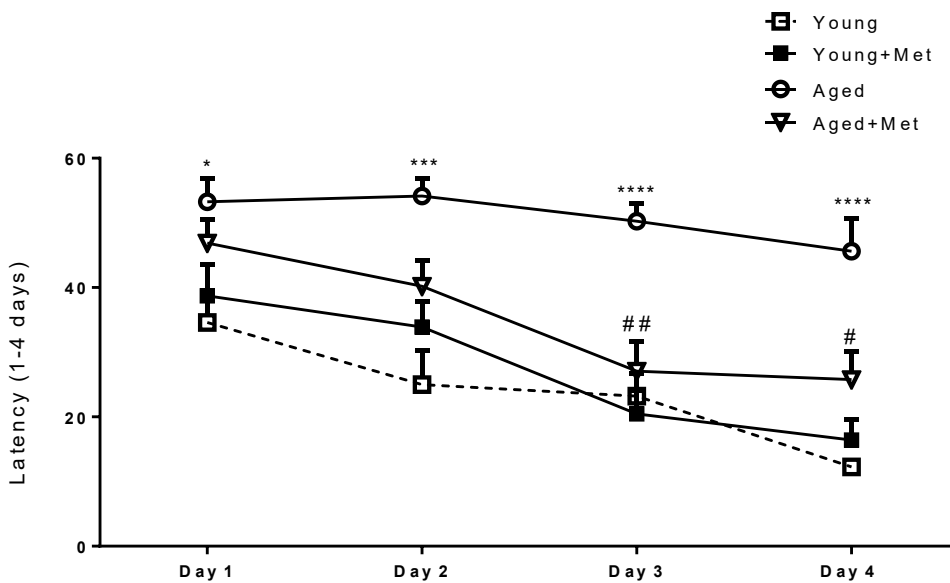
Latency (s) to find the platform of Young, Young+Met, Aged, Aged+Met groups in MWM test.
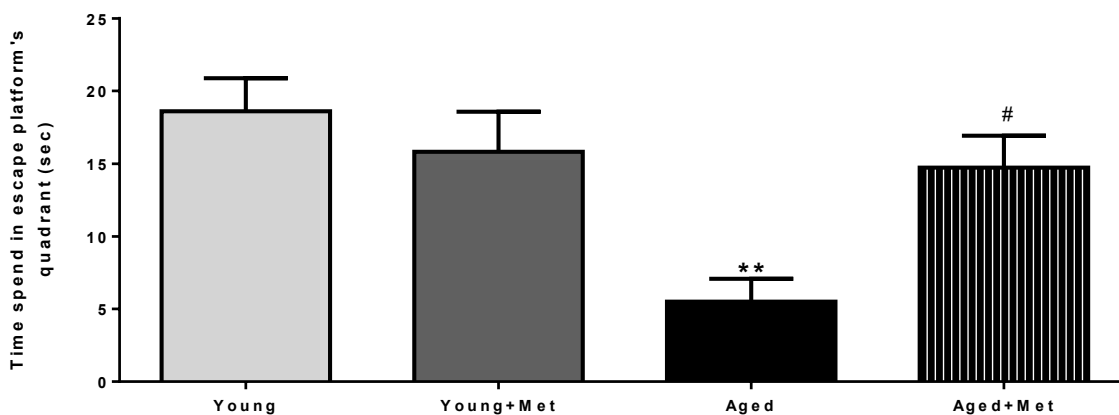
Time spent in the escape platform quadrants of Young, Young+Met, Aged, Aged+Met groups in MWM test
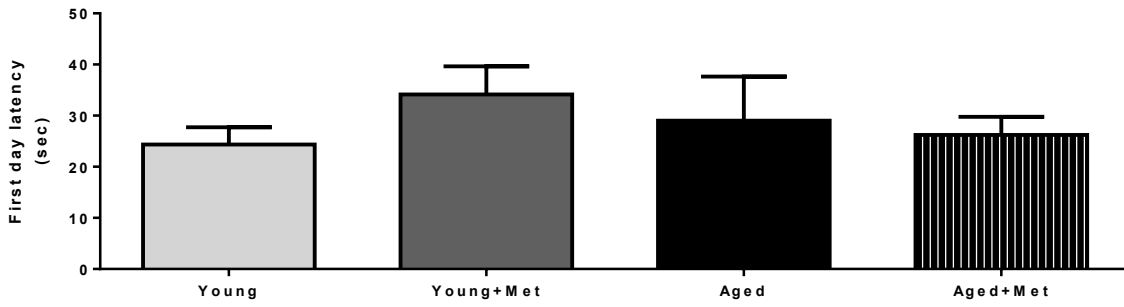
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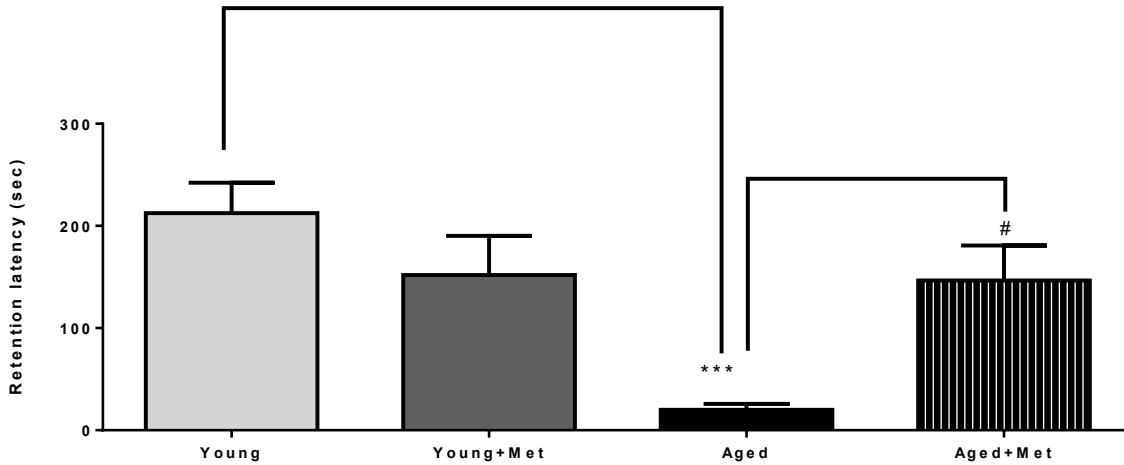
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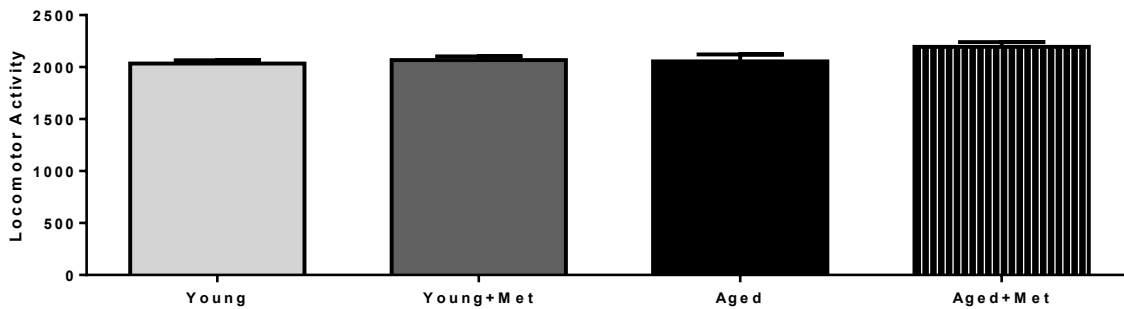
Locomotor activity of Young, Young+Met, Aged, Aged+Met groups

[Abstract:0412]

0412 - Pycnogenol and curcumin attenuates cognitive deficits and biochemical parameters in type-2 diabetes mellitus-induced Alzheimer's disease on rats

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ABSTRACT

OBJECTIVE: Alzheimer's disease (AD), the most common form of dementia, affects more than 35 million people worldwide. AD is characterized by progressive memory loss and gradually diminished cognitive function in people older than 65 years of age, and the pathophysiological mechanisms of these symptoms are not fully understood. However, misfolded protein accumulation called amyloid beta (Aβ) aggregates and neurofibrillary tangles containing hyperphosphorylated tau protein in AD brain are the triggers of oxidative and inflammatory damage and consequently cause synaptic dysfunction and neuronal death. The incidence of Alzheimer's Disease and Type-2 Diabetes Mellitus (T2DM) increases with age and development of one increases risk of other' [1]. T2DM enhanced by high-fat hypercaloric diets, reduced physical activity and/or genetic predisposition is characterized high blood pressure, hyperglycemia, insulin resistance, dyslipidemia and abdominal obesity that increase the likelihood of heart disease and coronary events. Interestingly, these characteristics are also reported to be important indicators for patients with a risk of progression to AD from mild cognitive impairment. In addition, Aβ aggregates, neurofibrillary tangles, oxidative and inflammatory damage, synaptic dysfunction and neuronal death in brain are associated with various mechanisms of T2DM.

As mentioned above, T2DM and AD are two very similar pathologies and have been shown in a variety of studies in which several drugs from both groups may be effective in one another. As research has turned to new targeted therapies that can cope with both diseases, it may be possible to weaken or even prevent the consequences of cumulative neuropathological events with the onset of treatment in the early stages of T2DM in the future. It is shown that many drugs from metformin, one of the classical drugs of T2DM, to peroxisome proliferator-activated receptor-γ agonists and glucagon-like peptide-1 agonists developed in recent years have beneficial effects in AD. In addition to the drugs mentioned above, the effects of plants and extracted compounds from plants are being investigated in AD. Many of these are used in the treatment of AD or in support of drug treatment.

Pycnogenol extracted from pine (Pinus sp.) tree bark and curcumin extracted from turmeric (Curcuma longa) rhizome have been shown to have potential effects on T2DM and AD [4, 5]. In a study of the effects of pycnogenol and vitamin E on intracerebroventricular streptozotocin (STZ)-induced cognitive impairment and oxidative damage in rats, pycnogenol and vitamin E were administered intraperitoneal to the rats for three weeks. In the study of cognitive impairment assessed by passive avoidance test and Morris' water maze test (MWMT), it has been shown that pycnogenol and vitamin E ameliorate cognitive performance and hippocampus choline acetyltransferase activity through STZ administration. In an investigation of the effects of pycnogenol on the formation of reactive oxygen species (ROS) induced by Aβ in a mouse feochromocytoma cell line, it has been shown that pycnogenol suppresses ROS production, as well as caspase-3 activation, DNA fragmentation and eventually protection against Aβ-induced apoptosis. Curcumin, the major component of turmeric, has been shown in a variety of *in vitro* and *in vivo* studies in which AD inhibits progression by many mechanisms. Curcumin inhibits Aβ fibril formation and prevents cell damage induced by Aβ peptides. By inhibiting cell death, they improve neuronal survival and reduce inflammatory stress. They also decrease tau hyperphosphorylation and neurofibrillary tangles.

In our study, we investigated the effects of pycnogenol and curcumin and comparison of each other on T2DM and AD in T2DM-induced AD model induced by high-fat diet (HFD) and low dose STZ administration and illumination of possible effects mechanisms on these diseases. For this purpose, the effects and mechanisms of action in AD were compared when they were administered single and combination of pycnogenol and curcumin. In addition, the effects and mechanism of action of pycnogenol and curcumin, and their differences with rivastigmine, which has FDA approval for use in AD, were also evaluated.

METHODS: Animal experiments were carried out with approval of Marmara University Animal Experiments Local Ethics Committee (permission number: 19.2018.mar). Adult female and male Sprague-Dawley rats (300-350 g) (n=8 in each group) were divided into 6 groups: Control, Alzheimer, Pycnogenol (10 mg/kg) [2], Curcumin (80 mg/kg) [3], Pycnogenol and Curcumin, and Rivastigmine groups. The rats were housed under controlled temperature (20-22), in humidity (40-60%) and light (12 h/12 h light/dark regime)-regulated rooms.

Although there are several models to induce T2DM in rats, most models are not suitable for the onset and development of the disease or the clinical situation in humans. Some genetic models may not appeal to people as a whole due to the high heterogeneity in genetic diversity. In models induced with high-dose STZ injection, the development of hyperglycemia primarily depends directly on pancreatic beta cell damage and is due to insulin deficiency rather than insulin resistance and shows more typical features of T1DM than T2DM. In contrast, rats fed a HFD develop obesity, hyperinsulinemia and insulin resistance; hyperglycemia and diabetes may not be fully explained. Therefore, in this study, the ideal model for T2DM was tried to be induced with the combination of the last two models, and this model is defined as T2DM-induced AD model in the literature. This model was induced by feeding with HFD for 8 weeks and administration of low dose STZ at the end of 4th week. 3 days after STZ administration, rats with a blood glucose level above 200 mg/dl were considered as diabetes and then treatments began on the 5th week of experiment and continued to the end of the 8th week. Anxiety and locomotor activities of rats were assessed by open field test (OFT); cognitive deficits were assessed by new object recognition test (NORT) and MWMT.

In OFT, rats' behavior was recorded on video for 5 minutes and evaluated the time spent in the central area, the number of squares passed and number of grooming and rearing of rats. The number of squares passed was considered as a measure of locomotor activity. The number of rearing was used to indicate discovery behavior. The time spent in the central area and the number of grooming was used to indicate rats' anxiety behavior. In NORT, exploration of identical and novel objects was defined if rats licked, sniffed or touched the object. Based on the exploration time of each object, the discrimination index and preferential index were calculated. In MWMT, rats were subjected to learning, which was evaluated for reaching the platform. On the 5th day of MWMT, 24 hours after the previous training session, probe tests were initiated in which the escape platform was removed and rats allowed the float freely for 60 seconds in tank. The time to reach the target quadrant in the probe trial and the time spent in the target quadrant in the both training and probe trials were calculated.

On end of the 8th week, all rats were decapitated. Insulin in rat pancreas, hippocampus, and brain cortex; and Aβ 1-42 in rat hippocampus and brain cortex are measured with ELISA method. The results of the tests were analyzed by one-way ANOVA followed by the Bonferroni method as a post-test and represented as mean ± S.E.M. P values <0.05 were considered significant. Data analysis was performed using GraphPad Prism 6.5 software (San Diego, USA).

RESULTS: According to result, there was no differences number of squares passed, rearing and grooming of rats in OFT. Time spent in central area was increased in treatments group in comparison with Alzheimer group (p<0.05). In NORT, control rats spent more time exploring the novel object to familiar object in the retention trial. There were no significant differences between time spent exploring the familiar and novel object in the retention trial in Alzheimer group. However, treatment groups spent significantly more time to exploring novel object compared to familiar one compared to Alzheimer group (p<0.05). In MWMT, latency to platform was higher in Alzheimer group compared to control group; but it was decreased in treatment groups compared to Alzheimer group (p<0.05). Time spent in target quadrant was decreased in Alzheimer group compared to control group, increased in treatment groups compared to Alzheimer group (p<0.05). Time to reach target quadrant was increased in Alzheimer group compared to control group, decreased in treatment groups compared to Alzheimer group (p<0.05).

ELISA analyzes were performed on the tissues taken after the rats were decapitated. Insulin levels were studied in the pancreas, hippocampus and cortex of rats. Insulin levels in pancreas were lower in Alzheimer group compared to control group (p<0.01), while in treatment groups, insulin levels increased compared to Alzheimer group (p<0.05). Similarly, in the hippocampus and cortex, insulin levels decreased in Alzheimer group compared to control group (p<0.05), while it was higher in treatment groups than Alzheimer group (p<0.05). Aβ 1-42 levels were increased in the brain cortex compared to control group in Alzheimer group (p<0.05), while it decreased in treatment group compared to Alzheimer group (p<0.05). When Aβ 1-42 levels in the hippocampus were examined, no significant difference was found between groups.

DISCUSSION: Classical treatment for AD has some limitations, current treatments can only slow the progression of the disease rather than cure the disease, and can often be useful at the onset of the disease. For this reason, many patients benefit from complementary and alternative medicine to go beyond existing treatments. On the context of our study, the effects of pycnogenol and curcumin, which had potential effects on AD, in the T2DM-induced AD model were investigated.

In our study, OFT was performed in rats to examine possible abnormal motor behavior and anxiety disorders in AD. Consequently, there was no significant difference between the groups in locomotor activity and this result eliminated the possibility of changes in the cognitive tests of rats' locomotor activity, especially MWMT. The increase observed in the treatment group compared to Alzheimer group at the time spent in the central area, which one of the anxiety evaluation parameters, indicates that the pycnogenol and curcumin, the effects of which we observe, may improve the anxiety from the symptoms of AD.

NORT is a cognitive test based on rodents' behavior to discover new objects. In our study, it was shown that the discovery activity, discrimination index and preference index, which are NORT parameters, in Alzheimer group cause deterioration. Pycnogenol and curcumin improved on these NORT parameters.

MWMT, which is widely used in our study, was preferred to test the spatial learning memories of rats. The failure of rats to learn the position of the platform in the labyrinth in this test indicates that their spatial learning and memories are impaired. The platform that enables them to escape from the water in the maze acts as a motivation. In our study, the learning time in Alzheimer group increased compared the control group, which indicates that learning-memory was impaired. The correction of this situation with pycnogenol and curcumin shows that they have therapeutic effects of spatial memory impaired in rats. Moreover, compared to control group in Alzheimer group, the time spent in the target quadrant and the correction of the treatments support the therapeutic activities of pycnogenol and curcumin.

It is thought that a decrease in insulin transfer to the brain in T2DM is a trigger for neurodegeneration and cognitive impairment. The fact that plasma insulin level is higher and brain insulin level is lower in AD patients compared to healthy adults. The relation of dysfunctional insulin activity in the hippocampus with cognitive attenuation is also important for the epidemiological relationship between T2DM and AD. Postmortem studies in patient with AD have shown dysfunction in insulin signaling, which can be described as insulin resistance, including downregulation at insulin receptors and a decrease in insulin sensitivity. In addition, age-related insulin resistance is associated with chronic neuroinflammation, an early pathological feature of the neurodegenerative process leading to increased blood brain barrier permeability. Insulin resistance and abnormal insulin levels usually go together, and people with hyperinsulinemia were more likely to develop AD, and compared to those without diabetes, they impair cognition more severely. In ELISA analyzes, insulin levels, which are expected to increase in disease state in pancreas, hippocampus and cortex and which are among the basic dynamics of the relationship between AD and T2DM, were measured. While these levels were decreased in Alzheimer group, treatments improved. This shows that pycnogenol and curcumin can improve insulin levels. Decreasing brain insulin levels creates an environment for the occurrence of amyloidogenic events that directly connect T2DM and AD. In fact, insulin deficiency allows for constructive Aβ production by permanently activating glycogen synthase kinase-3-beta (GSK3β). High expression and activation of GSK3β in T2DM-generated rat models has been associated with impaired ability of insulin to activate glucose utilization and glucagon synthesis. There is also evidence that beta-secretase expression, which plays an important role in Aβ formation, is upregulated in the absence of insulin, which increases the extracellular accumulation of Aβ in the brain.

According to amyloid cascade hypothesis of AD, progressive neuronal loss is directly related to the accumulation of Aβ aggregates in the brain parenchyma, and these aggregates are also considered surface catalysts in the formation of dispersible neurotoxic Aβ oligomers. Fibrinogenic Aβ peptides are formed after sequential proteolytic cleavage. The Aβ 1-40 and Aβ 1-42 formed by this process are the most common Aβ isoforms. While Aβ is dominant, Aβ 1-42 also tends to be higher aggregated and found in Aβ stores in most AD brains. In addition, in pathological events associated with impaired synaptic plasticity and memory loss; soluble Aβ 1-42 oligomers appear more neurotoxic than Aβ fibrils. In ELISA analysis in rats, Aβ is expected to be higher in Alzheimer group in the hippocampus and cortex. According to the analysis in our study, Aβ levels in the AD group increased compared to control group, as expected and the treatments improved this situation. But no significant difference was found between the Aβ levels in the hippocampus between the groups. In our study, pycnogenol and curcumin succeeded in lowering Aβ levels in the brain cortex in AD. We have found that both single and combined pycnogenol and curcumin improved cognitive functions in T2DM-induced AD rats. The improvement in cognitive functions of pycnogenol and curcumin was probably due to its healing effects on insulin and Aβ levels. In the light of these findings, we suggest that pycnogenol and curcumin is beneficial in T2DM and AD.

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Keywords: Type 2 diabetes mellitus, Alzheimer's disease, pycnogenol, curcumin, T2DM-induced AD model.

[Abstract:0447]

0447 - Whole brain morphometric studies in sexually female adolescence by voxel based morphometry

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ABSTRACT

OBJECTIVE: The brain is vulnerable to adverse events in adolescence because of neuronal reorganization and psychosocial transition during puberty. The effects of childhood adverse events reach out to adulthood which are shown repeatedly in adult magnetic resonance imaging studies. However, studies investigating the immediate effects of adverse events on adolescent brain are scarce. In this study, we explored the effects of sexual abuse, one of the serious adverse effects that adolescence might have, on their brain structure. In this study, we focused on the short-term effects of sexual abuse on adolescent brain structures. Based on the previous studies investing childhood adverse event on adults, we hypothesized that prefrontal cortex and limbic areas (especially amygdala and stress sensitive hippocampus) are vulnerable to the effects of the sexual abuse during adolescence. We also determined the somatosensorial and visual associated areas as a priori regions as smaller gray matter (GM) volumes of these regions are reported in PTSD patients with sexual abuse history [1]. We used complementary approaches (i.e., voxel-based morphometry measurements) to investigate the GM alterations. GM volume is a function of surface area and thickness of the measured area while cortical thickness is a measurement of the radial distance between the inner and outer border of cortical GM and compared to volume analyses, more sensitive to the columnar architecture of the cortex because it spans the cortical layers.

METHODS: *Subjects*: We contacted 134 childhood abuse cases and 104 healthy control subjects for the study. As we have limited our interest to the effects of sexual abuse during adolescence, we included only the subjects with a history of sexual abuse during preadolescence and adolescence.. From the sexual abuse group 57 subjects and 33 healthy control subjects accepted to participate in the study. As sexually abused subjects are frequently victims of multiple kinds of trauma adolescents with multiple traumas (e.g., neglect) were not excluded. In total ninety adolescent female subjects between 13 to 18 years old (mean age: 16.5± 0.2) with no developmental delay are included in the study. Healthy control group was composed of female adolescents who responded to the local advertisements in schools. We included healthy subjects with similar age and education levels to the sexually abused group.

Exclusion criteria for both study groups were as follows: having a n Intelligence Quotient (IQ) score of 70 or below, a chronic medical illness like asthma or diabetes mellitus, a history of head injury with loss of consciousness longer than three minutes, any neurological illness, a pervasive developmental disorder, any personal or family history of psychotic disorders or bipolar disorder, a history of perinatal complications. Since

previous studies reported that antidepressant medications may affect hippocampal volumes; we excluded subjects that used antidepressants within four weeks prior to the study.

Voxel-based Morphometry

The images were manually reoriented to place their native-space origin at the anterior commissure using SPM12 (www.fil.ac.uk/spm/) running under Matlab R2016a (The Mathworks, Inc., Natick, MA, USA). The default settings that are described in detail in the manual of the Computational Anatomy Toolbox (CAT12) were used for the next steps of the VBM analysis (http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). We used the Diffeomorphic Anatomical Registration through an Exponentiated Lie (DARTEL) algebra algorithm [23] to improve the registration quality of the structural images. Structural MRI data preprocessing procedures were as follows. First, the original individual T1-weighted images were segmented into GM), WM, and cerebrospinal fluid (CSF). After segmentation, The CAT12 toolbox provided ratings of image data quality (IQR) that can be used to identify problems with the images by assessing basic image properties, noise and geometric distortions. All data appeared to have a good-to-excellent quality, so all images of 90 participants were used for further analysis. Second, the segmented GM and WM images for all the subjects were used to create a study-specific template using DARTEL. Next, the individual segmented images were warped to the study-specific template and spatially normalized to Montreal Neurological Institute (MNI) space. Finally, the modulated GM images were smoothed with an 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel. As a result; the smoothed, modulated GM images for each subject were obtained. To test the effects of sexual abuse on specific brain structures a priori regions were determined regarding the findings of previous studies and the hippocampus, parahipocampal gyrus, anterior cingulate cortex, amygdala, insula, orbitofrontal cortex, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, primary visual cortex, fusiform gyrus, precuneus, supramarginal gyrus, angular gyrus and superior temporal gyrus regions was identified using the Wake Forest University PickAtlas Toolbox, Version 2.0. that provides a method for generating region of interest (ROI) masks based on the Talairach Daemon database [2].

Statistical Analysis

We used age and IQ scores as confounding factors during the comparisons among the groups if otherwise stated. Total intracranial volume was also added as a covariate in the one-way analysis of variance (ANOVA) at VBM analyses. One-way ANCOVA was used to compare the GM volumes with SPM12 for VBM comparison. We reported the clusters with peak value of p <0.05 after family- wise error correction. We also reported the clusters if they had been reported in other studies that were specifically interest in the effects of sexual abuse on brain structures. In these *a priori* regions of interest, we considered an uncorrected *p*-value of 0.001 as the significance threshold. This threshold, with the *a priori* hypothesis present, was approximately equivalent to $p < 0.05$ corrected for multiple comparisons [3]. For *a priori* regions, we accepted cluster [k] > 50 (168.75 mm^3) continuous voxel as threshold size.

RESULTS: VBM analyses revealed that abused group had smaller gray matter volumes of right fusiform gyrus and left thalamus compared to those of controls. It was previously reported some areas might be specifically associated with sexually abuse in females. When these areas were determined as a priori regions for ROI analysis and the p value threshold was set to uncorrected 0.001, we observed smaller gay matter volumes in the visual cortices bilaterally but not in the primary somatosensorial areas.

DISCUSSION: In this study, we investigated the effects of sexual abuse, which is one of the most significant environmental adverse events in life -time, on the female adolescent brain structure and functionality. When we compared brain structures of 57 subjects with a history of sexual abuse with 33 control subjects, we found several differences. VBM analysis revealed that right fusiform gyrus, left thalamus and bilateral secondary visual cortex volumes were smaller in the abused group when compared with control group. Adult studies showed that primary and association areas of the visual system are sensitive to effects of the sexual abuse and the decrease in GM volume is correlated with the duration of exposure before age 12 with gradual impairment in visual memory. Other related regions like fusiform and middle occipital gyrus, which play a role in face recognition and processing, also had GM reduction in patients with PTSD that sexually abused before 18 years old. Our findings of reduced GM volume in the visual association areas and fusiform cortex extend the previous findings and suggest that the sensitivity of visual association and face processing areas to the effects of the sexual abuse continues during adolescence.

The presentation of only female adolescence data is one of the limitations of our study and the observed alterations might not reflect the male abused victims. The different maturation trajectory and hormonal status of male and female brains might lead to different structural alterations to similar stress factors among the genders VBM analyses revealed significantly smaller volume in the right fusiform gyrus and left thalamus. The alterations in visual perception and processing regions in sexually abused adolescence may reflect an adaptation to stress exposure, indicating an attenuation in sensory systems and pathways relaying recurrent aversive or traumatic experiences [5]. Further studies may have the potential to elucidate the biological basis of the detrimental behavioral effects of sexual trauma that will lead to improved strategies for the prevention and intervention of trauma related brain alterations. We suggest that the observed differences in gray matter volume and network architecture may therefore represent neural markers of aberration in brain regions associated with a broad range of autobiographical, emotional, cognitive and regulatory processes that might underpin increased risk for psychopathology. Clearly longitudinal studies up to adolescence are needed to scrutinize the role of altered brain structure as the biopsychological consequences of sexual abuse.

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[Abstract:0530]

0530 - Comparison of excessive mind wandering between adult adhd , bipolar disorder and healthy controls mind wandering as a cognitive marker ?

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ABSTRACT

INTRODUCTION: Attention Deficit Hyperactivity Disorder is most common neuropsychiatric disorder of childoodwit a deveopmental origin .ADHD presents in Aduktood mosly with comorbidity and Bipolar Disorder an important comorbidity of ADHD (Thapar 2016:339). (Sobanski,2006:31Mind Wandering (MW) is conceptualized as periods in time when attention and the contents of thoughts shift away from external sources and/or ongoing tasks to unrelated internal thoughtsExcessive spontaneous MW has been associated with functional impairment and implicated in psychopathologies such as ADHD (Franklin et al., 2017). Mental restlessness, a descriptive term encompassing excessive MW, has been reported as more common in ADHD than non ADHD individuals.

METHOD: İn order to compare excessively mind wandering phenomena in Adult ADHD and Bipolar Disorder, 93 patients diagnosed as Adult Adhd were compared with 85 patients diagnosed with Bipolar Disoder in remission in psychiatry outpatient setting and randomly selected 111 healthy controls were assesed.For this purpose 93 Adult ASDHD patients were evaluated in Kanuni Sultan Süleyman Research and Teaching Hospital assesed by a experineced psychiatric academician enrolled in ADHD.All patients are prveiosly diagnosed as ADHD mostly in Childhood. For Assesment; ASRS, Excessively Mind Wandering Scale are used for Assesment of ADHD symptoms.

Excessively mind Wandering Scale formerly developed by Asherson is a 12 item Scale previously reliability and validity of the scale were studied by Günay Aksoy in 2019.

Bipolar patients 81 in number were selected from the same psychiatric outpatient setting of this hospital.. The patients in remission were included in to the study.111 controls were randomly selected without any psychiatric disorder or any psychiatric history.

 STATİSTİCAL ANALYSİS: First sosciodemographic variables of the three group were assesed For this pupose ANOVA test were done. To test the homogenity of the variance Levene test were performed to select post hoc technique to determine.The homogenous results ere assesed by Benforrini test; heterogenous variance were assesed by Tamhane's T2 test.The effect size of the significant results of ANOVA were assesed by COHEN's calculation eta kare (η2) (0,01 ;small effect size, 0,06 medium effect size, 0,14 big effects size.

DISCUSSION: In the present study, we examined the comparison of excessive mind wandering ADHD symptomatology in Adult ADHD Bipolar patients and healthy controls . Our findings are in line with previous studies reporting MW are commonly observed and discrimantive in ADHD compared with controls. However our study is first study comparing MW with another psychopathology nearby healthy controls. MEWS scores were also found to be highly correlated with ADHD symptoms ,as proposed previously replicating previous studies of the association between spontaneous MW and ADHD. (Mowlem 2016,Bozhiolav 2018) Further our study shows Mw are also observed but less common in Bipolar Disorder which postulate MW could be discrimantive and a potetntial cogntive marker for ADHD . As known Adult ADHD requires a complex psychiatric evaluation for accurate Diagnosis. Neural correlates and implicated brain circuits related with MW generated much interest in literature. The DMN has been implicated as a potential source of self-generated thoughts unrelated to external goal-directed tasks; most active during the restingstate, when the person is awake but in a daydreaming or MW state. (Fox 2015) The network can beconceptualized as switching off during external goal-directed tasks, and switching on when there are internal self-generated thoughts. Reductions in default mode activity under rewarding conditions have been hypothesized to reflect reductions in excessive MW. ADHD is associated with spontaneous MW, rather than deliberate MW, and detrimental episodes of MW.(Jansen 2017)

   Comparison of the results from this 3 group revealed that excessive mind were statsitically significantly common in Adult ADHD compared with healthy controls imposing highly discriminatory for this disorder wheras excesively mind wandering were not significantly correlated with scores obtained both form Bipolar Disorder and Healthy Control (p=,268; p>,05). Mind wandering can be proposed as a discriminatory phenomna observed in Adult ADHD.

Summarized our findings suggest that adults with ADHD are highly susceptible to excessive spontaneous MW and may have a core difficulty controlling spontaneous thoughts unrelated to the current context. Excessive MW could therefore underlie many of the symptoms and impairments that characterize the disorder further discriminate this disorder from other psychopathologies and healthy control and could be accepted as a cognitive marker of ADHD counterpart of DMN in neural network basis.

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FINDINGS:

TablE-1: RESULT OF MWS OF ADHD , BIPOLAR AND CONTROLS

GROUP	VARİABLE	N	$\overline{X}$	SS
ADHD	MWS	93	24,53	5,85
BİPOLAR	MWS	85	11,64	7,07
NORMAL	MWS	111	10,05	5,97

The aritmetic mean of the MWS were significantl higher in ADHD group compared to Bipolar and controls . wheras aritmetic mean of Bipolar Group were significantly higher than healthy controls .Highest results are obtained from ADHD group.

Table 2.:Descriptive Statistical Analysis of Adhd , Bipolar and Controls and results Of ANOVA

Descriptive Statiscal Analyisi					ANOVA Res						η2
	Group	N	$\overline{x}$	Ss	Var. K.	KT	Sd	KO	F	p	
MWS	Dehb	93	24,53	5,85	İntergoup	12109,45	2	6054,72	153,753	,000*	,518
	Bipolar	85	11,64	7,07	İn Group	11262,55	286	39,38			
	Normal	111	10,05	5,97	Total	23372,00	288				

*P<,001

To test the hogenity of the variance Levene test were perfomed .The variance test revaled that the results were not homogenous ((F=5,52; p<,05) so post hoc Tamhane's Test T2 were performed.

Table 3: Results of Tamhane's T2 Post hoc Analysis of MEWS

Dependent Variables	(I) Group	(j) Group	Mean Variance (I-J)	Std. Dev.	p
MWS	ADHD	Bipolar	12,89*	,98	,000
		Normal	14,47*	,83	,000
	Bipolar	Adhd	-12,89*	,98	,000
		Normal	1,58	,95	,268
	Normal	Adhd	-14,47*	,83	,000
		Bipolar	-1,58	,95	,268

*p<,05

MWS were significantly higher in ADHD group according to Post Hoc Analysis compared to Bipolar Disorder and Controls.

[Abstract:0565]

0565 - Evaluation of clinical features and cognitions effect on utilization of smoking cessation treatment

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ABSTRACT

OBJECTIVE: Smoking is the leading preventable cause of illness and premature death worldwide. Tobacco use remains the leading preventable cause of disease and premature death with nearly six million deaths and hudreads of billion dollars in economic damage wordwide. Smoking prevalence has decreased in most Western countries, as an example in the United States over the past 50 years, the prevalence of cigarette smoking has decreased dramatically from 43% to 15.1% [1]. Nevertheless, the risk of death from cigarette smoking continues to increase worldwide and smoking is still leading preventible cause of deaths in United States too [2]. Turkey is among the countries with the highest rates of smoking and one of the countries with the highest smoking rate among men in Europe according to WHO [3]. Therefore, great importance is attached to the fight against tobacco addiction both in the world and in Turkey. Preventive health policies are developed and implemented for this purpose, and on the other hand, many researches are conducted to find more effective and successful treatments. Today, after countless studies, the success reached in smoking cessation treatment is still not at the desired level, but it is similar to other addiction treatments. Nicotine replacement therapy (NRT), bupropion, and varenicline have been proven effective to help people to quit. Also numerous trials showes cognitive and behaviorual methods are another afective way to quit and its best to combine them with pharmacotherapy. It is known that the vast majority of smokers wants to quit smoking and tries to quit but despite the availability of theese affordable, cost effective and available aids, very low number of smokers benefit from evidence-based smoking cessation treatment therefore more than 95% of smoking cessation efforts fail within a year [4]. In individuals with tobacco use disorders, if factors affecting treatment attendence will be detected, the group may be conduct to apply for treatment. This will increase the quitting success rates of tobacco addiction by 3 to 10 times according to the results of previous studies. Thus, it is thought that it will contribute to the field of mental health and public health both in terms of preventing diseases and deaths that will develop due to the continuation of tobacco usage and preventing the great social and financial burden of these diseases and the continuation of tobacco usage causes. Increasing utilization of smoking cessation services is an important goal. The aim of this study is to determine factors which effects utilization of treatments.

METHODS: Participants comprised of 234 patients between the ages of 18 and 65. Two groups were present in our study: 156 patients with smoke addiction, who were attended to smoking cessation treatment called Treeatment Seeker Group (TSG) and 78 smoker who tried to quit within the last year (had at least one, 24 hour lasted quit attempt) but never attend to any cessation treatment ever, called Non Treatment Group (NTG). TSG consisted from the patients who were attended to smoking cessation outpatient clinic between 10th of October – 10th December 2017 at Erenkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery of Istanbul. NTG consisted from patients who were attended to family health center at the same district, in terms of similarity of the sample group, between December 10, 2017 – February 10, 2018.

In the previous studies, it was concluded that the patients with lower dependency severity applied less to treatment. Therefore those who were measured as low or very low dependent from the Fagerström Nicotine Addiction Test were not included in the study to strengthen the impact of results. Also patients who have psychotic disorder history, mental retardation, severe physical and psychiatric disorders that lead to create difficulties to response questions and correspond the interview, or illiterate were excluded from the study.

The Ethics Committee approval was obtained before the study. Participants were informed about the interview and tests to be applied, written consent was taken from each participant. All participants had an interview with certified CBT therapist, their cognitions about smoking and

smoking cessation were gathered in that 45 minute session. Participants assessed with the socio-demographic data form, Fagerstrom Nicotine Dependency Test (FNDT), *State Trait Anxiety Inventory* (*STAI*), Anxiety Sensitivity Index (ASI), Cognitive Distortions Scale (CDS) and *Dysfunctional Attitude Scale* (DAS).

Statistical analyses were performed with IBM SPSS, version 16 for Windows. The normality control of continuous data was made by Kolmogorov Smirnov and Shapiro Wilk tests. Variables that don't show normal distribution were evaluated by MannWhitney U test. Normally distributed numerical data between two groups evaluated by Student T test. The statistical significance value was accepted as 0.05 in all analyzes.

RESULTS: Only significant difference between the two groups in terms of socio-demographic characteristics (see Table 1) was age (the avarage age of TSG was lower than NTG, 39,69±11,20 vs 44,01± 11,50). Also smoking characteristics (see Table 2) of the two groups were statistically similar. Years of smoking was 22,99±12,35 vs 20,72±10,59; avarage cigarette smoked per day was 22,33±8,41 vs 25,03±11,50 between NTG and TSG.

Even the study excluded very low and low level dependent patients, Nicotne dependence severity measured with FNDT showed TSG (6,48±1.88) had statistically higher scores than NTG (5,90±1.93). NTG had more quit attempt history (2,56±2,27 vs 2,04±1,85). Enviromental features about smoking were also similar between NTG and TSG: %33,3 vs %35,9 were not working, %59 vs %55,1 has smokers in their work place and only %7,7 vs %9 didn't have smokers in their work place. %32,1 vs %29,5 didn't get any advice from any healthcare professional ever to quit smoking, %44,9 vs %44,2 were adviced to quit and %23,1 vs %26,3 were adviced to quit and attend treatment from healthcare professional. %38,5 of NTG and %37,2 of TSG reported having psychical illness, %26,9 of NTG and %32,7 of TSG reported psychiatric illness history and there was no statistically significant difference between groups.

Readiness to quit, placing importance on quitting, self confidance to quit and placing importance on getting professional help were measured from likert scaled questions, all of them were significantly higher in the treatment seeker group. When placing importance to quit gathered at spesific topics as for health and for economic reasons, the importance of quitting smoking for health and and for economic reasons was statistically similar between groups. There were no significant differences between the two groups in terms of state and trait anxiety. ASI scores were significantly higher in the treatment seeker group (27,54±14.89 vs 22,83±12.11) (Table 3). General usage of cognitive distortions measured with CDS and results showed: *Mind reading* and *minimalizing the positive* was higher at both interpersonal(IP) and personal achievement(PA) domains; *should statements* was higher at only PA domain at the TSG. However when the same cognitive distorsions usage on smoking topic especially examined, only all-or-nothing thinking about using/quitting smoking was higher at TSG. At the NTG, all other cognitive distorsions about using/quiting smoking found similar with TSG. Labeling (1,83±3,17 vs 0,84±1,94), *mental filter* (3,31±3,08 vs 2,43±2,79), *should statements* (5,79±3,86 vs 4,47±3,57) and *minimizing the positive* (2,46±3,19 vs 1,59±2,50) were all statistically higher at the NTG on the topic of getting help to quit smoking (Table 4). At DAS, *autonomous attitudes* and *tentativeness* were same between groups but *perfectionistic attitudes* (44.36±16.67 vs 50.69±17.73) and *need for approval* (36.77±10.11 vs 39.88±10.46) were higher at TSG (Table 3).

DISCUSSION: Underutilization of smoking cessation treatment is a major problem which causes low quit rates and that costs a big burden to public health. Most of the studies about that topic are socio-demographic studies which gathers informaions from people who attends cessation treatment. No studies have been found in our literature search, comparing smokers who tries to quit appeals/dont appeals cessation treatment. It's well known that some cognitions and cognitive distortions effects quiting/continuing smoking habbit [5] so researching that on treatment utilization would be logical. In our study we aimed to find a changeable difference between smokers appeals/dont appeals cessation treatment, so we could aim that factors in future work and improve sucsess rates. Study results supported our hypothesis and points the reason of underutilizing smoking cessation treatements as inner bariers and cognitive distortions of patients about quiting and especially about getting treatment to quit. Founding similar socio-demographic characteristics between groups also strengthens that hypothesis.

We found similar anxiety scores between groups and we interpreted higher ASI score results at TSG as that; literature showes patients with higher anxiety sensitivity has more negative prospects about quitting and experience more withdrawal sypmptoms, so these problems they have and their need for help may lead them to get professional help.

One of the most important findings in the present study is, smokers had same cognitions about smoking but some cognitive distorsions about getting professional help to quit smoking were significantly higher in the smokers who wanted and tried to quit but didn't get any treatment. These cognitions can be aimed at both individual and community-based interventions and that can increase treatment utilization, which can boost quitting rates and have considerable effect at public health.

Perfectionistic attitudes, Need for approval, Autonomous attitudes, and Tentativeness
Perfectionistic attitudes, Need for approval, Autonomous attitudes, and Tentativeness

Keywords: Smoking, Nicotine addiction, Treatment utilization, Smoke cessation treatment, cognitive distortions

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TABLES

Table 1. Sociodemographic data of the study group

			Non Treatment Group	Treatment Seeker Group	p
Gender	Male		31 39,7%	80 51,3%	0,96
	Female		47 60,3%	76 48,7%	
Age	Mean±Std (Med)		44,01± 11,50 (44,00)	39,69±11,20 (37,00)	0,006
Marital status	Married		50 64,1%	84 53,8%	0,135
	Not married		28 35,9%	72 46,2%	
Income status	Low		10 12,8%	26 16,7%	0,372
	Moderate		65 83,3%	126 80,8%	
	High		3 3,8%	4 2,6%	
Employment status	Working		49 62,8%	101 64,7%	0,773
	Unemployed		29 37,2%	55 35,3%	
Education level / As the year successfully completed	Mean±Std (Med)		11,22±4,75 (11,00)	11,58±4,35 (12,00)	0,636

Table 2. Smoking characteristics of the study group

		Non Treatment Group	Treatment Seeker Group	p
Years of smoking	Mean±Std (Med)	22,99±12,35 (20,00)	20,72±10,59 (20,00)	0,183
Average numbers of cigarettes a day	Mean±Std (Med)	22,33±8,41 (20,00)	25,03±11,50 (20,00)	0,161
How many times did he/she quit smoking before (at least 24 hour tries)	Mean±Std (Med)	2,56±2,27 (2,00)	2,04±1,85 (2,00)	0,044
Longest quit lasts	Up to 1 week	34	72	0,978
		43,6%	46,2%	
	1 week to 1 mounth	16	25	
		20,5%	16,0%	
	1 to 3 mounth	9	19	
		11,5%	12,2%	
	3 to 6 mounth	8	11	
		10,3%	7,1%	
	6 mounth to 1 year	3	14	
		3,8%	9,0%	
	Longer than a year	8	15	
		10,3%	9,6%	

Table 3: Study groups; Anxiety, Anxiety Sensitivity, FNDT and Dysfunctional Attitude Scale scores

		Non Treatment Group Mean±Std (Med)	Treatment Seeker Group Mean±Std (Med)	p
STAI State Anxiety score		35.65±10.64 (34.00)	37.33±9.79 (36.00)	0,214
STAI2 Trait Anxiety score		43.00±8.81 (43.50)	44.38±9.33 (43.00)	0,394
Anxiety Sensitivity Index-3 total score		22.83±12.11 (21.50)	27.54±14.89 (25.50)	0,041
Fagerström Nicotine Dependency Test score		5.90±1.93 (6.00)	6.48±1.88 (6.00)	0,016
Perfectionistic attitudes (DAS)		44.36±16.67 (39.50)	50.69±17.73 (48.00)	0,004

Need for approval (DAS)	36.77±10.11 (36.00)	39.88±10.46 (39.00)	0,038
Autonomous attitudes (DAS)	29.04±7.30 (29.00)	27.92±6.89 (28.00)	0,159
Tentativeness (DAS)	18.54±4.96 (18.00)	19.03±4.92 (18.50)	0,499

Table 4:

Cognitive distorsions usage about getting help-treatment to quit smoking	Non Treatment Group Mean±Std (Med)	Treatment Seeker Group Mean±Std (Med)	p
Catastrophizing / About getting help-treatment to quit smoking	4,33±3,75 (4,00)	4,97±3,67 (5,00)	0,224
All-or-nothing thinking / About getting help-treatment to quit smoking	6,05±3,55 (6,00)	6,56±3,30 (7,50)	0,337
Emotional reasoning / About getting help-treatment to quit smoking	4,10±3,66 (4,00)	4,21±3,35 (5,00)	0,793
Labeling / About getting help-treatment to quit smoking	1,83±3,17 (0,00)	0,84±1,94 (0,00)	0,037
Mental filter/ About getting help-treatment to quit smoking	3,31±3,08 (3,00)	2,43±2,79 (1,00)	0,034
Overgeneralization / About getting help-treatment to quit smoking	1,63±2,69 (0,00)	1,56±2,57 (0,00)	0,900
Personalization / About getting help-treatment to quit smoking	2,46±3,49 (0,00)	2,24±3,49 (0,00)	0,326
Should statements / About getting help-treatment to quit smoking	5,79±3,86 (8,00)	4,47±3,57 (5,00)	0,008
Minimizing the positive / About getting help-treatment to quit smoking	2,46±3,19 (1,00)	1,59±2,50 (0,00)	0,027

Evaluation of cognitive distorsions usage on the topic of getting help to quit smoking in study group.

[Abstract:0581]

0581 - Prevalence and associated factors of adverse effects in young subjects treated with selective serotonin reuptake inhibitors: A chart review study from Turkey

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ABSTRACT

OBJECTIVE: SSRIs have been widely used medications among young population to treat psychiatric disroders with or without FDA approved indications (1,2). Although the overall efficacy and safety of SSRIs is supported by large controlled multicentre studies, adverse effects of SSRIs treatment in children and adolescents may be different from adults due mainly to the pharmacodynamic and pharmacokinetic developmental differences (3,4). It has been reported that adverse effects associated with SSRIs show significant differences across age groups (3,4). It is stated that children may be more susceptible to adverse effects related to SSRIs and this may be explained in part by biological immaturity (3,4). The majority of studies in the younger group have focused on the efficacy of SSRIs, and there are relatively few studies on the safety profile of SSRIs in children and adolescents with insufficient data on the recognition of adverse effects, relationships with SSRIs dose and type, and clinical and sociodemographic characteristics of the subjects (4). Additionally data regarding the safety and adverse effects of SSRIs in young population may sometimes come from studies in which participants received multiple psychotropic drugs during study period or had previous psychotropic drug use (5). Therefore it may be important to assess adverse effects of SSRIs treatment and potential relationships with sociodemographic and clinical variables in medication naïve subjects received SSRIs monotherapy.

In this retrospective chart review study we aimed to investigate the prevalence and nature of SSRIs related adverse effects among treatment naïve young population who recived SSRIs monotherapy and possible relationships with several clinical (i.e psychiatric diagnosis) and sociodemographic variables (i.e age, gender).

METHODS: *Participants and Procedure:* This study was conducted in Child and Adolescent Psychiatry Department in Istanbul Medical Faculty. Subjects of this study were among the children and adolescents who were referred to outpatient clinic during January-June 2018, and had received SSRI monotherapy for any psychiatric diagnosis. During the initial clinical interview subjects were assessed in terms of reason(s) for referral, provisional diagnosis and the need for a psychopharmacological treatment. The subjects then underwent a detailed clinical assessment including diagnostic interview if they were planned to start treatment with SSRIs. Inclusion criteria were a) receiving SSRI monotherapy, b) having complete and detailed psychiatric examination and assessment using routine clinical instruments for the efficacy and safety of SSRI monotherapy, c) having been followed up for at least 3 months of initiation of SSRI monotherapy. Among 85 subjects a total of 67 subjects met inclusion criteria and then included in the study.

Before SSRI treatment was started each subject was assessed by an experienced child psychiatry fellow and supervisor for a complete psychiatric diagnostic evaluation using DSM-5 criteria. After psychiatric diagnosis subjects were asked to fill out relavant instruments for measuring symptom severity such as anxiety and depressive symptoms. Afterthat they were started SSRIs treatment in routine clinical basis which includes fluoxetine and sertraline as the most commonly used SSRIs in that clinic. As a routine clinical practice each subject started SSRIs monotherapy was assessed after 2 or 3 weeks. Efficacy and safety of SSRIs treatment was evaluated using Clinical Global Impression Scale (CGI), The Screen for Child Anxiety and Related Disorders (SCARED), Children's Depression Inventory (CDI), Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale, and a screening tool for investigating SSRIs associated behavioral activation, mania, apathy and suisidality (SABAMAS). These scales were used in most of the clinical visits. For evaluation in this study we looked for the results at the end of 3 months of medication treatment.

Instruments

Sociodemographic Data

Several parameters including gender, age, education status, medical history, psychiatric diagnoses, family characteristics, and type, dosage and duration of SSRI treatment were coded depending on the information in patients' charts.

Clinical Global Impression Scale (CGI)

In the present study, the CGI-S which ranges from 1 to 7 with 1= normal or not at all ill, while 7= extremely ill and CGI-I which ranges 1 to 7 with 1=very much improved while 7= Very much worse, subscales were used to measure the symptom severity and improvement.

Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale

UKU is a frequently used 48-item scale that measures adverse effects and tolerability related to psychotropic medication. It investigates side effects in four domains including psychic, neurological, autonomic and others for the last 3 days with severity scores changing 0 (no or doubtful side effects) to 3 (severe side effects).

SSRI Associated Behavioral Activation, Mania, Apaty and Suicidality (SABAMAS)

SABAMAS was previously developed by the author (M.C) and used in the clinical practice to investigate four domains of adverse effects including behavioral activation (8 items), mania (3 items), apathy (4 items) and suicidality (3 items) that may emerge during treatment with SSRIs. It consists of a total of 18 items scored from 0 (no adverse effect) to 3 (severe adverse effect that requires medication discontinuation). The internal consistency was measured using Cronbach's alpha coefficient. The Cronbach α coefficient of the SABAMAS in the study was 0.78.

RESULTS: A total of 67 subjects aged 5 to 17 years old (10,82 ± 3,63 years) were included in the study. Almost half of the subjects were male (n=33; 49.3%) and more than half of the subjects were under 10 years of age (n=35, 52.2%). Most frequent diagnoses were social anxiety disorder (SAD) (n=48; 71.6 %), generalized anxiety disorder (GAD) (n=29; 43.3%), attention defict hyperacitivity disorder (ADHD) (n=28; 41.8%), and specific phobia (SP) (n=17; 25.4%). Most frequent diagnoses for SSRI treatments were anxiety disorders (n=50; 74.6%) and obsessive-compulsive disorder (n=10; 14.9%). Most frequently prescribed SSRIs were sertraline (n=43;64.2%) and fluoxetine (n=20; 29.9%). There was a history of diagnosed psychiatric disorder(s) in the first degree relatives in majority of the subjects (n=50; 74.6%). The rates of diagnosed psychiatric disorder(s) in mothers and fathers were 41.8 percent (n=28) and 23.9 percent (n=16) respectively. Table 1 shows clinical and sociodemographic characteristics of the subjects.

At the end of 12th week of SSRI treatment 23.8 percent of the subjects (n=16) had at least one adverse effect in SABAMAS and 70.1 percent (n=47) had at least one side effect in UKU. While irritability was the most frequent adverse effect (n=13;19.4%) in SABAMAS, nausea/vomiting was the most frequent side effect in UKU (n=15, %22.4). No one of the subjects developed neurological side effects in UKU during treatment. Table 2 and 3 show details of SABAMAS and UKU respectively.

Binary logistic regression was used to assess variables predicting behavioral activation, autonomic and psychic adverse/side effects. Regression models for behavioral activation (R^2=0.338, p=0.007), psychic (R^2=0.210, p=0.047) and autonomic (R^2=0.390, p=0.001) adverse/side effects were statistically significant. Behavioral activation was associated with the age of the subject (B= 6.4, CI: 1.05; 39.3, p=0.044), diagnosis of OCD in the subject (B= 6.3, CI: 1.05; 39.3, p=0.034), and psychiatric disorder(s) in the father (B= 4.9, CI: 1.1; 22.7, p=0.036). Psychic adverse/side effects were associated with the diagnosis of MDD in the subject (B=13.6, CI: 1.3; 141.6, p=0.029).

Autonomic adverse/side effects were associated with the age of the subject (B= 0.05, CI: 0.006; 0.488, p=0.009), diagnosis of SAD in the subject (B= 25.5, CI: 2.8; 255.9, p=0.004), and history of incubator (B= 10.3, CI: 1.4; 74.5, p=0.020). Results of binary regression models for the variables predicting behavioral activation, psychic and autonomic adverse/side effects are presented in table 4.

In our study, none of the cases developed bipolar shift and neurological adverse / side effects. The frequency of apathy and suicidal behavior was less than the behavioral activation, autonomic, and psychological adverse/side effects. Medication was discontinued in 13 subjects (19.4%) due to adverse/side effects. The most frequent adverse effect that led to medication discontinuation was behavioral activation (irritability) that occurred in 6 subjects. Table 5 shows details of medication discontinuation.

DISCUSSION: In the current study, children and adolescents using SSGI were evaluated for different side effects for 12 weeks. Behavioral activation, psychological and autonomic side effects are the most common side effects / adverse events in SSRI-treated patients. Nausea / vomiting in autonomic side effects, concentration problems and sedation in psychological side effects , and irritability in behavioral activation were commonly seen. In our study, side effects emerged in 58.2% (n = 39) of children using SSGI and 19.4% (n = 13) of them had to discontinue treatment. The most common reason for discontinuation was behavioral activation. Side effects encountered during the treatment are one of the important causes of treatment incompatibility and failure. IIt is important to inform patients and their relatives about the side / adverse effects correctly at the beginning of the treatment, to follow these cases carefully during the treatment and to manage it correctly when determined, in terms of treatment compliance and treatment success.

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Table 1. Clinical and Sociodemographic Characteristics of the Subjects

	n	%
Age	10,82 ⏥ 3,63 years	
Gender		
Female	34	50.7
Male	33	49.3
Psychiatric disorders		71.6
Social anxiety disorder	48	43.3
Generalized anxiety disorder	29	41.8
Attention deficit hyperactivity disorder	28	27.1
Predominantly inattentive	19	13
Combined	9	25.4
Specific phobia	17	17.9
Obsessive-compulsive disorder	12	16.4
Separation anxiety disorder	11	11.9
Tic disorders	8	9
Major depressive disorder	6	6
Enuresis	4	3
Post-traumatic stress disorder	2	1.5
Panic disorder	1	1.5
Encopresis	1	1.5
Oppositional defiant disorder	1	
Indications of SSRI initiation		
Anxiety disorders	50	74.6
Obsessive-compulsive disorder	10	14.9
Major depressive disorder	6	9
Post-traumatic stress disorder	1	1.5
Type of SSRI		
Sertraline	43	64.2
Fluoxetine	20	29.9
Paroxetine	2	3
Escitalopram	2	3
Mean doses of SSRIs		
Sertraline	41.2±18.6	
Fluoxetin	16.9±7.9	
Paroxetin	10.0±0.0	
Escitalopram	3.5±0.7	

Table 2. SSRI Associated Behavioral Activation, Mania, Apathy and Suicidality (SABAMAS)

	Severity			N (%)
	Mild	Moderate	Severe	
Behavioral activation				13 (19.4)
Irritability	8	4	1	13 (19.4)
Oppositional behaviors	5	4	-	9 (13.4)
Excessive talking	3	4	-	7 (10.4)
Aggressive behaviors	2	3	2	7 (10.4)
Hyperactivity	4	2	-	6 (9)
Risky behaviors	1	2	-	3 (4.5)
Talking with unfamiliar people	1	-	-	1 (1.5)
Self injurious behaviors				-
Manic shift				0 (0)

Euphoria				-
Grandiosity				-
Hypersexuality				-
Apathy				2 (3)
Laziness	-	2	-	2 (3)
Not to care anything	-	2	-	2 (3)
Emotional blunting				-
Passiveness/feeling empty				-
Suicidality				2 (3)
Suicidal ideation	-	2	-	2 (3)
Suicidal behaviour	-	-	1	1 (1.5)
Suicide attempt	-	-	1	1 (1.5)

Table 3. UKU Side Effects				
	Severity			N (%)
	Mild	Moderate	Severe	
Psychic				25 (37.3)
Concentration difficulties	2	5	3	10 (14.9)
Astheniat/lassitude/increased fatigability	3	5	2	10 (14.9)
Sleepiness/sedation	2	2	-	4 (6)
Failing memory	1	2	-	3 (4.5)
Depression				-
Tension/inner unrest	-	5	1	6 (9)
Increased duration of sleep	4	-	-	4 (6)
Reduced duration of sleep	6	-	1	7 (10.4)
Increased dream activity	2	1	-	3 (4.5)
Emotional indifference	1	1	-	2 (3)
Autonomic				20 (29.9)
Accommodation disturbances				-
Increased salivation				-
Reduced salivation				-
Nausea/vomiting	7	5	3	15 (22.4)
Diarrhoea	1	1	-	2 (3)
Constipation	1	-	-	1 (1.5)
Micturition disturbances				-
Polyuria/polydipsia	-	1	-	1 (1.5)
Orthostatic dizziness	6	1	-	7 (10.4)
Palpitations/tachycardia	1	-	-	1 (1.5)
Increased tendency to sweating				-
Other				6 (9)
Rash	2	-	-	2 (3)
Headache	2	2	-	4 (6)

Table 4. Results of Binary Logistic Regression Models for the Variables Predicting Behavioral Activation, Psychic and Autonomic Adverse/Side Effects		
Model 1: Binary logistic regression analysis for predictors of behavioral activation adverse/side effects (R²=0.338 , p=0.007)		
Variables	OR (95%CI)	Significant (p)
BMI (Weight/Height²)	1.04 (0.88-1.22)	0.612

Comorbidity (Absance → Presence)	1.73 (0.24-12.16)	0.578
Age (Above 10 → Below 10)	6.44 (1.05-39.38)	0.044
Diagnosis of OCD (Absance → Presence)	6.35 (1.15-35.04)	0.034
Psychiatric diagnosis in the father (Absance → Presence)	4.95 (1.10-22.17)	0.036
Model 2: Binary logistic regression analysis for predictors of psychic adverse/side effects (R²=0.210 , p=0.047)		
BMI (Weight/Height²)	0.92 (0.81-1.06)	0.272
Psychiatric diagnosis in the father (Absance → Presence)	1.96 (0.53-7.17)	0.309
Diagnosis of SAD (Absance → Presence)	2.63 (0.66-10.51)	0.170
Diagnosis of MDD (Absance → Presence)	13.63 (1.30-144.66)	0.029
History of incubator (Absance → Presence)	2.14 (0.40-11.29)	0.368
Model 3: Binary logistic regression analysis for predictors of autonomic adverse/side effects (R²=0.390 , p=0.001)		
BMI (Weight/Height²)	0.83 (0.69-1.03)	0.054
Comorbidity (Absance → Presence)	1.57 (0.33-7.48)	0.568
Age (Above 10 → Below 10)	0.053 (0.006-0.48)	0.009
Diagnosis of SAD (Absance → Presence)	25.54 (2.88-225.94)	0.004
History of incubator (Absance → Presence)	10.35 (1.43-74.59)	0.020
Note: Bold data, p<0.05 (significance). CI;Confidence Interval. OCD; Obsessive Compulsive Disorder. SAD; Seperation Anxiety Disorder. MDD: Major Depressive Disorder		

Table 5. Details of Medication Discontinuation

Case	*Age (years)/ Gender*	*Indication for SSRI Treatment*	*SSRI Medication and Dosage That Adverse(s) Effect Emerged*	*Adverse Effect(s) Led to Discontinuation*
1	7/F	Separation anxiety disorder	Fluoxetine 10 mg/day	Apathy
2	9/F	Separation anxiety disorder	Sertraline 50 mg/day	Rash
3	10/F	Social anxiety disorder	Paroxetine 10 mg/day	Behavioral activation
4	15/M	Obsessive-compulsive disorder	Sertraline 50 mg/day	Sedation
5	16/F	Generalized anxiety disorder	Sertraline 50 mg /day	Tooth grinding

6	13/F	Social anxiety disorder	Sertraline 50 mg/day	Headache
7	5/F	Obsessive-compulsive disorder	Fluoxetine 5 mg/day	Behavioral activation
8	8/M	Generalized anxiety disorder	Sertraline 25 mg/day	Behavioral activation
9	8/F	Obsessive-compulsive disorder	Sertraline 25 mg/day	Behavioral activation
10	10/M	Generalized anxiety disorder	Sertraline 25 mg/day	Suicidal ideation
11	8/M	Social anxiety disorder	Sertraline 25 mg/day	Behavioral activation
12	15/F	Major depressive disorder	Fluoxetine 20 mg/day	Suicide attempt
13	6/M	Obsessive-compulsive disorder	Fluoxetine 10 mg/day	Behavioral activation

[Abstract:0586]

0586 - Extracting face measurements on children for adhd classification

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ABSTRACT

OBJECTIVE: Attention Deficit Hyperactivity Disorder (ADHD) is characterized by lack of attention, hyperactivity and impulsivity, which starts in early childhood and often continues up to the adolescence and early adulthood. The studies conducted reports its frequency varies between 2-12% throughout the world. ADHD has been started to be investigated under the heading of neurodevelopmental disorders together with DSM-V and, as with many neurodevelopmental disorders, the search for biomarkers for use in the diagnosis of ADHD has recently been increasing. The final focus of the new researches is on identifying phenotypes of ADHD [1-5].

In this paper, our aim is to investigate the face features obtained from the computer vision algorithms that can help the pediatric psychiatrist to diagnose ADHD. In order to realize this aim, facial expressions in the study have been examined. Face recognition problem have been studied in many areas such as security, biometric data analysis, personal data protection and diagnosis in the field of computer vision for many years. The main purpose in face recognition is to detect human faces from photos or videos and then more deeply find out the facial expressions or emotions. The eyes, nose and forehead are distinct individual characteristics of the human face. The researchers have focused on identifying these facial biometric features based on the localization, size and intersection on the face in recent years. We use physical measurement defined as landmark on the face images obtained from the ADHD and healthy subjects for the classification [6-9].

This study aimed to investigate whether the individuals diagnosed with ADHD differ from healthy individuals according to face features applied to machine learning algorithms.

METHODS: Participants: Forty children diagnosed with ADHD and without any comorbid psychopathology and intellectual disability were included as a case group and Forty children without any psychopathology and intellectual disability were included as a control group. All participants were selected by taking into account genetic, gender, nutrition, climate and age factors that effect to facial region development. An acute and/or chronic medical disease, nutritional problems and having a history of trauma/surgery in the head/facial region were exclusion criteria of this study. All participants and their parents were informed in details and informed consent was obtained from the parents. The scenario was obtained as follows; all participants were asked to sit in a table near their parent in order to feel relax. Two photographs of the facial region of children, one from the front and one from the left side were taken.

Face Landmark Detection: Measuring exact feature point on the face represented as face landmark is necessary to extract facial features. For this purpose, we used Google Cloud Vision API in the Firebase ML SDK to extract the face landmark. It is a single development kit that includes Cloud Vision API, Tensor Flow Lite and Neural Network API within the Firebase ML kit SDK. The Google Cloud Vision API offers pre-trained machine learning models. In this way, many basic problem in computer vision such as face recognition, object recognition, and location recognition can be performed robustly and accurately. Using face contour methods, 131 face landmarks on the face surface are extracted from each of the images. Figure 1 shows number of the landmarks in facial region. The x and y axes of landmarks on the face are obtained within face contour method.

Feature Extraction

Facial geometric features are used to determine ADHD disorders based on landmarks. At first, the distance between the landmarks are calculated according to the selected landmarks. In Table 1 describe the number of the lengths depicted by Figure-2 between the coordinate of the landmarks and corresponding their definitions. For instance, the first feature represents forehand width that is calculated using Euclid distance between Y4

and Y32 landmarks in the vertical direction. Then, 256 distance ratio which is another geometric features are extracted from the landmarks shown in Algorithm 1.

CLASSIFICATION: Since we have two class labels of ADHD in the dataset, we use binary classification algorithms as Naive Bayes, k-NN and SWM which are state of the algorithms. The details of each classifier are as follows.

1) Navie Bayes (NB): The Naive Bayes classification algorithm is based on Bayes Theorem that defines the conditional probabilities of the each class. The prior observation is important issue to calculate the probability of the conditions. Our goal is to find the decision rule according to highest probability that also reduce the risk factor. Since we are dealing with two-class, the following Bayes' decision rule is obtained

$$if \ P(w_1|x) > P(w_2) \ \ decide \ w_1 \ \ otherwise \ decide \ w_2$$

where w_1 is the ADHD class and w_2 is the healthy class. The performance of Naive Bayes algorithm is faster than the other algorithms.

2) The k-nearest neighbors (k-NN): The basic idea under the k-NN algorithm is to assign an input vector x to the neighbor class w_i where i=1,2 based on majority voting. We used Euclidian metric to calculate the closest neighbors. If the data is linearly separable in the feature space, k-NN algorithms achieve highly robust performance in two-class problem.

3) Support Vector Machine (SVM): SVM is initially developed for two-classes and then extended to multi-classes which is more difficult to estimate. The idea is that the classification data is assigned to classes by finding optimum hyperplane which separates the data into classes. We used linear SVM to train the features.

Statistical Analysis: Statistical analyzes were performed using Statistical Package for Social Sciences (SPSS) Statistics 20.0 program. For comparison of non-normally distributed variates, Mann-Whitney U test; for comparison of normally distributed variates among the groups, Student t-test was used. The Pearson Chi-Square and Fisher's Exact Tests were used to assessing the distribution of categorical variables. Spearman correlation analysis was performed to determine the relationship between normally distributed variates. Moreover, children diagnosed with genetic syndrome and living in different geographies from the study geographic were excluded from the study. Pearson correlation was performed to determine the relationship between non-normally distributed variates. Statistical significance level was accepted as p <0.05.

RESULTS: A total of 80 children were included in the study, 71.2% (n=57) of the participants were male, and 29.8% (n=23) were female and the mean age was 10.48 ± 2.2. Nose Width, Forehead Height 1, Forehead Height 2, Upper Face Depth measurements were shown statistically significant differences between case and control groups. After we performed logistic analysis, Lenght of Nose Width and Upper Face Dept relevant as an independent risk factor for ADHD.

We used the scikit-learn library in Phyton for all our training and test experiments. All data are randomly partitioned to %80 training and %20 test. Navie Bayes, k-NN and SVM algorithms are used as classifier. Table- 2 shows the precision and recall results for all classification algorithms.

DISCUSSION: ADHD is one of the most common psychiatric disorder in childhood, nevertheless, many cases cannot be diagnosed in the early period. It was stated that the most common cause of diagnostic delay is the lack of biological marker to be used for early diagnosis of ADHD. Studies stated that nose wing width may be related to the neurodevelopmental disorder group. Similar to the literature, we found a strong relationship between the diagnosis of ADHD, a neurodevelopmental disorder, and nasal width length. The depth of the upper face depth was strongly associated with the diagnosis of ADHD. The brain and face develop simultaneously in the embryonic process, and therefore, face phenotype occurs in parallel with the changes in the brain. The prefrontal cortex volumes of individuals diagnosed with ADHD were found to be 5% smaller than those of healthy children. In the present study, the shorter upper face debts in the case group may be related to the small volume of the prefrontal cortex, the projection of the forehead [4-5].

It is concluded from experiments that 93% accuracy rate is obtained with SVN classifier. Although the data set is unbalanced and contains a few numbers of images, it is observed that the accuracy rate is significantly very high.

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TABLO I: COORDINATES AND DEFINITION OF THE LENGTHS

#	Coordinates	Length
1	Y4 – Y32	Forehead length
2	Y56 – Y80	Biocular length
3	Y64 – Y72	Intercantal length
4	Y36 – Y46	Upper Face length
5	Y128 – Y130	Nose length
6	Y88 – Y98	Mouth length
7	Y12 – Y24	Lower Face Length
8	Y72 – Y80	Eye Length
9	(X34 – X38) * 2	Forehead Height 2
10	(X34 – X38) * 2 + (X38 – X56)	Forehead Height 1
11	X18 – X56	Face Height
12	X126 – X129	Nose Length
13	X18 – X129	Lower Face Depth
14	(X9, Y9) – (X126, Y126)	Upper Face Depth
15	(X9, Y9) – (X129, Y129)	Lower Face Depth
16	(X9, Y9) – (X18, Y18)	Ear Length
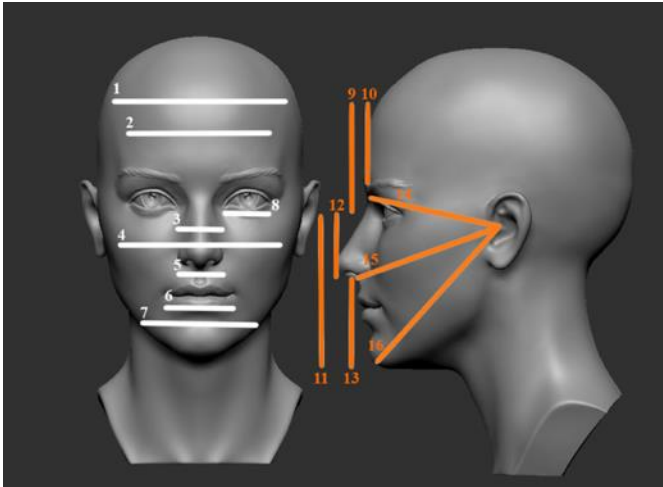
Figure-2 The length features representation based on landmarks

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Algorithms 1 Extracting Ratio Features

Input: $Length_1 \ldots Length_{16}$
Output: $Ratio$

1: **function** LOOP($Length[\,]$)
2:     $Ratio \leftarrow 0$
3:     $N \leftarrow length(A)$
4:     **for** $u \leftarrow 1$ to 16 **do**
5:         **for** $l \leftarrow 1$ to 16 **do**
6:             **return** $Ratio \leftarrow Length(u)/Length(l)$
7:         **end for**
8:     **end for**
9: **end function**

TABLO II: CLASSIFICATION RESULTS BASED ON LENGTH FEATURES AND RATIO FEATURES

	Precision		Recall	
	Ratio	Length	Ratio	Length
SVM ADHD	1	0,57	0,86	0,57
SVM Control	0,90	0,67	1	0,67
KNN ADHD	1	0,22	0,5	0,33
KNN Control	0,55	0,43	1	0,30
Naif Bayes ADHD	0,67	0,89	0,80	0,67
Naif Bayes Control	0,90	0,43	0,82	0,75

[Abstract:0601]

0601 - Functional brain connectivity under resting state and cognitive task: an eeg study

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ABSTRACT

OBJECTIVE: NETWORK Theory is a science that aims to examine systems that are connected with each other through physical or virtual connections. Interrelated structures are transformed into mathematical graph structures by representing them with "nodes" and "links" [15]. Network parameters are used for the analysis of nodes and links. With this method, the relationships between nodes and links are revealed. Although studies on the discovery of the anatomical features of the human brain started in ancient times, the knowledge about how the human brain works is very limited. One of the methods used to investigate how the brain works is brain network analysis [16]. The brain network is a mathematical representation of real human brain architecture [11]. Images and signals from devices such as electroencephalography (EEG), functional MRI (fMRI), magnetoencephalography (MEG), and multielectrode array (MEA) are used to create the brain network [3]. The nervous system produces signals that can be measured externally due to its structure. Using the EEG device, signals are recorded on the human skull using electrodes. EEG signals provide information about the functional state of the brain [2]. The functional brain network obtained using EEG provides information on the diagnosis of neurological and psychiatric diseases [17,18]. Electrodes on the scalp that record the electrical activity of the region in which they are placed are defined as "knots", and the connections between the electrodes are defined as "links" [1].From the mathematical representation of nodes and links, the brain network is obtained. Nodes represent brain regions, while links represent anatomical, functional or effective connections [12]. The network is named differently according to the node and link types of the brain network. The brain network is examined under three main headings: structural connectivity, functional connectivity and effective connectivity. Structured brain network; is the physical network between the anatomical regions of the brain. The functional brain network is the electrical signal-based network between regions. The effective connectivity network is the network that consists of the interaction of the whole system with each other [5]. Functional brain networks are obtained using EEG signals. Functional brain networks are time-dependent and only provide information on the duration of the signal recording. In this respect, it is one of the biological networks class that changes over time in network theory classification [4]. The functional brain network is analyzed and interpreted using complex network parameters. For example, the "average path length" of the complex network parameters is the length of the shortest path between the two nodes. The average path length shows the speed of the transfer of information between the brain regions. If the network has a low average path length value, it indicates that information is transmitted at high speeds between the relevant regions [1].

METHODS: The EEG records used in our study were taken from the Physionet database [6]. Dataset includes records from 36 volunteers. EEG recordings were made by Zyma et al. [7]. EEG recordings were recorded in two different scenarios, at resting state and during mental arithmetic task. The 23-channel Neurocom device was used to record EEG signals. All electrodes are placed on the scalp in accordance with the international 10/20 placement protocol. Ear electrodes (A1 and A2) are selected as reference. All recordings are 60 seconds duration and artifact-free. The sampling frequency is 500 Hz.

Mental arithmetic task: During the EEG recording, it was given to the Volunteers to subtract two numbers in series as a mental arithmetic task. Each EEG trial started with subtract 4-digit and 2-digit numbers (e.g., 2833 and 67). The correct and incorrect results of each volunteer were recorded separately. According to these results, volunteers are labeled as successful and unsuccessful. Detailed information about EEG recording can be accessed from Ref. [7].

In our study, the beta band in the spectrum of EEG between 12-30 hz, which appeared under cognitive functions such as mental activity, problem solving and focusing, was analyzed [13]. We used HERMES to get connectivity matrices from EEG signals. HERMES is a toolbox designed to examine brain connectivity from neurophysiological data for the MATLAB environment [19]. PLV (Phase Locking Value) method in the literature was used to obtain the connectivity matrix. With this method, an unidirectional and weighted functional connection matrix is obtained. PLV

method examines the phase difference between two signals whose relationship is examined. The distribution of the phase difference of the two signals examined on the unit circle is determined. A weight value between 0 and 1 is defined between the two signals examined at the end of the process. The relationship decreases as the weight value approaches 0, and the relationship increases as you approach 1. The PLV method is formulated as follows [9,10].

Functional connectivity matrices are calculated for rest and mental processes for women and men. In addition, regardless of gender, connectivity matrices of successful individuals and unsuccessful individuals were calculated for rest and mental processes. In connectivity matrices, disruptive noise occurs because all areas of the brain are in relationship. Low weight (weak link) links were removed using the threshold value to make the network more meaningful by clearing the disturbing noise between the nodes. Using the threshold values, parameters of the brain network were calculated. If we briefly explain the related parameters; Strength parameter is the sum of all link weights divided by the number of nodes. The average path length is the shortest path length between nodes. The average Clustering coefficient is the average neighbor ratio of the neighbors of the nodes. Density parameter is the number of links available divided by the maximum number of links possible [14]. Brain Connectivity Toolbox for MATLAB was used to calculate network parameters [20].

RESULTS: Adjacency matrices according to genders and successes are given in figure 3.

When the average weights of adjacency matrices in women and men are compared, it is seen that the average weight in women is more intense than men in resting state. However, during mental processes, the average weight of men exceeds the average weight of women. The average weight for women decreases slightly during the transition from rest to mental tasks. When the functional brain network of rest and mental processes is examined in successful and unsuccessful individuals, it is seen that the average brain network of successful individuals is higher in both cases. The functional network of the successful group, regardless of gender, appears to be denser and contain more connections.

"Strength", "Avg. Clustering Coeff. "," Density "values are higher than the male brain. These parameters show that the female brain is more active and conscious at rest. As the average path length of the brain decreases, the speed of communication increases as the distance between the nodes decreases. From this point of view, the average path length of the male brain at rest is higher than that of women. This indicates that the communication speed of the male brain at rest is lower than that of women.
When the functional brain network for men and women was examined under mental processes, it was seen that the indicators in figure 4 were reversed. Strength, which are indicators of the activity of the brain, "Avg. Clustering Coeff. "," Density "values increased for men and women. Compared to rest status for women and men, there has been an increase in mental processes. This is an indication that the male brain is more active and more motivated than the female brain under mental processes. Similarly, the average path length value was higher in women than in men. In Figure 4, the average path length was the opposite.

Rest status parameters of Successful / Unsuccessful individuals in Figure 6 are better than successful individuals. In this case, it can be said that the brains of successful individuals are more active, more connected and faster.

When the parameters are analyzed under the Successful / Unsuccessful Mental Processes in Figure 7, it is seen that the brains are more active, more connected and faster than the unsuccessful individuals as in Figure 6.
Discussion:As a result of the examination of the functional brain networks obtained from the EEG records using the PLV method, it was observed that there was a difference in terms of network theory parameters between resting status and mental processes by gender. It was also observed that there was a similar difference between successful / unsuccessful individuals regardless of gender. As a result, it has been observed that the female brain is more active and connected than the male brain at rest. The male brain was observed to be more connected and motivated than the female brain during mental processes. Similarly, when the functional brain networks of successful and unsuccessful individuals were compared, it was observed that the brains of successful individuals were more active and more communicative than the unsuccessful individuals during rest and mental activity.

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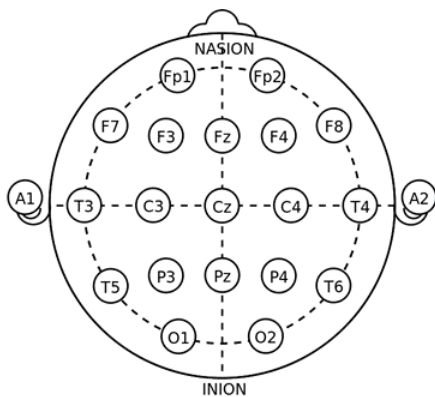
Figure 1: 10/20 EEG placement protocol [8].

Resting state: EEG recordings of the subjects taken at rest. It was recorded just before mental arithmetic procedures.
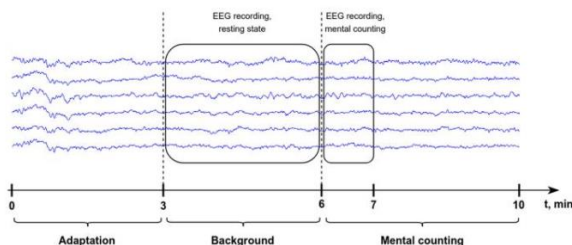
Figure 2: EEG data collection during the experiment [7].

$$PLV = \left| \frac{1}{N} \sum_{n=1}^{N} e^{i\Delta\varphi_{rel}(t_n)} \right|$$
$$= \sqrt{cos\Delta\varphi_{rel}(t)^2 + sin\Delta\varphi_{rel}(t)^2} \quad (1)$$
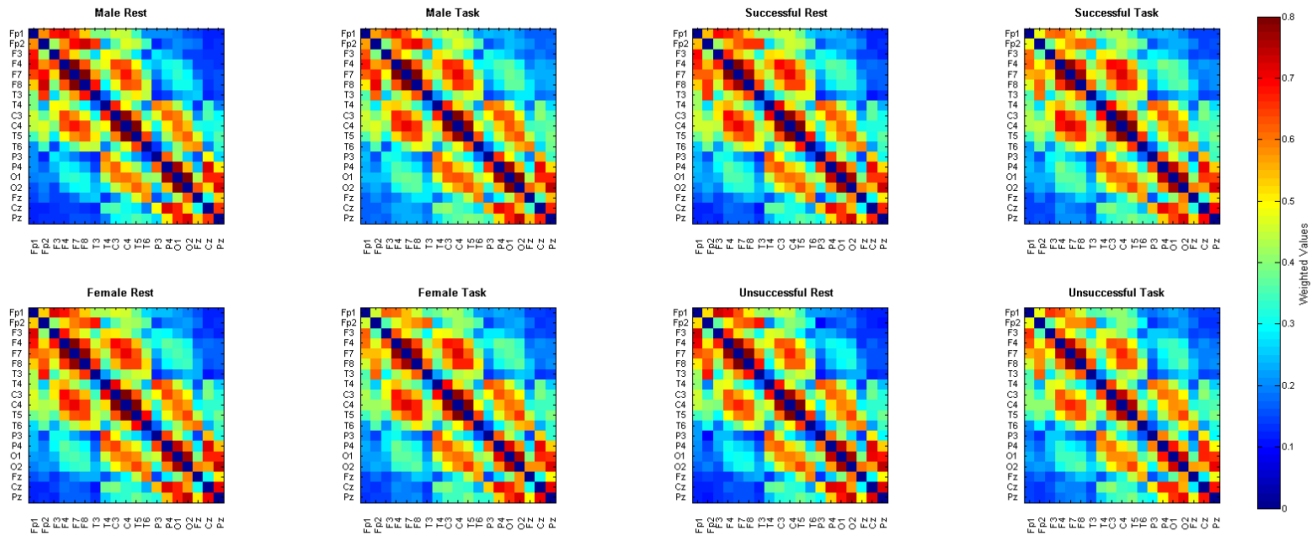
Figure 3: Adjacency matrices regarding male/female, rest/task and successful/unsuccessful status of the individuals

	Functional Brain Network	
	Rest	Task
Male	0,4175	0,4437
Woman	0,4316	0,4186
Successful	0,4331	0,4269
Unsuccessful	0,4150	0,4197

Table 1: Average link weights of adjacency matrices

Figure 4: Network parameters under resting condition of male/female volunteers. (a) Strength, (b) Avg. Path Length, (c) Avg. Clustering Coeff., (d) Density.	Figure 5: Network parameters under cognitive task condition of male/female volunteers. (a) Strength, (b) Avg. Path Length, (c) Avg. Clustering Coeff., (d) Density
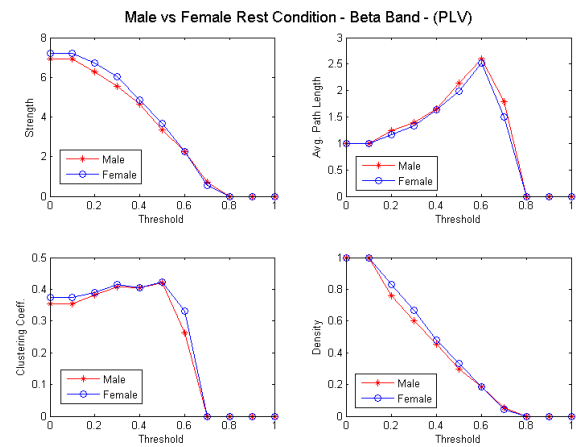
Figure 6: Network parameters under resting condition of successful/unsuccessful volunteers. (a) Strength, (b) Avg. Path Length, (c) Avg. Clustering Coeff., (d) Density.

Figure 7: Network parameters under arithmetic task condition of successful/unsuccessful volunteers. (a) Strength, (b) Avg. Path Length, (c) Avg. Clustering Coeff., (d) Density
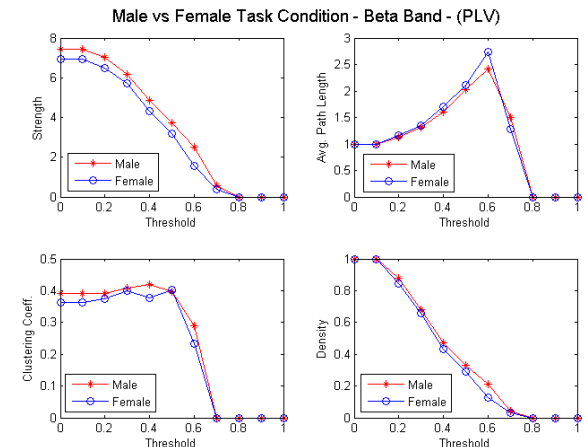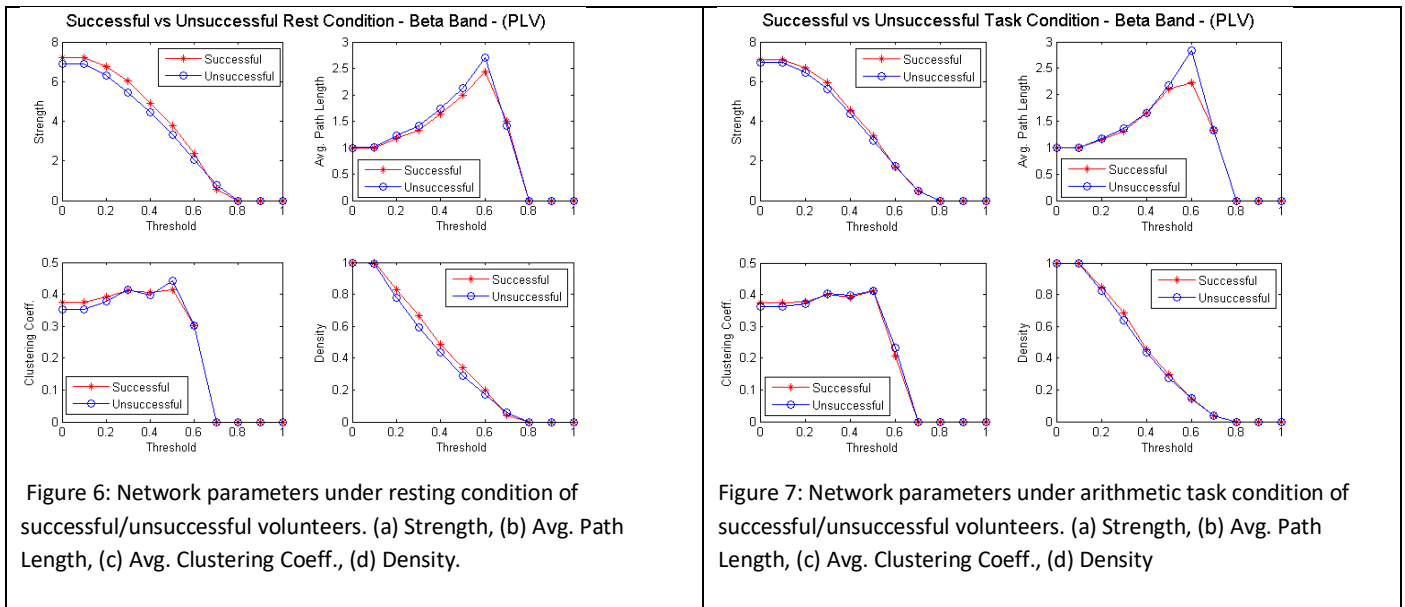
[Abstract:0611]

0611 - Detailed assessment of asymmetry of brain regions in major depressive disorder

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ABSTRACT

OBJECTIVE: Major Depressive Disorder (MDD) is a mental disorder which can be widely seen throughout life and progress with serious impairments in functionality; but its etiology still remains unclear [1,2]. Classification of MDD subtypes aims to better define its biological basis and clarify the uncertainty in the heterogeneity of depressive disorders [3]. Neuroimaging studies with the purpose of reaching the biological basis of MDD showed that; both functional and structural differences in brain can be seen in MDD patients [2]. Magnetic resonance imaging (MRI), one of the neuroimaging methods, is widely used to identify pathophysiological findings in different parts of the brain [4]. While the gold standard for segmentation is to manually analyze the data in MRI studies, automatic approaches with several potential advantages over manual segmentation, are increasingly used due to time limitations. These model based approaches assume that algorithms can reliably identify anatomical regions, regardless of interpersonal differences or pathological changes in neuroanatomy and/or analysis of MRI brain data. Fully automatic segmentation approaches such as volBrain (http://volbrain.upv.es, Manjón ve Coupé 2016) have been developed in order to eliminate the effects of these confounding factors [5, 6].

Brain imaging studies using positron emission tomography (PET) and MRI measurements have found evidence of abnormalities in multiple brain areas including prefrontal cortex (PFC), superior temporal cortex, anterior cingulate cortex (ACC), amygdala, insula, basal ganglia and cerebellum but lateralization of these abnormalities in right or left brain hemispheres is not fully focused on the right and left sides of the brain are asymmetrical in terms of anatomy and function [7]. And most imaging studies are not specifically designed to study hemispheric asymmetry. Structural MRI studies found smaller hippocampal volumes in patients with MDD compared to healthy controls, and two meta-analyzes reported that the right hemisphere hippocampal volumes were larger than the left [8, 9]. In the literature, a meta-analysis study was carried out showing that the bilateral caudatus, left putamen and left nucleus accumbens were less responsive to the award stimuli [10, 11]. Hypoactivation of the right caudate has been reported during the processing of positive stimuli in depressive patients [12]. The reduced activity of the right caudate during failure to recognize positive emotions was also found in a study on treatment-resistant patients with MDD [7]. Neuroimaging studies may provide valuable clinical data regarding the role of biological infrastructure and clarify the possible clinical effects of neurophysiological alterations in MDD.

In the literature, fully automatic segmentation studies such as volBrain have not been implemented in neuroimaging studies on MDD before so with this study, by obtaining the results of detailed volumetric measurements from 3 Tesla MRI data. We aimed to examine the biological infrastructure of MDD and evaluate the usability of volBrain application in clinical studies.

METHODS: Recruitment period between September 2016 and January 2020, involved inclusion of 20 patients, 10 cases and 10 controls, who were referred to the psychiatry outpatient clinics of our hospital and met the inclusion criterion of the study and their 3 Tesla MRI data were gathered retrospectively from Recep Tayyip Erdogan University (RTEU) Medicine Faculty Image Archiving and Communication System (PACS).

Inclusion criterion of the study were; being 18-85 years old, having a diagnosis of depressive disorder in the hospital automation system with no additional comorbid psychiatric or neurological diagnosis and/or treatment, having volumetric axial T1 brain sequences taken via 3 Tesla GE Discovery Magnetic Resonance (MR) 750W GEM ENAB device which were evaluated as "normal" by the Department of Radiology. Patients who had comorbid psychiatric/neurological comorbidities, were younger than 18 or older than 85, whose MRI data was not from his/her depression time period or had abnormalities in their MRI reports evaluated by the Department of Radiology were excluded from the study. Same MRI sequences were obtained from control group who were matched with case group in regard of sociodemographic characteristics and had similar medical history with the case group. Same inclusion criterion were applied to case group.

MATERIALS

1. RTEÜ Training and Research Hospital Electronic Sociodemographic data form: A form that will be created by researchers to evaluate the sociodemographic and clinical data of the patients

2. Brain MR images: Volumetric axial T1 sequence brain sequences were obtained wia 3 tesla GE Discovery Magnetic Resonance (MR) 750W GEM ENAB device.

3. Volbrain: Automatic and reliable quantitative MRI is an internet based brain image analysis program. Sequences of case and controls will be transformed into a different rar file for each individual which is suitable for Volbrain via supplementary computer program then included in the Volbrain analysis (https://volbrain.upv.es/members.php).

RESULTS: The study included 10 patients with MDD and 10 ~~healthy~~ controls. No statistically significant difference was found between the mean age of the MDD group was 60.4 ± 21.3 years and the mean age of the control group was 58.7 ± 20.1 years; Mann Whitney U Test, p=0.912), gender (p=0.371; Pearson Chi-Square test). In our study, right and left volumes of whole brain white and gray matter, cerebrum, cerebellum, caudate, putamen, thalamus, globus pallidus, hippocampus, amygdala, accumbens regions were measured and proportioned (right / left). It was calculated that the right / left (R / L) volüme ratios of nucleus caudatus were lower in the case group than in the control group (p=0.035). No statistical differences were found for other investigated brain regions.

CONCLUSIONS: In the literature, compared to other neuroanatomical structures, the decrease in the volume of nucleus caudatus has been found to be consistent in many previous studies [11, 13]. In our study with Volbrain, the results regarding caudat volumes were compatible with the literature. In line with the literature, the results obtained with the application of Volbrain may be meaningful in terms of the reliability of its use in clinical investigations. Additionally, morphometric results suggest that anhedonia, which is one of the two criteria that should be found in order to diagnose major depressive disorder, is related to caudate volume. Relationship between detailed psychiatric examination and volume measurements via MRI might be valuable for the future studies on psychiatric disorders [14]. It is unclear whether the reduced caudate volume makes individuals susceptible to anhedonia or more severe depression, or if these neurophysiologcal alterations are results of the processes going on in MDD itself [11]. Relatively small sample size being as single center study, retrospective design and confounding effects of medications, might be counted as limitations of this study; but using a fairly new and previously unused method can make this study valuable. Another implication of this study is that; pathophysiological mechanisms of MDD may be related to decrease in nucleus caudatus volumes and R / L ratios. Volbrain is a newly introduced fully automatic segmentation technique. It is likely that fully automated segmentation techniques, which can be uploaded to cloud storage systems, will play an important role in volumetric brain analysis in the near future. Volbrain application being a fully automatic segmentation technique can contribute to the reduction of the differences between manual measurements between clinicians and support the achievement of objective and reliable results. Decrease in R / L ratios that be found in our study is in line with the literature. Research on fully automatic segmentation techniques might be the driving force behind fully understanding biological foundations of MDD in the future. Successfull implementation of Volbrain in our study suggests that Volbrain may be an important part of clinical applications in many other neuropsychiatric disorders in the near future.

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[Abstract:0632]

0632 - Do peripheral inflammatory markers discriminate the clinical stage of schizophrenia? A perspective from trait-or-state dilemma

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ABSTRACT

Objective:Although increasing evidence implicates inflammatory processes in the pathophysiology of schizophrenia, it remained unclarified that to what extent enhanced inflammatory tone plays a role in the relapse-remission cycle of the disorder. Numerous blood-derived inflammatory markers including the neutrophil/lymphocyte-ratio (NLR), platelet/lymphocyte-ratio (PLR), monocyte/lymphocyte-ratio (MLR), red-cell distribution width (RDW), and mean platelet volume (MPV) have been examined in schizophrenia; however, research into discrimination of clinical stages of schizophrenia via inflammatory markers is insufficient. C-reactive protein (CRP) is a well-documented circulating marker for systemic inflammation, and albumin is a negative acute-phase protein. However, the CRP/albumin ratio (CAR) is suggested to be a better indicator of an inflammatory response than CRP or albumin alone [1]. The neutrophil/albumin ratio (NAR), which has recently only been studied in patients with cancer, because higher NAR indicates an enhanced inflammatory status that worsens cancer prognosis and treatment response [2]. Furthermore, CAR and NAR which are novel biomarkers of the systemic inflammatory response have not been studied in schizophrenia, yet. In this study, our aims were as follows: (1) to examine CAR and NAR as novel peripheral inflammatory markers in patients with both acutely exacerbated and remitted schizophrenia, and to compare them between patient and control groups; (2) to reveal whether peripheral inflammatory markers discriminated patients and controls and whether these markers varied between patients with acute exacerbation and remission; and (3) to determine optimum cut-off levels of CAR and NAR for the diagnosis of schizophrenia.

Methods: This cross-sectional retrospective study included data of patients who were admitted to the outpatient unit or the inpatient clinic in the Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery within a six-month period between September 15th, 2018, and March 15th, 2019. Patient data, which were retrieved anonymously by the researchers upon the permission of the institute board, was extracted from the electronic medical records of the hospital without any accessible personal identifying information of the patients except their hospital registration number. Inclusion criteria for patients were as follows: aged 18-65 years and being admitted or hospitalized with a primary diagnosis of schizophrenia (ICD-10 codes between F20.0-F20.9). Exclusion criteria were as follows: presence of a comorbid psychiatric disorder, systemic diesease or pregnancy. A comparison group of healthy controls consisted of 445 individuals who visited our outpatient unit for purposes of pre-employment health check-ups or employee medical examinations, coded with ICD-10 Z00.00, aged 18-65 years, and without any previous psychiatric or medical diagnosis coded in the hospital electronic database.

Preliminarily, data of 1498 patients who attended the outpatient unit or were admitted to the inpatient clinic within the designated time frame were screened. Six hundred eighteen patients were included in the study. The patients were assigned to two groups as schizophrenia-acute exacerbation(AE) and schizophrenia-remission(R). Schizophrenia-AE defined patients with a psychiatric admission with an acute relapse or following the first 24 h of psychiatric hospitalization, and schizophrenia-R represented patients who were admitted to the outpatient setting for a routine follow-up. The study was approved by the local ethics committee[IRB: 03.05.2016 – 2016/523].

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) for Mac OS, Version 23.0 software. A Chi-square test and an independent sample t-test were used for comparisons of categorical and parametric variables between the patient and the control groups. For the comparison of inflammatory markers amongst the schizophrenia-AE, schizophrenia-R, and control group, one-way analysis of variance(ANOVA) was used, and Tukey's honestly significant difference(HSD) test was performed for post-hoc analysis of pairwise comparisons. Pearson's rank correlation test was performed to analyze associations between peripheral inflammatory markers with each other and with clinical characteristics. Receiver operating characteristic(ROC) analysis was used to show the use of CAR and NAR in differentiating between patients with schizophrenia and healthy controls. A binomial logistic regression analysis was performed to examine the predictive power of inflammatory markers for the diagnosis of schizophrenia. A p-value of less than 0.05 was considered statistically significant.

Results: Descriptive characteristics of the study population are presented in Table 1. There were no differences between the patient and control groups with regard to sex; however, age was higher in the patient group compared with the healthy controls. The duration of illness and number of hospital stays did not differ between the patient groups, whereas the total duration of hospital stays of patients in remission was longer than was for patients with acute exacerbations.

An independent sample t-test showed that the inflammatory markers were significantly higher in patients with schizophrenia than in control subjects(p<0.001). The results of one-way ANOVA revealed that there were statistically significant differences between the schizophrenia-AE, schizophrenia-R, and control groups in terms of inflammatory markers. Further, post-hoc analysis using Tukey's HSD test was performed and it was found that none of inflammatory markers except NAR differed between the schizophrenia-AE and schizophrenia-R groups. All markers were strongly significantly higher in patients with schizophrenia-AE compared with healthy controls(p<0.001). Additionally, all markers, except MLR and MPV were significantly higher in patients with schizophrenia-R than in controls (p<0.05)(Table 2).

The results of Pearson's rank correlation test, with which we examined bivariate correlations of inflammatory markers with each other, showed that except CAR-MPV, NAR-MPV, PLR-MPV, and MLR-MPV relationships, there were statistically significant and positive correlations between inflammatory markers with each other. CAR, NAR, NLR, PLR, MLR and RDW were not significantly correlated with clinical variables. However, MPV was significantly and negatively correlated with the number of hospital stays and total duration of hospital stays.(Table 3)

The ROC analysis revealed that a CAR value lower than 95% (95% CI: 0.863-0.902) and 0.388 as a cut-off, differentiated patients with schizophrenia from healthy controls with a sensitivity of 81% and a specificity of 81% (area under the curve (AUC) 0.882, p<0.001), and 0.885 as a cut-off value for NAR (95% CI: 0.712-0.770) differentiated patients with schizophrenia from healthy controls with a sensitivity of 68% and a specificity of 67.5% (AUC 0.741, p<0.001)(Figure 1).

The hypothesized relationship between the diagnosis of schizophrenia CAR and NAR was further tested in a binomial logistic regression analysis. Sex, CAR, NAR, NLR, PLR, MLR, RDW, and MPV were entered in the first step of the analysis. We decided not to test the predictive value of age because the mean age of patients was significantly higher than that of controls, which implied that age would have a substantial effect on the diagnosis of schizophrenia. The logistic regression analysis indicated that CAR (p<0.001), NAR (p=0.001), and MPV (p=0.001) were significant predictors of diagnosis.

Conclusion: The principal findings of the present study were peripheral inflammatory markers were increased in a relatively large sample of patients with schizophrenia compared with healthy controls. This is the first study to examine CAR and NAR in a psychiatric population.

The CAR is a novel biochemical marker of systemic inflammatory response and has been associated with poor survival and treatment response in various cancer types, inflammatory activity in autoimmune diseases, and sepsis [3]. In addition, CAR has a weak but significant correlation with NLR [4]; however, in our study, CAR was strongly correlated with other peripheral inflammatory markers including NLR.

We also found that none of the peripheral inflammatory markers, except NAR, differed between patients with schizophrenia-AE and schizophrenia-R, which may support the notion that inflammation is rather a trait-related phenomenon in schizophrenia. Our findings are consistent with the insight that inflammation is not directly associated with clinical relapse; it rather reflects a pathophysiologic process that may be related to the occurrence of schizophrenia.

We constructed ROC curves to determine optimum cut-off levels of CAR and NAR for the diagnosis schizophrenia. The cut-off value of CAR found in our study was 0.388 with a sensitivity of 81% and a specificity of 81%, and 0.885 as a cut-off value for NAR had lower sensitivity and specificity. To date, few studies have reported cut-off levels of peripheral inflammatory biomarkers such as NLR, IL-6, and the high sensitivity-CRP/IL-10 ratio; however; insufficient power of sensitivity and/or specificity for these markers were denoted. Our finding suggests that CAR, as an inflammatory biomarker, may be used to support the diagnosis of schizophrenia.

According to the logistic regression analyses, CAR, NAR, and MPV were significantly predictive of a diagnosis of schizophrenia. In a previous study, logistic regression analysis failed to demonstrate a significant predictive value of MPV for the diagnosis of schizophrenia[5], and the predictive values of CAR and NAR for schizophrenia have not yet been studied. Our findings suggest that a combination of inflammatory markers including CAR and NAR could be used to reflect the increased inflammatory status in schizophrenia.

This study showed that, except NAR, peripheral inflammatory markers did not significantly vary between patients with relapse and remission, suggesting that inflammation is rather a trait marker for schizophrenia. Additionally, we brought CAR and NAR as peripheral trait biomarkers, which may reflect enhanced inflammatory signalling in schizophrenia, to the relevant literature. On the other hand, both biomarkers should be further examined in larger patient groups.

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Table 1: Descriptive Variables of the Study Groups

	Patients n=618	Controls n=445	χ^2 / t	df	p
Sex			0.00	1	0.98
Male	310	223			
Female	308	222			
Age	39.68+10.564	31.22+9.69	13.515	1001	<0.001*

	Patients		t	p
	Acute Exacerbation (n=439)	Remission (n=179)		
Duration of illness (years)	11.35+9.06	12.88+8.72	1.928	0.54
No. of hospital stay	4.62+5.77	4.31+6.08	-0.601	0.54
Total duration of hospital stay (months)	4.09+5.85	6.30+13.1	2.179	0.03*

Note: χ^2: Chi-square, t: Student's t-test

*p<0.05 statistically significant

Table 2: Comparison of Peripheral Inflammatory Markers Between the Groups

	PATIENTS		CONTROLS							
	Schizophrenia-AE	Schizophrenia-R		T	P^{1A}	F	P^{2B}	P^{3C}	P^{4C}	P^{5C}
CAR	1.54±2.05	1.34 ±1.35	0.23 ±0.21	16.316	<0.001	97.895	<0.001	0.283	<0.001	<0.001
NAR	1.16 ±0.43	1.06 ±0.37	0.83 ±0.32	13.487	<0.001	88.94	<0.001	0.007	<0.001	<0.001
NLR	2.27 ±1.41	2.09 ±1.17	1.65 ±0.6	9.3	<0.001	6.411	<0.001	0.162	<0.001	<0.001
PLR	125.03 ±58.95	123.27 ±62.07	108.93 ±36.57	5.256	0.001	11.969	<0.001	0.921	<0.001	0.005
MLR	0.28 ±0.13	0.26 ±0.10	0.24 ±0.20	3.21	<0.001	88.94	0.002	0.253	0.001	0.496
RDW	13.93 ±2.58	13.95 ±2.91	12.92 ±5.32	4.064	<0.001	8.255	<0.001	0.997	0.001	0.010
MPV	9.36 ±1.94	9.2 ±1.72	8.90 ±1.86	3.568	<0.001	6.804	0.001	0.615	0.001	0.158

[A]Student's t-test; [B]One-way ANOVA; [C]Tukey-HSD for ANOVA post-HOC

p1: patients *vs.* controls

p2: schizophrenia-AE *vs.* schizophrenia-R *vs.* controls

p3: schizophrenia-AE *vs.* schizophrenia-R

p4: schizophrenia-AE *vs.* controls

p5: schizophrenia-R *vs.* controls

Schizophrenia-AE: acute exacerbation, Schizophrenia-R: remission, CAR: C-reactive protein/ albumin ratio, NAR: Neutrophil/ albumin ratio, NLR: Neutrophil/ lymphocyte ratio, PLR: Platelet/ lymphocyte ratio, MLR: Monocyte/ lymphocyte ratio, RDW: Red-cell distribution width, MPV: Mean platelet volume

*p<0.05 statistically significant

Table 3: Pearson Rank correlation coefficients between inflammatory markers and clinical variables

	Age	Duration of illness (yrs.)	No. of hospital stay	Total duration of hospital stay (mos.)
CAR[a]	0.084*	0.071	0.021	-0.001
NAR[a]	0.052	0.043	0.042	-0.002
NLR[b]	0.038	0.032	-0.017	-0.026
PLR[a]	0.127**	0.043	-0.018	-0.032
MLR[c]	0.034	0.013	0.009	-0.017
RDW[c]	0.024	0.007	-0.011	-0.067
MPV[a]	-0.015	-0.056	-0.099*	-0.148**

Note:

[a]Statistical significance was not observed for CAR-MPV, NAR-MPV, and PLR-MPV correlations (p>0.05), while observed for other bivariate correlations; [b]significantly correlated with all other inflammatory markers ($p<0.05$); [c]RDW-MLR is not significantly correlated; significant correlation existed with other markers ($p<0.05$)

r: Pearson Rank correlation coefficient

*Correlation is significant at the .05 level (two-tailed).

**Correlation is significant at the .01 level (two-tailed)

Figure 1: Receiver Operating Characteristic (ROC) Curves for The Diagnostic Ability of CAR and NAR (patient *vs.* control)
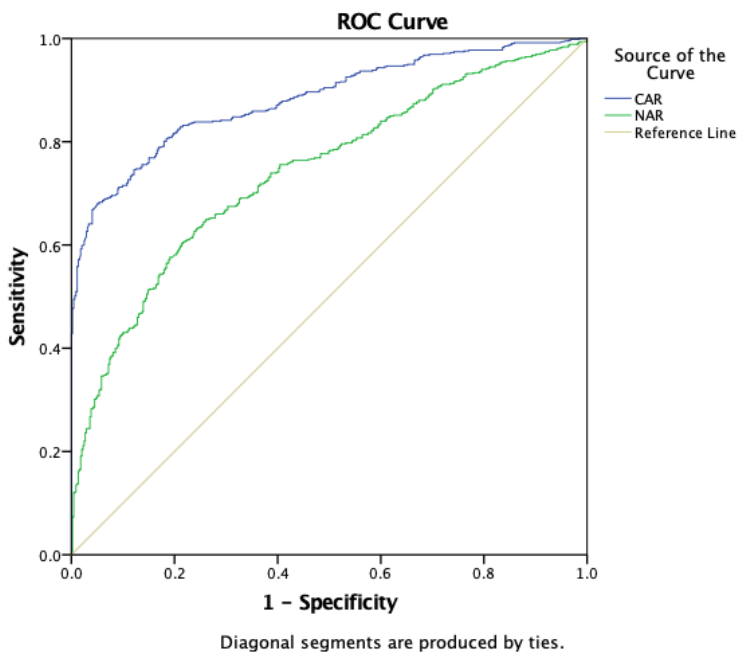
Legend: ROC curves for CAR and NAR values for the diagnosis of schizophrenia. CAR: AUC 0.882 (95% CI=0.863 to 0.902), p<0.001; NAR: AUC 0.741 (95% CI=0.712 to 0.770), p<0.001

AUC: Area under the ROC curve

[Abstract:0640]

0640 - The retrospective evaluation of the children who applied to the health board of disability

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ABSTRACT

OBJECTIVE: Disability is defined as an impairment, limited functioning and restricted participation in daily life, and the difficulties of the interaction between the individual and environmental factors which prevent people from living their life equally with others. Understanding the difficulties and needs and being aware of disabilities are primary to remove the barriers. Disabilities, either congenital or not, cover orthopedic, sensory, speaking, mental, chronic disorders. Preventions should address the barriers that people with disabilities struggle with besides treatments of their health conditions [1].

There are many struggles to measure disability and to suggest that each type of disability needs a certain type of special care. Because people with disabilities can experience different disadvantages even if they have the same health condition. Contextual factors (environmental and personal) are important as well as health conditions to understand disabilities [1].

Disability prevalence among children aged 0-14 is estimated to be 93 million (%5.1) by World Health Organization (WHO), however, it varies according to the measurement methods or definition of disability [1]. Prevalence of the children with disabilities aged 0-19 years in Turkey is estimated to be 8.78% [2] consistent with the review showing child disability prevalence from 0.4% to 12.7% in low- and middle-income countries [3].

In Turkey, people with disabilities apply to the health board of disability at hospitals to benefit from disability-related services. Related doctors examine the people who applied to the health board of disability to specify their disabilities and special care needs. Information from at least two different contexts (school, family ext.) or follow-up, observation, psychometric tests is usually required to diagnose a psychiatric disorder of children. Some of the children with disabilities see a child psychiatrist for the first time at the health board of disability, however, it is important to get a diagnosis, determine comorbidities and receive treatments.

Many children with disabilities have difficulties benefit from healthcare, education, and disability-related services. Disability is understood as a human right and development issue, however, the science behind disability is not very well studied and there is a lack of information about its epidemiology to improve the policies and to meet the needs of people with disabilities [1]. And also rates of the history of psychotropic medication use and admission to child psychiatry outpatient clinic of the children applied to the health board aren't known. Establishing these rates will help to predict if children with disabilities get a diagnosis, determine comorbidities, and receive treatments. This study aims to enlighten on the approach and arrangements for children with disabilities by determining the follow-up and treatment in psychiatry by evaluating the patients who apply for the health board of disability.

METHODS: The children, aged 0-18 years and applied to the health board of Şırnak Cizre Dr. Selahattin Cizrelioğlu State Hospital in one month to benefit healthcare, education, and disability-related services, were evaluated. Their gender, age, complaint of admission, history of psychotropic medication use, admission to child psychiatry outpatient clinic and health board, diagnoses, and special care need levels were recorded.

Complaints of admission were distinguished as other medical causes, developmental disability, academic difficulty, speech problems, autism, behavioral problems, movement disorders. Diagnoses were recorded as intellectual disability, specific learning disorder, speech disorders, autism spectrum disorder, no active psychopathology, and follow-up recommendation. Special care need levels were recorded as ''no special needs (SN) '', ''SN'', ''mild SN'', ''moderate SN'', ''advanced SN'', ''very advanced SN'', ''significant SN'', ''special condition needs''.

The data were analyzed with Statistical Package for Social Sciences (SPSS) and descriptive statistical methods were used. Before data analysis, the Kolmogorov Smirnov test was used for a normality evaluation of the continuous variables. The ages were normally distributed. The data were presented with frequencies and percentages. Statistical significance was established at $p < 0.05$.

RESULTS: A total of 107 patients applied to the health board in 1 month to benefit healthcare, education, and disability-related services. The mean age of the children was 8.86 ranging from 4 months to 17,5 years. There were 66 (61.7%) male children.

The complaints of these patients were 36 (33.6%) other medical causes, 29 (27.1%) developmental disability, 28 (26.2%) academic difficulty, 8 (7.5%) speech problems, 4 (3.7%) autism, 1 (0.9) behavioral problems, 1 (0.9%) movement disorders. It was determined that 89 (83.2%) patients did not apply to the child psychiatry outpatient clinic before, 94 (87.9%) patients didn't use any psychotropic medication and 50 (46.7%) patients didn't apply to the health board before.

The diagnosis of the children were 45 (42%) intellectual disabilities, 13 (12.1%) specific learning disorders, 6 (5.6%) speech disorders, 5 (4.7%) autism spectrum disorders, while no active psychopathology was detected in 26 (24.3%) children and follow-up was recommended for 12 (11.2%) patients. Special requirement levels were 38 (35.5%) ''no special needs (SN) '', 30 (28%) ''SN'', 17 (15.9%) ''mild SN'', 5 (4.7%) ''moderate SN'', 8 (7.5%) ''advanced SN'', 2 (1.9%) ''very advanced SN'', 1 (0.9%) ''significant SN'' and 6 (5.6%) ''special condition needs''.

DISCUSSION: Despite the frequency of children with disabilities and the importance of this issue, the studies about psychiatry admissions and treatments of psychiatric disorders of children with disabilities are limited. In this study, the children who applied to the health board for one month were analyzed concerning their former treatment or follow-up.

The prevalence of male children (61.7%) was found higher than female children in this study consistent with the findings of the other studies done in Turkey which have a rate ranging from 61.6% to 67,8% of male children applied to health board [4,5]. However, these findings of Turkey aren't in conformity with global findings which establish a higher rate of women with disabilities [1]. These low rates of female children who applied to health boards in Turkey show that they get less disability-related services and there is a need to reach especially female children with disabilities to provide their rights.

In this study, it was found that most of the applicants have psychiatry-related complaints and psychiatry-related disabilities, eventually. Most of the children were diagnosed with intellectual disabilities. Specific learning disorders, speech disorders, autism spectrum disorders followed it, respectively. There were 35.5% of children who didn't get a psychiatric diagnosis and didn't need special care related to psychiatric disorders at the moment of health board application. Most of the children needed special care. Mild special care, advanced special care, special condition care, moderate special care, very advanced special care, and significant special care followed it. These special need levels are specified according to ''The Implementing Regulation on Special Needs Assessment for Children'' which has been developed to create a standard language and framework by the ministry of health in Turkey.

Although the applications of the health board of disability were largely due to psychopathologies, the number of children who were admitted to the child psychiatry outpatient clinic and/or used psychotropic medication was found to be in the minority. It is known that children with disabilities frequently have other psychiatric disorders that are needed to be treated either their disabilities are related to psychiatry or not. However, this study shows that the majority of children with disabilities neither applied to the child psychiatry outpatient clinic nor used any psychotropic medication, while their application prevalence for health boards is higher. These findings indicate that there is a deficit in the access of children with disabilities to psychiatric admissions and possible treatments.

This study has some important limitations. The relatively small sample size and recruiting the children from one hospital record prevent the findings to be generalized. On the other hand, accessing the data of psychiatry admission or psychotropic medication use of the children, and providing information about the region are strengths of this study.

In conclusion, some fewer female children benefit from disability-related services, and the prevalence of children with disabilities who are admitted to child psychiatry and get treatment is low. It is suggested to investigate the reasons that hinder the admissions of children with disabilities for their mental health, and to provide arrangements for their follow-up and treatment. Further studies recruiting a larger sample size from multiple centers are needed to have a better understanding of general demographic information, psychiatric follow-up, and treatment rates of children with disabilities.

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[Abstract:0648]

0648 - Vortioxetine has anticonvulsant activity on the pentylenetetrazole ınduced kindling model in rats

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ABSTRACT

Background: Epilepsy is a devastating neurological disorder that is characterized by recurrent convulsions. Approximately 1/3 of patients are drug-resistant and could not be treated enough while current drugs treat over half of the patients. Besides, the current drugs have severe side effects that decrease treatment compliance. For these reasons, epilepsy patients need novel drug approaches for a more comfortable life. Several studies have indicated a close relationship between serotonin and epilepsy. It has been well known that the drugs increasing synaptic serotonin levels had beneficial effects on both generalized and focal epileptic seizures while decreasing the synaptic serotonin levels caused a decrease in epileptic seizure threshold in the chemical, electrical and audiogenic induced seizures [1, 2]. It has been proved that genetically epileptic susceptible rats had a decreased brain concentration of serotonin in rodent brain whereas fluoxetine, a selective serotonin reuptake inhibitor, decreased the convulsions in the different animal models of epilepsy [3-5]. Molecular studies have shown that especially 5-HT1A, 5-HT2C, 5-HT3, 5-HT4 and 5-HT7 receptors play important roles in the etiopathogenesis of epilepsy. When the role of 5-HT1A is investigated, it

has been seen that certain studies proved the epileptic activities of 5-HT1A receptor antagonism and potential antiepileptic activities of its agonists even though there were contrary results [6]. Furthermore, it has been indicated that 5-HT2C receptor knockout mice show sensitivity to audiogenic convulsions and agonists of these receptors improve epileptic seizures penicillin-induced and genetically modified epileptic rodents [7,8]. It has been known that activation of the 5-HT3 receptors causes the excitatory postsynaptic potentials via entries of positive ions to the postsynaptic cells and contributes excessive postsynaptic discharge which is a component of epilepsy pathogenesis. It has been demonstrated 5HT3 receptor antagonists, ondansetron and granisetron, have antiepileptic activities in preclinical models of epilepsy. Furthermore, studies have shown that stimulation of the 5HT7 receptors increased the convulsion frequency while its antagonist had anticonvulsant activity in the temporal lobe epilepsy models of rodents [9]. Vortioxetine is one of the latest antidepressant drugs which was approved by the Food and Drug Administration (FDA) in September 2013. It has been known that vortioxetine's mechanism of action is different from other SSRI drugs since it modulates various serotonin receptors. It has been shown that vortioxetine block the serotonin reuptake transporter with a high affinity like SSRIs. Besides, it has been proved that vortioxetine shows agonistic effects on 5HT1A and partial agonist on 5HT1B receptors while it antagonizes the serotonergic 5HT3 and 5HT7 receptors [10]. All the information mentioned above considered together, it has been thought that vortioxetine might be a valuable antiepileptic drug candidate with its unique pharmacological profile for epilepsy. A limited number of studies showed that vortioxetine improved penicillin-induced epileptiform activities in rodents [11]. Herein, we first investigated the behavioral and electrophysiological effects of vortioxetine on the pentylenetetrazole (PTZ) induced kindling model of rats.

Material and Methods: Male Wistar albino rats were divided into three groups as PTZ (n=6, 35 mg/kg, i.p.), PTZ+Vortioxetine (n=6, 10 mg/kg, i.p.), and PTZ+Topiramate as a positive control (n=6, 10 mg/kg, i.p). According to Fisher and Kittner's chronic epilepsy kindling scale, injections were given regularly at a dose of 35 mg/kg, three times a week. Animals showing the five or more times stage three and above convulsions were considered to be kindled. PTZ group received 35 mg/kg intraperitoneal (i.p) PTZ injection 3 three times a week. Later, the kindled animals were taken to the surgical operation. The rats were anesthetized with 90 mg/kg ketamine and 10 mg/kg xylazine, and an incision was opened in the scalp about a 3 cm long. Bregma was detected after cleaning the membrane on bone tissue. Using a hand drill, holes were drilled in 4 different points of the skull. Stainless steel screws were placed in three of these holes to contact the cortex (right frontal cortex, right occipital cortex, left occipital cortex) for electrocorticogram recording. After a small jack outlet is connected to these screws, it is fixed with acrylic and left to dry. After this 30-minute procedure, the animal was injected intraperitoneally with 50 mg/kg ampicillin to prevent infection for 3 days. To relieve pain, at the dose of 10 mg/kg xylazine was injected after surgery. After the surgical procedure, the animal was left to rest for a week. After a week, the jack input inserted into the jack output that is inserted through the surgical procedure and this input is connected to the PowerLab data acquisition system. In this way, an Electrocorticogram record was obtained from the brain and these records were analyzed offline. Electrophysiological records were divided into one-minute sections and the total spikes were calculated automatically with the macro commands included in the Chart v5.1 (ADInstruments, Australia) software. All of the electrophysiological records were converted to numerical data via Microsoft Excel. Changes in inter-group measurements were calculated by using suitable tests for the data in the SPSS v22.0. According to the results obtained from the tests, changes with a p-value below 0.05 were considered significant.

Results: In behavioral analyzes, vortioxetine and topiramate treatments decreased (p<0.01 for both group) the convulsion severities according to Fisher and Kittner's scale compared to the PTZ group in rats. Interestingly, the rats injected with vortioxetine and especially topiramate tended to decrease the latency for the first myoclonic jerks. In the electrocorticographic study, vortioxetine and topiramate decreased the total spike number in 30 min in the brain compared to the PTZ group (p<0.001 per group).

Conclusion: In this study, we firstly reported that vortioxetine had beneficial effects on behavioral and electrophysiological deficits of the chronic PTZ kindling model of epilepsy in rats. We suggest that our findings were results of its unique pharmacological profile including serotonergic receptor affinities closely related to epilepsy pathogenesis rather than a surprising effect of vortioxetine. Besides, these effects of vortioxetine should be supported by further studies because our report is one of the pioneer studies showing its therapeutical effect on epileptic activities in rats. In further studies, it may be valuable to focus potential underlying mechanism of its therapeutical effects other than the serotonergic approach. Moreover, because epilepsy is a complex disorder including many subtypes and different drugs are used for the treatment depending on convulsion form. To conclude, we have suggested that these effects of vortioxetine mentioned in our study are valuable and worth investigating when considering the limitation of treatments in epilepsy.

Keywords: Vortioxetine, Pentylentetrazole, Epilepsy, Topiramate

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[Abstract:0890]

0890 - Choroid plexus enlargement in early-course psychosis

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ABSTRACT

Objective: Psychosis is a severely debilitating chronic brain disorder. While the disorder's pathophysiology remains elusive, evidence from several fields suggests an essential role of neuroinflammation, especially around disease onset.

Neuroimaging provides a way to study potential structural correlates of neuroinflammation in-vivo, and, indeed, prior imaging studies have reported brain changes suggestive of neuroinflammation in the early stages of psychosis [1,2]. While this previous work has focused on gray and white matter brain structures, postmortem evidence also implicates the choroid plexus (ChP) as a potential regulator of the neuroinflammatory response in psychosis. The ChP responds to peripheral inflammatory signals by producing proinflammatory cytokines and modulating immune cells' transmigration into the brain, and postmortem studies have demonstrated an increase of proinflammatory gene expression in the ChP in psychosis [3]. However, given its complex shape and difficulties of automatic segmentation, in-vivo morphological studies of the ChP are sparse. Still, computer tomography imaging studies identified an association between the presence and size of ChP calcification and psychotic symptom severity. Moreover, the two only magnetic resonance imaging (MRI) studies reported ChP enlargements in individuals with psychosis [4,5]; however, the significance of these findings is limited, given that the applied automatic segmentation methods have not been validated.

In the present study, we aim to extend this previous work by examining the ChP volumes in individuals with early-course psychosis (ECP) and matched healthy controls (HC), applying a newly developed and validated manual segmentation method.

Methods

Participants

Imaging and clinical data were collected as part of the Early Psychosis Human Connectome Project. All participants provided informed written consent, and the review board of Harvard Medical School approved the study.

We included 42 individuals with ECP and 30 HC in the present study. Exclusion criteria for all subjects were an IQ less than 70, contraindication to undergoing an MRI scan, the DSM-5 diagnosis of substance-induced psychosis, or psychotic disorder due to a medical condition, and known brain damage. Additional exclusion criteria for HC were a history of a DSM-5 diagnosis or psychiatric treatment and a history of a first-degree family member diagnosed with a schizophrenia spectrum disorder. Individuals with psychosis were diagnosed with a DSM-5 non-affective or affective psychosis defined by the Structured Clinical Interview for DSM-5 - Research version (SCID-5-RV) or DSM-5-RV interview and were within the first five years after disease onset. We administered the Positive and Negative Symptom Scale (PANSS) to determine symptom severity in ECP group. Last, we calculated lifetime chlorpromazine equivalent dosages (CPZ) for individuals with ECP with complete medication information.

Image acquisition

We utilized a 3T Siemens Magnetom Prisma with a 32-channel head coil to collect a whole brain, high-resolution three-dimensional (3D) T1-weighted magnetization prepared rapid gradient echo sequence (MPRAGE).

Preprocessing and manual segmentation

Structural T1 images underwent visual quality control, were realigned and centered. Subsequently, brain masks were generated using 3D Slicer software and edited manually.

Based on the guidance of three neuroanatomists who contributed to establishing the presented method, we decided to focus our segmentation on the trigonum collaterale in the lateral ventricle, which contains the most reliably identifiable and sizable portion of the choroid plexus. We identified the start of the trigonum collaterale in the coronal view on the first slice in which the ventricular "walls" are not attached to one and another (Figure 1 A). To determine the last slice, we identified the transition of the trigonum collaterale into the occipital horn in the sagittal and axial views (Figure 1 B).

We primarily utilized the coronal view to segment the ChP in the trigonum collaterale. ChP voxels surrounded by clearly identified ChP tissue and located immediately next to a hypointense non-ChP voxel were included. In the case of two adjacent voxels with the same density at the boundary, we only added the inner one (Figure 2A, red arrow) and excluded the outer one (Figure 2A red circle). After the segmentation in the coronal view, editing was conducted in the axial and sagittal view, making sure not to include grey or white matter, especially at the boundaries of the lateral ventricles (Figure 2B and 2C, green arrow), thalamus (Figure 2B, yellow arrow), and corpus callosum (Figure 2C, blue arrow). Finally, the 3D view was used to check for holes, gaps, and islands of (non-) ChP tissue, which we then eliminated manually.

Figure 2: Manual segmentation of the Choroid Plexus using Slicer ® (A) Axial view (B) Coronal view (C) Sagittal view.

We extracted the left and the right ChP volume measurements and normalized them (by dividing ChP volumes by total intracranial volume, as derived from Freesurfer). Our method yielded inter- and intra-rater reliability above 0.9.

Statistical Analyses

For statistical analyses, we used SPSS version 26. We compared normalized left, and right ChP volumes applying ANCOVAs corrected for age and sex between ECP and HC. Next, we calculated partial correlation analysis (corrected for age and sex) between normalized ChP volumes and positive and negative symptom severity and CPZ in ECP group.

Discussion: The present study is the first to assess the differences in ChP volume between individuals with ECP and HC using a novel manual segmentation method of the ChP. Our results demonstrate significantly higher left and right ChP volumes in individuals with ECP, when compared to HC. We do not observe correlations between the ChP volume and symptom severity or medication.

Our findings align with the two previous studies that reported increased ChP volumes in individuals with psychosis compared to healthy individuals applying automated FreeSurfer segmentation [4,5]. Interestingly these previous studies has also reported an association between the ChP volume and peripheral immune-inflammatory markers, further suggesting the critical role of the ChP in regulating the neuroinflammatory response in psychosis. Additionally, other imaging and postmortem studies have described pathologies during the early phases of the disorder that might indicate an acute neuroinflammatory response [1,2].

In the present study, we did not observe an association between ChP volume and symptom severity or medication, suggesting that the ChP enlargement might be an inherent marker for ECP. These findings align with one of the previous studies, which also did not demonstrate a relation between ChP volume and symptom severity [4]. One could speculate that the lack of correlations might indicate that the enlargement of the ChP is primarily associated with peripheral rather than central inflammation. Previous studies have demonstrated peripheral inflammation in individuals with psychosis, and one postmortem study showed that the ChP responds to peripheral inflammatory signals by upregulating proinflammatory genes in psychosis [3]. Thus, more extensive longitudinal studies are required to better characterize the ChP over the illness trajectory and its interaction with peripheral markers and brain structure. These studies should further investigate other variables that might influence the ChP, such as comorbidities, substance abuse, or hormonal regulation.

Conclusion

In summary, the present study demonstrated ChP enlargements in individuals with ECP, which might indicate a neuroinflammatory response that happens around disease onset. In light of this finding, we can say that ChP may serve as a promising target for novel therapeutic strategies, given its critical role in neuroinflammatory processes in psychosis.

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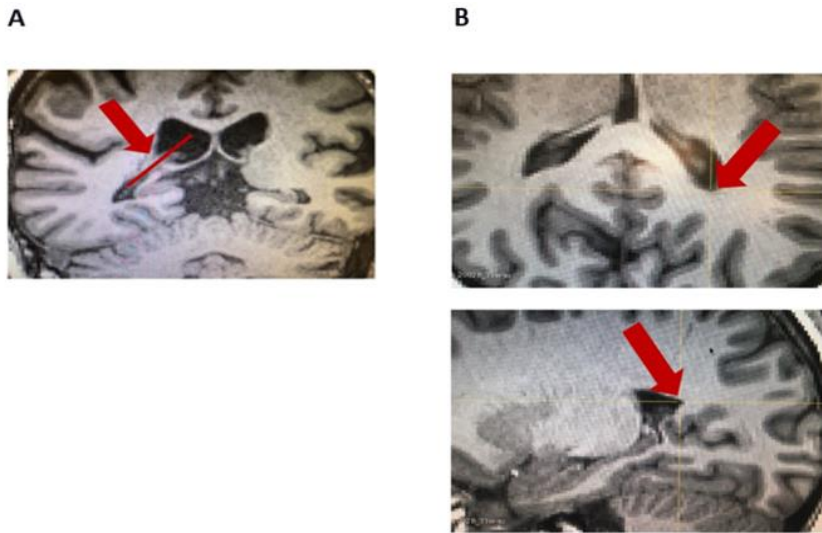
Figure 1: Identification of the (A) start and (B) end of the trigonum collaterale.
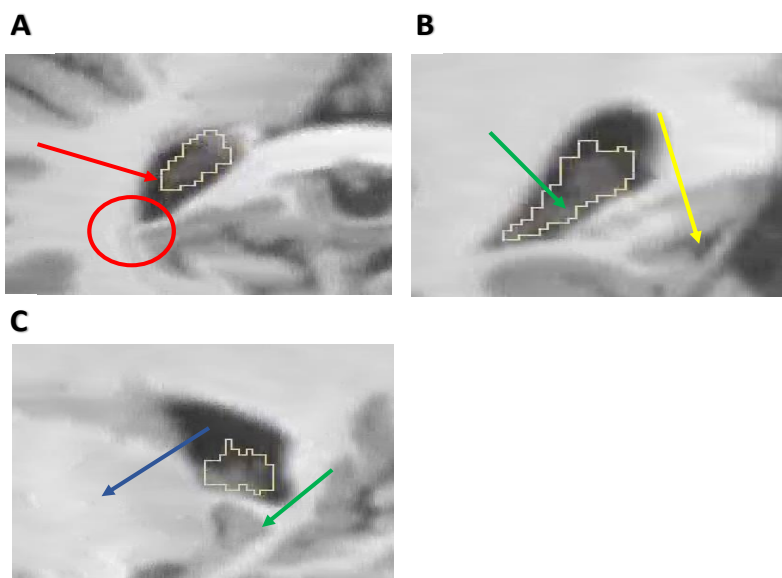
Table 1: Demographical variables

Variables	Healthy Controls	Early-Course Psychosis	Test statistic
n (%)	30 (41.66%)	42 (58.33%)	
Age in years (mean±std)	25.03±4.52	21.74±4.41	t =-3.094, df =70, p <.001
Sex (n/%)	F: 12/40% M: 18/60%	F: 16/38.1% M: 26/61.9%	X^2 =.027, p =.87
Education in years (mean±std)	15.77±2.09	13.09±1.59	t =5.40, df =53, p <.001
Duration of illness in years (mean±std)		1.78±1.17	
PANSS Total (mean±std)		47.38±9.81	
PANSS Negative Symptoms (mean±std)		12.61±4.79	
PANSS Positive Symptoms (mean±std)		13.27±4.16	

std: standard deviation; PANSS: Positive and Negative Symptom Scale

ChP volume comparisons

Individuals with ECP demonstrated significantly larger left (F =19.66, df =1, p <.0001) and right (F =18.93, df =1, p <.0001) ChP volumes than HC (Table 2).

Table 2: Group comparison for ChP volumes

Variables	Healthy Controls	Early-Course Psychosis	Test statistic
Normalized ChP volume left hemisphere in mm³ (mean±std)	.00092±.00019	.0011±.00020	ANCOVA, corrected for age and sex, F =19.66, df =1, p <.0001*
Normalized ChP volume right hemisphere in mm³ (mean±std)	.00087±.00016	.0011±.00019	ANCOVA, corrected for age and sex, F =18.93, df =1, p <.0001*

ChP: Choroid Plexus; std: standard deviation; *: p <.01 (after Bonferroni correction)

Correlation analyses

No correlation was shown between the normalized left and right ChP volumes and PANSS total, positive, and negative scores. We also did not observe a significant correlation between left and right ChP volumes and CPZ (Table 3).

Results

Demographics

For demographical information, please see Table 1.

Table 3: Correlations between ChP volumes and clinical variables in Early-Course Psychosis

Clinical variables	Partial correlation	
	Normalized ChP volume left hemisphere	Normalized ChP volume right hemisphere
PANSS Total	r =.12, p =.53	r =-.15, p =.45
PANSS Positive	r =.23, p =.24	r =.032, p =.87
PANSS Negative	r =.049, p =.81	r =-.25, p =.21
CPZ	r =-.34, p =.13	r =.040, p =.86

ChP: Choroid Plexus; PANSS: Positive and Negative Symptom Scale; CPZ: lifetime chlorpromazine equivalent dosages

[Abstract:0891]

0891 - The relationship between test anxiety and metacognitive beliefs among university students

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ABSTRACT

Introduction: Cognitive test anxiety is characterized as extreme anxiety that inhibits efficient use through previously acquired information during testing and leads to a reduction in success. Furthermore, metacognitive belief is referred to as the brain mechanisms that incorporate control, monitoring, organization, and evaluation of cognition. As it involves a wide range of activities, psychopathological cognitive patterns are likely to be derived from maladaptive functioning in metacognition. Additionally, the metacognitive perspective believes that anxiety is one of the most important forms of metacognitive inconsistencies that underlie anxiety disorders [1]. Recent studies have suggested that metacognitive beliefs have a significant impact on test anxiety [1-2]. There is concern about whether metacognition and cognitive anxiety tests are intimately related.

The object of the study was to investigate the relationship between cognitive test anxiety and metacognitive beliefs among university students.

Methods: *Participants and Procedure:* Three hundred-thirty university students participated in the study. The data was acquired from Turkish university students. The research was announced on the Internet and social media sites and conducted via an online survey platform. The snowball method was applied to conduct the data. All participants who voluntarily participated in the study were informed about the nature of the study and their right to withdraw from it at any time. All participants signed informed consent for participation in the study. The study was approved by the Institutional Review Board of the International University of Sarajevo (03/03/2021; IUS-REC-01-465/2021).

Instruments

Socio-demographic Scale: Socio-demographic form was developed by the authors and included questions on the patient's gender, age, educational level, and other basic sociodemographic information.

Cognitive Test Anxiety Scale-Revised (CTAR): The Cognitive Test Anxiety Scale-Revised is a measurement tool developed to assess only the cognitive domain of test anxiety. The scale is one-dimensional, and the Turkish version consists of a 23-item questionnaire. Two items were removed for the Turkish version of the scale [3]. Each item on CTAR is rated on a 4-point Likert scale; (1) do not agree to (4) agree very much. All the items of the Cognitive Test Anxiety Scale are collected, and a single cognitive exam anxiety score is obtained. It demonstrates that as the score obtained from the scale increases, cognitive test anxiety increases.

Metacognition Questionnaire (MCQ-30): The Metacognition Questionnaire-30 is a short version of the original MCQ. It demonstrates individual differences in five factors important in the metacognition of psychological disorders. It has been widely used to detect the existence of such metacognitions in both clinical and non-clinical populations [4]. In this study, the Turkish version of the MCQ-30 was used, which was established by Tosun and Irak [5]. Each item on MCQ-30 is rated on a 4-point Likert scale; (1) do not agree to (4) agree very much. MCQ-30 scores go from 30 to 120 focuses, and higher scores demonstrate a more considerable obsessive metacognitive movement. The five determinants are evaluated by the measure, which includes: positive beliefs about worry, cognitive self-consciousness, cognitive confidence, negative beliefs about the uncontrollability of thoughts and danger, and beliefs about the control thoughts.

Statistical Analysis: Statistical Package for Social Sciences (SPSS) version 22.0 was used for statistical analysis [6]. Descriptive data were presented as mean and standard deviation. Pearson Bivariate correlations were used to identify the correlations between socio-demographic variables, CTAR scores, and MCQ-30 scores. A multiple linear regression analysis was then conducted to predict the cognitive test anxiety based on the MCQ-NB and MCQ-CC.

Results: The mean age of the participants was 22,33 (*SD* = 2.37). Data analysis suggests that among participants, 31.2% (*n* = 103) were males and 68.8% (*n* = 227) were females. Pearson's correlation equation detected a positive correlation between the negative beliefs about uncontrollability and danger (MCQ-NB), cognitive self-consciousness (MCQ-CSC), the need to control thoughts (MCQ-NCT), and cognitive confidence (MCQ-CC) subtests with the CTAR. On the other hand, when the sociodemographic variables were conducted, results revealed that only age was negatively correlated with the MCQ-CSC (See table 1). Results from linear regression analysis yielded a significant and positive association between MCQ-NB and MCQ-CC subcategories (See table 2).

Discussion: Cognitive test anxiety consists of individuals' cognitive reactions to or internal dialogues about assessment situations before, during, and after assessment tasks [7]. The cognitive component is the factor that was found to be most consistently associated with a decrease in performance [8]. Apart from the traditional correlational studies and meta-analyses, pathway analyses have also confirmed that cognitive test anxiety and performance have the strongest link to each other [9]. Furthermore, metacognitive beliefs foresee the experience of negative emotions such as anxiety. In their research findings, Spada et al. [1] have showed that metacognitive beliefs have a positive and significant relationship with anxiety and stress.

The present study examined the potential associations between metacognitive beliefs and cognitive test anxiety. According to the results of our study, negative beliefs about uncontrollability and danger and cognitive confidence factors may influence cognitive test anxiety in young adults. Congruently, researchers have found a relationship between test anxiety and metacognitive beliefs. Results of that study showed a strong association between 'negative beliefs about uncontrollability and danger of worry'. In their study, researchers suggested that, also 'cognitive

confidence' might play an essential role in test anxiety [9]. Moreover, Matthews et al. [10] have observed that anxiety symptoms decreased with the improvement of negative metacognitive beliefs. Our findings from the present study support the put forward and point out the importance of implementing a metacognitive intervention for students with high cognitive test anxiety. Additionally, interventions targeting these factors may help young people manage cognitive test anxiety.

There were several limitations in the present study. Sample characteristics (small number of undergraduate students and large female distribution) and the variables (e.g., ethnicity and culture) that are not included in the study may limit the generalizability of the research findings. Future studies should be designed to include a large group of individuals and various variables. Despite these limitations, this study is the first to suggest that the effect of metacognitions on cognitive test anxiety in young adults. We believe that our findings provide lightning in the relationship between metacognitive beliefs and cognitive test anxiety.

Keywords: anxiety; cognitive test anxiety; metacognitive beliefs; university students; young adults

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Table 1. Correlation Coefficients Between Age, CTAR-T and MCQ'subtests

		CTAR-T	MCQ-CC	MCQ-PBW	MCQ-CSC	MCQ-NB	
Age	1	-	-	-	-	-	-
CTAR-T	-.047	1	-	-	-	-	-
MCQ-CC	-.044	.338**	1	-	-	-	-
MCQ-PBW	-.046	.235**	.202**	1	-	-	-
MCQ-CSC	-.122*	.415**	.407**	.323**	1	-	-
MCQ-NB	-.103	.499**	.309**	.356**	.643**	1	-
MCQ-NCT	-.075	.376**	.332**	.478**	.545**	.679**	1

Correlation is significant at the 0.05 level (2-tailed).

**. *Correlation is significant at the 0.01 level (2-tailed).*

Notes for Table: CTAR-T: Cognitive Test Anxiety Scale-Revised Total Score (M=43.37, SD=11.53), MCQ-CC: Metacognition (Lack of) Cognitive Confidence subtest (M=13.40, SD=3.67), MCQ-PBW: Metacognition Positive Beliefs about Worry subtest (M=13.32, SD=3.65), MCQ-CSC: Metacognition Cognitive Self-Consciousness subtest (M=16.42, SD=2.92), MCQ-NB: Metacognition Negative Beliefs about Uncontrollability and Danger subtest (M=14.54, SD=4.01), MCQ-NCT: Metacognition Need to Control Thoughts subtest (M=15,57, SD=3.46).

Table 2. The predictor variables of test anxiety

Variables		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	13.397	3.354		3.994	.000
	MCQ-NB	1.101	.177	.383	6.206	.000
	MCQ-CC	.570	.161	.182	3.536	.000
Notes for Table 2: MCQ-NB: Metacognition Negative Beliefs about Worry subtest, MCQ-CC: Metacognition Cognitive Confidence subtest						

[Abstract:0953]

0953 - Evaluation of the macrophage migration inhibitory factor (MIF) −173 G/C polymorphism in bipolar disorder and its relationship with clinical parameters and scale scores

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ABSTRACT

OBJECTIVE: Macrophage migration inhibitory factor (MIF) is a potent cytokine that is responsible for both the innate and acquired immune response and is involved in the pathogenesis of many inflammatory and autoimmune diseases. The *MIF* gene is localized to the q11.23 region on chromosome 22. In studies about the variants in the promoter region of the *MIF* gene, the −173 C allele in the rs755622 variant was associated with increased transcription activity and increased MIF protein production (1). In the previous study, it was seen that the *MIF* gene played an essential role for the age of illness onset and impairment of insight in schizophrenia (2). We hypothesized that the *MIF* −173 G/C variant could be also associated with the pathogenesis of BD. To our knowledge, this is the first study that has examined the relationship between *MIF* −173 G/C variant and BD. This study aims to investigate the relationship between clinical features of BD and *MIF* −173 G/C variant in patients with BD by comparing genotype distributions of MIF gene variant between patients and healthy controls considering clinical parameters.

METHODS: Patient Selection: A sample of 104 patients with BD consecutively admitted to the Bakirkoy Mazhar Osman Mental Health and Neurology Training and Research Hospital outpatient clinic in the period of January-June 2018; additionally, 100 healthy volunteers were included in the study which was designed as a case-control study. The study was approved by the Local Committee of Bakirkoy Mazhar Osman Mental Health and Neurology Training and Research Hospital (07.11.2017/81).

Diagnoses and Symptom Measurement: The participants were informed in detail about the study, and written consents of all the participants were obtained. The interview was initiated by filling out data forms that included sociodemographic and clinical information. Afterward, the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) was used to confirm the diagnosis according to DSM-IV-TR criteria, and the presence of any psychiatric diagnosis was decided as the basis for exclusion from the study in healthy control group. The Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (HAM-D), The Clinical Global Impression Scale (CGI) were administered to patients with BD.

Inclusion and Exclusion Criteria: Subjects of 18 to 65 years of age, of either gender, were literate, agreed on the participation in the study, diagnosed with a BD according to the SCID-I interview, had no other systemic/neurological disease that may affect cognitive functions (dementia, epilepsy, Parkinson disease, head trauma accompanied by loss of consciousness) included in the study. We had excluded subjects who had mental retardation, neurodevelopmental disorders such as autism, a diagnosis of axis-1 disorder other than BD as a result of the SCID-I interview, BD secondary to a general medical condition, dementia or brain damage.

DNA Analyses: Blood samples were obtained from participants at the Istanbul Faculty of Medicine Laboratory of Medical Biology to isolate their deoxyribonucleic acid (DNA) material. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used to determine the *MIF* −173 G/C variant.

Statistical Analyses: Statistical analysis was performed using IBM SPSS version 21.0 (IBM Corp. released 2012; Armonk, NY, USA). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, percentage. Pearson chi-square test or Fisher's exact test was used for the comparison of discrete variables. The odds ratio (OR) and the 95% confidence interval (CI) were also calculated. The Shapiro Wilk test evaluated the suitability of continuous variables to normal distribution. Intergroup comparisons of continuous variables were

performed by Mann Whitney U testing. Genotype distributions in both the patients and the healthy controls were analyzed according to the Hardy-Weinberg Equilibrium (HWE). Statistical significance was accepted as p <0.05 for the results of all analyses.

RESULTS: One hundred and four patients with BD (62 female/ 42 male) were evaluated according to their clinical parameters and scale scores, as shown in Table-1. The clinical specifiers of the patients are presented in Table-2. When the *MIF* −173 G/C genotype (GG, GC, CC) and the allele frequencies (G, C) of patients with BD were compared with the control group, the *MIF* genotype distribution of BD was found to be significantly different from the control group (OR: 0.521, 95%Cl: 0.278-0.975; p=.040). The percentage of the GG genotype was found to be statistically higher in the BD group compared to the control group. The *MIF* −173 G/C allele frequency of the BD group was also found to be significantly different from the control group (OR: 0.575, 95%Cl: 0.330-1.001; p=.049). The percentage of the G allele was found to be statistically higher in the BD group than the control group (Table-3).

Comparing the scale scores (HAM-D, YMRS, CGI-S, CGI-I) and clinical parameters (number of manic episodes, depressive episodes, total episodes, age of onset, duration of disease and number of hospitalizations) regarding the *MIF* −173 G/C genotype (GG, GC/CC) distributions in patients with BD, the CGI-I score was significantly different between the groups of *MIF* −173 G/C genotype (p=.029) (Table-4). The CGI-I score of the group containing the genotype of the mutation allele (GC/CC) was statistically lower than the group containing the GG genotype. Also comparing the *MIF* −173 G/C genotype and allele frequency distributions between the two groups according to the presence of clinical specifiers (psychotic features, atypical features, seasonal pattern, mixed features, rapid cycling history, peripartum onset) in the BD patient group it was shown that there were no statistically significant differences in terms of clinical specifiers (p>0.05) (data not shown).

DISCUSSION: In our study, the data analysis of 204 participants (104 BD patients and 100 healthy volunteers) revealed that *MIF* −173 G/C genotype and allele frequency distributions in BD groups were significantly different from the control group. The percentage of GG genotype and G allele of the BD group was found to be statistically higher than the control group. When we research the studies of inflammation-related gene variants in the literature, the increasing number of evidence suggests that *MIF* gene variants have a role in depression and schizophrenia. These studies have shown MIF as a monitoring biomarker. Musil et al. found that patients with depression had significantly elevated serum MIF and reduced serum TGF-β concentrations compared to the control group. They suggested that MIF is a promising new candidate in the neuro-immune interaction that may be related to depressive symptoms, altered immune system, and hypothalamic–pituitary–adrenal (HPA) axis (3). Again, Okazaki et al. reported that serum MIF levels were significantly higher in patients with schizophrenia than in controls and were positively correlated with the antipsychotic dose. These high levels of MIF in serum may potentially be biomarkers for schizophrenia, and the association with the antipsychotic dose may be explained with an alternative etiological mechanism besides the dopamine antagonist effect in the treatment (4).

Comparing the scale scores and clinical parameters about the *MIF* −173 G/C genotype distributions in patients with BD, the CGI-I score was significantly different between the groups of *MIF* −173 G/C genotype (GG, GC/CC). As known, the CGI-I is used to evaluate how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the treatment. When we classified the groups according to the presence of mutation alleles (GG, GC/CC) (homozygosis normal, heterozygosis/ homozygosis mutant), the CGI-I score of the group containing genotype of mutation allele (GC/CC) was statistically lower than the group containing genotype of GG. This result showed that the treatment response of the group containing the genotype of the mutation allele was better. Although BD itself appears to be the most inheritable disease in all psychiatric disorders, genetic studies of treatment response are predominantly related to predictors of lithium response. Some studies in the literature provide evidence about supporting the anti-inflammatory effects of lithium through different mechanisms. Lithium reduces the synthesis of pro-inflammatory enzymes and molecules (IL-1, TNF-α, PG, NO, iNOS, COX-2, and PLA2) during treatment and organizes in vitro microglial activity. It was also shown that valproic acid down-regulates the arachidonic acid signal cascade by inhibiting COX-1 and COX-2 synthesis in the rat brain similar to lithium. Thus, valproate and other antiepileptic agents used as mood stabilizers (carbamazepine, lamotrigine, oxcarbazepine, and topiramate) have been shown to significantly reduce a cytokine synthesis in vitro (5).

Our study's first limitation is the inability to include drug-naïve first-episode patients with BD. The second limitation was the small sample size, which can limit the statistical power. Also, in our study, *MIF* −173G/C variant was examined, but it was impossible to know the other functional MIF −794 CATT$_{5-8}$ microsatellite variant of BD.

In conclusion, we found that the *MIF* −173G/C variant may be related to BD and the treatment response. Also, in our study, the presence of GG genotype and G allele was found to be disadvantageous both in terms of an occurrence of a BD diagnosis as well as the treatment response of BD in the Turkish population. Confirmation of the present findings with other gene variants in different ethnic populations covering more extensive regions will provide a better understanding of the association between inflammation-related gene variants and BD.

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TABLES:

Table-1: The Clinical Parameters and Scale Scores of Patients

Bipolar Disorder (N:104)		
	Mean ± SD	
Age of onset (year)	25.68±8.51	
Duration of disease (year)	15.73±10.49	
Number of Hospitalization	3.28±4.2	
Dep. episode	1.17±2.32	
Manic episode	4.02±4.58	
Total episode	5.57±5.25	
HAM-D	14.78±9.09	
YMRS	9.39±10.87	
CGI-S	4.96±0.94	
CGI-I	2.18±0.87	

(Abbreviations: SD, standard deviation; dep., depressive; HAM-D, hamilton depression rating scale; YMRS, young mania rating scale; CGI-S, clinical global impression scale-severity; CGI-I, clinical global impression scale-improvement)

Table-2: The Clinical Specifiers of Patients with Bipolar Disorder

Clinical Specifiers		N	%
Atypical Features	No	82	79
	Yes	22	21
Mixed Features	No	80	77
	Yes	24	23
Seasonal Pattern	No	58	55.7
	Yes	46	44.3
Hist. of Rapid Cyc.	No	75	72.1
	Yes	29	27.9
Psychotic Depression	No	88	84.6
	Yes	16	15.4
Psychotic Mania	No	55	52.9
	Yes	49	47.1
Postpartum Onset	No	94	90.4
	Yes	10	9.6

(Abbreviations: hist., history; cyc., cycling)

Table-3: Comparison of MIF −173G/C Genotype Distribution of Patients with the Control Group

	Genotype	Bipolar Disorder	Healthy Control		OR	95% CI	p
		n= [a] (%)	n=100 (%)				
MIF	GG	82 (78.8)	66 (66)		0.521*	0.278-0.975*	**.040***
	GC	20 (19.2)	31 (31)		1.887*	0.989-3.600*	**.052***
	CC	2 (1.9)	3 (3)		0.634[&]	0.104-3.876[&]	**.678[&]**
Allele							
	G	184 (88.5)	163 (81.5)				
	C	24 (11.5)	37 (18.5)		0.575*	0.330-1.001*	**.049***

Abbreviations: [a]n= 104; OR, odds ratio; CI, confidence interval; *Pearson chi-square; &Fisher's Exact Test; HWE mid-p, Hardy-Weinberg equilibrium mid-p adjustment.

Table-4: Comparison of Scale Scores and Clinical Parameters According to *MIF* –173G/C Genotype Distribution in Patients

	GG		GC/CC		
	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	p*
HAM-D score	14(0-41)	15.62 ±9.38	11(0-26)	11.68±7.31	.093
YMRS score	6.5(0-42)	9.89±10.84	1(0-35)	7.54±11.01	.104
CGI-S score	5(2-7)	4.97±0.91	5(3-7)	4.90±1.06	.781
CGI-I score	2(1-5)	2.28±0.87	2(1-3)	1.81±0.79	.029
Dep. episode	0(0-10)	1.32±2.50	0(0-6)	0.59±1.33	.224
Manic episode	2(0-21)	3.86±4.29	3(1-21)	4.63±5.61	.581
Total episode	4(1-23)	5.53±4.96	3.5(1-27)	5.72±6.33	.825
Age of onset	24(13-52)	26.09±8.83	24(10-34)	24.1±7.16	.641
Duration of disease	13.5(0.5-40)	15.05±10.05	20(2-40)	18.27±11.87	.256
Number of hospt.	2(0-21)	3.39±4.14	2(0-21)	2.90±4.47	.594

* Mann Whitney U test

(Abbreviations: SD, standard deviation; min, minimum; max, maximum; CGI-S, clinical global impression scale-severity; CGI-I, clinical global impression scale-improvement; HAM-D, hamilton depression rating scale; YMRS, young mania rating scale; dep., depressive; hospt., hospitalization)

[Abstract:0961]

0961 - Effects of selective serotonine reuptake ınhibitors treatment on oxidative stress in patients with obsessive compulsive disorder

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ABSTRACT

Introduction: Obsessive Compulsive Disorder (OCD) is a psychiatric disorder with a prevalence of 2-3% in the population, leading to significant functional impairment. Features of OCD such as etiology, clinical presentation and response to treatment are quite heterogeneous. Many studies have been conducted to investigate the etiology of OCD. However, definitive links between biochemical and neuroanatomical models of OCD etiology have not yet been established. In some recent studies investigating the etiology of OCD, it has been suggested that oxidative stress (OS) and free radical damage play a role in the etiology (1).

Reactive oxygen radicals are chemically very active, harmful molecules that carry one or more unpaired electrons in their final orbitals. OS causes disease through toxic effects on carbohydrate, protein, lipid and deoxyribonucleic acid (DNA) metabolism. Recent studies have shown that oxidative markers increase and antioxidant markers decrease in many psychiatric disorders. In addition, studies examining the effects of psychotropic drugs on OS show that antidepressants have positive effects (2). However, the number of studies investigating the effects of selective serotonin reuptake inhibitors (SSRI) on OS in obsessive-compulsive disorder is very limited.

8-hydroxy-2'-deoxyguanosine (8-OHdG) is a marker of OS and mitochondrial dysfunction. The level of 8-OHdG in blood and urine is a direct indicator of oxidative DNA damage, and measurement of 8-OHdG in these body fluids is the most commonly used method for detecting oxidative DNA damage. There is no study in the literature investigating the effect of SSRI on oxidative DNA damage and oxidative metabolism in OCD.

Aim of the study

In this study, we aimed to investigate oxidative DNA damage and oxidative metabolism in OCD, and the effects of SSRI on OS in this group. As a secondary outcome, we aimed to compare the effects of fluoxetine and sertraline used in the initial treatment of OCD in our clinic on OS parameters.

Materials and Methods: This study is a single-centre, prospective, randomised controlled trial. Approval for the study was obtained from the Medical Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine with decision number 03.01.2018/155. In addition,

approval was obtained from the Ministry of Health, Turkish Medicines and Medical Devices Agency, Department of Clinical Research, with decision number 09.03.2018 / E.46711.

Among the patients who applied to Necmettin Erbakan University Meram Faculty of Medicine Psychiatry outpatient clinic between 01.08.2017 and 01.08.2018, those diagnosed with OCD according to DSM V criteria were included in the study. The exclusion criteria were:

• Chronic metabolic (hyperthyroidism, hypothyroidism, diabetes, etc.) medical disease,

• Comorbid psychiatric disease or tic disorder,

• Alcohol and substance abuse,

• Smoking,

• Pregnancy,

• Moderate and severe mental retardation,

• History of severe head trauma,

• Antioxidant agent use in the last 1 month (vitamin E, vitamin C, N-acetyl cysteine),

• Xanthine oxidase inhibitor use (allopurinol, folic acid),

• Severe neurological disease (Epilepsy, Parkinson's disease, etc.),

• Obesity

Forty-one patients who met the diagnostic and exclusion criteria were identified. Forty healthy hospital employees were included in the study as a control group. The exclusion criteria for this group were the same as for the patient group.

To compare the baseline status before treatment in terms of total antioxidant status (TAS,), total oxidant status (TOS), and 8-OHdG of the OCD patients, 5 ml of blood was collected once from the control group at the beginning of the study. In the OCD group, 5 ml of blood was collected before SSRI treatment and at the 8th week of treatment. Measurements were performed by the biochemistry department of Meram Faculty of Medicine using the serums obtained from the blood samples. TAS and TOS measurements were made with Relassay brand kit (Relassay, Turkey). The oxidative stress index (OSI) was obtained by dividing TOS by TAS. JaICA kit (JaICA, 8-OHdG ELISA High Sensitivity kit, Japan) was used to measure 8-OHdG in serum.

Sociodemographic and clinical data were collected from both groups before the study. The Yale-Brown Obsession Compulsion Rating Scale (Y-BOCS) was administered to the OCD group twice, at baseline and at week 8 of treatment, to assess the quality and severity of obsessive-compulsive symptoms and to evaluate response to treatment. Statistical analyzes were performed using SPSS version 22.0. Statistical significance was $p < 0.05$.

Results

Forty-one patients in the OCD group and 40 healthy volunteers in the control group were enrolled in the study. There was no significant difference between the groups in terms of socio-demographic characteristics.

There were no significant differences in TAS, TOS, OSI, and 8-OHdG levels between patients and control groups in the pretreatment phase. After 8 weeks of antidepressant treatment, 8-OHdG levels had decreased compared to pre-treatment levels (p:0.004). Furthermore, there was a significant positive correlation between patients' pre-treatment 8-OHdG levels and the rate of change of the YBOC-S compulsive subscale (r:0.46 p:0.014). Moreover, a negative correlation was found between patients' post-treatment 8-OHdG levels and the rates of change of the YBOC-S total and compulsive subscales (r:-0.38 p:0.049). Nevertheless, TAS, TOS and OSI showed no significant changes after antidepressant treatment. The rate of decrease in TOS and OSI with treatment was significantly higher in the patient group receiving fluoxetine than in the patient group receiving sertraline. (p:0.028 p:0.025)

Discussion: In recent years, many studies have been carried out to understand the mechanism of SSRI. While there are many studies on the effects of SSRI on OS in major depression (MD), studies in OCD are limited. There is no study investigating the effect of SSRI on oxidative DNA damage and oxidative metabolism in OCD. Our study is important as it is the first study in this field.

Although the results of studies investigating OS markers in OCD are conflicting, the general opinion on this topic is that OS indicators are high and antioxidant status is low in OCD. A few studies with inadequate methodology have yielded variable results regarding TAS, TOS, and OSI levels in OCD (3). We did not find a statistically significant difference in OS parameters between OCD patients and the control group. Although the role of OS in various psychiatric diseases has been better explained (4), the studies (including our study) in this field in OCD are not sufficient to explain the effects of OS on the development and nature of obsessions and compulsions.

TAS, TOS and OSI, which are the parameters we used in our study, were mostly evaluated in studies related to MD (5). When we evaluate the results of these studies, we see that there is a negative correlation between the disease and TOS and OSI, and a positive correlation with TAS. In studies examining changes in OS parameters with treatment of MD, the lack of standard treatment protocols and inconsistent results prevent a clear interpretation. It would be appropriate to use similar statements for 8-OHdG in patients with MD. An association with MD has been demonstrated, but the results of response to antidepressant treatment are inconsistent. As a direct indicator of DNA damage, 8-OHdG was the most important parameter evaluated in our study. We found a significant decrease in 8-OHdG levels after 8 weeks of SSRI treatment in OCD patients, but we did not observe a similar change in TAS, TOS and OSI levels. We interpret this difference to mean that 8 weeks of treatment may not be sufficient to detect significant changes in the levels of TAS, TOS, and OSI. While there was a positive correlation between pre-treatment 8-OHdG level and rate of decline in YBOC-S compulsion score, a negative correlation between post-treatment 8-OHdG level and rate of decline in YBOC-S total and obsession score, the absence of this relationship in other OS parameters supports our opinion.

When we assessed the differences in OS parameters between patients taking fluoxetine and sertraline, we found that the rate of decrease in TOS and OSI levels was significantly higher in the fluoxetine group. This can be interpreted as the better antioxidant effect of fluoxetine, but since our current data are not sufficient, further well-designed studies on this topic are needed.

As a result, we did not detect any difference between the two groups in terms of pretreatment OS parameters, and we interpreted this situation as OS not playing an active role in the etiology of OCD. However, we have demonstrated that 8-OHdG levels may be a useful parameter for monitoring response to SSRI treatment in OCD patients.

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[Abstract:0992]

0992 - Investigation of the relationship between inflammatory markers and clinical features in adolescents with non suicidal self injury and suicide attempt

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ABSTRACT

Introduction: International Society for the Study of Self- Injury (ISSS) group defined self-injury as "voluntary damage to the tissues of the body by the person himself/herself without the intention of death or social sanction" and found it appropriate to use the common term 'non-suicidal self injury' (NSSI). The fact that suicidal behaviour and NSSI have been differentiated in this definition and that a clear definition of NSSI has been made is vital for successful treatment of adolescents and to make a correct conceptualization (1). Addressing these two behaviours together leads to confusion, and actually covers the fact that these two phenomena serve different purposes. Suicidal behaviour is a term that includes all the thoughts and behaviours of an individual that involve the purpose of ending his/her own life knowingly and willingly. The relationships between SA and NSSI are complicated in adolescents. A great number of factors which play a role in the aetiology of NSSI in adolescents are also accepted as risk factors in adolescents who have attempted suicide. In adolescents who have attempted suicide, similar psychiatric diseases are seen with adolescents who show NSSI and individual characteristics in the aetiology such as impulsivity, anger, despair and childhood traumas are similar to familial risk factors (2). As a result, clinic groups in NSSI and SA should be revealed in more detail phenomenologically, their associations with each other should be found and similar and different aspects between these two groups should be determined.

The relationship between NSSI and SA and neuroinflammation can be bilateral. First of all, the perception of threat that leads an individual to think about suicide activates biological stress reactions and inflammatory responses are also in these stress reactions. Secondly, inflammatory response increasing with any reason can be creating a predisposition for suicide attempt by affecting the suicide-associated areas in the brain. In metaanalysis studies conducted so far investigating the association between suicide behaviour and immune dysregulation, the parameters which have been shown to have the strongest association are IL-6, TNF-α hsCRP (3).

The aim of our study is to evaluate the inflammatory and clinical parameters that are thought to have a role in the pathogenesis of NSSI and SA and to find out the posNSSIle relationship between these. This relationship can clarify the psychopathological mechanisms underlying NSSI and SA behaviours and also can be useful for determining goals for interventions to prevent these behaviours.

Method

Participants

This study was conducted with the data obtained from patients who referred to the emergency service with SA, patients who were followed in our department with a diagnosis of NSSI according to DSM-5 and healthy volunteering adolescents between the ages of 12 and 18.

38 adolescents included in the NSSI group met the diagnostic criteria of self-injurious behaviour according to DSM-5 criteria as a result of clinical psychiatric examination and assessments and the criterion of having shown self-injurious behaviour within the last month. 38 adolescents included in the SA group met the criteria that the patient expressed having attempted suicide at the admission to the emergency service and that the patient's attempt was evaluated as having a death intention as a result of clinical assessment. 48 adolescents in the control group included adolescents between the ages of 12 and 18 who were age and gender matched with the NSSI and SA group, who had not previously or presently received a psychiatric diagnosis, who had not used psychopharmacological treatment and who did not have a chronic medical disease.

Adolescents who had diseases that could affect the immune system (chronic diseases such as autoimmune disease, allergy, diabetes, cancer or acute infection), mental retardation IQ<70, autism spectrum disorder, organic brain syndrome, psychotic disorders, bipolar disorder, and alcohol use were excluded from the study.

Instruments

Interview Form. The interview form was developed by the authors and included questions about the patient's age, gender and other basic sociodemographic information.

K-SADS-PL, : K-SADS-PL DSM-5 November 2016 is a semi-structured interview chart. Beck Depression Scale: It was developed by Beck et al. In this 21-item scale which consists of how an individual feels within the last week, each question consists of 4 options scored between 0 and 3.

Beck Anxiety Scale, It is a 21-item Likert type scale scored between 0 and 3 and it measures the frequency of anxiety symptoms experienced by the individual.

Beck Hopelessness Scale, It was developed by Beck et al. to determine the level of hopelessness about the future. It is a 20-item self-report scale.

Barratt Impulsivity Scale, It is a 30-item, Likert type self-report scale measuring impulsivity. Higher scores taken from the scale show higher impulsivity degree.

Trait Anger and Anger Expressions Scale, The scale, which measures anger and anger expression, was developed by Spielberger et al. in 1983 and it consists of 34 items and 4 subscales as anger in, anger expression, anger control and trait anger.

Adverse Childhood Experience Scale, It is a self-report scale developed by Bernstein et al. to examine the abuse experiences of individuals before the age of 18. It is a 5-Likert type scale consisting of 40 items, 16 of which are adversely scored.

Analysis of inflammatory markers

IL-6 Determination : The samples were studied with Roche cobas e 601 model device with electrochemiluminescence method. (Roche Diagnostic GmbH D-68298 Mannheim/Germany) was centrifuged and the serums separated were kept at -800C.

hs-CRP Determination : It was studied with nephelometric method on Siemens Dade Behring Nephelomether 100 model analyzer (Siemens Healthcare Diagnostic Product GmBH, Emil-von – Behring-Str. 76, 35041 Marburg/Germany).

TNF-α Determination: It was analyzed with ELISA method on Biotek, SYNERGY H1 model device (Wuhan USCN Business Co.,Ltd. USCN life science KIT INC. No.33 ZhenHun Road, Wuhan Hubei4300056 PRC).

Hemogram Determination: It was analyzed with fluorescence flow cytometry method with Sysmex XN-1000 model device (Symex Corporation 1-5-1 Wakinohama-Kai gandori, Chuo-ku, Kobe 6510073, Japan).

Statistical Analysis: SPSS (Statistical Package Fort the Social Sciences version 22.0) program was used for analyses. Kolmogorov Smirnov normality test was conducted on variables that included quantitative data and it was found that they were not normally distributed. Mann Whitney U and Kruskal Wallis variance analysis were used in the analysis of qualitative data. Chi-square test was used in the analysis of quantitative data to find out significance between groups. Spearman correlation test was used to find out the association between variables in our study. $p<0.05$ was accepted as statistically significant.

Results: NSSI, SA and control groups were similar in terms of age (p=0,830), gender (p=0,070), state of smoking (p=0,604), BMI (p=0,233) and family sociodemographic characteristics and psychiatric diagnosis. When the groups were compared in terms of inflammatory parameters, while NLR (p= 0,023) and TNF-a (p=0,001) were significantly higher in NSSI and SA group when compared with the control group, IL-6 was significantly higher in NSSI and control group (Table 1). When the correlations between inflammatory parameters which were found to have significant differences between groups and clinical characteristics were examined, it was found that NLR and IL-6 were correlated with sexual abuse and depression scores, while TNF-α was correlated with anxiety, depression, despair, impulsivity, anger and abuse scores (table 2).

CONCLUSIONS:

Advancements in the field of immunology and genetic increase our understanding about how immunological processes can affect brain development and functions. For this reason, researches on immune system changes are among the most current topics in psychiatry researches. Evidence suggesting that immunological abnormalities have a posNSSIle role in the pathogenesis of NSSI and suicide attempt has been increasing in recent years with increasing number of studies conducted. It is thought that demonstration of immunological dysregulation can be a marker in NSSI and SA or an adjuvant biological factor in understanding pathogenesis. In the metaanalysis of studies investigating the association between suicidal behaviour and immune dysregulation, the parameters which have been shown to have the strongest association are IL-6, TNF-α hsCRP (5). The easiest and practically clinically available evidence of immune dysregulation is peripheral NLR MLR and PLR values. While studies in literature mostly focus on suicidal behaviour, there are few studies conducted on humans about NSSI. In addition, there are also few studies which examine the clinical characteristics which are known to be risk factors for NSSI and SA and inflammatory markers together.

In our study, we examined a total of 124 adolescents, 38 diagnosed with NSSI, 38 diagnosed with SA and 48 healthy controls. When it is considered that the inflammatory markers we examined can be affected by factors such as age, gender, smoking and BMI, it is important for the groups that we analyzed to be similar in terms of these factors. NSSI and SA are frequently evaluated together since they have common risk factors and because of their comorbidity. However, the fact that these two different phenomena were evaluated as separate groups in our study is important in terms of finding out the differences between. In addition, the fact that these two groups are similar in terms of psychiatric diagnoses is also important in terms of excluding the effect of psychiatric diseases which have an influence on the inflammatory parameters examined. Our result that the NLR obtained was associated with depression and sexual abuse scores in NSSI and SA groups brings to mind that NLR can have a mediator role in sexual abuse and depression increasing the risk of NSSI and SA behaviours. The result that IL-6 was significantly higher in SA group when compared with the other two groups and SA group associated with sexual abuse and depression scores brings to mind that IL-6 can have a specific role for SA on a specific mediator route. As a conclusion, longitudinal studies are needed which research the

hypothesis that especially depression and sexual abuse, which are clinical characteristics known to increase the risk of NSSI and SA behaviours, play a role in the pathogenesis through inflammatory parameters.

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Table 1. Comparison of inflammatory markers by groups

	NSSI median(min-max)	SA Median(min-max)	Control Median(min-max)	p*
NLR	1,7(0,8-4,8)	1,8(0,7-6,3)	1,4(0,7-5,5)	0,023
MLR	0,2(0,1-0,5)	0,2(0,1-20,5)	0,2(0,1-0,4)	0,625
PLR	130(68-236)	116(62-288)	120(68-207)	0,791
IL-6(pg/ml)	1,50(0-10)	2,50(1-15)	1,50(1-7)	0,001
TNF-α (pg/ml)	55,61(7,8-357,2)	43,1(0,7-1001)	6,02(0,2(0,2-156)	0,001
hsCRP(mg/l)	0,30(0,2-1,2)	0,2(0,2-5,5)	0,2(0,2-12,1)	0,721

*: Kruskal Wallis H NSSI: Non Suicidal Self İnjury SA: Suicide Attempt min:minimum max:maksimum NLr: Neutrophil lymphocyte ratio MLR: monocyte lymphocyte ratio PLR: platelet lymphocyte ratio IL-6: interleukin 6 TNF-α: tumor necrosis factor alpha hsCRP: high sensitivity C-reactive protein pg / ml: picogram / milliliter mg / ml: milligram / milliliter

Table 2. Correlations of inflammatory parameters with clinical features

	r	p
NLR-BDS	+0,242	0,007
NLR-ACES-sexual abuse	+0,234	0,009
IL-6-BDS	+0,196	0,001
IL-6- ACES-sexual abuse	+0,291	0,029
TNF-α - BAS	+0,387	0,001
TNF-α -BDS	+0,345	0,001
TNF-α -BIS	+0,231	0,010
TNF-α -BHS	+0,220	0,016
TNF-α - ACES-sexual abuse	+0,237	0,008
TNF-α - ACES-physical abuse	+0,185	0,040
TNF-α - ACES-emotional abuse	+0,291	0,001
TNF-α -SÖTÖ-trait anger	+0,238	0,008
TNF-α -SÖTÖ-trait expression	+0,247	0,006

r: correlation coefficient p: significance value NLR: Neutrophil lymphocyte ratio IL-6: interleukin 6 TNF-α: tumor necrosis factor alpha

[Abstract:0970]

0970 - Sociodemographic and clinical characteristics of patients requesting magnetic resonance imaging in the psychiatry service

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ABSTRACT

INTRODUCTION: Magnetic resonance imaging (MRI) has an important place in better understanding the etiology of psychiatric diseases and in the development of diagnostic approaches. In this study, it was aimed to determine the sociodemographic and clinical characteristics of patients who were hospitalized in a psychiatry service and requested MRI.

METHODS: The files of 100 patients who were hospitalized and requested MRI at Akdeniz University Hospital Psychiatry Service between January 1, 2020 and January 1, 2021 were retrospectively scanned.

RESULTS: The mean age of the patients was 39.53 ± 18.19 years (min: 18, max 81) and 45% of them were women (n = 45). 61% (n = 61) of the patients were single and 39% (n = 39) were married. 35% (n = 35) had children and 82% (n = 82) were unemployed.MRI was requested due to 75% (n = 75) first-attack disease etiology, 19% (n = 19) forgetfulness, 3% (n = 3) epileptic seizures and 3% (n = 3) intense agitation. MRI results; 68% (n = 68) normal.MRI was requested for first-attack etiology in 89.6% (n = 60) of psychotic disorder patients and 80.6% (n = 54) were found to be normal.

CONCLUSION: In our study, it was found that MRI was requested to determine the etiology of first-attack disease in young and psychotic disorder patients. The prevalence of radiological findings in first-episode psychosis patients ranges from 5% to 17%. However, most of the findings do not require intervention. In our study, in accordance with the literature, MRI was found to be normal in 80.6% of psychosis patients and the findings found in MRI did not require any intervention. In patients receiving inpatient treatment in the psychiatry service, the most common reason for MRI is the first episode of psychosis and MRI is mostly normal or there are findings that do not require intervention.

Keywords: psychiatric disorders, imaging, etiology

[Abstract:1027]

1027 - Evaluation of bdnf-related blood mirna levels of patients with major depressive disorder: a comparative study

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ABSTRACT

Introduction : Depression is a serious and life-threatening mental disorder of unknown cause, manifested by anhedonia and low self-esteem. Sometimes the symptoms can be severe and persistent and affect patients' quality of life(1).
The molecular and cellular mechanisms of depression are still not fully elucidated. New evidence suggests that changes in gene expression play a role in the pathogenesis of depression(2). The brain-derived neurotrophic factor (BDNF) gene is involved in the pathophysiology of many psychiatric disorders, including depression(3). The BDNF protein is a neurotrophin and contributes to neuronal development and plasticity. BDNF is also involved in maintaining higher brain functions such as cognitive functions(4). Because it is difficult to assess BDNF levels directly from the patient's brain, studies have focused on measuring BDNF levels in the blood. Serum BDNF levels were found to be lower in patients with depression than in healthy individuals(6). This indicates that serum BDNF levels may be a candidate biomarker for the diagnosis of major depressive disorder(MDD).
Considerable effort has been made to identify the factors that regulate BDNF levels. One of these is microRNA(miRNA), which has been studied extensively recently. miRNAs are endogenous small non-coding ribonucleic acids that regulate post-transcriptional gene expression by targeting mRNAs(8). MiRNAs are required for different cellular processes, including metabolism, differentiation, and apoptosis in both animals and plants(9). MiRNAs have been shown to play a role in the pathogenesis of neuropsychiatric disorders, including MDD.
Considering the important roles of BDNF and miRNAs in the pathogenesis of depression, we aimed to determine the relationship between miRNAs regulating serum BDNF levels and depression and to show their usability as a candidate biomarker in the diagnosis of MDD. We also aimed to evaluate the relationship of these miRNAs with clinical features and childhood trauma.

Materials and Methods: Between February 1, 2020 and August 1, 2020, 48 patients who were diagnosed with MDD according to the DSM-5 diagnostic criteria and met the inclusion and exclusion criteria of the Health Sciences University Konya Beyhekim Training and Research Hospital Psychiatry Clinic were recruited.

The patient group consisted of MDD patients with a HAM-D score of ≥ 18 and no psychotropic drug use in the last 6 months.

The control group consisted of 48 healthy volunteers who were matched with the patient group in terms of age, gender and education parameters, who did not have a diagnosis and treatment for a psychiatric disease in the past and still, at the end of the psychiatric evaluation. Exclusion criteria were the presence of any neurological disease in both groups, alcohol and/or substance abuse other than smoking, and obesity (BMI≥30 kg/m2).

Sociodemographic Data Form, The Hamilton Depression Rating Scale(HAM-D), Childhood Trauma Scale(CTQ), Suicide Probability Scale(PSS), Coping Attitudes Rating Scale(COPE), and Montreal Cognitive Assessment Scale(MoCA) were administered to the participants.

Physical examinations of the patients and healthy volunteers included in the study were performed, height and weight parameters were measured and BMI values were calculated. Blood samples of the patients and control group were taken. The obtained sera were stored at -80 oC until the study day and the tests for miR-206, miR-155-5p, miR-134-5p, let-7a-3p were studied on the working day. Statistical evaluations and analyzes were applied according to the results obtained. The sera were thawed on the working day and all samples were studied with the Real Time PCR method on the same day.

Statistical Package for Social Sciences(SPSS), Version 26.0 was used for data analysis. The level of significance in the analyzes was accepted as $p<0.05$.

Results: There was no statistically significant difference between the patient and control groups in terms of gender, age, education period and education level ($p>0.05$). The comparison of the sociodemographic data of the patient and control groups is shown in Table1.

Linear Regression analysis was applied to determine the variables that predicted MiR-206 levels. All variables were analyzed one by one, but a model could not be formed because a variable with a significant relationship could not be determined.

Discussion: In our study, miR-206 level was found to be significantly higher in the MDD patient group compared to healthy controls. Many studies have shown that BDNF may be the direct target gene of miR-206. MiR-206 levels of mice exposed to social isolation and control group mice were compared; It was found that the miR-206 level was higher and the BDNF level was lower in the social isolation group(10). When the changes in miRNA expression with ketamine treatment were examined; MiR-206 expression was decreased in the hippocampus of rats after ketamine infusion. This supports that BDNF is the direct target gene of miR-206(11). When we searched the literature, we could not find any study investigating the relationship between miR-206 and MDD in humans. Our study in accordance with the preclinical studies; This increase in miR-206 level shows that it can be a candidate biomarker in the diagnosis of MDD.

We found that the plasma miR-134-5p level in MDD patients was significantly lower than in healthy controls. Brain-specific miR-134; it is involved in pathways that regulate synaptic plasticity(12). The effect of acute and chronic stress exposure on miRNA level was investigated; It has been shown that miR-134 level increases in the amygdala of mice following acute stress, and miR-134 level decreases with chronic stress(13).

With chronic mild stress exposure, decreased miR-134 expression and low BDNF expression were detected in the basolateral amygdala of mice. When these mice were given ginsenoside Rb1 for antidepressant effect, an increase in miR-134 expression and activation of the BDNF system were observed(14). Consistent with existing studies, our study shows that the decrease in miR-134-5p level may be a candidate biomarker in the diagnosis of MDD.

As a result of the regression analysis, MoCA, CTQ physical abuse and COPE dysfunctional coping attitudes were determined as the variables predicting miR-134-5p level.

Stress-coping-like behaviors were studied in socially defeated mice. After imipramine treatment in these mice, an increase in miR-135 level and an increase in behaviors such as coping with stress were observed(15). Our study shows that there may be a relationship between dysfunctional coping attitudes and miR-134-5p.

We could not find any study investigating the relationship between childhood trauma and miR-134-5p in the literature. As a result of our study; We think that childhood traumas may have contributed to the development of depression by causing a decrease in miR-134-5p levels.

Spatial learning and memory impairments were detected in rats that formed a depression model with chronic mild stress. MiR-134 and BDNF levels were measured in the hippocampus of rats before and after resveratrol treatment. An improvement in cognitive functions and an increase in hippocampal miR-134 and BDNF levels were detected in rats with resveratrol treatment(16). Similarly, in our study, it was shown that there may be a relationship between cognitive functions and miR-134-5p levels.

Conclusion: MiR-206 level was found to be higher in the MDD patient group compared to the control group. MiR-134-5p level was found to be significantly lower in the group of patients with MDD compared to healthy controls. As a result of the regression analysis, it was determined that miR-134-5p and miR-206 levels were diagnostic predictors for the diagnosis of MDD. As a result of the regression analysis, MoCA, CTQ physical abuse and COPE dysfunctional coping attitudes were determined as the variables predicting miR-134-5p level.

Although there are preclinical studies, there is no clinical study evaluating the relationship between MDD and miR-134-5p and miR-206 levels in the literature to the best of our knowledge. The fact that it is the only study evaluating miR-134-5p and miR-206 levels in MDD patients makes our study valuable. Low serum miR-135-5p level and high miR-206 level; Although it needs to be supported by more comprehensive studies, it is promising both as a biomarker that can help clinicians in the diagnostic sense and as a treatment agent that can be used in the treatment of MDD in the long term.

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Table1.Sociodemographic Characteristics of Patients and Healthy Controls

		Patient Group (n=48)	Control Group (n=48)	p
Gender, n(%)				0.81
	Woman	35 (72.9)	35 (72.9)	
	Boy	13 (27.1)	13 (27.1)	
Age (years) Mean ± SD		36.9±12.8	36.5±11.8	0.98
Total Study Period (years), Mean ± SD		9.9±4.8	10.4±4.2	0.66
Education Level, n(%)				0.97
	Primary education	22 (45.8)	22 (45.8)	
	High school	11 (22.9)	11 (22.9)	
	University	15 (31.3)	15 (31.3)	
Place of Residence, n(%)				0.004
	Town center	38 (79.2)	47 (97.9)	
	Other	10 (20.8)	1 (2.1)	
Marital Status, n (%)				0.07
	single	12 (25)	13 (27.1)	
	married	27 (56.3)	33 (68.8)	
	Other	9 (18.8)	2 (4.2)	
Living Condition, n (%)				0.72
	Family	44 (91.7)	43 (89.6)	
	Alone	4 (8.3)	5 (10.4)	
Working Status, n(%)				<0.001
	working	16 (33.3)	48 (100)	
	can't work	7 (14.6)		
	Housewife	16 (33.3)		
	Other	9 (18.8)		
Socioeconomic Status, n(%)				0.002
	Lower	13 (27.1)	2 (4.2)	
	Mid-Upper	35 (72.9)	46 (95.8)	
Smoking, n(%)		26 (54.2)	15 (31.3)	0.023
BMI, Mean ± SD		25.6	26	0.24

mean±sd= mean ± standard deviation, n=number of subjects, p= statistical significance BMI: Body Mass Index

The age at which the patients were first diagnosed (age of onset of the disease) was 31.1±11.9. 70.8% of the patients (n=34) had a previous depressive episode and the mean number of depressive episodes was 1.3±1.3. 33.3% (n=16) of the patients had a previous suicide attempt. Comparison of the clinical features of the patient and control groups is shown in Table 2.

Table2. Clinical Characteristics of the Patients

Mean ± SD, n(%)		Hasta (n=48)
Disease Onset Age		31.1±11.9
Previous Depressive Episode, n(%)		34 (70.8)
Number of Previous Depressive Episodes, Mean ± SD		1.3±1.3
Previous Depression Treatment, n(%)		26 (54.2)
History of Hospitalization, n(%)		6 (12.5)
Number of Hospitalizations		0.2±0.4
Suicide Attempt, n(%)		16 (33.3)
History of ECT, n(%)		1 (2.1)
Inpatient, n(%)		9 (18.8)
Duration of Current Depressive Episode (Months)		11±16.3
Determinants of Current Depressive Episode		
	Anxiety	45 (93.8)
	Mixed	10 (20.8)
	Melancholia	45 (93.8)
	Atypia	14 (29.2)
	Psychotic	1 (2.1)
Psychiatric Disease in the Family		19 (39.6)
	Psychotic disorder	1 (2.1)
	BDB	1 (2.1)
	Depressive disorder	11 (22.9)
	Anxiety disorder	3 (6.3)
	Alcohol-substance addiction	3 (6.3)

mean±sd= mean ± standard deviation, n=number of subjects, p= statistical significance ECT=Electroconvulsive Therapy

There was a significant statistically significant difference between the HAM-D, CTQ and subscales, PSS and subscale scores compared between the patient and control groups (p<0.001) (Table 3,4,5).

Tablo 3 Comparison of HAM-D, CTRS, and IAS Scores of Patients and Healthy Controls

	Patient Group (n=48) Mean±SD	Control Group (n=48) Mean±SD	p
HAM-D	26.3±4.9	1.6±1.7	<0.001
CTQ total score	55.8±16	42.2±3.5	<0.001
emotional abuse	10.8±5.4	5.8±1.5	<0.001
emotional neglect	13.7±5.6	7.4±2.8	<0.001
physical abuse	7.3±3.6	5.1±0.8	<0.001
physical neglect	7.8±5.3	5.7±1	<0.001
sexual abuse	7.1±5.3	5.1±0.3	0.16
PSS total score	82.9±19.8	44.6±6	<0.001
Despair	26.2±5.7	14.2±2.4	<0.001
Hostility	15.5±4.7	8.6±1.5	<0.001
Negative self-perception	24.6±5.7	13.3±3.4	<0.001
suicidal ideation	16.6±7.3	8.4±1	<0.001

mean±sd= mean ± standard deviation, n=number of people, p= statistical significance HAM-D=Hamilton Depression Scale CTRS=Childhood Traumas Scale IPS=Suicide Probability Scale

Table4 Comparison of MoCA Scale Scores of Patients and Healthy Controls

	Patient Group n=48 n(%), mean±sd	Control Group n=48 n(%), mean±sd	p
MoCA total	24.3±5	31±3.2	<0.001
Visual-Spatial-Administrative Functions	2.5±1.4	4.1±0.9	<0.001
Naming	2.6±0.4	2.9±0.3	0,002
Attention	4.2±1.7	4.9±1.2	0.02
Language	1.5±1	2.6±0.7	<0.001
Abstract Thinking	0.9±0.7	1.4±0.6	0,001
Delayed Recall	2±1.2	4.2±0.9	<0.001
Orientation	5.6±0.5	5.9±0.2	0.002

mean±sd= mean ± standard deviation, n=number of subjects, p= statistical significance MoCA=Montreal Cognitive Assessment Scale

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[Abstract:1028]

1028 - Maternal prenatal stress and depression-like behavior associated with hippocampal and cortical neuroinflammation in the offspring: An experimental study

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ABSTRACT

Objective

Prenatal stress was shown to increase the likelihood of pregnancy and delivery problems, negatively impacting neonatal health, growth, and bonding with the mother. Although intrauterine exposure to stress may induce long-term cognitive, emotional, behavioral, psychological, and immunological abnormalities, data on the molecular basis of these changes are limited.

Maternal, fetal, and placental hypothalamic-pituitary-adrenal (HPA) axis activation is observed in response to stress during pregnancy. Glucocorticoids affect fetal brain development but can also cause the immune system and inflammatory response dysregulation. Moreover, recent data revealed increased cytokine levels in depression led to studies investigating the mechanisms that trigger cytokine-mediated immune responses. One of the danger signal recognition receptors that play an important role in the interaction between the inflammatory response and behavior is the Node-like receptor (NLR). Danger signals reaching macrophages and microglia due to stress or cell damage lead to activation of NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) [1].

Another important mechanism includes deregulation of mTOR (mechanistic target of rapamycin) signaling that potentially contributes to psychiatric diseases [2]. Transient receptor potential melastatin (TRPM) is a calcium-permeable channel that senses oxidative stress and contributes to the calcium influx associated with neuropsychiatric disorders such as depression, mental retardation, schizophrenia.

This experimental study aimed to test the hypothesis that intrauterine stress exposure as an environmental factor may contribute to subsequent depression-like comorbidities associated with neuroinflammation, particularly in the hippocampus and the cortex. For this purpose, we assessed anxiety and depression-like behavior and hippocampal NLRP3, ASC (apoptosis related speck like protein containing a caspase activation and recruitment domain), Caspase-1 (cas-1), and Cas-3, mTOR, and TRPM expressions in the temporal and prefrontal cortices of the offspring in the experimental maternal prenatal stress rat model.

Methods

The study was subject to local animal ethics committee approval (the Animal Ethics Committee, Suleyman Demirel University 07.01.2021-01/09). All experiments were performed in accordance with the ARRIVE (Animal Research: Reporting in Vivo Experiments) guidelines in 2.0. Wistar Albino nulliparous female rats were randomly matched with male rats. The day on which sperm was detected in the vaginal smear was determined as day 0 of pregnancy. Then, pregnant rats were divided into two groups (n=6, each): (1) controls and (2) pregnancy stress. Rats in the pregnancy stress group were subjected for 21 days to the chronic unpredictable mild stress (CUMS) model stressors including food and water deprivation for 24 hours, exposure to a wet cage for 4 hours, moistened sawdust for 4 hours, tilted cage for 4 hours, empty cage for 4 hours, social stress for 4 hours, physical restraint for 4 hours, and disruption of the light-dark cycle (24 hours), and tail squeezing for 1-minute. The control animals were kept separate from the stressed animals in another room.

To avoid the effect of offspring born in the same litter (litter effect), two live rat pups (one female and one male) from each term delivery were randomly selected. Puppies were reared with their mothers and weaned on postnatal day (PND) 21. Behavioral tests were performed between days 15-19 of pregnancy for the mother rats and PND 30-34 for the pups. Plasma corticosterone level was measured to evaluate the stress response of the hypothalamus-pituitary-adrenal (HPA) axis. Open field test (OFT), forced swimming test (FST), and sucrose preference tests (SPT) were implemented every other day. Postpartum rats and pups (on PND 35) were euthanatized, and brain tissues harvested.

ELISA was used to test the IL-1β and IL-18 content in the hippocampus using rat-specific commercial kits. Hippocampal NLRP3, ASC, and Caspase-1 gene expressions were evaluated by RT-PCR. The sequences of the primers used in the study are given in Table 1. Samples were histopathologically evaluated. Immunohistochemical analyses included Caspase-3, TRPM-2, and mTOR staining of the temporal and prefrontal cortex with semiquantitative grading.

Student's t-test, Mann Whitney U test, and one-way ANOVA paired t- test were used for statistical comparisons with the level of significance set at < 0.05.

Results

Exposure to prenatal stress was associated with increased depression and anxiety-like behavior with significantly higher immobile and lower mobile period in the FST (p=0.015 and p=0.014 respectively) and significantly higher resting (p=0.044) and lower moving periods (p=0.033) as compared to control mothers. Number of line crosses (p=0.045) and defecation (p= 0.047) in the OFT were also significantly higher in pregnant rats administered prenatal stress. For the SPT, exposure to stress during pregnancy resulted in decreased maternal intake of sucrose water (p=0.041). Both mean serum cortisol and hippocampal IL-1β and IL-18 levels were also found to be significantly increased in pregnant rats exposed to maternal stress (for all comparisons, p<0.05), revealing increased maternal stress and inflammatory parameters with validation of the experimental model.

The FST results of the in utero stress-exposed pups revealed significantly higher resting (p=0.044) and lower moving periods (p=0.033). During the OFT, the offspring born following antenatal stress exposure spent lower time in center and inner part of the apparatus with lower number of walling compared to control pups (p=0.003, p=0.038, p=0.016 respectively), reflecting more anxiety and decreased explorative behavior (Table 1). Stress-exposed offspring also preferred less sucrose water compared to controls (p=0.021) in the SPT. Mean serum cortisol (p=0.004), hippocampal IL-1β (p=0.011), and IL-18 levels (p=0.009) of the offspring with antenatal stress were significantly higher than those of the controls (Table 2). No gender effect was found regarding these parameters (for all, p>0.05).

Hippocampal NLRP3 (FC=2.60, p=0.035; FC=2.28, p=0.022, respectively), ASC gene (FC=4.76, p=0.0001; FC=5.04, p=0.013, respectively), Caspase-1 (FC=3.39, p=0.010, FC=1.86, p=0.006, respectively) expression levels were significantly increased in both female and male offspring born to mothers exposed to prenatal stress compared to control offspring (Figure 1).

Neuronal degeneration and increased Caspase-3, mTOR, and TRPM immunostaining in the prefrontal and temporal cortices of both female and male offspring (p<0.05 for all comparisons except p<0.01 for Caspase-3 in the male cortex and female temporal cortex) compared to the control group were shown (Figure 2). Male pups seemed to be histologically more susceptible to these changes (Table 4).

Discussion

The results of the present study reveal that prenatal stress is associated with increased maternal and offspring depression and anxiety-like behavior with apparent neuroinflammation and injury in the offspring hippocampus and brain cortex.

There is accumulating evidence that early life stress leads to immune activation leading to release of proinflammatory cytokines. Activation of NLRP3 inflammasome induces the release of mature IL-1β and IL-18, which activate different signaling pathways that cause proliferation of pro-inflammatory cells such as astrocytes and macrophages and induce neuronal damage [3]. Consistent with this view, we demonstrated that prenatal stress leads to activation of NLRP3 inflammation in the hippocampus and increased levels of hippocampal proinflammatory cytokines IL-1β and IL-18. Neuroinflammation mediated by NLRP3 during early brain development may result in morphological and functional abnormalities, as well as depression and anxiety in adolescence and adulthood. It can be hypothesized that the NLRP3 inflammasome is critical in the initiation of inflammatory cascades in the hippocampus during prenatal stress, which may ultimately result in depression and anxiety.

The signaling cascade of mTOR is activated by neurotrophic factors and neurotransmitters that suppresses autophagy and enhances protein-lipid synthesis in the central nervous system and contribute to normal neuronal differentiation during fetal development. Reduced mTOR signaling is associated with neurodegeneration, while excess activation signaling causes abnormal development and brain malformation [4]. Numerous mTOR inhibitors have been developed and are approved for clinical uses. In our study, increased expression of mTOR was associated with prenatal stress. Modulation of mTOR signaling as a strategy to prevent prenatal stress-associated changes in fetal brain warrants future studies.

TRPM have been implicated in playing direct roles in Ca^{2+}-mediated neuronal death. They play a pivotal role in secondary injury processes including edema formation, apoptosis, oxidative stress, and necrosis, because of the influx of cations into neurons. Highest expression levels of TRPM in the CNS and both channels are implicated in post-ischemic CNS injury [5]. Caspase 3 expression involved neurodegeneration, synaptic plasticity, reactive gliosis, and neurogenesis. In our study, increased neuronal TRPM expressions in association with increased Cas-3 in maternal stress-exposed offspring indicated that maternal stress may be associated with offspring brain injury.

Study limitations include lack of data on the long-term effects of exposure to stress at different gestational ages. While rodent models are useful in demonstrating causality between prenatal stress and offspring outcomes by selectively manipulating variables in a controlled way, definitive mechanistic interpretation for humans is difficult with the findings obtained. There is a need for more detailed studies on gender-specific, behavioral, structural and epigenetic neurobiological changes transmitted between generations according to the timing and type of environmental exposure to prenatal stressors.

In conclusion, exposure to antenatal stress can lead to depression-like behavior in the infant, mainly driven by hippocampal NLRP3 inflammasome activation, and cortical neuroinflammation and neurodegeneration. Future perspectives include NLRP3-targeted therapies with anti-inflammatory and anti-apoptotic effects against adverse prenatal effects of maternal stress.

Keywords: prenatal stress, neuroinflammation, NLRP3, depression, inflammasome

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Table 1. Primers used in RT-PCR analysis

Gene	Forward primer	Reverse primer
NLRP3	5'-TTTCCCAGACCCTCATGTTG-3'	5'-GGTGCTGAGACTTGAGAAGAG-3'
ASC	5'-ACAAGATGAGGAAGCTCTTTAGC-3'	5'-CACCAAGTAGGGCTGTGTTT-3'
Caspase-1	5'-TGAAAGACAAGCCCAAGGTTAT-3'	5'-CCTCTTCGGGAGTTCCCTACT-3'
ACTB	5'- ACCACCATGTACCCAGGCATT-3'	5'-CCACACAGAGTACTTGCGCTCA-3'

Table 2: Open Field Test Data of Offspring

Groups	Permanence time outer	Permanence time inner	Permanence time center	Total lenght	Walling	Rearing	No of urination	No of defecation	No of line crosses
Control Pups	284,36± 6,84	12,83± 3,41	5,11± 2,40	3548,97± 434,05	23,50± 3,91	2,5± 1,97	1,16± 1,06	2,08± 1,62	185,33± 45,30
PNS	288,92± 6,22	9,19*± 4,80	2,55*± 1,55	3519,49± 362,99	19,21*± 4,42	1,35± 1,25	1,85± 1,25	3,21± 1,88	169,35± 36,37
p values	p=0.88	p=0.038	p=0.003	p=0.85	p=0.0016	p=0.08	p=0.19	p=0.11	p=0.32

'*' denotes a significant difference when compared with control group ($p < 0.05$) for each data.

Table 3. Cortisol, IL-1β and IL-18 levels of Offspring

	Cortisol (plasma)	IL-1β (hippocampus)	IL-18 (hippocampus)
Control pups (n=12)	318,61±85,71	78,38±17,66	34,66±6,4
PNS (n=12)	422,30*±71,16	107,51*±8,47	48,06*±6,5
p values	0,004	0,011	0,009
Sex and group interaction p values	0,356	0,980	0.384

'*' denotes a significant difference when compared with control group ($p < 0.05$) for each data.

Table 4. Statistical analysis results of the immunohistochemical scores

			Cas-3	mTOR	TRPM
Mother	Temporal cortex	Control	0.14±0.14	0.14±0.14	0.14±0.14
		Stress	0.28±0.18	0.28±0.18	0.28±0.18
		p value	>0.05	> 0.05	> 0.05
	Prefrontal cortex	Control	0.00±0.00	0.14±014	0.14±0.14
		Stress	0.42±0.20	0.42±0.20	0.42±0.20
		p value	< 0.05	< 0.05	< 0.05
	Temporal cortex	Control	0.00±0.00	0.14±0.14	0.14±0.14
		Stress	1.14±0.37	1.28±0.48	1.42±0.53

Male offspring		p value	< 0.01	< 0.05	< 0.05
	Prefrontal cortex	Control	0.00±0.00	0.14±0.14	0.14±0.14
		Stress	1.85±0.69	2.28±0.75	2.28±0.75
		p value	< 0.01	< 0.05	< 0.05
Female offspring	Temporal cortex	Control	0.00±0.00	0.14±0.14	0.14±0.14
		Stress	1.42±0.53	1.42±0.53	1.57±0.53
		p value	< 0.01	< 0.05	< 0.05
	Prefrontal cortex	Control	0.00±0.00	0.14±0.14	0.14±0.14
		Stress	1.85±0.37	1.71±0.75	1.71±0.75
		p value	< 0.05	< 0.05	< 0.05

*Data expressed mean±standard deviation (SD).

A

HPC NLRP3 mRNA

B

HPC ASC mRNA

C
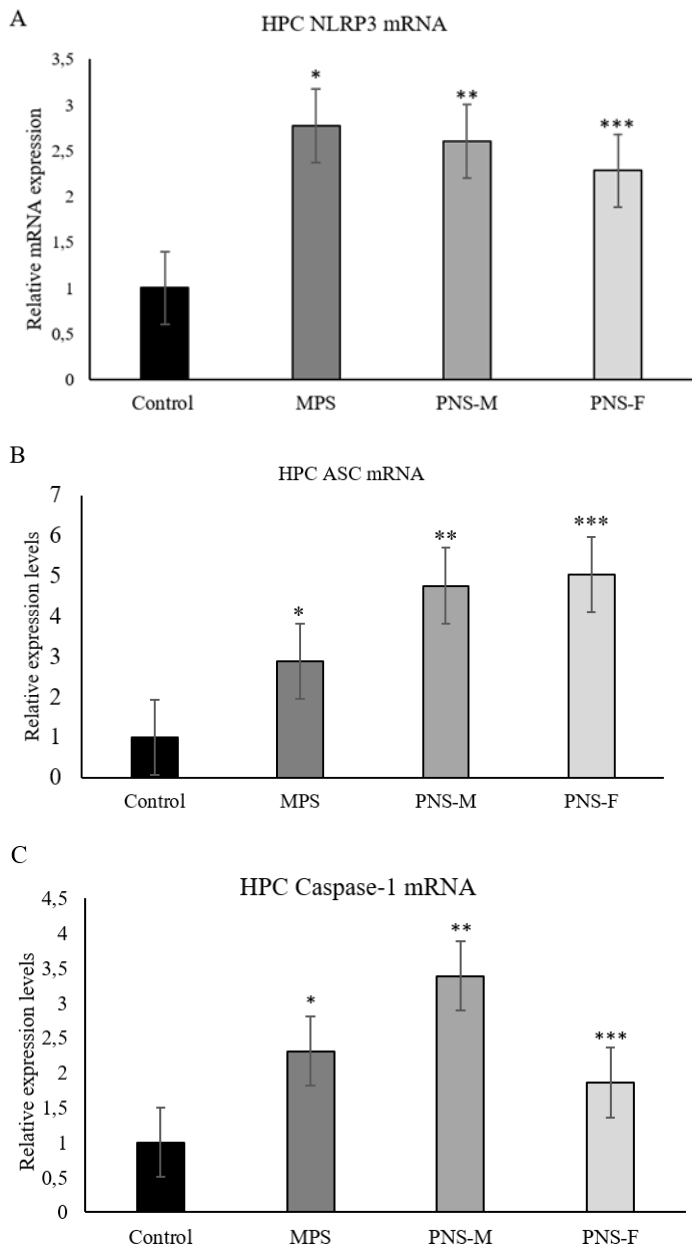
HPC Caspase-1 mRNA

Figure 1. Mean±SEM relative expression in hippocampus of (a) NLRP3 mRNA, (b) ASC mRNA, (c) Caspase-1 mRNA of control and prenatal stress mother rats' and their offspring. MPS, maternal prenatal stress; PNS-M, prenatal stress-male; PNS-F, prenatal stress-female; NLRP3, NOD-like receptor protein-3; ASC, apoptosis speck like protein containing a CARD. Data are presented as normalized mRNA expression in log2(2−ΔΔCT). *normalized to control mother rat group. **control normalized to the male offspring rat group. ***control pup normalized to female offspring rat group.
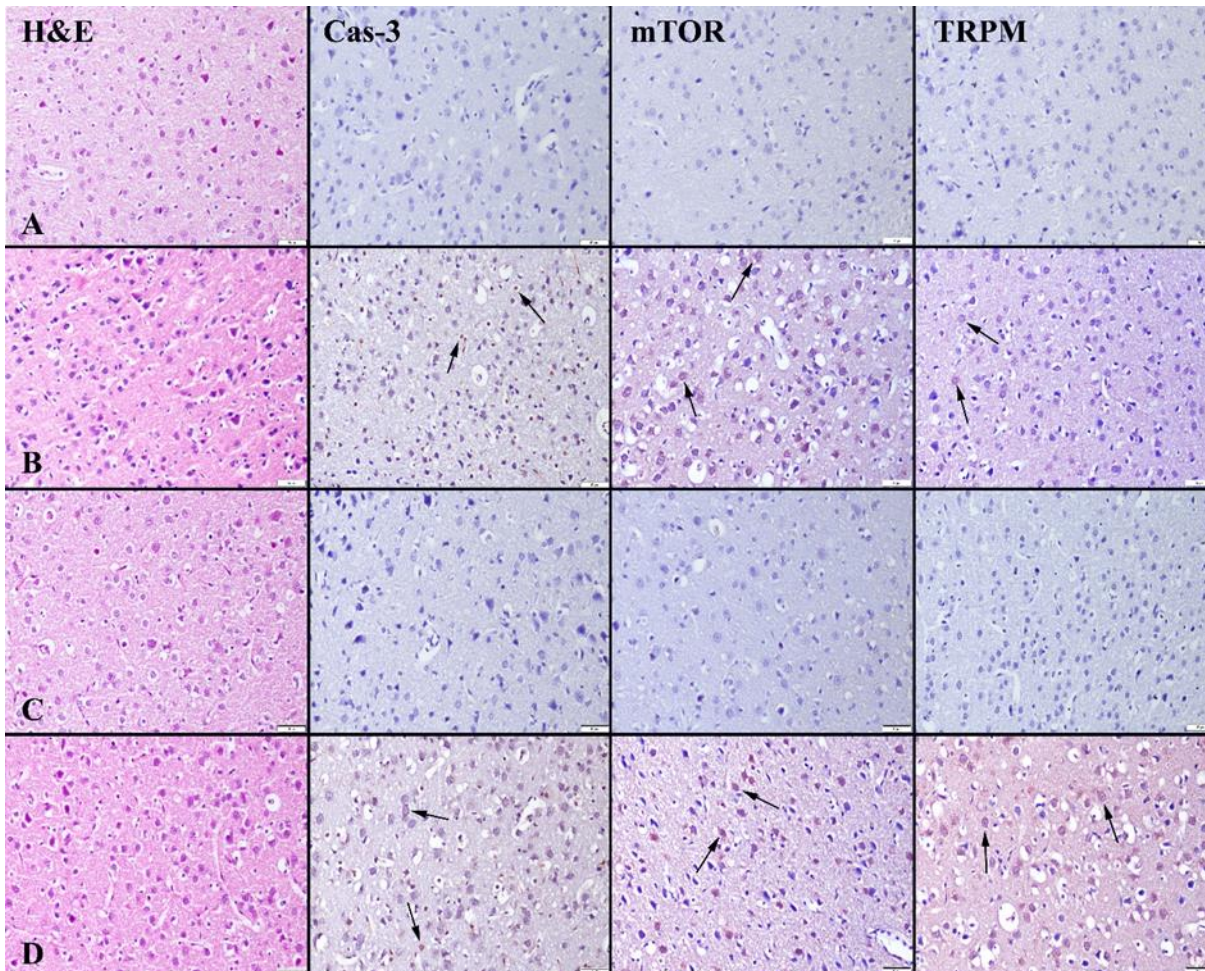
Figure 2. Representative histopathological and immunohistochemical pictures of offsprings between the groups. (A) Normal tissue architecture and negative expression in temporal cortex control group. (B) Relatively normal tissue histology but increased expressions (arrows) in temporal cortex in stress group. (C) Normal tissue histology and negative expression in prefrontal cortex in control group. (D) Almost normal tissue histology but increased expressions in prefrontal cortex in stress group, H&E (first column) and Streptavidin Biotin peroxidase method, scale bars=50μm.

[Abstract:1031]

1031 - Investigation of cox-2-765g→c and cox-2-1195a→g genes in autısm spectrum disorder

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ABSTRACT

Introduction: Autism spectrum disorder (ASD) is a neurodevelopment disorder that characterized by difficulties in social interaction and communication and the presence of restricted interests and stereotypic, repetitive behaviors. According to the epidemiological data, ASD is a common neurodevelopment disorder, which is affecting 1 in 68 children. Although ASD is a relatively common neurodevelopmental disorder, we have little information about its etiology. Complex interactions between genes and environment may explain this unique and different brain development for this neurodevelopmental disorder. Some neurobiological factors such as genetic, neurochemical, neurophysiological and neuroanatomical have been emphasized in the possible etiology of ASD. The COX2/PGE2-mediated signaling system is one of the possible etiological candidate pathways.

Arachidonic acid (AA) is released from cell membranes through the activity of phospholipase A2 (PLA2) in the healthy brain. Cyclooxygenase-1 and -2 (COX1 and COX2) enzymes convert AA to Prostaglandin E_2 (PGE2) and other prostanoid metabolites. COX2 expression is typically inducible in the periphery by inflammation and has constitutively expressed in the neurons of brain. Compared with in peripheral tissues, COX2 expression levels are significantly higher in the whole brain neurons, particularly in the hippocampus and cerebral cortex. Some fundamental brain functions such as dendritic spine formation, synaptic plasticity, memory and learning is mediated by normal COX2/PGE2-mediated signaling system. PGE2 is the predominant metabolite of COX enzymatic activity and is the major lipid mediator molecule in the nervous system and according to the

recent literature there are considerable evidence of abnormal PGE2 signaling on the developing brain of children with ASD. Possible molecular abnormal COX2/PGE2 signaling mechanisms may affect brain development and associated to ASD.

The clinical studies show that both genetic and environmental factors related COX2/PGE2 pathway may contribute ASD pathogenesis. In some studies conducted patients with ASD increased PLA2 activity, decreased total AA and increased PGE2 levels have been reported. As a PGE2 analogue, misuse of misoprostol for the termination of pregnancy was found increased risk of ASD. The developing brain is vulnerable to various environmental factors like inflammation, oxidative stress, pollution, heavy metals, pesticides and drugs like acetaminophen and nonsteroidal anti-inflammatory drugs such as acetominofen, because of disrupted PGE2 signaling pathway and this factors have been linked to ASD. In a Korean genetic study polymorphism of Ptgs2, which gene that encodes the COX2 enzyme, has been associated with ASD.

In our study, the relationship between COX-2 gene variants and autism, previously shown to be associated with ASD in different populations and animal experiments, was examined in the Turkish population.

Methods: Study population The study group consisted of 101 patients diagnosed with ASD between the ages of 2-18 and the biological parents of these patients, followed by the Department of Child and Adolescent Psychiatry at Istanbul University, Istanbul Medical Faculty. Participation in the study was determined on a voluntary basis and written and verbal informent consent was obtained from all participants. All participants were evaluated with sociodemografic form, Child Autism Rating Scale(CARS) and psychiatric examination based on the DSM-IV. Blood samples of trios (patient and their biological parents) were studied in the Department of Molecular Medicine of the Istanbul University Institute for Experimental Medicine. Ethics committee approval was obtained from Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee.

Polymorphism analysis

DNA isolation

Blood specimens were collected in tubes containing EDTA and DNA samples were extracted from whole blood by a salting out procedure (22). After the genomic DNA was isolated, COX-2-765G→C and COX-2-1195A→G polymorphisms were made. For COX-2-765G→C, forward 5'-TATTATGAGGAGAATTACTCGC-3' with reverse 5'-GCTAAGTTGCTCACAGAGAT-3' and for COX-2-1195A→G polymorphism forward 5'-CCCTGAGCACTACCCATGAT-3' with reverse 5'-GCCTTCATAGGAGATACTGG-3' Polymerase chain reaction (PCR) was performed using primers. COX-2-765G→C and COX-2-1195A→G DNA regions amplified by PCR were cut with AcyI and HpyCH4IV restriction enzymes, respectively. The cutting samples were evaluated under UV transilluminator after running on 3% agarose gel stained with ethidium bromide with appropriate size marker.

Statistical analysis

In our study, the nonparametric X2(Chi square) test was used to measure the significance of the distribution of the risk alleles of the COX 2 gene in the patient and control groups. Fisher's exact test was used if the number in any cell of the 2*2 contingency table was >5. Relative risk at 95% confidence intervals (CI) was calculated as the odds ratio (OR). Allelic and genotypic distributions of trios were tested using transmission disequilibrium test (TDT) and haplotype relative risk test(HRR). The standard TDT method in Haploview (http://www.broad.mit.edu/mpg/haploview/) was used to test the family-based association for each individual polymorphism and haplotype. The relative risk of the candidate gene in ASD was calculated using the HRR tables. Values for P ≤ 0.05 were considered as statistically significant. Some of the tests were applied within the SPSS software program and some of them were applied using the GraphPad software program.

Results

COX-2-765 gene evaluations were performed with 91 trios. TDT evaluation was performed only with data obtained from heterozygous parents (n=50). In total, 26 C alleles were transmitted from parents, while 30 C alleles were non-transmitted. When all samples for the COX-2-765 gene were examined with the TDT, which only counts the heterozygous parent-to-child transmission and tests this link, it was seen that the inheritance to the child with ASD did not reach the level of statistically significance (p:0,2248).

HRR calculations performed with 91 trios and no significant difference was found between the C and G alleles in parent-to-child transmission (p=0,3348). There was no significant difference between the case and control groups in terms of CG, CC and GG ratios (p=0,8775).

COX-2-1195 gene evaluations were performed with 85 trios. TDT evaluation was performed only with data obtained from heterozygous parents (n=32). In total, 21 G alleles were transmitted from parents, while 13 G alleles were non-transmitted. When all samples for the COX-2-1195 gene were examined with TDT, which only counts heterozygous parent-to-child transmission and tests this link, it was seen that heredity to child with ASD was higher and this reached the level of statistically significance (p:0,0262).

HRR calculations performed with 85 trios and it was found no statistically significant difference between G and A alleles in parent-to-child transmission (p=0,1064). There was no significant difference between the case and control groups in terms of AG, AA and GG ratios (p=0,3733).

Discussion

ASD is a neurodevelopmental disorder with an increasing prevalence in recent years. However, there are relatively few studies on possible causes of ASD and associated risk factors. In previous studies there are neurobiological studies and as well as studies related to environmental risk factors. Genetic studies are also prominent among neurobiological studies. In addition to being the first study in Turkey with the COX 2 gene in children and adolescents with ASD, it is one of the very few studies conducted with human subjects with ASD in the world.

When the studies on COX-2 are reviewed, we see that the possible role of COX-2 in different neurodegenerative and psychiatric diseases is emphasized. There are various studies on the role of COX-2 in the pathogenesis of Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Bipolar Disorder, and Schizophrenia. In addition, over-expression of COX-2 is associated with neurotoxicity in

acute diseases such as hypoxia, ischemia, and seizures. However, it is still controversial whether the role of COX-2 in inflammatory and neurodegenerative brain pathologies is beneficial or harmful.

In the study by Yoo HJ et al., PTGS2 (the gene encoding cox-2) polymorphisms were evaluated in 151 Korean family trios (mother, father, and child) whose children had ASD. In this study, the A allele of rs2745557 was found to be preferentially transmitted in ASD (p<0.01) and the GAAA haplotype was found to be significantly associated with ASD.

In our study, when the COX-2-765 gene was examined with TDT and HRR, it was seen that heredity to child with ASD did not reach statistically significance. When the COX-2-1195 gene was examined by TDT, it was seen that the inheritance was higher in child with ASD and this reached statistically significance. When the same sample was examined with HRR, no significant transition was found for the COX-2-1195 gene. The study by Yoo HJ et al. to examine the relationship between PTGS2 (the gene encoding COX-2) and ASD phenotype in Korean trios is the first human study in this area. Our study also supports the positive results obtained in the study of Yoo HJ et al. In both studies, it was determined that there was a significant relationship between ASD and COX-2 gene. However, this association needs to be replicated in larger populations.

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Table 1: COX-2-765 TDT Results

COX-2-765 TDT	C	G	TOTAL	Chi-square, df	p value	Odds ratio (95% CI)
Transmitted	26	30	56	0.5714, 1	0,2248	0,7511 (0.3573 - 1.579)
Non-Transmitted	30	26	56			
TOTAL	56	56	112			

Table 2: COX-2-765 HRR Results

COX-2-765 HRR	Case	Control	Total	Chi-square, df	p value	Odds ratio (95% CI)
C	28	31	59	0.1821, 1	0,3348	0,8856 (0.5068-1.548)
G	154	151	305			
TOTAL	182	182	364			
CG	22	25	47	0.2613, 2	0,8775	
CC	3	3	6			
GG	66	63	129			
TOTAL	91	91	182			

Table 3: COX-2-1195 TDT Results

COX-2-1195 TDT	G	A	TOTAL	Chi-square, df	p value	Odds ratio (95% CI)
Transmitted	21	13	34	3.765, 1	0,0262	2,609 (0.9809 - 6.942)
Non-Transmitted	13	21	34			
TOTAL	34	34	68			

Table 4: COX-2-1195 HRR Results

COX-2-1195 HRR	Case	Control	Total	Chi-square, df	p value	Odds ratio (95% CI)
A	142	150	292	1.553, 1	0,1064	0,6762 (0.3644 - 1.255)
G	28	20	48			
TOTAL	170	170	340			
AG	26	18	44	1.971, 2	0,3733	
AA	58	66	124			
GG	1	1	2			
TOTAL	85	85	170			

[Abstract:1033]

1033 - Comparison of executive functions with borderline ıntellectual functioning, attention deficit hyperactivity disorder and healthy groups using the event-related potentials method

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ABSTRACT

Objective: In this study, it will be evaluated whether there is a difference in executive function performances between individuals with Attention Deficit Hyperactivity Disorder (ADHD) and those with Borderline Intellectual Functioning, and to what extent this difference differs from the healthy group. In addition, by evaluating the executive functions of all three groups through Event-Related Potentials, it will be investigated whether there is a difference in the electrical waves obtained between the three groups and how the deterioration in executive functions is reflected on the electrical waves.

Methods: Between the ages of 10-18, who applied to the Outpatient Clinic of Atatürk University Faculty of Medicine Department of Child and Adolescent Psychiatry and Diseases, 20 individuals diagnosed with ADHD, 20 individuals diagnosed with Borderline Intellectual Functioning, and 20 age-matched healthy individuals with the study group were included in the study. In the study, sociodemographic data form and Developmental and Mental Health Assessment (DAWBA) were applied, and DSM-V based clinical interviews were conducted. ADHD was diagnosed with DAWBA. In the study, only individuals with no loss of intellectual functioning who were diagnosed with Oppositional Defiance disorder were included in the diagnosis of ADHD as a comorbid. The group diagnosed with Borderline Intellectual Functioning; It consisted of individuals who had an IQ between 70-85 as a result of the WISC-R Intelligence Test (Wechsler Intelligence Scale for Children) who did not have any psychopathology. In order to evaluate executive functions, Stroop task was applied, and electrical activity in the brain was recorded through Event-Related Potentials (ERP) during the test process.

The Stroop material was created in the computer environment using the MATLAB program within the scope of the study. Before starting the Stroop task, baseline EEG was recorded for 45 seconds. There were 5 sessions in the Stroop task and 15 stimuli were shown in each session. These 15 stimuli are the stimuli on which the colors "Red", "Blue", "Yellow", "Green" are written. The subject is asked to press the left button of the mouse when the stimulus that is compatible with the color name written on the screen comes (compatible stimulus), and not to press the left button of the mouse when the stimulus that is incompatible with the color name written on the screen comes (incompatible stimulus). 70% of the stimuli are compatible and 30% are incompatible. After 5 sessions of the Stroop task were completed, a 45-second baseline EEG was recorded again. Total Stroop task time is approximately 8 minutes.

Obtained behavioral parameters; Total of correct response, Correct response latency (reaction time), Total of incorrect response, Incorrect response latency, commission error and omission error.

The data obtained from the research were evaluated using the SPSS (The Statistical Package for Social Sciences) 24.0 package program. Statistically p<0.05 values were considered significant.

Results: In the sample of our study; while 5 (25%) of the ADHD group were girls, 15 (75%) were boys and the mean age was 12 (12.5 ± 2). While 11 (55%) of the Borderline Intellectual Functioning group were girls and 9 (45%)) was male and the mean age was 12 (12.2 ± 1.4). The mean age was 12 (12.3 ± 2) in the control group, with 10 girls (50%), 10 boys (50%). There was no statistically significant difference between the three groups in terms of gender distribution and mean age. As a result of DAWBA for all three groups; There was no psychiatric comorbid condition in the ADHD group.

Correct reaction times on the Stroop task were found to be statistically significantly longer in individuals with a diagnosis of borderline intellectual functioning than in the other two groups.

In individuals diagnosed with ADHD, the number of comission error was found to be statistically significantly higher.

In individuals diagnosed with Borderline Intellectual Functioning, a statistically significant difference was found between the number of correct, wrong numbers and omission error in the Stroop task compared to the control group.

In our study, the amplitude of the P300 electrical wave obtained by ERP during the Stroop task, in which executive functions were evaluated, was found to be statistically significantly higher in individuals with borderline intellectual functioning compared to the other two groups.

Discussion: In the Stroop task, individuals with ADHD were found to have significant performance impairment compared to the other two groups in behavioral data related to possible inattention and impulsivity symptoms. In the literature, commission error has been found to be associated with impulsivity (1). In this context, it was thought that impulsivity being the main symptom of ADHD may have contributed to the results obtained.

The Stroop task is a test that evaluates cognitive capacity as well as attention (2). In the Stroop task, performance impairment was found in behavioral data thought to be related to the cognitive capacities of individuals diagnosed with Borderline Intellectual Functioning. It was thought that the long reaction time obtained in our study may be related to the slow processing speed of individuals with borderline intellectual functioning. In addition, an increase in amplitude was observed in our study, which supports the long reaction time and cognitive slowness. In the literature, it is stated that individuals with borderline intellectual functioning have a slower processing speed than individuals with normal cognitive development (3).

Keywords: ADHD, Borderline Intellectual Functioning, Event-related potentials, Stroop task, executive functions

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[Abstract:1039]

1039 - Investigation of the effects of olanzapine and l-carnitine on rat testicular tissue

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ABSTRACT

Introduction: Environmental toxicants, occupational exposures, and drug-induced adverse reproductive effects are essential indicators of male infertility. The male reproductive system may be the target of drug toxicity. Continuous exposure to antipsychotic drugs alters hypothalamic-pituitary and gonadal hormones or non-hormonal mechanisms in men, leading to impaired sexual function, spermatogenesis process, as well as epididymal maturation (1). Olanzapine is atypical, in other words, a second-generation antipsychotic that acts through dopamine and serotonin receptors (2). There are studies in the literature that Olanzapine is associated with male infertility through sexual dysfunction (3, 4).

Oxidative stress is an imbalance between the formation of Reactive Oxygen Species (ROS) and antioxidant defense mechanisms (5). This imbalance leads to damage to biomolecules and cells that are vital to the whole organism. ROS are products of normal cellular metabolism and play an essential role in stimulating signaling pathways in animal cells in response to changes in intracellular and extracellular environmental conditions (6). Oxidative stress can seriously damage proteins, lipids, DNA, and organelles. It is a process directly related to inflammation and causes the secretion of a large number of cytokines and chemokines in inflammatory cells (7).

L-Carnitine is a biologically active stereoisomer of 3-carboxy-2-hydroxy-N, N, N-trimethyl-1-propanamine. L-Carnitine has been shown to have beneficial effects on parameters such as motility, maturation, and fertilization capacity in male germ cell lines through its antioxidant and radical scavenging properties (11-13). L-Carnitine has significant effects on the male reproductive system, notably on sperm count and motility (14).

Spermatozoa are immobile when they reach the epididymis. As it passes through the epididymis, as a result of post-gonadal modification with an increase in L-Carnitine in the epididymal fluid, spermatozoa mature, and tail movement is observed (15). L-Carnitine is known to be effective in improving fertilization ability with post-gonadal modification (16).

Due to the severe side effects of Olanzapine, especially its sexual dysfunction and adverse effects on the reproductive system, drug use is often interrupted. It is aimed to investigate the role of L-Carnitine in Olanzapine-induced testicular damage, which has limited studies on structural changes in the reproductive system.

Materials And Methods: Animal experiments were approved by the local animal ethics committee of Suleyman Demirel University (Ethics No: 14-03, dated 13.04.2018). 24 adult male Spraque-Dawley rats weighing 280-300 g were housed at 21-22 °C and 60% ± 5% humidity, with a 12-hour light, 12-hour dark cycle. All rats were fed with standard commercial chow (Korkuteli Yem, Antalya, Turkey), ad libitum food and water.

They were divided into 6 groups with 8 animals in each group. Olanzapine doses were determined as 2 and 4 mg/kg, which are equivalent to the high doses used in humans (0.5 and 2.5 mg/kg/day) according to the literature review (2, 17, 18).

Olanzapine was dissolved in distilled water and administered by oral gavage to experimental animals in a volume of 1 mL/100 g. The duration of administration was determined as 42 days, based on repeated dose oral toxicity studies and literature review, during which possible reproductive system damage could be detected (19, 20).

Based on the literature review, the dose of L-Carnitine administered to the experimental animals was determined as 200 mg/kg/day as an intraperitoneal (i.p.) injection (21, 22).

Control group (Control) (n=8): For 6 weeks, i.p. normal saline (SF) and oral gavage were applied in the same injection volume as the other groups.

Low dose olanzapine group (LOZN) (n=8): Olanzapine was administered by oral gavage at a dose of 2 mg/kg/day for 6 weeks.

High dose olanzapine (HOZN) (n=8): Olanzapine was administered by oral gavage at a dose of 4 mg/kg/day for 6 weeks.

Low dose olanzapine + L-Carnitine (LOZN + LC) (n=8): Olanzapine + 200 mg/kg i.p. L-Carnitine was administered by oral gavage at a dose of 2 mg/kg/day for 6 weeks.

High-dose olanzapine + L-Carnitine (HOZN+LC) (n=8): Olanzapine at a 4 mg/kg/day dose by oral gavage + 200 mg/kg i.p. L-Carnitine was administered for 6 weeks.

L-Carnitine (LC) (n=8): 200 mg/kg i.p. L-Carnitine was administered for 6 weeks.

The weights of the rats in the experimental groups were measured before the first drug administration and 24 hours after the last administration. During the experiment, weighing process was , repeted weakly. At the end of the 6 weeks, rats that were given ketamine/xylazine (80-100 mg/kg-6-8 mg/kg) anesthesia i.p. were sacrificed by collecting a high amount of blood from V. cava inf.

Histopathological Analyses

In the histopathological examinations, the tissues were washed in running water overnight using the immersion fixation method in 10% neutral formalin solution, and then they were subjected to dehydration, clearing, infiltration, and embedding processes. Sections of 4-micron thickness were taken from the prepared paraffin blocks using a Leica-type slide microtome. Preparations were stained with Hematoxylin-Eosin for histological evaluation. The stained samples were examined under an Olympus BX50 type binocular microscope, and images were obtained and evaluated.

Isolated epididymides were kept in Petri dishes with 2 ml of stock solution. For the evaluation of epididymal spermatozoa, the epididymides, which were divided into two, were placed in a stock solution with a Petri dish. It was kept at 37°C for 10-15 minutes to float and separated into 1 ml Eppendorf tubes. Sperm samples were evaluated after vortexing. They were evaluated with the Olympus CX21 (40X) stereomicroscope and Makler camera at 36.5ºC. All groups were kept confidential and scored by the same person by making five different counts of each sample. For total motility, five different samples were prepared for each group. A minimum of 200-300 sperm samples were counted for optimization. Progressive motility was determined as (a+b), non-progressive (c), and immotile as (d). Total motility was determined as (a+b) based on WHO 2010.

Biochemical Analyses

Rat testis and epididymis tissues were removed and washed with phosphate buffer (8 g/L NaCl, 0.224 g/L KCl, 0.2 g/L KH2PO4, 1.14 g/L Na2HPO4, pH 7.4) to remove blood and contamination. Left testicular tissues were used to determine the levels of testicular malondialdehyde (MDA), Interleukin-1 beta (IL-1B), Interleukin-6 (IL-6), Total Antioxidant Status (TAS), Total Oxidant Status (TOS), and Oxidative Stress Index (OSI) based on the experimental procedure determined by the manufacturer of the respective kits.

Some of the left testicular tissues were used for biochemical analyses. After weighing the tissue samples, they were homogenized in 750 L PBS in a homogenizer (Tissuelyser II, QIAGEN, Germany) for about 3 minutes at 30 frequencies. During the homogenization processes, care was taken to keep the samples under cold conditions. The homogenate was centrifuged at 10,000 g, and the resulting supernatants were stored at -80˚C until analysis. MDA, IL-1B, IL-6, TAS, TOS levels were measured from the supernatants as an indicator of oxidative stress.

Results: Evaluation of MDA, IL-1B, IL-6, TAS, TOS, OSI, FSH, LH, Testosterone in Testicular Tissue

MDA: Malondialdehyde; IL-1B: Interleukin-1 beta; IL-6: Interleukin-6; TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index; LC: L-Carnitine group; LOZN: Low-dose Olanzapine group; LOZN+LC: Low-dose Olanzapine+L-Carnitine group; HOZN: High-dose Olanzapine group; HOZN+LC: High-dose Olanzapine+L-carnitine group; Kruskal-Wallis test

A statistically significant difference was found in MDA, IL-1B, and TOS values, the parameters measured in testicular tissue (F=12.277, p=0.031, F=14.561, p=0.012, F=16.342, p=0.006, respectively). There was no statistically significant difference in IL-6, TAS, and OSI values (p>0.05).

When the MDA values were examined, there were statistically significant differences between Control and LOZN (LOZN>Control, p=0.031), Control and LOZN+LC (LOZN+LC>C, p=0.001), Control and HOZN+LC (HOZN+LC>C, p=0.019), LOZN and HOZN+LC groups (HOZN>LOZN+LC, p=0.04).

When the IL-1β values were examined, there were statistically significant differences between the Control and DOZN (LOZN>Control, p=0.028), Control and LOZN+LC (LOZN+LC>C, p=0.035), LC and LOZN (LOZN>LC, p=0.011), LC and LOZN+LC (LOZN+LC>LC, p=0.014), HOZN and LOZN (HOZN>LOZN, p=0.032), HOZN+LC and LOZN (HOZN+LC>LOZN, p=0.009), HOZN+LC and LOZN+LC groups (HOZN+LC>LOZN+LC, p=0.012).

When the TOS values were examined, there was a statistically significant difference between the groups HOZN+LC and LOZN (LOZN>HOZN+LC, p=0.003), HOZN and HOZN+LC (HOZN>HOZN+LC, p=0.005), LC and LOZN (LOZN>LC, p=0.049), LOZN and LOZN+LC (LOZN>LOZN+LC, p=0.005), and HOZN and LOZN+LC groups (HOZN>LOZN+LC, p=0.010).

Histopathological Findings

Testicular samples of all groups in our study were observed in terms of the basement membrane, seminiferous tubule structures, and interstitial space structures, and cells cytoplasm and nuclei by light microscopic examination. The samples in the control group were observed to be normal in terms of the examined areas. In the light microscopic examination of LC group testis samples, it was observed that it maintained its normal appearance in the interstitial area, seminiferous tubule structure, and lumen. It was also observed that spermatogenesis continued.

In the light microscopic examination of rat testis samples in the LOZN group, the basement membrane, seminiferous tubule structures, cytoplasm and nuclei of leydig cells in the interstitial area, vascular structures, sertoli cells, spermatogonia, and spermatogenic series cells were observed in a smooth structure, while edema was observed in the interstitial area. Spermatogonia were localized between sertoli cells and were observed in the tail lumen towards the head tubule wall.

Light microscopic examinations of rat testis samples from the LOZN+LC group were similar to the control and L-Carnitine groups. There was no interstitial edema observed in the LOZN group. It was observed that the seminiferous tubule structures were normal, with the normal histological appearance in terms of interstitial area features and cells.

In the light microscopic examination of rat testis samples from the HOZN group, occasional deteriorations and losses in the basal membrane seminiferous tubule structures, and congestion and edema in the interstitial structure were observed. Some openings in the seminiferous tubule lumens and occasional losses in the interstitial areas were observed. Organizational disorders were occasionally observed in the germinal epithelium. Deterioration and decrease in spermatogenic series in cells were noted. In the light microscopic examination of rat testis tissue samples from the HOZN+LC group, features similar to the HOZN group were observed in the basal membrane and seminiferous tubule structures. It was observed that there were improvements (decreases) in the losses in the interstitial areas in the opening of the seminiferous tubules compared to the HOZN group. It has been understood that the degeneration in the cells continues with the decrease.

Control group Lower Interstitial area (Arrow), Germ Cell Series (Star) (A). Seminiferous Tubule Lumen (Star), Interstitial area (Arrow) (B) belonging to LC Group. Interstitial area (Arrow) of the LOZN Group (C). Interstitial area (Arrow) of LOZN+LC Group (D). Vacuolization (Circle), Interstitial area (Arrow), congestion and edema (Arrow) in cells belonging to the HOZN Group (E). Interstitial area (Arrow), vasculature (Arrowhead), Spermatogenic Series cells (Star) belonging to the HOZN Group (F). Interstitial area of HOZAN+LC Group (Arrow), Spermatogenic Series cells (Star), Separation in Seminiferous tubules (Arrowhead) (G), H&E (X200)

Discussion: The effects of Olanzapine on testicular histology have been demonstrated with few studies in the literature (19, 24). In the study of De Siqueira Bringel et al., germ cell desquamation, multinucleated giant cells, vacuolization in Sertoli cells, necrotic and apoptotic germ cells were observed in rats treated with 5 and 10 mg/kg Olanzapine (19).

These histopathological changes observed, parallel to our study, show that Olanzapine has degenerative effects on testicular tissue, and this effect is dose-dependent. In the study of Soliman et al., It was stated that it caused epithelial desquamation, epithelial detachment, and apoptotic changes in the germ cells of the rat testis in the group receiving Olanzapine, and vacuolization, endoplasmic reticulum dilatation, and lipid accumulation were shown in Sertoli cells (24). Unlike our study, they detected histopathological changes in testis with a lower dose (0.5 mg/kg/day) of Olanzapine administration. This effect was thought to be related to the use of Olanzapine for a longer period (14 weeks), even at low doses.

The positive effects of L-Carnitine on testicular tissue and the male reproductive system have been shown in many studies (25- 28). In the study of Deliktas et al., the protective effect of L-Carnitine on ischemia and reperfusion injury caused by testicular torsion was investigated. Histologically, degeneration of germinal epithelial cells, edema of interstitial tissue, and color changes in spermatocytes were observed after ischemia-reperfusion. After administration of L-Carnitine, histological improvement was found close to normal (25).

Some results were obtained in our study. First, considering the histopathological changes, the opening of the seminiferous tubule lumens, losses in the interstitial areas, organizational disorders in the germinal epithelium, and degeneration of the cells may be an indicator of the testicular toxicity of Olanzapine . The milder findings in the LOZN group and the more severe degenerative findings in the HOZN and HOZN+LC groups suggest that this effect is dose-dependent. Olanzapine-induced testicular degenerative changes were observed less in the HOZN+LC group than in the HOZN group, indicating that L-Carnitine may positively affect Olanzapine-induced testicular degeneration. Second, the decrease in sperm count due to the damage caused by Olanzapine was reversed with L-Carnitine treatment, resulting in a significant increase in sperm count. Third, it was concluded that abnormal sperm morphology and degenerative histological findings in testicular structure in high-dose Olanzapine administered groups might be associated with Olanzapine-induced oxidative stress in testicular tissue. In accordance with the literature, it was concluded that L-Carnitine may have a positive effect on sperm morphology and testicular degeneration by reducing oxidative damage.

In the light of the findings of our study, it is noteworthy that there is a limited number of studies showing that Olanzapine causes histopathological changes in testicular tissue, the mechanisms of these changes have not yet been clarified, and studies suggesting that Olanzapine has effects on oxidative stress in other organs. Our study is the first to investigate the effects of Olanzapine and L-Carnitine on testicular tissue through oxidative stress parameters. Further animal and human studies are required to fully comprehend the effects of Olanzapine and L-Carnitine on testicular tissue.

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Table 1. MDA, IL-1B, IL-6, TAS, TOS, OSI Values of the Groups

	Controls (n=7)	LC (n=8)	LOZN (n=7)	LOZN+LC (n=8)	HOZN (n=8)	HOZN+LC (n=8)	P
MDA (nmol/g)	0.909±0.158	1.107±0.114	1.122±0.113	1.225±0.161	1.006±0.283	1.137±0.133	0.031
IL-1B (pg/mL)	1.388±0.189	1.268±0.481	1.664±0.174	1.629±0.124	1.415±0.241	1.379±0.196	0.012
IL-6 (pg/mL)	1.387±0.115	1.418±0.125	1.368±0.122	1.419±0.104	1.335±0.111	1.323±0.163	0.636
TAS (mmolTrolox Equivalent/L)	1.288±0.323	1.890±1.212	1.734 ±1.207	1.350±0.861	0.983±1.163	1.550 ±1.073	0.533
TOS (µmol H2O2 Equivalent/ L)	26.386±4.292	25.320±6.311	33.590±12.076	22.531±3.30	31.999±8.579	22.106±2.136	0.006
OSI	2.157±0.623	1.751±0.888	2.496±1.519	2.069±2.150	4.160±5.584	2.340±1.735	0.643

Figure 3. Comparison of Intergroup Histopathological Results
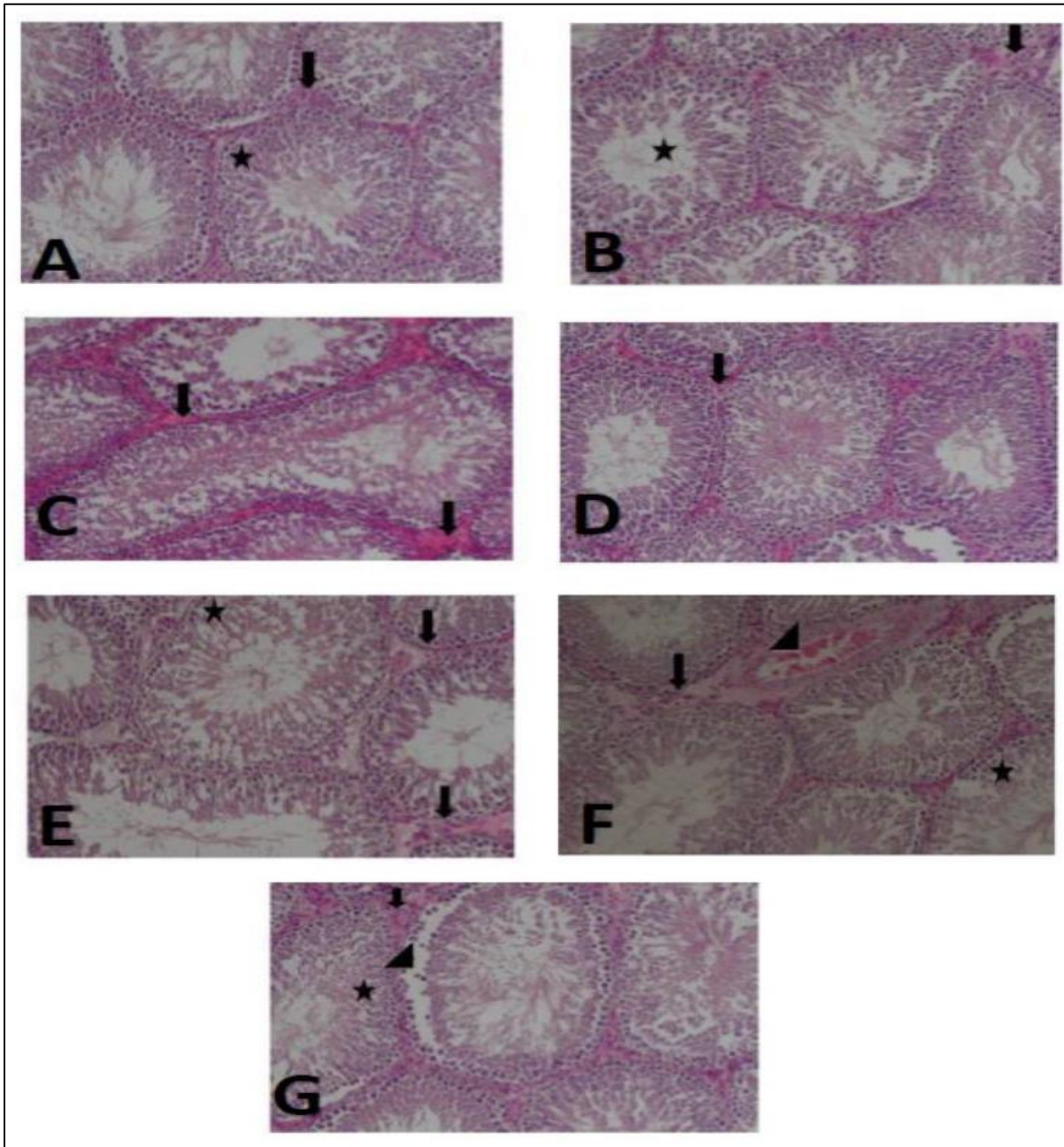
[Abstract:1067]

1067 - Increased plateletcrit and platelet distribution width in patients with panic disorder and generalized anxiety disorder

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ABSTRACT

OBJECTIVE: Panic disorder (PD) and generalized anxiety disorder (GAD) are among the most common mental disorders. Platelet volume indices (PVI) are hematological biomarkers that show platelet activity. Peripheral platelets are widely used as indicators of central serotonin metabolism because they reflect central serotonergic function. Platelet overactivity increases the tendency of coagulation. The aim of this study is to evaluate and compare PVI in patients with PD and GAD.

METHODS: The data of 49 patients with PD, 47 patients with GAD and 50 healthy controls were retrospectively analyzed. The following PVI were evaluated in complete blood count (CBC); PLT (Platelet count), MPV (Mean Platelet Volume), P-LCR (Platelet - Large Cell Ratio), PCT (Plateletcrit), PDW (Platelet Distribution Width) and P-LCC (Platelet Large Cell Count). Sociodemographic data form for all participants, Panic and Agoraphobia

Scale (PAS) and Hamilton Anxiety Rating Scale (HAM-A) for PD patients, State-Trait Anxiety Inventory and HAM-A for GAD patients were evaluated and compared with platelet parameters.

RESULTS: PCT and PDW levels of PD and GAD patients were found to be significantly higher than the control group (Table I, Figure 1). PCT values and PAS scores of PD patients were positively correlated (Table II). A positive correlation was also found between HAM-A score and PDW in GAD patients (Table II). ROC analysis showed that PCT> 2.58 had 73.5% sensitivity and 68% specificity for PD. PCT>2.53 had a sensitivity of 70.2% and a specificity of 63.6% for GAD (Figure 2a and 2b).

CONCLUSION: Elevated PCT and PDW levels are correlated with PD and GAD positively. PD and GAD patients who have high PCT and PDW levels can easily be identified during routine complete blood count (CBC) analysis and could possibly benefit from preventive antithrombotic treatment.

KEYWORDS: Panic disorder, plateletcrit, generalized anxiety disorder, platelet distribution width

INTRODUCTION: Generalized anxiety disorder (GAD) is defined as a disorder that occurs almost every day for at least 6 months, with symptoms such as excessive anxiety, inability to control sadness, restlessness, easy fatigue, distractibility, irritability, muscle tension, and sleep disorders. On the other hand, the most basic feature of panic disorder (PD) is recurrent and unexpected panic attacks. Panic attacks typically begin abruptly with intense fear and anxiety, and symptoms such as dyspnea, suffocation, dizziness, fainting, and palpitations may occur.

Because peripheral platelets reflect central serotonergic function, they are considered indicators of central serotonin (5-HT) metabolism. Serotonin is an important factor in the pathophysiology of anxiety disorders and is involved in platelet aggregation. Platelets contain 5-HT2A receptors and 5-HT transporter (5-HTT) in their membranes. Increased PVI are thought to be closely associated with thrombotic events particularly ischemic cardiovascular diseases (CVDs) and stroke. PVI are hematological biomarkers that show platelet activity. Platelet overactivity increases the tendency to coagulate. Although there are various studies on some PVI in PD and GAD patients, there is no definite opinion. In this study, we aimed to evaluate PVI in PD and GAD patients.

METHODS

Inclusion and exclusion criteria

A total of 96 patients between the age of 18 to 65 years diagnosed with PD (n=49) and GAD (n=47) according to DSM-V criteria who admitted to the Elazig Mental Health and Diseases Hospital between 1 June 2020 and 2021 were included in the study. Between the same dates, 50 healthy individuals (age range, 18-65) without any psychiatric diagnosis were included in the control group. Mental retardation, organic disease, cognitive or neurological impairment, alcohol or substance use, smoking, pregnancy, breastfeeding, hematological disease, and drug use that would affect platelet activity were determined as exclusion criteria for all participants. Of the patients, 16 patients were excluded from the study due to neurological disease, 20 due to smoking, 5 pregnancy, 9 patients using thrombolytic drugs, 8 patients due to alcohol or substance use, 17 patients over 65 years of age, and 20 patients due to lack of data. As for the control group, 22 people were excluded from the study due to smoking, 2 pregnancy, and 13 people due to lack of data.

The study was approved by Elazig Fırat University Clinical Research Ethics Committee (No: 2021/08-49). Since the study conducted retroprospectively , written consent form was not obtained from the patients.

Hematological Analysis

All blood samples were obtained from the antecubital vein after 12 hours of fasting. Samples were analyzed by drawing into vacuum tubes containing 15% K3 ethylene diamine tetraacetic acid (EDTA)-anticoagulant tubes (Sarstedt, Essen, Belgium). Complete blood count (CBC) parameters were evaluated using the Sysmex XN-450 hematology analyzer (Sysmex Corporation, Kobe, Japan) according to the manufacturer's instructions. PLT (Platelet count), MPV (Mean Platelet Volume), P-LCR (Platelet Large Cell Ratio), PCT (Plateletcrit), PDW (Platelet Distribution Width), and P-LCC (Platelet Large Cell Count) were evaluated as platelet parameters. The P-LCC value was calculated by dividing the product of PLT and P-LCR by 100.

Data collecting

Sociodemographic Data Form: It contains information such as age, gender, disease history, educational status, background, family history, alcohol, substance or cigarette use, and medications used.

Panic and Agoraphobia Scale (PAS): It rates the severity of panic attack by considering phobic avoidance, anticipatory anxiety, restriction in social relations, and belief in physical illness. This scale was developed by Bandelow. Turkish validity and reliability study was done by Tural et al. A high score indicates high disease severity.

State-Trait Anxiety Inventory (STAI): STAI-I and STAI-II consist of two 20-item scales. While STAI-I shows how an individual feels at a certain moment and under certain conditions, STAI-II shows how the individual generally feels. Its Turkish validity and reliability were evaluated by Öner N and LeCompte A. A high score indicates a high level of anxiety.

Hamilton Anxiety Rating Scale (HAM-A) : It was developed by Hamilton in order to determine the level of anxiety and symptom distribution and to measure the change in severity. Evaluates both somatic and cognitive anxiety symptoms. The total score ranges from 0 to 56. The Turkish validity and reliability study was performed by Yazıcı et al.

Sociodemographic data form for all participants, PAS and HAM-A for PD patients, STAI and HAM-A for GAD patients were evaluated and compared with platelet parameters.

Statistical analysis

All data were analysed with the Statistical Package for Social Science (SPSS) for Windows 26.0 package program. The conformity of the variables to the normal distribution was measured with the Kolmogorov-Smirnov test. Since all continuous variables were normally distributed, they were

expressed with mean and standard deviation (SD). Continuous data were analyzed with the One-way Anova test. Bonferroni test was performed to determine which group had a significant difference. The results were interpreted with a 95% (p<0.05) confidence interval.

RESULTS

PDW values were found to be significantly higher in PD and GAD patients compared to the control group (Table I, Figure 1). However, there were no statistically significant differences between the PD, GAD, and control groups in terms of PVI (Table I). Pearson correlation analysis showed that PCT values and PAS score were positively correlated in PD patients (Table II). No correlation was found between other platelet indices and PAS and HAM-A scores (Table II). On the other hand, a positive correlation was observed between HAM-A and PDW in GAD patients (Table II). However, no correlation was found between other platelet indices and STAI-I, STAI-II and HAM-A scores. ROC analysis showed that PCT> 2.58 had 73.5% sensitivity and 68% specificity for PD. PCT>2.53 had a sensitivity of 70.2% and a specificity of 63.6% for GAD (Figure 2a and 2b).

DISCUSSION: In this study, in which platelet parameters were evaluated, it was revealed that PCT and PDW levels were higher in PD and GAD patients compared to healthy people. Platelets are responsible for the pathophysiology of inflammatory and thrombotic processes cardiovascular events and stroke. PCT is the percent volume of platelets in the blood and is calculated wıth the formula of "PCT = platelet count × MPV/10,000". The platelet count in the blood is kept in balance through regeneration and elimination. There is evidence that PVI are significantly correlated with thrombotic events and may predict the prognosis of acute ischemic stroke. It was also shown that PCT may be a biomarker in inflammatory diseases.

PDW is the distribution width of platelets of different sizes. PDW elevation indicates anisocytosis in platelets. Therefore, PDW is an indicator of volume variability in platelet size. PDW is considered a specific marker of platelet activation. PDW was also associated with the severity of acute coronary syndrome. In some studies, PDW was found to be higher in PD patients than in healthy controls and can be considered an effective marker [1]. In other studies, changes in MPV and increase in PDW in PD patients were found to be risky for the development of CVDs. In this study, increased PDW in PD was found to be consistent with previous studies. Although platelet parameters in PD and GAD have been studied before, there is not enough data on PCT.

Serotonin is emphasized in the etiology of both PD and GAD. In cases of increased stress and anxiety, serotonin binds to 5 HT-2 receptors on platelets and triggers aggregation. Anxiety may play a role in vascular events such as MI by increasing platelet activity [2]. It has been found that 5-HT reuptake in platelets is increased in patients with PD and accompanying major depression [3]. In this study, PCT values and PAS scores were positively correlated in PD patients. On the other hand, a positive correlation was found between HAM-A score and PDW in GAD. The increase in these platelet volüme indices may be due to the serotonin metabolism, which is impaired by the severity of the disease.

Platelet indices are important tools that should be used to predict acute thrombotic events. PCT and PDW can be easily detected during routine CBC analysis and patients may benefit from preventive treatment. Therefore, more attention should be paid to these parameters in PD and GAD patients.

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Table 1. Comparison of laboratory data

	Panic disorder (N=49)	Generalized anxiety disorder (N= 47)	The Normals (N=50)	P values
PLT(10³/mm³)	266,32±53,18	274,10±89,59	249,52±36,85	NS
MPV (fL)	10,33±1,16	10,40±1,06	10,68±0,97	NS
PDW(fL)	15,98±0,42	15,98±0,39	12,85±2,51	P<0.0001[a],p<0.0001[b], NS[c]
PLC-R (%)	29,99±7,19	29,92±7,51	32,13±8,14	NS
PLCC (10³/mm³)	78,64±20,13	78,71±19,24	78,85±18,25	NS
PCT(Plateletcrit) (%)	2,83±0,44	2,80±0,73	0,29±0,04	P<0.0001[a],p<0.0001[b], NS[c]

a: Panic disorder versus normal group

b: Generalized anxiety disorder versus normal group,

c: Generalized anxiety disorder versus panic disorder.

PLT: Platelet, PDW: Platelet distribution width, PLC-R: Platelet Large Cell-Ratio, PLCC: Platelet Large Cell Count, MPV: Mean Platelet Volume, PCT: Plateletcrit

Table 2. Pearson correlation analysis between Panic disorder, Generalized anxiety disorder(GAD) and then normals

	PCT		PDW	
	r	p	r	p
PAS (panic disorder)	0.006		0.005	0.973
HAMA (panic disorder)	0.056	0.702	0.115	0.433
HAMA (GAD)	0.344	0.180	0.452	0.001
STAI-I (GAD)	-0,038	0,799	0,082	0,585
STAI-II (GAD)	0,045	0,764	0,272	0,065

Figure Legend

Figure 1: Comparison of PCT and PDW between the panic disorder, GAD and the normals

(a)　　　　　　　　　　　(b)

Figure Legend

Figure 2a: ROC analysis for PCT cut off predicting panic disorder. AUC: Area under the curve; CI: Confidence interval; ROC: Receiver operating characteristics.
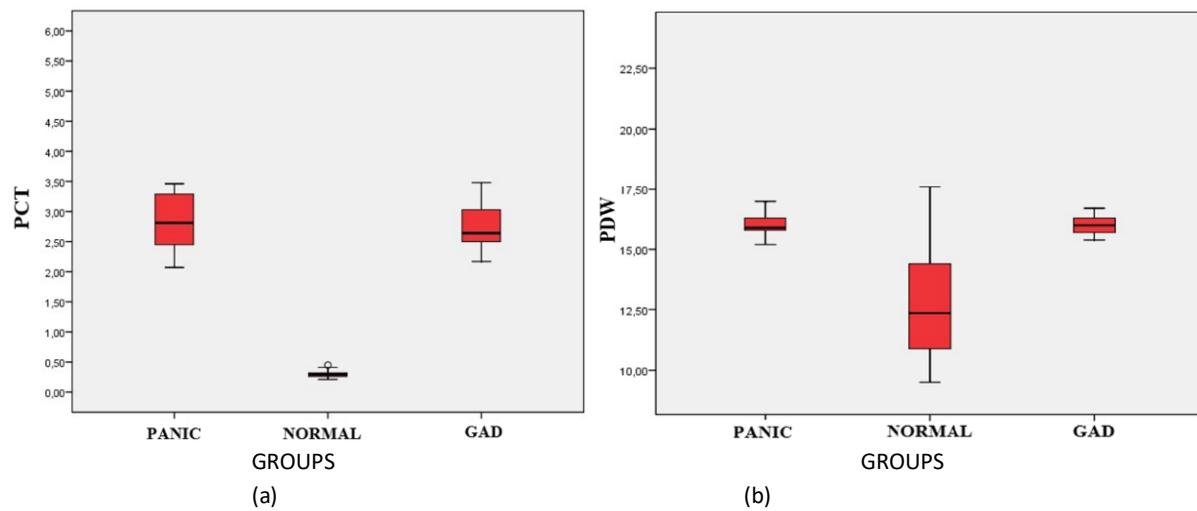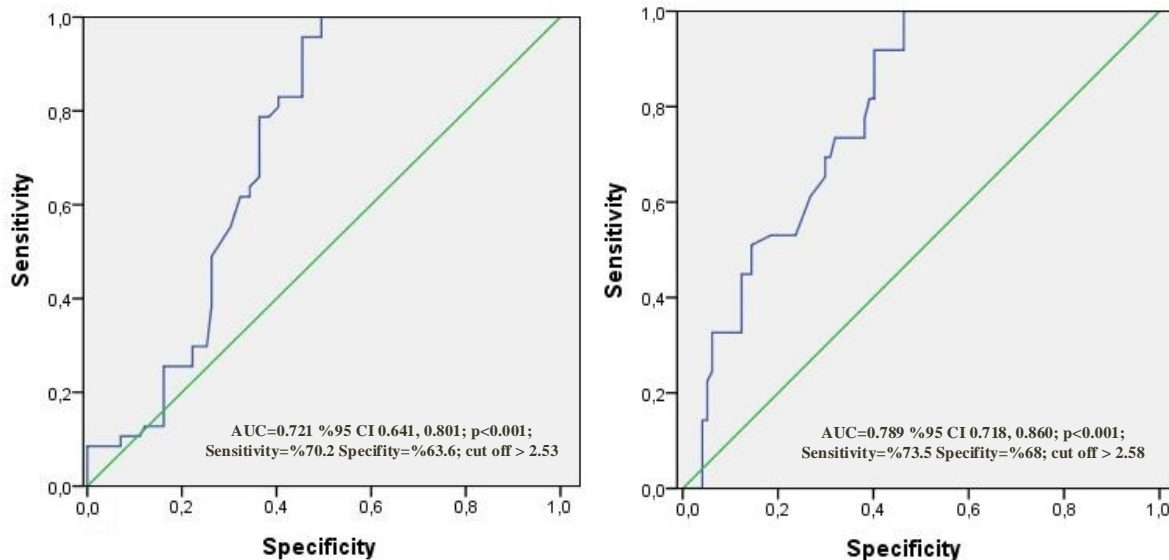
Figure 2b: ROC analysis for PCT cut off predicting generalized anxiety disorder. AUC: Area under the curve; CI: Confidence interval; ROC: Receiver operating characteristics.

AUC=0.721 %95 CI 0.641, 0.801; p<0.001;
Sensitivity=%70.2 Specificity=%63.6; cut off > 2.53

AUC=0.789 %95 CI 0.718, 0.860; p<0.001;
Sensitivity=%73.5 Specificity=%68; cut off > 2.58

(a)　　　　　　　　　　　(b)

[Abstract:1078]

1078 - Melanopsin gene polymorphism in seasonal depression and bipolar disorder

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ABSTRACT

INTRODUCTION: Seasonal affective disorder (SAD) is used to define recurrent mood episodes with a seasonal pattern. Depressive episodes mostly occur during fall and winter, hypmanic and mnic episodes ocur during spring and summer. Depressive symptoms in SAD include the full spectrum of symptoms subsumed under major depressive disorder with seasonal pattern specifier (MDD SP), however, the majority of MDD SP patients show atypical presentation, which includes hypersomnia, increased appetite, and weight gain due to carbohydrate craving/consumption. MDD SP is similar to bipolar disorder (BD) with these atypical symptoms and recurrent course. Also, BD and MDD SP involve irregularities in daily or circadian rhythms, such as changes in the timing of sleep, melatonin release, and body temperature (1-3). Melatonin is a hormone produced by the pineal gland that responds to darkness by causing sleepiness. Melanopsin is involved in the circadian rhythms and melatonin suppression. Melanopsin is photosensitive protein present in the retinal ganglion cells. Melanopsin receptors project to non-visual centers of the brain including the suprachiasmatic nucleus. Roeklein et al. found that all of the SAD patients have T/T allele of P10L variant of melanopsin gene (RS2675703) and this variant is associated with SAD. In a previous study done in Mexico, they found that P10L variant of melanopsin gene is associated with chronic insomnia. However, this variant is not investigated in bipolar patients before. This study investigates genetic polymorphism of melanopsin gene in bipolar disorder and seasonal depression and healthy controls.

METHODS: Patients were recruited from the outpatient and inpatient clinics of psychiatry department of Adnan Menderes University Medicine Faculty Hospital. Signed voluntary consent form is taken and peripheral blood is obtained and stored – 4 degrees celcius. Patients with comorbid anxiety disorders, eating disorders, schizoaffective disorder and mental retardation were exluded. DNA was isolated from peripheral blood samples with the QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's instructions. DNA purity and concentration were measured using a NanoDrop 1000 Spectrophotometer V3.7 (Thermo Scientific, USA). In the study, gene polymorphisms in the intronic region of melatonin, which was not previously studied bipolar depression patients but thought to be associated with depression, were selected by scanning the GWAS and ExAC databases and the literature on other psychiatric diseases. SNPs located in the intron regions of the identified genes and associated with some psychiatric diseases were identified by real-time PCR (LightCycler 480, Roche) using an SNiP panel from the manufacturer. Manufacturer-supplied probes identified single-base changes/SNPs enabling polymorphism analysis. SNPs were analyzed by melting curve analysis at the end of amplification. Data analysis was performed by melting curve genotyping with LightCycler 480 software. We investigated OPN4, RS2675703 Melatonin.

RESULTS: Study group consists of 85 (43 males and 42 females) volunteers. 39 patients with bipolar disorder, 14 patients with MDD SP, 32 healthy controls. The average age of the bipolars is 34.79±9.52, SAD patients is 38.35±8.67, HC is 29.09±5.08. There is no statistically significant difference between bipolar and MDD SP patients (p= 0.211). However, there are statistically significant difference between MDD SP patients and HC (p=0.002) and bipolar and HC (p=0.002) in terms of age. The distribution of all three genotypes (C/C, C/T, and T/T) of melanopsin gene between MDD SP and bipolar disorder did not differ (p=0.402). None of the patients with MDD SP (p<0.0001) and bipolar disorder (p<0.0001) have homozygous C/C genotype when compared with healthy controls (HC). None of the HC have T/T genotype. T/T genotype is present in 48.7 % of bipolar patients (19 patients), in 35.7% of MDD SP patients (5 patients), C/T genotype is present in 51.3 % of bipolar patients (20 patients), in 64.3% of MDD SP patients (9 patients).

CONCLUSION: This is the first study that has ever been carried out to investigate the relationship between melanopsin gene and bipolar disorder. OPN4 polymorphism is examined before by Rocklein et al. (2009) and and they found that T/T is associated with SAD and all the SAD patients have T/T allele. They reported that T allele increased the risk SAD 5.6 times. They included MDD, bipolar I and II patients with SP. Another study reported that T allele of OPN4 polymorphism is associated with chronic insomnia (Mexica). In line with previous study, our results demonstrated that C/T and T/T variants is present in bipolar disorder and MDD SP. However, 6 of the bipolar patients have the diagnosis of seasonal pattern in our study. According to the results of this study, T allele may be a risk factor for recurrent mood disorders independent of seasonality and MDD SP may be a variant of bipolar spectrum.

These findings support that melanopsin variants may predispose to mood disorders. But, further research is needed to demonstrate this relationship.

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[Abstract:1091]

1091 - An investigation of the relationship between childhood traumas and separation anxiety disorder for medical college students

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ABSTRACT

OBJECTIVE: Separation Anxiety Disorder (SEPAD) was classified in the section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" criteria for the disorder until the fifth version of Diagnostic and Statistical Manuel of Mental Disorders (DSM-5) [1]. In DSM-5 the core features of SEPAD remained the same, however the wording of the criteria updated to a more suitable form of SEPAD symptoms in adulthood such as a place for avoiding behaviors can be workplace in addition to school or attachment figure could be a child of someone other than a caregiver [1]. Moreover, DSM-5 indicated that the age for onset of SEPAD must not be under age 18, it could be seen after age [1]. Several anxiety disorders have been linked to childhood traumatic life events (CTLE) in the literature [2,3]. The most well-known anxiety disorders which are linked with CTLE are panic disorder, post-traumatic stress disorder (PTSD), and phobias [2,3]. The present article aims to investigate the prevalence of SEPAD in a sample of medical students. In addition, we aimed to investigate the relationships between SEPAD and childhood traumatic life experiences (CTLE) in the present population.

METHODS: Informed consent was obtained from all the participants in the present study and researchers followed the rules belongs to the World Health Organization Declaration of Helsinki. Appropriate permission (Decision number: 2017/147) was received from the Clinical Research Ethics Committee of the university on 23.10.2017.

The sample of this study consisted of 369 medical school students who are in their first four years in a medical school in Turkey. The Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS) was applied for all participants by researchers. After this interview, participants were asked to fill in the socio-demographic form, Separation Anxiety Symptoms Inventory (SASI), Adult Separation Anxiety Questionnaire (ASA), and Childhood Trauma Questionnaire (CTQ).

All analyses were conducted with the use of Statistical Package for Social Sciences (SPSS-26.0) for Windows. All continuous variables were tested for normality and homogeneity of variance. The student's t-test was used for normally distributed data, and Mann–Whitney U test was used for data that were not normally distributed. The Kruskal Wallis test was used to compare more than one group that was not normally distributed. Correlations between continuous variables were evaluated using Spearman's correlation test. A p-value below 0.05 was considered statistically significant.

RESULTS: The sample of the present study consisted of 369 people in total, 221 (59.9%) of the participants were female and 148 (40.1%) were male. 32.8% of the participants were in the first grade, 22.2% of the participants were in the second grade, 22.5% of participants were in the third grade, and 22.5% of the participants were in the fourth grade of medical school. The mean age was 20.06±1.86. Regarding SEPAD based on SCI-SAS, the rate of those with significant childhood SEPAD is 14.9% (n: 55), the rate of those with adult SEPAD is 20.1% (n: 74) in the present study. In terms of examining all participants based on CTQ, we examine all participants based on CTQ cutoff scores for sub-scores and total CTQ scores to see rates of each childhood trauma sub-type in all participants. According to this examination in all participants, the rate of those who suffered emotional neglect in their childhood was 62.1% (n: 229), the rate of those who suffered physical neglect was 36.3% (n: 134), the rate of those who suffered emotional abuse was 23.3% (n: 86), the rate of those who were physically abused was 15.7% (n:58), the rate of those who were sexually abused was 16.3% (n:60).

In terms of examining the relationship between SEPAD and CTLE, we compared CTQ scores in the groups which were divided based on their SCI-SAS scores. Participants were divided into groups based on their SCI-SAS scores as those who showed significant symptoms on the child and adult sub-scales of SCI-SAS (who scored 2 or higher out of at least 3 questions). A statistically significant difference was found in emotional abuse and sexual abuse sub-scores between participants who met childhood separation anxiety criteria of SCI-SAS (n:55 14.9%) and those who did not (n:314 85.1%) (Z=-2.810, p=0.005; Z=-2.080), p=0.038, respectively). A statistically significant difference was found in physical abuse and sexual abuse sub-scores between participants who met adult separation anxiety criteria of SCI-SAS (n:74 20.1%) and those who did not (n:314 85.1%) (Z=-2.524, p=0.012; Z=-2.068), p=0.039, respectively;) (Table-3).

CONCLUSIONS: The present study aimed to investigate SEPAD and CTLE characteristics in a young population who are student at a medical school in Turkey and to compare CTLE characteristics within groups based on SEPAD diagnosis through self-reported scales.

Since SEPAD is a new diagnosis for adults with DSM-5, we could not find any study about the prevalence of SEPAD especially in college students so far. In United States, National Comorbidity Survey Replication indicated lifetime prevalence for adult SEPAD as 6.6% and for child SEPAD as 4.1% [4]. In the present study, we found that both adult and childhood SEPAD is very common in medical students (20.1%, 14.9% respectively). There is a growing body of literature with mounting evidence showing that CTLE can trigger a mental disorder or worsen the prognosis of existing disorder [2,3]. There are several studies in the literature showing that especially some specific childhood trauma types in a relationship with specific mental disorders [2,3]. However, we could not find any study which examine the relationship between childhood trauma sub-type and SEPAD in the literature so far. According to findings of the present study in terms of the relationship between CTLE and SEPAD, we can see that CTLE were strongly in a relation with both childhood and adult SEPAD. In terms of trauma sub-type especially sexual abuse seems to be in a relation with both childhood and adult SEPAD. CTLE may have a key role in the progress of SEPAD. Trauma during the childhood has several effects on brain. CTLE can lead to learned helplessness and emotion dysregulation [3]. Additionally, CTLE influence early attachment relations, and this cause several problems in the interpersonal relationships during lifetime [2]. Therefore, it is very crucial to work with CTLE in individuals with mental disorders and clinicians should query about CTLE for SEPAD patients to improve treatment modals and prognosis. Moving forward, future studies should investigate differences between characteristics of CTLE in larger clinical samples in different ages groups with SEPAD.

Keywords: childhood trauma, medical school, separation anxiety disorder, traumatic life experiences

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TABLES

Table-1 The socio-demographic characteristics of participants and the correlations between socio-demographic characteristics and CTQ, SASI, and ASA scores

		n(%)	Mean(SD)	CTQ	SASI	ASA
Age	Female	221(59.9)	19.93(1.7)	-0.126	0.155*	0.010
	Male	148(40.1)	20.26(1.86)	0.138	0.216**	0.036
	Total	369(100)	20.06(1.77)	-0.004	0.196**	0.042
Duration for living away from home			2.89(2.32)	-0.026	0.187**	-0.005
			Median(min-max)			
Number of Sibling			2(0-11)	0.150**	-0.059	-0.004
Sibling rankings			1(1-9)	0.094	0.014	0.084
*: mann-whintney u CTQ: Childhood Trauma Questionnaire, SASI: Separation Anxiety Symptoms Inventory, ASA: Adult Separation Anxiety Questionnaire, SCI-SAS: Structured Clinical Interview for Separation Anxiety Symptoms						

Table 2: The correlations between physical and mental health conditions, monthly income and CTQ, SASI, and ASA scores

			CTQ		SASI		ASA	
		n %	Mean (SD)	p*	Mean (SD)	p*	Mean (SD)	p*
Physical Illness	Yes	29 (7.9)	34.06 (8.7)	0.870	49.8 (7.2)	0.016	83.2 (13.3)	0.182
	No	340 (92.1)	34.232 (10.6)		49.1 (6.2)		84.3 (12.0)	
Mental disorder	Yes	24 (6.5)	38.1 (12.9)	0.117	46.5 (9.1)	0.251	73.7 (10.5)	<0.01
	No	345 (93.5)	33.9 (10.2)		49.3 (6.0)		84.9 (11.9)	
Housing conditions	Living with family	46 (12.5)	34.0 (9.7)	0.600	49.5 (5.5)	0.398	83.7 (12.6)	0.398
	Living with friends	92 (24.9)	33.9 (12.9)		49.7 (6.3)		83.7 (12.7)	
	Staying at dormitory	179 (48.5)	34.3 (9.1)		48.7 (6.4)		84.5 (11.5)	
	other	52 (14.1)	34.5 (10.9)		49.5 (6.6)		84.3 (13.0)	
Monthly income perception	Good	96 (26.0)	33.7 (13.4)	0.005**	49.0 (6.9)	0.527	82.9 (13.1)	0.478
	Medium	259 (70.2)	33.9 (8.8)		49.1 (6.1)		84.7 (11.9)	
	Low	14 (3.8)	41.9 (13.3)		51.1 (5.1)		84.2 (9.2)	
*: Mann-Whintney U Test **KRUSKAL-WALLİS Test, CTQ: Childhood Trauma Questionnaire, SASI: Separation Anxiety Symptoms Inventory, ASA: Adult Separation Anxiety Questionnaire, SCI-SAS: Structured Clinical Interview for Separation Anxiety Symptoms								

Table-3: The comparison of total CTQ and CTQ sub-scores of participants in terms of their SEPAD characteristics

	Childhood SEPAD				**Adult SEPAD**			
	+* (n:55 %14.9)	- (n:314 %85.1)	z	p	+** (n:74 %20.1)	- (n:295 %79.9)	z	p
	Mean± SD	Mean± SD			Mean± SD	Mean± SD		
Emotional Abuse	7.7±3.4	6.6±2.7	-2.810	0.005	7.2±3.3	6.6±2.7	-1.384	0.166
Physical Abuse	5.7±5.0	5.7±5.6	-0.964	0.335	5.7±2.2	5.7±5.8	-2.524	0.012
Emotional Neglect	9.2±3.9	9.1±3.7	-0.012	0.991	9.4±3.1	9.1±3.7	-0.558	0.577
Physical Neglect	7.4±2.4	7.0±2.2	-1.367	0.171	7.1±2.2	7.0±2.7	-0.810	0.418

Sexual Abuse	5.7±1.6	5.4±1.6	-2.080	0.038	5.5±1.1	5.4±1.7	-2.068	0.039
Total CTQ	35.8±10.8	33.9±10.4	-1.511	0.131	35.1±9.6	33.9±10.6	-1.238	0.216
Mann-Whitney U Test. SEPAD: Seperation Anxiety Disorder, CTQ: Childhood Trauma Questionnaire, SASI: Separation Anxiety Symptoms Inventory, ASA: Adult Separation Anxiety Questionnaire, SCI-SAS: Structured Clinical Interview for Separation Anxiety Symptoms, *:Participants who met childhood SEPAD criteria based on SCI-SAS, **: Participants who met adult SEPAD criteria based on SCI-SAS,								

[Abstract:1122]

1122 - Sodium-glucose co-transporter inhibitor dapagliflozin enhanced cognitive deficits in diabetes mellitus-induced Alzheimer's disease rat model

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ABSTRACT

OBJECTIVE: Alzheimer's disease (AD) is identified with increasing memory loss and other cognitive-e functions and it is the most observed type of dementia. There is a rising interest in clarifying role of insulin resistance, hyperinsulinemia and type 2 diabetes mellitus (T2DM) in pathogenesis of AD, cognitive impairment, neuronal cytoskeletal lesions associated with AD and Aβ accumulation in brain [1-2]. AD and T2DM are very similar pathologies, and several studies have shown that various drugs from both groups may be effective in another [3-4]. As research has turned to new targeted therapies that can cope with both diseases, it may be possible to weaken or even prevent consequences of cumulative neuropathologic events with onset of treatment in early stages of T2DM in future.

Effects of sodium-glucose co-transporter (SGLT)2 inhibitors are unknown on AD. Studies with SGLT2 inhibitors, dapagliflozin [5], empagliflozin, and canagliflozin, have shown that they improve cognitive function. Another aspect that makes SGLT inhibitors remarkable for AD was found in molecular docking studies. According to molecular docking studies, various SGLT inhibitors perform AChE inhibition as well as SGLT inhibition. It is stated that the described results may form base of future dual treatment against diabetes and diabetes-related neurological disorders. As an antidiabetic SGLT2 inhibitor of dapagliflozin, it is thought to have effects on AD with its acetylcholinesterase activity due to its structural properties along with regulation glucose metabolism.

In this project, we intended that effects of selective SGLT2 inhibitor dapagliflozin and non-selective SGLT inhibitor phlorizin was investigated and compared with rivastigmine on both T2DM and AD in T2DM-induced AD model.

METHODS: The permission for animal experiments was approved by Marmara University Animal Experiments Local Ethics Committee (permission number: 86.2017.mar). Forty adult female and male Sprague-Dawley rats (300-350 g) (n=8 in each group) were obtained from Marmara University Experimental Animal Implementation and Research Center. Rats were kept under controlled room (temperature 20-22 ºC, humidity 40-60% and 12 h/12 h light/dark cycle). Rats were randomly divided into 5 groups: Control group (CON), Alzheimer group (ALZ), Dapagliflozin (1 mg/kg) treatment group (ALZ+DAP), Phlorizin (30 mg/kg) treatment group (ALZ+PHL), and Rivastigmine (0.3 mg/kg) treatment group (ALZ+RIV). All treatments began on 5st week of experiment and continued to end of 8st week. On end of 8st week, all rats were decapitated. In our project, diabetes-induced Alzheimer's model was planned to occurred by feeding with high fat diets for 8 weeks and administration of low dose streptozotosin at end of 4. week. 3 days after streptozotosin administration. Then treatments were started for 4 weeks. During experiment, locomotor activities were assessed by open field test (OFT); cognitive deficits were assessed by new object recognition test (NORT) and Morris's water maze test (MWMT).

In OFT, time spent in central area, number of squares passed, and number of rearing and grooming of rats were evaluated. Number of squares passed, rearing and grooming was considered a measure of locomotor activity of rats. In NORT, rats' licking, smelling, sniffing or touching objects was defined as object exploration. Exploration time of each object were evaluated. In MWMT, rats were subjected for 4 days of learning to reach platform. On day 5, in probe trial, time to reach target quadrant and time spent in target quadrant were calculated.

At end of 8 weeks, all rats were decapitated; cerebral cortex samples were collected for biochemical analysis. Biochemical analyzes were measured by ELISA and it was evaluated levels of amyloid beta (Aβ) 1-42, SGLT2, phospho-tau (p-tau), and glycogen synthase kinase-3beta (GSK-3β).

The statistical analyses were performed by one-way variance analysis (ANOVA) followed by Bonferroni method as a post-test and represented as mean ± S.E.M. P values <0.05 were considered significant. Data analysis was performed using GraphPad Prism 6.5 software (San Diego, USA). This study was supported by Marmara University Scientific Research Projects Committee (project number: SAG-C-DRP-110718-0445).

RESULTS: Results of behavior tests are given in Figure 1. In OFT, there was no significant difference between groups when number of squares crossed, rearing and grooming were evaluated. In NORT, control rats spent more time exploring novel object than familiar object (p<0.05). No significant difference was observed between time to explore familiar and new objects in ALZ. In ALZ+DAP, ALZ+PHL, and ALZ+RIV, exploring time novel object was found to be higher compared to familiar object (p<0.05, p<0.01, and p<0.05, respectively). In MWMT, time to reach target quadrant was found to be higher in ALZ compared to CON (p<0.01), and it was decreased in ALZ+DAP (p<0.01) and ALZ+RIV (p<0.01) compared to ALZ. No significant difference was observed in ALZ+PHL compared to ALZ. Considering time spent in target quadrant, ALZ spent less time in target quadrant compared to CON (p<0.01). There was no significant difference in treatment groups compared to ALZ.

ELISA results are given in Figure 2. Aβ levels were significantly higher in ALZ compared to CON (p<0.01); ALZ+DAP (p<0.05), ALZ+PHL (p<0.001), and ALZ+RIV (p<0.01) reduced this elevation. When p-tau results are examined, it is observed that there is a significant increase in ALZ compared to CON (p<0.001), and a significant decrease in other groups compared to ALZ (p<0.01 in ALZ+DAP and ALZ+PHL, p<0.001 in ALZ+RIV). While SGLT2 levels increased in ALZ compared to CON (p<0.01), a decrease was observed in ALZ+DAP (p<0.05) and ALZ+RIV (p<0.05) compared to ALZ; no significant difference was observed in ALZ+PHL compared to ALZ. When the GSK-3β results are evaluated, it is observed that the GSK-3β levels increased in ALZ compared to CON (p<0.001) and decreased in ALZ+DAP (p<0.05) and ALZ+RIV (p<0.05) compared to ALZ.

CONCLUSIONS: OFT was performed to assess locomotor activity before other behavioral experiments. There was no significant difference between groups in terms of crossed square, rearing and grooming numbers. It is important that there is no difference in locomotor activity between rats, so that other behavioral experiments are not affected by this. The NORT was conducted to assess short-term memory. According to our test results, the absence of a significant difference between exploration times of familiar and novel objects in the ALZ indicates that learning-memory is impaired. In treatment groups, rats showed more interest in novel object than familiar object, indicating that te short-term memory impaired in ALZ improved with the treatments. MWMT is used to investigate three-dimensional learning and memory functions in rats. In this test, ability of the rat to find platform hidden in target quadrant is investigated with help of clues in the environment. Time to reach target quadrant on the probe test day and time spent in target quadrant were used as learning-memory evaluation parameters. When platform is removed in probe test, the increase in time spent in target quadrant with the platform indicates that rat has gained learning skills. The shortening of time to reach target quadrant indicates that learning-memory function is improved. In our study, while time to reach target quadrant was prolonged in ALZ, dapagliflozin and rivastigmin treatments shortened this time. In addition, the decrease in time spent by ALZ in the target quadrant compared to CON proves that learning memory is impaired in AD-related rats. Treatments did not affect time spent in this quadrant.
It is known that Aβ and p-tau levels increase in AD. In our study, level of Aβ increased in ALZ, while treatments decreased the increased Aβ. In addition, p-tau was also increased in ALZ and decreased in treatments compared to ALZ. Results show that AD was successfully induced in our study, with all of treatment groups improving AD. In addition, when SGLT2 levels are examined, it is seen that SGLT2 increased in ALZ, and selective SGLT2 inhibitor dapagliflozin and AChE inhibitor rivastigmine decreased increased SGLT2 level compared to ALZ. GSK-3β, one of the proteins associated with T2DM and AD, was similarly elevated in AD, while dapagliflozin and rivastigmine decreased it.
In our study, in which effects of dapagliflozin and phlorizin were estimated and compared with rivastigmine, it was observed that when behavioral experiments and ELISA results were evaluated as a whole, AD was successfully induced and dapagliflozin and phlorizin cured AD similarly to rivastigmine. Additionally, selective SGLT2 inhibitor dapagliflozin was found to be more successful than non-selective SGLT inhibitor phlorizin.

Keywords: Alzheimer's disease, Dapagliflozin, Phlorizin, Rivastigmin, Diabetes mellitus.

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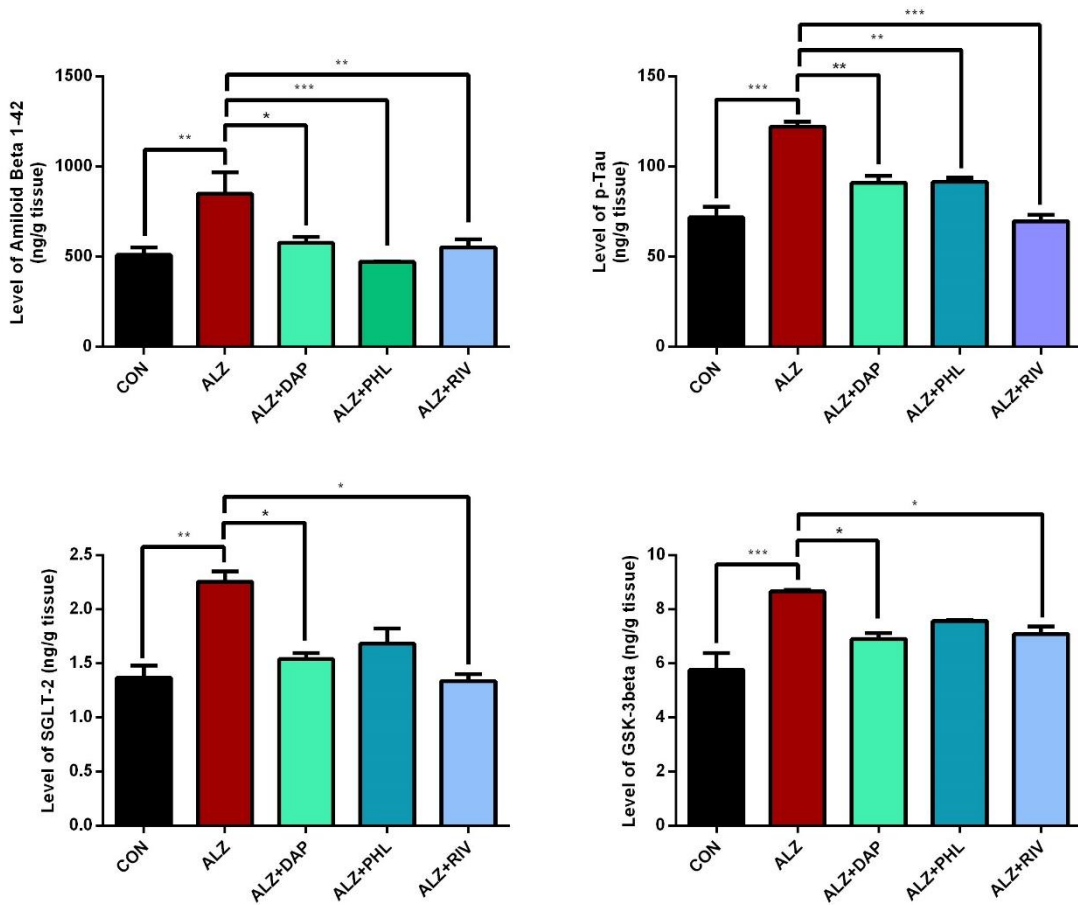
Figure 2: (a) Level of Aβ 1-42, (b) Level of p-tau, (c) Level of SGLT2, (d) Level of GSK-3β. One-way variance analysis (ANOVA) and Bonferroni post hoc test were used for statistical analyses. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (p-tau: phosphor-tau, SGLT-2: sodium-glucose co-transporter, GSK-3beta: glycogen synthase kinase-3beta, CON: control group, ALZ: Alzheimer group, ALZ+DAP: Alzheimer+Dapagliflozin group, ALZ+PHL: Alzheimer+Phlorizin group, ALZ+RIV: Alzheimer+Rivastigmin group, F: Familiar object, N: Novel object)
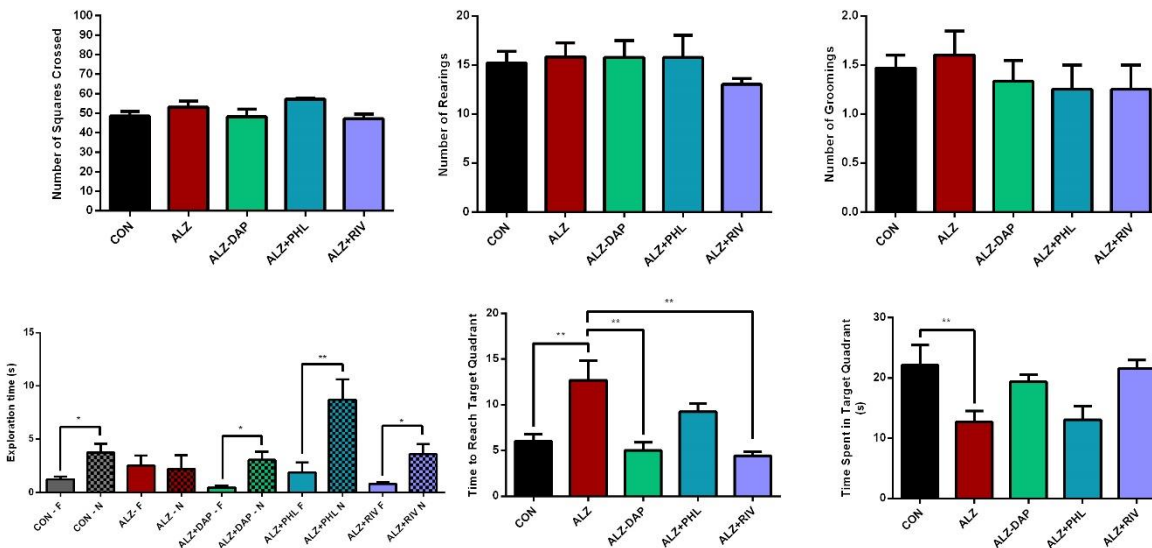
Figure 1: (a) Number of squares crossed, (b) number of rearings, and (c) number of groomings in open field test. (d) Exploration time (s) in novel object recognition test. (e) Time to reach target quadrant and (f) time spent in target quadrant in Morris's water maze test. One-way variance analysis (ANOVA) and Bonferroni post hoc test were used for statistical analyses. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (CON: control group, ALZ: Alzheimer group, ALZ+DAP: Alzheimer+Dapagliflozin group, ALZ+PHL: Alzheimer+Phlorizin group, ALZ+RIV: Alzheimer+Rivastigmin group, F: Familiar object, N: Novel object)

[Abstract:1124]

1124 - Relationship between dissociation and self injury in adolescents with child sexual abuse history

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ABSTRACT

OBJECTIVES: Prevention strategies are gaining importance in the management of suicide and NSSI, as suicide attempts and NSSI can have serious consequences such as death. Identifying risk factors for suicide and self-mutilation is thought to have a central role in prevention {Formatting Citation}. Based on the literature, dissociative symptoms, characteristics of perpetrator and characteristics of event can be seen as factors which must be considered when determining risky situations in terms of suicide and non-suicidal injury. However, the findings are mostly based on studies examining adults with a history of childhood sexual abuse (1)(3). Although it is known that the risk of suicide and NSSI increases in adolescence in the presence of a history of sexual abuse, the relevant risk factors need to be investigated further. Therefore, in this study, it is planned to investigate suicidality and NSSI in adolescent girls who had sexually abused in relation with dissociative symptoms, properties of event and perpetrator.

METHOD: Detailed psychiatric interviews with the participants were conducted by a child psychiatrist experienced in forensic psychiatric cases. Data on family structure, family history, psychiatric history, data about trauma and perpetrator such as age of the child at the time of the first and last occurrence of the event, age and proximity of the perpetrator, how and how many times did the event happen, history about suicide attemps and NSSI was collected by the interviews. Dissociative symptoms were measured by Adolescent Dissociative Experiences Scale and Child Dissociative Checklist. Adolescent Dissociative Experiences Scale (A-DES): is developed by Armstrong et al to screen dissociative behaviour in children. Turkish reliability and validity study was conducted by Zoroğlu et al. Child Dissociative Checklist (CDC) is developed by Frank Putnam in order to evaluate dissociative symptoms in children. Zoroğlu et al adapted the scale to Turkish.

RESULTS: While the frequency of receiving psychological treatment was higher in those who attempted suicide (p<0.001), no relationship was found with other sociodemographic variables (p>0.05 for each). No relationship was found between NSSI and sociodemographic variables (p>0.05 for each). (Table1)In the study group, the median age was 16.0 (15.0-17.0) years in those with suicide attempts, while the median age was 16.0 (15.0-17.5) years in those with NSSI. There was no relationship between the presence of suicide attempt and age, number of siblings, age of father, age of mother, age of first trauma, and age difference with the perpetrator (p>0.05 for each). Similarly, no relationship was found between NSSI and age, number of siblings, age of father, age of mother, age of first trauma, and age difference with the perpetrator (p>0.05 for each). (Table 2)

CDC scores, A-DES scores and Some Characteristics of Trauma
While no correlation was found between CDC total scores and suicide attempt (p:0.068), CDC total scores were higher in those with NSSI (p<0.001). In the study, the median A-DES total scores were 66.00 (27.00-115.00) in the group with suicide attempt and 69.00 (53.00-115.00) in the group with NSSI. While no correlation was found between A-DES total scores and suicide attempt (p:0.060), A-DES total scores were higher in those with NSSI (p:0.001). (Table 3)

Among those who attempted suicide in the study group, 51.2% had incest trauma (N:22), and 86.7% had genital touching (N:39). Also, trauma was repeated in 77.8% of those who attempted suicide (N:35). Kendine zarar verme davranışı olanların ise %51,1'i ensest (N:23), %81,3'ü genital temas var (N:39) ve %71,1'i mükerrer (N:37) olarak tespit edildi. Among those who had NSSI in the study group, 51.1% had incest trauma (N:23), and 81.3% had genital touching (N:39). Also, trauma was repeated in 71.1% of those who had NSSI (N:37). While suicide attempt and NSSI were more frequent in those with genital touching (respectively p:0.003; p:0.048), there was no relationship between presence of incest trauma, repetition and diagnosis of PTSD, depression, anxiety disorder, panic disorder or OCD. (Table 4)

Determinants of Suicide Attempt and NSSI
When the variables affecting presence of suicide attempt in the study group were examined in the logistic regression analysis, it was determined that presence of psychiatric treatment (OR: 9,092 95%CL: 1,523-54.290) and NSSI (OR: 8,177 95%CL: 2,012-33.233) increased the risk for presence of suicide attempt. (Table 5) When the variables affecting presence of NSSI in the study group were examined in the logistic regression analysis, it was determined that CDC total scores (OR:1,276%95CL: 1,066-1,528) and presence of suicide attempt (OR: 8,097 %95CL: 1,962-33,422) increased the risk for presence of NSSI. (Table 6)

CONCLUSIONS: In this study, in adolescent girls who had sexually abused, dissociative symptoms were found to be significantly associated with NSSI, but not with suicide. Sexual abuse history by genital touching were significantly higher in girls with suicide and NSSI history. However genital touching was not found as a predictor of suicide or NSSI in regression analysis. While psychiatric disease history and NSSI were found as predictor for suicide, dissociative symptoms and suicide were found as predictor for NSSI.

Suicide and NSSI are thought to be related with similar trajectories and risk factors such as impaired problem solving, adverse childhood experiences and psychopathologies (1) (2). Nevertheless, it is thought that self-harm without the desire to die may function by different

mechanisms from suicide (2). While desire to end unbearable psychological pain and hopelessness have role in suicidal attempts, with NSSI, a person can shift the focus from psychological pain to physical pain. Dissociation is another way to get rid of mental pain in sexually abused individuals (24). Dissociation is defined as division of personality in case of traumatic effect in those with insufficient personality integration. Dissociation can lead to impairment in consciousness, memory, identity and perception of the environment. Although dissociation is a response to trauma that sometimes serves as an adaptive mechanism, dissociative symptoms can be perceived as a challenging or even threatening experience (14). NSSI is sometimes executed to feel real and alive (1) and the relationship between NSSI and dissociation may be due to that function. Our results suggested that one of the functions of NSSI may be to relieve distress from dissociative symptoms. In the literature, there is a study which reported association of dissociation with suicidality and NSSI was conducted in general adolescent population. Dissociation was reported as the most powerful predictor for both suicidality and NSSI (4). It was frequently reported that children and adults with child sexual abuse history have higher suicide and NSSI rates. In this study, associated and predictive factors of suicide and NSSI were investigated in sexually abused adolescent girls. Dissociation and suicidal attempt history were found as predictors of NSSI. In consistent with previous studies (4), this result contributes to the literature on sexually abused adolescent girls.

Our results on suicidality and dissociation was different from previous studies. Although dissociation was reported as associated with suicidality in psychiatric and general populations (4), in sexually abused girls no association was obtained. This can be caused by that dissociative symptoms occur to cope with trauma and are more common in traumatic population. Therewithal, parallel with the literature (2), suicide and NSSI are found predictive for each other. It can be thought that adolescents who try to harm themselves have the potential to repeat it.

Characteristics of perpetrator and sexual abuse might be related with self harm. Of these, only genital touching was found associated with suicide and NSSI though not found as a predictor. It was previously reported that child rape have worse sequelae than abuse in terms of psychopathology. In sexually abused girls, a history of abuse through genital touching can be considered as a risk for self-harm. But, in the literature, there are results which was reported that some characteristics about event such as type of abuse, age when abused, relationship to perpetrator, and number of abuse incidents are not associated with negative outcomes depend on sexual trauma. Therefore, it can be thought that personal factors and differences may be more important than the variables related to the event.

As conclusion, in this study, dissociative symptoms were found as predictive factor for NSSI, but not significantly associated with suicidality in sexually abused adolescents. Suicide attempt and NSSI were found to be predictive of each other and self harm behaviors can be considered to be repetitive. Also, except for genital touching, it was determined that the characteristics of the perpetrator and the event were not related to suicide or NSSI.

Keywords: child, adolescent, sexual abuse, dissociation, suicide, self injury

Tablo 1. Distribution of some categorical variables according to the presence of suicide attempt and NSSI in the study group

TABLE 1		Suicidal Attempt					NSSI				
		Yes		No		p	Yes		No		p
		N	%	N	%		N	%	N	%	
Gender	Boy	2	4,4%	4	7,3%	0,554 x2	1	2,1%	5	9,6%	0,113 x2
	Girl	43	95,6%	51	92,7%		47	97,9%	47	90,4%	
Father	Alive	41	91,1%	51	96,2%	0,293 x2	43	91,5%	49	96,1%	0,113 x2
	Dead	4	8,9%	2	3,8%		4	8,5%	2	3,9%	
Father's employment	Not working	3	7,3%	5	10,4%	0,397 x2	6	14,6%	2	4,2%	0,167 x2
	Working	32	78,0%	40	83,3%		30	73,2%	42	87,5%	
	Retired	6	14,6%	3	6,3%		5	12,2%	4	8,3%	
Father's education	Illiterate	0	0,0%	1	2,0%	0,759 x2	0	0,0%	1	2,0%	0,142 x2
	Primary school	22	55,0%	28	56,0%		23	56,1%	27	55,1%	
	Secondary school	3	7,5%	6	12,0%		7	17,1%	2	4,1%	
	High school	12	30,0%	13	26,0%		8	19,5%	17	34,7%	
	College or higher	3	7,5%	2	4,0%		3	7,3%	2	4,1%	
Moher's employment	Not working	29	65,9%	40	75,5%	0,229 x2	30	65,2%	39	76,5%	0,215 x2
	Working	13	29,5%	13	24,5%		14	30,4%	12	23,5%	
	Retired	2	4,5%	0	0,0%		2	4,3%	0	0,0%	
Mother's education	Illiterate	4	9,3%	5	9,4%	0,353 x2	6	13,6%	3	5,8%	0,285 x2
	Primary school	24	55,8%	33	62,3%		22	50,0%	35	67,3%	
	Secondary school	6	14,0%	9	17,0%		9	20,5%	6	11,5%	
	High school	8	18,6%	3	5,7%		6	13,6%	5	9,6%	
	College or higher	1	2,3%	3	5,7%		1	2,3%	3	5,8%	
Parents	Together	27	64,3%	37	68,5%	0,663 x2	26	57,8%	38	74,5%	0,083 x2
	Seperated	15	35,7%	17	31,5%		19	42,2%	13	25,5%	
Settlement	Province	24	53,3%	23	41,8%	0,900 x2	27	56,3	25	48,1	0,109x2

	Town	18	40,0%	22	40,0%		20	41,7	20	38,5	
	Village	3	6,7%	5	9,1%		1	2,1	7	13,5	
Psychiatric treatment history	Yes	38	84,4%	30	54,5%	*0,001* x2	35	72,9%	33	63,5%	0,311 x2
	No	7	15,6%	25	45,5%		13	27,1%	19	36,5%	

NSSI: Non-suicidal self-injury, x2: Chi Square Test

Tablo 2. Distribution of some numerical variables according to the presence of suicide attempt and NSSI in the study group

	Suicidal Attempt						Test value	NSSI						Test value
	Yes			No				Yes			No			
	Median	IQR 25	IQR 75	Median	IQR 25	IQR 75	p	Median	IQR 25	IQR 75	Median	IQR 25	IQR 75	p
Age	16,00	15,00	17,00	16,00	14,00	17,00	0,428	16,00	15,00	17,50	16,00	14,00	17,00	0,231
Sibling Number	3,00	2,00	3,00	2,00	1,00	3,00	0,168	2,50	2,00	3,00	3,00	1,50	3,00	0,943
Father's Age	47,00	43,00	52,00	44,00	40,00	50,00	0,115	45,00	42,50	52,00	44,00	40,50	50,00	0,253
Mother's Age	41,50	38,00	48,50	41,00	37,00	43,00	0,109	41,50	39,00	47,00	40,00	37,00	45,00	0,059
Age at first trauma	9,42	7,00	13,00	11,50	8,00	13,00	0,114	11,25	8,00	13,00	10,00	8,00	13,00	0,430
Age difference with perpetrator	19,00	8,00	36,00	22,00	8,67	36,50	0,581	19,00	7,08	36,00	20,00	8,00	34,92	0,765

NSSI: Non-suicidal self-injury, IQR: Inter Quantile Range

Tablo 3. Distribution of CDC and A-DES total scores according to the presence of suicide attempt and NSSI in the study group

	Suicidal Attempt						Test value	NSSI						Test value
	Yes			No				Yes			No			
	Median	IQR 25	IQR 75	Median	IQR 25	IQR 75	p	Median	IQR 25	IQR 75	Median	IQR 25	IQR 75	p
CDC total	9,00	6,00	13,00	5,00	2,00	11,00	0,068	9,00	8,00	13,00	4,00	2,00	9,00	<0,001
A-DES total	66,00	27,00	115,00	53,00	16,00	69,00	0,060	69,00	53,00	115,00	26,00	10,00	69,00	0,001

A-DES: Adolescent Dissociative Experiences Scale, CDC: Child Dissociative Checklist, NSSI: Non-suicidal self-injury, IQR: Inter Quantile Range

Tablo 4. Distribution of some risk factors according to the presence of suicide attempt and NSSI in the study group

		Suicidal Attempt				Test value	NSSI				Test value
		Yes		No			Yes		No		
		N	%	N	%	p	N	%	N	%	p
Perpetrator 1	Not incest	21	48,8	27	50,0	0,909	22	48,9	26	50,0	0,913
	Incest	22	51,2	27	50,0		23	51,1	26	50,0	
Genital Temas	No	6	13,3	22	40,0	0,003	9	18,8	19	36,5	0,048
	Yes	39	86,7	33	60,0		39	81,3	33	63,5	
Repetetion	No	35	77,8	43	78,2	0,961	37	77,1	41	78,8	0,832
	Yes	10	22,2	12	21,8		11	22,9	11	21,2	
PTSD	No	4	8,9	8	14,5	0,387	4	8,3	8	15,4	0,278
	Yes	41	91,1	47	85,5		44	91,7	44	84,6	
Depression	No	38	84,4	40	72,7	0,159	41	85,4	37	71,2	0,085
	Yes	7	15,6	15	27,3		7	14,6	15	28,8	
AD/PD/OCD	No	44	97,8	54	98,2	0,886	47	97,9	51	98,1	0,954
	Yes	1	2,2	1	1,8		1	2,1	1	1,9	

PTSD: Post Traumatic Stress Disorder, AD: Anxiety Disorder, PD: Panic Disorder, OCD: Obsessive Compulsive Disorder

Tablo 5. Variables affecting the presence of suicide attempt in logistic regression analysis

	B	S.E.	p	OR	%95 CI
History of psychiatric treatment (ref:no)	2,207	,912	,015	9,092	1,523-54,290
CDC total	,073	,095	,439	,929	0,772-1,119
A-DES total	-,004	,008	,645	1,004	0,988-1,020
Genital touching (ref:no)	-,469	,713	,511	1,598	0,395-6,464
NSSI (ref:no)	2,101	,715	,003	8,177	2,012-33,233

CI, confidence interval; OR, odd's ratio; SE, standard error. Model dependent variable: suicide attempt , Model content: History of psychiatric treatment, CDC total score, A-DES total score, Genital touching, NSSI. A-DES: Adolescent Dissociative Experiences Scale, CDC: Child Dissociative Checklist, NSSI: Non-suicidal self-injury

Tablo 6. Variables affecting the presence of NSSI in logistic regression analysis

	B	S.E.	p	OR	%95 CI
History of psychiatric treatment (ref:no)	-1,154	,858	,178	3,171	0,591-17,030
CDC total	-,244	,092	,008	1,276	1,066-1,528
A-DES total	-,002	,008	,837	,998	0,983-1,014
Genital touching (ref:no)	-,565	,739	,444	1,790	0,413-7,497
Suicide attempt (ref:no)	2,092	,723	,004	8,097	1,962-33,422

CI, confidence interval; OR, odd's ratio; SE, standard error. Model dependent variable: NSSI , Model content: History of psychiatric treatment, CDC total score, A-DES total score, Genital touching, Suicide attempt. A-DES: Adolescent Dissociative Experiences Scale, CDC: Child Dissociative Checklist, NSSI: Non-suicidal self-injury

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Brief Poster Reports

[Abstract:0297]

0297 - Investigation of *adora2a* expression profile in patients with autism spectrum disorder

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ABSTRACT

INTRODUCTION: Autism spectrum disorder (ASD) is a neurodevelopmental disorder with early onset symptoms characterized by deficits in communicative and social skills, repetitive behaviors and/or restricted interests. With a heritability ratio of more than 90 percent, genetic factors play an important role in ASD etiology.

Among many other chromosomal regions, a region near the middle of the chromosome 22, 22q11.2, deserves a particular interest in terms of ASD genetics. Various genetic alterations in this region including deletions, duplications and copy number variations (CNV) have been associated with ASD previously[1] and genetic variants on this region are observed approximately 1% of individuals with ASD[2].

One of the candidate genes within this loci, Adenosine A_{2A} receptor gene *(ADORA2A),* is located on the 22q11.23 region and have been associated with various neuropsychiatric disorders including ASD, attention deficit/hyperactivity disorder (ADHD), depression, Tourette's disorder, panic disorder, schizophrenia and Parkinson's disease. *ADORA2A* encodes one of the four G-protein coupled adenosine receptors, Adenosine A_{2A} receptor, and expressed in various tissues including brain, liver, blood and immune system. It is thought to have roles in mediating locomotion, sleep-wake cycle, fine-tuning of synaptic plasticity, glial activity and neuroinflammation. Epigenetic factors are shown to influence the expression of *ADORA2A* expression through controlling the promoter regions of the gene.

In a case-control study conducted by Freitag and colleagues, 98 subjects with ASD and 234 controls were genotyped for eight SNPs in *ADORA2A* and found a nominal association with ASD for CC genotype of rs2236624. Authors also reported other SNPs as associated with increased social interaction (rs3761422), nonverbal communication (rs5751876) and repetitive behavior (rs35320474) [3]. In addition, it is shown that treatment with adenosine A_{2A} receptor agonists results in decreased stereotypic behavior in animal models of autism[4].

In this case-control study, we aimed to examine gene expression profile of *ADORA2A* gene in a group of children with ASD compared to healthy controls in Turkey.

METHODS

Participants

Study group of this study was drawn from children and adolescents who have been followed with the diagnosis of ASD at Child and Adolescent Psychiatry Department of Istanbul Medicine Faculty, Istanbul University. A total of 93 children and adolescents aged between 2 to 18 years old were included in the study. Diagnosis of ASD of the subjects were confirmed by the authors through detailed clinical examination based on DSM-5 criteria. Exclusion criteria for the study were: a) having evidence of severe/profound intellectual disability, b) having a diagnosis of genetic, metabolic or progressive neurologic disease and c) parents disagreed to participate to the study and rejected signing informed consent. CARS and ABC were applied to evaluate symptom severity and/or accompanying behavioral and emotional difficulties. As the control group, age and gender matched children and adolescents without history of any neurodevelopmental/psychiatric disorder (n=105) were recruited from General Pediatric Outpatient Clinic of Istanbul Medicine Faculty, Istanbul University. They were also undergone detailed clinical examination by the authors to make sure they meet inclusion criteria. This study was approved by Istanbul Medical Faculty Ethical Committee and supported by a grant from Scientific Research Project Coordination Unit of Istanbul University (project ID no: TTU-2018-30570).

Instruments

Interview Form. Interview form was developed by authors and included questions on patient's date of birth, gender, contact information and other basic sociodemographic information.

Childhood Autism Rating Scale (CARS). CARS is a frequently used, valid and reliable scale developed by Schopler et al. to assess disease severity and differentiate individuals with ASD and those with other developmental delays.

Aberrant Behavior Checklist (ABC). ABC is a useful tool for evaluating inappropriate and maladaptive behaviors which has been translated into more than 25 languages and is used commonly worldwide in subjects with ASD and developmental delay.

Gene Expression Analysis

Total RNA was extracted from whole blood using Hybrid-R™ (GeneAll, Seoul, South Korea, catalog no: 315-150) and transcribed into complementary DNA with Ipsogen® cDNA Synthesis Kit according to the manufacturer's instructions (Qiagen GmbH, Hilden, Germany, catalog no: 679923). The quantity, quality and integrity of RNA were assessed on Qubit 4 fluorometer (Thermo Fisher Scientific Inc, Wilmington, DE, USA). Real-Time Quantitative PCR analysis was performed using Thermo Scientific RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific Inc, Wilmington, DE, USA, catalog no: K1622) by using three reference genes (*ABL-1, CUL1* and *ZNF207).* The primer sequences of the

ADORA2A gene used for the amplification were (forward) 5'-CAT CTT CAG TCT CCT GGC CA-3' and (reverse) 5'-ACC CAG CAG ATG GCA ATG ATG-3'. Relative changes in gene expression were analyzed with the ΔCT method.

Statistical Analysis

R 3.4.0 and Statistical Program for Social Sciences (SPSS for Windows, 21.0) were used for statistical analyses. Descriptive data were presented as mean and standard deviation. Shapiro Wilkins test used for assessing normal distribution of data. Mann-Whitney U test or independent samples t-test were used for comparison of continuous data according to the distribution of the data. *p* value <0,05 was considered to be statistically significant.

RESULTS: The mean age of the study group was 9.06 ± 3.57 and 86% were male (n=83); whereas mean age of the control group was 9.22 ± 3.86 and 86.7% were male (n=91). No significant difference was found between the study groups in terms of age (p=0.763) or gender (p=0.895). There was no significant difference in terms of age (*p*=0.763) and gender (*p*=0.895) between the study and control groups. There was no statistically significant difference between the two groups in terms of mother's (t=1.511; p=0.133) and father's age (t=0.822, *p*=0.412) at birth.

Mean CARS score of the study group was 41.98 ± 4.37 (33 to 51.50) and mean scores of ABC subscales were: 20.39 ± 9.01 for *Hyperactivity/Noncompliance*; 20.97 ± 9.89 for *Lethargy/Social Withdrawal*; 6.28 ± 4.87 for *Stereotypic Behavior*; 1.43 ± 2.13 for *Self-Injurious Behavior* and 6.11 ± 3.14 for *Other Behaviors*.

Gene Expression Analyses

Gene expression profile of housekeeping genes and *ADORA2A* is shown in Figure 1. When groups are analyzed separately, *ADORA2A* expression level was not different in terms of gender (Z=-0.188, p=0.851 for the study group; Z=0.891, p=0.373 for the control group) and was not correlated with age (r=-0.66, p=0.532 for the study group; r=-0.178, p=0.70 for the control group). When groups compared, *ADORA2A* expression level was found to be 1.33-fold increased in study group (mean=3.32) compared to control group (mean=2.91) (p=0.001)(Figür 2).

Regarding the *ADORA2A* gene expression level and its correlations with different phenotypic characteristics of subjects with ASD, there was a negative correlation between *ADORA2A* expression level and CARS score (r=-0.216; p=0.038). On subscales of ABC, *ADORA2A* expression level was in a positive correlation with scores of *Stereotypic Behaviors* was (r=-0.207, p=0.046). No such significant correlation was observed for the other subscales of ABC. Correlations between *ADORA2A* expression level and phenotypic characteristics are presented in Table 1.

CONCLUSIONS: *ADORA2A* is expressed in plenty amounts in both ventral and striatal structures. Striatum is known to be associated with restricted and repetitive behaviors in ASD, as well as social reward systems. Striatal neurons expressing $A_{2a}R$ have mediating roles on dopaminergic and glutamatergic neurotransmission. It is hypothesized that the increased expression of *ADORA2A* may facilitate the release of excitatory neurotransmitters resulting in excitotoxicity. In animal models of autism, inactivation of adenosine A_{2A} receptor was found to be associated with higher level of sociability in mice and, central expression of expression *ADORA2A* were found to regulating the neuroimmune development and repetitive behavior of autistic mice. In mouse models of 22q11.2 duplication syndrome, it is shown that deletion of this chromosomal region (which includes *ADORA2A*) may interfere with the activity of the parvalbumin-producing interneurons. More specifically, decreased expression of cytokine C-X-C chemokine receptor type 4 may increase the propensity for neurodevelopmental disorders including ASD and schizophrenia, since these receptors play an important mediating role in neuronal migration and placement during the early development. In addition, it is also known that *ADORA2A* has regulatory role in neuroimmune development and blood-brain barrier permeability. In human studies, abnormalities of *ADORA2A* expression was found in several demyelinating diseases and spinal cord injuries. In animal models of ASD, *ADORA2A* expression was found to be associated with neuroimmunological changes associated with ASD [4].

This is the first study to evaluate the peripheral expression of *ADORA2A* in individuals with ASD in comparison with healthy controls. We have found a higher level of peripheral expression of *ADORA2A* in children and adolescents with ASD when compared with healthy controls. We also found a positive correlation with ASD severity (as evaluated on CARS) and increased symptoms of stereotypic behavior (as evaluated on ABC). As the first case-control study of *ADORA2A* gene expression in children and adolescents with ASD, our study may provide a basis for future studies in this area.

Table 1. Correlations Between *ADORA2A* Expression Level and Phenotypic Characteristics							
		CARS	*Hyperactivity /Noncompliance*	*Lethargy /Social Withdrawal*	*Stereotypic Behavior*	*Self-Injurious Behavior*	*Other Behaviors*
ADORA2A	R	-0.076	-0.035	0.089	-0.207	-0.157	-0.011
	p*	0.467	0.741	0.395	0.046	0.133	0.917
*Spearman Correlation Test							
CARS: Childhood Autism Rating Scale; ABC: Aberrant Behavior Checklist							

Figure 1.Gene Expression Profile of Housekeeping Genes and ADORA2A
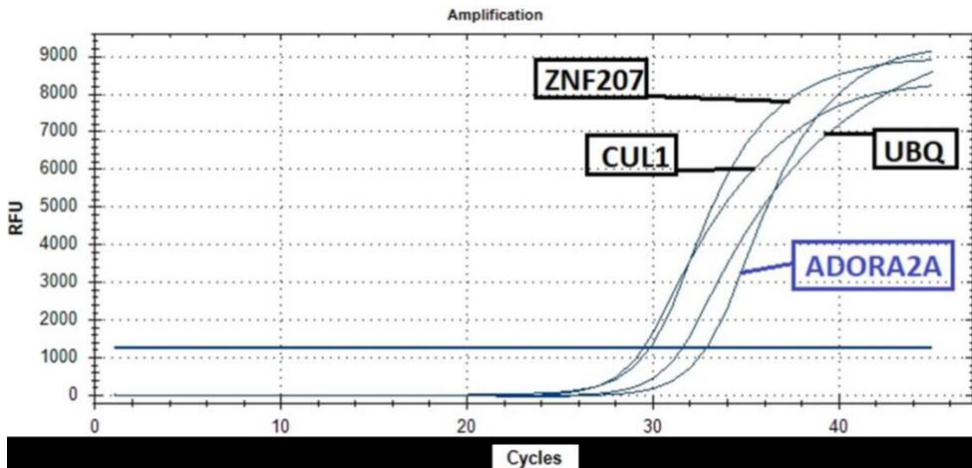
Figür 2.Boxplot showing the relationship between *ADORA2A* expression data of   control and patient samples
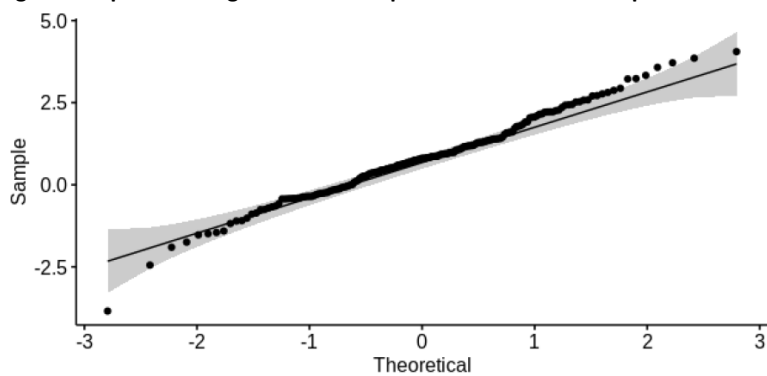
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[Abstract:0892]

0892 - The relationship between mindfulness, metacognitive beliefs and social anxiety among university students

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ABSTRACT
Introduction
Although, social anxiety disorder (SAD) also known as social phobia [1], is a relatively frequent anxiety disorder (AD) among young adults, with current prevalence estimates reaching up to 36 percent [2], which is significantly higher than previous estimates of 12 percent [3]. Social anxiety disorder (SAD) is widespread and associated with major psychological distress, its etiology is yet to be fully explored. The approach of Mindfulness is used in many different concepts; also it has been used to reduce the effects of social anxiety levels. In addition, maladaptive cognitions have been extensively investigated and presented as a maintenance factor of social anxiety.

Up to our knowledge, no previous study has all together considered these factors as potential predictors of SAD among young adults. Accordingly, Jankowski & Holas (2014) proposed that mindfulness may be conceptualised in terms of metacognition, moreover, its effects could be comprehended better if reviewed together with metacognitions [4]. For that reason, we assume that both dysfunctional metacognitions and low mindfulness levels may be associated with SAD. The purpose of the study is how metacognitions and Mindfulness may affect SAD.

Methods

Participant

Five hundred and thirty-one college students were reached in the study. The individuals were college students attending the International University of Sarajevo. We placed an advertisement on the internet and made an announcement through social media platforms for participant recruitment. All students were right to withdraw from participation at any stage of the study without penalty. The inclusion criteria was to be able to fill in the applied forms/tests. Fourteen participants who reported a psychiatric disorder: cannabis use disorder (3), attention deficit and hyperactivity disorder (1), major depressive disorder (3), obsessive compulsive disorder (3), and bipolar disorder (4), were excluded from the study. Two participants could not complete the tests. All participants approved the informed consent in a written format.

Institutional Review Board of the International University of Sarajevo approved the study (IUS REC-01-760/1/2020).

Instruments

Sociodemographic form

This instrument is created to gather general information about participants (e.g. age, gender, education, marital status, financial status) were documented with the sociodemographic form prepared by the researchers.

Liebowitz Social Anxiety Scale Self-Report (LSAS-SR)

Liebowitz Social Anxiety Scale Self-Report (LSAS-SR) evaluates a variety of social situations considered challenging for persons with SA. The scale has 24 items, 13 of them assess performance anxiety while 11 measure social interaction anxiety [5]. LSAS-SR scores are interpreted in the following way: 50-65 = moderate SAD; 65-80 = marked SAD; 80-95 = severe SAD; and greater than 95 = very severe SAD [6].

Five-Facet Mindfulness Questionnaire (FFMQ)

Five-Facet Mindfulness Questionnaire (FFMQ) is a 39-item scale that encompasses five mindfulness facets: observing (noticing internal and external experiences like thoughts, feelings, or sensations); describing (describing internal experiences with words); acting with awareness (concentrating on one's actions at a certain moment in contrast to acting automatically); non-judging of inner experience (holding a non-evaluative attitude toward feelings and thoughts); and non-reactivity to inner experience (letting feelings and thoughts come and go, without being strongly influenced by them). Higher FFMQ scores imply elevated mindfulness levels [7].

Metacognition Questionannire-30 (MCQ-30)

Metacognition Questionannire-30 (MCQ-30) is a short version (30-item) of the 65-item Metacognitions Questionnaire. The items are divided into five subscales: positive beliefs about worry; negative beliefs about uncontrollability and danger; need to control thoughts; cognitive confidence; and cognitive self-consciousness [8].

Statistical Anaylses

In this study, SPSS 23 and AMOS 24 programs were used for statistical analyses. Descriptive statistics analysis, means, standard deviations (SD), frequencies, and percentages were produced via SPSS 23.0 software.

Correlations among the main variables were evaluated using Pearson's product moment bivariate correlation coefficients. AMOS 24.0 program was used to reveal the relationship in structural equation modelling comprised of mindfulness, metacognition, and SA.

Results

515 participants aged between 18 and 30 attended to this study (Mean=22.67, SD=3.89). 71.8% of the participants were male (n=370) and 28.2% of the participants were female (n=145).

Pearson's correlations analyses detected the positive correlation between metacognitions and social anxiety (SA), while Mindfulness was negatively correlated with both SA and metacognitions. Likewise, structural equation modeling analyses specified that Mindfulness has a negative effect on both SA and metacognitions, whereas metacognitions positively affect SA.

Discussion

This study implies that both metacognitions and mindfulness factors may influence SAD in young adults. These results seem to be consistent with earlier studies which have reported that dysfunctional metacognitions are positively correlated with anxiety disorders. Our findings support the put forward the negative associations between mindfulness and anxiety disorders, including PD [9] and GAD [10]; as well as negative association of mindfulness with dysfunctional metacognitions. Accordingly, Barlow et al. (2004) proposed that Mindfulness-based therapy (MBT) is helpful in diminishing anxiety symptoms in various disorders and problems, most likely because it affects emotional avoidance and rumination, which are both factors associated with anxiety disorders [11]. Toneatto & Nguyen (2007) suggested that regular mindfulness practice may alleviate the anxiety symptoms because it decreases the amount of ruminative thoughts when faced with stressors [12].

This study is the first to suggest that mindfulness mediates the effect of metacognitions on SAD in young adults. We propose that focusing concurrently on metacognition and mindfulness factors while treating SAD may potentially result in better outcomes for young adults.

Due to the fact that this is a preliminary research conducted on this topic, further work needs to be done to establish the effects of clinical interventions aimed at metacognitions and mindfulness for alleviating the harmful effects of SAD among young adults.

Our findings might point out the importance of treatment management in mindfulness therapies of social anxiety disorders. Interventions targeting these factors may help young people manage SAD. Additionally, targeting the inappropriate metacognitions would be beneficial for social anxiety, pointing out more reasonable targets across inappropriate metacognitions.

Keywords: *social anxiety; social anxiety disorder; metacognitions; mindfulness; young adults*

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Table 1: The means, standard deviations, and min-max values of the observed variables

Scale and sub-dimensions		Mean	SD	Min-max
Metacognition	MCQ1	14,43	3,90	6-24
	MCQ2	14,77	3,54	6-24
	MCQ3	14,51	4,08	6-24
	MCQ4	15,26	3,88	6-24
	MCQ5	16,90	3,34	6-24
Mindfulness	MF1	26,86	5,26	12-40
	MF2	28,11	6,03	8-40
	MF3	26,25	5,03	13-37
	MF4	22,80	5,58	8-38
	MF5	20,84	4,41	8-35
Social Anxiety	Anxiety	45,74	12,75	23-87
	Avoidance	44,28	13,08	23-95

Notes for Table 1: MCQ1: Positive beliefs about worry, MCQ2: Negative beliefs about uncontrollability and danger, MCQ3: Cognitive confidence, MCQ4: Need to control thoughts, MCQ5: Cognitive awareness, MF1: Observation, MF2: Description, MF3: Mindful actions MF4: Non-judgmental inner critic, MF5: Non-reactivity

Table 2: Correlations among the observed variables

Variables	Metacognition	Mindfulness	Social avoidance	Social anxiety
Metacognition	1	-	-	-
Mindfulness	-,292*	1	-	-
Social avoidance	,303*	-,532*	1	-
Social anxiety	,345*	-,551*	,884*	1

Direct and indirect effects and 95% confidence intervals for the final model

Variables	B	SE	95%CI-Lower Bounds	95%CI-Upper Bounds	P
Total effect					
MF > SA	-.655	.039	-.721	-.573	.010
Direct effect					
MF > SA	-.572	.053	-.691	-.493	.003
MF > MCQ	-.434	.068	-.556	-.305	.009
MCQ > SA	.192	.059	.077	.309	.008
Indirect effect					
MF > MCQ > SA	-.083	.028	-.155	-.040	.004

MF: Mindfulness, SA: Social anxiety (total), MTC: Metacognition

[Abstract:0940]

0940 - Investigation of antidepressant treatment effects on hippocampus and hypothalamus endoplasmic reticulum stress in experimentally depressed rats

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ABSTRACT

INTRODUCTION: Depression is a syndrome characterized by slowness in thought, speech, psychomotor and psychophysiological processes, stagnation, worthlessness, powerlessness, reluctance, hopelessness, in addition to a sad and/or anxious mood. The ER is an important organelle required for processes such as protein synthesis, modification and folding, synthesis of phospholipids and steroids and calcium balance. If ER dysfunction occurs for any reason, ER stress occurs, which causes folded proteins to accumulate in the extracellular space. (1).

Increasing evidence shows that endoplasmic reticulum (ER) stress is involved in the pathophysiology of depression and this change is thought to be reduced with antidepressants.(2) measurement of ER stress markers CALR (calreticulin), GRP78 (HSPA5; heat shock protein family A member 5), ATF4 (activating transcription factor 4), eIF2α (Eukaryotic Translation Initiating factor 2α), XBP-1 (X-box binding protein), HSP47 (heat shock protein 47) mRNA gene expression will be helpful in understanding this pathway.

In this study, it was hypothesized that ER stress is involved in the etiology of depression and that the antidepressant response begins with a decrease in ER stress..

METHOD: Adult female rats in which depression was created with the chronic mild stress model were administered 2 different doses of sertraline for 14 days. Afterwards, all animals were decapitated with mild sedation after forced swim test was applied on the 22nd day, the hippocampus and hypothalamus regions were dissected and stored at -80 ˚C.

Chronic Mild Stress (CMS) Model

In the wet cage application, 333 g of sawdust is wetted with 1.5 liters of water and the food is kept above at an angle of 60 degrees. A bell ringing for 1 second every 10 seconds was applied in noise stress (60 db). Swimming stress was performed by swimming the rats in rollers for 10 min. Restraint stress was performed with physical restraint apparatuses. For hunger stress, the feeds were collected from the cages at 16:00 and put into the cages at 09:00 the next day. After the osmotic pumps were placed, restraint from stressors and swimming were applied for one week in order to heal the back parts of the animals, and the application of other stressors was continued. Forced swim test (5 min) was applied on the 8th day. (Table-1)

Placement of Osmotic Mini-Pumps and Drug Applications

Animals showing depression-like behavior as a result of FST were anesthetized and osmotic mini-pumps implanted in the middle of the two scapulae. Sertraline, which was prepared by dissolving with DMSO at different doses, was prepared in a total volume of 2 ml. The animals in the control group were implanted with the same volume of DMSO osmotic pumps.

Immobilization frequency, immobilization time and percentage of movement were determined in the video recording system for the diagnosis of depression with forced swim test.

Forced Swim Test

The transparent plexiglass cylinder is filled 30 cm with water at a temperature of approximately 25°C. The rats were allowed to swim for 15 minutes on the first day, then dried and placed back in their cages. The next day, rats were left in the water for 300 seconds, recorded with a video camera, and scored as swimming, climbing, and immobilization at 5-second intervals.

Total RNA Isolation from Tissue Samples

RNA isolation was performed with the TRIzol method. The determination of the concentration and quality of the total RNA samples was controlled by spectrophotometric and agarose gel electrophoresis method. A260/A280 and A260/230 ratios were evaluated in the nanodrop device to determine phenol, protein and genomic DNA (gDNA) contaminations. In order to determine the quality of RNA samples, RNA bands stained with ethidium bromide (EtBr) were evaluated with a UV-transluminator.

Purification of gDNA Contamination of Total RNA Samples

10 µg total RNA was made up to 100 µl volume with DNAse-I reaction mix. RNA samples were kept at 37 °C for 10 minutes by adding 2 U of DNAse-I enzyme. In order to stop the reaction, 1 µl of 0.5 M EDTA was added and incubated at 75 °C for 10 minutes.

Reverse Transcriptase (RT) Reaction

To produce single-stranded cDNA from 2µg/20µl total RNA, 1µl OligodT and 1µl Randomhexamer were added to 2µg/20µl total RNA and kept in a water bath at +70°C for 5 minutes, then 8µl of 5X cDNA reaction mixture, 2µl of RNAse inhibitor, 4µl of dNTP was added and kept in a +25°C water bath for 5 minutes. Then, 2µl of Reverse Transcriptase enzyme was added and incubated in a water bath. The reaction was stopped by standing in a +70°C water bath for 10 minutes. Obtained cDNA samples were stored at -20 ºC.

Design of Primer

The primer design of the target genes used in the study was created using the IDT PrimerQuest program. The primary sequence information of phosphoglyceratekinase 1 (PGK) and cyclophylin A (CycA) genes, which were determined as reference genes, were taken from the literature.

Real-Time Quantitative Polymerase Chain Reaction (qPCR)

Expression quantitation analysis of target and reference genes was performed using real-time PCR device. Sybr Green, a dye that binds to double-stranded DNA, was used for the reaction. Melting curve analysis was carried out by heating the temperature at 95 °C for 1 minute and decreasing it to 55 °C, gradually increasing it again to 95 °C. The obtained Ct (threshold cycle) values were recorded. To confirm the accuracy of the products, it was carried out on a 2% agarose gel for 30 minutes at 120 volts.

Ethical Approval

This study was conducted with the approval of the Ethics Committee of Necmettin Erbakan University, KONUDAM Experimental Medicine Application and Research Center, dated 16.01.2020 and numbered 2020-011.

Statistical analysis: In the analysis of gene expression data, Ct values showing the expression levels of the genes that are the subject of the study were normalized with the Ct values of PGK1 and CYCA reference genes, and $2(-\Delta Ct)$ values were determined. Differences observed in gene expression levels between groups were compared with one-way analysis of variance (ANOVA) using the SPSS package program. In the results obtained, those with a p value below 0.05 were considered statistically significant.

RESULTS: Hippocampus ATF4 gene expression was statistically significantly increased in the depression group compared to the control. Hippocampus ATF4 gene expression was statistically significantly decreased in the depression+1 mg/kg sertraline group and depression+10 mg/kg sertraline group compared to the depression group. (Figure 1)

Hippocampus GRP78 gene expression was statistically significantly decreased in the depression+1 mg sertraline group compared to the depression group. (Figure-2)

In the hypothalamus, CALR gene expression was statistically significantly decreased in the depression+1 mg/kg sertraline group compared to depression. Hippocampal CALR expression was statistically significantly decreased in the depression+10 mg/kg sertraline group compared to the depression group. (Figure-3)

Hypothalamic eIF2α gene expression was found to be statistically significantly increased in the depression+10 mg/kg sertraline group compared to the other three groups. (Figure-4)

There was a statistically significant decrease in hypothalamus HSP47 gene expression in both treatment groups compared to the depression group. (Figure-5)

Hypothalamic XPB1 gene expression was found to be statistically significantly decreased in the depression+1 mg/kg sertraline group compared to the depression group. In addition, XPB1 gene expression in the hypothalamus was statistically significantly decreased in the depression+1 mg/kg sertraline group compared to the control. Hippocampal XPB1 gene expression was statistically significantly decreased in the depression+10 mg/kg sertraline group compared to the depression group. (Figure-6)

Discussion: Although it is stated in the current literature that ER stress may play a role in depression, there are not enough studies published on how ER stress changes with treatment in depression.

The finding of increased hippocampal ATF4 expression in depression coincides with the knowledge of Timberlake et al. (3) that ATF4 gene expression is increased in the hippocampus tissues of rats with learned helplessness and supports our hypothesis that there is increased ER stress in depression. In addition, after sertraline treatment, a decrease in ATF4 gene expression level was detected in the hippocampus compared to the depression group. This finding supports the hypothesis that ER stress will decrease with effective treatment of depression.

GRP78 gene expression is increased in the temporal cortex of depressed patients who died by suicide.(4) In our study, however, no change was observed in GRP78 expression in depression. A decrease in the amount of hippocampal GRP78 in the depression+1 mg/kg sertraline group compared to the depression obtained in our study supports our hypothesis that effective treatment of depression provides a decrease in ER stress level..

In our study, it was observed that CALR gene expression was not statistically significantly different in depression compared to control. Consistent with this data, in a study conducted by Bown et al. (5), no significant change was observed in CALR gene expression in patients who died after a suicide attempt. This result suggests that more studies are needed to reach a consistent data. In addition, reduction of hypothalamic and hippocampal CALR gene expression with treatment supports our hypothesis that antidepressant treatment reduces ER stress. In the current literature, no study has been seen in this context.

There is no study in the literature with HSP47 with any mental illness or antidepressant treatment. The reduction of hypothalamic HSP47 gene expression with treatment confirms our hypothesis that ER stress is expected to decrease with antidepressant treatment in depression.
In the study of Timberlake et al. (3), increased hippocampal XBP1 gene expression was reported in mice with learned helplessness. In our study, although no increase was observed in XPB1 gene expression in depression, hippocampal XBP1 gene expression decreased in depression+10 mg/kg sertraline group compared to depression.

Our current study shows that ER stress plays a key role in the pathophysiology of depression and this process can be reversed with effective antidepressant treatment. In future studies, there is a need for human studies that can confirm the data obtained in our study and to elucidate the mechanisms by which the change in ER stress occurs.

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Table-1: Implementation of chronic mild stress protocol

DAY	MORNING			AFTERNOON			NIGHT		
	TIME	STRESSOR	DURATION	TIME	STRESSOR	DURATION	TIME	STRESSOR	DURATION
0	OPEN FIELD TEST BASAL EVALUATION								
1	09.00	RESTRAINT	45 min	12.00	NOISE	4 HOUR	---------	---------	---------
2	09.00	WET CAGE				7 HOUR	---------	---------	---------
3	09.00	RESTRAINT	45 min	12.00	SWIM	10 min	16.00	STARVATION	ALL NIGHT
4	09.00	NOISE	4 hour	14.00	RESTRAINT	45 min	---------	---------	---------
5	09.00	SWIM	10 DK	---------	---------	---------	16.00	TILTED CAGE	ALL NIGHT
6	09.00	NOISE	4 hour	---------	---------	---------	16.00	LIGHT ON	ALL NIGHT
7	09.00	RESTRAINT	45 min	13.00	FST TRAINING	15 min	---------	---------	---------
8	09.00	OPEN FIELD TEST	---------	12.00	FST	Placement of osmotic mini-pumps			
9	09.00	NOISE	4 hour	16.00	LIGHT ON	ALL NIGHT	---------	---------	---------
10	09.00	STARVATION			TILTED CAGE		---------	---------	---------
11	09.00	WET CAGE	7 hour		---------	---------	---------	---------	---------

12	10.00	NOISE	4 hour		TILTED CAGE	ALL NIGHT			
13	09.00	WET CAGE	7 hour				---------	---------	---------
14	09.00	RESTRAINT	45 min				16.00	STARVATION	ALL NIGHT
15	09.00	NOISE	4 hour	16.00	LIGHT ON	ALL NIGHT	---------	---------	---------
16	09.00	RESTRAINT	45 min	12.00	NOISE	4 HOUR	---------	---------	---------
17	09.00	WET CAGE	7 hour	16.00	---------	--------	---------	---------	---------
18	09.00	RESTRAINT	45 min	12.00	SWIM	10 min	16.00	STARVATION	ALL NIGHT
19	09.00	NOISE	4 hour	14.00	RESTRAINT	45 min	---------	--------	--------
20	09.00	SWIM	10 min	16.00	TILTED CAGE	ALL NIGHT	---------	---------	---------
21	09.00	RESTRAINT	45 min	13.00	FST TRAINING	---------	---------	---------	---------
22	TERMINATION OF EXPERIMENTS AND BEHAVIOR TESTS								

[Abstract:1101]

1101 - Digital video analysis of emotional facial movements of the children with attention deficit hyperactivity disorder[¥]

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ABSTRACT

[¥]This brief report is based on the data used in the doctorate thesis of the first author

OBJECTIVE: It is aimed to investigate emotion recognition abilities and to assess the emotional expressions of faces with digital face analysis in the children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).

METHODS: The 6-12 years-old children with ADHD (n=56) who did not prescribed any psychiatric drug for at least the last three months, and health control subjects (n=45) who had an intelligence score of at least 80 were included into the study. To measure emotion recognition skills, the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA2) tests were administered. A group of participants watched three, 7-minute scenes from cartoon videos and facial expressions were video recorded. Openface Software was used for video analysis.

RESULTS: When the ADHD group was subtyped according to the clinical appearence, compared to the other groups, the children in the attention deficit predominant group had worse performance in DANVA child faces and total scores. As we divide the ADHD group according to the comorbidity, the Learning Disorder (LD) comorbid group had more mistake on emotion recognition from the posture and total scores of DANVA. According to the digital face analysis, among Machine Learning algorithms, the Deep Learning had the best differentiation capacity using only Facial Action Units (AU's). On the other hand, Video 1, which included predominantly the sad emotions was found to be the best differentiator between ADHD and control groups. In Video 1, AU12 (lip corner puller), AU07 (lid tightener), AU09 (nose wrinkler), AU45 (eye blink), and AU06 (cheek raiser) were the most discriminators.

CONCLUSIONS: Theemotion recognition levels of children in the ADHD group showed significant differences, in terms of clinical subtype and comorbid disorder. The results suggest that the Machine Learning methods has a promising capacity for the differentiation of ADHD diagnosis, which is one of the most common neurodevelopmental disorder.

OBJECTIVE : Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental and psychiatric disorder characterized with attention and impulse control problems and hyperactivity.[1] The children with ADHD may have impairments in academic, social and behavioral functioning. In addition, the executive function problems despite other clinical symptoms are important in terms of daily well being of these children. The executive functions include planning, cognitive flexibility, working memory and some roots of social capability such as emotion recognition and empathy formation.[2] Several studies that investigated the emotion recognition abilities reported some disturbances in the children with ADHD. These children have more difficulty in comprehension of emotions from the facial expressions, tone in the voice, body gestures compared to the children without ADHD.[3] On the other hand, predicted difference or impairments in facial emotional expressions of the children with ADHD may have devastating effects on social interaction and empathy performance. In this study, we aimed to investigate the facial emotional expressions of the children with ADHD with an objective methodology. For this, we used computerized analysis of facial movements and we employed several machine learning procedures to compare the children with ADHD with the typical growing peers. As a consequence, we collected novel data for an original and pionering method to be used and developed in the era of clinical assessments in child and adolescent psychiatry

METHODS: The 6-12 year-old children diagnosed with ADHD (n=56) who did not use any medication for at least last 3 months, had an IQ score more than 80 were included. As a control group, the typical growing peers (n=45) are the participants. The mothers and teachers of the participants completed Turgay Screening and Assessment Instrument for Disruptive Behavior Disorders (TURGAY) and Social Reciprocity Scale (SRS). The mothers also filled the Brief Symptom Inventory (BSI) for themselves. The Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2) was used to evaluate the emotion recognition abilities of the children. The sample is also investigated for the facial emotional movements while they were watching 7-minutes cartoon parts and they were video recorded. The OpenFace Software is used for the video analysis. We measured the difference between ADHD and control cases in terms of facial action differences by using several machine learning procedures such as Support Vector Machines (SVM) and naive-bayes. We produced Receiver Operating Characteristic (ROC) curves and Area Under Curve (AUC) scores by the performance tests.

RESULTS: Compared to the control group, the children with ADHD had lower maternal and paternal ages, lower level of maternal and paternal education and Weschler IQ scores. In accordance with hypohesis, the group with ADHD had significantly higher maternal and teacher SRS scores. As the IQ scores were controlled, the difference in SRS scores remained. On the other hand, the significant difference found in DANVA-2 total scores in favor of control group disappeared when the IQ scores were controlled. As we subdivided the ADHD group according to the clinical subtype, compared to the children in other subgroups, the children with inattentive subgroup had statistically significant worse performance in DANVA-2. The ADHD group with Learning Disorder (LD) had worse performance on DANVA-2 compared to the ADHD group without LD. The best perfoming machine learning algoritm was found to be the Deep Learning methods where the Action Units (AU) are used. The video part 1 –that is consist of sad images at most- was found to be most discriminating video for distinguishing the children with or without ADHD. As we assessed the most discripinating AU in Video !, we found that the AU12 (lip corner puller), AU07 (lid tightener), AU09 (nose wrinkler), AU45 (eye blink), and AU06 (cheek raiser).

CONCLUSIONS: This is the first study that investigated tha emotional facial movements of the children with ADHD by using machine learning procedures on digital facial analysis. As nonverbal behaviors are the basic components in social interaction, and the facial movements are the basic elements of nonverbal behavior, the investigation of facial micromimics is crucial in the examination of mental status. For a better, objective and more detailed affect assessment in terms of psychiatric examination we still need more complicated and computer assisted technologies. The predicted and -until now only- theorized differences in facial movements in the children with neurodevelopmental disorders should be under further investigations. As we hypotized, in this study we found significant differences in SRS and DANVA-2 scores between ADHD and control groups. We also collected data on facial movements and found several parameters that have discriminaing capacity for some facial AU's. In addition, we found significant correlations with AU differences and DANVA and/or SRS scores. There is only one study similar to our design, where the authors evaluated the difference between LD patients and control group in terms of facial AU's.[4] They reported significant differences in four AU's (AU2, AU4, AU12, AU25). In that study, AU2, which is the outer brow raiser of musculus frontalis was reported as the chief discriminating muscle action. This muscle is used in surprising conditions and the children with LD had less AU2 movement. The authors concluded that this difference suggests that the children with LD have less ability on emotion recognition and they miss the surprising emotions.[4] In our study, the discriminating capacity of the Video 1, which has sad actions at most and AU12 difference which is associated with lip movements suggest that the children with ADHD had less emotional expression in terms of sad feelings. These findings necessiate further investigations. Nevertheless, the original and pionering nature of this study is promising for additional studies based on similar study design. These findings could be assessed the basics for a different era of psychiatric assessment in the future settings.

Keywords: ADHD (attention deficit hyperactivity disorder), facial recognition, emotion recognition, FACS (facial action coding system), Openface

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Table 1. The Group Differences in Correct Answer Scores in DANVA-2

		V1AU12	V1AU07	V1AU09	V1AU45	V1AU06
Social Reciprocity Scale		r:0,268	r:0,142	r:0,615	r:0,325	r:0,278
		p:0,227	p:0,529	p:0,002*	p:0,140	p:0,211
DANVA adult face recognition		r:-0,052	r:0,072	r:-0,008	r:0,064	r:-0,066
		p:0,817	p:0,750	p:0,970	p:0,776	p:0,769
DANVA child face recognition		r:-0,392	r:0,497	r:-0,301	r:-0,010	r:-0,468
		p:0,071	p:0,019*	p:0,173	p:0,966	p:0,028
DANVA posture recognition		r:-0,137	r:0,056	r:-0,208	r:-0,471	r:-0,383
		p:0,544	p:0,803	p:0,354	p:0,027*	p:0,079

		ADHD (n:56) Median (Q1-Q3)	Control (n:45) Median (Q1-Q3)	statistics	p	ANCOVA	p^a
Child face	LD (12 quest.)	9 (8-10)	9 (9-10)	Z:-1,470	0,142		
	HD (12 quest.)	10 (9-11)	10 (9-11)	Z:-0,640	0,522		
	Total	19 (17-20)	19 (18-21)	Z:-1,288	0,198		
Adult face	LD (12 quest.)	8 (6-9)	8 (7-9)	Z:-2,066	0,039*	F:1,219	0,273
	HD (12 quest.)	10 (8-11)	10 (10-11)	Z:-1,885	0,059		
	Total	18 (14-19)	19 (17-20)	Z:-2,293	0,022*	F:2,473	0,120
Posture (16 questions)		9 (7-10)	9 (8-11)	Z:-1,983	0,047*	F:0,065	0,800
General total (64 quest.)		45 (40-47)	47 (45-50)	Z:-3,071	0,002*	F:1,639	0,204
		Ort±SS	Ort±SS				
'Fearful' correct number		10,88±2,2	11,76±1,6	T:-2,133	0,036*	F:0,222	0,639
'Angry' correct number		8,94±2,2	9,79±2,7	T:-1,608	0,112		
'Sad' correct number		12,33±2,4	13,15±2,2	T:-1,573	0,120		
'Happy' correct number		14,08±1,7	14,44±1,4	T:-1,044	0,299		

Note: Z:Mann-Whitney-U. F:ANCOVA. a: p value in ANCOVA, where WISC-R total score is controlled. *p<0,05 HD: High density, LC: Low density

Table 2. Best performance scores of the algoritms

|	Facial Action Coding System	Density
Video 1 AU12	Lip corner puller	0.224
Video 1 AU07	Lid tightener	0.168
Video 1 AU09	Nose wrinkler	0.118
Video 1 AU45	Eye blink	0.117
Video 1 AU06	Cheek raiser	0.116

Table 3. The correlations between AU's and emotion regognition ability scores

*p<0.05. Pearson correlations

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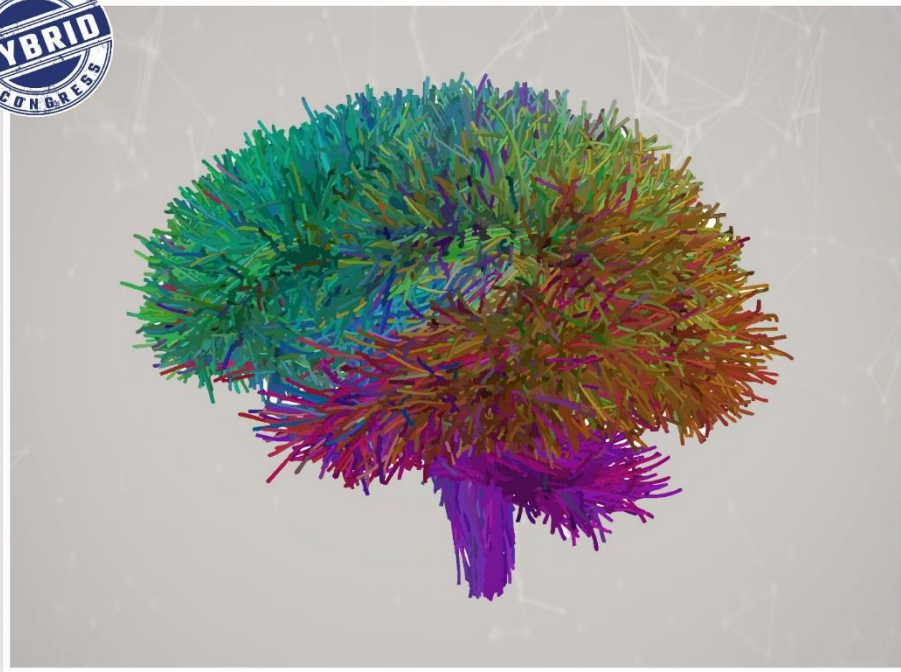
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