functional cerebellar abnormalities in patients with schizophrenia[4]. Thus, it is possible that some of the eye-tracking deficits associated with schizophrenia risk seen during ketamine challenge are mediated by shared cerebellar pathophysiology. Glutamate is the major excitatory neurotransmitter of the Central Nervous System (CNS), and it is crucially needed for numerous key neuronal functions. Yet, excess glutamate causes massive neuronal death and brain damage by excitotoxicity—detrimental over-activation of glutamate receptors. Glutamate-mediated excitotoxicity is the main pathological process taking place in many types of acute and chronic CNS diseases and injuries.

Successful attenuation of ketamine-induced deteriorations has been described for typical and atypical antipsychotics such as haloperidol, clozapine and olanzapine, and anti-epileptics such as lamotrigine, a glutamate agonist. Phencyclidine was also found related with vertical nystagmus. Risperidone treatment has previously been shown to improve antisaccade performance in schizophrenia patients after switching from typical antipsychotics to risperidone and in antipsychotic-naive first-episode patients.

With regard to smooth pursuit performance, no beneficial effects of risperidone on ketamine-induced smooth pursuit eye movements (SPEM) deficits were found. Some studies have investigated the effects of antipsychotics on SPEM in first-episode and chronic schizophrenia patients[3]. No treatment effect on predictive pursuit in first-episode patients but a worsening in SPEM performance in antipsychotic-treated, chronic schizophrenia patients compared with non-treated chronic patients has been observed. Hence patients' pursuit performance deficits seem to persist despite pharmacological treatment, possibly even representing cumulative adverse effects of typical and atypical antipsychotics on the pursuit system.

A neural circuitry involving the cerebellum has been proposed to have a central role in integrating and coordinating SPEM and saccadic information. It could be argued that NMDA receptor blockage in areas involved in frontal-thalamic-cerebellar circuits such as frontal eye fields, thalamus, and cerebellum would be likely to cause disruption in SPEM. We suggest that VEP is also responsible for the same mechanism. An involvement of a glutamatergic imbalance in cortical-subcortical-cerebellar circuits underlying the integrative theory of cognitive dysmetria may be assumed[5].

In conclusion, we suggest VEP as a physical examination sign for psychiatric disorders. Our findings are preliminary and should be investigated by further studies. Increased glutamatergic activity is associated with many psychiatric disorders as well as VEP in the brain; therefore, VEP may be used as a practical physical examination sign and may be helpful in diagnosis. Further studies are needed in order to show if VEP is an indicator of parental proneness or can be used as a phenotype. It should be examined more deeply if VEP's item can be used as endophenotype, genetic transition, connection with prognostic or disease susceptibility and response to treatment.

Keywords: eye sign, psychopathology, endophenotype

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[Abstract:0548] ***Genetic psychiatry***

No association between DNA methylation in BDNF gene and schizophrenia patients in Turkish population

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INTRODUCTION: Schizophrenia is a multifactorial disorder. Genetic and environmental factors are involved in the etiology of schizophrenia. Although genetic factors are risk factors for schizophrenia, it is assumed that some environmental factors are required for the manifestation

of disease[1]. Epigenetic mechanisms regulate gene functions without causing change in the nucleotide sequence of DNA. These regulations are reversible; the most commonly studied epigenetic mechanisms are DNA methylation and histone modification[2]. DNA methylation and epigenetic mechanisms are associated with psychiatric disorders such as depression, psychotic disorders, post-traumatic stress disorder, autism, eating disorders, and substance dependence[3]. Epigenetics has an important role in gene and environment interactions. This means environmental factors influence the genomic expressions through epigenetic mechanisms. DNA methylation is caused by coupling of a methyl group to CpG sites with the DNA methyltransferase enzyme. A normal level of DNA methylation is required for controlling genomic expressions. Brain Derived Neurotropic Factor (BDNF) is a neurotrophin that regulates synaptic transmission and plasticity, and it has a role in proliferation, differentiation, survival and death of neuronal and non-neuronal cells. It has been suggested that BDNF may play a role in the pathophysiology of schizophrenia. Genetic studies show an association between BDNF and schizophrenia. In this study we aimed to investigate the DNA methylation status of the BDNF gene in patients with schizophrenia.

METHODS: The study included 49 patients (aged 35.31±10.35 years, 33 male and 16 female) with schizophrenia and 65 unrelated healthy controls (aged 35.18±9.05 years, 46 male and 19 female). Volunteers in the control group had no personal or familial history of schizophrenia. Individuals with known major health problems, diabetes and malignancies were excluded from the study. Patients were diagnosed with schizophrenia according to the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). The severity of schizophrenia symptoms in the patients was evaluated using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression severity scale (CGI-S). DNA was extracted from blood samples by using salt-chloroform method. Determination of methylation pattern of CpG islands was based on the principle that bisulfite treatment of DNA would result in conversion of unmethylated cytosine residues into uracil, whereas methylated cytosine residues would remain unmodified. Methylation-specific PCR was performed with primers specific for either methylated or unmethylated DNA. The primers were designed for 2 different CpG islands in the BDNF promoter. 100 ng DNA samples were treated with EpiMark Bisulfite Conversion Kit (Catalog No: E3318, New England Biolabs), in accordance with the manufacturer's standard instructions. The collected data were analyzed using the SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Both descriptive and analytical statistics were used. Chi-square/Fisher's Exact test was used to compare categorical variables. To compare the continuous variables, t test was used.

RESULTS: The mean ages and the gender distribution of the study groups were similar. There were no significant differences in the methylated or un-methylated status for each area between schizophrenia patients and controls (Table 1). When patients were compared with clinical parameters such as duration of the illness, CGI-S, PANSS scores, BMI, and methylated or un-methylated status for each areas, we did not find any significant difference ($p>0.05$).

DISCUSSION: This study found no difference in methylation status of two regions of the BNDF gene between schizophrenia patients and healthy controls. Although the methylation status of some other genes has been studied in schizophrenia patients, there are limited studies about the methylation status of the BNDF gene in schizophrenia patients. However, in one study BDNF gene methylation status and BDNF gene expression were investigated in schizophrenia patients; BDNF gene methylation was found lower, BDNF gene expression higher in schizophrenia patients compared to controls. The methylation status of some genes other than BDNF has been studied in schizophrenia patients, e.g., MB-COMT and RELN. One study found hypomethylation in the MB-COMT gene and increased transcript levels of MB-COMT in schizophrenia patients. In that study, it is suggested that MB-COMT hypomethylation is a major risk factor for schizophrenia. Another study shows hypermethylation of the RELN promoter. But in contrast to these other studies, it shows that there is no difference in methylation status of COMT and RELN genes in schizophrenia patients compared to healthy controls[4]. As far as we can understand from these studies, data on DNA methylation status in patients with schizophrenia are conflicting. However, there must be an association with DNA methylation and schizophrenia according to our hypothesis, and again the methylation status must be different in schizophrenia patients compared to controls. Bu our findings do not support our hypothesis. As mentioned above, there are inconsistent results in methylation studies. Several other factors such as patients' received antipsychotics or analyzing methylation in blood may affect the methylation status. In a study which examined the effect of antipsychotics on DNA methylation, it is found that clozapine and quetiapine reduced DNA methylation, but there are no similar effects of haloperidol and risperidone on the DNA methylation status. Another study in animals shows that clozapine reduced BDNF methylation and increased social interaction[5]. The authors are aware of some limitations of this study. First, we analyzed DNA methylation in peripheral blood, which does not reflect directly the central nervous system. Second, this is a naturalistic and cross-sectional study and patients were continuing their medication. Therefore, antipsychotics received may have affected the methylation status. DNA methylation is a dynamic and reversible process, and many other environmental factors also affect methylation. For these reasons, examining the methylation status and protein levels of the BDNF gene in certain intervals throughout the treatment period in the same patients may be more worthwhile. In conclusion, there were no differences in BDNF gene methylation status between schizophrenia patients and healthy controls. Further studies are necessary with more patients, and the limitations referred in this paper should be considered.

Keywords: DNA methylation, BDNF gene, schizophrenia

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[Abstract:0549] ***Genetic psychiatry***

Cannabinoid receptor 1 (CNR1) gene polymorphisms in schizophrenia patients: Rs6454674 polymorphism is associated with disease severity

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INTRODUCTION: It is considered that schizophrenia is caused by a combination of multiple elements, such as genetic, biological, environmental, and psychological factors. According to this view, people may have a genetic predisposition for schizophrenia, but the disease may not emerge if some other factors are not added. Among these factors are birth complications that can cause mutagenesis or a change in gene expression, biological factors such as nutrition, and to a lesser extent certain environmental impacts including psychological factors. The endocannabinoid system contributes to the regulation of memory, cognition, emotion, and stress. In addition, it contributes to a spectrum of personality traits in normal individuals and a susceptibility to mood disorders. Endogenous cannabinoids have been found to be higher in the cerebrospinal fluid of schizophrenic patients[1]. It has been reported that endocannabinoids cause GABAergic inhibition and dopaminergic increase in the mesolimbic and nigro-striatal systems, which play a role in the neurobiology of schizophrenia[2]. There are limited studies about CNR-1 gene polymorphism in schizophrenia. In this study, we investigate cannabinoid receptor 1 (CNR1) gene polymorphisms in schizophrenia patients.
METHODS: CNR1 gene polymorphisms were studied in 66 schizophrenia patients and 65 healthy controls. To obtain genomic DNA, proteinase K digestion and salt-chloroform method were used. Clinical Global Impression severity scale (CGI-S) and Positive and Negative Syndrome Scale (PANSS) were administered for evaluating the severity of schizophrenia symptoms. CNR1 gene polymorphism has been determined by using polymerase-chain- reactions (PCR), Restriction Fragment Length Polymorphism (RFLP), and SSCP (Single Strand Conformation Polymorphism) methods for the Rs6454674, Rs806368, and Rs1049353 sites.
RESULTS: There was no difference in CNR 1 gene polymorphisms between schizophrenia patients and control groups (Rs6454674 T/G; p=0.973, Rs806368 T/C; p=0.349, Rs1049353 A/G; p=1). CGI-S, PANSS total, PANSS positive, PANSS negative and PANSS general psychopathology scores were significantly lower in schizophrenia patients with RS6454674 polymorphism than non-polymorphism.
CONCLUSION: Various theories have been proposed to explain the relationship between cannabis use and schizophrenia. It has been suggested that patients with schizophrenia use cannabis for self-medication, or that psychosis arises as a result of the use of cannabis, or that there are genetic and biological similarities between schizophrenia and cannabis use disorder. Considering this data, it is hypothesized that the endocannabinoid system (ECS) has a role in schizophrenia. In accordance with this hypothesis, endocannabinoid levels were studied in cerebrospinal fluid (CSF) and blood of schizophrenia patients. These studies show increased cannabinoid levels in CSF and blood of schizophrenia patients, and it is suggested that ECS alterations take a part in the pathophysiology of schizophrenia. Nevertheless, genetic studies have not shown this relationship conclusively. CNR genes are studied with various methods in schizophrenia. But results are conflicting and do not support clearly the relation between ECS and schizophrenia[3]. However, the result clarified that use of cannabis is a risk factor for onset of schizophrenia especially in vulnerably people[4]. We also found that there were no differences in CNR1 gene polymorphisms between schizophrenia patients and healthy controls. Our finding is consistent with previous studies which did not find any relationship between CNR1 gene polymorphisms and schizophrenia[5]. In conclusion, the results suggested that there may be an association between CNR1 gene polymorphisms and clinical symptoms and disease severity in schizophrenia patients.
Keywords: endocannabinoid system, cannabinoid receptor 1, gene polymorphism, schizophrenia

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