The Association Between The Extended Psychosis Phenotype and COMT val158met and BDNF val66met Polymorphisms

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SUMMARY

Objective: Psychotic disorders were previously associated with catechol-O-methyltransferase (COMT) val[158]met (rs4680) and brain-derived neurotrophic factor (BDNF) val[66]met (rs6265) polymorphisms. This article evaluates the association between COMT/BDNF polymorphisms and the extended psychosis phenotype which covers not only schizophrenia but also subclinical expressions of psychotic experiences.

Method: The participants of this study were part of the TürkSch (Izmir Mental Health *Survey* for Gene-Environment Interaction in Psychoses), a longitudinal study Psychotic experiences and disorders were screened 437. The extended psychosis phenotype was grouped into four: (1) no psychotic experiences (n: 194), (2) subclinical psychotic experiences (n: 87), (3) clinically relevant psychotic experiences (n: 104), and (4) schizophrenia-like disorders (n: 52). BDNF rs6265 was genotyped occurred in every participant whereas COMT rs4680 genotyping could be done on 366 individuals.

Results: There was no association between the extended psychosis phenotype and BDNF rs6265/COMT rs4680 polymorphisms. The frequency of met carriers in the BDNF rs6265genotype was slightly higher in individuals with subclinical psychotic experiences than in the group with no psychotic experiences, which was just below the significance level (p=0.08).

Conclusion: The lack of an association between different expression levels of the extended psychosis phenotype and the BDNF rs6265/COMT rs4680 polymorphism might be related to sample characteristics, underlying gene-gene, gene-environment and gene-environment-gene interactions.

Keywords: Psychosis, schizophrenia, COMT, BDNF, genetics

INTRODUCTION

Schizophrenia and other psychotic disorders are psychiatric diagnoses with core symptoms of delusions and hallucinations, and with uncertain aetiology (van Os and Kapur, 2009). Genetic predisposition is the most important risk factor in the disorder. Environmental factors are also playing an important role for the transition from subclinical expression into a disorder (van Os et al. 2010, van Winkel et al. 2010). Psychotic experiences, which are milder forms of symptoms of psychotic disorders, such as delusions and hallucinations, can be observed in the general population (Linscott and van Os 2013). There is continuity in prevalence phenomenology, and impairment among subthreshold experiences and psychotic disorders, as well as in terms of risk factors (Binbay et al. 2012b, Linscott and van Os 2013). Subthreshold psychotic experiences particularly increase in adolescence and can disappear overtime or can transform into a permanent subsequent psychotic disorder (Cougnard et al. 2007, Kaymaz and van Os 2010, Kelleher et al. 2010, van Os 2014).

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The extended psychosis phenotype is a spectrum of transient psychotic experiences at one end (for example, feel like hearing a sound for a few times, thinking that someone is talking behind, without any impairment due to these experiences, and without help-seeking), and schizophrenia and other psychotic disorders at the other end (Kaymaz and van Os 2010, Binbay et al. 2012b, Linscott and van Os 2013). The extended psychosis phenotype may emerge in different appearances as a result of gene-environment interaction (Cougnard et al. 2007, van Os et al. 2010, van Winkel et al. 2010). Examining the genes associated with the recurrence, permanence transition of transient psychotic experiences to a psychotic disorder may provide important insights for comprehensive evaluation of psychoses (Kaymaz and van Os 2010, Kelleher et al. 2010, van Os 2014).

Catechol-o-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) are two genes that are associated with psychotic experiences and disorders (Fan et al. 2005, Munafo et al. 2005, Williams et al. 2007, Okochi et al. 2009, Notaras et al. 2015a, Notaras et al. 2015b).

BDNF val^{66}met and psychosis

BDNF plays a significant role in neuro-developmental processes like growth and differentiation of nerve cells, maintenance of neuronal functions, synaptic regulation and cognitive functions (Numakawa et al. 2010, Bekinschtein et al. 2008). BDNF val^{66}met polymorphism (rs6265) occurs when alanine is replaced with guanine in the 196th nucleotide of pro-BDNF gene (Egan et al. 2003). This alteration causes a change in the amino acid chain, and methionine replaces valine. This polymorphism does not change BDNF activity, instead cellular transfer and release of pro-BDNF are affected (Egan et al. 2003, Soliman et al. 2010).

The association between BDNF val^{66}met polymorphism and schizophrenia are contradictive (Kawashima et al. 2009, Notaras et al. 2015b, Kheirollahi et al. 2016). Although it is not associated with schizophrenia directly, it is likely to affect the age of onset, emerging symptoms, treatment response, cognitive functions, and even brain structure (Notaras et al. 2015b). In addition, it can be involved in gene-environment interactions contributing to schizophrenia (van Winkel et al. 2010, Buckley et al. 2011) and can be related to subthreshold psychotic experiences (Simons et al. 2009, Alemany et al. 2011).

COMT val^{158}met and psychosis

COMT is the major regulator of dopamine and other catecholamines in the prefrontal cortex and is responsible for extra-neuronal dopamine metabolism (Hong et al. 1998, Kapur 2003). COMT gene, located in chromosome 22q11 allele, is intensively expressed in the hippocampus and the prefrontal cortex (Lachman et al. 1996a, Lachman et al. 1996b). COMT has important effects on dopamine functioning in the prefrontal cortex, which has a substantial place in schizophrenia pathophysiology (Tunbridge et al. 2004).

COMT val158 met polymorphism (rs4680) is formed when methionine replaces valine on the 4th exon of the gene (Lachman et al. 1996b, Chen et al. 2004). It has been shown that the enzymatic activity of val allele is 40% higher which leads to lower dopamine levels in the prefrontal cortex (Chen et al. 2004). The decrease in dopamine level can be associated with impairment in data processing, resulting in development of psychotic symptoms (Weinberger 2002, Kapur 2003). On the other hand, there is an inverse U-shaped relation between dopamine levels and frontal lobe activities. According to this, COMT has a favorable effect on frontal lobe functioning in a narrow window (Winterer and Weinberger 2004, Howes et al. 2004). Thus, COMT polymorphism is inadequate for psychosis solitarily, and frontal functioning is of importance as well.

There are a number of studies examining the relation between COMT and/or BDNF polymorphisms and psychotic disorders or experiences (Simons et al. 2009, Pelka-Wysiecka et al. 2013, Ramsay et al. 2013). Nevertheless, there is no study analyzing the distribution of these genes in the appearances of extended psychosis phenotypes, from syndromic end to the subthreshold experiences.

In this study, the distribution of COMT val158 and BDNF val66 polymorphisms along the extended psychosis phenotype was examined in a community based participants.

METHODS

Data is based on the TürkSch (İzmir Mental Health Survey for Gene-Environment Interaction in Psychosis) study (Binbay et al. 2011) which collected longitudinal data on the individual and social (neighbourhoods and family) risk factors, and genetic associations of the extended psychosis phenotype (Binbay et al. 2011, Binbay et al. 2012b, Topuzoglu et al. 2015). The TürkSch study had a general population based sample and the sample was screened twice for the extended psychosis phenotype, as well as other psychiatric symptoms in 2008 (T1) and 2014 (T2) (Elbi et al. 2016). In both waves of the screenings, blood samples were collected for genetic analysis. This report shows results on the genetic analysis of a subpopulation of the TürkSch study.

Design

Both assessments of TürkSch study were approved by the Ege University ethics committee and participants provided written informed consent. Individuals were randomly selected from the 6000 addresses, which were provided by the Turkey's

Statistic Institute (TurkStat), from the wider Izmir metropolitan area using a multistage sampling procedure. Each address was, visited by trained lay interviewers in 2008 and 2014. In the first screening (T1), 4011 individuals aged 15-64 were interviewed (Binbay et al. 2011). In the second screening (T2), each address of every respondent in T1 was visited and finally 2185 of them were re-interviewed after 6 years (Elbi et al. 2016). During the interviews, psychotic experiences were evaluated, and also, demographic, familial and social features, smoking habit, alcohol and substance abuse, depressive and manic episodes, traumatic life events, and any help-seeking for psychiatric problems were collected (Binbay et al. 2011, Elbi et al. 2016).

To evaluate the genetic associations of the extended psychosis phenotype, individuals with any expression of psychosis phenotype (from subclinical psychotic experiences to psychotic disorders) and control individuals (no expression of psychosis phenotype) were recruited from the general population based sample of the first screening wave (T1).

Screening and diagnostic interview

Psychosis phenotype was screened with the Composite International Diagnostic Interview (CIDI) 2.1 (Andrews and Peters 1998). The CIDI is a fully structured interview developed by the World Health Organization (Robins et al. 1988). The reliability and validity of the Turkish version of the CIDI was studied as a part of a national study in 1997 (Kılıç and Göğüş 1997). The extended psychosis phenotype was based on an operational assessment of frequency, related distress, help-seeking and impairment due to psychotic experience. The items of the G section (psychosis module) in CIDI were rated dichotomously indicating presence or absence of the particular evaluated delusional or hallucinatory psychotic experience. For each endorsed item, underlying condition (e.g. substance-related) frequency, duration, help-seeking, severity and impairment associated with psychotic experience were evaluated. For each psychotic experience, a severity score was established based on the evaluation (Binbay et al. 2011, Binbay et al. 2012b).

For the clinical and subclinical screenings, an algorithm was estabelihed, which was based on afomentioned severity score of the psychitc experience (Binbay et al. 2011). Eventually, individulas were identified as probable case of psychotic disorder with a severity score above 3, a diagnosis of psychotic disorder or bipolar affective disorder, ongoing antipsyuhotic medication, or any suspicious interview rated by the interviewer. All probable cases were recontacted by the TürkSch study team and invited for a clinical reappraisal with the research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al. 1995, Çorapçıoğlu et al. 1999). All clinical evaluations were performed from January 2008 to January 2009 by a clinician (HE, KA, TB) or by an experienced psychologist (NZ) in the hospital or in the respondents' houses.

Sample

The individuals were divided into four groups: Group 1: individuals without any expression of psychosis (control group), group 2: individuals with subclinical psychotic experiences, group 3: individuals with psychotic experiences leading to distress, and group 4: individuals with a diagnosis of DSM-IV schizophrenia or other psychotic disorders.

74.3% (n= 2930) of the T1 sample didn't endorsed any psychotic experience. 15.6% (n= 625) had subclinical psychotic experiences, 7.6% (n= 307) had psychotic experiences leading to distress, and 2.5% (n= 99) had a diagnosis of DSM-IV disorders with a psychotic symptom (schizophrenia and other psychotic disorders, affective psychoses, psychotic disorders due to somatic illness or substance abuse) (Binbay et al. 2012a).

The genotyped sample covered 52 out of 57 of individuals with a DSM diagnosis of schizophrenia and other psychotic disorders, which were clinically interviewed with SCID-I. Other groups included individuals matched or at least similar for age and sex with individuals with a diagnosis of DSM-IV schizophrenia and other psychotic disorders. In order to collect data of individuals for other three groups, 6.4% (n= 194) of individuals without any expression of psychosis (control group), 14.1% (n= 87) of individuals with subclinical psychotic experiences, and 33.9% (n= 104) of individuals with psychotic experiences leading to distress were re-contacted, evaluated and included. Thirty-four individuals (5 schizophrenia and other psychotic disorder; 12 individuals without any expression of psychosis; 10 individuals with subclinical psychotic experiences and 7 individuals with psychotic experiences leading to distress) were re-contacted, evaluated, but excluded due to lack of informed consent. When reached and unreached individuals in the groups of subclinical psychotic experiences and psychotic experiences were compared, there was no difference in sex and marital status. However, individuals recruited for genotyping had significantly higher mean of age in both groups than individuals not genotyped (means of age were 34.4 vs 44.7 and 35.4 vs. 42.3, respectively).

Genotyping

Blood sampling was performed only for T1 respondents providing a written informed consent. A two cc EDTA Blood sample was used to isolate DNA. Gene regions of polymorphisms of COMT $val^{158}met$ (rs4680) and BDNF $val^{66}met$ (rs6265) were amplified with corresponding primers. Restriction fragment length polymorphism technique was conducted to reveal fragments relevant to SNP region. Obtained fragments

Table 1. Demographic and Clinical Variables for Psychosis Phenotype

	No history of psychotic experiences (n: 194)		Subthreshold psychotic experiences (n: 87)		Psychotic experiences (n: 104)		Schizophrenia and other psychotic disorders (n: 52)		Total			
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Statistics**	**p**
Gender												
Male	91	47.0	37	42.5	33	31.7	27	52	188	43.0	χ^2= 8.29, df=3	0.040
Female	103	53.0	50.0	57.5	71.0	68.3	25.0	48.8	249	57.0		
Education												
≤8 years	111	57.2	58	66.7	71	68.3	35	67.3	275	63.0	χ^2= 4.93, df=3	0.177
>8 years	83	42.8	28	33.3	33	31.7	17	32.7	162	37.0		
Marital status												
Married	136	70.1	56	64.4	62	59.6	25	48.1	279	63.9	χ^2= 10.18; df=6	0.117
Unmarried	43	22.2	21	24.1	29	27.9	19	36.5	112	25.6		
Divorced/widow	15	7.7	10	11.5	13	12.5	8	15.4	46	10.5		
Health insurance												
Retirement Fund	38	19.6	10	11.5	8	7.7	8	15.4	64	14.6	χ^2= 12.15; df=6	0.059
Green Card	16	8.3	12	13.8	15	14.4	9	17.3	52	11.9		
SSK/Bagkur	140	72.1	65	74.7	81	77.9	35	67.3	321	73.5		
Employment Status												
Employed	71	36.6	25	28.7	38	36.5	12	23.1	146	33.4	χ^2= 8.94; df=9	0.443
Unemployed	15	7.7	12	13.8	8	7.7	7	13.5	42	9.6		
Retired	38	19.6	18	20.7	15	14.5	10	19.2	81	18.5		
Unregistered employment	70	36.1	12	36.8	43	41.3	23	44.2	168	38.4		
Family history of psychiatric disease												
No	134	69.1	49	56.3	66	63.5	30	57.7	279	63.8	χ^2=17.59; df=6	0.007
Yes, CPD	44	22.7	33	37.9	30	28.8	11	21.2	118	27.0		
Yes, SPD	16	8.2	5	5.8	8	7.7	11	21.1	40	9.2		
Result of the clinical interview												
No comorbidity	85	43.8	20	23.0	8	7.7	-	-				
Depressive Disorder	71	36.6	53	60.9	65	62.5	9	17.3				
Bipolar Disorder	11	5.7	4	4.6	12	11.5	-	-				
Anxiety Disorder	17	8.8	6	6.9	11	10.6	6	11.5				
Other	10	5.1	4	4.6	8	7.7	7	13.5				
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age	45.3	12.9	44.7	13.3	42.3	13.7	44.3	12.6	44.3	13.2	F(3. 433): 0.73	0.866

CPD: Common psychiatric disorder (depression, anxiety disorder, somatization disorder, conversion disorder etc.); SPD: Severe psychiatric disorder (Schizophrenia, other psychotic disorders, bipolar disorder); M: Mean; SD: Standard Deviation; * Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I) was used. For the participants with multiple psychiatric comorbidities, the primary psychiatric condition is coded. On the other hand, participants with comorbidities who have DSM-IV diagnosis of schizophrenia and psychotic disorders were also presented in the table. Depressive disorders include major depressive disorder and dysthymic disorder; bipolar disorder includes bipolar II disorder, cyclothymic disorder and bipolar disorder not otherwise specified: anxiety disorder includes generalized anxiety disorder, panic disorder, post-traumatic stress; other includes alcohol and substance abuse and somatoform disorders.

were separated according to their lengths by agarose gel electrophoresis. Both COMT (rs4680) and BDNF (rs6265) had three polymorphisms as Val/Val, Val/Met, Met/Met. Since the Met/Met genotype of BDNF (rs6265) had low frequency, the genotypes for this SNP were included in the analyses as a binary variable (Met allele carriers and Val homozygotes). BDNF (rs6265) was genotyped in each participated individual (n= 437) whereas due to financial limits COMT (rs4680) was genotyped in 336 of individuals who provided blood samples.

Statistical analyses

All analyses were conducted using the software package STATA, version 12.0 (StatCorp 2011). Group differences in genotype and allele frequency were analyzed with Hardy-Weinberg equilibrium test. Kolmogorov-Smirnov test was used to assess to normal distribution of the data. χ^2 was used for independent categorical variables, t-test was used for continuous variables, and linear or logistic regression was used for analyses including multiple independent variables. The associations were given as odds ratios (OR) or B co-efficient with 95% confidence interval. In this report, psychosis continuum was evaluated as a phenomenological concept, not a statistical feature. Therefore, the extended psychosis phenotype included categories of psychotic experiences with different levels of impairment and severity. Logistic regression was used to evaluate the associations between psychosis phenotype and genotype. In regression analysis reference group was control group without any expression of psychosis, and compared groups included individuals with subclinical psychotic experiences, individuals with psychotic experiences leading to distress, and individuals with a diagnosis of DSM-IV schizophrenia and other psychotic disorders. In all analyses, $p<0.05$ were used for statistical significance.

RESULTS

The sociodemographic and clinical characteristics of each group is presented in Table 1. Sex and family history of psychiatric disorders were the only sociodemographic features that were different between groups. The number of female participants was higher than male participants in all groups other than the group "individuals with a diagnosis of DSM-IV schizophrenia and other psychotic disorders" (χ^2= 8.29, p= 0.040). Family history of any psychiatric disorders was higher in all three groups of psychosis phenotype compared to group 1 (individuals without any expression of psychosis). Family history of severe psychiatric disorder was more common in group 4, schizophrenia and other psychotic disorder group when compared to group 1 (control group) and individuals with subclinical psychotic experiences (χ^2:17.6, p=0.007).

Table 2 shows COMT and BDNF genotype characteristics of the sample stratified by the extended psychosis phenotype. In all groups, val/val genotype was the most common variant among BDNF rs6265 genotypes and Met/met genotype was the least common. Among the groups of psychosis phenotype, no significant difference was found with respect to BDNF rs6265 genotypes. In all groups, val/val genotype was the most common variant among COMT rs4680 genotypes. Of the extended psychosis phenotype groups, there was a significant difference in terms of COMT rs 4680 genotypes.

Table 2. Distribution of COMT and BDNF polymorphisms for Psychosis Phenotype

	No history of psychotic experiences (n: 194)		Subthreshold psychotic experiences (n: 87)		Psychotic experiences (n: 104)		Schizophrenia and other psychotic disorders (n: 52)		Total			
	N	%	N	%	N	%	N	%	N	%	Statistics	p
BDNF rs6265												
GG (Val/Val)	127	65.5	66	75.9	77	74.0	35	67.3	305	69.8	χ^2= 4.94; df=6	0.551
GA (Val/Met)	59	30.4	19	21.8	24	23.1	14	26.9	116	26.5		
AA (Met/Met)	8	4.1	2	2.3	3	2.9	3	5.8	16	3.7		
Total	194	100	87	100	104	100	52	100	437	100		
COMT rs4680												
GG (Val/Val)	61	41.2	37	48.0	40	44.9	22	42.3	160	43.7	χ^2= 2.40; df=6	0.879
GA (Val/Met)	48	32.4	26	33.8	29	32.6	19	36.5	122	33.3		
AA (Met/Met)	39	26.4	14	18.2	20	22.5	11	21.2	84	23.0		
Total	148	100	77	100	89	100	52	100	366	100		

Table 3. Relationship between psychosis phenotypes and COMT and BDNF polymorphisms according to those with no psychotic experiences (multinomial logistic regression)

	Subthreshold psychotic experience cf no psychotic experience			Psychotic experience cf no psychotic experience			Schizophrenia and other psychotic disorders cf no psychotic experience		
	OR*	95% CI	p	OR*	95% CI	p	OR*	95% CI	p
BDNF rs6265									
GG (Val/Val)	ref	-	-	ref	-	-	ref	-	-
GA+AA** (Met+)	0.6	(0.3-1.1)	0.08	0.7	(0.4-1.2)	0.15	0.9	(0.5-1.8)	0.79
COMT rs4680*									
GG (Val/Val)	ref	-	-	ref	-	-	ref	-	-
GA (Val/Met)	0.9	(0.5-1.6)	0.73	0.9	(0.5-1.7)	0.81	1.1	(0.5-2.2)	0.80
AA (Met/Met)	0.6	(0.8-1.2)	0.14	0.7	(0.4-1.5)	0.39	0.8	(0.3-1.8)	0.52

* It was corrected for age and gender. ** Since the Met carriers are few, the group was formed as Val / Val and Met + (homozygous or heterozygous) cf: controlled for.
OR: Odds ratio; CI: Confidence Interval

Table 3 presents regression coefficients of the association between COMT and BDNF genotype on the one hand and the extended psychosis phenotype on the other. All categories within the extended psychosis phenotype were compared with no psychotic experiences. Since BDNF met/met genotype group was small (n: 16), the val/met subgroup as "met carrier" was added. This combined group was involved in the analysis. Age and sex were also added to the regression model for the associations between genotypes and psychosis phenotypes. After regression analysis, no significant association was found between genotypes and different phenotypes of extended psychosis (Table 3). Only, in individuals with subclinical psychotic experiences, the probability of carrying the allele that codes methionine in the genotypes for BDNF rs6265 polymorphism was lower than individuals without any expression of psychosis (control group) not statistically significant (OR= 0.6, 95% CI= 0.3-1.1, p= 0.08).

DISCUSSION

In this report, the relationship between the extended psychosis phenotype and COMT $val^{158}met$ and BDNF $val^{66}met$ polymorphisms was evaluated. Although the association between psychotic experiences and several genetic polymorphisms was examined, this is the first study that evaluates different levels of extended psychosis phenotype with individuals without any expression of psychosis. There was no significant association between BDNF $val^{66}met$ and COMT $val^{158}met$ polymorphisms and the extended psychosis phenotype.

In the BDNF $val^{66}met$ polymorphism, though there are studies indicating increased schizophrenia risk in the val allele carriers (Muglia et al. 2003, Neves-Pereira et al. 2005), it was also reported that met allele is related to increased risk of schizophrenia (Kheirollahi et al. 2016). However, recent meta-analyses and other studies have shown no relationship between BDNF $val^{66}met$ polymorphism and schizophrenia (Kawashima et al. 2009, Notaras et al. 2015a, Notaras et al. 2015b).

While there is no adequate data regarding the association between BDNF and schizophrenia, the BDNF functions in brain (Bekinschtein et al. 2008, Numakawa et al. 2010) is thought to have a role in pathophysiology of schizophrenia (Buckley et al. 2011, Nurjono et al. 2012). In addition, BDNF is thought to have a regulator effect on social stress (Alemany et al. 2011). Likewise, studies have shown that met carriers go through anxiety-related behaviour and paranoia in view of stressful life events (Chen et al. 2006, Simons et al. 2009). On the other hand, contradictory relation between BDNF $val^{66}met$ polymorphism and schizophrenia can be based on gene-environment interactions (van Winkel et al. 2010, Buckley et al. 2011). In this study, the lack of an association between BDNF $val^{66}met$ polymorphism and the extended psychosis phenotype may be related to possible unmeasured environmental exposures.

COMT is a gene that was thought to have a strong association with schizophrenia and psychosis for many years. Therefore, numerous studies have been carried out (Lachman et al. 1996a, Lachman et al. 1996b, Hong et al. 1998). Nonetheless, findings are complex and contradictory (Munafo et al. 2005, Williams et al. 2007, Okochi et al. 2009). Recently, a meta-analysis reported a significant association between schizophrenia and COMT $val^{158}met$ polymorphism which was more apparent in some demographic characteristics (for example being Caucasian) (Gonzalez-Castro et al. 2016). It is suggested that there is a relation between COMT and psychosis (Tunbridge et al. 2004) since COMT enzyme is the main regulator of dopamine in prefrontal cortex (Lachman et al. 1996b, Chen et al. 2004) and psychosis accompanies the deletion of chromosome region in which it is coded (Kapur 2003).

On the other hand, higher enzyme activity of val allele in COMT $val^{158}met$ polymorphism can lead to relatively more decrease in dopamine levels, impairment in data processing

periods, and thereby leading to development of psychotic symptom (Weinberger 2002, Winterer and Weinberger 2004). Hence, neurocognitive testing showed that dorsolateral prefrontal cortex activity was worse in schizophrenia patients carrying val/val polymorphism (Egan et al. 2001, Ceaser et al. 2013). However, dopamine levels can remain high for a long time in an individual carrying the met allele with low enzyme activity, and as a result, a predisposition to psychotic experiences can emerge (Howes et al. 2004). The relationship between COMT and schizophrenia can vary according to sex and ethnic groups (Williams et al. 2007). In this study, having no association between COMT $val^{158}met$ polymorphism and the extended psychosis phenotype may be due to relative small sample size and as well as unmeasured environmental factors.

There are also a number of studies that examine both gene polymorphisms in psychosis (Simons et al. 2009). In adolescents aged between11 and 15 years no association was found between BDNF $val^{66}met$ and COMT $val^{158}met$ polymorphisms and psychotic experiences (Ramsay et al. 2013). Furthermore there was no difference between schizophrenia patients, their unaffected relatives and healthy controls in terms of BDNF and COMT polymorphisms (Shaikh et al. 2011, Walshe et al. 2012). Also there was no relationship between BDNF and COMT polymorphisms, age of onset of schizophrenia and clinical symptoms (Numata et al. 2007).

This study has limitations. First, the study has a cross-sectional design, which makes it impossible to establish a cause and effect relation. Second, due to the sampling method, psychotic experience prevalence and genotype characteristics may be different within the group not volunteered to participate in the study. People displaying gene-phenotype relation might have been excluded and a possible relation between COMT, BDNF and psychosis phenotype may have been overlooked. Third, other features (for e.g. epigenetic) that could not be determined in this research may have formed an important restriction regarding the relation between genotype and phenotype. Fourth, the sample size is relatively small for a gene-environment interaction research. As power analysis was not carried out for genetic analyses, an existent relation might not have been identified. This might have resulted in a type II error (depending on sampling method). Fifth, there may be some ambiguous environmental factors affecting the relationship between researched genes and psychosis phenotype, which do not take place in this study. Therefore, possible gene-environment interactions may also have affected the result.

Together with these limitations, this study has the characteristic of being the first study with a community based sample, examining BDNF and COMT genotype distribution in a sample including all appearances of extended psychosis phenotype from syndromal disorder to subthreshold experiences.

CONCLUSION

The relationship between BDNF and COMT and extended psychosis phenotype is contradictory and complex. The complexity of psychosis phenotype, the fact that genetic effects on brain can only be examined indirectly, and numerous mixing factors being present are main obstacles to finding a certain relation. The contradictory results of studies examining the relationship between genotype and psychosis phenotype, are possibly related to the presence of multifactor mechanisms such as gene-gene interaction, gene-environment interaction, and gene-gene-environment interaction.

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REFERENCES

Alemany S, Arias B, Aguilera M et al (2011) Childhood abuse, the BDNF-$val^{66}met$ polymorphism and adult psychotic-like experiences. Br J Psychiatry, 199: 38-42.

Andrews G and Peters L (1998) The psychometric properties of the Composite International Diagnostic Interview. Soc Psychiatry Psychiatr Epidemiol, 33: 80-8.

Bekinschtein P, Cammarota M, Katche C et al (2008) BDNF is essential to promote persistence of long-term memory storage. Proc Natl Acad Sci U S A, 105: 2711-6.

Binbay T, Alptekin K, Elbi H et al (2012a) İzmir Kent Merkezinde Şizofreni ve Psikotik Belirtili Bozuklukların Yaşamboyu Yaygınlığı ve İlişkili Oldukları Sosyodemografik Özellikler. Turk Psikiyatri Derg 23: 149-60.

Binbay T, Drukker M, Elbi H et al (2012b) Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. Schizophr Bull 38: 992-1002.

Binbay T, Elbi H, Alptekin K et al (2011) Psikozlarda Gen-Çevre Etkileşimi için İzmir Akıl Sağlığı Araştırması (TürkSch): Amaç ve Yöntem. Turk Psikiyatri Derg 22: 65-76.

Buckley PF, Pillai A and Howell KR (2011) Brain-derived neurotrophic factor: findings in schizophrenia. Curr Opin Psychiatry 24: 122-7.

Ceaser A, Csernansky JG and Barch DM (2013) COMT influences on prefrontal and striatal blood oxygenation level-dependent responses during working memory among individuals with schizophrenia, their siblings, and healthy controls. Cogn Neuropsychiatry 18: 257-83.

Chen J, Lipska BK, Halim N et al (2004) Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 75: 807-21.

Chen ZY, Jing D, Bath KG et al (2006) Genetic variant BDNF ($val^{66}met$) polymorphism alters anxiety-related behavior. Science 314: 140-3.

Cougnard A, Marcelis M, Myin-Germeys I et al (2007) Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. Psychol Med 37: 513-27

Çorapçıoğlu A, Aydemir Ö, Yıldız M et al (1999) DSM-IV Eksen I Bozuklukları (SCID-I) için yapılandırılmış klinik görüşme, klinik versiyon. Ankara: Hekimler Yayın Birliği.

Egan MF, Goldberg TE, Kolachana BS et al (2001) Effect of COMT Val108/158

Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 98: 6917-22.

Egan MF, Kojima M, Callicott JH et al (2003) The BDNF val[66]met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell, 112: 257-69.

Elbi H, Binbay T, Alptekin K et al (2016). Psikoz Benzeri Yaşantı-Psikotik Bozukluk İlişkisi, Psikotik Bozukluğa Dönüşüm İçin Risk Faktörleri, Gen- Çevre Etkileşimi: Toplum Tabanlı Örneklemde Bir İzlem Çalışması (112S476). İzmir.

Fan JB, Zhang CS, Gu NF et al (2005) Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. Biol Psychiatry 57: 139-44.

First MB, Spitzer RL, Gibbon M et al (1995) Structured clinical interview for DSM-IV axis I disorders. New York: New York State Psychiatric Institute.

Gonzalez-Castro TB, Hernandez-Diaz Y, Juarez-Rojop IE et al (2016) The Role of a Catechol-O-Methyltransferase (COMT) val[158]met Genetic Polymorphism in Schizophrenia: A Systematic Review and Updated Meta-analysis on 32,816 Subjects. Neuromolecular Med 18: 216-31.

Hong J, Shu-Leong H, Tao X et al (1998) Distribution of catechol-O-methyltransferase expression in human central nervous system. Neuroreport 9: 2861-4.

Howes OD, McDonald C, Cannon M et al (2004) Pathways to schizophrenia: the impact of environmental factors. Int J Neuropsychopharmacol, 7 Suppl 1: S7-S13.

Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160: 13-23.

Kawashima K, Ikeda M, Kishi T et al (2009) BDNF is not associated with schizophrenia: data from a Japanese population study and meta-analysis. Schizophr Res 112: 72-9.

Kaymaz N and van Os J (2010) Extended psychosis phenotype--yes: single continuum--unlikely. Psychol Med 40: 1963-6.

Kelleher I, Jenner JA and Cansy M (2010) Psychotic symptoms in the general population – an evolutionary perspective. Br J Psychiatry 197: 167-9.

Kheirollahi M, Kazemi E and Ashouri S (2016) Brain-Derived Neurotrophic Factor Gene val[66]met Polymorphism and Risk of Schizophrenia: A Meta-analysis of Case-Control Studies. Cell Mol Neurobiol 36: 1-10.

Kılıç C, Göğüş A (1997) Uluslararası Bileşik Tanı Görüşmesi 2.1. Dünya Sağlık Örgütü ve Hacettepe Üniversitesi Tıp Fak. Psikiyatri A.D. İşbirliği Merkezi, Ankara.

Lachman HM, Morrow B, Shprintzen R et al (1996a) Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. Am J Med Genet 67: 468-72.

Lachman HM, Papolos DF, Saito T et al (1996b) Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 6: 243-50.

Linscott RJ and van Os J (2013) An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med 43: 1133-49.

Muglia P, Vicente AM, Verga M et al (2003) Association between the BDNF gene and schizophrenia. Mol Psychiatry 8: 146-7.

Munafo MR, Bowes L, Clark TG et al (2005) Lack of association of the COMT (Val158/108 Met) gene and schizophrenia: a meta-analysis of case-control studies. Mol Psychiatry 10: 765-70.

Neves-Pereira M, Cheung J, Pasdar A et al (2005) BDNF gene is a risk factor for schizophrenia in a Scottish population. Mol Psychiatry 10: 208-12.

Notaras M, Hill R and van den Buuse M (2015a) The BDNF gene val[66]met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy. Mol Psychiatry 20: 916-30.

Notaras M, Hill R and van den Buuse M (2015b) A role for the BDNF gene val[66]met polymorphism in schizophrenia? A comprehensive review. Neurosci Biobehav Rev 51: 15-30.

Numakawa T, Suzuki S, Kumamaru E et al (2010) BDNF function and intracellular signaling in neurons. Histol Histopathol, 25: 237-58.

Numata S, Ueno S, Iga J et al (2007) Interaction between catechol-O-methyltransferase (COMT) Val108/158Met and brain-derived neurotrophic factor (BDNF) val[66]met polymorphisms in age at onset and clinical symptoms in schizophrenia. J Neural Transm (Vienna) 114: 255-9.

Nurjono M, Lee J and Chong SA (2012) A Review of Brain-derived Neurotrophic Factor as a Candidate Biomarker in Schizophrenia. Clin Psychopharmacol Neurosci 10: 61-70.

Okochi T, Ikeda M, Kishi T et al (2009) Meta-analysis of association between genetic variants in COMT and schizophrenia: an update. Schizophr Res 110: 140-8.

Pelka-Wysiecka J, Wronski M, Jasiewicz A et al (2013) BDNF rs 6265 polymorphism and COMT rs 4680 polymorphism in deficit schizophrenia in Polish sample. Pharmacol Rep 65: 1185-93.

Ramsay H, Kelleher I, Flannery P et al (2013) Relationship between the COMT-val[158]met and BDNF-val[66]met polymorphisms, childhood trauma and psychotic experiences in an adolescent general population sample. PLoS One, 8: e79741.

Robins LN, Wing J, Wittchen HU et al (1988) The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 45: 1069-77.

Shaikh M, Hall MH, Schulze K et al (2011) Do COMT, BDNF and NRG1 polymorphisms influence P50 sensory gating in psychosis? Psychol Med 41: 263-76.

Simons CJ, Wichers M, Derom C et al (2009) Subtle gene-environment interactions driving paranoia in daily life. Genes Brain Behav 8: 5-12.

Soliman F, Glatt CE, Bath KG et al (2010) A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 327: 863-6.

StataCorp (2011) Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.

Topuzoglu A, Binbay T, Ulas H et al (2015) The epidemiology of major depressive disorder and subthreshold depression in Izmir, Turkey: Prevalence, socioeconomic differences, impairment and help-seeking. J Affect Disord 181: 78-86.

Tunbridge E, Burnet PW, Sodhi MS et al (2004) Catechol-o-methyltransferase (COMT) and proline dehydrogenase (PRODH) mRNAs in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression. Synapse 51: 112-8.

van Os J (2014) The many continua of psychosis. JAMA Psychiatry 71: 985-6.

van Os J and Kapur S (2009) Schizophrenia. Lancet 374: 635-45.

van Os J, Kenis G and Rutten BP (2010) The environment and schizophrenia. Nature 468: 203-12.

van Winkel R, Esquivel G, Kenis G et al (2010) REVIEW: Genome-wide findings in schizophrenia and the role of gene-environment interplay. CNS Neurosci Ther 16: e185-92.

Walshe M, Vassos E, Picchioni M et al (2012) The Association between COMT, BDNF, and NRG1 and Premorbid Social Functioning in Patients with Psychosis, Their Relatives, and Controls. Scientifica (Cairo) 2012: 560514.

Weinberger DR (2002) Schizophrenia, the prefrontal cortex, and a mechanism of genetic susceptibility. Eur Psychiatry 17 Suppl 4: 355s-62s.

Williams HJ, Owen MJ and O'Donovan MC (2007) Is COMT a susceptibility gene for schizophrenia? Schizophr Bull 33: 635-41.

Winterer G and Weinberger DR (2004) Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends Neurosci 27: 683-90.