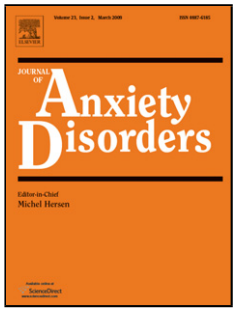

Title: The Interaction Between *Comt* And *Bdnf* Variants Influences Obsessive-Compulsive-Related Dysfunctional Beliefs

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THE INTERACTION BETWEEN *COMT* AND *BDNF* VARIANTS INFLUENCES OBSESSIVE-COMPULSIVE-RELATED DYSFUNCTIONAL BELIEFS

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Abstract

Cognitive models emphasize the importance of dysfunctional beliefs as overimportance/need to control thoughts, perfectionism, intolerance of uncertainty, responsibility, and overestimation of threat in Obsessive-Compulsive Disorder (OCD). Twin studies suggest that these beliefs are significantly heritable, but candidate genes associated with them have not been analyzed. We genotyped the Val158Met in the *COMT* gene and Val66Met variant in the *BDNF* gene in 141 OCD patients and analyzed their single and interactive effects on the Obsessive Beliefs Questionnaire (OBQ-44). Variability in dysfunctional beliefs was not affected by the *COMT* or *BDNF* genotype in isolation, but we detected a significant *COMT* x *BDNF* interaction effect on responsibility/overestimation of threat and overimportance/need to control thoughts scores. Subjects with the *BDNF* Met-present and the *COMT* Met-present genotype showed higher scores on responsibility/overestimation of threat. An interaction between dopaminergic and neurotrophic functional gene variants may influence dysfunctional beliefs hypothesized to contribute to the development of OCD.

Keywords: Obsessive-Compulsive disorder, cognition, dysfunctional beliefs, COMT, BDNF, OBQ-44

1. **Introduction**

Contemporary cognitive models of obsessive-compulsive disorder (OCD) emphasize the relevance of dysfunctional beliefs in the development and maintenance of the disorder (Clark & Purdon, 1995; P. M. Salkovskis, 1985). According to these models, it is not the patient's intrusive thoughts *per se*, that are problematic, instead, anxiety and compulsive behaviors arise from erroneous and maladaptative beliefs about the meaning and consequences of these thoughts (Abramowitz, Nelson, Rygwall, & Khandler, 2007). Six main intercorrelated domains of dysfunctional beliefs have been associated with obsessive-compulsive symptoms: 1) overimportance of thoughts, 2) need to control these thoughts, 3) perfectionism, 4) intolerance of uncertainty, 5) inflated personal responsibility and 6) overestimation of threat (OCCWG, 2005). The first two domains, overimportance of thoughts and the need to control them, involve a number of beliefs, i.e., that the mere presence of unwanted thoughts indicates that these thoughts are highly meaningful and have ethical or moral consequences, that having these thoughts increases the probability that the corresponding behavior or event will occur, and that complete control over such intrusions is both necessary and possible. Perfectionism and intolerance of uncertainty involve the belief that it is necessary and possible to be perfect and certain, and that one is unable to cope with imperfection and ambiguity. Finally, inflated responsibility and overestimation of threat include exaggerated estimates of the probability and costs of negative events, as well as the belief that one has the special power to cause, and the duty to prevent, such events.

Initial cognitive models focused almost exclusively on the role of environmental factors in the development of OC-related beliefs including aversive events during childhood and adolescence, strict moral or religious upbringing or high parental criticism (Rachman, 2004; P. Salkovskis, Shafran, Rachman, & Freeston, 1999). Nevertheless, a recent twin study in non-clinical subjects suggests that these dysfunctional beliefs are significantly heritable, with genetic factors accounting for 32% to 40% of their variance (Taylor & Jang, 2010). To our knowledge, there have been no previous attempts to analyze candidate genes associated with these OC-related dysfunctional beliefs in an OCD population.

Several molecular genetic studies have reported an association between gene variants and certain anxiety-related traits, such as increased anticipatory worry or fear of uncertainty – constructs that are in some way similar to OC-dysfunctional beliefs. The catechol-O-methyl-transferase (*COMT*) and the brain-derived neurotrophic factor (*BDNF*) genes are two of the most broadly investigated genes in relation with these personality traits. In the *COMT* gene, mapped to 22q11.1-q11.2, with a size of about 27Kbp and 345

identified polymorphisms, there is a polymorphism (rs4680) due to a G-to-A transition at codon 158 which results in a valine (val) to methionine (met) substitution. Carriers of the Val158 allele synthesize an enzyme with enhanced thermo stability (Lachman et al., 1996), which displays a 40% higher brain activity than the Met158 allele at normal body temperature. Since the two alleles behave additively, the heterozygotes will display an intermediate activity (Weinshilboum, Otterness, & Szumlanski, 1999). The low-activity Met allele, reported to be related to higher extracellular dopamine levels in prefrontal cortical areas, has been associated with better performance on executive cognition tasks (Dumontheil et al., 2011) while the Val allele has been associated with advantageous processing of aversive stimuli (Mier, Kirsch, & Meyer-Lindenberg, 2010). Discrepant results for the relationship between the Val158Met COMT polymorphism and personality traits have been reported (see (Calati et al., 2011) for a review). Regarding those more closely related to OC-dysfunctional beliefs, whereas the Met genotypes have been associated with both increased anticipatory worry and fear of uncertainty – two subscales of the Harm Avoidance construct in Cloninger's Temperament and Character Inventory (TCI)- in two studies (Enoch, Greenberg, Murphy, & Goldman, 2001; Hashimoto et al., 2007) -; Kim and colleagues, (Kim, Kim, Kim, Lee, & Kim, 2006) described a lower tendency for harm avoidance in Met/met homozygotes. On the other hand, Lang et al. (Lang, 2007) found that the Val/Val genotype was related to increased sensation seeking, mainly because of elevated adventure seeking, disinhibition, and boredom tendencies. Finally, in a recent study of female patients with eating disorders, subjects with the low activity Met allele scored higher on the Eating Disorder Inventory (EDI) perfectionism subscale (Mikolajczyk, Grzywacz, & Samochowiec, 2010).

The *BDNF* gene, located at chromosome position 11p12-13, plays a major role in neuronal survival, activity-dependent neuroplasticity, and learning. A non-synonymous variant in the 5' pro-BDNF sequence, corresponding to a functional Val66Met amino acid change, affects intracellular trafficking and secretion of BDNF, with the Met variant being associated with a deficit in activity-dependent release of BDNF and reduced dendritic arbor complexity(Chen et al., 2006). A recent meta-analysis by Frustaci and colleagues (Frustaci, Pozzi, Gianfagna, Manzoli, & Boccia, 2008) reported on the association between the Met/Met genotype and higher Harm Avoidance compared to BDNF Val carriers, with the largest difference at the expense of anticipatory worry and fear of uncertainty (Itoh, Hashimoto, Kumakiri, Shimizu, & Iyo, 2004; Jiang et al., 2005). Regarding other personality traits, an association between the Met/Met genotype and increased reward dependence and extraversion on the TCI has also been described

in healthy Japanese females (Itoh et al., 2004). Nevertheless, other work has failed to identify significant relationships between BDNF Val66Met variants and TCI scores in healthy populations (Zhang et al., 2002).

The aim of our study was to explore the possible association between dysfunctional beliefs hypothesized to contribute to the development and maintenance of OCD and two functional polymorphisms of *COMT* and *BDNF* genes as well as to investigate possible interactions between these gene variants. Based on previous studies, we hypothesized that the COMT Met158 allele and the BDNF Met66 allele would predispose OCD individuals to higher dysfunctional belief scores.

2. Material and Methods

2.1. Participants

One hundred and forty-one Caucasian Spanish outpatients with OCD (80 males and 61 females) were included in the study. Subjects were recruited from the OCD Clinic at Bellvitge Hospital (Barcelona, Spain), between 2008 and 2010. To be included in the study, patients had to fulfil DSM-IV criteria for OCD (APA, 1994) for a period of at least one year. Diagnoses were made on the basis of structured interviews conducted independently by two trained psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV)(First MB, 1997). Exclusion criteria were age under 18 or over 65 years, psychoactive substance abuse/dependence (either current or in the past six months), psychotic disorders, mental retardation and severe organic or neurological pathology except tic disorder. Comorbidity with other DSM-IV Axis I disorders was not considered an exclusion criterion provided that OCD was the main diagnosis and the primary reason for seeking medical assistance (Table 1). Written informed consent was obtained from each subject after a full description of the study, which was approved by the hospital's ethics committee.

- Insert Table 1 here-

2.2. Genotyping

DNA was extracted from peripheral blood using standard methods. For genotyping, from the dbSNP public database (http://www.ncbi.nlm.nih.gov/SNP/) we selected the non-synonymous mutation Val158Met (rs4680) in the *COMT* gene and the Val66Met functional variant (rs6265) in the *BDNF* gene.

Both SNPs were genotyped at the Madrid Node of the Centro Nacional de Genotipado (http://www.cegen.org) with the KASPar assay system. The Competitive Allele Specific PCR (KASPar) (Kbiosciences, Hoddesdon, Hertfordshire, UK) is a homogeneous fluorescent genotyping system, which uses a technique based on allele specific oligo extension and fluorescence resonance energy transfer (FRET) for signal generation. The chemistry involves two competitive allele specific tailed forward primers and one common reverse primer. It has shown high reproductibility, a concordance rate >99.5% with Taqman and an error rate <0.3%

2.3. Measures

A clinician-administered version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)(Goodman et al., 1989) and the 21-item Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960) was used to assess the severity of obsessive-compulsive symptoms. The clinician-administered version of the Y-BOCS Symptom Checklist (Goodman et al., 1989) was used to ascertain the presence of five previously identified symptom dimensions designated as “Symmetry/ordering”, “Hoarding”, “Contamination/cleaning”, “Aggression/checking”, and “Sexual/religious obsessions”(Mataix-Cols, Rauch, Manzo, Jenike, & Baer, 1999).

The short version of the Obsessive Beliefs Questionnaire, the 44-item OBQ (OBQ-44), was used to assess dysfunctional beliefs linked to OCD symptoms. The OBQ-44 consists of three subscales: perfectionism and intolerance of uncertainty (PC, 16 items), overimportance of thoughts and need to control these thoughts (ICT, 12 items) and responsibility and overestimation of threat (RT, 16 items). Respondents were asked to indicate their general level of agreement with each of the 44 statements on a 7-point scale ranging from 0 (disagree very much) to 7 (agree very much). The OBQ is the best measure available, in terms of reliability, validity and content coverage, for assessing dysfunctional beliefs related to OCD (OCCWG, 2005). In this study we used the validated Spanish version of the OBQ-44 (Ruiz, Gavino, & Godoy, 2008), which retains the psychometric properties of the English version.

2.4. Statistical analysis

The Hardy-Weinberg equilibrium for genotype frequencies was calculated using chi-square tests. A multivariate analysis of covariance (MANCOVA) and a post hoc MANCOVA were used to examine the single and interactive effects of COMT and BDNF genotypes on the three subscales of the OBQ-44 as

well as on Y-BOCS scores. To reduce possible sources of variance, the MANCOVA model included genotype, Y-BOCS scores and sex as main factors and age and HDRS scores as covariates to control for the effects of comorbid depressive symptomatology. The data were analyzed using SPSS18.0 for Windows (SPSS Inc., Chicago, IL, USA). The significance level was established at $p<0.05$ (two-tailed), due to the exploratory nature of our study and the fact that significant correlations between scores on the OBQ-44 subscales have been consistently reported (Taylor, Coles et al., 2010). This gave us sufficient power (0.8) to detect a medium effect size (Cohen's d = 0.47) between the two main genotypes, corresponding to 12.1 points on RT scores, 10.7 points on PC and 7.1 points on ICT scores.

3. Results

The allelic distributions of the *COMT* and *BDNF* polymorphisms were in accordance with the Hardy-Weinberg equilibrium (p= 0.5 for *BDNF*; p= 0.8 for *COMT*).

The COMT polymorphism was available for 132 OCD subjects (93.6% of the sample) and the BDNF polymorphism for 134 subjects (95.0% of the sample). For the COMT polymorphism, the most prevalent genotype was Val/Met (n = 65, 49.2%), followed by Val/Val (n = 36, 27.2%) and Met/Met (n = 31, 23.4%). The COMT genotype distribution in the present sample was similar to previous Spanish reports (Hoenicka et al., 2009). For the BDNF polymorphism, the most prevalent genotype was Val/Val (n = 85, 63.4%), followed by Val/Met (n = 42, 31.3%) and Met/Met (n = 7, 5.2%). The genotype distribution in the present sample was comparable to previous Spanish reports (Aguilera et al., 2009). In genotype analyses, based on the findings in previous functional studies related to BDNF and COMT genotypes, the Val/Val homozygote (Met-absent genotype, for BDNF n = 85, for COMT n = 36) was compared to the Val/Met and Met/Met groups (Met-present genotype, for BDNF n = 49, for COMT n= 96).

The COMT genotype showed a significant effect on Y-BOCS scores (F= 4.2, p= 0.04, partial eta squared 0.03), while no main effects of the BDNF genotype and COMT x BDNF interaction on OCD severity were detected. Comorbid depressive symptoms assessed by the HDRS showed a significant effect on Y-BOCS scores (F= 72.8, p< 0.001, partial eta squared= 0.3) as well as on two subscales of the OBQ-44: responsibility and overestimation of threat (F= 6.9, p=0.01, partial eta squared= 0.05) and perfectionism and intolerance of uncertainty (F= 6.2, p= 0.01, partial eta squared= 0.04).

No main effects of the COMT or the BDNF genotype on dysfunctional beliefs scores were found. However, there were significant multivariate *COMT* x *BDNF* interaction effects on two OBQ-44 scores:

responsibility and overestimation of threat (F= 5.7, p=0.01, partial eta squared= 0.04) and overimportance/need to control thoughts (F= 5.9, p= 0.01, partial eta squared= 0.04) (Table 2). Post-hoc MANCOVA analysis detected that the multivariate effect on OBQ-44 scores originated from the significant effects of *COMT* x *BDNF* interaction on responsibility and overestimation of threat scores, with subjects with the Met-present genotype of BDNF and the Met-present genotype of COMT showing significantly higher scores on this subscale (p= 0.02) (see Table 3 and Table 4 for post-hoc analysis).

-Insert Table 2, 3 and 4 here-

4. Discussion

To our knowledge, this is the first attempt to explore the candidate genes associated with the dysfunctional beliefs hypothesized to contribute to the pathophysiology of OCD. Our results support the notion that allelic variation at the *BDNF* and *COMT* locus is associated with variability in certain OC-related dysfunctional beliefs –responsibility/overestimation of threat and overimportance/need to control thoughts-, and that this effect results from the interaction of at least two genes. Specifically, OCD subjects with the Met-present genotype of BDNF and the Met-present genotype oft COMT, showed increased responsibility and overestimation of threat scores. Interestingly, a recent study by Taylor et al. (Taylor, Coles et al., 2010) suggests that among all dysfunctional beliefs, these two – responsibility and threat overestimation – are particularly important for predicting OC symptoms. Moreover, in Taylor & Jang's twin study (Taylor & Jang, 2010), while all cognitive domains shared similar contributing environmental features, responsibility and threat overestimation appeared to be shaped by specific genetic factors.

In line with our observations, several studies have reported an interaction between neurotrophic and dopaminergic gene variants in both personality traits and cognitive functions. Hünnerkopf and colleagues (Hunnerkopf, Strobel, Gutknecht, Brocke, & Lesch, 2007) observed that healthy individuals with at least one copy of the DAT 9-repeat allele at the variable number of tandem repeat polymorphism in the 3'-untranslated region of the dopamine transporter gene SLC6A3 (DAT VNTR), who were also carriers of the Val66Met BDNF Met allele, exhibited lower neuroticism scores on the Revised NEO-Personality Inventory and lower scores on the Harm Avoidance dimension of Cloninger's TPQ than Val66Met BDNF Met non-carriers. Kang et al. (Kang, Song, Namkoong, & Kim, 2010) described a gene x gene interaction between *COMT* and *BDNF* functional polymorphisms influencing the boredom susceptibility scores of

the Sensation Seeking Scale in a group of healthy Korean females, with COMT Met-present genotype subjects who also had the BDNF Met-absent genotype showing significantly higher boredom susceptibility. The same *BDNF* x *COMT* interaction, modulated by age, was reported to influence executive functioning and working memory in a sample of 318 healthy Caucasians (Nagel et al., 2008). Finally, Han and colleagues (Han et al., 2008) observed that in schizophrenic patients, those with the *BDNF* Met/met genotype who were also COMT Met carriers showed significantly poorer cognitive flexibility than the other genotype groups.

Structural and functional magnetic resonance studies suggest that the Met allele of the *BDNF* Val66Met polymorphism, which mitigates neurotrophic capacity, may have an impact on brain regions implicated in the cognitive control of emotions. Met carriers have been reported to show increased activation in limbic structures, such as the amygdala (Lau et al., 2008; Montag, Reuter, Newport, Elger, & Weber, 2008), the anterior cingulate cortex or the bilateral insula (Mukherjee et al., 2011) in response to emotional cues, as well as decreased subgenual anterior cingulate cortex grey matter volume (Gerritsen et al., 2011). Regarding the *COMT*, several functional brain imaging studies support a role for the Val158 Met functional polymorphism in affective processing and emotional regulation. The Met allele has been associated with greater reactivity to emotionally negative stimuli, as evidenced by increased activation or greater connectivity between prefrontal and associated limbic areas, including the ventro-lateral prefrontal cortex, orbitofrontal cortex, amygdala, hippocampus and parahippocampal gyrus (Drabant et al., 2006; Rasch et al., 2010; Smolka et al., 2005) . It has been hypothesized that carriers of the *COMT* Met 158 allele display impaired flexibility in processing and integrating affectively relevant information. This dopamine-mediated implicit processing bias may lead to increased sensitivity and exaggerated arousal responses in the face of negative environmental cues, which may be conceptually similar to what cognitive theories label as “overestimation of threat”. Nevertheless, since we did not detect a direct association between the *COMT* Val158Met polymorphism and overestimation of threat scores, at least in our sample, this dopaminergic influence appears to be modulated by neurotrophic factors.

Although the *COMT* Val158Met and the *BDNF* Val66Met polymorphisms are among the most widely studied genetic variants in relation with OCD, the published results are conflicting (see (Katerberg et al., 2010; Katerberg et al., 2009) for a review) . This inconsistency has been partly attributed to the heterogeneity within the clinical diagnostic category of OCD. The use of endophenotypic strategies has been postulated as a useful tool to disentangle the complex genetic basis of the disorder (Rajender et al.,

2011). An endophenotype is described as a heritable quantitative trait associated with increased genetic risk for a disorder, present both in patients and in their clinically unaffected relatives (Gottesman & Shields, 1973). Rector et al. (Rector, Cassin, Richter, & Burroughs, 2009) recently reported that OBQ scores tend to be higher in unaffected first-degree relatives of OCD patients than in relatives of non-OCD controls. If our results on the association between certain candidate genes and OC-related dysfunctional beliefs are confirmed, OC-related dysfunctional beliefs might be postulated as a useful endophenotype for OCD. In this regard, Taylor and Jang already suggest that, besides other direct genetic and environmental factors, OC symptoms are indirectly influenced by genetic and environmental factors which exert their influence through their effects on dysfunctional beliefs (Taylor & Jang, 2010), thereby supporting their possible role as an endophenotype.

Our study has several limitations that should be addressed in further work. First, due to the limited sample size, it constitutes an exploratory analysis that needs confirmation in independent larger sample. Our sample size limits the power of the study to detect small effects as those normally described in genetic-association studies for psychiatric disorders and may at least partially explain our negative results regarding certain cognitive dimensions. On the other hand, only two well-known polymorphisms in the *COMT* and *BDNF* genes were analyzed. Additional common gene variants thought to be involved in the pathophysiology of personality traits, such as the triallelic serotonin transporter-linked polymorphic region (5-HTTLPR) or the dopamine receptor D4 VNTR polymorphism, should be considered in further research. Cluster analytic studies have noted that obsessive beliefs are endorsed by only approximately 50% of OCD patients (see (Bradbury, Cassin, & Rector, 2011) for a review), suggesting that cognitive assessment of OCD should be broadened beyond the OBQ to encompass other cognitive domains, such as perceived memory deficits or metacognition, which may be relevant to OCD. OC-related beliefs are present in the general population (Taylor, Afifi, Stein, Asmundson, & Jang, 2010), so further research is needed to define whether the association between *COMT* x *BDNF* genetic variants and responsibility and threat overestimation can be replicated in healthy subjects as well as in other forms of psychopathology (i.e., anxiety, mood or eating disorders), in which cognitive distortions may also play a role. A gene x environment interaction was not explored in our study, and constitutes a challenging option. Children with a biologically based selective attention bias to threat may become particularly distressed by childhood trauma, learning experiences, or parental admonitions to act in a highly responsible or perfectionist manner, and this interaction may contribute to the development of beliefs concerning an

inflated sense of personal responsibility or perfectionism. Finally, future neuroimaging studies should seek out how dysfunctional beliefs are related to neurocircuitry dysregulations, in an attempt to delineate the neuroanatomical basis of these cognitive distortions.

In summary, our data suggest that an interaction between dopaminergic and neurotrophic functional gene variants influences responsibility/overestimation of threat and overimportance/need to control thoughts, two dysfunctional belief domains that are hypothesized to contribute to the development and maintenance of OCD. Integrating biological and cognitive models of OCD – currently two very distant theories – represents a unique challenge for future research, which will ultimately help us to improve our knowledge of the etiology of obsessions and compulsions as well as to develop better comprehensive therapeutic approaches for OCD patients.

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Table 1. Clinical and sociodemographic characteristics of 141 OCD patients included in the study.

Characteristics	OCD patients (n=141)
Age, years, mean ± SD (range)	35.5 ± 9.3 (18-62)
Male/female	80/61
Years of education, years, mean ± SD	11.7 ± 3.2
Age at onset of OCD, years, mean ± SD	20.2 ± 8.8
Y-BOCS score, mean ± SD	
Global	26.9 ± 6.5
Obsessions	13.5 ± 3.3
Compulsions	13.4 ± 3.9
HDRS score, mean ± SD	15.0 ± 6.1
OBQ-PC, mean ± SD (range)	67.7 ± 22.6 (16-112)
OBQ-ICT, mean ± SD (range)	42.1 ± 15.1 (12-84)
OBQ-RT, mean ± SD (range)	62.2 ± 25.7 (16-112)
Comorbid diagnosis, *n* (%)	
Any comorbid diagnosis	63, 44.6%
Affective disorders	31, 21.9%
Major depressive disorder	19
Dysthymia	7
Depressive disorder NEC	3
Bipolar disorder	2
Anxiety disorders other than OCD	24, 17.0%
Tics disorder or GT	20, 14.1%
Eating disorders	9, 6.3%
Symptom dimensions (present, *n*, %)	
Aggressive/checcking	102, 72.3%
Contamination/cleaning	61, 43.2%
Sexual/religious	38, 26.9%
Hoarding	20, 14.1%
Symmetry/ordering	52, 36.8%
Psychiatric Family History, n, %	
Any psychiatric diagnosis	73, 51.7%
OCD	28, 19.8%
Anxiety disorders other than OCD	19, 13.4%
Affective Disorders	32, 22.6%
Tic disorders or GT	6, 4.2%

Note. GT, Gilles de la Tourette syndrome; HDRS, Hamilton Depression Rating Scale; NEC, not elsewhere classified; OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; OBQ-PC: Obsessive Beliefs Questionnaire- Perfectionism and intolerance of uncertainty; OBQ-ICT: Obsessive Beliefs Questionnaire- overimportance of thoughts and need to control these thoughts; OBQ-RT: Obsessive Beliefs Questionnaire-responsibility and overestimation of threat.

Table 2. Gene-gene interaction analysis for the OBQ-44 and Y-BOCS scores by MANCOVA (Wilks' Lambda).

		F	Sig.	Partial Eta Squared
Age	YBOCS	0,1	0,7	0,001
	OBQ44 resp/threat	0,2	0,6	0,002
	OBQ44 perf/uncertain	1,8	0,1	0,015
	OBQ44 imp/control	5,0	0,2	0,040
HDRS	YBOCS	72,8	**< 0,001**	0,372
	OBQ44 resp/harm	6,9	**0,01**	0,053
	OBQ44 perf/uncertain	6,2	**0,01**	0,049
	OBQ44 imp/control	0,8	0,3	0,007
COMT	YBOCS	4,2	**0,04**	0,034
	OBQ44 resp/threat	0,2	0,5	0,002
	OBQ44 perf/uncertain	0,2	0,6	0,002
	OBQ44 imp/control	0,08	0,7	0,001
BDNF	YBOCS	0,2	0,6	0,002
	OBQ44 resp/threat	0,01	0,8	0,000
	OBQ44 perf/uncertain	0,1	0,7	0,001
	OBQ44 imp/contro	0,03	0,8	0,000
COMT & BDNF	YBOCS	3,0	0,08	0,024
	OBQ44 resp/threat	5,7	**0,01**	0,045
	OBQ44 perf/uncertain	3,5	0,06	0,028
	OBQ44 imp/control	5,9	**0,01**	0,046

Note. HDRS: Hamilton Depression Rating Scale; YBOCS: Yale-Brown Obsessive-Compulsive scale; COMT: catechol-O-methyl-transferase; BDNF: brain-derived neurotrophic factor gene; resp/threat: responsibility and overestimation of threat; perf/uncertain: Perfectionism and intolerance of uncertainty; imp/control: Overimportance of thoughts and need to control thoughts

Table 3. Scores on each OBQ-44 subscales for the interaction effect of the genotypes of the COMT and BDNF in 141 OCD subjetcs.

COMT	BDNF	n	OBQ-44 Perfectionism and intolerance of uncertainty (mean, SD)	OBQ-44 Overimportance/ need to control thoughts (mean, SD)	OBQ-44 Responsibility and overestimation of threat (mean, SD)
V/V	V/V	22	75.4 (5.0)	46.4 (3.4)	69.2 (5.6)
Met carrier	V/V	62	64.0 (2.9)	40.4 (1.9)	58.5 (3.2)
V/V	Met carrier	14	66.7 (5.9)	37.2 (4.0)	56.3 (6.7)
Met carrier	Met carrier	33	72.7 (3.8)	45.3 (2.6)	71.3 (4.4)

Note. COMT: catechol-O-methyl-transferase; BDNF: brain-derived neurotrophic factor gene; VV: Val/Val; SD: Standard deviation.
Information on interactive effects was missing in 10 OCD patients.

Table 4. Post hoc MANCOVA of the interactive effects of COMT and BDNF genotypes on the three subscales of the OBQ-44.

OBQ44	Genotype		Significance	95% Confidence Interval for Difference	
Responsibility and overestimation of threat	COMTVal/Val & BDNF Val/Val	COMT=Met carr & BDNF=Val/Val	0,110	-2,460	24,006
		COMT=Val/Val & BDNF=Met carr	0,145	-4,547	30,487
		COMT=Met carr & BDNF=Met carr	0,778	-16,408	12,313
	COMT Met carr & BDNF Val/Val	COMT=Val/Val & BDNF=Val/Val	0,110	-24,006	2,460
		COMT=Val/Val & BDNF=Met carr	0,770	-12,661	17,055
		COMT=Met carr & BDNF=Met carr	**0,021**	-23,681	-1,961
	COMT Val/Val & BDNF Met carr	COMT=Val/Val & BDNF=Val/Val	0,145	-30,487	4,547
		COMT=Met carr & BDNF=Val/Val	0,770	-17,055	12,661
		COMT=Met carr & BDNF=Met carr	0,064	-30,914	,879
	COMT Met carr & BDNF Met carr	COMT=Val/Val & BDNF=Val/Val	0,778	-12,313	16,408
		COMT=Met carr & BDNF=Val/Val	**0,021**	1,961	23,681
		COMT=Val/Val & BDNF=Met carr	0,064	-,879	30,914

OBQ44	Genotype		Significance	95% Confidence Interval for Difference	
Perfectionism and intolerance of uncertainty	COMTVal/Val & BDNF Val/Val	COMT=Met carr & BDNF=Val/Val	0,058	-,388	23,039
		COMT=Val/Val & BDNF=Met carr	0,269	-6,816	24,195
		COMT=Met carr & BDNF=Met carr	0,676	-10,020	15,402
	COMT Met carr & BDNF Val/Val	COMT=Val/Val & BDNF=Val/Val	0,058	-23,039	,388
		COMT=Val/Val & BDNF=Met carr	0,692	-15,788	10,516
		COMT=Met carr & BDNF=Met carr	0,078	-18,248	,978
	COMT Val/Val & BDNF Met carr	COMT=Val/Val & BDNF=Val/Val	0,269	-24,195	6,816
		COMT=Met carr & BDNF=Val/Val	0,692	-10,516	15,788
		COMT=Met carr & BDNF=Met carr	0,400	-20,069	8,071
	COMT Met carr & BDNF Met carr	COMT=Val/Val & BDNF=Val/Val	0,676	-15,402	10,020
		COMT=Met carr & BDNF=Val/Val	0,078	-,978	18,248
		COMT=Val/Val & BDNF=Met carr	0,400	-8,071	20,069

OBQ44	Genotype		Significance	95% Confidence Interval for Difference[a]	
Overimportance of thoughts and need to control thoughts	COMTVal/Val & BDNF Val/Val	COMT=Met carr & BDNF=Val/Val	0,134	-1,896	13,977
		COMT=Val/Val & BDNF=Met carr	0,086	-1,317	19,694
		COMT=Met carr & BDNF=Met carr	0,805	-7,538	9,687
	COMT Met carr & BDNF Val/Val	COMT=Val/Val & BDNF=Val/Val	0,134	-13,977	1,896
		COMT=Val/Val & BDNF=Met carr	0,486	-5,762	12,059
		COMT=Met carr & BDNF=Met carr	0,134	-11,479	1,547
	COMT Val/Val & BDNF Met carr	COMT=Val/Val & BDNF=Val/Val	0,086	-19,694	1,317
		COMT=Met carr & BDNF=Val/Val	0,486	-12,059	5,762
		COMT=Met carr & BDNF=Met carr	0,095	-17,647	1,419
	COMT Met carr & BDNF Met carr	COMT=Val/Val & BDNF=Val/Val	0,805	-9,687	7,538
		COMT=Met carr & BDNF=Val/Val	0,134	-1,547	11,479
		COMT=Val/Val & BDNF=Met carr	0,095	-1,419	17,647

Highlights

This is the first attempt to explore the candidate genes associated with dysfunctional beliefs hypothesized to contribute to the development and maintenance of OCD.

Allelic variation at the *BDNF* and *COMT* locus was associated with variability in OC-related dysfunctional beliefs, and this effect results from the interaction of the two genes.

OCD subjects with the Met-present genotype of BDNF, who were also Val/Met or Met/Met COMT genotype, showed significantly higher scores on responsibility and overestimation of threat subscales.

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