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The impact of the Val158Met COMT polymorphism on context processing in patients on the schizophrenia spectrum and their relatives

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ABSTRACT

Introduction: The level of dopamine in the prefrontal cortex (PFC) appears to play a fundamental role in cognitive alterations in schizophrenia. The Val158Met polymorphism of the catechol-O-methyltransferase (COMT) enzyme impacts dopamine availability in the prefrontal cortex and can thus influence cognitive functioning. Among the different cognitive deficits found in schizophrenia patients, context processing deficits have been noted as a specific characteristic of schizophrenia, for which the cerebral substrate appears to be located in the dorsolateral PFC. In this study, we examine the impact of the Val158Met COMT polymorphism on context processing in a sample of patients on the schizophrenia spectrum, their relatives, and healthy control subjects evaluated using the Dot Probe Expectancy Task (DPX).
Methods: Forty patients on the schizophrenia spectrum, 26 relatives, and 63 healthy control subjects were genotyped and performed the DPX test. Results: Both patients and their relatives demonstrated deficits in context processing influenced by the Val158Met COMT polymorphism. Compared with the other subjects, the Val/Val subjects showed poorer performance on context processing tasks.
Conclusions: Deficits in context processing in schizophrenic patients and their families are influenced by the Val158Met COMT functional polymorphism, likely as a consequence of reduced dopamine availability in the PFC.

1. Introduction

Cognitive deficits are a primary characteristic of schizophrenia that significantly impact patient functioning (Bowie et al., 2006; Green et al., 2000). Among other hypotheses, it has been postulated that the primary cognitive alterations in schizophrenia (working memory and executive functions) are due to dysfunction in the frontal lobe, specifically hypodopaminergia in the prefrontal cortex (PFC). Dopaminergic tone in the PFC is essential for cognitive functioning. The catechol-O-methyltransferase (COMT) enzyme is vital for the regulation of dopamine levels in the PFC (review: Tunbridge et al., 2006). A functional polymorphism of the COMT gene (rs4680) significantly impacts the dopamine levels in the PFC. The Val allele is associated with greater enzymatic activity and, therefore, with greater dopamine degradation in the synapses of the PFC (Chen et al., 2004; Lachman et al., 1996). This genetic polymorphism, although weakly linked to the risk of a schizophrenia diagnosis (Glatt et al., 2003), is a good candidate for understanding the relationships between dopamine levels in the PFC and cognitive functioning.

Many studies have investigated the link between cognition and the Val158Met COMT polymorphism in both healthy controls and clinical populations with varied results (review: Dickinson and Elvevåg, 2009). One of the first links between the COMT enzyme and executive functions (Egan et al., 2001) has been replicated in other studies (Joober et al., 2002; Mattay et al., 2003; Rosa et al., 2004), yet other groups have been unable to reproduce the results (Diaz-Asper et al., 2008; Ho et al., 2005; Tsai et al., 2003). Other cognitive phenotypes have also been studied including working memory, attentional control, and episodic memories, with both positive (Blasi et al., 2005; Goldberg et al., 2003) and negative results (Bilder et al., 2002; Stefanis et al., 2004).

Many of the studies that explore the association between cognition and the gene that encodes the COMT enzyme use neuropsychological examinations, which are sensitive to differences among clinical groups but do not have the ability to accurately determine differences between genotypes (MacDonald et al., 2007). One strategy that could prove useful in detecting cognitive differences between genotypes is to employ cognitive paradigms that evaluate specific cognitive functions or dysfunction instead of generalized deficits, which could aid in the study of their biological correlates.

Numerous tests have demonstrated the ability to identify specific deficits in cognitive functions dependent on the PFC. Among these

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Table 1
Demographic and clinical characteristics.

	Patients	Relatives	Controls	ANOVA/ $\chi 2$
N	40	26	63	
Age	37.2 (10.18)	49.27 (14.54)	36.36 (11.85)	$F = 11.64$; gl = 2/126; $p < 0.001$
Sex	20F/20M	16F/10M	36F/27M	$\chi 2 = 1.41$; p = NS
Level of Education				
None	0%	4%	0%	
Primary School	9.4%	18%	1.7%	
Secondary Education	37.5%	18%	8.7%	
Baccalaureate	19%	23%	43%	
University	34.1%		46.6%	
Years of Education	12.06 (3.27)	11.45 (4.5)	13.54 (2.45)	$F = 4.33$; gl = 2/126; $p = 0.01$
COMT Genotype[1]	21VV/17VM/2MM	8VV/12VM/6MM	14VV/34VM/15MM	
BPRS	9.5 (6.9)			
PANSS-P	12 (3.3)			
PANSS-N	19.2 (10.9)			
PANSS-PG	34.2 (13.36)			
CGI	3.21 (0.86)			
GAF	64.64 (10.78)			
Length of Illness	13.86 (8.57)			
Diagnosis (DSM-IV):				
Schizophrenia	27			
Schizoaffective Disorder	6			
Brief Psychotic Disorder	4			
Schizotypal Personality Disorder	2			
Delusional Disorder	1			
Atypical Antipsychotics	95%			

[1] VV = Val/Val; VM = Val/Met; MM = Met/Met.

tests is the Dot Pattern Expectancy Task (DPX), which evaluates a specific prefrontal cognitive function, context processing. The cognitive construct of context processing resembles the goal maintenance construct and involves cognitive control functions. The deficits in context processing appear to be specific to schizophrenia, detectable in the early stages of the illness, and not significantly affected by antipsychotic treatments (Barch et al., 2003). Various studies have shown context processing deficits to be a stable cognitive feature of schizophrenia (Cohen et al., 1999; Delawalla et al., 2008; Javitt et al., 2000; Jones et al., 2010; MacDonald and Carter, 2003; MacDonald et al., 2003; Stratta et al., 1998). Context processing also appears to be linked to the functioning of the dorsolateral PFC (MacDonald and Carter, 2003) and is thus likely linked to the dopaminergic system (Cohen and Servan-Schreiber, 1992). A link has also been described between context processing and the Val158Met COMT polymorphism in healthy control subjects (Leung et al., 2007; MacDonald et al., 2007). Individuals with the Val/Val genotype (low dopamine availability in the PFC) show selective deficits in goal maintenance in the DPX test.

In this study, we investigate the effect of the Val158/108Met COMT polymorphism on context processing in patients on the schizophrenia spectrum, their first-degree relatives, and healthy control subjects using a cognitive neuroscience paradigm (the DPX). According to our hypothesis, subjects with a Val/Val genotype should perform worse on the context processing test due to the reduced dopamine availability in the PFC.

2. Methods

2.1. Subjects

A total of 129 subjects were recruited for this study. Each subject was genotyped for the Val158/108Met COMT polymorphism and evaluated with the DPX. The clinical sample was recruited from psychiatry examination rooms of a general hospital (University Clinic of Navarra). Patient interviews and diagnoses were performed by research psychiatrists following the Structured Clinical Interview for the DSM-IV (SCID). In the clinical sample group, 40 subjects were found to be within the schizophrenia spectrum (schizophrenia, 27 patients; schizoaffective disorder, six patients; delusional disorder, one patient; brief psychotic disorder, four patients; and schizotypal personality disorder, two patients). A total of 26 subjects were first-degree relatives of the patients who were free of psychotic disorders, and 63 subjects were healthy controls. Both the relative and control groups were evaluated using the non-pathological version of the SCID. All patients were undergoing antipsychotic treatments at the time of the evaluation. Participation in the study was voluntary, and none of the subjects were paid for their participation. All subjects were Caucasian and native Spanish speakers. After receiving a description of the study, the subjects signed informed consent forms. The study was approved by the Ethical Committee of Clinical Investigation and followed the ethical principles of the international standards required for performing human research.

The clinical and demographic data for the sample are shown in Table 1. Clinical symptoms were evaluated using the following scales: the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndromes Scale (PANSS), Clinical Global Impression (CGI), and the Global Assessment of Functioning Scale (GAF). All patients presented with chronic forms of schizophrenia (average duration 13.86 ± 8.57 years) and were treated with antipsychotic medication (95% took antipsychotic drugs).

2.2. Genotyping

DNA was extracted from blood and saliva samples using a Qiamp DNA Blood Mini Kit from Qiagen. Genotyping of the single nucleotide polymorphism (SNP) Val158Met (rs4680) was performed via allelic discrimination using real-time polymerase chain reaction (RT-PCR) with a 7300 HT thermal cycler and TaqMan probes (TaqMan® SNP Genotyping Assays, Applied Biosystems). Ten percent of the samples were randomly selected to repeat the genotyping process for quality

control. The distribution of the genotypes in the three groups followed the Hardy-Weinberg equilibrium model.

2.3. Computer-based Cognitive Test

The cognitive function of context processing was evaluated with the DPX (MacDonald et al., 2005), which consisted of a modified version of the AX continuous performance task (AX-CPT) expectancy test designed by Cohen et al. (Servan-Schreiber et al., 1996). The test contains pairs of letters, and the subject is tasked with indicating the letter X when it is preceded by the letter A (an AX pair). Any other letter pair sequence should be ignored. The test is used to evaluate context processing; the context of the first letter is needed to determine whether the second letter fulfills the objective. Errors involving BX pairs reflect a difficulty in representing and maintaining the context; in these errors, X is selected as the objective, even though it is not preceded by A. Errors involving AY pairs reflect proper context representation (of the letter A) and are normally found in healthy subjects, signifying a suitable capacity for context processing. Errors involving all pairs of letters (AX, AY, BX, and BY) reflect the presence of generalized deficits.

The DPX uses the same principles as the AX-CPT expectancy test but with patterns of dots from the Braille alphabet rather than Latin letters, resulting in an increase in difficulty in each of the conditions and, therefore, a reduced test time. This test has been described in full in other studies (Jones et al., 2010; MacDonald et al., 2005). The duration of the DPX was 20 minutes. It was presented in four blocks, each of which consisted of 40 pairs of letters. The different pairs were presented in different percentages (70% AX, 12.5% AY, 12.5% BX, and 5% BY). The high proportion of AX presentation creates a tendency to select any letter that follows A as the objective. This manipulation of the pair percentages produces a greater number of AY errors in healthy subjects and of BX errors in subjects that have difficulty in controlling the tendency to select X when it is not preceded by the letter A.

2.4. Statistical analysis

The statistical analysis was performed with SPSS 15.0. Demographic differences between the groups were analyzed with analysis of variance (ANOVA) and χ^2 tests. To study context processing, the analysis was focused on the AY and BX pairs, which specifically measure this element of cognitive function. Error analysis was performed with analysis of covariance (ANCOVA) using genotype (Val/Val, Val/Met, and Met/Met) as the between-subject factor, letter pairs (AY and BX) as the within-subject factor, and age and years of schooling as covariables. Data from all groups were combined to perform an analysis by genotype; separate analyses were performed within each group (patients, relatives, and controls). Post-hoc tests were performed, and Bonferroni corrections were used to correct for multiple comparisons.

3. Results

The results of the DPX are shown in Fig. 1. A general ANCOVA of errors showed a significant interaction between genotype, letter pairs, and group ($F = 3.07, P < 0.001$). The proportion of errors by genotype is shown in Tables 2 and 3. First, the effect of genotype on the entire sample was examined. The ANCOVA showed a significant interaction between genotype and pairs of letters (AY, BX) ($F = 7.57, P < 0.001$),

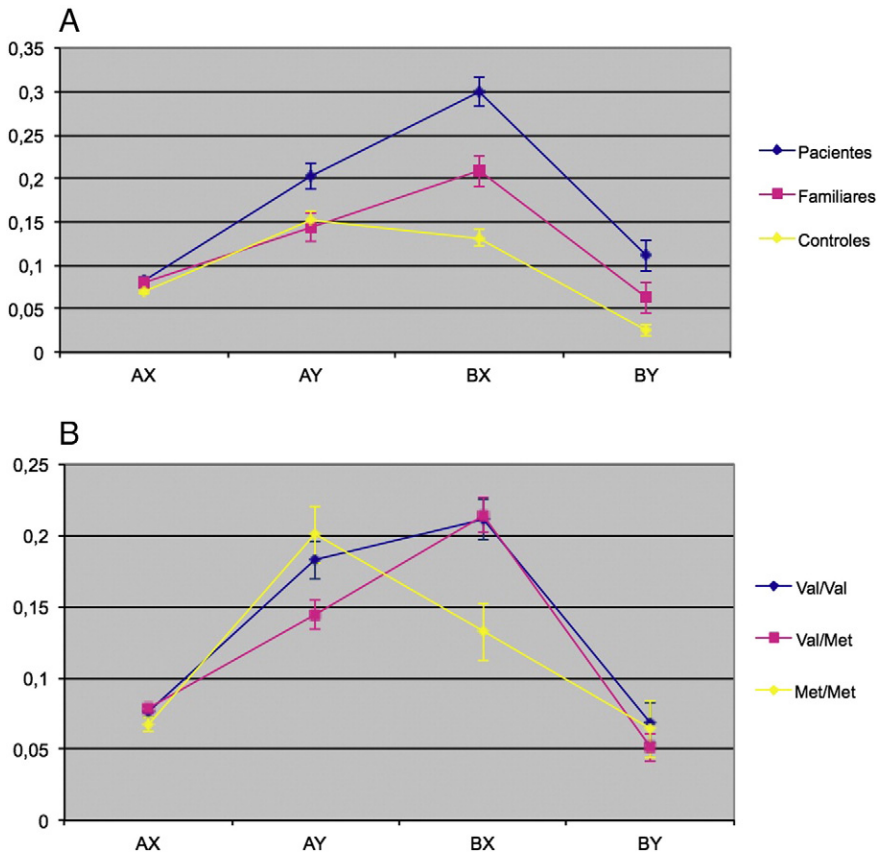

Fig. 1. DPX performance. A, Performance by group. B, Performance by Val158Met COMT genotype.

Table 2
Errors in context processing.

	VV			VM			MM		
Type of error	M (SD)			M (SD)			M (SD)		
AX	0.08 (0.004)			0.08 (0.003)			0.07 (0.005)		
AY	0.18 (0.013)			0.14 (0.01)			0.2 (0.02)		
BX	0.21 (0.014)			0.21 (0.012)			0.13 (0.02)		
BY	0.07 (0.014)			0.05 (0.01)			0.06 (0.02)		
Total	0.11 (0.004)[1]			0.1 (0.003)[1]			0.09 (0.005)[1]		
	Patients[2]			Relatives[2]			Controls[2]		
	VV	VM	MM	VV	VM	MM	VV	VM	MM
Type of error	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
AX	0.08 (0.006)	0.09 (0.007)	0.02 (0.01)	0.08 (0.01)	0.06 (0.01)	0.11 (0.01)	0.07 (0.01)	0.07 (0.004)	0.06 (0.006)
AY	0.23 (0.02)	0.18 (0.02)	0.08 (0.04)	0.13 (0.03)	0.1 (0.02)	0.24 (0.04)	0.14 (0.02)	0.14 (0.01)	0.2 (0.03)
BX	0.31 (0.02)	0.31 (0.02)	0.05 (0.04)	0.13 (0.03)	0.24 (0.03)	0.25 (0.04)	0.1 (0.02)	0.16 (0.01)	0.08 (0.02)
BY	0.13 (0.03)	0.1 (0.03)	0 (0)	0.02 (0.02)	0.02 (0.02)	0.2 (0.06)	0.01 (0.01)	0.04 (0.01)	0.01 (0.01)

M = Mean.
SD = Standard deviation.
VV = Val/Val genotype; VM = Val/Met genotype; MM = Met/Met genotype.
[1] ANOVA ($F = 2.36$; $p = 0.095$).
[2] ANCOVA: significant interaction between genotype, group, and pairs of letters ($F = 3.07$; $p < 0.001$).

driven primarily by a greater number of BX errors than AY errors in Val/Val and Val/Met subjects, while Met/Met subjects committed more AY than BX errors. We did not find a primary effect of genotype ($F = 0.92, P = 0.4$) or a primary effect of pairs of letters with respect to the rate of errors ($F = 0.08, P = 0.7$). The three genotype groups performed slower in response to the AY pairs than the BX pairs, with the largest difference in reaction time found in the Met/Met group, which demonstrated poor performance with AY pairs (thus reflecting good context maintenance).

Then, error analyses were performed for each group separately. In the patient group, the ANCOVA showed a primary effect of genotype ($F = 5.11$; $P < 0.05$); patients with the Val/Val genotype committed more errors than either the Val/Met or Met/Met patients (Val/Val > Val/Met > Met/Met). No significant interaction between genotype and pairs of letters was observed (F = 2.78; p = 0.06), although patients with the Val/Val and Val/Met genotypes committed more BX than AY errors. In the relatives group, there was also an effect of genotype ($F = 6.24$; $P = 0.002$) in which the Val/Val relatives committed more errors than the Val/Met and Met/Met relatives. The Val/Met and Met/Met relatives committed more BX errors than AY errors, but this interaction was not significant between genotype and letter pairs ($F = 1.6$; $P = 0.2$). In addition, we did not observe a primary effect of pairs of letters ($F = 1.6$; $P = 0.2$), although relatives committed more BX than AY errors. In the control group, the ANCOVA showed a significant interaction between genotype and pairs of letters ($F = 5.4$; $P = 0.004$). In this group, Val/Val subjects and Met/Met subjects committed more errors for AY than for BX pairs. A primary effect of letter pairs was also observed ($F = 8.61$; $P = 0.003$); healthy control subjects committed more AY than BX errors.

Table 3
Results of the DPX: BX-AY difference.

	M (SD)		ES
VV vs. VM	0.07 (0.31)	0.07 (0.23)	0.01
VM vs. MM	0.07 (0.23)	−0.07 (0.22)	0.61
VV vs. MM	0.07 (0.31)	−0.07 (0.22)	0.49
VV Patients vs. MM Patients[a]	0.16 (0.38)	0.11 (0.27)	0.16
VV Relatives vs. MM Relatives[a]	−0.001 (0.1)	0.88 (0.08)	10.58
VV Controls vs. MM Controls[a]	−0.04 (0.21)	−0.01 (0.21)	0.14

M = Mean.
SD = Standard deviation.
ES = Effect size.
VV = Val/Val subjects; VM = Val/Met subjects; MM = Met/Met subjects.
[a] MM = both VM and MM groups.

4. Discussion

In this study, we investigated the impact of the Val158Met COMT genotype on context processing in patients on the schizophrenia spectrum and in their relatives using the DPX. Our results demonstrated a relationship between the Val158Met COMT polymorphism and context processing.

Links between cognitive activity and the COMT genotype have been inconsistent in the literature. In samples of healthy controls, some studies have found positive associations (Blasi et al., 2005; Bruder et al., 2005; Papaleo et al., 2008), while others have found no association (Stefanis et al., 2004). In patients with schizophrenia, both positive (Egan et al., 2001; Goldberg et al., 2003; Wirgenes et al., 2010) and negative (Bilder et al., 2002; Liao et al., 2009; Mata et al., 2008) associations between the COMT genotype and cognition have been published. Patients with schizophrenia seem to show a similar pattern to healthy patients; those with a homozygous Met genotype appear to show better cognitive performance than those with a homozygous Val genotype. A recent meta-analysis on the effects of the Val158Met COMT polymorphism on cognition (Barnett et al., 2008) concluded that there is weak evidence of an association between this polymorphism and cognitive function. There are multiple explanations for why this lack of association has been claimed. First and most importantly, researchers regularly employ neuropsychological batteries to study cognitive function; these batteries study neurophysiological dominions, which tend to be compound constructions and, therefore, difficult to associate with any one specific genetic variant. Additionally, different versions of the batteries are used in different studies, making it difficult to interpret results across studies.

The development of cognitive neuroscience paradigms that viably evaluate the function of a specific neural system is a promising approach to evaluate the association between genes and cognition (Green et al., 2008). Based on this principle, we used the DPX in our study. Our results support the finding of a link between the Val158Met COMT polymorphism and context processing in healthy controls and patients with schizophrenia.

According to the theory of context processing, evaluated using variants of the AX-CPT expectancy test, subjects with a deficit in

context processing should show an alteration in performance with the BX letter pair, while those with intact context processing would commit more errors involving the AY pair (MacDonald, 2008). The pattern of errors in this task is more indicative of deficits in context processing than the total number of errors. As described in the results and shown in Fig. 1, both patients and their relatives performed better with the AY pairs than with the BX pairs, implying poor context processing, while the healthy controls showed better performance with the BX pairs than with the AY pairs, reflecting better context processing. The subjects that developed a tendency to respond (i.e., recognize a response as the objective) when they recognized the letter A committed more errors with the AY pairs than subjects with deficits in context processing who were incapable of using the context provided by the first letter of the pair. The most common pattern shown in studies on schizophrenia using variants of the AX-CPT expectancy test is an interaction of groups and type of letter pair, caused by a disproportionately worse performance with BX pairs than with AY pairs by patients (Barch et al., 2001, 2003; Javitt et al., 2000).

There is evidence to suggest that deficits in context processing are endophenotypic markers of the risks of schizophrenia because healthy relatives of patients with schizophrenia also showed deficits in context processing (Delawalla et al., 2008; MacDonald et al., 2003). Studies with the DPX have also shown that healthy relatives of patients with schizophrenia exhibit deficits in context processing (MacDonald et al., 2005). Our study showed that relatives, as well as patients, exhibit a primary effect of genotype; Val/Val and Val/Met subjects demonstrated a poorer performance in the BX condition than in the AY condition, reflecting a deficit in context processing and supporting the idea that deficits in context processing are, consequently, a valid endophenotype of schizophrenia.

This study has a number of limitations. The groups consisted of subjects with different age ranges; the relatives were older than the patients and the controls because the majority of first-degree relatives were the parents of the patients. Therefore, an analysis was performed including age as a covariable, and the results were similar. Nevertheless, we propose that age is an important factor that should be taken into account. Medication could be a source of potential bias as well. At the time that the sample of clinical patients was obtained, all were undergoing antipsychotic treatment. Although it is possible that the medication could contribute to poor cognitive performance, numerous studies have shown that cognitive deficits in patients with schizophrenia are present even though the antipsychotic treatment controls for positive symptoms. A study by Barch et al. (2003), comparing medicated and unmedicated patients with respect to their first schizophrenic episode showed that deficits in context processing are present even before treatment. The size of the sample was another limitation of our study. Individual genes could have relatively small effects on the cognitive phenotype, and thus larger samples should be studied to produce more viable conclusions and to reproduce our results. The Val158Met COMT polymorphism is also associated with impulsivity, which could explain the larger number of errors in patients with the Val/Val genotype.

The results of this study suggest that the use of cognitive neuroscience measures, linked specifically to the neural circuitry and with molecular characteristics related to the products of specific genes, may be a promising approach to establish informative links between the genotype and cognitive phenotype in the field of psychiatric genetics.

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