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Impact of COMT genotype on cognition in schizophrenia spectrum patients and their relatives

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ABSTRACT

Cognitive impairment in schizophrenia is a core feature and seems to be related mainly to dopaminergic dysfunction in the prefrontal cortex (PFC). The functional polymorphism Val158Met of the COMT (catechol-*O*-methyltransferase) gene could mediate the relationship between cognition and dopamine activity in PFC. The present study tested the influence of this polymorphism on the cognitive performance of schizophrenia spectrum patients and their relatives, using some subtests of the neuropsychological battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery, and evaluated the impact of this polymorphism on a specific prefrontal cognitive function using a cognitive neuroscience paradigm. A Group of 74 schizophrenia spectrum disorder patients, 48 relatives and 67 controls performed some subtests of the MATRICS Consensus Cognitive Battery. In addition, 40 schizophrenia spectrum disorder patients, 26 relatives and 63 controls performed the Dot Pattern Expectancy Task (DPX) to study context processing. For the neuropsychological battery, no differences in any of the cognitive domains were found according to genotype. The DPX task was sensitive to genotype effects in patients as well as in relatives. Context processing deficits in schizophrenia patients and their relatives may be mediated by COMT genotype. The influence of the COMT genotype on cognition is more relevant in specific cognitive tasks related to prefrontal function. These results should be replicated in larger samples.

1. Introduction

Cognitive deficits in schizophrenia are a core feature of the illness, and have an enormous impact on everyday functioning (Green et al., 2000; Bowie et al., 2006). The main cognitive deficits in schizophrenia (working memory and executive functioning) have been hypothesized to be related to frontal lobe dysfunction, and in particular to hypodopaminergia in the prefrontal cortex (PFC). Dopaminergic tone in the PFC is crucial for cognitive performance. The catabolic enzyme catechol-*O*-methyltransferase (COMT is important for regulating dopamine levels in PFC (for a review: Tunbridge et al., 2006). The functional polymorphism of the COMT gene (rs4680) has a substantial impact on dopamine levels in the PFC. The Val allele is associated with greater enzymatic activity, and therefore with faster dopamine degradation in prefrontal synapses (Lachman et al., 1996; Chen et al., 2004). This genetic polymorphism, though weakly associated with the risk of schizophrenia (Glatt et al., 2003), is a good candidate for understanding the relationships between dopamine levels in the PFC and cognitive performance.

An important number of studies have investigated the association between cognition and the Val158Met COMT polymorphism in healthy research participants and in clinical populations, yielding heterogeneous results (for a review: Dickinson and Elvevåg, 2009). One of the first reported associations between COMT and executive functioning (Egan et al., 2001) has been replicated repeatedly (Joober et al., 2002; Mattay et al., 2003; Rosa et al., 2004), although some other groups have not replicated it (Tsai et al., 2003; Ho et al., 2005; Diaz-Asper et al., 2008). Other cognitive phenotypes have also been studied – working memory, attentional control and episodic memory – with both positive (Goldberg et al., 2003; Blasi et al., 2005) and negative results (Bilder et al., 2002; Stefanis et al., 2004). The majority of the association studies between cognition and COMT use neuropsychological tests that, although having high discriminating power to detect group differences, may not have such power to discriminate among genotypes. It might be more useful to apply cognitive paradigms that assess specific rather than generalized deficits, and which therefore may be more linked to the underlying neurobiology.

There are several tasks that have been shown to identify a specific deficit in prefrontal cognition. Among them, the Dot Pattern

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Expectancy Task (DPX) is capable of evaluating a specific prefrontal cognitive function, context processing, while discriminating from a more general cognitive dysfunction. Context processing may be considered an element of the central executive in Baddeley's working memory model (Baddeley, 1986). It overlaps with the construct of goal maintenance and implies cognitive control. Context processing deficits have been shown to be specific to schizophrenia, a trait feature, and therefore detectable at the earliest stages of the illness, and are not strongly affected by atypical antipsychotic treatment (Barch et al., 2003). As a stable cognitive feature of schizophrenia, context processing deficits have been replicated in several studies (Stratta et al., 1998; Cohen et al., 1999; Javitt et al., 2000; MacDonald and Carter, 2003; MacDonald et al., 2003; Delawalla et al., 2008; Jones et al., 2010). Interestingly, context processing has also been linked to the function of the dorsolateral prefrontal cortex (DLPFC) (MacDonald and Carter, 2003) and thus may be related to the dopamine system (Cohen and Servan-Schreiber, 1992). Moreover, context processing has been shown to be associated to the Val158Met COMT polymorphism in healthy control samples (Leung et al., 2007; MacDonald et al., 2007). Individuals with the Val/Val genotype (less dopamine availability at the PFC) have been found to have selective goal maintenance deficits on the DPX task.

In this study, we examined the impact of the COMT Val158/108Met polymorphism on cognition in schizophrenia patients, their first-degree relatives and healthy controls, using several subtests of a standard neuropsychological battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery, as well as a more cognitive neuroscience-driven paradigm (context processing assessed through the DPX task).

2. Methods

2.1. Subjects

The 189 subjects were genotyped and underwent neuropsychological testing. The clinical sample was recruited from the outpatient clinic of a general hospital. Patients were interviewed by expert psychiatrists, and were diagnosed based on the Structured Clinical Interview for DSM-IV (SCID). From the total sample, 74 subjects were schizophrenia spectrum disorder patients: Schizophrenia ($n=44$), Schizoaffective Disorder ($n=16$), Delusional Disorder ($n=4$), Brief Psychotic Disorder ($n=5$) and Schizotypal Personality Disorder ($n=5$); 48 were non-psychotic first-degree relatives of the patients; and 67 were healthy controls from the community. A subset of the sample that underwent neuropsychological testing also completed the DPX task. This sample comprised 40 schizophrenia spectrum patients, 26 first-degree relatives and 63 healthy controls. All patients were receiving antipsychotic treatment at the moment of the assessments.

Patients were recruited from the outpatient clinics at the University Hospital of Navarre and controls were recruited using local advertisements. Relatives and controls did not have any mental disorder. They were evaluated using the Non-Patient version of the SCID. Participants were not reimbursed; their participation in the study was voluntary. All subjects were Spanish Caucasians and used Spanish (their native language) in the assessments.

Written informed consent was obtained after a complete description of the study to the subjects. This study was approved by the Ethical Committee of Clinical Research and followed the principles of the internationally recognized standards for the ethical conduct of human research.

Clinical and demographic information of the sample is shown in Table 1. Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), the Global Clinical Impression Scale (GCI) and the Global Assessment of Functioning (GAF) scale. The patients were clinically stable, had a chronic course of the illness (mean in years: 17.81 ± 11.11) and were under antipsychotic medication (atypical antipsychotics in 89% of the sample, typical antipsychotics in the remaining 11%).

2.2. Genotyping

DNA was extracted from blood and saliva samples using the Qiamp DNA Blood Mini Kit, Qiagen. Genotyping of SNP Val158Met (rs4680) was performed by allelic discrimination in a Real Time polymerase chain reaction (RT-PCR) with the thermal cycler 7300 HT using TaqMan probes (TaqMan® SNP Genotyping Assays, Applied Biosystems). As a quality control, 10% of the samples were randomly selected to repeat the genotyping process. All the samples replicated the genotype that was initially assigned. The distribution of genotypes was in accordance with Hardy-Weinberg equilibrium in the three group samples.

2.3. Neuropsychological evaluation

Neuropsychological assessment was performed using seven of the nine subtests of the MATRICS battery with the addition of the matrix reasoning subtest from the WAIS-III battery. The assessment covered the following cognitive domains: speed of processing (assessed by: Category fluency, Digit symbol and Trail Making Test A), non-verbal working memory (assessed by the Spatial Span from the Wechsler Memory Scale III), verbal working memory (assessed by the

Table 1
Demographic and clinical characteristics.

	Patients	Relatives	Controls	ANOVA/χ^2
Neuropsychological evaluation (MATRICS)				
N	74	48	67	
Age	41.42 (13.4)	51.73 (12.61)	35.24 (12.11)	$F=23.43$; $df=2/186$; $p<0.001$
Gender	40 F/34 M	28 F/20 M	39 F/28 M	$\chi^2=0.32$; $p=$NS
COMT genotype*	26 vv/36 vm/12 mm	17 vv/20 vm/11 mm	17 vv/35 vm/15 mm	
BPRS	14.23 (5.13)			
PANSS-P	11 (4.88)			
PANSS-N	15.16 (6.17)			
PANSS-PG	27.45 (10.72)			
GCI	3.21 (0.86)			
GAF	64.64 (10.78)			
Illness duration	17.81 (11.11)			
Diagnoses (DSM-IV):				
Schizophrenia	44			
Schizoaffective disorder	16			
Brief psychotic disorder	5			
Schizotypal personality disorder	5			
Delusional disorder	4			
Atypical antipsychotics	89%			
Context processing evaluation (DPX task)				
N	40	26	63	
Age	37.2	49.27	36.13	$F=11.64$; $df=2/126$; $p<0.001$
Gender	20 F/20 M	16 F/10 M	36 F/27 M	$\chi^2=1.41$; $p=$NS
COMT genotype	21 vv/17 vm/2 mm	8 vv/12 vm/6 mm	14 vv/34 vm/15 mm	

* vv=val/val; vm=val/met; mm=met/met.