Progress in Neuro-Psychopharmacology & Biological Psychiatry 71 (2016) 176–182

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

The influence of the COMT genotype in the underlying functional brain activity of context processing in schizophrenia and in relatives

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ARTICLE INFO

Article history:
Received 12 June 2016
Received in revised form 8 July 2016
Accepted 11 July 2016
Available online 13 July 2016

Keywords:
Schizophrenia
DPX
Context-processing
fMRI
Relatives
COMT

ABSTRACT

Context processing deficits have been shown to be present in chronic and first episode schizophrenia patients and in their relatives. This cognitive process is linked to frontal functioning and is highly dependent on dopamine levels in the prefrontal cortex (PFC). The catechol-O-methyltransferase (COMT) enzyme plays a prominent role in regulating dopamine levels in PFC. Genotypic variations in the functional polymorphism Val^{158}Met COMT appear to have an impact in dopamine signaling in the PFC of healthy subjects and schizophrenia patients. We aimed to explore the effect of the Val^{158}Met COMT polymorphism on brain activation during the performance of a context processing task in healthy subjects, schizophrenia spectrum patients and their healthy relatives. Methods: 56 participants performed the Dot Probe Expectancy task (DPX) during the fMRI session. Subjects were genotyped and only the Val and Met homozygotes participated in the study. Results: Schizophrenia spectrum patients and their relatives showed worse performance on context processing measures than healthy control subjects. The Val allele was associated with more context processing errors in healthy controls and in relatives **compared to patients**. There was a greater recruitment of frontal areas (supplementary motor area/cingulate gyrus) during context processing in patients relative to healthy controls. Met homozygotes subjects activated more frontal areas than **Val** homozygotes subjects. Conclusions: The Val^{158}Met COMT polymorphism influences context processing and on its underlying brain activation, showing less recruitment of frontal areas in the subjects with the genotype associated to lower dopamine availability in PFC.

1. Introduction

Cognitive impairment in schizophrenia is a critical feature of the illness, has a negative impact on functioning (Bowie et al., 2008; Green, 1996) and is not very much improved by existing antipsychotic treatments. A variety of cognitive deficits are present in schizophrenia (selective attention, speed of processing, executive functioning, working memory, episodic memory, language and learning) (Lesh et al., 2011; MacDonald, 2008), although there is an ongoing debate whether these deficits reflect a general cognitive impairment or are related to a specific cognitive domain dysfunction (Sheffield et al., 2014).

Context processing deficits are present in chronic and first episode schizophrenia patients (Barch et al., 2001; Barch and Braver, 2005; Braver et al., 1999; Braver and Cohen, 1999; Cohen and Servan-Schreiber, 1993), in their healthy siblings (MacDonald et al., 2003) and are an early predictor of risk for psychosis (Niendam et al., 2014). Context processing impairments in schizophrenia could contribute to patients' deficits in working memory, attention and executive functioning (Jones et al., 2010; MacDonald, 2008). Context processing refers to the processes involved in the representation and active maintenance of goals or rules based on internal or external cues to produce appropriate behavioral responses (Barch and Smith, 2008; Servan-Schreiber et al., 1996).

Context processing has been studied through the expectancy AX-continuous performance task (AX-CPT) and several imaging studies have shown activation in dorsolateral prefrontal cortex (DLPFC), anterior cingulate and inferior parietal cortex (Barch et al., 2001; Holmes et al., 2005; MacDonald and Carter, 2003; Paxton et al., 2008; Perlstein et al., 2001). The CNTRICS initiative (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) has proposed the Expectancy Dot Pattern Task (DPX), a further modification of the AX-CPT, to assess goal maintenance or context processing (Barch et al., 2009a).

Cognitive processes linked to frontal functioning, are highly dependent on dopamine levels in the prefrontal cortex (PFC) (Seamans and Yang, 2004). The extracellular levels of dopamine in the PFC are

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http://dx.doi.org/10.1016/j.pnpbp.2016.07.005
0278-5846/

particularly dependent on the catechol O-methyltransferase (COMT) enzyme due to the relative absence of DA transporters (Scatton et al., 1985; Tunbridge et al., 2004) in this brain area.

Natural variations (functional polymorphisms) in the COMT gene determine the activity of the main enzyme that catabolizes cortical dopamine and in turn it affects dopamine signaling in the PFC in **healthy subjects** and in schizophrenic patients. Val homozygotes of the Val^{158}-Met polymorphism (rs4680) have relatively higher COMT activity than Met homozygotes, and therefore have lower PFC dopamine levels (Chen et al., 2004; Lachman et al., 1996). There is a large body of literature on COMT's effect on brain function, particularly with respect to working memory and executive functions (Bertolino et al., 2004; Caldu et al., 2007; Chang et al., 2007; de Frias et al., 2010; Egan et al., 2001; Mattay et al., 2003; Meyer-Lindenberg et al., 2005). The main repeated finding is greater activation of the DLPFC in Val homozygotes compared to Met homozygotes for the same level of performance, which has been interpreted as "inefficient" PFC function (Egan et al., 2001; Mier et al., 2010).

The aim of this study was to explore the effect of COMT **Val^{158}Met** polymorphism on brain activation during the performance of a context processing task, the DPX task, in healthy subjects, schizophrenia spectrum patients and their healthy relatives. We predicted that Val homozygotes will be less efficient in the activation of brain areas related to context processing than Met homozygotes, requiring the recruitment of additional brain regions when performing the DPX task. With regard to behavioral performance, we predict that the Met homozygote subjects will show better performance on the DPX task than Va homozygotes subjects in all the diagnostic groups.

2. Methods

2.1. Subjects

Patients were recruited from the outpatient clinics at the University Hospital of University of Navarra. We contacted with first-degree unaffected relatives of the patients and asked for their voluntary collaboration in the study. Controls were recruited using local advertisements. Relatives and controls did not have any mental disorder, as assessed using the non-patient version of the SCID. Participants were not reimbursed; their participation in the study was voluntary. All subjects were **Caucasians** and used **Spanish** as their native language in the assessments.

The study was approved by the Ethical Committee of Clinical Research and was in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained after complete description of the study to the subjects.

Clinical and demographic information of the sample is represented in Table 1. Fifty six subjects underwent cognitive testing and fMRI scanning. Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndromes Scale (PANSS). Patients were clinically stable, had a chronic course of the illness (mean duration in years: 16.12 ± 11.48) and were under antipsychotic medication (88% of the sample were taking atypical antipsychotics while 18% were taking typical antipsychotics).

2.2. Genotyping

DNA was extracted from blood and saliva samples using Qiamp DNA Blood Mini Kit, Qiagen. Genotyping of SNP **Val^{158}Met** (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). 10% of the samples were randomly selected to repeat the genotyping process as a quality control. All the samples replicated the genotype that was initially assigned. Only Val and Met homozygotes were selected as we aimed at comparing the brain activation of the high (Val **homozygotes**) and low (Met **homozygotes**) activity genotypes.

Table 1
Demographic and clinical characteristics.

	Patients	Relatives	Controls	ANOVA/Chi square
N	15	16	20	
Age (years)	39.33 ± 12.96	57.06 ± 10.27	32.7 ± 11.21	$F = 20.66$; df = 2; $p < 0.001$
Gender (female/male)	3F/12M	7F/9M	12F/8M	$\chi^2 = 5.6$; df = 2; $p = 0.06$
COMT genotype	9VV/6MM	9VV/7MM	10VV/10MM	$\chi^2 = 0.36$; df = 2; $p = 0.83$
BPRS	11 ± 7.96			
PANSS-P	11 ± 4.14			
PANSS-N	15 ± 6.55			
PANSS-PG	24 ± 8.25			
Illness duration (years)	16.63 ± 11.12			
Antipsychotic treatment (atypical/typical/both)	13/3/1			

Abbreviations: VV = val/val; MM = met/met; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale.

2.3. Task

Participants performed the Dot Probe Expectancy task (DPX) during the fMRI session. The DPX (MacDonald et al., 2005a, 2005b) is based on the same principle **as** the expectancy AX-CPT but instead of letters, the DPX uses dots representations (Fig. 1). In the AX-CPT, subjects are presented with a series of cues and probes and have to identify the target sequence, when an X probe is immediately preceded by an A cue (AX trials). Any other sequence of cues and probes is considered a non-target (AY, BX and BY trials). Target sequence trials are the most frequent and create a prepotent tendency to make a target response when the target probe occurs. In the DPX, participants are presented with dot representations and they are instructed as in the expectancy AX-CPT. For simplicity, throughout the manuscript, we will refer to the trial types with their "letter" description with the understanding that those letters are actually represented by dot patterns in the DPX. Errors in BX trials reflect the inability to represent and maintain context because the X-probe is considered as a target when it actually is not preceded by an A. Errors in AY trials may reflect a strong representation of

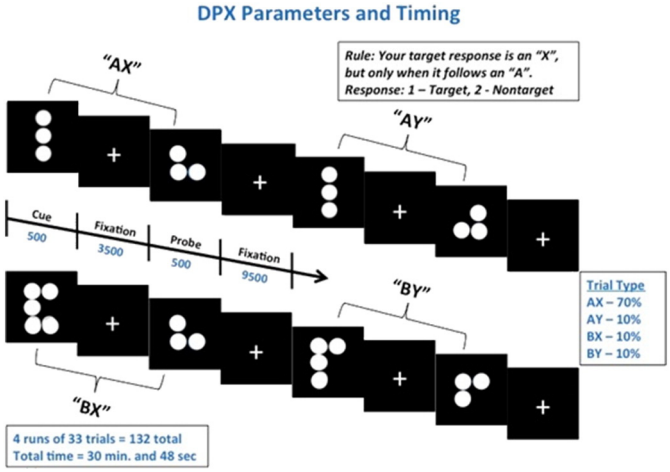

Fig. 1. Task parameters for the DPX.