Journal of Psychiatric Research 47 (2013) 989–994

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Gene–environment interaction on cognition: A twin study of childhood maltreatment and *COMT* variability

Ximena Goldberg [a,b], Mar Fatjó-Vilas [a,b], Silvia Alemany [a,b], Igor Nenadic [c], Cristobal Gastó [b,d], Lourdes Fañanás [a,b,*]

[a] Departament de Biologia Animal, Facultat de Biologia, Universitat de Barcelona, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain
[b] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[c] Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany
[d] Departament de Psiquiatria, Institut de Neurociències, Hospital Clínic de Barcelona, and Instituto de Investigaciones Biomédiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

ARTICLE INFO

Article history:
Received 13 August 2012
Received in revised form
2 February 2013
Accepted 6 February 2013

Keywords:
Genotypic variability
Childhood maltreatment
Gene–environment interaction
Twin-based design
Individual differences

ABSTRACT

The functional variant Val[158]Met in the coding sequence of *COMT* gene is involved in the modulation of dopamine availability in the prefrontal cortex in both clinical and general population samples. It has been suggested that the interplay between this genotype and early environmental factors could be used to predict the observed variation in cognitive flexibility. However, other genetic variants and environmental factors may confound the association and produce the inconsistent results commonly found in the literature. In the present study we aimed at testing putative interaction mechanisms between childhood maltreatment and *COMT* genotypic variability that might explain a proportion of the observed variability of cognitive flexibility in the population. Our design was based on a sample of adult monozygotic twins, which allowed us to test these effects free from potential genetic and shared-environmental confounding factors. Results showed that unique environmental effects of childhood maltreatment significantly impacted cognitive performance among Met/Met subjects. Interestingly, the direction of the association indicated that exposure to early stressful experiences was associated with enhanced cognitive flexibility in this genotype group. These results suggest that *COMT* may operate as a plasticity gene that provides differential cognitive capacity to respond to environmental stressors.

1. Introduction

Alterations in the dopamine system within the fronto-striato-thalamic circuits have been suggested to contribute to the cognitive impairments observed in schizophrenia and normal aging (Cropley et al., 2006), while dopamine levels in the prefrontal cortex seem to be crucial for the functioning of prefrontal-related cognitive flexibility in the general population (Amstadter et al., 2012; Goldman-Rakic et al., 2000). These findings have promoted the search for genes with a role in the metabolism of dopamine that may help explain both its impairment in brain disorders and the normal variation of higher-order cognitive functions. One of the most widely studied candidate genes involved in this neurotransmission system is the gene coding for catechol-O-methyltransferase (*COMT*), which is responsible for the extraneuronal degradation of synaptically released dopamine (Greenwood and Parasuraman, 2003).

The involvement of *COMT* gene in human cognition is related to a functional polymorphism Val[158]Met (Lachman et al., 1996). By increasing or decreasing the enzymatic activity of the protein, this functional variant affects dopaminergic pathways related to prefrontal cognitive functioning (Meyer-Lindenberg et al., 2006; Slifstein et al., 2008). Val[158] homozygotes present an increased activity of the enzyme that leads to cortical hypodopaminergia (thus increasing the risk for deficits in cognitive flexibility) while the opposite effects have been identified in Met[158] homozygotes (Caldu et al., 2007; Chen et al., 2004; de Frias et al., 2005). However, recent meta-analyzes posit that the effect of *COMT* genotype on prefrontal cognitive flexibility may be weaker than initially believed (Barnett et al., 2008; Dickinson and Elvevag, 2009).

Interestingly, when the focus of the studies changes from cognitive flexibility to sensitivity to stress, reports show a different pattern of results: Val carriers are usually found to show a decreased affective reactivity to stress than Met carriers (Collip et al., 2010). The latter commonly present impaired emotional

* Corresponding author. Departament de Biologia Animal, Facultat de Biologia, Universitat de Barcelona, Av. Diagonal 643, Edifici Margalef, 2°, 08028 Barcelona, Spain. Tel.: +34 93 402 14 16x208; fax: +34 93 403 57 40.
E-mail address: lfananas@ub.edu (L. Fañanás).

0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.02.002

processing as evidenced by a greater prefrontal activation in response to negative emotional stimuli (Smolka et al., 2005).

These findings have encouraged a model of interaction between *COMT* genotypic variants and environmental stressors that may be involved in mechanisms of emotion processing associated with the phenotypic variability of stress-sensitivity (Caspi and Moffitt, 2006; Henquet et al., 2006; Stefanis et al., 2007). In this regard, in the present study we aimed at testing the hypothesis that similar mechanisms concerning exposure to environmental stress might be implicated in the observed variation of cognitive flexibility in the population.

Two key limitations have been raised to gene–environment interaction studies. Firstly, the action of other genetic components may confound the results if genetic variation is not controlled for in the study (Barnett et al., 2011). Secondly, the specific effects of the measured environmental stressor may be confounded with those of other environmental variables not included in the model (Duncan and Keller, 2011). A monozygotic twin-pairs design provides an exceptional opportunity to overcome these limitations (Arseneault et al., 2008). Examining the value of cognitive performance with respect to the subject's and co-twin's stressful experiences allows the effects of these events to be decomposed into those attributable to within-pair differences and those attributable to between-pair differences (MacGregor et al., 2000). In genetically identical individuals, the effects of within-pair differences are free from confounding factors that are common to both twins (i.e. genetic and shared-environmental components of the variance), and are therefore a measure of the unique environmental effects of the stressful event in a genetically-informative design (Carlin et al., 2005). Any genetic association with the environmental variance of monozygotic twin pairs indicates a differential capacity of that genotype to respond to environmental factors (Birley et al., 1997).

Childhood maltreatment and neglect, and general deprivation of normal parental care during infancy, are environmental stressors especially noteworthy given their impact on normal adult development of higher-order cognition (Cicchetti and Toth, 2005; Gilbert et al., 2009). The objective of the present study was to examine the putative interaction effects between *COMT* Val^{158}Met polymorphism and the unique environmental effect of childhood adversity on cognitive flexibility, over and above other genetic and shared-environmental components. To achieve this objective we used a monozygotic-twin based design, which allowed us to control for the effects of the multiple factors that might be involved in the association.

2. Materials and methods

2.1. Sample

The initial sample consisted of 234 adult Caucasian subjects recruited from the University of Barcelona Twin Registry (Alemany et al., 2012). Twins between 17 and 65 years old with no personal history of neurological disorders or substance dependency were included. A further exclusion criterion was a personal history of psychiatric medical treatment, which excluded 16 subjects. The final sample comprised 218 healthy adult subjects with a mean age of 33.27 years, SD = 12.5 and mean years of education of 17.4, SD = 3. Gender distribution showed that 62.8% of the twins were women.

Zygosity was assessed by genotyping 16 highly polymorphic microsatellite loci (SSRs; PowerPlex® 16 System Promega Corporation). Identity on all the markers can be used to assign monozygosity with greater than 99% accuracy (Guilherme et al., 2009). Zygosity analysis of all 109 twin pairs showed that 85 were monozygotic (170 subjects) and 24 were dizygotic (48 subjects). Written informed consent was obtained after a detailed description of the study objectives and design, which were approved by the local ethics committee. All procedures were carried out in accordance with the Declaration of Helsinki.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood cells using the Real Extraction DNA Kit (Durviz S.L.U., Valencia, Spain) or from buccal mucosa by means of a cotton swab and a BuccalAmp DNA Extraction Kit (Epicentre® Biotechnologies, Madison, WI, USA). Genotyping of the *COMT* Val^{158}Met (rs4680) single nucleotide polymorphism (SNP) was determined using Applied Biosystems Taqman 5′-exonuclease assays. The final volume PCR reaction was 5 μL, using 10 ng of genomic DNA, 2.5 μL of TaqMan Master Mix, and 0.125 μL of 40x genotyping assay. The cycling parameters were as follows: 95 °C for 10 min, followed by 40 cycles of denaturation at 92 °C for 15 s and annealing/extension at 60 °C for 1 min. Polymerase chain reaction plates were read on an ABI PRISM 7900HT instrument with SDS v2.1 software (Applied Biosystems).

2.3. Childhood adversity

We used an adapted version of the Adverse Childhood Experiences Questionnaire (Felitti et al., 1998), which included parental loss and bullying. Nineteen items addressed three types of experiences of abuse (emotional, physical, and sexual), two of neglect (physical and emotional), and exposure to household dysfunction (substance abuse, mental illness, violent treatment of mother, criminal behavior, and parental separation or divorce). The test–retest reliability for every question in the questionnaire and for the total score are reported in the good to excellent range (Dube et al., 2004), and no evidence of response rate bias has been found (Edwards et al., 2001).

The count of adverse childhood experiences was used to obtain a total Childhood Adversity Score (CAS) for each subject that was designed to assess their cumulative impact on childhood development (Anda et al., 2006).

2.4. Cognitive assessment

The subjects were assessed using the computerized version of the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993). The primary outcome measure was the widely used perseverative errors score, a valid index of cognitive flexibility in behavioral programming that includes abstract reasoning and the ability to develop and maintain an appropriate problem-solving strategy to achieve a goal (Demakis, 2003). This is one of the most sensitive measures for assessing frontal cortical functions as impaired performance has been associated with prefrontal cortex activation alterations due to cortical dysregulation of dopaminergic neurotransmission (Meyer-Lindenberg et al., 2002).

WCST perseverative error scores were standardized to a z metric with a mean of zero and a standard deviation of 1, which allows for the interpretation of β coefficients as the standard deviation unit change in performance. Lower scores indicate better performance (i.e. lower number of perseverative errors).

2.5. Statistical analyzes

All analyzes were conducted using Stata.9 software (StataCorp, 2005). In all cases we used a generalized least squares approach (generalized estimating equations), which explicitly allows for the correlational structure present in any given twin-pair sample (Hanley et al., 2003). This method of estimation takes into account a common