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Gene-environment interaction as a predictor of early adjustment in first episode psychosis

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ABSTRACT

Background: This study aims to explore the gene-environment interaction hypothesis applied to pre-symptomatic neurodevelopmental phenotypes of first episode psychosis (FEP), that is, genetic factors might increase vulnerability to the effects of environmental adverse conditions occurring at later stages of development.
Methods: We constructed a schematic 'two-hit' model, with Val/Val homozygosity for the catechol-*O*-methyltransferase (*COMT*) Val158Met polymorphism as the 'first hit' and history of obstetric complications and parental socioeconomic status as 'second hits'. Early adjustment, measured using the Premorbid Adjustment Scale, was considered the main outcome. The study population comprised 221 adolescents and adults with FEP and 191 sex- and age-matched controls.
Results: The interaction between the Val/Val *COMT* genotype and a positive history of obstetric complications plus low parental socioeconomic status was significantly associated with poorer early adjustment. These results were observed both in FEP individuals and in controls, and remained significant after controlling for age, sex, and diagnosis.
Conclusions: Individuals carrying Val/Val seem to be more sensitive to the synergistic effect of environmental factors acting early in neurodevelopment, which leads to vulnerability phenotypes such as impaired early adjustment.

1. Introduction

The 'two hit' hypothesis of psychosis proposes that individual genetic factors affecting the earliest stages of neurodevelopment ('first hit') might increase vulnerability to the pathological effects of environmental adverse conditions ('second hits') occurring at later stages of development (Giovanoli et al., 2013; Niwa et al., 2013). This increased vulnerability would in turn impact the neurodevelopmental mechanisms involved in the pathogenesis of psychosis, thus increasing the risk of developing a psychotic disorder (Arango et al., 2014). Of course, the development of psychosis is likely to be more complex than the binary 'two hit' model (Davis et al., 2016). It appears influenced by manifold process involving genetic risk interfacing with multiple environmental hits occurring at key periods of neurodevelopmental activity (Marin, 2016).

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The 'two hit' (or rather, 'multi-hit') effect might be expressed before the emergence of psychotic symptoms in the form of neurodevelopmental phenotypes, such as impaired adjustment early in life. Poor adjustment in childhood and adolescence may be a marker of vulnerability to psychosis (Arango et al., 2014) or a manifestation of the underlying processes of the neurodevelopmental disturbances related to psychosis (Cuesta et al., 2015).

Within this framework, gene variants involved in the pathophysiology of psychosis might act as 'first hits' (Schizophrenia-Working-Group-of-the-Psychiatric-Genomics-Consortium, 2014), while environmental factors considered to increase risk for psychosis, such as history of obstetric complications (OCs) (Moreno et al., 2009) and low parental socio-economic status (SES) (Agerbo et al., 2015), might act as 'second hits'. Although the role of the catechol-*O*-methyltransferase (*COMT*) gene psychosis is controversial (Costas et al., 2011; Farrell et al., 2015), polymorphisms within the COMT gene have been reported to interact with psychosocial stress in the development of psychosis (Caspi et al., 2005). The COMT gene, which encodes *COMT*, the enzyme responsible for degradation of extracellular dopamine in the brain, contains a functional polymorphism (Val158Met). The Val variant is associated with increased COMT activity, which results in reduced dopamine neurotransmission in the prefrontal cortex (Meyer-Lindenberg et al., 2006) and greater predisposition to the stress-related hyperactivity of the mesolimbic dopaminergic system (Ira et al., 2014). These processes may leave Val carriers of the Val158Met polymorphism more sensitive to the effects of environmental factors (Caspi et al., 2005).

Both genetic and early environmental factors have been independently related to outcome in patients with psychosis (Collip et al., 2013; van Dam et al., 2015). However, to our knowledge, no previous studies have analyzed the effect of their potential interaction on early (and premorbid) adjustment. Here, we explore the effect of the interaction between genetic risk factors (*COMT* Val158Met polymorphism) and early environmental risk factors (history of OC and parental SES) on social and academic adjustment during childhood and early adolescence in subjects with first episode psychosis (FEP) and healthy controls. We hypothesized that participants with a higher number of 'hits' would be more impaired than participants with no or only one hit (Feigenson et al., 2014).

2. Methods

2.1. Participants

All the participants were from the "Phenotype–genotype and environmental interaction. Application of a predictive model in first psychotic episodes" (PEPs) study. PEPs is a multicenter, naturalistic, longitudinal, 2-year follow-up study designed to evaluate clinical, neuropsychological, neuroimaging, biochemical and genetic variables in adolescents and adults with FEP in Spain. Patients were age- and sex-matched with healthy controls. Recruitment took place between April 2009 and April 2011. The complete methodology of the PEPs study is described in detail elsewhere (Bernardo et al., 2013).

The patients included in the PEPs study met the following inclusion criteria: age between 7 and 35 years, presence of psychotic symptoms of <12 months' duration, fluency in Spanish and provision of written informed consent by participants and/or their parents or legal guardians. The exclusion criteria were: mental retardation according to DSM-IV-TR criteria (including both an intelligence quotient below 70 and impaired functioning), history of head trauma with loss of consciousness and somatic conditions with mental repercussions. Healthy controls also had to be fluent in Spanish and provide their written informed consent. The exclusion criteria for controls were the same as for patients, with the added criterion of current or past psychotic disorder or major depression. The study was approved by the institutional review boards of all participating clinical centers.

The current report is based on genetic, demographic, and premorbid data gathered at baseline. Initially, 335 FEP patients and 253 controls were included in the PEPs study. For the purposes of the present study, only participants with complete COMT genotype information, history of OC, parental SES and premorbid adjustment data were included. Further, participants aged 15 years or less were excluded from this specific study, so as to ensure that the premorbid functioning assessed corresponded to a period prior to the onset of the full-blown first psychotic episode. Therefore, the final sample for this report consisted of 412 individuals: 221 patients with FEP and 191 healthy controls.

2.2. Measures

2.2.1. Demographic and clinical assessment

Demographic data were collected for all participants. Diagnoses were determined according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria with the Structured Clinical Interview for DSM I and II (SCID-I and II) (First et al., 1997a; First et al., 1997b) for adults, and the Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version (K-SADS-PL) (Kaufman et al., 1997; Soutullo, 1999) for participants aged under 18 years. The diagnostic interviews were administered both at baseline and at 2-years follow-up.

For diagnostic categorization, and in order to avoid the problem of diagnostic instability (Fraguas et al., 2008), we used the diagnosis established at the most recent clinical assessment available for each patient.

Patients were grouped into 3 diagnostic categories: 1) schizophrenia spectrum disorders (SSD), including schizophrenia, schizophreniform and schizoaffective disorders; 2) broad affective spectrum psychoses (AfP), which included bipolar disorders I and II and depressive episodes with psychotic symptoms; and 3) other psychoses (OPs), which included brief psychotic disorders, psychoses not otherwise specified, and toxic psychoses.

2.2.2. COMT Val158Met genotyping

Blood samples were collected from participants in EDTA tubes (K2EDTA BD Vacutainer EDTA tubes; Becton Dickinson, Franklin Lakes, New Jersey) at the enrolment. DNA was extracted using the MagNA Pure LC DNA isolation Kit III and an LC MagNA Pure system (Roche Diagnostics GmbH, Mannheim, Germany). The DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware), and 2.5 μg of genomic DNA was sent for genotyping using the GoldenGate® assay with the Veracode genotyping system (Illumina, San Diego, USA) at the Madrid Node of the Spanish National Genotyping Centre (CeGen).

Hardy-Weinberg equilibrium was verified separately for patients ($\chi^2 = 0.158$; df = 2; p = 0.691) and controls ($\chi^2 = 0.160$; df = 2; p = 0.689).

Participants (both patients and controls) were then classified according to the three COMT Val158Met allelic variants as Val/Val, Val/Met and Met/Met.

2.2.3. Assessment of history of OC

History of OC was recorded at baseline using the Lewis-Murray Scale of Obstetric Data (Lewis et al., 1989), which retrospectively rates information on both prenatal and perinatal OC. It has been reported that mothers provide reports as accurate as those obtained from medical records (Rice et al., 2007). History of OCs was classified dichotomously as positive (any OC) or negative (no history of OC).

2.2.4. Parental SES assessment

Parental SES was assessed at baseline using the Hollingshead-Redlich Index of Social Position (Hollingshead and Redlich, 1958). This is a commonly used system that estimates parental SES based upon parental occupation and educational levels (years of education and

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