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Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis

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ABSTRACT

Schizophrenia and other psychoses are complex disorders with high rates of cognitive impairment and a considerable degree of genetic and environmental influence on its etiology. Whether cognitive impairment is related to dimensional scores of familial liability is still matter of debate. We conducted a cross-sectional study including 169 patients with psychotic disorders and 26 healthy controls. Attention, memory and executive functions were assessed, and familial loading scores for schizophrenia and mood disorders were calculated. The relationships between familial liability and neuropsychological performance were examined with Spearman's correlation coefficients. In addition, patients were classified into three groups by family loading tertiles, and comparisons were performed between the patients in the top and bottom tertiles. Low familial loading scores for schizophrenia showed a significant association with poor executive functioning and delayed visual memory. And these results were also achieved when the subset of psychotic patients in the two extreme tertiles of family loadings of schizophrenia and mood disorders were compared. Low familial liability to schizophrenia seems to be a contributing factor for the severity of cognitive impairment in patients with a broad putative schizophrenia spectrum diagnosis.

1. Introduction

Schizophrenia and other psychoses are complex disabling disorders with a lifetime prevalence of 3.06%, ranging from 0.07 to 0.87 across the psychosis subtypes (Perala et al., 2007). Typically, most psychoses arise in late adolescence or early adulthood, and symptoms are heterogeneous, varying greatly between diagnoses and patients. Though the etiology of psychoses is not yet fully established growing evidence from twin, adoption and family studies and from nationally representative samples indicate a substantial role for a genetic involvement with population heritability estimates as high as 70–85% (Lichtenstein et al., 2009). Further, there is convincing evidence that environmental influences act upon the genome by means of epigenetic mechanisms and are involved in the aetiopathogenesis of major psychoses (Rutten and Mill, 2009). In addition, genetic influences on many psychiatric and substance use disorders are likely to be dynamic, changing their action over the course of neurodevelopment; therefore, the timing of genetic effects seems to be crucial to determining different developmental outcomes (Paus et al., 2008). Indeed, the most widely held view is that neither genes nor environment are solely responsible for individual variation, and virtually all traits and diseases show gene–environment interactions (Caspi and Moffitt, 2006).

Family history is a risk factor for many complex diseases of public health significance (Yoon et al., 2003). Specifically, family history has historically served as an important validator for definitions of psychiatric disorders (Aberg et al., 2012). Further, it has been proposed that stratifying patients by their family antecedents may reduce heterogeneity and facilitate the identification of genetic

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risk factors (Murray et al., 1985). On the other hand, an intriguing finding in psychosis research is that, despite schizophrenia and other psychoses running in families, most affected individuals do not have family history of the illness (Welham et al., 2009).

There is now increasing evidence suggesting that cognitive dysfunction is a reliable and stable feature of psychosis (Barch and Ceaser, 2012) and that it predicts psychosocial functioning and functional capacity better than clinical manifestations in schizophrenia patients (Bowie et al., 2008). Moreover, an association between bipolar disorder and cognitive impairment has repeatedly been described even for euthymic patients. And a recent meta-analysis provided strong support to verbal memory learning, digit span and visuomotor disturbances as robust measures of cognitive impairment in bipolar disorder (Bourne et al., 2013).

The familiality of cognitive impairment in schizophrenia and affective disorders has been previously studied using categorical classifications differentiating between familial and non-familial or sporadic disorders (Anglin et al., 2009; Gur et al., 2007). This categorical approach cannot, however, account for the individual lifetime risk of psychosis for patients and relatives and does not allow estimation of the familial load as an indicator of position on a liability continuum.

These studies addressed the influence of antecedents of schizophrenia or psychosis in the cognitive functioning of schizophrenic or bipolar patients but little is known regarding the influence of family loading of mood disorders on cognitive performance in these patients. However, there is evidence reporting that euthymic healthy first-degree relatives of bipolar patients showed impairment in cognitive domains, such as response inhibition, set shifting, verbal memory and target detection (Bora et al., 2010), and processing speed, working memory, and declarative memory (Glahn et al., 2010). Both studies lend support to the presence of cognitive impairment in family members of patients with affective disorders.

The primary aim of this study was to examine whether familial liability to schizophrenia and to mood disorder was associated with cognitive impairment in patients with psychotic disorders.

2. Methods

2.1. Participants

We conducted a cross-sectional study including a sample of 169 patients recruited from our inpatient unit ($n=133$, 78.7%) and our outpatient clinic ($n=36$, 21.3%). Patients were included if they were clinically stable and had a diagnosis of psychotic disorder. Psychotic disorders included DSM-IV schizophrenia, schizophreniform disorder, schizoaffective disorder, affective disorder with a current episode with psychotic symptoms, brief psychotic disorder, atypical psychosis and delusional disorder (APA, 1994). Exclusion criteria were: a clear-cut affective episode without psychotic symptoms; major sensory or motor disabilities; mental retardation or any diagnosed brain disorder; and a primary diagnosis, or clinically dominant secondary diagnosis, of severe substance abuse. In addition, severely psychotic, aggressive or 'involuntarily admitted' patients were not included in the study.

We selected 26 healthy controls matched to the patient group for epidemiological variables (age, sex and years of education). Inclusion criteria for controls were: no history of (1) psychiatric disorders, (2) neurological disorders, or (3) severe medical illness, as well as (4) no family history of psychiatric or neurological disorders.

All patients and controls gave written informed consent to participate in this study, according to the guidelines of the Ethical Committee of our Hospital. Patients were on antipsychotic medication at standard doses. For the analysis, these doses were transformed to chlorpromazine equivalent units (Woods, 2003).

2.2. Procedures

2.2.1. Diagnostic assessment

The psychiatric assessment was carried out using an expanded version of the Manual for the Assessment of Schizophrenia (MAS) (Landmark, 1982; Peralta and Cuesta, 2005). The best consensus method was used to decide on the final diagnosis of each patient on the basis of all available information (Leckman et al., 1982). Good to excellent results were found for inter-rater reliability between coauthors MJC and VP in the scores for symptoms and diagnosis from the 'expanded MAS' interview (Peralta and Cuesta, 2005). Psychopathological symptoms were assessed with the Scale for the Assessment of Positive symptoms and the Scale for the Assessment of Negative symptoms (SAPS and SANS respectively) (Andreasen, 1984a, 1984b).

2.2.2. Neurocognitive tests

Participants underwent a comprehensive battery of neuropsychological tests covering a wide range of cognitive functions. These cognitive assessments were carried out during periods when patients had recovered from acute symptoms, to avoid as far as possible bias related to acute psychopathological status. Recovery from the acute episode was defined as remission of the acute psychotic episode that caused the admission. Thus, patients were evaluated before discharge of the admission (Table 1). Further, the neuropsychologist (AZ) was held blinded to psychopathological status and diagnosis.

The battery included tests assessing attention, memory and executive functions (Cuesta et al., 2007). Briefly, the Spanish adaptation of the Edinburgh Handedness Inventory (Oldfield, 1971; Peña-Casanova, 1990) was used as a measure of laterality and the Wechsler Adult Intelligence Scale (WAIS) Information subtest (Wechsler, 1981) as an index of premorbid intelligence. Performance on processing speed was measured with the Trail Making A test. Part B of the Trail Making Test (Reitan and Wolfson, 1993) and the Stroop Color Word Test (Golden, 1978) were used to assess executive function. Executive functioning was also assessed with the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993) and a Verbal Fluency test, which consisted of naming as many animals as possible in 1 min (Peña-Casanova, 1990). Memory performance was assessed with the immediate and delayed verbal and visual memory tasks of our battery, which are very similar to the Immediate Memory tests of the Wechsler Memory Scale. Specifically, these Memory and Verbal Fluency tasks were subtests of a neuropsychological battery adapted to the Spanish population that has been described in detail elsewhere (Peña-Casanova, 1990).

2.2.3. Familial loading score

To assess family psychiatric history considering up to first-degree relatives, we employed the Family History-Research Diagnostic Criteria (FH-RDC; Endicott et al., 1978), these being included within our 'expanded MAS' interview. The FH-RDC has shown an acceptable level of validity and excellent test–retest reliability compared with direct interviews (Weissman et al., 2000). Data on lifetime diagnoses of the first-degree family members were collected from multiple sources: direct interviews with the patients and at least two of their relatives, and psychiatric records. Discrepancies in diagnoses of any first-degree family member of patients were resolved by consensus between two experienced clinicians (MJC and VP).

To estimate the familial loading of the patients the family loading score (FLS) designed by Pak Sham was used (Verdoux et al., 1996). The FLS is an original and simple method to provide a measure of illness familiality on the basis of the family size and age structure together with widely accepted prevalence estimators of the illness, such as lifetime and age-related risks. Lifetime risk of schizophrenia in a first-