TITLE:
FAMILIAL LIABILITY TO SCHIZOPHRENIA AND MOOD DISORDERS AND COGNITIVE IMPAIRMENT IN PSYCHOSIS

AUTHORS:
Manuel J. Cuesta[a, b]*; Amalia Zarzuela[a, b]; Ana M. Sánchez-Torres[a, b, e]; Ruth Lorente-Omeñaca[a, b, e]; Lucía Moreno-Izco[a, b]; Julio Sanjuán[c, d]; Victor Peralta[a, b].

[a] Psychiatric Department, Complejo Hospitalario de Navarra, Pamplona (Spain).
[b] IdiSNA, Navarra Institute for Health Research, Spain.
[c] Spanish Mental Health Network (CIBERSAM), University of Valencia, Valencia, Spain
[d] Clinic Hospital (INCLIVA), Valencia, Spain
[e] Department of Basic Psychology I, Faculty of Psychology, National Distance Education University (UNED), Madrid, Spain

***Corresponding author**
Manuel J. Cuesta
Psychiatric Department, Complejo Hospitalario de Navarra
Irunlarrea 4
31008 Pamplona, Spain
Tel: +34 848 422488
Fax: +34 848 429924
e-mail: mcuestaz@cfnavarra.es

Amalia Zarzuela
Psychiatric Department, Complejo Hospitalario de Navarra
Irunlarrea 4
31008 Pamplona, Spain
Tel: +34 848 422488
Fax: +34 848 429924
e-mail: amalia.zarzuela.ituarte@cfnavarra.es

Ana M. Sánchez-Torres
Psychiatric Department, Complejo Hospitalario de Navarra
Irunlarrea 4
31008 Pamplona, Spain
Tel: +34 848 422488
Fax: +34 848 429924
e-mail: am.sanchez.torres@navarra.es

Ruth Lorente-Omeñaca
Psychiatric Department, Complejo Hospitalario de Navarra
Irunlarrea 4
31008 Pamplona, Spain
Tel: +34 848 422488
Fax: +34 848 429924
e-mail: rlorente_omenaca@hotmail.com

Lucía Moreno-Izco
Psychiatric Department, Complejo Hospitalario de Navarra
Irunlarrea 4
31008 Pamplona, Spain
Tel: +34 848 422488
Fax: +34 848 429924
e-mail: lucia.moreno.izco@navarra.es

Julio Sanjuán
Faculty of Medicine, University of Valencia
Blasco Ibáñez, 15
46010 Valencia, Spain

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Tel: +34 963983379
Fax: +34 963864767
e-mail: julio.sanjuan@uv.es

Victor Peralta
Psychiatric Department, Complejo Hospitalario de Navarra
Irunlarrea 4
31008 Pamplona, Spain
Tel: +34 848 422488
Fax: +34 848 429924
e-mail: victor.peralta.martin@cfnavarra.es

***Highlights**

1. The relationships between familial liability to schizophrenia and mood disorders and neuropsychological performance were examined.
2. Low familial liability to schizophrenia was associated with poor executive functioning and delayed visual memory.
3. Low familial liability to mood disorders was not associated with cognitive performance.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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 aetiology. 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.

Keywords: Schizophrenia, Psychosis, Bipolar disorder, Cognitive functioning, Relatives

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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 aetiology of psychoses is not yet fully established growing evidence from twin, adoption and family studies and from nationally representative samples indicates a substantial role for a genetic involvement with population heritability estimates as high as 70 to 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 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).

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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,

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

(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, b).

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

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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 one minute (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-degree relative is 10% but only 0.5% for probands without familial antecedents of schizophrenia. Despite the lifetime risk of illness for sporadic schizophrenia is unknown; it is assumed that it should be lower than the lifetime risk for schizophrenia in general population (1%). It is also assumed that the age-range at risk is 15-50, and that in this range risk increases linearly with age from zero to the lifetime risk. Thus, a FLS is intended to summarize the extent of psychiatric morbidity in a family using a continuous measure of liability (Peralta and Cuesta, 2007; Suvisaari et al., 1998; Verdoux, et al., 1996). In the present study, two FLS were calculated for each patient by modifying the aforementioned formula for two

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

lifetime risk estimates: one for schizophrenia, and one for mood disorder, and FLS values were log transformed. A dimensional FLS score of 0 indicates equal likelihood of their illness being familial or sporadic, and a positive score indicates greater likelihood of it being familial, while a negative score implies greater likelihood of it being sporadic. To compute diagnostic liability, we used for the schizophrenia FLS, the first-degree antecedents of Schizophrenia and Other psychotic Disorders, such as it is included in DSM-IV. Likewise, antecedents of bipolar disorder type I and major depressive disorder in first-degree relatives were gathered by means of the FH-RDC to compute mood disorder FLS.

2.3. Statistical procedures

For neuropsychological tests and domains, scores were standardized (z-score) to the baseline performance of the healthy comparison group. Spearman's rank order correlation coefficients were calculated to examine the relationships between familial liability scores and the twelve neuropsychological scores to account for the skewed distribution of neuropsychological scores. Non-parametric statistical methods were used for comparisons between groups by means of the Kruskal-Wallis rank sum test. All statistical tests were two-tailed. P values of 0.05 or lower were considered statistically significant.

In order to correct for multiple testing in the study the Bonferroni correction was used. The nominal alpha level=0.05 was divided by the number of correlations between schizophrenia and mood FLS scores and cognitive tests to account for Bonferroni correction. Thus the critical p-value for $p \leq 0.05$ was set at $p \leq 0.004$ (0.05/12) after the Bonferroni correction.

Moreover, partial correlation analyses were undertaken to account for the putative influence of duration of illness, medication and negative symptoms on the associations between familial loadings and neuropsychological scores.

3. Results

The study sample has been described previously elsewhere (Cuesta, et al., 2007). Table 1 shows the demographic, educational and clinical data of the sample, as well as the means and standard deviations in the neuropsychological tests. Patients and controls did not differ significantly in age, years

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

of education and gender distribution. Supplementary table 1 describes the diagnostic composition of the "affective disorder with psychotic symptoms" patient group.

A total of 917 first-degree relatives were identified for the sample. The mean FLS for schizophrenia and mood disorder in our sample were 0.05±0.68 (-0.92 to 4.71) and 0.00±0.61 (-0.92 to 4.42), respectively.

We found moderate to high associations between lower familial loading scores of schizophrenia and higher cognitive impairment in executive and memory domains. As shown in Table 2, low schizophrenia FLS was significantly correlated with poor WCST performance and with poor delayed visual memory score. Mood disorder FLS did not reach the critical level for significant correlations with cognitive performance after Bonferroni correction.

Partial correlation analyses on the resulting significant associations after allowing for the influence of duration of illness, medication (chlorpromazine equivalent doses) and negative symptoms were carried out. Partial correlations remained significant, however, only for the association between schizophrenia FLS score and delayed visual memory test after allowance for confounding factors ($r=0.18$, $p\leq0.034$). However, the reduction of the strength of significant associations after the inclusion of covariates was mainly related to the strong correlations between two of the covariates (negative symptoms and duration of illness) with WCST perseverative responses ($r=0.19$, $p\leq0.013$ and $r=0.29$, $p\leq0.001$, respectively). And these two covariates did not show any significant correlation with schizophrenia and mood disorder FLS scores.

To further analyze to what extent the above differences in neuropsychological performance could be related to familial loading for schizophrenia or mood disorder, the patient population was divided into three groups based on their FLS. Since FLS is a continuous variable, we used tertiles to split results into three groups and classify patients as having respectively high, intermediate or low familial loading for schizophrenia or mood disorder. Hereon, these groups are referred to as familial, intermediate or sporadic. Comparisons were made using Kruskal-Wallis non-parametric tests between familial and sporadic to assess whether there were any statistically significant differences in neuropsychological tests. We entered in these analyses those neuropsychological tests that showed Spearman correlations with schizophrenia or mood disorder FLS scores at $p\leq0.05$. Since they were only five neuropsychological tests (Trail Making A, WCST perseverative responses, WCST number of categories and Inmediate visual and

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

delayed visual memory tests) the Bonferroni correction for α at $p \leq 0.05$ in these analyses was set at $p \leq 0.01$ ($p \leq 0.05/5$).

The sporadic schizophrenia group showed significantly poorer cognitive performances in delayed visual memory scores and in WCST perseverative responses than its respective familial group in the patient population (Table 3).

Given that we examined a mixed sample of psychosis patients with predominant diagnoses of DSM-IV schizophrenia (n=108, 64%), we reanalyzed the data considering only those patients in the schizophrenia subgroup. Differences in neuropsychological test scores between sporadic and familial schizophrenia patients stratified in the subset of schizophrenia patients were no longer significant. And the same statistical analyses were applied to the subset of non-schizophrenia patients (n=61) yielding that non-schizophrenia patients with low familial liability to schizophrenia showed significantly poorer performance on the immediate visual memory test.

No statistical significant differences were found between family loading of mood disorder and cognitive performance in any of the three groups (total sample, schizophrenia and non-schizophrenia subgroups) (Table 3).

4. Discussion

This study sought to evaluate whether familial liability to schizophrenia or mood disorder was associated with cognitive impairment in patients with psychotic disorders. There were three main findings. First, we observed that low familial loading scores for schizophrenia were significantly related to impairment in delayed visual memory and one measure of executive performance (WCST perseverative responses). Second, familial loading scores for mood disorders did not show significant associations with cognitive performance. And third, when comparisons were narrowed and focussed only on the two extreme tertiles of familial loadings for schizophrenia and mood disorders (by excluding patients with intermediate familial loadings), psychosis patients with low schizophrenia family loadings but not low mood disorder family loadings showed significantly poorer cognitive performance in executive functioning and delayed visual memory than its respective familial forms. These significant differences were not demonstrated in the examination of the subset of patients with diagnosis of schizophrenia

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

(N=108) but in the non-schizophrenia psychosis subset of patients (N=61) with low schizophrenia family loadings showed significantly poorer immediate visual memory than its respective familial forms.

At first, these results seem to be at odds with considerable evidence showing greater cognitive dysfunction in schizophrenia patients with a positive family history of schizophrenia (Sautter et al., 1997a; Sautter et al., 1997b; Wolitzky et al., 2006). Similarly, they do not appear to be in agreement with studies reporting a gradient of cognitive impairment, which ranged from a severe disturbance in patients with schizophrenia to a moderate impairment in their well relatives regarding healthy controls (Gur, et al., 2007). Likewise, it has been reported that a history of affective illness in schizophrenia patients was related to the best performance on IQ tests and executive function measures (Anglin, et al., 2009); and that bipolar disorder is linked, at least in men, with high intelligence (Gale et al., 2013). However, there are also negative results (Roy et al., 1994; Sitskoorn et al., 2004) and there certain methodological shortcomings hampering the strength of previous studies. For instance, many previous studies were based exclusively upon the division into familial and sporadic patients. This distinction might hinder the identification of potential patients who are at risk at the time of the study but they have not yet developed the illness. And it does not take into account either differences in age and family structure between families or estimations of individual lifetime risk, which are needed to quantify the specific morbid risk of relatives (Van Os et al., 1997). In addition, psychiatric antecedents should be assessed using standardized instruments and information collected from individual family informants rather than from patients alone.

Heritability estimates for schizophrenia and bipolar disorder have been recently reduced from 0.81 to 0.67 and from 0.85 to 0.62 (Lichtenstein, et al., 2009; Wray and Gottesman, 2012). However, they continue to be relatively high, as well as in other complex diseases, and they are higher than those reported for major depression (0.32)(Wray and Gottesman, 2012). In this regard, caution is warranted against making direct genetic interpretations (Tenesa and Haley, 2013).

Furthermore, it has been suggested that heritability estimates for cognitive impairment associated with schizophrenia may be considerably lower (between 40-70%) than those reported, leaving room for gene-environment interplay in the aetiology of the illness (van Os et al., 2010). This is in agreement with recent findings from a longitudinal population-based study in Sweden that notably reduced the contribution of the shared genetic origin of cognition (premorbid IQ) and psychosis compared to previously reported values (Fowler et al., 2012).

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

While there is some consensus in the literature that supports the idea that degrees of relatedness to individuals with psychotic illness are closely associated with cognitive functioning, there is also mounting evidence supporting the view that pervasive and protective factors during neurodevelopment can have great importance for the future cognitive functioning of individuals (Plomin and Daniels, 2011). For instance, serious obstetric complications or preterm births are known risk factors for both abnormalities in cerebral cortical growth, which is associated with impairment in cognitive development and learning (Baron and Rey-Casserly, 2010), and an increased risk of developing schizophrenia (Demjaha et al., 2012). Moreover, it was found that a low birth weight and hypoxic insults at delivery were strongly associated with poor neuropsychological performance at age 7 in a large epidemiological study of pregnancy, birth, and development (Demjaha, et al., 2012). Further, interactions between genes involved in neurovascular function or regulated by hypoxia that interacted with obstetric complications might increase the risk for schizophrenia (Nicodemus et al., 2008). On the contrary, nurturing environments providing stable affective contexts may temper early stressful experiences, which could potentially negatively influence cognitive processes in psychiatric disorders (Goldberg et al., 2012).

Thus, environmental factors acting either directly or indirectly by gene–environment interactions or by epigenetic mechanisms may affect brain developmental trajectories and open "windows of vulnerability" either to developing psychosis (Brown, 2011) or facilitating the emergence of cognitive impairment associated with psychoses.

In our study, specific environment factors were not controlled for and we assumed that environmental factors could be present in both sporadic and familial groups. However, providing that the aforementioned results in the literature suggest that both familial and environment factors may affect to the development of cognitive impairment, it could be hypothesized that patients with a sporadic form of schizophrenia or a lower degree of familial loading of the disorder may need comparatively more severe environmental insults to develop the illness than the psychoses arising within affected families. This might explain sporadic patients having greater disturbances and consequently greater cognitive impairment than familial patients. In this respect, results from early studies on neuroimaging showed that, for instance, cerebral ventricular enlargement and grey matter volume were more related to environmental factors than to a family history of major psychiatric disorder (Reveley et al., 1984) and there is recent evidence suggesting that prefrontal volume reductions are not related to the same familial influences as

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

those that increase schizophrenia liability (Owens et al., 2012); these findings would be in agreement with a potential role for other contributing causes such as environmental factors.

4.1. Limitations

There are several limitations affecting that need to be considered. Firstly, retrospectively collected data on family psychiatric history is not exempt of errors and is a potential source of bias affecting the study. On the other hand, we used the FH-RDC method, which is regarded as one of the best standardized methods, and we collected information from at least two members of the family plus the patient to gather the most reliable data possible. Moreover, we combined dimensional and categorical analyses of FLS scores to provide a deeper understanding of our results since most previous research found that genetic antecedents were associated with lower cognitive performance. Thus we dichotomized the sample using the two extreme tertiles of family loading of schizophrenia, mood disorders and psychosis, thereby excluding patients with an intermediate loading in whom the importance of familiality was less clear and hence their classification would have been less reliable.

Secondly, the sample size of the healthy control group was not comparable to patients' group. However, we decided to include it as a better approach than using normative data because our healthy control group was matched to the patient group for epidemiological variables (age, sex and years of education). Moreover, our control group was not used for the computing of the family loading scores.

Thirdly, familiality is not the same as heritability (Kendler and Neale, 2009) since it does not address genetic causes directly and caution is warranted in assuming an environmental origin of sporadic forms of psychosis by neglecting the putative genetic or gene-environment interaction both with the psychosis and its associated cognitive impairment. Our results could seem, at first, to be at odds with studies demonstrating that psychopathological domains have been shown to exhibit high degrees of familiality (McGrath et al., 2009) but a very common finding across studies is the relative lack of a close relationship between symptoms and cognition (Cuesta and Peralta, 1995).

Fourth, we included a broad putative schizophrenia spectrum diagnosis to subsume patients with a mixed group of non-pure affective psychoses since an ever-increasing volume of research data underlines the inconclusiveness of the validity of the schizophrenia construct as presently defined (Jablensky, 2010). However, when we reanalyzed the data considering only subsets of patients we

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

obtained similar results replicating our analyses in the non schizophrenia subset of patients but not in the subset of patients with schizophrenia diagnosis. Hence, appropriate caution is warranted before further research can be conducted to replicate our findings.

Fifth, a possible enrichment of familial liability for any diagnostic categories might have biased the distribution of affected relatives and might have lead to the inclusion of less sporadic cases in the schizoaffective and affective disorders with psychotic symptoms groups regarding the schizophrenia group. However, an examination of schizophrenia and mood disorders FLS scores by DSM IV diagnostic groups allowed us to discard this bias in familial liability when the groups are considered separately. In addition, no differences in enrichments of familial liability between the two extreme tertiles of either schizophrenia or mood disorder FLS scores were found by DSM IV diagnostic breakdowns (Supplementary Table 2).

Finally, our interpretation about the contribution of environment factors in the cognitive impairment of our patients should be considered tentative since we did not control specifically for them. In conclusion, low familial liability to schizophrenia seems to be a contributing factor for the severity of cognitive impairment in delayed visual memory and a measure of executive functioning (WCST Perseverative responses) in patients with a broad putative schizophrenia spectrum diagnosis.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Acknowledgments

This work was supported by grants from the Government of Navarra (11/101 and 87/2014); the Carlos III Health Institute of the Spanish Economic Affairs and Competitiveness (ERDF Funds; 08/I/1026 and 11/02831).

References

Aberg, K., Adkins, D.E., Liu, Y., McClay, J.L., Bukszar, J., Jia, P., Zhao, Z., Perkins, D., Stroup, T.S., Lieberman, J.A., Sullivan, P.F., van den Oord, E.J., 2012. Genome-wide association study of antipsychotic-induced QTc interval prolongation. Pharmacogenomics Journal 12(2), 165-172.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). American Psychiatric Association, Washington.

Anglin, D., Stanford, A.D., Harkavy-Friedman, J.M., Goetz, R., Rosenfield, P., Malaspina, D., 2009. Family history of affective illness in schizophrenia patients: symptoms and cognition. Schizophrenia Research 110(1-3), 24-27.

Barch, D.M., Ceaser, A., 2012. Cognition in schizophrenia: core psychological and neural mechanisms. Trends in Cognitive Sciences 16(1), 27-34.

Baron, I.S., Rey-Casserly, C., 2010. Extremely preterm birth outcome: a review of four decades of cognitive research. Neuropsychology Review 20(4), 430-452.

Bora, E., Yücel, M., Pantelis, C., 2010. Neurocognitive markers of psychosis in bipolar disorder: A meta-analytic study. Journal of Affective Disorders 127(1-3), 1-9.

Bourne, C., Aydemir, O., Balanza-Martinez, V., Bora, E., Brissos, S., Cavanagh, J.T., Clark, L., Cubukcuoglu, Z., Dias, V.V., Dittmann, S., Ferrier, I.N., Fleck, D.E., Frangou, S., Gallagher, P., Jones, L., Kieseppa, T., Martinez-Aran, A., Melle, I., Moore, P.B., Mur, M., Pfennig, A., Raust, A., Senturk, V., Simonsen, C., Smith, D.J., Bio, D.S., Soeiro-de-Souza, M.G., Stoddart, S.D., Sundet, K., Szoke, A., Thompson, J.M., Torrent, C., Zalla, T., Craddock, N., Andreassen, O.A., Leboyer, M., Vieta, E., Bauer, M., Worhunsky, P.D., Tzagarakis, C., Rogers, R.D., Geddes, J.R., Goodwin, G.M., 2013. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatrica Scandinavica 128(3), 149-162.

Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biological Psychiatry 63(5), 505-511.

Brown, A.S., 2011. The environment and susceptibility to schizophrenia. Progress in Neurobiology 93(1), 23-58.

Caspi, A., Moffitt, T.E., 2006. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nature Reviews. Neuroscience 7(7), 583-590.

Cuesta, M.J., Peralta, V., 1995. Cognitive disorders in the positive, negative, and disorganization syndromes of schizophrenia. Psychiatry Research 58(3), 227-235.

Cuesta, M.J., Peralta, V., Zarzuela, A., 2007. Empirical validation of competing definitions of schizophrenia: a poly-diagnostic study of cognitive impairment in non-affective psychosis. Schizophrenia Research 95(1-3), 39-47.

Demjaha, A., MacCabe, J.H., Murray, R.M., 2012. How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. Schizophrenia Bulletin 38(2), 209-214.

Endicott, J., Andreasen, N.C., Spitzer, R.L., 1978. Family history-research diagnostic criteria (FH-RDC). New York State Psychiatric Institute, New York.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Fowler, T., Zammit, S., Owen, M.J., Rasmussen, F., 2012. A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. Archives of General Psychiatry 69(5), 460-466.

Gale, C.R., Batty, G.D., McIntosh, A.M., Porteous, D.J., Deary, I.J., Rasmussen, F., 2013. Is bipolar disorder more common in highly intelligent people? A cohort study of a million men. Molecular Psychiatry 18(2), 190-194.

Glahn, D.C., Almasy, L., Barguil, M., Hare, E., Peralta, J.M., Kent, J.W., Jr., Dassori, A., Contreras, J., Pacheco, A., Lanzagorta, N., Nicolini, H., Raventos, H., Escamilla, M.A., 2010. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. Archives of General Psychiatry 67(2), 168-177.

Goldberg, X., Fatjo-Vilas, M., Munoz, M.J., Campanera, S., Miret, S., Minano, M.J., Aguilera, M., Miralles, M.L., Navarro, M.E., Lazaro, L., Guitart, M., Barrantes-Vidal, N., Fananas, L., 2012. Increased familiarity of intellectual deficits in early-onset schizophrenia spectrum disorders. World Journal of Biological Psychiatry 13(7), 493-500.

Golden, C.J., 1978. Stroop color and word test. A manual for clinical and experimental uses. Stoelting Co., Wood Dale, Illinois.

Gur, R.E., Nimgaonkar, V.L., Almasy, L., Calkins, M.E., Ragland, J.D., Pogue-Geile, M.F., Kanes, S., Blangero, J., Gur, R.C., 2007. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. American Journal of Psychiatry 164(5), 813-819.

Heaton, R., Chelune, G., Talley, J., Kay, G., Curtiss, G., 1993. Wisconsin Card Sorting Test. Psychological Assessment Resources, Odessa, FL.

Jablensky, A., 2010. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. Dialogues Clin Neurosci 12(3), 271-287.

Kendler, K.S., Neale, M.C., 2009. "Familiality" or heritability. Archives of General Psychiatry 66(4), 452-453.

Landmark, J., 1982. A manual for the assessment of schizophrenia. Acta Psychiatrica Scandinavica. Supplementum 298, 1-88.

Leckman, J.F., Sholomskas, D., Thompson, W.D., Belanger, A., Weissman, M.M., 1982. Best estimate of lifetime psychiatric diagnosis: a methodological study. Archives of General Psychiatry 39(8), 879-883.

Lichtenstein, P., Yip, B.H., Bjork, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M., 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373(9659), 234-239.

McGrath, J.A., Avramopoulos, D., Lasseter, V.K., Wolyniec, P.S., Fallin, M.D., Liang, K.Y., Nestadt, G., Thornquist, M.H., Luke, J.R., Chen, P.L., Valle, D., Pulver, A.E., 2009. Familiality of novel factorial dimensions of schizophrenia. Archives of General Psychiatry 66(6), 591-600.

Murray, R.M., Lewis, S.W., Reveley, A.M., 1985. Towards an aetiological classification of schizophrenia. Lancet 1(8436), 1023-1026.

Nicodemus, K.K., Marenco, S., Batten, A.J., Vakkalanka, R., Egan, M.F., Straub, R.E., Weinberger, D.R., 2008. Serious obstetric complications interact with hypoxia-regulated/vascular-expression genes to influence schizophrenia risk. Molecular Psychiatry 13(9), 873-877.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1), 97-113.

Owens, S.F., Picchioni, M.M., Ettinger, U., McDonald, C., Walshe, M., Schmechtig, A., Murray, R.M., Rijsdijk, F., Toulopoulou, T., 2012. Prefrontal deviations in function but not volume are putative endophenotypes for schizophrenia. Brain 135(Pt 7), 2231-2244.

Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nature Reviews. Neuroscience 9(12), 947-957.

Peña-Casanova, J., 1990. Test Barcelona. Masson, Barcelona.

Perala, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppa, T., Harkanen, T., Koskinen, S., Lonnqvist, J., 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Archives of General Psychiatry 64(1), 19-28.

Peralta, V., Cuesta, M.J., 2005. The underlying structure of diagnostic systems of schizophrenia: a comprehensive polydiagnostic approach. Schizophrenia Research 79(2-3), 217-229.

Peralta, V., Cuesta, M.J., 2007. The relationship between syndromes of the psychotic illness and familial liability to schizophrenia and major mood disorders. Schizophrenia Research 91(1-3), 200-209.

Plomin, R., Daniels, D., 2011. Why are children in the same family so different from one another? International Journal of Epidemiology 40(3), 563-582.

Reitan, R., Wolfson, D., 1993. The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation. Neuropsychology Press, Tucson, AZ.

Reveley, A.M., Reveley, M.A., Murray, R.M., 1984. Hypothesis for the etiology of schizophrenia: a genetic perspective. Psychopharmacology Bulletin 20(3), 505-508.

Roy, M.A., Flaum, M.A., Gupta, S., Jaramillo, L., Andreasen, N.C., 1994. Epidemiological and clinical correlates of familial and sporadic schizophrenia. Acta Psychiatrica Scandinavica 89(5), 324-328.

Rutten, B.P., Mill, J., 2009. Epigenetic mediation of environmental influences in major psychotic disorders. Schizophrenia Bulletin 35(6), 1045-1056.

Sautter, F.J., McDermott, B.E., Cornwell, J., Wilson, A.F., Johnson, J., Vasterling, J.J., 1997a. Neuropsychological deficits in probands from multiply-affected schizophrenic families. Journal of Psychiatric Research 31(5), 497-508.

Sautter, F.J., McDermott, B.E., Cornwell, J.M., Borges, A., Johnson, J., Vasterling, J.J., Marcontell, D.K., 1997b. A comparison of neuropsychological deficits in familial schizophrenics, nonfamilial schizophrenics, and normal controls. The Journal of Nervous and Mental Disease 185(10), 641-644.

Sitskoorn, M.M., Aleman, A., Ebisch, S.J., Appels, M.C., Kahn, R.S., 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophrenia Research 71(2-3), 285-295.

Suvisaari, J.M., Haukka, J., Tanskanen, A., Lonnqvist, J.K., 1998. Age at onset and outcome in schizophrenia are related to the degree of familial loading. British Journal of Psychiatry 173, 494-500.

Tenesa, A., Haley, C.S., 2013. The heritability of human disease: estimation, uses and abuses. Nature Reviews. Genetics 14(2), 139-149.

van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. Nature 468(7321), 203-212.

Van Os, J., Marcelis, M., Sham, P., Jones, P., Gilvarry, K., Murray, R., 1997. Psychopathological syndromes and familial morbid risk of psychosis. British Journal of Psychiatry 170, 241-246.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Verdoux, H., van Os, J., Sham, P., Jones, P., Gilvarry, K., Murray, R., 1996. Does familiality predispose to both emergence and persistence of psychosis? A follow-up study. British Journal of Psychiatry 168(5), 620-626.

Weissman, M.M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., Olfson, M., 2000. Brief screening for family psychiatric history: the family history screen. Archives of General Psychiatry 57(7), 675-682.

Welham, J., Isohanni, M., Jones, P., McGrath, J., 2009. The antecedents of schizophrenia: a review of birth cohort studies. Schizophrenia Bulletin 35(3), 603-623.

Wolitzky, R., Goudsmit, N., Goetz, R.R., Printz, D., Gil, R., Harkavy-Friedman, J., Malaspina, D., 2006. Etiological heterogeneity and intelligence test scores in patients with schizophrenia. Journal of Clinical and Experimental Neuropsychology 28(2), 167-177.

Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. Journal of Clinical Psychiatry 64(6), 663-667.

Wray, N.R., Gottesman, I., 2012. Using summary data from the danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Front Genet 3, 118.

Yoon, P.W., Scheuner, M.T., Khoury, M.J., 2003. Research priorities for evaluating family history in the prevention of common chronic diseases. American Journal of Preventive Medicine 24(2), 128-135.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Contributors

Manuel J. Cuesta and Victor Peralta designed the study, analyzed the data and wrote the first draft of the manuscript. Amalia Zarzuela performed the neuropsychological assessment. Manuel J. Cuesta, Amalia Zarzuela, Ana M. Sánchez-Torres and Ruth Lorente designed the neuropsychological battery and participated in the analysis and interpretation of cognitive results. Lucía Moreno and Julio Sanjuan cooperated in the interpretation of familial data and in comments to the definitive version of the manuscript.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Conflict of interest:

None.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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 aetiology. 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.

Keywords: Schizophrenia, Psychosis, Bipolar disorder, Cognitive functioning, Relatives

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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 aetiology of psychoses is not yet fully established growing evidence from twin, adoption and family studies and from nationally representative samples indicates a substantial role for a genetic involvement with population heritability estimates as high as 70 to 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 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).

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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,

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

(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, b).

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

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

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 one minute (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-degree relative is 10% but only 0.5% for probands without familial antecedents of schizophrenia. Despite the lifetime risk of illness for sporadic schizophrenia is unknown; it is assumed that it should be lower than the lifetime risk for schizophrenia in general population (1%). It is also assumed that the age-range at risk is 15-50, and that in this range risk increases linearly with age from zero to the lifetime risk. Thus, a FLS is intended to summarize the extent of psychiatric morbidity in a family using a continuous measure of liability (Peralta and Cuesta, 2007; Suvisaari et al., 1998; Verdoux, et al., 1996). In the present study, two FLS were calculated for each patient by modifying the aforementioned formula for two

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

lifetime risk estimates: one for schizophrenia, and one for mood disorder, and FLS values were log transformed. A dimensional FLS score of 0 indicates equal likelihood of their illness being familial or sporadic, and a positive score indicates greater likelihood of it being familial, while a negative score implies greater likelihood of it being sporadic. To compute diagnostic liability, we used for the schizophrenia FLS, the first-degree antecedents of Schizophrenia and Other psychotic Disorders, such as it is included in DSM-IV. Likewise, antecedents of bipolar disorder type I and major depressive disorder in first-degree relatives were gathered by means of the FH-RDC to compute mood disorder FLS.

2.3. Statistical procedures

For neuropsychological tests and domains, scores were standardized (z-score) to the baseline performance of the healthy comparison group. Spearman's rank order correlation coefficients were calculated to examine the relationships between familial liability scores and the twelve neuropsychological scores to account for the skewed distribution of neuropsychological scores. Non-parametric statistical methods were used for comparisons between groups by means of the Kruskal-Wallis rank sum test. All statistical tests were two-tailed. P values of 0.05 or lower were considered statistically significant.

In order to correct for multiple testing in the study the Bonferroni correction was used. The nominal alpha level=0.05 was divided by the number of correlations between schizophrenia and mood FLS scores and cognitive tests to account for Bonferroni correction. Thus the critical p-value for $p \leq 0.05$ was set at $p \leq 0.004$ (0.05/12) after the Bonferroni correction.

Moreover, partial correlation analyses were undertaken to account for the putative influence of duration of illness, medication and negative symptoms on the associations between familial loadings and neuropsychological scores.

3. Results

The study sample has been described previously elsewhere (Cuesta, et al., 2007). Table 1 shows the demographic, educational and clinical data of the sample, as well as the means and standard deviations in the neuropsychological tests. Patients and controls did not differ significantly in age, years

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

of education and gender distribution. Supplementary table 1 describes the diagnostic composition of the "affective disorder with psychotic symptoms" patient group.

A total of 917 first-degree relatives were identified for the sample. The mean FLS for schizophrenia and mood disorder in our sample were 0.05±0.68 (-0.92 to 4.71) and 0.00±0.61 (-0.92 to 4.42), respectively.

We found moderate to high associations between lower familial loading scores of schizophrenia and higher cognitive impairment in executive and memory domains. As shown in Table 2, low schizophrenia FLS was significantly correlated with poor WCST performance and with poor delayed visual memory score. Mood disorder FLS did not reach the critical level for significant correlations with cognitive performance after Bonferroni correction.

Partial correlation analyses on the resulting significant associations after allowing for the influence of duration of illness, medication (chlorpromazine equivalent doses) and negative symptoms were carried out. Partial correlations remained significant, however, only for the association between schizophrenia FLS score and delayed visual memory test after allowance for confounding factors ($r=0.18$, $p\leq0.034$). However, the reduction of the strength of significant associations after the inclusion of covariates was mainly related to the strong correlations between two of the covariates (negative symptoms and duration of illness) with WCST perseverative responses ($r=0.19$, $p\leq0.013$ and $r=0.29$, $p\leq0.001$, respectively). And these two covariates did not show any significant correlation with schizophrenia and mood disorder FLS scores.

To further analyze to what extent the above differences in neuropsychological performance could be related to familial loading for schizophrenia or mood disorder, the patient population was divided into three groups based on their FLS. Since FLS is a continuous variable, we used tertiles to split results into three groups and classify patients as having respectively high, intermediate or low familial loading for schizophrenia or mood disorder. Hereon, these groups are referred to as familial, intermediate or sporadic. Comparisons were made using Kruskal-Wallis non-parametric tests between familial and sporadic to assess whether there were any statistically significant differences in neuropsychological tests. We entered in these analyses those neuropsychological tests that showed Spearman correlations with schizophrenia or mood disorder FLS scores at $p\leq0.05$. Since they were only five neuropsychological tests (Trail Making A, WCST perseverative responses, WCST number of categories and Inmediate visual and

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

delayed visual memory tests) the Bonferroni correction for α at $p \leq 0.05$ in these analyses was set at $p \leq 0.01$ ($p \leq 0.05/5$).

The sporadic schizophrenia group showed significantly poorer cognitive performances in delayed visual memory scores and in WCST perseverative responses than its respective familial group in the patient population (Table 3).

Given that we examined a mixed sample of psychosis patients with predominant diagnoses of DSM-IV schizophrenia (n=108, 64%), we reanalyzed the data considering only those patients in the schizophrenia subgroup. Differences in neuropsychological test scores between sporadic and familial schizophrenia patients stratified in the subset of schizophrenia patients were no longer significant. And the same statistical analyses were applied to the subset of non-schizophrenia patients (n=61) yielding that non-schizophrenia patients with low familial liability to schizophrenia showed significantly poorer performance on the immediate visual memory test.

No statistical significant differences were found between family loading of mood disorder and cognitive performance in any of the three groups (total sample, schizophrenia and non-schizophrenia subgroups) (Table 3).

4. Discussion

This study sought to evaluate whether familial liability to schizophrenia or mood disorder was associated with cognitive impairment in patients with psychotic disorders. There were three main findings. First, we observed that low familial loading scores for schizophrenia were significantly related to impairment in delayed visual memory and one measure of executive performance (WCST perseverative responses). Second, familial loading scores for mood disorders did not show significant associations with cognitive performance. And third, when comparisons were narrowed and focussed only on the two extreme tertiles of familial loadings for schizophrenia and mood disorders (by excluding patients with intermediate familial loadings), psychosis patients with low schizophrenia family loadings but not low mood disorder family loadings showed significantly poorer cognitive performance in executive functioning and delayed visual memory than its respective familial forms. These significant differences were not demonstrated in the examination of the subset of patients with diagnosis of schizophrenia

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

(N=108) but in the non-schizophrenia psychosis subset of patients (N=61) with low schizophrenia family loadings showed significantly poorer immediate visual memory than its respective familial forms.

At first, these results seem to be at odds with considerable evidence showing greater cognitive dysfunction in schizophrenia patients with a positive family history of schizophrenia (Sautter et al., 1997a; Sautter et al., 1997b; Wolitzky et al., 2006). Similarly, they do not appear to be in agreement with studies reporting a gradient of cognitive impairment, which ranged from a severe disturbance in patients with schizophrenia to a moderate impairment in their well relatives regarding healthy controls (Gur, et al., 2007). Likewise, it has been reported that a history of affective illness in schizophrenia patients was related to the best performance on IQ tests and executive function measures (Anglin, et al., 2009); and that bipolar disorder is linked, at least in men, with high intelligence (Gale et al., 2013). However, there are also negative results (Roy et al., 1994; Sitskoorn et al., 2004) and there certain methodological shortcomings hampering the strength of previous studies. For instance, many previous studies were based exclusively upon the division into familial and sporadic patients. This distinction might hinder the identification of potential patients who are at risk at the time of the study but they have not yet developed the illness. And it does not take into account either differences in age and family structure between families or estimations of individual lifetime risk, which are needed to quantify the specific morbid risk of relatives (Van Os et al., 1997). In addition, psychiatric antecedents should be assessed using standardized instruments and information collected from individual family informants rather than from patients alone.

Heritability estimates for schizophrenia and bipolar disorder have been recently reduced from 0.81 to 0.67 and from 0.85 to 0.62 (Lichtenstein, et al., 2009; Wray and Gottesman, 2012). However, they continue to be relatively high, as well as in other complex diseases, and they are higher than those reported for major depression (0.32)(Wray and Gottesman, 2012). In this regard, caution is warranted against making direct genetic interpretations (Tenesa and Haley, 2013).

Furthermore, it has been suggested that heritability estimates for cognitive impairment associated with schizophrenia may be considerably lower (between 40-70%) than those reported, leaving room for gene-environment interplay in the aetiology of the illness (van Os et al., 2010). This is in agreement with recent findings from a longitudinal population-based study in Sweden that notably reduced the contribution of the shared genetic origin of cognition (premorbid IQ) and psychosis compared to previously reported values (Fowler et al., 2012).

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

While there is some consensus in the literature that supports the idea that degrees of relatedness to individuals with psychotic illness are closely associated with cognitive functioning, there is also mounting evidence supporting the view that pervasive and protective factors during neurodevelopment can have great importance for the future cognitive functioning of individuals (Plomin and Daniels, 2011). For instance, serious obstetric complications or preterm births are known risk factors for both abnormalities in cerebral cortical growth, which is associated with impairment in cognitive development and learning (Baron and Rey-Casserly, 2010), and an increased risk of developing schizophrenia (Demjaha et al., 2012). Moreover, it was found that a low birth weight and hypoxic insults at delivery were strongly associated with poor neuropsychological performance at age 7 in a large epidemiological study of pregnancy, birth, and development (Demjaha, et al., 2012). Further, interactions between genes involved in neurovascular function or regulated by hypoxia that interacted with obstetric complications might increase the risk for schizophrenia (Nicodemus et al., 2008). On the contrary, nurturing environments providing stable affective contexts may temper early stressful experiences, which could potentially negatively influence cognitive processes in psychiatric disorders (Goldberg et al., 2012).

Thus, environmental factors acting either directly or indirectly by gene–environment interactions or by epigenetic mechanisms may affect brain developmental trajectories and open "windows of vulnerability" either to developing psychosis (Brown, 2011) or facilitating the emergence of cognitive impairment associated with psychoses.

In our study, specific environment factors were not controlled for and we assumed that environmental factors could be present in both sporadic and familial groups. However, providing that the aforementioned results in the literature suggest that both familial and environment factors may affect to the development of cognitive impairment, it could be hypothesized that patients with a sporadic form of schizophrenia or a lower degree of familial loading of the disorder may need comparatively more severe environmental insults to develop the illness than the psychoses arising within affected families. This might explain sporadic patients having greater disturbances and consequently greater cognitive impairment than familial patients. In this respect, results from early studies on neuroimaging showed that, for instance, cerebral ventricular enlargement and grey matter volume were more related to environmental factors than to a family history of major psychiatric disorder (Reveley et al., 1984) and there is recent evidence suggesting that prefrontal volume reductions are not related to the same familial influences as

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

those that increase schizophrenia liability (Owens et al., 2012); these findings would be in agreement with a potential role for other contributing causes such as environmental factors.

4.1. Limitations

There are several limitations affecting that need to be considered. Firstly, retrospectively collected data on family psychiatric history is not exempt of errors and is a potential source of bias affecting the study. On the other hand, we used the FH-RDC method, which is regarded as one of the best standardized methods, and we collected information from at least two members of the family plus the patient to gather the most reliable data possible. Moreover, we combined dimensional and categorical analyses of FLS scores to provide a deeper understanding of our results since most previous research found that genetic antecedents were associated with lower cognitive performance. Thus we dichotomized the sample using the two extreme tertiles of family loading of schizophrenia, mood disorders and psychosis, thereby excluding patients with an intermediate loading in whom the importance of familiality was less clear and hence their classification would have been less reliable.

Secondly, the sample size of the healthy control group was not comparable to patients' group. However, we decided to include it as a better approach than using normative data because our healthy control group was matched to the patient group for epidemiological variables (age, sex and years of education). Moreover, our control group was not used for the computing of the family loading scores.

Thirdly, familiality is not the same as heritability (Kendler and Neale, 2009) since it does not address genetic causes directly and caution is warranted in assuming an environmental origin of sporadic forms of psychosis by neglecting the putative genetic or gene-environment interaction both with the psychosis and its associated cognitive impairment. Our results could seem, at first, to be at odds with studies demonstrating that psychopathological domains have been shown to exhibit high degrees of familiality (McGrath et al., 2009) but a very common finding across studies is the relative lack of a close relationship between symptoms and cognition (Cuesta and Peralta, 1995).

Fourth, we included a broad putative schizophrenia spectrum diagnosis to subsume patients with a mixed group of non-pure affective psychoses since an ever-increasing volume of research data underlines the inconclusiveness of the validity of the schizophrenia construct as presently defined (Jablensky, 2010). However, when we reanalyzed the data considering only subsets of patients we

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

obtained similar results replicating our analyses in the non schizophrenia subset of patients but not in the subset of patients with schizophrenia diagnosis. Hence, appropriate caution is warranted before further research can be conducted to replicate our findings.

Fifth, a possible enrichment of familial liability for any diagnostic categories might have biased the distribution of affected relatives and might have lead to the inclusion of less sporadic cases in the schizoaffective and affective disorders with psychotic symptoms groups regarding the schizophrenia group. However, an examination of schizophrenia and mood disorders FLS scores by DSM IV diagnostic groups allowed us to discard this bias in familial liability when the groups are considered separately. In addition, no differences in enrichments of familial liability between the two extreme tertiles of either schizophrenia or mood disorder FLS scores were found by DSM IV diagnostic breakdowns (Supplementary Table 2).

Finally, our interpretation about the contribution of environment factors in the cognitive impairment of our patients should be considered tentative since we did not control specifically for them. In conclusion, low familial liability to schizophrenia seems to be a contributing factor for the severity of cognitive impairment in delayed visual memory and a measure of executive functioning (WCST Perseverative responses) in patients with a broad putative schizophrenia spectrum diagnosis.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Acknowledgments

This work was supported by grants from the Government of Navarra (11/101 and 87/2014); the Carlos III Health Institute of the Spanish Economic Affairs and Competitiveness (ERDF Funds; 08/I/1026 and 11/02831).

References

Aberg, K., Adkins, D.E., Liu, Y., McClay, J.L., Bukszar, J., Jia, P., Zhao, Z., Perkins, D., Stroup, T.S., Lieberman, J.A., Sullivan, P.F., van den Oord, E.J., 2012. Genome-wide association study of antipsychotic-induced QTc interval prolongation. Pharmacogenomics Journal 12(2), 165-172.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). American Psychiatric Association, Washington.

Anglin, D., Stanford, A.D., Harkavy-Friedman, J.M., Goetz, R., Rosenfield, P., Malaspina, D., 2009. Family history of affective illness in schizophrenia patients: symptoms and cognition. Schizophrenia Research 110(1-3), 24-27.

Barch, D.M., Ceaser, A., 2012. Cognition in schizophrenia: core psychological and neural mechanisms. Trends in Cognitive Sciences 16(1), 27-34.

Baron, I.S., Rey-Casserly, C., 2010. Extremely preterm birth outcome: a review of four decades of cognitive research. Neuropsychology Review 20(4), 430-452.

Bora, E., Yücel, M., Pantelis, C., 2010. Neurocognitive markers of psychosis in bipolar disorder: A meta-analytic study. Journal of Affective Disorders 127(1-3), 1-9.

Bourne, C., Aydemir, O., Balanza-Martinez, V., Bora, E., Brissos, S., Cavanagh, J.T., Clark, L., Cubukcuoglu, Z., Dias, V.V., Dittmann, S., Ferrier, I.N., Fleck, D.E., Frangou, S., Gallagher, P., Jones, L., Kieseppa, T., Martinez-Aran, A., Melle, I., Moore, P.B., Mur, M., Pfennig, A., Raust, A., Senturk, V., Simonsen, C., Smith, D.J., Bio, D.S., Soeiro-de-Souza, M.G., Stoddart, S.D., Sundet, K., Szoke, A., Thompson, J.M., Torrent, C., Zalla, T., Craddock, N., Andreassen, O.A., Leboyer, M., Vieta, E., Bauer, M., Worhunsky, P.D., Tzagarakis, C., Rogers, R.D., Geddes, J.R., Goodwin, G.M., 2013. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatrica Scandinavica 128(3), 149-162.

Bowie, C.R., Leung, W.W., Reichenberg, A., McClure, M.M., Patterson, T.L., Heaton, R.K., Harvey, P.D., 2008. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biological Psychiatry 63(5), 505-511.

Brown, A.S., 2011. The environment and susceptibility to schizophrenia. Progress in Neurobiology 93(1), 23-58.

Caspi, A., Moffitt, T.E., 2006. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nature Reviews. Neuroscience 7(7), 583-590.

Cuesta, M.J., Peralta, V., 1995. Cognitive disorders in the positive, negative, and disorganization syndromes of schizophrenia. Psychiatry Research 58(3), 227-235.

Cuesta, M.J., Peralta, V., Zarzuela, A., 2007. Empirical validation of competing definitions of schizophrenia: a poly-diagnostic study of cognitive impairment in non-affective psychosis. Schizophrenia Research 95(1-3), 39-47.

Demjaha, A., MacCabe, J.H., Murray, R.M., 2012. How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. Schizophrenia Bulletin 38(2), 209-214.

Endicott, J., Andreasen, N.C., Spitzer, R.L., 1978. Family history-research diagnostic criteria (FH-RDC). New York State Psychiatric Institute, New York.

Fowler, T., Zammit, S., Owen, M.J., Rasmussen, F., 2012. A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. Archives of General Psychiatry 69(5), 460-466.

Gale, C.R., Batty, G.D., McIntosh, A.M., Porteous, D.J., Deary, I.J., Rasmussen, F., 2013. Is bipolar disorder more common in highly intelligent people? A cohort study of a million men. Molecular Psychiatry 18(2), 190-194.

Glahn, D.C., Almasy, L., Barguil, M., Hare, E., Peralta, J.M., Kent, J.W., Jr., Dassori, A., Contreras, J., Pacheco, A., Lanzagorta, N., Nicolini, H., Raventos, H., Escamilla, M.A., 2010. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. Archives of General Psychiatry 67(2), 168-177.

Goldberg, X., Fatjo-Vilas, M., Munoz, M.J., Campanera, S., Miret, S., Minano, M.J., Aguilera, M., Miralles, M.L., Navarro, M.E., Lazaro, L., Guitart, M., Barrantes-Vidal, N., Fananas, L., 2012. Increased familiarity of intellectual deficits in early-onset schizophrenia spectrum disorders. World Journal of Biological Psychiatry 13(7), 493-500.

Golden, C.J., 1978. Stroop color and word test. A manual for clinical and experimental uses. Stoelting Co., Wood Dale, Illinois.

Gur, R.E., Nimgaonkar, V.L., Almasy, L., Calkins, M.E., Ragland, J.D., Pogue-Geile, M.F., Kanes, S., Blangero, J., Gur, R.C., 2007. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. American Journal of Psychiatry 164(5), 813-819.

Heaton, R., Chelune, G., Talley, J., Kay, G., Curtiss, G., 1993. Wisconsin Card Sorting Test. Psychological Assessment Resources, Odessa, FL.

Jablensky, A., 2010. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. Dialogues Clin Neurosci 12(3), 271-287.

Kendler, K.S., Neale, M.C., 2009. "Familiality" or heritability. Archives of General Psychiatry 66(4), 452-453.

Landmark, J., 1982. A manual for the assessment of schizophrenia. Acta Psychiatrica Scandinavica. Supplementum 298, 1-88.

Leckman, J.F., Sholomskas, D., Thompson, W.D., Belanger, A., Weissman, M.M., 1982. Best estimate of lifetime psychiatric diagnosis: a methodological study. Archives of General Psychiatry 39(8), 879-883.

Lichtenstein, P., Yip, B.H., Bjork, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M., 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373(9659), 234-239.

McGrath, J.A., Avramopoulos, D., Lasseter, V.K., Wolyniec, P.S., Fallin, M.D., Liang, K.Y., Nestadt, G., Thornquist, M.H., Luke, J.R., Chen, P.L., Valle, D., Pulver, A.E., 2009. Familiality of novel factorial dimensions of schizophrenia. Archives of General Psychiatry 66(6), 591-600.

Murray, R.M., Lewis, S.W., Reveley, A.M., 1985. Towards an aetiological classification of schizophrenia. Lancet 1(8436), 1023-1026.

Nicodemus, K.K., Marenco, S., Batten, A.J., Vakkalanka, R., Egan, M.F., Straub, R.E., Weinberger, D.R., 2008. Serious obstetric complications interact with hypoxia-regulated/vascular-expression genes to influence schizophrenia risk. Molecular Psychiatry 13(9), 873-877.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1), 97-113.

Owens, S.F., Picchioni, M.M., Ettinger, U., McDonald, C., Walshe, M., Schmechtig, A., Murray, R.M., Rijsdijk, F., Toulopoulou, T., 2012. Prefrontal deviations in function but not volume are putative endophenotypes for schizophrenia. Brain 135(Pt 7), 2231-2244.

Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nature Reviews. Neuroscience 9(12), 947-957.

Peña-Casanova, J., 1990. Test Barcelona. Masson, Barcelona.

Perala, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppa, T., Harkanen, T., Koskinen, S., Lonnqvist, J., 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Archives of General Psychiatry 64(1), 19-28.

Peralta, V., Cuesta, M.J., 2005. The underlying structure of diagnostic systems of schizophrenia: a comprehensive polydiagnostic approach. Schizophrenia Research 79(2-3), 217-229.

Peralta, V., Cuesta, M.J., 2007. The relationship between syndromes of the psychotic illness and familial liability to schizophrenia and major mood disorders. Schizophrenia Research 91(1-3), 200-209.

Plomin, R., Daniels, D., 2011. Why are children in the same family so different from one another? International Journal of Epidemiology 40(3), 563-582.

Reitan, R., Wolfson, D., 1993. The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation. Neuropsychology Press, Tucson, AZ.

Reveley, A.M., Reveley, M.A., Murray, R.M., 1984. Hypothesis for the etiology of schizophrenia: a genetic perspective. Psychopharmacology Bulletin 20(3), 505-508.

Roy, M.A., Flaum, M.A., Gupta, S., Jaramillo, L., Andreasen, N.C., 1994. Epidemiological and clinical correlates of familial and sporadic schizophrenia. Acta Psychiatrica Scandinavica 89(5), 324-328.

Rutten, B.P., Mill, J., 2009. Epigenetic mediation of environmental influences in major psychotic disorders. Schizophrenia Bulletin 35(6), 1045-1056.

Sautter, F.J., McDermott, B.E., Cornwell, J., Wilson, A.F., Johnson, J., Vasterling, J.J., 1997a. Neuropsychological deficits in probands from multiply-affected schizophrenic families. Journal of Psychiatric Research 31(5), 497-508.

Sautter, F.J., McDermott, B.E., Cornwell, J.M., Borges, A., Johnson, J., Vasterling, J.J., Marcontell, D.K., 1997b. A comparison of neuropsychological deficits in familial schizophrenics, nonfamilial schizophrenics, and normal controls. The Journal of Nervous and Mental Disease 185(10), 641-644.

Sitskoorn, M.M., Aleman, A., Ebisch, S.J., Appels, M.C., Kahn, R.S., 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophrenia Research 71(2-3), 285-295.

Suvisaari, J.M., Haukka, J., Tanskanen, A., Lonnqvist, J.K., 1998. Age at onset and outcome in schizophrenia are related to the degree of familial loading. British Journal of Psychiatry 173, 494-500.

Tenesa, A., Haley, C.S., 2013. The heritability of human disease: estimation, uses and abuses. Nature Reviews. Genetics 14(2), 139-149.

van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. Nature 468(7321), 203-212.

Van Os, J., Marcelis, M., Sham, P., Jones, P., Gilvarry, K., Murray, R., 1997. Psychopathological syndromes and familial morbid risk of psychosis. British Journal of Psychiatry 170, 241-246.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Verdoux, H., van Os, J., Sham, P., Jones, P., Gilvarry, K., Murray, R., 1996. Does familiality predispose to both emergence and persistence of psychosis? A follow-up study. British Journal of Psychiatry 168(5), 620-626.

Weissman, M.M., Wickramaratne, P., Adams, P., Wolk, S., Verdeli, H., Olfson, M., 2000. Brief screening for family psychiatric history: the family history screen. Archives of General Psychiatry 57(7), 675-682.

Welham, J., Isohanni, M., Jones, P., McGrath, J., 2009. The antecedents of schizophrenia: a review of birth cohort studies. Schizophrenia Bulletin 35(3), 603-623.

Wolitzky, R., Goudsmit, N., Goetz, R.R., Printz, D., Gil, R., Harkavy-Friedman, J., Malaspina, D., 2006. Etiological heterogeneity and intelligence test scores in patients with schizophrenia. Journal of Clinical and Experimental Neuropsychology 28(2), 167-177.

Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. Journal of Clinical Psychiatry 64(6), 663-667.

Wray, N.R., Gottesman, I., 2012. Using summary data from the danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Front Genet 3, 118.

Yoon, P.W., Scheuner, M.T., Khoury, M.J., 2003. Research priorities for evaluating family history in the prevention of common chronic diseases. American Journal of Preventive Medicine 24(2), 128-135.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Contributors

Manuel J. Cuesta and Victor Peralta designed the study, analyzed the data and wrote the first draft of the manuscript. Amalia Zarzuela performed the neuropsychological assessment. Manuel J. Cuesta, Amalia Zarzuela, Ana M. Sánchez-Torres and Ruth Lorente designed the neuropsychological battery and participated in the analysis and interpretation of cognitive results. Lucía Moreno and Julio Sanjuan cooperated in the interpretation of familial data and in comments to the definitive version of the manuscript.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Conflict of interest:

None.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

5. Table(s)

Table 1: Demographic, educational and cognitive test variables of patient and control groups

	Patients (n= 169)	Control group (n= 26)	F or x^2	p
Age	33.28 ± 9.22	31.15 ± 7.89	1.246	0.266
Education (years)	10.96 ± 3.04	12.08 ± 2.09	3.165	0.077
Gender: males (%)	109/60 (64.4%)	16/10 (61.5%)	0.86	0.770
Age at onset	23.77 ± 6.9			
Duration of illness (years)	9.51±7.18			
Psychopathological scores				
SAPS Total Score at admission	10.43 ± 3.86			
SANS Total Score at admission	11.86 ± 5.38			
SAPS Total Score at cognitive assessment	4.05 ± 3.53			
SANS Total Score at cognitive assessment	7.56 ± 5.24			
DSM IV Diagnostic breakdowns				
Schizophrenic disorder	108 (64%)			
Schizophreniform disorder	7 (4%)			
Schizoaffective	12 (7%)			
Affective disorder with psychotic symptoms	31 (18%)			
Brief Psychotic Disorder	6 (4%)			
Atypical Psychosis	3 (2%)			
Delusional disorder	2 (1%)			
Drugs				
Chlorpromazine equivalents doses	480.34 ± 475.14			
Biperidene doses (mg)	2.28 ± 2.88			
Neuropsychological tests			t	p
Edinburgh test	13.19 ±. 6.64	14.80 ± 7.31		n.s.
Information (WAIS)	12.86 ±. 4.51	12.07 ± 1.62		n.s.
Word Fluency	16.44 ±. 4.91	21.69 ± 5.53	-5.25	0.0001
Trail Making test A (seconds)	66.80 ±53.86	37.23 ± 13.01	2.78	0.0060
Trail Making test B (seconds)	164.73 ± 112.87	69.77 ± 26.75	4.26	0.0001
WCST Perseverative responses	26.25 ±18.75	12.77 ± 8.39	3.6	0.0004
WCST number of categories	3.99 ± 2.00	5.50 ± 1.20	-3.74	0.0002
Stroop Color-Word score	32.24 ± 8.43	45.54 ± 7.27	-7.61	0.0001
Stroop interference Task	43.05 ± 7.66	46.92 ± 7.47		n.s.
Inmediate Verbal Memory	10.76 ± 4.01	17.48 ± 3.14	-8.16	0.0001
Delayed Verbal Memory	12.33 ± 3.95	18.15 ± 3.12	-7.17	0.0001
Inmediate Visual Memory	7.76 ± 2.38	9.0 ± 1.09	-2.63	0.0092
Delayed Visual Memory	9.29 ± 3.82	13.61 ± 1.96	-5.71	0.0001

WCST: Wisconsin card sorting test.
n.s.: non significant

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Table 2: Spearman coefficient correlations between familial scores (for schizophrenia and mood disorder) and cognitive performance[a]

	Familial loading for	
Neuropsychological tests	**Schizophrenia**	**Mood Disorders**
Information (WAIS)	-0.02	-0.08
Word Fluency	0.03	0.11
Trail Making form A	-0.10	-0.20 / p≤ 0.02
Trail Making form B	-0.09	-0.09
Perseverative responses (WCST)	-0.27/ **p≤ 0.001**	-0.18/ p≤ 0.015
Number of Categories (WCST)	0.16/ p≤ 0.034	0.07
Stroop Color-Word score	0.01	0.02
Stroop Interference score	-0.09	-0.11
Immediate Verbal Memory	0.01	0.06
Delayed Verbal Memory	0.03	0.05
Immediate Visual Memory	0.16/ p≤ 0.038	-0.01
Delayed Visual Memory	0.28/ **p≤ 0.001**	0.07

[a]= The critical p-value for p≤ 0.05 was set at p≤0.004 after the Bonferroni correction.

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.

Table 3: Median differences in neuropsychological tests between groups classified by extreme tertiles of familial loading scores for schizophrenia, mood disorder and psychosis [a]

	Groups classified by extreme tertiles of familial loading for			
Neuropsychological tests	**Schizophrenia**		**Mood Disorders**	
	K-W	**p≤**	**K-W**	**p≤**
TOTAL SAMPLE (n=169)				
Perseverative responses (WCST)	**7.848**	**0.006**		ns
Delayed Visual Memory	**9.501**	**0.002**		ns
SCHIZOPHRENIA PATIENTS (n=108)				
Perseverative responses (WCST)	3.962	0.047		ns
Delayed Visual Memory	4.536	0.033		ns
NON-SCHIZOPHRENIA PATIENTS (n=61)				
Perseverative responses (WCST)	3.081	0.051		
Inmediate Visual Memory	**7.195**	**0.007**		ns
Delayed Visual Memory	5.162	0.023		ns

[a]=The critical p-value for p≤ 0.05 was set at p≤0.01 after the Bonferroni correction.

7. Optional e-only supplementary files

Click here to download 7. Optional e-only supplementary files: Supplementary Table 1.docx

Familial liability to schizophrenia and mood disorders and cognitive impairment in psychosis.
Cuesta MJ, Zarzuela A, Sánchez-Torres AM, Lorente-Omeñaca R, Moreno-Izco L, Sanjuán J, Peralta V.
Psychiatry Res. 2015 Jun 30;227(2-3):258-64. doi: 10.1016/j.psychres.2015.03.024.