Substantial Genetic Link Between IQ and Working Memory: Implications for Molecular Genetic Studies on Schizophrenia. The European Twin Study of Schizophrenia (EUTwinsS)

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While evidence is accumulating to support specific neurocognitive deficits as putative endophenotypes for schizophrenia, the heritability of these deficits in healthy subjects and whether they share common genetic influences, is not well established. In the present study, 529 healthy adult twins from two centers within the European Twin Study Network on Schizophrenia (EUTwinsS) were assessed on two domains that are consistently found to be particularly compromised in schizophrenia. Specifically, Intellectual Quotient Score (IQ) and the Letter–Number Sequencing Test (LNS), a measure of working memory, were measured in all twins. Latent variable components were explored through structural equation modeling, and common genetic underpinnings were examined using bivariate analyses. Results showed that the phenotypic correlation between IQ and working memory is substantial, indicating a strong genetic component. These findings support the use of IQ and LNS as putative endophenotypes for schizophrenia and highlight the potential for molecular genetic studies using twin data to elucidate the genetic basis of neurocognitive abnormalities in schizophrenia.

How to Cite this Article:

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memory was almost entirely attributed to shared genetic variance (95.5%). We discuss the potential use of a combined measure of IQ and working memory to improve the power of molecular studies in detecting the genetic mechanisms underlying schizophrenia. © 2013 Wiley Periodicals, Inc.

**Key words:** cognition; heritability; endophenotypes; healthy population; etiology

**INTRODUCTION**

Schizophrenia is a severe mental illness that represents the fifth most important cause of years lost due to disability worldwide [WHO 2004]. Its inheritance appears in line with other complex genetic diseases, where the phenotype expresses the combined influence and interaction of multiple genes [Stefansson et al., 2009; Greenwood et al., 2011; Ayalew et al., 2012]. However, the substantial variation in the clinical presentation of patients with schizophrenia introduces important limitations to unravel the underlying causes of this disorder.

One strategy to reduce this heterogeneity is to focus on characteristics of the illness whose expression is biologically less complex than the clinical syndrome, known as endophenotypes. The endophenotype strategy aims at identifying predisposing genes for schizophrenia by indexing processes pathophysiologically more proximal to genetic effects than the complex clinical manifestations of the disorder [Gottesman and Gould, 2003; Kendler and Neale, 2010]. In this regard, neurocognitive deficits are among the most promising endophenotypes for schizophrenia, since they constitute solid indicators of increased risk for the disorder and further present a clear neurobiological foundation [Gur et al., 2011].

Deficits in general intellectual ability (as measured with the intellectual quotient or IQ) and in the executive component of working memory have consistently been revealed in patients with schizophrenia [Gur et al., 2007; Toulopoulou et al., 2010] and are detectable even years before the onset of symptoms [Cannon et al., 2002; Barnett et al., 2012]. Furthermore, these domains have been proposed to be specifically altered in unaffected family members of the patients suggesting that these cognitive deficits in healthy relatives could be caused by common variants of risk for the disease [Toulopoulou et al., 2007; Owens et al., 2010; Owens et al., 2011; Goldberg et al., 2012].

A key controversial topic regarding the validity of all candidate endophenotypes, including neurocognitive, is that the observed heritabilities tend to be lower than the reported heritability (h²) of around 80% for the phenotype of schizophrenia [Flint and Munafo, 2007]. The proportion of genetic influence on the executive control aspect of working memory as assessed by the widely used letter–number sequencing test (LNS) was found to be around 40% [Greenwood et al., 2007]. Interestingly, IQ shows higher h² ranging up to 87% [Deary et al., 2010]. But this later domain has been linked to genetically complex morphological brain structures such as total brain size as well as a large number of genetic variants [Davies et al., 2011], which challenges its validity as an endophenotypic trait.

For this reason, research on schizophrenia and on other genetically complex brain diseases now tend to focus on the combined use of genetically overlapping endophenotypes. This approach based on the correlation structure between two traits might be valuable for the design of gene mapping studies [Aukes et al., 2008; Greenwood et al., 2012]. The rationale behind this approach is that if one gene or set of genes contribute to more than one of these neurobiological traits (a mechanisms known as pleiotropy), then a combination of such endophenotypes based on the magnitude of genetic correlations may be useful to detect those underlying genes [Braff et al., 2007].

Studies on the normal variability of the neurocognitive domains proposed as candidate endophenotypes for schizophrenia provide valuable information concerning the heritability of these traits. In the present study, we aimed to test the potential use of a combined measure of neurocognitive traits proposed as candidate endophenotypes (IQ and working memory) by examining its genetic architecture in a sample of adult healthy twins.

**MATERIALS AND METHODS**

Cognitive data were available from 529 healthy adult twins (264 twin pairs) drawn from two research institutions forming part of the European Twin Study Network on Schizophrenia (EUTwinsS). For the present study, one sample was drawn from London, United Kingdom—Institute of Psychiatry—and the other from Barcelona, Spain—Universitat de Barcelona. Recruitment at each site has been described in detail elsewhere [Toulopoulou et al., 2007, 2010; Alemany et al., 2012]. Briefly, both sites conducted recruitment among healthy twins between 17 and 65 years of age from local Twin Registers and by advertisement in national media.

Clinical assessment was carried out on all twin pairs using the Structured Clinical Interview for DSM-IV [First et al., 1997] and/or the General Health Questionnaire [Sánchez-López and Dresch, 2008] and the Schedule for Affective Disorders and Schizophrenia—Lifetime Version [Spitzer and Endicott, 1978]. Healthy twins were included when no personal or family history of psychosis, no personal history of neurological disorder or a systemic illness with known neurological complications and no current substance misuse or dependency could be detected. Written informed consent was obtained from all participants following a detailed description of the aims and design, after the study was approved by the local Ethics Committees.

Zygosity was confirmed by genotyping highly polymorphic microsatellite loci (SSRs) and a standardized twin likeness questionnaire [Cohen et al., 1975]. The combined sample included 186 monozygotic (MZ) twin pairs and 78 dizygotic (DZ) twin pairs. Demographic characteristics for the complete sample according to zygosity group are shown in Table I.

**Neurocognitive Assessment**

A standardized protocol was used in both sites that included:

Letter–number sequencing test (LNS) [Wechsler, 1997]. Performance in this test involves categorizing letters and numbers that are presented in an unordered sequence into separate classes, and reordering the stimuli. It provides a measure of a central executive
component of working memory, which concerns maintenance and complex manipulation of various forms of information.

General Intellectual Ability [Wechsler, 1997]. A full-scale Intelligence Quotient (IQ) score was derived from the assessment of the Wechsler Adult Intelligence Scale in the London sample. A short-form score derived from the same scale was used in the Barcelona sample that included the subtests of Vocabulary, Information, Block Design and Matrix Reasoning. This combination has high reliability and validity scores, of 0.963 and 0.922, respectively [Sattler, 2008]. Participants in both sites were administered the test according to the procedures described in the Administration and Scoring Manual.

Statistical Analysis

Demographic distributions of age, gender, and years of education across sites were explored using independent samples t-test and $\chi^2$-test based on one randomly selected member of each twin pair. The selection of one twin in each pair is a widely used method employed to control for the non-independence of data found in any family-based study [Rebollo et al., 2006]. Within-trait and between-trait correlations were examined to determine whether LNS and IQ were associated.

Structural equation modeling on twin data enables the estimation of latent variance components based on the contrast between MZ and DZ twins, where the relative contribution of genetic and environmental effects to the total phenotypic variance can be estimated [Boomsma et al., 2002]. In our study, genetic model fitting was applied to estimate the model parameters including additive genetic effects (A), common environmental effects shared between twins (C) and unique environmental influences not shared by the twins (E) [Rijsdijk and Sham, 2002].

To estimate the genetic overlap between IQ and LNS we used a bivariate approach. This allowed us to decompose the covariance of traits into estimates of their genetic correlation ($r_g$), shared-environmental correlation ($r_e$), and nonshared environmental correlation ($r_n$). A genetic correlation of 1.0 implies that all additive genetic influences on the first trait also impact on the second trait. However, these correlations do not consider the heritability of each assessed trait, and therefore it could be possible that a putative large genetic correlation explained only a limited part of the phenotypic covariance between the traits. Further analyses were run to combine the results of the heritability estimates with those resulting from this analysis in order to calculate the part of the phenotypic correlation due to genetic and environmental effects [Rijsdijk et al., 2005; Hall et al., 2007].

We compared the fit of the ACE model to the saturated statistics, and to models dropping either additive genetics effects, shared environment, or both. Absence of significance of the parameter indicates that the observed values do not significantly diverge from the expected values. Sources of variation were computed in Mx [Neale et al., 1999].

RESULTS

Statistically significant differences in age and years of education were found across sites ($P < 0.001$ and $P < 0.01$, respectively). Thus, the analyses were run using the standard residual values for each neurocognitive test adjusted for age, gender, years of education, and site [Zeegers et al., 2004].

Mean LNS score for the complete sample was 11.29 (SD = 2.99) and mean IQ score = 107.47 (SD = 13.97). The phenotypic correlation ($r_{ph}$) between LNS and IQ was 0.45 (95% CI = 0.36 to 0.53). Within-trait and between-trait correlations for the MZ and DZ pairs suggested an important genetic component in the origin of
IQ and LNS (Table II), which was further tested using structural genetic modeling.

Both LNS and IQ showed significant influences of genetic and unique-environmental effects, and comparison of the fit of the variance decomposition models showed that AE was the best-fitting model for these measures. The standardized estimates for this best-fitting model were $A = 0.77$ (95% CI = 0.70 to 0.82) for IQ and $A = 0.57$ (95% CI = 0.46 to 0.66) for LNS.

We performed bivariate analyses on IQ and LNS to test the extent to which these measures shared the same genetic variance. The most parsimonious model of the variance decomposition for this analysis was a model in which additive genetic influences and unique environmental influences significantly contributed to the phenotype, while dropping the shared-environmental influences did not result in a worst fit ($\chi^2 = 1.96, P = 0.58$).

The decomposition of the shared etiological causes suggested that the phenotypic correlation ($r_{ph}$) between LNS and IQ was due to shared genetic influences ($r_a = 0.66, 95\% CI = 0.53 to 0.77$), while unique environment influences were not shared between the two traits. Figure 1 shows the bivariate pathway model and results. The statistical power of this analysis in our study based on the combined sample size of 264 twin pairs and at the 0.05 significance level was high (0.889).

When the heritability estimates of each trait were considered in the analysis, the part of the phenotypic correlation that could be attributed to genetic factors was $r_{ph-a} = 0.43$ (calculated as $r_{ph-a} = \sqrt{h^2_{iq} * r_a * h^2_{wm}}$), and to unique environmental influences was $r_{ph-e} = 0.016$ (calculated as $r_{ph-e} = \sqrt{e^2_{iq} * r_e * e^2_{wm}}$). That is, 95.5% [(0.43/0.45) × 100] of the phenotypic correlation between IQ and LNS was accounted for by shared genetic influences.

**DISCUSSION**

In the present study we explored the shared genetic origins of two neurocognitive domains previously proposed as putative endophenotypes for schizophrenia, namely IQ and LNS. We found that 95.5% of the phenotypic correlation between IQ and LNS was attributed to shared genetic influences. The proportion of genetic components affecting the phenotypic correlation between these traits was larger than the proportion of genetic influences found for each endophenotype taken individually. In this regard, our results provide support to earlier limited findings for the use of multivariate measures in studies aimed at identifying the genetic architecture of schizophrenia [Schork et al., 2007; Aukes et al., 2009; Owens et al., 2010].

The association between working memory and intelligence in healthy individuals is one that has been previously acknowledged. In line with our results, these studies have provided evidence of a strong relationship between these domains using measures of event-related potential, visual working memory tasks and factor analyses [Luciano et al., 2001; Hansell et al., 2005; Unsworth, 2010]. To our knowledge, the association between IQ and LNS has not yet been reported, although LNS is a robust index of working memory widely used in endophenotypic studies of schizophrenia. We found that these domains shared 66% of their genetic origin, suggesting that the same set of genes contribute to the phenotypic expression of these putative endophenotypes in a healthy population. Therefore, combining these domains might provide studies with a more robust estimate of the constructs they measure.

Molecular studies of specific genes associated with intelligence and working memory are in line with a putative genetic overlap. Some of these genes have also been proposed as candidate genes for schizophrenia [Harrison and Weinberger, 2005]. The COMT gene, which codes for the catechol-O-methyl transferase enzyme involved in the modulation of catecholamines such as dopamine, has been associated with both intelligence performance [Barnett et al., 2007] and working memory, specifically with the letter–number sequencing task [Bruder et al., 2005; Dickinson and Elvevag, 2009]. Dystrobrevin binding protein-1 (dysbindin), a gene that influences glutamate signaling, has also been found in association with these cognitive endophenotypes [Burdick et al., 2007; Fatjo-Vilas et al., 2011]. In this regard, the large number of genes implicated in the expression of intellectual ability might be reduced if genetic overlap with working memory is considered in the analyses.

Two main limitations need acknowledgement in our study. In first place, given the very large sample sizes required to detect shared environmental effects on neurocognition, our study may be under-powered to reflect this component on the measures assessed. Secondly, it is possible that a deviation from a 1:1 in the MZ:DZ ratio may lead to a decrease in power for detecting moderate heritabilities [Martin et al., 1978; Neale et al., 1994]. Nevertheless,
we could confirm statistical power to perform the analyses in this sample.

In brief, our study posits the genetic overlap of the neural pathways involved in intelligence (IQ) and the executive control processes of working memory (LNS) and highlights the genetic underpinnings of individual differences in cognitive domains. The common components found provide biological support to the existence of influencing processes shared between these two putative endophenotypes. In the interpretation of our results, potential differences between healthy controls and clinical samples should be considered as heritability estimates may decrease when diagnosis of schizophrenia is included in the analysis [Chen et al., 2009]. However, our study was based on similar measures to those used in studies of patients and indeed our findings complement the limited existing literature on this issue. Such identification of highly heritable and genetically correlated traits can potentially improve the ability of molecular studies to detect particular genetic mechanisms concerning the phenotype, while the combined use of genetically overlapped neurocognitive traits could enhance the detection of risk associated with schizophrenia. Further research including specific genetic variants will probably lead to the examination of a putative causal course and the joint action of sets of candidate genes in these processes.

ACKNOWLEDGMENTS

The authors would like to thank the twins, whose voluntary participation made this work possible. This work was supported by: European Twins Study Network on Schizophrenia Research Training Network (grant number EU TwinsS, MRTN-CT-2006-035987); Spanish Ministry of Science and Innovation (grant number SAF2008-05674-C03-00); Spanish Ministry of Science and Innovation, Health Institute Carlos III, Center of Biomedical Research in Network of Mental Health (CIBERSAM); the National Alliance for Research on Schizophrenia and Depression through a NARSAD Young Investigator Award to T.T.; a Research Training Fellowship from the Wellcome Trust to M.P.; and Marie Curie grant from the European Twin Study Network on Schizophrenia at the University of Barcelona Node (grant number EU TwinsS, MRTN-CT-2006-035987) to X.G. All funding sources had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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