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The nature of schizotypy among multigenerational multiplex schizophrenia families

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Abstract

Identification of endophenotypes (Gottesman & Gould, 2003; Gottesman & Shields, 1972) that genetically correlate with schizophrenia and are genetically homogeneous is an important strategy for detecting genes that affect schizophrenia risk. Symptoms of schizotypy may familially correlate with schizophrenia; however, there are critical limitations of the current literature concerning this association. The present study examined the genetic architecture and genetic associations between schizotypy and schizophrenia among multigenerational, multiplex schizophrenia families. Genetic schizotypy factor scales were developed that genetically correlated with schizophrenia, although some relations were unexpected in direction suggesting minimization of “psychotic-like” symptoms. These genetic schizotypy factor scales did not genetically correlate with major depressive disorder or substance dependence indicating specificity to schizophrenia. The results highlight the possibility of significant response bias in schizophrenia families, particularly among close relatives, and suggest an important consideration when acquiring self-report information. This is a topic that deserves future study as the origins of this putative bias in relatives are unclear. In addition, the results support the identification of genetic schizotypy factors as a promising technique for maximizing genetic correlation of endophenotypes with schizophrenia.

Keywords

Schizotypal; Endophenotype; Relatives; Behavior genetics; Factor analysis

To the degree that a putative endophenotype (Gottesman & Gould, 2003; Gottesman & Shields, 1972) approximates genetic homogeneity and is genetically correlated with schizophrenia, the more likely it is to be useful in detecting specific risk genes (Pogue-Geile

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& Yokley, 2010). There is evidence that symptoms of schizotypal personality disorder [schizotypy (Meehl, 1962)] may be genetically correlated with schizophrenia (Lien et al., 2010; Ritsner, Karas, & Ginath, 1993), although there are substantial methodological limitations present in the current literature (Pogue-Geile & Tarbox, in press; Yin-Ju et al., 2009). Yet, even if symptoms of schizotypal personality disorder are found at a higher rate in relatives compared to controls, their sensitivity to specific schizophrenia risk genes would be compromised to the extent that these symptoms are themselves genetically heterogeneous. This is problematic from the standpoint that to be useful in genetic studies, an endophenotype must be sensitive to as few schizophrenia risk genes as possible and have limited sensitivity to non-schizophrenia risk genes.

Data from genetically-related individuals permit estimation of the unique contributions of genetic and environmental effects on a particular phenotype (e.g., schizotypal personality disorder symptom). A phenotype that is strongly influenced by genetic effects (i.e., high heritability) is ideal as this suggests minimal impact of environmental effects, although a highly heritable phenotype can still be genetically heterogeneous, including effects of both multiple schizophrenia risk and non-risk genes. It is therefore necessary to estimate both heritability and genetic homogeneity when evaluating a promising phenotype. Phenotypic covariation of observed symptoms among family members can be separated into genetic and environmental variance components. Furthermore, genetic covariance among variables (e.g., symptoms of schizotypal personality disorder) can be represented in terms of a set of genetic factors (Boomsma & Dolan, 1998; Boomsma, Molenaar, & Orlebeke, 1990). Regarding schizotypal personality disorder, genetic factors would reflect relative genetic homogeneity among schizotypal personality disorder symptoms, absent confounding effects of environmental variance. Consequently, schizotypal personality disorder genetic factors may be particularly sensitive to genetic liability to schizophrenia and useful in gene identification efforts using linkage and association methods.

Aims of the Current Study

This multigenerational, multiplex family study sought to examine associations between schizotypal personality disorder symptoms and genetic liability to schizophrenia among non-psychotic relatives of schizophrenia probands, with the ultimate goal of evaluating the utility of schizotypal symptoms as endophenotypes in genetic studies of schizophrenia. The following specific aims were addressed:

1. Construction of genetically homogeneous and uncorrelated schizotypal personality disorder genetic factor scales;
2. Estimation of heritabilities of these schizotypal personality disorder genetic factor scales;
3. Calculation of genetic correlations between the schizotypal personality disorder genetic factor scales and schizophrenia;
4. Calculation of genetic correlations between the schizotypal personality disorder genetic factor scales and two additional psychiatric diagnoses represented in this sample, major depressive disorder (MDD) and substance dependence, to evaluate scale specificity.

Method

Participants

Pedigree and control participants were recruited as part of a large, multisite schizophrenia multiplex family study (Gur et al., 2007). The participants in this study were 640 European-

American pedigree members from 43 multigenerational multiplex families and 88 non-psychotic control individuals demographically matched to the pedigree members. All participants provided written informed consent according to the guidelines of the University of Pittsburgh or University of Pennsylvania Institutional Review Boards.

Index probands—Potential probands were identified through consumer and mental health organizations located in Pennsylvania, Delaware, Indiana, Kentucky, Michigan, New Jersey, Ohio, and West Virginia. Probands were at least 18 years old, European-American, met DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder, depressed type, and had at least one first-degree relative who also was at least 18 years old, European-American, met DSM-IV criteria for either schizophrenia or schizoaffective disorder, depressed type, and might be willing to participate. All diagnoses were established by consensus based on diagnostic interviews (see below). Each proband was further required to have at least 10 first- to fourth-degree relatives possibly willing to participate. Potential probands were excluded according to the following criteria: unable to provide signed informed consent, unwilling to provide consent to contact family members, psychosis due to a substance use disorder, medication, medical/neurological condition, or pervasive developmental disorder by DSM criteria, existence of a medical condition that may cause neurocognitive deficits, IQ < 70, or lack of proficiency in English. Forty-three index probands met inclusion criteria and were enrolled in the study. The majority of probands were diagnosed with schizophrenia (n = 41); two were diagnosed with schizoaffective disorder, depressed type.

Index relatives—First- to fourth-degree relatives of each index proband who were 15 years of age or older at the time of recruitment and resided within the contiguous United States were eligible for participation. Potentially eligible relatives were identified by the probands and other enrolled family members and gave permission to be contacted by phone. Eligibility was established via a brief phone screening. Exclusion criteria were minimal: existence of a medical condition that may cause neurocognitive deficits, or lack of proficiency in English. In person interviews were scheduled with eligible relatives who agreed to participate.

Affected pedigree members: Of the 597 first through fourth degree index relatives initially recruited through the index proband, 60 were diagnosed with either schizophrenia (n = 51) or schizoaffective disorder, depressed type (n = 9) (see Table 1). These 60 affected index relatives, along with the 43 index probands, comprised the group of 103 affected pedigree members; there was an average of 2.4 affected individuals per family.

Unaffected pedigree members: The remaining 537 index relatives were not diagnosed with either schizophrenia or schizoaffective disorder, depressed type, and thus were “unaffected” pedigree members. The following additional hierarchical diagnoses were represented among the unaffected relatives (n): schizoaffective disorder, bipolar type (4); other psychotic disorder (e.g., substance or medically related, psychosis NOS) (16); and bipolar disorder (9). The following non-hierarchical, non-exclusive diagnoses also were represented: cluster A personality disorder (schizotypal, paranoid, or schizoid) (25); MDD (with psychotic features or a diagnosis of a cluster A personality disorder) (10); MDD (without psychotic features or diagnosis of a cluster A personality disorder) (110); other mood disorder (59); substance-related disorder (153); and dementia (2).

Controls—Non-psychotic, European-American individuals age 18–84, who did not have a first-degree relative with a psychotic disorder, were eligible for inclusion in the control group. Recruitment procedures implemented at the University of Pittsburgh were designed

to achieve a representative control group that was on average matched on age, sex, and location of residence to the index relatives enrolled in the study. Potential control individuals residing in the regions from which the majority of index probands and relatives had been recruited were initially contacted through random digit dialing. Interested potential control individuals completed a telephone screening to assess the following exclusion criteria: they or a first-degree relative had been diagnosed with a schizophrenia spectrum disorder or other psychotic disorder, recent exacerbation of non-psychotic psychiatric symptoms (e.g., psychiatric hospitalization or a dose increase of psychiatric medication in the past month), electroconvulsive therapy in the past six months, treatment for alcohol or substance disorder in the past six months, medical condition that could produce psychiatric symptoms or neurocognitive deficits (e.g., Alzheimer's disorder), history of head injury resulting in cognitive changes, or sensory or physical impairments that could interfere with completion of study measures.

For the larger study, controls were recruited from both the University of Pittsburgh and the University of Pennsylvania. However, schizotypy symptom data were available only for the 88 control individuals enrolled through the University of Pittsburgh. As presented in Table 1, the following non-hierarchical, non-exclusive diagnoses were present among the 88 controls (n): MDD without psychotic features (24); other mood disorder (4); and substance-related disorder (16). By design, none of the 88 control individuals met criteria for schizophrenia, schizoaffective disorder, or any other psychotic disorder.

Assessments

Diagnostic assessment—Lifetime, multi-axial diagnoses based on DSM-IV criteria were established by consensus conference by licensed psychiatrists and psychologists who were blind to subject identity and group status (proband, relative, control). All interviews were conducted by trained interviewers with established reliability ($\kappa > 0.80$) and under the supervision of the investigators. Reliability and training among interviewers was reviewed at semi-annual meetings. Interviewers were not blind to participant group status.

All participants were administered the Diagnostic Interview for Genetic Studies 2.0 (DIGS) (Nurnberger et al., 1994) to assess current and lifetime psychiatric diagnoses and medical history. Furthermore, at least one relative of each proband was administered the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) to gather additional diagnostic information about family members. Considerable effort was made to interview each participant in person. On the rare occasions when an in-person appointment was not feasible, interviews were conducted by phone. If available, medical records were also reviewed.

Schizotypal personality disorder assessment—Non-psychotic pedigree members and controls were assessed for symptoms of schizotypal personality disorder using a modified version of the Structured Interview for Schizotypy (SIS; Kendler, Lieberman, & Walsh, 1989), which is included as part of the DIGS 2.0.1 The SIS is a semi-structured interview specifically designed to assess schizotypal symptoms and is widely regarded as the most comprehensive interview available for this purpose (Kendler et al., 1993).

The version of the SIS used in this study consists of two sections, the interview itself and post-interview behavior ratings. The interview is composed of 14 scales: Social Isolation, Introversion, Sexual Anhedonia, Sensitivity (i.e. to remarks made about them by others), Social Anxiety, Restricted Emotion, Anger to Perceived Slights, Suspiciousness,

¹By convention, individuals meeting criteria for any psychotic disorder, including probands and “unaffected” relatives diagnosed with a non-schizophrenia psychotic disorder (e.g., MDD with psychotic features), were excluded from assessment of schizotypal personality disorder.

Pathological Jealousy, Ideas of Reference: Being Watched, Ideas of Reference: Remarks, Magical Thinking, Psychotic-like Phenomena (i.e., thought disorder), and Illusions (auditory and visual). The post-interview behavior ratings are completed based on the interviewer's observation of the respondent and include: Affect, Rapport, Guardedness, Organization of SpeechThought, Odd/Eccentric Behavior, Social/Interpersonal Functioning, and Irritability.

SIS scale scores: For each case, scale scores [range: 0 (no pathology) to 6 (marked pathology)] were generated by dividing the sum of the completed items in that scale by the number of completed items. To maximize the number of quantitative items available for each scale, items missing responses due to the design of the SIS interview (e.g., items not clinically applicable to the participant) were coded as '0' if skipped due to absence of pathology or '6' if skipped due to presence of marked pathology. Missing responses due to any other reason were coded as missing. Cases missing responses for the majority of items in a particular scale were excluded from that scale. The Expectation-Maximization (EM) algorithm in SPSS, using the student's *t* distribution, was utilized to impute missing SIS scale data.

Six SIS scales: Suspiciousness, Ideas of Reference: Being Watched, Ideas of Reference: Remarks, Magical Thinking, Illusions, and Odd/Eccentric Behavior, were dichotomized such that a rating of 0 (no pathology) was retained and any rating greater than 0 was given a score of 1 because genetic analyses failed to converge due to extreme scale skewness. These six scales remained dichotomized for all analyses. Seven additional scales (Social Anxiety, Irritability, Anger to Perceived Slights, Pathological Jealousy, Guardedness, Rapport, and Psychotic-like Phenomena) also required dichotomization to complete one or more genetic analysis. These scales can be assumed to be continuous, except where expressly noted that the dichotomized form was used.

SIS group characteristics: SIS data were available for 480 unaffected pedigree members and 88 controls. As noted above, pedigree members diagnosed with any psychotic disorder were excluded from SIS administration, and an additional 24 unaffected relatives were not administered the SIS due to logistical problems unrelated to diagnosis (e.g., refusal, lost to follow-up). SIS data from relatives with diagnoses of dementia (2) and bipolar disorder (8) were excluded from analyses. Relatives diagnosed with a cluster A personality disorder (25) were retained in these analyses so as not to truncate the distribution of symptom severity assessed by the SIS. Table 1 presents demographic and clinical characteristics of the 480 unaffected relatives and 88 control individuals for whom SIS data were available.

Analyses

All univariate analyses of heritability and bivariate analyses of genetic correlation were completed using SOLAR (Sequential Oligogenic Linkage Analysis Routines) (Almasy & Blangero, 1998) to accommodate the complex pedigree structure of the families included in this study. SOLAR is a comprehensive software package for genetic variance components analysis of quantitative-trait data in pedigrees of varying size and complexity. In SOLAR, all dichotomous variables (including diagnostic and trait variables) were modeled as threshold traits, all continuous variables were fit to a *t*-distribution due to skewness, and analyses were corrected for proband-based ascertainment. In these analyses, estimates of heritability and genetic correlation assume that shared environment effects are zero or uncorrelated with genetic relatedness. Analyses not involving examination of pedigree structure were conducted in SPSS or Mplus (Muthen & Muthen, 1998–2010).

Covariates—Age, sex, education, MDD (without psychotic features), and substance dependence (includes alcohol dependence) were selected as possible covariates in analyses.

A number of SIS scales were correlated with age, sex, and education, as well as MDD and substance dependence. Since the effects of education and the diagnostic variables may not necessarily be spurious, analyses were run twice: first with only age and sex as covariates and a second time with the addition of education, MDD, and substance dependence as covariates. Age and sex are covariates in all reported analyses; in each analysis, results were comparable when education, MDD, and substance dependence were added as covariates.

Results

SIS Genetic Factors

Genetic factor analysis—To examine the degree to which genetic effects were shared among the 21 individual SIS scales, bivariate genetic correlations were calculated among all SIS scales while controlling for age and sex in the unaffected pedigree sample. An exploratory factor analysis of the genetic correlations among SIS scales was then performed in Mplus. Factor structure was extracted using unweighted least squares, and Varimax (orthogonal) rotation was applied to reflect the fact that genetic variants segregate independently (unless they are in linkage disequilibrium). Genetic correlations among SIS scales indicate the degree to which participants' ratings are correlated due to common genetic effects. Thus, SIS scales that load strongly on the same genetic factor should be influenced, in part, by the same genetic effects. Six interpretable orthogonal genetic factors were identified using the Kaiser-Guttman rule (eigenvalues > 1), and this solution was consistent with the results of a scree test. Together, the six genetic factors accounted for 87% of the variance in the SIS scales.

The correlations (loadings) of the SIS scales with each of the six genetic factors, along with factor eigenvalues, are reported in Table 2. The first genetic factor, "Paranoid Fears", most strongly reflects the following SIS scales: Social Anxiety, Pathological Jealousy, Sensitivity, Psychotic-like Phenomena, Ideas of Reference (Remarks and Watched), Introversion, and Suspiciousness. Additional scales (e.g., Anger to Perceived Slights) also load above .40, but are more strongly correlated with other factors. This combination of scales suggests that this genetic factor primarily represents paranoid fears and ideas of reference.

The scales that are primarily correlated with the second genetic factor, "Interpersonal Deficits", are Organization of Speech/Thought, Rapport, Affect, Social/Interpersonal Functioning, Irritability, Guardedness, and Social Isolation. Note that all of these scales, except Social Isolation, reflect interviewer observation (not self-report). A few scales that loaded most strongly on the first factor (Paranoid Fears), such as Suspiciousness and Ideas of Reference: Watched, also show moderate correlation with the second factor. Restricted Emotion loaded above .40 as well, but was more strongly correlated with another factor (Constricted Affect). The Interpersonal Deficits factor thus seems best characterized as communication and interpersonal deficits.

The third genetic factor, "Perceptual Distortions", is most strongly represented by the unexpected combination of Sexual Anhedonia and Illusions and is moderately correlated with Psychotic-like Phenomena. As these scales are negatively correlated with this factor, a higher factor score would reflect less sexual anhedonia and fewer perceptual distortions. For ease of communicating the results below, the sign of the Perceptual Distortions factor will be reversed in the following analyses such that from here forward, a higher Perceptual Distortions factor score will correspond to greater pathology on these SIS scales.

The fourth genetic factor presented in Table 2, "Constricted Affect", primarily consists of the Restricted Emotion scale, although Introversion, Affect, Social/Interpersonal Functioning, and Illusions also have loadings greater than .40 (−.40 in the case of Illusions).

As the Illusions scale is negatively correlated with this factor, a lower rating on Illusions contributes to a higher score on this factor.

The fifth genetic factor, “Eccentric Behavior”, is correlated most strongly with Odd/Eccentric Behavior (interviewer observation) and shows moderate correlation with Ideas of Reference: Remarks. This factor might best be described as eccentricities of thought and behavior. These scales are negatively correlated with this factor, so a higher factor score on Eccentric Behavior would indicate less eccentric and unconventional thinking and behavior. As with the third factor, the sign of the Eccentric Behavior factor will be reversed in the following analyses so from here on, a higher Eccentric Behavior factor score reflects greater pathology on these SIS scales.

Lastly, Anger to Perceived Slights and Magical Thinking are strongly correlated with the sixth genetic factor “Unusual Beliefs”, as is Ideas of Reference: Watched. Thus, this factor is predominantly characterized by hostility and atypical beliefs.

Genetic Intercorrelations of SIS Genetic Factor Scales

Genetic factor scores were estimated by the standard regression method (Loehlin, 2004), and calculations were completed using the SPSS Matrix-End Matrix function. Bivariate genetic correlations were calculated among the genetic factor scales while controlling for age and sex in the combined unaffected pedigree and control sample. As can be seen in Table 3, the SIS genetic factor scales were genetically uncorrelated with each other as predicted.

Heritability of SIS Genetic Factor Scales

Heritabilities of the genetic factor scales were next estimated for the six SIS genetic factors in the combined unaffected pedigree and control sample. As presented in Table 4, all factors were significantly heritable ($h^2 = 0.25$ to 0.58 , $p < .001$).

Genetic Correlations of SIS Genetic Factor Scales with Diagnoses

Schizophrenia—Genetic correlations with schizophrenia were estimated for each of the SIS genetic factor scales in the combined unaffected pedigree and control sample; these data are presented in Table 4. Significant negative genetic correlations with schizophrenia were found for the Eccentric Behavior ($R_g = -0.52$, $p = .046$) and Unusual Beliefs ($R_g = -0.45$, $p = .022$) genetic factor scales, and a non-significant, positive genetic correlation with schizophrenia was observed for the Interpersonal Deficits genetic factor scale ($R_g = 0.27$, $p = .194$).

Contrary to expectation, the negative genetic correlation between Eccentric Behavior and schizophrenia indicates that relatives who are closely related to an individual with schizophrenia tend to display less unconventional thinking and odd social behavior, and report fewer ideas of reference, compared to more distant relatives. Similarly, the negative genetic correlation between Unusual Beliefs and schizophrenia indicates that close relatives of schizophrenia patients tend to be low on hostility, and report fewer unusual beliefs, superstitions, and feelings of being scrutinized or singled out in public.

Although non-significant, the positive genetic correlation between Interpersonal Deficits and schizophrenia suggests that as predicted, relatives who are closely related to an individual with schizophrenia may be perceived to demonstrate more atypical speech, low emotionality, constricted or suspicious affect, irritability, and social withdrawal compared to more distant family members. None of the genetic correlations with schizophrenia exceeded the conservative Bonferroni threshold for adjusting for multiple testing ($.05/6 = .008$).

Major Depressive Disorder—Genetic correlations with major depressive disorder (MDD, without psychotic features) were estimated for each of the SIS genetic factor scales, controlling for age and sex, and are reported in Table 5. In contrast to the findings for schizophrenia, none of the genetic factors were significantly genetically correlated with MDD.

Substance Dependence—Genetic correlations with substance dependence also were calculated for each of the SIS genetic factor scales (controlling for age and sex). These data are presented in Table 5 and indicate no significant genetic correlation with substance dependence. Of all six factors, the positive genetic correlation for Paranoid Fears most closely approached significance. As such, individuals who are closely related to someone with substance dependence may tend to report traits such as interpersonal hypersensitivity, distrust, and persecutory ideation.

Discussion

The aim of this multigenerational, multiplex family study of schizophrenia was to construct genetically homogeneous and uncorrelated schizotypal personality disorder genetic factor scales, estimate heritabilities of the genetic factor scales, and calculate genetic correlations between the genetic factor scales and schizophrenia, major depressive disorder (MDD), and substance dependence. The findings can be summarized as follows and are discussed below:

1. Six uncorrelated, schizotypal personality disorder genetic factors were identified, accounting for 87% of the variance in all SIS scales.
2. All schizotypal personality disorder genetic factor scales were significantly heritable. Thus, the difference among individuals on a particular factor scale was importantly caused by genetic effects.
3. Two of the genetically distinct schizotypal personality disorder factor scales, Eccentric Behavior and Unusual Beliefs, were significantly negatively genetically correlated with schizophrenia.
4. None of the six schizotypal personality disorder genetic factor scales were significantly genetically correlated with MDD or substance dependence.

Schizotypy Genetic Factors

To date, factor analyses of schizotypal personality disorder symptoms among relatives of schizophrenia patients have been exclusively “phenotypic” in nature. Phenotypic factors reflect both genetic and environmental covariance and thus confound the effects of genes and environment on symptoms of schizotypal personality disorder. This study is the first to examine the genetic factor structure of schizotypy in an attempt to disentangle genetic and environmental effects. This exploratory factor analysis suggested that six genetic factors best accounted for the genetic covariance among SIS scales, a solution similar to the five traits of “borderline schizophrenia” originally proposed by Kety and colleagues (Copenhagen Adoption Study; Kety, Rosenthal, Wender, & Schulsinger, 1968).

All six genetic factors were significantly heritable and genetically uncorrelated with each other, and thus appear to reflect six distinct, latent genetic variables. The modest heritabilities obtained for the schizotypy genetic factors (h^2 mean = 0.45, range: 0.25 to 0.58) and the individual SIS scales (h^2 mean = 0.47, range: 0.18 to 0.74) are consistent with previous heritability estimates for schizotypal personality disorder in relatives of schizophrenia patients (estimated at 0.61; Torgersen et al., 2000). This suggests that on average, approximately half the variance of schizotypy traits can be attributed to genetic

effects, although this percentage varies considerably across traits, ranging from approximately 20% to over 70%. Given that schizophrenia has an estimated heritability of approximately 0.80 (Cardno et al., 1999), but is not itself apparently associated with one or a few genes of large effect, it is clear that high heritability does not necessarily indicate utility in identifying schizophrenia “risk” genes (Pogue-Geile & Yokley, 2010). Alternatively, if less than 50% of a trait’s variance is attributable to genetic effects, but that genetic variance is correlated with the effects of only one or a small number of “risk” genes, such traits could be useful in detecting genetic associations.

Schizotypy Genetic Factor Scales and Genetic Correlation with Schizophrenia

Two genetic factor scales, Eccentric Behavior and Unusual Beliefs, were significantly negatively genetically correlated with schizophrenia. These results suggest that during the interview, close relatives of schizophrenia probands reported fewer atypical beliefs, superstitions, and feelings of being scrutinized in public, and were observed by the interviewer to display less unconventional thinking, odd social behavior, and hostility, compared to more distant relatives. The negative direction of the significant genetic correlations for the Eccentric Behavior and Unusual Beliefs factor scales was not predicted. In an effort to understand these unexpected findings, several possible explanations were considered.

First, it certainly may be that the significant negative correlations we observed were simply a result of chance. A Bonferroni correction suggests assuming a significance threshold of .008 for the six SIS genetic factors. Utilizing these guidelines, all six genetic factors would remain significantly heritable. However, none of the genetic correlations with schizophrenia would remain significant; therefore, Bonferroni corrected results would indicate no genetic association between schizotypal personality disorder symptoms and schizophrenia. Although Bonferroni correction is conservative, it is possible that these significant negative genetic correlations with schizophrenia are due to chance. Similarly, it may be that these unexpected negative genetic correlations with schizophrenia are spurious given that the interviewers were not blind to participant group status. However, most hypotheses of rater bias effects would predict inflated positive genetic correlations with schizophrenia, not negative.

It is also possible that first-degree relatives from multiplex families may be somehow different on measures of schizotypy compared to first-degree relatives from simplex families, perhaps due to differences in expression of risk genes or environmental experiences. As such, the negative genetic correlations between schizotypal symptoms and schizophrenia in the current multiplex sample may be valid, but could differ from findings in simplex families. Recent evidence suggests a similar phenotypic factor structure of schizotypal personality disorder symptoms in multiplex and simplex families, however (Lien, et al., 2010).

A final potential explanation for the negative genetic correlations observed for Eccentric Behavior and Unusual Beliefs is that during the interview, closer relatives were especially likely to underreport unusual ideas, beliefs, and behavior. As familial relatedness to schizophrenia probands decreased, bias against reporting unusual thoughts and behavior in turn became increasingly rare. This situation would produce a negative familial correlation between the more “unusual” or “positive” symptoms of schizotypy (e.g., magical thinking) and schizophrenia in the current study.

The notion of response bias against “positive” or psychotic-like symptoms in relatives of schizophrenia patients was first suggested more than two decades ago by Katsanis, Iacono and Beiser (1990) and Clementz, Grove, Katsanis, and Iacono (1991). Both reports indicated that first-degree relatives scored lower (endorsed less pathology) than controls on the

Perceptual Aberration Scale (Chapman, Chapman, & Raulin, 1978), despite scoring higher (greater pathology) than controls on the Social and Physical Anhedonia scales (Chapman, Chapman, & Raulin, 1976). Since that time, several studies have reported similar findings using the Chapman Scales as well as questionnaire and interview measures of schizotypal personality disorder (Huxley et al., 1993). For example, Appels et al., (2004) reported that parents of schizophrenia patients endorsed significantly fewer unusual experiences and beliefs compared to controls on the Schizotypal Personality Questionnaire (SPQ; Raine, 1991). In fact, in our recent review of schizotypy in relatives, results of available studies published between 1991 and 2009 supported a medium to large effect of social-interpersonal symptoms among first-degree relatives compared to controls (mean $d = 0.67$), but only a small effect of cognitive-perceptual symptoms (mean $d = 0.37$) (Tarbox & Pogue-Geile, 2011).

Models of reporting bias

The results of the current study and others suggest two possible models of reporting bias in relatives of schizophrenia patients. First, a response bias among relatives could occur due to increased “exposure” to the schizophrenia proband and reluctance to endorse positive schizotypal symptoms associated with their relative’s illness. In this situation, biased responding among close relatives could be entirely due to shared environmental effects rather than schizotypal suspiciousness associated with genetic liability to schizophrenia. This hypothesis implies that in family studies, closer degree relatives will show lower self-reported positive symptoms than more distant relatives due to their increased exposure to a proband. This will be detected as a negative “genetic” correlation with schizophrenia because in family studies like the current one genetic and shared environmental similarity are confounded. In addition, under this model it could also be hypothesized that these self-report ratings should be uncorrelated with observer-rated pathology within relatives. This is predicted because the observer ratings arise primarily due to relatives’ own pathology, whereas the self-report bias comes from a different (presumably uncorrelated) source – degree of exposure to the proband.

A second, but not mutually exclusive model is that increased genetic liability to schizophrenia does elevate schizotypy symptoms, including suspiciousness, leading to heightened guardedness and underreporting among close relatives irrespective of their experience with the schizophrenia proband. In this case, some relatives may adopt a reporting stance of broad symptom minimization that includes both positive and negative schizotypy. As above, this scenario would predict that closer relatives to a schizophrenia proband would show lower self-report symptoms compared to more distant relatives due to genetic effects on suspiciousness. However, this second model could also be hypothesized to predict a negative correlation between self-report positive symptom ratings and observed pathology within relatives because those individual relatives observed to be most pathological would also tend to be most suspicious and thus under-report symptoms.

The construction of the SIS provides an opportunity to further examine these models of response bias. The SIS instrument consists of two types of scales, those rated based on the participant’s self-report responses to interview questions and those rated after the interview based on the interviewer’s observation of the participant. Post-hoc examination of genetic correlations between the individual SIS scales and schizophrenia (provided in Table 6) show first, that the observer-rated SIS scales were on average positively genetically correlated with schizophrenia (R_g : mean = 0.19; range = -0.04 to 0.47), with only one of seven (14%) showing a negative genetic correlation. Furthermore, among the observer ratings, “Guardedness” showed the strongest positive genetic correlation with schizophrenia ($R_g = 0.47$). Of note, performance on a computerized neurocognitive battery, which also is less likely to be influenced by response bias, was positively genetically correlated with

schizophrenia in this multiplex sample such that first-degree relatives showed greater cognitive impairments than less closely related family members (Gur, et al., 2007; Yokley et al., in press). These findings support an association between genetic relatedness to schizophrenia and observed pathology among relatives.

Second, in contrast to observation ratings, self-report SIS scales had a mean genetic correlation with schizophrenia of $R_g = -0.02$ (range: -0.35 to 0.25), and 50% (7 of 14) of the scales were negatively genetically correlated with schizophrenia. The three self-report scales most strongly negatively correlated with schizophrenia were (R_g): Ideas of Reference: Watched (-0.35), Magical Thinking (-0.30), and Illusions (-0.23) (all involving psychotic-like phenomena), whereas the strongest positive genetic correlations were for Social Isolation (0.25), Sexual Anhedonia (0.18), and Anger to Perceived Slights (0.18). This suggests that underreporting may be primarily restricted to positive schizotypy symptoms, rather than a generalized minimization of pathology. Other studies also suggest that relatives of schizophrenia patients do not appear to demonstrate generalized defensive underreporting as measured by the K scale on the Minnesota Multiphasic Personality Inventory (MMPI). The K scale is a sensitive measure of underreporting developed to adjust scores on MMPI clinical scales that may have been spuriously minimized by defensive response bias (Greene, 1980). Two studies found that relatives scored higher than controls on the K scale, but the differences were small and probably not significant (MacCrimmon, Cleghorn, Asarnow, & Steffy, 1980; Moldin, Gottesman, Erlenmeyer-Kimling, & Cornblatt, 1990). In another study, MMPI K-scale items were interspersed within the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) and relatives scored significantly lower (less-defensive) than controls (although curiously both groups scored higher than “normal” suggesting perhaps something unusual about the control group or measurement instrument (Calkins, Curtis, Grove, & Iacono, 2004). These observations also support underreporting of specific psychosis-like pathology in relatives, but not necessarily due to a generalized defensiveness such as that measured by the K scale.

Third, correlations within relatives between the three self-report SIS scales most negatively genetically correlated with schizophrenia (all positive schizotypy symptoms - Ideas of Reference: Watched, Magical Thinking, and Illusions) and the seven observer-rated SIS scales are also informative. Ideas of Reference: Watched showed small, but significant positive correlations with all observer ratings (r : mean = 0.16 ; range = 0.09 to 0.20) and correlations for Magical Thinking were also in the positive direction with five reaching significance (r : mean = 0.11 ; range = 0.03 to 0.16), whereas the Illusions scale was not correlated with any observer ratings (r : mean = 0.02 ; range = -0.07 to 0.06). As such, self-reported positive schizotypy symptoms were either modestly positively correlated, or uncorrelated with ratings of observed pathology within relatives. This lack of negative within-person correlations between self-report and observer ratings is not consistent with the second model of bias (underreporting due to genetically influenced suspiciousness). Instead, these correlations are somewhat, although not unambiguously, more supportive of the first model of bias based on relatives' exposure to probands, which predicts self-report and observer ratings to be uncorrelated.

Although the results of these post-hoc analyses, along with previous reports, may be somewhat more consistent with the first “exposure” model of reporting bias described above, which suggests that reluctance to endorse positive schizotypy symptoms is affected by shared environmental experience with a relative with schizophrenia, the most definitive evidence needed to distinguish between these two models of bias is information from adoptive and reared apart biological relatives, which unfortunately is not available in the current study. Without adoption data we cannot know for certain if the observed negative

familial correlations reflect genetically influenced suspiciousness or reluctance to endorse psychotic-like experiences due to shared environmental knowledge.

There are a few adoption studies that provide relevant data, although they do not decisively resolve this issue. Comparisons between adoptive relatives of schizophrenia adoptees and non-schizophrenia control adoptees have found that adoptive mothers of schizophrenia probands are less guarded compared to adoptive mothers of controls (Rimmer et al., 1979; Wender, Rosenthal, & Kety, 1968). These findings are inconsistent with the model that bias is an effect of shared environmental exposure to a proband, although perhaps adoptive parent knowledge that they are genetically unrelated to the proband served to reduce parent guardedness. Important data from reared apart biological relatives of schizophrenia probands are available from Ingraham's report from the Danish adoption studies. These data indicate that suspicion, flat affect, and withdrawal were the only schizotypal symptoms significantly increased among reared apart biological relatives of schizophrenia adoptees compared to controls, whereas positive psychotic-like symptoms were not significantly increased (Ingraham, 1995). However, it is unclear if these data support genetic effects on bias, because the statistical analysis was one-tailed and thus appropriately did not indicate whether biological relatives reported significantly decreased positive psychotic-like symptoms (which would suggest underreporting due to genetic effects), or simply reported no significant differences from controls.

Schizotypy Genetic Factor Scales and Genetic Correlation with MDD and Substance Dependence

In contrast to schizophrenia, none of the six genetic factor scales were significantly genetically correlated with either MDD or substance dependence. The possible exception is Paranoid Fears, which may share a proportion of genetic effects with liability to substance dependence. The low genetic correlations of these factor scales with MDD and substance dependence in this sample support a degree of specificity to schizophrenia, or to positive symptoms in particular. Of course, replication in general population samples of MDD and substance dependence probands and their relatives is necessary to clarify generalizability, but inflation of results due to schizophrenia risk genes seems unlikely as these diagnoses were not genetically correlated with schizophrenia in this sample.

Limitations

Large multiply affected families represent a minority of families of schizophrenia patients, thus comparisons between our results and those obtained from simplex family studies may not be straightforward. Given that the MDD and substance dependence "probands" in the current study were also relatives of schizophrenia patients, generalizability of these results also should remain tentative until they can be replicated in a general population sample of individuals with these diagnoses. In addition, the family design of this study prevented the separate examination of effects that were due to genes and those that were due to shared environmental effects. As in the case of twin studies, this family study presumes no correlation between genetic effects and shared environmental effects. However, as noted above, without adoptive relatives in the current study, we cannot know for sure if the observed negative "genetic" correlations reflect guardedness due to genetic effects or due to shared environmental experience.

Conclusion

This study examined the nature of schizotypy among multigenerational, multiplex schizophrenia families. Genetic schizotypy factors and factor scores were derived using genetic factor analysis and evaluated for genetic correlation with schizophrenia. Two

genetically homogeneous and independent schizotypy factor scales were identified that were sensitive to genetic effects on schizophrenia, but not MDD or substance dependence, and thus may potentially be sensitive and specific indexes of schizophrenia risk genes. Identification of genetic factors thus appears to be a promising technique for maximizing genetic correlation of endophenotypes with schizophrenia. However, given the negative genetic associations with schizophrenia, it is unclear if these particular genetic schizotypy factor scales could be useful in this regard. Definitive evaluation of the utility of genetic factor scales in identifying schizophrenia risk genes requires utilization in genome-wide bivariate linkage and genetic association analyses. In addition, the negative direction of these genetic correlations supports minimization of “psychotic-like” symptoms among close relatives of schizophrenia patients, despite other observed pathology, perhaps due to genetically influenced suspiciousness or shared environmental exposure to a relative’s illness. These results underscore that response bias in schizophrenia families is an important consideration when acquiring self-report information and warrants future study to better delineate the origins of this bias.

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References

- Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *American Journal of Human Genetics*. 1998; 62:1198–1211. [PubMed: 9545414]
- Appels MCM, Sitskoorn MM, Vollema MG, Kahn RS. Elevated levels of schizotypal features in parents of patients with a family history of schizophrenia spectrum disorders. *Schizophrenia Bulletin*. 2004; 30(4):781–790. [PubMed: 15954190]
- Boomsma DI, Dolan CV. A comparison of power to detect a QTL in sib-pair data using multivariate phenotypes, mean phenotypes, and factor scores. *Behavior Genetics*. 1998; 28(5):329–340. [PubMed: 9926615]
- Boomsma DI, Molenaar PCM, Orlebeke JF. Estimation of individual genetic and environmental factor scores. *Genetic Epidemiology*. 1990; 7:83–91. [PubMed: 2184093]
- Calkins ME, Curtis CE, Grove WM, Iacono WG. Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. *Schizophrenia Bulletin*. 2004; 30(2):317–325. [PubMed: 15279049]
- Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders. *Archives of General Psychiatry*. 1999; 56:162–168. [PubMed: 10025441]
- Chapman LJ, Chapman JP, Raulin ML. Scales for physical and social anhedonia. *Journal of Abnormal Psychology*. 1976; 85(4):374–382. [PubMed: 956504]
- Chapman LJ, Chapman JP, Raulin ML. Body-image aberration in schizophrenia. *Journal of Abnormal Psychology*. 1978; 87:399–407. [PubMed: 681612]
- Clementz BA, Grove WM, Katsanis J, Iacono WG. Psychometric detection of schizotypy: Perceptual aberration and physical anhedonia in relatives of schizophrenics. *Journal of Abnormal Psychology*. 1991; 100(4):607–612. [PubMed: 1757676]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Gottesman, II.; Shields, J. *Schizophrenia and Genetics: A Twin Study Vantage Point*. New York, NY: Academic Press; 1972.
- Greene, RL. *The MMPI: An interpretive manual*. New York, NY: Grune & Stratton; 1980.

- Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, et al. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *American Journal of Psychiatry*. 2007; 164(5):813–819. [PubMed: 17475741]
- Huxley NA, Pogue-Geile MF, Garrett AH, Brunke JJ, Hall JK, Crown J. Is there a familial relationship between psychotic-like symptoms and schizophrenia? [Abstract]. *Schizophrenia Research*. 1993; 9:118.
- Ingraham, LJ. Family-genetic research and schizotypal personality. In: Raine, A.; Lencz, T.; Mednick, SA., editors. *Schizotypal Personality*. Cambridge: Cambridge University Press; 1995. p. 19-42.
- Katsanis J, Iacono W, Beiser M. Anhedonia and perceptual aberration in first-episode psychotic patients and their relatives. *Journal of Abnormal Psychology*. 1990; 99(2):202–206. [PubMed: 2348016]
- Kendler KS, Lieberman JA, Walsh D. The structured interview for schizotypy (SIS): A preliminary report. *Schizophrenia Bulletin*. 1989; 15:559–571. [PubMed: 2623438]
- Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon family study III. Schizophrenia-related personality disorders in relatives. *Archives of General Psychiatry*. 1993; 50:781–788. [PubMed: 8215802]
- Kety, SS.; Rosenthal, D.; Wender, PH.; Schulsinger, F. The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. In: Rosenthal, D.; Kety, SS., editors. *The Transmission of Schizophrenia*. Oxford: Pergamon Press; 1968.
- Lien Y-J, Tsuang H-C, Chiang A, Liu C-M, Hsieh MH, Hwang T-J, et al. The multidimensionality of schizotypy in nonpsychotic relatives of patients with schizophrenia and its applications in ordered subsets linkage analysis of schizophrenia. *American Journal of Medical Genetics Part B*. 2010; 153B:1–9.
- Loehlin, JC. *Latent variable models: An introduction to factor, path, and structural equation analysis*. Fourth ed.. Mahwah, NJ: Lawrence Erlbaum Associates; 2004.
- MacCrimmon DJ, Cleghorn JM, Asarnow RF, Steffy RA. Children at risk for schizophrenia: Clinical and attentional characteristics. *Archives of General Psychiatry*. 1980; 37:671–674. [PubMed: 7387338]
- Maxwell, ME. *Manual for the Family Interview for Genetic Studies (FIGS)*. Bethesda, MD: Clinical Neurogenetics Branch, Intramural Research Program, National Institute of Mental Health; 1992.
- Meehl PE. Schizotaxia, schizotypy, schizophrenia. *American Psychologist*. 1962; 17:827–838.
- Moldin SO, Gottesman II, Erlenmeyer-Kimling L, Cornblatt BA. Psychometric deviance in offspring at risk for schizophrenia: I. Initial delineation of a distinct subgroup. *Psychiatry Research*. 1990; 32:297–310. [PubMed: 2388968]
- Muthen, LK.; Muthen, BO. *Mplus User's Guide*. Sixth ed.. Los Angeles, CA: Muthen & Muthen; 1998–2010.
- Nurnberger JI, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, et al. NIMH Genetics Initiative: Diagnostic Interview for Genetic Studies: rationale, unique features, and training. *Archives of General Psychiatry*. 1994; 51:849–859. [PubMed: 7944874]
- Pogue-Geile, MF.; Tarbox, SI. Schizophrenia spectrum disorders. In: Cooper, D., editor. *Encyclopedia of the Human Genome*. 2nd ed.. Vol. 5. Chichester, UK: John Wiley & Sons, Ltd.; (in press)
- Pogue-Geile MF, Yokley JL. Current research on the genetic contributors to schizophrenia. *Current Directions in Psychological Science*. 2010; 19(4):214–219.
- Raine A. The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin*. 1991; 17(4):555–564. [PubMed: 1805349]
- Rimmer J, Cole S, Jacobson B, Kety SS, Rosenthal D, Schulsinger F, et al. Personal and social characteristics differentiating adoptive relatives of schizophrenics and nonschizophrenics: A preliminary report based on interviews. *Comprehensive Psychiatry*. 1979; 20(2):151–158. [PubMed: 421450]
- Ritsner M, Karas S, Ginath Y. Relatedness of schizotypal personality to schizophrenic disorders: Multifactorial threshold model. *Journal of Psychiatric Research*. 1993; 27(1):27–38. [PubMed: 8515386]

- Tarbox SI, Pogue-Geile MF. A multivariate perspective on schizotypy and familial association with schizophrenia: A review. *Clinical Psychology Review*. 2011; 31(7):1169–1182. [PubMed: 21855827]
- Torgersen S, Lygren S, Oien PA, Skre I, Onstad S, et al. A twin study of personality disorders. *Comprehensive Psychiatry*. 2000; 41(6):416–425. [PubMed: 11086146]
- Wender, P.; Rosenthal, D.; Kety, SS. A psychiatric assessment of the adoptive parent of schizophrenics. In: Rosenthal, D.; Kety, SS., editors. *The Transmission of Schizophrenia*. London: Pergamon; 1968. p. 234-250.
- Yin-Ju L, Hui-Chun T, Abigail C, Chih-Min L, Ming HH, Tzung-Jeng H, et al. The multidimensionality of schizotypy in nonpsychotic relatives of patients with schizophrenia and its applications in ordered subsets linkage analysis of schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2009; 153B(1):1–9.
- Yokley JL, Prasad KM, Chowdari KV, Talkowski ME, Wood JA, Gur RC, et al. Genetic associations between Neuregulin-1 SNPs and neurocognitive function in multigenerational, multiplex schizophrenia families. *Psychiatric Genetics*. (in press).

Table 1

Characteristics of affected and unaffected pedigree members and controls

Group	Total, n	Demographics			Diagnosis, n ^d				
		Age, yrs: mean (sd)	Sex: % male	Education, yrs: mean (sd)	Cluster A	MDD	Other mood	Substance dependence	No diagnosis
Affected Pedigree Members	103	47.1 (12.8)	57.3	12.3 (2.7)	n/a	0	9	30	n/a
Unaffected Pedigree Members	480 ^b	44.6 (17.8)	46.0	13.3 (2.9)	25	103	41	102	258
1 st Degree ^c	84	49.8 (17.6)	41.7	13.4 (3.0)	3	19	7	18	48
2 nd Degree	110	45.5 (21.0)	51.8	13.0 (3.2)	10	20	5	17	65
3 rd Degree	110	44.9 (13.8)	51.8	13.7 (2.6)	2	24	11	23	61
4 th Degree	132	36.3 (16.0)	40.9	13.0 (2.8)	9	30	17	38	56
Non-Bio Relative ^d	44	56.1 (13.3)	40.9	14.0 (2.9)	1	10	1	6	28
Controls	88	51.9 (17.5)	40.9	15.2 (2.4)	0	24	4	16	51

^aDiagnoses of Cluster A personality disorders, major depressive disorder, without psychotic features (MDD), other mood disorders (e.g., depressive disorder, NOS), and substance abuse/dependence disorders are non-hierarchical and not exclusive, and therefore do not sum to total n.

^b 480 unaffected pedigree members for whom SIS data were available.

^c Relatedness to index proband.

Note: As these are multiplex pedigrees, each family included at least two affected individuals. Therefore, an unaffected family member could have a different degree of relatedness to affected relatives (e.g., first degree relative of the index proband, but third degree relative of another affected family member).

^d Non-biological relatives include step-relatives and spouses.

n/a - not applicable

Table 2

Correlations of SIS Scales and SIS Genetic Factor Scales

SIS Scale (r)	SIS Genetic Factor Scale					
	Paranoid Fears	Interpersonal Deficits	Perceptual Distortions	Constricted Affect	Eccentric Behavior	Unusual Beliefs
Social Anxiety	0.94	0.10	-0.08	0.22	-0.23	0.08
Pathological Jealousy	0.91	0.38	0.09	-0.01	0.04	0.27
Sensitivity	0.87	-0.03	-0.28	-0.25	-0.03	0.27
Psychotic-like Phenomena [*]	0.86	0.15	-0.49	-0.11	0.01	0.15
Ideas of Reference: Remarks [*]	0.76	-0.01	0.09	-0.07	-0.44	0.30
Introversiion	0.72	0.22	-0.21	0.56	-0.24	-0.10
Suspiciousness [*]	0.60	0.53	0.23	-0.38	-0.05	0.25
Ideas of Reference: Watched [*]	0.58	0.46	0.25	-0.04	-0.39	0.58
Organization of Speech/Thought [†]	0.30	1.00	-0.28	0.13	0.03	-0.07
Rapport [†]	-0.03	0.93	0.10	0.22	-0.20	0.23
Affect [†]	0.03	0.73	0.21	0.49	-0.08	0.15
Social/Interpersonal Functioning [†]	0.38	0.70	0.13	0.45	-0.16	0.28
Irritability [†]	0.07	0.67	-0.05	0.04	-0.17	-0.10
Guardedness [†]	0.07	0.62	-0.27	-0.06	0.04	0.15
Social Isolation	0.42	0.55	0.34	0.38	0.32	0.21
Sexual Anhedonia	0.04	0.11	-0.87	0.21	0.10	<0.01
Illusions [*]	0.47	-0.04	-0.76	-0.48	-0.16	0.21
Restricted Emotion	-0.14	0.47	-0.12	0.91	-0.17	0.02
Odd/Eccentric Behavior ^{†*}	0.32	0.28	0.03	0.19	-0.92	0.09
Anger to Perceived Sights	0.57	0.03	-0.08	0.32	0.04	0.83
Magical Thinking [*]	0.36	0.29	-0.33	-0.32	-0.18	0.68
Eigenvalues	9.70	4.48	2.21	1.77	1.27	1.05

Note: Sample is unaffected pedigree members (n = 480). Covariates are age and sex. Boldface: r |.40|.

* Dichotomized scale: symptoms absent = 0, present = 1.

[†] Interviewer observation – other scales are based on participant self-report.

Genetic Correlations among SIS Genetic Factor Scales

Table 3

SIS Genetic Factor Scales	SIS Genetic Factor Scales				
	Paranoid Fears	Interpersonal Deficits	Perceptual Distortions ^a	Constricted Affect	Eccentric Behavior ^a Unusual Beliefs
Paranoid Fears					
Interpersonal Deficits	<0.01 (.985)				
Perceptual Distortions ^a	0.18 (.193)	-0.13 (.498)			
Constricted Affect	-0.06 (.733)	0.19 (.403)	-0.26 (.065)		
Eccentric Behavior ^a	-0.03 (.839)	-0.21 (.319)	-0.03 (.855)	-0.05 (.752)	
Unusual Beliefs	-0.15 (.361)	-0.02 (.939)	0.05 (.745)	0.06 (.717)	-0.09 (.641)

Note: Sample is unaffected pedigree members and controls (n = 568). Covariates are age and sex. Values are R_G (p).

^aDirection of scale is reversed.

Table 4

SIS Genetic Factor Scales: Heritability and Genetic Correlations with Schizophrenia

SIS Genetic Factor Scales	Heritability		Genetic Correlation with Schizophrenia	
	h^2	p-value	R_g	p-value
Paranoid Fears	0.56	<.001	0.08	.630
Interpersonal Deficits	0.25	<.001	0.27	.194
Perceptual Distortions ^a	0.58	<.001	-0.04	.789
Constricted Affect	0.50	<.001	0.04	.815
Eccentric Behavior ^a	0.40	<.001	-0.52	.046
Unusual Beliefs	0.40	<.001	-0.45	.022

Note: Sample is unaffected pedigree members and controls ($n = 568$). Covariates are age and sex. Boldface: $p < .050$.

^aDirection of scale is reversed.

Table 5

SIS Genetic Factor Scales: Genetic Correlations with MDD and Substance Dependence

SIS Genetic Factor Scale	Genetic Correlation with MDD		Genetic Correlation with Substance Dependence	
	Rg	p-value	Rg	p-value
Paranoid Fears	0.19	.313	0.36	.082
Interpersonal Deficits	−0.25	.371	0.39	.153
Perceptual Distortions ^a	−0.22	.286	−0.23	.237
Constricted Affect	−0.27	.206	0.42	.109
Eccentric Behavior ^a	−0.07	.746	−0.34	.121
Unusual Beliefs	0.17	.466	0.27	.265

Note: Sample is unaffected pedigree members and controls (n = 568). Covariates are age and sex.

^aDirection of scale is reversed.

Table 6**Genetic Correlations of SIS Scales and Schizophrenia**

Scale	Genetic Correlation with Schizophrenia	
	R _g	p-value
Observation		
Guardedness [†]	0.470	.043
Organization of Speech/Thought [†]	0.259	.210
Social/Interpersonal Functioning [†]	0.212	.238
Affect [†]	0.217	.260
Irritability ^{†*}	0.209	.375
Rapport [†]	0.016	.948
Odd/Eccentric Behavior ^{†*}	−0.035	.898
Self-Report		
Social Isolation	0.247	.140
Sexual Anhedonia	0.184	.334
Anger to Perceived Slights [*]	0.178	.510
Suspiciousness [*]	0.177	.438
Pathological Jealousy	0.161	.364
Psychotic-like Phenomena	0.035	.907
Introversion	0.029	.884
Sensitivity	−0.034	.848
Restricted Emotion	−0.041	.822
Social Anxiety [*]	−0.111	.614
Ideas of Reference: Remarks [*]	−0.199	.364
Illusions [*]	−0.226	.211
Magical Thinking [*]	−0.304	.099
Ideas of Reference: Watched [*]	−0.350	.099

Note: Sample is unaffected pedigree members and controls (n = 568). Covariates are age and sex.

^{*} Dichotomized scale: symptoms absent = 0, present = 1.

[†] Interviewer observation – other scales are based on participant self-report.