THE NATURE OF SCHIZOTYPY AMONG MULTIGENERATIONAL MULTIPLEX SCHIZOPHRENIA FAMILIES

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Identification of endophenotypes (I. I. Gottesman & Gould, 2003; I. I. Gottesman & Shields, 1972) that correlate with familial liability to schizophrenia and are maximally sensitive to a homogeneous subset of risk genes is an important strategy for detecting genes that affect schizophrenia risk. Symptoms of schizotypy may correlate with familial liability to schizophrenia; however, there are critical limitations of the current literature concerning this association. The present study examined the genetic architecture and genetic association between schizotypy and genetic liability to schizophrenia among multigenerational, multiplex schizophrenia families. Genetic schizotypy factors were identified that significantly correlated with genetic liability to schizophrenia, although some relations were unexpected in direction. These genetic factors did not correlate with genetic liability to major depressive disorder or substance dependence. Results suggest that genetic schizotypy factors may have the potential to be particularly useful endophenotypes in genetic linkage analyses of schizophrenia.

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1.0 INTRODUCTION.

Family, twin, and adoption studies suggest that schizophrenia is a highly heritable disorder [estimated at approximately 0.80 (Cardno et al., 1999)]. However, despite numerous attempts to identify specific genes contributing substantially to the risk for schizophrenia, the only promising candidates are those that contribute a small degree of risk. This implies that the diagnosis of schizophrenia most likely is associated with numerous genes of small effect rather than any single gene variant (O'Donovan, Williams, & Owen, 2003; Pogue-Geile & Gottesman, 2007). Consistent with this idea is substantial evidence that genetic liability to schizophrenia is present in non-psychotic relatives of schizophrenia patients. One of the most convincing demonstrations of this came from Gottesman and Bertelsen's (1989) follow up of Fischer's (1971) Danish sample of discordant monozygotic (MZ) and dizygotic (DZ) twins and their offspring. The risk for schizophrenia in the offspring of unaffected MZ co-twins was substantially higher than that in the offspring of unaffected DZ co-twins (17.4% in offspring of MZ co-twins, 2.1% in offspring of DZ co-twins), supporting the presence of "unexpressed" genetic liability in non-schizophrenia relatives that is correlated with degree of genetic relatedness to an affected individual and that can be transmitted to offspring.

Even in the absence of psychosis, genetic liability to schizophrenia may indeed produce observable effects in these "unaffected" relatives. For example, research with non-psychotic adult relatives has revealed "sub-clinical" neuropsychological deficits and behavioral patterns

that are similar to, but less severe than those of schizophrenia patients, including reduced performance on tasks of executive functioning, verbal and visual memory, auditory attention, visual scanning and sequencing, and social perception (e.g., Faraone, Seidman et al., 1995; Faraone et al., 2000; Thompson, Watson, Steinhauer, Goldstein, & Pogue-Geile, 2005; Toomey, Seidman, Lyons, Faraone, & Tsuang, 1999). Similar observations have been noted in children of schizophrenia patients, including poor performance on measures of inhibition, working memory, and verbal abilities, as well as problematic social behavior (e.g., solitary play, passivity, social anxiety, disruptiveness, aggression), poor peer relationships, and reduced social competence, compared to age-matched, non-high-risk peers (e.g., Asarnow, 1988; Davalos, Compagnon, Heinlein, & Ross, 2004; Davies, Russell, Jones, & Murray, 1998; Niemi, Suvisaari, Haukka, & Lonnqvist, 2005; Olin & Mednick, 1996; Tarbox & Pogue-Geile, 2008).

The presence of "sub-clinical" deficits among non-schizophrenia relatives suggests that these phenotypes are more sensitive to genetic liability to schizophrenia than is the diagnosis of schizophrenia itself, and perhaps could be used to search more powerfully for individual genes contributing to schizophrenia risk. Accordingly, an important strategy is the identification of such supplementary phenotypes [i.e. "endophenotypes" (I. I. Gottesman & Gould, 2003; I. I. Gottesman & Shields, 1972)] that correlate with the familial liability to schizophrenia in the absence of psychosis. To be most useful for understanding schizophrenia, these phenotypes should also be sensitive to schizophrenia liability in particular, rather than simply be an indication of liability to psychopathology in general (Faraone, Kremen et al., 1995).

However, even if a putative phenotype is elevated in relatives, its sensitivity to specific risk genes would be compromised to the extent that it is itself genetically heterogeneous. Thus, to the degree that a putative endophenotype approximates genetic homogeneity and correlates

with genetic liability to schizophrenia, the more likely it is to enhance sensitivity to specific risk genes.

1.1 SCHIZOTYPAL PERSONALITY DISORDER AND LIABILITY TO SCHIZOPHRENIA.

1.1.1 Historical Roots.

The belief that "sub-clinical" cognitive and interpersonal deficits of non-psychotic relatives are important in the conceptualization of schizophrenia liability is not new. For example, observations of abnormal interpersonal functioning in the family members of schizophrenia patients (e.g., social isolation/withdrawal, suspiciousness, irritability, eccentricity) can be found among the earliest descriptions of schizophrenia (Dementia Praecox) by Kraeplin (1919) and Bleuler (1911) (among others), both of whom hypothesized the existence of a "latent schizophrenia" syndrome among relatives (I. I. Gottesman, 1991; Kendler, 1985). In the decades following the early writings of Kraeplin and Bleuler, similar observations have been recorded and integrated into influential theories of schizophrenia liability.

Contemporary models of schizophrenia liability can be traced back to the work of Sandor Rado and Paul Meehl, who built upon the observations of Kraeplin and Bleuler and extended the idea of "latent schizophrenia". Rado (1953) introduced the term "schizotype" (schizophrenic genotype) to describe non-psychotic individuals who displayed schizophrenic traits such as anhedonia, reduced affect, and interpersonal impairments, and thus seemed to share a common genetic liability with schizophrenia. Meehl (1962) proposed that the sub-clinical, "schizophrenia-

like" characteristics observed in relatives were manifestations of the interaction between an inherited "neural integrative defect" predisposing to schizophrenia, which he termed "schizotaxia", and the environmental experiences of that individual. According to Meehl, the typical outcome of this interaction was a specific personality organization characterized by traits previously described by Kraeplin (1919) and Bleuler (1911): interpersonal aversiveness, anhedonia, ambivalence, and cognitive slippage. After Rado (1965), Meehl referred to this syndrome as "schizotypy" and to these individuals as "schizotypes". He theorized that although a subset of schizotaxic individuals would develop schizophrenia, schizotypy would be the more typical manifestation of inherited liability to schizophrenia. Meehl's model became the foundation for a number of important and productive contemporary research strategies aimed at investigating the nature of liability to schizophrenia (e.g., Faraone, Green, Seidman, & Tsuang, 2001; I. I. Gottesman & Gould, 2003; Lenzenweger, 2006).

1.1.2 Development of Diagnostic Criteria.

The first significant effort to develop diagnostic criteria for Bleuler's concept of "latent schizophrenia", and to clarify the role of genetic factors in this syndrome, was undertaken by Kety and colleagues in the context of the Copenhagen Adoption Study (Kety, Rosenthal, Wender, & Schulsinger, 1968). Kety et al. (1968; Kety et al., 1994) confirmed the presence of schizophrenia-like traits among the biological relatives of adoptees with schizophrenia, and demonstrated that the prevalence of these traits among biological relatives of adoptees with schizophrenia was significantly greater than in the biological relatives of controls. These findings provide strong support that this syndrome is associated with genetic liability to schizophrenia.

Kety grouped these schizophrenia-like traits into five categories (interpersonal deficits, atypical speech, cognitive/perceptual distortions, affective deficiencies, and neurotic symptoms) and proposed the diagnosis "borderline schizophrenia" to describe this syndrome. The criteria for this proposed diagnosis were subsequently modified by Spitzer et al. (1979) and incorporated into the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III; American Psychiatric Association, 1980) as Schizotypal Personality Disorder (for reviews see Kendler, 1985; Siever & Gunderson, 1983).

In the current edition of the DSM (DSM-IV-TR), schizotypal personality disorder (SPD) is described as a "…pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior..." (American Psychiatric Association, 2000). The full diagnostic criteria are provided in Table 1. As can be seen, deficits in social and interpersonal functioning are core features of this diagnosis.

1.1.3 Current Status.

The observations of Kety and colleagues continue to find support. Recent data from family, twin, and adoption studies suggests that SPD is highly heritable (estimated at .61; Torgersen et al., 2000) and among non-psychotic adult relatives of schizophrenia patients, the incidence of SPD is estimated to be between 4.2% and 14.6% (Tsuang, Stone, & Faraone, 1999) compared to 2-3% among the general population (Raine, 2006) [odds ratio (OR) estimated at 5.0 (Kendler & Gardner, 1997)]. Furthermore, an analysis of genome-wide linkage data by Fanous et al. (2007) provides support for genetic correlation between schizotypy and schizophrenia.

Specificity to schizophrenia liability also has been examined. These results indicate that the prevalence of SPD is significantly greater in non-psychotic relatives of schizophrenia patients (6.9%) than in relatives of patients with schizoaffective disorder (2.8%) , affective psychosis (2.5%), or non-psychotic affective disorders (2.3%) (K.S. Kendler et al., 1993; Pogue-Geile, 2003), although there are some contradictory findings (e.g., Erlenmeyer-Kimling et al., 1995; Kety et al., 1994). It has been further estimated that a considerable number of relatives not meeting criteria for the diagnosis of SPD may nevertheless display subclinical schizotypal traits (Tsuang et al., 1999).

Although SPD may also occur in the general population, the etiology of this diagnosis in non-relatives is likely to be heterogeneous (MacDonald, Pogue-Geile, Debski, & Manuck, 2001). Furthermore, the nature of the deficits associated with SPD in non-relatives is controversial. Some researchers have argued that there may be important differences in symptom presentation between relatives of schizophrenia patients diagnosed with SPD and general population cases (for reviews, see Kendler, 1985; Tsuang, Stone, Tarbox, & Faraone, 2002). For example, it has been suggested that in relatives, SPD may be more often characterized by social and affective deficits, whereas SPD diagnosed in the general population may be characterized by perceptual aberrations and odd beliefs (Thaker, Moran, Adami, & Cassady, 1993; Torgersen, 1985; Torgersen et al., 2002). However, this distinction is not consistently observed (e.g., Condray & Steinhauer, 1992). Thus at present, the true extent and source of these observed differences is not clear, but nevertheless suggests limitations to the study of SPD in the general population.

1.2 REVIEW OF SPD SYMPTOMS IN RELATIVES OF SCHIZOPHRENIA PROBANDS.

An important step for further investigating the putative association between schizotypal impairments and genetic risk for schizophrenia is to assess the degree to which SPD is elevated among non-psychotic relatives of schizophrenia patients. Although it is interesting to know if the SPD diagnosis itself is associated with schizophrenia liability, the degree to which individual symptoms of SPD are correlated with genetic liability to schizophrenia may be particularly informative. If schizotypy is associated with schizophrenia liability, then we would expect non-psychotic relatives of schizophrenia patients to have more severe symptoms of SPD compared to healthy controls, and perhaps greater severity of SPD symptoms than relatives of individuals with other psychiatric disorders. To examine the current evidence for elevation of schizotypy in non-psychotic relatives of schizophrenia patients, we next review studies that examined SPD symptoms among relatives of schizophrenia patients in contrast to non-psychiatric controls and/or relatives of other psychiatric groups.

1.2.1 Methodological Considerations.

Before reviewing this set of studies, there are a few key methodological issues relevant to the task of evaluating and synthesizing these data that should be discussed. These include use of first-degree index relatives, control sample composition and matching to index relatives, measurement of schizotypal traits, defining the factor structure of schizotypy, symptom-level comparisons, and variability in reported statistics. The data examined in this review are

presented in Tables 2 – 4, and include information relevant to the methodological points highlighted here.

Foremost, in familial liability schizophrenia studies, first-degree relatives are primarily recruited for the index relative sample. Although understandable, exclusive use of first-degree relatives raises two primary concerns. First, for several reasons, first-degree relatives tend to be a heterogeneous group. For example, first-degree relative samples may include parents, siblings, and/or offspring of patients. Although all first-degree relatives, these individuals differ in their risk for schizophrenia [relative risk: parents ~ 5%, siblings and offspring ~ 10% (K. S. Kendler et al., 1993)], in their experience of living with an individual with schizophrenia, and in prevalence of SPD. For example, reports suggest that SPD may be more than twice as prevalent in the parents of schizophrenia probands compared to siblings (Roscommon Family Study; K.S. Kendler et al., 1993), perhaps an effect of diminished reproductive fitness in schizophrenia (Kendler, 1986). If assessed at the same point in time, age differences among parents, siblings, and offspring is another potential source of heterogeneity that may affect results. In addition, although many studies do exclude relatives with a personal history of psychosis, this is not always the case; inclusion of "unscreened" relatives could inflate index/control differences. These sources of variation among first-degree relatives can obscure meaningful group differences and make comparisons across studies more difficult.

In addition to heterogeneity, exclusive use of first-degree relatives provides only one source of data on non-psychotic individuals with elevated genetic liability to schizophrenia. Thus, any observed association with schizophrenia liability is based solely on two data points, the first-degree relative sample and the control group, making non-linear genetic effects difficult to detect and potentially leading to erroneous conclusions. In contrast, non-first-degree relatives

are an underutilized resource that could help clarify differences between relatives and comparison samples. At present, the strength of familial correlation of schizotypal traits across multiple degrees of relationship to schizophrenia remains virtually untested (although see Ritsner, Karas, & Ginath, 1993)

A second key methodological issue pertains to the characteristics of the comparison group(s) and the extent to which this group is matched demographically to the index relatives. Control groups typically consist of individual control probands or, less often, relatives of control probands. Use of relatives of control probands, rather than the initially screened control individuals, is a stronger technique for minimizing confounds with recruitment strategy and increasing demographic representativeness. Control groups also vary in terms of how thoroughly they are screened for psychiatric illness, ranging from "no diagnosis" (psychiatrically healthy individuals whose relatives also are healthy), to "unscreened" (individuals and their relatives may or may not have psychiatric diagnoses). Both extremes can be problematic, as a "supernormal" control group can inflate index/control differences (Kendler, 1990), and confound the effect of relatedness to a schizophrenia proband with relatedness to any psychiatric ill individual. However, completely unscreened controls may inadvertently include individuals who themselves have a schizophrenia-spectrum diagnosis. To limit such confounds, moderate screening combined with careful demographic matching of comparison groups to the index relatives is probably best. Alternatively, given their shared family of origin, non-first-degree relatives of schizophrenia probands may actually constitute a more appropriate comparison group for assessing first-degree relatives than unrelated individuals, avoiding many of the problems of ascertaining non-relative controls.

Third, the type of instrument used to assess SPD symptoms can affect the outcome and interpretation of results. Use of different measures may influence the factor structure of schizotypal symptoms and there is evidence that compared to interview-based measures, questionnaires may be less sensitive to certain schizotypal traits in relatives, particularly social deficit symptoms of schizotypy (Catts, Fox, Ward, & McConaghy, 2000; Kendler, Thacker, & Walsh, 1996), and perhaps behavioral eccentricities. Consequently, measurement differences may lead to inconsistencies regarding which schizotypal traits appear most salient in relatives, and may be misleading regarding the strength of association with familial liability to schizophrenia. Given the concerns about questionnaire measures, in our review we tend to weight results from interview-based assessments more heavily.

Fourth, there is an ongoing debate regarding the phenotypic factor structure purported to underlie schizotypal traits in relatives. Proposed factor solutions range from two (Siever & Gunderson, 1983; Widiger, Frances, Warner, & Bluhm, 1986) to seven (Kendler, McGuire, Gruenberg, & Walsh, 1995) and seem to depend a large part on study methodology, including sample characteristics and use of questionnaire versus interview measures. Recently, Bergman et al. (2000) tested five models using data from interview measures of SPD conducted with adult, first-degree relatives of schizophrenia patients and concluded that the best fit was provided by the following three-factor model: 1) social-interpersonal symptoms (i.e. “negative schizotypy”), including excessive social anxiety, lack of close friends or confidants, constricted affect, and suspiciousness; 2) cognitive-perceptual symptoms (i.e. “positive schizotypy”), characterized by ideas of reference, odd beliefs/magical thinking, and unusual perceptual experiences; suspiciousness also loaded on this factor; and 3) disorganized symptoms of odd speech and odd behavior. A variation of this factor structure of SPD was identified in patients with personality

disorders in which paranoid symptoms defined the third factor instead of disorganized symptoms (A.J. Bergman et al., 1996). Several recent studies, including those using both interview and questionnaire measures, also have reported three schizotypy factors (typically identifying disorganization as the third factor). Accordingly, the data reviewed below are organized into the three dimensions suggested by Bergman et al. (2000): social-interpersonal, cognitive-perceptual, and disorganized. For studies that provided alternate factor solutions, we present those data with the factor (from the three-factor solution) that best approximates the associated symptoms.

A fifth methodological issue is that symptom-level comparisons are not consistently reported, even when factor comparisons are significant. Although there are similarities among symptoms within a single factor, each symptom represents a relatively unique deficit or behavior. Thus, examination of individual SPD symptoms among groups can help clarify if specific symptoms account for group differences, or if the contribution of multiple deficits is most important. When available, we review symptom-level group comparisons along with the factor comparisons.

Lastly, indexes of association, such as odds ratios and effect sizes, are very helpful for determining the strength of an association; however, there is substantial variability in which indexes are reported. This can hinder comparisons across studies and if a uniform index is desired, necessitates conversion of one index into another. There are a number of suggested methods for such transformations depending on the available statistics, which although useful, raises the concern that transformed indexes may not be entirely equivalent due to variation in the original statistics. Furthermore, such transformation calculations are not always feasible given the data provided.

1.2.2 Review of SPD Symptoms in Relatives versus Non-Relatives.

With these methodological points in mind, we now review studies that compared adult relatives of schizophrenia patients, psychiatrically healthy controls, and/or adult relatives of patients with other psychiatric diagnoses on the social-interpersonal, cognitive-perceptual, and disorganization dimensions of SPD. These data are presented in Tables 2 - 4. As our focus here is on the relation between the symptoms of SPD and familial liability to schizophrenia, we only included studies that assessed factors and/or individual symptoms of SPD rather than just the presence of diagnosis itself. Whenever possible, we present results for both the factors and the symptoms underlying those factors.

Effect sizes are presented to aid in the comparison of results across studies. When possible, all reported indices are converted to Glass' standardized mean difference statistic 'd' [relatives mean – control mean / control standard deviation (Smith, Glass, & Miller, 1980)]. As a group, relatives of schizophrenia patients are predicted to be more heterogeneous than healthy controls, therefore Glass' 'd' is more appropriate than Cohen's 'd', which uses the pooled standard deviation of relatives and controls. However, given that effect size transformations discussed in the current meta-analysis literature most often utilize Cohen's 'd', in some instances it was more feasible to transform reported indices to Cohen's 'd' rather than Glass' 'd' (Cohen, 1987; Haddock, Rindskopf, & Shadish, 1998; Hasselblad & Hedges, 1995; Johnson & Eagly, 2000; Rosenthal, 1994). To the extent that the standard deviation of the relatives is larger than that of the controls, Cohen's 'd' will result in a more conservative estimate of effect size than Glass' 'd'. Mean effect sizes were calculated for factor comparisons by weighting each 'd' by the inverse of the conditional variance of 'd' (Shadish & Haddock, 1994). On occasion, Cohen's 'd' was included in these calculations along with Glass' 'd'; use of both indices in this calculation

may result in an underestimation of the mean effect size. Cohen (1987) suggests the following guidelines for interpretation of effect size 'd': 0.2 = small, 0.5 = medium, 0.8 = large.

1.2.2.1 Social-Interpersonal Symptoms.

Index Relatives vs. Healthy Controls.

Factor-level comparisons. Seven studies reported comparisons between first-degree relatives of schizophrenia patients and psychiatrically healthy controls; these data are presented in Table 2 (Appels, Sitskoorn, Vollema, & Kahn, 2004; Calkins, Curtis, Grove, & Iacono, 2004; Grove et al., 1991; Kendler et al., 1995; Kremen, Faraone, Toomey, Seidman, & Tsuang, 1998; Squires-Wheeler et al., 1997; Yaralian et al., 2000). The largest reported effect (d = 1.65), suggesting worse social-interpersonal functioning among relatives, came from a comparison of unscreened first-degree relatives and no-diagnosis controls, and thus could reflect inflated index/control differences (Grove et al., 1991). The other large effect (d = 1.10) was obtained by the New York High Risk Study (Squires-Wheeler et al., 1997). Their sample consisted only of offspring of schizophrenia patients, a sizeable minority of which will develop schizophrenia; therefore, elevated pathology among this sample of relatives could reflect "prodromal" effects. Methodologically, one of the most persuasive reports is from the Roscommon Family Study (Kendler et al., 1995), given the large sample size, moderate screening of relatives, and use of relatives of control probands to obtain a more representative control sample. This study reported moderate elevation of social-interpersonal symptoms in first-degree relatives compared to control relatives (d = 0.27 to 0.67)[1]. It is interesting that all non-significant effects were reported

[1] Effect sizes estimated from odds ratios reported by Kendler et al. (1995) utilized Cohen's 'd' index of association (relative M – control M/pooled SD) (Cohen, 1987), and may underestimate effect size.

by studies that used questionnaire-based assessment of SPD (Appels et al., 2004; Kremen et al., 1998; Yaralian et al., 2000), perhaps a result of low sensitivity of these measures to detect social-interpersonal symptoms among relatives. Although, Calkins et al. (2004) did find a moderate effect (d = 0.55), similar to the Roscommon Family Study, using a questionnaire measure. In sum, the results of these studies best support a medium effect of elevated social-interpersonal symptoms among first-degree relatives of schizophrenia patients compared to psychiatrically healthy controls.

Symptom-level comparisons. Two of these studies also reported social-interpersonal symptom-level comparisons between first-degree relatives of schizophrenia patients and healthy controls. Yaralian et al. (2000) reported significant elevation among relatives only for paranoid ideation, whereas Calkins et al. (2004) reported significant effects for elevated social anxiety, no close friends, and constricted affect, but no differences for suspiciousness. Overall, the results from Calkins et al. are more consistent with the medium effect suggested by the factor comparisons. Possibly, the non-significant effects reported by Yaralian et al. were a result of limited power due to the small number of index relatives in their sample. Of course, since the majority of studies did not report comparisons for individual social-interpersonal symptoms, the effects detected by Calkins et al. are hardly conclusive and thus await further study.

Index Relatives vs. Other Diagnoses.

Factor-level comparisons. Table 2 also presents comparisons between first-degree relatives of schizophrenia patients and relatives of patients diagnosed with affective disorder or alcohol/drug abuse on social-interpersonal symptoms of SPD. Factor-level comparisons with relatives of affective disorder patients were reported by three studies (Kendler et al., 1995; Schurhoff, Laguerre, Szoke, Meary, & Leboyer, 2005; Squires-Wheeler et al., 1997). The largest effect (d = 0.87) was reported by Kendler et al. (1995) indicating elevated suspiciousness among index relatives compared to affective disorder relatives. However, neither of the other two studies reported on suspiciousness. In contrast, Schurhoff et al. (2005) reported no difference between index relatives and relatives of bipolar patients; although, of the three studies, this was the only one to use questionnaire-based assessment. This study also limited the comparison group to relatives of bipolar disorder patients which, given the proposed etiologic similarities between schizophrenia and bipolar disorder, may have increased similarity between the relative groups. Finally, Kendler et al. (1995) and Squires-Wheeler et al. (1997) both reported small to medium effect sizes indicating elevated symptoms of negative schizotypy in index relatives versus affective disorder relatives, although as noted above, comparisons with offspring of schizophrenia patients as reported in the New York High Risk Study (Squires-Wheeler et al., 1997) may tend to inflate group differences. Taken together, the few available results suggest a small to medium effect of elevated social-interpersonal factor symptoms in relatives of schizophrenia patients compared to affective disorder relatives. Lastly, one study reported factor-level comparisons between index relatives and relatives of individuals diagnosed with alcohol/drug abuse, and found no difference between groups (d = 0.01) (Yaralian et al., 2000).

Any conclusions regarding relatives of alcohol/drug abuse patients of course await additional studies.

Symptom-level comparisons. Two studies conducted symptom-level comparisons between first-degree relatives of schizophrenia patients and relatives of affective disorder patients. Torgersen et al. (1993) reported small to medium effects of greater social anxiety (d = 0.32) and inappropriate affect (d = 0.30) in index relatives; similarly, Lyons et al. (1994) reported that index relatives were significantly elevated on inadequate rapport (which was replaced by "inappropriate affect' when the DSM-III was updated to DSM-III-R) compared to affective disorder relatives. Together, the results of these two studies thus support a small to medium effect of elevated inappropriate affect in index relatives compared to affective disorder relatives, although additional studies are needed to confirm this finding. Comparisons between index relatives and relatives of individuals diagnosed with alcohol/drug abuse again were reported only by Yaralian et al. (2000). Their results suggested a medium to large effect of heightened paranoid ideation among index relatives that approached significance (d = 0.60; p=.06). This finding of course awaits replication.

1.2.2.2 Cognitive-Perceptual Symptoms.

Index Relatives vs. Healthy Controls.

Factor-level comparisons. All of the studies listed in Table 2 also reported results pertaining to the cognitive-perceptual symptoms of SPD; these data are presented in Table 3. Two of the largest effects (d = 1.02; d = 0.51), suggesting elevated cognitive-perceptual symptoms among first-degree relatives, were reported by Yaralian et al. (2000) and Grove et al. (1991), respectively. However, the samples of relatives in these studies were unscreened for

psychiatric illness, which could have inflated index/control differences. Kremen et al. (1998) also reported a medium to large effect of elevated cognitive-perceptual symptoms (d = 0.65), particularly among male first-degree relatives; although this result does not appear inflated, it is unclear how comparable it is to results for mixed sex samples. Of the remaining results, the small elevations of cognitive-perceptual symptoms in relatives reported by Kendler et al. (1995) and Calkins et al. (2004) are the most convincing (d = 0.36 and d = 0.24, respectively). However, the significant, negative effect reported by Appels et al. (2004), suggesting less pathology among parents of schizophrenia patients compared to controls, is particularly striking. Theory regarding fitness effects would instead tend to predict elevated schizotypy among index parents, although perhaps this negative finding reflects parents' unwillingness to endorse cognitive-perceptual symptoms of SPD. At this point, it is difficult to interpret or dismiss this negative effect. Considered together, current results seem to best support a small effect of elevated cognitive-perceptual factor symptoms among index relatives compared to controls.

Symptom-level comparisons. Three studies reported on cognitive-perceptual symptom-level comparisons between first-degree relatives of schizophrenia patients and healthy controls. For unusual perceptual experiences, Yaralian et al. (2000) reported a large, although likely inflated (due to unscreened index relatives), positive effect (d = 1.02) indicating elevated symptoms in relatives compared to controls, whereas Calkins et al. (2004) found a small positive effect (d = 0.38). Yaralian et al. (2000) also reported elevated ideas of reference (d = 0.87) and paranoid ideation (d = 0.75) among relatives, but again perhaps index/control differences were inflated. In contrast, Appels et al. (2004) observed a significant negative association for unusual perceptual experiences and magical thinking, suggesting that index relatives endorse fewer of these symptoms than controls. As noted above, these results could perhaps reflect parents'

reluctance to endorse cognitive-perceptual symptoms of SPD. At this point, any conclusions are difficult; a small effect of unusual perceptual experiences is perhaps most likely given these results.

Index Relatives vs. Other Diagnoses.

Factor-level comparisons. As can also be seen in Table 3, none of the three studies that compared first-degree relatives of schizophrenia patients and relatives of affective disorder patients on the cognitive-perceptual factor reported significant results. In contrast, the single comparison with relatives of individuals diagnosed with alcohol/drug abuse did find a significant elevation among index relatives (d = 0.79) (Yaralian et al., 2000). Thus, these results argue against differences between index relatives and affective disorder relatives on cognitive-perceptual symptoms, but suggest that these symptoms may be elevated in index relatives compared to alcohol/drug abuse relatives.

Symptom-level comparisons. Two studies reported individual cognitive-perceptual symptom comparisons between index relatives and relatives of affective disorder patients, and reported no group differences (Lyons et al., 1994; Torgersen et al., 1993). Yaralian et al. (2000) reported large, albeit non-significant, elevations on unusual perceptual experiences, ideas of reference, and paranoid ideation among index relatives compared to alcohol/drug abuse relatives. These results are generally congruent with results of cognitive-perceptual factor comparisons discussed above.

Disorganized Symptoms.

Index Relatives vs. Healthy Controls.

Factor-level comparisons. Most, but not all of the studies presented in Tables 2 and 3 also reported results pertaining to the disorganized symptoms of SPD; these data are presented in Table 4. Kendler et al. (1995) reported the largest elevation on the disorganized factor among index relatives versus controls (d = 0.96). In their study, the disorganized factor included "cognitive slippage" and "odd speech", but did not include "odd behavior", perhaps contributing to the larger effect. Given possible screening-related inflation of index/control differences reported by Yaralian et al. (2000), the remaining studies support, at best, a slight elevation of disorganized SPD symptoms among relatives compared to controls (Appels et al., 2004; Calkins et al., 2004; Kremen et al., 1998); although use of questionnaire assessments may have limited sensitivity to detect these types of symptoms. It is worth noting that in the literature, the disorganized dimension of schizotypy is generally considered to be less "stable" than the social-interpersonal and cognitive-perceptual factors. This is consistent with the variability of results for this factor (range: d = 0.17-0.96), and that two studies did not report a separate disorganized factor (Grove et al., 1991; Squires-Wheeler et al., 1997).

Symptom-level comparisons. Two studies (Calkins et al., 2004; Yaralian et al., 2000) presented comparisons for individual disorganized symptoms and both reported non-significant findings. As noted, questionnaire assessments may have low sensitivity to disorganized speech and behavior. Overall, these results are consistent with minimal differences between first-degree relatives and controls, but cannot rule out possible elevation of disorganized symptoms in index relatives that are more easily detectable using interview measures.

Index Relatives vs. Other Diagnoses.

Factor-level comparisons. Table 4 also presents the results of comparisons between first-degree relatives of schizophrenia patients and relatives of other psychiatric groups on the disorganized factor of SPD. Comparisons between relatives of schizophrenia patients and relatives of either affective disorder (Kendler et al., 1995; Schurhoff et al., 2005) or alcohol/drug abuse probands (Yaralian et al., 2000) failed to yield significant results, arguing against specificity of disorganized symptoms to liability to schizophrenia.

Symptom-level comparisons. Two studies reported individual symptom comparisons between index relatives and relatives of affective disorder patients. Torgersen et al. (1993) found a significant, albeit modest, elevation of odd speech among index relatives (d = 0.30), whereas Lyons et al. (1994) reported no group differences. Yaralian et al. (2000) also found no differences between index relatives and alcohol/drug abuse relatives on individual disorganized symptoms. These results generally support no specificity of disorganized symptoms to schizophrenia liability.

1.2.3 Summary of SPD Review.

The data reviewed above indicate that social-interpersonal symptoms of SPD are moderately elevated among first-degree relatives of schizophrenia patients compared to psychiatrically healthy controls, and thus are potentially sensitive to liability to schizophrenia. Social-interpersonal symptoms also may differentiate relatives of schizophrenia patients from relatives of affective disorder patients, but not from relatives of substance abuse probands, suggesting the possibility of limited specificity to schizophrenia liability.

Results support a small effect of cognitive-perceptual symptoms of SPD among first-degree relatives of schizophrenia patients compared to healthy controls, suggesting some sensitivity to schizophrenia liability. Cognitive-perceptual symptoms do not appear specific to schizophrenia liability compared to affective disorders. Although, results tentatively suggest that cognitive-perceptual symptoms may differentiate index relatives from relatives of substance abuse patients.

Lastly, current evidence supports a slight elevation of disorganized symptoms of SPD in index relatives compared to controls; however, a more substantial effect cannot be ruled out. Disorganization symptoms do not appear specific to schizophrenia liability compared to affective disorders or substance abuse, however.

1.2.4 Limitations.

The findings from this review could be consistent with possibility that some symptoms of schizotypy may correlate with familial liability to schizophrenia. However, there are critical limitations of the current literature that raise doubt about the validity of this association.

First, for all of the available studies, index relative samples consisted only of first-degree relatives of schizophrenia patients. As described in our discussion on methodology, although first-degree relatives are extremely useful, they only provide one point of view. Extended families can provide additional information on the nature of liability to schizophrenia. Furthermore, although most studies did control for at least age and sex to minimize spurious group differences, only one study utilized relatives of control probands to improve representativeness (Kendler et al., 1995), and none of the studies made use of non-first-degree relatives as a comparison group. The addition of liability data from extended schizophrenia

families to data provided by first-degree relatives could lead to more confident conclusions regarding the relation between SPD symptoms and schizophrenia liability.

A second limitation pertains to assessment of SPD. Half of the available studies relied on questionnaires to provide data on SPD symptoms. This limits conclusions foremost because of concerns that questionnaires are differentially sensitive across symptoms of SPD, requiring that data obtained from questionnaires be viewed with reservation. Furthermore, comparisons between questionnaire- and interview-based results are not straightforward, limiting the extent to which data across multiple studies can be evaluated.

Third, results were reported only for phenotypic SPD factors (e.g., the social-interpersonal factor) and related symptoms. 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 as limited sensitivity to non-schizophrenia risk genes as possible. Sensitivity (i.e. power) is compromised to the extent that the endophenotype is itself genetically heterogeneous. Although the identified SPD factors represent phenotypically similar SPD symptoms, these phenotypic factors reflect both genetic and environmental effects on associations with schizophrenia liability. Thus, genetic homogeneity of phenotypic SPD factors is uncertain and correlations with genetic liability to schizophrenia cannot be adequately assessed.

Data from genetically-related individuals permit estimation of the unique contributions of genetic and environmental effects on a particular variable (e.g., SPD symptom). A variable 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 variable can still be genetically heterogeneous, including effects of both schizophrenia risk and non-risk genes. Phenotypic

covariation of observed variables among family members can be separated into genetic and environmental variance components. Cross-relative correlations of variables can be calculated and just as phenotypic factors are derived from a matrix of correlations among observed variables, genetic factors can be derived from a matrix of genetic variance correlations among relatives[2]. As such, genetic variance and covariance among variables (e.g., SPD symptoms) can be represented in terms of a set of genetic factors (Boomsma & Dolan, 1998; Boomsma, Molenaar, & Orlebeke, 1990). SPD genetic factors thus would reflect genetic homogeneity among SPD symptoms, absent confounding effects of environmental variance, and consequently may be particularly sensitive to genetic liability to schizophrenia.

1.3 AIMS OF THE CURRENT STUDY.

Identification of endophenotypes (I. I. Gottesman & Gould, 2003; I. I. Gottesman & Shields, 1972)] that correlate with familial liability to schizophrenia, and are maximally sensitive to a homogeneous subset of risk genes, is an important strategy for enhancing detection of genes that affect schizophrenia risk. Although a number of studies have compared relatives of schizophrenia patients with non-psychiatric controls on symptoms of SPD, there are substantial methodological limitations present in the current literature. Second, only a small number of studies have included comparisons with relatives from other diagnostic groups and comparison diagnoses are limited primarily to affective disorders, with only one report on substance abuse.

[2] Environmental factors also could be derived from environmental correlations in this manner.

Such a narrow selection of diagnostic comparison groups makes it difficult to discern the extent of any specificity to schizophrenia liability.

This family study was designed to systematically examine associations between SPD 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. Furthermore, this study addressed a number of the methodological limitations present in the literature to date, by 1) utilization of data from first through fourth-degree relatives of schizophrenia probands, 2) assessment of symptoms of SPD using the Structured Interview for Schizotypy (SIS; Kendler, Lieberman, & Walsh, 1989), which is currently regarded as the gold standard for assessment of SPD, 3) use of genetic factors and genetic factor scores to examine the association between schizotypy and genetic liability to schizophrenia, and 4) comparison with relatives of major depressive disorder and substance dependence probands. The following specific aims were addressed:

1) Estimation of heritabilities of individual symptoms of schizotypal personality disorder (SPD), as assessed by the SIS;
2) Calculation of genetic correlations between individual symptoms of SPD (SIS scales) and schizophrenia;
3) Construction of genetically homogeneous and uncorrelated SPD factors;
4) Estimation of heritabilities of these SPD genetic factors;
5) Calculation of genetic correlations between the SPD genetic factors and schizophrenia;
6) Calculation of genetic correlations between the SPD genetic factors and two additional psychiatric diagnoses represented in this sample, specifically major depressive disorder (MDD) and substance dependence.

2.0 METHOD.

2.1 PARTICIPANTS.

The participants in this study were 597 European-American, first- through fourth-degree relatives of 43 Schizophrenia or Schizoaffective Disorder, Depressed Type probands from 43 multigenerational multiplex families, and 88 European-American non-psychotic control individuals demographically matched to the relatives. All participants provided written informed consent according to the guidelines of the University of Pittsburgh or University of Pennsylvania Institutional Review Boards, and were remunerated for their participation in the study and for travel expenses.

2.1.1 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. Participating index probands were at least 18 years old, European-American, met DSM-IV diagnostic criteria for schizophrenia, 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 who might be 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.

2.1.2 Index Relatives.

First- to fourth-degree relatives of each schizophrenia 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. Relatives were then contacted by an interviewer who provided information about the study and conducted a brief screening. Exclusion criteria were minimal: existence of a medical condition that may cause neurocognitive deficits, or lack of proficiency in English. Interviews were scheduled with those eligible relatives who agreed to participate.

2.1.3 Control Probands.

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 pedigree members (probands and relatives) enrolled in the study. Age and sex matching was achieved by creating age bins (e.g., 18-20, 21-30, 31-40) and calculating the percentage of male and female family members within each bin. Age and sex recruitment targets necessary to achieve equivalent percentages for controls were then calculated. To match on location of residence, controls recruited at the University of Pittsburgh resided in one of the following five geographic regions, defined by telephone area code, from which the majority of index probands and relatives had been recruited: Pittsburgh, PA, Detroit, MI, Columbus, OH, Cleveland, OH, and Dayton, OH. Within these regions, all potential control individuals were initially contacted through random digit dialing by the University Center for Social and Urban Research (UCSUR) at the University of Pittsburgh.

Interested individuals identified through the University of Pittsburgh 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 (evidenced by, for example, 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.

University of Pennsylvania controls were identified by approaching eligible individuals already known by the staff, meeting with their friends, and word of mouth. These individuals were then screened either in person or over the phone. Exclusion criteria were: lifetime diagnosis

of a psychotic disorder, a history of psychotic disorders in the family, current treatment with psychotropic medication, or diagnosis of any neurological disorder.

2.2 ASSESSMENTS.

2.2.1 Diagnostic Assessment.

Lifetime, multiaxial diagnoses based on DSM-IV criteria were established by consensus conference by licensed psychologists and psychiatrists 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. Considerable effort was made to interview each participant in person, either at their home, at a community facility (e.g., a library), or at the interviewer's office. On the rare occasions when an in-person appointment was not feasible, interviews were conducted by phone. If available, medical records were also reviewed.

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, except controls recruited at the University of Pennsylvania. The DIGS 2.0 is a semi-structured interview designed to evaluate the presence of select Axis I psychiatric disorders based on DSM-IV diagnostic criteria. The following diagnoses were assessed: Schizophrenia, Schizoaffective Disorder, other psychotic disorder, Major Depressive Disorder (MDD), Bipolar Disorder, Dysthymia, Cyclothymia, Alcohol Abuse and Dependence, and Substance Abuse and

Dependence. Instead of the DIGS, the controls recruited at the University of Pennsylvania were administered a brief diagnostic screening interview to assess current and lifetime psychiatric and medical diagnoses, including substance use disorders, and family history of psychiatric illness. Lastly, at both sites 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.

2.2.2 Schizotypal Personality Disorder Assessment.

Non-psychotic index relatives and University of Pittsburgh controls were assessed for symptoms of Schizotypal Personality Disorder (SPD) using a modified version of the Structured Interview for Schizotypy (SIS), which is included as part of the DIGS 2.0 (Kendler et al., 1989)[3]. 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. The SIS was developed and tested by Kendler and colleagues in the context of the Roscommon Family Study (K.S. 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 85 items across 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,

[3] By convention, individuals meeting criteria for any psychotic disorder, including schizophrenia/schizoaffective probands and relatives diagnosed with a psychotic disorder, were excluded from the assessment of SPD.

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). Each scale is composed primarily of multiple choice items, as well as some open-ended items for clarification. A global rating is generated for each scale to quantify the clinical significance of the respondent's answers. All multiple choice items and global ratings in the interview are scored using a 0 – 6 Likert scale with the following anchors: 0 – no pathology, 2 – mild pathology/possible clinical significance, 4 – moderate pathology, 6 – marked pathology.

The post-interview behavior ratings consist of 28 additional items designed to be rated following the interview based on the interviewer's observation of the respondent. The following five scales (22 items) are rated and a global score is generated for each: Affect, Rapport, Suspiciousness/Guardedness, Organization of Speech/Thought, and Odd/Eccentric Behavior. The remaining six items assess Social/Interpersonal Functioning, Irritability, (respondent's) Reaction to Interview Length, Openness in Responding, Level of Understanding of the Questions, and Overall Quality/Reliability of the Interview. All post-interview ratings are scored using a 0 – 4 Likert scale with the following anchors: 0 – good, 1 – fair to good, 2 – fair, 3 – poor, 4 – very poor.

All of the 19 available SIS scales [Social Isolation, Introversion, Sexual Anhedonia, Sensitivity, Social Anxiety, Restricted Emotion, Affect, Rapport, Anger to Perceived Slights, Suspiciousness, Suspiciousness/Guardedness[4], Pathological Jealousy, Ideas of Reference: Being Watched, Ideas of Reference: Remarks, Magical Thinking, Psychotic-like Phenomena, Illusions, Organization of Speech/Thought, and Odd/Eccentric Behavior] and two of the additional post-interview items (Social/Interpersonal Functioning and Irritability) were included in the current

[4] For clarity, "Suspiciousness/Guardedness" will be referred to as "Guardedness" from here forward.

study. The DSM-IV-TR criteria for SPD, the corresponding SIS scales, and characteristics associated with high scale ratings are presented in Table 5. The remaining four post-interview items (Reaction to Interview Length, Openness in Responding, Level of Understanding of the Questions, and Overall Quality/Reliability of the Interview) were not selected as they assess specific factors related to the interview experience, and are not intended to assess symptoms of SPD. For simplicity, the two post-interview items included in this study (Social/Interpersonal Functioning and Irritability) are referred to as "scales" from here forward to avoid confusion with the individual items that comprise the scales.

2.2.2.1 SIS Scale Scores.

An overall mean item score was generated for each SIS scale. Open-ended items were excluded as these did not yield a quantitative score. To maximize the number of quantitative items available for each scale, items missing responses due to the design of the SIS interview (i.e., items not clinically applicable to the participant were skipped) were coded as follows: items skipped do to absence of pathology were coded '0'; items skipped due to presence of marked pathology were coded '6'. Missing responses due to any other reason were coded as missing. Cases missing responses for more than 50% of the items in a particular scale were excluded from that scale, except due to the structure of the Introversion scale, cases missing responses for more than 60% of the items in this scale were excluded. Thus, for each scale, only cases with 50% or more of the items completed (40% or more for Introversion) were retained. 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.

2.3 ANALYSES.

All univariate analyses of heritability and bivariate analyses of genetic correlation among SIS scales and with schizophrenia 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, and analyses were corrected for proband-based ascertainment. It is important to note that in these analyses, estimates of heritability and genetic correlation assume that shared environment effects are zero or uncorrelated with degree of genetic relatedness. Analyses that did not involve examination of pedigree structure were conducted in SPSS and Mplus.

3.0 RESULTS.

3.1 SAMPLE CHARACTERISTICS.

3.1.1 Sample Selection and Attrition.

Forty-three families consisting of 1610 pedigree members (43 index probands, 1567 first- to fourth- degree relatives) met the initial inclusion criteria described above; 676 of whom (43 probands, 633 relatives) were enrolled as study participants. DIGS data were collected on 639 pedigree members (42 probands[5], 597 relatives[6]); a mean of 14.9 individuals per family provided DIGS data. Although attempts to recruit large families were generally successful, some family members were not administered the DIGS assessment due to scheduling difficulties or the participant being lost to follow-up. Table 6 presents the distribution of individuals per family for whom DIGS data were available; the table does not include participants without DIGS data, many of whom completed assessments not included in this study (e.g., neuropsychological testing). Table 7 presents the frequency distribution of the number of affected individuals (diagnosed with schizophrenia or schizoaffective disorder, depressed type) per family. In the case of four families, two affected individuals were initially identified, but upon later

[5] One additional proband was diagnosed as schizoaffective, depressed type in the context of a previous study and was not administered the DIGS.
[6] Includes 49 non-biological relatives (e.g., step-relatives, spouses)

consideration, consensus was that only one of these individuals met strict diagnostic criteria for schizophrenia or schizoaffective disorder, depressed type. As data had already been collected on these pedigrees, they were retained in the study.

Two-hundred thirty unrelated, non-psychotic control individuals met inclusion criteria and were enrolled in the MGI study. DIGS data were collected on the 88 of these control individuals (all of whom were recruited at the University of Pittsburgh).

3.1.2 Attrition Analyses.

Table 8 presents the demographic characteristics of the final sample of index probands, relatives, and controls who were administered the DIGS and utilized in the current study. For the relatives, demographics are presented by degree of relationship to the proband and by generation within the family. Thirty-six enrolled relatives were not administered the DIGS and thus were excluded from this study. The 36 relatives who were not administered the DIGS were significantly older [mean (sd) = 56.1 (20.9)] ($t = 3.06$, $p = .004$) and more likely to be recruited from the University of Pennsylvania (97.2%) ($\chi^2 = 22.48$, $p < .001$) than the relatives from whom DIGS data were collected [mean age (sd): 45.2 (17.7)]. There were no significant differences in sex or education.

One-hundred forty-two controls were not administered the DIGS, and thus were not included in this study. These controls (all recruited at the University of Pennsylvania) were significantly younger [mean (sd) = 40.6 (18.5)] than the 88 controls for whom DIGS data were available [51.9 (17.5)] ($t = 4.56$, $p < .001$). There were no significant differences in sex or education.

3.1.3 Group Demographic Comparisons.

Only individuals for whom DIGS data were available were included in these and subsequent analyses. The index proband group completed significantly fewer years of education ($t = -6.71$, $p < .001$) than the control group; there was a non-significant trend for age (probands < controls, $p = .051$). The total index relative group also was less educated ($t = -5.97$, $p < .001$) and was significantly younger ($t = -3.33$, $p = .001$) than the control group. Sex was not significant for either group comparison.

3.1.4 Group Clinical Characteristics.

3.1.4.1 Index Probands.

All 43 index probands were diagnosed with either schizophrenia (n = 41) or schizoaffective disorder, depressed type (n = 2). Of the 43 probands, two received an additional diagnosis of 'other mood disorder' (e.g. substance-induced, due to a general medical condition) and 11 were diagnosed with a substance-related disorder (non-hierarchical). Clinical characteristics for the probands, as well as for the relatives and controls, are presented in Table 9.

3.1.4.2 Index Relatives.

Of the 597 index relatives for whom DIGS data were available, 60 were diagnosed with either schizophrenia (n = 51) or schizoaffective disorder, depressed type (n = 9). These diagnosed relatives, along with the index probands, comprise the group of 103 "affected" pedigree members; Table 7 provided the frequency distribution of affected pedigree members per family. For simplicity, from here forward we use the designation 'schizophrenia' to refer to the 103

"affected" individuals (diagnosed with schizophrenia or schizoaffective disorder, depressed type).

As presented in Table 9, the following additional hierarchical diagnoses were represented in the index relative group (n): schizoaffective disorder, bipolar type (4); bipolar disorder (9); and other psychotic disorder (e.g., substance or medically related, psychosis-nos) (16). The following non-hierarchical, non-exclusive diagnoses also were represented among the index relatives: cluster A personality disorder (schizotypal, paranoid, or schizoid) (25); MDD (without psychotic features or diagnosis of a cluster A personality disorder) (110), MDD (with psychotic features or a diagnosis of a cluster A personality disorder) (10); other mood disorder (59); substance-related disorder (153); and dementia (2).

3.1.4.3 Controls.

As described above, the exclusion criteria for control individuals were relatively minimal to achieve a control group that was representative of the general population from which the index relatives were drawn. Table 9 presents the clinical characteristics of the control group. By design, none of the 88 control individuals met criteria for schizophrenia, schizoaffective disorder, depressed type, or any other psychotic disorder. 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).

3.1.5 SIS Group Characteristics.

Of the 597 relatives who were administered the DIGS, SIS data were available for 480 individuals. Relatives were excluded from SIS administration for the following reasons (n):

affected (schizophrenia or schizoaffective disorder, depressed type) (60), schizoaffective disorder, bipolar type (4), other psychotic disorder (16), MDD with psychotic features (3), and logistical problems unrelated to diagnosis (e.g., refusal, lost to follow-up) (24). SIS data from relatives with diagnoses of dementia (2) and bipolar disorder (8) also were excluded from the current 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. All 88 University of Pittsburgh controls were administered the SIS. Table 10 presents the demographic and diagnostic characteristics of the 480 non-psychotic index relatives and 88 University of Pittsburgh controls whose SIS data were included in the following analyses.

3.2 SCALE DEVELOPMENT.

As noted above, for relatives and controls, the overall score for each SIS scale was the mean rating of the completed items in that scale. Table 11 presents the frequency of cases with missing items and Table 12 presents descriptive statistics for each SIS scale. The internal consistency (Cronbach's alpha) of each scale was examined in the combined sample (relatives and controls) to determine if the global rating for that scale should be included in the calculation of the overall scale score. Results indicated that for all scales, inclusion of the global rating increased internal consistency; thus, the global rating was included in the calculation of each scale score. The corrected item-total correlation between the global rating and the summed interview items in the combined sample was between 0.80 and 0.92 for all but three scales (Restricted Emotion = 0.70, Sexual Anhedonia = 0.62, Psychotic-like Phenomena = 0.51), which also argued for including the global ratings in the calculation of the total scale scores.

The distribution of SIS scale scores was inspected for outliers and all scores were deemed valid. Scale scores also were inspected for skewness. As expected, all individual SIS scales were significantly skewed among relatives, ranging between 0.7 and 3.7 (in relatives, SE for all scales = 0.1) (see Table 12). The scales that were found to be most skewed in the relatives were Guardedness (skewness = 3.3), Irritability (3.5), and Odd/Eccentric Behavior (3.7). All scales also were significantly skewed in the controls (range = 0.7 – 5.3, SE for all scales = 0.3), with the exception of Sensitivity (skewness = 0.3). In the controls, Guardedness, Irritability, and Odd/Eccentric Behavior were again among the most skewed (skewness = 4.2, 3.5, and 4.3, respectively), as were Rapport (3.0) and Organization of Speech/Thought (5.3).

Mean differences between relatives and controls were tested for all individual SIS scales and results are presented in the last two columns in Table 12. As a group, relatives were rated on average significantly higher (more pathological) than controls on 14 of the 21 SIS scales: Social Isolation, Social/Interpersonal Functioning, Social Anxiety, Affect, Rapport, Anger to Perceived Slights, Suspiciousness, Guardedness, Pathological Jealousy, Ideas of Reference: Being Watched, Ideas of Reference: Remarks, Psychotic-like Phenomena, Organization of Speech/Thought, and Odd/Eccentric Behavior.

Of the 480 relatives and 88 controls that comprised the final study sample, 96 relatives and 9 controls were missing data for at least one SIS scale. The Expectancy-Maximization (EM) algorithm in SPSS, using the student's t distribution, was utilized to impute the missing SIS scale data. The EM imputation method is a maximum likelihood estimation procedure. It is generally robust to violations of normality and thus it is an appropriate imputation method for these data. Covariates were not included in the imputation procedure. Estimates of skewness for the imputed

scale scores were equivalent to the non-imputed scores for all scales in both the relatives and controls.

Estimates of genetic correlation and heritability could not be calculated in SOLAR for six SIS scales (Suspiciousness, Ideas of Reference: Being Watched, Ideas of Reference: Remarks, Magical Thinking, Illusions, and Odd/Eccentric Behavior) due to failure to converge. Consequently, these six scales were dichotomized such that a rating of 0 (no pathology) was retained and any rating greater than 0 was given a score of 1. These six scales remained dichotomized for all subsequent 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 individual analyses. These scales can be assumed to be continuous, except where expressly noted that the dichotomized form was used. Dichotomized scales were modeled as threshold traits within SOLAR in the analyses that follow. Given the degree of skewness present in the continuous SIS scales, continuous data were fit to a t-distribution in SOLAR.

3.3 COVARIATES.

The following demographic and diagnostic variables were selected for use as possible covariates in subsequent analyses: age, sex, education, MDD (without psychotic features), and substance dependence (includes alcohol 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 education and the diagnostic variables also included.

3.3.1 Heritability of Covariates.

"Heritabilities" of the demographic and diagnostic covariates were estimated in the combined pedigree (probands and relatives) and control sample, while correcting for age and sex (heritability for age corrected for sex and vice versa). Heritability (h^2) indicates the proportion of variation that is due to genetic effects. In the case of the covariates, it is useful to know the proportion of genetic variation prior to controlling for these effects. As can be seen in Table 13, all covariates except sex demonstrated significant heritability (h^2 = 0.27 to 0.61, $p \leq .002$). Although significant heritability was expected for education and the diagnostic variables, generally age would not be expected to be "heritable". However, the pedigree structure of the sample resulted in the inclusion of a number of sibling pairs such that more closely related individuals tended to be more similar in age.

3.3.2 Genetic Correlation of Covariates and Schizophrenia.

The demographic and diagnostic covariates also were examined for "genetic correlations" with schizophrenia in the combined pedigree and control sample while adjusting for age and sex (Table 14). Genetic correlation (R_g) is an estimate of the proportion of genetic effects that are shared between two variables. Although sex was not "genetically" correlated with schizophrenia, a significant positive genetic correlation was found for age. Although not predicted, the pedigree structure of the sample is such that individuals more closely related to schizophrenia patients tended to be older compared to more distant relatives. Negative genetic correlations were found for education (R_g = -0.26, p = .012) and MDD (R_g = -0.50, p = .002), indicating that close relatives of schizophrenia patients received fewer years of education and were less likely to be

depressed than more remote relatives. Substance dependence was not significantly genetically correlated with schizophrenia.

3.3.3 Covariates and SIS Scales.

Correlations between the covariates and SIS scales in the combined relative and control sample were calculated next. As can be seen in Table 15, age, sex, and education were significantly negatively correlated with a number of SIS scales (52%, 38%, and 48% of the scales, respectively). This indicates that the responses of relative and control participants who were younger, male, and/or had fewer years of education tended to be rated as more pathological compared to the other participants. MDD and substance dependence were significantly positively correlated with 48% and 71% of the scales, respectively, indicating these diagnoses were associated with more pathological scale ratings. Finally, diagnosis of a cluster A personality disorder was significantly correlated with 90% of the scales, signifying that as expected, individuals with a diagnosis of a cluster A personality disorder were rated as more pathological on the SIS scales compared to individuals without such a diagnosis.

3.4 INDIVIDUAL SIS SCALES.

3.4.1 Heritability of SIS Scales.

Heritability was estimated for each SIS scale in the combined pedigree and control sample. For each SIS scale, heritability was estimated first using age and sex as covariates, and then a more

conservative test was applied by taking into account all the covariates identified above: age, sex, education, MDD, and substance dependence. As can be seen in Table 16, when age and sex were entered as covariates, all scales showed significant heritability (h^2 = 0.18 to 0.74, $p \leq .010$). When all demographic and diagnostic covariates were entered, the results did not substantially change (h^2 = 0.19 to 0.76, $p \leq .015$). Heritability of a cluster A personality disorder diagnosis also was calculated, and was found to be significant (h^2 = 0.64, p = .013).

3.4.2 Genetic Correlation of SIS Scales and Schizophrenia.

The genetic correlation with schizophrenia was estimated for each of the SIS scales in the combined pedigree and control sample. As in the analyses above, the genetic correlation first was estimated using age and sex as covariates; a more conservative test then was applied by controlling for all the demographic and diagnostic covariates (age, sex, education, MDD, substance dependence). As presented in Table 17, when age and sex were entered as covariates, a significant positive genetic correlation with schizophrenia was found for one scale, Guardedness, indicating that individuals closely related to a schizophrenia patient were more likely to be rated by interviewers as appearing guarded and suspicious during the interview. Trends towards significant negative genetic correlations with schizophrenia were found for Magical Thinking and Ideas of Reference: Watched. This suggests that individuals with a close relative with schizophrenia were less likely to report unusual beliefs, superstitions, and feeling scrutinized in public. Negative correlations for Magical Thinking and Ideas of Reference: Watched were unexpected findings, and perhaps reflect close relatives' guardedness when asked about unusual thoughts, beliefs, and experiences. When all demographic and diagnostic covariates were entered, Guardedness remained significantly genetically correlated with schizophrenia and the

negative correlation between Ideas of Reference: Watched and schizophrenia attained significance. The genetic correlation of a cluster A diagnosis and schizophrenia also was calculated and contrary to hypotheses, cluster A personality disorder was not significantly genetically correlated with schizophrenia ($R_g = 0.23$).

3.4.3 Intercorrelation of SIS Scales.

3.4.3.1 Phenotypic.

Bivariate correlations were calculated among all 21 SIS scales in the pedigree sample while controlling for age and sex. As can be seen in Table 18, the SIS scales are, as expected, highly intercorrelated. An exploratory factor analysis of the phenotypic intercorrelations of the SIS scales was performed in Mplus for the combined pedigree and control sample. Factor structure was extracted using unweighted least squares and Varimax (orthogonal) rotation was applied. Four interpretable phenotypic factors, accounting for 52% of the variance across scales, were identified using the Kaiser-Gutterman rule (eigenvalues > 1); this solution was consistent with the results of a scree test. Table 19 presents the correlations (loadings) of the individual SIS scales on the four SIS phenotypic factors. The first factor, “Observed Behavior”, consists of all seven SIS scales that are rated based on interviewer observation of the participant. The remaining three phenotypic factors, “Cognitive-Behavioral”, “Social-Interpersonal”, and “Paranoid” closely correspond to factor solutions identified in previous studies (A.J. Bergman et al., 1996).

3.4.3.2 Genotypic.

To examine the proportion of genetic effects shared among the 21 individual SIS scales, bivariate genetic correlations were calculated next, and are presented in Table 20. These data indicate the scales on which participants' ratings are correlated due to shared genetic factors. For example, ratings on Social Isolation and Introversion are positively phenotypically correlated (Table 18) and this relation is substantially influenced by genetic effects (Table 20).

3.5 SIS GENETIC FACTORS.

An exploratory factor analysis of the genetic correlations among SIS scales was performed in Mplus for the combined pedigree and control sample. As this factor analysis is based on genetic correlations, SIS scales that load strongly on the same genetic factor should be influenced, in part, by the same genetic effects. Factor structure was extracted using unweighted least squares and Varimax (orthogonal) rotation was applied. Six interpretable genetic factors were identified using the Kaiser-Gutterman rule and this solution was consistent with the results of a scree test. Together, the six genetic factors accounted for 87% of the genetic variance across SIS scales. The correlations (loadings) of the SIS scales with each of the six genetic factors are reported in Table 21.

The first genetic factor presented in Table 21, "Paranoid Fears", most strongly reflects the SIS scales Social Anxiety, Pathological Jealousy, Sensitivity, Psychotic-like Phenomena, Ideas of Reference: Remarks, Introversion, Suspiciousness, and Ideas of Reference: Watched. Anger to Perceived Slights also is correlated with this factor, although most strongly loads on the sixth factor (Unusual Beliefs). The combination of these scales suggests that this genetic factor

primarily represents paranoid fears and ideas of reference. As these scales are positively correlated with this factor, more pathological ratings on these scales are associated with higher factor scores.

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. 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. This factor seems best characterized as communication and interpersonal deficits. As these correlations are in the positive direction, SIS scale ratings of greater deficits are associated with higher scores on this factor.

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, greater sexual anhedonia and increased perceptual distortions contribute to a lower factor score. For ease of communicating the results below, the sign of the Perceptual Distortions factor will be reversed in all the following such that from here forward, greater pathology on these SIS scales is associated with a higher Perceptual Distortions factor score.

The fourth genetic factor presented in Table 21, “Restricted Emotions”, primarily consists of the Restricted Emotion scale, although Introversion, Affect, and Social/Interpersonal Functioning also positively correlate with this factor. As such, a higher factor score reflects more constricted expression of emotion/affect and social anhedonia. Illusions is negatively correlated

with this factor and as such, a lower rating on Illusions also contributes to a higher score on this factor.

The fifth genetic factor, "Eccentric Behavior", is correlated most strongly with Odd/Eccentric Behavior and also shows moderate correlation with Ideas of Reference: Remarks and Ideas of Reference Watched. This factor might best be described as eccentricities of thought and behavior. These scales are negatively correlated with this factor, so increased eccentric and unconventional thinking and behavior would contribute to lower factor scores. As with the third factor, the sign of the Eccentric Behavior factor also will be reversed; so from here on, greater pathology on these SIS scales is associated with a higher Eccentric Behavior factor score.

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. As these scales are positively correlated with this factor, more pathological ratings are associated with higher factor scores.

3.5.1 Calculation of Genetic Factor Scores.

Genetic factor scores were estimated by the standard regression method (Loehlin, 2004), and calculations were completed using the SPSS Matrix-End Matrix function. Beta weights for each genetic factor were calculated from the genetic correlations among SIS scales (predictors) and the correlations of the SIS scales with the SIS genetic factors (that which is being predicted). Specifically, beta weights were derived by multiplying the inverse of the SIS scale genetic intercorrelation matrix by the matrix of correlations between the SIS scales and genetic factors using the formula: $\mathbf{B} = \mathbf{R}^{-1}\mathbf{S}$, where **B** is the matrix of beta weights, **R** is the matrix of genetic correlations among SIS scales, and **S** is the matrix of correlations between the SIS scales and the

genetic factors. The resulting matrix of beta weights is presented in Table 22. These beta weights subsequently were applied to the standardized observed SIS scale scores (z-scores) to yield predicted genetic factor scores on each of the six SIS genetic factors for each participant: **F = Z*B**, where **F** is the matrix of predicted genetic factor scores, **Z** is the matrix of standardized SIS scale scores, and **B** is the matrix of beta weights derived above (Loehlin, 2004).

3.5.2 Intercorrelation of SIS Factor Scores.

Bivariate genetic correlations were calculated among the six genetic factor scores in the combined pedigree and control sample while controlling for age and sex. As can be seen in Table 23, the factor scores are genetically uncorrelated with each other as expected.

3.5.3 Heritability of SIS Factor Scores.

Heritabilities of the genetic factor scores were estimated for the six SIS genetic factors in the combined pedigree and control sample. As presented in Table 24, all factors were significantly heritable when controlling for age and sex (h^2 = 0.25 to 0.58, $p < .001$) and when accounting for all demographic and diagnostic covariates (h^2 = 0.25 to 0.57, $p < .001$).

3.5.4 Genetic Correlations of SIS Genetic Factor Scores with Schizophrenia.

Next, genetic correlations with schizophrenia were estimated for each of the SIS factors in the combined pedigree and control sample; these data are presented in Table 25. When age and sex were entered as covariates, significant negative genetic correlations with schizophrenia were

found for the Eccentric Behavior and Unusual Beliefs genetic factors. A non-significant, positive genetic correlation with schizophrenia was observed for Interpersonal Deficits. Eccentric Behavior and Unusual Beliefs remained significantly genetically correlated with schizophrenia when the additional demographic and diagnostic covariates were entered.

Taking into account the correlations between individual SIS scales and SIS genetic factors, as well as the beta weights applied to the scales, high factor scores on Eccentric Behavior predominantly reflect high ratings on Odd/Eccentric Behavior and Ideas of Reference: Remarks; elevated factor scores on Unusual Beliefs primarily reflect high ratings on Anger to Perceived Slights, Magical Thinking, and Ideas of Reference: Watched. As such, 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, or feelings of being scrutinized/singled out in public. Although unpredicted, these findings are consistent with the genetic correlations between the individual SIS scales and schizophrenia reported above.

For Interpersonal Deficits, high scores are particularly indicative of elevated ratings on Organization of Speech/Thought, Rapport, Social/Interpersonal Functioning, Irritability, and Restricted Emotion. 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 tend to demonstrate more atypical speech, low

emotionality, constricted or suspicious affect, irritability, and social withdrawal compared to more distant family members.

3.5.5 Genetic Correlations of SIS Genetic Factor Scores with Major Depressive Disorder.

Next, genetic correlations with major depressive disorder (MDD, without psychotic features) were estimated for each of the SIS genetic factors in the combined pedigree and control sample, and are reported in Table 26. In contrast to the findings for schizophrenia, none of the genetic factors were significantly genetically correlated with MDD, although there was a non-significant negative genetic correlation for Perceptual Distortions. High scores on this factor reflect elevated ratings on Sexual Anhedonia, Illusions, and Psychotic-like Phenomena. This suggests that close relatives of an individual with MDD may tend to report less sexual anhedonia and fewer perceptual distortions than more remote relatives.

3.5.6 Genetic Correlations of SIS Genetic Factor Scores with Substance Dependence.

Genetic correlations with substance dependence also were calculated for each of the SIS genetic factors in the combined pedigree and control sample and these data are presented in Table 27. Of all six factors, the positive correlation with Paranoid Fears most closely approached significance. This factor is prominently characterized by high ratings of Social Anxiety, Pathological Jealousy, Sensitivity, Ideas of Reference: Remarks, Introversion, Suspiciousness, Social Isolation, and Illusions. 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.

4.0 DISCUSSION.

The aims of this multigenerational, multiplex family study of schizophrenia were to: 1) estimate heritabilities of individual symptoms of schizotypal personality disorder (SPD), as assessed by the SIS, 2) calculate genetic correlations between individual SIS symptom scales and schizophrenia, 3) construct genetically homogeneous and uncorrelated SPD (SIS) factors, 4) estimate heritabilities of the genetic factors, 5) calculate genetic correlations between the genetic factors and schizophrenia, and 6) calculate genetic correlations between the genetic factors and two additional psychiatric diagnoses represented in our sample, specifically major depressive disorder (MDD) and substance dependence. This study also sought to improve on methodological constraints present in the previous literature. The findings can be summarized as follows, and are discussed in more detail below:

1) All individual SIS scales were highly heritable, suggesting that endorsement of symptoms of SPD was strongly influenced by genetic effects.

2a) The individual SIS scale, Guardedness, demonstrated a significant, positive genetic correlation with schizophrenia.

2b) The individual SIS scale, Ideas of Reference: Watched, showed a significant, negative genetic correlation with schizophrenia; similarly, the Magical Thinking scale demonstrated a negative genetic correlation with schizophrenia that trended toward significance.

3) Six uncorrelated, genetic factors were constructed, accounting for 87% of the variance across all SIS scales.

4) All genetic factors were highly heritable. Thus, the degree to which an individual was elevated on a particular factor was in part driven by genetic effects.

5a) Two of the genetically distinct SIS factors, Eccentric Behavior and Unusual Beliefs, were significantly negatively genetically correlated with schizophrenia.

5b) The Interpersonal Deficits genetic factor showed a positive, albeit non-significant, genetic correlation with schizophrenia.

6a) None of the six SIS genetic factors were significantly genetically correlated with MDD. The highest non-significant (negative) correlation with MDD was found for Perceptual Distortions.

6b) Likewise, none of the SIS factors showed a significant genetic correlation with substance dependence, although a positive trend was observed for Paranoid Fears.

The following discussion is broadly organized into four sections. First, we discuss the current results in the context of prior studies of schizotypal traits and genetic liability to schizophrenia. Second, we address the implications of the current results for the potential utility of SPD symptoms as endophenotypes in genetic analyses of schizophrenia. Third, we discuss the limitations of this investigation, and fourth, we conclude with suggestions for future directions for this line of research.

4.1 SPD AND GENETIC LIABILITY TO SCHIZOPHRENIA.

The results of this study address three important and interrelated topics pertaining to schizotypy, schizophrenia, and contributing genetic effects. The first topic discussed below is the nature of the genetic contribution to schizotypal personality traits in non-psychotic relatives, including the genetic factor structure of SPD traits. The second topic of discussion is the genetic relation between symptoms of SPD and the schizophrenia phenotype. Third, we discuss the genetic relation between SPD symptoms and non-psychotic, psychiatric diagnosis phenotypes.

4.1.1 Genetic Effects on Symptoms of SPD.

4.1.1.1 Individual SIS Scales.

The significant heritabilities of the SIS scales indicate that characteristics of SPD observed among this sample of relatives of schizophrenia patients were strongly influenced by genetic effects; a finding that is consistent with the results of the few previous studies that have examined this question (Kendler & Hewitt, 1992; Torgersen, 1985). Furthermore, the results of the current study support strong genetic intercorrelations among particular groups of SIS scales, suggesting that multiple genetic factors contribute to the presence (or absence) of SPD symptoms. Thus, for example, there is a high likelihood that two closely related individuals (e.g., siblings) will endorse the same type and/or intensity of SPD symptoms. Additionally, if say, they both endorse Social Anxiety, then it is quite likely that both will endorse Introversion as well.

4.1.1.2 SIS Genetic Factors.

To date, factor analyses of SPD 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 SPD. This study was 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 variance among SIS scales, a solution similar to the five traits of "borderline schizophrenia" originally proposed by Kety et al. (Copenhagen Adoption Study; Kety et al., 1968). All six genetic factors were highly heritable. Furthermore, these factors were genetically uncorrelated with each other, and thus appear to reflect six distinct, latent genetic variables.

Comparison with Previous Studies.

It is interesting to compare the results of the novel genetic factor analysis reported here with the three SPD phenotypic factors most often reported (Social-Interpersonal, Cognitive-Perceptual, Disorganized) (A. J. Bergman et al., 2000), and similar to the phenotypic factors observed in this sample. First, the SPD symptoms previously observed to load on the "Social-Interpersonal" phenotypic factor[7] primarily contributed to one of two genetic factors: Paranoid Fears or Interpersonal Deficits, with a tertiary loading on Constricted Affect for a small subset of symptoms.[8] This divergence among social-interpersonal SPD symptoms may perhaps reflect two relatively distinct symptom clusters each influenced by different genetic effects. Presumably, in

[7] Social Isolation, Introversion, Sexual Anhedonia, Social/Interpersonal Functioning, Sensitivity, Social Anxiety, Restricted Emotion, Affect, Rapport, Anger to Perceived Slights, Suspiciousness (also reported to load on the Cognitive-Perceptual factor), Guardedness, Irritability, and Pathological Jealousy.
[8] Although arguably, all six of the genetic factors each include an interpersonal component.

previous phenotypic factor analyses, these symptoms loaded together on the same factor due to environmental covariance.

Second, of the SPD symptoms that typically characterize the "Cognitive-Perceptual" phenotypic factor[9], all but one were at least moderately correlated with the Paranoid Fears genetic factor. The exception, Magical Thinking, was a substantial contributor only to Unusual Beliefs. It seems that most observed cognitive-perceptual symptoms of SPD do share a portion of their genetic variance, perhaps associated with paranoia.

Lastly, the "Disorganized" phenotypic factor[10] is frequently noted in the literature as being less "stable" than the other two phenotypic factors, and is not consistently identified as a separate factor in phenotypic analyses of SPD symptoms (e.g., A. J. Bergman et al., 2000; Grove et al., 1991). Our results provide support for this observation as the two "disorganized" SIS scales, Organization of Speech/Thought and Odd/Eccentric Behavior, loaded on separate genetic factors (Interpersonal Deficits and Eccentric Behavior, respectively). As atypical speech and odd behavior appear to be genetically dissimilar, it is understandable that they do not always combine to form a separate phenotypic factor.

4.1.2 Genetic Association of SPD Symptoms and Schizophrenia.

We next focus our discussion on the results as they relate to the genetic correlations between SPD symptoms and schizophrenia. We first discuss the genetic relation of the individual SIS

[9] Ideas of Reference: Being Watched, Ideas of Reference: Remarks, Magical Thinking, Psychotic-like Phenomena, Illusions, and Suspiciousness.
[10] Organization of Speech/Thought and Odd/Eccentric Behavior

scales and schizophrenia. Second, we focus on the SIS genetic factors and schizophrenia, including potential explanations for the negative genetic correlations observed in this study.

4.1.2.1 Individual SIS Scales.

Three individual SIS scales, Guardedness, Magical Thinking, and Ideas of Reference: Watched, were found to be significantly (or nearly so) genetically correlated with schizophrenia. Foremost, Magical Thinking and Ideas of Reference: Watched were negatively correlated with schizophrenia. Both scales are based on the participants' self-report responses to the interview items. As such, close relatives of individuals with schizophrenia, who presumably share a greater proportion of schizophrenia risk genes with a proband compared to more distant relatives, were less likely to report feeling singled out and scrutinized in public, and endorsed fewer culturally unusual beliefs and paranormal experiences compared to more distant relatives. These results suggest that referential ideation of being watched and magical thinking each share a portion of their genes with schizophrenia; although in both cases, the shared genetic effects that increase risk for schizophrenia contribute to lower reported levels of these SPD symptoms.

Conversely, the Guardedness scale was significantly positively genetically correlated with schizophrenia. This scale is rated after the interview based on the interviewer's observations of the participant. Thus, elevation on this scale indicates that the participant appeared particularly suspicious, vigilant, and guarded to the interviewer. This finding suggests that a portion of the genetic effects that increase risk for schizophrenia also contribute to higher levels of observed guarded behavior. Although it would seem plausible that observed heightened levels of guardedness would be consistent with an individual's reluctance to divulge experiences of magical thinking and referential ideation, the Guardedness scale actually showed a significant positive phenotypic correlation with Magical Thinking and Ideas of Reference: Watched, and

was not genetically correlated with either scale. This suggests that the negative correlations observed for Magical Thinking and Ideas of Reference: Watched may not be due to elevated guardedness; however, the Guardedness scale reflects a small subset of behaviors and may not fully capture a participant's willingness to self-report on these symptoms.

It is unclear why the remaining individual SIS scales were not especially genetically correlated with schizophrenia. This is particularly surprising given the well replicated finding that as a group, relatives of schizophrenia patients are elevated on symptoms of SPD compared to normal controls. If relatives adopted a guarded response style throughout the interview, it likely would be reflected in all of the interview scales. However, as with Magical Thinking and Ideas of Reference: Watched, the Guardedness SIS scale actually showed significant positive phenotypic correlations, and non-significant genetic correlations, with the majority of the other SIS scales. Again, this suggests that the general lack of significant correlations between the SIS scales and schizophrenia may not be due to an overall guarded approach to the interview; however, as noted above, it must be cautioned that the Guardedness scale may have limited sensitivity in this area.

4.1.2.2 SIS Genetic Factors: Negative Genetic Correlations.

Eccentric Behavior and Unusual Beliefs.

At the level of the SIS genetic factors, a significant negative genetic correlation with schizophrenia was found for the Eccentric Behavior and Unusual Beliefs factors. These results suggest that during the interview, close relatives of schizophrenia probands reported fewer atypical beliefs, superstitions, 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. These results also indicate that a significant proportion of latent genetic effects that contribute to increased genetic risk for schizophrenia, also contribute to lower scores on the Eccentric Behavior and Unusual Beliefs factors. As these factors are not genetically correlated with each other, we can infer the presence of two genetically distinct latent variables, each of which separately influences schizophrenia liability.

The negative direction of the significant genetic effects for the Eccentric Behavior and Unusual Beliefs factors, as well as the two individual SIS scales noted above (Magical Thinking and Ideas of Reference: Watched), was quite surprising. These genetic correlations indicate that as an individual's genetic similarity (to a schizophrenia proband) increases, symptoms such as odd behavior, hostility, magical thinking, and referential ideation actually decrease. Although we cannot know for certain, there are a few plausible explanations for this unexpected finding that we address next. First, these negative genetic correlations may be spurious due to confounding variables in the data. Second, the observed negative genetic effects may accurately reflect the characteristics of this particular sample, but do not generalize to the general population of families of individuals with schizophrenia. Third, the negative genetic correlations observed in this sample also may be relevant to the general population of affected families.

Negative Genetic Correlations are Spurious.

Alpha error. It may be that the significant negative correlations we observed were simply a result of chance. A Bonferroni correction suggests assuming a significance threshold of .002 for the 21 individual SIS scales, and .008 for the six SIS genetic factors. Utilizing these guidelines, all of the individual SIS scales but two (Sexual Anhedonia and Suspiciousness) and 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 relation between SPD symptoms and schizophrenia. Although Bonferroni correction is usually considered overly conservative with uncorrelated measures, it is possible that these significant negative genetic correlations with schizophrenia are due to chance.

Age. As discussed earlier, in this sample age was positively "genetically" correlated with schizophrenia, and negatively correlated with a number of individual SIS scales, including Ideas of Reference: Watched. Thus, close relatives of schizophrenia probands tended to be older, and older relatives tended to score lower (less pathologically) on these SIS scales, which could spuriously induce the observed negative genetic correlations between the SIS scales (and SIS factors) and schizophrenia. However, all analyses reported above controlled for age. Furthermore, when we examined the genetic correlations of the scales and factors with schizophrenia without controlling for age, the results did not substantially change. As an additional assessment of age effects, we examined the genetic correlations between the SIS scales and schizophrenia separately for each generation and continued to obtain a negative association. Finally, the interaction term between age and generation was not significant. Thus, although age effects seem a very reasonable explanation for our findings, further analyses did not provide strong support for this possibility.

Negative Genetic Correlations are Sample Specific.

Multiplex family design. Another possible explanation for the negative genetic correlations with schizophrenia is that by recruiting multiplex pedigrees we may have selected for families in which inherited risk genes that could be expressed have already been expressed (as schizophrenia) in those members. This could be a result of a higher frequency of risk alleles in these multiplex families. Alternatively, these families may not differ from simplex families in frequency of risk alleles; but instead, a greater proportion of available risk genes may have been

expressed, perhaps due to elevated environmental stress. If a greater number of multiplex family members with risk alleles actually develop schizophrenia, then relatives who do remain well are likely to be particularly low in genetic liability. Given this, non-psychotic first-degree relatives from multiplex families actually may be relatively less symptomatic on measures of schizotypy compared to first-degree relatives from simplex families. This could tend to produce a negative genetic correlation between schizotypal symptoms and schizophrenia in the current sample.

In contrast to this suggestion, the balance of theory and observation during the last two decades (I. I. Gottesman, 1991; I.I. Gottesman, McGuffin, & Farmer, 1987) supports a multifactorial model of schizophrenia liability which states that multiple genes, in combination with adverse environmental factors, form the basis of schizophrenia etiology. According to this model, liability to schizophrenia is distributed proportional to the number of genetic and environmental risk factors present. As liability to schizophrenia increases, so should the symptoms and deficits associated with this liability. Based on this model, non-psychotic relatives from multiplex schizophrenia families should have a higher degree of genetic loading for the disorder and as such, should display more symptoms of SPD than relatives from simplex families.

A small number of studies have compared non-psychotic relatives from multiplex and simplex schizophrenia families, although no studies were identified that assessed symptoms of SPD. Seidman and colleagues (Faraone et al., 2000; Seidman et al., 2009; Seidman et al., 2003) published a series of reports on neuroanatomical and neuropsychological functioning in non-psychotic (primarily first-degree) relatives from multiplex and simplex families of schizophrenia patients. These studies found that relatives from multiplex families had more neuroanatomical abnormalities, and greater neuropsychological deficits, compared to relatives from simplex

families. Furthermore, worse performance on neuropsychological tasks was correlated with greater neuroanatomical abnormalities among multiplex, but not simplex families. Together, this evidence indicates that relatives from multiplex families do show significantly more abnormalities than relatives from simplex families, at least on neuroanatomical and neuropsychological measures, suggesting that ascertainment of multiplex families is unlikely to result in the negative genetic correlations with schizophrenia observed in this study.

Negative Genetic Correlations are Valid.

Systematic underreporting. Finally, as suggested above, a plausible explanation for the negative genetic effects observed for Eccentric Behavior and Unusual Beliefs is that during the interview, first-degree relatives were especially likely to underreport unusual ideas, beliefs, and behavior: symptoms that they perhaps associated with their ill relative. First-degree relatives in particular tend to be very familiar with psychotic symptoms given the experience of having a child, sibling, or parent with schizophrenia. As genetic relatedness to a schizophrenia proband and familiarity with psychotic symptoms decrease, underreporting of unusual thoughts and behavior may in turn become increasingly rare. This situation would tend to produce a negative genetic correlation between the more "unusual" symptoms of schizotypy (e.g., magical thinking) and schizophrenia. Furthermore, close relatives may have tended to underreport on the SIS as a whole, which would offer a reasonable explanation for the non-significant results obtained for the other SIS genetic factors and individual SIS scales.

In the current study, the Interpersonal Deficits genetic factor (which contained the Guardedness SIS scale that was based on interviewer rating) was neither genetically nor phenotypically correlated with the Eccentric Behavior or Unusual Beliefs factors, which does not add support for underreporting as a possibility. However, the Interpersonal Deficits factor may

not completely capture guardedness during the interview and as such, may not be an infallible indicator of reluctance to divulge information.

There is a small literature concerning unusual beliefs and behaviors among first-degree relatives of schizophrenia patients that is relevant to this discussion. In our earlier review of SPD symptoms, results supported just a small effect of (elevated) cognitive-perceptual symptoms among first-degree relatives of schizophrenia patients compared to controls. One study (Appels et al., 2004) reported a negative association, suggesting that parents of schizophrenia patients endorsed significantly fewer unusual experiences and beliefs compared to controls; although the cause of this finding is unclear.

The Chapman Perceptual Aberration Scale (Chapman, Chapman, & Raulin, 1978) also has been used to compare first-degree relatives of schizophrenia patients and controls, and has been reported to correlate strongly with cognitive-perceptual symptoms of SPD in relatives (Clementz, Sweeney, Hirt, & Haas, 1991). Clementz, Grove, Katsanis, and Iacono (1991) and Katsanis, Iacono and Beiser (1990) both reported that non-psychotic first-degree relatives scored lower (less pathological) than controls on the Perceptual Aberration Scale, despite scoring as expected (less pathological than probands, but more-so than controls) on other Chapman scales (Social Anhedonia and Physical Anhedonia; Chapman, Chapman, & Raulin, 1976). Docherty and Sponheim (2008) and Glatt, Stone, Faraone, Seidman, and Tsuang (2006) also reported no differences between first-degree relatives and controls on the Perceptual Aberration Scale [and the Magical Ideation Scale (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994)], despite relatives being elevated on social and physical anhedonia.

Finally, a few investigations used bidirectional personality inventories in their assessment of relatives of schizophrenia patients. Gonzalez-Torrez et al. (2009) assessed schizophrenia

probands, their first-degree relatives, and controls using the Spanish version of the Temperament and Character Inventory (TCI; Cloninger, 1994). They reported that on the Novelty-Seeking temperament dimension, relatives tended to endorsed lower novelty-seeking compared to controls ($p = .081$), yet did not differ on the other temperament and character dimensions. Berenbaum, Taylor, and Cloninger (1994) also found no differences between relatives and controls on traits of Control, Harm Avoidance, or Traditionalism as assessed by the Multidimensional Personality Questionnaire (MPQ; Tellegen, 1982).

Together, these results indicate that close relatives of schizophrenia probands may not differ from, or may actually endorse less pathology than controls on symptoms such as magical thinking and ideas of reference. These reports thus corroborate that low ratings on these SPD symptoms for close relatives are not unique to this study. Therefore, it may be the case that the Eccentric Behavior and Unusual Beliefs genetic factors are sensitive to underreporting among relatives of schizophrenia patients, and thus could be analogous to the K scale (defensive underreporting) on the Minnesota Multiphasic Personality Inventory (MMPI).

4.1.2.3 SIS Genetic Factors: Positive Genetic Correlations.

Interpersonal Deficits.

In contrast to Eccentric Behavior and Unusual Beliefs, the Interpersonal Deficits genetic factor showed a positive, albeit non-significant, genetic correlation with schizophrenia. This suggests that during the interview, close relatives of schizophrenia probands were somewhat more likely to display atypical speech, appear disconnected or irritated with the interviewer, and endorse constricted affect or lack of emotionality compared to more remote family members. This

finding is congruent with observations of elevated schizotypal social-interpersonal deficits among relatives of schizophrenia patients compared to non-relatives noted in our earlier review.

Although not significant in the current study, we draw attention to this positive genetic correlation between Interpersonal Deficits and schizophrenia in light of accumulating evidence that social deficits may be an important piece of the genetic liability puzzle. First, prospective and retrospective studies consistently find that schizophrenia patients display greater social deficits and worse social adjustment in childhood and adolescence (prior to psychosis onset), compared to patients with affective disorders, healthy siblings, and controls (Cannon et al., 1997; Tarbox & Pogue-Geile, 2008; Willinger, Heiden, Meszaros, Formann, & Aschauer, 2001). Second, the level of social functioning attained prior to psychosis onset is an important correlate of individual variation in illness course and outcome (poor social functioning in childhood and adolescence tends to be associated with greater illness severity in adult schizophrenia patients), and this association tends to be stronger for schizophrenia than other psychiatric illnesses (Bromet, Harrow, & Kasl, 1974).

Although speculative, the results of the current study suggest the possibility of shared genetic effects that elevate interpersonal deficits and increase risk for schizophrenia, and thus offer additional support for an association between social deficits and liability to schizophrenia. However, it remains unclear why the Interpersonal Deficits factor fell short of reaching significance in this study, but perhaps was a result of systematic underreporting by close relatives.

4.1.3 Genetic Association of SPD Symptoms and MDD and Substance Dependence.

None of the six genetic factors were significantly genetically correlated with MDD. The highest non-significant (negative) correlation with MDD was found for Perceptual Distortions. Of note, MDD and schizophrenia were negatively genetically correlated, which would tend to inflate negative genetic correlations between MDD and the SIS genetic factors. This is not of particular concern here given the non-significant results. Likewise, none of the genetic correlations between the genetic factors and substance dependence reached significance, although a positive trend was observed between substance dependence and Paranoid Fears. As substance dependence was not genetically correlated with schizophrenia in this sample, inflation of results due to increased liability to schizophrenia does not seem likely.

Overall, it seems likely that genes contributing to liability to MDD do not substantially overlap with genes that influence SIS genetic factor scores. Similarly, genes that elevate risk for substance dependence are likely not shared with those that affect SIS genetic factor scores. The possible exception is Paranoid Fears, which may share a proportion of genetic effects with liability to substance dependence. Of course, replication of these results in general population samples of MDD and substance dependence probands and their relatives would clarify generalizability of these results.

4.2 SCHIZOTYPY AND THE SEARCH FOR SCHIZOPHRENIA RISK GENES.

To be most useful in genetic studies of schizophrenia, an endophenotype (I. I. Gottesman & Gould, 2003; I. I. Gottesman & Shields, 1972) should 1) be as sensitive as possible to individual

genes that affect risk for schizophrenia and 2) correlate with genetic liability to schizophrenia in the absence of psychosis. The current study attempted to address these requirements with the goal of evaluating symptoms of SPD as potentially useful endophenotypes. Prior to considering the direction of the effects, we first examine the overall fit between the current results and these criteria. We then address the impact of the observed negative genetic correlations on this fit.

4.2.1 Comparison of Results to Endophenotype Criteria.

The six SIS genetic factors were obtained from genetic correlations among SIS scales and were not genetically correlated with each other; therefore, each factor reflects a distinct, homogeneous set of latent genetic effects shared by a particular subset of SIS scales. Three of the SIS genetic factors, Eccentric Behavior, Unusual Beliefs, and Interpersonal Deficits, also demonstrated moderate to strong genetic correlations with schizophrenia among non-psychotic relatives. As such, each of these three genetic factors is sensitive to distinct, homogeneous subsets of genes that contribute to genetic liability to schizophrenia in this sample (i.e., "risk genes"); although Eccentric Behavior and Unusual Beliefs were negatively associated with schizophrenia (see below) and Interpersonal Deficits showed a non-significant trend. Furthermore, these three genetic factors were not genetically correlated with liability to MDD or substance dependence, suggesting a degree of specificity to schizophrenia risk genes. Of course, the specific genes represented by these factors, and the degree to which they influence risk for schizophrenia, remain unknown.

Although quite heritable, the majority of individual SIS scales were not strongly genetically correlated with schizophrenia in this sample. Thus, as separate phenotypes, individual

symptoms of SPD are unlikely to be useful in genetic studies, with the possible exception of Guardedness.

In sum, the current study provides evidence that the SPD genetic factors Eccentric Behavior, Unusual Beliefs, and perhaps Interpersonal Deficits as derived from the SIS, are a) sensitive to a "homogeneous" subset of genes that affect risk for schizophrenia and b) correlate with genetic liability to schizophrenia in the absence of psychosis, and more strongly correlate with schizophrenia liability than with liability to MDD and substance dependence. Therefore, these symptoms of SPD perhaps could be useful endophenotypes, at least in regards to these criteria. Of course, there are a number of issues that await clarification. For example, the degree of genetic homogeneity present within each factor cannot be determined in this study. As yet, there also are no guidelines by which to determine the level of genetic homogeneity necessary for an endophenotype to be useful.

4.2.2 Directionality of Genetic Correlations.

This leads to the next crucial question: can genetic factors that are negatively genetically correlated with schizophrenia risk be useful in genetic studies? To reach a conclusion, first it must be determined if the apparent negative genetic correlations of Eccentric Behavior and Unusual Beliefs with schizophrenia are indeed valid, replicable, and systematic findings that are not unique to this multiplex sample. If replicated, the preceding discussion suggests that underreporting by close relatives would be the most plausible explanation for these negative genetic correlations. As such, among non-psychotic relatives, underreporting of unusual ideas, beliefs, and behavior appears to be significantly (and positively) genetically correlated with schizophrenia.

The Eccentric Behavior and Unusual Beliefs genetic factors thus appear to be sensitive indexes of shared genetic effects between underreporting on these particular symptoms and liability to schizophrenia. In addition to odd beliefs and behavior, these indexes may be sensitive to genetic effects on underreporting throughout the SIS interview. As noted above, these factors could be conceptualized as comparable to the MMPI K scale, which is a sensitive measure of underreporting on the MMPI. Furthermore, these indexes appear to be relatively specific to underreporting among family members of schizophrenia patients, at least compared to relatives of MDD and substance dependence patients. Given the methodological strengths of this study, the evidence suggests that Eccentric Behavior and Unusual Beliefs may have potential to be useful endophenotypes of schizophrenia. Of course, future replications are needed.

4.3 LIMITATIONS.

4.3.1 Sample.

First, although the multiplex pedigree sample utilized in this study offers a number of exceptional benefits and opportunities for statistical genetic analyses, large multiply affected families represent a minority of those families that include an individual with schizophrenia. In fact, the majority of individuals with schizophrenia do not have any relatives with schizophrenia or a spectrum disorder (such as SPD). As such, comparisons between our results and those obtained from simplex family studies are not straightforward. In addition, interviewers were not blind to group status, and often provided SIS ratings for multiple individuals from the same family.

A second, similar issue pertains to the genetic correlations between the SIS genetic factors and MDD and substance dependence. As the individuals in our study with diagnoses of MDD or substance dependence were also relatives of schizophrenia patients, generalizability of these results should remain tentative until they can be replicated in a general population sample of individuals with these diagnoses.

Third, given the age range of our pedigree sample (15 – 85), it is important to be aware that a proportion of the younger relatives may convert to psychosis subsequent to being interviewed. This concern may be especially relevant for male first-degree relatives under 25 and female first-degree relatives under 30, as they are at highest overall risk for schizophrenia. In this sample, 6% of male first-degree relatives were younger than age 25, and 14% of female first-degree relatives were younger than age 30, at the time they were interviewed. Thus, taking final diagnostic status into consideration, a notable minority of male and female non-psychotic relatives included in this study may be misclassified as "unaffected", and in actuality belong to the "affected" group. This error would tend to inflate pathology, particularly among more closely related individuals, and increase the chance that positive genetic correlations between SIS genetic factors (and scales) would be erroneously identified. Given the negative correlations reported above, misclassification does not appear to be a particular concern in this study.

4.3.2 Proband Heterogeneity.

As indicated above, the SIS was not administered to individuals with a psychotic diagnosis. Consequently, SIS scale scores and genetic factor scores were not available for our sample of "affected" participants. Although analyses were planned and executed with this characteristic of the data in mind, this study was not able to calculate genetic correlations or perform genetic

factor analyses to directly compare components of genetic variance of SPD symptoms among probands, relatives, and controls.

On a related point, although this study takes a considerable step towards disentangling genetic and environmental covariance and reducing genetic heterogeneity of SPD symptom phenotypes, it was not possible to examine and minimize heterogeneity within the schizophrenia diagnosis phenotype itself, due to the small sample size of affected individuals. The polygenetic etiology of schizophrenia has been a significant hurdle for both molecular and behavioral genetic studies, and likewise is an issue that complicates interpretation of the current results.

Finally, 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. In this sample, it is thus assumed that shared environmental effects are either absent, or uncorrelated with degree of genetic relatedness to schizophrenia.

4.4 FUTURE DIRECTIONS.

The preceding discussion raises some interesting issues that could be pursued in future investigations. Foremost, the current results of course require replication to establish that the observed genetic correlations are not, in actuality, spurious. Second, a particularly frustrating limitation of this and many previous studies is the effect of genetic heterogeneity of the schizophrenia phenotype. Perhaps a useful next step would be to separate the schizophrenia phenotype into more genetically homogeneous components, as done here with SPD symptoms.

This strategy may help reduce the genetic "noise" within the schizophrenia phenotype and improve sensitivity to detect important associations.

A few studies have divided schizophrenia by positive and negative symptoms (phenotypes), and examined the association between these phenotypic "subgroups" of schizophrenia and SPD symptoms in relatives. For example, Fanous, Gardner, Walsh, and Kendler (2007) examined the relation between positive and negative symptoms in schizophrenia probands and SPD symptoms in first-degree relatives. They reported that negative symptoms of schizophrenia probands predicted suspicious behavior, odd speech, social dysfunction, and negative symptoms of SPD among first-degree relatives, and there was a trend for proband positive symptoms to predict positive schizotypal symptoms. Additionally, Baron, Gruen, and Romo-Gruen (1992) examined the association between risk for SPD in first-degree relatives and the predominant symptoms (positive or negative) experienced by the probands. They found that elevation of positive symptoms among probands, regardless of the level of negative symptoms, was the best predictor of SPD in relatives. Given the promise of this strategy using phenotypically-determined subgroups, dividing schizophrenia into genetic components could be particularly informative for guiding the search for schizophrenia risk genes.

Third, the measurement of schizotypal personality traits could provide an opportunity to improve sensitivity and specificity of these symptoms to liability to schizophrenia. As discussed earlier, the type of instrument (interview or questionnaire) used to assess SPD symptoms can affect the outcome and interpretation of results. Furthermore, all of the currently available measures evaluate symptoms of SPD exclusively on unidirectional scales. This understandably reflects the long held convention of diagnosing personality disorders as one would Axis I disorders, compared to using a more dimensional approach. This unidirectional approach seems

particularly true for measures of Cluster A personalities, perhaps because the associated traits seem outside the range of "normal" personality characteristics.

Given the findings of this and other studies, bidirectional measures could provide the opportunity to more accurately examine the range of schizotypy traits, perhaps confirming unidimensionality, and evaluate their specificity to schizophrenia. In addition, if measures of schizotypal personality traits were extended to include the full range of their potential expression, it would provide a more complete picture of schizotypy among relatives of schizophrenia patients and perhaps offer additional insight into how liability to (or protection from) schizophrenia is expressed. Lastly, genetic factors generated from the full range of schizotypy traits would likely be more sensitive and specific to shared genetic effects with schizophrenia compared to the genetic factors identified in this study.

Finally, the results of this investigation suggest that the Eccentric Behavior, Unusual Beliefs, and (perhaps) the Interpersonal Deficits genetic factors may be particularly sensitive (and specific?) to genetic effects that increase risk for schizophrenia, perhaps more so than some of the traditionally (phenotypically) identified risk markers. Thus, following the endophenotype strategy and in accordance with the primary motivation for this study, these genetic factors could be applied to genome-wide bivariate linkage analyses of schizophrenia. Taking this step would allow the utility of these particular genetic factors to be evaluated, as well as provide additional validation for the novel strategy of endophenotype design presented in this paper.

5.0 CONCLUSION.

This study examined the nature of schizotypy among multigenerational, multiplex schizophrenia families and addressed a number of the methodological limitations present in the literature to date. Genetic schizotypy factors and factor scores were derived, using a novel application of genetic factor analysis, and evaluated for genetic correlation with schizophrenia. Three genetically homogeneous and distinct schizotypy factors were identified that were especially sensitive to genetic effects on underreporting pathology and perhaps interpersonal deficits among non-psychotic relatives of schizophrenia probands, but not among relatives of MDD or substance dependence probands. Although their direction was unexpected, these genetic factors may have the potential to be particularly useful endophenotypes in genetic linkage analyses of schizophrenia.

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APPENDIX 1

TABLES

Table 1. DSM-IV-TR Diagnostic Criteria for Schizotypal Personality Disorder (301.22)

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1) Ideas of reference (excluding delusions of reference).

2) Odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations).

3) Unusual perceptual experiences including bodily illusions.

4) Odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped).

5) Suspiciousness or paranoid ideation.

6) Inappropriate or constricted affect.

7) Behavior or appearance that is odd, eccentric, or peculiar.

8) Lack of close friends or confidants other than first-degree relatives.

9) Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self.

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder.

Table 2. Social-Interpersonal SPD Symptoms in Relatives

Study	Characteristics of the Relatives of Schizophrenia Probands					Schizotypy Assessment		Comparison with Psychiatrically Healthy Controls**				Comparison with Relatives of Non-Schizophrenia Probands				
	Relationship to Proband (n)	Sex % male	Age mean (SD)	Ethnicity % Caucasian	Psychiatric Status	Measure (instrument type)	Factor / Symptom	screening criteria (n)	match to schiz relatives	effect size	p value	proband diagnosis	screening criteria (n)	match to schiz relatives	effect size	p value
Grove et al, 1991	parents, sibs, half-sibs (61)	46.0%	35	n/a	unscreened	SSP (interview)	Social-Interpersonal Factor	no diagnosis (18)	n/a	**d^1 = 1.65**	p = 0.0001					
Torgersen et al, 1993	non-twin, 1st degree relatives (134)*	41.8%	53.6 (13.7)	n/a	no schiz	SCID-II (interview)	Social Anxiety					major depression	non-twin, 1st degree relatives; no schiz (65)	age, sex	d^5 = 0.32	p = 0.02
							Social Isolation								n/a	n.s
							Inapropriate Affect								d^5 = 0.30	p = 0.04
							Suspiciousness								n/a	n.s
Lyons et al, 1994	parents, sibs, offspring (34)	50.0%	49.2	n/a	≥ 3 symptoms of SPD	SIDP (interview) SANS, SAPS (clinician ratings)	Social Anxiety					affective d/o	parents, sibs, offspring; ≥ 3 symptoms of SPD (14)	age, sex, education	n/a	n.s
							Social Isolation								n/a	n.s
							Inadequate rapport								n/a	p < 0.05
							Suspiciousness								n/a	n.s
Kendler et al, 1995 (Roscommon Family Study)	1st degree relatives (314)	n/a	n/a	n/a	no schiz or schizoaff	SIS (interview)	Negative Schizotypy Factor	1st degree relatives of unscreened control probands; no schiz or schizoaff (575)	n/a	**d^3 = 0.62**	p = 0.0001	affective d/o	1st degree relatives; no schiz or schizoaff (183)	n/a	**d^3 = 0.34**	p = 0.02
							Poor Rapport									
							Aloofness/Coldness									
							Guardedness									
							Odd behavior									
							Avoident Symptoms Factor			**d^3 = 0.27**	p = 0.003				**d^3 = 0.35**	p = 0.001
							Social Isolotion									
							Social Anxiety									
							Hypersensitivity									
							Apparent Anxiety									
							Social Dysfunction Factor			**d^3 = 0.67**	p = 0.0008				n/a	
							Low Motivation									
							Low Occupational Functioning									
							Suspiscious Behavior Factor			**d^3 = 0.50**	p = 0.004				**d^3 = 0.87**	p = 0.02
							Hypervigilance									
							Irritability									
Squires-Wheeler et al, 1997 (New York High Risk Study)	offspring (48)	n/a	24.3 (1.9)	100.0%	unscreened	PDE (interview)	Negative Schizotypy Factor	unscreened offspring of no diagnosis parents (84)	age, ethnicity	**d^2 = 1.10**	p < 0.01	affective d/o	unscreened offspring (40)	age, ethnicity	**d^2 = 0.41**	n.s.
							No Close Friends									
							Constricted/Inappropriate Affect									
							Poverty of Speech									
							Poverty of Emotion									
							Indifference									
							Odd Behavior/Appearance									

Table 2. Social-Interpersonal SPD Symptoms in Relatives (cont.)

Kremen et al, 1998	1st degree relatives (40)	22.5%	m: 40.8 (13.9) f: 42.9 (11.6)	m: 88.9% f: 77.4%	no psychosis or substance abuse	SPQ (questionnaire)	Social-Interpersonal Factor	no psychopathology on the MMPI-168 (≤ 70) (44)	age, sex, ethnicity	**d^5 = 0.41** m: n/a f: n/a	n.s. ($p < 0.07$)‡ n.s. n.s.				
Yaralian et al, 2000	relatives (13)	92.3%	29.9 (7.3)	76.9%	unscreened	SPQ (questionnaire) Social Anxiety No Close Friends Constricted Affect Paranoid Ideation†	Social-Interpersonal Factor	no family history of schiz-spectrum or alcohol/drug abuse (51)	age, sex, ethnicity	**d^2 = 0.08** n/a n/a n/a d^4 = 0.75	n.s. n.s. n.s. n.s. p = 0.021	alcohol /drug abuse	unscreened relatives (38)	age, sex, ethnicity	**d^2 = 0.01** n/a n/a n/a d^4 = 0.60	n.s n.s n.s n.s n.s. (p = 0.06)
Appels et al, 2004	parents (36 couples)	50.0%	median: 54.9	n/a	no psychosis or substance abuse	SPQ (questionnaire) Social Anxiety No Close Friends Constricted Affect Suspiciousness†	Negative Schizotypy Factor	no psychotic, affective, substance, or personality diagnoses (26 couples)	age, sex, handedness, education, IQ	n/a	n.s.				
Calkins et al, 2004	parents, sibs, offspring (124)	49.2%	46.5 (15.3)	n/a	no psychosis	SPQ (questionnaire) Social Anxiety No Close Friends Constricted Affect Suspiciousness†	Social-Interpersonal Factor	no diagnosis (109)	sex	**d^1 = 0.55** d^1 = 0.53 d^1 = 0.52 d^1 = 0.36 n/a	p < 0.001 p < 0.001 p < 0.001 p < 0.01 n.s.				
Schurhoff et al, 2005	parents, sibs, offspring (85)	44.7%	53.9 (15.2)	n/a	no schiz or bipolar	SPQ (questionnaire)	Negative Schizotypy Factor					bipolar d/o	parents, sibs, offspring; no schiz or bipolar (95)	age, sex	**d^2 = 0.00**	n.s
Mean Effect Size for Factor-Level Comparisons[6]										**d = 0.59**					**d = 0.37** (affective disorders)

PDE - Personality Disorder Examination
SANS - Scale for the Assessment of Negative Symptoms
SAPS - Scale for the Assessment of Positive Symptoms

SCID-II - Structured Clinical Interview for DSM-III-R Personality Disorders
SIDP - Structured Interview for DSM-III Personality Disorders

SIS - Structured Interview for Schizotypy
SPQ - Schizotypal Personality Questionaire
SSP - Schedule for Schizotypal Personalities

unscreened - psychiatric diagnoses not excluded
no diagnosis - all psychiatric diagnoses excluded
schiz - schizophrenia

schizaff - schizoaffective disorder

MMPI - Minnesota Multiphasic Personality Inventory

SPD - Schizotypal personality disorder
m - male
f - female

[1] - Glass' d (relative M - control M / control SD)
[2] - Glass' d calculated by current author
[3] - Cohen's d (relative M - control M / pooled SD) transformed from odds ratio: $d = \ln o(\sqrt{3}/\pi)$ (Hasselblad & Hedges,1995)
[4] - Cohen's d transformed from t: $d = t(n_1+n_2)/\sqrt{df}(\sqrt{n_1 n_2})$; [pooled, equal variences assumed] (Rosenthal, 1994)
[5] - Cohen's d transformed from chi square: $r_\varphi = \sqrt{X^2/n}$; $d = 2r/\sqrt{1-r^2}$ (Johnson and Eagly, 2000)
[6] - Mean effect sizes were calculated for factor comparisons by weighting each 'd' by the inverse of the conditional variance of 'd' (Shadish & Haddock, 1994)

n/a - not reported, not able to calculate
n.s. - not significant ($p > 0.05$)
† - On the SPQ, suspiciousness/paranoid ideation loads on both the social-interpersonal and cognitive-perceptual factors
‡ - trend of significant group-by-sex interaction ($p < 0.06$)
empty cells: comparisons not reported

* Torgersen et al, 1993 also reported results for MZ and DZ twins - all comparisons were not significant. As the results were uniformly not significant, they were not listed in this table in order to conserve space

** Unless otherwise noted, healthy control groups are comprised of individual control probands

Table 3. Cognitive-Perceptual SPD Symptoms in Relatives

Study	Characteristics of the Relatives of Schizophrenia Probands					Schizotypy Assessment		Comparison with Psychiatrically Healthy Controls**				Comparison with Relatives of Non-Schizophrenia Probands				
	Relationship to Proband (n)	Sex % male	Age mean (SD)	Ethnicity % Caucasian	Psychiatric Status	Measure (instrument type)	Factor Symptom	screening criteria (n)	match to schiz relatives	effect size	p value	proband diagnosis	screening criteria (n)	match to schiz relatives	effect size	p value
Grove et al, 1991	parents, sibs, half-sibs (61)	46.0%	35	n/a	unscreened	SSP (interview)	Cognitive-Perceptual Factor	no diagnosis (18)	n/a	**d[1] = 0.51**	n.s. (p = 0.056)					
Torgersen et al, 1993	non-twin, 1st degree relatives (134)*	41.8%	53.6 (13.7)	n/a	no psychosis	SCID-II (interview)	Illusions Ideas of Reference Magical Thinking					major depression	non-twin, 1st degree relatives; no schiz (65)	age, sex	n/a n/a n/a	n.s. n.s. n.s.
Lyons et al, 1994	parents, sibs, offspring (34)	50.0%	49.2	n/a	≥ 3 Symptoms of SPD	SIDP (interview) SANS, SAPS (clinician ratings)	Illusions Ideas of reference Magical ideation					affective d/o	parents, sibs, offspring; ≥ 3 symptoms of SPD (14)	age, sex, education	n/a n/a n/a	n.s n.s n.s
Kendler et al, 1995 (Roscommon Family Study)	1st degree relatives (314)	n/a	n/a	n/a	no schiz or schizoaff	SIS (interview)	Positive Schizotypy Factor Illusions Ideas of reference Suspiciousness Depersonalization Recurrent suicidal threats	1st degree relatives of unscreened control probands; no schiz or schizoaff (575)	n/a	**d[3] = 0.36**	p = 0.005	affective d/o	1st degree relatives; no schiz or schizoaff (183)	n/a	n/a	n.s
Squires-Wheeler et al, 1997 (New York High Risk Study)	offspring (48)	n/a	24.3 (1.9)	100.0%	unscreened	PDE (interview)	Positive Schizotypy Factor Unusual perceptual experiences Odd beliefs/magical thinking Ideas of reference Suspiciousness Circumstantial/tangential speech	unscreened offspring of no diagnosis parents (84)	age, ethnicity	**d[2] = 0.25**	p < 0.05	affective d/o	unscreened offspring (40)	age, ethnicity	**d[2] = -0.08**	n.s.
Kremen et al, 1998	1st degree relatives (40)	22.5%	m: 40.8 (13.9) f: 42.9 (11.6)	m: 88.9% f: 77.4%	no psychosis or substance abuse	SPQ (questionnaire)	Cognitive-Perceptual Factor	no psychopathology on the MMPI-168 (≤ 70) (44)	age, sex, ethnicity	**d[5] = 0.65** m: n/a f: n/a	p < 0.004‡ p < 0.006 n.s					

Table 3. Cognitive-Perceptual SPD Symptoms in Relatives (cont.)

Yaralian et al, 2000	relatives (13)	92.3%	29.9 (7.3)	76.9%	unscreened	SPQ (questionnaire)	Cognitive-Perceptual Factor	no family history of schiz-spectrum or alcohol/drug abuse (51)	age, sex, ethnicity	**d^2 = 1.02**	p < 0.003	alcohol /drug abuse	unscreened relatives (38)	age, sex, ethnicity	**d^2 = 0.79**	p < 0.012
							Unusual Percep.Experiences			d^4 = 0.87	p < 0.01				d^4 = 0.94	n.s.
							Ideas of Reference			d^4 = 0.87	p = 0.01				d^4 = 0.49	n.s
							Magical Thinking			n/a	n.s.				n/a	n.s
							Paranoid Ideation†			d^4 = 0.75	p = 0.021				d^4 = 0.60	n.s. (p = 0.06)
Appels et al, 2004	parents (36 couples)	50.0%	median: 54.9	n/a	no psychosis or substance abuse	SPQ (questionnaire)	Positive Schizotypy Factor	no psychotic, affective, substance, or personality diagnoses (26 couples)	age, sex, handedness, education, IQ	n/a (-)	p = 0.027					
							Unusual Percep.Experiences			n/a (-)	n.s. (p = 0.053)					
							Ideas of Reference			n/a (-)	n.s.					
							Magical Thinking			n/a (-)	p = 0.016					
							Suspiciousness†			n/a (-)	n.s.					
Calkins et al, 2004	parents, sibs, offspring (124)	49.2%	46.5 (15.3)	n/a	no psychosis	SPQ (questionnaire)	Cognitive-Perceptual Factor	no diagnosis (109)	sex	**d^1 = 0.24**	n.s. (p = 0.08)					
							Unusual Percep.Experiences			d^1 = 0.38	p < 0.05					
							Ideas of Reference			n/a	n.s.					
							Magical Thinking			n/a	n.s.					
							Suspiciousness†			n/a	n.s.					
Schurhoff et al, 2005	parents, sibs, offspring (85)	44.7%	53.9 (15.2)	n/a	no schiz or bipolar	SPQ (questionnaire)	Positive Schizotypy Factor					bipolar d/o	parents, sibs, offspring; no schiz or bipolar (95)	age, sex	**d^2 = 0.10**	n.s
Mean Effect Size for Factor-Level Comparisons[6]										**d = 0.37**					**d = 0.04** (affective disorders)	

PDE - Personality Disorder Examination
SANS - Scale for the Assessment of Negative Symptoms
SAPS - Scale for the Assessment of Positive Symptoms

SCID-II - Structured Clinical Interview for DSM-III-R Personality Disorders
SIDP - Structured Interview for DSM-III Personality Disorders
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SSP - Schedule for Schizotypal Personalities

unscreened - psychiatric diagnoses not excluded
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schiz - schizophrenia

schizaff - schizoaffective disorder

MMPI - Minnesota Multiphasic Personality Inventory

SPD - Schizotypal personality disorder
m - male
f - female

[1] - Glass' d (relative M - control M / control SD)
[2] - Glass' d calculated by current author
[3] - Cohen's d (relative M - control M / pooled SD) transformed from odds ratio: $d = \ln(\sqrt{3}/\pi)$ (Hasselblad & Hedges,1995)
[4] - Cohen's d transformed from t: $d = t(n_1+n_2)/\sqrt{df}(\sqrt{n_1 n_2})$; [pooled, equal variences assumed] (Rosenthal, 1994)
[5] - Cohen's d transformed from chi square: $r_\varphi = \sqrt{X^2/n}$; $d = 2r/\sqrt{1-r^2}$ (Johnson and Eagly, 2000)
[6] - Mean effect sizes were calculated for factor comparisons by weighting each 'd' by the inverse of the conditional variance of 'd' (Shadish & Haddock, 1994)

n/a - not reported, not able to calculate
n.s. - not significant (p > 0.05)
† - On the SPQ, suspiciousness/paranoid ideation loads on both the social-interpersonal and cognitive-perceptual factors
‡ - significant group-by-sex interaction (males > females, p < 0.007)
(-) - effect is negative (relatives < controls)
empty cells: comparisons not reported

* Torgersen et al, 1993 also reported results for MZ and DZ twins - all comparisons were not significant. As the results were uniformly not significant, they were not listed in this table in order to conserve space

** Unless otherwise noted, healthy control groups are comprised of individual control probands

Table 4. Disorganized SPD Symptoms in Relatives

Study	Characteristics of the Relatives of Schizophrenia Probands					Schizotypy Assessment		Comparison with Psychiatrically Healthy Controls**				Comparison with Relatives of Non-Schizophrenia Probands				
	Relationship to Proband (n)	Sex % male	Age mean (SD)	Ethnicity % Caucasian	Psychiatric Status	Measure (instrument type)	Factor Symptom	screening criteria (n)	match to schiz relatives	effect size	p value	proband diagnosis	screening criteria (n)	match to schiz relatives	effect size	p value
Torgersen et al, 1993	non-twin, 1st degree relatives (134)*	41.8 %	53.6 (13.7)	n/a	no psychosis	SCID-II (interview)	Odd speech					major depression	non-twin, 1st degree relatives; no schiz (65)	age, sex	d^5 = 0.30	p = 0.03
Lyons et al, 1994	parents, sibs, offspring (34)	50.0 %	49.2	n/a	≥ 3 Symptoms of SPD	SIDP (interview) SANS, SAPS (clinician ratings)	Odd speech					affective d/o	parents, sibs, offspring; ≥ 3 symptoms of SPD (14)	age, sex, education	n/a	n.s.
Kendler et al, 1995 (Roscommon Family Study)	1st degree relatives (314)	n/a	n/a	n/a	no schiz or schizoaff	SIS (interview)	Odd Speech Factor Cognitive slippage Odd speech	1st degree relatives of unscreened control probands; no schiz or schizoaff (575)	n/a	**d^3 = 0.96**	p = 0.003	affective d/o	1st degree relatives; no schiz or schizoaff (183)	n/a	n/a	n.s
Kremen et al, 1998	1st degree relatives (40)	22.5 %	m: 40.8 (13.9) f: 42.9 (11.6)	m: 88.9% f: 77.4%	no psychosis or substance abuse	SPQ (questionnaire)	Disorganized Factor	no psychopathology on the MMPI-168 (≤ 70) (44)	age, sex, ethnicity	**d^5 = 0.22**	n.s.					
Yaralian et al, 2000	relatives (13)	92.3 %	29.9 (7.3)	76.9%	unscreened	SPQ (questionnaire)	Disorganized Factor Odd behaviors Odd speech	no family history of schiz-spectrum or alcohol/drug abuse (51)	age, sex, ethnicity	**d^2 = 0.49** n/a n/a	n.s. n.s. n.s.	alcohol/drug abuse	unscreened relatives (38)	age, sex, ethnicity	**d^2 = 0.25** n/a n/a	n.s n.s n.s
Appels et al, 2004	parents (36 couples)	50.0 %	median: 54.9	n/a	no psychosis or substance abuse	SPQ (questionnaire)	Disorganized Factor Odd Behaviors Odd Speech	no psychotic, affective, substance, or personality diagnoses (26 couples)	age, sex, handedness, education, IQ	n/a	n.s.					
Calkins et al, 2004	parents, sibs, offspring (124)	49.2 %	46.5 (15.3)	n/a	no psychosis	SPQ (questionnaire)	Disorganized Factor Odd Behaviors Odd Speech	no diagnosis (109)	sex	**d^1 = 0.17** d^1 = 0.11 d^1 = 0.17	n.s. n.s. n.s.					
Schurhoff et al, 2005	parents, sibs, offspring (85)	44.7 %	53.9 (15.2)	n/a	no schiz or bipolar	SPQ (questionnaire)	Disorganized Factor					bipolar d/o	parents, sibs, offspring; no schiz or bipolar (95)	age, sex	**d^2 = -0.16**	n.s
Mean Effect Size for Factor-Level Comparisons[6]										**d = 0.73**						

Table 4. Disorganized SPD Symptoms in Relatives (cont.)

SANS - Scale for the Assessment of Negative Symptoms
SAPS - Scale for the Assessment of Positive Symptoms
SCID-II - Structured Clinical Interview for DSM-III-R Personality Disorders
SIDP - Structured Interview for DSM-III Personality Disorders
SIS - Structured Interview for Schizotypy
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SSP - Schedule for Schizotypal Personalities

unscreened - psychiatric diagnoses not excluded
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m - male
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[1] - Glass' d (relative M - control M / control SD)
[2] - Glass' d calculated by current author
[3] - Cohen's d (relative M - control M / pooled SD) transformed from odds ratio: $d = \ln(\sqrt{3}/\pi)$ (Hasselblad & Hedges,1995)
[5] - Cohen's d transformed from chi square: $r_\varphi = \sqrt{X^2/n}$; $d = 2r/\sqrt{1-r^2}$ (Johnson and Eagly, 2000)
[6] - Mean effect size was calculated for factor comparisons by weighting each 'd' by the inverse of the conditional variance of 'd' (Shadish & Haddock, 1994)

n/a - not reported, not able to calculate
n.s. - not significant ($p > 0.05$)
empty cells: comparisons not reported

* Torgersen et al, 1993 also reported results for MZ and DZ twins - all comparisons were not significant. As the results were uniformly not significant, they were not listed in this table in order to conserve space

** Unless otherwise noted, healthy control groups are comprised of individual control probands

Table 5. DSM-IV-TR Criteria for Schizotypal Personality Disorder and Corresponding SIS Scales

DSM-IV-TR Criterion	SIS Scale	Characteristics associated with high scale ratings
Lack of close friends or confidants	Social Isolation	Few friends; little contact with others, including friends and relatives; lacks desire for more contact
	Introversion	Prefers/desires being alone; quiet and reserved around others
	Social/Interpersonal Functioning	Lacks meaningful friendships; absence of social interactions/activities
	Sexual Anhedonia	Absence of sexual relationships; low drive for sexual relations
Excessive social anxiety associated with paranoid fears	Sensitivity	Hypersensitive to criticism; easily upset
	Social Anxiety	Worries about what people think of them; worries about appearing foolish
Inappropriate or constricted affect	Restricted Emotion	Lacks strong feelings, convictions, and/or emotional reactivity; low desire to express feelings/affection
	Affect	Flat, inappropriate, and/or labile affect, appears cold towards interviewer
	Rapport	Poor eye contact; body language suggests detachment from interviewer; absence of emotional rapport
Suspiciousness or paranoid ideation	Anger to Perceived Slights	Easily insulted; perceives criticism when none was intended; quick to react with anger
	Suspiciousness	Believes people are untrustworthy; holds grudges; believes they were, or will be taken advantage of/victimized
	Pathological Jealousy	Easily and frequently feels jealous without justification; suspicious about partners' fidelity
	Irritability	Irritable or argumentative towards interviewer and/or others with whom they have contact
	Guardedness	Appeared hypervigilant; made suspicious comments; perceived hidden meaning in the interview questions
Ideas of reference	Ideas of Reference: Being Watched	Sense of being watched or scrutinized in public; singled out for special attention
	Ideas of Reference: Remarks	Sense of being talked about and/or laughed at in public
Odd beliefs or magical thinking	Magical Thinking	Can read others' minds or others are reading their mind; can foretell or affect the future; sense the presence of and/or feel influenced by unseen forces or spirits; highly superstitious
	Psychotic-like Phenomena	Thoughts/feelings come into their mind which do not belong; thoughts are being put into or taken out of their head by an outside agency or power; their thoughts can be heard by others
Unusual perceptual experiences	Illusions	Mistakes objects for people or animals; hears whispering, their name called, or other sounds; senses the presence of an unseen person or force
Odd thinking and speech	Organization of Speech/Thought	Speech during interview is frequently digressive, tangential, or circumstantial; presence of derailment and loose associations; rate of speech is pressured or unusually slow.
Behavior or appearance that is odd, eccentric, or peculiar	Odd/Eccentric Behavior	Presence of odd movements, tics, posture, or gait; socially inappropriate toward interviewer (either overly familiar or hostile); talking and/or laughing to themselves; expresses inappropriate humor

Table 6. Number of Individuals with DIGS per Family

Individuals with DIGS per family, n	Frequency of family size in DIGS sample, n
2	2
3	3
4	1
5	1
6	2
7	4
8	4
9	1
10	2
11	2
12	1
13	3
14	1
15	2
16	3
17	1
20	1
23	1
24	2
29	1
32	1
34	1
36	1
42	1
70	1
Mean family size = 14.86	

Table 7. Number of Affected (Schizophrenia/Schizoaffective Disorder, Depressed) Individuals per Family

Affected individuals per family, n	Frequency of families in DIGS sample, n
1	4
2	27
3	7
4	2
5	2
6	1
Mean per family = 2.4	

Table 8. Demographics of Proband, Relative, and Control Participants with DIGS Data

Participant Group		Total, n	Age, yrs: mean (sd), range	Sex: % male	Education, yrs: mean (sd)	Site: % Pitt
Proband		42[1]	46.4 (13.1), 20-82	58.1	12.3 (2.2)	41.9
Biological Relative		597	45.2 (17.7), 15-87	47.2	13.2 (3.0)	42.7
1st Degree	Total	150	49.8 (15.9), 16-87	46.7	13.0 (3.0)	46.0
	Parents	39	66.2 (11.7), 40-87	35.9	12.4 (3.3)	48.7
	Siblings	96	47.0 (11.1), 21-84	50.0	13.2 (3.1)	43.8
	Children	15	25.8 (8.5), 16-47	53.3	12.8 (2.5)	53.3
2nd Degree	Total	129	46.2 (21.3), 15-87	51.2	12.8 (3.2)	43.4
	Grandparents	5	72.4 (4.4), 69-80	60.0	10.8 (4.6)	80.0
	Uncles/Aunts	55	65.5 (11.8), 41-87	52.7	12.4 (3.1)	41.8
	Half-Siblings	4	29.0 (5.5), 21-33	75.0	10.8 (1.5)	50.0
	Nephews/ Nieces	65	29.0 (10.0), 15-56	47.7	13.5 (3.1)	41.5
3rd Degree	1st Cousins	124	44.5 (13.5), 15-77	51.6	13.8 (2.8)	54.8
4th Degree	2nd Cousins	145	36.4 (16.3), 15-82	42.8	13.0 (2.8)	42.1
Non-Biological Relative		49	55.7 (13.4), 26-79	40.8	14.0 (2.8)	2.0
Controls		88	51.9 (17.5), 19-84	40.9	15.2 (2.4)	100.0

[1] One proband was diagnosed as schizoaffective, depressed type in the context of a previous study and was not administered the DIGS.

Table 9. Clinical Characteristics by Group

Diagnosis[1], n	Participant Group														
	Proband	Relatives' Degree of Relatedness													Control
		All	First				Second						Third	Fourth	Non-bio	
			Total	Parent	Sibling	Child	Total	Grand-parent	Uncle/ Aunt	Half-sibling	Nephew/ Niece		First cousin	Second cousin	Step-rels, Spouses	
Total	43	597	150	39	96	15	129	5	55	4	65		124	145	49	88
Schiz/schizaff-dep	43	60	49	8	40	1	4	0	1	0	3		2	4	1	0
Schiz	41	51	42	6	35	1	4	0	1	0	3		2	3	0	0
Schizaff-d	2	9	7	2	5	0	0	0	0	0	0		0	1	1	0
Schizaff-bp	0	4	2	0	2	0	1	0	1	0	0		1	0	0	0
Bipolar	0	8	1	0	1	0	3	1	1	0	1		2	1	1	0
Other psychosis	0	16	7	1	6	0	3	0	2	0	1		2	3	1	0
Cluster A pd	0	25	3	1	2	0	10	1	5	0	4		2	9	1	0
Schizotypal	0	19	2	0	2	0	6	0	4	0	2		2	8	1	0
Paranoid	0	3	1	1	0	0	2	1	1	0	0		0	0	0	0
Schizoid	0	3	0	0	0	0	2	0	0	0	2		0	1	0	0

Table 9: Clinical Composition (cont.)

Diagnosis[1], n	Participant Group													
	Proband	Relatives' Degree of Relatedness												Control
		All	First				Second					Third	Fourth	Non-bio	
			Total	Parent	Sibling	Child	Total	Grand-parent	Uncle/ Aunt	Half-sibling	Nephew/ Niece	First cousin	Second cousin	Step-rels, Spouses	
Total	43	597	150	39	96	15	129	5	55	4	65	124	145	49	88
Total MDD	0	120	22	8	13	1	27	1	6	1	19	25	33	13	24
No psychosis or Cluster A	0	110	22	8	13	1	22	1	3	1	17	25	31	10	24
With psychosis or Cluster A	0	10	0	0	0	0	5	0	3	0	2	0	2	3	0
Other mood	2	59	15	3	11	1	8	0	2	0	6	13	22	1	4
Substance d/o	11	153	42	7	32	3	29	1	12	2	14	28	45	9	16
Dementia	0	2	1	0	1	0		0	1	0	0	0	0	0	0

[1] Diagnoses of schizophrenia, schizoaffective disorder-depressed type, schizoaffective disorder-bipolar type, bipolar disorder, and other psychotic disorders are hierarchical as presented. Diagnoses of cluster A personality disorders, major depressive disorder (MDD), other mood disorders, substance disorders, and dementia are non-hierarchical and not exclusive except where noted.

Table 10. Characteristics of Pedigree and Control Participants for whom SIS Data were Available

			Demographics			Diagnosis, n[1]				
Group		Total, n	Age, yrs: mean (sd), range	Sex: % male	Education, yrs: mean (sd)	Cluster A	MDD	Other mood	Substance Dep.	No diagnosis
Relatives		480	44.6 (17.8), 15-85	46.0	13.3 (2.9)	24	103	41	102	258
1st Degree	Total	84	49.8 (17.6), 16-82	41.7	13.4 (3.0)	3	19	7	18	48
	Parents	26	67.1 (10.2), 49-82	42.3	12.7 (3.1)	1	7	0	5	17
	Siblings	44	47.8 (11.2), 21-75	38.6	14.0 (3.1)	2	11	6	10	22
	Children	14	24.3 (6.4), 16-39	50.0	12.9 (2.5)	0	1	1	3	9
2nd Degree	Total	110	45.5 (21.0), 15-85	51.8	13.0 (3.2)	10	20	5	17	65
	Grand-parents	4	70.5 (1.3), 69-72	50.0	12.5 (2.9)	1	1	0	0	2
	Uncles/Aunts	46	64.9 (11.9), 41-85	54.3	12.6 (3.1)	5	3	1	8	30
	Half-Siblings	4	29.0 (5.5), 21-33	75.0	10.8 (1.5)	0	1	0	2	1
	Nephew/Nieces	56	28.9 (9.4), 15-51	48.2	13.5 (3.2)	4	15	4	7	32
3rd Degree	1st Cousins	110	44.9 (13.8), 15-77	51.8	13.7 (2.6)	2	24	11	23	61
4th Degree	2nd Cousins	132	36.3 (16.0), 15-78	40.9	13.0 (2.8)	9	30	17	38	56
Non-Bio Relative[2]		44	56.1 (13.3), 26-79	40.9	14.0 (2.9)	1	10	1	6	28
Controls		88	51.9 (17.5), 19-84	40.9	15.2 (2.4)	0	24	4	16	51

[1] Diagnoses of Cluster A personality disorders, Major depressive disorder (MDD), Other mood disorders, and Substance disorders are non-hierarchical and not exclusive.

[2] Non-biological relatives include step-relatives and spouses.

Table 11. Excluded and Included Relative and Control Cases and Missing Data for Each SIS Scale

			Relatives			Controls			Mean Group Difference	
Scale	Items, n	Alpha	Cases, n	Mean (sd)	Skewness[1]	Cases, n	Mean (sd)	Skewness[2]	F	p-value
Social Isolation	10	0.8	478	1.50 (0.98)	1.7	88	1.01 (0.62)	2.1	20.7	<.001
Introversion	17	0.9	480	1.53 (1.30)	0.7	88	1.32 (1.22)	0.7	2.0	.153
Sexual Anhedonia	4	0.8	365	1.02 (1.31)	2.1	53	0.95 (1.11)	2.2	0.1	.709
Social/Interpersonal Functioning	1	n/a	443	0.69 (0.89)	1.2	88	0.31 (0.55)	2.1	14.9	<.001
Sensitivity	8	0.9	479	2.08 (1.38)	0.4	88	1.85 (1.24)	0.3	2.1	.147
Social Anxiety	7	0.8	479	1.27 (0.98)	1.1	88	0.92 (0.82)	1.2	10.1	.002
Restricted Emotion	9	0.7	479	1.44 (0.75)	0.7	88	1.32 (0.66)	0.8	2.0	.158
Affect	5	0.8	447	0.34 (0.46)	1.6	87	0.18 (0.30)	1.9	10.1	.002
Rapport	4	0.9	446	0.35 (0.62)	2.2	87	0.19 (0.42)	3.0	5.0	.026
Anger to Perceived Slights	8	0.8	479	1.16 (1.35)	1.2	88	0.69 (1.05)	1.7	9.6	.002
Suspiciousness	20	0.9	479	1.07 (0.95)	1.4	88	0.69 (0.76)	1.5	12.1	.001
Guardedness	3	0.9	447	0.17 (0.46)	3.2	88	0.04 (0.17)	4.2	7.1	.008
Irritability	1	n/a	447	0.11 (0.38)	3.5	88	0.13 (0.42)	3.5	0.1	.810
Pathological Jealousy	6	0.8	479	0.79 (1.26)	1.7	88	0.35 (0.78)	2.6	10.0	.002
Ideas of Reference: Being Watched	10	0.9	478	0.69 (1.15)	2.0	88	0.42 (0.84)	2.5	4.5	.035
Ideas of Reference: Remarks	10	0.9	479	0.61 (0.98)	1.8	88	0.33 (0.64)	1.9	6.8	.009
Magical Thinking	23	0.9	479	0.45 (0.67)	2.6	88	0.38 (0.42)	1.0	0.9	.335
Psychotic-like Phenomena	10	0.7	478	0.55 (0.51)	1.7	88	0.43 (0.45)	2.0	3.9	.049
Illusions	8	0.8	478	0.66 (0.76)	2.1	88	0.53 (0.62)	1.8	2.4	.120
Organization of Speech/ Thought	6	0.8	447	0.20 (0.43)	2.5	88	0.06 (0.22)	5.3	8.2	.004
Odd/ Eccentric Behavior	4	0.8	447	0.12 (0.33)	3.7	88	0.03 (0.14)	4.3	5.8	.016

Table 12. SIS Scale Descriptive Characteristics and Mean Relative and Control Group Differences

			Relatives			Controls			Mean Group Difference	
Scale	Items, n	Alpha	Cases, n	Mean (sd)	Skewness[1]	Cases, n	Mean (sd)	Skewness[2]	F	p-value
Social Isolation	10	0.8	478	1.50 (0.98)	1.7	88	1.01 (0.62)	2.1	20.7	<.001
Introversion	17	0.9	480	1.53 (1.30)	0.7	88	1.32 (1.22)	0.7	2.0	.153
Sexual Anhedonia	4	0.8	365	1.02 (1.31)	2.1	53	0.95 (1.11)	2.2	0.1	.709
Social/Interpersonal Functioning	1	n/a	443	0.69 (0.89)	1.2	88	0.31 (0.55)	2.1	14.9	<.001
Sensitivity	8	0.9	479	2.08 (1.38)	0.4	88	1.85 (1.24)	0.3	2.1	.147
Social Anxiety	7	0.8	479	1.27 (0.98)	1.1	88	0.92 (0.82)	1.2	10.1	.002
Restricted Emotion	9	0.7	479	1.44 (0.75)	0.7	88	1.32 (0.66)	0.8	2.0	.158
Affect	5	0.8	447	0.34 (0.46)	1.6	87	0.18 (0.30)	1.9	10.1	.002
Rapport	4	0.9	446	0.35 (0.62)	2.2	87	0.19 (0.42)	3.0	5.0	.026
Anger to Perceived Slights	8	0.8	479	1.16 (1.35)	1.2	88	0.69 (1.05)	1.7	9.6	.002
Suspiciousness	20	0.9	479	1.07 (0.95)	1.4	88	0.69 (0.76)	1.5	12.1	.001
Guardedness	3	0.9	447	0.17 (0.46)	3.2	88	0.04 (0.17)	4.2	7.1	.008
Irritability	1	n/a	447	0.11 (0.38)	3.5	88	0.13 (0.42)	3.5	0.1	.810
Pathological Jealousy	6	0.8	479	0.79 (1.26)	1.7	88	0.35 (0.78)	2.6	10.0	.002
Ideas of Reference: Being Watched	10	0.9	478	0.69 (1.15)	2.0	88	0.42 (0.84)	2.5	4.5	.035
Ideas of Reference: Remarks	10	0.9	479	0.61 (0.98)	1.8	88	0.33 (0.64)	1.9	6.8	.009
Magical Thinking	23	0.9	479	0.45 (0.67)	2.6	88	0.38 (0.42)	1.0	0.9	.335
Psychotic-like Phenomena	10	0.7	478	0.55 (0.51)	1.7	88	0.43 (0.45)	2.0	3.9	.049
Illusions	8	0.8	478	0.66 (0.76)	2.1	88	0.53 (0.62)	1.8	2.4	.120
Organization of Speech/ Thought	6	0.8	447	0.20 (0.43)	2.5	88	0.06 (0.22)	5.3	8.2	.004
Odd/ Eccentric Behavior	4	0.8	447	0.12 (0.33)	3.7	88	0.03 (0.14)	4.3	5.8	.016

Alpha: Cronbach's Alpha calculated on the total combined sample (relatives and controls)

n/a: Not applicable; Cronbach's Alpha not calculated because scale consists of 1 item

[1] For relatives, standard error of skewness for all scales = 0.1

[2] For controls, Standard error of skewness for all scales = 0.3

Table 13. Heritability of Demographic & Diagnostic Covariates in the Combined Pedigree & Control Sample

Demographic and Diagnostic Covariates	Heritability h^2	p-value
Age	0.271	<.001
Sex*	0.078	.257
Education	0.607	<.001
MDD*	0.442	.001
Substance Dependence*	0.403	.002

Note: Covariates = age and sex (age corrected for sex, sex corrected for age)

* Dichotomized variables: Sex: male = 0, female = 1; MDD and Substance Dependence: diagnosis absent = 0, present = 1

Table 14. Genetic Correlation of Demographic and Diagnostic Variables with Schizophrenia in the Combined Pedigree and Control Sample

	Genetic Correlation with Schizophrenia	
Demographic and Diagnostic Variables	R_g	p-value
Age	0.293	.037
Sex*	-0.129	.681
Education	-0.259	.012
MDD*	-0.503	.002
Substance Dependence*	0.116	.455

Note: Covariates = age and sex (age corrected for sex, sex corrected for age)

* Dichotomized variables: Sex: male = 0, female = 1; MDD, Substance Dependence: diagnosis absent = 0, diagnosis present = 1

Table 15. Correlations between Covariates and SIS Scales in the Combined Relative and Control Sample

Scale	Age	Sex*	Education	MDD*	Substance Dependence*	Cluster A*
Social Isolation	-0.042 (.315)	**-0.154 (<.001)**	**-0.237 (<.001)**	0.075 (.074)	**0.227 (<.001)**	**0.346 (<.001)**
Introversion	0.041 (.325)	**-0.127 (.002)**	0.007 (.870)	**0.116 (.006)**	0.063 (.133)	**0.200 (<.001)**
Sexual Anhedonia	-0.034 (.419)	0.061 (.149)	**-0.092 (.029)**	**-0.087 (.039)**	**-0.124 (.003)**	0.040 (.341)
Social/Interpersonal Functioning	**-0.093 (.026)**	**-0.115 (.006)**	**-0.245 (<.001)**	**0.138 (.001)**	**0.255 (<.001)**	**0.402 (<.001)**
Sensitivity	-0.072 (.087)	**0.171 (<.001)**	-0.008 (.847)	**0.219 (<.001)**	**0.118 (.005)**	**0.176 (<.001)**
Social Anxiety	**-0.187 (<.001)**	0.042 (.318)	-0.071 (.092)	**0.187 (<.001)**	**0.187 (<.001)**	**0.285 (<.001)**
Restricted Emotion	**-0.158 (<.001)**	**-0.278 (<.001)**	**-0.215 (<.001)**	**-0.115 (.006)**	0.043 (.311)	**0.086 (.041)**
Affect	**-0.157 (<.001)**	**-0.138 (.001)**	**-0.238 (<.001)**	0.015 (.722)	**0.147 (<.001)**	**0.328 (<.001)**
Rapport	**-0.132 (.002)**	-0.068 (.108)	**-0.205 (<.001)**	-0.008 (.842)	0.060 (.156)	**0.270 (<.001)**
Anger to Perceived Slights	**-0.201 (<.001)**	-0.058 (.169)	**-0.119 (.005)**	**0.085 (.042)**	**0.250 (<.001)**	**0.157 (<.001)**
Suspiciousness*	**-0.121 (.004)**	-0.044 (.300)	-0.078 (.065)	0.046 (.279)	0.080 (.057)	0.058 (.170)
Guardedness	-0.031 (.461)	-0.015 (.724)	-0.043 (.312)	0.026 (.542)	**0.120 (.004)**	**0.357 (<.001)**
Irritability	-0.060 (.155)	-0.023 (.588)	-0.070 (.098)	0.010 (.809)	**0.103 (.014)**	**0.170 (<.001)**
Pathological Jealousy	**-0.183 (<.001)**	0.026 (.539)	**-0.100 (.017)**	**0.160 (<.001)**	**0.230 (<.001)**	**0.147 (<.001)**
Ideas of Reference: Being Watched*	**-0.138 (.001)**	0.012 (.783)	-0.080 (.058)	**0.104 (.013)**	**0.098 (.020)**	**0.134 (.001)**
Ideas of Reference: Remarks*	**-0.190 (<.001)**	**-0.107 (.011)**	**-0.106 (.011)**	0.081 (.055)	0.068 (.109)	**0.207 (<.001)**
Magical Thinking*	0.004 (.922)	0.044 (.292)	0.012 (.781)	0.044 (.302)	**0.116 (.006)**	**0.093 (.028)**
Psychotic-like Phenomena	0.001 (.999)	-0.042 (.321)	-0.049 (.242)	**0.189 (<.001)**	**0.181 (<.001)**	**0.237 (<.001)**
Illusions*	**-0.135 (.001)**	-0.011 (.796)	0.078 (.065)	0.067 (.112)	0.075 (.073)	**0.095 (.023)**
Organization of Speech/ Thought	-0.052 (.216)	-0.076 (.072)	**-0.182 (<.001)**	0.040 (.341)	**0.115 (.006)**	**0.279 (<.001)**
Odd/ Eccentric Behavior*	0.006 (.879)	**-0.082 (.051)**	**-0.117 (.005)**	-0.032 (.452)	**0.129 (.002)**	**0.194 (<.001)**

Note: Values in table are R (p); Bold: $p \leq .05$

* Dichotomized variables: Sex: male = 0, female = 1; Diagnosis/symptoms: absent = 0, present = 1

Table 16. Heritability of SIS Scales in Combined Pedigree and Control Sample

	Heritability			
	Cov: age, sex*		Cov: age, sex*, education, MDD*, substance dependence*	
Scale	h^2	p-value	h^2	p-value
Social Isolation	0.392	<.001	0.303	<.001
Introversion	0.393	<.001	0.404	<.001
Sexual Anhedonia	0.181	.006	0.191	.006
Social/Interpersonal Functioning	0.320	<.001	0.254	.001
Sensitivity	0.442	<.001	0.458	<.001
Social Anxiety	0.450	<.001	0.431	<.001
Restricted Emotion	0.401	<.001	0.312	<.001
Affect	0.361	<.001	0.305	<.001
Rapport*	0.404	<.001	0.395	.001
Anger to Perceived Slights	0.323	<.001	0.237	.002
Suspiciousness*	0.742	.010	0.728	.008
Guardedness*	0.660	<.001	0.679	<.001
Irritability*	0.707	<.001	0.757	<.001
Pathological Jealousy*	0.522	<.001	0.437	<.001
Ideas of Reference: Being Watched*	0.571	<.001	0.568	<.001
Ideas of Reference: Remarks*	0.521	<.001	0.511	<.001
Magical Thinking*	0.675	<.001	0.685	<.001
Psychotic-like Phenomena	0.306	<.001	0.290	<.001
Illusions*	0.718	<.001	0.731	<.001
Org Speech/Thought*	0.406	<.001	0.414	<.001
Odd/Eccentric Behavior*	0.460	<.001	0.412	<.001

* Dichotomized variables: Sex: male = 0, female = 1; Diagnosis/symptoms: absent = 0, present = 1

Table 17. Genetic Correlations of SIS Scales & Schizophrenia in the Combined Pedigree & Control Sample

	Genetic Correlation with Schizophrenia			
	Cov = Age, sex*		Cov = Age, sex*, education, MDD*, substance dependence*	
Scale	Rg	p-value	Rg	p-value
Social Isolation	0.247	.140	0.175	.376
Introversion	0.029	.884	0.066	.731
Sexual Anhedonia	0.184	.334	0.176	.340
Social/Interpersonal Functioning	0.212	.238	0.151	.525
Sensitivity	-0.034	.848	0.055	.785
Social Anxiety*	-0.111	.614	-0.088	.696
Restricted Emotion	-0.041	.822	-0.216	.300
Affect	0.217	.260	0.154	.479
Rapport	0.016	.948	-0.114	.653
Anger to Perceived Slights*	0.178	.510	-0.162	.551
Suspiciousness*	0.177	.438	0.145	.552
Guardedness	**0.470**	**.043**	**0.536**	**.026**
Irritability*	0.209	.375	0.214	.350
Pathological Jealousy	0.161	.364	0.146	.470
Ideas of Reference: Watched*	**-0.350**	**.099**	**-0.391**	**.052**
Ideas of Reference: Remarks*	-0.199	.364	-0.205	.354
Magical Thinking*	**-0.304**	**.099**	**-0.266**	**.158**
Psychotic-like Phenomena	0.035	.907	0.131	.562
Illusions*	-0.226	.211	-0.172	.344
Organization of Speech/Thought	0.259	.210	0.206	.377
Odd/Eccentric Behavior*	-0.035	.898	-0.275	.318

Note: All scales were significantly different from 1 (or -1)

* Dichotomized variable: Sex: male = 0, female = 1; Diagnosis/symptoms: absent = 0, present = 1

Table 18. Correlations among SIS Scales in the Pedigree Sample

SIS Scale	Social Isol.	Introv.	Sexual Anhed.	Social/ Interp.	Sensit.	Social Anxiety	Restrict Emot.	Affect	Rapport	Anger Slights	Suspic.*	Guard.	Irritab.	Pathol. Jealous	Watch*	Remar*	Magic Think.*	Psychot Phen.*	Illus.*	Speech/ Thou.	Odd/ Eccent.*
Social Isolation																					
Introversion	**0.434 (<.001)**																				
Sexual Anhedonia	**0.111 (.015)**	**0.206 (<.001)**																			
Social/Interp. Functioning	**0.567 (<.001)**	**0.435 (<.001)**	0.045 (.327)																		
Sensitivity	**0.210 (<.001)**	**0.373 (<.001)**	0.001 (.975)	**0.322 (<.001)**																	
Social Anxiety	**0.333 (<.001)**	**0.522 (<.001)**	0.012 (.799)	**0.397 (<.001)**	**0.631 (<.001)**																
Restricted Emotion	**0.282 (<.001)**	**0.261 (<.001)**	**0.163 (<.001)**	**0.265 (<.001)**	-0.006 (.904)	**0.121 (.008)**															
Affect	**0.367 (<.001)**	**0.259 (.001)**	-0.003 (.954)	**0.628 (<.001)**	**0.193 (<.001)**	**0.243 (<.001)**	**0.287 (<.001)**														
Rapport	**0.321 (<.001)**	**0.238 (<.001)**	0.009 (.837)	**0.546 (<.001)**	**0.174 (<.001)**	**0.194 (<.001)**	**0.238 (<.001)**	**0.793 (<.001)**													
Anger to Perc. Slights	**0.256 (<.001)**	**0.215 (<.001)**	-0.033 (.474)	**0.337 (<.001)**	**0.469 (<.001)**	**0.359 (<.001)**	0.034 (.464)	**0.244 (<.001)**	**0.185 (<.001)**												
Suspicious.*	**0.120 (.009)**	**0.183 (<.001)**	0.023 (.616)	**0.131 (.004)**	**0.242 (<.001)**	**0.168 (<.001)**	0.046 (.314)	**0.103 (.025)**	**0.097 (.034)**	**0.148 (.001)**											
Guarded.	**0.226 (<.001)**	**0.111 (.016)**	-0.081 (.077)	**0.292 (<.001)**	**0.211 (<.001)**	**0.169 (<.001)**	0.008 (.861)	**0.416 (<.001)**	**0.379 (<.001)**	**0.207 (<.001)**	0.045 (.329)										
Irritability	**0.214 (<.001)**	**0.123 (.007)**	-0.024 (.604)	**0.362 (<.001)**	**0.113 (.013)**	**0.162 (<.001)**	**0.140 (.002)**	**0.496 (<.001)**	**0.408 (<.001)**	**0.273 (<.001)**	0.045 (.323)	**0.422 (<.001)**									
Pathological Jealousy	**0.234 (<.001)**	**0.235 (<.001)**	**-0.134 (.003)**	**0.379 (<.001)**	**0.409 (<.001)**	**0.428 (<.001)**	0.085 (.064)	**0.199 (<.001)**	**0.123 (.007)**	**0.427 (<.001)**	**0.089 (.052)**	**0.114 (.012)**	**0.176 (<.001)**								
Ideas of Ref. Watched*	**0.176 (<.001)**	**0.176 (<.001)**	0.018 (.697)	**0.197 (<.001)**	**0.308 (<.001)**	**0.399 (<.001)**	0.050 (.274)	**0.123 (.007)**	**0.160 (<.001)**	**0.303 (<.001)**	**0.175 (<.001)**	**0.161 (<.001)**	**0.090 (.050)**	**0.231 (<.001)**							
Ideas of Ref. Remarks*	**0.135 (.003)**	**0.151 (.001)**	-0.078 (.089)	**0.230 (<.001)**	**0.316 (<.001)**	**0.394 (<.001)**	0.004 (.926)	**0.119 (.009)**	**0.128 (.005)**	**0.314 (<.001)**	**0.124 (.006)**	**0.107 (.019)**	**0.116 (.011)**	**0.291 (<.001)**	**0.302 (<.001)**						
Magical Thinking*	**0.106 (.021)**	**0.104 (.023)**	0.074 (.106)	**0.133 (.003)**	**0.239 (<.001)**	**0.175 (<.001)**	-0.043 (.351)	0.031 (.495)	**0.101 (.027)**	**0.245 (<.001)**	**0.155 (.001)**	**0.117 (.011)**	**0.115 (.012)**	**0.175 (<.001)**	**0.335 (<.001)**	**0.203 (<.001)**					
Psychotic. Phenomena*	**0.091 (.046)**	**0.246 (<.001)**	**0.103 (.024)**	**0.015 (.001)**	**0.368 (<.001)**	**0.297 (<.001)**	-0.004 (.935)	0.071 (.124)	0.086 (.061)	**0.306 (<.001)**	**0.157 (.001)**	**0.127 (.005)**	0.078 (.089)	**0.229 (<.001)**	**0.251 (<.001)**	**0.278 (<.001)**	**0.350 (<.001)**				
Illusions*	-0.003 (.949)	**0.120 (.009)**	0.038 (.408)	0.056 (.223)	**0.282 (<.001)**	**0.234 (<.001)**	**-0.094 (.040)**	-0.067 (.142)	-0.002 (.957)	**0.213 (<.001)**	**0.095 (.038)**	0.060 (.191)	0.025 (.583)	**0.167 (<.001)**	**0.195 (<.001)**	**0.293 (<.001)**	**0.333 (<.001)**	**0.408 (<.001)**			
Org. Speech/ Thought	**0.301 (<.001)**	**0.163 (<.001)**	0.053 (.249)	**0.532 (<.001)**	**0.279 (<.001)**	**0.226 (<.001)**	0.048 (.293)	**0.519 (<.001)**	**0.524 (<.001)**	**0.240 (<.001)**	0.081 (.075)	**0.309 (.001)**	**0.274 (<.001)**	**0.233 (<.001)**	**0.143 (.002)**	**0.136 (.003)**	**0.161 (<.001)**	**0.135 (.003)**	0.047 (.304)		
Odd/Eccent. Behavior*	**0.251 (<.001)**	**0.167 (<.001)**	-0.043 (.349)	**0.410 (<.001)**	**0.169 (<.001)**	**0.189 (<.001)**	**0.163 (<.001)**	**0.472 (<.001)**	**0.416 (<.001)**	**0.216 (<.001)**	0.073 (.111)	**0.296 (<.001)**	**0.333 (<.001)**	**0.226 (<.001)**	**0.157 (.001)**	**0.124 (.007)**	0.086 (.061)	**0.124 (.006)**	-0.007 (.874)	**0.381 (<.001)**	

Note: Cov = age, sex; Values in table are R (p); Bold: $p \leq .05$; * Dichotomized scale: symptoms absent = 0, present = 1

Table 19. Correlation of SIS Scales and SIS Phenotypic Factors

	Genetic Correlation			
Scale	I. Observed Behavior	II. Cognitive-Perceptual	III. Social-Interpersonal	IV. Paranoid
Affect	**0.869**	-0.054	0.210	0.094
Rapport	**0.792**	0.056	0.196	0.010
Social/Interpersonal Functioning	**0.615**	0.030	**0.376**	**0.365**
Organization of Speech/Thought	**0.585**	0.126	0.101	0.150
Irritability	**0.559**	0.061	-0.002	0.097
Odd/Eccentric Behavior*	**0.535**	0.037	0.065	0.160
Guardedness	**0.511**	0.126	-0.063	0.110
Psychotic-like Phenomena*	0.055	**0.600**	0.089	0.206
Magical Thinking*	0.101	**0.573**	0.005	0.086
Illusions*	-0.054	**0.569**	-0.040	0.163
Ideas of Reference: Watched*	0.128	**0.368**	0.058	**0.312**
Introversion	0.112	0.135	**0.632**	**0.371**
Social Isolation	**0.346**	0.002	**0.454**	0.281
Sexual Anhedonia	-0.066	0.168	**0.426**	-0.196
Restricted Emotions	0.189	-0.116	**0.415**	0.030
Social Anxiety	0.119	0.238	0.280	**0.701**
Sensitivity	0.133	**0.361**	0.102	**0.614**
Pathological Jealousy	0.189	0.130	-0.007	**0.586**
Anger to Perceived Slights	0.258	**0.303**	-0.017	**0.478**
Ideas of Reference: Remarks	0.111	**0.319**	-0.040	**0.401**
Suspiciousness*	0.061	0.199	0.123	0.153
Factor Eigenvalue	5.529	2.544	1.543	1.238

Note: Cov = age, sex; Bold: R $\geq$ .300

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

Table 20. Genetic Correlations among SIS Scales in the Pedigree Sample

Scale	Social Isol.	Introv.	Sexual Anhed.	Social/ Interp.	Sensit.	Social Anxiety	Restrict Emot.	Affect	Rapport	Anger Slights	Suspic.*	Guard.	Irritab.	Pathol. Jealous	Watch*	Remark*	Magic Think.*	Psychot Phen.*	Illus.*	Speech/ Thou.	Odd/ Eccen.*
Social Isolation																					
Introversion	**0.519 (.012)**																				
Sexual Anhedonia	-0.242 (.365)	0.457 (.081)																			
Social/Interp. Functioning	**0.725 (.001)**	**0.657 (.001)**	0.038 (.887)																		
Sensitivity	0.198 (.295)	**0.645 (<.001)**	0.050 (.832)	0.233 (.247)																	
Social Anxiety	**0.385 (.049)**	**0.838 (<.001)**	0.013 (.962)	**0.571 (.005)**	**0.848 (<.001)**																
Restricted Emotion	**0.561 (.002)**	**0.534 (.004)**	0.298 (.288)	**0.667 (.001)**	-0.306 (.085)	0.214 (.250)															
Affect	**0.610 (.005)**	**0.454 (.029)**	-0.042 (.874)	**0.865 (<.001)**	-0.149 (.462)	0.260 (.191)	**0.819 (<.001)**														
Rapport	**0.621 (.017)**	0.263 (.291)	0.005 (.987)	**0.886 (.001)**	-0.073 (.756)	0.186 (.422)	**0.719 (.002)**	**0.950 (<.001)**													
Anger to Perc. Slights	**0.562 (.012)**	**0.472 (.022)**	0.292 (.274)	**0.631 (.005)**	**0.624 (.001)**	**0.706 (.001)**	0.308 (.121)	0.245 (.312)	0.177 (.535)												
Suspicious.*	0.479 (.132)	0.339 (.264)	-0.093 (.758)	0.489 (.129)	**0.515 (.048)**	0.493 (.091)	-0.362 (.225)	0.397 (.209)	0.538 (.134)	0.480 (.133)											
Guarded.	0.301 (.198)	0.168 (.471)	0.157 (.656)	0.438 (.069)	0.215 (.327)	0.062 (.757)	0.330 (.132)	0.305 (.143)	**0.454 (.001)**	0.256 (.370)	0.185 (.679)										
Irritability	0.421 (.213)	0.305 (.355)	0.039 (.913)	0.367 (.378)	-0.009 (.978)	0.165 (.569)	0.522 (.067)	0.286 (.398)	0.560 (.088)	-0.034 (.937)	0.309 (.482)	**0.675 (.001)**									
Pathological Jealousy	**0.767 (<.001)**	**0.703 (.001)**	0.107 (.690)	**0.743 (<.001)**	**0.713 (<.001)**	**0.873 (<.001)**	0.025 (.903)	0.242 (.252)	0.187 (.446)	**0.818 (<.001)**	**0.958 (.003)**	0.309 (.185)	0.427 (.229)								
Ideas of Ref. Watched*	**0.481 (.021)**	**0.460 (.020)**	-0.106 (.657)	**0.720 (<.001)**	**0.716 (<.001)**	**0.675 (<.001)**	0.096 (.614)	**0.536 (.008)**	**0.682 (.001)**	**0.836 (.001)**	**0.818 (.006)**	0.446 (.136)	0.425 (.117)	**0.928 (<.001)**							
Ideas of Ref. Remarks*	0.238 (.254)	**0.410 (.051)**	-0.194 (.415)	**0.497 (.013)**	**0.673 (<.001)**	**0.839 (<.001)**	-0.046 (.814)	0.066 (.750)	0.143 (.519)	**0.638 (.003)**	0.517 (.099)	0.118 (.695)	-0.006 (.982)	**0.806 (<.001)**	**0.877 (<.001)**						
Magical Thinking*	0.223 (.271)	0.259 (.190)	0.204 (.356)	0.335 (.088)	**0.753 (<.001)**	**0.406 (.033)**	-0.188 (.294)	0.135 (.481)	**0.399 (.056)**	**0.749 (<.001)**	**0.608 (.016)**	0.343 (.209)	0.191 (.422)	**0.572 (.006)**	**0.685 (<.001)**	0.367 (.071)					
Psychotic. Phenomena*	**0.314 (.050)**	**0.687 (<.001)**	**0.466 (.053)**	0.279 (.126)	**0.996 (<.001)**	**0.918 (<.001)**	-0.120 (.479)	0.066 (.710)	0.283 (.144)	**0.607 (.001)**	**0.550 (.003)**	0.339 (.200)	0.105 (.637)	**0.742 (<.001)**	**0.486 (.004)**	**0.761 (<.001)**	**0.597 (<.001)**				
Illusions*	-0.222 (.260)	0.075 (.688)	**0.583 (.024)**	-0.033 (.866)	**0.835 (<.001)**	**0.506 (.005)**	-0.315 (.073)	**-0.374 (.052)**	-0.165 (.424)	0.267 (.166)	0.320 (.228)	0.344 (.190)	0.013 (.956)	**0.407 (.031)**	0.136 (.479)	**0.612 (.001)**	**0.818 (<.001)**	**0.923 (<.001)**			
Org. Speech/ Thought	**0.614 (.014)**	**0.485 (.041)**	0.573 (.064)	**0.963 (<.001)**	0.313 (0.133)	**0.520 (.020)**	**0.540 (.035)**	**0.820 (.002)**	**0.931 (<.001)**	0.095 (.736)	0.653 (.088)	**0.766 (.002)**	**0.685 (.036)**	**0.653 (.003)**	0.445 (.059)	0.171 (.461)	0.383 (.077)	**0.467 (.027)**	0.197 (.343)		
Odd/Eccent. Behavior*	0.082 (.721)	**0.727 (.001)**	-0.022 (.937)	**0.589 (.008)**	0.177 (.411)	**0.531 (.018)**	**0.440 (.041)**	0.330 (.157)	0.463 (.055)	0.278 (.241)	0.413 (.220)	0.063 (.857)	0.446 (.117)	0.407 (.079)	**0.733 (.001)**	**0.661 (.008)**	0.437 (.074)	0.215 (.284)	0.207 (.342)	0.357 (.162)	

Note: Cov = age, sex; Values in table are Rg (p); Bold: $p \leq .05$; * Dichotomized scale: symptoms absent = 0, present = 1

Table 21. Correlations of SIS Scales and SIS Genetic Factors

	Correlation					
Scale	I. Paranoid Fears	II. Interpersonal Deficits	III. Perceptual Distortions	IV. Constricted Affect	V. Eccentric Behavior	VI. Unusual Beliefs
Social Anxiety	**0.943**	0.097	-0.081	0.216	-0.225	0.079
Pathological Jealousy	**0.914**	0.380	0.090	-0.005	0.035	0.270
Sensitivity	**0.871**	-0.028	-0.278	-0.248	-0.031	0.273
Psychotic-like Phenomena*	**0.856**	0.153	**-0.493**	-0.110	0.011	0.153
Ideas of Reference: Remarks*	**0.761**	-0.005	0.094	-0.069	**-0.439**	0.299
Introversion	**0.716**	0.222	-0.206	**0.563**	-0.236	-0.104
Suspiciousness*	**0.601**	**0.533**	0.225	-0.382	-0.051	0.248
Ideas of Reference: Watched*	**0.580**	**0.458**	0.246	-0.039	-0.385	**0.576**
Organization of Speech/Thought	0.303	**1.002**	-0.282	0.133	0.030	-0.074
Rapport	-0.030	**0.933**	0.099	0.217	-0.204	0.232
Affect	0.028	**0.733**	0.214	**0.492**	-0.075	0.149
Social/Interpersonal Functioning	0.381	**0.702**	0.125	**0.454**	-0.164	0.277
Irritability	0.070	**0.673**	-0.045	0.043	-0.167	-0.103
Guardedness	0.074	**0.617**	-0.272	-0.055	0.043	0.150
Social Isolation	**0.423**	**0.553**	0.335	0.384	0.324	0.206
Sexual Anhedonia	0.039	0.112	**-0.873**	0.211	0.095	0.004
Illusions*	**0.474**	-0.037	**-0.757**	**-0.476**	-0.160	0.214
Restricted Emotion	-0.139	**0.474**	-0.121	**0.908**	-0.168	0.019
Odd/Eccentric Behavior*	0.317	0.280	0.031	0.193	**-0.918**	0.086
Anger to Perceived Slights	**0.572**	0.025	-0.076	0.321	0.041	**0.827**
Magical Thinking*	0.362	0.288	-0.330	-0.322	-0.179	**0.680**
Factor Eigenvalue	9.700	4.477	2.208	1.768	1.272	1.046

Note: Cov = age, sex; Bold: R $\geq$ .400

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

Table 22. Beta Weights for Deriving Genetic Factor Scores

Scale	I. Paranoid Fears	II. Interpersonal Deficits	III. Perceptual Distortions	IV. Constricted Affect	V. Eccentric Behavior	VI. Unusual Beliefs
Social Anxiety	0.201	-0.119	-0.163	0.023	0.217	0.021
Pathological Jealousy	0.236	-0.109	0.137	0.105	0.129	-0.0431
Sensitivity	0.206	0.046	0.074	0.018	0.102	0.012
Psychoticlike Phenomena*	0.088	0.117	-0.194	-0.167	0.070	-0.129
Ideas of Reference: Remarks*	0.150	-0.100	0.141	0.055	-0.366	-0.046
Introversion	0.229	-0.077	-0.031	0.204	-0.233	-0.414
Suspiciousness*	0.170	0.046	0.159	-0.336	0.031	-0.180
Ideas of Reference: Watched*	-0.016	0.007	0.232	0.088	-0.066	0.407
Organization of Speech/Thought	0.031	0.291	-0.094	-0.076	0.198	-0.109
Rapport	-0.334	0.569	-0.077	-0.315	0.061	0.306
Affect	0.217	-0.378	0.156	0.508	-0.247	-0.256
Social/Interpersonal Functioning	-0.145	0.544	0.028	-0.166	-0.009	0.014
Irritability	-0.012	0.239	0.013	-0.084	-0.100	-0.145
Guardedness	-0.020	-0.011	-0.147	-0.112	0.010	-0.063
Social Isolation	0.118	0.051	0.139	0.210	0.356	0.0298
Sexual Anhedonia	-0.082	0.077	-0.380	0.174	0.121	0.136
Illusions*	0.104	-0.159	-0.243	-0.008	-0.183	-0.128
Restricted Emotion	-0.007	-0.202	-0.075	0.468	-0.064	0.109
Odd/Eccentric Behavior*	-0.051	-0.05957	-0.042	0.006	-0.594	-0.098
Anger to Perceived Slights	-0.063	-0.11606	-0.055	0.098	0.194	0.559
Magical Thinking*	-0.146	-0.0151	-0.206	-0.102	-0.139	0.433

* Dichotomized scales: symptoms absent = 0, present = 1

Table 23. Genetic Correlations among the SIS Genetic Factors in the Combined Pedigree & Control Sample

Factor	Paranoid Fears	Interpersonal Deficits	Perceptual Distortions[1]	Constricted Affect	Eccentric Behavior[1]	Unusual Beliefs
I. Paranoid Fears						
II. Interpersonal Deficits	0.004 (.985)					
III. Perceptual Distortions[1]	0.182 (.193)	-0.126 (.498)				
IV. Constricted Affect	-0.055 (.733)	0.194 (.403)	-0.256 (.065)			
V. Eccentric Behavior[1]	-0.032 (.839)	-0.212 (.319)	-0.027 (.855)	-0.054 (.752)		
VI. Unusual Beliefs	-0.151 (.361)	-0.017 (.939)	0.050 (.745)	0.064 (.717)	-0.085 (.641)	

Note: Cov = age, sex; Values in table are R_g (p)

[1]Direction of scale is reversed

Table 24. Heritability of SIS Genetic Factor Scores in the Combined Pedigree and Control Sample

	Heritability			
	Cov: age, sex*		Cov: age, sex*, education, MDD*, substance dependence*	
Factor	h^2	p-value	h^2	p-value
I. Paranoid Fears	0.560	<.001	0.565	<.001
II. Interpersonal Deficits	0.246	<.001	0.245	<.001
III. Perceptual Distortions	0.576	<.001	0.564	<.001
IV. Constricted Affect	0.500	<.001	0.436	<.001
V. Eccentric Behavior	0.396	<.001	0.389	<.001
VI. Unusual Beliefs	0.400	<.001	0.381	<.001

* Dichotomized variables: Sex: male = 0, female = 1; Diagnosis: absent = 0, present = 1

Table 25. Genetic Correlations of SIS Genetic Factor Scores and Schizophrenia in the Combined Pedigree and Control Sample

	Genetic Correlation with Schizophrenia			
	Cov = Age, sex*		Cov = Age, sex*, education, MDD*, substance dependence*	
Factor	R_g	p-value	R_g	p-value
I. Paranoid Fears	0.076	.630	0.085	.615
II. Interpersonal Deficits	0.270	.194	0.198	.380
III. Perceptual Distortions[1]	-0.038	.789	0.024	.862
IV. Constricted Affect	0.040	.815	-0.047	.794
V. Eccentric Behavior[1]	**-0.522**	**.046**	**-0.445**	**.048**
VI. Unusual Beliefs	**-0.446**	**.022**	**-0.468**	**.015**

Note: all scales were significantly different from 1 (or -1); Bold: $p \leq .05$

* Dichotomized variable: Sex: male = 0, female = 1; Diagnosis absent = 0, present = 1

[1]Direction of scale is reversed

Table 26. Genetic Correlations of SIS Genetic Factor Scores and MDD in the Combined Pedigree and Control Sample

	Genetic Correlation with MDD			
	Cov = Age, sex*		Cov = Age, sex*, education, substance dependence*	
Factor	Rg	p-value	Rg	p-value
I. Paranoid Fears	0.194	.313	0.169	.379
II. Interpersonal Deficits	-0.249	.371	-0.282	.336
III. Perceptual Distortions[1]	-0.219	.286	-0.306	.151
IV. Constricted Affect	-0.273	.206	-0.270	.250
V. Eccentric Behavior[1]	-0.073	.746	-0.065	.769
VI. Unusual Beliefs	0.170	.466	0.172	.457

Note: all scales were significantly different from 1 (or -1)

* Dichotomized variable: Sex: male = 0, female = 1; Diagnosis absent = 0, present = 1

[1]Direction of scale is reversed

Table 27. Genetic Correlations of SIS Genetic Factor Scores and Substance Dependence in the Combined Pedigree and Control Sample

	Genetic Correlation with Substance Dependence			
	Cov = Age, sex*		Cov = Age, sex*, education, MDD*	
Factor	Rg	p-value	Rg	p-value
I. Paranoid Fears	0.359	.082	0.421	.088
II. Interpersonal Deficits	0.390	.153	0.290	.381
III. Perceptual Distortions[1]	-0.232	.237	-0.156	.493
IV. Constricted Affect	0.415	.109	0.365	.268
V. Eccentric Behavior[1]	-0.344	.121	-0.362	.165
VI. Unusual Beliefs	0.268	.265	0.210	.464

Note: all scales were significantly different from 1 (or -1)

* Dichotomized variable: Sex: male = 0, female = 1; Diagnosis absent = 0, present = 1

[1]Direction of scale is reversed