

Familiarity of Novel Factorial Dimensions of Schizophrenia

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Context: Factor analysis of the signs and symptoms of schizophrenia yields dimensional phenotypes that may relate to underlying genetic variation. Examination of familiarity of factor scores can demonstrate whether they are likely to be of use in genetic research.

Objective: To produce a broader set of factorial phenotypes that are tested for familiarity including core symptoms of schizophrenia and additional indicators of social, work, and educational dysfunction.

Design: The study used psychiatric assessment data collected from several large samples of individuals with schizophrenia who have participated in family or case-control genetic studies (1988-2006) in the Epidemiology-Genetics Program in Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland. Seventy-three signs and symptoms were selected from direct assessment interviews and consensus diagnostic ratings (integrating interview data, medical records, and informant reports).

Setting: Study participants were recruited from across the United States, and a few additional participants were recruited from Canada, Greece, Italy, Poland, and Israel. Assessments generally were performed in the individuals' homes.

Participants: Forty-three percent of 1199 volunteers had largely white European backgrounds. The remaining individuals were recruited for family and case-control studies with focus on Ashkenazi Jews. All individuals had a consensus diagnosis of schizophrenia (including schizoaffective disorder) using *DSM-III* or *DSM-IV* criteria.

Main Outcome Measures: The 73 indicators were subjected to principal components factor analysis, and factor scores representing 9 dimensions were analyzed for familiarity.

Results: The 9 factors include the often-reported delusions, hallucinations, disorganization, negative, and affective factors; novel factors included child/adolescent sociability, scholastic performance, disability/impairment, and prodromal factors. All 9 factors demonstrated significant familiarity (measured by a heritability statistic), with the highest scores for disability/impairment (0.61), disorganization (0.60), and scholastic performance (0.51).

Conclusions: The factor scores show varying degrees of familiarity and may prove useful as quantitative traits and covariates in linkage and association studies.

Arch Gen Psychiatry. 2009;66(6):591-600

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SCHIZOPHRENIA (SZ) IS A DISABLING complex disease with a prevalence of about 1%,¹ typically arising in late adolescence or early adulthood. Symptoms, which include delusions, paranoia, anhedonia, hallucinations, lack of motivation, and cognitive and affective disturbances, can vary substantially between patients and over time. The etiology of SZ remains unknown; however, twin, adoption, and family studies suggest genetic involvement with heritability estimated to be as high as 70% to 85%.^{2,3} It has been suggested that 3 or 4 loci with likely epistatic interactions might be involved in SZ susceptibility.⁴ Linkage stud-

ies have implicated more than a dozen chromosomal regions⁵; however, various meta-analytic methods have not substantially reduced this number.^{6,7} Genome-wide significance has been demonstrated only for regions on chromosomes 13q⁸ and 1q.⁹ Association studies have followed linkage studies or investigated functional candidate genes,^{10,11} with some promising results; however, findings have not been conclusively replicated.¹²

It is reasonable to posit that the complexity of the SZ phenotype reflects, at least in part, the complexity of the underlying genetics. Researchers have increasingly pursued methods for reliably measuring simplified attributes of SZ in the hope that

genetic associations with such intermediate phenotypes will be more easily detected.¹³ The application of data reduction techniques such as factor analysis to clinical signs and symptoms has been used to delineate several dimensions of SZ¹⁴⁻²⁵ such as the positive (delusions and hallucinations), disorganization (in thought and behavior), and negative (deficit symptoms such as apathy and avolition) dimensions.¹³ However, differences in the symptoms ascertained, the scope of data collected (eg, cross-sectional and lifetime), data sources (eg, informant, individual, and medical record), recruitment sources, sample composition, and measurement error all contribute to variations in factor structure results.

The present study presents a principal components factor analysis (PCFA) of 73 indicators that include not only the frequently analyzed positive, disorganization, negative, and affective features of SZ but also additional elements such as social and occupational deterioration as well as earlier signs of dysfunction such as troubled child/adolescent sociability and scholastic performance. The objectives of the study were to determine the factors that best describe the interrelationships among these indicators in a sample of 1199 individuals and to examine the familiarity of these factor scores for potential use in genetic studies.

METHODS

PARTICIPANTS

Individuals participated in institutional review board–approved studies within the Epidemiology-Genetics Program in Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland. For simplification, they can be grouped into 2 categories: 513 outbred (OB) individuals (94% European Caucasian backgrounds and 6% African American) and 686 Jews of European ancestry including 685 Ashkenazi Jews (AJ) (89% full AJ and 11% partly AJ) and 1 Sephardic Jew. We asked about the heritage and country of origin of all 4 grandparents to establish the full AJ classification. Recruitment criteria have been previously described.^{8,26} Most OB individuals were examined between April 18, 1988, and December 14, 1996, and the Jewish participants between July 25, 1996, and May 24, 2006. Most OB individuals were ascertained for multiplex family (ie, more than 1 affected family member) studies: 77% have an affected relative in the data set vs 13% of AJs (most of the latter were ascertained for case-control studies).

We began the OB studies using a modified Diagnostic Interview Schedule²⁷⁻³⁰; we included a broader range of psychosis items, used experienced clinicians (M.H.T. and J.R.L. among others) (ie, with a master's, PhD, or MD degree) rather than lay interviewers, and encouraged interviewers to break from the probe flow when necessary to clarify information. Interviews were audiotaped for quality control. Approximately halfway into the OB assessments, we switched from the modified Diagnostic Interview Schedule (49% of OB individuals) to the Diagnostic Interview for Genetic Studies (DIGS)³¹ and from a *DSM-III-R*³² consensus diagnostic checklist (46% of OB individuals) to a *DSM-IV*³³ consensus checklist. All AJs were interviewed using the DIGS and were rated using the *DSM-IV* checklist. A total of 47 interviewers participated during the 18-year period. To maintain standardization, the interviewers were supervised by a lead psychologist (one from 1988 to 1995 and one of us [M.H.T.] from 1995 onward) who conducted train-

ing and follow-up monitoring (review of audiotaped interviews).

The consensus diagnostic procedure was identical for OB and AJ individuals, with at least 2 diagnosticians reviewing data from the interview, medical records, and informants to form consensus on diagnoses and key criteria. A total of 31 diagnosticians participated during the 18 years; one of us (G.N.) oversaw diagnostic committee meetings throughout this period to maintain standardization.

In total, 1199 individuals from 921 families met criteria for inclusion in the studies and gave informed consent to participate. There were 428 women (36%) and 771 men (64%) with a consensus research diagnosis of SZ (n=1018 [85%]) or schizoaffective disorder (n=181 [15%]). Their mean (SD) age at assessment was 40.7 (11.9) years, and at onset of psychosis was 21.1 (6.3) years.

INDICATOR SELECTION

Since initiation of the Epidemiology-Genetics Program, we have made a fundamental effort to measure a broad range of phenomena representing the clinical heterogeneity of SZ with the goal of eventually sorting out which aspects are related to genetic variation. The supposition behind this effort is that SZ is likely several related disorders with varying and sometimes overlapping genetic underpinnings, some of which affect clinical and course features. While we respect the operational rigor that current diagnostic systems supply, we recognize that no symptoms are pathognomonic for SZ. We, therefore, embedded both the modified Diagnostic Interview Schedule and the DIGS with a common set of items related not only to the major criteria of SZ but also to antecedent and concurrent signs. **Table 1** lists the 73 lifetime indicators chosen for the PCFA, all coded 1 (present) or 0 (absent). The indicators are largely related to *DSM-IV* diagnostic criteria (Table 1). In contrast to most factor analytic studies that focus only on SZ criterion A items (some with attention to mania and depression), we included indicators representing the broader domains of psychopathology as articulated, for example, by Carpenter³⁵; items related to SZ criteria B and C, and associated signs/symptoms and course of illness variables, as well as affective spectrum indicators,^{36,37} all of which have been studied in efforts to diagnose or subtype SZ. Table 1 gives indicators from our interviews vs the consensus diagnostic checklist. Also footnoted are items relating to criteria B and C, which were adapted from the Premorbid Adjustment Scale³⁴ and embedded in our interviews; we rated these child and adolescent items regardless of age at onset of psychosis. We considered including age at onset of psychosis in the factor analysis but chose to withhold it as a potentially powerful characteristic for genetic dissection on its own.

PCFA AND MISSING DATA IMPUTATION

Commercially available software (SAS version 9.1; SAS Institute, Inc, Cary, North Carolina) was used for the analyses. Indicator missing data rates varied from approximately 2% to 44% (mean, 16%; median, 14%; Table 1). A small portion of the missing data are owing to missing interviews (approximately 5% of individuals did not complete an interview because of refusal, incapacitation, or location [we have only summaries of the assessments conducted in Italy]). Four interview items (among the top 12 indicators for missing data) were not added until adoption of the DIGS (Table 1). However, the primary reason for missing data is that the interviewer or diagnostician judged information insufficient to code a given indicator. For example, 7 of the 9 indicators with 30% or more missing data dealt with prodromal symptoms (in the year preceding psychosis

Table 1. Seventy-three Indicators Included in the Principal Components Factor Analysis: Prevalence, Missing Rates, and Diagnostic Relevance^a

Indicator	Proportion With Symptom/Attribute	Proportion With Missing Data	Relevance to <i>DSM-IV</i> Diagnostic Criteria
≥3 Panic disorder symptoms ^b	0.11	0.10	Panic disorder criterion A
Abnormal birth or early development^c	0.16	0.28	Other
Affective symptoms early in course of psychosis	0.53	0.17	Course of illness
Affective syndrome prominent and simultaneous (or antedates psychosis) and never 1 wk of psychotic symptoms in absence of affective symptoms	0.02	0.10	Course of illness
Akathisia	0.14	0.07	Associated signs/symptoms
Alogia	0.34	0.23	SZ criterion A7
Anhedonia	0.44	0.14	Associated signs/symptoms
Apathy	0.69	0.22	SZ criterion A7
Attended therapeutic school	0.11	0.11	SZ criterion B
Auditory hallucinations (first rank and non-first rank)	0.82	0.02	SZ criteria A2/A4
Bizarre behavior	0.58	0.23	SZ criterion A6
Catatonic behavior	0.11	0.08	SZ criterion A6
Committed assault	0.42	0.09	Other
Criterion A for obsessive-compulsive disorder ^b	0.12	0.15	Obsessive-compulsive disorder criterion A
Delusions of guilt	0.22	0.09	SZ criterion A3
Delusions of influence	0.25	0.14	SZ criterion A1
Delusions of reference	0.78	0.09	SZ criterion A3
Established adult independence^d	0.48	0.18	SZ criterion B
Flat affect	0.55	0.06	SZ criterion A7
Generalized anxiety for >6 months ^b	0.09	0.12	Generalized anxiety disorder criterion A
Good/fair adolescent peer relations^d	0.76	0.18	SZ criterion B
Good/fair adult sociability^d	0.46	0.16	SZ criterion B
Good/fair childhood peer relations^d	0.84	0.16	SZ criterion B
Good/fair elementary school adaptation^d	0.88	0.16	SZ criterion B
Good/fair elementary school performance^d	0.93	0.16	SZ criterion B
Good/fair high school adaptation^d	0.76	0.21	SZ criterion B
Good/fair high school performance^d	0.84	0.20	SZ criterion B
Good intimate relationships^d	0.14	0.19	SZ criterion B
Good/fair adolescent sociability^d	0.71	0.17	SZ criterion B
Good/fair childhood sociability^d	0.77	0.16	SZ criterion B
Grandiose delusions	0.55	0.08	SZ criterion A3
History of occupational deterioration	0.78	0.21	SZ criterion B
History of occupational impairment	0.43	0.23	SZ criterion B
Inappropriate affect	0.36	0.07	Associated signs/symptoms
Incoherence/loose associations	0.53	0.16	SZ criterion A5
Learning disability/hyperactivity^c	0.15	0.32	SZ criterion B
Lives alone or institutionalized, vs with family/friends^c	0.56	0.25	SZ criterion B
Major depression criterion A: ≥5 symptoms in 2-wk period	0.56	0.20	Major depression criterion A
Mania criterion A: ≥1 wk of euphoric or irritable mood	0.41	0.11	Mania criterion A
Negative formal thought disorder (poverty of speech and of speech content)	0.28	0.06	Associated signs/symptoms
Nihilistic delusions	0.05	0.11	SZ criterion A1
No affective syndrome (in psychotic illness)	0.33	0.12	Course of illness
Occupational disability at time of interview^c	0.61	0.30	SZ criterion B
Olfactory hallucinations	0.15	0.10	SZ criterion A4
Parkinsonian signs	0.14	0.07	Associated signs/symptoms
Persecutory delusions	0.87	0.03	SZ criterion A3
Poor insight	0.65	0.02	Associated signs/symptoms
Premorbid personality disorder	0.18	0.23	Course of illness
Primary delusional perception (delusional misinterpretation of real perception)	0.03	0.13	SZ criterion A1
Primary delusions (nonrational meanings arising with no apparent cause)	0.05	0.13	SZ criterion A1
Prodromal impaired hygiene	0.28	0.41	SZ criterion C
Prodromal lack of interest or energy	0.54	0.35	SZ criterion C
Prodromal odd beliefs/magical thinking	0.34	0.42	SZ criterion C
Prodromal peculiar behavior	0.34	0.37	SZ criterion C
Prodromal role impairment	0.71	0.29	SZ criterion C
Prodromal social isolation/withdrawal	0.68	0.31	SZ criterion C
Prodromal unusual perceptions	0.22	0.44	SZ criterion C
Remitting course	0.05	0.08	Course of illness
School performance deterioration	0.49	0.19	SZ criterion B
Seizures or convulsions	0.11	0.11	Other
Self-damaging acts	0.45	0.05	Other
Self-neglect	0.44	0.07	SZ criterion A6
Severe psychotic disorder	0.33	0.11	Course of illness
Somatic hallucinations	0.19	0.13	SZ criterion A1
Some college or more vs none	0.55	0.10	Other
Sudden onset (within 3 mo)	0.27	0.37	Course of illness
Tactile hallucinations	0.15	0.10	SZ criterion A4
Tardive dyskinesia	0.12	0.07	Associated signs/symptoms
Thought broadcasting	0.20	0.14	SZ criterion A1
Thought echo	0.07	0.13	SZ criterion A1
Thought insertion	0.21	0.14	SZ criterion A1
Thought withdrawal	0.11	0.14	SZ criterion A1
Visual hallucinations	0.41	0.11	SZ criterion A4

Abbreviations: *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); SZ, schizophrenia.

^a Items in bold were embedded in the modified Diagnostic Interview Schedule and Diagnostic Interview for Genetic Studies, except as noted in note c (below); items not in bold are from the Consensus Diagnostic Checklist.

^b Affective spectrum indicators.

^c Not included in the modified Diagnostic Interview Schedule but was included in the Diagnostic Interview for Genetic Studies.

^d Adapted from Premorbid Adjustment Scale.³⁴

onset) and suddenness of onset; these events occurred on average 20 years before the interview and illustrate the care with which raters made their codings. We used multiple imputation (SAS Proc MI; SAS Institute, Inc) using the Markov chain Monte Carlo method to replace missing data with pseudorandom draws from the simulated multidimensional distributions. Three to 10 imputations are usually sufficient³⁸; we generated 5 imputation data sets, which were analyzed individually using PCFA (SAS Proc Factor; SAS Institute, Inc) with varimax rotation. Although our primary goal was generation of orthogonal dimensional scores for genetic analyses, we also conducted an oblique rotation using imputation data set 1 (obvarimax method³⁹) to examine intercorrelations among factor scores not constrained to be orthogonal.

Underextraction or overextraction of factors is considered a critical problem in factor analysis. Often-used methods for deciding on the number of factors include the Kaiser criterion (eigenvalue >1) and examination of the scree plot of descending eigenvalues to determine a point at which the eigenvalues level off⁴⁰; however, the former method tends to result in specification of too many factors and the latter method can be unreliable.^{41,42} We, therefore, used 2 statistically based methods for factor number determination: parallel analysis and the Velicer Minimum Average Partial correlation method.⁴¹⁻⁴⁴ Ten thousand parallel analyses were run with random multivariate normal data. The Velicer Minimum Average Partial test was conducted using correlation matrices from each of the 5 imputation data sets. Simulation studies have shown that both of these methods for factor number determination are accurate.⁴⁴

Factor scores were calculated using the score option (SAS Institute, Inc) within the factor procedure, which generates scoring coefficients for each indicator-factor combination based on the factor structure. Raw indicator values for a given individual are standardized, multiplied by the appropriate scoring coefficient, and summed to produce the factor scores. The 5 sets of 9 factor scores (1 for each imputation data set) were averaged into 1 set of 9 for familiarity analyses. Pearson intercorrelations with age at onset of psychosis were also examined.

FAMILIARITY ANALYSES

We calculated heritability estimates for the factor scores using the ASSOC program from the Statistical Analysis for Genetic Epidemiology (SAGE) package (version 5.4.1).⁴⁵ For a given sample made up of pedigrees of related individuals, some of whom have been measured on a given quantitative trait, ASSOC partitions the variance of the trait into components that reflect (depending on model specification) additive polygenic effects vs sibship effects, nuclear family effects, marital effects, and random individual environment effects. Heritability is calculated as the ratio of polygenic variance to total variance. Note that, while the ASSOC program produces a heritability statistic for a given trait, our specialized sample ascertainment does not permit this to be interpreted as an estimate of heritability in a general population. We interpret heritability simply as an index of familiarity within this sample. We calculated heritability with and without an adjustment (adding a covariate coded 1 for individuals with SZ with affected relatives in the analysis vs 0 for singletons) to illustrate the attenuation of some of the observed heritability values if one adjusts for a degree of within-family sameness produced by ascertaining mainly multiplex families.

Although the factor scores have an assumed underlying normal distribution, not all of the generated distributions met this expectation. We tested several transformation methods to normalize the distributions, as preferred for both heritability analyses and quantitative trait locus linkage analyses⁴⁶: the George-

Elston modulus power transformation⁴⁷ (implemented in SAGE), the Box-Cox power transformation,⁴⁸ and the natural log power transformation (the latter 2 implemented with STATA Release 8.0; Stata Corp, College Station, Texas). The final transformations chosen are given in Table 3 ("Results" section); the transformed score distributions were also standardized to have a mean of zero and variance of unity. The transformed factor scores in extended pedigrees were analyzed for their polygenic and random variance components. Familiarity analysis included the 1199 individuals with SZ plus 553 additional individuals (without factor scores) from these families needed to delineate the relationships among the affected members (eg, unaffected parents added to connect 2 affected siblings). Of the 1199 individuals with SZ, 714 were singletons. The SAGE ASSOC program treats these individuals as coming from pedigrees of size 1 each and uses these observations in producing the variance estimates underlying the heritability calculations.

RESULTS

FACTOR ANALYSIS

The Velicer Minimum Average Partial Correlation Test suggested 8 components in each of the 5 imputation data sets. The parallel analysis, however, indicated that 15 factors could be extracted (**Figure**). We examined solutions sequentially from 8 to 15 factors using each of the 5 imputation data sets, and solutions for 8 or 9 factors were consistent across the 5 imputation data sets, whereas expanding beyond this introduced more substantive variability in the later factors. The difference between the 8- and 9-factor solutions was that several types of hallucinations separated from most delusion symptoms as the ninth factor rather than loading with delusions on a single factor. We chose to keep the 9-factor model. While previous studies have achieved both types of solutions (a single positive symptom factor^{17,22,49,50} vs separate delusion vs hallucination factors^{51,52}), the hallucination items had slightly higher factor loadings when coalescing on the ninth factor than when mixing with delusions in the 8-factor model. The 9 components accounted for 35.4% of the total variance in imputation data set 1 (**Figure**).

Table 2 gives primary factor loadings with absolute values greater than or equal to 0.30 from the varimax rotated 9-factor solution using imputation data set 1; similar loadings were obtained for the other 4 data sets. Although the 0.30 cutoff is lower than in some studies, it permits display of indicator relationships that are milder yet significant (eg, loadings on the hallucination factor). Negative loadings indicate an inverse relationship; for example, individuals with more disability/impairment tend to have a nonremitting course. The full set of loadings is given in eTable 1 (<http://www.archgenpsychiatry.com>). The schneiderian factor is so named because it is dominated by indicators historically known as first-rank symptoms (eg, thought insertion and withdrawal, thought echo and broadcasting, delusions of influence, and primary delusional perception), which Schneider considered to be core features of SZ.³³

Age at onset showed weak correlations with several factors including hallucinations ($r = -0.12$; $P < .002$), child/adolescent sociability ($r = 0.09$; $P < .006$), scholastic performance ($r = 0.20$; $P < .001$), disability/impairment

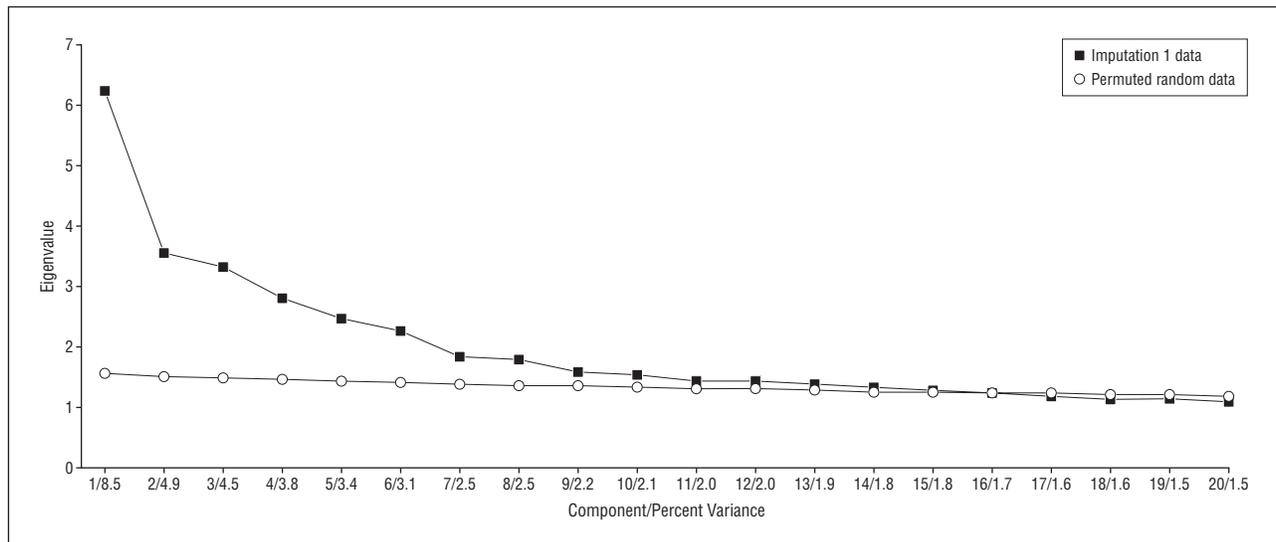


Figure. Comparison of eigenvalues from principal components factor analysis of imputation 1 data (1199 individuals) vs 10 000 parallel analyses of permuted random data. Notes: Permuted random data eigenvalues represent the 95th percentile value for each component, over the 10 000 parallel analyses (ie, analyses of 10 000 permuted data sets). Although not shown, the eigenvalues for imputation 1 data remain at or above 1.0 through component 23; that is, the Kaiser rule would result in extraction of 23 components. Attempting to judge the number of factors to extract based on the scree plot also presents difficulties (different judges may disagree on the cutoff point). With use of parallel analytic techniques, the permuted random data values yield a 15-factor solution. This is also true when using permutations of the imputation 1 data set for the 10 000 parallel analyses (eigenvalues are almost identical to the permuted random data results shown here).

($r = -0.10$; $P < .003$), and the prodromal factor ($r = -0.09$; $P < .003$). Oblique factor loadings are given in eTable 2. Many of the oblique factors were significantly intercorrelated; however, most associations were weak (eg, $r < 0.15$; eTable 3).

FAMILIARITY OF FACTORS

The heritabilities of the 9 varimax factors are given in **Table 3**, calculated for 207 families with multiple affected members and 714 singletons, with and without adjustment for ascertainment bias. The method of factor score transformation along with the relevant transformation parameters for each factor (λ_1 for the George-Elston modulus power transformation and k for the natural log power transformation) are given in Table 3. All factors showed statistically significant heritabilities whether adjusted or not. Unadjusted values varied from 0.27 for child/adolescent sociability to 0.61 for disability/impairment. **Table 4** gives the predominance of affected sibling pairs existing in the multiplex families included in the heritability analyses (affected-pair correlations were produced using the SAGE FCOR program).

COMMENT

At least 5 of the 9 PCFA factors (hallucinations, disorganization, negative, schneiderian, and affective) cover previously often-described dimensions of psychotic disorders.^{14,16,17,20,51,54-59} In these studies, dimensions have sometimes been broken down (eg, affective is separated into mania and depression in studies that include a greater variety of affective indicators) or combined (eg, delusions and hallucinations often join as positive symptoms). This variation is not unusual. Jablensky points out

that “factor-analytical studies suggesting ‘established’ dimensions or syndromes of schizophrenia should be viewed with caution, considering the diversity of clinical populations and the limitations of the instruments used to generate the input data.”^{13(p821)} Four of the dimensions we studied are somewhat novel, not in their pertinence to aspects of SZ but in their description through factor analysis (these include the childhood/adolescent sociability, scholastic performance, disability/impairment, and prodromal factors). However, aspects of asociality have been factor analyzed in the adult context (eg, as disordered relating^{52,55,60,61}).

The disorganization and negative factor heritabilities are consistent with studies that show familial aggregation for similar or related dimensions^{57,62-66} and studies that link these dimensions to increased risk of psychosis or SZ in relatives.^{23,25,67} Familiarity of disorganization seems to be most consistent across studies. A recent meta-analysis of sib-pair studies supports the familiarity of disorganization but shows more equivocal results for reality distortion (delusions or hallucinations) and the psychomotor poverty dimension (related to our negative dimension).⁶⁸ Similarly, another recent sib-pair study by Vassos et al⁶⁹ supported the familiarity of a positive/disorganized factor (as well as positive/delusional and dysphoric factors) but not a negative factor.

Substantial literature exists on the deficit syndrome of SZ,^{24,70} defined by enduring negative symptoms that are not secondary to other conditions such as depression, anxiety, or drug effects.²³ The indicators with major loadings on the negative factor (Table 1) encompass the deficit syndrome domain; however, our assessment does not establish the duration criterion of the deficit syndrome. Still, the mild but significant inverse relationship between the affective and negative factors when ob-

Table 2. Factor Loadings Greater Than or Equal to the Absolute Value of 0.30 for the 9-Factor Principal Components Factor Analysis (1199 Individuals, Varimax Rotation)^a

Affective Factor	Value	Disorganization Factor	Value	Prodromal Factor	Value
Affective symptoms early in course	0.82	Incoherence/loose associations	0.55	Prodromal role impairment	0.75
Major depression criterion A	0.81	Bizarre behavior	0.52	Prodromal lack of interest, energy	0.74
Mania criterion A	0.66	Inappropriate affect	0.50	Prodromal social isolation/withdrawal	0.70
Self-damaging acts	0.36	Self-neglect	0.49	Prodromal impaired hygiene	0.59
No affective syndrome (in psychotic illness)	-0.85	Poor insight	0.46	Prodromal odd beliefs/magical thinking	0.57
		Grandiose delusions	0.34	Prodromal peculiar behavior	0.57
		<i>Prodromal peculiar behavior</i>	<i>0.34</i>	Prodromal unusual perceptions	0.53
		Committed assault	0.33	Sudden onset (within 3 mo)	-0.50
		Persecutory delusions	0.31		
		<i>Prodromal odd beliefs/magical thinking</i>	<i>0.30</i>		
Child/Adolescent Sociability Factor	Value	Hallucination Factor	Value	Schneiderian First-Rank Symptoms Factor	Value
Good/fair childhood sociability	0.78	Visual hallucinations	0.47	Thought insertion	0.67
Good/fair childhood peer relations	0.75	Auditory hallucinations	0.37	Delusions of influence	0.60
Good/fair adolescent sociability	0.69	Tactile hallucinations	0.36	Somatic hallucinations	0.56
Good/fair adolescent peer relations	0.66	<i>Olfactory hallucinations</i>	<i>0.33</i>	Thought withdrawal	0.54
Good/fair elementary school adaptation	0.40	Catatonic behavior	0.30	Thought broadcasting	0.53
<i>Good/fair adult sociability</i>	<i>0.32</i>			Thought echo	0.44
				Primary delusions	0.40
				Olfactory hallucinations	0.36
				Primary delusional perception	0.35
				<i>Tactile hallucinations</i>	<i>0.35</i>
				Delusions of reference	0.33
				Delusions of guilt	0.30
Disability/Impairment Factor	Value	Negative Factor	Value	Scholastic Factor	Value
History of occupational deterioration	0.69	Alogia	0.63	Good/fair high school adaptation	0.73
Occupational disability at time of DIGS	0.62	Flat affect	0.62	Good/fair high school performance	0.71
History of occupational impairment	0.53	Negative formal thought disorder	0.61	Some college or more vs none	0.54
Lives alone or institutionalized vs with family/friends	0.47	Apathy	0.56	Good/fair elementary school performance	0.43
	0.40	Anhedonia	0.56	<i>Good/fair elementary school adaptation</i>	<i>0.38</i>
Severe psychotic disorder	-0.35	<i>Severe psychotic disorder</i>	<i>0.38</i>	Learning disability/hyperactivity	-0.42
Good intimate relationship	-0.35	<i>Self-neglect</i>	<i>0.30</i>	Attended therapeutic school	-0.51
<i>Sudden onset (within 3 mo)</i>	<i>-0.40</i>	<i>Poor insight</i>	<i>0.30</i>	School performance deterioration	-0.66
Remitting course		Good/fair adult sociability	-0.38		
		Established adult independence	-0.39		

Abbreviation: DIGS, Diagnostic Interview for Genetic Studies.

^a Italicized indicators have a stronger primary loading on another factor but still have a secondary loading greater than or equal to the absolute value of 0.30.

Table 3. Heritability Estimates for 9 Sets of Factor Scores (1199 Individuals)

Variable	Unadjusted			Transformation Parameter^a	Adjusted for Multiplex Ascertainment		
	h²	SE	P Value		h²	SE	P Value
Affective	0.44	0.13	<.001	$\lambda_1 = 2.99$	0.43	0.12	<.001
Child-adolescent sociability	0.27	0.14	.02	$k = -5.93$	0.23	0.14	<.05
Disorganization	0.60	0.11	<.001	$\lambda_1 = 1.37$	0.52	0.12	<.001
Hallucination	0.43	0.12	<.001	$k = -12.50$	0.43	0.12	<.001
Disability/impairment	0.61	0.12	<.001	$k = -9.33$	0.48	0.12	<.001
Negative	0.53	0.12	<.001	$\lambda_1 = 1.55$	0.38	0.13	<.002
Schneiderian	0.39	0.12	<.001	$k = 2.06$	0.38	0.12	<.001
Prodromal	0.36	0.12	<.001	$k = -7.84$	0.35	0.12	<.001
Scholastic	0.51	0.13	<.001	$k = -6.13$	0.46	0.14	<.001

^a λ_1 indicates George-Elston modulus power transformation was used; k indicates that the natural log power transformation was used (4 was added to raw scores to make them nonnegative before determining the power transformation parameter).

liquely rotated ($r = -0.15$, eTable 3) reinforces the supposition that the negative symptoms in this sample are not secondary to depression. The positive loading for poor insight (0.30) on the negative factor (Table 2) is consistent with research that associates this illness feature with the deficit syndrome.⁷¹ Likewise, the positive load-

ings for self-neglect (0.30) and severe psychotic disorder (0.39) and negative loading for remitting course (-0.22, eTable 1) are all consistent with the finding of poorer outcome for individuals with deficit syndrome.²³

The schneiderian factor heritability is consistent with several other studies that have demonstrated significant

sib-pair correlations for this nuclear syndrome.^{72,73} While the heritability estimate of Cardno et al⁷³ (0.71) is quite a bit higher than in the present study, it came out of a more ideal sample of monozygotic and dizygotic twins. Our schneiderian factor contains some indicators that are not first rank and this, along with sample characteristics and randomness introduced by multiple imputation, may account for the difference.

We are unaware of previous studies in probands and relatives with SZ that demonstrate familial aggregation of child/adolescent sociability, scholastic performance, disability/impairment, or prodromal factors. However, Vassos et al⁶⁹ included Premorbid Adjustment Scale and Global Assessment of Functioning Scale scores (scale scores, not factor scores) in their sib-pair study and found evidence of familiarity for both of these (our child/adolescent sociability and scholastic performance factors draw heavily on the Premorbid Adjustment Scale items, and our disability/impairment factor likely reflects some aspects of the variation captured by the Global Assessment of Functioning Scale).

The lowest heritabilities were found for the child/adolescent sociability factor (0.27) and the prodromal factor (0.36). The prodromal indicators are affected most by missing data. They involve subclinical behaviors and internal experiences in the year immediately before the illness was diagnosed (on average, almost 20 years before the interview). Likewise, individual recall of the childhood/adolescent sociability indicators might be more affected than for other signs, given the greater passage of time. It is also possible that prodromal and asociality symptoms characterize SZ variants more commonly produced by environmental exposures or de novo genetic events⁷⁴⁻⁷⁷ and that this accounts for the lower heritabilities. Nevertheless, the familial aggregation for these dimensions is statistically significant, which suggests that genetic analyses may still be warranted. By way of indirect comparison with the familiarity estimate for child/adolescent sociability, a healthy-twin study of the extraversion factor (from the NEO-PI-R personality questionnaire) estimated heritability to be 0.53.⁷⁸

Premorbid maladjustment has been associated with earlier age at onset and more likelihood of negative symptoms.⁷⁹ We observed a mild association of the child/adolescent sociability and scholastic performance factors with age at onset; however, even with oblique rotation, we did not find an association of the negative dimension with these factors (eTable 3).

The scholastic factor in part reflects cognitive functioning, a complex domain that has been deeply explored in SZ; specific cognitive phenotypes⁸⁰ and endophenotypes⁸¹⁻⁸³ are being pursued as vehicles for subtyping SZ. Scholastic performance has been studied in healthy populations and is strongly related to genetic factors; for example, a recent twin study suggested a heritability for academic achievement of 0.72 to 0.76, substantially correlated with verbal IQ.⁸⁴ The present study cannot answer the question as to whether the scholastic performance factor variation is also related to SZ susceptibility per se. However, studies implicate cognitive dysfunction as a precursor to SZ.^{85,86} In addition, the endophenotypic nature of various cognitive deficits for SZ has been

Table 4. Affected Pairs Contributing to Heritability Calculations (Correlations for Disorganization Factor)

Pairs	Count	Pair Correlation	SE
Parent/offspring	48	0.37 ^a	0.14
Sibling/sibling	215	0.24 ^b	0.07
Sister/sister	31	0.13	0.19
Brother/brother	86	0.38 ^b	0.10
Brother/sister	98	0.19	0.10
Grandparent	6	-0.36	0.41
Avuncular	53	-0.05	0.16
Half-sibling	4	0.19	0.45
Cousin	29	-0.10	0.19

^a $P < .02$.

^b $P < .001$.

established; thus, to the extent that the scholastic performance factor carries some of this cognitive variation, it may be reflecting variation related to SZ susceptibility. The present study also suggests that the scholastic performance variation is not simply a proxy for other illness aspects, as seen in the relatively low correlations of the scholastic performance factor with other factors when obliquely rotated (eTable 3).

Although the scholastic performance factor is an admittedly blunt metric for cognitive problems and is likely affected by contaminating influences (eg, socioeconomic status), it fits into a line of research by MacCabe et al,⁸⁷ who tested educational markers as a means for subtyping SZ. MacCabe et al⁸⁷ compared 2 groups of inpatients with SZ on OPCRIT⁸⁸ and other case note-rated symptoms, as well as on principal component factor scores. Their 46 university-educated patients vs 48 non-university-educated patients were matched by sex and age at diagnosis. University-educated individuals had significantly lower scores on a principal component made up of SZ symptoms and significantly higher scores on a reactive depression component, which suggests that they might represent a subtype. They were also more likely to have experienced a psychosocial stressor before onset and had a less chronic course of illness. A more recent study by MacCabe et al⁸⁹ in a Swedish birth cohort showed that the risk of adult-onset SZ and other psychosis is significantly related to poorer scholastic achievement at age 15 to 16 years, ruling out confounding by socioeconomic status, parental educational achievement level, migrant status, low birthweight, and hypoxia.

A key strength of the present study is the inclusion of indicators of social adaptation, school/occupational dysfunction, and prodromal symptoms, rounding out the more typically analyzed items characterizing psychosis per se. While studies vary in the types of assessments conducted, there can be opportunities for replication when similar domains are measured using well-operationalized tools even if these are not identical to those in the present study (eg, the DIGS and Premorbid Adjustment Scale). Use of the relatively large sample of individuals tends to produce more stable factor analytic solutions, increasing the likelihood of replication. Using statistical methods for factor number determination is also a strength, although even the best 2 methods showed divergence. The relatively large pool of indicators (73) was well divided among the various factors so that 8 of 9 fac-

tors have at least 4 to 5 substantial loadings (greater than or equal to the absolute value of 0.40). The hallucination factor is weaker in this regard. The affective factor is somewhat limited in the number of indicators loading on it. Inclusion of a greater number and variety of affective symptoms would likely result in generation of separate mania and depression factors. Another limitation is the ascertainment of some of the indicators (especially child and adolescent period items) primarily from individual reports via the diagnostic interview. It is possible that issues of recall and reporting bias can arise here more than with the SZ symptom indicators, which benefit from the addition of medical record and informant or clinician information used for consensus diagnosis. However, countering this potential weakness was our reliance on professional clinical examiners who could make in-depth probes and who held judgments in abeyance when the interview information proved weak. Despite the introduction of imputed values for missing data, we observed substantively sensible factors that show significant evidence of familial aggregation. The percentage of variance accounted for (35.4%) is somewhat lower than in many studies but likely is owing to the greater diversity of indicators here and the use of multiple imputation (introducing randomness).

CONCLUSIONS

A lingering question is whether alternative phenotypes with modest-to-moderate heritabilities (such as the present collection) can perform usefully in genetic studies of a disorder with a high heritability (eg, 70%-85% for SZ). In favor of this possibility, it must be emphasized that, although SZ is associated with relatively high heritability, this does not imply that strong or even moderate genetic effects lead to susceptibility. A common hypothesis is that SZ susceptibility arises from multiple genes of modest effect. If these loci have different phenotypic expressions (related to some of the dimensions explored in this study), the power to detect genetic associations will be greater for the quantitative measures vs discrete phenotypes. We are exploring the use of the factor scores as phenotypes in quantitative trait locus linkage and association studies. Other potential uses are as covariates or stratification variables. The factor scores may also prove useful in the eventual clinical characterization of individuals known to share a specific genetic variant that increases their susceptibility to SZ.

Submitted for Publication: August 11, 2008; final revision received October 8, 2008; accepted November 23, 2008.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grants ROI MH57314 and ROI MH068406 from the National Institute of Mental Health (Dr Pulver). The SAGE software package is supported by US Public Health Service

Resource grant RR03655 from the National Center for Research Resources.

Additional Information: The eTables are available at <http://www.archgenpsychiatry.com>.

Additional Contributions: Paul Costa Jr, PhD, provided valuable advice during the planning phase of the factor analysis. We thank the individuals and their families who participated in this study and continue to support this research program.

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