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Comparison of the Heritability of Schizophrenia and Endophenotypes in the COGS-1 Family Study

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Background: Twin and multiplex family studies have established significant heritability for schizophrenia (SZ), often summarized as 81%. The Consortium on the Genetics of Schizophrenia (COGS-1) family study was designed to deconstruct the genetic architecture of SZ using neurocognitive and neurophysiological endophenotypes, for which heritability estimates ranged from 18% to 50% (mean = 30%). This study assessed the heritability of SZ in these families to determine whether there is a "heritability gap" between the diagnosis and related endophenotypes. *Methods:* Nuclear families ($N = 296$) with a SZ proband, an unaffected sibling, and both parents ($n = 1366$ subjects; mean family size = 4.6) underwent comprehensive endophenotype and clinical characterization. The Family Interview for Genetic Studies was administered to all participants and used to obtain convergent psychiatric symptom information for additional first-degree relatives of interviewed subjects ($N = 3304$ subjects; mean family size = 11.2). Heritability estimates of psychotic disorders were computed for both nuclear and extended families. *Results:* The heritability of SZ was 31% and 44% for nuclear and extended families. The inclusion of bipolar disorder increased the heritability to 37% for the nuclear families. When major depression was added, heritability estimates dropped to 34% and 20% for nuclear and extended families, respectively. *Conclusions:* Endophenotypes and psychotic disorders exhibit comparable levels of heritability in the COGS-1 family sample. The ascertainment of families with discordant sibpairs to increase endophenotypic contrast may underestimate diagnostic heritability relative to other studies. However, population-based studies also report significantly lower heritability estimates for SZ. Collectively, these findings support the importance of endophenotype-based strategies and the dimensional view of psychosis.

Key words: schizophrenia/psychosis/endophenotypes/cognition/biomarkers/heritability

Introduction

Schizophrenia (SZ) is a severe and persistent psychotic disorder that is characterized by significant cognitive impairments and psychosocial disability.[1] Previous meta-analyses of twin studies have indicated a substantial heritability of this disorder ranging from 44% to 87% with a mean of 81%.[2] Although a broad range of heritability estimates have been obtained using a variety of sampling strategies (eg, twin concordance rates, parent-offspring correlations, sibling correlations, and multiplex families), it is the estimate of 81% that is perhaps most commonly

reported in the literature.[3,4] Yet, as some have suggested, twin studies may overestimate the heritability of SZ.[5,6] Indeed, recent population-based studies have begun to challenge this figure and suggest that the actual heritability of SZ may be lower.[7,8] Other studies of families ascertained through a SZ proband have even found "scant evidence" of heritability of this illness.[9] Although the heterogeneous nature of SZ may be in part responsible for the discrepant estimates, variations in ascertainment strategy likely contribute to this wide range of heritability estimates for SZ.[5,10,11]

The Consortium on the Genetics of Schizophrenia (COGS) explores quantitative neurocognitive and neurophysiological endophenotypes related to SZ as a means for understanding the genetic determinants of SZ. The first phase of COGS (COGS-1) focused on the recruitment of families via SZ probands with at least 1 unaffected sibling, and both parents available for evaluation in order to maximize contrast between and within families. Heritability estimates for 12 SZ-related endophenotypes ranged from 18% to 50% in the COGS-1 families with a mean of 30%.[12,13] In parallel, association, linkage, and copy number variation (CNV) studies have begun to elucidate the genomic substrates of these endophenotypes and of SZ itself in this cohort.[12,14,15]

Considering the often cited heritability estimate of SZ of 81%, there appears to be a significant "heritability gap" between illness and endophenotype heritability. This study, therefore, aimed to examine the heritability of SZ (alone and in combination with related serious psychiatric illnesses) in the COGS-1 families for a comparison with established heritability estimates of the endophenotypes in the same families. Given the COGS-1 ascertainment criteria, we hypothesized that SZ would be significantly heritable, albeit at lower levels than previously derived from twin- and multiplex family-based designs. We also hypothesized that expanding the diagnostic category in relatives to include bipolar disorder (BPD) would increase the illness heritability observed in accordance with the emerging dimensional view of psychotic disorders. In contrast, with the diagnostic group in relatives further expanded to include major depressive disorder (MDD), we anticipated a reduction in the observed heritability through a broadening of the diagnostic boundary beyond psychosis. Lastly, as study inclusion criteria required the enrollment of intact families, we hypothesized that COGS-1 patients would exhibit significantly lower levels of clinical symptoms and have a higher functional status than a cohort of patients enrolled at the same COGS laboratories as part of subsequent ongoing COGS-2 case-control study that does not require family member participation.

Methods

Subjects

COGS-1 families were ascertained at 7 sites through the identification of probands who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for SZ via the administration of the Diagnostic Interview for Genetic Studies (DIGS).[16] Each family consisted of a proband with SZ, at least 1 unaffected sibling, and both parents, with blood samples for DNA extraction required for all subjects and endophenotype testing required for the proband and unaffected sibling. Additional affected and unaffected siblings were included whenever possible. Families missing 1 or both parents were accepted if 2 or more additional siblings were available, regardless of affected status. This ascertainment strategy was designed to provide greater potential for phenotypic contrasts between and within families. The ascertainment and screening methods, inclusion/exclusion criteria, and continuous clinical quality assurance procedures are detailed elsewhere.[17] The final COGS-1 data set, included in this article, consisted of 296 predominantly nuclear families comprising 1366 subjects with an average family size of 4.6 members (range 4–14). The majority of the families (62%) consisted of a single sibling pair discordant for SZ, with sibships of 3 accounting for 26% of families and larger sibships accounting for 12%. A total of 1286 subjects had DNA available for genotyping, and of these, 1004 subjects were assessed for the 12 quantitative neurocognitive and neurophysiological endophenotypes.[12] Detailed descriptions of the assessment procedure for the endophenotypes are provided elsewhere.[13,17–22]

The Family Interview for Genetic Studies (FIGS)[23] was administered to all participants in order to obtain convergent psychiatric diagnoses for first-degree relatives of interviewed participants. Although 1297 subjects were directly assessed via the DIGS, psychiatric diagnoses were obtained from the FIGS for an additional 1952 family members who did not participate in endophenotype testing. Using best-estimate consensus diagnostic information, we were able to extend the nuclear families to comprise 3304 subjects with a mean family size of 11.2 and diagnoses available for 3249 subjects. Table 1 illustrates the differences between the nuclear families used for our previous endophenotype studies and the extended families that we were able to construct using FIGS information provided by participating subjects. FIGS information was only used when information was obtained from reliable first-degree informants in accordance with the original purpose of this instrument.[23] For example, the mother of the proband could provide diagnostic information for her parents and siblings, none of whom were directly interviewed for this study. Figure 1 shows an example of the best-estimate consensus summary information obtained and how FIGS information was used to extend the nuclear families.

To determine whether the COGS-1 requirement of participation of at least 3 additional family members, including at least 1 unaffected sib, resulted in a study ascertainment bias that favored a less-severe form of SZ, COGS-1 SZ

Table 1. Sample Description

	Nuclear Families[a]	Extended Pedigrees[b]
Family information		
Number of families	296	296
Average size	4.6	11.2
Average generations	2.0	2.7
Relative pairs		
Sibling	714	4113
Half-sibling	17	40
Parent-child	1530	4644
Grandparent-grandchild	18	2368
Avuncular	8	3294
Cousin	0	235
Subjects		
Total subjects	1366	3304
Males/females	736/630	1508/1795
SZ	321	391
BPD	25	60
MDD	201	296
Other disorder	2	53
Never mentally ill	748	2449
Unknown diagnosis	69	49
Relative frequency		
SZ	24.8%	12.0%
SZ + BPD	26.7%	13.9%
SZ + BPD + MDD	42.2%	23.0%

Note: BPD, bipolar disorder; MDD, major depressive disorder; SZ, schizophrenia.
[a]Nuclear families include 1297 subjects directly diagnosed via the Diagnostic Interview for Genetic Studies, as well as 1337 subjects that provided Family Interview for Genetic Studies information for all included family members and additional nonparticipating subjects.
[b]Extended pedigrees include additional subjects indirectly diagnosed via the Family Interview for Genetic Studies information obtained from directly assessed first-degree relatives.

probands were compared to a sample of 1189 SZ patients who were recruited and evaluated as part of the subsequent and ongoing 3000 person COGS-2 case-control study, which does not require the participation of family members. In this context, clinical symptoms for both COGS-1 and COGS-2 SZ patients were assessed using the Scale for the Assessment of Negative Symptoms[24] and the Scale for the Assessment of Positive Symptoms.[25] A modified Global Assessment of Functioning Scale[26] was used for assessing participants' overall level of functional status across psychological, social, and occupational domains via an anchored measure in accordance with our previously published methods.[26–28]

Statistical Analyses

Pedstats was used to determine the number of informative relative pairs for each endophenotype.[29] Heritability analyses of the diagnostic categories were conducted via SOLAR v.4.3.1,[30] consistent with our previous methods

for estimating the heritability of the quantitative endophenotypes.[12,13] Although variance component methods were used for the endophenotypes, SOLAR uses a liability threshold model to accommodate discrete traits, implemented in separate maximization routines that are generally identical to those used for quantitative trait maximization. The null hypothesis of no heritability ($h^2 = 0$) is tested by comparing a full model, which assumes that some fraction of the phenotypic variation is explained by genetic factors, to a reduced model, which assumes that no variation is explained by genes, using likelihood ratio tests. The bias introduced by our discordant sibpair ascertainment strategy necessitated a correction to better reflect the true mean of the disorder in the analysis. We, therefore, fixed the mean of each diagnostic category to more accurately reflect the population prevalence using the corresponding critical z values. We estimated the prevalence of SZ and BPD each as 1% and MDD as 16.2%.[31] We used z values of 2.33 for the SZ model, 2.05 for the SZ + BPD model, and 0.91 for the SZ + BPD + MDD model. Comparisons of severity of clinical symptoms, functional status, and endophenotype deficits were performed in SPSS version 20 using ANOVA adjusted for age, sex, and site of ascertainment as necessary.[12]

Results

The heritability of SZ was determined to be 31% for the nuclear and 44% for the extended families (table 2). When the clinical diagnostic phenotype was broadened to include a history of a serious psychotic mental disorder (ie, SZ or BPD), heritability estimates rose to 37% for the nuclear families and remained at 44% for the extended families. In contrast, when MDD was added as a nonpsychotic, clinically impaired group, heritability estimates for the nuclear and extended families dropped to 34% and 20%, respectively (table 2).

Anticipating that the discordant sibpair design may have selected for families with fewer affected individuals and perhaps more sporadic vs familial cases of SZ, we examined the effects of positive vs negative family history. An assessment of the extended families revealed 62 (21%) of COGS-1 families exhibited a positive family history of SZ, defined as a minimum of 2 family members with SZ. When family history was broadened to include SZ or BPD, 97 families (33%) were defined as having a positive family history. As one would expect, restricting the analysis to the subset of families with multiple affected members significantly increased the heritability estimates for SZ and SZ + BPD to approximately 80%, consistent with estimates observed in previous twin and multiplex family studies. Another 96 families (32%) had no evidence of family history for any psychiatric illness, and the SZ proband was the only affected family member. These probands may thus represent sporadic cases of SZ. The remaining 103 families (35%) had a family history of MDD in addition to the SZ proband, and some portion of
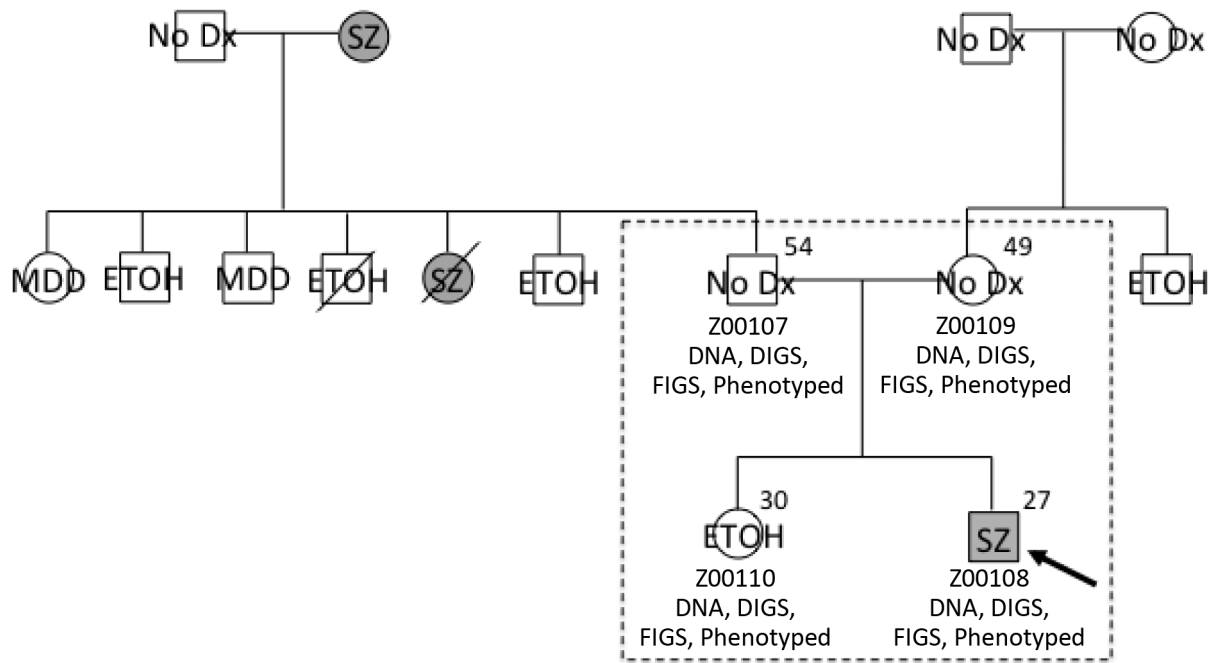
Fig. 1. Example of a nuclear family from the COGS-1 database that was extended using FIGS information. A dashed box indicates members of the nuclear family, all of whom directly participated in the study. The age of each participating subject is indicated in the upper righthand corner and subject IDs are given, along with an indication of whether DNA was collected and whether DIGS, FIGS, or endophenotypes are available for the subject. DIGS-based diagnoses are indicated for each participating member, and FIGS-based diagnoses are indicated for additional first-degree relatives of a participating member with additional diagnostic information below as relevant. Squares indicate males and circles indicate females, and diagonal lines indicate the subject is deceased. COGS-1, Consortium on the Genetics of Schizophrenia; DIGS, Diagnostic Interview for Genetic Studies; ETOH, alcohol dependence; FIGS, Family Interview for Genetic Studies; MDD, major depressive disorder; no Dx, never mentally ill; SZ, schizophrenia.

Table 2. Heritability (h^2) Estimates for Each Diagnostic Category and Family Set, Indicating the Numbers of Unaffected, Discordant, and Affected Relative Pairs for Each Model

Family Set	Diagnoses	Informative Relative Pairs[a]			$h^2 \pm$ SE	P value
		Sibling	Parent-Offspring	Other[b]		
Nuclear	SZ	219/466/17	747/561/8	16/21/1	0.31 ± 0.02	<.0001
	SZ + BPD	206/464/32	712/580/24	16/21/1	0.37 ± 0.32	<.0001
	SZ + BPD + MDD	121/422/159	461/669/186	13/12/13	0.34 ± 0.03	<.0001
Extended	SZ	3141/876/42	3713/759/16	3648/2017/90	0.44 ± 0.04	<.0001
	SZ + BPD	3032/953/74	3571/873/44	3411/2205/139	0.44 ± 0.17	<.0001
	SZ + BPD + MDD	2523/1261/275	2925/1310/253	2624/2779/352	0.20 ± 0.04	<.0001

Note: Abbreviations are explained in the first footnote to table 1.
[a]Informative relative pairs are listed as unaffected/discordant/affected for each diagnostic and relationship category.
[b]Other includes half-sibling, grandparent-grandchild, avuncular, and cousin pairs.

probands from these families likely represent sporadic cases of SZ as well. The COGS-1 families thus seem to reflect a SZ sample that includes combinations of both familial and sporadic cases of SZ.

We further assessed whether the recruitment of intact families may have biased the sample to favor the recruitment of SZ probands with a milder form of illness. A comparison of all COGS-1 probands, regardless of family history, with SZ patients collected as singleton cases in COGS-2 revealed no differences in symptom

severity or global functioning (see table 3), providing further evidence that COGS-1 SZ probands are symptomatically representative of a population-based sample that includes both familial and sporadic cases of SZ.

Conclusions

Heritability of SZ in the COGS-1 family sample was estimated at 31% and 44%, derived from nuclear and extended families, respectively. At first blush, this appears

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Table 3. Comparison of Demographic and Clinical Characteristics of SZ Patients Recruited as Part of COGS-1 Family Study vs the COGS-2 Case-Control Design

| | Comparison of COGS-1 vs COGS-2 Schizophrenia Patients | | | | | | |
| | COGS-1: 3 Additional Family Members Required | | | COGS-2: No Additional Family Members Required | | | Effect Size |
	N	Mean	SD	N	Mean	SD	(d)
Age*	295	34.39	11.02	1189	46.42	11.06	1.00
Education*	294	13.73	2.09	1189	12.55	2.10	0.55
Age of onset	290	22.56	5.52	1174	21.89	7.07	0.10
GAF	279	45.56	13.43	1172	43.99	8.53	0.01
SANS total	289	10.17	5.91	1187	10.91	5.64	0.13
SAPS total	289	6.56	4.15	1183	6.69	4.05	0.16

Note: COGS, Consortium on the Genetics of Schizophrenia; GAF, Global Assessment of Functioning; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.
No significant differences in global clinical symptoms or functional characteristics were detected. The COGS-1 family study, however, enrolled SZ patients who were significantly younger and had higher levels of education.
*$P < .001$.

to be discordant with the commonly cited figure of SZ heritability as 81%, derived primarily from twin studies,[2] although more recent population-based studies have yielded lower heritability estimates for SZ.[7,8] Specifically, the a priori inclusion of BPD in combination with SZ as a broad psychosis phenotype caused a modest increase in the heritability from 31% to 37% in the nuclear families. This finding supports the concept of psychosis as a dimensional phenotype[32] and may reflect the shared genetic architecture among SZ and BPD, which was recently estimated to be 68% from common variation.[33] Further broadening of the clinical phenotype via the addition of nonpsychotic MDD for a more general assessment of severe mental illness, however, significantly deflated the heritability estimates in both the nuclear and extended families relative to the SZ + BPD diagnostic category. This is perhaps not surprising, because the shared genetic etiology between MDD and SZ or BPD appears to be much lower (47% and 43%, respectively).[33]

Many researchers now utilize quantitative endophenotypes to deconstruct the genetic architecture of SZ.[34] Endophenotypes are laboratory-based neurocognitive, neurophysiological, imaging, or metabolic measures that show deficits in SZ patients and their clinically unaffected relatives.[3,34–36] Endophenotypes need not necessarily be more heritable than the clinical disorders. Their utility lies in the presumably "cleaner" and measurable signals they produce as a result of being more closely tied to the underlying neurobiological processes, compared to the conglomeration of traits and symptoms embedded in the diagnosis. As objective and reliable quantitative traits, endophenotypes also have more power to detect genetic associations than categorical clinical diagnoses. Many endophenotypes are even amenable to translational animal model studies for revealing neurobiological

substrates associated with diseases.[37–40] In the COGS-1 sample, the heritability estimates for SZ are equivalent to the mean heritability estimate for the 12 endophenotypes of 30% (range: 18%–50%) with 7 of the COGS-1 endophenotypes exhibiting higher heritability estimates than the diagnosis of SZ in the nuclear families.

Heritability reflects the genetic contributions to a disorder. In the narrow sense, heritability refers to additive genetic factors, which are typically common variants of relatively small effect that can be detected by association methods.[12,14,41–45] These common variants are passed vertically through multiple generations of family members putatively leading to familial forms of SZ, but they also contribute to sporadic cases of the disorder. A large population-based study recently suggested that additive genetic effects account for 64% of SZ risk,[8] and another study suggested that common single nucleotide polymorphisms explain approximately 23% of the total risk.[33] In the broad sense, heritability refers to all genetic sources of risk, irrespective of allele frequency or effect size, and also includes rare copy number variants (CNVs) or single nucleotide variants (SNVs) of large effect, nonadditive genetic effects, and gene-environment interactions. Although highly penetrant, variants arising de novo appear to play a significant role in SZ risk,[46–51] they do not segregate within families and are thus not reflected in heritability estimates. They may, however, explain some of the variation attributed to environment and contribute to some sporadic cases of SZ. It is also possible that some de novo mutations occur in "hotspots," or vulnerable regions, that are sources of frequent mutation, which may mimic the relatively low-risk profile of common variation and serve as a mechanism whereby risk variation subject to negative selective pressure can be replenished.[52] Thus, SZ liability likely

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involves a combination of segregating variants (common single nucleotide polymorphisms, rare SNVs, and CNVs) and de novo variation (highly penetrant CNVs and damaging coding SNVs) in the context of environmental factors.[15,52] This model is consistent with familial vs sporadic cases, evolution, and observed phenotypic heterogeneity, because each case would presumably display a unique risk profile.[15]

The COGS-1 sample allowed for a direct comparison of the heritability estimates for SZ and endophenotypes. The COGS-1 ascertainment strategy of recruiting intact families with siblings discordant for SZ in an extensive study could bias the sample in a number of ways.[17] First, this discordant sibpair design, which was chosen to enhance the study of quantitative endophenotypes associated with an illness, may lead to lower heritability estimates of the illness itself, as we have found. Second, families exhibiting evidence of bilineal transmission were excluded, which may have similarly created a downward bias on the heritability of SZ in our sample. Thus, our selection strategy may have inadvertently excluded more densely affected families for which unaffected siblings might be rare or for which affected members potentially show greater impairment and would therefore be less willing to participate in this study. Such families may also be less likely to be intact due to the dysfunction caused by multiple cases of illness. In contrast to our expectations, however, when COGS-1 probands were compared with COGS-2 singleton SZ cases, there were no apparent differences in clinical symptom severity or functional status, suggesting that the COGS-1 probands are representative of broader population-based samples, at least based on these more global characteristics. One might also speculate that this COGS-1 ascertainment strategy would yield a preponderance of sporadic rather than familial cases of SZ. Of the SZ probands, 33% had at least 1 other family member with a psychotic illness and likely represent familial cases; 32% of families exhibited no family history of any serious mental illness and were likely sporadic. Many of the remaining probands likely also represented sporadic cases with no family history of psychosis. In fact, sporadic cases may be the norm for SZ. Recently, Yang et al[53] showed that for a disease such as SZ, 83%–90% of cases are predicted to appear sporadic with a lack of affected first-, second-, or third-degree relatives, which is consistent with both common polygenic and highly penetrant de novo mutation models. The prevalence of sporadic vs familial SZ was recently examined in the Swedish population study of more than 9 million people; only 3.8% of families had more than 1 affected member.[8] Thus, the COGS-1 sample does not appear to contain a preponderance of sporadic SZ, but rather reflects a mixture of both sporadic and familial forms of illness. This characterization of families will serve as a valuable platform for future molecular and endophenotypic studies of these samples.

For over a century,[54–56] family studies of psychiatric disorders have demonstrated the substantial contribution of genetic factors to risk of illness,[57–61] forming the basis for contemporary molecular approaches. The first family study of SZ—or rather dementia praecox—was conducted by Rudin[54] in Kraepelin's clinic from 1907–1911, reported in 1916,[57] see also.[62–64] An important strength of the current study is the method of directly interviewing as many relatives as possible ($n = 1297$) using the DIGS and FIGS. This resource-intensive approach allowed us to later obtain convergent psychiatric information for first-degree relatives of directly interviewed individuals and substantially expand the total sample ($N = 3304$) for heritability analyses of SZ. Although reliance on informants can result in an underreporting of psychiatric disorders in families with some inherent diagnostic uncertainty,[58] the FIGS was developed to minimize these possibilities through the use of structured assessment procedures anchored with specific diagnostic criteria.[23] Rather than a decrease in heritability that would be expected with either an underreporting of psychiatric illness in families or a loss of diagnostic fidelity, FIGS information actually increased the heritability estimates in our sample, particularly for models using a broad psychosis phenotype (SZ + BPD).

The COGS, Bipolar and Schizophrenia Network on Intermediate Phenotypes, and other studies attempt to address the imprecision in our current diagnostic symptom through advancing the use of reliable, laboratory-based neurocognitive and neurophysiological measures for use as endophenotypes in genomic studies and biomarkers in clinical outcome studies.[65–67] The current analyses are only one step in a larger strategy of examining endophenotype structure. Even if there were to be an illness vs endophenotype "heritability gap," the endophenotypes are still extremely informative regarding the pathophysiology and genetics of this illness. These results support the continued use of endophenotypes to illuminate the mechanisms contributing to SZ and related psychoses. We anticipate that the ongoing COGS-2 case-control study will shed further light on the genomic and neurobiological substrates of SZ.

Acknowledgments

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