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Factor structure and heritability of endophenotypes in schizophrenia: Findings from the Consortium on the Genetics of Schizophrenia (COGS-1)

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ABSTRACT

Background: Although many endophenotypes for schizophrenia have been studied individually, few studies have examined the extent to which common neurocognitive and neurophysiological measures reflect shared versus unique endophenotypic factors. It may be possible to distill individual endophenotypes into composite measures that reflect dissociable, genetically informative elements.
Methods: The first phase of the Consortium on the Genetics of Schizophrenia (COGS-1) is a multisite family study that collected neurocognitive and neurophysiological data between 2003 and 2008. For these analyses, participants included schizophrenia probands ($n = 83$), their nonpsychotic siblings ($n = 151$), and community comparison subjects ($n = 209$) with complete data on a battery of 12 neurocognitive tests (assessing domains of working memory, declarative memory, vigilance, spatial ability, abstract reasoning, facial emotion processing, and motor speed) and 3 neurophysiological tasks reflecting inhibitory processing (P50 gating, prepulse inhibition and antisaccade tasks). Factor analyses were conducted on the measures for each subject group and across the entire sample. Heritability analyses of factors were performed using SOLAR.
Results: Analyses yielded 5 distinct factors: 1) Episodic Memory, 2) Working Memory, 3) Perceptual Vigilance, 4) Visual Abstraction, and 5) Inhibitory Processing. Neurophysiological measures had low associations with these factors. The factor structure of endophenotypes was largely comparable across probands, siblings and controls. Significant heritability estimates for the factors ranged from 22% (Episodic Memory) to 39% (Visual Abstraction).
Conclusions: Neurocognitive measures reflect a meaningful amount of shared variance whereas the neurophysiological measures reflect largely unique contributions as endophenotypes for schizophrenia. Composite endophenotype measures may inform our neurobiological and genetic understanding of schizophrenia.

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1. Introduction

Identifying genes that are associated with schizophrenia is a key step in identifying potentially remediable biological pathways for the development of novel treatments. Endophenotypes (e.g., neurocognitive and neurophysiologic measures) reflect components of liability narrower than the broad clinical diagnosis of schizophrenia and may facilitate the search for susceptibility genes and biological pathways to illness (Gottesman and Gould, 2003; Braff et al., 2007a,b). Individual endophenotypes are heritable (Greenwood et al., 2007), and believed to reflect variation among a smaller number of genes than the very large array of genes implicated in schizophrenia (Gottesman and Gould, 2003; Braff et al., 2007a,b; Ripke et al., 2014). The goal of the first phase of the Consortium on the Genetics of Schizophrenia (COGS-1) was to investigate the genetic basis of endophenotypes for schizophrenia.

Considerable support existed in the literature for the selection of neurocognitive (Gur et al., 2007; Stone and Seidman, in press) and neurophysiological (Turetsky et al., 2007) endophenotypes for COGS-1. Reports of COGS-1 data for individual endophenotypes have focused on working memory (Horan et al., 2008), verbal declarative memory (Stone et al., 2011), P50 gating (Olincy et al., 2010), prepulse inhibition (Swerdlow et al., 2007), antisaccade performance (Radant et al., 2010), and N100 amplitude (Turetsky et al., 2008). In addition to demonstrating significant heritability of COGS endophenotypes (Greenwood et al., 2007), previous work demonstrates that these endophenotypes have salient genetic associations to relevant neurobiological gene networks involving candidate genes, for example, in glutamate transmission (e.g. NRG1, ERBB4) (Greenwood et al., 2011; Greenwood et al., 2013).

Relationships among endophenotypic measures have rarely been addressed, yet they have practical and theoretical significance. From a practical perspective, the degree of independence and overlap among measures can guide investigators in their choice of measures. These issues are relevant to the study cost, subject burden and other study design decisions when there are multiple potential measures. Because there is no consensus on the most genetically informative individual measures or the number or type of underlying endophenotypic dimensions, analyses of shared versus unique contributions can help identify the utility of individual measures. Importantly, reduction of many overlapping individual endophenotypes into a modest number of latent factors will improve statistical power by both increasing the reliability of measurement of the underlying constructs and by limiting the number of statistical comparisons.

To date, most work has been devoted to identifying individual endophenotypes or bivariate relationships between endophenotypes. In particular, relatively few studies have examined the interrelationships among multiple neurocognitive and neurophysiological measures and virtually none have done so in large samples. For example, modest but significant correlations among three neurocognitive endophenotypes of attention, declarative memory and executive functioning were demonstrated in non-psychotic relatives of patients with schizophrenia, but not in normal controls (Toomey et al., 1998). In addition, P50 gating and prepulse inhibition (PPI)—two operational measures of inhibitory function—are uncorrelated in both normal control subjects (Schwarzkopf et al., 1993; Light and Braff, 2001) and schizophrenia patients (Braff et al., 2007a,b). More recently, a principal components analysis of a large number of potential endophenotypes in controls, schizophrenia probands and relatives was carried out (Dickinson et al., 2011), but like most prior studies, did not include neurophysiological measures nor report heritabilities.

The COGS-1 dataset is particularly well suited to address questions about interrelationships among measures because of its intensive ascertainment of neurocognitive and neurophysiological endophenotypes. Among the key questions are: 1) What is the factor structure of the endophenotypes? 2) To what extent are the factors correlated with each other? 3) Is the factor structure of endophenotypes comparable across different groups of subjects? 4) Are composite multivariate endophenotypic factors significantly heritable?

2. Methods

COGS-1 is a seven-site NIMH-funded project designed to assess endophenotypes and perform genetic analyses on individuals with schizophrenia, their biological first-degree relatives, and community comparison subjects (CCS; Calkins et al., 2007). The institutional review boards of each site approved the study. All subjects provided written informed consent and received compensation for participating.

Each site followed identical protocols for recruitment, diagnosis, endophenotype assessment and collection of blood for DNA. Consortium-wide quality assurance procedures were exercised throughout the study. Families were recruited through a proband with schizophrenia and minimally included at least either: a) one nonpsychotic sibling and both parents; or b) one parent and at least two siblings. Additional siblings were included whenever possible.

2.1. Subjects

Subjects who received endophenotype assessment were 18–65 years old and fluent in English. Exclusion criteria for probands and CCS included a: history of electroconvulsive therapy in the past 6 months; positive drug or alcohol screen; diagnosis of substance abuse disorder in the past 30 days or substance dependence in the past 6 months; estimated premorbid IQ < 70; a history of head injury with loss of consciousness exceeding 15 min; a seizure disorder; any ocular, neurological, or systemic medical problem likely to cause neurocognitive or neurophysiological performance deficits; and inability to provide informed consent. Similar inclusion criteria were applied to relatives. CCS were excluded if they had a history of any DSM-IV Cluster A Personality Disorder, psychosis, or a first- or second-degree family history of psychosis.

All subjects were administered a modified version of the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), the Family Interview for Genetic Studies (NIMH, 1992), and other clinical measures (see Calkins et al., 2007), and a review of medical records was performed. Premorbid IQ was estimated using the Wide Range Achievement Test, Third Edition (WRAT-3) Reading subtest (Jastak and Wilkinson, 1993). All probands met DSM-IV diagnostic criteria for schizophrenia, were stable clinically (i.e. no psychiatric hospitalization in the previous month), and were tested as outpatients.

Data were collected between 2003 and 2008. 1984 subjects consented to enter the study. The maximum number of participants who completed any COGS-1 measure was 1495 because parents > age 65 were excluded from endophenotype testing. In addition, valid neurophysiological measurement was limited by factors such as the number of subjects in which P50 conditioning ratios could be accurately determined. Each endophenotypic measure had a different completion rate.

Given our interest in the factor structure of the endophenotypes, we focused only on the sample that validly completed all endophenotypic measures: probands $N = 83$, nonpsychotic siblings $N = 151$, and CCS $N = 209$. Parents of probands were excluded from the factor analyses (FA) to maintain comparable age ranges across the groups. Subsequent description of the subjects will be limited to those in this "factor analyzed (FA) sample."

Participants were on a range of medications at the assessment: probands ($n = 80$ [96.0%] on antipsychotics, $n = 2$ unmedicated [2.4%], $n = 1$ other medications [1.6%]; CCS ($n = 164$ [78.5%], no medications, $n = 45$ [21.5%] other medications, none on anti-psychotics); siblings ($n = 101$, 66.9%, no medications, $n = 50$ [33.1%] other medications, none on antipsychotics).

2.2. Endophenotypic measures

Each endophenotype variable is described here briefly, and is more fully detailed elsewhere (Calkins et al., 2007; Greenwood et al., 2007; Swerdlow et al., in this issue). There were 12 neurocognitive endophenotypes: 1. Vigilance—The Degraded Stimulus version of the

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Continuous Performance Test (DS-CPT) with performance indexed by target/nontarget discrimination (d') (Nuechterlein and Asarnow, 1999) as well as target reaction time; 2. The CPT Identical Pairs version (CPT-IP) d' (Cornblatt et al., 1988) requires memory of the prior stimulus to determine whether the current one is a target; 3. Verbal Memory—The California Verbal Learning Task, Second Edition (CVLT-II), total recall score for 16 verbally presented items summed over 5 learning trials (Delis et al., 2000); 4. Working Memory—The Letter–Number Span test (LNS) score measures verbal information storage with manipulation (Gold et al., 1997).

We used a modified version of the University of Pennsylvania Computerized Neurocognitive Battery (Penn CNB) (Gur et al., 2001), excluding measures of attention and verbal and working memory to avoid redundancy with those detailed above. Included were the tests for Abstraction and Mental Flexibility (ABF), Face Memory (FMEM), Spatial Memory (SMEM), Spatial Processing (SPA), Sensori-motor (S-M) Dexterity, Emotion Recognition (EMO), and motor speed (C-TAP). Each test of the Penn CNB is measured as "efficiency", a combination of accuracy (percent correct) and speed (median response time in ms), which is calculated as accuracy/$\log_{10}$ (speed) and expressed as standard equivalents (Z-scores).

There were three neurophysiological endophenotypes. Prepulse inhibition (PPI) was measured as the percent inhibition of the startle reflex in response to a weak prestimulus using a 60 ms prepulse interval (onset asynchrony) (Braff et al., 1978). P50 gating (P50S) was measured as the ratio of the amplitudes of the P50 event-related potentials generated in response to the conditioning and test stimuli that are presented with a 500 ms interstimulus interval (Freedman et al., 1997). The Antisaccade Task (AS) performance was measured as the ratio of correct antisaccades to total interpretable saccades (Radant et al., 2010).

2.3. Statistical analyses

For demographic comparisons by group, one-way ANOVAs for continuous variables and Chi-square tests for categorical variables were used. When the omnibus tests showed significant differences between the groups, they were followed up with post-hoc contrasts.

We conducted a maximum likelihood FA on the endophenotype measures. We determined the number of factors by requiring that the covariance structure implied by the estimated factor structure was not significantly different from the observed covariance structure and that this outcome was supported by the scree plot based on the eigenvalue-decomposition of the sample covariance matrix. Five factors were thus identified. From this factor structure we identified the key endophenotypes for each factor, first by identifying for each variable the factor on which it loaded highest. Next, all variables in which this highest loading was below .30 were excluded, as they did not show strong association with any factor. Third, we determined for each factor the lowest loading of the variables we linked with it in the first step. Then all variables not selected in the first step that had higher loadings on the factor were considered to be associated with this factor. This last step was to ensure that variables that cross-load heavily were also linked with the factor with which they were secondarily associated. To maximize generalizability across different samples, the factor scores were estimated using unit weighting. To ensure that the structure created by an exploratory FA of the whole sample was equally applicable to each of the subsamples and did not disproportionally reflect one of the samples, we additionally fit a confirmatory FA based on this factor structure on each of the subsamples using EQS 6.2.

For the 296 families included in COGS-1, heritability estimates were computed for the five factors using the variance component methodology implemented in SOLAR v.4.3.1 (Almasy and Blangero, 1998), as we have described in our initial report of endophenotype heritabilities (Greenwood et al., 2007). In this maximum likelihood method, 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 distribution of values for each factor was analyzed to eliminate large departures defined as greater than three standard deviations from the mean. Factor scores from 11 individuals were removed to improve the distribution of Factor 1 only. A correction was made for ascertainment bias, since the families were recruited through the identification of a proband with schizophrenia and are thus not representative of the general population (Beaty and Liang, 1987). The heritability estimates for each factor were adjusted as necessary for covariates (e.g., age, sex, and site of data collection) explaining a significant portion of the trait variance. Bivariate genetic correlations (ρ_G) were also computed using SOLAR as the component of the overall correlation that is due to pleiotropy (i.e., the influence of a gene or set of genes on both factors simultaneously), which was obtained from the kinship information in the families (Almasy et al., 1997).

3. Results

3.1. Demographic and clinical characteristics

Table 1 shows no significant differences among the schizophrenia probands, siblings of probands, and CCS on age, parental education, or handedness. Probands included a significantly higher proportion of males, with lower education and reading scores than CCS, and lower education than siblings. The overall sample is comprised of 49% males with a mean age of about 35 years, 15.1 years of education, 15.6 years of parental education, and with WRAT-3 standardized reading scores in the higher end of the average range (~107).

3.2. Factor structure

Five factors were identified with the combined sample, with 10 of the 15 endophenotypes associated with one factor, three (CVLT total recall, Antisaccade proportion correct, spatial memory efficiency) cross-loading onto two factors, and two representing independent dimensions (C-TAP/finger tapping, P50) that were not associated with the others (Table 2). The analyses were then replicated in the three subsamples (Probands, Siblings, CCS) to ensure that the factor structure was not based on group differences. The results in the three subsamples did not show a markedly different structure from the combined sample, supporting the notion that the factor structure within the groups is fundamentally similar (see Supplemental Table 1).

Four of the five factors primarily reflected neurocognitive performance, emphasizing: 1) Episodic Memory, 2) Working Memory, 3) Perceptual Vigilance, and 4) Visual Abstraction. A fifth, inhibitory processing factor had loadings from the AS and PPI measures. The loadings indicate that P50 gating index is relatively independent of all five factors. Motor speed (finger tapping) is also only weakly associated with the factors, with a maximum loading of .22 with any factor score.

In the combined sample, correlations among the factors ranged from 0.00 to 0.68 (Table 3), suggesting that some factors were independent of each other while others were moderately associated. Perceptual vigilance had the smallest multiple R, suggesting that this factor shares less common variance with the other factors than the other four factors. The correlation matrices among estimated factor scores within each diagnostic group showed that the three groups had reasonably similar ICCs: probands with schizophrenia had the highest mean intraclass correlation coefficient between factors (ICC = .407) compared to siblings (ICC = .319) and CCS (ICC = .270) (see Supplemental Table 1). This pattern suggests that probands perform more equally poorly or well on multiple factors compared with the other diagnostic groups.

To determine if this factor structure was equally applicable to all three of the subgroups we used a hierarchical multigroup confirmatory FA. In a first step we tested if the measurement model was identical across the three groups by constraining all factor loadings to be identical

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Table 1
Demographic characteristics of the three groups.

Variable/group	Overall sample ($n = 443$)	CCS (1) $n = 209$	Proband (2) $n = 83$	Sibling relative (3) $n = 151$	Overall group differences	Post-hoc group comparisons
Age	34.8 (11.9)	34.8 (12.7)	32.4 (10.0)	35.9 (11.4)	$F_{(2,440)} = 2.40$ $P = .09$	
Sex (% males)	217 (49%)	88 (42%)	63 (76%)	66 (44%)	$Xc^2(2) = 30.85$ $P < .01$	1 vs 2: c^2 (1) = 28.3 $p < .01$ 1 vs 3: c^2 (1) = 0.1 $p = .76$ 2 vs 3: c^2 (1) = 23.3 $p < .01$
Personal education	15.1 (2.7)	15.5 (2.2)	13.7 (2.0)	15.1 (2.3)	$F_{(2,440)} = 20.6$ $P < .01$	1 vs 2: $p < .01$ 1 vs 3: $p = .09$ 2 vs 3: $p < .01$
Parent education $n = 430$	15.6 (3.1)	15.3 (3.1) $N = 199$	15.9 (3.3) $N = 81$	16.0 (3.0) $N = 150$	$F_{(2,427)} = 2.21$ $P = .11$	
Handedness					c^2 (4) = 5.65	
Right	388 (88%)	189 (91%)	65 (81%)	134 (89%)	$P = .23$	
Left	46 (10%)	16 (8%)	14 (18%)	16 (11%)		
Ambidextrous $n = 438$	4(1%)	2 (1%) $N = 207$	1 (1%) $N = 80$	1 (1%) $N = 151$		
WRAT3 Reading Standard Score $n = 442$	107.0 (9.8)	108.4 (9.7) $N = 209$	104.5 (11.0) $N = 83$	106.5 (9.1) $N = 150$	$F_{(2,439)} = 5.0$ $P < .01$	1 vs 2: $p < .01$ 1 vs 3: $p = .07$ 2 vs 3: $p = .14$

CCS = community comparison subjects.

across groups, and determining if this constraint leads to a significant decrease in the model fit. The constrained model fit not differently than the unconstrained model ($\chi^2(20) = 15.8$, $p = .73$). In a second step we tested if both the factor loading and the correlations between factors were identical across groups constrained the measurement and the structural model to be identical across all groups. Again, this constraint did not significantly decrease model fit (i.e. ($\chi^2(38) = 48.6$, $p = .12$).

3.3. Heritability of factors

All five factors were found to be significantly heritable ($p < 0.0001$) in the 296 COGS families. Factor 4 (Visual Abstraction) produced the highest heritability estimate of 39%, whereas heritability estimates for the other factors range from 22 to 29% (Table 4). Significant genetic correlations were observed between all factors ($\rho_G = 0.32$–0.82, $p < 0.05$) (Table 5). However, using a conservative Bonferroni correction, Perceptual Vigilance was independent of all other factors. In addition to being the most heritable factor, Visual Abstraction demonstrated the strongest and most robust ($p < 0.005$) genetic correlations with Episodic Memory ($\rho_G = 0.82$) and Inhibitory Processing ($\rho_G = 0.60$).

4. Discussion

These findings extend previous investigations of cognitive factors and their deficits in schizophrenia. Based on 15 neurocognitive and neurophysiological measures five factors were identified, with a similar structure across the 3 subsamples. Four of the five factors largely involved neurocognitive performance: 1) Episodic Memory, 2) Working Memory, 3) Perceptual Vigilance, and 4) Visual Abstraction. The fifth factor reflected Inhibitory Processing and involved significant loadings from two of the three neurophysiological measures (PPI and AS). Each of these factors was shown to be significantly heritable. Moreover, a number of the factors demonstrated highly significant genetic correlations with each other.

Table 2
Rotated factor matrix for the complete sample[a] ($N = 443$).

Factors					
	Episodic memory	Working memory	Perceptual vigilance	Visual abstraction	Inhibitory processing
DS-CPT[b] reaction time for targets	−.147	.007	**−.984**	−.023	−.092
DS-CPT[b] d′[c]	.067	.234	**.409**	.290	.205
CPT-IP[d] d′ (4 digits)	.240	**.443**	.148	.024	.284
CVLT[e] Total recall, trials 1–5	**.514**	**.324**	.142	.088	−.136
Letter number sequence total for reorder	.242	**.714**	.038	.051	−.024
Abstraction & mental flexibility efficiency	.208	.309	.069	**.515**	−.069
Face memory efficiency	**.673**	.051	.028	.004	.026
Spatial memory efficiency	**.497**	.299	.066	**.310**	−.018
Spatial ability efficiency	.261	.281	.065	**.486**	.215
Emotional recognition efficiency	**.620**	.157	.081	.081	.020
Mouse practice z (motor speed)	**.386**	.131	.253	.265	.031
Finger tapping z (motor) speed	.123	.180	.194	.224	.089
Antisaccade proportion correct	**.390**	.291	.068	.257	**.338**
PPI[f] 60 ms	−.037	.000	.052	.000	**.309**
P50 conditioning test	−.017	−.101	.019	.224	−.010

Note—Efficiency Measures from University of Pennsylvania Computerized Neurocognitive Battery (Penn CNB) combine accuracy and speed of performance.

[a] Extraction Method: Maximum Likelihood; Rotation Method: Varimax with Kaiser Normalization; Rotation converged in 6 iterations, Chi Square (40 *df*) = 56.923, $p = 0.04$. Loadings considered part of the measurement model are highlighted.

[b] DS-CPT—Degraded Stimulus Continuous Performance Test.

[c] d′ ("d prime") = target / nontarget discrimination during vigilance.

[d] CPT-IP = Continuous Performance Test—Identical Pairs.

[e] CVLT = California Verbal Learning Test, second edition.

[f] PPI + Prepulse Inhibition.

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Table 3
Correlation matrices between factors within the three groups comprising the factor analyzed sample ($n = 443$).

Factors	Episodic memory	Working memory	Perceptual vigilance	Visual abstraction	Inhibitory processing
Episodic memory	–	.66	.00	.68	.40
Working memory	.66	–	.06	.51	.27
Perceptual vigilance	.00	.06	–	.19	.09
Visual abstraction	.68	.51	.19	–	.27
Inhibitory processing	.40	.27	.09	.27	–
Multiple R	.79	.66	.27	.70	.41

Homogeneity: ICC = .319.

These results show that, despite robust performance deficits in widespread cognitive domains in schizophrenia, cognitive deficits are separable into several neuropsychologically meaningful factors. This cognitive domain strategy was also a central theme in the development of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al., 2004), and one that has been utilized and replicated across multiple studies (Dickinson et al., 2004; Genderson et al., 2007). Our findings are also consistent with recent factor analytic results indicating that the structure of separable factors is relatively similar for schizophrenia probands, siblings, and controls (Dickinson et al., 2011).

The findings also extend our understanding of the meaning and significance of endophenotypes in schizophrenia research. First, we noted a distinct difference between neurocognitive and neurophysiological measures. The neurocognitive performance measures cohered well into identifiable cognitive factors, whereas the neurophysiological factors (all considered measures of inhibitory processes), shared relatively little common variance. Only AS and PPI had meaningful loadings on the inhibitory processing factor. P50 gating did not load at an interpretable level on any factor. This pattern indicates that, while all of the neurophysiological measures presumably reflected aspects of inhibition, they may measure distinctly different components of this complex, multifaceted construct. In addition, the loading of AS on 3 of 4 cognitive factors (albeit weakly, <.40) shows that it has stronger associations to higher cognitive functions than the other 'inhibitory' measures. Overall, the identification of five neuropsychologically meaningful endophenotypic factors supports the use of a battery of measures covering a number of domains to effectively index the separable dimensions when examining relationships of cognition to neurobiological substrates and outcome.

These findings extend the literature on endophenotypes by showing that the derived factors are heritable and genetically correlated. While heritability values for the individual measures have been established in a previous COGS-1 report (Greenwood et al., 2007), the current study found novel, separable underlying dimensions that are also significantly heritable. This strategy reduces the likelihood of false positive findings obtained with individual putative endophenotypic measures and strengthens the notion that underlying, identifiable constructs can be used to classify a smaller but meaningful set of heritable endophenotypes. Moreover, it adds to the evidence that these factors do reflect endophenotypes, as the literature on heritability of endophenotypes is relatively modest (Stone and Seidman, in press). The observance of genetic correlations between all factors with the exception of Perceptual Vigilance may reflect a shared cognitive component between the factors that is more prominent in some than others.

It is possible that the FA strategy, by distilling individual measures into core components also reduces some of the "noise" inherent in the measures. If so, this approach might yield increased power of factor-analytic derived measures over individual measures. This finding will be followed up by genomic analyses to determine if these heritable factors have greater power to be associated with specific schizophrenia candidate genes than do individual measures.

4.1. Strengths of the study

Studies of relationships and factors derived from endophenotypes have been much more limited than those evaluating individual constituent measures. This partly reflects the difficulty of obtaining large sample studies of quality assured measures across sites: a barrier overcome by the COGS multi-site strategy (Calkins et al., 2007).

Another important strength of these analyses was that participants had complete data for all measures. While this was necessarily a limited subset of the entire COGS-1 sample (only a subset of subjects had valid data on all measures), the acquisition of a large sample allowed us to choose this option and maintain a sufficient sample for FA. Finally, the complete FA sample represents the best estimate of the true relationship between the measures as these subjects have completed all measures and there was no need for any data imputation.

4.2. Limitations

The major limitation is the loss of subjects due to the requirement of complete data from all measures. This loss was greatest among probands with schizophrenia, and occurred most often on the P50 measure. While combining neurocognitive and neurophysiological measures is a methodological strength, the downside is the greater technical vulnerability of some neurophysiological measures, making it difficult to collect complete data on every measure. Moreover, our decision to conduct FA on the sub-sample with complete data limits the generalizability of the results. Nonetheless, subjects with incomplete data may be those most affected by fatigue during testing, potentially making their available data less reliable than for subjects with complete data. Furthermore, the COGS multi-site strategy still allowed us to have the power to reach novel and reliable findings.

Table 4
Heritability estimates for the five factors in 296 COGS-1 families.

				Covariate *P* values			
Factor	*N*	$h^2_r \pm$ SE	*P* value	Age	Sex	Site	Variance due to covariates
Episodic memory (1)	713	0.22 ± 0.06	<0.0001	<0.0001	0.013	ns	0.18
Working memory (2)	957	0.27 ± 0.06	<0.0001	<0.0001	0.047	0.021	0.15
Perceptual vigilance (3)	885	0.29 ± 0.06	<0.0001	<0.0001	ns	0.032	0.03
Visual abstraction (4)	898	0.39 ± 0.06	<0.0001	<0.0001	<0.0001	ns	0.19
Inhibitory processing (5)	640	0.29 ± 0.07	<0.0001	0.002	0.0001	ns	0.05

Key: h^2_r = residual heritability after adjustment for significant covariates; SE = standard error; variance = the proportion of the variance in the factor explained by all significant covariates.
ns = nonsignificant *p* values (>0.05).

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Table 5
Genetic correlations (ρ_G) observed between the five factors.

	Factor 1—episodic memory	Factor 2—working memory	Factor 3—perceptual vigilance	Factor 4—visual abstraction
Factor 2—working memory	**0.62 ± 0.13***			
Factor 3—perceptual vigilance	0.25 ± 0.17	**0.34 ± 0.15**		
Factor 4—visual abstraction	**0.82 ± 0.08***	**0.49 ± 0.13***	**0.32 ± 0.13**	
Factor 5—inhibitory processing	**0.41 ± 0.16**	0.31 ± 0.17	0.15 ± 0.17	**0.60 ± 0.13***

Significant correlations ($p < 0.05$) are indicated in bold, with those surpassing a conservative Bonferroni correction for multiple comparisons ($p < 0.005$) further indicated with an asterisk.

4.3. Future directions

In considering the original goals associated with a focus on endophenotypes, it is currently the case that identification of endophenotypes has not led to substantial discoveries of new risk genes for schizophrenia. However, this is likely due to the relatively small samples of participants with endophenotypic measures available for genetic analyses. Genetic findings using diagnoses of schizophrenia and most other psychiatric disorders have finally become robust after tens of thousands of subjects became available in the latest analyses (e.g., Ripke et al., 2014). Thus, in order to avoid a Type II error with respect to conclusions about the value of endophenotypes in relation to genetic understanding of schizophrenia, studies with substantially larger samples need to be conducted.

It is also true that multiple genetic approaches utilizing neurocognitive measures may yet improve the understanding of the genetic architecture of schizophrenia. The recently published study by Toulopoulou et al. (2014) is an example of the value of different genetic approaches. The authors in that study suggest that endophenotypes can help in identifying susceptibility genes for schizophrenia. In a large twin study (626 pairs) using reciprocal causation models they reported that "cognitive deficits lie *upstream* of the liability for schizophrenia with about a quarter of the variance in liability to schizophrenia explained by variation in cognitive function." (p.1). This finding for cognition was in contrast with the finding that "brain volume changes lay *downstream* of schizophrenia liability, with 4% of brain volume variation explained directly by variation in liability". (p.1). Their data support the idea that schizophrenia liability is expressed partially through cognitive deficits and they propose that the relevant loci to be discovered will ultimately have a larger effect size on cognitive function than on the diagnosis of schizophrenia. The findings are encouraging from a genetic perspective, they represent non-trivial effects, and the resulting hypotheses can be tested.

Another issue to be addressed is the idea that the factors tend to have lower heritabilities than some of the individual endophenotypes reported previously from our group (Greenwood et al., 2007). It may turn out to be the case that factor scores will be less related to genes than are individual test scores. A related question is how the magnitude of the heritabilities of factors compares to the heritability of schizophrenia. Some new findings from our group shed light on this complex question (Light et al., 2014). They show that heritabilities vary considerably depending on whether they are calculated from twin, population, or family studies. Light et al. (2014) showed that the heritability of schizophrenia was 31% and 44% for nuclear and extended families in our COGS-1 family study, compared to average heritabilities of the endophenotypes of about 30%. Thus, endophenotypes and psychotic disorders manifest fairly comparable heritability in the COGS-1 family sample. The COGS-1 ascertainment of families with discordant sib-pairs to increase endophenotypic contrast appears to yield lower diagnostic heritability relative to other methods that have demonstrated heritabilities of ~81%. Stone and Seidman's (in press) review of neurocognitive endophenotypes in schizophrenia also showed a range of heritabilities depending on the sampling method used. These differing findings lead us to be cautious about concluding that the heritabilities of endophenotypes are lower than expected.

In conclusion, these findings both confirm and extend previous investigations of endophenotypic factors in schizophrenia. Based on the utilization of 15 measures obtained from a well-characterized sample of DSM-IV schizophrenia probands, their siblings, and community comparison subjects, five distinct heritable factors emerged that may have neurobiological, genetic and treatment implications. The five endophenotypic factors may also be valuable as key RDoC cognitive dimensions (Cuthbert and Insel, 2013) that underlie several related psychiatric diagnoses. Replication with the substantially larger COGS-II sample (see Braff, in this issue), with identical measures, will test further the explanatory power of endophenotypes for understanding the genetics of schizophrenia.

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Conflicts of interest

Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen.

Dr. Lazzeroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Nuechterlein has received unrelated research support from Janssen Scientific Affairs, Genentech, and Brain Plasticity, Inc., and has consulted to Genentech, Otsuka, Janssen, and Brain Plasticity, Inc. Dr. Swerdlow has been a consultant for Genco Sciences, Ltd. All other authors declare that they have no conflict of interest.

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