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Consortium on the Genetics of Schizophrenia (COGS) assessment of endophenotypes for schizophrenia: An introduction to this Special Issue of schizophrenia research

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ABSTRACT

Background: The COGS is a multi-site NIMH-sponsored investigation of the genetic basis of 12 primary and multiple secondary quantitative endophenotypes in schizophrenia.

Methods: Since 2003, COGS has completed studies using a family-based ascertainment strategy (COGS-1), and a case-control ascertainment strategy (COGS-2) (cumulative “n” > 4000).

Results: COGS-1 family study confirmed robust deficits in, and heritability of, these endophenotypes in schizophrenia, and provided evidence for a coherent genetic architecture underlying the risk for neurocognitive and neurophysiological deficits in this disorder. COGS-2 case-control findings, many reported herein, establish a foundation for fine genomic mapping and other analyses of these endophenotypes and risk genes for SZ. Several reports in this Special Issue compare findings of endophenotype deficits generated by fundamentally different COGS-1 vs. COGS-2 ascertainment strategies. Despite the expectation that family-based and case-control designs would establish demographically and potentially biologically distinct patient cohorts, findings generally revealed comparable patterns of endophenotype deficits across studies. The COGS-2 case-control design facilitated the accrual of a larger “n”, permitting detailed analyses of factors moderating endophenotype performance. Some COGS-2 endophenotypes not assessed in COGS-1 are also reported, as is a new factor analytic strategy for identifying shared vs. unique factors among the COGS endophenotypes which can be used to develop composite variables with distinct genetic signatures.

Discussion: The path to date of COGS-1 endophenotype and genetic findings, followed by replication and extension in COGS-2, establishes benchmarks for endophenotype deficits in SZ and their moderation by specific factors, and clear expectations for informative findings from upcoming COGS-2 genetic analyses.

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1. Introduction

This Special Issue describes findings from The Consortium on the Genetics of Schizophrenia (COGS)—a multi-site NIMH sponsored-collaboration that investigates the genetic basis of 12 primary and multiple secondary candidate endophenotypes in schizophrenia patients and their relatives (COGS-1). The COGS strategy has been to acquire endophenotype measures across multiple geographically distributed sites to maximize sample ascertainment and hence the power for genetic linkage and association studies (Calkins et al., 2007). COGS-1 findings of robust deficits in endophenotypes in schizophrenia patients have been published (Radant et al., 2007, 2010; Horan et al., 2008; Turetsky et al., 2008; Olincy et al., 2010; Stone et al., 2011), as have reports of significant heritability of these measures (Greenwood et al., 2007; Light et al., 2014), as well as genomic evidence for significant associations and linkage findings with several of the primary endophenotypes and individual genes and a 42-gene network of suspected importance to schizophrenia (Greenwood et al., 2011, 2013). Based on these COGS-1 findings, a second, larger case-control study was initiated (COGS-2), powered for the analysis of moderating factors as well as advanced genomic strategies.

One vexing issue in schizophrenia research, and particularly in studies of its genetic architecture, relates to its heterogeneity, reflected in differences across a variety of domains, including symptoms, functional outcome, neuroimaging and other biomarkers, and family structure. Differences in family structure may be of particular relevance to the search for schizophrenia risk genes. For example, two schizophrenia patients might present with comparable clinical features: Patient 1 might present as part of a narrowly defined intact family structure (at least one unaffected full sibling available for genotyping and endophenotyping, along with parents available at least for genotyping), and Patient 2 might present as an isolated case, without any identifiable family members. These two distinct presentations might suggest different forms of schizophrenia, conceivably with different heritability and genetic architectures. Such differences might also manifest themselves in the nature or magnitude of endophenotypic deficits, since these endophenotypes, by definition, are shaped by the genes that underlie the neurobiological abnormalities that give genesis to the symptoms that define this disorder. For this reason, studies such as COGS-1 that use a family-based strategy for ascertainment of affected probands within a narrowly defined family structure vs. the COGS-2 case-control ascertainment strategy, which ignored family history of schizophrenia, might be expected to result in distinct cohort characteristics and to generate different endophenotypic and, potentially, genetic results. One explicit goal of the COGS has been to test this hypothesized difference in endophenotypic and genetic characteristics of schizophrenia as assessed via family-based vs. case-control ascertainment strategies.

The COGS approach to schizophrenia endophenotypes assumes that endophenotype data can be acquired with high fidelity and reliability across multiple geographically dispersed test sites, and that schizophrenia-related deficits will be comparable across these sites. For several endophenotypes, these assumptions were confirmed in reports published from COGS-1 studies (Horan et al., 2008; Olincy et al., 2010; Radant et al., 2007; Swerdlow et al., 2007; Stone et al., 2011; Turetsky et al. 2008). The COGS-2 case-control design is sufficiently powered to not only confirm these COGS-1 findings, but also to assess across these test sites a number of experimental factors believed—based on the published literature—to moderate these endophenotypes. Published reports suggest that overlapping but not identical factors moderate the several COGS-2 schizophrenia

endophenotypes, but these reports span many different small samples using non-standardized methodologies. The moderation of schizophrenia-linked endophenotypes by a carefully considered list of neurocognitive and neurophysiologically meaningful factors was thus assessed in several reports in this Special Issue, leveraging the statistical power of this large case-control sample. These factors included test site, sex, age, race, antipsychotic use (none, first generation, second generation, or mixed), smoking status and parental education. An interim (“mid-way”) report of another COGS-2 endophenotype—prepulse inhibition (PPI) of acoustic startle—and its moderation by these factors was recently published as a “stand-alone” article in *Schizophrenia Research* (Swerdlow et al., 2014).

Findings from the COGS-1 family-based study confirmed the presence of robust deficits in schizophrenia probands and their first-degree relatives in several different quantitative neurocognitive and neurophysiological measures, including the Letter-Number Span (Horan et al., 2008), the California Verbal Learning Test (Stone et al., 2011), P50 suppression (Olincy et al., 2010), N100 ERP amplitude (Turetsky et al. 2008) and antisaccade performance (Radant et al., 2007, 2010). Significant heritability of these and other schizophrenia endophenotypes was demonstrated (Greenwood et al., 2007; Light et al., 2014), and performance in these measures was shown to be significantly associated with single nucleotide polymorphisms of specific candidate schizophrenia risk genes, many of which contribute to potentially important shared signaling networks (Greenwood et al., 2011). Linkage analyses were suggestive of association for several endophenotypes in regions thought to contain genes that are both physiologically plausible for these endophenotypes and potentially consistent with pathophysiological models for schizophrenia (Greenwood et al., 2013). One important goal of COGS-2 was to use the relative ease (compared to family-based studies) of case-control recruitment to acquire a large sample of carefully characterized schizophrenia and healthy comparison subjects (HCS) across the COGS sites, and to leverage this greater power towards GWAS strategies and fine mapping of chromosomal regions identified in COGS-1 to potentially harbor genes associated with schizophrenia endophenotypes. To date, collection and quality assurance of all COGS-2 endophenotype data have been completed, and genetic materials have been submitted for analysis to the Psychiatric Genetics Consortium (PGC), using the 550 K PGC “PsychChip” platform (Sullivan, 2010).

While criteria for case and control subject inclusion and exclusion for the COGS studies were uniform across the COGS-1 and -2 data collection sites, it is important to note that different endophenotypes are impacted and potentially confounded by different subject characteristics (e.g. auditory sensitivity of ERP measures vs. visual sensitivity of AS measures); as a result, the reports of different endophenotypes in this Special Issue inevitably included different numbers of overlapping but not identical subjects. Measure-specific inclusion criteria and sample characteristics for each of the COGS-1 and COGS-2 measures covered in this Special Issue are described in this overview, and the factor analysis of COGS-1 measures (Seidman et al., 2014-in this issue) necessarily includes a more restricted sample of subjects with valid data across all endophenotypes. Lastly, statistical analyses of several different measures described in this issue can be approached in a variety of ways, using categorical (ANOVA) and continuous (regression) strategies, along with more advanced analytic tools. The prospective decision of the COGS investigators was to apply statistical analyses to each measure in a manner that is consistent with the broader published literature for that measure. In the analysis of moderating factors, given the large sample size of COGS-2, it was important to limit primary

and exploratory analyses to 2-factor interactions, to avoid the analysis and forced interpretation of a large number of statistically significant results of dubious biological importance.

This Special Issue includes an Overview by the COGS Director (D.L. Braff), this Introduction and seven reports that describe novel data from COGS-2, in some instances in conjunction with data from COGS-1 to assess the impact of ascertainment strategy on the endophenotypes, and a report of a factor analysis of COGS-1 measures. Collectively, these reports form an important foundation for interpreting the findings that will emerge from the ongoing COGS genetic analyses.

2. Methods

2.1. Participants

COGS-1 data were collected at 7 sites: University of California at San Diego (UCSD) and Los Angeles (UCLA), University of Colorado (CUHSC), Mount Sinai School of Medicine (MSSM), University of Pennsylvania (PENN), Harvard Medical School (HMS) and University of Washington (UW). Participant selection for all COGS-1 studies has been described in detail in several reports, including a comprehensive overview of COGS-1 procedures and methods (Calkins et al., 2007), and the many COGS-1 studies cited in the accompanying articles in this Special Issue. Thus, COGS-1 methodologies will be described only briefly herein. COGS-2 data collection included five of the 7 COGS-1 sites, with UCHSC and HMS exiting as collection sites. Local institutional review boards of each site approved the COGS-2 study. All endophenotyped participants were 18–65 years old, able to understand and provide informed consent and were compensated for their participation.

In the family-based COGS-1 design, diagnoses were established via the Diagnostic Interview for Genetics Studies (DIGS) (Nurnberger et al., 1994), the Family Interview for Genetic Studies (FIGS) (NIMH, 1992), and a Best-Estimate Final Diagnosis (BEFD) procedure based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia. Criteria for family eligibility included: 1) a proband met DSM-IV criteria for schizophrenia based on BEFD procedures, 2) both biological parents were available for genotyping, and 3) ≥ 1 full sibling unaffected with schizophrenia was available for endophenotyping and genotyping. First-degree biological relatives included parents and siblings of the proband. Proband having only one available parent but 2 or more available siblings (≥ 1 unaffected by schizophrenia) were also included, as were probands having no available parents but 3 or more available siblings (≥ 1 unaffected by schizophrenia). Multigenerational families were included when an additional relative (e.g., nephew or child of the proband) met criteria for schizophrenia, and the proband had living parents and at least one unaffected sibling available.

COGS-1 exclusion criteria are seen in Table 1. Families that included only a proband with schizoaffective disorder (either bipolar or depressed subtype) were not included. Additionally, families with evidence of “parental bilineality” or no “contrast” in sibships (all sibs have a diagnosis of schizophrenia) were not included. For subjects who met eligibility requirements, all available first-degree family members completed diagnostic and most endophenotype testing. HCS also participated in all components of testing, including diagnostic and endophenotype assessment. To parallel psychiatric comorbidity in relatives of probands, nonpsychotic axis I psychopathology was accepted in approximately 30% of HCS, but clinical stability and/or remission was required.

Table 1
Exclusion criteria for COGS-1 and COGS-2.

| Exclusion criterion | All participants | COGS-1 | | COGS-2 | |
|---|------------------|---------|-----|---------|-----|
| | | Proband | HCS | Patient | HCS |
| Does not meet family inclusion criteria (see text) | X | | | | |
| Does not meet diagnostic criteria for SZ | | X | | | |
| Does not meet diagnostic criteria for SZ or schizoaffective disorder, depressed type | | X | | X | |
| Adopted or family history unknown | X | | | | X |
| Outside study age range of 18–65 | X | | | X | X |
| Unable to understand consent due to language or competency | X | | | X | X |
| Physically unable to participate in testing of at least one endophenotype | X | | | | |
| Physically unable to participate in testing of at least two endophenotypes | | | | X | X |
| Previous endophenotype testing in the last 1 mo | X | | | X | X |
| Previous neuropsychological testing in the last 3 mo | X | | | X | X |
| Positive illicit drug or alcohol screen at the time of testing | | X | X | X | X |
| Severe systemic illness that interferes with ability to be endophenotyped | X | | | X | X |
| Parents not living (unless sibship is large) or unavailable for genotyping | | X | | | |
| Both parents diagnosed with SZ | | X | | | |
| Siblings unavailable for endophenotyping and genotyping | | X | | | |
| All siblings diagnosed with SZ | | X | | | |
| Electroconvulsive treatment in the last 6 mo | | X | X | X | X |
| Alcohol or substance abuse in the past 1 mo | | X | X | X | X |
| Alcohol or substance dependence not in remission for 6 mo | | X | X | X | X |
| Significant head injury (loss of consciousness > 15 min and/or neurological sequelae) | | X | X | X | X |
| Neurological illness (e.g., seizures, stroke, Parkinson disease) | | X | X | X | X |
| Less than one 1 month psychiatrically stable | | X | X | | |
| Estimated premorbid IQ < 70 per Wide Range Achievement Test-Third Edition | | X | X | X | X |
| History of psychosis in themselves or a family member (1st or 2nd degree) | | | X | | |
| History of psychosis in themselves or a family member (1st degree) | | | | | X |
| Current Axis I mood disorder | | | | | X |
| Cluster A personality disorder | | | X | | X |
| Current treatment with antipsychotic agents | | | X | | X |
| Current treatment with any psychoactive medication | | | | | X |
| Participated in COGS-1 testing | | | | X | X |
| First-degree relative who has already participated in this study | | | | X | X |

2.2. Assessments

Diagnoses in COGS-2 were established by a modified version of the Structural Clinical Interview for DSM-IV (SCID) (First et al., 1995, 1996) with additional items from the DIGS and FIGS. All COGS-2 patients met DSM-IV criteria for schizophrenia or schizoaffective disorder, depressed type. HCS were included if they had 1) no current or past psychotic disorder, 2) a known (identifiable) biological family history, 3) no history of psychosis in a 1st degree relative, 4) no current Axis I mood disorder, 5) no Cluster-A Axis II disorder, and 6) no current regular treatment with psychoactive medication. Exclusion criteria for all COGS-2 participants are seen in Table 1.

In addition to diagnostic assessments, COGS-1 and COGS-2 participants received clinical assessments and endophenotype measurements, seen in Table 2. Assessments were generally divided over two days for COGS-1, while for COGS-2, assessments and testing for HCS often were completed in a single day. This was not uniformly the case, and at some sites, COGS-1 endophenotype testing was split over two days, and COGS-2 HCS assessments were sometimes divided over two days. COGS-1 endophenotype testing was completed in one of two orders, roughly balanced across groups, to assess any impact of test order on endophenotype measures. Some minor variations in test order were introduced among COGS-1 sites that completed CNB testing on day 1, vs.

Table 2
Diagnostic and clinical instruments and endophenotype measures in COGS-1 and COGS-2.

| COGS-1 | COGS-2 | |
|--------------------------------|---------------------------------------|---|
| Day 1—clinical assessment | Day 1—clinical assessment | |
| Probands, Relatives, HCS | Patients | HCS |
| DIGS (including SANS/SAPS) | SCID I/P w/additional items from DIGS | SCID I/NP w/additional items from DIGS |
| FIGS | FIGS and pedigree analysis | FIGS and pedigree analysis |
| BPRS | MMSE | MMSE |
| GAF | GAF | GAF |
| Day 2—endophenotype assessment | | SANS/SAPS-modified version from the DIGS |
| Test order A | Test order B | SOF |
| P50 | CVLT | RFS |
| AS | DS-CPT | UPSA-B |
| PPI | LNS | Day 2—endophenotype assessment |
| Break | CPT-IP | PPI |
| SANS/SAPS | PENN CNB | AS |
| PENN CNB | SANS/SAPS | CPT-IP |
| CPT-IP | Break | CPT-DS |
| LNS | PPI | LNS |
| CVLT | AS | CVLT |
| DS-CPT | P50 | PENN CNB |
| | | Event-related potentials: mismatch negativity (MMN), P300 |

Abbreviations:

| | |
|-----------|--|
| DIGS: | Diagnostic Interview for Genetics Studies |
| FIGS: | Family Interview for Genetic Studies. |
| BPRS: | Brief Psychiatric Rating Scale—Expanded, Anxiety Scale |
| MMSE: | Mini-Mental State Exam |
| GAF: | Global Assessment of Functioning Scale |
| SANS: | Scale for the Assessment of Negative Symptoms |
| SAPS: | Scale for the Assessment of Positive Symptoms |
| SOF: | Scale of Functioning |
| RFS: | Role Functioning Scale |
| UPSA-B: | UCSD Performance-based Skills Assessment—Brief |
| AS: | Antisaccade measurements |
| P50: | P50 event-related potentials suppression |
| PENN CNB: | U. Pennsylvania Computerized Neurocognitive Battery |
| LNS: | Letter—number span test. |
| CVLT: | California Verbal Learning Test, Version II |
| CPT: | Continuous performance task (DS = degraded stimulus version; IP = identical pairs version) |

others that included the CNB in day 2. Based on some potentially confounding COGS-1 order effects (Light et al., 2007), COGS-2 testing utilized a relatively fixed, single order, though even this order had some minor variations across sites; for example, some COGS-2 sites completed the UCSD Performance-based Skills Assessment (UPSA-B; Patterson et al., 2001) testing during day 1, while others did so during day 2. Nonetheless, Table 2 shows the “modal” division of testing across days, and order of testing within days, that held for the vast majority of COGS subjects.

All COGS-1 endophenotype measures except P50 event-related potential gating (P50 gating) were included in COGS-2, using COGS-1 equipment, test parameters, analytic strategies and QA procedures (Calkins et al., 2007). One COGS-1 endophenotype was modified slightly to enhance its sensitivity (Continuous Performance Task (CPT)) and two new neurophysiological endophenotypes (mismatch negativity (MMN) and P300 amplitude) were added to COGS-2.

2.3. Data management and analyses

Methods for COGS-1 data flow are described in detail in Calkins et al. (2007) and the associated COGS-1 reports, and were substantially repeated for COGS-2. Specific statistical approaches to each endophenotype differed, in order to conform to the general statistical strategies used in the published literature for each measure. A unique attribute of COGS, and particularly COGS-2, is the sample sizes of the schizophrenia vs. HCS comparisons for each endophenotype; while large samples are common among the many genomic studies of the “fuzzy” DSM-defined entity of schizophrenia, the COGS samples provide a definitive assessment of multiple quantitative laboratory-based schizophrenia endophenotypes. From an analytic standpoint, this uniquely high-powered endophenotype database presented both opportunities and challenges. For example, subgroups of patients that would generally be quite small in single-site studies (e.g. schizophrenia patients taking no antipsychotics) were sufficiently large to allow meaningful analyses of many different potentially important factors that moderate endophenotype expression in schizophrenia cohorts. For some endophenotypes, these robust analyses of moderating factors might be important if not unique additions to the literature. Even with this large sample, however, there were some variables for which cell sizes remained small, and in these cases, a consensus was reached to limit the number of separate subgroups to those with samples adequate to support meaningful contrasts.

Another statistical implication of a large study sample with several potentially important moderating factors (Table 3) is that levels of statistical significance identified via analyses of variance or similar strategies might be highly dependent on the number of factors entered into the analyses, and the number of levels of interactions that are explored among these factors. The generic approach to this analytic challenge for COGS studies within any given endophenotype was to limit analyses to pair-wise contrasts with diagnosis, unless specific a priori hypotheses justified otherwise. In addition to the moderating factors shown in Table 3, exploratory analyses of clinical and demographic independent variables to endophenotype performance were pursued where appropriate. Comparisons across endophenotypes (e.g. the relationship of performance on endophenotypes A to B, e.g. AS to MMN) were generally limited to two types: 1) relationship of specific neurocognitive to neurophysiological measures; and 2) an omnibus factor analytic approach across all COGS-1 endophenotypes, which is the focus of the report by Seidman et al. (2014-in this issue).

3. Sample characteristics

Sample characteristics divided by test site in COGS-1 and COGS-2 HCS, COGS-1 schizophrenia probands and COGS-2 schizophrenia patients, are seen in Tables 4A and 4B, for all subjects who generated valid data for at least one endophenotype.

Table 3
Putative moderating factors in analyses of COGS endophenotypes.

| Factor | Example of putative moderating impact | Reference |
|------------------------|--|------------------------|
| Test site | COGS-1 site differences in CVLT performance | Stone et al. (2011) |
| Age | Significant reduction in MMN amplitude with increasing age | Kiang et al. (2009) |
| Sex | Superior immediate recall in women vs. men on CVLT | Ragland et al. (2000) |
| Antipsychotic (AP) use | "Normalized" PPI with 2nd generation AP use in COGS-2 SZ patients | Swerdlow et al. (2014) |
| Smoking status | Nicotine reduces AS errors in SZ patients | Rycroft et al. (2006) |
| Parental education | Significantly greater CNB performance with higher levels of parental education | Gur et al. (2001) |

Based on these data, some general observations are possible regarding the overall COGS samples. First, COGS-1 probands were younger than COGS-2 schizophrenia patients; this is true across the full study samples (COGS-1 vs. COGS-2), and was also evident for each of the 5 sites that tested subjects in both studies (all p 's < 0.0001). Second, COGS-1 probands were more educated than COGS-2 patients, and the same is true of their respective parents (all p 's < 0.0001). Third, while there was some variability across sites, overall sex distributions for both COGS-1 probands and COGS-2 patients strongly favored males, and this was significantly more marked in COGS-2 vs. COGS-1 (Chi-square = 5.61, p < 0.02); by contrast, among HCS, women were more heavily represented compared to men in both COGS-1 and COGS-2 samples. Fourth, antipsychotic (AP) use differed slightly between studies, with COGS-1 probands less likely than COGS-2 patients to receive no antipsychotics (3.6% vs. 8.6%; Chi-square = 9.36, p < 0.003), though the clear majority of affected individuals in both studies received 2nd generation antipsychotics (89.8% vs. 83.7%). In general, these findings support the prediction that different ascertainment strategies might identify patients with different characteristics.

For some factors, including age, sex and race, differences in COGS-1 vs. COGS-2 cohorts were site-specific. For example: at UCLA, HCS were older in COGS-2 vs. COGS-1; at UW, HCS were more likely to be female in COGS-1 vs. COGS-2; and at PENN, COGS-2 patients were more likely than COGS-1 probands to be African American. In COGS-2, African Americans were significantly more represented among East Coast sites (PENN, MSSM) than West Coast sites (UCSD, UCLA and UW); PENN and MSSM also had the greatest representation of African American probands among COGS-1 sites. Other subtle differences in sample characteristics across sites and studies are seen in Tables 4A and 4B, but a global assessment of these data suggests far more similarities than differences across studies and sites in terms of the characteristics of HCS, as well as those of affected subjects.

Table 4A
COGS-1 and COGS-2 HCS characteristics across test sites (mean (SD)).

| Test site | UCSD | UCLA | UW | PENN | MSSM | Harvard | Colorado |
|--------------------------|------------------|------------------|-----------------|------------------|------------------|---------------|-----------------|
| COGS-1 HCS (N) | 81 | 71 | 72 | 72 | 76 | 62 | 73 |
| COGS-2 HCS (N) | 222 | 217 | 219 | 207 | 196 | | |
| COGS-1 M:F | 26:55 | 36:35 | 27:45 | 36:36 | 36:40 | 30:32 | 28:45 |
| COGS-2 M:F | 95:127 | 131:86 | 109:110 | 97:110 | 89:107 | | |
| COGS-1 Age (y) | 42.8 (12.8) | 33.7 (9.4) | 32.5 (12.6) | 36.7 (12.1) | 38.1 (13.8) | 37.8 (14.3) | 31.0 (9.3) |
| COGS-2 Age (y) | 40.2 (12.8) | 46.5 (8.2) | 37.1 (14.7) | 32.7 (12.4) | 35.6 (12.4) | | |
| COGS-1 Race (%) | 64.2: 11.1: 24.7 | 52.1: 21.1: 26.8 | 75.0: 6.9: 18.1 | 48.6: 31.9: 19.4 | 42.1: 21.1: 36.8 | 74.2: 0: 25.8 | 74.0: 6.8: 19.2 |
| Cauc: AA: Other | | | | | | | |
| COGS-2 Race (%) | 50.5: 17.1: 32.4 | 61.3: 25.8: 12.9 | 71.7: 7.8: 20.5 | 52.2: 34.8: 13.0 | 46.9: 34.7: 18.4 | | |
| Cauc: AA: Other | | | | | | | |
| COGS-1 Smokers | 90.1: 9.9 | 87.3: 12.7 | 88.9: 11.1 | 84.7: 15.3 | 82.9: 17.1 | 83.9: 16.1 | 86.3: 13.7 |
| %Never: Now | | | | | | | |
| COGS-2 Smokers | 79.7: 10.4: 9.9 | 82.9: 3.7: 13.4 | 87.7: 0.0: 12.3 | 91.8: 0.0: 8.2 | 87.8: 0.5: 11.7 | | |
| %Never: Past: Now | | | | | | | |
| COGS-2 # cigs/day | 7.0 (6.2) | 9.9 (6.4) | 6.9 (5.4) | 7.3 (6.1) | 8.1 (7.2) | | |
| COGS-1 Educ'n (y) | 14.9 (2.2) | 14.8 (2.1) | 15.5 (2.4) | 15.3 (2.6) | 15.4 (2.3) | 15.3 (3.0) | 16.4 (1.6) |
| COGS-2 Educ'n (y) | 14.8 (2.1) | 14.8 (1.7) | 15.1 (2.4) | 14.8 (2.3) | 15.5 (2.4) | | |
| COGS-1 Father Educ'n (y) | 13.8 (3.0) | 14.4 (3.6) | 15.1 (3.2) | 13.8 (3.8) | 13.3 (4.4) | 13.9 (3.5) | 15.9 (3.4) |
| COGS-2 Father Educ'n (y) | 13.7 (3.7) | 13.5 (3.2) | 14.3 (3.4) | 14.6 (3.2) | 14.4 (3.5) | | |
| COGS-1 Mother Educ'n (y) | 13.2 (2.5) | 14.0 (3.2) | 14.8 (2.3) | 13.9 (3.1) | 13.3 (3.5) | 14.0 (2.9) | 15.2 (2.5) |
| COGS-2 Mother Educ'n (y) | 13.3 (3.2) | 13.4 (2.8) | 14.3 (3.4) | 14.1 (2.9) | 14.5 (3.4) | | |

4. Summary of endophenotype findings

Detailed findings with specific COGS-1 and COGS-2 endophenotypes are found in the accompanying manuscripts in this Special Issue. A brief summary of these findings is found in Table 5.

Overall, moderate-to-large effect size deficits in all primary endophenotypes were detected in COGS-2 patients; the general patterns of deficits were comparable across COGS-1 and COGS-2 studies.

5. Discussion

The COGS platform has obtained high fidelity and reliable endophenotypic data from a definitively large number of individuals with schizophrenia as well as HCS, using two different ascertainment strategies: the COGS-1 family-based design and the COGS-2 case-control design. Differences in age, sex distribution, education, parental education, IQ and antipsychotic use were detected across these two studies. Despite these differences, what is most notable in the comparisons across studies is the substantial degree of similarity in the schizophrenia-based deficits in endophenotype performance between COGS-1 and COGS-2 schizophrenia participants. While the relative magnitude of specific deficits varied across measures and ascertainment strategies, each performance deficit detected in one ascertainment strategy was paralleled by a deficit in the same measure in the other ascertainment strategy. Thus, despite any a priori expectations based on assumptions of the subject characteristics identified by different ascertainment strategies, or the impact of testing patients with more intact family structures vs. putatively more isolated individual patients, the general profile of neurocognitive and neurophysiological deficits detected with family-based vs. case-control COGS ascertainment designs was strikingly similar. This result is generally consistent with Gottesman's conceptualization of endophenotypes as being

Table 4B
COGS-1 proband and COGS-2 patient characteristics across test sites (mean (SD)).

| Test site | UCSD | UCLA | UW | PENN | MSSM | Harvard | Colorado |
|--------------------------|----------------------|---------------------|----------------------|------------------------|---------------------|-------------------|---------------------|
| COGS-1 Prob (N) | 47 | 52 | 52 | 45 | 48 | 47 | 51 |
| COGS-2 Pts (N) | 355 | 263 | 249 | 273 | 270 | | |
| COGS-1 M:F | 31:16 | 38:14 | 40:12 | 31:14 | 33:15 | 42:5 | 44:7 |
| COGS-2 M:F | 239:116 | 193:70 | 192:57 | 172:101 | 180:90 | | |
| COGS-1 Age (y) | 36.3 (11.8) | 34.3 (10.5) | 35.5 (10.3) | 33.4 (11.2) | 36.9 (12.2) | 32.8 (10.7) | 36.1 (11.3) |
| COGS-2 Age (y) | 46.6 (11.0) | 48.6 (10.5) | 46.3 (11.8) | 44.1 (11.3) | 45.9 (10.2) | | |
| COGS-1 Race (%) | 66.0: 4.3: 29.8 | 61.5: 3.8: 34.6 | 78.8: 0: 21.2 | 64.4: 20.0: 15.6 | 41.7: 16.7: 41.7 | 78.7: 0: 21.3 | 76.5: 2.0: 21.6 |
| Cauc: AA: Other | | | | | | | |
| COGS-2 Race (%) | 54.6: 18.3: 27.0 | 46.0: 38.4: 15.6 | 53.0: 22.1: 4.9 | 24.9: 67.0: 8.1 | 37.0: 55.2: 7.8 | | |
| Cauc: AA: Other | | | | | | | |
| COGS-1 Smokers | 51.1: 48.9 | 48.1: 51.9 | 51.9: 48.1 | 55.6: 44.4 | 55.3: 44.7 | 48.9: 51.1 | 64.0: 36.0 |
| % Never:Now | | | | | | | |
| COGS-2 Smokers | 30.7: 11.8: 57.5 | 39.2: 6.5: 54.4 | 57.8: 0.4: 41.8 | 47.3: 0.4: 52.4 | 39.3: 4.1: 56.7 | | |
| % Never:Past:Now | | | | | | | |
| COGS-2 # cigs/day | 15.0 (10.1) | 16.3 (9.9) | 11.3 (6.8) | 13.5 (9.5) | 11.2 (7.8) | | |
| COGS-1 Educ'n (y) | 13.0 (2.0) | 13.7 (1.9) | 13.1 (1.8) | 14.1 (2.1) | 13.8 (2.2) | 12.9 (2.0) | 13.6 (2.4) |
| COGS-2 Educ'n (y) | 12.3 (2.0) | 12.9 (1.9) | 13.2 (1.9) | 12.5 (2.3) | 11.9 (2.1) | | |
| COGS-1 Father Educ'n (y) | 15.4 (3.3) | 15.0 (4.2) | 14.9 (3.7) | 15.2 (3.1) | 13.8 (4.5) | 14.8 (2.9) | 15.9 (3.5) |
| COGS-2 Father Educ'n (y) | 12.9 (3.3) | 12.4 (4.1) | 13.1 (3.5) | 12.6 (3.7) | 11.8 (3.0) | | |
| COGS-1 Mother Educ'n (y) | 14.6 (3.3) | 13.9 (3.6) | 14.5 (3.6) | 14.5 (2.5) | 14.2 (3.8) | 14.5 (3.2) | 15.1 (2.4) |
| COGS-2 Mother Educ'n (y) | 12.4 (3.2) | 12.3 (3.5) | 12.7 (2.8) | 12.7 (3.2) | 11.9 (3.3) | | |
| AP's COGS-1 (%) | 10.9: 4.3: 78.3: 6.5 | 1.9: 9.6: 88.5: 0 | 2: 3.9: 78.4: 15.7 | 2.2: 6.7: 82.2: 8.9 | 0: 17: 68.1: 14.9 | 0: 2.2: 91.1: 6.7 | 8.7: 2.2: 80.4: 8.7 |
| None: 1st: 2nd: both | | | | | | | |
| AP's COGS-2 (%) | 9.0: 4.8: 72.4: 13.8 | 5.5: 7.0: 80.1: 7.4 | 14.5: 7.2: 70.7: 7.6 | 10.3: 11.4: 66.2: 12.1 | 3.3: 9.4: 82.4: 4.9 | | |
| None: 1st: 2nd: both | | | | | | | |

independent of variations in state-related symptom profiles (Gottesman and Gould, 2003).

Among the measures acquired uniquely from COGS-2 case-control participants, schizophrenia patients exhibited at least medium-to-large effect-size deficits in CPT performance, and in the amplitude of MMN, P3a and P300 event related potentials. While we cannot compare these findings vs. results obtained with these measures in a family-based study, the magnitudes of these COGS-2 deficits match or exceed those reported in smaller, single-site studies reported in the literature. In a recent report in *Schizophrenia Research*, we described deficits in another schizophrenia endophenotype—prepulse inhibition of acoustic startle (PPI)—in over 1400 subjects from the COGS-2 sample (Swerdlow et al., 2014). The PPI deficits detected in this COGS-2 sample reproduced those reported in many previous studies of PPI in

schizophrenia, and exhibited the expected characteristic sensitivity to prepulse intervals (most robust deficits in cases elicited by prepulses with 60 ms intervals) and antipsychotic use (deficits most robust in unmedicated patients and “normalized” by 2nd generation APs).

As studies designed specifically to identify genes conferring risk for schizophrenia, COGS-1 and COGS-2 are not designed to draw definitive conclusions regarding other aspects of endophenotype performance in schizophrenia. For example, several of reports in this Special Issue describe the complex issue of antipsychotic medication effects on quantitative endophenotype scores in the COGS-1 and COGS-2 samples. Most generally, a subject's antipsychotic medication status can be stratified into several different levels, e.g. 1. not taking antipsychotics; 2. taking first generation antipsychotics; 3. taking second generation antipsychotics; and 4. taking both first and second generation

Table 5
Summary of endophenotype findings.

| Authors | Putative endophenotype | Primary dependent measure(s) | Study, sample size (affected: HCS) | Effect size difference ^a , affected subjects vs. HCS | Associations/significant moderating factors ^b |
|---------------------|------------------------|---|---|---|--|
| Gur et al. | CNB | Performance accuracy Performance speed | COGS-1, 328: 497 COGS-2, 1195: 1009 | COGS-1, 0.2–0.89 COGS-2, 0.5–1.17 | COGS-1: Age, parental education, symptoms, functioning COGS-2: Age, parental education, symptoms, functioning |
| Stone et al. | CVLT-II | Trials 1–5 free recall total correct | COGS-1, 324: 510 COGS-2, 1356: 1036 | COGS-1, 1.10 COGS-2, 0.93 | COGS-1: Site, age, gender, WRAT-3 reading COGS-2: Site, age, gender, parental education, smoking, medications |
| Radant et al. | AS | % correct | COGS-1, 285: 495 COGS-2, 996: 906 | COGS-1, 1.06 COGS-2, 1.01 | COGS-1: Site, age, gender COGS-2: Site, age, gender |
| Lee et al. | LNS | LNS Reorder, # correct | COGS-1, 149: 190 COGS-2, 1377: 1037 | COGS-1, 0.94 COGS-2, 1.08 | COGS-2: Medications, smoking |
| Nuechterlein et al. | CPT | DS-CPT d' CPT-IP 3-digit d' CPT-IP 4-digit d' | COGS-2, 1140: 972 COGS-2, 1190: 999 COGS-2, 1152: 986 | 0.57 1.13 1.14 | MMSE score, education, functional capacity, substance history, smoking |
| Light et al. | MMN | MMN amplitude, P3a amplitude | COGS-2, 877: 753 | MMN: 0.96 P3a: 0.93 | Medications, smoking, clinical and functional status |
| Turetsky et al. | P300 | P300 amplitude | COGS-2, 587: 649 | 0.62 | Positive symptoms, race, smoking status, substance history |

Abbreviations: CNB: Penn Computerized Neurocognitive Battery; CVLT-II: California Verbal Learning Test (second edition); WRAT-3: Wide Range Achievement Test 3; AS: antisaccade task; LNS: Letter-Number Span; CPT: Continuous Performance Task; d': signal/noise discrimination; DS-CPT: Degraded Stimulus CPT; CPT-IP: Identical Pairs CPT; MMSE: Mini-Mental State Examination score; MMN: Mismatch Negativity; P300: P300 event related potential amplitude; P3a: amplitude of the P3a component of the P300.

^a Cohen's *d*, for simple main effects of diagnosis on primary dependent measure, using raw data unadjusted for moderating factors or interactions with other variables. See individual papers for detailed descriptions of adjusted analyses.

^b See individual papers for specific effects of moderating variables on endophenotype performance

antipsychotics. The algorithm for using this information in the interpretation of endophenotype performance is complicated by many factors, not the least of which is the fact that self-reports of antipsychotic use are notoriously inaccurate (Lieberman et al., 2005). Both COGS-1 and COGS-2 studies have cross-sectional designs, and the antipsychotic regimen at the time of COGS testing for any given patient reflects a complex, often non-biologically-based and geographically-specific rationale. For example, schizophrenia patients may not take antipsychotics based on their mild level of their symptoms, or their sensitivity to adverse effects of antipsychotics, or their limited access to mental health treatment, or their non-adherence to prescribed regimens. Some cross-sectional studies demonstrate endophenotype deficits in schizophrenia patients who are not taking antipsychotics, and that these deficits are reduced or not present among patients taking second generation antipsychotics (including studies from COGS (Swerdlow et al., 2014)); in these instances, it is parsimonious to conclude that the observed deficit likely reflects a process closely linked to schizophrenia rather than antipsychotics per se. However, this pattern is not always observed, and in some cases, endophenotype deficits among COGS cohorts in this Special Issue are least pronounced among antipsychotic-free patients, and most pronounced among patients taking antipsychotics. The cause–effect explanation for this latter pattern of findings is simply not discernible based exclusively on findings from the COGS cross-sectional study designs. In some instances, data from prior longitudinal, randomized controlled trials indicates that antipsychotics reduce these same endophenotype deficits, making it very unlikely that the smaller deficits in antipsychotic-free patients in COGS are due to causal antipsychotic effects. Thus, each paper in this Special Issue has relevant data on this topic of antipsychotic associations with quantitative schizophrenia endophenotypes, but definitive explanations for the observed patterns will depend on prospective studies of drug effects with more complex cross-over or randomized, parallel-group longitudinal designs.

The cumulative experience of the COGS project on endophenotypes and schizophrenia to date confirms that with careful attention to standardization of methods and equipment, quality assurance oversight and centralized data processing, it is possible to harness the testing capacity and access to schizophrenia patients afforded by the use of multiple, geographically dispersed sites, and to collect high-fidelity and reliable measures of highly heritable endophenotype deficits in schizophrenia patients. The COGS-2 endophenotype findings suggest that it will now be possible to engage the larger COGS-2 sample, facilitated by a case–control design, to attempt GWAS and fine-mapping of genetic loci responsible for these deficits. This large cohort also allows for analytic strategies that employ endophenotype ranking and cumulative endophenotype loading, as well as gene burden analyses. While this approach has not yet been applied to COGS-2 data, the Seidman et al. findings (2014-in this issue) suggest that potent signals for identifying the genetic underpinning of heritable neurocognitive and neurophysiological deficits in schizophrenia may come from the identification of a factor structure that reflects shared, genetically informative neurobiological processes.

The overarching rationale behind the COGS studies reflects the expectation that genes associated with deficits in specific, quantifiable domains of function (e.g. working memory) or processes with known or suspected neural substrates (e.g. sensorimotor gating) should be more readily connected to underlying biological mechanisms, compared to genes associated with the more complex and “fuzzy” clinical phenotype of schizophrenia per se. This expectation is supported by COGS-1 findings, in which many of the genes showing strongest associations with the endophenotypes shared overlapping biological mechanisms (e.g. glutamate signaling) and showed significant pleiotropic associations with multiple endophenotypes (Greenwood et al., 2011). Past efforts to understanding the genetics of schizophrenia have yielded many failures to replicate findings, based perhaps on the difficult-to-standardize clinical phenotype of the schizophrenia diagnosis, but also

on the use of different ascertainment strategies and variance introduced by factors such as age, sex, race, antipsychotic use, smoking and education. In this Special Issue of *Schizophrenia Research*, we describe our large-scale efforts to examine the potential impact of ascertainment strategies and moderating factors on rigorously standardized, quantitative endophenotype performance in the COGS-1 and COGS-2 samples. Ultimately, the full value of the COGS approach to identifying the genomic variation associated with endophenotype deficits in schizophrenia will be realized if knowledge of these genes and/or their related networks contributes in a meaningful way to our understanding of the pathophysiology or therapeutics of schizophrenia, including its antecedent risks and our ability to predict its course and treatment sensitivity.

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Contributors

Dr. Swerdlow wrote the first draft of this manuscript. Drs. Gur and Braff provided valuable edits to the manuscript. Each of the authors played a leadership role in the organization and operation of the COGS for both COGS-1 and COGS-2 studies.

Conflict of interest

Drs. Braff and Gur report no financial relationships with commercial interests. Dr. Swerdlow has been a paid Consultant for Genco Sciences, Inc.

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