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Genome-wide Association of Endophenotypes for Schizophrenia From the Consortium on the Genetics of Schizophrenia (COGS) Study

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IMPORTANCE The Consortium on the Genetics of Schizophrenia (COGS) uses quantitative neurophysiological and neurocognitive endophenotypes with demonstrated deficits in schizophrenia as a platform from which to explore the underlying neural circuitry and genetic architecture. Many of these endophenotypes are associated with poor functional outcome in schizophrenia. Some are also endorsed as potential treatment targets by the US Food and Drug Administration.

OBJECTIVE To build on prior assessments of heritability, association, and linkage in the COGS phase 1 (COGS-1) families by reporting a genome-wide association study (GWAS) of 11 schizophrenia-related endophenotypes in the independent phase 2 (COGS-2) cohort of patients with schizophrenia and healthy comparison participants (HCPs).

DESIGN, SETTING, AND PARTICIPANTS A total of 1789 patients with schizophrenia and HCPs of self-reported European or Latino ancestry were recruited through a collaborative effort across the COGS sites and genotyped using the PsychChip. Standard quality control filters were applied, and more than 6.2 million variants with a genotyping call rate of greater than 0.99 were available after imputation. Association was performed for data sets stratified by diagnosis and ancestry using linear regression and adjusting for age, sex, and 5 principal components, with results combined through weighted meta-analysis. Data for COGS-1 were collected from January 6, 2003, to August 6, 2008; data for COGS-2, from June 30, 2010, to February 14, 2014. Data were analyzed from October 28, 2016, to May 4, 2018.

MAIN OUTCOMES AND MEASURES A genome-wide association study was performed to evaluate association for 11 neurophysiological and neurocognitive endophenotypes targeting key domains of schizophrenia related to inhibition, attention, vigilance, learning, working memory, executive function, episodic memory, and social cognition.

RESULTS The final sample of 1533 participants included 861 male participants (56.2%), and the mean (SD) age was 41.8 (13.6) years. In total, 7 genome-wide significant regions ($P < 5 \times 10^{-8}$) and 2 nearly significant regions ($P < 9 \times 10^{-8}$) containing several genes of interest, including *NRG3* and *HCN1*, were identified for 7 endophenotypes. For each of the 11 endophenotypes, enrichment analyses performed at the level of $P < 10^{-4}$ compared favorably with previous association results in the COGS-1 families and showed extensive overlap with regions identified for schizophrenia diagnosis.

CONCLUSIONS AND RELEVANCE These analyses identified several genomic regions of interest that require further exploration and validation. These data seem to demonstrate the utility of endophenotypes for resolving the genetic architecture of schizophrenia and characterizing the underlying biological dysfunctions. Understanding the molecular basis of these endophenotypes may help to identify novel treatment targets and pave the way for precision-based medicine in schizophrenia and related psychotic disorders.

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Schizophrenia is a severe and persistent psychotic disorder with a prevalence of approximately 1% and a heritability of as much as 80%.¹ Large-scale genome-wide association studies (GWAS) using a case-control design have detected many common variants that collectively account for as much as 7% of risk for schizophrenia.² Several of the implicated genes are consistent with leading hypotheses regarding pathophysiology, such as *DRD2* (OMIM 126450), the target of most effective antipsychotics, and genes involved in glutamate signaling (eg, *GRM3* [OMIM, 601115], *GRIN2A* [OMIM, 138253], and *GRIAI* [OMIM, 138248]). The identification of the complement component 4 gene (*C4* [OMIM, 120810]) within the major histocompatibility complex region and its relation to synaptic pruning is particularly intriguing.³ However, most of the genetic risk for schizophrenia remains unexplained, and the pathways by which the implicated variants contribute to the clinically observable signs and symptoms are largely unknown to date.

To achieve large samples for GWAS, clinically diverse patients are typically grouped together by diagnosis, ignoring the broad range of deficits associated with schizophrenia and possibly obscuring salient genetic signals. As stable biomarkers of the underlying brain dysfunctions, endophenotypes hold promise for parsing the clinical heterogeneity of schizophrenia and refining the genetic signal.⁴ Because endophenotypes provide laboratory-based measures of specific neurobiological functions with characteristic impairment in schizophrenia (eg, inhibition, memory, and executive function), they are less subjective than the clinical symptoms used for diagnosis. As quantitative measures of genetic liability to schizophrenia, endophenotypes provide increased efficiency and as much as a 10-fold increase in power compared with comparably sized case-control studies.^{5,6} Endophenotypes are also amenable to the use of animal models and neuroimaging in humans to facilitate direct investigations of underlying neurobiological processes.^{7,8} Finally, many neurocognitive endophenotypes are associated with poor real-world functioning and have been endorsed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative and the US Food and Drug Administration as targets for the development of new treatments in schizophrenia.⁹ For example, targeted cognitive training has been shown to improve verbal memory in patients with schizophrenia, with a resultant increase in real-world functioning.¹⁰ The endophenotype strategy thus complements large-scale genomic investigations of diagnosis and provides important neurobiological context.

The Consortium on the Genetics of Schizophrenia (COGS)¹¹ has previously reported the significant heritability of 11 neurophysiological and neurocognitive endophenotypes related to dysfunction across key domains, including aspects of inhibition, attention, learning, episodic and working memory, executive function, complex cognition, and social cognition. Such endophenotypes are intrinsic to the clinical presentation of schizophrenia, with clear deficits observed in patients with schizophrenia compared with healthy comparison participants (HCPs) and intermediate values observed for unaffected first-degree relatives.¹¹⁻¹⁶ Candidate gene association and

Key Points

Question Can a genome-wide association study of neurophysiological and neurocognitive endophenotypes identify genes related to the underlying molecular dysfunctions in schizophrenia?

Findings A total of 7 regions exceeding a conventional genome-wide significance threshold ($P < 5 \times 10^{-8}$) were associated with various endophenotype deficits, and the genes within these regions largely implicate glutamate and axonal dysfunctions as well as other neurobiologically salient targets. Many regions of interest were identified, including 39 previously associated with a schizophrenia diagnosis.

Meaning These results suggest that the use of quantitative endophenotypes in genomic studies may provide an important, strong inference-based strategy for understanding the molecular basis of schizophrenia and may suggest novel treatment targets.

linkage analyses of the COGS phase 1 (COGS-1) families implicated a network of genes related to neuregulin and glutamate signaling pathways and synaptic plasticity as underlying endophenotype deficits in schizophrenia,¹⁷⁻¹⁹ consistent with the findings of other studies evaluating common, rare, and de novo variation in relation to a schizophrenia diagnosis.^{2,20,21} Herein we report the initial findings from the GWAS of these endophenotypes in the independent phase 2 (COGS-2) cohort of patients with schizophrenia and HCPs, which confirm and extend previous results and show consistency with studies of schizophrenia diagnosis in large samples.

Methods

Participants

Recruitment for the COGS study was conducted in 2 phases and reflects a carefully coordinated effort across multiple academic sites with standardized methods for diagnostic evaluation and endophenotype testing.²² The COGS-2 sample of 726 unrelated patients with schizophrenia and 667 HCPs of self-reported European or admixed European ancestry was collected through recruitment at the University of California, San Diego; UCLA (University of California, Los Angeles); Icahn School of Medicine at Mount Sinai, New York, New York; University of Pennsylvania, Philadelphia; and University of Washington, Seattle. We also included a sample of 396 HCPs of self-reported European ancestry collected as an adjunct to the COGS-1 family sample, which additionally involved recruitment at the University of Colorado Health Sciences Center, Denver, and Harvard University, Boston, Massachusetts. All participants underwent standardized psychiatric interviews using the Structured Clinical Interview for *DSM-IV* to obtain consensus diagnoses.²³ All patients with schizophrenia met criteria for schizophrenia, and HCPs were excluded for psychosis, bipolar disorder, current depression, alcohol and/or substance abuse, or a first-degree relative with a history of psychosis. Participants ranged from 18 to 65 years of age and received urine toxicology screens before assessment. The HCPs were matched as a group to the patients with schizophrenia

on age, sex, ancestry, and parental educational attainment. Written informed consent was obtained for each participant after a detailed description of study participation. This study was approved by the local institutional review board at each COGS site.

Data for COGS-1 were collected from January 6, 2003, to August 6, 2008; data for COGS-2, from June 30, 2010, to February 14, 2014. Detailed descriptions of the rationale and assessment procedures for the 11 endophenotypes have been previously published.^{24,25} Prepulse inhibition of the startle response at 60 milliseconds was used to evaluate inhibition. The proportion correct on the antisaccade task was used to evaluate oculomotor inhibition and directed attention. The degraded stimulus version of the Continuous Performance Test signal/noise discrimination was used to measure perceptual-load vigilance. Total correct responses on the California Verbal Learning Test, trials 1 to 5, and correct reordering on the Letter-Number Span were used as measures of learning and working memory, respectively. The University of Pennsylvania Computerized Neurocognitive Battery included tests of abstraction and mental flexibility, face memory, spatial memory, spatial processing, sensorimotor dexterity, and emotion recognition to measure functioning across additional cognitive domains, including executive function, episodic memory, complex cognition, and social cognition. All endophenotype data underwent a rigorous quality assurance process before analysis. The correlations between the endophenotypes are presented in the eTable in [Supplement 1](#).

Genotyping

The 1789 participants were genotyped using the PsychChip, which was developed by the Psychiatric Genomics Consortium and contains a 240 000 genome-wide marker grid, 240 000 exome markers, and 50 000 custom content markers for psychiatric illness. Genotype calls from AutoCall, Birdseed, and zCall algorithms were merged to form a single consensus file. Using the Psychiatric Genomics Consortium RICOPILI (Rapid Imputation and Computational Pipeline; <https://github.com/Ripkelab/ricopili>), standard quality control filters were applied to remove 41 participants with poor genotype call rates (<0.98). An additional 27 participants were removed for sex discrepancies, sampling error, or relatedness. Single-nucleotide polymorphisms (SNPs) were removed for low minor allele frequency (<0.01), poor genotype call rates (<0.98), and deviation from Hardy-Weinberg equilibrium among HCPs ($P < 10^{-6}$). Ancestry was confirmed via comparison with the 1000 Genomes Project Consortium phase 3 and Human Genome Diversity Project reference populations.^{26,27} After the removal of 188 population outliers, the largest ancestral groups included participants of European (523 patients with schizophrenia and 506 HCPs from COGS-2 and 321 HCPs from COGS-1; $>95\%$ European) and Latino (100 patients with schizophrenia and 83 HCPs from COGS-2; approximately 60% European and 30% Native American and $>90\%$ European and Native American combined) ancestry. Genotype data were imputed to the 1000 Genomes Project Consortium phase 3 reference panel,²⁶ and a second round of quality control filters was applied as above to generate a

final data set consisting of 1533 participants (623 patients with schizophrenia and 910 HCPs) and more than 6.2 million variants with a genotyping call rate of greater than 0.99.

Statistical Analysis

Data were analyzed from October 28, 2016, to May 4, 2018. The final data set was stratified by study (COGS-1 or COGS-2), case status (SZ case or HCP), and ancestry (European or Latino) for analysis. Principal components were calculated for each data set separately to correct for residual population stratification and genotype pool discrepancies. Association was performed using linear regression in PLINK, adjusting for age, sex, and the first 5 principal components, with a λ of less than 1.1 observed for each data set.²⁸ Results were combined across data sets using weighted meta-analysis to adjust for sample size.²⁹ Quantile-quantile plots for each analysis are provided in the eFigure in [Supplement 1](#).

The combined sample has 80% power to detect a single variant accounting for 2.5% of the variance in a given endophenotype at the standard genome-wide significance threshold of $P < 5 \times 10^{-8}$. To the extent that the endophenotypes follow a polygenic model influenced by common variation, we expect that the same alleles contributing to endophenotype deficits in schizophrenia when aggregated in high density also influence endophenotype variation in the general population. As such, the inclusion of HCPs provides greater phenotypic range and increased power to detect associated variants, whereas the inclusion of patients with schizophrenia provides the appropriate context for the analyses. GWAS are intended to be hypothesis generating, yet a stringent statistical threshold designed to eliminate all false-positive results at a certain probability necessarily comes at the expense of an increased false-negative rate, obscuring any true associations that might fail to reach genome-wide significance. Indeed, several studies have demonstrated that subthreshold GWAS findings ($P < 10^{-4}$) are enriched for SNPs that regulate gene expression.^{30,31} We have thus used an additional threshold of $P < 10^{-4}$ to generate a broader set of SNPs potentially enriched for true associations, allowing for the exploration of patterns across endophenotypes and facilitating cross-study comparisons. A complete listing of SNPs exceeding the $P < 10^{-4}$ threshold for each endophenotype is provided in [Supplement 2](#).

Results

We included a total of 1533 participants (672 women [43.8%] and 861 men [56.2%]; mean [SD] age, 41.8 [13.6] years). Seven regions exceeding a conventional genome-wide significance threshold of $P < 5 \times 10^{-8}$ were identified, along with 2 regions nearly reaching genome-wide significance, as shown in [Figure 1](#) and detailed in [Table 1](#). The antisaccade task produced a significant peak ($P = 3.5 \times 10^{-8}$) on chromosome 9q31 within an olfactory gene family region and a nearly significant peak ($P = 5.3 \times 10^{-8}$) on chromosome 12p13 that spanned the cation-dependent *PHCI* (OMIM 602978) and *M6PR* (OMIM 154540) genes. The Continuous Performance Test produced

Figure 1. Results of the Genome-wide Association Analyses of 11 Endophenotypes for Schizophrenia

Significance is indicated on the y-axis as the $-\log(P)$. A total of 7 regions exceeded the conventional genome-wide significance threshold of $P < 5 \times 10^{-8}$ (red line) with 2 additional regions nearly reaching significance ($P < 9 \times 10^{-8}$). The blue line indicates $P = 1 \times 10^{-5}$. The University of Pennsylvania Computerized Neurocognitive Battery consisted of the following tests:

abstraction and mental flexibility (ABF), emotional recognition (EMO), face memory (FMEM), sensorimotor dexterity (SM), spatial memory (SMEM), and spatial processing (SPA). AS indicates antisaccade task; CVLT, California Verbal Learning Test; DSCPT, degraded stimulus Continuous Performance Test; LNS, Letter-Number Span; and PPI, prepulse inhibition of the startle response.

a significant peak on chromosome 5p15 near the *BASPI* gene (OMIM 605940). Multiple associations were also observed for the Computerized Neurocognitive Battery measures. Abstraction and mental flexibility produced a significant ($P = 1.5 \times 10^{-8}$)

on chromosome 10q23 near the *NRG3* gene (OMIM 605533). Face memory produced a significant peak ($P = 4.2 \times 10^{-8}$) on chromosome 3p21 in the *KIF15* gene (OMIM 617569). Spatial processing produced significant peaks on chromosome 14q11

Table 1. Summary of Significantly Associated Regions

Endophenotype	Chromosome	Position ^a	Lead SNP in Region	Effect Size (95% CI) ^b	P Value for Meta-analysis ^c	P Value for EA ^c	Nearest Gene	Genes Within 100 kb
Face memory	3p21	44813350 to 44874489	rs73076581	-0.72 (-1.00 to -0.45)	4.2 × 10 ⁻⁸	4.2 × 10 ⁻⁸	KIF15	ZNF502, ZNF501, TMEM42, TGM4
Continuous Performance Test	5p15	17439886 to 17443654	rs7706512	0.21 (0.14 to 0.28)	2.5 × 10 ⁻⁸	1.2 × 10 ⁻⁶	BASP1	None
Spatial memory	5p12	44791335 to 45215941	rs187763903	-0.72 (-0.98 to -0.47)	8.3 × 10 ⁻⁸	6.8 × 10 ⁻⁶	HCN1	None
Sensorimotor dexterity	9q21	72488418	rs140830767	-1.11 (-1.58 to -0.64)	4.0 × 10 ⁻⁸	3.3 × 10 ⁻⁶	C9orf135	None
Antisaccade task	9q31	107334694 to 107499546	rs77038697	-0.24 (-0.31 to -0.16)	3.5 × 10 ⁻⁸	3.5 × 10 ⁻⁸	OR13C9	OR13C4, OR13C3, OR13C8, OR13C5, OR13C2, OR13D1, NIPSP3A
Abstraction and mental flexibility	10q23	85685084 to 85719133	rs11200733	-0.56 (-0.20 to -0.07)	1.5 × 10 ⁻⁸	6.1 × 10 ⁻⁸	NRG3	None
Antisaccade task	12p13	9082391 to 9135281	rs117302528	-0.20 (-0.28 to -0.13)	5.4 × 10 ⁻⁸	3.7 × 10 ⁻⁷	PHC1	A2ML1, M6PR, KLRG1
Spatial processing	14q11	23364106 to 23473706	rs45543740	-0.62 (-0.82 to -0.41)	1.7 × 10 ⁻⁸	5.8 × 10 ⁻⁸	AJUBA	REM2, RBM23, PRMT5, HAUS4, PSMB5, PSMB11, ACIN1
Spatial processing	19q12	44813350 to 44874489	rs4805491	-0.46 (-0.61 to -0.31)	3.8 × 10 ⁻⁸	6.0 × 10 ⁻⁷	CCNE1	URI1

Abbreviations: EA, European ancestry; SNP, single-nucleotide polymorphism.

^a Indicates hg19 region spanned by SNPs tagged by the lead SNP. The boundaries of each gene are expanded by 20 kb on each side to capture putative regulatory elements.

^b Calculated from the lead SNP from the meta-analysis and the corresponding lower and upper bounds, respectively, of the 95% CI.

^c Indicates *P* value of lead SNP.

in the *AJUBA* gene (OMIM 609066; $P = 1.7 \times 10^{-8}$) and chromosome 19q12 near the *CCNE1* gene (OMIM 123837; $P = 3.8 \times 10^{-8}$). Spatial memory produced a nearly significant peak ($P = 8.3 \times 10^{-8}$) on chromosome 5p12 near the *HCN1* gene (OMIM 602780). Sensorimotor dexterity produced a significant association ($P = 4.0 \times 10^{-8}$) with the *C9orf135* gene (HGNC 31422) on chromosome 9q21.

In total, 1070 independent regions of association were identified at an enrichment threshold of $P < 10^{-4}$, including 128 regions of shared association across 2 or more endophenotypes. These regions are summarized in Supplement 2 and include the major histocompatibility complex region on chromosome 6, as well as several other candidate genes and regions previously identified for schizophrenia diagnosis. Of the 108 regions previously identified for schizophrenia diagnosis by the Psychiatric Genomics Consortium Schizophrenia Working Group, 39 were associated with 1 or more COGS endophenotypes, as shown in Table 2.² In addition, as shown in Figure 2, most genes in the previously reported gene network defined through linkage and association studies of the COGS-1 families were at least nominally significant ($P < .01$) in the independent COGS-2 GWAS of patients with schizophrenia and HCPs, including all 8 genes that were found to be pleiotropic across multiple endophenotypes.¹⁷

Discussion

These initial GWAS of neurophysiological and neurocognitive deficits in schizophrenia have identified promising associations for multiple genomic regions and genes involved in critical neurodevelopmental processes. At an enrichment threshold, we found support for the gene network identified

through candidate gene association and linkage studies of the COGS-1 families.¹⁷⁻¹⁹ In addition to implicating glutamate dysfunction in schizophrenia, many of the genes in this network and those newly identified through GWAS of these endophenotypes form part of the *DISC1* (OMIM 605210) regulome for which rare, disruptive variants have been associated with schizophrenia and low cognitive ability in childhood.³² Such convergence at the pathway level may be more likely to be observed and more meaningful than concordance at the level of an individual gene or SNP in illuminating the underlying neurobiological dysfunction in schizophrenia. Finally, 39 of the genomic regions associated in this study of schizophrenia-related endophenotypes overlap with the 108 regions previously identified by the Psychiatric Genomics Consortium study of schizophrenia diagnosis and may be helpful in refining the association signal.²

By and large, the regions meeting genome-wide significance harbor genes that appear to play a role in key cellular and neurodevelopmental processes and have previously shown association with schizophrenia and related disorders, such as bipolar disorder, autism spectrum disorder, and intellectual dysfunction. For example, the chromosome 9q31 region found to be significantly associated with oculomotor antisaccade dysfunction has previously been implicated in a linkage analysis of psychotic bipolar disorder (log of odds, 3.55),³³ and de novo chromosomal abnormalities in this region have been observed in patients with schizophrenia.^{34,35} The associated SNPs are located within a region containing several genes from the olfactory receptor family 13, subfamily C. Olfactory dysfunction has been observed in schizophrenia and may even serve as an early warning or prodromal sign of schizophrenia onset.³⁶ The antisaccade task also produced a nearly significant association to chromosome 12p13 in the *PHC1* gene, which func-

Table 2. Regions of Association Overlap Between the COGS Endophenotypes and Schizophrenia Diagnosis^a

PGC Region	Peak PGC P Value	Gene	Endophenotype Association
Chromosome 1: 2372401 to 2402501	8.7×10^{-10}	<i>PLCH2</i> ^b	PPI (rs114330159, $P = 2.5 \times 10^{-5}$) ^c ; LNS (rs12744097, $P = 3.0 \times 10^{-5}$)
Chromosome 1: 97792625 to 98559084	3.4×10^{-19}	<i>DPYD</i> , ^b <i>MIR137</i>	FMEM (rs1520668, $P = 7.4 \times 10^{-6}$) ^d ; EMO (rs78891607, $P = 5.2 \times 10^{-5}$)
Chromosome 1: 243503719 to 244002945	3.7×10^{-9}	<i>AKT3</i> , ^e <i>SDCCAG8</i>	AS (rs55777167, $P = 3.2 \times 10^{-6}$) ^d
Chromosome 2: 185601420 to 185785420	1.5×10^{-12}	<i>ZNF804A</i> ^b	AS (rs151076669, $P = 5.2 \times 10^{-5}$)
Chromosome 2: 225334096 to 225467796	1.1×10^{-8}	<i>CUL3</i> ^b	SM (rs140109470, $P = 5.5 \times 10^{-7}$)
Chromosome 3: 2532786 to 2561686	2.7×10^{-11}	<i>CNTN4</i> ^b	SM (rs11129200, $P = 2.0 \times 10^{-6}$); PPI (rs146541530, $P = 9.1 \times 10^{-5}$) ^b
Chromosome 3: 52541105 to 52903405	4.3×10^{-11}	<i>NISCH</i> , <i>STAB1</i> , <i>NTSDC2</i> , <i>SMIM4</i> , <i>PBRM1</i> , ^e <i>GNL3</i> , ^e <i>GLT8D1</i> , ^e <i>SPCS</i> , ^e <i>NEK4</i> , ^b <i>ITIH1</i> , ^e <i>ITIH3</i> , ^e <i>ITIH4</i> , ^e <i>MUSTN1</i> , ^e <i>TMEM110</i> ^e	EMO (rs34184137, $P = 4.0 \times 10^{-5}$)
Chromosome 4: 103146888 to 103198090	8.0×10^{-15}	<i>SLC39A8</i> ^b	CVLT (rs192068, $P = 9.8 \times 10^{-5}$)
Chromosome 4: 176851001 to 176875801	9.5×10^{-9}	<i>GPM6A</i> ^b	SM (rs114201782, $P = 6.9 \times 10^{-7}$) ^b
Chromosome 5: 45291475 to 45393775	5.1×10^{-9}	<i>HCN1</i> ^e	SMEM (rs187763903, $P = 8.3 \times 10^{-8}$); SM (rs73917002, $P = 4.0 \times 10^{-5}$)
Chromosome 5: 88581331 to 88854331	4.6×10^{-9}	<i>MEF2C</i> ^{c,e}	SPA (rs114097435, $P = 4.7 \times 10^{-5}$) ^b
Chromosome 5: 137598121 to 137948092	4.7×10^{-9}	<i>GFRA3</i> , <i>CDC25C</i> , <i>FAM53C</i> , <i>KDM3B</i> , ^e <i>REEP2</i> , ^e <i>EGR1</i> , ^e <i>ETF1</i> , ^b <i>HSPA9</i> , ^e <i>CTNNA1</i>	CVLT (rs154067, $P = 4.3 \times 10^{-6}$)
Chromosome 5: 140023664 to 140222664	4.9×10^{-8}	<i>CD14</i> , ^b <i>TMC06</i> , ^e <i>NDUFA2</i> , ^e <i>IK</i> , ^e <i>WDR55</i> , ^e <i>DND1</i> , ^e <i>HARS</i> , ^e <i>HARS2</i> , ^e <i>ZMAT2</i> , ^e <i>PCDHA1-10</i>	SPA (rs12659563, $P = 7.8 \times 10^{-5}$)
Chromosome 5: 151941104 to 152797656	1.1×10^{-10}	<i>GRIA1</i> ^{c,e}	FMEM (rs177521, 4.5×10^{-5})
Chromosome 6: 73132701 to 73171901	2.7×10^{-8}	<i>RIMS1</i> ^b	AS (rs10665509, $P = 8.0 \times 10^{-5}$)
Chromosome 6: 84279922 to 84407274	8.2×10^{-10}	<i>SNAP91</i> ^b	FMEM (rs1171121, $P = 9.4 \times 10^{-6}$); SMEM (rs583637, $P = 2.9 \times 10^{-5}$)
Chromosome 6: 96459651 to 96459651	1.6×10^{-9}	<i>FUT9</i> ^b	SM (rs4240598, $P = 9.6 \times 10^{-6}$); EMO (rs9399876, $P = 5.0 \times 10^{-5}$)
Chromosome 7: 1896096 to 2190096	8.2×10^{-15}	<i>MAD1L1</i> ^b	AS (rs6969832, $P = 1.5 \times 10^{-5}$)
Chromosome 7: 24619494 to 24832094	2.9×10^{-8}	<i>MPP6</i> , <i>DFNA5</i> , <i>OSBPL3</i> ^b	SMEM (rs2391082, $P = 1.9 \times 10^{-5}$)
Chromosome 7: 110034393 to 111205915	3.0×10^{-13}	<i>IMMP2L</i> ^{b,f}	FMEM (rs35648000, $P = 7.4 \times 10^{-5}$)
Chromosome 8: 4177794 to 4192544	1.1×10^{-8}	<i>CSMD1</i> ^b	CVLT (rs2688282, $P = 8.2 \times 10^{-5}$) ^d ; ABF (rs17066292, $P = 3.6 \times 10^{-5}$); SMEM (rs72507671, $P = 6.1 \times 10^{-6}$); EMO (rs10081576, $P = 7.9 \times 10^{-5}$)
Chromosome 8: 89340626 to 89753626	1.2×10^{-8}	<i>MMP16</i> ^e	LNS (rs78075875, $P = 8.1 \times 10^{-5}$)
Chromosome 9: 84630941 to 84813641	3.6×10^{-9}	<i>TLE1</i> ^b	SM (rs149799159, $P = 5.3 \times 10^{-5}$)
Chromosome 10: 18681005 to 18770105	2.0×10^{-12}	<i>CACNB2</i> ^e	AS (rs11012693, $P = 5.0 \times 10^{-6}$)
Chromosome 11: 46342943 to 46751213	1.3×10^{-11}	<i>CREB3L1</i> , ^e <i>DGKZ</i> , ^e <i>MDK</i> , ^e <i>CHRM4</i> , ^b <i>AMBRA1</i> , ^e <i>HARBI1</i> , <i>ATG13</i> , <i>ARHGAP1</i> <i>ZNF408</i> , <i>F2</i> , <i>CKAP5</i>	SMEM (rs61882689, $P = 8.3 \times 10^{-5}$)
Chromosome 11: 133808069 to 133852969	3.9×10^{-11}	<i>IGSF9B</i> ^e	FMEM (rs117439990, $P = 6.9 \times 10^{-5}$)
Chromosome 12: 2321860 to 2523731	3.2×10^{-18}	<i>CACNA1C</i> ^b	SM (rs7956107, $P = 1.9 \times 10^{-6}$)
Chromosome 12: 92243186 to 92258286	4.6×10^{-8}	<i>C12orf79</i> ^{b,f}	SM (rs78503948, $P = 9.3 \times 10^{-5}$) ^d
Chromosome 12: 103559855 to 103616655	4.8×10^{-8}	<i>C12orf42</i> ^e	LNS (rs11838301, $P = 9.3 \times 10^{-5}$)
Chromosome 14: 30189985 to 30190316	1.4×10^{-8}	<i>PRKD1</i> ^b	CVLT (rs45525431, 6.3×10^{-6}); SPA (rs138940224, $P = 9.1 \times 10^{-6}$)
Chromosome 14: 72417326 to 72450526	4.9×10^{-9}	<i>RGS6</i> ^b	ABF (rs2108709, $P = 1.8 \times 10^{-5}$)

(continued)

Table 2. Regions of Association Overlap Between the COGS Endophenotypes and Schizophrenia Diagnosis^a (continued)

PGC Region	Peak PGC P Value	Gene	Endophenotype Association
Chromosome 15: 70573672 to 70628872	1.8×10^{-8}	<i>TLE3</i> ^e	AS (rs35122286, $P = 5.8 \times 10^{-5}$)
Chromosome 15: 78803032 to 78926732	2.4×10^{-13}	<i>IREB2</i> , ^b <i>AGPHD1</i> , ^e <i>PSMA4</i> , ^e <i>CHRNA5</i> , ^e <i>CHRNA3</i> , <i>CHRNA4</i>	EMO (rs117028191, $P = 5.6 \times 10^{-6}$)
Chromosome 16: 9875519 to 9970219	1.3×10^{-18}	<i>GRIN2A</i> ^b	AS (rs4782090, $P = 5.3 \times 10^{-5}$)
Chromosome 16: 29924377 to 30144877	4.6×10^{-11}	<i>SEZ6L2</i> , ^e <i>ASPHD1</i> , ^e <i>KCTD13</i> , ^e <i>TMEM219</i> , ^e <i>TAOK2</i> , ^b <i>HIRIP3</i> , ^e <i>INO80E</i> , ^e <i>DOC2A</i> , ^e <i>C16orf92</i> , ^e <i>FAM57B</i> , ^e <i>ALDOA</i> , ^e <i>PPP4C</i> , ^e <i>TBX6</i> , ^e <i>YPEL3</i> , <i>GDPD3</i> , <i>MAPK3</i>	SM (rs10445105, $P = 9.1 \times 10^{-5}$)
Chromosome 19: 19374022 to 19658022	3.6×10^{-10}	<i>NCAN</i> , ^e <i>HAPLN4</i> , ^e <i>TM6SF2</i> , ^e <i>SUGP1</i> , ^b <i>MAU2</i> , ^e <i>GATAD2A</i> , ^e <i>TSSK6</i> , <i>NDUFA13</i> , <i>CILP2</i> , <i>PBX4</i>	SPA (rs78844461, $P = 9.9 \times 10^{-5}$)
Chromosome 19: 50067499 to 50135399	4.7×10^{-8}	<i>RCN3</i> , ^b <i>NOSIP</i> , ^e <i>PRRG2</i> , ^e <i>PRR12</i> , ^e <i>RRAS</i> , <i>SCAF1</i>	ABF (rs148832708, $P = 1.0 \times 10^{-5}$) ^d
Chromosome 20: 37361494 to 37485994	1.5×10^{-11}	<i>SLC32A1</i> , ^e <i>ACTR5</i> , ^b <i>PPP1R16B</i> ^e	PPI (rs111764110, $P = 8.5 \times 10^{-5}$); SPA (chromosome 20: 37254033, $P = 5.3 \times 10^{-5}$) ^g
Chromosome 22: 42315744 to 42689414	1.7×10^{-9}	<i>SREBF2</i> , <i>TNFRSF13C</i> , <i>SHISA8</i> , <i>CENPM</i> , <i>SEPT3</i> , ^e <i>WBP2NL</i> , ^e <i>NAGA</i> , ^e <i>FAM109B</i> , ^e <i>SMDT1</i> , ^e <i>NDUFA6</i> , ^e <i>CYP2D6</i> , ^e <i>TCF20</i> ^b	AS (rs11703217, $P = 3.0 \times 10^{-6}$)

Abbreviations: ABF, abstraction and mental flexibility; AS, antisaccade task; COGS, Consortium on the Genetics of Schizophrenia; CVLT, California Verbal Learning Test; EMO, emotion recognition; FMEM, face memory; LNS, Letter-Number Span; PGC, Psychiatric Genomics Consortium; PPI, prepulse inhibition of the startle response; SM, sensorimotor dexterity; SMEM, spatial memory; SNP, single-nucleotide polymorphism; SPA, spatial processing.

^a For a subset of the 108 regions associated with schizophrenia diagnosis in the most current data set from the Psychiatric Genomics Consortium Schizophrenia Work Group, the peak *P* value and regional coordinates are indicated as originally reported, along with all genes within 100 kb, arranged according to genomic position.² For each COGS endophenotype meeting the enrichment threshold of $P < 1 \times 10^{-4}$, the lead SNP and corresponding *P* value

are listed.

^b Indicates gene within 20 kb of a COGS lead SNP.

^c The association is within 100 kb of the gene.

^d Association of the indicated endophenotype to this region derives from a single SNP with $P < 1 \times 10^{-4}$.

^e Indicates gene within 100 kb of a COGS lead SNP.

^f PGC-SCZ2-associated region lists the nearest gene within 500 kb although the endophenotype association is more proximate.

^g The association is within 100 kb of the *ACTR5* gene.

tions in early neurodevelopment and is associated with microcephaly.³⁷ *M6PR*, located 10 kb downstream of the lead SNP in this region, plays a critical role in lysosome function and is associated with neuronal ceroid lipofuscinosis, for which vision loss is an early sign.^{38,39} The Continuous Performance Test, a measure of vigilance, produced a significant peak on chromosome 5p15 near *BASPI*, which is involved in neuronal axon growth and guidance and has previously been identified in a GWAS of mood-incongruent psychotic symptoms in bipolar disorder.⁴⁰ A long history of findings implicate neurodevelopmental axon formation dysfunction in schizophrenia,⁴¹⁻⁴³ and bipolar disorder shows substantial clinical and genetic overlap with schizophrenia as part of the psychosis dimension.^{44,45} Face memory produced a significant peak on chromosome 3p21 in *KIF15*, which colocalizes in dendrites and growth cones of axons with microtubules and is differentially expressed in fetal vs mature astrocytes.⁴⁶ *KIF15* is also a target of microRNA miR-192-5p, which has been shown to be downregulated in schizophrenia.⁴⁷

Spatial processing produced a significant association to 14q11 within the *AJUBA* gene, which encodes a scaffold protein that is expressed in the cerebellum, cortex, hippocampus, and retina. *AJUBA* interacts with *SLC1A2* (OMIM 600300), a candidate gene for schizophrenia, and plays a role in the regulation of microRNA-mediated gene silencing.⁴⁸ Spatial processing also produced a significant association to *CCNE1* on 19q12, which is part of the *DISC1* regulome and has been shown to be upregulated in schizophrenia.^{32,49} Sensorimotor dexter-

ity produced a significant peak on chromosome 9q21 in *C9orf135*, which is associated with cognitive function.⁵⁰ However, this association derived from a single SNP and requires further validation.

Abstraction and mental flexibility produced a significant peak on chromosome 10q23 near *NRG3*, which influences neuroblast proliferation, migration, and differentiation by signaling through *ERBB4* (OMIM 600543). Many studies have implicated *NRG3* as a susceptibility locus for schizophrenia.⁵¹⁻⁵⁴ Specifically, genetic variants of *NRG3* are associated with cognitive and psychotic symptom severity in schizophrenia and may result from differential prefrontal cortical expression of the gene.^{51,55,56} Finally, *NRG3* knockout mice exhibit behaviors that are consistent with psychotic disorders in humans.⁵⁷ These data are consistent with prior reports of association for *NRG1* and *ERBB4*, suggesting that pathogenic variation in the ErbB-neuregulin pathway may underlie cognitive functioning and risk for psychosis.^{17,19,54,58-60}

Spatial memory produced a nearly significant peak on 5p12 near *HNCN1*, which is highly expressed in the frontal cortex and regulates neuronal excitability, rhythmic activity, and synaptic plasticity. Several lines of evidence in human and animal studies have suggested that hyperpolarization-activated cyclic nucleotide-gated (HCN) channels may play a role in psychiatric and neurological disorders. Common variation in *HNCN1* is associated with schizophrenia and educational attainment, and rare inherited and de novo variants are associated with a broad phenotypic spectrum that includes neonatal epi-

Figure 2. Interaction Network of Genes Identified for the 11 Endophenotypes Through Association and Linkage Analysis of the Consortium on the Genetics of Schizophrenia (COGS) Samples

Genes are represented as nodes with solid lines representing direct protein-protein interactions and dashed arrows representing more indirect effects on expression, activation, or inhibition. Genes and interactions in black revealed association (blue box) or linkage (red box) with 1 or more endophenotypes, whereas those in gray represent other interacting genes. Those with pleiotropic associations to at least 4 endophenotypes in the COGS families are shown in bold. Genes with additional evidence of association in the genome-wide association study (GWAS) of the independent cases with

schizophrenia and healthy comparison participants are indicated in green, with a solid box representing genes meeting the enrichment threshold of $P < 1 \times 10^{-4}$ and a dashed box representing nominal significance ($P < .01$). C indicates genes identified as associated with a schizophrenia diagnosis through GWAS of common variants; R, those identified by studies of rare and de novo variation. *CTNNA2*, *CSMD1*, and *ZNF804A* were prominent genes in these analyses with external support from studies of schizophrenia diagnosis but do not directly connect into the defined network.

leptic encephalopathy, generalized seizures, intellectual disability, and autistic spectrum disorders.^{2,61-63} Interestingly, spatial memory also produced an association with *SHANK3* (OMIM 606230), an interacting partner of *HCN1*, mutations of which have similarly been shown to predispose to autism.⁶⁴ Sensorimotor dexterity revealed an association with another HCN channel, *HCN2* (OMIM 602781). Studies suggest that a reduction of HCN function through knockout of *HCN1* or *HCN2* in the dorsal hippocampus induces antidepressant behaviors in rodents, suggesting a potential treatment target for depression.^{65,66} Of particular relevance to the observed association in this study, studies of *HCN1* knockouts have revealed a role for this gene in spatial learning and memory.^{67,68} An imbalance of *HCN1* and *HCN2* expression in the hippocampal CA1 area is also associated with impairments in spatial learning and memory associated with drug abuse.⁶⁹

Strengths and Limitations

Although shared genetic substrates appear likely, this is not a study of schizophrenia but rather a study of neurophysiological and neurocognitive deficits that occur in the general population but are more pronounced in the context of schizophrenia and have implications for treatment.⁷⁰ In addition, although

our sample may appear modest by current case-control GWAS standards, it is suitable for the identification of genomic substrates underlying deficits in quantitative schizophrenia-related endophenotypes, which are labor intensive to acquire but provide increased efficiency compared with case-control designs.^{5,6} Future analyses of the complete COGS sample and other ongoing collaborations designed to increase power will provide opportunities to gain additional mechanistic insight into schizophrenia. GWAS of the COGS-1 families and the COGS-2 patients with schizophrenia and HCPs of African ancestry may allow us to replicate and extend these initial results as well as increase power for enrichment analyses. Sequencing of the COGS-1 families is pending completion to allow for an assessment of common vs rare variation in relation to family history, endophenotype deficit load, and clinical severity.⁷¹

The question of when and how to adjust for multiple tests remains challenging. In recent years, GWAS have converged toward use of $P < 5 \times 10^{-8}$ as a default threshold for genome-wide significance to facilitate comparisons across studies and avoid the alternative in which each study selects its own correction from a possible multitude of complex algorithms that increase opportunities for “p-hacking,” that is, choosing which analytical strategy to report based on the significance of the resulting *P* values.

We have similarly used this threshold to account for the multiple testing of SNPs, although no correction was made for the multiple testing of endophenotypes, because each represents a distinct subject of scientific inquiry in numerous independent studies and publications. Although we believe the GWAS of each endophenotype has intrinsic interest of its own and could be published separately, we have opted to combine these results into a single report to allow for patterns of association to emerge. Also, as we previously demonstrated, *P* values are so highly variable that even under ideal circumstances, an initial $P < 5 \times 10^{-8}$ can vary from 2×10^{-16} to .007 in an identical replication study, even without considering multiple testing issues.^{72,73} This observation holds true for other thresholds, suggesting that any significance threshold is somewhat arbitrary and cannot eliminate the possibility of false-positive and/or false-negative findings.

Conclusions

Although some important considerations exist for interpretation of these findings, the present study has identified neurobiologically relevant genomic substrates for key neurophysiological and neurocognitive deficits in schizophrenia, reinforcing the goals of endophenotype-based projects.^{74,75} As many of the 11 endophenotypes have been endorsed as targets for the development of novel treatments for schizophrenia, a better understanding of the corresponding cellular and molecular processes may pave the way for precision-based medicine in schizophrenia and perhaps other psychiatric illnesses with a shared genetic liability.

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