Original Investigation

Variability in Working Memory Performance Explained by Epistasis vs Polygenic Scores in the *ZNF804A* Pathway

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IMPORTANCE We investigated the variation in neuropsychological function explained by risk alleles at the psychosis susceptibility gene *ZNF804A* and its interacting partners using single nucleotide polymorphisms (SNPs), polygenic scores, and epistatic analyses. Of particular importance was the relative contribution of the polygenic score vs epistasis in variation explained.

OBJECTIVES To (1) assess the association between SNPs in *ZNF804A* and the *ZNF804A* polygenic score with measures of cognition in cases with psychosis and (2) assess whether epistasis within the *ZNF804A* pathway could explain additional variation above and beyond that explained by the polygenic score.

DESIGN, SETTING, AND PARTICIPANTS Patients with psychosis (n = 424) were assessed in areas of cognitive ability impaired in schizophrenia including IQ, memory, attention, and social cognition. We used the Psychiatric GWAS Consortium 1 schizophrenia genome-wide association study to calculate a polygenic score based on identified risk variants within this genetic pathway. Cognitive measures significantly associated with the polygenic score were tested for an epistatic component using a training set (n = 170), which was used to develop linear regression models containing the polygenic score and 2-SNP interactions. The best-fitting models were tested for replication in 2 independent test sets of cases: (1) 170 individuals with schizophrenia or schizoaffective disorder and (2) 84 patients with broad psychosis (including bipolar disorder, major depressive disorder, and other psychosis).

MAIN OUTCOMES AND MEASURES Participants completed a neuropsychological assessment battery designed to target the cognitive deficits of schizophrenia including general cognitive function, episodic memory, working memory, attentional control, and social cognition.

RESULTS Higher polygenic scores were associated with poorer performance among patients on IQ, memory, and social cognition, explaining 1% to 3% of variation on these scores (range, $P = .01$ to .03). Using a narrow psychosis training set and independent test sets of narrow phenotype psychosis (schizophrenia and schizoaffective disorder), broad psychosis, and control participants (n = 89), the addition of 2 interaction terms containing 2 SNPs each increased the R^2 for spatial working memory strategy in the independent psychosis test sets from 1.2% using the polygenic score only to 4.8% ($P = .11$ and .001, respectively) but did not explain additional variation in control participants.

CONCLUSIONS AND RELEVANCE These data support a role for the *ZNF804A* pathway in IQ, memory, and social cognition in cases. Furthermore, we showed that epistasis increases the variation explained above the contribution of the polygenic score.

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Genome-wide association studies (GWASs) have been at the forefront of identifying candidate genes for schizophrenia. One of the genetic variants achieving genome-wide significance for psychosis was rs1344706 in the zinc finger binding protein 804A (*ZNF804A*).[1] Several independent replication studies[2,3] and a recent meta-analysis[4] have supported an association between schizophrenia and the risk allele of this single nucleotide polymorphism (SNP). The gene *ZNF804A*, which is expressed in the brain, is believed to encode a protein with a C2H2 zinc finger domain. This suggests a role in the regulation of gene expression through DNA and/or RNA binding.[5] The gene *ZNF804A* has been reported to show an association with brain activity and structure.[6,7] A recent study by Hill et al[8] assessed the effects of its knockdown on the cellular transcriptome, which linked *ZNF804A* to cell adhesion molecules, suggesting a role in neural migration, neurite outgrowth, and synapse formation, which are hypothesized to be aberrant in schizophrenia.

Several studies have linked *ZNF804A* to cognition, based on imaging studies,[6,9] traditional neuropsychological measures,[10-12] and measures of social cognition.[13,14] The results of these studies deviate from what would be expected in that while the rs1344706 risk allele appears to convey impairments in cognition in control individuals based on behavioral and imaging studies,[11,15-17] the literature points to preserved cognition in patients.[10,12,18,19] Although some studies suggest that *ZNF804A* is associated with impaired social cognition in control participants, it is uncertain whether *ZNF804A* might also confer a disadvantage to patients because only 1 study[14] has assessed patients. If *ZNF804A* confers risk for psychosis, why does the risk allele–carrying patient population show preserved cognitive function? The answer may lie in the impact of *ZNF804A* embedded within its functional pathway. The development of complex traits, such as psychosis, is likely to involve the contribution of a large number of independent and/or interacting genetic variants, mostly of modest effect.[20,21] In case-control analyses, polygenic scores (a simple or weighted summation of the top sets of SNPs) have been shown to predict case status in related disorders and explain a significant percentage of variability.[22] Limiting this polygenic risk score to include variants within genes shown to be altered by *ZNF804A* knockdown,[8] we investigated whether more of the variance in patients' neuropsychological function can be explained than is explained by single variants. We used the *P* values and odds ratios from the Schizophrenia Psychiatric GWAS Consortium 1 (PGC1) schizophrenia case-control analysis[23] to rank SNPs for inclusion in the polygenic score. As variation in complex traits is thought to include both polygenic and epistatic components, we examined whether epistasis between SNPs within the *ZNF804A* pathway could explain variation above that explained by the polygenic score alone. We used half of the narrow psychosis (schizophrenia and schizoaffective disorder) set as a training set to test for pairwise epistasis among all SNPs included in the polygenic score, then assessed whether adding these interactions to the regression model containing the polygenic score increased the R^2 among 3 independent test sets including (1) additional narrow psychosis cases, (2) broad psychosis (bipolar disorder, major depressive disorder, and psychosis not otherwise specified), and (3) healthy control participants.

Methods

Participants

Four hundred twenty-four cases and 89 healthy participants who completed a full neuropsychological assessment battery and for whom GWAS data were available were included. Cases were clinically stable patients with a *DSM-IV* diagnosis of schizophrenia (n = 282), schizoaffective disorder (n = 58), bipolar disorder (n = 61), major depressive disorder with psychotic features (n = 11), or psychosis not otherwise specified (n = 12) recruited from 5 sites across Ireland (**Table 1**). Inclusion criteria required that participants were clinically stable at neuropsychological assessment, aged 18 to 65 years, had no history of comorbid psychiatric disorder, no substance abuse in the preceding 6 months, no prior head injury with loss of consciousness, and no history of seizures. Diagnosis was confirmed by trained psychiatrists using the Structured Clinical Interview for *DSM-IV-TR*.[24] Additional diagnostic details and clinical sample characteristics, including symptom severity (Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive Symptoms)[25,26] and medication dosage, are detailed elsewhere.[10] Healthy control participants were recruited via online and poster advertising. They were aged 18 to 65 years, with no history of substance abuse in the preceding 6 months, no prior head injury with loss of consciousness, no history of seizures, and no personal history of psychosis or in their first-degree relatives. All assessments were conducted in accordance with the relevant ethics committees' approval from each participating site. All participants had 4 grandparents born in Ireland and provided written informed consent.

Cognitive Assessment

Participants completed a neuropsychological assessment battery designed to target the cognitive deficits of schizophrenia including general cognitive function, episodic memory, working memory, attentional control, and social cognition. General cognitive functioning (IQ) was measured using selected subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) from the Wechsler Adult Intelligence Scale,[27] yielding a full-scale, verbal, and performance IQ. Episodic memory was assessed using the logical memory subtest from the Wechsler Memory Scale III.[28] Working memory was assessed using the spatial working memory task (SWM) from the Cambridge Neuropsychological Test Automated Battery[29] and letter-number sequencing from the Wechsler Memory Scale III.[28] Attentional control was assessed using the Continuous Performance Task-Identical Pairs version,[30] the Intradimensional-Extradimensional shift task (IDED) (Cambridge Neuropsychological Test Automated Battery),[29] and the Sustained Attention to Response Task.[31] Social cognition was assessed using the Reading the Mind in the Eyes Task[32] and the Internal, Personal, and Situational Attributions Questionnaire (IPSAQ),[33] which yields 2 bias scores; externalizing bias (EB), which in-

Table 1. Participant Demographics and Neurocognitive and Clinical Measures

Characteristic	Patients		Healthy Participants (n = 89)
	Psychosis Narrow (n = 340)	Psychosis Broad (n = 424)	
Psychosis subtype, No.			NA
Schizophrenia	282	282	
Schizoaffective disorder	58	58	
Bipolar disorder		61	
Major depressive disorder		11	
PNOS		12	
Male:female ratio	2.6:1	2.2:1	1.4:1
Age, mean (SD), y	41.3 (12.2)	41.3 (12.4)	36.27 (12.8)
Age at onset, mean (SD), y	22.8 (7.2)	23.2 (7.5)	NA
Chlorpromazine equivalent, mean (SD), mg/d	589.8 (562.4)	555.5 (540.7)	NA
SAPS/SANS, mean (SD)			NA
Manic	−0.18 (0.95)	0.04 (1.09)	
Depression	0.16 (1.07)	0.23 (1.06)	
Positive	−0.02 (0.99)	−0.12 (0.95)	
Disorganized	−0.22 (0.76)	−0.31 (0.78)	
Negative	0.39 (0.9)	0.32 (0.87)	
Cognition: full-scale IQ, mean (SD)	89.6 (17.8)	90.3 (18.3)	124.6 (13.3)

Abbreviations: NA, not applicable; PNOS, psychosis not otherwise specified; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

dicates a propensity to attribute positive events to oneself rather than to other people, and a personalizing bias, which indicates a propensity to attribute negative events to other people rather than to situational factors.

Genotyping

Genotyping was conducted on DNA extracted from blood in patients and saliva in control participants. Single nucleotide polymorphism data were obtained from a recent GWAS using the Affymetrix SNP Array 6.0 platform, conducted as part of the Wellcome Trust Case Control Consortium 2, described in detail elsewhere.[34]

Statistical Analysis

Polygenic scores[22] for variants located within the *ZNF804A* pathway were calculated starting with all available SNPs within 20 Kb of genes in the *ZNF804A* pathway[8] (eTable 1 in Supplement). Target alleles at these SNPs were identified as risk associated based on the PGC1 GWAS. Two polygenic scores for each individual were calculated. The count polygenic score was based on the simple sum of the number of risk-associated alleles they carried averaged across the total number of valid genotypes for that individual. The weighted polygenic score was based on the count polygenic score, with the exception that each SNP was weighted by the log of the odds ratio from the PGC1. We used 3 *P* value thresholds from the PGC1 case-control analysis as arbitrary thresholds as in a previous polygenic analysis[22] (thresholds and number of SNPs: $P < 1.0e^{-05}$, n = 10; $P < .05$, n = 218; and $P < .50$, n = 1525). As individual *ZNF804A* SNPs have been associated with cognition, we examined whether an association observed between the pathway-based polygenic score remained after removing all *ZNF804A* SNPs (n = 27). A subset of the Wellcome Trust Case Control Consortium 2 sample was included in the PGC1 schizophrenia case-control analysis, thus the samples are not entirely independent. However, the outcome of interest in the PGC1 was case status, whereas in the present study the outcome of interest was cognition in cases with psychosis. As suggested in the supplementary materials of the original polygenic score report,[22] we used all genotyped SNPs in genes within the *ZNF804A* pathway without pruning for linkage disequilibrium.

Association Analysis

Polygenic Scores

Associations between *ZNF804A* polygenic score and the phenotypes of IQ, episodic memory, working memory, attention, and social cognition were tested in multiple regression analyses implemented in SPSS version 17[35] or the R Statistical Computing Environment.[36] In each case, scores for each neuropsychological phenotype were entered as dependent variables, controlling for age and sex as necessary.

Polygenic Scores Plus Epistatic Effects

To test whether additional variation could be explained by epistasis beyond that explained by the polygenic score, we developed a novel approach within the context of the regression models previously described. To reduce multiple testing, we restricted our search for epistasis to the models where the polygenic score accounted for a small, but significant, amount of variation in the neuropsychological phenotype in broad or narrow psychosis including SWM strategy, IPSAQ-EB, and performance IQ. First, we created equal-sized training and test sets from the narrow psychosis cases (n = 170). Second, to obtain a stable and consistent estimate of the *P* value from 2-SNP interactions, we took 100 bootstrap samples with replacement from the narrow psychosis training sample and performed linear regression analysis for all possible pairs of SNPs falling under the threshold at hand (SWM threshold $P \leq .05$, SNPs:

Table 2. Significant Variance Explained (R^2) and Associated *P* Values for *ZNF804A* Polygenic Score Regression on Neuropsychological Phenotypes[a]

	R^2 (*P* Value)					
	Narrow Psychosis			Broad Psychosis		
	P Value Threshold					
Phenotype	.00001	.05	.50	.00001	.05	.50
Performance IQ including *ZNF804A*	0.009 (.26)	0.001 (.51)	0.002 (.41)	**0.012 (.03)**	<0.001 (.78)	0.004 (.21)
IPSAQ-EB including *ZNF804A*	**0.030 (.01)**	0.0070 (.21)	0.0030 (.43)	**0.025 (.01)**	0.0040 (.28)	0.0030 (.39)
SWM strategy including *ZNF804A*	0.010 (.09)	**0.017 (.03)**	0.003 (.35)	0.0040 (.23)	**0.013 (.03)**	0.0020 (.41)
SWM strategy excluding *ZNF804A*[b]	0.010 (.11)	**0.017 (.03)**	0.003 (.36)	0.0040 (.23)	0.011 (.05)	0.0010 (.47)

Abbreviations: IPSAQ-EB, Internal, Personal, and Situational Attributions Questionnaire–Externalizing Bias; SWM, spatial working memory.

[a] Bolded numbers indicate *P* < .05.

[b] Only the significant *P* value threshold for SWM strategy (*P* < .05) included *ZNF804A* single nucleotide polymorphisms.

n = 218; IPSAQ-EB and performance IQ threshold $P < 1.0e^{-05}$, SNPs: n = 10). For performance IQ and IPSAQ-EB, the 10 SNPs were all on chromosome 10 and in tight linkage disequilibrium (range, r^2 = 0.6-1.0), which led to collinearity in the interactions and were not tested further. For SWM, the linear regression model in the training data contained the unweighted polygenic score plus an epistatic term, which was the product of the risk-associated alleles at 2 SNPs. The unweighted polygenic score was used so the alleles comprising the score were on the same scale of measurement as those used in the interactions; however, the use of the weighted score did not change the results (discussed below). The average *P* value from the 100 replicates was used to determine which interactions would be evaluated using the 3 independent test sets, using an uncorrected *P* < .05 threshold estimated from the training set. To account for linkage disequilibrium, a further condition was that only the interaction with the smallest *P* value containing a particular SNP would be tested for replication in the independent test sets and all other interactions containing that SNP would not be considered for replication due to collinearity. This led to 3 significant 2-SNP interaction terms, independent of one another, being brought forward for replication in the 3 test sets. R^2 values on the independent test sets were calculated as the square of the correlation between the fitted values for the test set based on the model estimated from the training data and the observed values from the test set.

Results

Demographic and Clinical Measures

Demographic and clinical characteristics for patients and healthy participants appear in Table 1. The characteristics of the broad psychosis group were compared with the narrow psychosis group and with the control group using *t* tests. No significant differences were observed between the narrow and broad psychosis groups for age, sex, age at onset, full-scale IQ, medication dosage as measured by chlorpromazine equivalents, or positive and negative symptoms, with the exception of the mania factor where the broad psychosis group scored significantly higher. The patient group contained significantly more men than the healthy group, was significantly older at the time of assessment, and had a significantly lower full-scale IQ.

ZNF804A Pathway Polygenic Score

ZNF804A weighted polygenic scores were associated (uncorrected *P* < .05) with measurements of both general and social cognition, including SWM, IPSAQ-EB, and performance IQ, although the effect size was moderate (1.2%-3%) (**Table 2**; results for all phenotypes are in eTable 2 in Supplement). Larger *ZNF804A* polygenic scores were predictive of poorer performance on performance IQ in the broad psychosis group at the threshold of $P = 1.0e^{-05}$, but did not predict performance IQ in the narrow psychosis group (Table 2). The IPSAQ-EB demonstrated significant association with the *ZNF804A* polygenic score among broad and narrow psychosis at a threshold of $P = 1.0e^{-05}$. Patients with psychosis who had greater polygenic scores demonstrated a decreased IPSAQ-EB score, suggesting that these patients were less likely to show what is known as a self-serving bias: the adaptive tendency to attribute causality for negative events to external factors and positive events to oneself. Among both narrow and broad psychosis groups, a higher *ZNF804A* polygenic score led to significantly poorer performance on SWM strategy at a threshold of *P* = .05.

To determine whether the polygenic score results were powered by *ZNF804A* SNPs, we excluded all variants in *ZNF804A* and reassessed association with the polygenic score; the results were virtually unchanged (Table 2), with the exception of SWM strategy, which showed a slightly reduced R^2 and larger *P* value in the narrow psychosis set (results for all phenotypes are in eTable 3 in Supplement).

Epistasis Within the *ZNF804A* Pathway

As just described, we tested for additional variation in SWM explained by 2-SNP epistasis in the narrow psychosis training set. Because of linkage disequilibrium, 112 average *P* values across 100 bootstrap samples of the training set were less than .05; however, of these, only 3 were completely independent of the other sets and thus only these 3 interaction terms were brought forward for replication in the 3 independent test sets.

Table 3. Increase in R^2 Values Using Epistasis in Conjunction With *ZNF804A* Polygenic Scores Across the Narrow Psychosis Test Set and Broad Psychosis Set[a]

Model	Narrow Train R^2	*P* Value	Narrow Test R^2	*P* Value	Broad R^2	*P* Value	Total Test Case R^2	*P* Value	Control R^2	*P* Value
Polygene count score	0.017	.12	0.013	.17	0.013	.34	0.012	.11	0.03	.11
Polygene count score + rs17186340T:rs140512A	0.13	$6.70e^{-005}$	0.027	.05	0.05	.06	**0.035**	**.006**	0.0069	.45
Polygene count score + rs17186340T: rs140512A + rs2295984T:rs34138673G	0.16	$2.70e^{-005}$	**0.04**	**.02**	**0.062**	**.04**	**0.048**	**.001**	0.001	.77

[a] Bolded numbers indicate $P < .05$.

Beginning with SWM strategy, adding the most significant interaction (rs17186340:rs140512) to the model containing the polygenic count score led to an increase of 1.4% in the narrow psychosis test set ($P = .05$), 3.7% in the broad psychosis test set ($P = .04$), and a combined case test set increase of 2.3% ($P = .006$) (**Table 3**). Although adding this interaction increased the variation explained in 2 independent sets of cases, it did not increase variation explained in control participants ($R^2 = 0.0069$, $P = .45$). Adding a second interaction term to the model (rs2295984:rs34138673) further increased the variation explained in cases: in the narrow psychosis test set, the R^2 increased by 1.3% ($P = .02$) to a total of 4.0%; in the broad psychosis test set, the R^2 increased further by 1.2% ($P = .04$) for a total variation explained of 6.2%; and in the combined set of cases, the R^2 increase was 1.3% ($P = .001$) for a total of 4.8%. In control participants, adding the second interaction did not increase the variation explained ($R^2 = 0.001$, $P = .77$). The third epistatic term did not increase the R^2 values in any independent test set and thus was not considered further.

To test whether the increase in R^2 was attributable to strongly associated SNPs contained in the interactions themselves, interaction SNPs were tested individually for association with SWM strategy in a model containing the polygenic count score. Two SNPs were associated with SWM strategy at an uncorrected $P < .05$ and both were in the second interaction term (rs17186340:rs34138673). The improvement in R^2 values from the narrow psychosis training set model containing the polygenic count score plus rs17186340 on the narrow psychosis, broad psychosis, and total test cases set were $5.89e^{-06}$, $9.1e^{-04}$, and $8.0e^{-05}$, respectively. Results for the same analysis using rs34138673 were 0.0056, 0.013, and 0.0079, respectively, indicating that the interaction term explained more variation than either single SNP.

To see whether the type of polygenic score influenced the amount of variation explained, the weighted polygenic score was substituted for the count polygenic score and R^2 values were calculated for the case test sets. In the narrow psychosis test set, the use of the weighted polygenic score in the 3 models (polygenic only, 1 and 2 interactions) increased the R^2 value by $9.1e^{-04}$ – 0.001 vs models containing the count polygenic score, whereas the use of the weighted polygenic score in broad psychosis reduced the R^2 value by $4.7e^{-04}$ – 0.0061 vs the count polygenic score, suggesting the choice of polygenic score was trivial in this instance. When strongly associated SNPs with very large or very small effect sizes (odds ratios) are present, we would expect to see differences between using the count or weighted score.

Discussion

We used polygenic scores to investigate whether *ZNF804A* pathway schizophrenia risk–associated alleles were associated with neuropsychological function among 424 patients with psychosis. Higher *ZNF804A* polygenic scores were significantly associated with poorer performance in IQ, working memory, and biased social cognition and explained 1% to 3% of the variation in these measures, consistent with estimates previously reported in general intelligence in control individuals.[37] Removal of the SNPs within *ZNF804A* reduced the R^2 values only slightly, suggesting the combined contribution of genes within the pathway was driving the association. Furthermore, we showed that considering epistasis along with the polygenic score resulted in more than 3 times the amount of variation explained in 2 independent test sets of cases (range, total R^2 = 4.0%-6.2%). Because the SNPs participating in interactions were not in *ZNF804A*, we provide further evidence that this gene was not the key contributor to our pathway-based results. Thus, our findings are not inconsistent with previous studies showing preserved cognitive function in cases is associated with *ZNF804A*. Although the polygenic score explained a similar amount of variation in control participants, improvements due to epistasis were specific to psychosis cases.

Although previous studies have shown that the risk allele of *ZNF804A* rs1344706 shows differential effects in cases and control participants,[10-19] we showed that, at the pathway level, the effect of the combination of schizophrenia risk alleles leads to poorer performance in patients with psychosis on measures of intelligence, working memory, and social cognition. The 4 SNPs participating in epistasis that increased the R^2 values in our test sets were near *STAC* (rs17186340), *MAPK8IP2* (rs140512), and flanking either side of *FAM46A* (rs2295984 and rs34138673). In mice, *Stac* is expressed in the brain, neurons, and postsynaptic densities; within the brain, the expression is highest in the hippocampus and cerebellum.[38,39] A *Stac* knockout mouse model showed reduced social interaction, impaired learning, and deficits in exploration of novel environments.[39] *MAPK8IP2* is located within the Chr22q13.3 deletion region associated with autism spectrum disorders and

Phelan-McDermid syndrome, which is characterized by developmental delay. Also known as JIP2, it is a scaffold protein that is necessary for N-methyl-D-aspartic acid receptor function and modulates signal transduction.[40] *FAM46A* is expressed in adult human brain and shows higher expression in human fetal brain.[41] The SNPs participating in the second interaction term, rs2295984 and rs34138673, are located on either side of *FAM46A*, approximately 19.5 kbp apart, possibly indicating a promoter and/or enhancer role.

How can we reconcile previous research that has shown the risk allele at *ZNF804A* rs1344706 is associated with less impaired cognition in patients with psychosis with the results of the present study, which showed that the polygenic score from the *ZNF804A* pathway was associated with poorer performance IQ, working memory, and social cognition? The *P* values from the PGC1 were used to select SNPs for inclusion in the polygenic score, and the smallest *ZNF804A P* value was .002 for rs1344706. Therefore, the set with the most stringent threshold did not include any *ZNF804A* SNPs, and this set was negatively associated with IQ and social cognition. For working memory, the removal of the *ZNF804A* SNPs at a threshold of $P = .05$ would have included 12 of the 27 SNPs with *P* values ranging between .002 and .05. We have shown that the removal of these SNPs did not lead to significant differences in the magnitude of association between the polygenic score and working memory. The use of the weighted polygenic score would have ensured a weak contribution of these SNPs because they were not strongly associated with schizophrenia in the PGC1 and they comprised only 5.5% of the total number of SNPs at that threshold. Interestingly, the PGC1 *P* values for the 4 SNPs participating in epistasis ranged between .007 (rs2295984) and .04 (rs17186340), showing that although they are marginally associated with schizophrenia, they would not have been considered for follow-up. As was the case with the previous use of the polygenic score,[22] we showed that the polygenic score and epistatic models based on a narrow psychosis training sample were able to significantly account for variation in working memory in 2 independent psychosis samples, but they were not able to predict variation in control participants. Although the control sample size was modest (n = 89), the broad psychosis sample was of a similar size (n = 84) so a lack of statistical power cannot fully explain the inability to account for additional variation in control participants.

Interestingly, the 10 SNPs in linkage disequilibrium that comprised the most strongly associated polygenic score for IPSAQ-EB and performance IQ included 5 SNPs in *CNNM2* and 5 SNPs either 3′ or 5′ of the gene. This gene is strongly associated with schizophrenia[23,42,43] and we and other groups have shown variation within the gene is associated with gray matter volume in patients with schizophrenia[44,45] and with attributional style.[45] Our results support a polygenic contribution of variation within and around this gene weakly contributing to attributional style and performance IQ.

We have introduced a novel method to evaluate the combined effect of the polygenic score and epistasis, which is both simple and computationally tractable. The addition of the epistatic terms also increased the interpretability of the model, as it is difficult to determine which genes were contributing signal to the polygenic score. We showed that the results estimated on the training sample were generalizable to 2 independent test sets of patients—one with narrow psychosis and the other with non-schizophrenia psychosis—similar to previous studies' use of the polygenic score.[22] In both instances, the variation explained by our epistatic terms was much larger than that explained by the polygenic score itself: the polygenic score explained 1.2% to 1.3% of variation, whereas increases in R^2 using our novel approach in the test sets were between 2.7% and 4.9%. Epistasis is thought to be a key element in complex phenotypes[20,21] and has been shown to influence the risk for schizophrenia and inefficient dorsolateral prefrontal cortex processing during a working memory task in healthy control individuals.[20,21,46,47] The potential limitations of our study included modest sample sizes and the fact that we may not have captured all variation (especially rare variation) in the genes in the *ZNF804A* pathway because of our reliance on SNPs from a GWAS.

Conclusions

To our knowledge, this study is the first to investigate the role of the *ZNF804A* pathway in the cognitive decline commonly observed among patients with psychosis. We have identified 3 new candidate genes for working memory in the *ZNF804A* pathway: *STAC*, *MAPK8IP2*, and *FAM46A*. Perhaps more critically, we introduced an improvement in the use of polygenic scores by adding an epistatic component that explained additional variation in working memory that was specific to cases with psychosis.

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