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# Associations Between Schizophrenia Polygenic Liability, Symptom Dimensions, and Cognitive Ability in Schizophrenia

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[+ Supplemental content](#)

**IMPORTANCE** Schizophrenia is a clinically heterogeneous disorder. It is currently unclear how variability in symptom dimensions and cognitive ability is associated with genetic liability for schizophrenia.

**OBJECTIVE** To determine whether phenotypic dimensions within schizophrenia are associated with genetic liability to schizophrenia, other neuropsychiatric disorders, and intelligence.

**DESIGN, SETTING, AND PARTICIPANTS** In a genetic association study, 3 cross-sectional samples of 1220 individuals with a diagnosis of schizophrenia were recruited from community, inpatient, and voluntary sector mental health services across the UK. Confirmatory factor analysis was used to create phenotypic dimensions from lifetime ratings of the Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, and the MATRICS Consensus Cognitive Battery. Analyses of polygenic risk scores (PRSs) were used to assess whether genetic liability to schizophrenia, other neuropsychiatric disorders, and intelligence were associated with these phenotypic dimensions. Data collection for the cross-sectional studies occurred between 1993 and 2016. Data analysis for this study occurred between January 2019 and March 2021.

**MAIN OUTCOMES AND MEASURES** Outcome measures included phenotypic dimensions defined from confirmatory factor analysis relating to positive symptoms, negative symptoms of diminished expressivity, negative symptoms of motivation and pleasure, disorganized symptoms, and current cognitive ability. Exposure measures included PRSs for schizophrenia, bipolar disorder, major depression, attention-deficit/hyperactivity disorder, autism spectrum disorder, and intelligence.

**RESULTS** Of the 1220 study participants, 817 were men (67.0%). Participants' mean (SD) age at interview was 43.10 (12.74) years. Schizophrenia PRS was associated with increased disorganized symptom dimension scores in both a 5-factor model ( $\beta = 0.14$ ; 95% CI, 0.07-0.22;  $P = 2.80 \times 10^{-4}$ ) and a 3-factor model across all samples ( $\beta = 0.10$ ; 95% CI, 0.05-0.15;  $P = 2.80 \times 10^{-4}$ ). Current cognitive ability was associated with genetic liability to schizophrenia ( $\beta = -0.11$ ; 95% CI,  $-0.19$  to  $-0.04$ ;  $P = 1.63 \times 10^{-3}$ ) and intelligence ( $\beta = 0.23$ ; 95% CI, 0.16-0.30;  $P = 1.52 \times 10^{-10}$ ). After controlling for estimated premorbid IQ, current cognitive performance was associated with schizophrenia PRS ( $\beta = -0.08$ ; 95% CI,  $-0.14$  to  $-0.02$ ;  $P = 8.50 \times 10^{-3}$ ) but not intelligence PRS.

**CONCLUSIONS AND RELEVANCE** The findings of this study suggest that genetic liability for schizophrenia is associated with higher disorganized dimension scores but not other symptom dimensions. Cognitive performance in schizophrenia appears to reflect distinct contributions from genetic liabilities to both intelligence and schizophrenia.

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The clinical heterogeneity of schizophrenia and related psychotic disorders has long been recognized. Factor analyses of symptoms related to schizophrenia have consistently resulted in positive, negative, and disorganized dimensions.<sup>1,2</sup> Studies have also identified dimensions relating to cognitive ability, which, although not considered a core diagnostic feature, has been consistently shown to be impaired in schizophrenia.<sup>3,4</sup> A better understanding of the different factors underlying these symptom dimensions could contribute to the development of novel treatments for schizophrenia; currently available treatments predominantly affect only positive symptoms.

The genetic contribution to clinical variation between patients across symptom dimensions has been of interest for some time. Familial aggregation for a disorganized symptom dimension has been found in studies of affected sib-pairs<sup>5,6</sup> and multigeneration families,<sup>7</sup> although twin-based analysis has indicated that this aggregation is substantially a genetic effect (heritability;  $h^2 = 84\%$ ).<sup>1</sup> The disorganized dimension also demonstrates patterns of familial aggregation consistent with it being a marker of genetic loading for psychotic disorders.<sup>2</sup> Evidence for familial aggregation of the positive and negative dimensions is less consistent, but the negative dimension has also been associated with genetic loading for psychotic disorders.<sup>8</sup>

Recent genomic studies have used polygenic risk scores (PRSs) to assess the association between schizophrenia genetic liability and phenotypic dimensions. The schizophrenia PRS has been reported to be associated with a combined disorganized/negative dimension<sup>9,10</sup> and with negative symptoms.<sup>4,11,12</sup> However, many of these studies have not assessed disorganized symptoms or are based on a dimensional structure that combines disorganized symptoms with either negative symptoms<sup>9,10,13</sup> or cognition.<sup>3</sup> Furthermore, there is emerging evidence that indicates the structure of negative symptoms may not be unidimensional and that at least 2 substructures can be reliably identified: diminished expressivity and diminished motivation and pleasure.<sup>14,15</sup> The association of genetic liability with other psychiatric disorders on symptom dimensions in schizophrenia is unclear.

Cognitive ability in the general population is a highly heritable trait.<sup>16</sup> However, studies investigating the genetic source of the cognitive deficits observed in individuals with schizophrenia and the association with schizophrenia genetic liability have reported inconsistent findings.<sup>17-19</sup>

In this genetic association study, we aimed to examine which phenotypic dimensions of schizophrenia are associated with genetic liability to schizophrenia as indexed by PRSs. We addressed gaps in previous studies by defining each of the commonly found symptom dimensions and cognitive ability as distinct phenotypic dimensions and conducted a meta-analysis across 3 samples that used a common approach to phenotypic assessment. We also investigated the association between phenotypic dimensions and genetic liability to psychiatric and cognitive traits other than schizophrenia.

## Key Points

**Question** Are phenotypic dimensions in schizophrenia associated with genetic liability to schizophrenia, other neuropsychiatric disorders, and intelligence?

**Findings** In this cross-sectional genetic association study of 1220 individuals with schizophrenia, analyses indicated that higher levels of disorganized symptoms, but not other symptom dimensions, and lower levels of current cognitive ability were significantly associated with schizophrenia polygenic risk scores. Current cognitive ability was also associated with intelligence polygenic risk scores.

**Meaning** The findings of this study suggest that variation in disorganized symptoms and cognitive ability in schizophrenia are markers of schizophrenia common genetic liability; cognitive performance in schizophrenia may reflect distinct contributions from genetic liabilities to both intelligence and schizophrenia.

## Methods

### Participants

This genetic association study included a total of 1220 individuals with schizophrenia. Participants came from 3 schizophrenia sample collections, all previously reported: the CardiffCOGS ( $n = 697$ ),<sup>20</sup> Cardiff F-series ( $n = 383$ ),<sup>21</sup> and Cardiff Affected-Sib ( $n = 140$ ) samples<sup>5</sup> (eTable 1 in the Supplement provides demographic characteristics). All studies had the relevant UK National Health Service ethical approval, and written informed consent was obtained for all study participants. All participants underwent a comprehensive clinical research interview based on the Schedules for Clinical Assessment in Neuropsychiatry<sup>22</sup> and met *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*<sup>23</sup> or *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*<sup>24</sup> criteria for a diagnosis of schizophrenia or schizoaffective disorder, depressed type. Recruitment to each study was from community, inpatient, and voluntary sector mental health services across the UK. The Cardiff Affected-Sib sample included a single affected individual from families with 2 or more siblings diagnosed with schizophrenia. The study was conducted at the MRC Centre for Neuropsychiatric Genetics and Genomics at Cardiff University, UK. Data collection for the cross-sectional studies occurred between 1993 and 2016. Data analysis for this study occurred between January 2019 and March 2021. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline.

### Phenotype Measures

In each of the 3 samples, the Scale for the Assessment of Positive Symptoms<sup>25</sup> and the Scale for the Assessment of Negative Symptoms<sup>26</sup> were scored on a lifetime worst basis using information from the Schedules for Clinical Assessment in Neuropsychiatry interview and lifetime psychiatric clinical case notes. Measures of cognition were available in the CardiffCOGS sample only: we used the MATRICS Consensus Cognitive Battery domain and composite scores<sup>27</sup> as a measure of

current cognitive ability and the National Adult Reading Test<sup>28</sup> as a measure of estimated premorbid IQ. eTable 2 in the [Supplement](#) details the phenotype measures used.

Trained psychiatrists or psychology graduates completed the clinical ratings and cognitive assessments under the supervision of study principal investigators (consultant psychiatrists) (A.G.C., S.Z., M.J.O., M.C.O., and J.T.R.W.), and regular interrater reliability was measured. The Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms ratings had good interrater reliability in each sample, with  $\kappa$  values ranging from 0.72 to 0.95. Interrater reliability for research diagnosis was described in a previous publication.<sup>29</sup>

### Genetic Data

All samples were genotyped on the Illumina HumanOmniExpress (version 8 or 12). Details relating the quality control and imputation of genetic data are provided in eAppendix 1 in the [Supplement](#). Genetic principal components representing ancestry were derived using PLINK, version 2.0<sup>30</sup> using single-nucleotide variants with low levels of linkage disequilibrium ( $r^2 < 0.2$  and 500-kilobyte window; criteria used by the Psychiatric Genomics Consortium<sup>31</sup>). All genetic analyses were restricted to individuals of European ancestry as assessed by principal components. Our sample contained too few participants of non-European ancestry to analyze. First-degree relatives ( $\pi > 0.4$ ) both within and between samples were identified, and 1 member of each related pair was removed, preferentially retaining samples that had more complete phenotype data and otherwise removed at random.

### Polygenic Risk Scores

Polygenic risk scores were calculated using PRSice<sup>32</sup> following a widely applied method<sup>33</sup> and using default parameters unless otherwise stated. Criteria used by the Psychiatric Genomics Consortium<sup>31</sup> were applied to select common single-nucleotide variants (minor allele frequency,  $> 0.10$ ) of high-quality (imputation score,  $> 0.9$ ) in relative linkage equilibrium ( $r^2 < 0.2$ , 500-kilobyte window) that were present in all 3 samples. We excluded the extended major histocompatibility complex region (25–34 megabytes) given its complex linkage disequilibrium structure. The PRSs for schizophrenia were calculated for each study participant using summary statistics from the largest available genome-wide association study<sup>34</sup> after excluding the samples included in this study (summary statistics derived specifically for the purposes of this study by the Psychiatric Genomics Consortium Schizophrenia Working Group). Scores were also calculated using the largest available genome-wide association study for bipolar disorder,<sup>35</sup> major depression,<sup>36</sup> autism spectrum disorder,<sup>37</sup> attention-deficit/hyperactivity disorder (ADHD),<sup>38</sup> and intelligence.<sup>16</sup> The first 5 genetic principal components were included as covariates when generating each PRS. We selected the PRSs based on single-nucleotide variants associated with a threshold of  $P \leq .05$  in the genome-wide association study sample for the primary analysis given that single-nucleotide variant inclusion at this threshold gives the best prediction of schizophrenia,<sup>31</sup> but as a secondary sensitivity test, we also looked across a range

of  $P$  value thresholds:  $5 \times 10^{-8}$ ,  $1 \times 10^{-7}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-5}$ ,  $1 \times 10^{-4}$ , 0.001, 0.05, 0.1, 0.2, 0.5, and 1.0.

### Statistical Analysis

A confirmatory factor analysis (CFA) framework was used to estimate phenotype-derived dimension scores. First, CFA of symptom and cognition measures was conducted on the CardiffCOGS sample because CardiffCOGS had comprehensive ratings for cognition and other symptoms not measured in the other samples. Next, we fitted a multiple-group CFA model solely of symptom ratings that were available across all 3 samples.

The lavaan package<sup>39</sup> for R was used to identify all CFA models. A series of prespecified models were examined in the CardiffCOGS sample (detailed in eTable 2 in the [Supplement](#)) using empirically derived and validated measurement models from previous publications.<sup>5,14</sup> The Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms measures were global scores of symptom categories, with the exception of inappropriate affect, and were included on an ordinal (0–5) scale in the CFA models. All MATRICS Consensus Cognitive Battery domain scores were included on a continuous scale. Otherwise, we used default parameters of the lavaan package, including fixing the first indicator variable to 1, automatically adding residual variances, and allowing latent variables to be correlated.

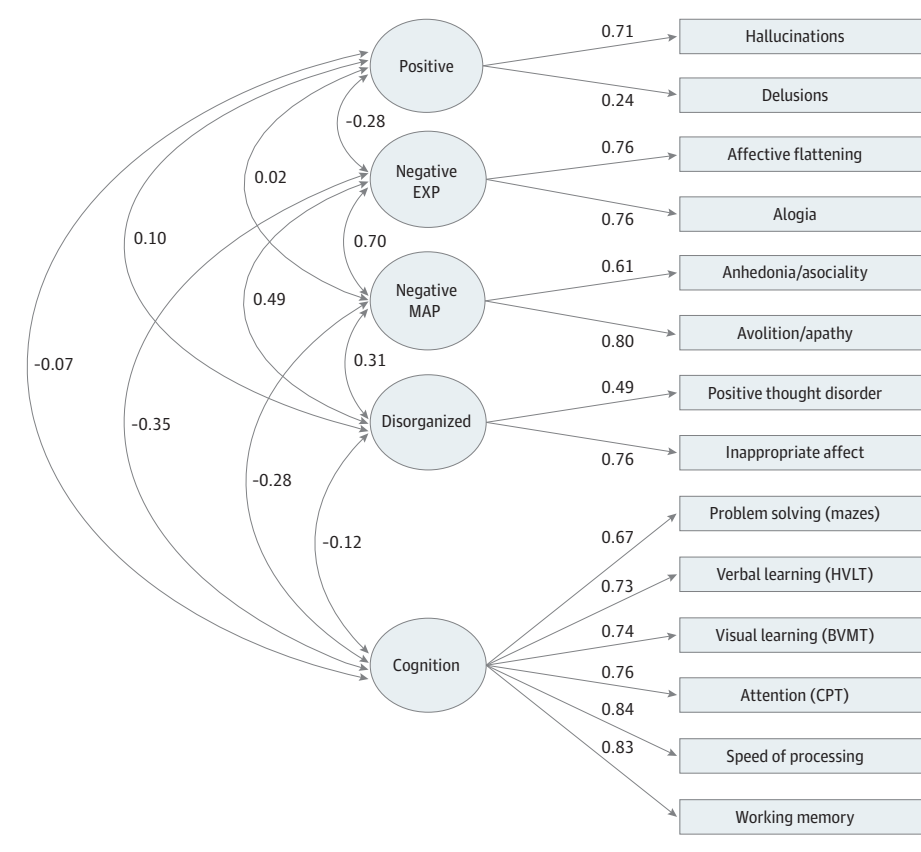
The model that was considered to have the best fit was selected for further analyses. Model fit was guided by both theoretical knowledge and standard interpretations of goodness-of-fit indices,<sup>40,41</sup> including (1) the standardized root mean square residual ( $< 0.08$ ), (2) the root mean square error of approximation ( $< 0.06$ ), and (3) the comparative fit index ( $> 0.95$ ). eAppendix 2 in the [Supplement](#) provides further details of goodness-of-fit indices. Phenotype dimension scores were calculated for each study participant from the CFA model.

Polygenic risk scores and phenotype dimension scores were standardized before analysis. Each phenotype dimension (considered the dependent variable) was regressed on the schizophrenia PRS using linear regression and including sex, age at interview, and the first 5 genetic principal components as covariates. For the multisample analysis,  $\beta$  values were meta-analyzed using the R package meta,<sup>42</sup> with a fixed-effect model weighted by the SE. To control for multiple testing, a Bonferroni correction was applied for the number of phenotype dimensions tested. In secondary analyses, we also tested the association of PRSs for bipolar disorder, depression, ADHD, autism spectrum disorder, and intelligence with each phenotype dimension. A Bonferroni correction was applied for testing 5 disorder PRSs multiplied by the number of phenotype dimensions. In CardiffCOGS, we also tested the correlation of estimated premorbid IQ with the derived cognitive dimension via Pearson correlation and assessed the association between premorbid IQ and schizophrenia PRS via linear regression.

## Results

A total of 1220 individuals were included in the study; 817 were men (67.0%), 403 were women (33.0%), and the mean (SD) age

Figure 1. Five-Factor Structure of Phenotype Dimensions in Schizophrenia



Structure of 5-factor phenotype dimensions derived by confirmatory factor analysis (CFA) in the CardiffCOGS sample. Boxes on the right detail contributing phenotypes, and circles represent latent factors created by CFA. Solid lines represent standardized factor loadings, and curved lines represent the correlation among phenotype dimensions. BVMT indicates Brief Visuospatial Memory Test-Revised; CPT, Continuous Performance Test: Identical Pairs; negative EXP, negative symptoms of diminished expressivity; HVLTL, Hopkins Verbal Learning Test; and negative MAP, negative symptoms of diminished motivation and pleasure.

Table 1. Association of Schizophrenia PRS and Phenotype Dimensions From 5-Factor Model

Phenotype dimension	CardiffCOGS (n = 662)			
	$\beta$ (95% CI)	SE	R <sup>2</sup>	P value <sup>a</sup>
Positive	-0.03 (-0.11 to 0.05)	0.039	<0.001	.422
Negative				
Diminished expressivity	0.09 (0.02 to 0.17)	0.039	0.007	.015
Motivation and pleasure	0.04 (-0.03 to 0.12)	0.039	<0.001	.258
Disorganized	0.14 (0.07 to 0.22)	0.039	0.019	$2.80 \times 10^{-4}$
Cognition	-0.11 (-0.19 to -0.04)	0.036	0.012	$1.63 \times 10^{-3}$

Abbreviation: PRS, polygenic risk score.

<sup>a</sup> Determined with regression analyses.

at study interview was 43.10 (12.74) years. eTable 1 in the Supplement provides demographic information specific to each sample.

The CFA models fitted in the CardiffCOGS sample are detailed in eTable 2 in the Supplement. The optimal model had 5 phenotypic dimensions relating to positive symptoms, negative symptoms of diminished expressivity, negative symptoms of motivation and pleasure, disorganized symptoms, and cognitive ability. Figure 1 details the factor loadings of contributing phenotypes from the optimal model, which fitted the data well at the global level: comparative fit index, 0.99; root mean square error of approximation, 0.04; 95% CI, 0.03-0.05; and standardized root mean square residual, 0.05.

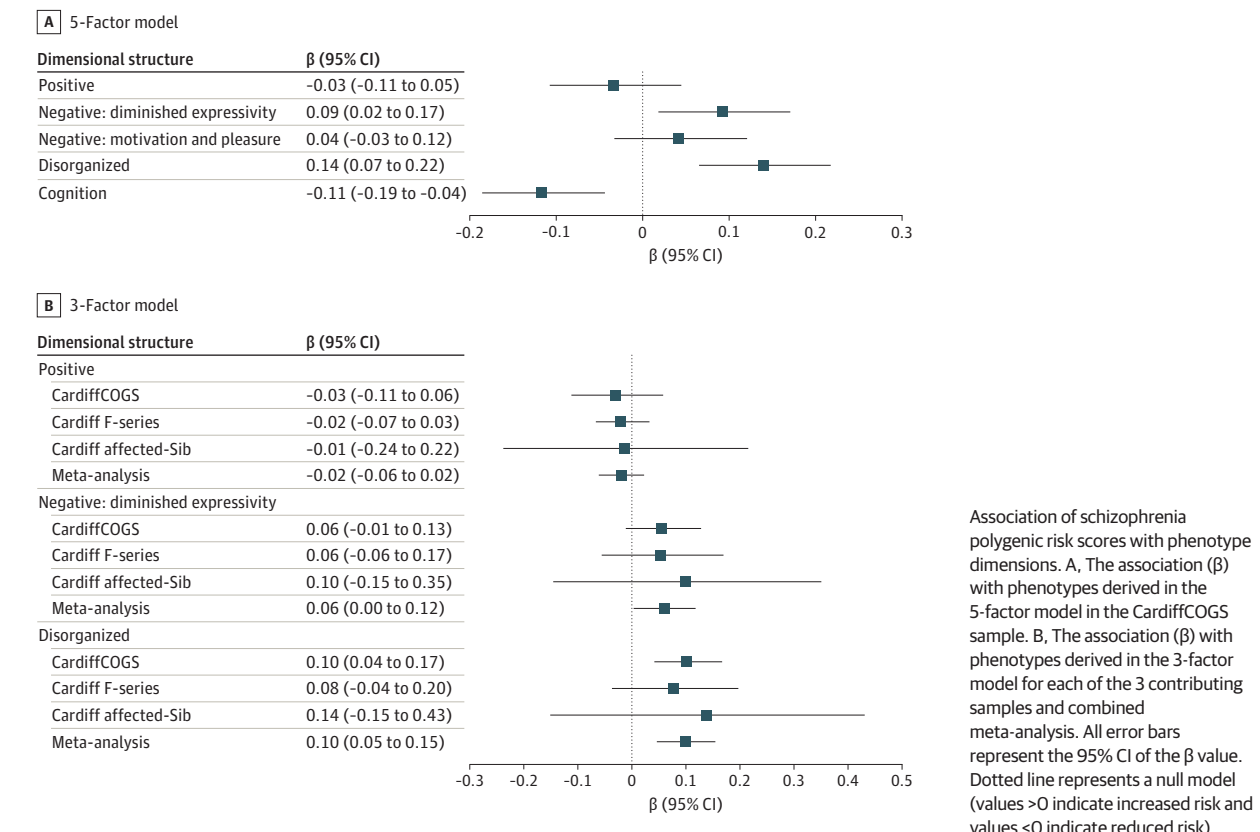
A 3-factor CFA model was fitted across all 3 samples for positive symptoms, negative symptoms of diminished expres-

sivity, and disorganized symptoms. The 3-factor model was a good fit for the data in each sample; therefore no further post hoc modifications to the model were made (eFigure 1 in the Supplement details factor loadings and fit measures). The CFA dimension scores derived from the 5-factor and 3-factor models were highly correlated (0.92-0.98).

### Genetic Liability

Table 1 and Figure 2 detail the associations between schizophrenia PRS and the phenotype dimensions from the CardiffCOGS 5-factor model. Schizophrenia PRS was significantly associated with higher scores on the disorganized dimension ( $\beta = 0.14$ ; 95% CI, 0.07-0.22;  $P = 2.80 \times 10^{-4}$ ) and lower current cognitive ability ( $\beta = -0.11$ ; 95% CI, -0.19 to -0.04;  $P = 1.63 \times 10^{-3}$ ). The dimension of negative symptoms of diminished expressivity was associated at  $P < .05$  ( $\beta = 0.09$ ; 95% CI, 0.02-

Figure 2. Association of Schizophrenia Polygenic Risk Score and Phenotype Dimensions



0.17;  $P = .015$ ) but did not survive a Bonferroni correction for the 5 dimensions tested ( $P < .01$ ). These associations were consistent across different  $P$  thresholds for single-nucleotide variant inclusion in the PRS (eTable 3 in the Supplement), but as expected, the optimal threshold was our primary  $P$  threshold of .05, which typically captures maximum heritability. To assess whether the phenotypic dimensions were independently associated with the PRS, we regressed the schizophrenia PRS against all phenotype dimensions simultaneously. In this model, the dimensions relating to disorganized symptoms and current cognitive ability remained significantly associated with schizophrenia PRS, whereas the dimension of negative symptoms of diminished expressivity did not (eTable 4 in the Supplement).

To confirm the findings applied to raw symptoms scores, we tested the association between schizophrenia PRS and summed raw phenotype scores used to create the symptom dimensions and the MATRICS Consensus Cognitive Battery composite score for cognition, as opposed to the latent factors defined by CFA, and found that schizophrenia PRS was associated only with disorganized symptoms ( $\beta = 0.24$ ; 95% CI, 0.11-0.37;  $P = 2.12 \times 10^{-4}$ ) and current cognitive ability ( $\beta = -0.13$ ; 95% CI, -0.23 to -0.04;  $P = 4.63 \times 10^{-3}$ ) (eFigure 2, eTable 5 in the Supplement). Schizophrenia PRS was associated with both of the variables used to create the disorganized dimension when entered into the same model simultaneously: positive formal thought disorder ( $\beta = 0.10$ ; 95% CI,

0.02-0.18;  $P = .01$ ) and inappropriate affect ( $\beta = 0.08$ ; 95% CI, 0.01-0.16;  $P = .04$ ). Schizophrenia PRS remained associated with the disorganized and cognitive dimensions when controlling for potential confounders of age at the onset of psychosis and treatment resistance to antipsychotics (eTable 6 in the Supplement).

In a meta-analysis of the multisample 3-factor model (Table 2, Figure 2B), schizophrenia PRS was significantly associated with the disorganized dimension ( $\beta = 0.10$ ; 95% CI, 0.05-0.15;  $P = 2.80 \times 10^{-4}$ ) after correction for multiple testing, but not with the dimensions relating to negative symptoms of diminished expressivity ( $\beta = 0.06$ ; 95% CI, 0.00-0.12;  $P = .038$ ) or positive symptoms ( $\beta = -0.02$ ; 95% CI, -0.06 to 0.02;  $P = .367$ ). Tests for heterogeneity (Cochran  $Q$  and  $I^2$ ) indicated that the studies in the meta-analysis had consistent outcomes for all phenotype dimensions studied.

Figure 3 and eTable 7 in the Supplement detail the associations between the 5-factor phenotype dimensions in CardiffCOGS and PRSs for bipolar disorder, depression, autism, ADHD, and intelligence at the threshold  $P \leq .05$ . The only association that survived a Bonferroni correction for the number of tests conducted ( $n = 25$ ;  $P < .002$ ) was between the intelligence PRS and current cognitive ability ( $\beta = 0.23$ ; 95% CI, 0.16 to 0.30;  $P = 1.52 \times 10^{-10}$ ).

In meta-analysis for the 3-factor model, none of the PRSs for bipolar disorder, depression, autism, ADHD, or intelli-

**Table 2. Meta-analysis of Schizophrenia PRS and Phenotype Dimensions From Multisample 3-Factor Model**

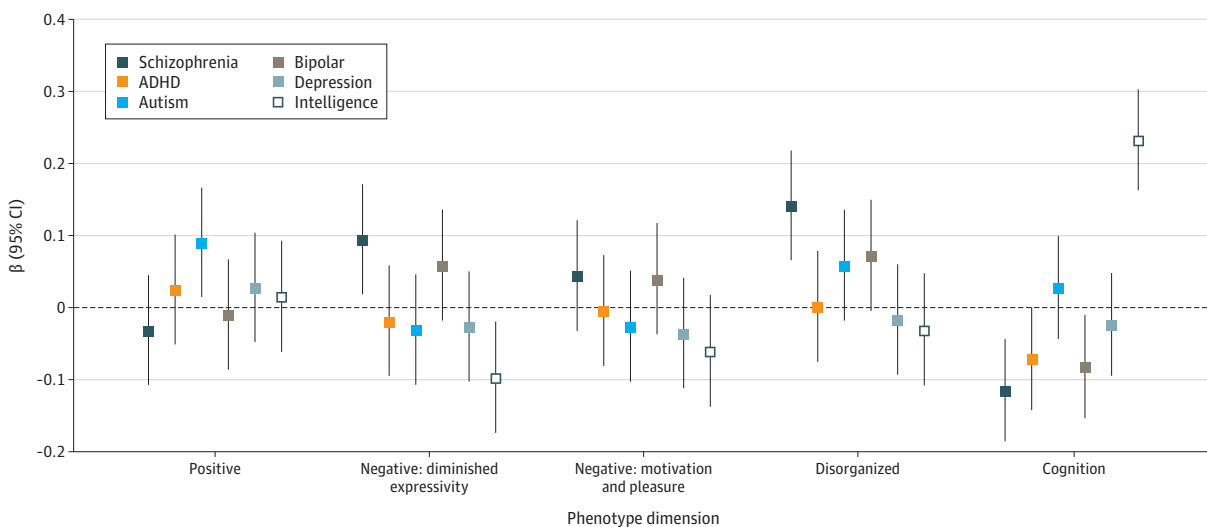
Symptom dimension	CardiffCOGS (n = 697) <sup>a</sup>			Cardiff F-series (n = 383)			Cardiff affected-sib (n = 140)			Meta-analysis (n = 1220)			
	β (95% CI)	SE	P value	β (95% CI)	SE	P value	β (95% CI)	SE	P value	β (95% CI)	P value	Q	Q P value
Positive	-0.03 (-0.11 to 0.06)	0.043	.533	-0.02 (-0.07 to 0.03)	0.025	.501	-0.01 (-0.24 to 0.22)	0.114	.922	-0.02 (-0.06 to 0.02)	.367	0.04	.978
Negative: diminished expressivity	0.06 (-0.01 to 0.13)	0.035	.098	0.06 (-0.06 to 0.17)	0.057	.321	0.10 (-0.15 to 0.35)	0.125	.414	0.06 (0.00 to 0.12)	.038	0.12	.942
Disorganized	0.10 (0.04 to 0.17)	0.032	1.14×10 <sup>-3</sup>	0.08 (-0.04 to 0.20)	0.059	.179	0.14 (-0.15 to 0.43)	0.147	.342	0.10 (0.05 to 0.15)	2.80×10 <sup>-4</sup>	0.20	.903

Abbreviation: PRS, polygenic risk score.

<sup>a</sup> The sample size for CardiffCOGS is larger than in the 5-factor model owing to the inclusion of 35 individuals who were missing data for either cognitive

ability or negative symptoms of motivation and pleasure and thus excluded from the 5-factor model.

**Figure 3. Association of Polygenic Risk Scores and 5-Factor Phenotype Dimensions**



Association of polygenic risk scores (PRSs) for schizophrenia, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, bipolar disorder, depression, and intelligence with phenotype dimensions derived from the

5-factor model in CardiffCOGS. Error bars represent the 95% CI of the β value. Dotted line represents a null model (values >0 indicate increased risk and values <0 indicate reduced risk).

genetics were significantly associated with any of the symptom dimensions after correction for multiple testing (eTable 8 in the Supplement).

The intelligence PRS was strongly associated with premorbid IQ as measured by the National Adult Reading Test ( $\beta = 0.33$ ; 95% CI, 0.26-0.41;  $P = 4.76 \times 10^{-17}$ ), whereas the schizophrenia PRS was not ( $\beta = -0.04$ ; 95% CI, -0.12 to 0.04;  $P = .323$ ). Premorbid IQ and the current cognitive ability dimension had a Pearson correlation of 0.50. We added premorbid IQ as a covariate in the regressions of the current cognitive ability dimension, as defined in the 5-factor CFA model, on the PRSs for schizophrenia and intelligence—a method that has been demonstrated to be preferable to the creation of change scores.<sup>43</sup> The association between current cognitive ability and schizophrenia PRS remained significant ( $\beta = -0.08$ ; 95% CI, -0.14 to -0.02;  $P = 8.50 \times 10^{-3}$ ), whereas the comparison with intelligence PRS did not ( $\beta = 0.06$ ; 95% CI, -0.01-0.12;  $P = .08$ ).

## Discussion

In this study, we found evidence that higher levels of disorganized symptoms and lower levels of current cognitive ability were significantly associated with schizophrenia PRS, suggesting that these phenotypes are markers of increased genetic liability to schizophrenia. We also found that current cognitive performance in schizophrenia reflects genetic liabilities to both schizophrenia and intelligence.

Our first notable finding relates to the association between schizophrenia PRS and disorganized dimension scores in individuals with schizophrenia based on lifetime worst ratings; we found a significant association in the 5-factor model derived in our largest sample and in a meta-analysis of a 3-factor model across 3 samples. This finding is consistent with a twin study that found that the disorganized symptom dimension was a marker of genetic loading for psychotic disorders.<sup>2</sup>

We noted little evidence that the disorganized dimension was significantly associated with genetic liability to other neuropsychiatric disorders or intelligence, suggesting some specificity with schizophrenia genetic liability.

Previous studies assessing the relationships between schizophrenia PRS and symptom dimensions in schizophrenia have reported associations with a combined negative/disorganized dimension.<sup>9,10</sup> Follow-up analyses in one of these studies of raw symptom scores found that this signal appeared to be influenced by the disorganized rather than the negative symptom scores.<sup>10</sup> Our study clarifies the associations between schizophrenia PRS and symptom dimensions by including distinct disorganized and negative dimensions in the primary analysis. We found that, although schizophrenia PRS was nominally associated with the dimension relating to negative symptoms of diminished expressivity in our largest sample, this association attenuated when included in a model with the disorganized dimension and was not associated in the meta-analysis of the 3-factor model or with the raw phenotypes. Thus, our findings suggest that the association with genetic liability to schizophrenia is principally associated with disorganized rather than negative symptoms. These findings support the importance of developing better assessments and capturing subjective and observed data for disorganized symptoms in schizophrenia research, which may have particular relevance for clinical studies into basic symptoms<sup>44</sup> and genetic high risk.

The lack of association between genetic liability for schizophrenia and positive symptoms is consistent with previous studies in individuals with schizophrenia.<sup>2,9,10,13</sup> Our study extends these findings to show that, in people with schizophrenia, there is no association between positive symptoms and genetic liability for bipolar disorder, depression, ADHD, autism, or intelligence.

The second key finding from this study concerns the associations between schizophrenia PRS, intelligence PRS, and current cognitive ability. Although both sets of PRSs were associated with current cognitive ability, the intelligence PRS, but not the schizophrenia PRS, was associated with premorbid IQ as estimated by the National Adult Reading Test. Moreover, when adding premorbid IQ as a covariate, the association between current cognitive ability and schizophrenia PRS remained significant, but the association with intelligence PRS did not. These results suggest that current cognitive ability in individuals with schizophrenia is partly a function of premorbid IQ, influenced by genetic variants that contribute to variation in intelligence in the general population and additionally influenced by schizophrenia risk alleles. The latter could affect cognitive ability via processes intrinsic to schizophrenia pathophysiologic factors and/or via consequences of having schizophrenia, such as medication effects or social isolation. It is of interest that a recent study of 22q11.2 deletion syndrome also found evidence of an association between decline in intelligence and schizophrenia PRS.<sup>45</sup> Another possibility is that schizophrenia PRS predominantly influences fluid intelligence (primary component of the MATRICS Consensus Cognitive Battery) as opposed to crystallized intelligence (primary component of the National Adult Reading Test), which

may be more related to intelligence PRS.<sup>46</sup> The genetic basis of cognitive impairment in schizophrenia is an important area for future research given the association between cognitive impairment and poor functional outcome in schizophrenia.<sup>47</sup> Studies investigating the association between schizophrenia PRS and cognitive ability in patients with schizophrenia have reported inconsistent findings,<sup>4,17</sup> which may be owing to differences in the duration between schizophrenia onset and cognitive assessment and the aspects of cognition measured.<sup>48</sup>

The phenotypic correlation between the disorganized and cognitive ability dimensions in our study was low ( $-0.12$ ), consistent with previous studies,<sup>49</sup> and in the model including all dimensions, schizophrenia PRS was significantly associated with both the disorganized and cognitive ability dimensions. These findings suggest that disorganized symptoms and current cognitive ability in patients with schizophrenia are independent markers of genetic liability to schizophrenia. In addition to disorganized symptoms and cognitive ability being influenced by common schizophrenia genetic risk factors, these and the other phenotypes assessed might be influenced by rarer schizophrenia genetic risk factors, genetic factors independent of schizophrenia liability, and a range of environmental factors.<sup>1</sup>

### Strengths and Limitations

A key strength of this study is the use of 3 independent samples, each with well-characterized symptom data derived from both interview and clinical case records focusing on lifetime symptoms. The symptom dimensions were identified from the Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms in all 3 samples, thus allowing for relatively high consistency of symptom dimension measures. The study included cognitive ability as well as symptom dimensions as distinct phenotypes and optimized phenotypic structure using confirmatory factor analysis.

However, the study findings should be interpreted in the context of several limitations. The results presented in this study are limited by the fact that cognitive data were not available in 2 of the samples, and thus these results require replication in other samples that have dimensional phenotypes including disorganized symptoms and cognitive measures. The lifetime symptom scores were based in part on retrospective reports during interviews, but their use in conjunction with contemporaneous clinical records will have increased the accuracy of the phenotypic measures. In addition, our analyses consisted of individuals of White European ancestry because the sample contained too few participants of non-European ancestry to analyze thoroughly. Thus, further studies are required to establish the generalizability of these findings to all people with schizophrenia.

### Conclusions

The results of this study suggest that variation in disorganized symptoms and cognitive ability in schizophrenia are independent markers of the extent to which individuals carry common genetic risk variants for schizophrenia. Moreover, cog-



nitive performance in schizophrenia reflects genetic liabilities to both schizophrenia and intelligence. Further investigation of the genetic basis of these phenotypes and

underlying mechanisms may have potential to improve diagnosis, prognosis, and development of treatments for aspects of schizophrenia currently associated with poor outcomes.

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