Copy Number Variant Risk Scores Associated With Cognition, Psychopathology, and Brain Structure in Youths in the Philadelphia Neurodevelopmental Cohort

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IMPORTANCE Psychiatric and cognitive phenotypes have been associated with a range of specific, rare copy number variants (CNVs). Moreover, IQ is strongly associated with CNV risk scores that model the predicted risk of CNVs across the genome. But the utility of CNV risk scores for psychiatric phenotypes has been sparsely examined.

OBJECTIVE To determine how CNV risk scores, common genetic variation indexed by polygenic scores (PGSs), and environmental factors combine to associate with cognition and psychopathology in a community sample.

DESIGN, SETTING, AND PARTICIPANTS The Philadelphia Neurodevelopmental Cohort is a community-based study examining genetics, psychopathology, neurocognition, and neuroimaging. Participants were recruited through the Children's Hospital of Philadelphia pediatric network. Participants with stable health and fluency in English underwent genotypic and phenotypic characterization from November 5, 2009, through December 30, 2011. Data were analyzed from January 1 through July 30, 2021.

EXPOSURES The study examined (1) CNV risk scores derived from models of burden, predicted intolerance, and gene dosage sensitivity; (2) PGSs from genomewide association studies related to developmental outcomes; and (3) environmental factors, including trauma exposure and neighborhood socioeconomic status.

MAIN OUTCOMES AND MEASURES The study examined (1) neurocognition, with the Penn Computerized Neurocognitive Battery; (2) psychopathology, with structured interviews based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children; and (3) brain volume, with magnetic resonance imaging.

RESULTS Participants included 9498 youths aged 8 to 21 years; 4906 (51.7%) were female, and the mean (SD) age was 14.2 (3.7) years. After quality control, 18 185 total CNVs greater than 50 kilobases (10 517 deletions and 7668 duplications) were identified in 7101 unrelated participants genotyped on Illumina arrays. In these participants, elevated CNV risk scores were associated with lower overall accuracy on cognitive tests (standardized β = 0.12, 95% CI, 0.10-0.14; P = 7.41 × 10⁻²⁶); lower accuracy across a range of cognitive subdomains; increased overall psychopathology; increased psychosis-spectrum symptoms; and higher deviation from a normative developmental model of brain volume. Statistical models of developmental outcomes were significantly improved when CNV risk scores were combined with PGSs and environmental factors.

CONCLUSIONS AND RELEVANCE In this study, elevated CNV risk scores were associated with lower cognitive ability, higher psychopathology including psychosis-spectrum symptoms, and greater deviations from normative magnetic resonance imaging models of brain development. Together, these results represent a step toward synthesizing rare genetic, common genetic, and environmental factors to understand clinically relevant outcomes in youth.
Deletions or duplications of genomic segments known as copy number variants (CNVs) are major contributors to liability for complex diseases, including mental illness. Many so-called genomic disorders, historically characterized by sets of clinical features and now linked to specific recurrent CNVs, are associated with autism, schizophrenia, and intellectual disability.1-5 For example, up to 25% of individuals with 22q11.2 deletion syndrome develop schizophrenia.6 Multiple recurrent CNVs have also been associated with cognitive outcomes7,8 and depressive symptoms in adults.9 However, most clinically relevant CNVs are ultra-rare, with frequencies too low for sufficiently powered tests of genomewide association.10 In the clinical setting, screening children with neurodevelopmental disorders using chromosomal microarrays identifies potentially causal CNVs in 10% to 15% of cases.11-13 Yet the association of CNVs (especially nonrecurrent CNVs) with psychiatric morbidity has only been sparsely explored.

Despite continued advances, serious obstacles limit the diagnostically and prognostic potential of CNVs in psychiatry. Many CNVs exhibit variable penetrance and expressivity.1 This interindividual phenotypic variability highlights the importance of simultaneously considering other risk factors, including common genetic variation, environmental factors, and cumulative burden of multiple CNVs.14-16 Another limitation is that pathogenicity of ultra-rare CNVs is, in essence, binary in the clinical context (ie, disease causing or not), in contrast with continuous measures of symptomatology in contemporary psychiatric phenotyping.17 Notably, recent work leveraged annotations of haploinsufficient genes 18,19 (genes whose function is sensitive to copy number loss) to derive CNV risk scores that predict IQ loss and autism risk for both recurrent and nonrecurrent CNVs.20-22 For example, IQ quantitative models estimated a negative effect size of 2.6 IQ points for deletions and 0.8 IQ points for duplications per unit of predicted haploinsufficiency intolerance, successfully predicting IQ in recurrent pathogenic CNVs.21 These studies motivate further research to characterize associations between CNV risk scores and dimensional measures of psychopathology as well as finer-grained measures of cognitive performance beyond IQ.

To advance work on quantitative models of CNV-related developmental outcomes, there are also compelling reasons to investigate a combined framework that integrates common genetic and environmental factors. It is well established that exposures to long-term and acute environmental stressors are strongly associated with interindividual variability in domains of cognition and psychopathology.23-26 Moreover, the multiple hit model of cumulative genetic and environmental impacts has support from numerous sources.27-30 Complementarily, the cumulative impact of common variants, as quantified by polygenic scores (PGSs), explains significant variance in many complex traits, eg, approximately 3% of variance in general intelligence (g)31,32 and up to 7% of liability for schizophrenia.33 Moreover, PGSs may have greater predictive power in at-risk individuals, including individuals with genomic disorders.10

In the present study, associations between CNVs and developmental outcomes were investigated in the Philadelphia Neurodevelopmental Cohort (PNC), a well-characterized community sample where CNVs have not previously been examined. The PNC included comprehensive clinical assessments, cognitive batteries, and brain magnetic resonance images (MRIs) during the critical period of adolescence.33,34 This allowed the present study to assess, in concert, subdomains of cognition and clinical symptomatology; neuroimaging phenotypes; common genetic variation in the form of PGSs; and environmental risk factors, eg, socioeconomic burden and history of trauma exposure. We aimed to (1) evaluate, in a large developmental cohort, the previously reported quantitative association between CNV risk scores and cognition; (2) examine associations between CNV risk scores and subdomains of clinical symptomatology as well as measures of deviation from typical brain development indexed by MRI; and (3) investigate models that integrate CNV risk scores with PGSs and environmental factors. We hypothesized that risk scores derived from integrating all CNV-associated genes, weighted by intolerance or dosage sensitivity scores,35 would be preferentially associated with cognitive and clinical symptom domains, combining with PGS and environmental factors to explain interindividual variation in a range of developmental outcomes.

**Methods**

**Study Description**

Study procedures for the PNC33,34,36 (9498 participants aged 8 to 21 years) were approved by institutional review boards of Children’s Hospital of Philadelphia and University of Pennsylvania. All participants, parents, or guardians provided informed consent, and minors provided assent. Outcomes of interest included dimensional cognitive function37,38 and psychopathology39-44 (eMethods 1 in the Supplement). Associations with these outcome measures were hypothesized for environmental factors (eMethods 2 in the Supplement).36-45 CNV risk scores, including measures of total size, gene content, intolerance to haploinsufficiency, and dosage sensitivity (eTables 2 to 4 and eFigures 1 and 2 in the Supplement); and PGSs, including autism

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**Key Points**

**Question** How do copy number variants (CNVs) combine with common genetic variants and environmental factors to help explain variability in cognition and psychopathology in a community sample?

**Findings** In this community-based cohort study including 9498 youths in the Philadelphia Neurodevelopmental Cohort, elevated CNV risk scores were associated with lower cognitive ability and more subtly associated with both higher overall psychopathology and higher psychosis-spectrum symptoms. Statistical models of cognitive and psychopathological outcomes were significantly improved when CNV risk scores were combined with polygenic scores and quantitative measures of environmental stress.

**Meaning** It is important to integrate rare genetic, common genetic, and environmental factors in investigations of clinically relevant developmental outcomes.
spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder (MDD), schizophrenia, and intelligence (g) (eMethods 5 in the Supplement). Owing to current genomewide association study (GWAS) limitations, PGSs could only be reliably calculated in individuals in the European ancestry cohort. The subset of PNC participants who underwent brain MRI were also analyzed using a measure of deviation from a normative model of brain development and its association with CNV risk scores (eMethods 6 in the Supplement). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Statistical Analysis
As in prior work, cognitive and psychopathological outcomes were age-normalized prior to subsequent analyses. Biological sex and self-identified race were included as demographic covariates in statistical models, along with 10 ancestry principal components (eMethods 4 in the Supplement). Models were evaluated systematically by the stepwise inclusion of CNV risk scores, environmental stressors, and PGSs, using multivariable linear and logistic regression in the stats package in R version 3.6.3 (The R Foundation). All β coefficients reported were standardized to provide a measure of effect size. Using the summary.lm function in R, t statistics were calculated from each β estimate and its standard error, and 2-tailed P values indicated the probability of observing as large a t statistic under the null hypothesis that β = 0. Correction for multiple comparisons was performed via the Benjamini-Hochberg false discovery rate, with a threshold for statistical significance of adjusted P less than .05.

Results
Participants included 9498 youths aged 8 to 21 years; 4906 (51.7%) were female, and the mean (SD) age was 14.2 (3.7) years. The CNV sample after quality control comprised 7543 unrelated youths, 7101 genotyped on Illumina Infinium Beadchip arrays (aged 8 to 21 years; mean [SD] age, 14.2 [3.7] years; African American, 1818 [26%]; European American, 4482 [63%]; other race [including American Indian, Asian, Native Hawaiian or Other Pacific Islander, and multiracial], 801 [11%]; eTable 1 in the Supplement). In these participants, 18 185 total CNVs (10 517 deletions, 7668 duplications) were identified (Figure 1A). CNV risk scores were quantified in terms of the cumulative size of deletions or duplications; total number of genes encompassed by CNVs; intolerance scores, measured by genes’ probability of loss intolerance or the inverse loss-of-function observed/expected upper bound fraction (1/LOEU); and dosage sensitivity scores, measured by the probability of haploinsufficiency (pHI) in deletions and probability of triplosensitivity (pTS) in duplications (eTables 2 to 4 and eFigures 3 and 4 in the Supplement).

CVN Risk Score Associations With Cognition
To determine if CNVs had the hypothesized, cumulative association with cognitive outcomes, regression models were run with overall accuracy (a proxy for generalized intelligence) and multiple subdomains of cognition, showing robust associations with measures of CNV burden scores (eg, association between total CNV deletion size and overall accuracy: standardized β = −0.08; 95% CI, −0.11 to −0.06; P = 1.28 × 10⁻¹³), intolerance and dosage sensitivity scores (eg, association between CNV pHIscore and overall accuracy: β = −0.12; 95% CI, −0.14 to −0.10; P = 7.41 × 10⁻²⁶; Table 1). There was little evidence of specificity with respect to CNV associations with distinct cognitive domains (Figure 1B and C; eFigure 1 in the Supplement).

If CNV risk scores that incorporate annotations of intolerance and dosage sensitivity improve associations with clinically relevant outcomes, then these models should outperform simpler models based on CNV burden. This prediction was borne out, and pHI/pTS scores outperformed other annotations as measured by a decrease in Akaike information criteria (AIC) (Table 1). Because the distribution of CNV risk scores was positively skewed consistent with benign CNVs comprising the large majority (Figure 1A; eFigures 3 and 4 in the Supplement), logarithmic and categorical transformations of CNV risk scores were analyzed and also showed strong associations with outcomes (eg, log[probability of loss intolerance deletions]; β = −0.10; 95% CI, −0.13 to −0.08; P = 2.90 × 10⁻¹⁵; pHIGreater than 0 vs pHI of 0; β = −0.16; 95% CI, −0.24 to −0.09; P = 3.24 × 10⁻⁴).

According to the multiple hit hypothesis, CNVs and environmental stressors are expected to jointly affect neurodevelopmental outcomes. Adding information about neighborhood-level socioeconomic factors and individual-level trauma exposures did strengthen associations with cognitive outcomes in addition to CNVs (eg, for overall accuracy; model with pHI/pTS and covariates: AIC = 18 922; model with environmental factors and covariates: AIC = 18 555; model with pHI/pTS and environmental measures: AIC = 18 419) (Table 2; eFigure 5 in the Supplement).

CNV Risk Score Associations With Psychopathology
Compared with the association with cognitive phenotypes, CNV risk scores had subtler but significant associations with psychopathology (Table 2). Specifically, higher pHIsensitivity scores were associated with higher overall psychopathology (β = 0.03; 95% CI, 0.00-0.05; P = 2.21 × 10⁻⁵), externalizing symptoms (β = 0.03; 95% CI, 0.00-0.05; P = 2.59 × 10⁻²) and psychosis-spectrum symptoms (β = 0.05; 95% CI, 0.03-0.08; P = 3.48 × 10⁻³) (Figure 1B and C). Higher pHIs were also associated with higher odds of categorical psychiatric diagnoses (psycosis spectrum: β = 0.13; 95% CI, 0.06-0.20; P = 4.61 × 10⁻⁴; ADHD: β = 0.11; 95% CI, 0.04-0.18; P = 0.003; eTable 3 in the Supplement). CNV deletion risk scores were therefore associated with both categorical and dimensional psychopathology. In contrast to cognitive outcomes, we did not observe significant association between CNV duplication scores and psychopathology after false discovery rate correction. Similar to cognitive outcomes, adding information about environmental stressors improved models of psychopathology outcomes (eg, psychosis-spectrum symptoms; model with pHIPTS and covariates: AIC = 19 519; model with pHIPTS, and
Figure 1. Copy Number Variants (CNVs) Larger Than 50 Kilobases Identified in the Philadelphia Neurodevelopmental Cohort and the Association of CNV Risk Scores With Cognitive and Psychopathological Outcomes

A. CNVs across chromosomes. Left panel shows the total number of CNVs and the subset of genic CNVs encompassing at least 1 gene. Right panel shows the number of CNVs with risk scores greater than 0 or greater than 1. CNV risk scores were derived from the cumulative probability of haploinsufficiency (pHI; a measure of sensitivity to deletion) or probability of triplosensitivity (pTS; a measure of sensitivity to duplication). See Table 1 and eFigure 3 in the Supplement for additional information. B. Two-dimensional density plots of risk scores showing associations with overall cognition accuracy (top panel) and psychosis-spectrum symptomatology (bottom panel). C. Dot plots of effect sizes (standardized β coefficients) for associations of risk scores with 8 cognitive outcomes (top panel), and psychopathology outcomes generated via bifactor models (middle panel) and correlated traits factor models (bottom panel). Cognitive outcomes included speed and accuracy scores for specific and global measures; slow speed is summarized from items requiring deliberation, while fast speed indexes rapid decisions. All outcome measures were age-normalized. Additional covariates included self-identified race, sex, and 10 ancestry principal components. These analyses were generated based on the multiancestry sample of 7101 participants genotyped on illumina arrays that met quality-control criteria. P values were corrected for 34 comparisons using Benjamin-Hochberg false discovery rate (FDR). NS indicates not significant.
Table 1. Association of Copy Number Variant (CNV) Risk Scores With Overall Cognitive Accuracya

| CNV risk scores | Standardized β (95% CI) | P value | FDR-adjusted P value | Adjusted $r^2$ | AIC |
|-----------------|--------------------------|---------|----------------------|----------------|-----|
| **pHI**         |                          |         |                      |                |     |
| Deletion pHI    | −0.121 (−0.144 to −0.099) | 7.41 × 10^{-26} | 9.49 × 10^{-24} | 0.125         | 18 922 |
| Duplication pTS | −0.054 (−0.076 to −0.032) | 1.31 × 10^{-6} | 1.47 × 10^{-4}   |                |     |
| **pLI**         |                          |         |                      |                |     |
| Deletion        | −0.117 (−0.14 to −0.094)  | 1.03 × 10^{-23} | 1.30 × 10^{-21}   | 0.124         | 18 928 |
| Duplication     | −0.059 (−0.081 to −0.037) | 1.06 × 10^{-7} | 1.20 × 10^{-5}   |                |     |
| **LOEUF**       |                          |         |                      |                |     |
| Deletion        | −0.118 (−0.14 to −0.095)  | 2.94 × 10^{-24} | 3.73 × 10^{-22}   | 0.123         | 18 937 |
| Duplication     | −0.044 (−0.066 to −0.022) | 7.38 × 10^{-5} | .008               |                |     |
| **Log(pLI)**    |                          |         |                      |                |     |
| Deletion        | −0.103 (−0.126 to −0.081) | 2.90 × 10^{-19} | 3.63 × 10^{-17}   | 0.121         | 18 959 |
| Duplication     | −0.046 (−0.068 to −0.025) | 2.82 × 10^{-5} | .004               |                |     |
| **N genes**     |                          |         |                      |                |     |
| Deletion        | −0.092 (−0.114 to −0.069) | 1.85 × 10^{-15} | 2.29 × 10^{-13}   | 0.117         | 19 898 |
| Duplication     | −0.022 (−0.044 to 0.000)  | .049    | >.99                |                |     |
| **Total size**  |                          |         |                      |                |     |
| Deletion        | −0.084 (−0.106 to −0.062) | 1.28 × 10^{-13} | 1.57 × 10^{-11}   | 0.115         | 19 001 |
| Duplication     | 0.001 (−0.021 to 0.023)   | .91     | >.99                |                |     |
| **Log(1/LOEUF)**|                          |         |                      |                |     |
| Deletion        | −0.066 (−0.089 to −0.044) | 7.07 × 10^{-9} | 8.06 × 10^{-7}    | 0.113         | 19 021 |
| Duplication     | −0.013 (−0.035 to 0.009)  | .25     | >.99                |                |     |
| **pHI>0 / pTS>0**|                          |         |                      |                |     |
| Deletion pHI>0  | −0.162 (−0.238 to −0.085) | 3.24 × 10^{-5} | .004               | 0.111         | 19 038 |
| Duplication pTS>0 | −0.032 (−0.084 to 0.019) | .22     | >.99                |                |     |

Abbreviations: AIC, Akaike information criterion; FDR, false discovery rate; LOEUF, loss-of-function observed/expected upper bound fraction; pHI, probability of haploinsufficiency; PLOI, probability of loss intolerance; pTS, probability of triplosensitivity.

a Rows are sorted from lowest to highest AIC, where lower AIC indicates a superior model fit. Overall accuracy scores were age-normalized, and additional covariates included self-identified race, sex, and 10 ancestry principal components. This table was generated from the multiancestry sample of 7101 participants genotyped on Illumina arrays that met quality-control criteria, and P values were corrected for 16 comparisons using the Benjamini-Hochberg FDR.

Table 2. Models of Cognitive and Psychopathological Outcomes Associated With Copy Number Variant (CNV) Risk Scores Indexed by Dosage Sensitivity and Environmental Factorsa,b

| Outcome                  | Demographic covariates | CNV risk scores | Environmental factors | Environmental factors and CNV risk scores |
|--------------------------|------------------------|-----------------|-----------------------|------------------------------------------|
|                          | AIC        | Adjusted $r^2$ | AIC        | Adjusted $r^2$ | AIC        | Adjusted $r^2$ | AIC        | Adjusted $r^2$ |
| Overall accuracy         | 19 053     | 0.108           | 18 922     | 0.125           | 18 555     | 0.126           | 18 419     | 0.143           |
| Executive complex cognition accuracy | 18 752 | 0.148           | 18 646     | 0.161           | 18 291     | 0.166           | 18 181     | 0.179           |
| Memory accuracy          | 19 499     | 0.031           | 19 416     | 0.043           | 19 087     | 0.039           | 19 002     | 0.051           |
| Social cognition accuracy | 19 849  | 0.024           | 19 775     | 0.035           | 19 483     | 0.030           | 19 411     | 0.040           |
| Overall psychopathology  | 19 511     | 0.033           | 19 508     | 0.034           | 18 511     | 0.034           | 18 507     | 0.031           |
| Psychosis spectrum       | 19 527     | 0.032           | 19 519     | 0.034           | 18 620     | 0.015           | 18 608     | 0.015           |
| Externalizing            | 19 397     | 0.046           | 19 393     | 0.047           | 18 794     | 0.125           | 18 789     | 0.126           |
| Fear                     | 19 366     | 0.042           | 19 365     | 0.043           | 18 979     | 0.094           | 18 978     | 0.095           |
| Mood                     | 19 649     | 0.018           | 19 650     | 0.018           | 18 816     | 0.128           | 18 816     | 0.129           |

Abbreviation: AIC, Akaike information criterion.

a For dosage sensitivity, probability of haploinsufficiency was used for deletions and probability of triplosensitivity was used for duplications. For environmental factors, neighborhood socioeconomic status and trauma exposures were used.

b AIC and adjusted $r^2$ are shown for models with increasing complexity, from left to right: demographic covariates only (self-identified race, sex, and 10 ancestry principal components); CNV risk scores and demographic covariates; environmental factors and demographic covariates; and CNV risk scores, environmental factors, and demographic covariates. This table was generated from the multiancestry sample of 7101 participants genotyped on Illumina arrays that met quality-control criteria. All outcome measures were age-normalized.

environmental measures: AIC = 18 608) (Table 2; eFigure 5 in the Supplement).

Combined Analysis of CNV Risk Scores, PGSs, and Environmental Factors

Owing to current GWAS limitations, we focused on the European ancestry subcohort (n = 4482) to further assess models that included PGSs in addition to environmental factors and CNV risk scores. Compared with models including only CNV risk scores and environmental factors, the addition of PGSs improved models for both cognitive and psychopathology outcomes (eTable 4 in the Supplement). By far the strongest PGS associations were between the intelligence PGS and cognition (eg, overall accuracy: β = 0.27; 95% CI, 0.24-0.30; $P = 7.2 \times 10^{-7}$) (Figure 2; eFigure 6 in the Supplement). Other significant associations were between the MDD PGS and mood symptoms (β = 0.06; 95% CI, 0.03-0.09; $P = 3.58 \times 10^{-4}$) and cognition (eg, overall accuracy: β = 0.04; 95% CI, 0.01-0.07;
High CNV risk scores were positively associated with neuroimaging deviations from normative ranges (Figure 3). Of 920 multiancestry participants with structural imaging after quality control, 59 participants were characterized as having high CNV risk scores, defined as either total pHI greater than 1 (deletions) or pTS greater than 1 (duplications). Of these participants with high-risk scores, 32 of 59 (54%) were also categorized as high deviation based on neuroimaging normative models (eMethods 6 in the Supplement). An exploratory analysis was conducted to test for interactions effects between CNV risk scores and environmental factors or PGSs, and no interaction effects were significant after multiple comparisons correction (eMethods 7 and eTable 5 in the Supplement).

**Neuroimaging**

CNV duplication cumulative probability of triplosensitivity and PGSs for autism spectrum disorder, bipolar disorder, and schizophrenia. All outcome measures were age-normalized, and additional covariates included self-identified race, sex, and 10 ancestry principal components in all models. This analysis was conducted in the European ancestry sample and included 4482 individuals genotyped with Illumina arrays that met quality-control criteria, and P values were corrected for 90 comparisons using the Benjamini-Hochberg false discovery rate (FDR). NS indicates not significant.
Sensitivity Analyses

We performed a number of sensitivity analyses to investigate the robustness of reported findings (eMethods 8 in the Supplement). Using a literature-defined set of known pathogenic CNVs, we excluded 130 participants with known pathogenic CNVs, demonstrating that associations with CNV risk scores were not entirely due to effects of known pathogenic CNVs (although the degree of statistical significance and the strength of associations were altered for some of the outcome measures; eTables 6 and 7 and eFigure 8 in the Supplement). Further sensitivity analyses confirmed the robustness of the main results to the inclusion of X chromosome CNVs (eTable 8 in the Supplement), individuals genotyped with Affymetrix arrays (eTable 9 in the Supplement), the inclusion of demographic covariates (eTables 10 and 11 in the Supplement), and the inclusion of random effects to control for heterogeneity in array technology (eTable 12 and eFigure 9 in the Supplement).

Discussion

The present results constitute a step toward synthesizing rare genetic, common genetic, and environmental factors to improve our understanding of their associations with clinically relevant outcomes in youth. Our study shows the joint association of CNVs (recurrent or nonrecurrent), common genetic variation (PGSs), and measures of environmental stress with clinical and subclinical psychopathology and cognitive outcomes. In general, statistical significance and effect sizes were stronger for cognitive outcomes compared with psychopathological outcomes and for deletions compared with duplications, and models were improved by the addition of information about environmental factors and PGSs as well as CNV risk scores. CNV risk scores were also associated with deviations from a normative model of MRI-derived brain structure.51 We show that CNV-related associations can be investigated with CNV risk scores even in cohorts not powered for genomewide discovery, which often benefit from deeper phenotyping than is typical in large-scale genetic studies.
Our results suggest that CNV risk scores are associated with a range of dimensions of psychopathology, including the psychosis spectrum. Importantly, associations with the psychosis dimension persist when controlling for overall psychopathology, suggesting an association beyond that with general psychiatric morbidity. In addition, these associations persist when known pathogenic CNVs, such as 22q11.2 deletion syndrome, are excluded from models. While the lack of significant associations with some other psychiatric symptom domains may be a false-negative owing to insufficient statistical power, the association with psychosis is consistent with an impact by both recurrent and nonrecurrent CNVs on early neurodevelopmental mechanisms that mediate risk for psychosis symptoms.52-54

It is important to note that CNVs with high risk scores, based on computational annotations of deleted or duplicated genomic segments, are not necessarily pathogenic in the sense of a known clinical association from prior literature. Relevant clinical information could be provided even for ultra-rare CNVs, where case-control studies of multiple patients with the same structural variant are not feasible but elevated risk scores have been associated with psychopathology. Moreover, even known pathogenic CNVs have variable associations with dimensional outcome measures, which can be captured by risk scores, providing information beyond that afforded by a binary index of pathogenicity. Conceptually, CNV risk scores bear similarities to PGSs, where individuals with similar PGSs do not necessarily overlap in terms of specific common variants. While PGSs can be derived for specific psychiatric outcomes based on available GWAS, however, CNV risk scores are based on CNV burden, intolerance, and dosage sensitivity of encompassed genes.

The present study compares different CNV risk scores derived from gene-level annotations of intolerance and dosage sensitivity, including recently reported models that distinguish between haploinsufficiency and triplosensitivity (eMethods 4 in the Supplement). Prior research suggests differences between haploinsufficient and triplosensitive genes in size, distance from other genes, and precision of developmental regulation. Although deletions tend to be more damaging than duplications, both are associated with psychiatric illness, and mechanisms of pathogenicity are likely more variable for duplications than CNVs with high risk scores, PGSs, and environmental stressors, including neighborhood environment and individual-level trauma exposures (eMethods 7 in the Supplement). An important area of future work is to continue to investigate the possibility of convergent molecular or functional pathways mediating the association between CNV risk scores and developmental outcomes, and potentially optimizing risk scores for specific psychiatric contexts.

When PGSs were included in models in addition to CNV risk scores, results suggested stronger associations with cognition compared with weaker but significant associations with psychopathology dimensions, likely owing to various methodological and biological factors. Although surprising given the high-quality schizophrenia GWAS, the lack of significant correlation between schizophrenia PGS and psychotic-spectrum symptoms is consistent with prior studies, possibly reflecting that liability for adult schizophrenia generalizes poorly to subthreshold psychotic symptoms in youth.60-63 Studies of threshold psychotic symptoms in adults suggest that risk conferred by recurrent CNVs is augmented by high schizophrenia PGSs.16 Our observed associations between ADHD PGSs and externalizing symptoms, and between MDD PGSs and mood symptoms, are highly credible. The finding that MDD PGS has a positive association with overall accuracy, executive, and social cognition is surprising, but prior reports do suggest that subthreshold depressive symptoms may have positive associations with cognition (especially with social domains). Future work will continue to explore indices of common variant effects in developmental samples, where cross-disorder liability may be particularly important.

**Limitations**

Several additional methodological limitations should be noted. First, PGSs could only be reliably calculated on individuals with European ancestry. This limitation is not specific to our study but an unfortunate reality of racial bias in the underlying GWAS data that will hopefully be addressed by increasing diversity of genetic samples. Second, there was heterogeneity in the array technology used for PNC genotyping (eMethods 3, 4, 5, and 8 in the Supplement). Third, with respect to environmental stressors, temporal information about trauma was not collected, so early developmental traumatic events that may be particularly impactful could not be distinguished. Genetic trios were also not available, which would have allowed for characterization of de novo variants and parent-offspring correlation in outcome measures—especially in concert with more in-depth phenotyping of parents and familial environmental exposures (eMethods 9 and eFigure 11 in the Supplement). Fourth, neuroimaging normative models were derived from global tissue volumes, where centile scores can be reliably calculated relative to a robust population-based model. A goal for future work is to incorporate additional neuroimaging phenotypes into normative models.

The results of the present study are consistent with multiple hit hypotheses about functional outcomes. CNV risk scores, PGSs, and environmental stressors, including neighborhood environment and individual-level trauma exposures (previously analyzed without incorporating genetic information), were jointly associated with cognitive and psychopathological outcomes in a developmental sample. The lack of statistically significant interaction effects between these exposures should be interpreted cautiously, as larger samples are likely required to reliably disambiguate additive and interactive effects (eMethods 7 in the Supplement). Moreover, the clinical importance of multiple hits is supported even if only additive effects are considered.

**Conclusions**

This community-based cohort study suggests that integrating multiple domains of environmental and genetic exposure, including common genetic variation indexed by PGSs and rare genetic variation indexed by CNV risk scores, may improve our understanding of contributors to psychiatric and cognitive outcomes in neurodevelopment.
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