Single Nucleotide Polymorphism Heritability of a General Psychopathology Factor in Children

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Objective: Co-occurrence of mental disorders is commonly observed, but the etiology underlying this observation is poorly understood. Studies in adolescents and adults have identified a general psychopathology factor associated with a high risk for different psychiatric disorders. We defined a multi-informant general psychopathology factor in school-aged children and estimated its single nucleotide polymorphism (SNP) heritability. The goal was to test the hypothesis that child behavioral and emotional problems are under the influence of highly pleiotropic common autosomal genetic variants that nonspecifically increase the risk for different dimensions of psychopathology.

Method: Children from the Generation R cohort were repeatedly assessed between ages 6 to 8 years. Child behavior problems were reported by parents, teachers, and children. Confirmatory factor analysis estimated a general psychopathology factor across informants using various psychiatric problem scales. Validation of the general psychopathology factor was based on IQ and temperamental measures. Genome-wide complex trait analysis (GCTA) was used to estimate the SNP heritability (N = 2,115).

Results: The general psychopathology factor was associated with lower IQ, higher negative affectivity, and lower effortful control, but not with surgency. Importantly, the general psychopathology factor showed a significant SNP heritability of 38% (SE = 0.16, $p = .008$).

Conclusion: Common autosomal SNPs are pleiotropically associated with internalizing, externalizing, and other child behavior problems, and underlie a general psychopathology factor in childhood.

Key words: child behavior, psychopathology, comorbidity, genetic pleiotropy, SNP heritability

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Co-occurrence of mental disorders is commonly observed in clinical and epidemiological studies.[1,2] Family studies have shown familial co-aggregation for many common disorders such as depressive and anxiety disorders, but also attention-deficit/hyperactivity disorder (ADHD), conduct problems, and psychosis.[3,4] This coincides with the observation that many risk factors for psychopathology, like stressful life events,[5] are not disorder specific. Research suggests the existence of a general psychopathology factor, which is associated with high risk of developing a broad range of both internalizing and externalizing mental disorders and problems[6,7] in preschool children,[8] school-aged children,[9] adolescents,[10-12] and adults.[6] In one study, a latent general factor based on repeated assessments of psychiatric symptoms over a 20-year period explained on average 42% of the disorder variance.[13] In another large multi-ethnic adult sample, a general factor was estimated to explain between 29% and 67%, depending on the diagnosis.[14] The general psychopathology factor might be especially prominent in children, as it has been argued that psychiatric disorders are not as differentiated at young ages, although the notion has been recently challenged.[15] Most of the aforementioned studies used *DSM*-oriented scales; however, the general psychopathology factor was also replicated in studies using problem scales/items in general population samples.[12,15] Both assessment approaches show concurrent validity with *DSM* diagnoses (see e.g. Ebesutani *et al.*[16]); therefore, a general psychopathology factor can be estimated with a variety of instruments.

Given the consistent statistical evidence for common etiological pathways between psychopathology domains, the question arises to what extent these pathways are genetic. Twin studies have indicated that a common genetic factor influences a broad range of behavioral and emotional problems in child and adolescent study participants,[7,17-19] which can explain the observed co-occurrence to a large degree. However, as twin studies use familial information, it is unclear which specific genetic mechanisms are at play. It is unclear to what extent this heritability can be explained by common or rare variants, single nucleotide polymorphisms (SNP) or structural variants, additive effects, or nonadditive effects such as epistasis. Thus our goal was to test the hypothesis that the general psychopathology factor represents the additive effects of common SNPs, and to estimate the

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Supplemental material cited in this article is available online.

variance explained by these (SNP heritability). Various adult psychiatric diagnoses show substantial genetic correlations (up to 0.68) based on common autosomal variants[20]; however, the SNP heritability of a general psychopathology factor is unknown. To estimate the SNP heritability, we used genomic restricted maximum likelihood estimation (GREML), which estimates heritability by quantifying the extent to which individuals who share more SNP alleles also are more similar phenotypically.[21]

To test the hypothesis, we first defined general psychopathology factors using multi-informant data (i.e., parent, teacher, and child self-report measures), in a large population-based cohort: the Generation R study. Psychiatric research in young children that relies on a single informant, most often a parent, may bias results and inflate correlations between behavior subscales because of common method variance.[22] For the calculation of the general psychopathology factor score, we extended a validated model,[13] which has been replicated in adolescents,[12] by including autistic-like behaviors and accounting for the multiple informant context. To test the validity of our general factor, we examined its association with intelligence and temperament. Intelligence is an important criterion variable for several reasons: it is measured independently of psychopathology, and is an indicator of neurodevelopment. Furthermore, low IQ has previously been associated with general factors of psychopathology.[9,13] Higher levels of neuroticism have also been observed with a general risk for psychopathology.[8,13,19]

METHOD

Participants

This study features participants from a population-based birth cohort, the Generation R Study,[23] designed to identify early environmental and genetic predictors of development and health from fetal life onward. All participating children were born between April 2002 and January 2006. A total of 6,624 children were all repeatedly assessed during the ages 6 to 8 years, of whom 1,954 had complete data on all problem subscales of all instruments and were used in a confirmatory factor analysis (CFA) of the general psychopathology model. We established the associations between the subscales and the factor in the set with complete data and then applied this information to estimate factor scores in the incomplete dataset using multiple imputation (see Supplement 1, Method, available online). IQ information was available in 1,826 children with complete problem subscales, and temperament information was available in 1,933 children.

The sample used for the nongenetic analyses was multi-ethnic: the majority had a Dutch, Surinamese, Turkish, or Moroccan ethnic background. However, for GREML analyses, only children with genetic data and of European ancestry were eligible (n = 2,353). A total of 238 participants were removed from analysis due to excessive relatedness, resulting in a final GREML sample size of 2,115. All parents gave informed consent for their children's participation and teacher report. Study protocols were approved by the local ethics committee.

Instruments

The general psychopathology factor was estimated using parent, teacher, and self-reported measures, which were designed to assess common behavioral and emotional problems in the general population. We took a conservative approach to missing data. All children included in any analysis with incomplete data had at least 50% of observations complete and had been assessed with multiple instruments (see Figure S1, available online, for correlations among all subscales).

Child Behavior Checklist. The Child Behavior Checklist (CBCL) 1½–5 years was used to assess child behavioral problems in preschool-aged children.[24] Questionnaires were completed by the primary caregiver (92% mothers) when children were on average 6 years old (mean = 6.1 years, SD = 0.5 years). The CBCL includes seven subscales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, Aggressive Behavior, and a sumscore of other items.

Social Responsiveness Scale. The Social Responsiveness Scale (SRS) is a parent-report questionnaire assessing autistic-like traits in children.[25] A validated short-form was completed by the primary caregiver (91% mothers) when children were 6 years of age (mean = 6.2 years, SD = 0.5 years). Three subscales were used: Social Cognition, Social Communication, and Autistic Mannerism.

Conners' Parent Rating Scale–Revised. The Conners' Parent Rating Scale–Revised (CPRS-R) is a well-validated questionnaire assessing attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD).[26] It was completed by the primary caregiver (90% mothers) when children were 8 years of age (mean = 8.2 years, SD = 0.2 year). Three scales of the CPRS-R were used: ADHD Inattentive, ADHD Hyperactive-Impulsive, and ODD.

Teacher's Rating Form. Teachers were approached independently of parents at 7 years (mean = 6.8 years, SD = 1.3 years), and completed the Teacher's Rating Form (TRF) at 6 to 18 years.[27] The following subscales were used: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior.

Berkeley Puppet Interview. The Berkeley Puppet Interview (BPI) is a semi-structured interactive interview[28] conducted in our research center with the help of two identical dog hand puppets at 6 years of age (mean = 6.2 years, SD = 0.5 years). The two puppets made opposite statements, and the child was asked to indicate which statement described him/her best. The interview was videotaped and scored with high intercoder reliability.[29] Six subscales were used: Depression, Separation Anxiety, Overanxious, Oppositional Defiant, Overt Hostility, and Conduct Problems.

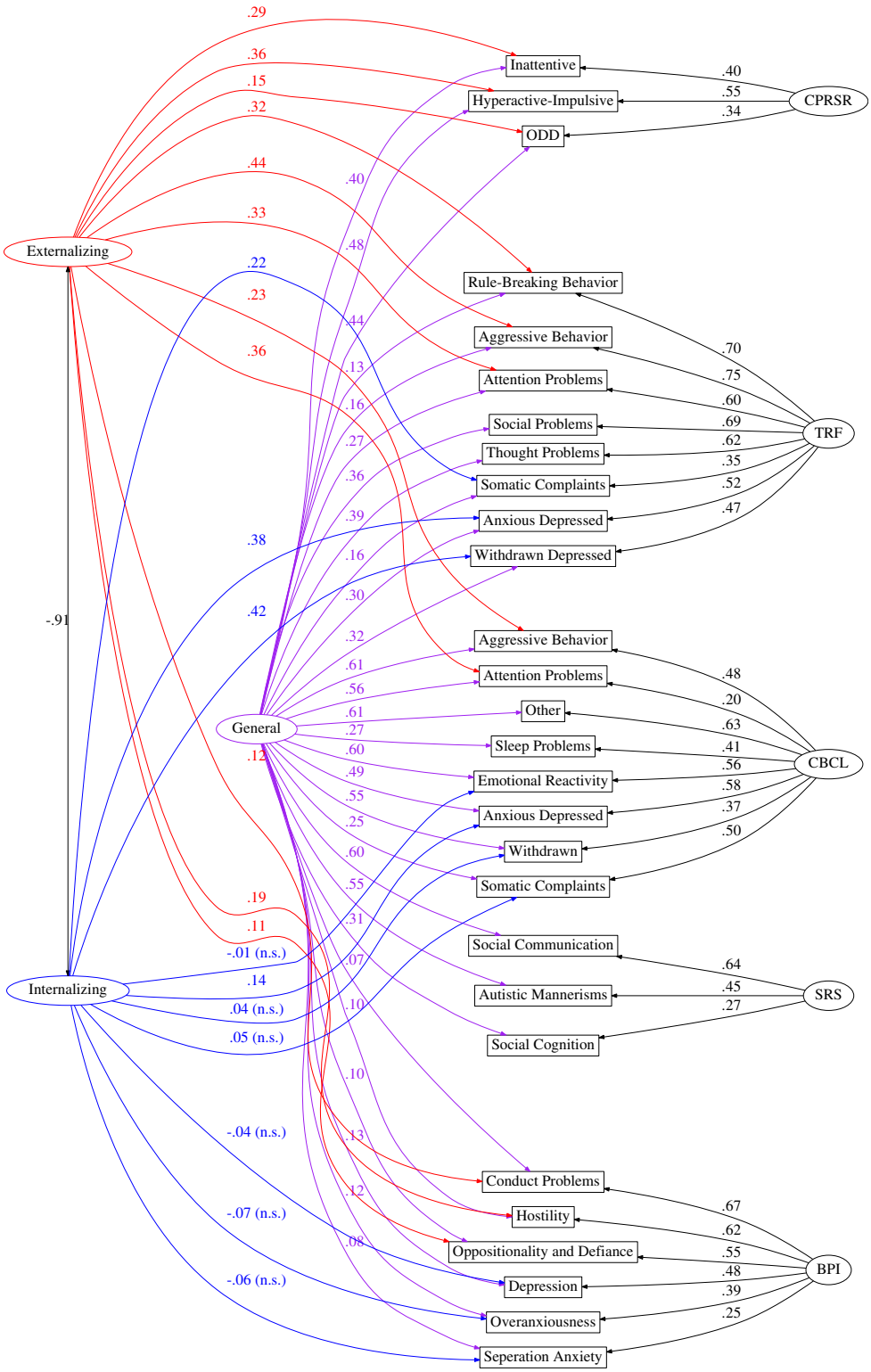
Validation Measures. Nonverbal cognitive abilities were assessed with the Snijder-Oomen nonverbal intelligence test.[30] This is a well-validated test administered at age 6 years. The mean IQ score was 103.9 (SD = 14.2).

We assessed temperamental dimensions (negative affectivity, surgency/extraversion, and effortful control) at age 6 years with the Child Behavior Questionnaire (Very Short Form), a parent-rated questionnaire.[31]

Genotyping and Quality Control

DNA was extracted from whole blood cells from cord blood and genotyped on Illumina 610K/660W platforms. Quality checks for each SNP included sample (≥97.5%) and SNP call rates (≥90%), minor allele frequency ≥1%, and deviation from the Hardy–Weinberg equilibrium ($p < 10^{-7}$). Samples were checked for excess heterozygosity, sex accuracy, relatedness, and missing data. After quality control, 504,617 autosomal SNPs remained. Genetic ancestry was investigated using multidimensional scaling. Participants were classified as of non–northwestern European ancestry when they exceeded 4-SDs difference with the mean European reference level (HapMap CEU) on any of the first four principal components. A

FIGURE 1 Path diagram of the general psychopathology factor model with standardized loadings. Note: Sex and age paths are not displayed. BPI = Berkeley Puppet Interview; CBCL = Child Behavior Checklist; CPRS-R = Conners' Parent Rating Scale–Revised; ODD = oppositional defiant disorder; SRS = Social Responsiveness Scale; TRF = Teacher Report Form.



total of 2,830 participants were classified as of European ancestry, and 2,901 as non–northwestern European. Principal components of ancestry used as covariates in this study were based on the European sample. (See Medina-Gomez *et al.* for further details on the genetic data in Generation R.[32])

Statistical Analyses

We performed the statistical analyses in four steps, as follows: the general psychopathology factor was estimated with a CFA; the general psychopathology factor was associated with IQ and temperament to confirm validity; factor scores were extracted and imputed; and the SNP heritability of the general factor score was estimated.

General Psychopathology Factor Model. The continuous subscales of specific child emotional and behavioral problems constituted the manifest (observed) variables. A latent variable loading on all subscales from all instruments was specified to represent the general psychopathology factor. Two other latent factors loaded on internalizing and externalizing problems. These were allowed to correlate; however, the correlations with the general psychopathology factor were constrained to 0. This bifactor model is adapted from the best-fitting models found in previous studies.[7,12,13] Consequently, the internalizing and externalizing factors represent effects specific to internalizing and externalizing problems, respectively, that cannot be explained by a general vulnerability to psychopathology. The general psychopathology factor in turn represents a general vulnerability, independent of these more specific effects. Sex and age were included as covariates.

To account for within-instrument bias, latent variables specific to the subscales of each instrument were introduced (Figure 1) that were not allowed to correlate with other latent variables. The assumption is that similarities between subscales measured by the same instrument, which are not shared with subscales of other instruments, capture bias due to common method variance. It is therefore important that these instrument-specific latent variables not be correlated with each other. If they were, they would also capture variances, which are shared with other instruments. These cross-instrument effects, however, should contribute to the general factor of psychopathology.

Confirmatory Factor Analysis. The CFA models were fit in a subsample with complete data on all subscales (n = 1,954) using standardized latent variables. Because of violations of assumption of multivariate normality, the maximum likelihood robust estimator was used. The general psychopathology model was formally compared to a simpler model without the general psychopathology factor, but otherwise identical model. Model fit was judged by the following: comparative fit index (CFI), Tucker–Lewis index (TLI), root-mean-square error of approximation (RMSEA), standardized root-mean-square residual (SRMR), and Bayesian information criterion (BIC). Lavaan 0.5-20 in R 3.2.3 was used for the CFA.[33,34] Factor scores were extracted from the CFA model, imputed, and used for further analyses (see Supplement 1, Method, available online).

Validation. To validate the general psychopathology factor, we extended the general psychopathology model to two structural equation models. In one model, IQ predicted the general and specific internalizing and externalizing factors, and in another model, the temperamental dimensions were the predictors.

SNP Heritability. Next, we estimated the variance explained by additive effects of autosomal SNPs using GREML as implemented in GCTA 1.24.7.[21,35] A potential source of bias is the ethnic admixture in the heterogeneous Generation R sample, because participants from different ethnicities, and thus distant genetic relatedness, might have concordant or discordant phenotypes due to environmental correlates of ethnicity and not genetic makeup. To minimize population stratification, we restricted analyses to children with European ancestry (2,830 of 5,731, of whom 2,353 had information on the phenotype). Moreover, we included four principal components of ancestry, which were estimated within the European sample,[32] as covariates (see Supplement 2, Method, available online, for measurement invariance tests between European and non–northwestern European ancestries). To reduce confounding due to shared environment, the conventional GRM cutoff 0.025 was used to exclude close relatives (second-degree cousins and closer) within the European sample (n = 238).[21] The final GREML sample with complete genetic information consisted of 2,115 children of European ancestry.

First, a genetic relatedness matrix (GRM) between unrelated participants was calculated based on autosomal SNPs. Second, restricted maximum likelihood was used to estimate the phenotype (general psychopathology factor scores) variance explained by the random effect of GRM. SNP heritabilities of the specific internalizing and externalizing factors from the general psychopathology factor model are not presented. Lower item count and loadings of these factors make factor score estimation problematic due to factor indeterminacy; thus SNP heritabilities of such factor scores could be misleading. A likelihood ratio test compared whether the inclusion of the GRM significantly improved model fit. The factor score was transformed using ln(score-lowest score+1) to normalize the total genetic effects and residuals distribution. All GREML results were similar for transformed and untransformed factor scores. The total genetic effects were similar for observations with and without imputation (see Supplement 1, Method, available online).

RESULTS

General Psychopathology Factor Model

All psychopathology subscales of all instruments/raters loaded significantly on the general psychopathology factor independent of the more specific internalizing/externalizing factors and the instrument-specific covariances (Table 1). Furthermore, although BIC penalizes models for greater complexity, the BIC was 1,358 points lower for the model including the general factor as opposed to the same model with the general psychopathology factor omitted, providing strong evidence for a difference in model fit (Table 2).[36]

The average loading of the individual psychopathology scales on the general factor was 0.34. Parent-rated subscales showed the highest average loadings (mean = 0.48); teacher ratings showed moderate average loadings (mean = 0.26); and child-report subscales showed modest but still significant average loadings (mean = 0.10). In the hierarchical model with the general factor, the internalizing and externalizing scales correlated strongly and negatively with each other ($r = -0.91$, SE = 0.18, $p < .001$). All externalizing subscales loaded significantly on the externalizing factor. Similarly, all teacher-reported internalizing subscales and the parent-reported Anxious/Depressed subscale loaded on the internalizing factor. No other internalizing subscale loaded on the internalizing factor in the model, including the general psychopathology factor. The instrument-specific latent factors showed moderate loadings ranging from 0.20 to 0.75 (Figure 1), indicating the magnitude of covariance unique to the measurement context.

IQ Associations

The general psychopathology factor was negatively associated with nonverbal IQ, the standardized path coefficient

TABLE 1 Standardized Factor Loadings of the General Psychopathology Factor Model

	General		Specific Ext		Specific Int	
Item	**Loading**	**SE**	**Loading**	**SE**	**Loading**	**SE**
Parent Report						
Emotional Reactivity (CBCL)	0.60***	0.06			−0.01	0.03
Anxious/Depressed (CBCL)	0.49***	0.06			0.14***	0.03
Somatic Complaints (CBCL)	0.25***	0.04			0.05	0.03
Withdrawn (CBCL)	0.55***	0.07			0.04	0.03
Attention Problems (CBCL)	0.56***	0.07	0.36***	0.07		
Aggressive Behavior (CBCL)	0.61***	0.09	0.23***	0.05		
Sleep Problems (CBCL)	0.27***	0.05				
Other (CBCL)	0.61***	0.05				
Social Cognition (SRS)	0.31***	0.04				
Social Communication (SRS)	0.60***	0.08				
Social Autistic Mannerisms (SRS)	0.55***	0.08				
ODD (CPRS-R)	0.44***	0.07	0.15*	0.07		
Inattentive (CPRS-R)	0.40***	0.04	0.29***	0.07		
Hyperactive-Impulsive (CPRS-R)	0.48***	0.07	0.36***	0.08		
Teacher Report						
Anxious/Depressed (TRF)	0.30***	0.06			0.38***	0.05
Withdrawn/Depressed (TRF)	0.32***	0.07			0.42***	0.06
Somatic Complaints (TRF)	0.16**	0.05			0.22***	0.05
Social Problems (TRF)	0.36***	0.05				
Thought Problems (TRF)	0.39***	0.08				
Attention Problems (TRF)	0.27***	0.05	0.33***	0.04		
Rule-Breaking Behavior (TRF)	0.13**	0.04	0.32***	0.06		
Aggressive Behavior (TRF)	0.16***	0.05	0.44***	0.05		
Child Self-Report						
Depression (BPI)	0.13***	0.03			−0.04	0.05
Separation Anxiety (BPI)	0.08**	0.03			−0.06	0.04
Over-Anxiousness (BPI)	0.12***	0.03			−0.07	0.05
Oppositionality and Defiance (BPI)	0.10**	0.03	0.11**	0.04		
Hostility (BPI)	0.10**	0.03	0.19***	0.04		
Conduct Problems (BPI)	0.07*	0.03	0.12**	0.04		
Specific Internalizing/Externalizing Correlations			**r**	**SE**		
Specific Int/Ext			−0.91***	0.18		

Note: n = 1,954. BPI = Berkeley Puppet Interview; CBCL = Child Behavior Checklist; CPRS-R = Conners' Parent Rating Scale–Revised; Ext = externalizing; Int = internalizing; SE = standard error; SRS = Social Responsiveness Scale; TRF = Teacher Report Form.
*p < .05; **p < .01; ***p < .001.

being −0.14 (SE = 0.04, $p = .001$). However, it was not statistically significantly associated with the specific internalizing ($\beta = -0.05$, SE = 0.05, $p = .371$) and externalizing factors ($\beta = -0.09$, SE = 0.05, $p = .060$).

Temperament Associations

Parent-reported temperamental negative affectivity was associated with the general psychopathology factor ($\beta = 0.52$, SE = 0.07, $p < .001$) but not with the specific internalizing factors ($\beta = -0.12$, SE = 0.09, $p = .197$) or specific externalizing factors ($\beta = 0.05$, SE = 0.08, $p = .537$). In contrast, parent-reported surgency showed no association with the general psychopathology factor ($\beta = -0.09$, SE = 0.07, $p = .169$), but a negative association with the specific internalizing factor ($\beta = -0.29$, SE = 0.10, $p = .004$) and a positive association with the specific externalizing factor ($\beta = 0.62$, SE = 0.04, $p < .001$). Effortful control was negatively associated with the general psychopathology factor ($\beta = -0.20$, SE = 0.04, $p < .001$), positively associated with the specific internalizing factor ($\beta = 0.11$, SE = 0.04, $p = .017$), and negatively associated with the specific externalizing factor ($\beta = -0.19$, SE = 0.03, $p < .001$).

SNP Heritability

We observed significant SNP heritability of the general psychopathology factor (SNP $h^2 = 38\%$, SE = 0.16, $p = .008$, genetic variance = 0.028, residual variance = 0.047, phenotypic variance = 0.076).

TABLE 2 Model Fit Indices of the General Psychopathology Factor (GPF) and the Same Model Without the General Psychopathology Factor (No GPF)

Model	CFI	TLI	RMSEA[a]	SRMR	BIC
GPF	0.890	0.854	0.048 (0.046, 0.050)	0.036	283891
No GPF	0.831	0.790	0.057 (0.056, 0.059)	0.104	285249

Note: n = 1,954. BIC = Bayesian information criterion; CFI = comparative fit index; RMSEA = root-mean-square error of approximation; SRMR = standardized root mean square residual; TLI = Tucker-Lewis index.

[a]*A 90% CI is given for RMSEA.*

DISCUSSION

In this study, a general psychopathology factor, underlying several diverse dimensions of externalizing, internalizing, and autistic-like behaviors, was observed in early school-age children. No single psychopathology subscale was disproportionately associated with this general factor. Importantly, GREML demonstrated substantial SNP heritability of the general psychopathology factor, suggesting that the shared effects responsible for co-occurrence are partly due to common SNPs. The three-informant design is an important strength of the current study because it allowed an estimation of the general psychopathology factor with lower risk of informant and context bias. This is a valuable extension of previous studies that reported on the effects of the general psychopathology factor for one informant only or separately for parental, teacher, or self-report. The multi-informant approach, however, reduces the chance that a general factor will partly reflect reporting tendencies. Another strength is the simultaneous inclusion of autistic-like behavior together with internalizing and externalizing problems. Although a previous study in children reported that a general factor explained various neurodevelopmental symptoms, internalizing behaviors were not included.[18] In the present study, not only externalizing but all internalizing problems and three autism-like behavior subscales loaded on the general psychopathology factor.

All child-rated scales loaded significantly on the general psychopathology factor and contributed meaningfully to the multi-informant internalizing and externalizing factors. This supports the view that children can report their problems at this young age. The lower loadings of the child-rated and teacher-rated scales compared to parent-rated scales in the general psychopathology factor model, however, might indicate limitations of these informants. Child developmental level, including short attention span, and difficulties reporting on complex constructs, are inherent challenges to obtaining valid self-reports at this young age, whereas teachers may know children less well. Alternatively, the lower loadings in the general psychopathology factor model might reflect our conservative within-instrument covariance correction: instrument-specific factors overcorrect for "true" covariance structures detected using a particular instrument or informant only. For example, high teacher-specific loadings may represent the teachers' specific insights from task-oriented settings and their ability to compare with other children. Parents have more limited insights in the school setting, but can judge children by their behavior outside of school and overall typically spend much more time with them than other informants. However, we took a conservative approach and argue that the likelihood of a true covariance pattern emerging in only one of many instruments is lower than the likelihood of error, and thus deliberately introduced the latent factors.

The criterion validity of the general factor was supported by associations with negative affectivity, effortful control, and IQ. The temperamental subscales Negative Affectivity and Effortful Control represent the disposition to show distress and the ability to self-control. Both traits have been hypothesized to relate to a broad range of disorders, perhaps due to eliciting maladaptive responses from family and peers or shared genetic origins,[37] and thus a general psychopathology factor was expected to be related. Indeed, previous studies also found evidence for robust associations of the general psychopathology factor with negative affectivity and poor effortful control/conscientiousness.[8,13,19] Temperamental surgency, which describes the tendency to experience positive emotions, was not related to the general factor. Particularly strong support for the criterion validity of our general factor comes from the correlation with IQ scores. If the general psychopathology factor was solely a spurious product of common method variance, it would not be correlated with IQ scores obtained in formal testing at our research center, independently of any questionnaire on psychopathology.

Perhaps most importantly, we observed that additive effects of common autosomal SNP variants underlie the general psychopathology factor. This heritable component was found to explain 38% (95% CI 6%-69%) of the general psychopathology factor variance in the European ancestry sample. This observed SNP heritability is very unlikely to occur under the assumption that the population heritable component is 0, and thus the finding strongly supports the hypothesis that the general factor of psychopathology reflects shared genetic influences.[6,7] However, the variance explained by common SNPs is difficult to quantify exactly because of the wide confidence intervals when estimating SNP heritabilities in samples with a few thousand participants.[38] Substantial residual variance remained, which can reflect environmental effects, non-additive effects, polygenic rare variants,[12,39] or structural variants, such as copy number variations, but which also includes the error term.

We previously reported SNP heritabilities for single parent-rated and teacher-rated instruments separately in participants from the Generation R and the Netherlands Twin Register cohorts.[40] These estimates ranged from 12% (parent-rated [CBCL] Internalizing and Externalizing scale)

to 71% (teacher-rated [TRF] attention problems). The present sample would have been underpowered to detect genetic effects if the SNP heritability of the general factor were in the lower range of previous estimates. However, the general psychopathology factor is based on the combined analyses of the previously reported and additional instruments. The combination of instruments and the expected increase in accuracy due to multiple informants formed the background of our hypothesis that the SNP heritability of the general factor would be in the middle or higher regions of previous estimates. This hypothesis was confirmed.

The results of the specific internalizing and externalizing factors in the general psychopathology factor model are intriguing. These factors are not the traditionally observed internalizing and externalizing domain scores as measured by their broadband scales. The factors represent specific influences on problematic behavior beyond those explained by the general vulnerability. Although previous studies found negative correlations between the specific factors of approximately $r = -0.47$ in adults and $r = -0.44$ in children,[12,13] the correlation in the current study was stronger ($r = -0.91$). This suggests the presence of a single internalizing/externalizing dimension in young children, once we account for the general psychopathology factor. Fitting a model with such a dimension is nearly equivalent to the original fit with two highly correlated factors (see Table S1 and S2, available online). The model implies that children scoring high on the externalizing end have more externalizing problems, less internalizing problems, and more surgency (see Table S3, available online) compared to children scoring in the center of the dimension (assuming equal scores on general psychopathology). The reverse patterns hold for children scoring high on the internalizing end; they have more internalizing and less externalizing problems and show less surgency. In contrast, this factor is not related to negative affectivity as is the general psychopathology factor. Such an alternative model needs further investigation and replication.

In conclusion, the results suggest that common autosomal SNPs are pleiotropically associated with internalizing, externalizing, autism-like, and other problematic behaviors in children. This may suggest that a substantial portion of the genetic variants underlying psychopathology could be missed in genome-wide association studies focusing on single disorders. Future genome-wide association studies should therefore incorporate the simultaneous analysis of diverse problems. Accounting for the interrelated nature of psychiatric disorders may help to unravel part of the complex genetic architecture of child psychopathology. &

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SUPPLEMENT 1

METHOD

Factor Score Estimation

GCTA 1.24.7 supports only observed variables as phenotype. For this reason, we estimated the factor scores of the latent factors using the regression method, which were then used for further GREML analyses. A limitation of this approach is that the relationship between the factors scores may differ slightly from the latent factors. The derived factor scores were based on a confirmatory factor analysis (CFA) fitted in a sample with only complete data (n = 1,954). We established the relationship between the subscales and the general and specific factors and thus were able to predict factor scores using multiple imputation. To ensure a reliable prediction, we restricted the estimation of missing factor scores to individuals with up to 50% missing subscales, resulting in a sample of 6,624. The median number of missing scales was 29%, with information from multiple informants being available in almost all cases (97%). We based the factor scores on multiply imputed values of the missing subscales. Specifically, we used MICE 2.25[1] to impute both missing subscales and factor scores, using the subscales as well as sex and age as predictors in the imputation model. We performed 100 imputations and obtained factor scores by averaging across simulations.

To normalize the distribution of total genetic effects and residuals, as estimated by the best linear unbiased prediction, all factor scores were transformed using ln(score-lowest score+1). This approach of investigating GREML's assumptions, and its limitations, was described by Kirkpatrick et al.[2]

The total genetic effect for the genetic psychopathology factor was similar between imputed and non-imputed factor scores. We did not use genetic information for the imputation; therefore, if the imputation were of poor quality, we would expect differences in the distribution of the total genetic effect between imputed and non-imputed distributions. We observe a 0.15-SD higher score mean for the total genetic effect and slightly narrower standard deviation (0.04-SD difference) for children with imputed data as opposed to those without. The similarity in total genetic effect distributions supports successful imputation of the factor score.

SUPPLEMENT 2

METHOD

Measurement Invariance of the Internalizing, Externalizing, and General Psychopathology Factors Across Ethnic Groups

The factor scores were derived from a confirmatory factor analysis (CFA), which included children with any ancestry; we thus implicitly assumed that children scoring equally on the factors would also score equally on the problem subscales regardless of whether they have European or non-European ancestry (strong invariance). We tested this assumption formally by sequentially comparing multigroup CFA models with no to strict equality constraints between European and non-European ancestries.[3,4]

We used a comparative fit index (CFI) cutoff of <0.01 to decide whether a simpler model with more constraints fits equally well as a more complicated model with less constraints. This fit measure was chosen because it has both been shown to be adequate for testing measurement invariance and because it can be based on a scaled test-statistic when facing non-normal data. It should be noted that performance of detecting measurement invariance in non-normal data has not been examined to the best of our knowledge.[4,5] We present the results for the general psychopathology factor model.

All following general psychopathology factor models are based on 888 children with European ancestry and 437 children without European ancestry, who had complete data on all variables in the general psychopathology factor model as well as genetic information on ancestry. The configural model, which applies the same factor structure to both ancestry groups but no other constraints, had a CFI of 0.890, which is of equivalent magnitude to the originally reported model without groups. Constraining the loadings to be equal between groups (weak invariance) led to an improved fit of 0.896. Additionally, constraining the intercepts to be equal (strong invariance) showed a nonsignificant decrease of the fit to 0.895. The strict fit, which imposes additionally equal residuals, led to a significant decrease in fit to 0.882.

SUPPLEMENTAL REFERENCES

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FIGURE S1 Pearson correlations among subscales in 1,954 children. Note: BPI = Berkeley Puppet Interview; CBCL = Child Behavior Checklist; CPRS-R = Conners' Parent Rating Scale–Revised; ODD = oppositional defiant disorder; SRS = Social Responsiveness Scale; TRF = Teacher Report Form.

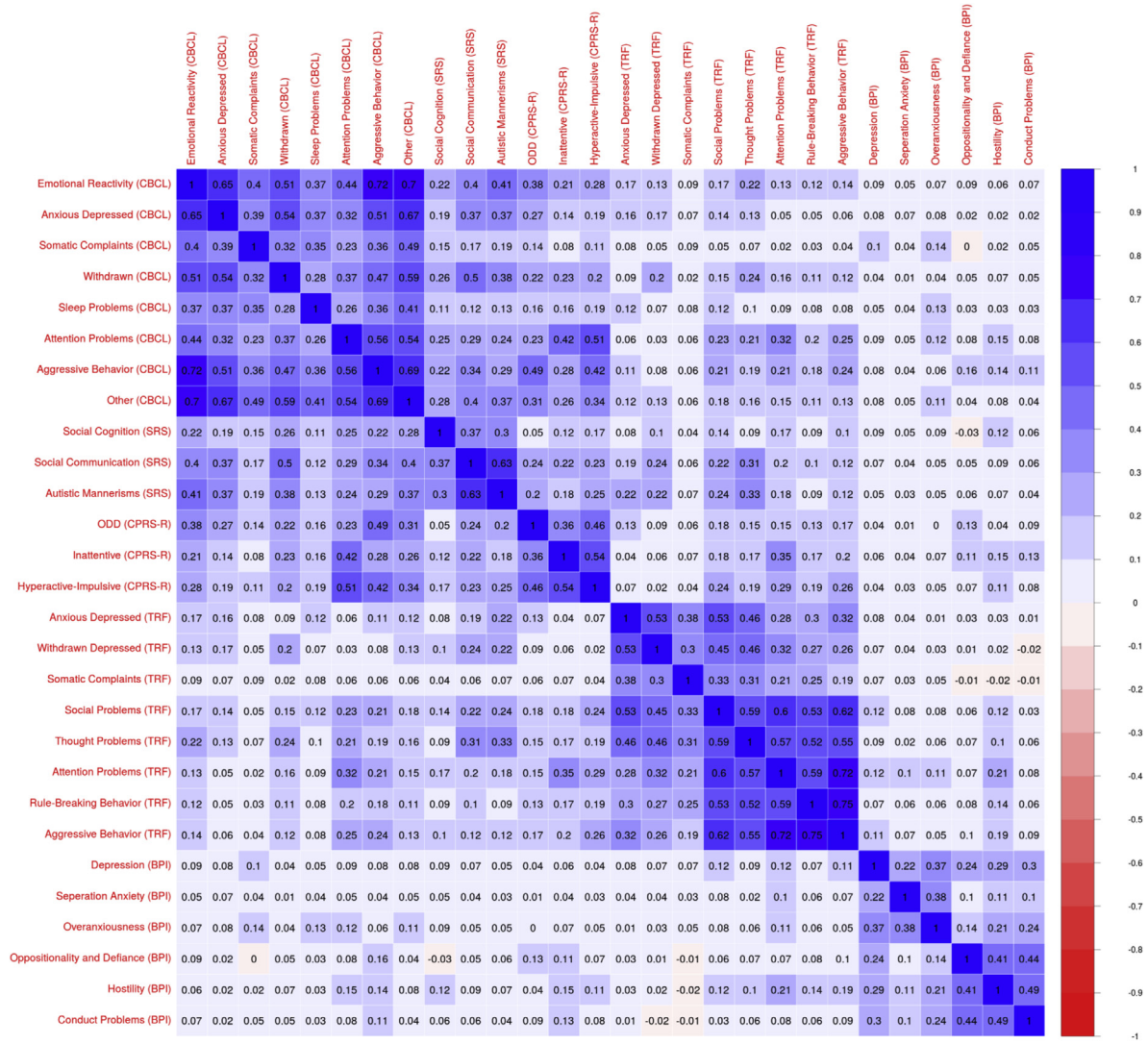

TABLE S1 Standardized Factor Loadings of a Model With a General Psychopathology Factor and Single Combined Dimensional Internalizing/Externalizing Factor

	General		Int/Ext Dimension	
Items	**Loading**	**SE**	**Loading**	**SE**
Emotional Reactivity (CBCL)	0.61***	0.06	0.01	0.03
Anxious Depressed (CBCL)	0.49***	0.05	−0.14***	0.03
Somatic Complaints (CBCL)	0.25***	0.04	−0.05	0.03
Withdrawn (CBCL)	0.54***	0.07	−0.04	0.03
Attention Problems (CBCL)	0.57***	0.06	0.35***	0.05
Aggressive Behavior (CBCL)	0.62***	0.08	0.22***	0.04
Sleep Problems (CBCL)	0.27***	0.05		
Other (CBCL)	0.61***	0.05		
Social Cognition (SRS)	0.31***	0.04		
Social Communication (SRS)	0.59***	0.07		
Social Autistic Mannerisms (SRS)	0.54***	0.07		
ODD (CPRS-R)	0.44***	0.06	0.14**	0.05
Inattentive (CPRS-R)	0.41***	0.04	0.27***	0.05
Hyperactive-Impulsive (CPRS-R)	0.49***	0.06	0.34***	0.06
Anxious Depressed (TRF)	0.30***	0.06	−0.36***	0.04
Withdrawn Depressed (TRF)	0.31***	0.07	−0.40***	0.04
Somatic Complaints (TRF)	0.16**	0.05	−0.21***	0.04
Social Problems (TRF)	0.36***	0.05		
Thought Problems (TRF)	0.39***	0.07		
Attention Problems (TRF)	0.27***	0.05	0.33***	0.04
Rule-Breaking Behavior (TRF)	0.13**	0.04	0.32***	0.06
Aggressive Behavior (TRF)	0.17***	0.04	0.44***	0.04
Depression (BPI)	0.13***	0.03	0.03	0.04
Separation Anxiety (BPI)	0.08**	0.03	0.05	0.03
Over Anxiousness (BPI)	0.12***	0.03	0.06	0.03
Oppositionality and Defiance (BPI)	0.10**	0.03	0.11**	0.03
Hostility (BPI)	0.11**	0.03	0.18***	0.04
Conduct Problems (BPI)	0.08**	0.03	0.11***	0.03

Note: n = 1,954. BPI = Berkeley Puppet Interview; CBCL = Child Behavior Checklist; CPRS-R = Conners' Parent Rating Scale—Revised; Ext = externalizing; Int = internalizing; ODD = oppositional defiant disorder; SRS = Social Responsiveness Scale; TRF = Teacher Report Form.
$^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$.

TABLE S2 Model Fit Indices of a Model With a General Psychopathology Factor and Single Combined Dimensional Internalizing/Externalizing Factor

Model	CFI	TLI	RMSEA[a]	SRMR	BIC
Int/Ext Dimension	0.891	0.856	0.048 (0.046, 0.049)	0.036	283885

Note: n = 1,954. BIC = Bayesian information criterion; CFI = comparative fit index; RMSEA = root-mean-square error of approximation; SRMR = standardized root-mean-square residual; TLI = Tucker-Lewis index.
[a]A 90% CI is given for RMSEA.

TABLE S3 Standardized Path Coefficients From Temperament to General Psychopathology Factor and a Combined Dimensional Internalizing/Externalizing Factor in a Structural Equation Model

	General		Int/Ext Dimension	
Temperament	**Coefficient**	**SE**	**Coefficient**	**SE**
Negative affectivity	0.53***	0.06	0.06	0.07
Surgency	−0.02	0.06	0.55***	0.04
Effortful control	−0.22***	0.04	−0.16***	0.03

Note: n = 1,933. Ext = externalizing; Int = internalizing; SE = standard error.
*p < .05; **p < .01; ***p < .001.