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Biological Psychiatry

The Genetic Architecture of Differentiating Behavioral and Emotional Problems in Early Life

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ABSTRACT

BACKGROUND: Early in life, behavioral and cognitive traits associated with risk for developing a psychiatric condition are broad and undifferentiated. As children develop, these traits differentiate into characteristic clusters of symptoms and behaviors that ultimately form the basis of diagnostic categories. Understanding this differentiation process—in the context of genetic risk for psychiatric conditions, which is highly generalized—can improve early detection and intervention.

METHODS: We modeled the differentiation of behavioral and emotional problems from age 1.5 to 5 years (behavioral problems − emotional problems = differentiation score) in a preregistered study of ∼79,000 children from the population-based Norwegian Mother, Father, and Child Cohort Study. We used genomic structural equation modeling to identify genetic signal in differentiation and total problems, investigating their links with 11 psychiatric and neurodevelopmental conditions. We examined associations of polygenic scores (PGS) with both outcomes and assessed the relative contributions of direct and indirect genetic effects in ∼33,000 family trios.

RESULTS: Differentiation was primarily genetically correlated with psychiatric conditions via a neurodevelopmental factor. Total problems were primarily associated with the neurodevelopmental factor and p-factor. PGS analyses revealed an association between liability to attention-deficit/hyperactivity disorder and differentiation ($\beta = 0.11$; 95% CI, 0.10 to 0.12) and a weaker association with total problems ($\beta = 0.06$; 95% CI, 0.04 to 0.07). Trio-PGS analyses showed predominantly direct genetic effects on both outcomes.

CONCLUSIONS: We uncovered genomic signal in the differentiation process, mostly related to common variants associated with neurodevelopmental conditions. Investigating the differentiation of early-life behavioral and emotional problems may enhance our understanding of the developmental emergence of different psychiatric and neurodevelopmental conditions.

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An emerging body of evidence suggests that genetic risk for psychiatric conditions is probabilistic in nature and overlaps substantially across domains (1–8). This overlap is underpinned by widespread pleiotropy of common genetic variants, with multiple pathways linking genetic variants to psychiatric outcomes (9,10). This extensive genomic overlap raises the question of how traits and behaviors associated with different behavioral and emotional conditions emerge through development.

The generalized nature of risk for psychiatric conditions has been explained by a general p-factor (11,12) with potential neurodevelopmental origins (3,13). Previous research has supported the heritability and predictive validity of the p-factor during childhood (12,14–16). However, even after accounting for a general p-factor, specific behavioral problems (i.e., undercontrolled and disruptive behavior) and emotional problems (i.e., negative mood and inhibition) remain associated with a range of outcomes (11). Similarly, specific genetic contributions to behavioral and emotional conditions in childhood account for important between-person differences after accounting for shared variance (17,18).

During early childhood, generalized risk for behavioral and emotional problems gives rise to their common co-occurrence (12), while specific risk factors may explain why some children display high levels of behavioral problems without emotional problems and vice versa. Given that behavioral and emotional problems in early childhood are associated with increased risk of developing behavioral and emotional conditions later in life (19–21), understanding the differentiation (i.e., difference in relative levels) of behavioral and emotional problems may provide useful insights into who is at risk for which conditions later in life. In a previous validation study, we demonstrated that the extent to which behavioral and emotional problems were differentiated from one another in early childhood predicted mental health later in childhood and adolescence over and above the total level of problems (22). Although differentiation has been recognized as a core proposal in the field of developmental psychopathology for decades (23), few studies have investigated it empirically. Direct investigations of differentiation have mostly focused on later childhood and adolescence and have yielded mixed results (24,25). However,

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studies that have shown decreasing correlations among symptoms of different mental health conditions as children grow older may be indicative of differentiation as a developmental process. Previous research has shown larger decreases in correlations among symptoms of mental health conditions that belong to the behavioral and emotional domains, respectively, than within either domain (24). Exploring the differentiation between behavioral and emotional problems during early childhood may shed light on the etiology of developing psychiatric conditions and facilitate early detection and prevention.

There are several plausible mechanisms by which behavioral and emotional problems might become differentiated across development. Differentiation may be due to genetic differences that are amplified over time, alongside exposure to environmental factors (26) and other stochastic events (27). We recently identified specific environmental factors associated with differentiation in early childhood (22). However, specific measures of the childhood environment tend to demonstrate weak associations with later mental health (28) and are frequently confounded by gene-environment correlations (29). Previous studies have shown that unmeasured traits in parents, indexed by genetic liabilities that are not transmitted to the child, may influence mental health in early life (30,31). Such indirect genetic effects are independent of direct genetic transmission and may be mediated via parenting behaviors (32,33). Alternatively, they may capture assortative mating or population structure (32). Larger samples of parent-offspring trios than have previously been available may be needed to detect specific indirect genetic effects, which may be small in magnitude or nonexistent for many childhood psychiatric traits (33–35). Furthermore, we lack a clear understanding of the patterning of indirect versus direct genetic effects across general and specific aspects of childhood behavioral and emotional problems.

In the current study, we applied genomic structural equation modeling (SEM) and polygenic score (PGS) analyses to investigate the genetic underpinnings of the differentiation of behavioral and emotional problems in early life. Using data from the Norwegian Mother, Father, and Child Cohort Study (MoBa), we explored the genetic architecture of differentiation, estimating genetic correlations with 11 psychiatric and neurodevelopmental conditions based on external summary statistics. To further characterize the links between differentiation and genetic liability to these conditions, we used previously established latent structures (5) incorporating a general p-factor and/or 4 specific factors accounting for variance that is shared among conditions. Finally, we estimated the relative contribution of direct and indirect genetic effects using genotyped parent-offspring trios. In parallel, we also conducted all analyses on measures of overall behavioral and emotional problems, presenting the findings together with those for differentiation to highlight how considering general and specific aspects in tandem can enhance our understanding of the whole.

METHODS AND MATERIALS

Sample

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (36,37). Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 40.6% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers, and 75,200 fathers. Ethical approval for this work was given by The Regional Committees for Medical and Health Research Ethics (2016/1702). We also used data from the Medical Birth Registry of Norway. See Supplemental Methods for further details.

Measures

Differentiation and Total Behavioral and Emotional Problems. Behavioral and emotional problems were assessed at ages 1.5, 3, and 5 years using the Child Behavior Checklist (CBCL). Differentiation was calculated as the difference between standardized behavioral and emotional problem scores at each time point (behavioral problems − emotional problems = differentiation score) (see Figure 1). This means that individuals with high scores have relatively more behavioral than emotional problems, and individuals with negative scores have the opposite. Differentiation was compared with total problems throughout (behavioral problems + emotional problems = total score). Differentiation and total problem scores at each time point were then standardized to a zero mean and unit variance. See Supplemental Methods and Table S1 for further details about the CBCL subscales.

Genomic Data and Quality Control. Blood samples were obtained from both parents during pregnancy and from mothers and children at birth. Genotype data were available for 56,150 children and 33,351 parent-offspring trios (Figure S1) (38). The genotyping and quality control procedures have been described elsewhere (39).

Covariates. We included child sex as a covariate in all models, and genotyping batch, imputation batch, and the 20 first principal components were included as covariates in genetic analyses.

Inclusion Criteria and Sample Size

We included all MoBa children with CBCL data from at least one time point (details in Supplemental Methods). Full information maximum likelihood was used to estimate parameters without biases that arose from a listwise deletion in the context of missing data (40). The total analytic sample comprised 79,028 children.

Preregistration

The preregistration of analyses and inference criteria can be accessed at https://osf.io/4rq3b/?view_only=ffe0d83f58ca4b5db72810b6d15780fc (with deviations described in Supplemental Methods).

Measurement Models

In all analyses, observed values for differentiation and total problems at ages 1.5, 3, and 5 years were modeled as the result of latent growth processes, each parameterized by an intercept and a linear slope. This decision was based on previously reported analyses that showed that an intercept-only model provided a worse fit to these data (22). The intercept

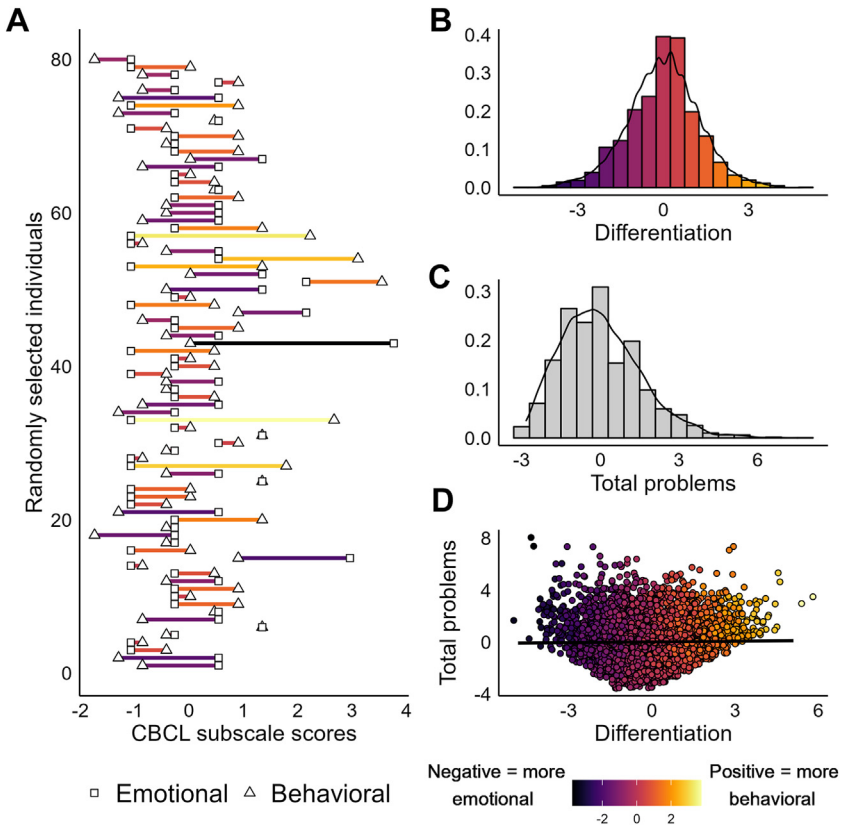

Figure 1. Operationalization of the differentiation and total problem scores. **(A)** Illustration of how the differentiation score is constructed based on individual scores on the behavioral and emotional subscales of the CBCL in 80 randomly selected individuals from the overall sample. **(B)** Distribution of the differentiation score in 3000 randomly selected individuals. **(C)** Distribution of the total problem score. **(D)** Correlation between differentiation and total scores, demonstrating that these are uncorrelated. CBCL, Child Behavior Checklist.

was set at 5 years to index the end point of the children's trajectories, and this end point was the focus of interpretation for all analyses. This model had 2 components. The first, referred to from here on as differentiation, was specified so that the latent intercept factor represented the extent of differentiation toward behavioral problems at age 5. For the second, referred to as total problems, the intercept represented the extent of total problems by age 5. For genomic analyses, a version of this measurement model was constructed at the genomic level with wave-specific genome-wide association studies (GWASs) as indicators (see Figure S2). We obtained these summary statistics by running GWASs of the differentiation and total scores at each time point (age 1.5, 3, and 5 years) in *REGENIE* version 3.1 (41). In PGS analyses, observed CBCL values at each time point were used as indicators.

Genomic SEM Analyses

Single Nucleotide Polymorphism Heritability of Differentiation and Genetic Correlations With Psychiatric Conditions. We estimated the single nucleotide polymorphism (SNP) heritability of differentiation and total problems from the summary statistics obtained by running multivariate GWASs in *GenomicSEM* (42) (Figure S2). Next, we estimated genetic correlations of differentiation and total problems with 11 psychiatric and neurodevelopmental conditions using linkage disequilibrium (LD) score regression (43,44). We constrained the cross-trait genetic covariance intercepts to zero if they were not significantly different from zero, because we did not expect significant sample overlap with MoBa in most cases. We used external GWAS summary statistics for attention-deficit/hyperactivity disorder (ADHD) (45), autism spectrum disorder (ASD) (46), schizophrenia (SCZ) (47), bipolar disorder (BIP) (48), major depression (MDD) (49), anxiety disorder (50), alcohol dependence (51), posttraumatic stress disorder (52), obsessive-compulsive disorder (53), anorexia nervosa (54), and Tourette syndrome (TS) (55). To avoid bias due to varying ascertainment across contributing cohorts, for each trait, we calculated the sample size as the sum of effective sample sizes for each GWAS meta-analysis (56).

Structural Models of Genetic Overlap Between Differentiation and Psychiatric Conditions. We incorporated genetic liability for the 11 psychiatric and neurodevelopmental conditions into genomic structural equation models with the differentiation and total problems (based on GWAS summary statistics for all inputs). We tested models parameterizing associations of differentiation and total problems with the 11 psychiatric and neurodevelopmental liabilities via 3 different, previously established (5) higher-order structures:

1. Four correlated factors (compulsive, psychotic, neurodevelopmental, and internalizing)

2. The factors specified as uncorrelated—apart from cross-loadings—domain-level factors that mediate effects of the 11 liabilities on a general p-factor (a hierarchical model)
3. The same 5 factors, but with the 11 liabilities loading directly on the p-factor and not on the domain-level factors (a bifactor model)

We report the results in terms of what proportion of the explained variance goes via differentiation versus total problems. We followed a similar procedure to that of Grotzinger *et al.* (5), including model fit comparisons to determine whether effects are best explained by the second-order p-factor or the first-order factors (see Figure S3 and Supplemental Methods).

PGS Analyses

We generated PGSs for the 11 psychiatric and neurodevelopmental conditions using LDpred2 (57), based on European samples from the most recent GWASs (at the time of analysis). In LDpred2, PGSs are calculated as a weighted sum of the effect sizes for all variants in common between the discovery sample and the target sample. The software adjusts GWAS effect sizes using LD information and a Bayesian framework to estimate the posterior mean effect size for each SNP, which improves prediction accuracy. All PGSs were standardized to zero mean and unit variance prior to analyses. We used a robust maximum likelihood estimator in all models.

Direct and Indirect Genetic Effects on Differentiation. We estimated indirect and direct genetic effects in a trio-PGS design (33) using 33,351 parent-offspring trios. In this model, the 11 PGSs for children and both parents were simultaneously included as predictors of differentiation and total problems. The inheritance of genetic variants from parents to children is random; therefore, the child's PGS conditional on their parent's PGS is random and will not be affected or biased by the indirect influence of parents' genes via their behavior. Accordingly, estimates of the child, maternal, or paternal PGS are mutually adjusted, and the association of the parents' PGSs together are an estimate of indirect genetic influence (33). We also conducted sensitivity analyses in which we restricted the sample to 27,330 unrelated trios.

Inference Criteria and Equivalence Testing. We used equivalence testing in all PGS analyses, testing whether the 90% CI of each effect size overlaps with prespecified equivalence bounds for the smallest effect size of interest (58). We set this at Cohen's d = 0.1, which can be considered as the lower bound of a small effect (see Supplemental Methods) (59). Type 1 error rates were adjusted in all models using false discovery rate (FDR) (60).

Analytic Software and Code. All modeling was carried out in R version 4.1.2, using version 0.6-15 of *lavaan* (61) and version 0.0.5 of the *GenomicSEM* (42) package. Wave-specific GWASs were conducted in *REGENIE* (41). The *phenotools* package version 0.2.9 was used to process the phenotypic data (62). Data preparation and analysis code are publicly available on GitHub (https://github.com/psychgen/genomics-differentiation).

RESULTS

Measurement Models

Descriptive statistics for the outcomes are provided in Table S2. The differentiation and total problem scores were

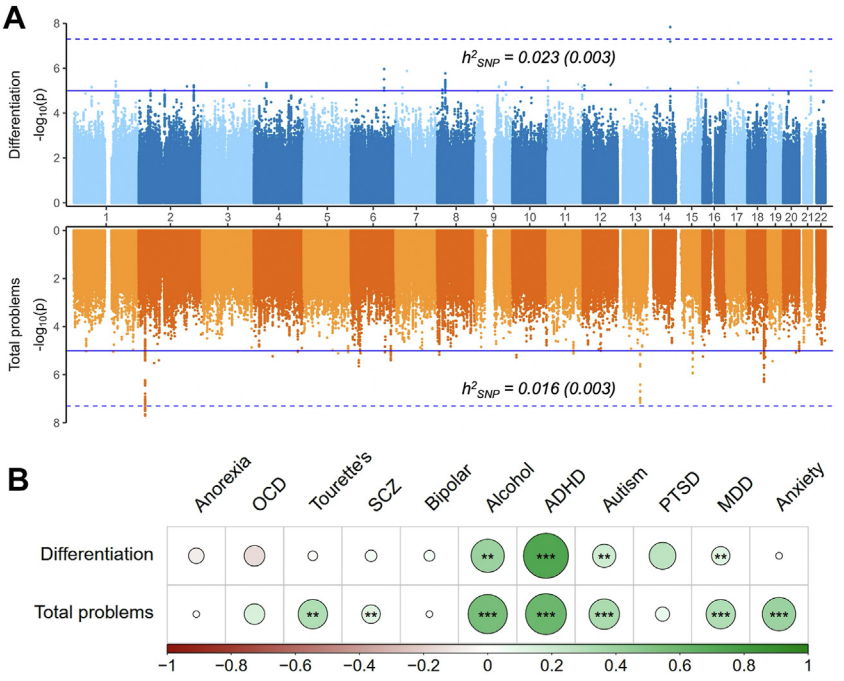

Figure 2. Genomic analyses of differentiation (in blue) and total behavioral and emotional problems (orange) and genetic correlations with 11 psychiatric conditions. **(A)** Results of multivariate genome-wide association studies of the differentiation intercept (top) and total problems (bottom). **(B)** Linkage disequilibrium score regression genetic correlations of 11 psychiatric and neurodevelopmental conditions with differentiation and total problems. The size and color of each circle corresponds to the strength of the genetic correlation. For differentiation, positive values (in green) indicate relatively more behavioral than emotional problems, and negative values (brown) indicate relatively more emotional than behavioral problems. $^{**}p < .01$, $^{***}p < .001$. h^2_{SNP} indicates single nucleotide polymorphism heritability (liability scale). ADHD, attention-deficit/hyperactivity disorder; MDD, major depression; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SCZ, schizophrenia.

empirically independent (see Figure 1 and Table S3). The latent growth model provided excellent fit to the data both at the phenotypic and genomic levels (Tables S4 and S5). There was significant variance in both the intercepts and slopes in the phenotypic model but only of the intercepts in the genomic model (see Supplemental Results).

SNP Heritability of Differentiation and Genetic Correlations With Psychiatric Conditions

We found genomic signal in the differentiation between behavioral and emotional problems in early life, which was genetically correlated with specific psychiatric and neurodevelopmental conditions. Based on longitudinal GWAS findings, the estimated SNP heritabilities were modest for both differentiation and total problems (Figure 2A). One genome-wide significant locus was identified in each of these GWASs (Figures S4–S7 and Table S6). Then, we estimated genetic correlations of differentiation and total problems with liability to 11 different psychiatric and neurodevelopmental conditions (Figure 2B and Figure S3). Liability to ADHD (r_g = 0.73; 95% CI, 0.62 to 0.86), alcohol dependence (r_g = 0.40; 95% CI, 0.14 to 0.66), autism (r_g = 0.20; 95% CI, 0.08 to 0.31), and depression (r_g = 0.12; 95% CI, 0.05 to 0.20) was associated with a propensity to develop more behavioral than emotional problems in early childhood, whereas none of the other conditions were genetically correlated with differentiation. The same conditions were similarly or more strongly associated with total problems (Figure 2B).

Structural Models of Genetic Overlap Between Differentiation and Psychiatric Conditions

To investigate whether any underlying factors accounted for the observed pattern of genetic correlations, we incorporated structural models of genetic liability to these 11 conditions (see Figure S8) (5). First, we specified correlated factor models with direct paths from differentiation and total problems to the 4 latent factors (compulsive, psychotic, neurodevelopmental, and internalizing) (see Figure 3A). In these models, differentiation and total problems were strongly associated with the neurodevelopmental factor in approximately equal measure (Figure 3B and Table S7). In addition, total problems were associated with the internalizing factor (9% of the variance was explained by total problems vs. 1% by differentiation).

In the hierarchical model (Figure 4A), the paths to the neurodevelopmental factor were again largest (Table S8), and 47% of the variance was explained by differentiation (vs. 53% by total problems) (Figure 4B). In addition, total problems were related to the p-factor (13% total problems vs. 2% differentiation) (Figure 4B) and the internalizing factor (33% total problems vs. 0% differentiation). The genetic associations of differentiation and total problems with the 11 conditions were better explained by the first-order factors than by p, indicating significant heterogeneity in the effects via the p-factor ($p < .001$). Results from a bifactor specification of the 5-factor model were highly consistent (see Table S9). In this model, there was also significant heterogeneity in the effects via the p-factor ($p < .001$).

Direct and Indirect Genetic Effects on Differentiation

Then, we explored associations of the 11 PGSs with differentiation and total problems. First, in a child-only model (Figure 5A and Table S10), the ADHD PGS showed the strongest association with differentiation toward behavioral problems (β = 0.11; 95% CI, 0.10 to 0.12, $p_{FDR} < .001$) and a weaker association with total problems (β = 0.06; 95% CI, 0.04 to 0.07; $p_{FDR} < .001$). The anorexia nervosa PGS was associated with differentiation toward emotional problems (β = −0.02; 95% CI, −0.04 to −0.01, p_{FDR} = .005). The MDD PGS (β = 0.04; 95% CI, 0.02 to 0.05; $p_{FDR} < .001$), TS PGS (β = 0.03; 95% CI, 0.02 to 0.04; $p_{FDR} < .001$), and SCZ PGS (β = 0.02; 95% CI, 0.01 to 0.04; p_{FDR} = .005) were associated with higher total problems, whereas the BIP PGS was associated with fewer problems (β = −0.03; 95% CI, −0.04 to −0.02; $p_{FDR} < .001$). Based on equivalence testing, the associations between the ADHD PGS and both outcomes and the association of the MDD PGS with total problems were outside the region of practical equivalence to zero (Figure S9). All other PGS associations could be considered as null in practical terms (although based on an arbitrary threshold).

In the multivariate trio-PGS model, most point estimates from the child-only models were unattenuated, apart from the association of the MDD PGS with total problems (Figure 6A and Table S11). Some point estimates increased, such as the direct effect of the anorexia nervosa PGS on differentiation (β = −0.05; 95% CI, −0.07 to −0.03; p_{FDR} = .001). This effect was outside the region of practical equivalence to zero (Figure S10). In univariate trio-PGS analyses, the pattern of results was highly similar (Tables S12 and S13).

We also tested whether these associations were explained by indirect or direct genetic effects based on the full sample of parent-offspring trios. Results showed that effects were primarily direct for both differentiation and total problems (Figure 5B). We found some modest evidence of indirect genetic effects (Figure 6; Figures S11 and S12; Table S14). This was for the maternal MDD PGS (β = 0.03; 95% CI, 0.01 to 0.05; p_{FDR} = .047) and the ASD PGS (β = 0.03; 95% CI, 0.01 to 0.05; p_{FDR} = .047), which were associated with higher total problems. The indirect effect of maternal autism liability fell within the region of practical equivalence to zero, whereas the MDD effect did not (Figure S11). When we restricted the sample to 27,330 unrelated trios, the pattern of results was similar, but the indirect effect of the MDD PGS became nonsignificant (Tables S15 and S16).

Note that the PGS results for linear change in differentiation and total problems (captured by the slope factor) were in a consistent direction but were less precise and smaller (Figure S13 and Tables S17–S19).

DISCUSSION

In this study, we investigated the genomic factors that contribute to the co-occurrence and differentiation of behavioral and emotional problems in early life. Our findings revealed systematic genomic signal in both differentiation and total problems. Overall, associations of genetic liabilities to psychiatric and neurodevelopmental conditions with differentiation were at least as strong as for total problems. Furthermore,

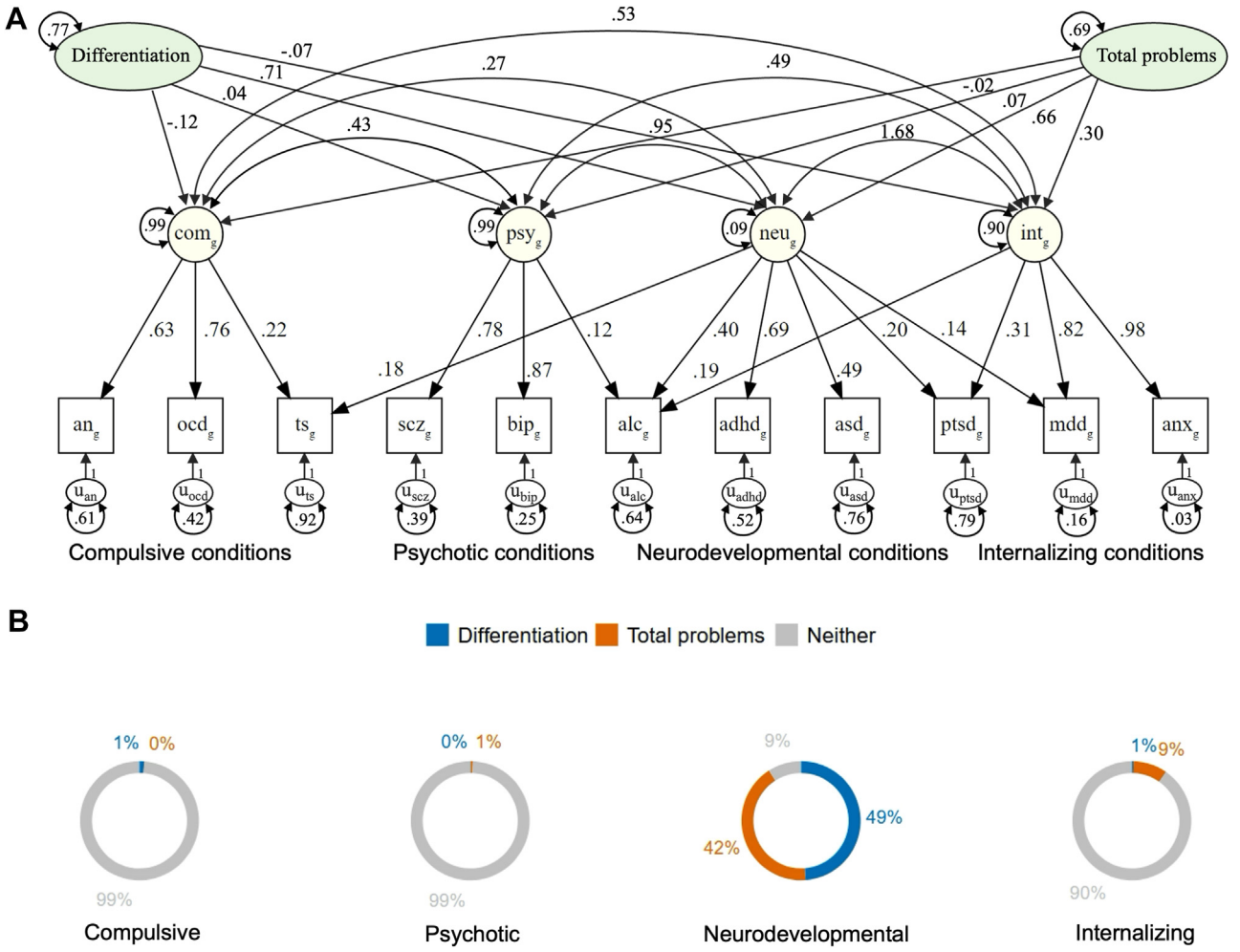

Figure 3. Four-factor genetic architecture of 11 psychiatric conditions and proportion of variance explained in each of the 4 factors by differentiation and total problems. **(A)** Standardized results from the model with differentiation/total problems predicting 4 correlated factors. **(B)** Proportion of variance explained in the 4 factors in **(A)** by differentiation vs. total problems. The colored percentages show the proportion of the variance that goes via differentiation vs. total problems, and the gray percentages show the residual variance. Note that because the latent factors are endogenous in our model, we could not use unit variance identification (i.e., fixing the variance to 1) to obtain standardized estimates (doing this results in model nonconvergence). Therefore, we used unit loading identification, and for that reason, the squared paths do not equal 1. Latent variables (common genetic factors) are represented as circles; manifest variables (genetic components of conditions) are squares; regression paths are depicted as single-headed arrows; (co)variances are double-headed arrows. adhd, attention-deficit/hyperactivity disorder; alc, alcohol dependence; an, anorexia nervosa; anx, anxiety disorder; asd, autism spectrum disorder; bip, bipolar disorder; com, compulsive; int, internalizing; mdd, major depression; neu, neurodevelopmental; ocd, obsessive-compulsive disorder; psy, psychotic; ptsd, posttraumatic stress disorder; scz, schizophrenia; ts, Tourette syndrome.

genomic structural equation modeling indicated that while the p-factor was associated with higher total problems only, liability to neurodevelopmental conditions was strongly associated with both differentiation and total problems. Consistent with Grotzinger *et al.* (5), the effects via the p-factor showed notable heterogeneity, suggesting limited informativeness of a genomic p-factor in explaining associations between childhood differentiation and total problems and later neurodevelopmental and psychiatric conditions. Trio model results indicated that genetic effects on differentiation and total problems were primarily direct, consistent with previous studies (18,33–35,63). These results underscore the value of looking not only at generalized liability such as that which is typically captured by the p-factor but also at domain-level sources of variability for both gene discovery and the investigation of etiological mechanisms.

We identified genetic correlations between differentiation and ADHD, autism, alcohol dependence, and depression. These conditions have been found to load on a shared neurodevelopmental factor (5). Here, one implication could be that genetic liability to conditions underpinned by neurodevelopmental processes may be associated with differentiation toward behavioral problems in early childhood. However, liability to ADHD could also be the driving factor behind these associations. In multivariate PGS analyses, where each score was adjusted for the others, liability to ADHD was the predominant predictor of differentiation toward behavioral problems.

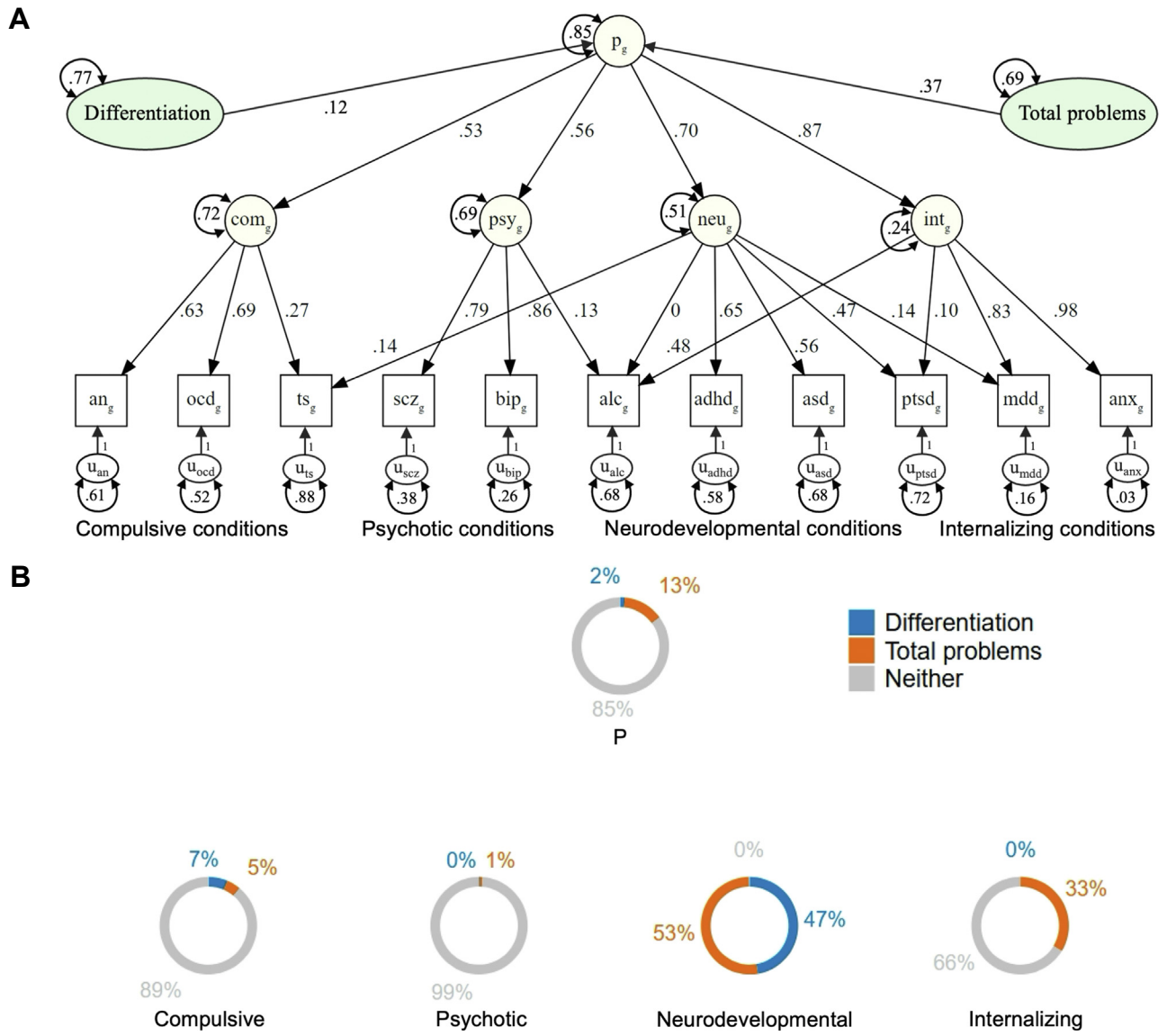

Figure 4. Five-factor genetic architecture of 11 psychiatric conditions and proportion of variance explained in the 5 factors by differentiation and total problems. **(A)** Standardized results from the hierarchical model with differentiation and total problems predicting the p-factor. A separate model was run with differentiation/total predicting the 4 first-order factors. **(B)** Proportion of variance explained in the 5 factors in **(A)** by differentiation vs. total problems. The colored percentages show the proportion of the variance that goes via differentiation vs. total problems, and the gray percentages show the residual variance. Note that because the latent factors are endogenous in our model, we could not use unit variance identification (i.e., fixing the variance to 1) to obtain standardized estimates (doing this results in model nonconvergence). Therefore, we used unit loading identification, and for that reason the squared paths do not equal 1. Latent variables (common genetic factors) are represented as circles; manifest variables (genetic components of conditions) are squares; regression paths are depicted as single-headed arrows; (co)variances are double-headed arrows. adhd, attention-deficit/hyperactivity disorder; alc, alcohol dependence; an, anorexia nervosa; anx, anxiety disorder; asd, autism spectrum disorder; bip, bipolar disorder; com, compulsive; int, internalizing; mdd, major depression; neu, neurodevelopmental; ocd, obsessive-compulsive disorder; psy, psychotic; ptsd, posttraumatic stress disorder; scz, schizophrenia; ts, Tourette syndrome.

An intriguing finding was the notably larger effect of the ADHD PGS for differentiation than for total problems. In apparent contrast, previous studies have found similar or stronger associations between liability to ADHD and a general p-factor than specific factors (15,16,18,64). Seemingly converging research has shown a positive association of ADHD PGS with the p-factor and specific behavioral problems and a slightly negative association with specific emotional problems (65). However, direct comparisons with previous studies are complicated by differences in measures and modeling strategy. In MoBa, the CBCL subscales are brief measures of aggression and attention difficulties for the behavioral domain and anxiety/emotional reactivity for the emotional domain. If ADHD liability is robustly associated with

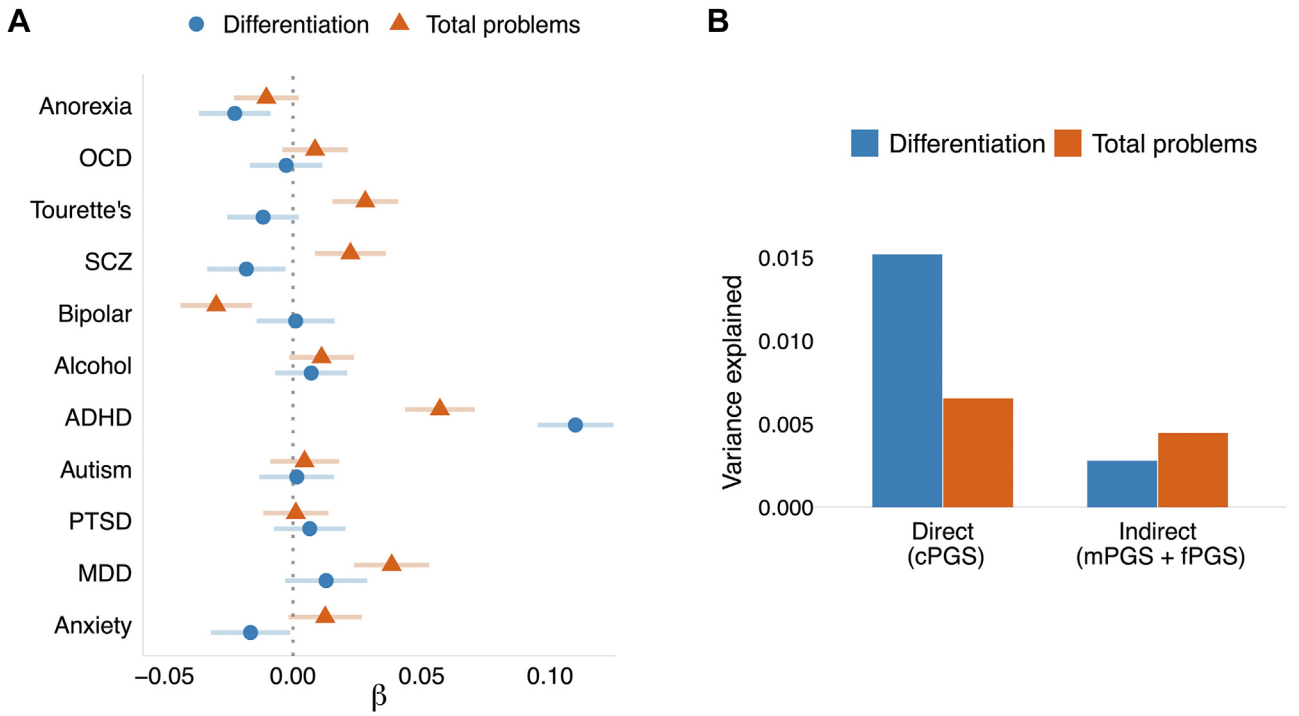

Figure 5. Associations of 11 polygenic scores with differentiation and total problems. **(A)** Standardized betas of associations of 11 PGSs with differentiation and total problems (~56,000). Note that for differentiation, positive values indicate relatively more behavioral than emotional problems, and negative values indicate relatively more emotional than behavioral problems. **(B)** Trio-PGS effects on differentiation and total problems, showing the variance explained by direct effects of all child PGSs (adjusting for parent's PGSs) and indirect effects of parents' PGSs (~33,000). ADHD, attention-deficit/hyperactivity disorder; cPGS, child's PGS; fPGS, father's PGS; MDD, major depression; mPGS, mother's PGS; OCD, obsessive-compulsive disorder; PGS, polygenic score; PTSD, posttraumatic stress disorder; SCZ, schizophrenia.

the former but not the latter, it may produce the pattern of findings observed here. Alternatively, children with a high burden of generalized genetic risk may display a broad range of problems from early in life, whereas children who predominantly display behavioral problems may be more likely to have specifically elevated liability to ADHD.

Leveraging a large sample of parent-offspring trios, we found modest evidence of indirect genetic effects on differentiation or total problems. There seemed to be small indirect effects of maternal liability to depression and autism on offspring total problems. Because mothers reported on offspring total problems, and no effect was identified for the fathers, these findings may reflect how mothers with high liability to depression or autism perceive and report on their children's behavior. First, one implication is that biases from population phenomena may not necessarily substantially inflate genetic associations with psychiatric traits [supported by multiple studies (18,33,34,63,66,67)]. Only the association of the MDD PGS with total problems was notably attenuated in the trio model (compared with the child-only model), which is consistent with recent within-sibship GWAS findings (66). Second, an implication for future studies is that any indirect effects of specific psychiatric PGSs on childhood outcomes may be small in magnitude (33,34). It is noteworthy that observational associations between parental psychiatric traits and offspring outcomes (68,69) are often assumed to be caused by parenting. If causal parental effects of the magnitude that have often been postulated as explanations for these observational associations existed, we would expect to see evidence of them as indirect genetic effects here, which we do not.

Overall, genetic liability to neurodevelopmental conditions was the most important contributor to early-life behavioral and emotional problems. First, a likely reason is that neurodevelopmental conditions (such as autism and ADHD) have an earlier age at onset than the other conditions studied here and are more often present in the studied age range. Second, recent evidence suggests that a distinguishing factor between liability to child and adult mental health problems is the key role of neurodevelopmental processes during childhood, which is relevant to broad aspects of mental health and not just neurodevelopmental conditions (70). Future GWASs with children would help to delineate these processes further because most current GWAS samples consist of adults.

Limitations

There are some limitations to our study. First, both differentiation and total problems exhibited very modest SNP heritabilities, which might have been attenuated by unreliability of the behavioral and emotional problem measurements, a common challenge in the field (71). Extracting stable signal over time and across different raters may be a way forward in childhood psychiatric genomics (72). Second, the estimates

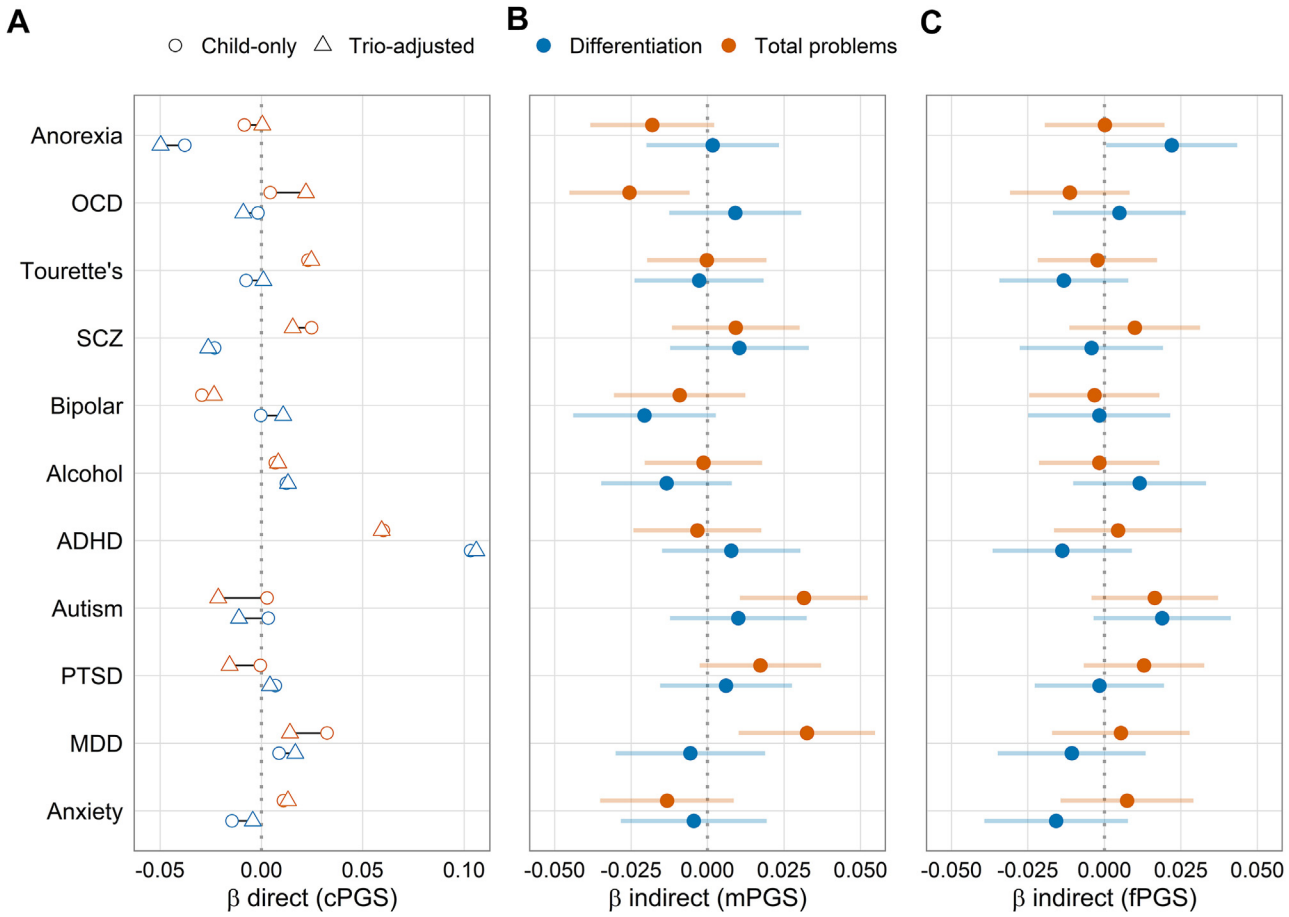

Figure 6. Direct and indirect genetic effects of 11 psychiatric PGSs on differentiation and total problems estimated in the total sample of parent-offspring trios. **(A)** Standardized betas of child-only and trio-adjusted direct effects estimated in ~33,000 trios. Note that to facilitate direct comparison, these child-only effects were estimated in the trio sample. **(B)** Mother's indirect genetic effects on offspring differentiation and total problems in early childhood. **(C)** Father's indirect genetic effects on offspring differentiation and total problems in early childhood. For differentiation, positive values indicate relatively more behavioral than emotional problems, and negative values indicate relatively more emotional than behavioral problems. ADHD, attention-deficit/hyperactivity disorder; cPGS, child's PGS; fPGS, father's PGS; MDD, major depression; mPGS, mother's PGS; OCD, obsessive-compulsive disorder; PGS, polygenic score; PTSD, posttraumatic stress disorder; SCZ, schizophrenia.

might have been affected by measurement (un)reliability of the difference scores. This is because difference scores are less reliable than their constituent components (i.e., behavioral and emotional problems) when these are positively correlated (73). To address these limitations, we modeled the outcomes using a latent growth process, which partitions out measurement error. Third, a limitation of all PGS analyses is that the size of the GWAS for each trait influences their predictive power. Therefore, PGSs for traits with larger GWASs are more likely to have detectable associations with our outcomes. This must be accounted for when comparing the different PGS associations between the 11 conditions. We mitigated this issue by conducting multivariate GWASs of the latent growth factors and modeling the overlap with the 11 conditions at the genomic level—via genetic correlations and path estimates. These estimates are much less variable with GWAS power than estimates based on PGSs. Finally, the generalizability of our results could be affected by nonrandom participation at baseline (74) and selective attrition over time. The presence of behavioral problems or ADHD in children has been identified as a predictor of attrition in similar cohorts (75), which would attenuate links with our predictors. We have previously reported some (although limited) attrition based on the CBCL subscales in this sample (22). Here, in part because the slope factor would be most affected by selective attrition, the focus of our interpretation was on the intercept factor.

Conclusions

The current study revealed systematic genomic influences on the differentiation of early-life behavioral and emotional problems. Liability to neurodevelopmental conditions contributed substantially to both differentiation and total problems, while the genomic p-factor was mainly associated with total problem development. By comparing differentiation to total problems, we identified key differences in polygenic predictors, thereby

shedding light on the genetic architecture of general and specific traits that underlie the development of behavioral and emotional conditions. Novel approaches to exploring the differentiation of behavioral and emotional traits across development hold promise for enhancing our ability to understand and eventually prevent the emergence of behavioral and emotional conditions.

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Data from MoBa and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway and can be made available to researchers, provided there is approval from The Regional Committees for Medical and Health Research Ethics, compliance with the European Union General Data Protection Regulation, and approval from the data owners. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to datasets for replication should apply through helsedata.no. Access to datasets requires approval from The Regional Committees for Medical and Health Research Ethics in Norway and an agreement with MoBa. GWAS summary statistics used to compute PGS are available from publicly available repositories from the Psychiatric Genomics Consortium website (https://www.med.unc.edu/pgc/download-results/).

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REFERENCES

1. Musliner KL, Mortensen PB, McGrath JJ, Suppli NP, Hougaard DM, Bybjerg-Grauholm J, *et al.* (2019): Association of polygenic liabilities for major depression, bipolar disorder, and schizophrenia with risk for depression in the Danish population. JAMA Psychiatry 76: 516–525.
2. Boyle EA, Li YI, Pritchard JK (2017): An expanded view of complex traits: From polygenic to omnigenic. Cell 169:1177–1186.
3. Schork AJ, Won H, Appadurai V, Nudel R, Gandal M, Delaneau O, *et al.* (2019): A genome-wide association study of shared risk across psychiatric disorders implicates gene regulation during fetal neurodevelopment. Nat Neurosci 22:353–361.
4. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, *et al.* (2013): Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 45:984–994.
5. Grotzinger AD, Mallard TT, Akingbuwa WA, Ip HF, Adams MJ, Lewis CM, *et al.* (2022): Genetic architecture of 11 major psychiatric disorders at biobehavioral, functional genomic and molecular genetic levels of analysis. Nat Genet 54:1–12.
6. Hindley G, Frei O, Shadrin AA, Cheng W, O'Connell KS, Icick R, *et al.* (2022): Charting the landscape of genetic overlap between mental disorders and related traits beyond genetic correlation. Am J Psychiatry 179:833–843.
7. Roelfs D, Alnæs D, Frei O, van der Meer D, Smeland OB, Andreassen OA, *et al.* (2021): Phenotypically independent profiles relevant to mental health are genetically correlated. Transl Psychiatry 11:202.
8. Pettersson E, Lichtenstein P, Larsson H, Song J, Attention Deficit/Hyperactivity Disorder Working Group of the iPSYCH-Broad-PGC Consortium, Autism Spectrum Disorder Working Group of the iPSYCH-Broad-PGC Consortium, Bipolar Disorder Working Group of the PGC, Eating Disorder Working Group of the PGC, Major Depressive Disorder Working Group of the PGC, Obsessive Compulsive Disorders and Tourette Syndrome Working Group of the PGC, Schizophrenia CLOZUK, Substance Use Disorder Working Group of the PGC, Agrawal A, *et al.* (2019): Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. Psychol Med 49:1166–1173.
9. Solovieff N, Cotsapas C, Lee PH, Purcell SM, Smoller JW (2013): Pleiotropy in complex traits: Challenges and strategies. Nat Rev Genet 14:483–495.

10. Andreassen OA, Hindley GFL, Frei O, Smeland OB (2023): New insights from the last decade of research in psychiatric genetics: Discoveries, challenges and clinical implications. World Psychiatry 22:4–24.
11. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, *et al.* (2014): The p factor: One general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2:119–137.
12. Allegrini AG, Cheesman R, Rimfeld K, Selzam S, Pingault JB, Eley TC, Plomin R (2020): The p factor: Genetic analyses support a general dimension of psychopathology in childhood and adolescence. J Child Psychol Psychiatry 61:30–39.
13. Xie C, Xiang S, Shen C, Peng X, Kang J, Li Y, *et al.* (2023): A shared neural basis underlying psychiatric comorbidity. Nat Med 29:1232–1242.
14. Murray AL, Eisner M, Ribeaud D (2016): The development of the general factor of psychopathology 'p factor' through childhood and adolescence. J Abnorm Child Psychol 44:1573–1586.
15. Brikell I, Larsson H, Lu Y, Pettersson E, Chen Q, Kuja-Halkola R, *et al.* (2020): The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. Mol Psychiatry 25:1809–1821.
16. Waszczuk MA, Miao J, Docherty AR, Shabalin AA, Jonas KG, Michelini G, Kotov R (2023): General v. specific vulnerabilities: Polygenic risk scores and higher-order psychopathology dimensions in the Adolescent Brain Cognitive Development (ABCD) Study. Psychol Med 53:1937–1946.
17. Hannigan LJ, Askeland RB, Ask H, Tesli M, Corfield E, Ayorech Z, *et al.* (2021): Genetic liability for schizophrenia and childhood psychopathology in the general population. Schizophr Bull 47:1179–1189.
18. Chen C, Lu Y, Lundström S, Larsson H, Lichtenstein P, Pettersson E (2022): Associations between psychiatric polygenic risk scores and general and specific psychopathology symptoms in childhood and adolescence between and within dizygotic twin pairs. J Child Psychol Psychiatry 63:1513–1522.
19. Caspi A, Moffitt TE, Newman DL, Silva PA (1996): Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. Arch Gen Psychiatry 53:1033–1039.
20. Scott J, Martin G, Welham J, Bor W, Najman J, O'Callaghan M, *et al.* (2009): Psychopathology during childhood and adolescence predicts delusional-like experiences in adults: A 21-year birth cohort study. Am J Psychiatry 166:567–574.
21. Mulraney M, Coghill D, Bishop C, Mehmed Y, Sciberras E, Sawyer M, *et al.* (2021): A systematic review of the persistence of childhood mental health problems into adulthood. Neurosci Biobehav Rev 129:182–205.
22. Askelund AD, Ask H, Ystrom E, Havdahl A, Hannigan LJ (2023): Exploring the differentiation of behavioural and emotional problems across childhood: A prospective longitudinal cohort study. JCPP Adv 3:e12176.
23. Lilienfeld SO, Waldman ID, Israel AC (1994): A critical examination of the use of the term and concept of comorbidity in psychopathology research. Clin Psychol Sci Pract 1:71–83.
24. Sterba SK, Copeland W, Egger HL, Jane Costello E, Erkanli A, Angold A (2010): Longitudinal dimensionality of adolescent psychopathology: Testing the differentiation hypothesis. J Child Psychol Psychiatry 51:871–884.
25. Richards JS, Hartman CA, Ormel J, Oldehinkel AJ (2024): Continuity of psychopathology throughout adolescence and young adulthood. J Clin Child Adolesc Psychol 53:623–636.
26. Hannigan LJ, Walaker N, Waszczuk MA, McAdams TA, Eley TC (2017): Aetiological influences on stability and change in emotional and behavioural problems across development: A systematic review. Psychopathol Rev 4:52–108.
27. Molenaar PC, Boomsma DI, Dolan CV (1993): A third source of developmental differences. Behav Genet 23:519–524.
28. Plomin R, Daniels D (1987): Why are children in the same family so different from one another? Behav Brain Sci 10:1–16.
29. Plomin R, DeFries JC, Loehlin JC (1977): Genotype-environment interaction and correlation in the analysis of human behavior. Psychol Bull 84:309–322.
30. Cheesman R, Eilertsen EM, Ahmadzadeh YI, Gjerde LC, Hannigan LJ, Havdahl A, *et al.* (2020): How important are parents in the development of child anxiety and depression? A genomic analysis of parent-offspring trios in the Norwegian Mother Father and Child Cohort Study (MoBa). BMC Med 18:284.
31. Eilertsen EM, Cheesman R, Ayorech Z, Røysamb E, Pingault JB, Njølstad PR, *et al.* (2022): On the importance of parenting in externalizing disorders: An evaluation of indirect genetic effects in families. J Child Psychol Psychiatry 63:1186–1195.
32. Kong A, Thorleifsson G, Frigge ML, Vilhjalmsson BJ, Young AI, Thorgeirsson TE, *et al.* (2018): The nature of nurture: Effects of parental genotypes. Science 359:424–428.
33. Pingault JB, Barkhuizen W, Wang B, Hannigan LJ, Eilertsen EM, Corfield E, *et al.* (2023): Genetic nurture versus genetic transmission of risk for ADHD traits in the Norwegian Mother, Father and Child Cohort Study. Mol Psychiatry 28:1731–1738.
34. Shakeshaft A, Martin J, Dennison CA, Riglin L, Lewis CM, O'Donovan MC, Thapar A (2024): Estimating the impact of transmitted and non-transmitted psychiatric and neurodevelopmental polygenic scores on youth emotional problems. Mol Psychiatry 29:238–246.
35. Martin J, Wray M, Agha SS, Lewis KJS, Anney RJL, O'Donovan MC, *et al.* (2023): Investigating direct and indirect genetic effects in attention-deficit/hyperactivity disorder using parent-offspring trios. Biol Psychiatry 93:37–44.
36. Magnus P, Birke C, Vejrup K, Haugan A, Alsaker E, Daltveit AK, *et al.* (2016): Cohort profile update: The Norwegian mother and child cohort study (MoBa). Int J Epidemiol 45:382–388.
37. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C, MoBa Study Group (2006): Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 35:1146–1150.
38. Paltiel L, Anita H, Skjerden T, Harbak K, Bækken S, Nina Kristin SN, *et al.* (2014): The biobank of the Norwegian Mother and Child Cohort Study – present status. Nor J Epidemiol 24:29–35.
39. Corfield EC, Frei O, Shadrin AA, Rahman Z, Lin A, Athanasiu L, *et al.* (2022): The Norwegian Mother, Father, and Child cohort study (MoBa) genotyping data resource: MoBaPsychGen pipeline v. 1. bioRxiv https://doi.org/10.1101/2022.06.23.496289.
40. Lang KM, Little TD (2018): Principled missing data treatments. Prev Sci 19:284–294.
41. Mbatchou J, Barnard L, Backman J, Marcketta A, Kosmicki JA, Ziyatdinov A, *et al.* (2021): Computationally efficient whole-genome regression for quantitative and binary traits. Nat Genet 53:1097–1103.
42. Grotzinger AD, Rhemtulla M, de Vlaming R, Ritchie SJ, Mallard TT, Hill WD, *et al.* (2019): Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. Nat Hum Behav 3:513–525.
43. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, *et al.* (2015): An atlas of genetic correlations across human diseases and traits. Nat Genet 47:1236–1241.
44. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, *et al.*, , Schizophrenia Working Group of the Psychiatric Genomics Consortium (2015): LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 47:291–295.
45. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51:63–75.
46. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51:431–444.
47. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, *et al.* (2022): Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604:502–508.
48. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, *et al.* (2021): Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet 53:817–829.
49. Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shirali M, *et al.* (2019): Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci 22:343–352.

50. Purves KL, Coleman JRI, Meier SM, Rayner C, Davis KAS, Cheesman R, *et al.* (2020): A major role for common genetic variation in anxiety disorders. Mol Psychiatry 25:3292–3303.
51. Walters RK, Polimanti R, Johnson EC, McClintick JN, Adams MJ, Adkins AE, *et al.* (2018): Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. Nat Neurosci 21:1656–1669.
52. Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE, *et al.* (2018): Largest GWAS of PTSD (N= 20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol Psychiatry 23:666–673.
53. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS) (2018): Revealing the complex genetic architecture of obsessive–compulsive disorder using meta-analysis. Mol Psychiatry 23:1181–1188.
54. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, *et al.* (2019): Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 51:1207–1214.
55. Yu D, Sul JH, Tsetsos F, Nawaz MS, Huang AY, Zelaya I, *et al.* (2019): Interrogating the genetic determinants of Tourette's syndrome and other tic disorders through genome-wide association studies. Am J Psychiatry 176:217–227.
56. Grotzinger AD, de la Fuente J, Privé F, Nivard MG, Tucker-Drob EM (2023): Pervasive downward bias in estimates of liability-scale heritability in genome-wide association study meta-analysis: A simple solution. Biol Psychiatry 93:29–36.
57. Privé F, Arbel J, Vilhjálmsson BJ (2021): LDpred2: Better, faster, stronger. Bioinformatics 36:5424–5431.
58. Lakens D, Scheel AM, Isager PM (2018): Equivalence testing for psychological research: A tutorial. Adv Methods Pract Psychol Sci 1:259–269.
59. Kruschke JK (2018): Rejecting or accepting parameter values in Bayesian estimation. Adv Methods Pract Psychol Sci 1:270–280.
60. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300.
61. Rosseel Y (2012): lavaan: An R package for structural equation modeling. J Stat Softw 48:1–36.
62. Hannigan LJ, Corfield E, Askelund AD, Askeland RB, Hegemann L, Jensen P, *et al.* (2021): phenotools: An R package to facilitate efficient and reproducible use of phenotypic data from MoBa and linked registry sources in the TSD environment Available at: https://osf.io/6g8bj/. Accessed November 22, 2023.
63. Karlsson Linnér R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA, *et al.* (2019): Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet 51:245–257.
64. Riglin L, Thapar AK, Leppert B, Martin J, Richards A, Anney R, *et al.* (2020): Using genetics to examine a general liability to childhood psychopathology. Behav Genet 50:213–220.
65. Neumann A, Jolicoeur-Martineau A, Szekely E, Sallis HM, O'Donnel K, Greenwood CMT, *et al.* (2022): Combined polygenic risk scores of different psychiatric traits predict general and specific psychopathology in childhood. J Child Psychol Psychiatry 63:636–645.
66. Howe LJ, Nivard MG, Morris TT, Hansen AF, Rasheed H, Cho Y, *et al.* (2022): Within-sibship genome-wide association analyses decrease bias in estimates of direct genetic effects. Nat Genet 54:581–592.
67. Selzam S, Ritchie SJ, Pingault JB, Reynolds CA, O'Reilly PF, Plomin R (2019): Comparing within- and between-family polygenic score prediction. Am J Hum Genet 105:351–363.
68. Goodman SH, Rouse MH, Connell AM, Broth MR, Hall CM, Heyward D (2011): Maternal depression and child psychopathology: A meta-analytic review. Clin Child Fam Psychol Rev 14:1–27.
69. McLaughlin KA, Gadermann AM, Hwang I, Sampson NA, Al-Hamzawi A, Andrade LH, *et al.* (2012): Parent psychopathology and offspring mental disorders: Results from the WHO World Mental Health Surveys. Br J Psychiatry 200:290–299.
70. Hughes DE, Kunitoki K, Elyounssi S, Luo M, Bazer OM, Hopkinson CE, *et al.* (2023): Genetic patterning for child psychopathology is distinct from that for adults and implicates fetal cerebellar development. Nat Neurosci 26:959–969.
71. Cheesman R, Selzam S, Ronald A, Dale PS, McAdams TA, Eley TC, Plomin R (2017): Childhood behaviour problems show the greatest gap between DNA-based and twin heritability. Transl Psychiatry 7:1284.
72. Cheesman R, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Purves KL, Pingault JB, Breen G, Rijsdij KF, *et al.* (2018): Extracting stability increases the SNP heritability of emotional problems in young people. Transl Psychiatry 8:223.
73. Edwards JR (1994): Regression analysis as an alternative to difference scores. J Manag 20:683–689.
74. Nilsen RM, Vollset SE, Gjessing HK, Skjaerven R, Melve KK, Schreuder P, *et al.* (2009): Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol 23:597–608.
75. Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, Lamberts K (2009): Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. Br J Psychiatry 195:249–256.