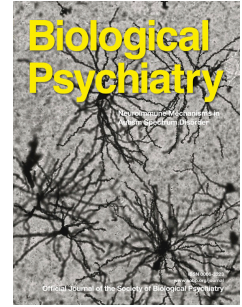# Journal Pre-proof

The genetic architecture of differentiating behavioral and emotional problems in early life

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The genetic architecture of differentiating behavioral and emotional problems in early life

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Running title: The genomics of differentiation in early life.

Keywords: differentiation; behavioral problems; emotional problems; attention-deficit/hyperactivity disorder; genomic structural equation modeling; trio polygenic score.

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 1.5-5 years (behavioral problems – emotional problems = differentiation score) in a pre-registered 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 ADHD and differentiation ($\beta=0.11$ [0.10,0.12]), and a weaker association with total problems ($\beta=0.06$ [0.04,0.07]). 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.

Introduction

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). The 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 in 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).

In 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 later developing behavioral and emotional conditions (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

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demonstrated that the extent to which behavioral and emotional problems are differentiated from one another in early childhood predicts 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, yielding mixed results (24,25). However, studies showing 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 belonging to the behavioral and emotional domains, respectively, than within either domain (24). Exploring the differentiation between behavioral and emotional problems in 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

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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 non-existent 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 apply genomic structural equation modeling and polygenic score 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 explore 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 use 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 estimate the relative contribution of direct and indirect genetic effects using genotyped parent-offspring trios. In parallel, we also conduct 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

Design

Sample

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (NIPH) (36,37). Participants were recruited from all over Norway from 1999-2008. 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 has been given by The Regional Committees for Medical and Health Research Ethics (2016/1702). We also used data from the Medical Birth Registry of Norway (MBRN). See Supplementary 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 problems 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 those with negative scores have the inverse. Differentiation was compared to total problems throughout (behavioral problems + emotional problems = total score). Differentiation and total problem scores at each time point were then standardized to zero mean and unit variance. See Supplementary 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 was available for 56,150 children and 33,351 parent-offspring trios (Figure S1) (38). The genotyping and quality control 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 in genetic analyses.

Inclusion criteria and sample size

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

Statistical analyses

The pre-registration of analyses and inference criteria can be accessed here (with deviations described in Supplementary 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 showing that an intercept-only model provided worse fit to these data (22). The intercept was set at 5 years to index the endpoint of the

children's trajectories, and this endpoint was the focus of interpretation for all analyses. This model had two components. The first, referred to from here on out as differentiation, was specified so that the latent intercept factor represented the extent of differentiation towards 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, this measurement model was constructed at the genomic level with wave-specific genome-wide association studies (GWAS) as indicators (see Figure S2). We obtained these summary statistics by running GWAS of the differentiation and total scores at each time point (age 1.5, 3, and 5 years) in *REGENIE* (41). In polygenic score analyses, observed CBCL values at each time point were used as indicators.

Genomic SEM analyses

SNP 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 GWAS 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 (*LDSC)* (43,44). We constrained the cross-trait genetic covariance intercepts to zero if they were not significantly different from zero, as 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), post-traumatic stress disorder (52),

obsessive-compulsive disorder (53), anorexia nervosa (AN) (54), and Tourette's 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 three different, previously established (5) higher order structures, namely: four correlated factors ("compulsive", "psychotic", "neurodevelopmental", and "internalizing"); 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); the same five 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 variance explained goes via differentiation versus total problems. We followed a similar procedure to 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; Supplementary Methods).

Polygenic score analyses

We generated PGS for the 11 psychiatric and neurodevelopmental conditions using LDpred2 (57), based on European samples from the most recent GWAS (at the time

of analysis). In LDpred2, PGS are calculated as a weighted sum of the effect sizes for all variants in common between the discovery sample and 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, improving prediction accuracy. All PGS were standardized to zero mean and unit variance prior to analyses. We used a robust maximum likelihood (MLR) 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 PGS 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 parents 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 PGS together are an estimate of indirect genetic influence (33). We also conducted sensitivity analyses restricting the sample to 27,330 unrelated trios.

Inference criteria and equivalence testing

We employed equivalence testing in all PGS analyses, testing whether the 90% confidence interval of each effect size overlaps with pre-specified equivalence bounds for the smallest effect size of interest (60). We set this at Cohen's $D = 0.1$, which can be considered as the lower bound of a small effect (see Supplementary Methods) (61). Type 1 error rates were adjusted in all models using the False Discovery Rate (FDR) (62).

Analytic software and code

All modeling was carried out in R v4.1.2, using v0.6-15 of *lavaan* (63) and v0.0.5 of the *GenomicSEM* (42) package. Wave-specific GWAS were conducted in *REGENIE* v3.1 (41). The *phenotools* package v0.2.9 was used to process the phenotypic data (65). Data preparation and analysis code is publicly available on Github.

Results

Measurement models

Descriptive statistics of the outcomes are provided in Table S2. The differentiation and total problem scores were empirically independent (see Figure 1; Table S3). The latent growth model provided excellent fit to the data both at the phenotypic and genomic levels (Tables S4, 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 Supplementary Results).

Figure 1 approximately here

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 GWAS (Figures S4, S5, S6, S7; Table S6). We then estimated genetic correlations of differentiation and total problems with liability to 11 different psychiatric and neurodevelopmental conditions (Figures 2B; S3). Liability to ADHD (r_g=0.73 [0.62,0.86]), alcohol dependence (r_g=0.40 [0.14,0.66]), autism (r_g=0.20 [0.08,0.31]), and depression (r_g=0.12 [0.05,0.20]) were associated with a propensity to develop

more behavioral relative to 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).

Figure 2 approximately here

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, both differentiation and total problems were strongly associated with the "neurodevelopmental" factor, in approximately equal measure (Figure 3B; Table S7). In addition, total problems were associated with the "internalizing" factor (9% of the variance was explained by total problems, versus 1% by differentiation).

Figure 3 approximately here

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 <0.001). 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 <0.001).

Figure 4 approximately here

Direct and indirect genetic effects on differentiation

We then explored associations of the 11 PGS with differentiation and total problems. First, in a child-only model (Figure 5A; Table S10), the ADHD$_{PGS}$ showed the strongest association with differentiation toward behavioral problems (β=0.11 [0.10,0.12], p_{FDR}<0.001), and a weaker association with total problems (β=0.06 [0.04,0.07], p_{FDR}<0.001). The AN$_{PGS}$ was associated with differentiation toward emotional problems (β=-0.02 [-0.04,-0.01], p_{FDR}=0.005). The MDD$_{PGS}$ (β=0.04 [0.02,0.05], p_{FDR}<0.001), TS$_{PGS}$ (β=0.03 [0.02,0.04], p_{FDR}<0.001), and SCZ$_{PGS}$ (β=0.02 [0.01,0.04], p_{FDR}=0.005) were associated with higher total problems, whereas the BIP$_{PGS}$ was associated with fewer problems (β=-0.03 [-0.04,-0.02], p_{FDR}<0.001). Based on equivalence testing, the ADHD$_{PGS}$ associations with both outcomes and the MDD$_{PGS}$ association 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 (albeit based on an arbitrary threshold).

Figure 5 approximately here

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In the multivariate trio-PGS model, most point estimates from the child-only models were unattenuated, apart from the MDD$_{PGS}$ association with total problems (Figure 6A; Table S11). Some point estimates increased, such as the direct effect of the AN$_{PGS}$ on differentiation (β=-0.05 [-0.07,-0.03], p_{FDR}=0.001). 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, 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 (Figures 6, S11, S12; Table S14). This was for the maternal MDD$_{PGS}$ (β=0.03 [0.01,0.05], p_{FDR}=0.047) and ASD$_{PGS}$ (β=0.03 [0.01,0.05], p_{FDR}=0.047), 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 major depression effect did not (Figure S11). When restricting the sample to 27,330 unrelated trios, the pattern of results was similar, but the indirect effect of the MDD$_{PGS}$ became non-significant (Tables S15, 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 less precise and smaller (Figure S13; Tables S17-S19).

Figure 6 approximately here

Discussion

In this study, we investigated the genomic factors contributing 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, 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. In line 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 (18,33–35,66). 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 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 the

multivariate PGS analyses, where each score is adjusted for the others, liability to ADHD was the predominant predictor of differentiation toward behavioral problems.

An intriguing finding was the notably larger ADHD$_{PGS}$ effect 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 (15,16,18,67). Seemingly converging research has shown a positive association of the ADHD$_{PGS}$ with the 'p-factor' and specific behavioral problems, and a slightly negative association with specific emotional problems (68). 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 the former but not the latter, that may produce the pattern of findings observed here. Alternatively, children with a high burden of generalized genetic risk might display a broad range of problems from early in life, whereas those 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. Since 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 (18,33,34,66,69,70)). Only the MDD$_{PGS}$ association with total problems was notably attenuated in the trio model (compared to the child-only model), which aligns with recent within-sibship GWAS findings (69). Second, an implication for future studies is that any indirect effects of specific psychiatric PGS on childhood outcomes may be small in magnitude (33,34). It is noteworthy that observational associations between parental psychiatric traits and offspring outcomes (71,72) are often assumed to be caused by parenting. If causal parental effects of the magnitude often postulated as explanations for these observational associations existed, we would have expected to see evidence of them as indirect genetic effects here - and 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 in childhood, relevant to broad aspects of mental health and not just neurodevelopmental conditions (73). Future GWAS in children would help to delineate these processes further, as 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 be attenuated by unreliability of the behavioral and emotional problem measurements – a common challenge in the field (74). Extracting stable signal over time and across different raters may be a way forward in childhood psychiatric genomics (75). Second, the estimates may be 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 (76). 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, PGS for traits with larger GWAS 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 GWAS 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 those based on PGS. Finally, the generalizability of our results could be affected by non-random participation at baseline (79) and selective attrition over time. The presence of behavioral problems or ADHD in children has been identified as predictors of attrition in similar cohorts (80), 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, our focus of interpretation was on the intercept factor.

Conclusion

In summary, our 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 associated mainly with total problem development. By comparing differentiation to total problems, we identified key differences in polygenic predictors, shedding light on the genetic architecture of general and specific traits underlying the development of behavioral and emotional conditions. Novel approaches to exploring the differentiation of behavioral and emotional traits across development hold promise in enhancing our ability to understand and eventually prevent the emergence of behavioral and emotional conditions.

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to publish or preparation of the manuscript. We are grateful to all the participating families in Norway who take part in this ongoing study.

Disclosures

O.A.A. is a consultant of cortechs.ai, and has received speaker's honoraria from Lundbeck, Janssen, and Sunovion, with no conflict of interest relevant to this work. The other authors report no biomedical financial interests or potential conflicts of interest.

Data availability

Data from MoBa and the MBRN used in this study are managed by the national health register holders in Norway (NIPH) and can be made available to researchers, provided approval from The Regional Committees for Medical and Health Research Ethics (REK), compliance with the EU General Data Protection Regulation (GDPR) 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 REK in Norway and an

agreement with MoBa. GWAS summary statistics used to compute polygenic scores

are available from publicly available repositories from the Psychiatric Genomics

Consortium website (https://www.med.unc.edu/pgc/download-results/).

Supplement Description:

Supplement Methods, Results, Figures S1-S13, Tables S1-S19

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Figure legends

Figure 1. Operationalisation 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.

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 GWAS of the differentiation intercept (top) and total problems (bottom).
B, LDSC 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. h^2_{SNP} = single nucleotide polymorphism heritability (liability scale); OCD, obsessive-compulsive disorder; SCZ, schizophrenia; ADHD, attention-deficit/hyperactivity disorder; PTSD, post-traumatic stress disorder; MDD, major depression. $*p <.05$; $**p <.01$; $***p <.001$.

Figure 3. 4-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 model with differentiation/total problems predicting 4 correlated factors.
B, Proportion of variance explained in the 4 factors in panel **A** by differentiation vs. total problems. The colored percentages show the proportion of the variance that goes via differentiation versus total problems, and the grey percentages show the residual variance. Note that since 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 non-convergence). We therefore 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; com, compulsive; psy, psychotic; neu, neurodevelopmental; int, internalizing;

an, anorexia nervosa; ocd, obsessive-compulsive disorder; ts, tourette's syndrome; scz,

schizophrenia; bip, bipolar disorder; alc, alcohol dependence; adhd, attention-deficit/hyperactivity

disorder; asd, autism spectrum disorder; ptsd, post-traumatic stress disorder; mdd, major depression;

anx, anxiety disorder.

Figure 4. 5-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 panel A by differentiation versus total problems. The colored percentages show the proportion of the variance that goes via differentiation versus total problems, and the grey percentages show the residual variance. Note that since 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 non-convergence). We therefore 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; p, p-factor; com, compulsive; psy, psychotic; neu, neurodevelopmental; int, internalizing; an, anorexia nervosa; ocd, obsessive-compulsive disorder; ts, tourette's syndrome; scz, schizophrenia; bip, bipolar disorder; alc, alcohol dependence; adhd, attention-deficit/hyperactivity disorder; asd, autism spectrum disorder; ptsd, post-traumatic stress disorder; mdd, major depression; anx, anxiety disorder.

Figure 5. Associations of 11 polygenic scores with differentiation and total problems.

A, Standardized betas of associations of 11 PGS with differentiation and total problems (N~56k). 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 PGS (adjusting for parent's PGS), and indirect effects of parent's PGS (N~33k). OCD, obsessive-compulsive disorder; SCZ, schizophrenia; ADHD, attention-deficit/hyperactivity disorder; PTSD, post-traumatic stress disorder; MDD, major depression; cPGS, child's polygenic score; mPGS, mother's polygenic score; fPGS, father's polygenic score.

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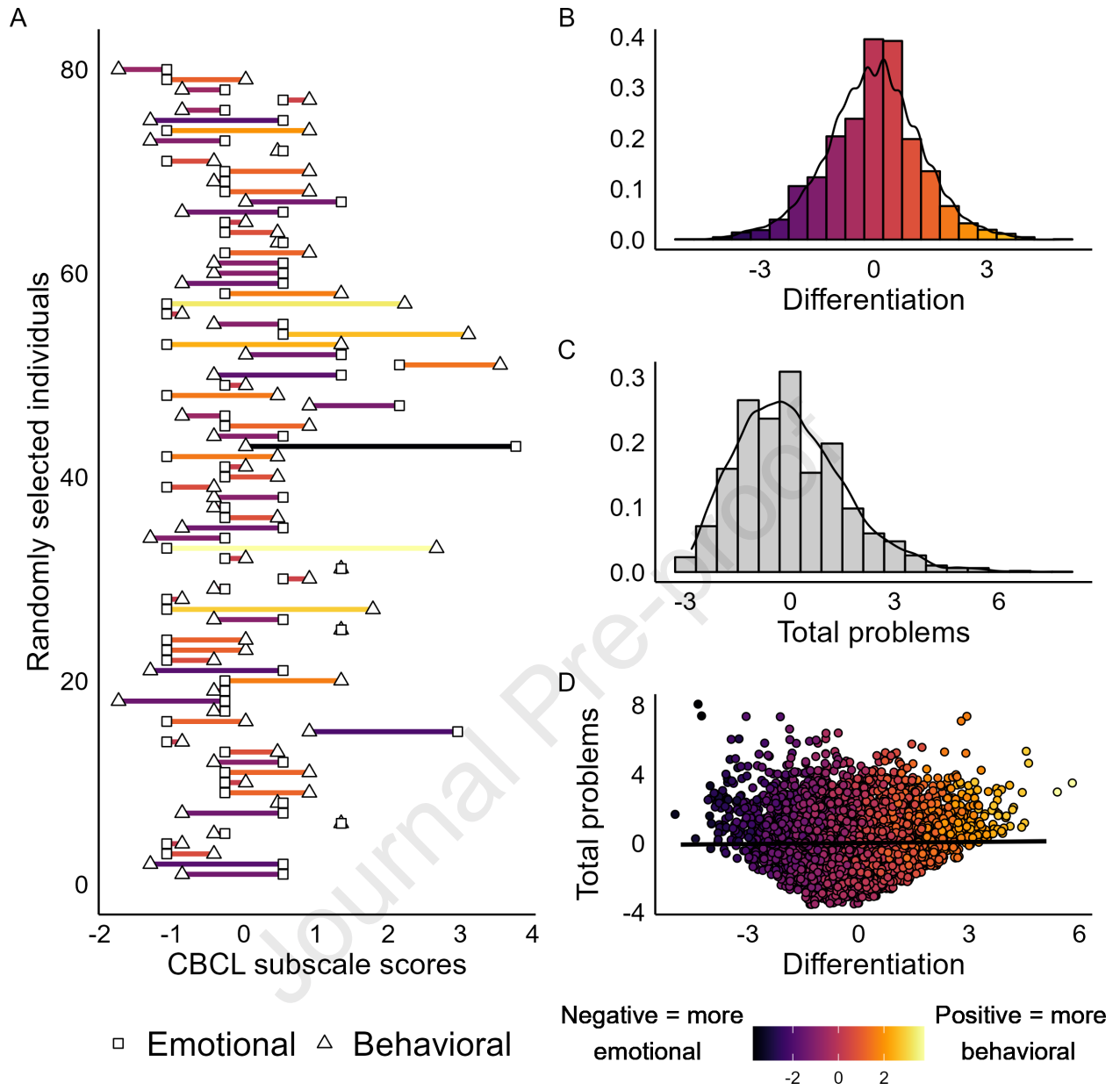
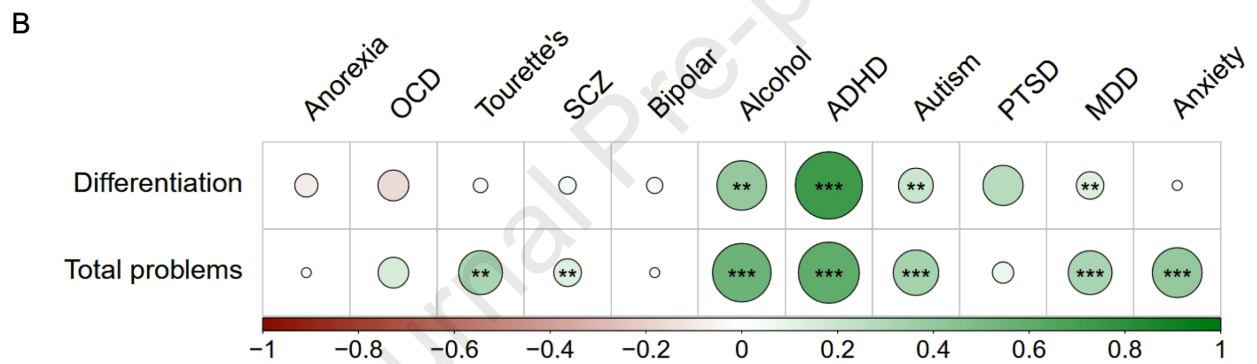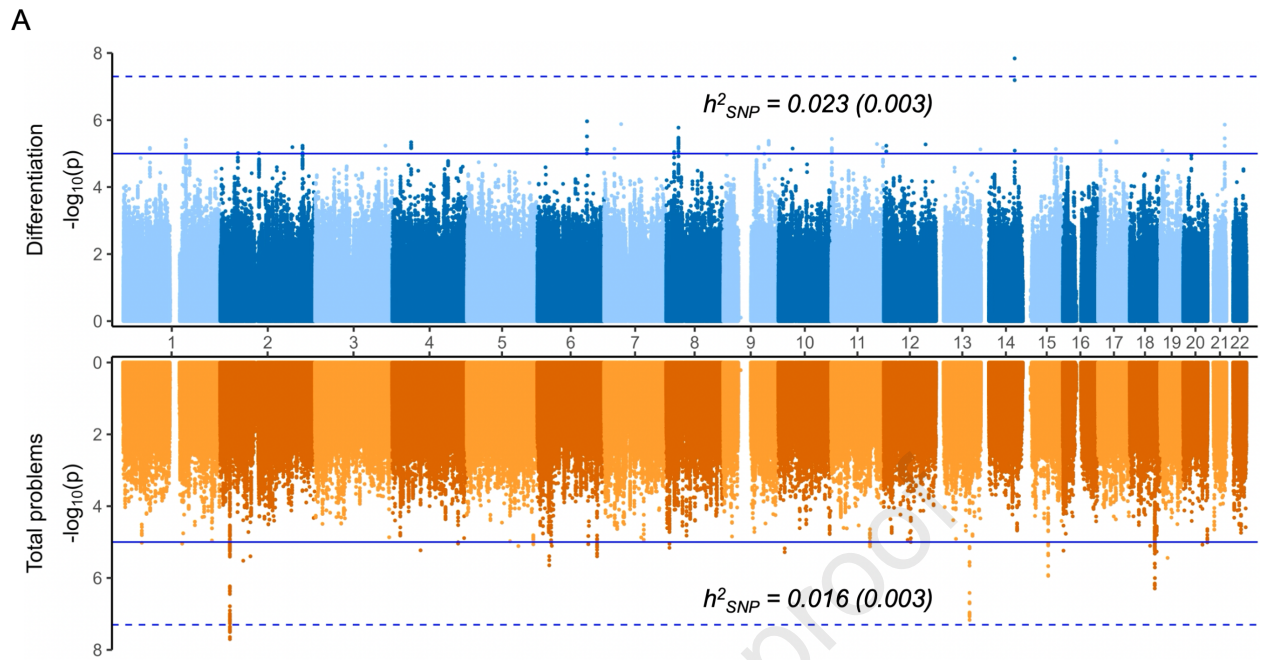**A,** Standardized betas of child-only and trio-adjusted direct effects, estimated in the ~33,000 trios. Note that to facilitate direct comparison, these child-only effects were estimated in the trio sample.
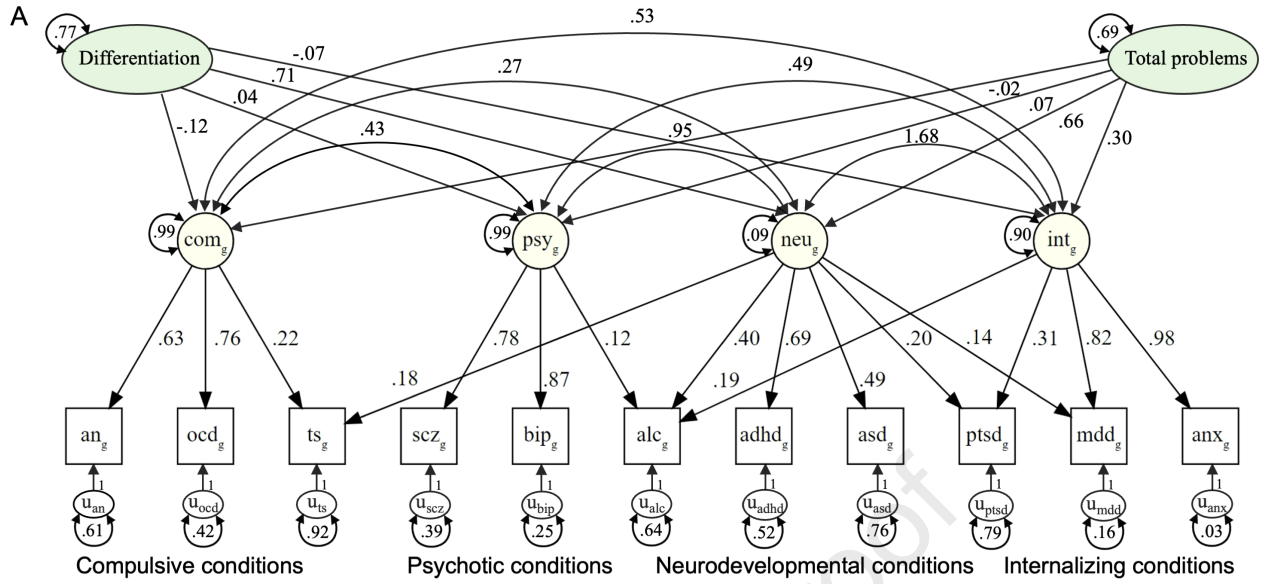**B,** Mother's indirect genetic effects on offspring differentiation and total problems in early childhood.
C, Father's indirect genetic effects on offspring differentiation and total problems in early childhood. For differentiation, positive values indicate relatively more behavioral than emotional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

A

Randomly selected individuals

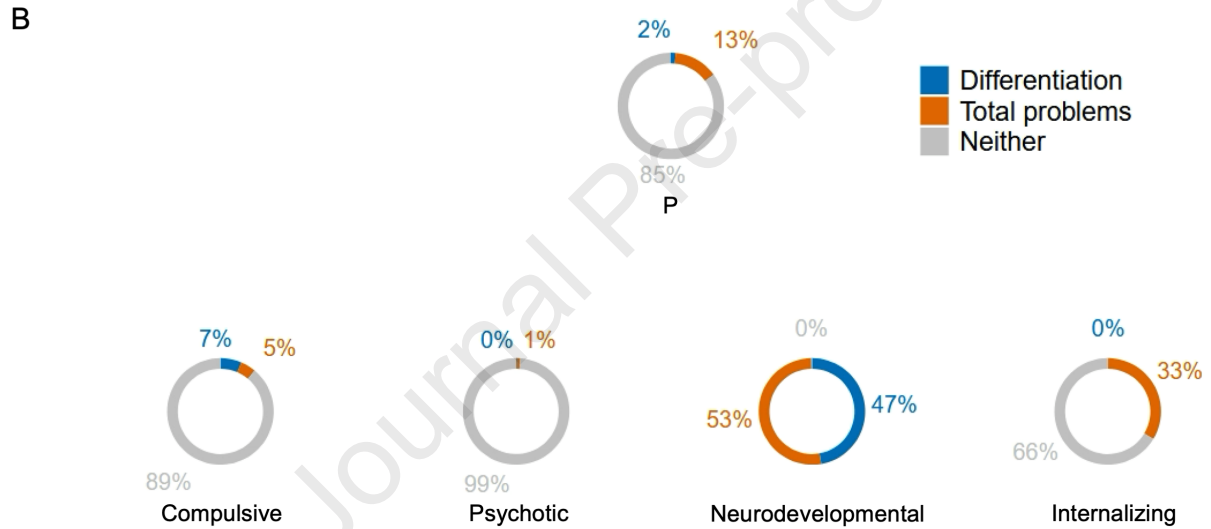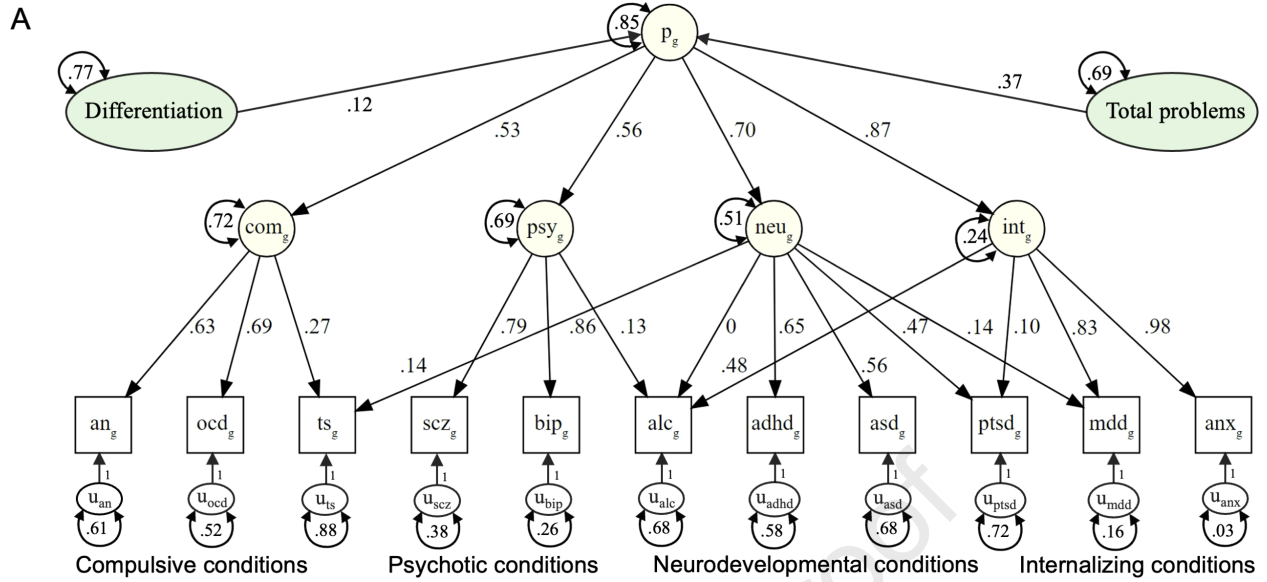CBCL subscale scores

□ Emotional   △ Behavioral

B

Differentiation

C

Total problems

D

Total problems

Differentiation

Negative = more
emotional

Positive = more
behavioral

A

$h^2_{SNP} = 0.023\ (0.003)$

$h^2_{SNP} = 0.016\ (0.003)$

B

A

.77 Differentiation

.53

-.07

.71

.27

.49

.69 Total problems

.04

.43

.95

-.02

.07

-.12

1.68

.66

.30

.99 com_g

.99 psy_g

.09 neu_g

.90 int_g

.63 .76 .22

.78 .12

.40 .69

.20 .14

.31 .82 .98

.18

.87

.19

.49

an_g ocd_g ts_g scz_g bip_g alc_g adhd_g asd_g ptsd_g mdd_g anx_g

u_an u_ocd u_ts u_scz u_bip u_alc u_adhd u_asd u_ptsd u_mdd u_anx

.61 .42 .92 .39 .25 .64 .52 .76 .79 .16 .03

Compulsive conditions   Psychotic conditions   Neurodevelopmental conditions   Internalizing conditions

B

■ Differentiation ■ Total problems ▮ Neither

1% 0%   99%   Compulsive

0% 1%   99%   Psychotic

9% 49% 42%   Neurodevelopmental

1% 9% 90%   Internalizing

A

B

A

B

A   ○ Child-only   △ Trio-adjusted

B   ● Differentiation   ● Total problems

C