Motivation and Cognitive Abilities as Mediators Between Polygenic Scores and Psychopathology in Children

Narun Pat, PhD, Lucy Riglin, PhD, Richard Anney, PhD, Yue Wang, BS, Deanna M. Barch, PhD, Anita Thapar, FRCPsych, FMedSci, PhD, Argyris Stringaris, MD, PhD, FRCPsych

Objective: Fundamental questions in biological psychiatry concern the mechanisms that mediate between genetic liability and psychiatric symptoms. Genetic liability for many common psychiatric disorders often confers transdiagnostic risk to develop a wide variety of psychopathological symptoms through yet unknown pathways. This study examined the psychological and cognitive pathways that might mediate the relationship between genetic liability (indexed by polygenic scores; PS) and broad psychopathology (indexed by $p$ factor and its underlying dimensions).

Method: First, which of the common psychiatric PSs (major depressive disorder [MDD], attention-deficit/hyperactivity disorder [ADHD], anxiety, bipolar disorder, schizophrenia, autism) that were associated with $p$ factor were identified. Then focused was shifted to 3 pathways: punishment sensitivity (reflected by behavioral inhibition system), reward sensitivity (reflected by behavioral activation system), and cognitive abilities (reflected by $g$ factor based on 10 neurocognitive tasks). We applied structural equation modeling on the Adolescent Brain Cognitive Development (ABCD) Study dataset ($n = 4,814; 2,263$ girls; 9–10 years old).

Results: MDD and ADHD PSs were associated with $p$ factor. The association between MDD PS and psychopathology was partially mediated by punishment sensitivity and cognitive abilities (proportion mediated = 22.35%). Conversely, the influence of ADHD PS on psychopathology was partially mediated by reward sensitivity and cognitive abilities (proportion mediated = 30.04%). The mediating role of punishment sensitivity was specific to emotional/internalizing. The mediating role of both reward sensitivity and cognitive abilities was specific to behavioral/externalizing and neurodevelopmental dimensions of psychopathology.

Conclusion: This study provides a better understanding of how genetic risks for MDD and ADHD confer risks for psychopathology and suggests potential prevention/intervention targets for children at risk.

Key words: ADHD, Adolescent Brain Cognitive Development, MDD, polygenic score, transdiagnostic psychopathology

The last decade has seen major advances in psychiatric genetics. However, fundamental questions remain about the psychological and cognitive links that associate genes with psychopathology. In the present study, we examined whether 3 psychological and cognitive mechanisms, similar to those proposed by the National Institute of Mental Health Research Domain Criteria (RDoC) —punishment sensitivity, reward sensitivity, and cognitive abilities—mediate the relation between genetic liability and psychiatric symptoms.

Genetic liability to psychiatric disorders, eg, major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia, can be captured by a composite of common gene variants identified from genome-wide association studies (GWASs), known as polygenic scores (PSs). Multiple gene variants associated with different psychiatric disorders have been identified, and these cut across current diagnostic classification, such that genes contributing to one disorder also influence other phenotypes, not necessarily specific to such disorder. For instance, PSs associated with case status for MDD, ADHD, and schizophrenia in discovery GWASs are associated with covariation among multiple psychiatric symptoms not limited to their respective disorders, assessed through a latent variable known as the psychopathology factor, or $p$ factor. It is unclear, however, what the mechanisms that explain this link between PSs and $p$ factor might be.
These mechanisms are likely to occur at multiple levels, including molecular, cellular, circuit, but also psychological and cognitive. The RDoC has emerged as a framework to investigate how components of these different levels contribute to psychopathology. Surprisingly little work has been done to examine which psychological and cognitive mechanisms mediate links between genetic risks and psychopathology. This is unfortunate, as at least some psychological and cognitive phenotypes can be measured with relatively high precision, and some may also be amenable to interventions. Understanding such mediating mechanisms may provide a foundation for effective early prevention and intervention strategies, an especially important goal in childhood given that most psychiatric disorders originate early in life. For this reason, our study focused on uncovering psychological and cognitive pathways between genetic liability (as indexed by PS) and psychopathology (as indexed by p factor) to provide causal mechanisms, mediation analyses still allow us to examine whether the variance of the relation between each identified PS and p factor is explained by the proposed mediators: punishment sensitivity (BIS), reward sensitivity (BAS), and cognitive abilities (g factor). Finally, to further investigate the specific roles of the mediators, we conducted follow-up mediation analyses on the 5 specific dimensions by which p factor was manifested. This allowed us to demonstrate detailed pathways for each mechanism to mediate specific sets of psychopathology.

Recently, p factor has been integrated into a transdiagnostic framework that empirically groups related symptoms together in a hierarchical order of dimensions. This framework has advantages over classical diagnostic systems (eg, DSM or ICD) in terms of predicting clinical outcomes, such as new onsets of future diagnoses, suicide attempts, and psychosocial impairments. This hierarchical structure has p factor at its apex to represent broad severity across different types of psychopathology. Moreover, p factor is manifested by lower, specific dimensions. Based on a recent large-scale study in children from the Adolescent Brain Cognitive Development (ABCD) Study dataset, at the lower level of this hierarchical structure are 5 specific dimensions of behavioral/externalizing, neurodevelopmental, emotional/internalizing, somatoform, and detachment items. These lower-level, specific dimensions make it possible to study mediating processes in greater granularity. Researchers can test which of the specific dimensions (in addition to p factor) are mediated by each mechanism. For instance, while PS for one disorder and p factor might be jointly mediated by 2 mechanisms, these 2 mechanisms might mediate different specific dimensions from the other, suggesting dissociable roles in the pathway from genetic risk to psychopathology.

Our aim here was to test possible missing mediating links between genetic risk and clinical symptoms. We did this by testing the hypotheses that motivational traits and cognitive abilities mediate between PSs for major psychiatric disorders and psychopathology (as indexed by p factor and its underlying dimensions). The first step was to identify which of the common psychiatric PSs were associated with p factor. Here we regressed p factor on PSs for common psychiatric disorders: MDD, ADHD, anxiety, bipolar disorder, schizophrenia, and autism. We used PSs of specific disorders as opposed to cross-disorders to demonstrate specific mediators for specific genetic risks for each disorder. Once identified, we conducted mediation analyses. While using mediation analyses on cross-sectional data does not provide causal mechanisms, mediation analyses still allow us to examine whether the variance of the relation between each identified PS and p factor is explained by the proposed mediators: punishment sensitivity (BIS), reward sensitivity (BAS), and cognitive abilities (g factor). Finally, to further investigate the specific roles of the mediators, we conducted follow-up mediation analyses on the 5 specific dimensions by which p factor was manifested. This allowed us to demonstrate detailed pathways for each mechanism to mediate specific sets of psychopathology.
METHOD

Sample

We used the baseline, cross-sectional data from ABCD Release 3, collected at 21 sites across the United States between September 1, 2016, and February 15, 2020 (https://doi.org/10.15154/1519007). The study recruited 11,099 children across races and ethnicities. Given the biases associated with generating PSs in samples that are ancestrally diverse, in line with others, we restricted our main analysis to children of homogeneous ancestry. To match with the discovery samples of the PSs (assessed by multidimensional scaling analysis of their genotype data; see below), we focused our main analysis on children of European ancestry. After additional quality controls (see below), the final sample included 4,814 children (2,263 girls; mean [SD] age = 9.94 [0.61] years). We also separately conducted an exploratory, supplemental analysis on 1,460 children of African ancestry (726 girls; mean [SD] age = 9.94 [0.60] years) (Figure S1, available online) using the same European ancestry-derived summary statistics. They were the second largest population based on the genotype data in the dataset, but their ancestry did not match with the discovery samples of the PSs: these analyses were therefore exploratory, as recent work showed lower predictive performance when nonmatched ancestry samples were used. The ABCD Study was approved by the institutional review board at multiple sites and obtained informed consent (parents) and assent (children).

Polygenic Score

Full details of genotyping have been published elsewhere (https://doi.org/10.15154/1519007). Briefly, the study used the Smokescreen array and genotyped from saliva and whole blood. The ABCD Study applied quality control based on calling signals and variant call rates and performed the Ricopili pipeline. The study imputed the quality-controlled genotype data with TOPMED reference (https://topmedimpute.readthedocs.io/en/latest/prepare-your-data/). We excluded children whose genetic data were collected from a problematic plate or had a subject-matching issue based on the study’s recommendations. For further quality control, we used the genotypecq function (https://github.com/ricanney/stata). We removed subjects with minimal or excessive heterozygosity, disproportionate levels of individual missingness (>2%), or insufficient sample replication (identical by descent <0.8). We also excluded single nucleotide polymorphisms based on minor allele frequency (<5%), call rate (<98%) or evidence for violations of Hardy-Weinberg equilibrium ($p < 1 \times 10^{-10}$). We included only children with low genetic relatedness (third-degree relative pairs or less; identical by descent < 0.0422). We considered children to be genetically similar to the ancestry reference if they were within 4 SDs of the mean of the top 4 principal components for the super population in phase 3 of the 1000 Genomes Project reference genotypes (see Figures S2 and S3, available online, for population structure principal components). After extracting children of the ancestry reference, we recomputed multidimensional scaling.

Using PLINK 1.9 via the summaryqc2score function (https://github.com/ricanney/stata), we computed each PS as the z-scored, weighted mean number of risk alleles in approximate linkage equilibrium, derived from imputed autosomal single nucleotide polymorphisms. We defined these risk alleles as alleles associated with case status in large-scale discovery GWASs of 6 major psychiatric disorders: MDD, ADHD, anxiety, bipolar disorder, schizophrenia, and autism. Note that for MDD, we used summary statistics based on diagnoses by clinicians and not based on self-reports used in 23andMe and UK Biobank as implemented in a more recent meta-analysis. For anxiety, we used a GWAS that involved a meta-analysis from various populations, as opposed to a more recent, larger study that analyzed only veterans, which may not be generalizable to other populations.

In the main analysis, we focused on risk alleles that passed the $p < .05$ threshold in the discovery GWASs to capture most of the variance in moderately powered GWASs. As an exploratory, supplementary analysis, we also used PSs at other thresholds from $p < .5$ to .0001 and applied Benjamini-Hochberg false discovery rate (FDR) to control for multiple testing across thresholds. In our structural equation modeling (SEM) that involved PSs, we also included control variables: 4 principal components (to control for population stratification) and sex.

Psychopathology: $p$ Factor and 5 Specific Dimensions

We assessed children’s psychopathology using the Child Behavior Checklist (CBCL), reported by parents as detailed previously. The CBCL included 119 items on a scale of 0 (not true) to 2 (very true or often true) that reflected emotional, behavioral, and ADHD problems occurring in the past 6 months. Following previous work, we removed low-frequency items and created composites for items that were highly correlated with each other. We captured $p$ factor and its lower, specific dimensions as latent variables in 2 confirmatory factor analysis (CFA) models.

First, the higher-order $p$ factor model (Figure 1A) allowed us to model $p$ factor in the mediation analyses. Here we had $p$ factor as the second-order latent variable and the 5
specific dimensions (behavioral/externalizing, neurodevelopmental, emotional/internalizing, somatoform, and detachment, as defined previously\textsuperscript{30}) as the first-order latent variables (ie, \( p \) factor was manifested by the 5 specific dimensions).

Second, the first-order model (Figure 1B) allowed us to model the 5 specific dimensions as correlated latent variables in the follow-up mediation analyses. We had the 5 specific dimensions as the first-order, correlated latent variables without \( p \) factor. Using this model, we could test associations between variables (PSs and mediators) and each of the 5 specific dimensions while controlling for the correlations among the specific dimensions.

**Motivation: Punishment (BIS) and Reward (BAS) Sensitivity**

We assessed children’s motivation through the BIS/BAS scale\textsuperscript{19} modified from the PhenX Toolkit (https://www.phenxtoolkit.org/), reported by children as detailed previously.\textsuperscript{51} The scale included 20 items (7 for BIS) on 4-point
Likert scale options (0 = not true; 3 = very true) that reflected punishment (BIS) and reward (BAS) sensitivity. The scale has been developed to have a 4-factor structure: 1 BIS and 3 BAS subscales (fun, drive, reward responsiveness). Following a recent factor analysis in children, we dropped 4 problematic items: 3 from the BIS and 1 from the BAS reward responsiveness. This resulted in 4 items per (sub)scale.

To evaluate the latent structure of the BIS/BAS scale, we ran a CFA model, similar to the classical \(^{19}\) and revised \(^{52}\) 4-factor models. In this model (Figure 1C), the BAS (as the higher-order variable) underlined the 3 BAS subscales (as the first-order variables). We then allowed the BIS and BAS to covary. We treated the BIS and BAS as latent mediators for the mediation analyses.

**Cognitive Abilities: g Factor**
We assessed children’s cognitive abilities through various cognitive tasks as detailed previously. \(^{11}\) Children completed these tasks on an iPad during a 70-minute in-session visit. We included 10 tasks in our model (including 7 tasks from the NIH Toolbox \(^{12}\)). First, the Flanker task measured inhibitory control. Second, the card sort task measured cognitive flexibility. Third, the pattern comparison processing task measured processing speed. Fourth, the picture vocabulary task measured language and vocabulary comprehension. Fifth, the oral reading recognition task measured language decoding and reading. Sixth, the picture sequence memory task measured episodic memory. Seventh, the Rey auditory verbal learning task measured auditory learning, recall, and recognition. Eighth, the list sorting working memory task measured working memory. \(^{12}\) Ninth, the Little Man task measured visuospatial processing via mental rotation. \(^{26}\) Tenth, the matrix reasoning task measured visuospatial problem solving and inductive reasoning. \(^{25}\)

As a preliminary analysis, we followed previous work \(^{11}\) by applying principal component analysis to evaluate the structure of cognitive abilities. As we assumed some similarity among the tasks, we used oblique (oblimin) rotations. The 4-component solution appeared to capture the cognitive tasks well, given minimal cross-loading. From this preliminary analysis, we then used CFA to capture the latent variable, g factor, the underlying cognitive abilities. In our higher-order g factor model (Figure 1D), we had g factor as the second-order latent variable. We also had 4 first-order latent variables in the model: executive functions (capturing the Flanker, card sort, and pattern comparison processing tasks), verbal (capturing the picture vocabulary and oral reading recognition tasks), memory (capturing the picture sequence memory, Rey auditory verbal learning, and list sorting working memory tasks) and spatial (capturing the Little Man and matrix reasoning tasks). We treated g factor as a latent mediator for the mediation analyses.

### Statistical Approach: Mediation Analyses With SEM
In our mediation analyses, we fit a series of latent variable models in successive steps. First, to identify which of the PSs are associated with p factor, we treated p factor from the higher-order p factor model as an outcome variable and 6 six PSs (MDD, ADHD, anxiety, bipolar disorder, schizophrenia, and autism) as explanatory variables. In this regression SEM, the association between each PS and p factor was already controlled for other PSs. Second, to ensure that the proposed mediators were related to p factor, we treated p factor as an outcome variable and the 3 proposed mechanisms (BIS, BAS, and g factor) as explanatory variables. Third, to demonstrate which of the 3 mediators were related to the PSs implicated by the first step, we treated the 3 proposed mediators as outcome variables and each of the selected PSs as an explanatory variable. Fourth, we examined the extent to which the relationship between each of the selected PSs and p factor was accounted for by the mediators implicated by steps 2 and 3. Here we treated each implicated PS (step 1) as an independent variable, mechanisms (steps 2 and 3) as mediators, and p factor as a dependent variable. We then conducted follow-up analyses to further examine the role of the mediators by exploring associations with the 5 specific dimensions from the first-order model. For these follow-up mediation analyses, we started by examining the association between the 5 specific dimensions (as outcome variables) and each of the PSs that was significantly associated with p factor (as an explanatory variable). Because the first-order model separately estimated correlations among the 5 specific dimensions, here we captured the unique associations between each specific dimension and PS (ie, controlling for the correlations among the dimensions). Only the 5 specific dimensions of psychopathology that were associated with each PS were used in the final follow-up mediation analyses. Finally, we tested the indirect effects, or how much the relationship between each significant PS and the specific dimensions of psychopathology was accounted for by the mediators. Given that we used specific dimensions as multiple endogenous (ie, dependent) latent variables, we further controlled for multiple testing by applying FDR to all joint indirect effects that included all mediators for each specific dimension. For latent variable modeling configurations, see Supplement 1, available online. For the R script for data preprocessing and latent variable modeling and their detailed outputs, see https://narunpat.github.io/MotivationCognitionMediationPolygenicScores/ MovCogMedPSPFactor_ABCD3_TestWGender_PC4_Mac.html.
FIGURE 2 The Relations Between Polygenic Scores, p Factor, and Proposed Mediators (Behavioral Inhibition System, Behavioral Activation System, and g Factor)
RESULTS
How Well Do the Proposed Latent Variable Models Fit the Data?
Figure 1 shows the results of CFA. All 4 proposed latent variable models had adequate model fit indices. Overall, the proposed latent variables (including \( p \) factor, 5 specific dimensions, BIS, BAS, and \( g \) factor) had good reliability (ie, internal consistency), reflected by OmegaL\(^\text{2,53} \) for second-order variables and Omega\(^\text{3,54} \) for first-order variables.

Which PSs Are Associated With \( p \) Factor?
Our first SEM tested the relationship between the 6 psychiatric PSs and \( p \) factor from the higher-order \( p \) factor model on children of European ancestry (Figure 2A, B). At \( p < .05 \) PS threshold, only the MDD and ADHD PSs showed unique associations with \( p \) factor. When examining the associations at different PS thresholds, we found that \( p \) factor was significantly associated with the ADHD PS across all 6 PS thresholds, but was only significantly associated with the MDD PS at 4 PS thresholds (\( p < .5 \) to \( < .01 \)). Given that the MDD and ADHD PSs showed associations with \( p \) factor at a similar magnitude at the prespecified \( p < .05 \) PS threshold and that these associations passed the FDR correction, we treated the MDD and ADHD PSs as independent variables in our subsequent mediation analyses on children of European ancestry. Note that we also conducted the same SEM on children of African ancestry at \( p < .05 \) PS threshold (see Figure S3, available online). However, none of the 6 psychiatric PSs were significantly associated with \( p \) factor in this population. Accordingly, we did not conduct further mediation analyses on children of African ancestry.

Are the Proposed Mechanisms Related to \( p \) Factor?
Next, we evaluated whether the proposed mediators were related to the main dependent variable, \( p \) factor (Figure 2C). Here we examined \( p \) factor in relationship to the BIS, the BAS, and \( g \) factor simultaneously, again allowing for the assessment of unique relationships. \( p \) factor was significantly associated with all proposed mediators: BIS, BAS and \( g \) factor.

Are the Proposed Mechanisms Related to MDD and ADHD PSs?
We then separately evaluated whether each of the PSs that were associated with \( p \) factor (MDD and ADHD PSs) were also related to each of the proposed mediators at \( p < .05 \) PS threshold. MDD PS (Figure 2D, E) was significantly related to the BIS and \( g \) factor, but not the BAS. The BIS and \( g \) factor were therefore included as mediators for MDD PS mediation analyses. ADHD PS (Figure 2F, G) was significantly related to the BAS and \( g \) factor, but not the BIS. The BAS and \( g \) factor were therefore included as mediators for the ADHD PS mediation analyses.

Do the Proposed Mechanisms Mediate Between Each PS and \( p \) Factor?
We then conducted the mediation SEM separately for MDD and ADHD PSs at \( p < .05 \) PS threshold. For the MDD PS mediation model, the BIS and \( g \) factor were included as mediators (Figure 3A, B). The association between MDD PS and \( p \) factor was partially mediated by both
the BIS (proportion mediated = 5.73%) and g factor (proportion mediated = 16.60%), together explaining 22.35% of the association.

The ADHD PS mediation model included the BAS and g factor as mediators at \( p < .05 \) PS threshold (Figure 3B). The association between the ADHD PS and \( p \) factor was partially mediated by both the BAS (proportion mediated = 6.404%) and g factor (proportion mediated = 23.637%). Thus, the 2 mediators together explained 30.040% of the association between the ADHD PS and \( p \) factor.

Which of 5 Specific Dimensions Are Associated With Each PS?

We then conducted follow-up mediation analyses to investigate the distinct roles of the mediators at the level of 5 specific dimensions for both the MDD PS and the ADHD PS. We first tested the relation between each of the 2 PSs and the 5 dimensions at \( p < .05 \) PS threshold. The MDD PS was significantly associated with all 5 specific dimensions (Figure 4A, B): all dimensions were therefore included in the follow-up mediation analyses for the MDD PS. The ADHD PS was statistically associated with externalizing, neurodevelopmental,
and somatoform, but not internalizing and detachment (Figure 4C, D); these 3 dimensions were therefore included in the follow-up mediation analyses for the ADHD PS.

Do the Proposed Mechanisms Mediate Between Each PS and Specific Dimensions?

For the MDD PS follow-up mediation model at \( p < .05 \) PS threshold (Figure 5A, B), joint indirect effects from all 5 specific dimensions passed the FDR correction (\( p_{FDR} = .004 - .018 \)). BIS specifically mediated the influence of MDD PS on internalizing (proportion mediated = 13.715%). \( g \) factor largely mediated the influence of MDD PS on externalizing (proportion mediated = 18.082%) and neurodevelopmental (proportion mediated = 32.237%) dimensions, but also on internalizing (proportion mediated = 5.747%) and somatoform (proportion mediated = 5.647%).

For the ADHD PS follow-up mediation model at \( p < .05 \) PS threshold (Figure 5C, D), joint indirect effects from the 3 included specific dimensions passed the FDR correction (\( p_{FDR} = < .001 - .019 \)). The BAS mediated the influence of the ADHD PS on externalizing (proportion mediated = 8.83%) and neurodevelopmental (proportion...
FIGURE 5 The Mediation Between Polygenic Scores (Major Depressive Disorder and Attention-Deficit/Hyperactivity Disorder) and Specific Dimensions of Psychopathology
mediated = 7.478%), whereas g factor mediated the influence of the ADHD PS on all 3 dimensions: externalizing (proportion mediated = 17.297%), neurodevelopmental (proportion mediated = 27.515%), and somatoform (proportion mediated = 15.246%).

DISCUSSION

In this study, we aimed to uncover the psychological and cognitive mechanisms mediating the relation between genetics and psychopathology. In particular, we tested whether 3 RDoC-based psychological and cognitive mechanisms—punishment sensitivity (BIS), reward sensitivity (BAS), and cognitive abilities (g factor)—mediated the relation between PSs for different psychiatric disorders and psychiatric symptoms across disorders (p factor and its specific dimensions). We first identified that, among the 6 common psychiatric PSs, MDD and ADHD PSs were associated with p factor in children. While we did not find a previously shown relation between schizophrenia PS and p factor, consistent with the previous reports.3,4 Moreover, MDD and ADHD PSs were related to our proposed mediation mechanisms. Importantly, the proposed mechanisms partially mediated the relation of the 2 PSs to p factor and its specific dimensions. Note that our observation that no associations were observed in children of African ancestry is in keeping with other studies that have observed low predictive power of PSs derived from a discovery sample when the target sample is of different ancestry.38

The relation of MDD PS to p factor was mediated by the BIS and g factor, whereas the relationship of ADHD PS to p factor was mediated by the BAS and g factor. Thus, the influence of MDD and ADHD PSs on psychopathology may be acting through both shared (g factor) and unique (BIS vs BAS) routes. Here we demonstrated 2 routes for MDD PS (punishment sensitivity and cognitive abilities) and 2 routes for ADHD PS that are partially dissociable from MDD PS (reward sensitivity and cognitive abilities). To further investigate the specificity of these pathways, we conducted follow-up mediation analyses on the 5 specific dimensions of psychopathology by which p factor was manifested. As discussed in more detail below, our results showed that the proposed psychological and cognitive mechanisms differentially mediated each of the 5 specific dimensions. Thus, together these data are consistent with the hypothesis that dissociable but complementary pathways mediate the influence of the MDD and ADHD PSs on p factor.

The mediating role of the BIS from MDD PS to p factor is consistent with studies associating the BIS with emotional/internalizing symptoms.17 When examining its detailed mediating pathways using specific dimensions of psychopathology, we found a high level of specificity in the mediation: the BIS was significantly related to only 1 PS (MDD PS) and 1 specific dimension of psychopathology (internalizing). Conversely, the mediating role of the BAS to ADHD PS and p factor is consistent with associating the BAS with neurodevelopmental and behavioral/externalizing symptoms.20,21 Similar to the BIS, the BAS also showed a high level of specificity in its mediation: it was significantly related to only 1 PS (ADHD PS) and 2 specific dimensions (neurodevelopmental and behavioral/externalizing symptoms). Together, these findings suggest that motivation-related mechanisms, punishment and reward sensitivity, mediated the influences of genetics in a specific manner.

Note: (A) Structural equation modeling testing the mediation between MDD PS and the 5 specific dimensions of psychopathology with the BIS and g factor as mediators using p < .05 PS threshold. This model demonstrated the following fit indices: robust, scaled comparative fit index = 0.815, Tucker-Lewis index = 0.807, and root mean squared error = 0.033 (90% CI = 0.033–0.034). The BIS mediated the relation between MDD PS and internalizing (indirect b = 0.011, SE = 0.094, 95% CI = 0.003–0.018, z = 2.831, p = .006), neurodevelopmental (indirect b = 0.015, SE = 0.0052, 95% CI = 0.005–0.025, z = 2.887, p = .004), internalizing (indirect b = 0.03, SE = 0.002, 95% CI = 0.000–0.006, z = 2.028, p = .043), and somatoform (indirect b = 0.031, SE = 0.002, 95% CI = 0.000–0.006, z = 2.026, p = .043). (B) Only the indirect effects of BIS on externalizing and neurodevelopmental survived the FDR correction when examining PSs across thresholds. While the indirect effect of BIS on internalizing was significant (p < .05) at multiple PS thresholds (5, 1, 0.5, 0.1, 0.01), none survived the FDR correction. (C) Structural equation modeling testing the mediation between ADHD PS and the 3 specific dimensions of psychopathology with BAS and g factor as mediators using p < .05 PS threshold. This model demonstrated the following fit indices: robust, scaled comparative fit index = 0.809, Tucker-Lewis index = 0.803, and root mean squared error = 0.033 (90% CI = 0.033–0.034). The BAS mediated the influence of the ADHD PS on externalizing (indirect b = 0.008, SE = 0.002, 95% CI = 0.004–0.013, z = 3.99, p = .001) and neurodevelopmental (indirect b = 0.007, SE = 0.002, 95% CI = 0.002–0.011, z = 3.078, p = .002), g factor mediated the influence of the ADHD PS on all 3 dimensions: externalizing (indirect b = 0.017, SE = 0.004, 95% CI = 0.010–0.024, z = 4.979, p < .001), neurodevelopmental (indirect b = 0.025, SE = 0.005, 95% CI = 0.015–0.035, z = 5.072, p < .001), and somatoform (indirect b = 0.006, SE = 0.002, 95% CI = 0.001–0.010, z = 2.831, p = .004). (D) All of these indirect effects survived the FDR correction when examining PSs across thresholds. The numbers overlaid black lines indicate standardized parameter estimates. The numbers on the right side next to each specific dimension of psychopathology indicate proportion mediated for the mediation pathways with significant indirect effects. Dotted lines indicate mediation paths with nonsignificant (p < .05) indirect effects. Yellow indicates independent variables; blue, mediators; green, dependent variables. ADHD = attention-deficit/hyperactivity disorder; BAS = behavioral approach system; BIS = behavioral inhibition system; ConVars = PS control variables (4 principal components and sex); Detach = detachment; DRW = BAS drive; EF = executive functions; Ext = externalizing; FDR = false discovery rate; Fun = BAS fun; g = g factor; Int = internalizing; MDD = major depressive disorder; mmr = memory; Neuro Dev = neurodevelopmental; PS = polygenic score; RR = BAS reward responsiveness; Scz = schizophrenia; Somatic = somatoform; sp = spatial; vrb = verbal. Please note color figures are available online.

*p < .05; **p < .01; ***p < .001.
Of note, we found relatively broad influences of the MDD PS on all specific dimensions of psychopathology, including both internalizing and externalizing dimensions. Yet, the MDD PS was specifically related to punishment sensitivity (BIS), but not reward sensitivity (BAS). This seems to suggest that other mediators may play a role in the relation between the MDD PS and other psychopathological dimensions beyond internalizing. g factor appears to be one of these mediators. The mediating role of g factor to both the MDD PS and the ADHD PS is in line with previous work showing relationships between cognitive abilities and broad psychopathology. In contrast to the 2 motivation-related mediators, g factor showed a broader role. That is, g factor mediated the influences between both the MDD PS and the ADHD PS and various specific dimensions of psychopathology. For both the MDD PS and the ADHD PS, g factor strongly mediated the contribution of genetic influences to the externalizing and neurodevelopmental dimensions, relative to other dimensions. g factor additionally, albeit weakly, mediated the link with the internalizing and somatic dimensions for the MDD PS and with the somatic dimension for the ADHD PS. Accordingly, we found that having genetic liability for MDD and/or ADHD had negative associations with cognitive abilities, which, in turn, may enhance the general risk to develop psychopathology. As such, cognitive abilities played a key role as a nonspecific factor that linked genetic liability with broad psychopathology, consistent with previous findings and theoretical perspectives of p factor.

We believe understanding the roles of the proposed psychological and cognitive mechanisms has research and clinical implications. As we showed here, the model fit indices and reliability (ie, internal consistency) indices of the proposed mechanisms were relatively high. This means that we can measure these mechanisms in children with precision using latent variable modeling. Moreover, punishment and reward sensitivity and cognitive abilities are shown to be altered via psychotherapy and other environment-altering interventions. Accordingly, they can be targeted for effective early prevention and intervention strategies for children at risk.

This study is not without limitations. First, as highlighted previously, while using PSs derived from GWASs is more reliable than using only a few common single nucleotide polymorphisms from selected genes (candidate-gene approach), PSs still explain only a small proportion of genetic liability to psychiatric disorders. The relatively small effect sizes of our results confirm this notion. Additionally, our use of the CBCL to define psychopathology did not allow us to investigate psychosis as another specific dimension. Thus, our definition of p factor may not be exhaustive. This may explain the nonsignificant relationship between schizophrenia PS and p factor, which is contradictory to previous studies. Next, we measured the mediators and psychopathology at the same time, making it difficult to empirically test the directionality of their relations. Fortunately, the ABCD Study is an ongoing longitudinal study that will provide additional data from the same children until they are 20 years old. Thus, we believe that our study will lay a foundation for future research to further empirically test the directionality of the effects found here, for instance, using the cross-lagged panel model. Further, we included only children with low genetic relatedness (more than third-degree relative pairs) to avoid inflated associations following recommendations. Nonetheless, this method may lower the statistical power. Future studies may implement a different approach to statistically account for relatedness without exclusion.

Finally, the generalizability of the findings is limited to children of European ancestry owing to the lack of summary statistics from well-powered GWASs for major psychiatric disorders done in non-European participants. When we applied European ancestry–derived summary statistics to children with African ancestry, we no longer saw the relation between psychiatric PSs and p factor. This is consistent with recent work showing lower predictive performance when nonmatched ancestry samples are used. This highlights the importance of having diverse populations in the GWASs and statistical approaches to deal with multi-ancestry and admixed cohorts so that genetic research can be more broadly applicable. Such shortcomings prohibited the full use of the ABCD Study even though the ABCD Study had been specifically designed to have a strength in the diversity of its participants.

In summary, in a large sample of children, the influences of genetic predispositions for MDD and ADHD on psychopathology were mediated by 3 RDoC mechanisms: punishment sensitivity, reward sensitivity, and cognitive abilities. These findings further our understanding of the structure of psychopathology and the pathways through which it relates to genetic architecture.
listing of the study investigators can be found at https://abcdstudy.org/scientists/workgroups/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or the ABCD consortium investigators. N.P., Y.W., and A.S. were supported by the Otago Medical Research Foundation Grant through the M. Begg Charitable Trust.

This work has been previously posted on a preprint server: https://www.medrxiv.org/content/10.1101/2020.06.08.20123877v3.

Author Contributions

Conceptualization: Pat
Data curation: Pat
Formal analysis: Pat, Riglin, Anney
Funding acquisition: Pat, Stringaris
Investigation: Pat
Methodology: Pat, Anney
Project administration: Pat

REFERENCES


Resources: Pat, Barch
Software: Pat, Anney
Supervision: Pat, Stringaris
Validation: Riglin, Barch, Thapar
Visualization: Pat, Wang

Writing — original draft: Pat, Stringaris
Writing — review and editing: Pat, Riglin, Barch, Thapar, Stringaris

Disclosure: Drs. Pat, Riglin, Anney, Barch, Thapar, and Stringaris and Mr. Wang have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Narun Pat, PhD (also known as Narun Pornpattananangkul, PhD), Department of Psychology, University of Otago, William James Building, 275 Leith Walk, Dunedin 9016, New Zealand, e-mail: narun.pat@otago.ac.nz

0890-8567/$36.00/©2021 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

https://doi.org/10.1016/j.jaac.2021.08.019
Sunderland M, Slade T. The relationship between internalizing psychopathology and
suicidality, treatment seeking, and disability in the Australian population. J Affect Disord.

Forbush KT, Hagen KE, Kite BA, Chapa DAN, Boheer BK, Gould SR. Understanding
eating disorders within internalizing psychopathology: A novel transdiagnostic,
compspsych.2017.06.009.

38. Duncan L, Shen H, Gelaye B,
Garavan H, Bartsch H, Conway K,
37. Gelaye B, Achenbach TM. Achenbach System of Empirically Based Assessment (ASEBA).
In: Cautin RL, Lilienfeld SO, eds. The Encyclopedia of Clinical Psychology. Malden, MA:

36. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genome wide meta-
analysis identifies genomic relationships, novel loci, and pleiotropic mechanisms across
528117.

35. Caspi A, Moffitt TE. All for one and one for all: Mental disorders in one
2018.17121383.

34. Pat et al. Meta-analysis of genome-wide association studies identify 44
risk variants and refine the genetic architecture of major depression. Nat Genet.

33. Kessler RC, Petukhova M, Zaslavsky AM. The role of latent internalizing and exter-

32. Ruderfer DM, Ripke S, McQuillin A, et al. Genomic dissection of bipolar disorder and
10.1016/j.cell.2018.05.046.

enriched in mutation-intolerant genes and in regions under strong background selection.


detects 102 independent variants and highlights the importance of the prefrontal brain

results from ~200,000 participants in the Million Veteran Program. Am J Psychiatry.

27. Barch DM, Albaugh MD, Avenevoli S, Achenbach TM. Achenbach System of Empirically Based Assessment (ASEBA).
In: Cautin RL, Lilienfeld SO, eds. The Encyclopedia of Clinical Psychology. Malden, MA:

10.1016/j.cell.2018.05.046.

25. Bogdan R, Baranger DAA. Agrawal A. Polymorphic risk scores in clinical psychology:
Bridging genomic risk to individual differences. Annu Rev Clin Psychol. 2018;14:

24. Choi SW, Mak TS, Reilly PF. Tutorial: A guide to performing polygenic risk score

ancestraly diverse populations: Opportunities, methods, pitfalls, and recommendations.
SUPPLEMENT 1. LATENT VARIABLE MODELING CONFIGURATIONS

For each CFA structure, we fixed latent factor variances to 1 so that we could estimate all factor loadings. We used robust estimators to deal with the non-normality of psychopathological phenotypes in this population-based study. To this end, we first used robust maximum likelihood estimation with robust (Huber-White) standard errors and scaled test statistics that also dealt with missing values via the full information maximum likelihood algorithm. However, if we encountered a nonconvergent problem with the maximum likelihood estimation, we treated data as ordinal and used the weighted least square mean and variance adjusted estimator instead. The weighted least square mean and variance adjusted estimator uses diagonally weighted least squares to estimate model parameters. To demonstrate model fit, we used scaled comparative fit index, Tucker-Lewis index and root mean squared error of approximation with 90% CI. We reported the robust versions of these indicators for the maximum likelihood estimation. For CFA, we also reported the reliability of the latent variables: OmegaL2 for second-order variables and Omega3 for first-order variables. These reliability indices reflect the internal consistency of the latent variables of interest. Model fits and reliability indices are shown in the captions to Figures S1–S3. We ran the analyses in R4.0.2 on the standardized data using lavaan (version 0.6-6) and semTools along with semPlot and qgraph for visualization (see https://narunpat.github.io/MotivationCognitionMediationPolygenicScores/MovCogMedPSPFactor_ABCD3_TestWGender_PC4_Mac.html for the script and detailed outputs).

SUPPLEMENTAL REFERENCES

FIGURE S1 The Relationships Between Polygenic Scores and the p Factor Among Children of African Ancestry

Note: Structural equation modeling using p < .05 PS threshold showed the following fit indices: robust, scaled comparative fit index \( = 0.795 \), Tucker-Lewis index \( = 0.790 \), and root mean squared error \( = 0.038 \) (90% CI: 0.037–0.039). From this model, none of the 6 PSs showed significant associations with the p factor at p < .05. ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; BIP = bipolar disorder; Con Vars = PS control variables (4 principal components and sex); Detach = detachment; Ext = externalizing; Int = internalizing; MDD = major depressive disorder; Neuro Dev = neurodevelopmental; PS = polygenic score; SCZ = schizophrenia; Somatic = somatoform.

FIGURE S2 Population Structure Principal Components for Children of European Ancestry in the Adolescent Brain Cognitive Development (ABCD) Study Dataset

Note: We used the super population in phase 3 of the 1,000 Genomes Project as reference genotypes. Red cluster indicates European super population; orange, American super population; green, African super population; blue, East Asian super population; purple, South Asian super population; yellow, children of European ancestry in the ABCD Study.
FIGURE S3 Population Structure Principal Components for Children of African Ancestry in the Adolescent Brain Cognitive Development (ABCD) Study Dataset

Note: We used the super population in phase 3 of the 1,000 Genomes Project as reference genotypes. Red cluster indicates European super population; orange, American super population; green, African super population; blue, East Asian super population; purple, South Asia super population; yellow, children of African ancestry in the ABCD Study.