Polygenic variation underlying educational attainment and ADHD indexes behavior ratings of executive functions in child psychiatry outpatients

Michael R. Capawana, PhD[1,2], Pieter J. Vuijk, PhD[3], Joanna Martin PhD[4], Alisha R. Pollastri, PhD[1,2], Gina A. Forchelli, PhD[1,2], Georgia G. Woscoboinik, BS[3], Sonia L. Tremblay, BA[3], Lauren E. Wolfe, BA[3], Ellen B. Braaten, PhD[1,2], Alysa E. Doyle PhD*[1, 2,3]

1) Department of Psychiatry, Massachusetts General Hospital (MGH)
2) Harvard Medical School
3) Center for Genomic Medicine (CGM), MGH
4) Centre for Neuropsychiatric Genetics & Genomics, School of Medicine, Cardiff University, Cardiff, United Kingdom

* Correspondence to: adoyle1@mgh.harvard.edu; CPZN 6.240, Massachusetts General Hospital, 185 Cambridge St., Boston, MA 02114

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Brief Biographical Statements for authors: Dr. Capawana is a staff psychologist at the Learning and Emotional Assessment Program (LEAP) at MGH. Dr. Vuijk is biostatistician in Dr. Alysa Doyle's laboratory in the Psychiatric and Neurodevelopmental Genetics Unit (PNGU) in the CGM at MGH. Dr. Martin is a Research Fellow affiliated with the Wolfson Centre for Young People's Mental Health and the Centre for Neuropsychiatric Genetics and Genomics at Cardiff University. Dr. Pollastri is Director of Research and Evaluation at the Think:Kids program at MGH. Dr. Forchelli is a staff psychologist at LEAP at MGH. Ms. Woscoboinik is a current research coordinator in the Doyle laboratory in PNGU at MGH. Ms. Tremblay is a former research coordinator in the Doyle laboratory in PNGU at MGH and is now a doctoral student in clinical psychology at the University of Colorado, Boulder. Ms. Wolfe is a former research coordinator in the Doyle laboratory in PNGU at MGH and is now a doctoral student in school and clinical psychology at the University of Virginia. Dr. Braaten is a writer and Executive Director of MGH LEAP, which is the source clinic for the current study. Dr. Doyle is PI of the grant under which data the current data were collected, Director of Research at LEAP, and a faculty member in PNGU at MGH. Drs. Doyle and Braaten previously worked under Dr. Joseph Biederman's mentorship in the MGH Pediatric Psychopharmacology Unit and remain grateful for his kindness and contributions to their careers.

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Abstract

Objective: We leveraged common genetic variation underlying ADHD, educational attainment (EA) and cognition (COG) to understand the nature of the Behavior Rating Inventory for Executive Functions (BRIEF) and its relationship to academic functioning. Method: Participants were 991 youth, ages 7 to 17, consecutively referred for neuropsychiatric evaluation. Polygenic scores (PGS) for ADHD, EA, and COG were related to the BRIEF using regression analyses. Structural equation models were used to examine the associations between the PGS, BRIEF and academic outcomes (math, reading, and special education services [EDPLAN]). Results: After modeling the PGS together, only the EA and ADHD PGS significantly associated with the BRIEF. The BRIEF partially mediated the relationships between EA PGS with math and EDPLAN and fully mediated the relationship between ADHD PGS and EDPLAN. Conclusion: Genetic data extend evidence that the BRIEF measures a construct relevant to educational success that differs from what is indexed by cognitive testing.

Introduction

Executive Functions (EFs), such as working memory, inhibition, and shifting, are a set of higher-order cognitive processes that assist with problem-solving and goal-directed behavior (Diamond, 2020; Guha, 2016; Miyake et al., 2000). Historically, EFs have been measured using psychometric tests that engage relevant cognitive capacities via performance-based tasks (Guha, 2016). Over time, a large literature has demonstrated that such tests show reduced performance, on average, in children with neuropsychiatric conditions (Doyle et al., 2018; Willcutt et al., 2008). Further, within and across diagnoses, variation in test scores associates with academic and social problems in youth (Biederman et al., 2004; Biederman et al., 2011; Colomer et al., 2017; Kouklari et al., 2018) and educational, occupational, and social difficulties in adults (Biederman et al., 2006; Evans et al., 2004; Green, 2006; Hagen et al., 2016). Thus, given the association between EFs and functional impairment across the lifespan, assessment of EFs is often sought in child clinical settings to identify youth who require support beyond treatment of their psychiatric symptoms (Biederman et al., 2022; Coghill, 2021).

In the last two decades, rating scales that aim to assess EF have also emerged. Neuropsychological testing, despite its well-documented validity, is not without limitations (Toplak et al., 2013). Evaluations can be costly and potentially challenging to access (Wright et al., 2017). Testing also assesses performance in controlled environments over a particular time duration, and thus its ability to capture functioning in everyday life has been questioned (Biederman et al., 2022; Chaytor et al., 2006). Questionnaires, like the widely-used Behavior Rating Inventory of Executive Function (BRIEF; (Gioia et al., 2000, 2015), were developed to provide a cost-effective, accessible and ecologically-valid option for evaluating EFs via informant observation and self-reflection. Over time, a robust literature has emerged to show that, like EF tests, rating scales that inventory the behavioral concomitants of EF show a relationship to academic (Biederman et al., 2008; Clark et al., 2010;

Colomer et al., 2017; Costa et al., 2017; Figuccio et al., 2019; Gerst et al., 2017; Gilboa et al., 2014; Locascio et al., 2010; Mann & Snover, 2015; Samuels et al., 2016), social (Freeman et al., 2017; Gilotty et al., 2002; Torske et al., 2017), adaptive (Gilotty et al., 2002; Kouklari et al., 2018; Pope et al., 2016), and occupational (Biederman et al., 2008) arenas.

Curiously, though, EF questionnaires and EF tests show a limited relationship with one another. For example, Toplak et al. (2013) conducted a comprehensive review of 20 studies that included 286 correlations between EF tests and questionnaires. Even in the quarter of the correlations that were statistically significant, the relationship between scales and tests was of relatively low magnitude (i.e., median correlation ~.2). Yet, studies that have directly examined both methods of assessment confirm that, despite their limited relationship, EF tests and questionnaires both relate to real world functioning. For example, Gerst et al. (2017) found that, despite modest correlations across measures, BRIEF subscales and EF tests related to reading comprehension and math in a youth sample. Moreover, in our own prior study of 692 child psychiatric outpatients (Pollastri et al., 2022), cognitive tests of EF and the BRIEF independently explained variance in academically related outcomes, (i.e. teacher-rated learning problems and study skills), despite their low correlation with one another.

Such findings raise questions about what exactly the BRIEF is measuring. Based on their review, Toplak et al. (2013) and others (e.g. Gerst et al., 2017) have posited that EF tests and questionnaires index different levels of the executive function construct, with the latter relating to aspects of the broad EF construct that relate to real world functioning not captured by tests. Yet, on a practical level, the possibility that EF tests are measuring the behavioral sequelae of psychopathology symptoms in psychiatric samples is also important to consider. In particular, a relationship with ADHD has emerged. For example, McAuley and colleagues (2010) found that while BRIEF scores were not significantly associated with psychometric EF tests in a clinical sample of children, they did index parent- and teacher-rated behavioral disruption, including of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms (inattention and hyperactivity) as well as other difficulties (e.g., relationship

quality, school truancy). Further, Biederman et al (2022) showed a relationship between the adult version of the BRIEF's total score (i.e., the General Executive Composite; GEC) and the severity of ADHD symptoms. Additionally, in our own sample (Pollastri et al., 2022), BRIEF subscales showed relationships with different psychiatric diagnoses and symptom dimensions, but the most robust association was ADHD. Specifically, the ADHD diagnosis related to all BRIEF subscales and the inattention symptoms related to six out of eight subscales, even after controlling for other psychopathology.

In the current study, we aimed to capitalize on progress in the field of psychiatric genetics to explore this issue further. Over the past decade, large-scale genome-wide association studies (GWAS) have yielded information about common genetic variation that underlies a range of psychiatric diagnoses and clinically-important constructs (Wray et al., 2021). We aimed to leverage this information to clarify the constructs that contribute to variation on the BRIEF and to determine the extent to which the BRIEF mediates the relationship between genetic risk and academic functioning. Our analyses focused on three constructs with relevance to the BRIEF based on the literature reviewed above: 1) general cognition as measured by psychometric tests (COG; (Savage et al., 2018) including those that tap into EF (Diamond, 2020); 2) educational attainment (EA; i.e., the years of schooling attained; (Lee et al., 2018), which is correlated with cognition to an extent but subsumes factors that relate to academic success generally; and 3) ADHD (Demontis et al., 2023). We generated polygenic scores (PGS) to quantify the genetic loading relevant to these constructs in child psychiatry outpatients and related them to scores on the BRIEF and indices of academic functioning. By doing so, we aimed to shed further light on the nature of the BRIEF itself as well as the role of the behavioral concomitants of EF that the BRIEF measures in risk mechanisms and child outcomes. Given the limited phenotypic relationship between the BRIEF and psychometric tests and its robust phenotypic relationships to school functioning and ADHD in the literature, we expected to find a relationship between the BRIEF and the biological underpinnings of EA and ADHD but not COG.

Method

Participants (N = 991) were from the ongoing Longitudinal Study of Genetic Influences on Cognition (LOGIC). The study was launched to study the trajectories of referred youth with neuropsychiatric symptoms and facilitate the clinical translation of genomic discoveries. LOGIC ascertains children and adolescents consecutively referred for evaluation, regardless of diagnosis. The source clinic is housed within the Psychiatry Department of an academic hospital and provides evaluations to assist with differential diagnosis and/or treatment/educational planning. To enroll, youth must contribute their clinical data. They are also asked to provide a DNA sample and to undergo supplemental assessments to create a uniform phenotype battery. The current analyses included the first child enrolled in a family, with the following characteristics: 1) ages 7 to 17 years; 2) Full Scale IQ (FSIQ) $\geq$ 70; 3) received the first edition of the BRIEF parent rating scale (BRIEF), which was part of the standard study battery; and 4) had completed genotyping and QC procedures. Their mean age was 11.3 $\pm$ 3.0 years, 62.6% were male. Full scale IQ (FSIQ) was 99.5 $\pm$ 13.3, as measured by the Wechsler Intelligence Scale appropriate to their age and via the edition that was current at their time of assessment (WISC-IV (Wechsler, 2004); WISC-V (Wechsler, 2015); WAIS-IV (Wechsler, 2008)).

The study was approved by the Mass General Brigham Institutional Review Board. After reviewing study procedures and risks, parents provided written informed consent for youth 7 to 17 years old. Youth 7 to 13 provided written assent and youth 14 to 17 co-signed the consent form.

We note that 644 of the 991 participants in this study were included in our prior, phenotypic paper on the BRIEF (Pollastri et al 2022), which examined different outcomes related to the school setting (i.e. teacher ratings).

Phenotypic Characteristics of the Sample:

Clinical Diagnoses: Youth in this clinical sample manifested a range of conditions and

comorbidity, which are summarized in Table 1 and detailed in the Supplementary Text. Participants received DSM-IV/ DSM-IV-TR diagnoses, reflecting the diagnostic system at the time of their enrollment, by faculty who were doctoral-level licensed psychologists or fellows under their close supervision. Our source clinic is an accredited training site for clinical psychology interns and post-doctoral fellows. It emphasizes thorough, diagnostic assessment, with information gathered from clinical interviews with parents/guardians and patients, review of medical records, and rating scales. Diagnoses were coded in the clinic record if the clinician determined that full DSM-IV-TR were met with the one exception that an ADHD diagnosis made at the time of the DSM-IV was allowed to co-occur with an Autism Spectrum Disorder (ASD), in anticipation of DSM-V. Because Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) were not coded in the clinical record if they were considered secondary to other factors, clinical CD and ODD diagnoses were enriched for research purposes when full DSM-IV criteria was met based on symptom-level parent reports using the Child Symptom Inventory - 4 (CSI-4; (Gadow & Sprafkin, 2002).

Medication**:** Detailed data regarding current use of psychotropic medication (dose, type, onset, offset) was obtained as part of the clinical evaluation and is provided in the Supplementary Text. Based on this information, we created a binary variable to indicate current use of one or more types of psychotropic medications versus non-use. This variable yielded a total of 41.6% (N = 412) youth using any psychotropic medication, with some youth taking more than one type of medication.

Genomic data:

DNA was collected via Oragene^{TM} saliva kits or blood venipuncture. Samples were genotyped at the Broad Institute of MIT and Harvard in two rounds related to availability of samples and funding. Round 1 included the Illumina Infinium PsychArray Beadchip v1.1 (PsychChip), and Round 2 included the Illumina Global Screening Array v.1 (GSA). Data were processed separately by chip for QC and imputation, and then harmonized and merged for further analysis. Relatedness analyses

(identity-by-descent and Mendel error analyses) were performed in PLINK in the context of the wider study population, and principal components analysis (PCA) was done using PCAiR (Conomos et al., 2015). Details of QC, imputation, and sample processing can be found in the Supplementary Text. After QC, this process yielded 1,068,808 high-quality SNPs.

We calculated polygenic scores (PGS) based on the summary statistics available for recent GWAS of our target constructs, which included COG (Savage et al., 2018), EA (Lee et al., 2018), and ADHD (Demontis et al., 2023) . We note that the summary statistics for EA exclude participants in the publication who were derived from the 23andMe resource. Scores were calculated using the continuous shrinkage method, PRS-CS (Ge et al., 2019). This strategy scores polygenic variation using all available HapMap3 SNPs (Vos et al., 2012). It adjusts the per-SNP effect sizes relative to their GWAS association signals, considering linkage disequilibrium (LD) information based on the European ancestry subset of the 1000 genomes phase 3 reference sample. The program PLINK (Purcell et al., 2007) was used to sum the SNP-level scores and create a PGS for each individual. Further details are provided in the Supplementary Text.

Our analyses for all three scores used a global shrinkage parameter of phi = 1, which reflects high polygenicity and is thus appropriate for the constructs being examined. We used the full sample regardless of ancestry (N = 991). As a sensitivity test, given the predominance of European ancestry in the source GWAS, we repeated analyses in the subgroup of individuals of European ancestry (N = 762 children [mean (SD) age = 11.4 (3.0) years; N (%) female = 277 (36.4%)], identified via the principal components analyses.

Measures:

EF rating scale:

The BRIEF parent form (1st edition) consists of 86 items on which parents rate their child's

behavior on a three-point Likert scale (Never, Sometimes, or Often). The BRIEF was normed on 2,271 children and has well-established test- retest reliability (Gioia et al., 2000; Gioia et al., 2002). It includes eight individual scales measuring different aspects of executive functioning, which in turn are grouped under two index scores. Behavioral Regulation Index (BRI) consists of the scales Inhibit, Shift, and Emotional Control, while the Metacognition Index (MI) consists of Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The Global Executive Composite (GEC) represents the total score, comprised of all scales. The GEC has high internal consistency validity (.97) and is the primary outcome for the current study.

Academic achievement:

Math and reading achievement were evaluated with Word Reading and Numerical Operations subtests from the Wechsler Individual Achievement Test – 2nd or 3rd Editions, depending on the date of participant enrollment (Wechsler, 2005, 2009). In both editions, the Word Reading subtest evaluates a child's ability to read individual sight words of increasing difficulty, while the Numerical Operations subtest examines a participant's ability to complete math computation problems of increasing difficulty. Both tests are untimed. Standard scores were calculated using age-based norms. Correlations between comparable tests from the WIAT-II and WIAT-III editions are high (r = .85 for Word Reading; r = .81 for Numerical Operations) (Pearson, 2010). All WIAT versions have widely recognized good to excellent psychometric properties (Breaux & Lichtenberger, 2016; Lichtenberger & Smith, 2005; McCrimmon & Climie, 2011; Pearson, 2002, 2010).

Special education services:

As a final, objective measure of difficulties in the school setting, we used the receipt of formal special education services, operationalized as being on an Individualized Education Program (N = 466 [47.0%]) or a 504 plan (N = 125 [12.6%]). These services were collapsed into one dichotomous variable representing special education services (EDPLAN).

Statistical analyses:

Question 1: Does polygenic variation underlying ADHD, EA, and COG associate with the BRIEF?

First, we used stepwise linear regression analyses to determine the association between each of the three polygenic scores and the BRIEF GEC in three separate analyses. We entered control variables (i.e., age, sex, use of psychotropic medication, genotyping chip, and the first 10 principal components of ancestry) in Step 1, followed by the relevant polygenic score in Step 2. The delta R^2 effect size (i.e., the difference between these steps) therefore reflects the strength of the specific association between each given polygenic score and the BRIEF.

Second, we conducted a backward regression analysis in which all three PGS were examined simultaneously and excluded, based on a criterion of $p > .15$ as recommended by Hosmer Jr. and colleagues (2013). We present full and final models and carried the significant scores from the final model through to analyses for Question 2.

Question 2. Does the BRIEF GEC mediate the relationship between genetic variation and academic functioning?

Building on the results of Question 1, and using the PGS from the final model, we conducted structural equation modeling (SEM) to examine whether and how the BRIEF mediates the association between genetic variation and academic functioning. As our goal was specifically to understand the potential role of the BRIEF, we first examined the correlations between the BRIEF and the three potential school outcome variables – reading, math, and EDPLAN – and carried forward the outcomes showing significant correlations with the BRIEF into the SEM. In all analyses, we controlled for age, sex, use of psychotropic medication, genotyping chip (PsychChip or GSA), and the first 10 principal components of ancestry. We used the Lavaan (Rosseel, 2012) package in R version 4.2.2 to perform the SEM, as this package can accommodate continuous and categorical variables in models. The SEM model predicting the quantitative academic achievement scores used maximum likelihood (ML)

estimation and the model predicting the dichotomous EDPLAN variable used diagonally weighted least squares (DWLS) estimator, which is suitable for categorical variables. To account for the possibility that the total effect between the independent variable and the outcome in the mediation models was not significant (Hayes, 2009; Shrout & Bolger, 2002), we used a bootstrapping approach (MacKinnon et al., 2004) to examine the indirect effect between the independent variable and the outcome using 5000 replications. STATA 14 was used for all other analyses. Benjamini-Hochberg FDR; 0.05 was used to correct for multiple testing.

Results

No differences were found with regard to the characteristics of youth genotyped with the PsychChip and GSA chip (Supplementary Table S1), with the exception of being on a special education plan ($\chi^2(1) = 6.14$, $p = .01$). Here, although proportionally more participants genotyped on the GSA chip had a positive EDPLAN status, the effect size was quite small (Cramer's $V = .08$). Nonetheless, we controlled for chip in subsequent analyses.

Question 1: Does polygenic variation underlying ADHD, EA, and COG associate with the BRIEF? As shown in Table 2, the correlation between the three PGS were significant. When considered individually, all three PGS were significantly associated with the BRIEF after controlling for potential confounders and correcting for multiple comparisons (Table 3). Notably, though, the effect sizes of the associations between ADHD PGS and EA PGS and the BRIEF were ~2 times larger than the effect size between COG PGS and BRIEF. In the subset of participants of European ancestry, only ADHD PGS and EA PGS were significantly associated with BRIEF (Supplementary Figure S2).

Using a backward regression approach examining the simultaneous association between all three PGS with the BRIEF, the final model included only ADHD PGS and EA PGS. These scores explained 1.39% of the variance in the BRIEF, with significant univariate effects for both ADHD PGS

(p = .029) and EA PGS (p = .016) (Table 4). In the subset of participants of European ancestry, the backward regression analysis yielded a similar final model with both ADHD PGS and EA PGS remaining as relevant predictors (R^2 = 1.13%), but only a significant univariate association between EA PGS (p = .04) and the BRIEF was found, likely due to reduced power in this smaller sample. (See Supplementary Tables S2 and S3.)

Question 2. Does the BRIEF GEC mediate the relationship between genetic variation and academic functioning? The correlations between the BRIEF and the three academic outcomes were as follows: Numerical Operations r = -.13 (p < .001), Word Reading r = .05 (p = .11), and EDPLAN rho = .24, p < .001). Because the association between Word Reading and the BRIEF was non-significant, SEM analyses were only conducted for Numerical Operations and EDPLAN. In the models predicting math achievement, the BRIEF showed a significant association with Numerical Operations (b = -.11, z = 3.34, p < .001). Further, EA PGS had a significant direct (b = .21, z = 5.65, p < .001) association to Numerical Operations as well as a significant indirect association through the BRIEF (b = .01, z = 2.01, p = .045). The direction of effect was as expected, with a low value (reflecting the "at risk" state for low EA) being detrimental to math achievement directly and through the behavioral concomitants of EF indexed by the BRIEF. In this model, ADHD PGS was also significantly associated with the BRIEF; however, it did not show a significant direct (b = .04, z = 0.97, p = .33) or indirect effect on math (b = -.01, z = 1.78, p = .075) in the same model as EA PGS (Figure 1).

In the SEM predicting special education services, the association between the BRIEF and EDPLAN was strong (b = .21, z = 5.20, p < .001) indicating that a high score on the BRIEF increased the risk of receiving formal special education services. Significant findings in the model further showed that EA PGS decreased the risk of being on an EDPLAN both directly (b = -.17, z = 3.75, p < .001) as well as indirectly through the behaviors indexed by the BRIEF (b = -.02, z = 2.27, p = .023). For the ADHD PGS, a high polygenic loading also indirectly related to EDPLAN status through

variation on the BRIEF (b = .02, z = 2.01, p = .045) but did not have an additional direct effect on this outcome (b = -.06, z = 1.29, p = .20; Figure 2).

Results for Question 2 analyses showed similar effect sizes in the European sample; however, some findings lost statistical significance due to the reduced power of the smaller sample. Findings are available in the Supplementary Figures S1 and S2.

Discussion

Questionnaires like the BRIEF were developed to assess the behavioral features of EF in an individual's daily environment. Because such measures are cost-efficient and have shown a relationship to real world functioning (Biederman et al., 2022; Biederman et al., 2008), they are frequently used in the assessment of youth with neuropsychiatric conditions. Yet, evidence for their limited correlation with psychometric tests of EF has coninuted to accumulate (e.g. Toplak et al., 2013). Thus, there has been curiosity and speculation regarding the underlying constructs being indexed by EF rating scales (Toplak et al., 2013).

In the current paper, we used polygenic variation from large-scale GWAS to extend our understanding of the BRIEF. Specifically, we related PGS from ADHD, EA, and COG to the BRIEF GEC. Results showed independent relationships between the BRIEF and polygenic variation underlying ADHD and EA. Further, the BRIEF partially mediated the relationships between EA PGS with math and special education services (EDPLAN) and fully mediated the relationship between ADHD PGS and EDPLAN. These findings suggest that the BRIEF indexes distinct biological underpinnings of ADHD and educational attainment, and represents behaviors that link the genetic variation underlying these constructs to functioning in the school setting.

Our first set of analyses set out to relate the BRIEF to common genetic variation representing putatively relevant constructs. Specifically, we examined genetic variation related to ADHD, which has phenotypically been linked to BRIEF scores in our (Pollastri et al., 2022) and other child

psychiatric samples (Biederman et al., 2004; Biederman et al., 2006; McAuley et al., 2010). We also examined genetic variation relevant to cognition (COG), as measured by the first principal component of psychometric tests batteries, given that the BRIEF was designed to measure a construct that is also captured by cognitive tests. Finally, we measured polygenic variation underlying years of education attained (EA) as it indexes the broad factors that contribute to this outcome. Although all scores showed significant relationships to the BRIEF when considered independently, only the relationships with ADHD and EA scores remained when the scores were considered together.

This pattern of relationships has implications for understanding the BRIEF. As shown in Table 2, the correlation between COG PGS and EA PGS was .59, which is considered large (Cohen, 1988), and indicates that these risk scores share ~35% of their variance. In univariate associations between the PGSs and the BRIEF, the effect size of EA PGS was more than 2 times as large as the effect size of COG PGS (R^2 = 0.94% versus R^2 = 0.43%, respectively). This shared variance was also reflected in the backward regression, where the strength of the association between EA PGS and the BRIEF increased (b = 0.93 versus b = 1.02) in the reduced model (which omitted the COG PGS) compared to the full model. These data suggest that some of the variance that links the genetic basis of educational attainment to the BRIEF overlaps with the genetic basis of cognition measured by psychometric tests. Yet, the genetic basis of educational attainment explained additional variance in the BRIEF over and above genetic variance relating to psychometrically-measured cognition. Further, while the phenotypic correlation of .40 between ADHD PGS and EA PGS indicated some (i.e.16%) shared variance, ADHD genetic risk also had an independent relationship to the BRIEF that did not overlap the genetic basis of educational attainment. In other words, genetic contributions to the BRIEF include genetic variation underlying educational attainment (which subsumes but extends beyond aspects of the genetic basis of cognitive test performance) as well as genetic variation relevant to ADHD that is non-overlapping with those constructs.

These genetic analyses extend evidence from the phenotypic literature suggesting that the BRIEF measures a construct that: 1) extends beyond what is measured by psychometric tests of cognition; 2) partially but not completely relates to ADHD risk; and 3) contributes to educational success. Such information is interesting to consider in the context of Toplak et al.'s (2013) discussion of several possible explanations for the low correlation between the BRIEF and EF tests. For example, these authors reference the possibility that psychometric tests and rating scales may reflect narrow versus broad definitions of a common construct (e.g. narrow versus broad EF). They also cite distinctions from the field of psychometrics, that consider "maximal" performance versus "typical" performance, which can occur with and without external constraints, respectively, such as one would have in a controlled testing environment. While the current study cannot speak to this precise interpretation of the BRIEF, our analyses are consistent with the BRIEF indexing a construct that is important to educational outcomes and that relates to but extends beyond what is measured by cognitive tests.

To further understand how the behavioral concomitants of the BRIEF relate to the real world, we then examined the extent to which the BRIEF served as a mediator of the relationship between genetic risk and different academic variables. This required us to first establish a relationship between the BRIEF and indices of academic functioning. In our sample, the BRIEF related to Numerical Operations and having an EDPLAN. Unlike the findings of Gerst and colleagues (2017), it did not relate to reading; however, we attribute this difference to our use of a straightforward measure of word reading and their use of a reading comprehension measure, which requires a more complex set of skills. Nonetheless, the fact that the BRIEF phenotypically related to math and EDPLAN status provides a constructive replication of the prior literature showing a relationship between the BRIEF and functioning in the academic setting (Biederman et al., 2008; Clark et al., 2010; Colomer et al., 2017; Costa et al., 2017; Figuccio et al., 2019; Gerst et al., 2017; Gilboa et al., 2014; Locascio et al., 2010; Mann & Snover, 2015; Samuels et al., 2016).

For both math and EDPLAN outcomes, the BRIEF served as a partial mediator of the relationship with EA PGS. Thus, the influence that genetic variation underlying educational attainment has on academic outcomes in our sample was manifested, in part, through the behavioral concomitants of EF represented in the BRIEF. The ADHD PGS behaved somewhat differently. It had a stronger relationship to the BRIEF itself than to Numerical Operations (with a trend level indirect effect on Numerical Operations in the SEM that included the EA PGS). Additionally, the BRIEF fully mediated the impact of the ADHD PGS on having an EDPLAN, suggesting that all of the genetic risk for ADHD that results in an EDPLAN in our sample was due to the behavioral correlates of EF measured by the BRIEF.

The current results have implications for the use of the BRIEF in the child clinical setting. The pattern of PGS correlations in our study is consistent with evidence from the literature (e.g. Pollastri et al., 2022; Gerst et al. 2017) that the BRIEF explains variation in academic functioning that is not captured by cognitive tests. Such results suggest that the BRIEF would not be redundant with psychometric tests if included together in an assessment battery. Further, the role of the BRIEF as a partial or full mediator in our SEM compels further study of whether the behaviors indexed by the BRIEF could be targets for early intervention to reduce school difficulties in youth who are genetically at risk for educational under-attainment and ADHD. This would be particularly relevant if continued advances in psychiatric genetics lead to PGS that explain a more substantial component of variance in the BRIEF.

It is indeed important to acknowledge that the PGS together explained only a small amount of variance in the BRIEF over and above the additional covariates in the model. Small magnitude associations such as this are common in the psychiatric genetics literature, as PGS scores only capture common additive variants of small effect and reflect the characteristics of their source GWAS. Nonetheless, the limited variance explained must be considered in terms of some methodological choices and limitations. First, our use of the BRIEF's global GEC score and a select set of PGS was

intentional so as to conduct hypothesis-driven analyses while maximizing the generalizability of findings to the current version of the BRIEF. Yet, it is possible that analyses relating specific index scales and a wider range of PGS scores would find more robust relationships. The source study for our data is ongoing and was initiated before the publication of the BRIEF-2 (Gioia et al., 2015). Due to the availability of genotyping, the current analyses only include participants who were administered the first edition of the measure. To maximize the relevance of our analyses to the BRIEF-2, we examined the total (i.e., GEC) score in our analyses. Just as psychometric tests of EF are known to have both "unity and diversity' (Miyake et al., 2000), the BRIEF includes scores at different levels of specificity, with correlated components. The overall GEC is a statistically sound choice, as it shows particularly high internal consistency validity (.97), and, importantly, for the purposes of the current study, has been linked to ADHD either directly (e.g. Biederman et al., 2022) or by implication in that all individual BRIEF scales showed an ADHD association (Pollastri et al., 2022). The use of this scale also promotes generalizability of results to the BRIEF-2 (Gioia et al., 2015; Hendrickson & McCrimmon, 2019), as the correlations between GECs from the two BRIEF editions is high (.97) even though the BRIEF-2 has a different factor structure than the BRIEF. Future papers should address whether individual Index scores in the BRIEF-2 (Behavior Regulation, Emotion Regulation, and Cognitive Regulation) show more robust relationships with relevant PGS scores.

Second, the COG PGS score was derived from the first principal component of a wide range of cognitive batteries and is thought to represent general ability. Though EF tests were included and general IQ overlaps and is correlated with EF (Diamond, 2020), this PGS is not based purely on tests of EF. Thus, we cannot rule out the possibility that a GWAS that targeted EF tests more specifically would yield a PGS with a higher magnitude relationship to the BRIEF. Third, the accuracy of PGS is tied to the sample size of the source GWAS studies, with larger studies reducing noise in the selection of relevant risk variants. The sample in the source study for the EA PGS (N = 766,345, excluding 23andMe participants) is substantially larger than the samples that the COG (N = 269,867 individuals)

and ADHD PGS (N = 38,691 cases and 186,843 controls) were based on. Moreover, the ADHD and COG GWAS arguably represent more multifactorial target phenotypes than EA. Thus, we are unable to rule out the possibility that the greater strength of the EA association was due to the statistical power and precision of its GWAS and that future iterations of the COG and ADHD PGS may explain a greater proportion of variance in the BRIEF as their sample sizes and precision increase. Fourth, we note that the PGS we used were developed on primarily European populations. We included non-Europeans in our primary analyses because limiting analyses to a less racially and ethnically diverse sample risks exacerbating existing health disparities. Our use of the sub-population of European participants showed generally comparable effect sizes. Nonetheless, we note that more representative source studies for genomic information – which are now actively being pursued in the field – may yield stronger associations for PGS in our overall sample. Finally, while the rates of diagnoses in the sample (Table 1) suggest that our findings may generalize to outpatient clinical settings, further studies are needed for confirmation.

Notwithstanding these issues, the current results provide a novel application of PGS to the literature on the BRIEF, a rating scale commonly used in child clinical settings. Results showed that the behaviors represented on the BRIEF relate to the heritable biology of 1) ADHD and 2) educational attainment, including but also beyond its overlap with the genetic basis of cognitive tests. Further, in our sample, the BRIEF was a partial mediator of the relationship between polygenic variation underlying educational attainment and school functioning (specifically math achievement and special education services). It is also a full mediator of the relationship between ADHD risk and special education services. Such data provide further evidence that the behaviors the BRIEF captures represent functionally important information relevant to school success. Results also suggest that the BRIEF serves as a bridge between genetic risk and outcomes in academic settings. Thus, further work exploring the BRIEF as an intervention target for youth who are genetically at risk for ADHD and educational under-attainment is warranted.

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Table 1. Characteristics of the clinical youth cohort, ages 7-17 (N = 991).

Variables	**Sample (N = 991)**
Age; Mean (SD)	11.3 (3.0)
Sex; N_{male} (%)	620 (62.6%)
Self- Reported Ethnicity; $N_{Hispanic}$ (%)*	106 (10.7%)
Self- Reported Race N(%)**	
Asian	25 (2.2%)
Black/ African American	54 (5.4%)
White/ Caucasion	846 (85.4%)
Mixed Race/Other	65 (6.6%)
Psychotropic Medication; N_{yes} (%)	412 (41.6%)
Full Scale IQ	99.5 (13.3)
Global Executive Composite (GEC)	60.4 (13.7)
GEC $N_{clinical\ range\ (t \geq 65)}$ (%)	503 (50.8%)
Numerical Operations***	97.8 (14.3)
Word Reading****	99.8 (14.3)
Education Plan; N_{yes} (%)	591 (59.6%)
Diagnoses*****	
ADHD	606 (61.2%)
Conduct Disorder	112 (11.3%)
ODD	189 (19.1%)

Anxiety Disorders	386 (39.0%)
Mood Disorders	201 (20.3%)
ASD	148 (14.9%)
Psychosis	29 (2.9%)
Number of Diagnoses	
0	166 (16.8%)
1	342 (34.5%)
2	235 (23.7%)
3	159 (16.0%)
≥4	89 (9.0%)

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; ODD = Oppositional Defiant Disorder; *Missing N = 1 (0.1%); **Missing N = 1 (0.1%);***Missing N = 42 (4.3%); ****Missing N = 49 (4.9%); *****Due to comorbidity, diagnoses exceed 100%

Table 2. Cross-correlations between the polygenic scores for ADHD, Educational Attainment and Cognitive Ability (N = 991).

Polygenic score	ADHD phi = 1	EA phi = 1	COG phi = 1
ADHD phi = 1	1		
EA phi = 1	-.40	1	
COG phi = 1	-.23	.59	1

Note. ADHD = Attention Deficit/Hyperactivity Disorder; EA = Educational Attainment; COG = Cognitive Ability;

All correlations $p < .0001$

Table 3. The effect of polygenic scores on the Global Executive Composite of the BRIEF using linear regression analyses, controlling for age, sex, psychotropic medication, genotyping chip, and the first 10 principal components of ancestry (N = 991).

Polygenic score	b	SE	t	p-value	ΔR^2(%)
ADHD phi = 1	1.28	0.42	3.04	.0024	0.85%
EA phi = 1	-1.29	0.40	3.20	.0014	0.94%
COG phi = 1	-0.87	0.40	2.16	.0308	0.43%

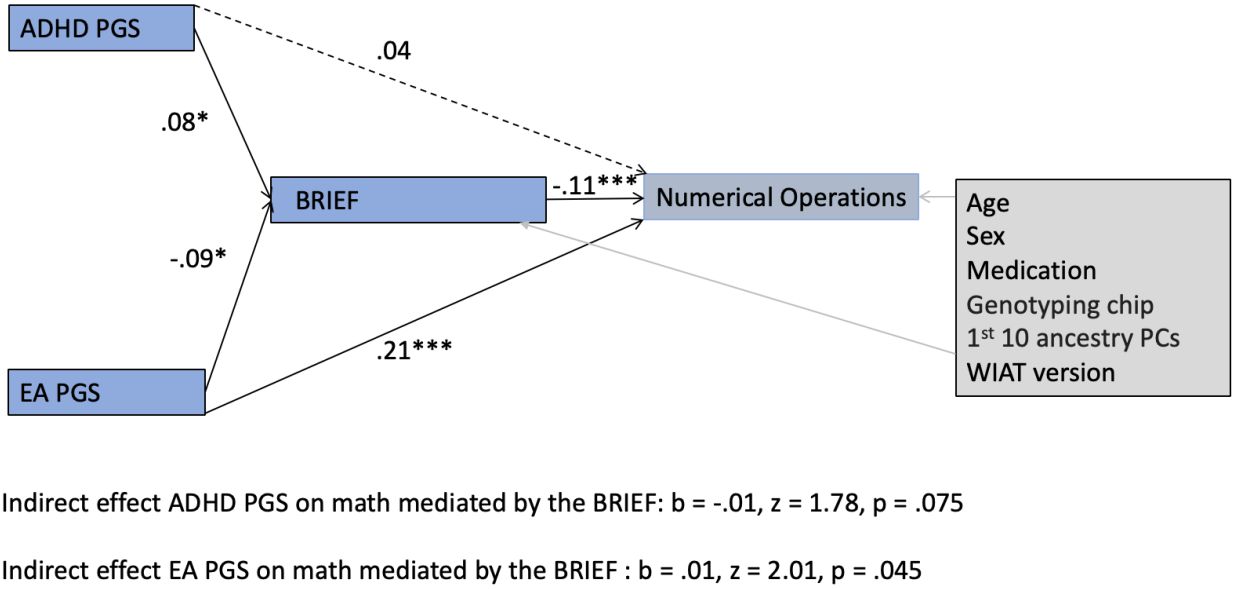
Note. ΔR^2(%) = explained variance attributed to the polygenic score in the analysis; ADHD = Attention Deficit/Hyperactivity Disorder; EA = Educational Attainment; COG = Cognitive Ability

Table 4. Backward regression examining the combined effect of the polygenic scores on the Global Executive Composite of the BRIEF using linear regression analyses controlling for age, sex, psychotropic medication, chip, and the first 10 principal components for ancestry (N = 991).

Polygenic score	b	SE	t	p-value	Test statistics
Full model					
ADHD phi = 1	0.95	0.44	2.17	.030	F(3,973) = 5.06; p = .0018,
EA phi = 1	-0.93	0.51	1.84	.066	ΔR^2(%) = 1.39%
COG phi = 1	-0.15	0.49	0.31	.757	
Final model					
ADHD phi = 1	0.96	0.44	2.19	.029	F(2,974) = 7.54; p = .0006,
EA phi = 1	-1.02	0.42	2.41	.016	ΔR^2(%) = 1.39%

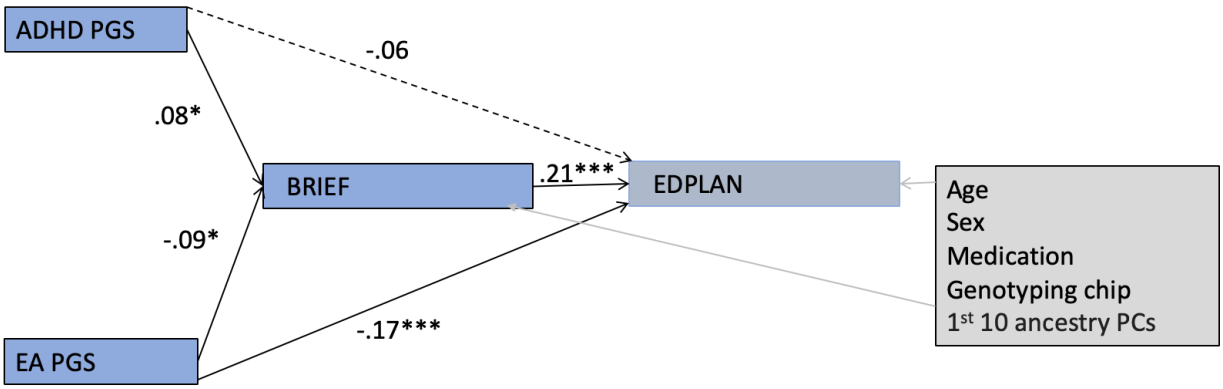
Note. ΔR^2(%) = explained variance attributed to the polygenic score in the analysis; ADHD = Attention Deficit/Hyperactivity Disorder; EA = Educational Attainment; COG = Cognitive Ability

Figure 1. SEM of ADHD and EA PGS as predictors of Numerical Operations and the mediating role of the BRIEF.



Note. SEM = Structural Equation Model; ADHD = Attention-Deficit/Hyperactivity disorder; EA = Educational Attainment; PGS = Polygenic Score; BRIEF = Behavior Rating Inventory of Executive Function; PCs = Principal Components; WIAT = Wechsler Individual Achievement Test

Figure 2. SEM of ADHD and EA PGS as predictors of special education services status and the mediating role of the BRIEF.



Indirect effect ADHD PGS on EDPLAN mediated by the BRIEF: b = .02, z = 2.01, p = .045

Indirect effect EA PGS on EDPLAN mediated by the BRIEF: b = -.02, z = 2.27, p = .023

Note. SEM = Structural Equation Model; ADHD = Attention-Deficit/Hyperactivity Disorder; EA = Educational Attainment; PGS = Polygenic Score; BRIEF = Behavior Rating Inventory of Executive Function; PCs = Principal Components

Supplemental Text

Quality control and imputation of genetic data

We excluded SNPs prior to imputation if they had the following characteristics: non-autosomal, excessive missingness (call rate <98%), low minor allele frequency (MAF<0.01), or Hardy-Weinberg disequilibrium test $p<10^{-6}$. We excluded samples if they showed a sex mismatch, had excessive missing data (call rate <98%) or were duplicates. SNPs were phased using Eagle-2 and imputed using Minimac-3, using data from the 1000 Genomes project phase-3 as the haplotype reference panel. We filtered imputed best guess genotypes, retaining only high-quality common markers (INFO>0.8 & MAF>0.01).

We also conducted relatedness and ancestry checks. Here, we merged SNPs that were common across the two genotyping chips, after excluding those with inconsistent alleles and ambiguous (AT/CG) SNPs. As we had some related individuals in the source data set, we ran identity-by-descent and Mendel analysis in PLINK where possible to exclude individuals not related as expected based on family structure. Mendelian errors in the remaining samples were set to missing. We ran a GWAS of genotyping batch and excluded SNPs with batch effects ($p<0.01$). We then merged the sample with the 1000 Genomes reference panel to perform a principal components analysis (PCA) on an LD-pruned set of common (MAF>0.05) markers. This analysis used PCAiR (Conomos et al., 2015), a package that provided a robust estimation of population structure while accounting for kinship. The full sample, including individuals of non-European ancestries, was used for primary analyses. We also used these analyses to identily a subgroup of individuals comprised of European ancestries for sensitivity analyses, given that this approximated the composition of the source GWAS. PCA (using PCAiR) was re-run on the final full sample, as well as again on the European subset, using the final set of markers (1,068,808 common autosomal SNPs), to extract the top 10 principal ancestry components (PCs).

Calculation of polygenic scores

For calculation of PGS, we filtered the discovery datasets for the three relevant constructs (ADHD, EA, and COG), using MAF>0.01 & INFO>0.8, and excluded variants if they were indels, non-autosomal, ambiguous/asymmetric, multi-allelic or duplicate position, or had inconsistent alleles across the target and discovery data. PGSs were calculated in PLINK after employing the PRS-CS (continuous shrinkage) method (Ge et al., 2019) by summing the number of alleles (weighted by the adjusted effect size) across the full set of SNPs for each person. The PGS were based on a total number of 219,742 common autosomal SNPs.

Frequencies of the specific diagnostic groups in the sample

The sample's specific psychiatric diagnoses were as follows: 61.2% (n=606) were diagnosed with ADHD, 11.3% (n=112) with Conduct Disorder, 19.1% (n=189) with Oppositional Defiant Disorder (ODD), 0.3% (n=3) with Panic Disorder, 10.7% (n=106) with Generalized Anxiety Disorder (GAD), 6.3% (n=62) with Social Phobia, 3.8% (n=38) with Separation Anxiety Disorder, 17.9% (n=177) with Anxiety Disorder – Not Otherwise Specified (NOS), 3.1% (n=31) with Bipolar Disorder, 7.9% (n=78) with Major Depressive Disorder (MDD), 1.1% (n=11) with Dysthymic Disorder, 8.2% (n=81) with Mood Disorder – NOS, 3.7% (n=37) with Autistic Disorder, 5.9% (n=58) with Asperger's Syndrome, 5.3% (n=53) with Pervasive Developmental Disorder – NOS, 0.5% (n=5) with Schizophrenia/ Schizoaffective Disorder, and 2.4% (n=24) with Prodromal Symptoms/ Psychotic Disorder – NOS.

Frequencies of psychotropic medications in the sample

The sample's specific psychotropic medication usage was as follows: 22.9% (n=227) children were taking stimulants, 10.8% (n=107) were on non-stimulant medication to treat ADHD (e.g., atomoxetine), 8.5% (n=84) were taking an atypical antipsychotic, 14.1% (n=140) were taking a Selective Serotonin Reuptake Inhibitor (SSRI), 4.1% (n=41) were taking a non-SSRI antidepressant, 2.3% (n=23) were taking a benzodiazepine, and 5.1% (n=51) were taking another type of psychotropic medication.

Supplementary Table S1. Comparison of youth genotyped with PsychChip and GSA on relevant variables.

Variables	PsychChip (N = 468)	GSA (N = 523)	Test statistic	p-value	Missing
Age; Mean (SD)	11.4 (3.0)	11.3 (2.9)	t (989)=0.25	.80	-
Sex; N_{male} (%)	302 (64.5%)	318 (60.8%)	$\chi^2(1)=1.46$	.23	-
Ancestry; $N_{European}$ (%)	370 (79.1%)	392 (75.0%)	$\chi^2(1)=2.35$	.13	-
Psych. Medication; N_{yes} (%)	189 (40.4%)	223 (42.8%)	$\chi^2(1)=0.52$	.47	-
Full Scale IQ	99.8 (13.4)	99.2 (13.2)	t (989)=0.73	.47	-
BRIEF GEC	60.4 (13.3)	60.3 (14.1)	t (989)=0.09	.92	-
GEC $N_{clinical\ range\ (t \geq 65)}$ (%)	240 (51.3%)	263 (50.3%)	$\chi^2(1)=0.10$	.75	-
Numerical Operations	97.3 (14.2)	98.1 (14.4)	t (947)=0.82	.41	42 (4.2%)
Word Reading	99.8 (14.6)	99.9 (14.0)	t (940)=0.10	.92	49 (4.9%)
Education Plan; N_{yes} (%)	260 (55.6%)	331 (64.3%)	$\chi^2(1)=6.14$	.01	-
Diagnoses*					
ADHD	276 (59.0%)	330 (63.1%)	$\chi^2(1)=1.77$	.18	-
Conduct Disorder	52 (11.1%)	60 (11.5%)	$\chi^2(1)=0.03$	.86	-
ODD	94 (20.1%)	95 (18.2%)	$\chi^2(1)=0.57$	.45	-
Anxiety Disorders	174 (37.2%)	212 (40.5%)	$\chi^2(1)=1.17$	.28	-
Mood Disorders	99 (21.2%)	102 (19.5%)	$\chi^2(1)=0.42$	.52	-
ASD	70 (15.0%)	78 (14.9%)	$\chi^2(1)=0.00$	.99	-
Psychosis	12 (2.6%)	17 (3.3%)	$\chi^2(1)=0.41$	.52	-
Number of Diagnoses			$\chi^2(4)=1.81$	.77	-
0	81 (17.3%)	85 (16.3%)			-
1	159 (34.0%)	183 (35.0%)			-
2	116 (24.8%)	119 (22.8%)			-
3	75 (16.0%)	84 (16.1%)			-
≥4	37 (7.9%)	52 (9.9%)			-

Note. BRIEF= Behavior Rating Inventory of Executive Functions; GEC= General Executive Composite; ADHD = Attention-Deficit/Hyperactivity Disorder; ASD = Autism Spectrum Disorder; ODD = Oppositional Defiant Disorder; *Due to comorbidity, numbers do not add up to 100%

Supplementary Table S2. European ancestry subsample (n=762): The effect of polygenic scores on the General Executive Component of the BRIEF using linear regression analyses controlling for age, sex, psychotropic medication, chip, and the first 10 principal components of ancestry.

Polygenic score	b	SE	t	p-value	ΔR^2(%)
ADHD phi = 1	1.11	0.48	2.32	.0209	0.64%
EA phi = 1	-1.20	0.46	2.63	.0087	0.82%
COG phi = 1	-0.82	0.45	1.83	.0673	0.40%

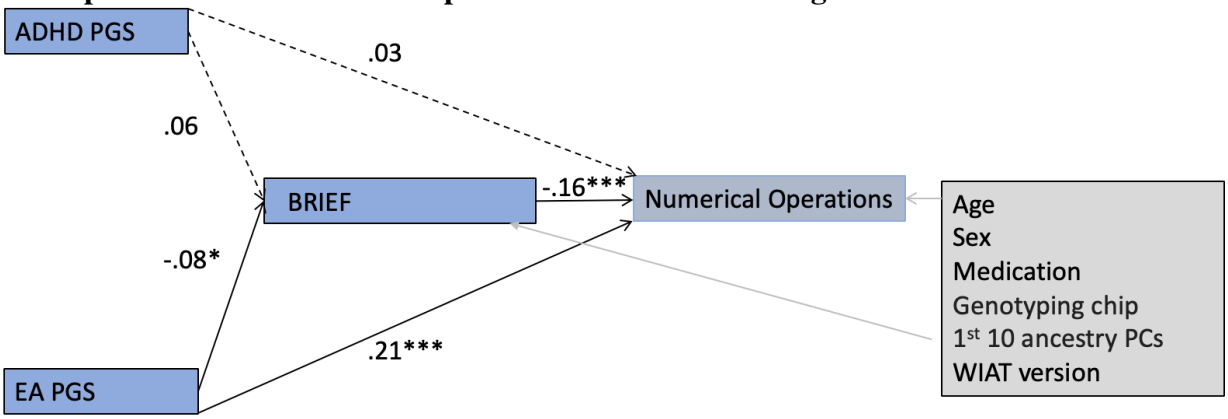
Note. ΔR^2(%) = explained variance attributed to the polygenic score in the analysis; ADHD = Attention Deficit/Hyperactivity Disorder; EA = Educational Attainment; COG = Cognitive Ability.

Supplementary Table S3. European ancestry subsample (n=762): The effect of polygenic on the main constructs of the BRIEF over and above COG PV using stepwise regression analyses controlling for age, sex, psychotropic medication, chip, and the first 10 principal components of ancestry

Polygenic score	b	SE	t	p-value	Test statistics
Full model					
ADHD phi = 1	0.81	0.50	1.61	.1087	F(3,744) = 3.21; p = .0226, ΔR^2(%)=1.14%
EA phi = 1	-0.89	0.58	1.53	.1257	
COG phi = 1	-0.14	0.56	0.25	.7992	
Final model					
ADHD phi = 1	0.81	0.50	1.62	.1053	F(2,745) = 4.79; p = .0086, ΔR^2(%)=1.13%
EA phi = 1	-0.98	0.48	2.05	.0411	

Note. ΔR^2(%) = explained variance attributed to the polygenic score in the analysis; ADHD = Attention Deficit/Hyperactivity Disorder; EA = Educational Attainment; COG = Cognitive Ability.

Supplementary Figure S1. European ancestry subsample (n=762): SEM of ADHD and EA PGS as predictors of Numerical Operations and the mediating role of the BRIEF.



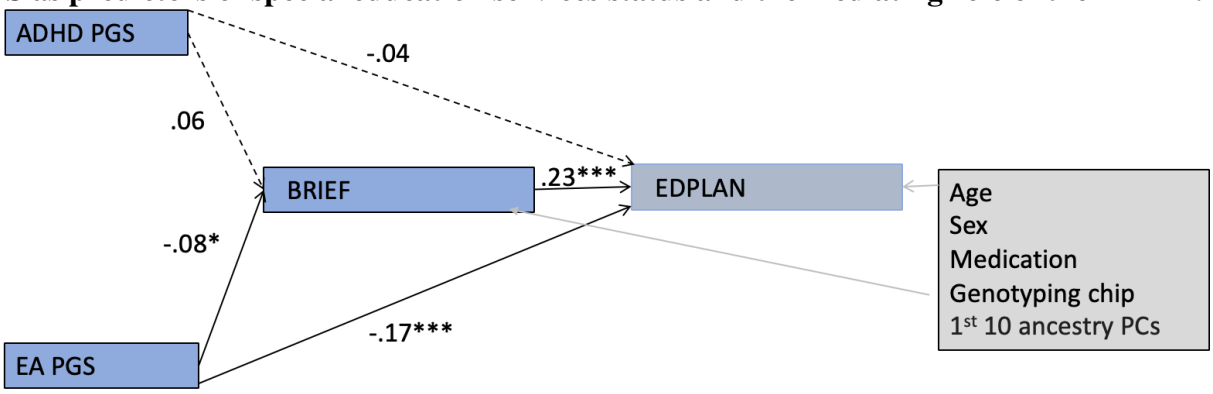
Direct effect the BRIEF on Numerical Operations: b = -.16, z = 4.43, p <. 001

Direct effect ADHD PGS on the BRIEF: b = .06, z = 1.57, p = .12
Direct effect of ADHD PGS on Numerical Operations: b = .03, z = 0.71, p = .48
Indirect effect ADHD PGS on Numerical Operations mediated by the BRIEF: b = -.01, z = 1.48, p = .14

Direct effect EA PGS on the BRIEF: b = -.08, z = 2.17, p = .030
Direct effect of EA PGS on Numerical Operations: b = .21, z = 5.34, p < .001
Indirect effect EA PGS on Numerical Operations mediated by the BRIEF : b = .01, z = 1.97, p = .048

Note. SEM = Structural Equation Model; ADHD = Attention-Deficit/Hyperactivity disorder; EA = Educational Attainment; PGS = Polygenic Score; BRIEF = Behavior Rating Inventory of Executive Function; PCs = Principal Components; WIAT = Wechsler Individual Achievement Test

Supplementary Figure S2. European ancestry subsample (n=762): SEM of ADHD and EA PGS as predictors of special education services status and the mediating role of the BRIEF.



Direct effect the BRIEF on EDPLAN: b = .23, z = 5.17, p <. 001

Direct effect ADHD PGS on the BRIEF: b = .06, z = 1.61, p = .11
Direct effect of ADHD PGS on EDPLAN: b = -.04, z = 0.95, p = .34
Indirect effect ADHD PGS on EDPLAN mediated by the BRIEF: b = .01, z = 1.49, p = .14

Direct effect EA PGS on the BRIEF: b = -.08, z = 2.03, p = .042
Direct effect of EA PGS on EDPLAN: b = -.17, z = 3.47, p < .001
Indirect effect EA PGS on EDPLAN mediated by the BRIEF: b = -.02, z = 1.91, p = .06

Note. SEM = Structural Equation Model; ADHD = Attention-Deficit/Hyperactivity Disorder; EA = Educational Attainment; PGS = Polygenic Score; BRIEF = Behavior Rating Inventory of Executive Function; PCs = Principal Components

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