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COMT and DAT1 polymorphisms moderate the indirect effect of parenting behavior on youth ADHD symptoms through neurocognitive functioning

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Abstract

Although gene $\times$ environment interactions contribute to youth attention-deficit/hyperactivity disorder (ADHD) symptoms, the pathways mediating these influences are unknown. We tested genetic moderation of indirect effects from parenting behavior to youth ADHD symptoms through multiple neurocognitive factors. Two hundred and twenty-nine youth with and without ADHD were assessed at baseline (Wave 1; ages 5–10) and at a 2-year follow-up (Wave 2; ages 7–13). At Wave 1, youth completed a neurocognitive battery including measures of response inhibition, visuospatial working memory, and fluid reasoning, and a standardized parent-child interaction task yielding observational measures of positive and negative parenting. At Wave 2, youth psychopathology was rated by parents and teachers using multiple methods (i.e., structured interview, rating scale). We employed moderated multiple mediation and compared conditional indirect effects across youth genotypes at two biologically plausible genetic loci. Controlling for parent ADHD symptoms as well as youth demographic factors and co-occurring externalizing symptoms, these genetic factors moderated the indirect effect from Wave 1 parenting to multi-method/informant Wave 2 ADHD symptoms through Wave 1 neurocognitive functioning. This preliminary study is the first to identify genetic moderation of mediated effects underlying ADHD symptoms, and suggests that specific gene $\times$ parenting interactions may underlie neurocognitive functioning deficits and subsequent ADHD.

Keywords

ADHD; COMT Val¹⁵⁸Met; DAT1; neurocognitive functioning; moderated mediation

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent and costly conditions in the United States. Eleven percent of American youth aged 4 to 17 are diagnosed with ADHD in their lifetime (Visser et al., 2014), and the associated annual costs

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range from \$143 to \$266 billion (Doshi et al., 2012). Beyond its significant public health burden, there is also unmet clinical need given that even the most effective pharmacologic and behavioral interventions for ADHD have critical limitations (e.g., costly, time consuming, short-term gains; Sonuga-Barke & Halperin, 2010). Thus, ADHD *prevention* strategies must be prioritized. Innovation in ADHD prevention requires elucidation of causal factors, and their mechanisms of influence, to highlight targets for early interventions that promote resilience (Sonuga-Barke & Halperin, 2010). Although individual differences in ADHD are sensitive to multiple putative causal influences (i.e., equifinality), including substantial heritability and diverse environmental predictors (Thapar, Cooper, Eyre, & Langley, 2013), the pathways mediating these influences are poorly characterized. The present study addresses this gap in knowledge directly.

Family, twin, and adoption studies converge around the significant heritability of ADHD, with estimates ranging from 75% to 90% (Hawi et al., 2015). However, candidate gene and genome-wide studies of ADHD have identified relatively few associated genetic variants, all of small effect, which collectively account for only a modest proportion of overall ADHD heritability (Hawi et al., 2015; Schachar, 2014). In fact, the total variation in ADHD attributable to common genetic variants (i.e., single nucleotide polymorphism-based heritability) ranges from 5% to 34% (Middeldorp et al., 2016), a small proportion of the high heritability estimated from behavioral genetic designs. Thus, the genetic architecture of ADHD remains elusive.

One potential source of this so called “missing heritability” is gene $\times$ environment interactions ($G \times E$). Both behavioral genetic (e.g., twin studies) and molecular genetic designs (e.g., candidate gene studies) have implicated $G \times E$ for ADHD. Among 6- to 11-year-old twins, positive parenting behavior moderated total genetic influences on child ADHD (Nikolas, Klump, & Burt, 2015). As reviewed by Nigg, Nikolas, & Burt (2010), specific functional polymorphisms (i.e., polymorphisms that alter gene function) also interact with psychosocial factors, and especially parenting behavior, to predict youth ADHD. Polymorphisms that influence dopaminergic activity may be especially sensitive to environmental interaction for ADHD. One such polymorphism is located in the dopamine transporter gene (DAT1; SLC6A3), which is implicated in ADHD etiology because the dopamine transporter is the site of action for psychostimulant medications (Gizer, Ficks, & Waldman, 2009). This 40-base pair variable number tandem repeat polymorphism commonly results in two alleles, 9-repeat and 10-repeat, with three possible genotypes: 9/9, 9/10, and 10/10. The DAT1 10/10 genotype is associated with increased dopamine transporter expression and availability but decreased binding compared to 9/9 and 9/10 genotypes (Heinz et al., 2000; Mill, Asherson, Browes, Souza, & Craig, 2002). In a comprehensive meta-analysis, the DAT1 10-repeat allele was significantly associated with youth ADHD, although heterogeneous effects across studies suggested that moderating factors are likely influential (Gizer et al., 2009). Several studies have also directly observed DAT1 $\times$ environment effects on youth ADHD, including exposure to family adversity (Laucht et al., 2007) and parenting (Li & Lee, 2013). Thus, we contend there is ample evidence that $G \times E$ may account for unexplained genetic variance underlying ADHD symptoms, and that DAT1 $\times$ environment interactions are implicated.

There is also preliminary evidence that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene may interact with environmental factors to predict youth ADHD. COMT plays a key role in the degradation of dopamine in the prefrontal cortex (Chen et al., 2004), which in turn is associated with the development of ADHD. The COMT Val¹⁵⁸Met polymorphism (rs4680) is characterized by a valine-to-methionine (Val/Met) substitution at codon 158 that results in three possible genotypes: Val/Val, Val/Met, and Met/Met. The Val allele confers decreased efficiency of dopamine catabolism and higher synaptic dopamine levels in the prefrontal cortex (Chen et al., 2004). The Val allele is also reliably associated with impaired prefrontal activation (Mier, Kirsch, & Meyer-Lindenberg, 2010). In turn, hypoactivation in fronto-striato-parietal networks that regulate executive functioning (EF) is central to the etiology of ADHD (Cortese et al., 2012). Although COMT Val¹⁵⁸Met was not reliably correlated with ADHD directly in a recent meta-analysis, significant heterogeneity across studies was observed, again suggesting possible moderating factors (Sun, Yuan, Shen, Xiong, & Wu, 2014). Additionally, youth COMT genotype $\times$ parenting behavior interactions have predicted externalizing problems that commonly co-occur with ADHD, such as alcohol use (Laucht et al., 2012) and aggression (Zhang, Cao, Wang, Ji, & Cao, 2016). Thus, in addition to DAT1, COMT Val¹⁵⁸Met is a logical candidate for further studies of $G \times E$ for ADHD.

Despite their likely role in youth ADHD symptoms, the mechanisms underlying putative $G \times E$ effects are essentially unknown. That is, it is unclear *how* $G \times E$ contribute to individual differences in ADHD. Thus, rather than testing simple genetic moderation of the *association* between environmental factors and ADHD symptoms (i.e., simple moderation), this study evaluated genetic moderation of *indirect effects* from environmental factors to youth ADHD symptoms through specific mediators (i.e., moderated mediation; Hayes, 2015). Based on their biological plausibility, we prioritized several higher-order neurocognitive domains as intermediate pathways from DAT1 $\times$ environment and COMT Val¹⁵⁸Met $\times$ environment predictions of ADHD symptoms. Longitudinal and meta-analytic evidence suggest that separable EF facets including response inhibition and visuospatial working memory reliably predict youth ADHD with medium to large effect sizes (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Although less studied than the traditional EF domains, there is also replicated evidence that fluid reasoning, which may subsume EF, predicts ADHD (Biederman et al., 2009; Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005; Morgan, Lee, & Loo, 2016; Tamm & Juranek, 2012); this association was also observed within a prospective longitudinal design where assessment of fluid reasoning temporally preceded ADHD symptoms (Morgan, Loo, & Lee, 2016), which is necessary to infer causal mediation (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Response inhibition, visuospatial working memory, and fluid reasoning also share key risk factors with ADHD across genetic and neural measures, underscoring their biological plausibility as mediators. Twin studies suggest considerable genetic overlap between ADHD and EF deficits (Coolidge, Thede, & Young, 2000). Additionally, meta-analytically implicated ADHD candidate genes and polygenic ADHD risk scores (i.e. calculated across many genes) predict reasoning and EF (Barnes, Dean, Nandam, O'Connell, & Bellgrove, 2011; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014). Moreover, working memory and response inhibition have been implicated as intermediary pathways from genetic influences

to ADHD (i.e., endophenotypes; Gallo & Posner, 2016; Kamradt, Nigg, Friderici, & Nikolas, 2016; Loo et al., 2008). Youth with ADHD consistently exhibit hypoactivation in fronto-striato-parietal networks that regulate working memory, response inhibition, and fluid reasoning, and in other relevant regions (e.g., cerebellum; Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Tamm & Juranek, 2012). Thus, based on the biological plausibility of ADHD symptoms as sequelae of poor response inhibition, visuospatial working memory, and fluid reasoning, there is strong evidence for their intermediary role in the development of ADHD.

While response inhibition, visuospatial working memory, and fluid reasoning reliably predict youth ADHD, these factors may in turn be *predicted by* COMT Val¹⁵⁸Met and DAT1 interactions with environmental factors. Interactions with parenting behavior are especially likely, given the contribution of positive (e.g., sensitivity) and negative parenting (e.g., maltreatment) to optimal and adverse neurocognitive development in young children, respectively (Bernier, Carlson, & Whipple, 2010; Blair et al., 2011; Blair, Raver, & Berry, 2014; Kundakovic & Champagne, 2015), and their contribution to youth ADHD (Thapar et al., 2013; Tung, Brammer, Li, & Lee, 2014). Like ADHD, fluid reasoning and EF domains are moderately to highly heritable (Friedman et al., 2008; Jacobs, van Os, Derom, & Thiery, 2007), but effects for associated genetic variants are relatively small (Davies et al., 2011; Loo et al., 2012; Robinson et al., 2015). Thus, similar to ADHD, these domains may be influenced by unmeasured $G \times E$. For example, although DAT1 directly predicted working memory, response inhibition, and fluid reasoning in youth with ADHD (Kamradt et al., 2016; Karama et al., 2008; Söderqvist et al., 2012), there have been multiple replication failures, indicating DAT1 may have a moderating rather than direct influence on neurocognitive deficits and subsequent ADHD (Kebir & Joobar, 2011). Likewise, COMT Val¹⁵⁸Met directly correlated with response inhibition, working memory, and IQ (Jin et al., 2016; Loo et al., 2012; Mione et al., 2015; Störmer, Passow, Biesenack, & Li, 2012), and with activation in the neural networks supporting EF and fluid reasoning (Bishop, Fossella, Croucher, & Duncan, 2008; van Rooij et al., 2015), but multiple studies have not found main effects (Kebir & Joobar, 2011). COMT genotype also interacted with parenting quality and maltreatment to predict youth EF and attention (Goldberg et al., 2013; Voelker, Sheese, Rothbart, & Posner, 2009). Thus, COMT Val¹⁵⁸Met $\times$ parenting and DAT1 $\times$ parenting interactions may predict the hypothesized neurocognitive deficits, which in turn, are strongly implicated in youth ADHD.

To review, although $G \times E$ are likely to influence ADHD symptoms, the pathways mediating these associations are unknown. We examined biologically plausible moderation by DAT1 and COMT Val¹⁵⁸Met polymorphisms of indirect effects from parenting behavior to ADHD symptoms in a prospective longitudinal sample of youth with and without ADHD (see Figure 1 for a conceptual model). To expand upon prior $G \times E$ investigations, the present study specifically aimed to test genetic moderation of indirect effects from positive and negative parenting to youth ADHD symptoms through youth response inhibition, visuospatial working memory, and fluid reasoning simultaneously in a multiple mediation framework.

Methods

Participants

Participants were 229 children with ($n = 120$) and without ($n = 109$) ADHD who were intensively evaluated at ages 5–10 (i.e., Wave 1), and followed prospectively for 2 years (i.e., Wave 2; complete demographic data and descriptive statistics are presented in Table 1). Families were recruited from a large metropolitan city in California via advertisements at local schools, pediatric offices, and self-help groups, and referrals from mental health providers. Recruitment materials encouraged parents of children with and without ADHD to contact the study staff to determine eligibility. Participants were required to be fluent in English and living with at least one biological parent at least half-time. Exclusion criteria consisted of an IQ below 70 or diagnosis of an autism spectrum or neurological disorder that prevented full study participation. ADHD status required a positive diagnosis on the Diagnostic Interview Schedule for Children–IV (DISC), a structured interview with the parent. Children meeting diagnostic criteria for other disorders (e.g., depression) were included in the non-ADHD group to enhance external validity.

Procedures

Initial study eligibility was determined during a telephone screening of 235 families. Eligible families ($n = 230$) were mailed rating scales and invited to complete a laboratory-based assessment (i.e., Wave 1); rating scales were also mailed to children's teachers. Each child attended the assessment with his or her primary caregiver, defined as the parent who spends the most time with the child. Only the primary caregiver provided parent data. After parents and children gave consent and assent, parents completed multi-method measures of child psychopathology while children completed neurocognitive assessments in a separate room; they also completed a parent–child interaction task that was videotaped for later coding of parenting behavior. At the time of the assessment, 82.67% of children were not regularly taking psychotropic medication of any kind. For the 17.33% of children who were normally medicated, parents and teachers were asked to provide ratings based on the child's unmedicated behavior, if possible. Additionally, parents were asked to have their child abstain from medication on the day of the assessment; however, this was not a requirement for study participation if the parent objected or had reason to believe that missing one day of medication was unsafe for the child. Thus, 6% of children completed the Wave 1 neurocognitive assessment with psychotropic medication. Two years later (i.e., Wave 2), families were invited for a laboratory follow-up consisting of assessment procedures highly parallel to Wave 1. Two hundred and twenty-nine families completed the laboratory-based assessment and returned completed or partially completed rating scales at Wave 1, of which 204 were retained at Wave 2. We employed Full Information Maximum Likelihood procedures (FIML; described below) so that analyses were conducted on the full sample of 229 youth. All study procedures were approved by the Institutional Review Board.

Measures

Genotype.—Child DNA was extracted from saliva using DNA Genotek Oragene Self-Collection Kits (DNA Genotek, Inc., Ottawa, Canada). DAT1 genotype frequencies were distributed in our sample as follows: 10/10 (57.08%, $n = 121$), 9/10 (35.85%, $n = 76$), and

9/9 (7.08%, $n = 15$). These frequencies did not deviate from Hardy-Weinberg equilibrium ($\chi^2(1) = 0.41, p = .52$). The COMT Val¹⁵⁸Met polymorphism (rs4680) was also genotyped. COMT genotype frequencies were distributed in our sample as follows: Val/Val (25.34%, $n = 56$), Val/Met (50.23%, $n = 111$), and Met/Met (24.43%, $n = 54$). These frequencies did not deviate from Hardy-Weinberg equilibrium ($\chi^2(1) = 0.01, p = .95$).

Parenting behavior.—We used the Dyadic Parent Child Interaction Coding System (DPICS; Eyberg, Nelson, Duke, & Boggs, 2005) to assess positive and negative parenting behavior. During an approximately 20-minute parent-child interaction task, parents were asked to first play along with their child during an activity of the child's choosing (e.g., drawing, playing with toy); they were then asked to select a new activity and have the child play along according to parental rules; finally, parents instructed the child to clean up the toys without assistance. Counts of discrete parent behaviors were coded continuously and two composite categories of parenting, praise and negativity, were created (Chronis et al., 2007; Chronis-Tuscano et al., 2008; Eyberg et al., 2001). Parental praise was counted when parents positively appraised their child's behavior, attributes, or actions. Parental negativity was counted when parents issued hostile or critical comments, negative commands, or sarcastic and condescending remarks. We totaled the counts of observed behaviors across each category, and divided by the total minutes that were coded to correct for slight variations in the coding times.

Interactions were coded by intensively trained research assistants. Training consisted of a full day of instruction followed by a 2-month practice period with weekly coding meetings to resolve disagreements and ensure ongoing reliability. Estimations of composite category reliability were established via random selection of 20% of cases to be coded by two raters; the intraclass correlations in the sample were .75 (negativity) and .88 (praise). The DPICS composite categories have demonstrated strong test-retest reliability (Chronis-Tuscano et al., 2008) and predictive validity (Chronis et al., 2007). For additional details regarding coding and psychometrics see Li and Lee (2013).

Neurocognitive functioning.—Fluid reasoning, response variability, and visuospatial working memory were assessed at Wave 1. Fluid reasoning was assessed with the Arithmetic subtest of the Wechsler Intelligence Scale for Children–IV (WISC; Wechsler, 2003), which requires subjects to mentally solve orally presented math problems. WISC Arithmetic loads onto multiple cognitive domains in traditional four-factor WISC-IV models, but there is replicated evidence that it loads strongly and exclusively onto fluid reasoning in superior five-factor models (e.g., factor loading = 0.79; Keith, Fine, Taub, Reynolds, & Kranzler, 2006; Weiss, Keith, Zhu, & Chen, 2013). Thus, while Arithmetic may be sensitive to working memory, verbal comprehension, and quantitative reasoning, it primarily reflects fluid reasoning, which may subsume working memory and quantitative reasoning (Keith et al., 2006; Weiss et al., 2013). Visuospatial working memory was assessed with the Dot Locations subtest of the Children's Memory Scale (CMS; Cohen, 1997), which requires subjects to recall the location of multiple dots on a grid over the course of three learning trials and following a distractor condition. Finally, response inhibition was assessed via the Stop Signal Reaction Time (SSRT) from the Stop Signal Task (SST; Logan, Schachar, &

Tannock, 1997). Subjects were asked to press a button to indicate whether an “X” or “O” was presented on the computer screen (i.e., go task). During 25% of the stimuli presentations, an auditory tone was presented to indicate that the child should not press the button (i.e., stop task). Thus, children were required to inhibit the prepotent response of pressing a button in the presence of the tone. The task was designed to adjust the presentation of the stop signal such that subjects successfully inhibit their responses on 50% of the stop trials; this allows for the determination of the SSRT, with longer times suggesting worse inhibition. The WISC, CMS, and SST have been extensively validated and demonstrate excellent psychometric properties (Cohen, 1997; Logan et al., 1997; Wechsler, 2003). We used scaled scores from the Arithmetic and Dot Locations tasks. Arithmetic and Dot Locations were correlated in this sample ($r_s = .20, p < .01$), but they were not related to the SSRT (respectively, $r_s = -.04, p = .52$; $r_s = -.05, p = .50$).

Youth psychopathology symptoms.—At Wave 2, youth ADHD symptom counts were determined with the DISC (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), a fully structured computer-assisted diagnostic interview that is conducted with the parent and keyed to Diagnostic and Statistical Manual of Mental Disorders–IV criteria (DSM; American Psychiatric Association, 1994). The DISC has been extensively validated and demonstrates excellent psychometric properties (Shaffer et al., 2000). Youth oppositional defiant disorder (ODD) and conduct disorder (CD) symptom counts were also extracted from the DISC to be used as covariates in models predicting DISC ADHD symptoms. Parents also completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), a normed 113-item rating scale yielding eight narrowband syndrome scales as well as broadband internalizing and externalizing scales. Each item was rated from 0 = “not true” to 2 = “very true/often true.” Additionally, teachers completed the Teacher Report Form (TRF; Achenbach & Rescorla, 2001), yielding parallel scales to the CBCL. Although the CBCL and TRF do not reflect ADHD diagnostic symptoms per se, they are (1) highly correlated with DSM-based symptom measures, (2) extensively validated and demonstrate excellent reliability and validity, and (3) can be easily combined as a single multi-informant measure to conservatively reduce the number of statistical tests (Achenbach & Rescorla, 2001). Thus, we used a mean composite of parent and teacher reported *T* scores from the Attention Problems scale ($r_s = .52, p < .001$), which includes inattention and hyperactivity/impulsivity items. Parent ratings were used exclusively when teacher data were missing ($n = 98$), given that youth with teacher data were similar to youth without teacher data with respect to age, sex, race-ethnicity, income, neurocognitive functioning, and ADHD symptoms ($p > .16$ for all tests suggesting that teacher data were missing at random). Mean CBCL/TRF composite scores for the Externalizing Problems scale were similarly calculated for use as a covariate in models predicting CBCL/TRF Attention Problems.

Parent ADHD symptoms.—Parental ADHD symptoms were self-reported at Wave 1 via the 18-item Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005). The ASRS has excellent reliability and validity (Adler et al., 2006). Items consisted of a 5-point scale and a total score was summed ($\alpha = .94$).

Statistical Analysis

Moderated mediation.—We first evaluated moderation of indirect effects from Wave 1 parenting behavior to Wave 2 youth ADHD symptoms through Wave 1 neurocognitive functions (i.e., SSRT, CMS Dot Locations, WISC Arithmetic) by COMT Val¹⁵⁸Met genotype via four moderated mediation models in Mplus 7.0 (Muthén & Muthén, 1998–2015). Models 1 and 2 separately predicted moderation of indirect effects from positive parenting to youth CBCL/TRF Attention Problems *T*Scores and DISC ADHD symptoms, respectively. Models 3 and 4 evaluated indirect effects from negative parenting to youth CBCL/TRF Attention Problems *T*Scores and DISC ADHD symptoms, respectively. Each of the four models simultaneously calculated: (1) path coefficients for the direct effects from all predictors (i.e., Wave 1 parenting behavior, COMT genotype, a COMT genotype $\times$ parenting interaction term, and the covariates) to all Wave 1 mediators; (2) path coefficients from parenting behavior, all mediators, and all covariates to Wave 2 ADHD symptoms; (3) point estimates of the conditional indirect effects (i.e., an indirect effect conditioned on a particular value of the moderator) from parenting to ADHD symptoms through each neurocognitive mediator for each genotype group; and (4) the difference between the conditional indirect effects (i.e., the index of moderated mediation; Hayes, 2015). Ninety-five percent bias-corrected (BC) confidence intervals (CIs) for the point estimates of the conditional indirect effects and the difference between these effects were calculated using 5,000 bootstrap simulations (statistical significance is assumed when the interval excludes zero). Bootstrapped CIs for indirect effects are statistically more powerful than traditional mediation techniques (Zhao, Lynch, & Chen, 2010) and robust to non-normal data (Preacher & Hayes, 2008). Next, the identical four moderated mediation models were reproduced, but featured DAT1 instead of COMT Val¹⁵⁸Met. Parenting behavior and genotypes were centered to avoid scaling artifacts. In all models testing moderation by youth DAT1 genotype, we compared youth with at least one copy of the 9-repeat allele (i.e., 9/9 or 9/10) to those with the 10/10 genotype, coded 0 = “9/9 or 9/10” and 1 = “10/10,” due to few 9/9 genotypes in the sample ($n = 15$) and based on prior studies of DAT1 and ADHD (e.g., Kamradt et al., 2016). Additionally, because results were consistent when COMT Val¹⁵⁸Met was coded additively (i.e., 0 = “Met/Met,” 1 = “Val/Met,” 2 = “Val/Val”) and dominantly (i.e., 0 = “Met/Met,” 1 = “Val/Met or Val/Val”), and because effects for Val/Met and Val/Val youth were directionally consistent and statistically similar, we present results from the dominant models to increase simplicity and facilitate interpretation (results from the additive models are available upon request).

Missing data.—Approximately 22% of youth were missing data on at least one key study variable (e.g., parenting behavior). Thus, we used FIML estimation to maximize sample size for all moderated mediation analyses described above. FIML optimally remedies missing data when data are missing at random or missing completely at random (MCAR). Evaluation of missing data patterns via Little’s MCAR Test (Little, 1988) indicated that data were indeed MCAR in the present sample ($\chi^2(1318) = 931.80, p = .99$).

Covariates.—All models described above controlled for co-occurring externalizing symptoms due to their significant etiologic and phenotypic overlap with ADHD (Cosgrove et al., 2011), and preliminary evidence that COMT Val¹⁵⁸Met and DAT1 are associated with

externalizing behavior secondary to ADHD (Kamradt et al., 2016; Thapar et al., 2013). Specifically, Wave 2 CBCL/TRF Externalizing Problems *T* scores were covaried in models predicting CBCL/TRF Attention Problems, and a sum of Wave 2 DISC ODD and CD symptoms was controlled in predictions of DISC ADHD symptoms. All models predicting DISC ADHD symptoms also controlled for youth sex; however, given our use of *T* scores, we did not adjust for sex in predictions of CBCL/TRF Attention Problems. We similarly did not adjust for youth age given our use of the scaled WISC Arithmetic and CMS Dot Locations scores as well as the CBCL/TRF Attention Problems *T* scores. Although, unlike the current study, population stratification is primarily a concern when samples consist of highly distinct strata (Hutchison, Stallings, McGeary, & Bryan, 2004), racial-ethnic differences in COMT Val¹⁵⁸Met and DAT1 allele frequencies may threaten internal validity. Thus, because population stratification is contingent on race-ethnicity being associated with both genotype and outcome variable (Hutchison et al., 2004), and youth COMT and DAT1 genotypes were non-randomly distributed by race-ethnicity in our sample (respectively, $\chi^2(8) = 17.28, p = .03$; $\chi^2(4) = 11.94, p = .02$), race-ethnicity was controlled in all moderated mediation models. Medication status was also controlled in all models given that 6% of youth were medicated on the day of Wave 1 neurocognitive testing. Finally, because parent characteristics may affect individual differences in youth ADHD, both directly and with respect to common genetic influences, we controlled for Wave 1 parental ADHD symptoms in all analyses. First, parental ADHD is associated with parenting behavior (Chronis-Tuscano et al., 2008). Second, gene-environment correlation (rGE) complicates definitive inferences of $G \times E$ (Jaffee & Price, 2007). For example, children's genetically-influenced traits may elicit non-random responses from the environment (i.e., evocative rGE), or environmental effects on child outcome (e.g., parenting) may reflect shared genetic influences (i.e., passive rGE). We controlled for parental ADHD symptoms to approximately account for these non-random associations.

Results

Moderated Multiple Mediation by COMT Val¹⁵⁸Met Genotype

We first evaluated moderation of the indirect effects of Wave 1 positive parenting behavior (i.e., parental praise) on Wave 2 CBCL/TRF Attention Problems through Wave 1 SSRT, CMS Dot Locations, and WISC Arithmetic by youth COMT genotype, controlling for youth race-ethnicity, medication status during Wave 1 neurocognitive testing, Wave 2 CBCL/TRF Externalizing Problems, and Wave 1 parent ADHD symptoms (the Attention Problems *T* scores are also adjusted for age and sex). Path coefficients generated by this model are presented in Figure 2. Although this was not a focus of the present study, the total effect of parental praise on CBCL/TRF Attention Problems (i.e., not adjusted for the mediators) and the indirect effects of parental praise on CBCL/TRF Attention problems through the neurocognitive mediators (i.e., not conditioned on youth genotype) are presented in Table 2. There was a significant positive *conditional* indirect effect through Arithmetic for Val/Val and Val/Met youth, but not Met/Met youth (Table 3), whereby parental praise was negatively correlated with Arithmetic, which in turn was negatively correlated with CBCL/TRF Attention Problems. A post hoc test of the difference between the conditional indirect effects (i.e., index of moderated mediation) revealed that the indirect effect through Arithmetic

differed significantly between Val/Val and Val/Met vs. Met/Met youth (Table 3). There were no significant conditional indirect effects through SSRT or Dot Locations domains (Table 3). These results were replicated in prediction of Wave 2 DISC ADHD symptoms, controlling for sex, race-ethnicity, medication status, Wave 2 DISC ODD/CD symptoms, and Wave 1 parent ADHD symptoms (the scaled Dot Locations and Arithmetic scores are also adjusted for age; the total effect and non-conditioned indirect effects from this model are presented in Table 2): there was a significant conditional indirect effect through Arithmetic for Val/Val and Val/Met youth ($B = 1.06$, $SE = 0.58$, $95\% CI = 0.20, 2.54$), but not Met/Met youth ($B = 0.17$, $SE = 0.20$, $95\% CI = -0.13, 0.63$), and these effects were significantly different ($B = 0.90$, $SE = 0.50$, $95\% CI = 0.07, 2.06$); no conditional indirect effects through SSRT or Dot Locations were observed. Thus, COMT Val¹⁵⁸Met moderated indirect effects from parental praise to Wave 2 ADHD symptoms through Arithmetic, but not SSRT or Dot Locations, across all methods and informants.

We then evaluated moderation of the indirect effects of Wave 1 negative parenting behavior (i.e., parental negativity) on Wave 2 ADHD symptoms through Wave 1 SSRT, CMS Dot Locations, and WISC Arithmetic by youth COMT genotype, controlling for the identical covariates from the positive parenting models above. No significant conditional indirect effects were observed from parental negativity to CBCL/TRF Attention Problems or DISC ADHD symptoms. Also, although this was not a focus of the present study, neither the total effect nor the indirect effects of parental negativity on CBCL/TRF Attention Problems were significant. In prediction of DISC ADHD symptoms, there were significant total and direct effects of parental negativity (respectively, $B = 3.40$, $SE = 1.20$, $p < .01$; $B = 3.22$, $SE = 1.16$, $p < .01$), but no indirect effects through the mediators.

Moderated Multiple Mediation by DAT1 Genotype

We also evaluated moderation of the indirect effects of Wave 1 parental praise on Wave 2 CBCL/TRF Attention Problems through Wave 1 SSRT, Dot Locations, and Arithmetic by youth DAT1 genotype, controlling for youth race-ethnicity, medication status, Wave 2 CBCL/TRF Externalizing Problems, and Wave 1 parent ADHD symptoms (the Attention Problems *T* scores are also adjusted for age and sex). Path coefficients generated by this model are presented in Figure 3. There was a significant positive conditional indirect effect through Arithmetic for 10/10 youth, but not 9/9 and 9/10 youth (Table 4), whereby parental praise was negatively correlated with Arithmetic, which in turn was negatively correlated with CBCL/TRF Attention Problems. A post hoc test of the difference between the two conditional indirect effects (i.e., index of moderated mediation) was significant (Table 4). No significant conditional indirect effects through SSRT or Dot Locations were observed (Table 4). These results were replicated in prediction of Wave 2 DISC ADHD Symptoms, controlling for youth sex, race-ethnicity, medication status, Wave 2 DISC ODD/CD symptoms, and Wave 1 parent ADHD symptoms (the scaled Dot Locations and Arithmetic scores are also adjusted for age): there was a significant conditional indirect effect through Arithmetic for 10/10 youth ($B = 0.92$, $SE = 0.54$, $95\% CI = 0.17, 2.40$), but not 9/9 and 9/10 youth ($B = 0.17$, $SE = 0.20$, $95\% CI = -0.14, 0.63$), and these effects were significantly different ($B = 0.75$, $SE = 0.46$, $95\% CI = 0.04, 1.93$); no conditional indirect effects through SSRT or Dot Locations were observed. Thus, DAT1 genotype moderated indirect effects

from parental praise to Wave 2 ADHD symptoms through Arithmetic, but not SSRT or Dot Locations, across all methods and informants.

Finally, we evaluated moderation of the indirect effects of Wave 1 parental negativity on Wave 2 ADHD symptoms through Wave 1 SSRT, Dot Locations, and Arithmetic by youth DAT1 genotype, controlling for the identical covariates from the positive parenting models above. No significant conditional indirect effects were observed from parental negativity to CBCL/TRF Attention Problems or DISC ADHD symptoms.

Discussion

We evaluated genetic moderation of indirect effects from positive and negative parenting behavior to youth ADHD symptoms through biologically plausible neurocognitive factors in a prospective study of youth with and without ADHD. Controlling for demographic factors, youth externalizing symptoms, and parent ADHD symptoms, both the COMT Val¹⁵⁸Met and DAT1 polymorphisms moderated indirect effects of positive parenting (i.e., parental praise), but not negative parenting (i.e., parental negativity), on multi-method/informant ADHD symptoms through fluid reasoning (i.e., Arithmetic). Specifically, there was a positive indirect effect from parental praise to ADHD symptoms through fluid reasoning for youth with the COMT Val/Val and Val/Met genotypes, but not for Met/Met youth; similarly, for DAT1, there was a positive indirect effect for 10/10, but not 9/9 and 9/10, youth. There was no moderation of indirect effects from both positive and negative parenting through response inhibition (i.e., SSRT) and visuospatial working memory (i.e., Dot Locations). These findings reflect novel, preliminary evidence that specific neurocognitive facets mediate $G \times E$ effects on the development of youth ADHD symptoms.

Although positive parenting is typically associated with optimal youth neurocognitive functioning (e.g., Bernier et al., 2010), the indirect effects observed in COMT Val/Val and Val/Met as well as DAT1 10/10 youth revealed an *inverse* relation of parental praise with fluid reasoning (*a* path), which in turn inversely predicted ADHD symptoms (*b* path). That higher parental praise correlated with lower fluid reasoning was somewhat surprising. One potential explanation for this finding is that specific forms of praise may hinder rather than promote fluid reasoning. There is replicated evidence that parental praise for children's efforts/actions promotes healthy motivation and attributions during challenging cognitive tasks, whereas praise for children's inherent characteristics (e.g., intelligence) predicts lower motivation, persistence, and performance with respect to both their overall achievement as well as tests of fluid reasoning specifically (Gunderson et al., 2013; Mueller & Dweck, 1998). Moreover, most parents infrequently engage in praise that explicitly labels children's actions/efforts (Leijten et al., 2016). Thus, the parental praise observed in this study was likely to be more child-focused than action-focused, although this was not formally evaluated. Also, whereas this study focused on praise, other studies on youth EF/reasoning focused on other dimensions of positive parenting (e.g., sensitivity). Despite their intercorrelations, these domains are separable (e.g., Johnston et al., 2002), and may differentially affect youth neurocognitive development. Finally, higher levels of child neurocognitive functioning have elicited increased positive parenting (Blair et al., 2014). Although our results, in contrast, suggest that increased positive parenting correlated with

lower fluid reasoning in COMT Val/Val and Val/Met as well as DAT1 10/10 youth, given that parenting behavior and fluid reasoning were assessed concurrently, we cannot rule out potential evocative effects. Thus, future research on genetic moderated mediation for youth ADHD should prioritize temporally ordered predictors, mediators, and outcomes as well as examine separable parenting dimensions (e.g., labeled vs. unlabeled praise).

That fluid reasoning statistically mediated conditional indirect effects underlying ADHD symptoms converges with prior evidence of fluid reasoning deficits as well as hypoactivation in brain regions that modulate fluid reasoning in youth with ADHD (e.g., Doyle et al., 2005; Tamm & Juranek, 2012). Additionally, these results are consistent with prior mediational studies in which other early risk factors (i.e., birth weight) indirectly predicted youth ADHD symptoms through fluid reasoning (Morgan et al., 2016; 2016). However, in contrast to the reliable inverse effect of fluid reasoning on youth ADHD, the main and interactive effects of COMT Val¹⁵⁸Met and DAT1 polymorphisms on neurocognitive functioning are inconsistent. Notably, the current study implicated Val/Val and Val/Met COMT genotypes as well as 10/10 DAT1 genotypes in moderated mediation effects for ADHD. Whereas the Val and 10-repeat alleles are thought to confer risk for ADHD (although direct main effects of the COMT polymorphism are unclear; Gizer et al., 2009), and the Val allele reliably predicts hypoactivation in brain regions critical to fluid reasoning (Mier et al., 2010), main or interactive associations of the COMT Met allele and DAT1 9-repeat allele with decreased neurocognitive function have also been observed (Goldberg et al., 2013; Karama et al., 2008). Thus, further studies must clarify the precise nature of COMT Val¹⁵⁸Met and DAT1 moderation of indirect effects through fluid reasoning to ADHD.

Several key limitations should be noted. First, although the sample size ($n = 229$) significantly exceeded that required to adequately power product-of-coefficients tests of mediation using resampling methods for path coefficients of even small effect ($n = 148$; Fritz & Mackinnon, 2007), larger samples may be required to test the more complex models examined herein (e.g., moderated mediation with multiple mediators). Thus, evaluation of visuospatial working memory and response inhibition as mediators of $G \times E$ effects on ADHD, including interactions with negative parenting, in larger samples is warranted. Second, WISC Arithmetic may tap other domains of functioning in addition to fluid reasoning (e.g., working memory, quantitative reasoning). Thus, we cannot rule out the possibility that the complexity of the constructs underlying Arithmetic confounded the observed findings. We await studies that disentangle these separable components to further improve traction on fluid reasoning pathways from $G \times E$ to ADHD. Finally, the challenges inherent to $G \times E$ research, including replication failure and false positives (Duncan & Keller, 2011), should be acknowledged, especially because this study did not include a built-in replication and the analyses did not survive stringent correction for multiple testing. Given the importance of balancing genetic discovery with costly replication, identification of novel genetic moderated mediation is only an initial step in elucidating putative genetic risk processes. The results described herein require further investigation, especially via experimental and longitudinal designs (van IJzendoorn & Bakermans-Kranenburg, 2012).

Whereas there is a growing literature on $G \times E$ underlying youth ADHD symptoms, this study is the first to explore mediators of these associations. We specifically found that

COMT Val¹⁵⁸Met and DAT1 polymorphisms moderated indirect effects of parental praise on multi-method/informant ADHD symptoms through fluid reasoning as assessed by WISC Arithmetic. In addition to validation of reliable ADHD risk factors, such as replicated $G \times E$, identification of biologically plausible risk processes is necessary to develop prevention strategies that will reduce the burden associated with this prevalent and costly condition (Sonuga-Barke & Halperin, 2010). Thus, given the likely centrality of $G \times E$ to the development of youth ADHD symptoms (Nigg et al., 2010), and the role of multiple mediating pathways (i.e., equifinality), continued examination of fluid reasoning and other diverse biologically plausible mediators of this association ultimately has potential to elucidate alterable processes in the etiology of ADHD.

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Figure 1.
Conceptual model of proposed moderated multiple mediation analysis.

Figure 2.

Path coefficients from the model estimating moderation by COMT Val¹⁵⁸Met polymorphism of indirect effects from Wave 1 positive parenting to Wave 2 youth CBCL/TRF Attention Problems through Wave 1 neurocognitive mediators, controlling for youth race-ethnicity, psychotropic medication status on the day of neurocognitive testing, Wave 2 CBCL/TRF Externalizing Problems, and Wave 1 parent ADHD symptoms (Attention Problems *T* scores are also adjusted for age and sex). *Note:* Numbers shown reflect unstandardized beta coefficients; ⁺*p* < .10 **p* < .05 ***p* < .01 ****p* < .001

Figure 3.

Path coefficients from the model estimating moderation by DAT1 polymorphism of indirect effects from Wave 1 positive parenting to Wave 2 youth CBCL/TRF Attention Problems through Wave 1 neurocognitive mediators, controlling for youth race-ethnicity, psychotropic medication status on the day of neurocognitive testing, Wave 2 CBCL/TRF Externalizing Problems, and Wave 1 parent ADHD symptoms (CBCL/TRF Attention Problems *T* scores are also adjusted for age and sex). *Note:* Numbers shown reflect unstandardized beta coefficients; ⁺ $p < .10$ * $p < .05$ ** $p < .01$ *** $p < .001$

Table 1.

Sample demographics and descriptive statistics

	% of sample		M (SD), range
Sex (female)	32.31	Family income	7.65 (2.20), 1–9
Ethnicity:		Age (W2), years	9.68 (1.34), 7–13
Caucasian	53.18	Parental Praise (W1)	0.52 (0.46), 0–2.67 *
African American	9.09	Parental Negativity (W1)	0.38 (0.37), 0–2.28 *
Hispanic/Latino	10.91	SSRT (W1), milliseconds	352.52 (115.04), 138.6–762.5
Asian	3.64	CMS Dot Locations (W1)	11.34 (3.14), 2–16
Mixed	23.18	WISC Arithmetic (W1)	11.11 (3.10), 3–19
COMT Val ¹⁵⁸ Met genotype		ADHD symptoms (W2)	
Val/Val	25.34	CBCL/TRF Attention	60.27 (9.49), 50–93
Val/Met	50.23	DISC ADHD symptoms	6.91 (5.51), 0–18
Met/Met	24.43	Externalizing symptoms (W2)	
DAT1 genotype		CBCL/TRF Externalizing	52.42 (9.06), 33–76
10/10	57.08	DISC ODD/CD symptoms	2.12 (2.24), 0–11
9/10	35.85	Parent ASRS total (W1)	25.57 (13.28), 0–68
9/9	7.08		

Note: Family income was assessed on an ordinal scale from 1 = “less than \$10,000” to 9 = “greater than \$75,000” annually; W2 = Wave 2; W1 = Wave 1; SSRT = Stop-Signal Reaction Time; CMS = Children’s Memory Scale; WISC = Wechsler Intelligence Scale for Children; ADHD = attention-deficit/hyperactivity disorder; CBCL/TRF = mean composite of parent and teacher *T* scores on the Child Behavior Checklist and Teacher Report Form; DISC = Diagnostic Interview Schedule for Children; ODD = oppositional defiant disorder; CD = conduct disorder; ASRS = Adult ADHD Self-Report Scale

* Values reflect the mean, standard deviation, and range calculated on the number of counts divided by the total minutes coded

Table 2.

Total effects of Wave 1 positive parenting on Wave 2 ADHD symptoms and indirect effects through the Wave 1 neurocognitive functions (i.e., not conditioned on youth genotypes)

	Point Est.	SE	95% BC Bootstrap CI	
			Lower	Upper
CBCL/TRF Attention Problems				
Indirect effect through SSRT	−0.104	0.208	−0.780	0.132
Indirect effect through CMS Dot	0.232	0.310	−0.101	1.112
Indirect effect through WISC Arithmetic	0.351	0.469	−0.408	1.400
Total effect of positive parenting	2.746	.011	0.147	5.546
DISC ADHD symptoms				
Indirect effect through SSRT	0.067	0.130	−0.090	0.492
Indirect effect through CMS Dot	0.062	0.150	−0.118	0.516
Indirect effect through WISC Arithmetic	0.167	0.198	−0.131	0.626
Total effect of positive parenting	2.269	0.948	0.423	4.168

Note: Boldface indicates significant conditional indirect effect and/or significant index of moderated mediation; the index of moderated mediation reflects the difference between the two conditional indirect effects; CBCL/TRF = mean composite of parent and teacher *T* scores on the Child Behavior Checklist and Teacher Report Form; DISC = parent reports on the Diagnostic Interview Schedule for Children; Point est. = point estimate of the indirect effect; BC Bootstrap CI = bias corrected confidence intervals; SSRT = Stop-Signal Reaction Time; CMS Dot = scaled score on the Dot Locations subtest of the Children's Memory Scale; WISC Arithmetic = scaled score on the Arithmetic subtest of the Wechsler Intelligence Scale for Children

Table 3.

Indirect effects of Wave 1 positive parenting on Wave 2 CBCL/TRF Attention Problems through Wave 1 neurocognitive functions conditioned on COMT Val¹⁵⁸Met genotype

			95% BC Bootstrap CI	
	Point Est.	SE	Lower	Upper
SSRT				
Met/Met	-0.104	0.208	-0.780	0.132
Val/Met and Val/Val	-0.037	0.367	-1.205	0.461
Index of Moderated Mediation	0.068	0.365	-0.297	1.540
CMS Dot Locations				
Met/Met	0.232	0.310	-0.101	1.112
Val/Met and Val/Val	0.484	0.719	-0.391	2.767
Index of Moderated Mediation	0.252	0.612	-0.701	1.854
WISC Arithmetic				
Met/Met	0.351	0.469	-0.408	1.400
Val/Met and Val/Val	2.798	1.311	0.751	5.863
Index of Moderated Mediation	2.447	1.098	0.531	4.868

Note: Boldface indicates significant conditional indirect effect and/or significant index of moderated mediation; the index of moderated mediation reflects the difference between the two conditional indirect effects; CBCL/TRF = mean composite of parent and teacher *T* scores on the Child Behavior Checklist and Teacher Report Form; Point est. = point estimate of the indirect effect; BC Bootstrap CI = bias corrected confidence intervals; SSRT = Stop-Signal Reaction Time; CMS Dot = scaled score on the Dot Locations subtest of the Children's Memory Scale; WISC Arithmetic = scaled score on the Arithmetic subtest of the Wechsler Intelligence Scale for Children

Table 4.

Indirect effects of Wave 1 positive parenting on Wave 2 CBCL/TRF Attention Problems through Wave 1 neurocognitive functions conditioned on DAT1 genotype

	Point Est.	SE	95% BC Bootstrap CI	
			Lower	Upper
SSRT				
9/9 and 9/10	-0.108	0.226	-0.824	0.155
10/10	-0.244	0.549	-2.187	0.313
Index of Moderated Mediation	-0.137	0.381	-1.515	0.217
CMS Dot Locations				
9/9 and 9/10	0.235	0.315	-0.100	1.157
10/10	0.392	0.677	-0.384	2.697
Index of Moderated Mediation	0.158	0.528	-0.634	1.649
WISC Arithmetic				
9/9 and 9/10	0.349	0.471	-0.416	1.369
10/10	2.308	1.230	0.426	5.192
Index of Moderated Mediation	1.959	1.031	0.143	4.257

Note: Boldface indicates significant conditional indirect effect and/or significant index of moderated mediation; the index of moderated mediation reflects the difference between the two conditional indirect effects; CBCL/TRF = mean composite of parent and teacher *T* scores on the Child Behavior Checklist and Teacher Report Form; Point est. = point estimate of the indirect effect; BC Bootstrap CI = bias corrected confidence intervals; SSRT = Stop-Signal Reaction Time; CMS Dot = scaled score on the Dot Locations subtest of the Children's Memory Scale; WISC Arithmetic = scaled score on the Arithmetic subtest of the Wechsler Intelligence Scale for Children