Published in final edited form as:

J Abnorm Child Psychol. 2017 April ; 45(3): 429–442. doi:10.1007/s10802-017-0264-y.

DRD4 Variants Moderate the Impact of Parental Characteristics on Child Attention-Deficit Hyperactivity Disorder: Exploratory Evidence from a Multiplex Family Design

Molly A. Nikolas¹ and Allison M. Momany¹

¹Department of Psychological and Brain Sciences, University of Iowa, E11 Seashore Hall, Iowa City, IA 52242, USA

Abstract

Parental ADHD symptomatology and related impairments have been robustly associated with youth ADHD across decades of work. Notably, these factors may impede typical development of child self-regulation capabilities through both neurobiological and interpersonal processes. High heritability of estimates for the disorder further suggest that these effects are likely genetically-mediated, at least in part. Variation within the dopamine D4 receptor gene (*DRD4*) has been shown to moderate parental influences on youth ADHD. Use of a multiplex family design (i.e., samples of families that included multiple affected members) may facilitate identification of additional gene variants of interest and advance understanding of gene-environment interplay in regard to parenting. Thirty multiplex families consisting of 114 individuals (66 youth, 48 parents) completed a multi-stage, multi-informant diagnostic and neurocognitive assessment, measures of parenting, and provided saliva samples for DNA analyses. Sanger sequencing of the *DRD4* gene yielded 16 rare variants; a polygenic risk score was computed for both parents and youth. Generalized estimating equations (GEE) examined the predictive effects of parental ADHD symptoms, parental neurocognitive functioning, and poor parenting dimensions on youth ADHD as well as moderation of these effects by parental and youth *DRD4* variants. Findings indicated that *parental DRD4* variants moderated the impact of parental ADHD and neurocognitive functioning on youth ADHD symptoms. *Youth DRD4* variants moderated the impact of parental inconsistent discipline on child ADHD. In all cases, stronger associations were observed for those individuals with more risk variants. These exploratory findings highlight the potential utility of a multiplex family design for examining the interplay between parent and child characteristics in predicting youth outcomes.

Correspondence to: Molly A. Nikolas.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human subjects were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in this study.

Keywords

Attention-deficit hyperactivity disorder; *DRD4*; Parenting; Gene-environment interplay

Attention-deficit hyperactivity disorder is a common and costly neurodevelopmental disorder characterized by pervasive and impairing problems with inattention, overactivity, and impulsivity (American Psychiatric Association 2013; Leibson et al. 2001; Pelham et al. 2007). It's been long recognized that ADHD tends to run in families (Faraone and Biederman 1994) and decades of twin research have converged on high heritability estimates for the disorder of around 70% (Burt 2009; Nikolas and Burt 2010). More recently, large-scale, whole-genome investigations are beginning to uncover variants that may be relevant to the pathophysiology of ADHD (Mooney et al. 2016). However, the family context has been posited to be crucial in moderating liability factors involved in the shaping of behavioral regulation among youth (Nigg et al. 2006). Parental characteristics have also been shown to predict individual differences in the developmental trajectories of symptoms, comorbid problems, and functional impairments among youth with ADHD specifically (see Deault 2010 for a review). Further, behavioral interventions aimed at reducing impairment and behavior problems among youth with ADHD frequently focus on improving parent-child interactions and reducing parenting stress (Heath et al. 2014), suggesting that parental characteristics likely play a key role in understanding the origins of the disorder and its course (Johnston and Mash 2001).

Notably, however, twin and adoption studies have also estimated shared environmental factors (i.e., factors common among siblings that also serve to increase sibling similarity) to be zero for ADHD (Burt 2009; Nikolas and Burt 2010). Similarly, the effects of non-shared environmental influences (i.e., factors that differ among siblings and serve to increase sibling dissimilarity) are also small throughout development (Chang et al. 2013). However, as outlined by Purcell (2002), interactive effects between genetic factors and shared environmental factors are captured in the additive genetic variance term (e.g., about 70% of the variance in ADHD), whereas interactive effects between genetic factors and non-shared environmental factors are captured in the non-shared environmental variance term (e.g., about 30% of the variance in ADHD). Initial studies of these gene $\times$ environment interaction effects (G $\times$ E) indicated some promise and positive effects, particularly when examining family context factors (Nigg et al. 2010). Therefore, examination of the impact of parental characteristics within the context of genetically-informed designs remains particularly important.

Conceptually, the development of behavioral and emotion regulation capacities in children has been hypothesized to include multilevel biological and contextual inputs and their interactions (Zelazo 2013). Parental ADHD symptoms and impairments may influence the development of regulatory neurobehavioral functions due to shared genetic and neurobiological risk. However, the presence of ADHD symptoms in parents may also alter the type of contextual inputs they provide that serve to shape effective regulatory strategies in children. For example, parental ADHD may impair parental scaffolding (i.e., direct guidance to children while engaging in a novel or challenging activity), stimulation (i.e.,

ability to provide opportunities for learning and cognitive enrichment), as well as the degree to which parents are warm and responsive to children's needs for care and attention. Ecological models focused on these factors have emphasized that impairments in parental responsiveness (i.e., consistency) may prevent the development of internalized regulatory strategies in children, leading to impairments in effortful control (Kochanska and Kim 2014). A recent review also demonstrated that problems in parental scaffolding, stimulation, and responsiveness are linked to later developmental deficits in children's executive functioning skills (Fay-Stammach et al. 2014). In line with this, there is strong evidence from animal studies that environmental stimulation and enrichment positively impacts neural growth and development, suggesting that factors that interfere with enrichment may alter the trajectories of neural development and increase risk for neurodevelopmental problems (Halperin and Healey 2011). Thus, parental ADHD symptoms and related impairments, including parental neurocognitive functioning, as well as the degree of consistency in parental responding may be particularly relevant contextual risk factors for ADHD that require further examination within the context of genetic risk.

Empirically, decades of research have established significant connections between parental ADHD and child ADHD. Focus on the role of parental characteristics, particularly parental ADHD, remains high given that between 25 and 30% of youth with ADHD also have a parent with ADHD (Faraone and Biederman 1994). Parental ADHD behaviors, particularly more persistent and impairing symptoms, have been associated with increased ADHD symptom severity among offspring (Agha et al. 2013). Prospective studies have also indicated that increased parental ADHD symptoms and impairments significantly predicted youth ADHD symptom severity and persistence during adolescence (van Lieshout et al. 2016). While associations between parental and youth ADHD symptom severity are not surprising, given the role of genetic factors in the etiology of ADHD, parental ADHD also appears to predict other behavioral problems across the externalizing spectrum (Buschgens et al. 2010).

Neurocognitive functioning among parents has also been linked to youth outcomes in several family designs, mainly within the context of searching for endophenotypes suitable for genetic analyses (Gottesman and Gould 2003). Overall, several of these studies have documented small to moderate associations between parental executive function (including response inhibition and working memory), visuospatial attention, and motor behavior and youth ADHD (Goos et al. 2009; Jester et al. 2009; Nigg et al. 2004; Nigg et al. 1997; Thissen et al. 2014). While the presence of such deficits in affected and unaffected relatives (Nigg et al. 2004; Nikolas and Nigg 2015) and their association with candidate genes of interest to ADHD (Kamradt et al. 2016) suggests potential for endophenotypes, it remains unclear if associations between parental neurocognitive function and youth ADHD symptoms indeed vary as a function of shared genetic factors or other indicators of genetic risk.

Furthermore, conceptual models regarding the intergenerational transmission of executive function and attention emphasize the potentially critical role of parental neurocognition in the development of child self-regulation (Deater-Deckard 2014). Under this model, self-regulation develops and operates within the context of parent-child relationships, and

parental attention, inhibitory control, and working memory may serve to modulate parental responsiveness to child behavior. Impairments in these areas of neurocognitive functioning, including in working memory, may impair the consistency of parental responsiveness or underpin hostile or critical responses to negative child behavior (Deater-Deckard et al. 2010). Thus, in addition to serving as markers of shared genetic risk, parental neurocognitive deficits may serve to exacerbate difficulties in the development of self-regulation in youth by impairing warm responsiveness or exacerbating negative or hostile responding. Such effects that may be particularly potent for youth who are genetically or neurobiologically vulnerable to developing self-regulation problems.

In line with this, parenting dimensions, particularly those characterized by inconsistency of responsiveness, have also been robustly associated with youth ADHD symptom severity (Ellis and Nigg 2009) and developmental trajectory and may be crucial in maintaining ADHD in early childhood (Campbell et al. 2000). Notably, recent work has also indicated that parenting dimensions, specifically the use of corporal punishment strategies, mediated associations between parental and offspring ADHD (Tung et al. 2015), suggesting that parenting dimensions may play a key role in understanding the transmission of ADHD. Along these lines, significant G×E effects involving inconsistent parental discipline have also been observed for ADHD (Martel et al. 2011), indicating that the impact of negative (or positive) parenting on youth functioning may be dependent upon inherited vulnerability factors.

Overall, there is strong evidence that parental characteristics, including parental ADHD symptoms, parental neurocognitive function, and parenting dimensions likely influence child ADHD symptom severity and course to some extent. However, the exact mechanisms are likely associated with or dependent upon shared genetic factors between parents and children. For example, recent work using a novel design of biologically-related and unrelated parents demonstrated that difficult temperament traits among youth may evoke hostile and negative parenting from mothers, which may then, in turn, exacerbate symptoms of ADHD (Harold et al. 2013). Parents with increased ADHD symptomatology and neurocognitive deficits may be less equipped to handle the behavioral demands of an overactive or impulsive child, and further respond with increased inconsistency or hostility, which may serve to influence and maintain ADHD symptoms across development (Johnston et al. 2016). Thus, consideration of both parental and youth genetic characteristics appears to be crucial when parsing the effects of parental characteristics on offspring ADHD.

In addition to large-scale, genome-wide studies of ADHD, improvements in gene sequencing platforms have allowed investigators to examine multiple polymorphic regions within candidate genes of interest. One such gene, the dopamine D4 receptor gene (*DRD4*), has been frequently linked to ADHD, including significant meta-analytic association (Gizer et al. 2009). The dopamine D4 receptor is a G-protein coupled receptor that is heavily expressed in brain areas hypothesized to be involved in the etiology of ADHD, including the prefrontal cortex and anterior cingulate, which comprise the executive attention network (Posner and Fan 2005). In addition to its meta-analytic association with ADHD, variation within *DRD4* has also been associated with individual differences in child executive functioning (Albrecht et al. 2014) and associated neural networks (Gilsbach et al. 2012).

There is substantial evidence that the executive attention network is heavily mediated by dopamine innervations (Posner and Rothbart 2009) and that functioning within this brain network is related to the development of self-regulation capabilities (Posner et al. 2007). In addition to genetic or neurobiological mechanisms, deficits or inconsistency of parental contextual input may also alter the functionality of brain regions that underpin child self-regulation, (such as the executive attention network, Deater-Deckard 2014), which may occur via mechanistic alterations in neurogenesis or synaptogenesis (Halperin and Healey 2011). Such influences may be particularly problematic for youth with genetic polymorphisms that may alter dopamine neurotransmission within these regions, including polymorphisms that alter functionality of the D4 receptor (Smith et al. 2013).

The use of a multiplex family design may be especially useful for identifying and examining such effects. These designs consist of multiple biologically-related family members with ADHD (or who are high on the related ADHD symptom dimensions of inattention-disorganization and hyperactivity-impulsivity). Hypothetically, these designs may provide a method of sampling individuals who possess a high degree of genetic or familial liability for ADHD, given the presence of ADHD-related problems among multiple, related individuals. The use of a multiplex family design can be especially useful for detecting and evaluating effects of less common polymorphisms (i.e., those with allele frequencies under 10%), while also oversampling for ADHD-related problems.

The purpose of the current study was to evaluate the impact of parental characteristics, including parental ADHD symptoms, parental neurocognitive function, and inconsistency in parental discipline on youth ADHD outcomes. Our specific goal was to evaluate whether the presence of multiple variants within the *DRD4* gene among both parents and children may moderate these associations and to test whether a multiplex family design may provide a feasible model for testing such relationships. We hypothesized that parental ADHD, parental neurocognitive function, and poor parenting dimensions would predict youth ADHD symptoms, and that those associations would indeed depend on variation within the *DRD4* gene among both parents and children. Specifically, we hypothesized that those parents and youth with more rare variants (which are hypothetically related to functional changes in the D4 protein) would evidence stronger associations between parental characteristics and child ADHD symptoms.

Method

Participants

Participants were children and their biological parents from 30 multiplex ADHD families (total $N = 114$). This included 66 youth (M age = 10.9 years, $SD = 2.5$, range 7–17 years, 63.6% male) and 48 adults (27 mothers, 21 fathers, M age = 41.9 years, $SD = 6.7$, range 29–69 years, 43.8% male). Families were recruited via newspaper advertisements, email listservs, and outreach to local child psychiatric and pediatric clinics in order to obtain as broad and as representative a sample as possible, while avoiding potential biases associated with a purely clinic-referred sample. A multi-stage, multi-informant assessment process was then used to identify eligible multiplex ADHD families. At stage one, families completed an initial eligibility screening online or via telephone. At this stage, families were deemed

eligible if they had (1) a history of ADHD (reported by a primary parent) in multiple members of their family, (2) at least one child between the ages of 8 and 14 years, and (3) at least three blood-related family members (i.e., full biological parents and siblings) that would be willing to participate in an in-person assessment. Additionally, all family members had to be fluent in English and have no history of intellectual disability, schizophrenia/psychosis, mania/bipolar disorder, autism spectrum disorder, or Tourette's syndrome. Of the 65 families that completed the screening, 40 were passed to stage two.

Following this initial screen, a telephone interview was completed at stage two with a primary parent to assess potential ADHD symptoms, diagnostic, and treatment history in all eligible family members. Primary parents provided yes/no ratings of five core ADHD symptoms deemed most predictive of subsequent diagnoses (Kessler et al. 2010) and answered questions about ADHD diagnostic and treatment history for each eligible family member. Each individual was considered for the ADHD group if they screened positive on at least three of the five ADHD symptoms and/or had a diagnostic and treatment history of ADHD. To be included in the in-person assessments, at least 50% of the family members identified as eligible to participate by the primary parent had to be above thresholds for potential inclusion in an ADHD group. Of the 40 families who completed this second stage of screening, 32 were deemed eligible to complete the in-person assessments at stages three and four.

At stage three, participating youth came to the laboratory with a primary parent to complete a diagnostic and neuropsychological evaluation. Diagnostic assessments of youth involved completion of a semi-structured interview with the primary parent and parent and teacher-report on a series of behavioral rating scales (about each child). Parents completed the ADHD, oppositional defiant disorder (ODD) and conduct disorder (CD) modules of the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-E, Puig-Antich and Ryan 1986) with a trained masters-level interviewer. Additionally, parents and teachers completed the ADHD Rating Scale (DuPaul et al. 1998), Conners-3 (Conners 2008), and ASEBA Child Behavior Checklist or Teacher Report Form (Achenbach and Rescorla 2001) about each participating child. While parents completed the diagnostic assessment, youth completed a testing battery assessing their intellectual and neurocognitive functioning (see below). Youth taking short-acting stimulant medications completed a wash-out for 24–48 h prior to the assessment ($M = 49.2$ h, $SD = 12.6$). Additionally, both parents and youth completed a series of questionnaires regarding parenting and family functioning.

Lastly, stage four involved in-person diagnostic and neuropsychological evaluations with each participating parent. This included administration of a semi-structured diagnostic interview to assess each parent's current and childhood symptoms of ADHD (Kessler et al. 2010), modeled after the Adult ADHD Clinical Diagnostic Scale (Adler and Cohen 2004). Following the diagnostic interview, parents completed the same neurocognitive testing battery as their children (see below) as well as rating scales assessing their broadband functioning (ASEBA Adult Self-Report, Achenbach and Rescorla 2001), their current and childhood ADHD symptoms (BAARS-IV, Barkley 2011a), their executive function deficits (Barkley Deficits in Executive Function Scale; BDEFS; Barkley 2011b), and impairment due to ADHD symptoms (Barkley Functional Impairment Scale, BFIS; Barkley 2011c).

Parents taking short-acting stimulant medications also completed a wash-out for 24–48 h prior to the assessment ($M = 51.2$ h, $SD = 14.4$). All participants also provided a saliva sample for DNA analyses via Oragene OG500 saliva collection kits (DNAGenotek) at stages three and four.

To determine final diagnostic status, all interview and rating scale data, including normed scores, were reviewed by the principal investigator (MAN). Inter-rater reliability was coded for a subset of interviews and was adequate for child reports of ADHD, ODD, and CD ($\kappa_s > 0.82$) and for parental self-report of current and childhood ADHD ($\kappa_s > 0.85$). For youth, both a current and a lifetime diagnosis was assigned for ADHD, ODD, and CD based on DSM-5 criteria and corroborating reports of cross-situational symptoms and impairment from both parents and teachers. Symptom counts were determined using an “or” algorithm for parent and teacher report of ADHD symptoms (i.e., a symptom is counted as present if endorsed by the parent or teacher, with no more than 3 unique symptoms per informant). For parents, childhood and current diagnoses were assigned based upon the appropriate symptom thresholds (6 for childhood, 5 for present functioning) from diagnostic interviews and behavioral rating scales. 30 families ($N = 114$ individuals, 66 youth and 48 parents) completed the stage 3 and 4 assessments. The final sample consisted of 50 youth (46% male) and 25 (76% male) parents meeting full DSM-5 criteria for ADHD (overall 75/114 family members with ADHD or 65.8% of the entire sample).

Measures

Neurocognitive Testing Battery—The neurocognitive testing battery employed was organized to capture multiple neuropsychological functions implicated in ADHD across a wide developmental range. Tests measured intellectual functioning, executive function performance including inhibition (Barkley 1997), working memory (Martinussen and Tannock 2006), and arousal (or activation; operationalized as signal detection sensitivity; Sergeant 2005). All participants (youth and their parents) completed the same battery of tests, which were administered in a fixed order. For the current study, we were particularly interested in parental neurocognitive function in the domains of response inhibition, working memory, and arousal, which correspond conceptually to the domains of neurocognitive impairments hypothesized to be relevant to intergenerational and interpersonal processes associated with the development of child self-regulation. These domains were assessed via the Stop-It task (response inhibition, Verbruggen et al. 2008), WISC-IV Digit Span (Wechsler 2008) and the Conners Continuous Performance Task (Conners 2000).

Parental Response Inhibition: Stop-it Task: Response inhibition was assessed via the Stop-It task (Verbruggen et al. 2008), based upon the original version by Logan (1994). During this choice reaction time task, participants saw either a circle or a square on a computer screen and were instructed to rapidly respond with the corresponding key on the keyboard (called Go Response trials). On 25% of trials, a tone sounded shortly after the shape (duration determined via a stochastic tracking procedure) was displayed, indicating that participant were to withhold their response. The task is presented in four blocks of 64 trials (one practice block and three test blocks) with adequate internal consistency ($\alpha = 0.88$ for non-ADHD participants, $\alpha = 0.85$ for ADHD participants). Several validity indices were

applied to each block of data, adapted from Nikolas and Nigg (2013). First, for a block to be considered valid, the probability of successfully stopping a response had to be between 25 and 75% (task aims for a 50% average stopping probability). Second, the hit rate percentage had to be above 90%, indicating that participants were engaged and correctly responding to the primary task. Lastly, reaction times within valid blocks were winsorized to be within ± 2.5 standard deviations of the mean. For a single participant's data to be included, they had to have at least one valid block of test trials (all parent participants had at least one valid block and the majority, 83%, had three valid blocks). Stop signal reaction time (SSRT), which indexes how much warning each participant needed to interrupt their prepotent response, was computed by subtracting the average stop signal delay from the average Go Response time; higher SSRT values indicated more impaired response inhibition.

Parental Working Memory: WISC-IV Digit Span: Working memory was assessed via the Digit Span subtest of the WISC-IV (Wechsler 2008). Participants complete three trials; forward, backward, and sequencing. On this task, participants are aurally presented with a sequence of digits and must repeat the digits back to the examiner. On the forward portion, participants repeated the digits exactly as presented; on the backward portion, participants repeated the digits in the reverse order of presentation; and on the sequencing portion, participants repeated the digits in chronological order from lowest to highest. Digit span backward is a commonly used index of verbal working memory and the raw score for trials correct served as the primary index of working memory in the analyses.

Parental Signal Detection (Arousal): Continuous Performance Task: The Conners' Continuous Performance Task (CPT), Version II (Conners 2000) was administered to assess vigilance and sustained attention. A series of letters rapidly appeared on the computer screen. Participants were instructed to press the spacebar on the keyboard with every letter presented, with the exception of the letter *X*. Stimuli were presented continuously for 14 min (across 4 quarters), with varying inter-stimulus intervals of 1 s, 2 s, or 4 s ($\alpha = 0.91$ for non-ADHD participants). Omission and commission errors were used to compute the *d*-prime value, which is a sensitivity index expressed in units of standard deviation. Higher *d*-prime scores reflect greater sensitivity in distinguishing the targets (all non *X*-letters) from the non-targets (*X* letters).

Parenting—Parents and youth completed the Alabama Parenting Questionnaire (APQ, Shelton et al. 1996). This 42-item scale assesses multiple dimensions of parenting relevant to ADHD and externalizing behaviors (Ellis and Nigg 2009). Past work has indicated that the APQ demonstrates adequate reliability (Ellis and Nigg 2009; Essau et al. 2006) and convergent validity, displaying significant overlap with parenting interview measures (Essau et al. 2006). The measure was completed by both parents and by children – parents completed a separate APQ for each participating child. Additionally, questions were read to children under the age of 12 in order to ensure comprehension of the items and completeness. The poor inconsistent discipline subscale from the APQ was of interest in the current study, as it has been previously associated with ADHD and externalizing spectrum psychopathology in youth (Ellis and Nigg 2009; Shelton et al. 1996; Ullsperger et al. 2016) and indexes the relevant construct of parental responsiveness and consistency. The

inconsistent discipline scale demonstrated adequate reliability for both youth ($\alpha = 0.73$) and parent report ($\alpha = 0.81$).

Gene Sequencing—DNA was isolated via saliva samples collected via the Oragene OG500 collection kit (DNA Genotek). DNA was first amplified via polymerase chain reaction; PCR reactions were incubated at 94 °C for 5 min followed by 35 amplification cycles (45 s at 94 °C, 45 s at 60 °C, 45 s at 72 °C) and a final extension at 72 °C for 7 min. Primers were designed to amplify the region containing the *DRD4* gene via Primer3. Primer sequences and optimal conditions are available from the author upon request. PCR products were sent for sequencing on an ABI 3730XL (Functional Biosciences). Chromatograms were transferred to a UNIX workstation, base-called with PHRED (v. 0961028), assembled with PHRAP (v. 0.970312), and viewed with the CONSED program (v. 4.0). Novel mutations were confirmed with sequencing in the reverse direction. Sequencing of *DRD4* resulted in approximately 86% coverage of the gene (Fig. 1). A large portion (715 base pairs) of *DRD4* was not sequenced due to the large simple tandem repeat occurring in exon III (also genotyped, but not included in the current report). In all, sequencing revealed 16 variants in this region. 12 were intronic variants, of which two were deletions and two were novel. Additionally, sequencing captured 2 known missense variants (G11R and V194G), 1 known frameshift deletion, and 1 novel synonymous variant. Variant frequencies in the current sample ranged from 0.09% to 37.3% (see Table 1 for details). For the purposes of this paper, each variant was classified as present or absent, such that those with one or two copies of the minor allele were distinguished from those homozygous for the major allele. A polygenic risk score was computed by summing the number of variants present for each individual (M number of variants = 2.2, $SD = 1.6$, range 0–6, see Table 1).

ADHD Symptom Measures—Youth ADHD symptom scores served as the primary outcome measures. Two scores were created for each child – one based on parental report on the symptom measures (ADHD Rating Scale and Conners 3) and one based on teacher report. Because of the low power to examine reports of child behavior separately by mothers and fathers, we created a mean parental composite for inattention and hyperactivity-impulsivity using both mother and father report (when both were available). Because within-informant correlations on the ADHD Rating Scale and Conners 3 were moderate for both parent report ($r = 0.49$, $p < 0.001$) and teacher report ($r = 0.42$, $p < 0.001$), we computed composites ADHD symptom scores by averaging standardized scores for both measures for each informant (i.e., a parental ADHD symptom score composite included mean standardized scores from the ADHD Rating Scale and the Conners 3). Both scales demonstrated good internal consistency for both informants (parent-report ADHD rating scale $\alpha = 0.95$, parent-report Conners 3 $\alpha = 0.92$; teacher report ADHD Rating scale $\alpha = 0.92$, teacher report Conners 3 $\alpha = 0.90$). Parental ADHD symptom scores were derived from self-report on the BAARS-IV (Barkley 2011a) current symptom scale, which demonstrated good internal consistency ($\alpha = 0.94$).

Measures for Supplementary Analyses—Prior recommendations for G×E work (Moffitt et al. 2005) have encouraged investigators to evaluate the robustness of any significant G×E findings in several ways. First, recommendations have suggested

substituting an alternative candidate environmental factor that was not conceptually hypothesized to interact with the genetic polymorphism(s) of interest (i.e., environments not anticipated to interact with rare variation across *DRD4*). Second, specificity of findings should be evaluated by examining related phenotypes as outcomes in G×E work. Lastly, interactions should be evaluated to determine if effects extend to variables not conceptually associated with the candidate gene or environment of interest, as a way of evaluating the possibility of spurious interactions within the data.

Alternative Candidate Environment: Family Recreation Activities: We elected to use both parental and child report on the family recreation activities scale from the Family Environment Scale (FES; Moos and Moos 2007) as an alternative candidate environment in our supplementary analyses. The FES consists of 90 statements requiring dichotomous (e.g., true/false) responses. The FES comprises 10 scales, each with 9 items; for our purposes, we elected to use the Active-Recreational scale, which indexes the degree to which family members regularly participate in recreational activities, as this was not hypothesized to interact with either parental or youth *DRD4* variants to predict youth ADHD symptoms. As with the APQ, we utilized both parent and child report, which each evidenced adequate internal consistency (parent report $\alpha = 0.86$, youth report $\alpha = 0.81$).

Evaluating Specificity: ODD and CD Symptoms: To evaluate specificity of G×E effects, our supplementary analyses also focused on examining G×E effects predicting related outcomes, including parent report and teacher report of both ODD and CD symptoms from the ADHD Rating Scale. Internal consistency was adequate for parental and teacher reports of both ODD (α parent = .89; α teacher = .90) and CD symptoms (α parent = .87; α teacher = .84).

Evaluating Spurious Interactions: Youth Word Reading: Recommendations for G×E work also suggest evaluating whether any significant G×E effects also predict another outcome variables that are not conceptually related to either the candidate gene or environment of interest. For this purpose, we elected to use child word reading score on the Wide Range of Achievement Test, 4th edition (Wilkinson and Robertson 2006), which has been demonstrated be a reliable and valid screening measure of academic achievement and is not hypothesized to be related to parental ADHD symptoms, parental neurocognitive functioning, or parental inconsistent discipline or variation in the *DRD4* gene.

Data Analytic Strategy

Bivariate correlations were first examined between parent and child symptoms, parent and child neurocognitive functioning, and parent and youth report of poor parenting dimensions. Primary analyses proceeded via generalized estimating equations (GEE), which is an extension of general linear model, but allows for examination of interactions between categorical, ordinal, and dimensional predictors with non-normal outcomes and with non-independent, nested data (as is the case in family studies, see Homish et al. 2010). To correct for the dependence of familial data, family number was entered as a repeated measure and the working correlation matrix was set to exchangeable. A series of GEE linear models was used to examine the main effects of our key predictors (parental ADHD symptoms, parental

neurocognitive function, poor parenting dimensions) on youth ADHD symptom scores as well as potential moderation of effects based on the number of both parental and youth *DRD4* variants. Because the effects of gene-environment correlation (rGE) can falsely emerge as G×E effects, we evaluated correlations between the number of parental and child *DRD4* variants and parental characteristics (e.g., ADHD symptoms, neurocognitive functioning, and inconsistent discipline). All correlations were not significantly different from zero (r s ranging from -0.10 to 0.11 , p s > 0.20). Further, because of our relatively small sample size as well as the exploratory nature of this sample, we also conducted a series of internal replication analyses by examining (1) both parent and teacher reports of ADHD symptoms as outcomes, (2) both response inhibition as well as arousal as indices of parental neurocognitive functioning, and (3) both youth and parent report of poor parenting dimensions as predictors.

In addition to these primary analyses, we also conducted secondary analyses to evaluate the robustness of any potential G×E effects. We did this by first substituting an alternative index of environmental exposure for which we had both youth and parent report (e.g., family recreational activity involvement from the Family Environment Scale) in place of our parental characteristics variables. We selected this variable as showed a small correlation with ADHD $r = -0.21$, $p = 0.04$), but is not a primary focus of our conceptual model, which posits that parental ADHD symptoms and impairments as well as associated problems with parenting impair critical input required for the adequate development of child self-regulation capabilities. Additionally, we evaluated other symptoms as outcomes in G×E models. First, we included parent and teacher report of other externalizing psychopathology (e.g., ODD and CD symptom scores assessed as part of the parent and teacher ADHD Rating scale). We also examined the robustness of models by evaluating a child outcome not hypothesized to be related to our model, child word reading score (assessed via the WRAT-4, Wilkinson and Robertson 2006).

Child sex and age were included as covariates in all models and stimulant medication use was covaried in analyses examining neurocognitive functioning and parenting measures as predictors. Associations are reported in terms of standardized b -values, along with 95% confidence intervals. Because of the small sample size and exploratory nature of the analyses, a false-discovery rate (FDR, Benjamini and Hochberg 1995) was used when evaluating multiple comparisons across informant, using a q -value of 0.05.

Results

Demographic and Descriptive Statistics

Demographic and descriptive statistics for the sample are presented in Table 2 for youth and parents. 75% of participating youth met criteria for ADHD, whereas just over 50% of participating parents met current or lifetime criteria for ADHD. There were also more males than females among participating youth, and rates of comorbid disruptive disorders among youth were also moderate. In contrast, there were slightly more mothers that participated than fathers. Families were predominately Caucasian and middle-class, which is consistent with demographics of the surrounding area.

Bivariate Correlations

Bivariate correlations are presented in Table 3. Parent ADHD symptoms were moderately correlated with youth ADHD symptoms; however, parental inattention was more strongly associated with youth inattention and parental hyperactivity-impulsivity was more strongly associated with youth hyperactivity-impulsivity. Parental neurocognitive functioning was also moderately associated with youth inattention. In regard to parenting, parental inattention was significantly correlated with youth reports of parental inconsistent discipline. Similarly, youth inattention was significantly correlated with parental reports of inconsistent discipline. Correlations between youth and parental neurocognitive functioning were also significant, as were parental and youth reports of parenting, although correlations were small in magnitude. However, the remaining analyses focus on parental ADHD symptoms, parental neurocognitive functioning (but not youth neurocognitive functioning), and youth and parent reports of parental inconsistent discipline as predictors of child ADHD symptoms.

Parental ADHD Symptoms

For our primary analyses, GEE were used to estimate the main effects of three classes of parental predictors (parental ADHD, parental neurocognitive functioning, and poor parenting dimensions) on child ADHD symptoms as well as the moderating effects of both youth and parent *DRD4* rare variants (sex and child age covaried). The nesting of family data was included in all models. Because our sample size is relatively small, we attempted to replicate findings by evaluating models using both parent and teacher reports of youth ADHD as outcomes. Results indicated that parental ADHD symptom scores were significantly associated with parent report of child ADHD symptoms, $b = 0.55$, 95% CI [0.08, 1.0], $p = 0.01$. However, this effect was moderated by the number of parental *DRD4* variants, $b = 0.19$, 95% CI [0.02, 0.36], $p = 0.01$, but not by the number of youth *DRD4* variants (see Table 4). We followed up this effect by examining correlations between parent and youth ADHD symptoms among parents with two or fewer *DRD4* variants compared to those with three or more *DRD4* variants (which represented the median and provided roughly equivalent cell sizes in each group). Findings indicated a small, but non-significant correlation between parental and youth ADHD symptoms for those with two or fewer parental *DRD4* variants, $r = 0.19$, $p = 0.29$, but a moderate and significant correlation between parental and youth ADHD symptoms for those with three or more parental *DRD4* variants, $r = 0.41$, $p = 0.03$. Notably, similar effects were found for teacher report of child ADHD symptoms. Parental ADHD symptom scores significantly predicted teacher-report of youth ADHD symptom scores, $b = 0.44$, 95% CI [0.06, 0.82], $p < 0.001$, an effect which was moderated by parental *DRD4* variants, $b = 0.14$, 95% CI [0.03, 0.26], $p = 0.01$. Further examination of this interaction indicated a moderate and significant correlation for those with 3 or more parental *DRD4* variants, $r = 0.31$, $p = 0.02$, but no significant correlation for those with two or fewer parental *DRD4* variants, $r = 0.17$, $p = 0.43$. Implementation of the FDR p -value (calculated at $p^* = 0.0333$; Benjamini and Hochberg 1995) indicated that both interaction effects survived corrections for multiple tests.

Parental Neurocognitive Functioning

Parental response inhibition (indexed via the stop-signal reaction time such that higher values indicate greater deficits) significantly predicted youth ADHD symptom scores, $b = 0.52$, 95% CI [0.14, 0.89], $p = 0.01$. Parental *DRD4* variants, but not youth *DRD4* variants, moderated this effect, $b = 0.17$, 95% CI [0.02, 0.32], $p = 0.04$, such that a stronger association emerged for those with three or more variants, $r = 0.49$, $p = 0.001$ compared to those with 2 or fewer parental *DRD4* variants, $r = 0.01$, $p = 0.58$. Similar effects were again found for teacher report of youth ADHD symptoms, such that the main effect of parental SSRT was significant, $b = 0.35$, 95% CI [0.03, 0.57], $p = 0.01$, as was the interaction between parental *DRD4* variants and parental SSRT, $b = 0.20$, 95% CI [0.04, 0.36], $p = 0.02$. Again, a stronger association emerged for those with three or more parental *DRD4* variants, $r = 0.43$, $p = 0.01$, compared to those with 2 or fewer, $r = 0.06$, $p = 0.66$. The corrected FDR p -value was $p = 0.025$, indicating that the main effects and the interaction predicting teacher report (but not the interaction predicting parent report) survived correction for multiple tests.

Parental working memory (indexed via the raw backward score on the WAIS-IV) predicted parent but not teacher reports of youth ADHD scores. A significant interaction emerged between parental working memory and parental *DRD4* variants, $b = -0.41$, 95% CI [-0.62, -0.20], $p < 0.001$. Again, a stronger association emerged for those with three or more parental *DRD4* variants, $r = 0.50$, $p < 0.001$, compared to those with 2 or fewer, $r = 0.15$, $p = 0.18$. In contrast, neither the main effect of parental working memory nor interactions involving child *DRD4* variants were significantly different from zero. The corrected FDR p -value was $p = 0.003$, indicating that the main effect and interaction predicting parent report survived correction for multiple tests.

Parental arousal (indexed via d -prime on the Conners Continuous Performance task, such that lower values indicate worse performance) did not statistically predict parent or teacher report of youth ADHD scores. However, a marginally significant interaction emerged between parental arousal and parental *DRD4* variants, $b = -0.35$, 95% CI [-0.57, -0.03], $p = 0.01$, when predicting parental report of youth ADHD. Again, effects were stronger for those with three or more parental *DRD4* variants, $r = -0.31$, $p = 0.03$, compared to those with two or fewer, $r = -0.03$, $p = 0.44$. Notably, however, this effect did not survive correction for multiple tests (see Table 4).

Parental Inconsistent Discipline

Both youth report and parental report of inconsistent discipline significantly predicted youth ADHD symptom scores, such that greater inconsistency of parental discipline was associated with increased symptomatology (see Table 5). However, youth *DRD4* variants moderated the effect of child-reported inconsistent discipline when examining both parent-report of ADHD symptoms, $b = 0.27$, 95% CI [0.06, .47], $p = 0.003$, and teacher report of ADHD symptoms, $b = 0.21$, 95% CI [0.002, 0.41], $p = 0.04$. Youth *DRD4* variants also moderated the effect parent-reported inconsistent discipline on parent, $b = 0.29$, 95% CI [0.10, 0.48], $p < 0.001$, and teacher reports of ADHD, $b = 0.26$, 95% CI [0.04, 0.48], $p = 0.01$. Results again revealed a stronger association between inconsistent discipline and

ADHD for those with three or more youth *DRD4* variants (parent report $r = 0.46$, $p < 0.001$; teacher report $r = 0.33$, $p = 0.005$) compared to those with two or fewer (parent report $r = 0.09$, $p = 0.24$; teacher report $r = 0.08$, $p = 0.51$). All three significant interactions survived correction for multiple tests, using the FDR corrected p -value of 0.018.

Supplementary Analyses

In line with recommendations for G×E work (Moffitt et al. 2005), we conducted follow-up analyses to evaluate the robustness of findings by first substituting an alternative candidate environmental factor that was not conceptually hypothesized to interact with *DRD4* (youth and parent report of family recreational activities from the Family Environment Scale). In all models, the interactions between parental *DRD4* variants and child *DRD4* variants and youth and parent report of family recreational activities were not significantly different from zero, all $ps > 0.21$. Next, we examined child ODD and CD symptoms as outcomes in G×E models to evaluate specificity of effects. All models involving interactions between parental *DRD4* variants and parental ADHD symptoms and parental neurocognitive functioning did not reveal any interactions that were significantly different from zero (all $ps > 0.32$). However, the interaction between child *DRD4* variants and parent-report of inconsistent discipline was significant in predicting parent report of ODD symptoms, $b = 0.25$, 95% CI [.01, 0.49], $p = 0.02$, again such that association between inconsistent discipline and ODD was stronger for those with three or more variants, $r = 0.39$, $p = 0.009$, compared to those with two or fewer, $r = -0.01$, $p = 0.85$. Interactions predicting CD symptoms were not significant. Similarly, we also examined child word reading as an outcome to determine if interactions extended to other variables that were not conceptually associated with parental ADHD characteristics or with variation within the *DRD4* gene (as a way of testing possibility of spurious interactions within the data). None of the parental characteristics significantly predicted child word reading, all $ps > 0.22$, and no interactions involving parent *DRD4* variants or child *DRD4* variants were significantly different from zero, all $ps > 0.49$.

Discussion

The current study set out to examine variation within the *DRD4* gene as a potential moderator of associations between parental characteristics and youth ADHD outcomes within a sample of multiplex families. Our exploratory findings indicated that parental *DRD4* variants moderated the associations between parental ADHD and neurocognitive function and child ADHD symptom scores. However, youth *DRD4* variants moderated the association between inconsistent discipline and child ADHD outcomes. In all cases, associations were stronger as the number of *DRD4* variants increased, indicating that variation within this gene, particularly among variants less common in the population, may be important for understanding the ways in which inputs from the environment, particularly parental influences, serve to shape ADHD outcomes in youth. While findings should be considered preliminary due to the small sample size, we implemented a set of replication tests by examining both parent and teacher report of ADHD outcomes, by implementing p -value corrections via FDR methods, and by evaluating other candidate environmental factors and outcomes that were not posited to be related to parental characteristics or variation within the *DRD4* gene.

While ours is one of the first studies to employ a multiplex family design to examine multiple genetic variants and their interaction with parental characteristics, findings are consistent with past work indicating potential interactive effects between genes involved in dopamine neurotransmission and parenting. Martel et al. (2011) previously reported G×E effects involving a variant in the promoter region of *DRD4* and inconsistent parenting in predicting inattentive ADHD symptoms. Similarly, Li and Lee (2012) documented interactions between the high-activity variant of the monoamine oxidase-A gene (MAO-A), a gene involved in dopamine degradation, and negative (but not positive) parenting dimensions in predicting ADHD inattentive symptoms among boys. Recent work has also extended G×E models to predict additional outcomes, with findings indicating that other psychosocial factors, including potential enriching environments (e.g., positive peer affiliation) may interact with *DRD4* variants to predict putamen volume (Richards et al. 2016). In line with this, G×E effects involving dopamine candidate genes have been extended to adults, such that the association between stressful life events and inattention severity among adults with ADHD was moderated by variation within *DRD4* (Sánchez-Mora et al. 2015). Thus, the current study adds to the growing body of work demonstrating that contextual factors that may influence the development and maintenance of self-regulation capabilities across development relevant to ADHD appear to depend on genetic liability to alterations in dopamine neurotransmission.

While findings from multiple samples using different designs and measurement methods have supported interactive effects between parenting and variation within the *DRD4* gene, it is important to note that parenting dimensions, both positive and negative, are likely not solely environmental. Past work has indicated that parenting dimensions are themselves influenced by genetic factors (Klahr and Burt 2014), which may manifest among parents via neurobiological influences on cognitive dysfunction, perhaps via deficits in executive functioning, self-regulation, and motivation among parents, which then, in turn impact their parenting behaviors (Johnston et al. 2012). In line with this, we also found evidence that parental response inhibition and parental ADHD symptoms were associated with poor parenting dimensions and with child ADHD outcomes. Notably, the impact of parental neurocognitive function and parental ADHD symptoms on child ADHD were moderated by *parental* variation in *DRD4*. Thus, future work in this area may benefit by examining the impact of parental psychopathology and parental neurocognitive function on youth outcomes as a function of both youth as well as parental genetic factors.

Detection of individual differences in neurobiological and neurocognitive functioning on parenting dimensions will be crucial for understanding how intergenerational transmission of ADHD may occur as well as for identifying novel intervention or prevention efforts. For example, it may become increasingly important to assess parental ADHD and neurocognitive functioning within the clinical context, given the potential impact these symptoms and impairments may have on parental responsiveness and parent-child communication. Given that the vast majority of clinical interventions for ADHD focus on parent management training, better characterization of how parental ADHD may influence the effectiveness of these treatments as well as identification of factors that may enhance treatment effects for parents with ADHD will likely remain crucial to efforts focused on improving treatment outcomes in youth with ADHD and externalizing psychopathology.

In addition, individual differences in child temperament also appear to influence parental behaviors (Klein et al. 2016). Such effects have been documented in very young children and have also shown to have lasting effects across development, which then serve to further exacerbate (or perhaps attenuate) youth behavioral and emotional problems (Barnett and Scaramella 2015). Additionally, there is some evidence that the impact of parenting on child behavior problems may be partially explained by effects of parenting on child temperament traits (Ullsperger et al. 2016). Future work will benefit from prospective, genetically-informed designs, which can then examine the independent, interactive, and reciprocal influences of parental and youth genetic and neurobiological factors, psychosocial stressors and enhancements (including both positive and negative parenting) on youth outcomes.

There are several noteworthy limitations to this work. First, our sample size was relatively small, which may have reduced our power for detecting effects, particularly moderation effects. As such, our findings should be considered exploratory and preliminary. Further, as with all genetic studies, findings need to be replicated, however, our findings are remarkably consistent with other larger G×E investigations involving variation in dopamine genes and parenting. We also evaluated findings using both parent and teacher reports of outcomes and managed issues with multiple testing via use of false-discovery rate methods to generate corrected *p*-values. Second, we relied on youth and parent report measures of parenting dimensions, which themselves may be biased, particularly among parents with ADHD (Lui et al. 2013). Third, we focused only on rare variants within the *DRD4* gene and elected not to include the commonly-genotyped variable number of tandem repeat polymorphism (VNTR) within exon III. Our future work plans to evaluate these variants in combination with the exon III VNTR. Fourth, our measure of parenting was based on parent and child reports. Future work would benefit by examining such associations with observational measures of parenting. Fifth, our polygenic risk score was largely based on allele frequency proportions and not on evidence of clear functional changes associated with particular genotypes. Future work should continue to explore the functional consequences of both rare and common variants on gene expression and efficiency of dopamine neurotransmission. Lastly, while multiplex families have been shown to be useful for identifying neurobiological influences on ADHD (Loo et al. 2010), future work should also elect to compare findings among multiplex and simplex families (as well as controls) to determine how genetic variation as well as parental and child characteristics co-segregate within families and interact together when predicting youth outcomes.

Overall, the current study adds to the growing body of literature indicating that the impact of parental characteristics on child ADHD symptoms varies depending on genetic variation among both parents and youth. Further, the study highlights the potential utility of a multiplex family design for examining whole-gene variation within candidate genes as well as associations between parent and child ADHD.

Acknowledgments

Funding This work was funded by the University of Iowa Institute for Clinical and Translational Science and CTSA Grant UL1RR024979 from the National Institutes of Health.

References

- Achenbach, T., Rescorla, L.A. Manual for the child behavior checklist and 2001 profile. Burlington: University of Vermont, Department of Psychiatry; 2001.
- Adler L, Cohen J. Diagnosis and evaluation of adults with attention deficit/hyperactivity disorder. *The Psychiatric Clinics of North America*. 2004; 27:187–201. [PubMed: 15063992]
- Agha SS, Zammit S, Thapar A, Langley K. Are parental ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD? *European Child & Adolescent Psychiatry*. 2013; 22:369–377. [PubMed: 23385540]
- Albrecht B, Brandeis D, Uebel-von Sandersleben H, Valko L, Heinrich H, Xu X, et al. Genetics of preparation and response control in ADHD: the role of DRD4 and DAT1. *Journal of Child Psychology and Psychiatry*. 2014; 55:914–923. [PubMed: 24521003]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th. Arlington: American Psychiatric Association Press; 2013.
- Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*. 1997; 121:65–94. [PubMed: 9000892]
- Barkley, RA. Barkley adult ADHD rating scale (BAARS-IV). New York: Guilford Press; 2011a.
- Barkley, RA. Barkley deficits in executive scale (BDEFS). New York: Guilford Press; 2011b.
- Barkley, RA. Barkley functional impairment scale (BFIS). New York: Guilford Press; 2011c.
- Barnett MA, Scaramella LV. Child fear reactivity and sex as moderators of links between parenting and preschool behavior problems. *Development and Psychopathology*. 2015; 27:1179–1190. [PubMed: 26439069]
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society*. 1995; 57:289–300.
- Burt SA. Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences. *Psychological Bulletin*. 2009; 135:608–637. DOI: 10.1037/a0015702 [PubMed: 19586164]
- Buschgens CJM, van Aken MAG, Swinkels SHN, Ormel J, Verhulst FC, Buitelaar JK. Externalizing behaviors in preadolescents: familial risk to externalizing behaviors and perceived parenting styles. *European Child & Adolescent Psychiatry*. 2010; 19:567–575. [PubMed: 20041337]
- Campbell SB, Shaw DS, Gilliom M. Early externalizing behavior problems: toddlers and preschoolers at risk for later maladjustment. *Development and Psychopathology*. 2000; 12:467–488. [PubMed: 11014748]
- Chang Z, Lichtenstein P, Asherson PJ, Larsson H. Developmental twin study of attention problems: high heritabilities throughout development. *JAMA Psychiatry*. 2013; 70:311–318. [PubMed: 23303526]
- Conners, CK. Manual for the Conners continuous performance test. 2nd. Toronto: Multi-Health Systems; 2000.
- Conners, CK. Conners rating scale. 3rd. Toronto: Multi-Health Systems; 2008.
- Deater-Deckard K. Family matters: intergenerational and interpersonal processes of executive function and attentive behavior. *Current Directions in Psychological Science*. 2014; 23:230–236. [PubMed: 25197171]
- Deater-Deckard K, Sewell MD, Petrill SA, Thompson LA. Maternal working memory and reactive negativity in parenting. *Psychological Science*. 2010; 21:75–79. [PubMed: 20424026]
- Deault LC. A systematic review of parenting in relation to the development of comorbidities and functional impairments in children with attention-deficit/hyperactivity disorder (ADHD). *Child Psychiatry and Human Development*. 2010; 41(2):168–192. [PubMed: 19768532]
- DuPaul, GJ., Power, TJ., Anastopoulos, AD., Reid, R. ADHD rating scale—IV: checklists, norms, and clinical interpretation. New York: Guilford Press; 1998.
- Ellis B, Nigg J. Parenting practices and attention-deficit/hyperactivity disorder: new findings suggest partial specificity of effects. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009; 48:146–154. [PubMed: 19065110]

- Essau CA, Sasagawa S, Frick PJ. Psychometric properties of the Alabama parenting questionnaire. *Journal of Child and Family Studies*. 2006; 15:595–614.
- Faraone SV, Biederman J. Is attention deficit hyperactivity disorder familial? *Harvard Review of Psychiatry*. 1994; 1:271–287. [PubMed: 9384859]
- Fay-Stammbach T, Hawes DJ, Meredith P. Parenting influences on executive function in early childhood: a review. *Child Development Perspectives*. 2014; 8:258–264.
- Gilsbach S, Neufang S, Scherag S, Vloet TD, Fink GR, Herpertz-Dahlmann B, Konrad K. Effects of the DRD4 genotype on neural networks associated with executive functions in children and adolescents. *Developmental Cognitive Neuroscience*. 2012; 2:417–427. [PubMed: 22727763]
- Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. *Human Genetics*. 2009; 126:51–90. [PubMed: 19506906]
- Goos LM, Crosbie J, Payne S, Schachar R. Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. *The American Journal of Psychiatry*. 2009; 166:711–717. [PubMed: 19448185]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *The American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Halperin JM, Healey DM. The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: can we alter the developmental trajectory of ADHD? *Neuroscience and Biobehavioral Reviews*. 2011; 35:621–634. [PubMed: 20691725]
- Harold GT, Leve LD, Barrett D, Elam K, Neiderhiser JM, Natsuaki MN, et al. Biological and rearing mother influences on child ADHD symptoms: revisiting the developmental interface between nature and nurture. *Journal of Child Psychology and Psychiatry*. 2013; 54:1038–1046. [PubMed: 24007415]
- Heath CL, Curtis DF, Fan W, McPherson R. The association between parenting stress, parenting self-efficacy, and the clinical significance of child ADHD symptom change following behavior therapy. *Child Psychiatry and Human Development*. 2014; 46(1):118–129.
- Homish GG, Edwards EP, Eiden RD, Leonard KE. Analyzing family data: a GEE approach for substance use researchers. *Addictive Behaviors*. 2010; 35:558–563. DOI: 10.1016/j.addbeh.2010.01.002 [PubMed: 20163918]
- Jester JM, Nigg JT, Puttler LI, Long JC, Fitzgerald HE, Zucker RA. Intergenerational transmission of neuropsychological executive functioning. *Brain and Cognition*. 2009; 70:145–153. [PubMed: 19243871]
- Johnston C, Mash EJ. Families of children with attention-deficit/hyperactivity disorder: review and recommendations for future research. *Clinical Child and Family Psychology Review*. 2001; 4:183–207. [PubMed: 11783738]
- Johnston C, Mash EJ, Miller N, Ninowski JE. Parenting in adults with attention-deficit/hyperactivity disorder (ADHD). *Clinical Psychology Review*. 2012; 32:215–228. [PubMed: 22459785]
- Johnston C, Williamson D, Noyes A, Stewart K, Weiss MD. Parent and child ADHD symptoms in relation to parental attitudes and parenting: testing the similarity-fit hypothesis. *Journal of Clinical Child and Adolescent Psychology*. 2016:1–10.
- Kamradt JM, Nigg JT, Friderici KH, Nikolas MA. Neuropsychological performance measures as intermediate phenotypes for attention-deficit/hyperactivity disorder: a multiple mediation analysis. *Development and Psychopathology*. 2016; :1–14. DOI: 10.1017/S0954579416000195
- Kessler RC, Green JG, Adler LA, Barkley RA, Chatterji S, Faraone SV, et al. Structure and diagnosis of adult attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 2010; 67:1168–1178. [PubMed: 21041618]
- Klahr AM, Burt SA. Elucidating the etiology of individual differences in parenting: a meta-analysis of behavioral genetic research. *Psychological Bulletin*. 2014; 140:544–586. [PubMed: 24016230]
- Klein MR, Lengua LJ, Thompson SF, Moran L, Ruberry EJ, Kiff C, Zalewski M. Bidirectional relations between temperament and parenting predicting preschool-age Children's adjustment. *Journal of Clinical Child and Adolescent Psychology*. 2016; :1–14. DOI: 10.1080/15374416.2016.1169537

- Kochanska G, Kim S. A complex interplay among the parent-child relationship, effortful control, and internalized, rule-compatible conduct in young children: evidence from two studies. *Developmental Psychology*. 2014; 50:8–21. [PubMed: 23527491]
- Leibson CL, Katusic SK, Barbaresi WJ, Ransom J, O'Brien PC. Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. *JAMA*. 2001; 285:60–66. [PubMed: 11150110]
- Li JJ, Lee SS. Association of positive and negative parenting behavior with childhood ADHD: interactions with offspring monoamine oxidase a (MAO-A) genotype. *Journal of Abnormal Child Psychology*. 2012; 40:165–175. [PubMed: 21826446]
- Logan, GD. A user's guide to the stop signal paradigm. In: Dagenbach, D., Carr, TH., editors. *Inhibitory processes inattention, memory, and language*. San Diego: Academic Press; 1994. p. 189–239.
- Loo SK, Hale ST, Hanada G, Macion J, Shrestha A, McGough JJ, et al. Familial clustering and DRD4 effects on electroencephalogram measures in multiplex families with attention deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:368–377. [PubMed: 20410729]
- Lui JHL, Johnston C, Lee CM, Lee-Flynn SC. Parental ADHD symptoms and self-reports of positive parenting. *Journal of Consulting and Clinical Psychology*. 2013; 81:988–998. [PubMed: 23796318]
- Martel MM, Nikolas M, Jernigan K, Friderici K, Waldman I, Nigg JT. The dopamine receptor D4 gene (DRD4) moderates family environmental effects on ADHD. *Journal of Abnormal Child Psychology*. 2011; 39:1–10. [PubMed: 20644990]
- Martinussen R, Tannock R. Working memory impairments in children with attention-deficit hyperactivity disorder with and without comorbid language learning disorders. *Journal of Clinical and Experimental Neuropsychology*. 2006; 28:1073–1094. [PubMed: 16840237]
- Moffitt TE, Caspi A, Rutter M. Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*. 2005; 62:473–481. [PubMed: 15867100]
- Mooney MA, McWeeney SK, Faraone SV, Hinney A, Hebebrand J, IMAGE2 Consortium. et al. Pathway analysis in attention deficit hyperactivity disorder: an ensemble approach. *American Journal of Medical Genetics Part B, Neuropsychiatric Genetics*. 2016; doi: 10.1002/ajmg.b.32446
- Moos, RH., Moos, BS. *Family environment scale*. 4th. Menlo Park: Mind Garden; 2007.
- Nigg JT, Swanson JM, Hinshaw SP. Covert visual spatial attention in boys with attention deficit hyperactivity disorder: lateral effects, methylphenidate response and results for parents. *Neuropsychologia*. 1997; 35:165–176. [PubMed: 9025120]
- Nigg JT, Blaskey LG, Stawicki JA, Sachek J. Evaluating the endophenotype model of ADHD neuropsychological deficit: results for parents and siblings of children with ADHD combined and inattentive subtypes. *Journal of Abnormal Psychology*. 2004; 113:614–625. [PubMed: 15535793]
- Nigg, JT., Hinshaw, SP., Huang-Pollock, C. Disorders of attention and impulse regulation. In: Cicchetti, D., Cohen, DJ., editors. *Developmental psychopathology, volume 3: risk, disorder, and adaptation*. 2nd. Hoboken: Wiley; 2006. p. 358–403.
- Nigg J, Nikolas M, Burt SA. Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:863–873. [PubMed: 20732623]
- Nikolas MA, Burt SA. Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: a meta-analysis. *Journal of Abnormal Psychology*. 2010; 119:1–17. [PubMed: 20141238]
- Nikolas MA, Nigg JT. Neuropsychological performance and attention-deficit hyperactivity disorder subtypes and symptom dimensions. *Neuropsychology*. 2013; 27:107–120. [PubMed: 23148496]
- Nikolas MA, Nigg JT. Moderators of neuropsychological mechanism in attention-deficit hyperactivity disorder. *Journal of Abnormal Child Psychology*. 2015; 43:271–281. [PubMed: 25037459]
- Pelham WE, Foster EM, Robb JA. The economic impact of attention deficit/hyperactivity disorder in children and adolescents. *Journal of Pediatric Psychology*. 2007; 32:711–727. [PubMed: 17556402]

- Posner, MI., Fan, J. Attention as an organ system. In: Pomerantz, JR., editor. *Topics in Intergrative Neuroscience*. New York: Cambridge University Press; 2005. p. 31-61.
- Posner MI, Rothbart MK. Toward a physical basis of attention and self regulation. *Physics of Life Reviews*. 2009; 6:103. [PubMed: 20161073]
- Posner MI, Rothbart MK, Sheese BE, Tang Y. The anterior cingulate gyrus and the mechanism of self-regulation. *Cognitive, Affective & Behavioral Neuroscience*. 2007; 7:391–395.
- Puig-Antich, J., Ryan, N. *Kiddie schedule for affective disorders and schizophrenia*. Pittsburgh: Western Psychiatric Institute; 1986.
- Purcell S. Variance components models for gene-environment interaction in twin analysis. *Twin Research*. 2002; 5:554–571. [PubMed: 12573187]
- Richards JS, Arias Vásquez A, Franke B, Hoekstra PJ, Heslenfeld DJ, Oosterlaan J, et al. Developmentally sensitive interaction effects of genes and the social environment on total and sub-cortical brain volumes. *PloS One*. 2016; 11:e0155755. [PubMed: 27218681]
- Sánchez-Mora C, Richarte V, García-Martínez I, Pagerols M, Corrales M, Bosch R, et al. Dopamine receptor DRD4 gene and stressful life events in persistent attention deficit hyperactivity disorder. *Neuropsychiatric Genetics: American Journal of Medical Genetics*. 2015; Part B. doi: 10.1002/ajmg.b.32340
- Sergeant JA. Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. *Biological Psychiatry*. 2005; 57:1248–1255. [PubMed: 15949995]
- Shelton KK, Frick PJ, Wootton J. Assessment of parenting practices in families of elementary school-age children. *Journal of Clinical Child Psychology*. 1996; 25:317–329.
- Smith HJ, Kryski KR, Sheikh HI, Singh SM, Hayden EP. The role of parenting and dopamine D4 receptor gene polymorphisms in children's inhibitory control. *Developmental Science*. 2013; 16:515–530. [PubMed: 23786470]
- Thissen AJAM, Rommelse NNJ, Altink ME, Oosterlaan J, Buitelaar JK. Parent-of-origin effects in ADHD: distinct influences of paternal and maternal ADHD on neuropsychological functioning in offspring. *Journal of Attention Disorders*. 2014; 18:521–531. [PubMed: 22628139]
- Tung I, Brammer WA, Li JJ, Lee SS. Parenting behavior mediates the intergenerational Association of Parent and Child Offspring ADHD symptoms. *Journal of Clinical Child and Adolescent Psychology*. 2015; 44:787–799. [PubMed: 24926775]
- Ullsperger JM, Nigg JT, Nikolas MA. Does child temperament play a role in the association between parenting practices and child attention deficit/hyperactivity disorder? *Journal of Abnormal Child Psychology*. 2016; 44:167–178. [PubMed: 25684446]
- van Lieshout M, Luman M, Twisk JWR, van Ewijk H, Groenman AP, Thissen AJAM, et al. A 6-year follow-up of a large European cohort of children with attention-deficit/hyperactivity disorder-combined subtype: outcomes in late adolescence and young adulthood. *European Child & Adolescent Psychiatry*. 2016; 25:1007–1017. [PubMed: 26837866]
- Verbruggen F, Logan GD, Stevens MA. STOP-IT: windows executable software for the stop-signal paradigm. *Behavior Research Methods*. 2008; 40:479–483. [PubMed: 18522058]
- Wechsler, D. *Manual for the Wechsler adult intelligence scale*. 4th. San Antonio: Pearson; 2008.
- Wilkinson, GS., Robertson, GJ. *Wide Range Achievement Test*. 4th. Lutz: Psychological Assessment Resources; 2006.
- Zelazo, PD. Developmental psychology: a new synthesis. In: Zelazo, PD., editor. *The Oxford handbook of developmental psychology, Body and mind*. Vol. 1. New York: Oxford University Press; 2013. p. 3-12.

Fig. 1. Sequencing coverage of DRD4

Note. Red bars represent the regions sequenced, blue bars and lines represent DRD4 exons and introns, respectively, and black bars represent Simple Tandem Repeats

Table 1

DRD4 sequencing variant information and frequencies in youth and parents

Variant	Description	Location	Minor Allele Frequency
rs 146,680,769	Intronic (C > T)	chr11: 637,294	5.4
rs 189,482,961 (G11R)	Missense (G > C)	chr11: 637,335	5.6
rs 554,375,713	Frameshift deletion (CCGCCACCTCCT/-)	chr11: 637, 357–637,549	2.8
rs752306	Intronic (C > T)	chr11: 637,622	9.7
rs 72,844,728	Intronic (G > A)	chr11: 637,933	37.3
rs 531,064,346	Intronic deletion (ACAC/-)	chr11: 638,987–638,990	26.9
rs 72,844,729	Intronic (C > T)	chr11: 638, 098	2.9
rs 72,844,730	Intronic (A > G)	chr11: 638,165	0.9
rs 189,353,842	Intronic (C > T)	chr11: 638,194	3.9
rs 559,464,313	Intronic (A > G)	chr11: 638,633	1.9
rs 556,789,901	Intronic deletion (A/-)	chr11: 639,085–693,090	27.8
Novel	Intronic deletion (C/-)	chr11: 639,111	27.3
Novel	Intronic (C > G)	chr11: 639, 241	4.5
rs 7,124,601	Intronic (C > A)	chr11: 639,273	32.7
rs 1,800,443 (V194G)	Missense (T > G)	chr11: 639,830	4.1
Novel G232G	Synonymous (C > G)	chr11: 639,945	3.9.

rs = reference SNP number, chr = chromosome. Location number reflects base pair position

Table 2

Demographic and descriptive statistics for youth and parents

	Youth	Parents
N	66	48
% Male	63.6	41.7
% Caucasian	84.8	85.4
Age (years)	10.9 (2.5)	41.9 (6.7)
Income (median range)+	—	50–75
% Stimulant Medication	56.1	16.7
Full Scale IQ	106.6 (12.1)	111.3 (14.9)
Inattention Symptoms	6.6 (2.5)	4.1 (3.0)
Hyperactivity-Impulsivity Symptoms	3.9 (3.1)	2.4 (2.4)
% ADHD	75.8	52.1
% ODD	48.5	—
% CD	15.2	—
Stop Signal RT (ms)	291.5 (72.9)	274.2 (51.7)
d' -prime	0.18 (0.36)	0.61 (0.48)
Digit Span Backward Raw Score	7.2 (1.6)	9.1 (2.2)
# <i>DRD4</i> variants	3.6 (2.4)	2.3 (1.6)
Inconsistent Discipline	13.2 (4.1)	14.6 (3.9)
Family Recreational Activities	6.2 (2.1)	6.6 (2.3)
Word Reading Score	99.6 (14.3)	103.2 (15.7)

Parenthetical values are standard deviations. Inattention and hyperactivity-impulsivity symptoms as well as diagnoses are based on “or” algorithm counts derived from KSADS-E interview and parent and teacher questionnaires. d' -prime is coded in units of standard deviations, such that higher scores reflect better discrimination of targets from non-targets. IQ = intelligence quotient, ODD = oppositional defiant disorder, CD = conduct disorder, RT = reaction time. + Income is reported in thousands of U.S. dollars. Parental ODD and CD were not included as part of the diagnostic assessment. Youth values of inconsistent discipline and family recreational activities are raw scores and are based on their report of parents, whereas parent values are also raw scores and based on parent report

Table 3

Bivariate correlations between parent and youth symptom scores, neurocognitive functioning, and poor parenting dimensions

Parent Variables						
Child Variables	Inatt	Hyper	SSRT	d-prime	Digit Span	Discipline
<i>Inatt</i>	0.48 ^{**}	0.11	0.23 [*]	-0.14	0.23 [*]	0.25 [*]
<i>Hyper</i>	0.16 ⁺	0.30 ^{**}	0.20 [*]	-0.12	0.06	0.10
<i>SSRT</i>	0.21 [*]	0.20 [*]	0.33 ^{**}	-0.17	0.17	0.21
<i>d-prime</i>	-0.18 ⁺	-0.10	-0.16	0.24 [*]	0.10	0.17
<i>Digit span</i>	-0.20 [*]	-0.19 [*]	-0.18 ⁺	0.20 [*]	0.17 ⁺	-0.22 [*]
<i>Discipline</i>	0.26 [*]	0.12	0.21 [*]	0.07	-0.21 [*]	0.29 [*]

⁺ $p < 0.10$,

^{*} $p < 0.05$,

^{**} $p < 0.01$.

Inatt = inattention, Hyper = hyperactivity-impulsivity, SSRT = parent stop-signal reaction time, Digit Span = Digit Span Backward raw score, Discipline = Inconsistent Discipline. Bolded values indicate correlation between parents and youth on same measure

Table 4

Parenting dimensions and DRD4 variants as predictors of youth ADHD symptom dimensions

	Outcome	
	Child ADHD (Parent Report)	Child ADHD (Teacher Report)
<i>Parental ADHD Symptoms</i>		
Parental ADHD	0.55 ** (0.08, 1.0)	0.44 ** (0.06, 0.82)
Child <i>DRD4</i> × Parental ADHD	0.07 (−0.05, 0.19)	0.03 (−0.20, 0.26)
Parent <i>DRD4</i> × Parental ADHD	0.19 * (0.02, 0.36)	0.14 * (0.03, 0.26)
<i>Parental Neurocognitive Functioning</i>		
Response Inhibition (SSRT)	0.52 ** (0.14, 0.89)	0.35 ** (0.03, 0.57)
Child <i>DRD4</i> × Response Inhibition	0.03 (−0.18, 0.24)	0.01 (−0.22, 0.24)
Parent <i>DRD4</i> × Response Inhibition	0.17 * (0.02, 0.32)	0.20 * (0.04, 0.36)
Working Memory (SSRT)	−0.59 ** (−1.02, −0.16)	0.28 (−0.10, 0.66)
Child <i>DRD4</i> × Working Memory	0.02 (−0.26, 0.30)	−0.01 (−0.42, 0.40)
Parent <i>DRD4</i> × Working Memory	−0.41 ** (−0.62, 0.20)	0.08 (−0.16, 0.32)
Arousal (<i>d</i> -prime)	−0.08 (−0.02, 0.18)	−0.06 (−0.05, 0.17)
Child <i>DRD4</i> × Arousal	−0.02 (−0.26, 0.22)	−0.004 (−0.10, 0.11)
Parent <i>DRD4</i> × Arousal	−0.15+ (−0.006, 0.30)	−0.10 (−0.02, 0.12)

*
 $p < 0.05$,**
 $p < 0.01$ .Values are standardized *b* estimates from generalized estimating equations, with parentheses representing the 95% confidence interval

Table 5

Parenting dimensions and DRD4 variants as predictors of youth ADHD symptom dimensions

	Outcome	
	Child ADHD (Parent Report)	Child ADHD (Teacher Report)
Youth Report of Parenting		
Inconsistent Discipline	0.37 (0.11,0.67)	0.30 ** (0.14, 0.46)
Child <i>DRD4</i> × Inconsistent Discipline	0.27 ** (0.06, 0.47)	0.21 * (0.002, 0.41)
Parent <i>DRD4</i> × Inconsistent Discipline	0.04 (−0.11, 0.19)	0.01 (−0.24, 0.26)
Parent Report of Parenting		
Inconsistent Discipline	0.39 ** (0.14, 0.64)	0.28 * (0.06, 0.50)
Child <i>DRD4</i> × Inconsistent Discipline	0.29 ** (0.10, 0.48)	0.26 * (0.04, 0.48)
Parent <i>DRD4</i> × Inconsistent Discipline	0.09+(0.002, 0.19)	0.03 (−0.11, 0.17)

*
 $p < 0.05$,**
 $p < 0.01$ .Values are standardized b estimates from generalized estimating equations, with parentheses representing the 95% confidence interval