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Diversity in Pathways to Common Childhood Disruptive Behavior Disorders

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Abstract

Oppositional-Defiant Disorder (ODD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are highly comorbid, a phenomenon thought to be due to shared etiological factors and mechanisms. Little work has attempted to chart multiple-level-of-analysis pathways (i.e., simultaneously including biological, environmental, and trait influences) to ODD and ADHD, the goal of the present investigation. 559 children/adolescents (325 boys) between the ages of 6 and 18 participated in a multi-stage, comprehensive diagnostic procedure. 148 were classified as ODD; 309 were classified as ADHD, based on parent, teacher, and clinician ratings. Children provided buccal or salivary samples of DNA, assayed for select markers in *DRD4* and *5HTT*. Parents completed the Alabama Parenting Questionnaire and the California Q-Sort. Children completed the Child Perception of Interparental Conflict Scale. Correlational associations consistent with multiple-level-of-analysis pathways to ODD and ADHD emerged. For ODD, children with the short allele of the *5HTT* promoter polymorphism had higher neuroticism and ODD symptoms regardless of level of self-blame in relation to inter-parental conflict, whereas children without this allele had more ODD symptoms only in the context of more self-blame for inter-parental conflict. For ADHD (and ODD), children homozygous for the long allele of *DRD4* 120bp insertion polymorphism had lower conscientiousness when exposed to inconsistent parenting, whereas children without this genotype were more resilient to effects of inconsistent discipline on conscientiousness. Thus, ODD and ADHD appear to demonstrate somewhat distinct correlational associations between etiological factors and mechanisms consistent with pathway models using a multiple-level-of-analysis approach.

Keywords

disruptive behavior disorders; ODD; ADHD; mediation; gene by environment interaction

Oppositional-Defiant Disorder (ODD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are common and impairing problems (Barkley, 2003; Campbell et al., 2006; Costello et al., 2003). For this reason, much research has focused on identifying the etiology and within-child mechanisms, or markers, that increase risk for these disorders. Commonly comorbid, ODD and ADHD co-occur in nearly fifty percent of cases (Angold, Costello, & Erkanli, 1999; Willcutt et al., in press). In line with this clinical phenomenology, it has become apparent that these childhood disruptive behavior disorders (DBD) share some common etiological and mechanistic factors, while at the same time having their own unique influences (Burt et al., 2005b; Coolidge, Thede, & Young, 2000; Tuvblad et al., 2009; Waldman et al., 2001). Lacking have been integrated models utilizing a multiple-level of analysis approach that simultaneously incorporates biological, environmental, and psychological influences to characterize the distinction and overlap of these conditions.

ODD, a behavioral disorder characterized by symptoms of angry/irritable mood, defiant and headstrong behavior, and vindictiveness (APA, 2000; Stringaris & Goodman, 2009), affects approximately ten percent of children (Angold, Costello, & Erkanli, 1999; Costello et al., 2003). ODD is associated with increased risk for other forms of psychopathology, including other DBDs, as well as mood and/or anxiety problems (Kerr, Lunkenheimer, & Olson, 2007; Lavigne et al., 2001; Pihlakoski et al., 2006). ODD, like other DBDs, is associated with later impairments in school and social functioning, even after accounting for other forms of psychopathology (Campbell et al., 2006; Spira & Fischel, 2005). Children with ODD often have conflictual family relations and low verbal intelligence compared to typically developing children (Speltz, McClellan, DeKlyen, & Jones, 1999).

ADHD, a developmental behavioral disorder characterized by symptoms of inattention, hyperactivity, and impulsivity (APA, 2000), as well as the personality trait of low conscientiousness (Martel & Nigg, 2006), affects approximately five percent of school-age children (Angold, Costello, & Erkanli, 1999; Costello et al., 2003). Despite improvement over time in some children, ADHD is substantially stable into adolescence and adulthood (Lahey & Willcutt, 2010) and is associated with increased risk for other forms of psychopathology, particularly other DBDs like ODD, as well as anxiety and mood problems (Biederman et al., 2006; Chronis-Tuscano et al., 2010; Kerr, Lunkenheimer, & Olson, 2007; Pihlakoski et al., 2006; von Stauffenberg & Campbell, 2007). Besides the general risks associated with all DBDs discussed above, ADHD is associated with poorer literacy skills and academic underachievement, more problematic interactions with peers, and increased medical and health risks (Barkley, 2003; Lahey et al., 1998; Spira & Fischel, 2005).

Based on their high comorbidity, it is not surprising that ODD and ADHD share several multifactorial etiological influences. Notably, these shared processes have involved both environmental and genetic/biological indicators of liability. Many aspects of the family environment have been associated with both ODD and ADHD (Bates, Pettit, Dodge, & Ridge, 1998; Campbell, Shaw, & Gillion, 2000; Denham et al., 2000; Pfiffner, McBurnett,

Rathouz, & Judice, 2005; Patterson et al., 1989; reviewed by Rothbaum & Weisz, 1994). Key among these are factors associated with family conflict (e.g., inter-parental conflict, coercive cycles, lack of warmth) and parental use of discipline such as inconsistent use of discipline (e.g., Burt et al., 2005a; Ellis & Nigg, 2009; Rothbaum & Weisz, 1994). Further, both ODD and ADHD appear to involve disruptions in amine functioning, particularly in frontal-striatal dopaminergic circuits and in ascending serotonergic circuits (Beauchaine, Hinshaw, & Pang, 2010). Supporting that conceptualization, candidate gene studies have confirmed that polymorphisms influencing transcription of genes involved in serotonergic and dopaminergic neurotransmission systems are risk factors for both ODD and ADHD (Burt & Mikolajewski, 2008; Faraone et al., 2005; Waldman & Gizer, 2006). Further, high neuroticism and low conscientiousness characterize children at risk for DBDs, including ODD and ADHD (Lahey et al., 2008; Martel & Nigg, 2006).

However, differential associations between etiological and mechanistic factors and ODD and ADHD have also been noted (Burt et al., 2005b; Coolidge, Thede, & Young, 2000; Jester et al., 2005; Waldman et al., 2001). High conflict family environments including influences such as high inter-parental conflict, coercive cycles, and low warmth parent-child relations may be more specifically associated with ODD as compared with ADHD (Katz & Gottman, 1993; Kochanska & Murray, 2000; Patterson, DeBaryshe, & Ramsey, 1989), whereas consistency of parenting may be particularly associated with ADHD (Ellis & Nigg, 2008; Martel et al., 2011; Nigg, Nikolas, & Burt, 2010). Further, genetic polymorphisms influencing serotonin neurotransmission may be more specifically associated with ODD (and Conduct Disorder) than ADHD, whereas genetic polymorphisms influencing dopamine neurotransmission appear to be more specifically associated with ADHD rather than ODD after controlling for symptom covariation (Faraone, 2005; Nikolas et al., under review; Waldman & Gizer, 2006). Likewise, from a personality perspective, high neuroticism appears to be more specifically associated with ODD, whereas low conscientiousness may be more specifically associated with ADHD (Martel & Nigg, 2006; Nigg et al., 2002; Pennington & Ozonoff, 1996). Thus, we can propose a partial dissociation in developmental risk, with ADHD somewhat more associated with dopaminergic dysfunction, poor effortful and/or cognitive regulation, and inconsistent parenting, whereas ODD may be somewhat more associated with serotonergic dysfunction, emotional dysregulation, and conflictual family environments, perhaps particularly children's self-blame associated with parental conflict.

Theoretically-Driven Multi-Level Pathways for ODD and ADHD

To evaluate such a proposal, it would be preferable to simultaneously examine variation in dopamine and serotonergic functioning, cognitive and emotional regulation, and the family environment of children with ODD and ADHD. Such studies, however, remain in short supply. Most prior literature has only included one or two of these three levels of analysis. For example, most work to date has focused on the relationship of ODD or ADHD to traits (e.g., Martel & Nigg, 2006), or genetics (e.g., Burt & Mikolajewski, 2008; Nikolas et al., under review), or family environmental factors (e.g., Ellis & Nigg, 2009; Patterson et al., 1989). Although a one- or two-levels-of-analysis approach is a good starting point for establishment of etiology/mechanism associations with psychopathology, such work is

necessarily limited in its ability to allow for a more nuanced and integrated picture of pathways to various forms of psychopathology. Based on work to date and available theory of the development of ODD and ADHD, specific multiple-level pathways to these disorders, simultaneously incorporating biological, environmental, and psychological influences, can now be hypothesized and correlational structure can begin to be characterized.

Empirical work beginning to trace more complex pathways to ODD suggests the importance of interactions between environmental and genetic influences. Particular genetic regions, such as the region associated with polymorphisms such as the 44-bp promoter polymorphism of the serotonin transporter gene (5HTTLPR), may influence sensitivity to adverse environmental events in children (Belsky & Pluess, 2009; Caspi et al., 2003; 2010; Kochanska, Philibert, & Barry, 2009), as well as adults (Karg, Burmeister, Shedden, & Sen, 2011). Specifically, youth with the “short” allele of 5HTTLPR exhibit reduced transcription efficiency, leading to reduced serotonin transporter protein and lower serotonin reuptake via programmatic genetic influences on the development of the serotonin system (see Greenberg et al., 1999; Kobiella et al., 2011; Lesch et al., 1996). In turn, children with this allele have increased problems with behavioral and emotional regulation when faced with environmental adversity (Caspi et al., 2010; Karg, Burmeister, Shedden, & Sen, 2011). Negative affective interactions between parents and between parent and child, including coercive cycles, low responsiveness, and children’s self-blame for inter-parental conflict seem to be the types of environmental adversity that are particularly important for the later development of ODD (Burke, Pardini, & Loeber, 2008; Kochanska, Philibert, & Barry, 2009; Lahey, Moffitt, & Caspi, 2003; Patterson, DeBaryshe, & Ramsey, 1989). Past theoretical and empirical work has indicated that youth appraisals of inter-parental conflict (rather than frequency or intensity of conflict) are the proximal processes by which conflict impacts youth behavior problems (Grych & Fincham, 1990). Further, past work has indicated that the topics of inter-parental disputes are differentially related to children’s reactions and behaviors, such that conflict regarding the child is linked to greater behavioral dysregulation than are other sources of inter-parental conflict (e.g., financial concerns, Cummings & Davies, 2002). Theoretically, self-blame associated with inter-parental conflict seems to predispose children to adopt a negative interpersonal style that then characterizes their interactions with others and may increase dispositional traits like neuroticism (Martel et al., 2010; Lengua, 2005; Pergamin-Hight, Bakersman-Kranenburg, van IJzendoorn, & Bar-Haim, in press). High neuroticism may, in turn, increase risk for the later development of ODD (Stringaris & Goodman, 2009; Tackett, 2006; Watson et al., 2006), serving as a useful early developmental phenotype of the disorder (Martel, 2009; Sonuga-Barke & Halperin, 2011). Thus, a theoretically multiple-level pathway to ODD might begin with 5HTTLPR influencing disruptions with serotonergic neurotransmission. These biological changes may then function to make children more susceptible to self-blame associated with inter-parental conflict-based parenting, which in turn lead to increases in neuroticism and subsequent ODD. Finding a correlational structure consistent with this possibility would be helpful for determining its plausibility.

In regard to ADHD, research indicates that ADHD is highly heritable. Meta-analysis of genetic association studies of ADHD implicates genes influencing dopaminergic neurotransmission. Perhaps the most widely studied marker of dopamine function is the

dopamine D4 receptor (*DRD4*), which has polymorphisms that are reliably associated with the disorder and that influences dopaminergic neurotransmission (Faraone et al., 2005; McCracken et al., 2000; Waldman & Gizer, 2006) since it is highly expressed in the prefrontal cortex. Several polymorphic regions of the gene, including a 120 bp promoter polymorphism, as well as a variable number of tandem repeat polymorphism (VNTR) in exon III, have been associated with ADHD (Gizer, Ficks, & Waldman, 2009). Recent research and meta-analysis suggests that consistency of parenting may moderate the relationship between *DRD4* and ADHD such that homozygosity for the *DRD4* promoter 120-bp tandem repeat insertion allele increases vulnerability for ADHD and ODD only in the presence of inconsistent parenting (Nigg, Nikolas, & Burt, 2010; Martel et al., 2010; Sonuga-Barke et al., 2009). Further, child traits like low conscientiousness are influenced by parenting (Lengua, 2005; van den Akker et al., 2010), have been associated with ADHD (Martel & Nigg, 2006; Parker, Majeski, & Collin, 2004), and mediate genetic influences on ADHD (Martel et al., 2010), suggesting that they may be useful developmental phenotypes of the disorder (Sonuga-Barke & Halperin, 2010). Thus, genes influencing dopaminergic neurotransmission may interact with negative environmental socialization influences such as inconsistent parenting that would then lead to decreases in childrens' conscientiousness which, in turn, leads to the manifestation of ADHD symptomatology.

Preliminary work utilizing a multiple-level-of-analysis approach has begun to provide some support for these pathway models via evaluation of gene by environment interactions (Martel et al., 2011; Nikolas et al., 2010; Sonuga-Barke et al., 2009) and trait mediation of gene-DBD associations (Martel et al., 2010). Such work suggests that family processes are more or less strongly associated with ADHD symptoms depending on *DRD4* genotype (Martel et al., 2011; Sonuga-Barke et al., 2009) and that inter-parental conflict interacts with the serotonin transporter promoter polymorphism (5HTTLPR) to predict ADHD symptoms (Nikolas et al., 2010). Further, temperament traits like neuroticism and conscientiousness appear to statistically mediate the associations between genetic risk or susceptibility and ADHD and ODD symptoms (Martel et al., 2010). Thus, these hypothesized multiple-level-of-analysis pathway models have garnered some preliminary support and appear promising with respect to describing childhood ODD and ADHD.

What remains unclear is whether a theoretically-driven multiple-level-of-analysis approach can clarify distinctions between ODD versus ADHD by evaluating whether the correlational structure among genetic alleles, environmental influences, and traits are consistent with pathway models. Although research has suggested some specificity of associations between etiology and mechanisms associated with ODD versus ADHD, these remain poorly validated and somewhat speculative. A multiple-level-of-analysis approach may shed light on specificity of associations with ODD and ADHD by suggesting distinctive pathways for ODD versus ADHD at more nuanced levels of analysis. That is, genes and environments may interact in partially distinguishable and specific ways in the development of ODD versus ADHD with differential effects on the within-child mechanisms of personality traits.

The goal of the current study was to further assess the utility of a multiple-level-of-analysis approach to evaluating specificity of pathways to ODD and ADHD using cross-sectional data to determine whether the correlational structure is consistent with pathway models

before investment in longitudinal study. It was hypothesized that (a) interactions between genetic alleles and parenting and (b) that pathways between etiological environmental and genetic factors and DBD would be mediated by within-child trait mechanisms for both ODD and ADHD, or moderated mediation. Specifically, based on prior work (Martel et al., 2010; Martel et al., 2011; Nikolas et al., 2010; Patterson et al., 1989; Sonuga-Barke et al., 2009), it was predicted that 5HTTLPR genotype would interact with child self-blame for inter-parental conflict to predict ODD symptoms, and that high levels of neuroticism would mediate the effects of this interaction on ODD symptoms. In regard to ADHD, it was predicted that *DRD4* promoter polymorphism genotype would interact with inconsistent parenting to predict ADHD symptoms and that low levels of conscientiousness would mediate the effects of this interaction on ADHD symptoms. Lastly, it was predicted that these sets of associations would be at least partially specific to ODD and ADHD.

METHOD

Participants

Overview—Participants were 559 children (325 boys) between the ages of six and 18 years ($M=11.5$, $SD=2.89$). Children were initially included in one of two groups: those classified as meeting DSM-IV criteria for ADHD ($n=309$) and non-ADHD comparison youth ($n=217$). Thirty-three additional children who were classified as having situational or sub-threshold ADHD (did not meet criteria for either ADHD or non-ADHD comparison group as explained below), were included to provide more complete coverage of the dimensional trait space of both personality and ADHD (Haslam et al., 2006; Levy, Hay, McStephen, Wood, & Waldman, 1997). The ADHD group included (a) 119 ADHD-Predominantly Inattentive type (ADHD-PI; these youth met DSM-IV criteria for six or more inattentive symptoms, plus impairment, onset, and duration, and in addition appeared by parent structured interview to have never in the past met criteria for combined type), (b) 1 ADHD-Predominantly Hyperactive-Impulsive type (ADHD-PHI; i.e., met criteria for six or more hyperactive-impulsive symptoms, plus impairment, onset, and duration, and never in the past met criteria for combined type), and (c) 189 ADHD-Combined type (ADHD-C; i.e., met criteria for six or more inattentive symptoms and six or more hyperactive-impulsive symptoms, plus impairment, onset, and duration). 148 children met DSM-IV criteria for Oppositional-Defiant Disorder (ODD); of these, 82% of children with ODD were also classified as ADHD (see Table 1). 43 additional children were subthreshold for ODD, but were included in analyses for a more continuous distribution of ODD symptoms. Children came from 447 families; 335 families had one child in the study, and 112 families had two children in the study. All parents and children completed informed consent, in conformity with local IRB, NIH, and APA ethical guidelines. Descriptive statistics for the entire sample are presented in Table 1.

Recruitment and Identification—In order to avoid the potential inferential bias that can result from identifying cases only through clinic referred cases (Berkson, 1946), a broad community-based recruitment strategy was used, with mass mailings to parents in local school districts and public advertisements, as well as fliers at local clinics. Families who initially volunteered then passed through a standard multi-gate screening process to establish

diagnostic groupings. At Stage 1, all families were screened by phone to rule out youth prescribed long-acting psychotropic medication for ADHD or other conditions (e.g., antidepressants, Strattera, Atomoxetine), neurological impairments, seizure history, head injury with loss of consciousness, other major medical conditions, or a prior diagnosis of mental retardation or autistic disorder. Prescription of psychostimulant medication was not an exclusionary criteria.

At Stage 2, parents and teachers of remaining eligible youth completed standardized rating scales, and parents completed a structured clinical interview to ascertain symptom presence, duration, and impairment. Children completed an IQ screen (a three- or four-subtest short form of the WISC-III or WISC-IV, Wechsler, 1991; 2003) and achievement testing. They had to have estimated full Scale IQ of greater than or equal to 75 for inclusion.

The diagnostic interview used depended on the year of data collection. For participants who participated between 1997 and 2001 ($N=218$), the Diagnostic Interview Schedule for Children (*DISC-IV*; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was completed with the parent by telephone or during on-campus visits with a trained interviewer. For participants who participated from 2002 to 2008, youth and their primary caregiver completed the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-E; Puig-Antich & Ryan, 1986), and the data from the interviews and parent and teacher rating scales were presented to a clinical diagnostic team consisting of a board certified child psychiatrist and licensed clinical child psychologist. Pooling the data across families that received the KSADS and the DISC was justified based on our analysis of agreement between the two methods in 430 youth (including some who were screened out for the study for other reasons) for whom a parent completed both a KSADS and a DISC-IV ADHD module. The two interviews agreed adequately for total number of symptoms (inattention, $ICC=.88$; hyperactivity, $ICC=.86$), presence of six or more symptoms of ADHD ($kappa=.79$), and presence of ADHD (defined as six or more symptoms + cross situational impairment; $kappa=.79$). Thus, it seemed that similar cases of ADHD were being identified using both methods, and that they could be pooled.

ODD Diagnosis and ODD and ADHD Symptoms—The structured diagnostic interview was used for establishing the presence of ODD based on *DSM-IV* criteria. ADHD and ODD symptom counts were obtained via separate parent and teacher report on the ADHD Rating Scale (DuPaul, Power, Anastopolous, & Reid, 1998) and the Swanson, Nolan, & Pelham Rating Scale-Fourth Edition (SNAP-IV; Swanson, 1992), symptom checklists that are routinely used in children and adults. Teacher-rated symptoms were utilized as the primary dependent variable in the current study to eliminate the potential confound of shared method variance between symptoms and parent-rated parenting style and personality traits.

Measures

Parenting—Parents completed the Alabama Parenting Questionnaire, a 42-item self-report questionnaire on parenting practices that was developed to assess parenting of children between preschool and adolescence (Cornell & Frick, 2007; Essau, Sasagawa, & Frick,

2006). Each item is rated on a Likert scale from one (never) to five (always). The scale assesses six domains: involvement, positive parenting, poor monitoring/supervision, inconsistent discipline, corporal punishment, and other discipline practices. These subscales exhibit satisfactory reliability (Ellis & Nigg, 2009; Essau, Sasagawa, & Frick, 2006), as well as satisfactory convergent validity, exhibiting significant correlations with conduct problems and interviews about parenting (Essau et al., 2006). Internal consistency in the current study was .74 for the six-item inconsistent parenting scale (e.g., “you let your child out of a punishment early;” “you threaten to punish your child and then do not do it;” Essau et al., 2006). This scale was emphasized in the current study based on our prior finding (Ellis & Nigg, 2009) demonstrating its association with ADHD.

Child Perception of Inter-parental Conflict—Children completed the Children’s Perception of Inter-parental Conflict Scale (CPIC; Grych, Seid, & Fincham, 1992), a measure devised for use with school-age children and early adolescents. The measure was completed with a staff person while the parent was absent. They were instructed to complete the measure in regard to the most familiar current relationship between parents or parental figures. Thus, the child could rate two parents living in the home, whether both biological parents ($n=348$) or a biological parent and a partner ($n=73$), or co-parents who were living apart if the child often observed their interactions ($n=114$). The CPIC consists of 48 items rated on a three-point scale. Recent factor analytic empirical validation of the scale items in the current sample and a cross-validation sample indicated that the instrument’s variance is best summarized in samples of this type by four latent factors: threat to self (6 items), conflict properties (11 items), triangulation/stability (13 items), and self-blame (9 items; e.g., “my parents usually argue because of things that I do;” “it’s usually my fault when my parents argue;” Nigg et al., 2009). In the current study, these were treated as manifest variables by summing the items to create each scale (after appropriate reversal of negatively-worded items). Child self-blame for inter-parental conflict was emphasized in the current study based on results by Counts et al. (2005) which found that children’s self blame (in that study, using the closely related original self blame scale suggested by Grych et al., 1990) was independently associated with both ADHD symptoms and DBD, after controlling for other associated risk factors, as well as due to theoretical considerations that a child’s perception of conflict may be more important than the objective measurement of conflict (Cummings & Davies, 2002; Grych & Fincham, 1990; Munroe, 2008). Importantly, behavioral genetic research indicates that non-shared environmental factors accounted for the majority of the variance (i.e., 72%) in self-blame appraisals (Nikolas, Klump, & Burt, 2012). This scale demonstrated adequate internal reliability ($\alpha=.81$) in the current data set.

Personality Traits—Parents completed the California Child Q-Sort (CCQ), specifically the common language version (Caspi et al., 1992), as a rating of children’s dispositional traits. The CCQ is a typical Q-Sort consisting of 100 cards which must be placed in a forced-choice, nine-category, rectangular distribution. The rater (in this case, the mother) describes the child by placing descriptive cards in one of the categories, ranging from one (least descriptive) to nine (most descriptive). To measure the Big Five Factors, scales developed for use with children and adolescents (John et al., 1994) were used. A composite score was generated by reverse-scoring selected items and computing the average. Scale

reliabilities were all above .70. Since item overlap between personality traits (specifically conscientiousness) and symptom scales could affect results, potential overlap among these measures was evaluated by independent judges based on conceptual similarity of items; agreement was 95 percent. In order to avoid the potential confound that could result from overlapping items, the three items that were judged to be overlapping between the conscientiousness scale and inattentive ADHD symptoms were removed from the conscientiousness scale. Reliability remained acceptable ($\alpha=.77$).

Genotyping—Buccal and salivary DNA samples were obtained from participating children. DNA samples were purified using a method by Meulenbelt (1995). The *DRD4* 120-bp tandem repeat polymorphism was assayed according to the method of McCracken et al. (2000) with only minor modifications to the amplification parameters. *DRD4* genotype was coded into two groups. Children with the short/short and long/short genotypes were coded as “low-susceptibility.” Children homozygous for the long allele were coded as “high susceptibility” based on prior reports of over-transmission of this genotype to ADHD (McCracken et al., 2000). The 44-bp promoter polymorphism of the serotonin transporter gene (5HTTLPR) was genotyped as follows. The “short” and “long” alleles of the 5HTTLPR were genotyped according to previous methodology (Lesch et al., 1996) with the following modifications to the primer sets (5'-GACTGAGCTGGACAACCACG-3' and 5'-GGTTGCCGCTCTGAATGCCA-3'). Genomic DNA was amplified in similar fashion as described above, with the substitution of *Taq* DNA Polymerase kit (Qiagen Inc., Valencia, CA), using standard kit protocol, including 1.5 mM $MgCl_2$, 0.2 mM dNTPs, Q Solution, and 0.7 μ M primer. PCR conditions utilized an annealing temperature of 63°C and a 45 second extension time. Genotypes were analyzed using a 2% agarose gel. The final products were 528 bp (long) and 484 bp (short). Based on prior work (e.g., Caspi et al., 2003), presence of the short allele of *5HTT* (s/s or l/s) was coded as “high susceptibility” with homozygosity of the long allele of *5HTT* coded as “low susceptibility.” Genotype frequencies were consistent with previous reports (see McCracken et al., 2000). When Mendelian errors were examined in 467 parent-child trios, only four errors (0.9%) were encountered. No significant deviations from the Hardy-Weinberg Equilibrium were detected for neither the *DRD4* or 5HTTLPR polymorphisms ($p>.78$; these analyses were conducted for the control group only so as to detect differences in the absence of expected associations).

Data Analysis

Missingness in the current study was minimal, or less than 5% for all key variables, and statistical power was adequate (.80) to detect small to medium effects ($d=.32$). Confirmatory mediation analyses were conducted in accordance with the stepwise procedures advocated by Baron and Kenny (1986) and using the powerful, state-of-the art bootstrapping approach recommended by Preacher, Rucker, and Hayes (2007) and MacKinnon and Fairchild (2009). Briefly, first, we assessed whether associations in individual pathways of the proposed models were significant using regression analyses, in line with Baron and Kenny's (1986) recommendations. Then, we utilized the Preacher, Rucker, & Hayes (2007) bootstrapping approach to mediation as a test of indirect effects. This method, available through an on-line macro that can run through SPSS (PASW) 18, provides an estimate of indirect effects and their significance using z-statistics generated from multiple resamples of the data set, a

procedure which increases estimate precision and statistical power. In addition, the macro calculates conditional indirect effects, or moderated mediation (and mediated moderation; i.e., indirect effects and pathway estimates that are conditional on a moderating variable) using *t*-statistics, followed by bootstrapped estimates and significance tests at specific levels of the moderator variable (see Preacher, Rucker, & Hayes, 2007 for more information). This strategy controls for gene-environment correlations by controlling for main effects and collinearity between variables (Cohen, Cohen, West, & Aiken, 2003). Since two sets of moderated mediation models were tested, significant associations between variables are not interpreted unless $p < .025$ (.05/2). Main analyses controlled for the possible confounding influences of inclusion of non-independent data, child age, child sex, and family income. In addition, ADHD models utilized the revised, non-overlapping conscientiousness scale described above.

RESULTS

Descriptive Statistics

As can be seen in Table 1, the ADHD, ODD, and ADHD+ODD group were younger and had a higher proportion of boys compared to the non-ADHD/ODD comparison group (both $p < .05$). As expected, children with ADHD, ODD, and ADHD+ODD exhibited high neuroticism and lower conscientiousness than non-ADHD/ODD comparison children ($p < .01$). In addition, per parental report, children in the clinical groups were exposed to higher levels of inconsistent parenting, and – based on their own report—they exhibited higher levels of self blame associated with inter-parental conflict (both $p < .01$). In contrast, there were no significant differences in the percentage of 5HTTLPR short alleles and *DRD4* promoter polymorphism long alleles in children with ADHD/ODD and those without (all $p > .10$). This is consistent with previous variability of findings regarding the main effect associations between specific candidate gene polymorphisms and ADHD (Faraone et al., 2005).

Initial bivariate correlations between environmental factors (i.e., inconsistent parenting and self-blame associated with inter-parental conflict), child personality traits (i.e., neuroticism and conscientiousness), and ODD and ADHD symptom counts were in the expected direction with more environmental risk and less adaptive personality traits (higher neuroticism and lower conscientiousness) associated with more ODD and ADHD symptoms (all $p < .01$; shown in Table 2). Thus, mediational analyses were pursued. As is possible with moderating variables, genetic susceptibility did not exhibit significant associations with ODD or ADHD symptoms. However, 5HTTLPR and *DRD4* promoter polymorphism genotypes were retained for examination as possible moderators of mediational pathways.

ODD Complex Pathway

Building on prior work, theory, and preliminary associations in our own data, neuroticism was examined as a possible mediator of the association between child self-blame in relation to inter-parental conflict and teacher-rated child ODD symptoms using hierarchical multiple regression and moderated mediation macros developed by Preacher, Rucker, and Hayes (2007) and controlling for child sex, child age, and non-independent data (i.e., siblings), as

dictated by significant differences between diagnostic groups in Table 1. Consistent with expectations, higher levels of child self blame for inter-parental conflict was significantly associated with higher neuroticism ($\beta=.14, p=.001$) and more ODD symptoms ($\beta=.14, p=.002$), and higher neuroticism was associated with increased ODD symptoms ($\beta=.26, p=.001$). As shown in Figure 1, when neuroticism was placed in the full mediational model, the pathway between child self-blame for inter-parental conflict and ODD symptoms dropped significantly (from $\beta=.14, p=.002$ to $\beta=.10, p=.02$), suggesting significant partial mediation (bootstrap $z=2.24, p=.03$).

Next, 5HTTLPR genotype was examined as moderator of mediational pathways. 5HTTLPR genotype significantly moderated the direct pathway between child self-blame for inter-parental conflict and ODD symptoms ($t=-2.03, p=.04$), but none of the other pathways (all $p>.9$). Specifically, for those homozygous for the long allele of 5HTTLPR, the pathway between child self-blame and ODD symptoms was significant ($\beta=.25, p=.001$). However, for those with one or two copies of the 5HTTLPR short allele, the pathway between child self-blame for inter-parental conflict and ODD symptoms was not significant ($\beta=.05, p=.36$). Overall, whereas children with the low-functioning polymorphisms of 5HTTLPR appeared predisposed to follow an indirect path from high self-blame in relation to inter-parental conflict through high neuroticism to high ODD symptoms, children with the high functioning form of 5HTTLPR (i.e., those homozygous for the long allele) appeared more likely to follow a direct path from high self-blame for inter-parental conflict to increased ODD symptoms.

Specificity of Model to ODD

When specificity of the model to ODD was checked by covarying ADHD symptoms, mediation and moderated mediation became marginally significant (bootstrap $z=1.6, p=.11$; $t=-1.71, p=.09$). However, when examining the model in relation to ADHD symptoms as an outcome, both mediation and moderated mediation became nonsignificant (bootstrap $z=1.32, p=.19$; $t=-.05, p=.96$). Thus, despite the moderate overlap between ADHD and ODD symptoms ($r=.42, p<.01$), the complex pathway involving 5HTTLPR, neuroticism, and self-blame appeared to be somewhat specific to ODD.

ADHD Complex Pathway

Again, building on prior work, theory, and preliminary associations in our own data, conscientiousness was examined as a possible mediator of the association between inconsistent parental discipline and teacher-rated child ADHD in the same manner as above and controlling for child sex, child age, family income, and nested data, as well as using the non-overlapping conscientiousness scale. Inconsistent parental discipline was significantly associated with lower child conscientiousness ($\beta=-.24, p=.001$) and more ADHD symptoms ($\beta=.21, p=.001$), and lower conscientiousness was significantly associated with more ADHD symptoms ($\beta=-.53, p=.001$). As shown in Figure 2, when conscientiousness was placed in the full mediational model, the pathway between inconsistent discipline and ADHD symptoms dropped significantly (from $\beta=.21, p=.001$ to $\beta=.08, p=.04$), suggesting significant partial mediation (bootstrap $z=3.56, p=.0004$).

Next, *DRD4* genotype was examined as moderator of mediational pathways. *DRD4* genotype significantly moderated the direct pathway between inconsistent discipline and conscientiousness ($t = -1.92, p = .05$), but none of the other pathways (all $p > .5$). Specifically, for those homozygous for the long allele of the *DRD4* 120 bp promoter polymorphism, the pathway between inconsistent discipline and low conscientiousness was significantly stronger compared to those with one or no copies of the long allele (*DRD4* long allele homozygotes: $\beta = -.30, p = .001$; *DRD4* 0 or 1 copies of long allele: $\beta = -.18, p = .01$). Overall, whereas homozygote children appeared more likely to exhibit low conscientiousness when exposed to inconsistent parenting, children without this *DRD4* genotype appeared somewhat more resilient to effects of inconsistent discipline on conscientiousness.

Specificity of Model to ADHD

When specificity of the model to ADHD was checked by covarying ODD symptoms, mediation held (bootstrap $z = 2.83, p = .005$), but moderated mediation did not ($t = -2.69, p = .09$). Further, when the model was examined with ODD as an outcome, mediation and moderated mediation were significant (bootstrap $z = 2.05, p = .04$; $t = -1.9, p = .05$), suggesting that this model was not specific to ADHD, but rather generalized across ADHD and ODD.

DISCUSSION

Although ODD and ADHD share many etiological and mechanistic influences, they are also characterized by unique influences. The current paper examined whether use of a theoretically-driven multiple-level-of-analysis approach might elucidate correlational associations consistent with distinct pathways to ODD and ADHD in a cross-sectional sample. Results revealed somewhat distinct associations for ODD and ADHD. For ODD symptoms, children homozygous for the long, high-functioning allele of 5HTTLPR exhibited increased ODD symptoms when they experienced high self-blame in relation to inter-parental conflict, whereas those children with one or more copies of the low-functioning short allele of 5HTTLPR appeared predisposed to follow an indirect route from high self-blame in relation to inter-parental conflict to ODD symptoms through high neuroticism. For ADHD, children homozygous for the long allele of the *DRD4* promoter appeared more likely to exhibit low conscientiousness when exposed to inconsistent parenting, whereas children without this *DRD4* genotype appeared somewhat more resilient to effects of inconsistent discipline on conscientiousness. This second model, however, was not entirely specific to ADHD as a similar model was supported in relation to ODD.

Largely in line study hypotheses (Martel et al., 2010; Nikolas et al., 2010), high child self-blame interacted with 5HTTLPR genotype to predict ODD symptoms, and this effect was partially accounted for by high levels of neuroticism. Children with the low-functioning short allele of 5HTTLPR appeared to exhibit high neuroticism and high ODD symptoms when exposed to environmental factors like inter-parental conflict. In contrast, children homozygous for the long allele of 5HTTLPR appeared more likely to follow a direct path from high self-blame in relation to inter-parental conflict to increased ODD symptoms without mediating effects of high neuroticism. These results support previous work in the notion that functional variation in 5HTTLPR may be differentially related to ODD (vs.

ADHD), such that those with the low-functioning allele display greater biological vulnerability for developing psychopathology (via effects on neuroticism), whereas those with high-functioning allele may require exposure to some type of environmental adversity in order to develop ODD (or other psychopathology; Caspi et al., 2010; Pergamin-Hight et al., in press). One possible implication of this finding is that, cognitive-behavioral treatment might be particularly efficacious for youth with the high-functioning 5HTTLPR long allele, particularly if it includes a component addressing child self-blame associated with inter-parental conflict.

The complex pathway to ADHD was also in line with theory, prior work, and study hypotheses (Martel et al., 2010; Martel et al., 2011; Sonuga-Barke et al., 2009). *DRD4* genetic risk or susceptibility interacted with inconsistent discipline to be significantly related to low conscientiousness, and low conscientiousness partially accounted for the pathway between this gene by environment interaction and ADHD symptoms. The association between inconsistent parenting and conscientiousness was stronger for those homozygous for the long allele of the *DRD4* promoter polymorphism, suggesting that these individuals were more vulnerable to, or even differentially susceptible to, the effects of inconsistent parenting on conscientiousness (Belsky et al., 2009).

However, the pathway was not entirely specific to ADHD. For ODD, there was also a significant interaction between *DRD4* genotype and inconsistent parenting in relation to low conscientiousness. Thus, the complex pathway to ADHD was not specific to ADHD, but rather seemed to generalize to ODD. These finding could be seen as consistent with a spectrum model of trait-psychopathology relations (Watson, Kotov, & Gamez, 2006). Extreme traits may serve as a marker of risk for ADHD and ODD, and low conscientiousness may be more general to childhood DBD including ODD and ADHD, consistent with Krueger's (2002) finding of a shared disinhibition factor associated with externalizing disorders in adults. Of course, more work, particularly longitudinal work, is needed on this topic.

The current findings suggest the utility of current evidence-based behavioral treatments for ADHD and ODD (Barkley, 2006; Eyberg, Nelson, & Boggs, 2008) that include a parenting component. Based on current study results, increasing consistency of parenting might be important for both children with and without genetic susceptibility. Of course, this is likely to be particularly important for ADHD, a highly heritable disorder (Faraone et al., 2005; Waldman & Gizer, 2006), due to the fact that parents with ADHD may be particularly likely to have difficulty being consistent with parenting practices. A second important treatment component, particularly for children with ODD, or ODD+ADHD, might be cognitive-behavioral treatment addressing child self-blame for interparental conflict. Furthermore, future longitudinal studies examining multi-level pathways for ADHD and ODD can aid in identification of common and specific causal processes operating for each disorder. Identification of these causal mechanisms then has great potential to inform novel treatment and prevention strategies.

Of course, the current results should be considered in light of study limitations. The current study was cross-sectional. Thus, the pathway models examined in the current model are only

illustrative. Since these types of pathway models appeared promising based on this cross-sectional data, future longitudinal research validating these types of pathway models will be important for establishing temporal ordering (e.g., it is just as possible that child neuroticism increases children's responsivity to conflictual parenting practices as vice versa), as well as for evaluating more complex models that allow for bidirectionality of influences (e.g., between neuroticism and self-blame for inter-parental conflict; between neuroticism and ODD). The current study utilized a community-recruited sample of children with ADHD. While this study design is strong in that it avoids clinical sample selection bias (Berkson, 1946), other kinds of selection bias are possible based on recruitment procedures and exclusionary criteria; therefore, the generalizability of study results is, of course, not known until results can be validated by replication in other kinds of samples (e.g., clinical and general population samples). Further, replication using a sample of children selected for ODD would help ensure that current results are not related to sampling or recruitment strategy or to relatively few cases of "pure" ODD which was a study limitation. Although multiple types of measures were utilized (e.g., biological assays, teacher report of symptoms, parent and child report of environmental variables), replication with other types of measurement approaches would be useful. For example, observational coding of parenting consistency and child personality traits might provide important information, even though they are found to correlate with parent-report measures (Forman et al., 2003; Kochanska, Murray, & Harlan, 2000). Child self blame for interparental conflict might be considered a family effect or a child personality effect; yet, initial behavioral genetic work examining self-blame specifically showed that non-shared environmental factors accounted for the majority of the variance (i.e., 72%) in self-blame appraisals (Nikolas, Klump, & Burt, 2012). In addition, it should be noted that parenting has a genetic component in addition to being an environmental influence on the child (Kendler & Baker, 2007), although any gene-environment correlation effects involving 5HTTLPR and *DRD4* were controlled for in the current study. Further, other genes beside the candidate genes examined in the current study might exert important effects on pathways due to the multifactorial nature of the etiology of these disorders; this is an important direction for future work. This includes the recently discovered third variant of 5HTTLPR, which initial evidence suggests has been found to change the functionality of the polymorphism. Finally, although no completely distinct pathway to ADHD was found in the present study, it is likely that other pathways are evident, and this is an important direction for future work.

In summary, the current study evaluated the utility of a multiple-level-of-analysis approach for evaluation of distinct influences on ODD and ADHD. Results revealed somewhat distinct etiological and mechanistic factors associated with ODD and ADHD. For ODD, children without the short allele of the 5HTTLPR promoter polymorphism appeared more likely to exhibit increased ODD symptoms when they experienced high self-blame for inter-parental conflict, whereas those children with at least one copy of the short allele of 5HTTLPR appeared to experience high neuroticism and ODD symptoms without exposure to high self-blame for inter-parental conflict. For ADHD (and ODD), children homozygous for the long allele of *DRD4* appeared more likely to exhibit low conscientiousness when exposed to inconsistent parenting, whereas children without *DRD4* genetic susceptibility appeared somewhat more resilient to effects of inconsistent discipline on conscientiousness.

These findings may have important implications for clinical assessment and personalization of treatment components.

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5HTTLPR long allele homozygotes: direct path= $.25^{**}$ / indirect path= $.22^{**}$
 5HTTLPR 1 or 2 short alleles: direct path= $.05$ / indirect path= $.02$

Figure 1.

ODD Complex Pathway

Note. $^{*}p < .05$. $^{**}p < .01$. Mediation bootstrap $z = 2.24$, $p = .03$ for those with 1 or 2 short alleles for 5HTTLPR. Moderation $t = -2.03$, $p = .04$.

Figure 2.

ADHD Complex Pathway

Note. $*p < .05$. $**p < .01$. Mediation bootstrap $z = 3.56$, $p = .0004$ for those with $DRD4$ 2 long alleles. Moderation $t = 1.92$, $p = .05$.

Figure 3.

Non-Specificity of ADHD Complex Model: ODD as Outcome

Note. $*p < .05$. $**p < .01$. Mediation bootstrap $z = 2.05$, $p = .04$ for those with *DRD4* long allele homozygotes. Moderation $t = -1.9$, $p = .05$.

Table 1

Descriptive Statistics on Sample

M(SD)	ADHD n=159	ODD n=26	ADHD+ODD n=122	Control n=176¹
Boys <i>n</i> (%)	108(67.9)	16(61.5)	83(68)	82(46.6)**
Ethnic Minority <i>n</i> (%)	44(27.7)	4(15.3)	32(26.2)	39(22.1)
Age	11.12(2.84)	11.12(2.74)	11.3(2.85)	12.1(3.02)*
Family income (thousands\$)	69.74(36.70)	88.27(71.7)	54.14(33.61)	78.87(55.98)**
CPIC Self-Blame	12.81(3.42)	10.72(2.11)	13.47(4.11)	10.38(2.23)**
Inconsistent Parenting	14.24(4.13)	13.96(3.33)	15.59(3.33)	12.76(4.29)**
Neuroticism	4.5(1.28)	3.85(1.02)	4.85(1.03)	3.81(1.06)**
Conscientiousness	4.18(1.34)	6.05(1.07)	3.66(1.11)	6.39(1.2)**
5HTTLPR <i>n</i> (%) presence of short allele	94(59.1)	18(69.2)	81(66.4)	116(65.9)
DRD4 <i>n</i> (%) homozygosity of long allele	113(71.1)	16(61.5)	82(67.2)	119(67.6)
ODD Symptoms	1.14(1.75)	1.38(1.89)	4.01(2.51)	.29(.73)**
ADHD Symptoms	8.99(4.88)	.54(1.57)	9.04(5.2)	1.2(2.4)**

Note.

¹= 76 children were identified as having subthreshold ADHD or ODD or were screened out of the study at a later point in time, but were included in study analyses because they had data on traits, environmental risk, and genetics. Self-blame in relation to inter-parental conflict from child report on the Child Perception of Inter-Parental Conflict Scale. Inconsistent parenting from parent report on the Alabama Parenting Questionnaire. Neuroticism and conscientiousness from parent report on the California Q-sort. ODD and ADHD symptoms from teacher report on the ADHD Rating Scale.

*
p<.05.

**
p<.01, via ANOVAs or chi-squares.

Table 2

Correlations Between Environmental Risk, Genetic Susceptibility, Traits, and ODD and ADHD Symptoms

	1	2	3	4	5	6	7	8
CPIC Self-Blame	1							
Inconsistent Discipline	.12**	1						
5HTT Susceptibility	.07	.01	1					
DRD4 Susceptibility	-.05	-.06	-.02	1				
Neuroticism	.14**	.14**	-.002	-.01	1			
Conscientiousness	-.31**	-.24**	.02	-.01	-.35**	1		
ODD Symptoms	.14**	.22**	-.02	-.002	.26**	-.4**	1	
ADHD Symptoms	.28**	.21**	-.06	.05	.22**	-.55**	.42**	1

Note.*
 $p < .05$.**
 $p < .01$.