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# Biopsychosocial Models of the Development of Childhood Disruptive Behaviors

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BIOPSYCHOSOCIAL MODELS OF THE DEVELOPMENT OF CHILDHOOD DISRUPTIVE  
BEHAVIORS

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A Dissertation  
Presented to  
the Faculty of Social Sciences  
University of Denver

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In Partial Fulfillment  
of the Requirements for the Degree  
Doctor of Philosophy

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by  
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August 2016  
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Title: BIOPSYCHOSOCIAL MODELS OF THE DEVELOPMENT OF CHILDHOOD DISRUPTIVE BEHAVIORS  
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## ABSTRACT

Hyperactivity/attention problems (HAP) and conduct problems (CP) are common and impairing disruptive behaviors in childhood and adolescence. Previous research has established that HAP and CP are highly comorbid, and that outcomes are worse for youth exhibiting both symptom clusters relative to youth with only one disruptive behavior type. Despite ample evidence that HAP and CP share common etiological factors and maladaptive outcomes, the nature of their developmental association remains unclear. This dissertation clarifies three important characteristics of comorbid HAP and CP development, in two replicate, longitudinal, population samples of youth. First, I test the theory that within-person variation in HAP relates to subsequent within-person in variation CP, but not vice versa. Second, I apply growth mixture modeling to identify comorbid HAP-CP developmental trajectories, as well as their uniquely associated risk factors. Finally, I attempt to replicate a well-known candidate gene by environment interaction as a predictor of CP. Altogether, these analyses expand the literature on the etiologies of HAP, CP, and their cross-construct relations.

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CHAPTER 1.  
INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is one of the most common and debilitating disorders affecting children and adolescents. The core features of ADHD, hyperactivity and attention problems (HAP), impact academic functioning, physical safety, social interactions, and self-esteem, among other domains. Moreover, youth with HAP who also demonstrate symptoms of conduct problems (CP) experience significantly greater difficulties in all of these domains, and are at higher risk for poor functional and mental health outcomes as adults.

Although the high comorbidity between HAP and CP among youth is well documented, the mechanisms by which youth develop these comorbid externalizing behaviors are not clear. Most strikingly, it is unknown why some youth exhibit HAP without CP, while others exhibit high severity symptoms in both clusters. The general consensus in the fields of child clinical and developmental psychology is that suboptimal environmental responses to HAP elicit symptoms of CP. However, this assumes a temporal relationship (i.e. wherein individual show HAP first and CP later) that has not been proven at the individual level. It is also unclear how suboptimal parenting would compare to negative interactions with school personnel or peer conflict as mediators of the HAP to CP trajectory.

The etiology of externalizing symptoms is thought to be largely genetic. However, in support of the hypothesis that maladaptive interpersonal relationships mediate the comorbidity between HAP and CP, estimates of heritability of CP are considerably lower than that of HAP. Moreover, behavioral interventions for HAP and CP have been effective for many youth, suggesting a gene by environment interaction, at least. Altogether, the literature suggests heterogeneous etiologies; yet, analyses of



comorbidity at the individual level are scant, and attempts to identify etiological subtypes, particularly for individual youth, are in early stages.

The current dissertation addresses some of the gaps in the extant literature by emphasizing multiple pathways to HAP-CP comorbidity, both at the individual and group levels. Biopsychosocial models of behavioral comorbidity are presented and include within-person fluctuations in behavior, environmental stressors, ontological models of comorbidity, and candidate gene by environment interactions. The overall goal of the study is to contribute to translational research on disruptive behavior disorders, which focuses on establishing more individually tailored diagnostics and treatment for affected youth and families.

CHAPTER 2.

EFFECTS OF WITHIN-PERSON VARIANCE IN HYPERACTIVITY/ATTENTION  
PROBLEMS ON SUBSEQUENT CONDUCT PROBLEMS IN YOUTH

Comorbidity between symptoms of hyperactivity/impulsivity and attention problems (HAP) and conduct problems (CP) has been a topic of great interest in the field of child psychology within the last two decades (Beauchaine, Hinshaw, & Pang, 2010; Loeber, Burke, Lahey, Winters, & Zera, 2000). These symptom clusters are core features of common childhood disorders, namely attention deficit hyperactivity disorder (ADHD), which is prevalent in about 6 - 11 percent of school age children (Willcutt, 2012) and oppositional defiant disorder (ODD) and conduct disorder (CD), which are estimated to affect 10 percent of the population (Nock, Kazdin, Hiripi, & Kessler, 2006; Nock, Kazdin, Hiripi, & Kessler, 2007). HAP and CP share phenotypic and genotypic latent traits as well as common negative outcomes, including peer problems, early adult arrest, substance abuse, and antisocial personality disorder (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009; Beauchaine et al., 2010; Loeber et al., 2000; Pennington, 2002; Tuvblad, Zheng, Raine, & Baker, 2009; Waschbusch, 2002). Yet, despite their high rates of comorbidity, overlapping etiological factors, and shared sequelae, HAP and CP are distinct symptom clusters, and only a proportion of youth with high levels of HAP also have elevated CP (Biederman, Newcorn, & Sprich, 1991).

One theory of comorbidity, the developmental cascades model (Masten & Cicchetti, 2010), describes interactions and transactions between two symptom clusters over time, and encompasses both direct and indirect effects. In line with this model, some research has indicated a developmental progression in which CP follows onset of HAP, specifically in the presence of harsh parenting (Beauchaine et al., 2010; Lahey, McBurnett, & Loeber, 2000). Patterson's proposed coercive cycle (Patterson, 1976; Patterson, DeGarmo, & Knutson, 2000) further specifies this pattern by describing

transactions in which HAP elicits inconsistent and coercive parenting practices, which in turn increase the child's propensity toward coercive and antisocial behaviors, which further elicits coercive parenting, and so on.

Although widely accepted as a viable explanation for the temporal pattern in which HAP precedes CP, Patterson's theory has not been adequately tested. For example, using structural equation modeling to test their own hypothesis, Patterson and colleagues (2000) found that a latent hyperactivity factor in fourth grade did not predict delinquency by ninth grade when early antisocial behaviors were included in the model. However, this analysis used only a few, distant time points and depended on latent traits across a group of youth. This approach could have masked acute temporal relations between early hyperactivity and antisocial behaviors, as well as individual variability in HAP-CP relational patterns.

Other studies have also reported that early childhood antisocial and aggressive behaviors mediate the association between early HAP and later CP (Cadoret & Stewart, 1991; Patterson, DeGarmo, & Knutson, 2000; Young, Heptinstall, Sonuga-Barke, Chadwick, & Taylor, 2005). Further, Lahey et al. (2009) found that early hyperactive symptoms at the behavioral level did not contribute unique variance to explain later CP once genetic and environmental factors influencing early CP were included in the model. This suggests that the longitudinal relation between the behavioral constructs may be accounted for by underlying genetic and environmental risk for CP.

Conflicting results with regard to the developmental progression of HAP and CP likely relate to the limitations of testing the developmental cascades model using few time points and/or between-person analyses, such as group comparisons. As Masten and

Cicchetti (2010) described, in order to truly model developmental cascades, multiple, repeated assessments over time are necessary. In order for Patterson's coercive cycle to be plausible, there must be some evidence that an individual's fluctuations in HAP severity at any given time point will relate to the same individual's subsequent CP just a short time later. In other words, if a youth is having a "severe HAP" month, then according to Patterson's theory, severe CP should follow soon thereafter. Thus, studies of associations between HAP and CP across only a few, distant time points do not adequately address Patterson's theory.

Additionally, most well executed studies that have targeted this question have focused on high-risk samples, often limited to clinically-referred boys. These restricted samples limit the amount of behavioral variance, which would underestimate the correlation between HAP and CP longitudinally. It is important to test these associations across the full spectrum of behaviors in order to maximize the statistical variance. The only potential drawback would be if the HAP-CP association only exists beyond a certain threshold of behavioral severity. If that is the case, one would only expect to find the association among youth with severe HAP and/or CP. While most research indicates that HAP exists along a continuum of behavioral severity (e.g. Arnett et al., 2012), the question of whether comorbid HAP and CP represent a unique categorical disorder is widely disputed (Waschbusch, 2002).

The current study aimed to fill a gap in the disruptive behavior literature by examining associations between within-person fluctuations in HAP and CP in a population sample from three salient age cohorts. The study design included ten repeated assessments over the course of 30 months. I used hierarchical linear modeling to test

three-level, repeated measures models of HAP and CP. I hypothesized that within-person fluctuations in HAP (wpHAP) would significantly predict within-person variation in CP (wpCP) at the subsequent time point, but not vice versa. Within-person variation in HAP and CP were defined as deviations from the youth's average HAP or CP severity, respectively.

Given that the influence of family environment on neuropsychological development is greater for younger youth (Nisbett, 2009), I proposed that Patterson's coercive cycle would be supported if the effect of wpHAP on later wpCP was stronger in younger youth. I further expected that the effect of wpHAP on subsequent wpCP would be stronger in the context of previously established risk covariates: more negative parenting, lower SES, and more severe average HAP (i.e. across all time points) (Barkley, Fisher, Edelbrock, & Smallish, 1991; Chronis et al., 2007; Loeber & Keenan, 1994; Patterson et al., 2000; Waschbusch, 2002). Additionally, I predicted that the association between wpHAP and later wpCP would be stronger for females, due to literature reporting a paradoxical gender effect wherein fewer females exhibit HAP, but among those who do, there are relatively higher rates of comorbid CP compared to males with HAP (Loeber & Keenan, 1994).

Prior literature has also documented a weaker association between harsh parenting and disruptive behavior outcomes in African American youth relative to Caucasian youth (Hill & Bush, 2001). The current sample included youth of varying ethnic and racial backgrounds; however, non-Caucasian youth in this sample included multiple racial identities, including many youth who identified as multi-racial, which limited power to test for race-specific effects. Thus, non-Caucasian youth were grouped together under the

category of “minority.” Given the crudeness of this measure, I did not expect to find significant effects of minority race on the lagged wpHAP-wpCP association.

Finally, I repeated all analyses testing for the opposite directional effect of wpCP on subsequent wpHAP, as a measure of discriminant validity for my hypotheses. I did not expect to find a significant effect of wpCP on subsequent wpHAP.

## **Methods**

### **Participants**

Youth in third, sixth, and ninth grades were recruited from schools in the greater Denver, CO and New Brunswick, NJ areas for enrollment in a multi-site, longitudinal study of mood disorders. Exclusionary criteria included autism spectrum or psychotic disorders, IQ less than 70, and non-English speaking. Recruitment procedures have been described in detail in previously published studies (Cohen, Young, Gibb, Hankin, & Abela, 2014; Hankin, Jenness, Abela, & Smolen, 2011). The current analyses only used data from participants who had completed at least three of the relevant time points. The final samples included 105 third grade, 119 sixth grade, and 104 ninth grade youth ( $n = 328$ ) recruited from Denver and 82 third grade, 108 sixth grade, and 102 ninth grade youth ( $n = 292$ ) from New Brunswick (total  $n = 620$ ). Participants’ ages ranged from 7 to 16 years at baseline.

Sample demographics are listed in Table 2.1. A minority of participants in each sample also had a sibling enrolled in the study. The Denver and New Brunswick samples did not differ with regard to percent female, minority ethnicity, average SES, average HAP or CP severity, or number of participants who scored greater than 1.5 standard deviations above established gender normative values on the strengths and difficulties

questionnaire (Bourdon, Goodman, Rae, Simpson, & Koretz, 2005) on average.

According to this threshold, the rates of youth with clinically elevated levels of HAP and CP ranged from 4.6 to 6.4 percent.

Table 2.1

*Sample Demographics*

	Denver	New Brunswick
<i>n</i>	328	292
Female	185 (56%)	160 (55%)
Minority Race	104 (32%)	108 (37%)
Siblings	76 (23%)	66 (23%)
SES (SD)	48.65 (11.26)	49.19 (11.74)
HAP Severity (SD)	2.75 (1.97)	2.74 (1.95)
CP Severity (SD)	1.15 (1.25)	1.16 (1.15)
Elevated HAP	15 (4.6%)	17 (5.8%)
Elevated CP	21 (6.4%)	14 (4.8%)

Minority Ethnicity = non-Caucasian. Siblings = participants with at least one sibling also in the study. SES = Hollingshead 4 factor index (Adams & Weakliem, 2011). Elevated HAP/CP = average SDQ *z*-score greater than 1.5 for HAP/CP scales.



## **Procedures**

The parent study was a prospective, multi-wave sequential cohort design aimed at studying internalizing symptoms in children and adolescents. I performed secondary analyses on disruptive behavior symptoms in these youth. Although the goal of the parent study was to examine internalizing symptoms, participants were recruited from the community and symptom rates were representative of the general population; thus, the purpose of the parent study had no effect on my results. Each youth and a parent participated in a baseline laboratory visit. Parents provided written consent for themselves and their youth. The youth provided written assent. Thereafter, every three months following the baseline visit, participants completed behavioral questionnaires for a total of 10 waves of follow-up assessment over 30 months. An additional laboratory visit took place at the 18-month follow-up. All procedures were approved by the University of Denver and Rutgers University institutional review boards.

## **Measures**

**Disruptive behavior symptoms.** Child HAP and CP symptoms were measured using the Strengths and Difficulties Questionnaire, Parent Report (SDQ; Goodman, 1997) every three months, from the 3- through 30-month follow-ups, for a total of 10 waves of data. The SDQ was not collected at the 18-month follow-up at the Denver site. The SDQ scales are highly correlated with other established parent-report measures of CP and HAP symptoms, including the Rutter scales (HAP  $r=.88$ ; CP  $r=.82$ ) (Goodman, 1997). Internal validity for the SDQ has been established for a large ( $N=9,878$ ) sample of children age 4-17 (Bourdon et al., 2005). The SDQ HAP and CP scales each comprise five items measuring symptoms characteristic of ADHD, ODD and CD (see Table 2.2). Both scales

are rated by a parent on a scale of 0 “not true” to 2 “certainly true.” Items were reverse coded when necessary such that higher scores reflected more symptoms.

The SDQ HAP scale was correlated with the SNAP-IV (Bussing et al., 2008), a DSM-IV checklist of ADHD symptoms that was collected at the 18-month follow-up. These correlations were conducted with subsamples that included only one random sibling from each family: Denver  $n = 289$  and New Brunswick  $n = 277$ . The SDQ HAP scale was correlated with the SNAP-IV inattention and hyperactivity/impulsivity subscales across all time points (inattention range:  $r = .64$  to  $.77$ ,  $p < .001$ ; hyperactivity/impulsivity range:  $r = .52$  to  $.66$ ,  $p < .001$ ). Parents also completed the externalizing scale of the Child Behavior Checklist 6-18 (CBCL; Achenbach, 2001) at baseline and the 18-month follow-up. The externalizing scale of the CBCL is subcategorized into delinquent behavior and aggressive behavior syndrome scales, which have been associated with covert and overt conduct problems, respectively (Achenbach & Ruffle, 2000). The CBCL externalizing scale measures symptoms related to ODD and CD, but not ADHD, which is a separate scale. SDQ CP scores were correlated with the CBCL aggressive behavior syndrome scale (range:  $r = .62$  to  $.76$ ,  $p < .001$ ) and the delinquent behavior syndrome scale (range:  $r = .58$  to  $.65$ ,  $p < .001$ ), suggesting that the SDQ CP items are reflective of both overt and covert conduct behaviors. As expected, correlations between the SDQ HAP and CBCL externalizing scales were weaker (range:  $r = .41$  to  $.62$ ,  $p < .001$ ), as were correlations between the SDQ CP and SNAP-IV scales (range:  $r = .38$  to  $.63$ ,  $p < .001$ ). The SDQ HAP and CP scales were modestly correlated with one another in this sample (range:  $r = .48$  to  $.62$ ,  $p < .001$ ), further supporting the SDQ as a valid measure of these two related, but independent, behavioral constructs.

Table 2.2

*Items in the HAP and CP Scales of the Strengths and Difficulties Questionnaire*

<u>HAP</u>	<u>CP</u>
1. Restless, overactive, cannot stay still for long	1. Often has temper tantrums or hot temper
2. Constantly fidgeting or squirming	2. Generally obedient, usually does what adults request
3. Easily distracted, concentration wanders	3. Often fights with other children or bullies them
4. Thinks things out before acting	4. Often lies or cheats
5. Sees tasks through to the end, good attention span	5. Steals from home, school, or elsewhere

**Socioeconomic status (SES).** SES was ascertained at baseline using a demographic parent report. Information about both parents’ education levels and specific occupations was used to calculate the Hollingshead Four-Factor Index (Adams & Weakliem, 2011).

**Race.** Minority status was defined as non-Caucasian, and included participants who identified as “mixed race” or “other.” The child’s race and ethnicity were reported by the parent as part of the baseline demographic questionnaire.

**Negative parenting.** Negative parenting was measured at baseline using the Alabama Parenting Questionnaire (APQ), which is a parent self-report. Three negative parenting subscales measuring poor monitoring/supervision, inconsistent discipline, and

corporal punishment were created following guidelines published by Shelton, Frick & Wootton (1996). Scales were averaged to create a single measure of negative parenting practices. The scales showed moderate internal validity in both the Denver and New Brunswick samples (*Chronbach's alphas* = .51 and .56, respectively).

### **Hierarchical Linear Modeling Analysis Plan**

Single level linear regression analyses were initially conducted with age, squared age, and cubed age as independent variables, to test for the shape of growth in within-person variation in CP and HAP severities. The linear model was the best fit for both wpCP and wpHAP. Next, three-level, nested hierarchical linear models were tested using HLM Version 6.08 (Raudenbush, Bryk, Cheong, & Cogdon, 2004). The overall model was similar to a cross-lagged structural equation model (SEM), except that only one outcome variable was modeled at a time. I opted to use HLM, rather than SEM, in order to test for moderation of the level 1 random slopes by both between-person and between-family variables. Variance was divided into within-person, time varying effects at level 1, between-person effects at level-2, and between-family effects at level-3.

At level 1, I tested the hypothesis that wpCP at each time point would be predicted by wpHAP severity at the previous time point (i.e. lagged wpHAP), controlling for the contemporaneous association with wpHAP and the autoregressive association with lagged wpCP. I tested both a one-time point lag and two-time point lag (three and six months, respectively) in wpHAP to allow for the possibility of a sleeper effect. Additionally, I included the interaction of lagged wpHAP and age to test the hypothesis that if coercive parenting mediated the wpHAP to wpCP progression, the association would be stronger in younger youth.

At level-2, I tested the hypothesis that the longitudinal association between within-person variation in HAP and CP would be even stronger for youth with more negative parenting and higher average HAP severity, as well as for females. Negative parenting was included at this level (between-person) rather than level-3 (between-family) because parents were asked to complete the APQ with a specific child in mind, and parenting practices can vary with each child, particularly in the presence of externalizing behavior.

At level-3, I tested the theory that higher family stress in the form of lower SES would increase the magnitude of the longitudinal association between within-person HAP and CP at the first level, and that minority ethnicity would not have an effect on this association.

There were no intercept moderators included at levels 2 or 3 because the outcome variable, wpCP, represented a time-varying deviation from an individual's average CP severity; thus, there were no between-person or between-family differences on the intercept. Altogether, I planned to test the following model with within-person, time-varying CP severity as the outcome:

$$\text{Level 1: } wpCP_{tik} = \beta_0 + \beta_1 \cdot Age_{tik} + \beta_2 \cdot wpHAP_{tik} + \beta_3 \cdot LagwpHAP_{tik} + \beta_4 \cdot LagwpHAP \times Age_{tik} + \beta_5 \cdot LagwpCP_{tik} + e$$

$$\text{Level-2: } \beta_0 = \gamma_{00} + u_0$$

$$\beta_1 = \gamma_{10} + u_1$$

$$\beta_2 = \gamma_{20} + u_2$$

$$\beta_3 = \gamma_{30} + \gamma_{32} \cdot AveHAP_{ik} + \gamma_{33} \cdot NegParent_{ik} + \gamma_{34} \cdot Sex_{ik} + u_3$$

$$\beta_4 = \gamma_{40} + u_4$$

$$\beta_5 = \gamma_{50} + u_5$$

$$\text{Level-3: } \gamma_{00} = \delta_{000}$$

$$\gamma_{10} = \delta_{100}$$

$$\gamma_{20} = \delta_{200}$$

$$\gamma_{30} = \delta_{300} + \gamma_{301} \cdot SES_k + \gamma_{302} \cdot Minority_k + V_{30}$$

$$\gamma_{40} = \delta_{400}$$

$$\gamma_{50} = \delta_{500}$$

Next, I tested the opposite model with wpHAP as the outcome, and lagged wpCP as the level 1 predictor of interest. I hypothesized that there would not be a statistically significant effect of lagged wpCP on later wpHAP.

Model specification was done incrementally (Snijders & Bosker, 2012), by adding predictors and random slopes one level at a time. All variables and random slopes that were significant at  $p < .05$  at initial entry into the model were retained in the final models, along with level 1 predictors of primary interest. Lastly, sample was added as a level 3

moderator of all significant level 1 and level 2 effects in order to test for replication of results.

## Results

### Preliminary Analyses

**Data transformation.** All variables were initially examined for normality. SDQ HAP and CP scores were winsorized to within three standard deviations of the mean at each time point, within sample. All variables then demonstrated skew and kurtosis values in the acceptable range (absolute value < 1.6).

**HAP and CP severities.** Participants' clinical severities for HAP and CP symptoms were estimated using sex-specific normative data collected on 9,878 7-17 year old youth from the National Health Interview Survey (Bourdon et al., 2005), available on the SDQ website ([www.sdqinfo.org/USnorm.html](http://www.sdqinfo.org/USnorm.html)). Results are reported by sample in Table 2.1. Altogether, 5% of participants scored at least 1.5 standard deviations above the sex norm for average HAP severity across all time points; 6% scored in this range for average CP severity.

### Within-Person CP Outcomes

When all level 1 variables were included in the model, wpCP at a given time point was negatively predicted by wpHAP lagged by one time point ( $b = -.07, p = .018$ ). This result was in the opposite direction of my prediction. Although age was not a significant predictor of wpCP ( $b = .00, p = .564$ ), there was a positive effect of the interaction between age and the lagged, wpHAP score on subsequent wpCP ( $b = .02, p < .001$ ). This interaction effect indicated that the association between lagged wpHAP and wpCP became more positive with age. As expected, contemporaneous wpHAP was positively

associated with wpCP ( $b = .19, p < .001$ ). Lagged wpCP negatively predicted wpCP ( $b = -.06, p = .006$ ).

As planned, I next checked for a sleeper effect by testing the predictive effect of within-person variance in HAP lagged by two time points (i.e. six months prior). This model resulted in non-significant beta values for the two-time point lagged wpHAP ( $b = .03, p = .250$ ), age ( $b = .00, p = .666$ ), and their interaction ( $b = .00, p = .745$ ). Thus, I reverted to the one-time point lagged level 1 model for the subsequent analyses.

I added random slopes for wpHAP, lagged wpHAP, the interaction term, and lagged wpCP; all four variances were statistically significant ( $p < .01$ ), indicating between-person variability. To compare effect sizes of the significant level 1 predictors, I removed them one at a time from the level 1 random model, and calculated a pseudo- $R^2$  as a proportion of the change in variance of the level 1 intercept. The association with concurrent wpHAP accounted for the greatest proportion of variance at 13%, followed by lagged wpCP (6%), lagged wpHAP (2%) and a negligible effect size for the interaction term.

Next, I retained these random slopes at level 1 and added the proposed level 2 moderators. Contrary to predictions, none of the proposed between-person variables (negative parenting, average HAP or sex) significantly moderated the association between lagged wpHAP and wpCP, which remained negative and statistically significant. Thus, all of the level 2 moderators were dropped from the model.

Next, I tested for an effect of lower SES at the between-family level (level 3) on the within-person association between lagged wpHAP and wpCP. I also tested for a moderating effect of minority ethnicity, although I expected that the non-Caucasian



sample was too ethnically and racially diverse to result in a significant interaction. Contrary to prediction, when both SES and minority status were included in the model, SES was not significant ( $b = .00, p = .929$ ), but non-Caucasian youth demonstrated a weaker (more negative) association between lagged wpHAP and wpCP outcomes ( $b = -.10, p = .010$ ) relative to Caucasian youth. For Caucasian youth, the effect of lagged wpHAP on subsequent wpCP was not statistically significant ( $b = -.05, p = .146$ ); however, the random slope was still significant ( $\sigma^2 = .11, p < .001$ ), indicating that minority status did not explain all of the between-person variance in the effect. Finally, I added sample as a moderator of all of the significant level 1 effects, including wpHAP, lagged wpHAP, lagged wpCP, and the interaction of age x lagged wpHAP. The purpose of this final analysis was to replicate results across both samples. As predicted, sample was not a significant moderator of any of the level 1 associations, indicating that the model fit equally well across both the Denver and New Brunswick samples.

Results of the final, three-level hierarchical linear model with lagged within-person variance in HAP predicting subsequent wpCP are reported in Table 2.3. As seen in Figure 2.1, the association between lagged wpHAP and wpCP was positive for older youth. However, minority and younger youth demonstrated a negative association. The final model accounted for 22% of the within-person variance in CP severity.

Table 2.3

*Three-Level Hierarchical Linear Model with Lagged wpHAP Predicting wpCP*

<i>Fixed Effects</i>	<i>Parameter</i>	<i>B (SE)</i>	<i>t (df)</i>
Intercept	Intercept $\delta_{000}$	-.03 (.04)	-.74 (410)
Age	Intercept $\delta_{100}$	.00 (.01)	.63 (2053)
Concurrent wpHAP	Intercept $\delta_{200}$	.18 (.02)***	10.11 (53)
Lagged wpHAP	Intercept $\delta_{300}$	-.05 (.03)	-1.47 (53)
	Minority $\delta_{301}$	-.10 (.04)**	-2.70 (53)
Lagged wpHAP x Age	Intercept $\delta_{400}$	.01 (.00)**	3.23 (53)
Lagged wpCP	Intercept $\delta_{500}$	-.08 (.03)**	-3.17 (53)
<i>Variance Components</i>	$\sigma^2$	$\chi^2 (df)$	
Level 1, $\sigma_e^2$	.46		
Level 2, $\sigma_0^2$	0	<i>Too few df</i>	
Level 3, $u_{00}^2$	0	248.04 (410)	
Concurrent wpHAP, $\sigma_2^2$	.03***	460.34 (262)	
Lagged wpHAP, $\sigma_3^2$	.11***	427.62 (262)	
Lagged wpHAPxAge, $\sigma_4^2$	.00**	432.44 (262)	
Lagged wpCP, $\sigma_5^2$	.06***	472.36 (262)	

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . Sample = New Brunswick sample.

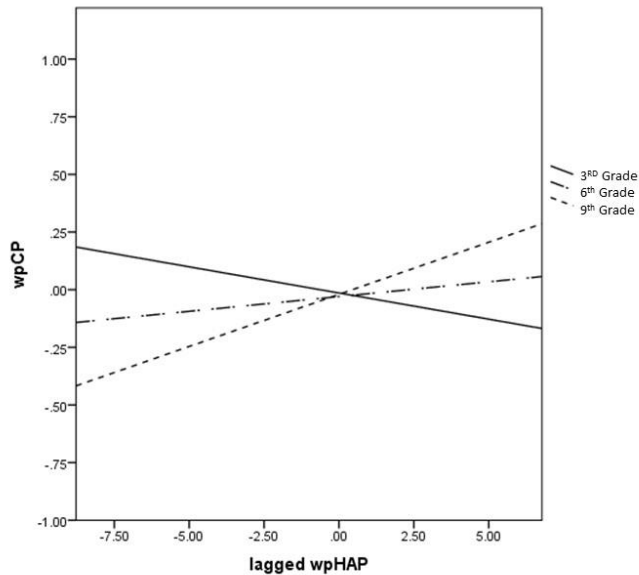


Figure 2.1 The effect of within-person variation in HAP on subsequent within-person variation in CP is more positive for older youth.

### Within-Person HAP Outcomes

As expected, within-person variation in HAP was not predicted by the one-time point lagged wpCP ( $b = .02, p = .729$ ). Further, neither age ( $b = -.01, p = .137$ ) nor the interaction between age and lagged wpCP ( $b = -.00, p = .942$ ) was significantly related to wpHAP outcomes. When the interaction term was removed, the lagged wpCP effect remained non-significant. Effect sizes as calculated by pseudo  $R^2$  were negligible for all level-1 predictors. As planned, I next tested the same level 1 model using wpCP lagged

by two time points. Again, the effect was not significant. These results were consistent with the original hypothesis that there would not be an association between lagged wpCP and wpHAP, as well as with literature supporting HAP as a developmental precursor of CP, but not vice versa. Thus, I did not continue to evaluate this comparison model beyond level 1.

### **Discussion**

These analyses tested the hypothesis that individual fluctuations in HAP severity would precede and predict individual fluctuations in CP, consistent with the developmental pattern described by Patterson's coercive cycle. My analyses differed from prior research (e.g. Gittelman, 1985; Loeber et al., 2000; Mannuzza et al., 2004) in that I tested the effects of within-person differences in behavioral severity over multiple time points, rather than executing between-person comparisons over just a few time points. As predicted, within-person variation in HAP did predict subsequent within-person CP variation, but not vice versa; however, the predicted effect was only evident in older youth, and the variance explained by the interaction term was very small. Among younger youth, a small, negative association was found, suggesting regression to the mean. Additionally, among non-Caucasian youth, the association between lagged wpHAP and wpCP was weaker than that for Caucasian youth (across all ages).

The results only partially supported the theory by Patterson and colleagues that HAP severity has an indirect effect on CP severity at the behavioral level; however, these results did not clarify the process by which HAP influences CP. Consistent with Patterson's theory, it is possible that youth with HAP elicit more coercive parenting, resulting in an indirect effect on CP. Alternatively, a direct effect of HAP on CP might

exist; an example of this would be that the impulsivity and impaired social skills associated with HAP (Laird, Jordan, Dodge, Pettit, & Bates, 2001) could cause youth to be more likely to engage in mildly antisocial behaviors, such as stealing or fighting, which could act as gateway behaviors to more frequent and severe forms of CP. A third possibility is that when youth engage in HAP-related behaviors, epigenetic and/or neuropsychological changes occur that increase the youth's risk for CP. A related example of this in the medical literature is an individual with Type II diabetes whose metabolic and inflammatory derangements increase his/her risk of developing coronary vascular disease. Many additional relations are possible, and most are probably not mutually exclusive.

Importantly, the effect size for the association between lagged wpHAP and later wpCP was very small, even when age was taken into account. Thus, these results do not conclusively support a transactional relation such as Patterson's coercive theory. An alternative explanation for the temporal relation between HAP and CP, wherein HAP typically emerges earlier, is that shared genetic and environmental etiologies for the two behaviors manifest differently as a function of age. For example, some polygenes that predispose a youth to HAP in childhood may likewise constitute risk for CP following puberty-related neuropsychological changes, negative peer- or family-interactions that are more likely to occur in older youth, or exposure to drugs and alcohol.

Younger youth did not show the expected pattern of lagged wpHAP predicting subsequent wpCP. This finding is inconsistent with Patterson and colleagues' hypothesis that coercive parenting is the environmental risk factor that mediates the association between HAP and CP. CP is also thought to be influenced strongly by deviant peer

associations (Gardner, Dishion, & Connell, 2008), and peer influences surpass those of parental influences as youth get older and spend more time away from the family environment. Thus, an alternative model in which deviant peer associations mediate the HAP to CP progression, is more consistent with the age moderation results.

On the other hand, the fact that non-Caucasian youth showed a weaker association between lagged wpHAP and subsequent wpCP is consistent with previous literature indicating a weaker effect of harsh parenting on CP in African American relative to European American youth (Hill & Bush, 2001). This result should be interpreted with caution, however, due to the level of diversity among the non-Caucasian youth, and the fact that I did not specifically test for negative parenting as a mediator. This issue certainly deserves further attention in future research.

One limitation of these analyses was that the sample did not include a very young cohort of children. Mediation by negative parenting may occur in children prior to third grade, with a transition to peer and other non-familial influences as youth get older. However, this does not explain the negative association between lagged wpHAP and later wpCP in the third grade cohort. Future examination of age as a moderator of HAP and CP comorbidity is warranted, preferably using mediation models and repeated measures of disruptive behaviors and environmental risk.

The community sample had a low base rate of disorder. The lack of significant moderation by average behavioral severity at the second level suggests that results applied to youth with extreme (i.e. disordered) behavior as well. This suggests that there is not a threshold of behavioral severity that is necessary to elicit the longitudinal association. This is likewise true for the lack of moderation by negative parenting, which

suggests that the HAP to CP progression is not more likely to occur in highly dysfunctional parenting environments. However, it would be helpful to replicate this finding in a population sample that is enhanced for behavioral disorders, to insure adequate variance exists at both the typical and disordered ends of the behavioral continuum.

These analyses were somewhat limited by the use of the SDQ to measure disruptive behaviors. Although a reliable instrument, the number of items comprising the HAP and CP scales was small, so I could not investigate specific associations among subtypes of symptom clusters, such as predominantly inattentive versus hyperactive/impulsive HAP, and aggressive versus covert CP. Previous literature suggests that the HAP to CP progression may be specific to the hyperactivity/impulsivity cluster of ADHD symptoms (Babinski, Hartsough, & Lambert, 1999). Thus, use of an expanded HAP measure might result in different findings for individual symptom subtypes. An additional limitation of the SDQ was that the scales measured only the dysfunctional ends of the symptom spectrums, and did not capture variance at the favorable ends of the distributions (e.g. good impulse control, high empathy). This limited variance in the behavioral severities and may have resulted in underestimated regression coefficients. Future research should aim to test these hypotheses using balanced and more in depth measurement tools at each time point.

CHAPTER 3.  
DUAL GROWTH MIXTURE MODELS OF HYPERACTIVITY/ATTENTION AND  
CONDUCT PROBLEMS IN YOUTH



Outcomes of hyperactivity/attention problems (HAP) and conduct problems (CP) in youth are highly variable, with some adolescents remitting entirely and others developing severe antisocial behaviors in adulthood. These heterogeneous sequelae have been linked to distinct developmental courses of HAP and CP (Broidy et al., 2003; Nagin & Tremblay, 2001; Schaeffer, Petras, Ialongo, Poduska, & Kellam, 2003; Shaw, Lacourse, & Nagin, 2005), which in turn relate to environmental, genetic and gene by environment risk factors (Beauchaine, Hinshaw, & Pang, 2010; Frick, 2012). Research on the co-occurrence of HAP and CP indicates that outcomes associated with comorbid symptom presentation are worse than those for either symptom cluster on its own (Waschbusch, 2002), but we do not know how the relation between the two trajectories is related to worse outcomes. Answering that question is a key goal of the current analyses, along with identifying risk and protective factors specifically associated with the joint developmental trajectories of these two symptom clusters. Thus far, extant research indicates that high CP trajectories are associated with high HAP, but high HAP is a less consistent predictor of high CP (Nagin & Tremblay, 2001; Shaw et al., 2005). However, these studies have been limited by use of 1) predominantly at-risk, male samples; 2) semiparametric mixture analyses, which do not allow for heterogeneity within classes; and/or 3) lack of trajectory analysis of HAP. The present analyses extend previous work in this area by applying growth mixture modeling (GMM) with auxiliary predictor variables (Muthén & Muthén, 2000; Muthén & Asparouhov, 2013) to identify risk factors associated with the joint latent growth trajectories of HAP and CP in a population sample of male and female youth.

## **Developmental Trajectories of HAP**

Much of the research on HAP trajectories has focused on behavioral subtypes. Youth with combined high hyperactive/impulsive and inattentive symptoms show a more pervasive and severe developmental trajectory than those with primarily only one symptom cluster or the other (Lahey, Pelham, Loney, Lee, & Willcutt, 2005), but this result is virtually inevitable if each symptom cluster has external validity in terms of predicting outcomes. In other words, children with more symptoms should have worse later outcomes, unless symptoms are developmentally unstable or lack external validity. The Lahey et al. (2005) study becomes more theoretically interesting if it is due, at least in part, to a subgroup with a different developmental trajectory, rather than just due to an additive effect of more symptoms being correlated with worse outcomes throughout the whole distribution. Since the overall consensus is that hyperactive/impulsive symptom severities typically decline with age, while inattentive symptoms remain stable or decrease slightly (for a review see Willoughby, 2003), children with the combined subtype at time 1 should tend to convert to the inattentive subtype at time 2, children with the inattentive subtype at time 1 should persist in that subtype at time 2, and the smaller hyperactive/impulsive only group at time 1 should tend to recover from ADHD by time 2. However, developmental change in HAP is not always linear; for example, Langberg et al. (2008) reported a slight increase or stabilization of ADHD symptoms associated with the youth's entrance into middle school. Additionally, some studies have found evidence of a subclass of youth whose hyperactive/impulsive symptoms increase during adolescence (Cuffe et al., 2001; Schaughency, McGee, Raja, Feehan, & Silva, 1994). In a study of both HAP and CP symptom trajectories in very young children, Shaw and

colleagues (2005) found that HAP fit a four-class developmental trajectory model, but none of these groups showed increasing severity with age. Hence, the results found by Lahey et al (2005) may be due in part to a subtype with a different developmental trajectory and not just to the additive effects of having more ADHD symptoms across both dimensions of ADHD.

### **Developmental Trajectories of CP**

Studies of CP growth have similarly converged on four distinct growth patterns, including two “high” and two “low” developmental trajectories (Haapasalo & Tremblay, 1994; Loeber, Tremblay, Gagnon, & Charlebois, 1989; Moffitt, 1993; Patterson, DeBaryshe, & Ramsey, 1989; Shaw, Gilliom, Nagin, & Ingoldsby, 2003). Clinical research and diagnostic criteria have emphasized age of symptom onset, as well as presence of callous/unemotional traits as distinguishing characteristics of developmental trajectories and severity of outcomes. Earlier onset CP has been linked to more severe antisocial outcomes (Moffitt, 1990; Patterson, Reid, & Dishion, 1992), while CP symptoms in the adolescent onset trajectory have been described as less severe (Frick, 2012; Moffitt, Caspi, Dickson, Silva, & Stanton, 1996). These subtypes have been linked to distinct etiological risk factors (e.g. familial risk for early onset and peer deviance with later onset; Hyde, Shaw, & Hariri, 2013), suggesting that each clinical classification represents a unique disorder, and the childhood onset and callous/unemotional forms of CP are not simply the result of additive risk and/or symptom severity.

### **HAP and CP Dual Trajectories**

Since there is evidence for distinct subgroups with different developmental trajectories within HAP and CP separately, it is important to understand their dual (i.e.

comorbid) trajectories, as these subgroups may arise from different developmental relations between HAP and CP across development. We already know that HAP and CP are among the most important child behavioral characteristics for predicting one another. Higher HAP symptom counts, combined inattentive and hyperactive/impulsive subtypes, and more pervasive HAP behaviors have all been linked to more severe CP, but the directional relation remains unclear (for review see Thapar, Van Den Bree, Fowler, Langle, & Whittinger, 2006).

In a population sample of girls and boys, van Lier, van der Ende, Koot & Verhulst (2007) found that the HAP developmental trajectory was predictive of a DSM-IV conduct disorder trajectory only in girls. However, the authors separated symptoms associated with DSM-IV oppositional defiant disorder from those associated with conduct disorder, minimizing the amount of variance in the CP clusters. Further, this study did not examine the opposite effect, i.e. the predictive validity of conduct disorder symptoms on HAP growth. Likewise, Schaeffer et al. (2003) found that concentration problems predicted high CP growth patterns among African American boys. However, this study did not model HAP severity longitudinally. In support of the opposite effect, Nagin and Tremblay (2001) and Shaw and colleagues (2005) both reported that high CP trajectories were significant predictors of high HAP trajectories in at-risk boys. Importantly, these results did not convey temporal relations between HAP and CP; rather they indicated probability of high HAP or CP trajectories given high severity of the opposite construct.

A study by Jester and colleagues (2005) is the only one in which GMM was used to classify joint trajectories of HAP and CP in male and female youth. They specified four classes described as healthy, comorbid, primarily HAP, and primarily aggressive.

Membership in the comorbid (i.e. high HAP and high aggressive) trajectory was predicted by parental alcoholism and a less positive family environment. This study was well executed in its use of GMM to examine parallel process models, but presented several limitations. First, by holding one construct constant to identify variance in the other, it did not allow identification of a potentially broader range of joint construct latent classes. Further, unlike other studies, only two latent classes were identified within each construct, and both followed a strictly linear trajectory. As with most studies of disruptive behavior in youth, Jester et al.'s sample comprised a group of at-risk youth which increased its clinical validity; but because it was not representative of the general population, its generalizability is unknown. From a Research Domain Criteria (RDoc; NIMH, 2008) perspective, it is important to test the developmental relations between HAP and CP symptoms dimensionally in a population sample. Additional predictor variables, such as child sex, parenting style, and extra-familial stress were also not examined.

### **Family Environment Risk**

HAP and CP share common family risk correlates, including low SES, negative parenting, and marital conflict/divorce (Biederman, Milberger, Faraone et al., 1995a; Biederman, Milberger, Faraone et al., 1995b; Counts, Nigg, Stawicki, Rappley, & Von Eye, 2005; Dodge, Greenberg, & Malone, 2008; Dodge, Coie, & Lynam, 2006; Hammen, Brennan, & Shih, 2004). Results have suggested that despite shared risk factors, HAP and CP symptoms also show unique associations with marital conflict and family adversity. Other studies reported no association between family adversity and

ADHD (McGee, Williams, & Silva, 1984). In contrast, Counts et al. (2005) reported that only conduct disorder symptoms were related to low SES.

The conflicting results with regard to disruptive behavior symptoms and family stress may relate to the lack of attention to the developmental nature of disruptive behavior symptoms in those studies. Those who have examined HAP and CP developmental trajectories have found that risk effects vary by age and gender. For example, Moffit (1990) reported increasingly strong associations between family adversity and CP between ages 7 and 13 years. Further, family risk factors may not predict overall levels of child behavior, but rather, the shape of change in the behavior over time.

Larsson, Dilshad, Lichtenstein & Barker (2011) employed GMM to test joint developmental trajectories of ADHD inattentive and hyperactive symptom clusters. They found that divorce was most common in youth with high hyperactivity or combined high inattention/hyperactivity symptom trajectories, while low SES was prevalent in all three affected trajectories (i.e. primarily inattentive, hyperactive, and combined). This study also confirmed an overall decrease in hyperactivity symptoms over time regardless of joint inattention/hyperactivity trajectory status. A review by Deault (2010) indicated that HAP is not associated with negative parenting practices once CP is controlled. Moreover, Chronis et al. (2007) reported that positive parenting protected against development of CP in children with high early HAP.

Earlier onset CP has been linked to adverse family environment factors (for review see Frick, 2012). However, the effects of family stress on CP development appear to interact with child characteristics. For example, Malone, Lansford, Castellino, Berlin,

Dodge, Bates & Pettit (2004) reported that in boys, marital separation or divorce predicted an increasing externalizing trajectory during elementary school, but only a short, limited spike in externalizing when the divorce/separation occurred in middle or high school. Further, girls showed no association between externalizing behavior and divorce at any age in this study.

Pasalich, Dadds, Hawes & Brennan (2011) demonstrated a unique mitigating effect of positive parenting in young children with CP and high callous/unemotional traits. Similarly, rejecting parenting has been associated with chronic versus desisting CP trajectories (Shaw et al., 2003). On the other hand, Silver, Measelle, Armstrong & Essex (2005) reported a main effect for low SES on high trajectories of teacher-rated externalizing symptoms in early elementary school, but no effect of harsh parenting, and no interaction of sex. However, this latter study did not examine the full trajectory of symptoms across adolescence. Hence, more research is needed to resolve these apparently conflicting findings regarding family environment risk.

### **Peer Environment Risk**

Difficulties with peer relations are commonly cited as correlates of both HAP and CP. A review by Hoza (2007) reported that youth with ADHD are rejected, less well-liked, and have worse self-awareness with regard to social skills. In the Multimodal Treatment Study of ADHD, these problems were found to relate uniquely to inattentive and hyperactive/impulsive symptoms, rather than to symptoms of CP or anxiety (Hoza et al., 2005). On the other hand, peer rejection has been reported to predict school-age CP even controlling for early aggression levels (Miller-Johnson, Coie, Maumary-Gremaud,

& Bierman, 2002). Those authors also found a partial mediation effect of peer rejection on the sequential association between HAP and later CP between first and fourth grade.

Some studies have emphasized the role of deviant peer associations in development of CP. Patterson's Social Interaction Model (Patterson et al., 1989) proposed that peer rejection leads to childhood externalizing behavior as well as affiliation with antisocial peers in adolescence. However, Laird et al. (2001) found that this was only true for youth who experienced time-limited peer rejection. Youth who were chronically rejected were unable to form friendships at all, thus eliminating the impact of deviant youth in that study. In a study by Gardner, Dishion & Connell (2008), the effect of deviant peer association on adolescent antisocial behavior was mediated by self-regulation, a child characteristic that is deficient in ADHD. Finally, Laird and colleagues (2001) reported that regardless of antisocial peer associations, peer rejection in childhood was predictive of adolescent externalizing problems, underscoring the importance of peer problems, rather than deviant peer relationships, for CP outcomes in youth. Again, more research is needed to clarify these conflicting results.

### **School Environment Risk**

Stress in the school environment has also been identified as prominent in youth with HAP and CP. Specific stressors include low achievement, poor teacher-student relationships, and expulsion. However, the direction of effects and developmental pattern of associations depends on the behavioral construct. For example, while HAP demonstrates reciprocal relations with academic and cognitive deficits (e.g. Arnett et al., 2012; Metcalfe, Harvey, & Laws, 2013), academic stress may precede CP (Hinshaw,



1992; Metcalfe et al., 2013). Further, the association between academic failure and CP weakens when family environment variables are controlled (Metcalfe et al., 2013).

Altogether, family, peer and academic stress have predictive value for disruptive behavior outcomes. However, no one has examined the associations between stressful events in these domains and the dual growth trajectories of HAP and CP, which may help resolve the conflicting findings. The current analyses will fill this gap in the literature by testing the equality of means across dual trajectory classes for stressors within the family, peer and academic domains.

### **Hypotheses**

Based on the extant literature, I formulated the following hypotheses for the current analyses. First, I predicted that consistent with previous research, I would identify four distinct growth trajectories for HAP and for CP. I predicted that consistent with van Lier et al. (2007) and Shaw et al. (2005) the HAP trajectories would follow 1) high stable, 2) moderate increasing, 3) moderate decreasing and 4) low stable trajectories. Within the CP construct, I expected four trajectories that would map onto previous results and age of onset subtypes: 1) high stable and 2) high decreasing as two subtypes of early onset type, 3) moderate increasing being equal to the adolescent limited subtype, and 4) low = unaffected. Since the four trajectories proposed for each symptom dimension, HAP and CP, cover most of the logical ground given floor and ceiling effects (if you start high you can only decrease or stay stable and if you start low you can only increase or stay stable), it is important to test the external validity of these trajectories by modeling dual trajectories and examining their relations to the risk factors discussed earlier. The key questions were 1) whether there would be evidence for a synergistic relation between

HAP and CP trajectories, not just an additive one, and 2) whether this dual trajectory analysis would identify meaningful subgroups with distinct constellations of risk factors.

## **Methods**

### **Participants**

Youth in third, sixth, and ninth grades were recruited from schools in the greater Denver, CO and New Brunswick, NJ areas for enrollment in a multi-site, longitudinal study of mood disorders. Exclusionary criteria included autism spectrum or psychotic disorders, IQ less than 70, and non-English speaking. Recruitment procedures have been described in detail in previously published studies (Cohen, Young, Gibb, Hankin, & Abela, 2014; Hankin, Jenness, Abela, & Smolen, 2011). The current analyses only used data from participants who had completed at least three of the relevant time points. The final samples included 105 third grade, 119 sixth grade, and 104 ninth grade youth ( $n = 328$ ) recruited from Denver and 82 third grade, 108 sixth grade, and 102 ninth grade youth ( $n = 292$ ) from New Brunswick (total  $N = 620$ ). Participants' ages ranged from 7 to 16 years at baseline.

Sample demographics are listed in Table 3.1. A minority of participants in each sample also had a sibling enrolled in the study. The Denver and New Brunswick samples did not differ with regard to percent female, minority ethnicity, average SES, average HAP or CP severity, or number of participants who scored greater than 1.5 standard deviations above established gender normative values for these symptoms (Bourdon, Goodman, Rae, Simpson, & Koretz, 2005). According to this symptom threshold, the rates of elevated HAP and CP ranged from 4.6 to 6.4 percent.

Table 3.1

*Sample Demographics*

	<u>Denver</u>	<u>New Brunswick</u>
<i>n</i>	328	292
Female	185 (56%)	160 (55%)
Minority Race	104 (32%)	108 (37%)
Siblings	76 (23%)	66 (23%)
SES (SD)	48.65 (11.26)	49.19 (11.74)
HAP Severity (SD)	2.75 (1.97)	2.74 (1.95)
CP Severity (SD)	1.15 (1.25)	1.16 (1.15)
Elevated HAP	15 (4.6%)	17 (5.8%)
Elevated CP	21 (6.4%)	14 (4.8%)

*Notes.* Siblings = participants with at least one sibling also in the study. SES = Hollingshead 4 factor index (Adams & Weakliem, 2011). Elevated HAP and CP = participants with average SDQ z score > 1.5 standard deviations above the mean for HAP and CP, respectively.

**Procedures**

The parent study is an ongoing, prospective, multi-wave sequential cohort design aimed at studying depression in children and adolescents. I performed secondary analyses on disruptive behavior symptoms in these youth. Each youth and a parent participated in

a baseline laboratory visit. Parents provided written consent for themselves and their youth. The youth provided written assent. Thereafter, every three months following the baseline visit, participants completed behavioral questionnaires for 10 waves of follow-up assessment over 30 months. An additional laboratory visit took place at the 18-month follow-up. All procedures were approved by the University of Denver and Rutgers University institutional review boards.

## **Measures**

**Disruptive Behavior Symptoms.** Child HAP and CP symptoms were measured using the Strengths and Difficulties Questionnaire, Parent Report (SDQ; Goodman, 1997) every 3 months, from the 3- through 30-month follow-ups, for a total of 10 waves of data. The SDQ was not collected at the 18-month follow-up at the Denver site. The SDQ scales are highly correlated with other established parent-report measures of CP and ADHD symptoms, including the Rutter scales (ADHD  $r = .88$ ; CP  $r = .82$ ) (Goodman, 1997). Internal validity for the SDQ has been established for a large ( $N = 9,878$ ) sample of children age 4-17 (Bourdon et al., 2005). The SDQ HAP scale comprises five items that measure both inattentive and hyperactive/impulsive symptoms. The SDQ CP scale comprises five items measuring symptoms typical of ODD and CD. Both scales are rated by a parent on a scale of 0 “not true” to 2 “certainly true.” Items were reverse coded when necessary such that higher scores reflected more symptoms. Specific HAP and CP items, as well as correlations with clinical measures of HAP (SNAP-IV) and CP (CBCL) were described in Chapter 1.

**Socioeconomic Status (SES).** SES was ascertained at baseline using a demographic parent report. Information about both parents’ education levels and specific

occupations was used to calculate the Hollingshead Four-Factor Index (Adams & Weakliem, 2011).

**Negative Parenting and Positive Parenting.** Parenting constructs were measured at baseline using the Alabama Parenting Questionnaire (APQ), which is a parent self-report. Three negative parenting subscales measuring poor monitoring/supervision, inconsistent discipline, and corporal punishment were created following guidelines published by Shelton, Frick & Wootton (1996). These scales were averaged to create a single measure of negative parenting practices. The scales showed moderate internal validity in both the Denver and New Brunswick samples (*Chronbach's alphas* = .51 and .56, respectively). The positive parenting scale consisted of five related items identified by Shelton and colleagues, and has previously established internal and external validity (Shelton et al., 1996).

**Peer and School Problems.** Problems in the peer and school domains were assessed every three months using both youth- and parent-report on the Adolescent Life Events Questionnaire (Hankin et al., 2011; Hankin & Abramson, 2002). The Peer and Academic stress domains consisted of twelve and five face-valid items, respectively. An event was counted as occurring if either the youth or the parent endorsed it and total number of stressful events in each domain were summed across all time points.

### **Statistical Methods**

Growth mixture models were executed in MPLUS 7.3 (Muthén & Muthén, 2012). HAP and CP growth curves were modeled using age as the time variable by rounding participants' ages at each assessment to the closest quarter of a year, and further binning youngest and oldest ages such that at least six participants fell into each age interval. This

resulted in a model that estimated behavioral change between ages 8.75 and 17.75 years, with measurements every three months, and a median  $n$  of 138 participants at each age time point. Ninety percent of the time points included at least 100 participants. Growth trajectories were modeled over two levels, with family affiliation at level two to account for the non-independence of sibling data. Due to the cross-sequential study design, there was insufficient power to run individual GMMs within each sample, sex, and minority status. Thus, I compared posterior probabilities among these variables to estimate the replicability of the findings across sample, sex, and minority status.

GMM has an advantage over traditional Latent Class Growth Analysis (LCGA) because, like standard growth modeling, GMM allows for heterogeneity in growth parameters within classes. GMM expands on growth modeling by identifying latent classes with random intercept and slope parameters (Muthén & Muthén, 2000). Additionally, I tested equality of means of risk variables using the auxiliary command in Mplus, which applies Wald Tests of equality of means across latent trajectory classes (Muthén & Asparouhov, 2013). In contrast to typical tests of distal outcome variables, inclusion of the risk variables in this approach did not affect the trajectory specifications. Similar to an ANOVA, this method compared mean values of variables of interest across previously identified classes of growth; however, unlike ANOVA, by modeling the predictor in the growth mixture model, the mean values are compared using posterior probability-based multiple imputations, rather than fixed classification. In other words, the predictor variables are tested for effects across the latent trajectory classes, rather than across groups of participants who are most likely to belong to each of the classes.

## Results

### Individual Growth Trajectory Identification

First, I identified the optimal number of classes for HAP and CP independently. For each behavioral construct, I used the Technical 11 output option in Mplus, which compares Bayesian information criterion (BIC; Schwarz, 1978) of the current model versus a model with one fewer class. A significant  $p$  value and lower BIC indicates a better fit. Because the computational load was high, I first ran each of the models without the BIC calculation, then specified the optimal seed generated by the first output in the OPTSEED command in Mplus, which reduced the computational stress and allowed us to re-run the model requesting the BIC comparison. HAP fit a three class model best, with the four class model demonstrating a non-significant change in BIC. In contrast, CP fit a two class model best. For both constructs, intercept, slope and quadratic parameters were retained as all three terms were significant in at least one of the latent classes. Hence, I found fewer than the predicted four trajectories for each symptom dimension, three for HAP and two for CP.

The three HAP trajectories showed comparable intercept values but distinct linear and quadratic patterns (see Table 3.2). The High HAP group had the highest intercept, with an increasing linear trajectory that peaked at age 14.81 years and decelerated thereafter. The Moderate HAP group showed linear stability in symptom severity across age, with a peak at age 12.58 and a slight decrease in later adolescence. The Low HAP group showed rapid decline in early symptom severity with the lowest point at age 16.05. This solution was similar to three of the trajectories identified in prior research (Nagin & Tremblay, 1999; Shaw et al., 2005; Van Lier et al., 2007); however, unlike these studies,

the current sample did not fit a fourth HAP trajectory. Further, I did not predict significant slopes in the High and Low trajectories, while I did expect to see moderate increasing and moderate decreasing trajectories. Thus, the predicted growth patterns did not map onto the results.

Table 3.2

*HAP Trajectory Latent Parameters*

	<u>High</u>	<u>Moderate</u>	<u>Low</u>
Intercept <i>M</i> (SE)	3.98 (1.65)*	3.48 (.49)***	3.51 (.29)***
Slope <i>M</i> (SE)	.97 (.48)*	.23 (.17)	-.73 (.09)***
Quadratic <i>M</i> (SE)	-.08 (.04)*	-.03 (.02)*	.05 (.01)***
Proportion	9%	36%	55%

*Notes.* *M* (SE) = Mean (standard error). Proportions based on estimated posterior probabilities

The two CP growth trajectories included Low and High intercept groups with opposite linear and quadratic growth patterns. The Low CP group showed a linear decrease over time, with a low trough at age 13.25 and a slight incline thereafter. The High CP group had a moderately severe intercept that peaked in severity at age 12.31 and decreased to moderate levels of CP by the end of adolescence. (see Table 3.3). The shape of the High CP latent trajectory was comparable to that identified by Van Lier and colleagues (2007). However, unlike that study and those by Nagin & Tremblay (1999) and Shaw et al. (2003), which found three- and four-class solutions, respectively, the



current analysis identified only two latent trajectories. The High CP trajectory showed a decrease in symptom severity overall; thus, it mapped onto the predicted high decreasing class. Severity of CP in the Low trajectory, as predicted, remained relatively stable overall. However, I did not see the expected high stable and moderate decreasing classes.

Table 3.3

*CP Trajectory Latent Parameters*

	<u>High</u>	<u>Low</u>
Intercept $M$ (SE)	2.74 (.60)***	1.16 (.12)***
Slope $M$ (SE)	.57 (.21)**	-.18 (.05)***
Quadratic $M$ (SE)	-.08 (.02)***	.02 (.01)***
Proportion	14%	86%

*Notes.*  $M$  (SE) = Mean (standard error). Proportions based on estimated posterior probabilities

**Parallel Process HAP and CP GMM**

With the growth classes identified in the individual models, I next tested for associations between the three HAP and two CP latent trajectory classes. I hypothesized that consistent with previous literature, CP trajectory would be a better indicator of HAP severity than vice versa. Thus, I predicted their developmental relation would be *asymmetrical*. It is virtually inevitable that HAP and CP trajectories will be correlated, given the high level of cross-sectional correlation between HAP symptoms and CP at each time point ( $r = .48$  to  $r = .63$ ). But a specific directional relation (asymmetry) is not

inevitable, since the high cross-sectional correlations would be equally consistent with either direction of relation or an equal one (reciprocal influence). Specifically, I expected that the High CP trajectory would predict greater odds of High HAP growth compared to Moderate HAP, but High HAP and Moderate HAP trajectories would not increase odds of the High CP trajectory. In other words, a High CP trajectory would rarely exist outside the context of a severe HAP trajectory, but High HAP would commonly exist absent of High CP.

To estimate the associations between trajectories, I ran a parallel process growth mixture model with user specified starting values for the intercept and growth parameters within each class. The starting values were the trajectory parameter means from the individual models, and were specified in order to reduce the computational load and retain the order of latent trajectory classes.

Consistent with the hypothesis, probability of a High HAP trajectory given a High CP trajectory was substantial (94%), while likelihood of Low HAP given High CP was low, only 6% (Table 3.4). Multinomial logistic regression showed a significant predictive effect of the High CP trajectory on the High (versus Low) HAP trajectory ( $b = 4.82$ ,  $SE = .78$ ,  $p < .001$ ,  $OR = 123.97$ ).

In contrast, youth in the High HAP trajectory were about equally likely to follow a High (58%) or Low (42%) CP trajectory (Table 3.4). However, the Low HAP trajectory was a significant predictor of CP development: given a Low HAP trajectory, there was a near perfect probability (99%) of following a Low CP trajectory (Table 3.5).

Table 3.4

*Probability of HAP Trajectory Given CP Trajectory*

		HAP		
		<u>High</u>	<u>Moderate</u>	<u>Low</u>
CP	High	94%	0%	6%
	Low	10%	14%	76%

*Note.* Proportions for the Latent Classes Based on Estimated Posterior

Probabilities

Table 3.5

*Probability of CP Trajectory Given HAP Trajectory*

		CP	
		<u>High</u>	<u>Low</u>
HAP	High	58%	42%
	Moderate	0%	100%
	Low	1%	99%

*Note.* Proportions for the Latent Classes Based on Estimated Posterior

Probabilities

### **Dual Trajectory Model**

Next, I modeled dual HAP and CP trajectories in a single latent class GMM, such that all six parameters (HAP and CP intercepts, slopes, and quadratic terms) were

modeled together in each specified class. Unlike previous studies that have identified dual trajectories by combining pairs of individual trajectory classes together, the current approach identified the best fit GMM for the data by integrating using both behavior processes. As with the individual models, I tested for the best fit for the number of classes using the BIC comparison. The dual trajectory model fit three classes best (Vuong-Lo-Mendell- Rubin Likelihood Ratio Test Value:  $2*\Delta-LL = -120.08$ ,  $df = 7$ ,  $p = .043$  versus the two class model, and  $2*\Delta-LL = 102.69$ ,  $df = 7$ ,  $p = .658$  versus the four class model).

Parameters for the three dual trajectory classes are listed in Table 3.6. Altogether, the first of the dual trajectories, which will be called Chronic, was characterized by high levels of both HAP and CP, and comprised an estimated 7% of the sample. The second trajectory, henceforth “Moderate” (22%), was characterized by initially moderate HAP and low CP, with a slight decrease in HAP, and a slight increase in CP over time, both with negative quadratic shapes. Finally, the third trajectory, “Low,” was the most common (72%) and was characterized by moderate HAP and low CP, which both showed linear decreases over time that decelerated after early adolescence (see Figures 3.1-3.3).

Consistent with the individual HAP trajectory GMM, the intercept means for all three latent trajectory classes were comparable and in the moderate severity range (about one-half standard deviation above the sample mean). I performed follow-up Wald Test comparisons using the Model Test command in Mplus in order to test equality of pairs of parameters across trajectory classes and determined that these intercepts were not significantly different across the three trajectories. In contrast, the HAP linear and quadratic slopes of the three trajectories were significantly different from one another ( $p < .01$ ). Thus, with regard to HAP severity, the three dual trajectories were distinguished

by their rates and shapes of HAP growth, rather than by starting levels in childhood. In contrast, the Chronic dual trajectory had a significantly more severe CP intercept than the other two trajectories ( $p < .05$ ), while the CP intercepts for Moderate and Low trajectories were not different. The CP intercept in the Chronic trajectory was almost two standard deviations above the sample mean. Both the Chronic and Moderate trajectories showed initial increases in CP severity; however, this increase decelerated for youth in the Chronic trajectory, such that they returned back to initial levels of CP by the end of high school. On the other hand, youth in the Moderate dual trajectory showed steady increase in severity that did not decelerate as rapidly as the Chronic trajectory. However, follow-up Wald Tests showed that neither the linear nor quadratic slopes in these two trajectories were significantly different from one another. The Low CP linear slope was negative, with a deceleration during high school ages; the linear and quadratic CP slopes for the Low dual trajectory were significantly different than the parameters in the other two trajectories ( $p < .01$ ).

Table 3.6

*Dual HAP-CP Trajectory Latent Parameters*

		<u>Chronic</u>	<u>High</u>	<u>Low</u>
HAP	Intercept	3.84 (1.26)**	3.34 (.55)***	3.57 (.21)***
	Linear Slope	.85 (.44)	.41 (.18)*	-.51 (.08)***
	Quadratic Slope	-.10 (.04)*	-.06 (.02)***	.04 (.01)***
	Peak/Trough Age	13.00	12.17	15.13
CP	Intercept	3.26 (.83)***	1.13 (.39)*	1.23 (.13)***
	Linear Slope	.61 (.32)	.46 (.13)***	-.29 (.05)***
	Quadratic Slope	-.07 (.03)*	-.05 (.01)***	.03 (.00)***
	Peak/Trough Age	13.11	13.35	13.58
Proportion		7%	21%	72%

*Notes.* Peak/Trough Age = age in years at which behavior is highest or lowest, depending on quadratic shape. Proportions are based on posterior probability estimates.

The Chronic and Low trajectories were comparable to dual trajectory combinations identified in previous studies (Nagin & Tremblay, 1999; Shaw et al., 2005; Van Lier et al., 2007). However, the Moderate dual trajectory was unique. While the HAP intercept in this trajectory was in the moderate range and showed an initial increase in severity through childhood, severity peaked in early adolescence and returned to the average range by late adolescence. In contrast, initial CP severity in the Moderate

trajectory was modest, but increased and maintained a severity level about one-half standard deviation above average by late adolescence. The Moderate dual trajectory was therefore consistent with developmental theory models in which HAP precedes emergence of less severe CP (Loeber & Keenan, 1994; Waschbusch, 2002). Beauchaine and colleagues (2010) hypothesized that this sequence was due entirely to environmental risk incurred by genetically predisposed youth. However, those authors specified emergence of HAP as early as toddlerhood. Further, they described youth for whom CP outcomes were severe, which would be more consistent with the Chronic dual trajectory. Thus, I proposed that the Chronic and Moderate dual trajectories reflected unique developmental patterns; thus the Chronic dual trajectory was not a more severe version of the Moderate dual trajectory.

### **Additive Severity GMM**

To begin to address the question of whether the Chronic dual trajectory was due to additive risk or synergistic relations between HAP and CP, I tested a single process disruptive behavior GMM by adding the HAP and CP severity scores at each time point. Unlike the dual trajectory model, the best fit GMM for the combined severity was only a single class. The overall trajectory showed stability in total disruptive behavior symptom severity over time, with a linear decrease over age ( $b = -.34$ ,  $SE = .09$ ,  $p < .001$ ) and a non-significant quadratic slope ( $b = .02$ ,  $SE = .01$ ,  $p = .054$ ). This indicates that, in contrast with the individual and dual HAP and CP GMM, the additive severity model does not adequately capture important developmental differences in disruptive behavior development. The results are supportive of a synergistic, rather than additive, association between HAP and CP.

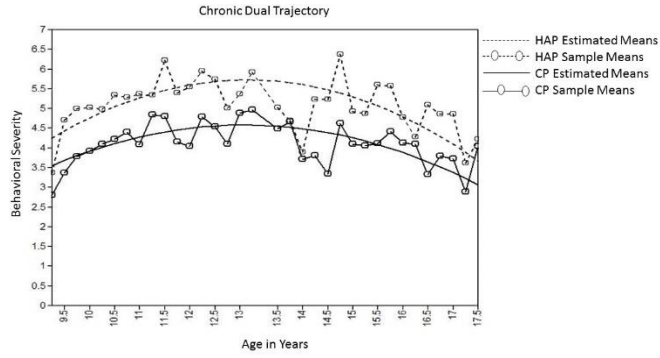


Figure 3.1. Estimated and sample means for the Chronic dual trajectory.

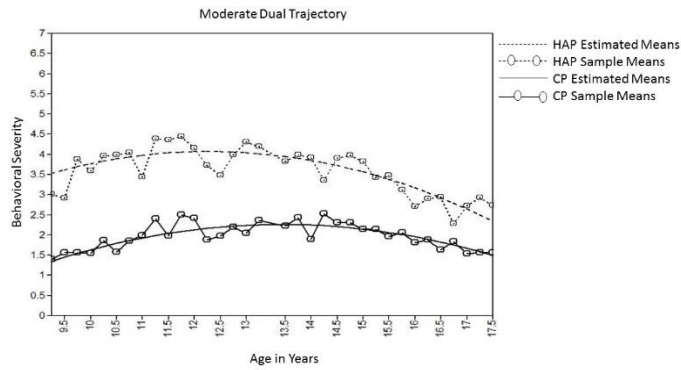


Figure 3.2. Estimated and sample means for the Moderate dual trajectory.

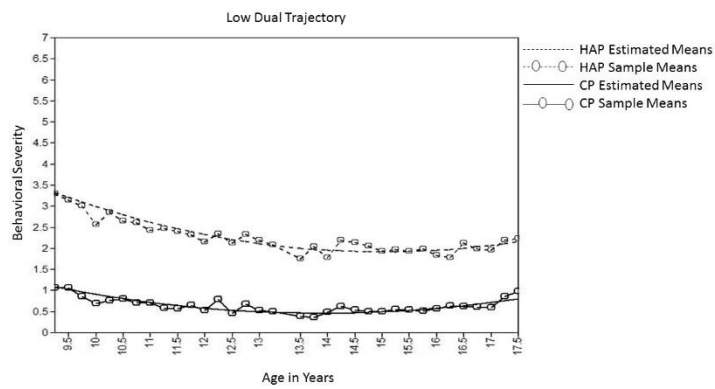


Figure 3.3. Estimated and sample means for the Low dual trajectory.



## **Hypotheses for Risk Variables**

To further address the issue of additive versus synergistic effects, I tested the associations between the dual process trajectories and environmental and child risk variables. I hypothesized that the Chronic trajectory would be associated with certain risks that the Moderate and Low trajectories would not, and this would further indicate that the Chronic trajectory was unique (synergistic) rather than just a more severe manifestation of the Moderate trajectory.

Given the paucity of previous research examining specific environmental risk correlates of joint HAP/CP developmental trajectories, the analyses were somewhat exploratory. However, prior research on the individual trajectories of each behavioral construct informed the hypotheses. Specific predictions regarding which dual trajectories would have the highest proportion or mean level of risk are listed along with results in Table 3.7.

I was unable to replicate the models across each sample individually, due to low power. Instead, I tested whether an equal number of participants from each sample was represented across all three dual trajectory groups, to estimate whether the dual trajectory model was appropriate for both samples. Likewise, I tested for differences in rates of sex and minority status participants across the dual trajectories. Rates of ADHD are significantly higher in males than females (Willcutt, 2012). However, prior research on sex differences has indicated that girls with high levels of HAP are more likely to have comorbid HAP and CP, and sex differences in rates of oppositional defiant and conduct disorders are inconsistently found, particularly in adolescents (Loeber, Burke, Lahey, Winters, & Zera, 2000; Waschbusch, 2002). Thus, I expected to see an equal distribution

of males and females in the Chronic trajectory, which represented a comorbid subtype. In contrast, I hypothesized that the Moderate trajectory would include more males than females, and that this sex difference would be a proxy for unique genetic risk. Different distributions of male sex in the Chronic versus Moderate trajectories would also indicate synergistic, rather than additive associations between HAP and CP.

There is limited research on racial and ethnic differences in rates of disruptive behavior disorders. Some studies have reported more incidence of HAP and CP in African American youth relative to Hispanic and White youth, while others have found no differences in incidence of conduct disorder or oppositional defiant disorder (Jaffee & Odgers, 2013; Nolan, Gadow & Sprafkin, 2001; Reid et al., 2000). More than one-third of the sample identified as non-White; however, the identified races were disparate and included youth identifying as multi-racial. As a result, I did not have power to examine equality of means of individual races across the dual trajectories; rather I described youth as either Caucasian or non-Caucasian. As this characterization was quite limited, I did not expect to find differences among the dual trajectories in their percentage of minority youth. I hypothesized that the three dual trajectories would be equally represented by Caucasian and non-Caucasian participants.

Within the family risk domain, I expected that the Chronic and Moderate trajectories would be associated with increased odds of divorce, based on previous research finding repeated associations between divorce and high levels of HAP and CP in young children, as well as brief increases in behavioral severity when divorce occurs in adolescence. As an explanation for the Moderate trajectory behavioral growth patterns, I hypothesized that divorce, absent of additional genetic or environmental risk, could

explain the increase in CP or the initial moderate levels of HAP that resolved over time. However, I expected that the Chronic trajectory would have higher rates of divorce than the Moderate trajectory, given potential gene-environment correlations among divorcing parents (i.e. higher rates of divorce among parents who themselves exhibit HAP and CP traits), as well as potential transactional effects between difficult child behaviors and marital stress. Thus, I did not expect divorce to provide support for a synergistic effect, as I still expected incrementally higher rates of divorce in the Moderate and Chronic trajectories, respectively. I did not expect the Low trajectory to have a significant odds ratio of divorce.

The literature on low SES and HAP is mixed, with some research finding that low SES is associated with all subtypes of ADHD (e.g. Larsson et al., 2011), and others finding no specific correlation between SES and HAP in youth (Waschbusch, 2002). On the other hand, severe CP and comorbid HAP-CP have been repeatedly associated with low SES (Frick, Kimonis, Dandreaux, & Farell, 2003). A meta-analysis by Waschbusch (2002) also found a distinction between referred and non-referred samples wherein the latter also reported low SES in youth with only HAP or CP but the former did not. Given the gene-environment correlation that exists as an explanation for low SES families, I predicted that this variable would be uniquely low in the Chronic trajectory, and thus would indicate synergy rather than additive effects for the Chronic dual trajectory.

Negative parenting has been uniquely associated with CP (Deault, 2010), and particularly with high chronic versus desisting levels of CP (Shaw et al., 2003). Thus, I expected that the Chronic dual trajectory would have higher odds of negative parenting relative to the other two trajectories. I further hypothesized that transactions between

negative parenting and behavioral severity over time could explain the linear increase in CP in the Moderate trajectory. However, I expected that in order to have a later onset CP than the Chronic trajectory, the youth would have less negative parenting than the Chronic trajectory due to a) better equipped parents or b) less severe initial behavior which would in turn elicit lower levels of negative parent-child interaction. Thus, I hypothesized that the Moderate trajectory would have less negative parenting than the Chronic trajectory, but more negative parenting than the Low trajectory, which would not support synergy, but would not rule it out.

On the other hand, given that positive parenting has been shown to have a mitigating effect on severe CP (Chronis et al., 2007; Pasalich et al., 2011), I expected to find more positive parenting in both the Moderate and Low dual trajectories than the Chronic trajectory. I theorized that the Moderate trajectory could include youth who might have been at early risk for chronic HAP and CP, but who maintained only moderate and later-onset CP symptoms due to mitigating effects of positive parenting. I expected comparable levels of positive parenting between the Moderate and Low latent trajectory classes. Significantly lower rates of positive parenting in the Chronic trajectory could support a synergistic etiology.

The current analyses measured stressful events related to peer relations, including rejection, arguments, bullying, and peer pressure. A meta-analysis by Waschbusch (2002) found that peer problems and social skills were particularly pronounced in comorbid HAP-CP relative to either HAP or CP alone. Other research has found that high severity HAP and CP youth were rejected early on and thus lacked opportunity for peer difficulties (Laird et al., 2001). Endorsement of the peer stress items on the ALEQ

generally depended on some interaction with peers; thus, if I expected that the Chronic dual trajectory represented youth who were entirely isolated by peers, I would not have hypothesized any peer problems in this trajectory due to lack of opportunity. However, given that I was testing a representative sample, I hypothesized that youth in the Chronic trajectory would include non-rejected as well as rejected youth, and would thus have moderate levels of peer problems, on average. With regard to the Moderate trajectory, I proposed that peer problems were a potential etiological risk factor that could explain the increase in CP over time. Thus, I expected comparable levels of peer problems in the Chronic and Moderate trajectories, and greater peer problems in these two groups relative to the Low trajectory. Thus, this risk variable would not support a synergistic hypothesis.

Finally, I hypothesized that the Chronic and Moderate trajectories would be associated with worse academic problems than the Low trajectory. Previous literature supports transactions between academic problems and elevated HAP in youth (e.g. Arnett et al., 2012; Metcalfe et al., 2013). These transactions would result in a stable or increasing level of behavioral severity over time; thus, I expected to see the worst academic problems associated with the Chronic trajectory. However, prior studies have also indicated that with regard to CP, academic stress precedes symptoms of conduct disorder (Hinshaw, 1992; Metcalfe et al., 2013). Given the positive linear slope in CP in the Moderate trajectory, I hypothesized that there might be worse academic problems in this class than in the Low class, and that academic problems might therefore explain the increase in CP behavioral severity among youth with initially modest levels of behavioral problems. As with peer problems, I expected that academic problems would be

comparable between the Chronic and Moderate trajectories, which would not indicate synergy.

In order to test the hypotheses regarding risk variables, I ran the three class, dual trajectory model using the Auxiliary (E) and (DCAT) commands in MPlus 7.3 to specify continuous and categorical auxiliary models, respectively. The benefit of this approach was that the effect of the risk variables on the overall GMM was minimized (Asparouhov & Muthén, 2014). Thus, the analyses tested equality of means of the risk variables across latent classes based on posterior probabilities, but the risk variables did not change the parameters or posterior probabilities of the latent classes themselves. One disadvantage of this approach was that the DCAT specification could not be used in conjunction with the complex (i.e. two level) analysis that I had specified to account for non-independence of sibling data. Thus, the results of the categorical auxiliary analyses did not correct for sibling relationships, which comprised 23% of the sample. This limitation would most likely result in Type I error; thus, I set the significance level at  $p < .01$  for the binary risk variable analyses.

Table 3.7

*Auxiliary Risk and Dual Trajectory Association Hypotheses and Results*

<u>Variable</u>	<u>Hypothesis</u>	<u>Results</u>
Sample	No differences	No differences
Male	Moderate >Chronic, Low	<b>No differences</b>
Minority	No differences	No differences
Divorce	Chronic > Moderate > Low	<b>Chronic &gt; Moderate, Low</b>
Low SES	Chronic > Moderate, Low	<b>Chronic&gt;Low</b>
Negative Parenting	Chronic > Moderate > Low	Chronic > Moderate > Low
Positive Parenting	Chronic < Moderate, Low	<b>No differences</b>
Peer Problems	Chronic, Moderate > Low	Chronic, Moderate>Low
Academic Problems	Chronic, Moderate > Low	Chronic, Moderate>Low

Note. Bold patterns in the third column indicate results that differed from the hypotheses.

**Child Risk Variables**

As predicted, there were no differences in sample origin across the three dual classes, with odds ratios ranging from .73 to 1.14 across all three classes, and no significant chi square difference across all three classes. Contrary to expectations, males and females were equally distributed across the three dual trajectories as well ( $OR = 1.00$  to 1.24). Minority status was slightly more likely in the Low trajectory ( $OR = 1.39$ ), but not in the Chronic or Moderate trajectories ( $OR = 1.22$  and 1.00, respectively), and there were no overall differences in minority stratification among classes. This suggests that

the final dual trajectory model was a good fit for both samples, as well as both sexes and (broadly speaking) minority as well as Caucasian youth.

### **Family Risk Variables**

Odds of parental divorce were large in the Chronic trajectory ( $OR = 5.26$ ), modest in the Moderate trajectory ( $OR = 1.57$ ), and insignificant in the Low trajectory ( $OR = 1.00$ ). The overall test of equality of means across the dual trajectories was significant, indicating differences in divorce rates across the three trajectories  $\chi^2(2) = 16.61, p < .001$ . As expected, pairwise comparisons indicated that the Chronic trajectory had significantly greater rates of divorce than both the Moderate ( $\chi^2(1) = 6.71, p = .010$ ) and Low ( $\chi^2(1) = 14.17, p < .001$ ) trajectories. Contrary to expectations, the Moderate and Low trajectories had comparable rates of divorce ( $\chi^2(1) = 2.32, p = .127$ ). These results suggest that a chronic, high trajectory of HAP and CP may be uniquely associated with divorce, which would support a synergistic etiology for the Chronic dual trajectory.

The overall test of equality of means showed that SES was not significantly different across the three dual trajectories, although there was a trend in that direction ( $\chi^2(2) = 5.66, p = .059$ ). Pairwise comparisons indicated that the Chronic trajectory had a significantly lower mean SES (43.99) than the Low (49.66:  $\chi^2(1) = 6.29, p = .012$ ) trajectory, but contrary to predictions, mean SES associated with the Moderate trajectory (47.73) was not significantly different from either of the other two trajectories. This result is harder to interpret with regard to additive versus synergistic effects; however, given that SES was lower in the Chronic trajectory relative to the Low trajectory, while the Moderate trajectory did not differ in SES from the Low trajectory, low SES appears to be



uniquely associated with the Chronic dual trajectory, which would be consistent with synergy.

The overall test of equality of means for negative parenting was statistically significant ( $\chi^2(2) = 31.11, p < .001$ ), indicating overall differences among the three dual trajectories. As predicted, the Chronic trajectory was associated with more negative parenting than both the Moderate ( $\chi^2(1) = 8.79, p = .003$ ) and Low ( $\chi^2(1) = 31.14, p < .001$ ) trajectories. Further, the Moderate trajectory had more negative parenting than the Low trajectory ( $\chi^2(1) = 14.38, p < .001$ ). This result could be consistent with either additive or synergistic effects for the Chronic dual trajectory.

The overall test of equality of means for positive parenting was not significant ( $\chi^2(2) = 2.11, p = .349$ ), nor were any of the pairwise tests, indicating that in this sample, positive parenting did not relate to dual HAP and CP latent growth trajectories.

### **Peer Problems**

There were significant differences in peer problems overall among the dual trajectories ( $\chi^2(2) = 16.86, p < .001$ ). As predicted, although the Chronic dual trajectory had the most severe peer problems, the severity was not significantly different from the level of peer problems in the Moderate trajectory ( $\chi^2(1) = 3.05, p < .081$ ). Both the Chronic and Moderate trajectories had significantly worse peer problems than the Low trajectory ( $\chi^2(1) = 16.24, p < .001$  and  $\chi^2(1) = 14.09, p < .001$ , respectively). These results indicate that in the current sample, chronic high levels of HAP and CP did not result in complete social isolation that would eliminate negative interactions measured by the ALEQ. Rather, the level of disruptive behavior symptoms experienced by the Chronic youth were sufficient to cause high levels of negative peer interactions. The comparable

association between peer problems for youth with a Moderate dual trajectory indicates that high initial levels of HAP may be sufficient to drive the peer problem association, and CP severity may increase in association with overall stress in peer relationships. Thus, as predicted, severity of peer problems did not suggest a synergistic effect for the Chronic dual trajectory, but also did not rule it out.

### **School Problems**

The overall chi square test for school problems was significant, indicating differences in mean school problem severity across the three dual trajectories ( $\chi^2(2) = 26.14, p < .001$ ). As predicted, school problems in the Chronic and Moderate trajectories were comparable ( $\chi^2(1) = 2.40, p = .122$ ), and both trajectories had worse school problems than the Low trajectory ( $\chi^2(1) = 21.24, p < .001$  and  $\chi^2(1) = 24.99, p < .001$ , respectively). Thus, as I hypothesized, school problems appeared to be associated both with high Chronic and Moderate trajectories of HAP and CP, and no synergistic effect was supported. As with peer problems, the comparable association with school problems for both the Chronic and Moderate trajectories indicates that initial high levels of HAP may place youth at risk for school problems, and consistent with previous literature, CP severity may increase in response to this stress.

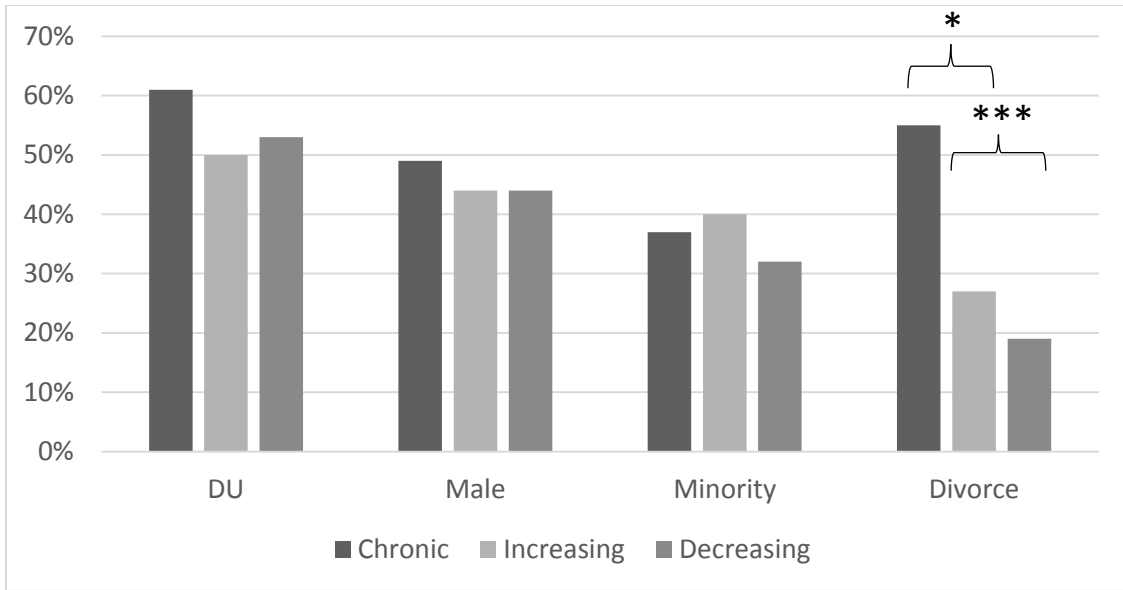


Figure 3.4. Binary predictors of dual growth trajectories. \* $p < .05$ , \*\*\* $p < .001$ .

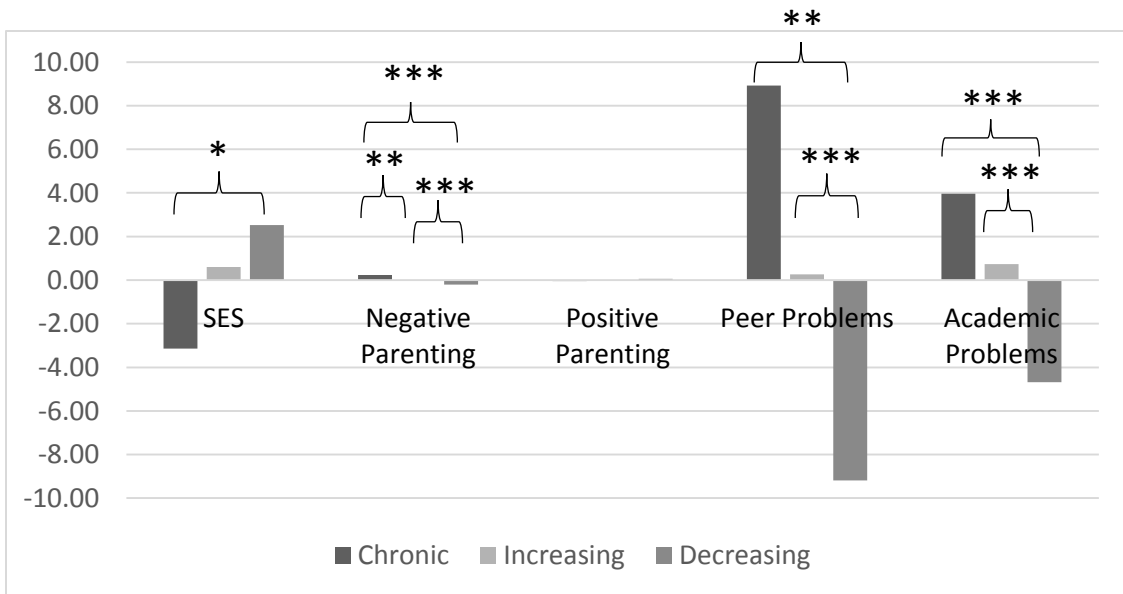


Figure 3.5. Continuous predictors of dual growth trajectories. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . Values are mean-centered for illustrative purposes.

## Discussion

In these analyses, I examined dual growth trajectories of HAP and CP symptoms in three cohorts of 3<sup>rd</sup>, 6<sup>th</sup> and 9<sup>th</sup> grade youth. The model fit three latent classes best for HAP trajectories, two classes for CP latent trajectories, three trajectory classes for the dual HAP and CP GMM, and only a single class for the additive disruptive behavior (i.e. HAP + CP) GMM. Previous research has typically identified four trajectory classes each for the individual behavioral constructs; however, these prior studies usually included high risk youth, unlike the population-based sample in the current analyses. The absence of the additional trajectories in the current sample is likely attributable to a) lack of behavioral variance in the population sample, and b) the age of the sample. Youth who are high on callous/unemotional traits are less common even among high risk youth, and they have been shown to show unique patterns of change in behavioral severity over time (Frick, Stickle, Dandreaux, Farrell, & Kimonis, 2005). The current, representative sample included only moderate levels of CP severity and thus there may not have been power to identify disparate growth patterns among the most severe youth. With regard to the age of the sample, Shaw and colleagues (Shaw et al., 2005) found that severity of the “moderate desister” HAP and CP trajectories nearly converged with that of the Low trajectory youth by age 10 years, indicating that the number of trajectory classes may decrease prior to third grade, when the current analyses began.

I found that a High CP trajectory was nearly always associated with a High HAP trajectory, while a High HAP trajectory predicted a High CP trajectory only about half the time. On the other hand, a Low HAP trajectory was a very strong predictor of a Low CP trajectory. These results corroborate earlier findings from at-risk, male samples

(Nagin & Tremblay, 2001; Shaw et al., 2005) indicating that high CP severity is a better predictor of high HAP severity. Altogether, these results indicate that severe CP rarely develops absent of severe HAP, but HAP symptoms are often present independent of CP. Further, this directional association suggests that while the etiology of a High CP trajectory is sufficient to likewise cause a High HAP trajectory, the opposite is not true.

The Moderate dual trajectory identified in these results was of particular interest, due to the unique developmental patterns for HAP and CP. This dual trajectory has not been identified in previous latent class analyses and might be a result of the statistical approach, which sought a solution for GMM using all HAP and CP latent parameters, rather than merely combining the trajectories identified in individual process models. The Moderate dual trajectory is consistent with a previously supported developmental sequence in which HAP precedes CP. This trajectory may also be consistent with the clinical diagnosis of adolescent onset conduct disorder; however, sample means for CP in this trajectory remained only slightly above the norm and thus would not meet diagnostic threshold in a clinical setting. Nonetheless, the results provide insight into development of CP symptoms among typically developing and low-risk youth. Further, this trajectory was equally likely to experience peer and academic problems as the Chronic trajectory, increasing its validity as an affected group despite below-threshold symptom presentation. Positive parenting was not associated with the Moderate trajectory, indicating that a particularly adaptive parenting environment did not account for the difference between Chronic and Moderate dual trajectory behavioral outcomes.

Males and females were equally represented in all three dual trajectories, indicating that unlike the sex disparity in ADHD diagnoses, dual HAP and CP

developmental trajectories do not show a sex difference. However, given that I could not test the best fit dual GMM in each sex separately, this is a question that deserves further investigation in future research. Likewise, the equal presence of both samples across the three dual trajectories indicates a good fit for the model in both samples. However, in order to truly replicate the findings I would have needed to test the models separately in each sample; unfortunately, I did not have sufficient power to do so.

I sought to clarify previous disagreement about whether chronic, comorbid HAP and CP represents a synergistic (i.e. unique) disorder or merely a more severe manifestation of the combined disruptive behavior constructs. I found that additively combining HAP and CP into single disruptive behavior ratings at each time point resulted in a very different GMM solution than the dual trajectory model, with only one class identified in the former compared to three in the latter. This indicates that differences among the Chronic, Moderate and Low dual trajectories were important, and did not merely represent additive effects. Further, the Chronic dual trajectory was uniquely associated with two of the auxiliary risk variables: divorce and low SES, consistent with prior research (for meta-analysis, see Waschbusch, 2002). Again, these tests of external validity for the Chronic versus Moderate dual trajectory suggest synergistic effects between high, chronic levels of HAP and CP. However, the results do not clarify the direction of effects between the Chronic dual trajectory and associated risk; while divorce and low SES may be uniquely associated with the Chronic dual trajectory, it is unclear whether the interaction of the behaviors results in family risk, or family risk (or some highly associated parental characteristic) leads to a Chronic dual trajectory, or whether there are bidirectional influences.

Future research could further clarify this issue by testing for equality of means of neuropsychological endophenotypes across the three trajectories, which would approach the question of a common versus distinct neuropsychological etiology for these three trajectories. Further, use of balanced likert scale measures of HAP and CP would allow examination of risk and etiological factors across the full spectra of behavioral severities. Due to the truncated measurement of HAP and CP in the SDQ (similar to other common disruptive behavior questionnaires), the full spectrum of adaptive behaviors in these domains, such as good attention and prosocial behaviors, is not captured (Arnett et al., 2013). This truncated variance limits the magnitude of correlation one can detect between disruptive behaviors and a more normally distributed variable, such as SES. Further, it limits conclusions about a) the number of developmental trajectories (as there may be additional dual trajectories within the Low class) and b) the association between risk variables and the full spectrum of HAP and CP developmental patterns.

Here I found a unidirectional relationship wherein CP trajectory predicted HAP trajectory, while in Chapter 1 I report a temporal relationship with individual fluctuations in HAP predicting CP in older youth. Importantly, the two sets of results are not contradictory. The results from Chapter 1 suggested that direct and/or indirect associations exist between within-person variation in HAP and CP in older youth. Here, the results suggest that the etiology of severe CP is shared by severe HAP, but not by less severe levels of HAP and CP. Thus, youth on a high CP trajectory are likely to also follow a high HAP trajectory. Together, these results are consistent with a model in which 1) on average, HAP develops earlier than CP, due to both shared and unique genetic and environmental risk; 2) for certain constellations of risk factors, HAP and CP

both manifest as severe; 3) for other constellations of risk, HAP may develop absent of CP, or both symptom clusters may be moderate to low in severity; and finally, 4) in older youth, at any level of overall behavioral severity, spikes in HAP severity predict spikes in CP severity within just a few months, via direct and/or indirect processes.

### **Limitations**

In addition to measuring a truncated spectrum of HAP and CP behaviors, the SDQ was a limitation of these analyses due to the measure's lack of attention to clinically identified subtypes of disorders associated with HAP and CP. Additional raters of child disruptive behaviors, such as teachers or testers, would have been welcome, given the possibility of rater bias when parents reported on both HAP and CP simultaneously. Further, the current analyses would have been strengthened by an additional cohort of very young children, in order to capture the full developmental trajectory from early childhood through late adolescence. Future research would benefit from a prospective study of youth beginning at birth and followed through adulthood, with multiple informants and using a more balanced measurement tool, although the logistical challenges of such a study are fully acknowledged by this author.

### **Strengths**

The current analyses aimed to address weaknesses in previous research on the developmental course and risk factors associated with dual HAP and CP trajectories. I used GMM to identify latent classes of HAP and CP growth trajectories, which allowed for heterogeneity within the classes. Unique to these analyses was the identification of the dual process latent class trajectories, as these were modeled by estimating both HAP and CP parameters, rather than forcing combinations of each of the individual trajectories.



The latter approach would have resulted in an over-estimation of the number of dual trajectories that fit the data best. Additionally, unlike in previous research, the effects of predictor variables on trajectory classifications did not affect identification of the latent trajectory classes in these analyses.

Additional advantages of my approach were that I tested both HAP and CP symptoms in two replicate samples of population youth. The importance of examining risk factors in typical youth was described by Frick (2012). As the majority of youth do not go on to develop significant psychopathology, population samples allow us to identify protective factors and growth patterns associated with healthy levels of HAP and CP symptoms in youth, which can in turn inform intervention strategies for those with unhealthy behavioral patterns. Finally, I measured both HAP and CP symptoms across ten time points, such that I was able to test for associations between the symptom trajectories, rather than treating one static symptom severity as a predictor of growth in the opposite symptom cluster.

CHAPTER 4.

LACK OF INTERACTION BETWEEN MAOA GENOTYPE AND NEGATIVE  
PARENTING FOR CONDUCT PROBLEMS IN A NORMATIVE SAMPLE OF  
YOUTH

Advances in genotyping technology over the past several decades have allowed researchers to test main effects of specific, *a priori* identified candidate gene variants as well as interactive effects of these candidate genes with environmental risk factors, known as candidate gene x environment interactions (cGxE). In the context of psychological development, cGxE are theoretically plausible explanations for individual variability in outcomes. Positive interaction results for cGxE analyses suggest that genotype moderates the correlation between environmental risk and behavior, and vice versa, such that a child with a certain genetic predisposition may be more vulnerable to maladaptive outcomes if he or she is exposed to a certain set of environmental risk factors. These results have implications for early identification of risk as well as individually tailored treatments.

With regard to disruptive behavior disorders, Caspi et al. (2002) published one of the most well-known cGxE studies, reporting that the effect of child maltreatment on adult CP outcomes was stronger for males who exhibited the low-acting functional polymorphism in the promoter region of the monoamine oxidase A (MAOA) gene. MAOA transcription is believed to influence behavioral regulation via regulation of norepinephrine, serotonin and dopamine expression. Genetic abnormalities in MAOA have been linked to aggression in mice and antisocial behavior in humans (Cases et al., 1995; Shih & Thompson, 1999; Brunner, Nelen, Breakefield, Ropers & van Oost, 1993). Thus MAOA was a reasonable candidate for the original cGxE study by Caspi and colleagues (2002). Attempts to replicate this groundbreaking study have since revealed mixed results; however, a follow-up study and meta-analysis conducted by the original

authors (Kim-Cohen et al 2006) reported pooled effect sizes ranging from .15 to .18 consistent with the original interaction.

Despite the theoretical support and promising clinical application of cGxE, there are several limitations to these statistical analyses that have recently been acknowledged (see Dick et al., 2015 for review). First, there is the well-known problem with replication bias toward positive results (Duncan & Keller, 2011). Second, and less obvious, is the susceptibility of cGxE to false positive results. As described by Duncan & Keller (2011) many studies with larger samples have not replicated positive findings reported by smaller samples. Sample sizes across the five studies included in the of MAOA x adverse childhood experiences on CP outcomes meta-analysis by Kim-Cohen (2006) ranged from 81 to 975; consistent with the concern voiced by Duncan & Keller (2011), the smallest sample (Nilsson, 2005) reported the largest effect. This illogical finding is suggestive of Type 1 error, and the small number of studies that met criteria for inclusion in the meta-analysis (two of which were published by the same authors who conducted the review) suggests that additional research is necessary, preferably by independent authors examining a large, population based sample. On the other hand, a second major criticism of cGxE research is that effect sizes for interaction terms are typically very small and thus difficult to detect in underpowered samples. Consistent with this concern, the meta-analysis by Kim-Cohen et al. (2006), included several studies that failed to replicate the original cGxE effect on their own. However, when analyzed together as part of the larger meta-analysis, the interaction was present, in the expected direction for all studies, and thus supportive of the original report.

There are many additional concerns regarding cGxE research that have been described during the past decade, most of which can be addressed by careful adherence to guidelines set forth by Dick et al. (2015), as well as by the editors of several peer-reviewed journals (e.g. Hewitt, 2012; Johnston, 2013). Of these recommendations, the most relevant to the current analyses include 1) careful selection of candidate genotypes that have previously been associated with theoretically relevant brain processes, 2) use of a large, representative sample and 3) replication of previously published results or use of a replication sample. The current analyses carefully addresses these three specifications in the following ways:

- 1) The candidate genotype identified is the low-activity MAOA functional polymorphism. The MAOA gene is known to influence speed of degradation of serotonin, norepinephrine, and dopamine in the synaptic cleft, with the low-activity polymorphism translating to less efficient degradation. Thus, it is implicated in regulation of neurotransmitters that relate to regulation of behavior and emotional response, which are deficient in individuals demonstrating CP.
- 2) The current sample derives from a large, longitudinal study of two replicate samples of third, sixth, and ninth grade cohorts. Participants were recruited from nonclinical settings, and severity levels of CP and family adversity were representative of the general population. Importantly, the sample included both males and females, the latter of which have commonly been overlooked in prior research.

- 3) After testing for a cGxE in the combined sample, I re-ran the analyses separately within each of the two replicate samples (described below) to test for replicability of the results.

## **Aims**

The goal of the current analyses was to expand on the results of Foley et al. (2004) and Caspi et al. (2002), who reported an interaction between the low-activity MAOA allele and childhood adversity that predicted higher odds of conduct disorder in youth. While these studies utilized male- and Caucasian-only samples, my sample of youth was representative of the United States population on gender and racial stratification.

Foley et al. (2004; page 740) modeled the CP outcome as binary. As described by those authors, logistic regressions were preferred over linear regressions (i.e. with a continuous outcome) due to the fact that the latter are sensitive to heteroscedasticity effects and are therefore less robust. Eaves (2006) has since reported that logistic regression is subject to false positive (Type II) error, relative to linear regression, making it a less desirable approach for these analyses. Thus, I first ran logistic regressions, and opted to run linear regressions next if the interaction term was significant. The measure of negative parenting used in the current analyses differed from the childhood adversity measures used in prior studies. The representative samples in the current analyses did not have high rates of maltreatment; thus, my goal was to test whether the cGxE effect documented in prior studies extends to normative levels of adverse childhood experiences.

Specific hypotheses were developed based on the results of Foley et al. (2004). First, I expected to find a significant main effect for negative parenting on CP outcome, but not for MAOA. However, I did expect to find a trend for the latter main effect in the expected direction; in other words, I expected that a greater percentage of low-MAOA youth would meet diagnostic threshold for CP, even if it was not statistically significant. Finally, I predicted that there would be a significant interaction between genetic risk and environmental risk such that youth with more negative parenting exposures would be more likely to meet diagnostic threshold for CP if they carried the low-MAOA genotype.

## **Methods**

### **Participants**

Youth in third, sixth, and ninth grades were recruited from schools in the greater Denver, CO and New Brunswick, NJ areas for enrollment in a multi-site, longitudinal study of mood disorders. Exclusionary criteria included autism spectrum or psychotic disorders, IQ less than 70, and non-English speaking. Recruitment procedures have been described in detail in previously published studies (Cohen, Young, Gibb, Hankin, & Abela, 2014; Hankin, Jenness, Abela, & Smolen, 2011). The final samples included 105 third grade, 119 sixth grade, and 104 ninth grade youth ( $n = 328$ ) recruited from Denver and 82 third grade, 108 sixth grade, and 102 ninth grade youth ( $n = 292$ ) from New Brunswick (total  $N = 620$ ). Participants' ages ranged from 7 to 16 years at baseline.

### **Procedures**

The parent study is an ongoing, prospective, multi-wave sequential cohort design aimed at studying depression in two replicate, representative samples of children and adolescents. I conducted secondary analyses on disruptive behavior symptoms in this

cohort. Each youth and a parent participated in a baseline laboratory visit during which parents provided written consent for themselves and their youth, and the youth provided written assent. During this initial visit, basic demographic information was collected by interview, and parents and youth completed behavioral questionnaires. The youth also gave saliva for DNA testing during this visit. Thereafter, every three months following the baseline visit, participants completed behavioral questionnaires for 10 waves of follow-up assessment over 30 months. An additional laboratory visit took place at the 18-month follow-up. All procedures were approved by the University of Denver and Rutgers University institutional review boards.

## **Measures**

**Conduct Problems.** At the 18-month follow-up, parents completed the externalizing scale of the Child Behavior Checklist 6-18 (CBCL; Achenbach, 2001), which measures symptoms associated with conduct disorder and oppositional defiant disorder. The CBCL has high test-retest reliability ( $r=.89$ ) and is correlated with the Quay and Peterson Revised Behavior Problem Checklist (Quay & Peterson, 1983). For the logistic regressions in the current analyses, the diagnostic threshold for CP was set at 1.5 standard deviations above gender normative values on the externalizing scale of the parent-report CBCL.

**Negative Parenting.** Parenting constructs were measured at baseline using the Alabama Parenting Questionnaire (APQ), which is a parent self-report. Three negative parenting subscales measuring poor monitoring/supervision, inconsistent discipline, and corporal punishment were created by averaging scores for relevant items as described by Shelton, Frick & Wootton (1996). Six items each comprised the poor



monitoring/supervision and inconsistent discipline scales, and three items comprised the corporal punishment scale.

**Genotyping.** Youth provided saliva cells for DNA collection via Oragene™ kits from DNA Genotek (Ottawa, Ontario, Canada). The 30 bp *MAOA* VNTR polymorphism was characterized following standard salting out and solvent precipitation methods. Primer sequences for the 30 bp VNTR in the promoter region of the *MAOA* open reading frame were: forward, 5' -ACAGCCTGACCGTGGAGAAG-3' (fluorescently labeled) and reverse, 5' -GAACGTGACGCTCCATTCGGA-3'. PCR products included five possible fragment sizes: 291, 321, 336, 351, and 381bp (2–5 repeats). Consistent with previous research (Haberstick et al., 2005; Caspi et al., 2002), the most common alleles were the 3R and 4R variants. Similar to Caspi et al. (2002) the 2R and 3R alleles were characterized as the low-activity *MAOA* genotype, and the 3.5R, 4R, and 5R alleles were characterized as high-activity.

## Results

### Preliminary Analyses

**Genetic variation.** Allelic variation among the male participants was similar to that reported by Foley and colleagues, with 1.5% showing the 2-repeat (low), 37% the 3-repeat (low), 0.4% the 3.5 repeat (high), 60% the 4-repeat (high), and 1.2% the 5-repeat (low) for a total of 40% of males exhibiting any low-activity (i.e. high risk) *MAOA* allele. Females were more difficult to categorize due to the fact that the *MAOA* gene is located on the X chromosome, of which females have two copies; it is impossible to determine which copy of the gene is active. However, approximately half the females were homozygous for either a high- or low-activity *MAOA* variant, and among those,

30% were categorized as the low-activity MAOA. Because the inclusion of females was important for the goal of expanding on previous cGxE findings in CP, I erred on the side of caution and ran the MAOA analyses only including females who were homozygous for either low- or high-activity MAOA repeat variants.

The resulting reduced sample of all males and homozygous females constituted a total  $N = 427$ . The females who were not included in the analyses due to heterozygosity of the MAOA allele did not differ from those who were included on SES, minority ethnicity, sample origin, negative parenting, percent exceeding diagnostic threshold for CP, or percentage who had siblings also in the study. Demographic information about the final reduced sample is listed in Table 4.1.

Table 4.1

*Sample Demographics*

<i>N</i>	427
% Low-Activity (risk) MAOA	36%
% Female	39%
% Caucasian	67%
Mean SES (SD)	49.43 (11.37)
Mean Age at Baseline (SD)	12.07 (2.42)
% Denver Sample	52%
% Meeting CP Threshold	8.2%

*Notes.* SES=Hollingshead four-factor index of socioeconomic status (Adams & Weakliem, 2011).. CP Threshold =  $\geq 1.5$  standard deviations above sample mean on CBCL Externalizing scale.

**CP outcomes.** Behavioral diagnostic threshold was defined as 1.5 standard deviations above the sample mean on the CBCL externalizing scale at the 18 month follow-up. The resulting rate of 8.2% of participants meeting research criteria for CP was lower than that in the Foley et al. study (11.5%). However, those authors counted a clinical symptom as endorsed if it was reported by any of several reporters. Further, a participant in the Foley and colleagues study was rated as positive for conduct disorder if he met criteria at any of four time points. Both of these criteria likely over-estimated the number of youth who would meet full diagnostic criteria in a clinical setting.

Following Foley et al. (2004) and Caspi et al. (2002), I initially counted the number of exposures to negative parenting as 0-3, with each scale score that was at least one standard deviation above the sample mean counting as a single exposure. This resulted in a highly skewed ordinal variable, with 67% having zero exposures, 23% one exposure, 9% two exposures, and 1% three exposures. Foley and colleagues encountered a similar limitation when attempting to replicate Caspi et al. (2002); they thus performed alternative analyses in which they combined all seven items pertaining to the relevant scales to create an ordinal variable pertaining to childhood maltreatment. In line with this, and with consideration of the fact that the APQ includes more than seven items pertaining to the three negative parenting scales, the items for each of the scale scores were instead averaged, and the mean of the three scales was used as a continuous measure of negative parenting exposure.

**Statistical approach and power analysis.** Mplus 7.3 was used to conduct two-level logistic regression analyses to test for competing main effects and interactions. Family membership was modeled at the second level to account for non-independence of sibling data, which included 23% of the sample. To estimate power, I compared the current sample with Foley et al (2004), who likewise used a population based cohort with an  $N$  slightly larger than ours, at  $N = 514$ . The sample in the study by Foley and colleagues comprised twin boys, which further limited their power due to non-independence of the twin data. The Foley et al. paper reported a small but statistically significant odds ratio (1.69,  $p = .04$ ) for the interaction term in a logistic regression. Given that in the present sample, the  $N$  was smaller, but fewer of the participants were siblings, I expected to have sufficient power to detect comparable effect sizes.

Additionally, I conducted a power analysis using G\*Power 3.1. I was unable to use this program to model the non-independent sibling effects, thus I cautiously estimated power using a further reduced sample size that only included one sibling from each family ( $n = 389$ ). The results indicated that even with this significantly reduced sample size, I would have 98% power to detect an odds ratio of 1.69 using a one-tailed logistic regression, as in Foley et al. (2004).

**Main effects.** As expected, youth meeting diagnostic criteria for CP experienced more negative parenting:  $b = 2.07$ ,  $SE = .55$ ,  $p < .001$ . As with Foley et al. (2004), there was no significant main effect for the low-activity MAOA allele on CP diagnosis:  $b = -.16$ ,  $SE = .38$ ,  $p = .665$ . Contrary to expectations, the association between low-activity MAOA and CP status was not even in the expected direction. Gene-environment correlations (rGE) are also theoretically relevant in childhood disruptive behaviors, because youth inherit both genes and environments from their parents. A plausible rGE in the current sample would be one in which a parent's genetic propensity for CP manifests as negative parenting. Unlike Foley et al. (2004), the level of negative parenting was not significantly related to MAOA genotype:  $b = .02$ ,  $SE = .04$ ,  $p = .678$ . Thus, there was no indication of rGE for these variables in my sample.

When the MAOA risk allele and negative parenting were entered into the logistic regression simultaneously, negative parenting showed a significant effect ( $b = 1.08$ ,  $SE = .26$ ,  $p < .001$ ) but MAOA did not ( $b = .01$ ,  $SE = .22$ ,  $p = .982$ ). This result is consistent with Foley et al. (2004).

**Interaction effect.** Although lack of both main effects would not generally support inclusion of an interaction term, the overall purpose of these analyses was to test

for cGxE. Further, in the case of a true interaction, it is possible for the interaction itself to suppress main effects. Thus, I next tested the model with the negative parenting x MAOA variant term included. As before, the effect of negative parenting was statistically significant, but MAOA was not. The interaction term was not statistically significant ( $b = .22$ ,  $SE = .68$ ,  $p = .742$ ;  $OR = 1.25$ ), but it was in the expected direction. The difference in magnitude of the association between negative parenting and CP across high- and low-activity MAOA groups was .08, which is smaller than the effect sizes reported in the meta-analysis by Kim-Cohen and colleagues (2006). Finally, I repeated all analyses using male participants only ( $n = 260$ ), to test the possibility that the effect was sex-specific; results of the male-only analyses were consistent with those for the overall sample. Likewise, I got consistent results when I tested the model with only Caucasian participants included ( $n = 288$ ).

As described above, I did not have adequate numbers of minority youth to test the model within specific non-Caucasia races. Because the interaction was not significant in any of these analyses, I did not attempt to replicate the results across both the Denver and New Brunswick samples, and I did not repeat the model using linear regression. Thus, I was unable to expand on Caspi and colleagues' original result to less severe childhood adversity within a normative sample.

## **Discussion**

The current analyses attempted to expand on previously published results supporting a gene by environment interaction between the low-activity MAOA allele and childhood adversity on CP in youth. I did not find a significant interaction effect, nor did I find effect sizes in the range of previously published reports. The results are consistent

with other studies that have failed to replicate the original report by Caspi and colleagues (2002), such as that by Haberstick and colleagues (2005) and Young, Smolen, Hewitt and Haberstick (2006).

My analyses constituted an extension of previous research in that I included females who were homozygous for the low- or high-activity MAOA allele. This particular cGxE has not been previously been studied in females, and evidence for differences in conduct problems between the sexes (e.g. Tiet, Wasserman, Loeber, McReynolds & Miller, 2001) supports further investigation of cGxE as a potential etiology of these differences. Although the results remained consistent when I examined males separately, this test reduced the sample size and power substantially, and is therefore not entirely conclusive. Similarly, although the sample was racially diverse, there was not sufficient power to test for effects of population stratification.

Additional limitations of these analyses include the measurement of behavior and adverse childhood experiences. Unlike the study by Foley and colleagues that I attempted to replicate, I did not have multiple informants of CP, and the CP measurement was not specific to the DSM-IV criteria for conduct disorder. Rather, the externalizing scale of the CBCL includes symptoms of both conduct disorder and oppositional defiant disorder, the latter of which might not be as strongly related to either adverse experiences or the MAOA risk allele. Further, the diagnostic threshold resulted in a smaller proportion of participants meeting research criteria for high CP, which could have limited the amount of variance. Additionally, only two of the three negative parenting scales were replications of Foley's three scales. The third scale in the current analyses, corporal punishment, did not explicitly mirror inter-parental violence, measured by Foley and

colleagues. Further, the amount of corporal punishment experienced by participants in the current sample was minimal and therefore very little variance was contributed by this scale. The original study by Caspi and colleagues (2002) measured more severe manifestations of childhood maltreatment than either the current analyses or those by Foley and colleagues; likewise, behavioral outcomes in the original study were more severe with inclusion of antisocial behaviors, criminality, and conduct disorder symptoms, and outcome was measured in adulthood. Thus, my analyses are not an exact replication of either Foley et al. (2004) or Caspi et al. (2002), and the lack of replication of results should thus be interpreted cautiously.

On the other hand, there is plenty of reason to remain skeptical of Caspi's original cGxE effect and the meta-analysis by Kim-Cohen and colleagues (2006). With regard to the latter report, only five studies were included in the meta-analysis, due to the authors' attempts to replicate the results using homogeneous and reliable measurement methods. Further, two of the included studies were by the same authors who conducted the meta-analysis, and a third was that of Foley et al. (2004), who as described above, did not carefully replicate measurement of behavior and adversity. Finally, only one included study failed to find the expected interaction on its own (Haberstick et al., 2005) and this study included the largest N and most closely replicated the methods of Caspi and colleagues' original report.

It is widely accepted that disruptive behavior disorders are polygenic, and heritability estimates of CD and ODD are small to moderate, with equally strong shared environment and individual environmental effects found for CD in particular (Bernalova, 2010; Hicks et al., 2004). Thus, it is implausible that a single cGxE effect would explain



even a modest amount of variance in the behavior. Further, a recent genome wide association study (GWAS) of CD (Dick et al., 2011) identified four genetic markers of CD symptoms, none of which were candidate genes in previous cGxE research.

Although it could be argued that the main cG effect is masked by the gene-environment interaction, this lack of convergence across investigative approaches warrants caution in interpretation of positive results.

Altogether, the current analyses contribute to several conflicting reports regarding the replicability of Caspi and colleagues' original cGxE finding for childhood adversity, the low-activity MAOA allele, and conduct disorder. Additional research that includes candidate genes identified by GWAS, both males and females, and greater variation in behavioral symptoms and environmental risk would be beneficial. Importantly, if the results of Foley et al. (2004) can be verified, this cGxE still constitutes a very small effect in the overall etiology of CP, and should be considered only one developmental pathway toward disruptive behavior disorders in youth.

CHAPTER 5.  
CONCLUSIONS

This dissertation examined cross-construct, developmental, and candidate gene by environmental explanations for the development of HAP and CP, using two large, representative samples of youth. In the first set of analyses, I focused on within-person variation, with the assumption that a youth's own externalizing behavior may affect development of comorbid phenotypes. The results indicated that within-person variability in HAP does indeed predict within-person variability in CP at the subsequent time point for older youth. However, the effect size was small, and more negative for younger and non-Caucasian youth. The results are partially consistent with a mediation model similar to that proposed by Patterson and colleagues. Yet, the results did not clarify the process by which HAP relates to CP, and suggest that environmental mediators may vary as a function of age.

In the second analyses, I examined group differences in development of these comorbid behaviors. The analyses resulted in three distinct developmental trajectories of comorbid HAP and CP, with the most severe, chronic trajectory demonstrating unique associations with family stress variables. The results supported Chronic HAP and CP as a unique dual trajectory that was not captured by a model of additive disruptive behavior severity, and which was uniquely related to high rates of divorce and low SES. In contrast, youth following either a Chronic or Moderate dual trajectory were equally at risk for problems in the peer and academic domains. These results supported the use of GMM to model comorbid development of HAP and CP, and underscored the importance of examining externalizing behavior in the context of development. Further, the results suggested that family adversity is particularly salient in the developmental model of comorbid HAP and CP.

Finally, I failed to replicate an effect of the interaction between the low-activity MAOA allele and negative parenting on CP outcomes. The sample included females and a less robust measurement of conduct disorder relative to previous studies, and was thus limited in its ability to exactly replicate the previous reports. Although cGxE is a theoretically plausible explanation for developmental disorders in youth, there are reasons to remain cautious of positive cGxE results reported in previous papers, including multiple studies that have failed to replicate the interaction effect using adequate samples. Further investigation of cGxE as an etiological explanation for CP in youth is warranted.

Altogether, the results of this dissertation indicate that severe comorbid HAP and CP may constitute a unique etiological subtype of disruptive behavior disorders, as they appear to relate to one another synergistically, rather than additively. However, for older youth with any level of behavioral severity, direct and/or indirect associations between the two behavioral clusters result in a temporal relationship wherein HAP precedes CP in brief time frames. Finally, disruptive behavior symptoms are highly polygenic, and cannot likely be explained well by a single candidate gene by environment interaction.

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