Homotypic and Heterotypic Comorbidity and Continuity of Depression and Conduct Problems from Elementary School to Adolescence

THESIS

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Abstract

Despite non-overlapping criterion sets, conduct disorder (CD) and depression co-occur at much higher rates than expected by chance, which may indicate shared etiology. In attempts to elucidate etiological pathways and devise more effective treatments, several research groups have sought to determine which disorder precedes the other. These studies suggest that CD often precedes depression and that depression often precedes CD. To date, however, most analyses have evaluated lagged associations across time points among highly comorbid samples in attempts to establish temporal precedence of CD versus depression via statistical control. Notably, statistical partialling has several limitations when disentangling comorbidity and continuity in psychopathology. To address these limitations, we use an accelerated longitudinal design to evaluate growth in parent-reported conduct problems (CPs) and depression from elementary school to adolescence among children who were assigned at ages 8-12 years into depressed only (n=27), conduct problem only (n=28), comorbid (n=81), and control (n=70) groups based on levels of symptoms. Steep growth in depressive symptoms was exhibited by all groups, including those who were asymptomatic at study entry, with the highest levels observed for depressed only and comorbid participants. In contrast, CPs remained high and stable among those in the CP only and comorbid groups, versus low and stable among depressed only and control participants. Thus, although CPs alone portend

prospective vulnerability to depression, depression alone does not portend prospective vulnerability to CPs. Possible etiological mechanisms are discussed.

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Fields of Study

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Chapter 1: Introduction

Traditionally, most psychiatric disorders of childhood and adolescence have been viewed as either distinct diagnostic entities, as exemplified in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013), or as variants along factor analytically-derived internalizing or externalizing dimensions (Achenbach & Edelbrock, 1983, 1991). When following the DSM-perspective, differential diagnosis is prioritized, which sometimes obscures common etiological mechanisms among internalizing disorders and among externalizing disorders (see e.g., Beauchaine, Zisner, & Sauder, 2017). Even empirically-based taxonomies, such as the Child Behavior Checklist (Achenbach & Edelbrock), which acknowledge shared liability *within* the internalizing and externalizing spectra, can reify—however unwittingly—distinctions *between* internalizing and externalizing disorders.

In recent years, it has become clear that strong distinctions between and among internalizing and externalizing disorders are not always warranted (see e.g., Beauchaine & Constantino, in press; Zisner & Beauchaine, 2016), and that *transdiagnostic* vulnerabilities to psychopathology extend both within *and* across the internalizing and externalizing spectra (e.g., Krueger, 1999; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011). As outlined in detail below, concurrent comorbidity rates are quite high both within and across internalizing and externalizing disorders. Moreover, many studies

show that (1) internalizing symptoms in early childhood predict continued internalizing impairment in later life (homotypic continuity; see Cicchetti & Natsuaki, 2014); (2) externalizing symptoms in early childhood predict continued externalizing impairment in later life (also homotypic continuity; see Beauchaine et al., 2017); and (3) internalizing and externalizing symptoms predict one another in later life (heterotypic continuity; see Drabick et al., 2006; Loth, Drabick, Leibenluft, and Hulvrshorn, 2014).

Homotypic Comorbidity and Continuity in Child and Adolescent Psychopathology

Exceedingly high rates of homotypic comorbidity and continuity have long been acknowledged in the child and adolescent psychopathology literatures (see Angold, Costello, Erkanli, 1999; Klein & Riso, 1993), and emerge regardless of whether categorical or empirically-based taxonomies are used for assessment. Moreover, progressions to increasingly severe internalizing and externalizing psychopathology across childhood and adolescence are well documented (e.g., Cicchetti & Natsuaki, 2014; Hinshaw, 2015; Moffitt, 1993). As reviewed in detail elsewhere, for many individuals, these progressions involve complex transactions between endogenous neurobiological vulnerabilities and exogenous environmental risk factors across development (e.g., Beauchaine & McNulty, 2013; Cicchetti, Rogosch, & Toth, 1997). Given space constraints, specific developmental processes associated with internalizing and externalizing progressions cannot be reviewed here (see Beauchaine et al., 2017; Cicchetti et al., 1997). Nevertheless, it is worth noting that neither concurrent comorbidity of nor continuity in internalizing and externalizing disorders are surprising given within-spectrum overlap of neural vulnerabilities, personality characteristics, and

symptoms (see e.g., Beauchaine, Zisner, & Hayden, in press; Beauchaine & Cicchetti, 2016).

Heterotypic Comorbidity and Continuity in Child and Adolescent Psychopathology

In contrast to homotypic comorbidity, heterotypic comorbidity—defined as co-occurrence of internalizing and externalizing disorders within individuals—has traditionally been more perplexing. Symptoms of DSM-defined disruptive behavior disorders and depressive/mood disorders are almost entirely exclusive, and separate internalizing and externalizing factors emerge consistently from structural models of large twin and population-based samples of children, adolescents, and adults (e.g., Achenbach & Edelbrock, 1983, 1991; Krueger, 1999; Lahey et al., 2011). Nevertheless, rates of heterotopic comorbidity far exceed levels expected of independent disorders (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Giliom & Shaw, 2004; Keiley, Bates, Dodge, & Pettit, 2000). In fact, depending on ascertainment method and age of participants, rates of comorbidity between conduct problems (CPs) and depressive disorders—the syndromes we evaluate in this paper—range from 15%-82% (Angold & Costello, 1993; Drabick, Gadow, & Sprafkin, 2006; Marmorstein & Iacono, 2003; Pliszka, Sherman, Barrow, & Irick, 2000; Zoccolillo, 1992).

Heterotypic continuity between internalizing and externalizing disorders is also quite common, with both CPs and depression in childhood conferring prospective vulnerability to one another in adolescence (e.g., Gilliom & Shaw, 2004; Kovacs, Paulauskas, Gatsonis, & Richards, 1988; Zoccolillo, 1992). On balance, there may be more support for CPs predicting future depression. In a recent meta-analysis of longitudinal studies

comprising 17,712 children ages 12 years or below at initial assessment, Loth et al. (2014) found that childhood externalizing disorders predicted adult depression in a preponderance of studies, and for the sample as a whole. Among younger children assessed initially in the preschool years, externalizing behaviors also predict later growth in internalizing symptoms (Gilliom & Shaw, 2004). Notably, however, Drabick et al. (2006) also found that depressive symptoms predicted future CD among 6-10-year-old boys with ADHD.

Current Study

In this study, we seek to clarify whether depression predicts later growth in CPs, CPs predict later growth in depression—or both—in a sample recruited at study entry for either (1) high depressive symptoms without CPs, (2) CPs without depressive symptoms, (3) comorbid CPs and depressive symptoms, and (4) no psychiatric morbidity. As noted above, many previous studies have evaluated lagged correlations across time to establish prediction of CPs by depression and prediction of depression by CPs using statistical control. This practice can distort relations between predictors and outcomes, and mask patterns of true comorbidity, both concurrently and over time. As reviewed by Miller and Chapmen (2001), when two assumedly different disorders share symptoms, psychological vulnerabilities, and neural substrates, statistical partialling creates mathematical entities that rarely exist in reality (e.g., depression without liability to anxiety). Partialling procedures can also obscure longitudinal relations between disorders (e.g., ADHD and later substance use) when "controlling for" or "partialling out" etiologically related conditions (e.g., conduct disorder; Beauchaine et al., 2010).

In addition, most studies conducted to date have evaluated comorbidity and continuity of internalizing and externalizing psychopathology among treatment-seeking samples, which differ from more naturalistic samples in initial levels of functional impairment, symptom severity and duration, and rates of comorbidity (Goodman et al., 1997). Thus, treatment-seeking samples may be biased toward worse long-term outcomes. Accordingly, we recruited 206 children, ages 8-12 years at study entry, and followed them across three annual assessments. By using an accelerated longitudinal design, we were able to evaluate parent-reported growth in depression and CPs from ages 8-15 years. Consistent with the literature reviewed above, we hypothesized that those in the CPs only group would exhibit growth in depression, but that those in the depressed only group would not exhibit growth in CPs. We hypothesized further that all clinical groups (including those with CPs only) would exhibit growth in depression across assessment waves. This hypothesis follows from population-based studies of growth in depression across childhood and adolescence (Merikangas et al., 2010; Rushton, Forcier, & Schectman, 2002), and from the literature reviewed above on heterotopic progression of psychopathology. Finally, we hypothesized that growth in CPs would be less pronounced, and restricted primarily to children who were already symptomatic at study entry.

Chapter 2: Method

Participants

Participants were recruited using advertisements placed in local newspapers, community publications, and city buses. These advertisements described characteristics of depression and CPs, and asked interested parents to call if they felt that their child fit one or both descriptions. We received 445 inquiries from parents who completed (1) a 30-min computerized, structured phone interview including *DSM-IV-TR* (American Psychiatric Association, 2000) major depressive disorder (MDD), dysthymia (DYS), ADHD, oppositional defiant disorder (ODD), and CD subscales from the Child Symptom Inventory (CSI-4; Gadow & Sprafkin, 1997); and (2) the anxious/depressed, aggression, and attention problems subscales from the Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983, 1991). Child-Symptom Inventory-4 items are assessed on 4-point scales (0 = *never*, 1 = *sometimes*, 2 = *often*, 3 = *very often*), with scores of 2 and 3 considered positive for each diagnostic criterion. Scores can also be summed dimensionally. In this study, we use dimensional scores for our primary analyses (described below), but we also report tentative diagnoses. Details regarding reliability and validity of these measures appear below. Responses were scored immediately by computer.

Based on these interviews, 212 children were assigned into the following four groups:

conduct problems (CPs; *n*=28), depression (DEP; *n*=27), comorbid (CMB; *n*=81) and control (CTR; *n*=70). To be included in the CPs group, children were required to meet *DSM-IV* criteria for ODD and/or CD on the CSI, and/or score at or above the 98th percentile ($T \geq 70$) on the CBCL aggression subscale. They could not meet criteria for depression or dysthymia, and were required to score $T \leq 60$ on the CBCL anxious/depressed subscale. To be included in the DEP group, children were required to meet *DSM-IV* criteria for major depression or dysthymia on the CSI, and/or score at or above the 98th percentile ($T \geq 70$) on the CBCL anxious/depressed subscale. They could not meet criteria for CD or ODD, and were required to score $T \leq 60$ on the CBCL aggression subscale. Children in the CMB group were required to meet criteria for both the CPs and DEP groups, with no CBCL exclusions. Finally, children in the CTR group had to be free of psychiatric diagnoses on all CSI scales, and score $T \leq 60$ on all CBCL subscales. Additional exclusion criteria included symptoms of psychosis, autism, or intellectual disability, as assessed during the structured phone interview. Of the 212 qualifying participants, 6 dropped out early and did not attend any lab sessions (described below). The final sample was therefore comprised of 206 children, including 134 boys and 72 girls. Racial composition was 61.7% Caucasian, 12.1% African American, 10.2% Hispanic, 6.3% Asian American, 2.4% Pacific Islander, and 1.5% American Indian. The remaining 5.8% either entered a race other than those listed above, or declined to respond.

Procedure

All procedures were approved by the local institutional review board, and researchers

obtained parental consent and child assent prior to each yearly lab session (see below). Following the structured phone interview in which parents completed the CSI-4 and CBCL, those who met inclusion criteria were invited to the lab for their first of three annual assessments (Year 1). As described in detail elsewhere (e.g., Kopp & Beauchaine, 2007), these assessments included collection of additional questionnaires and participation in a broader lab protocol that is not relevant to the current paper (see Beauchaine, Hong, & Marsh, 2008; Shannon, Beauchaine, Brenner, Neuhaus, & Gatzke-Kopp, 2007; Vasilev et al., 2009). Similar assessments were conducted at Years 2 and 3, when CSI-4, CBCL, and laboratory tasks were again administered. Parents were compensated $75 for participation at each annual assessment.

Measures

Child Symptom Inventory for DSM-IV (CSI-4; Gadow & Sprafkin, 1997). As described above, the CSI-4 assesses a wide range of DSM-IV psychiatric disorders of childhood. Parents completed the CD, ODD, ADHD, MDD, and dysthymia modules at each time point. Sensitivities and specificities vis-à-vis clinical diagnoses for the CSI scales used in this study range from .73 to .83, suggesting adequate validity (Gadow & Sprafkin, 1997). Reliabilities, as assessed via Cronbach's α coefficients calculated at each yearly assessment, ranged from .85-.90.

Child Behavior Checklist (CBCL; Achenbach, & Edelbrock, 1991). At Year 1, parents completed the anxious/depressed, aggression, and attention problems subscales of the CBCL for group assignment purposes (see above). Cronbach's αs ranged from .90-.93.

Analyses

Among the 206 children who were assigned to groups, 28 (13.6%) dropped out before Year 2, and 20 (9.7%) dropped out before Year 3. Participants who dropped out scored higher on all CSI and CBCL scales. Rather than omitting these participants, which would have introduced bias into outcomes and analyses, we imputed their data in SPSS 24. Analyses were conducted across 30 imputations, according to established guidelines (see Graham, 2009). Imputation provides more accurate estimates of missing data than mean substitution or simple regression-based substitution, and is preferable to omitting attritted participants.

We assessed growth in depressive symptoms by constructing multilevel models in Hierarchical Linear Modeling software, version 6.08 (HLM; Raudenbush, Bryk, & Congdon, 2004). Within-participant change in parent-reported depressive symptoms was modelled across the entire eight-year age span of participants at Level 1. As with all accelerated longitudinal designs, the sample size was somewhat smaller at age extremes (n = 51 at age 8, n = 81 at age 9, n = 123 at age 10, n = 111 at age 11, n = 117 at age 12, n = 73 at age 13, n = 47 at age 14, and n = 13 at age 15). Of note, however, HLM computes slopes across time and results do not depend on sample size at any specific age. Age at Year 1 was entered at Level 2 to control for individual differences at entry into the accelerated longitudinal design. Group differences in growth of depression were assessed by entering orthogonal contrast codes at Level 2[1]. Contrast 1 (C1) compared the CTR group to all clinical groups, Contrast 2 (C2) compared the CMB group to the DEP and

[1]Orthogonal contrast codes were constructed to ensure that all contrasts were independent, and to control for size differences between groups. Orthogonal coding provides numerous statistical advantages over other approaches, including lower probability of Type I error (see e.g., Pedhazur, 1997).

CPs groups, and Contrast 3 (C3) compared the DEP and CPs groups. Sex effects were evaluated as a possible covariate at Level 2 given well-documented sex differences in growth of depression across this age range (e.g., Nolen-Hoeksema, 1987; Kendler & Gardner, 2014). The full model for DSM depressive symptoms was as follows:

$$\text{Level 1: depression/dysthymia symptoms}_{ti} = \pi_{0i} + \pi_{1i}*(\text{age}_{ti}) + e_{ti}$$

$$\text{Level 2: } \pi_{0i} = \beta_{00} + \beta_{01}*(\text{sex}_i) + \beta_{02}*(C1_i) + \beta_{03}*(C2_i) + \beta_{04}*(C3) + \beta_{05}*(\text{age}_{Time1}) + r_{0i}$$

$$\pi_{1i} = \beta_{10} + \beta_{11}*(\text{sex}_i) + \beta_{12}*(C1_i) + \beta_{13}*(C2_i) + \beta_{14}*(C3_i) + \beta_{15}*(\text{age}_{Time1}) + r_{1i}$$

Note that we specify depression/dysthymia symptoms together since they are identical. Finally, to evaluate growth in CPs, we ran a parallel model with DSM conduct disorder (CD) symptoms as the outcome. For both sets of analyses, we restricted outcomes to symptoms of DSM disorders (depression, CD), since almost all of the existing literature on heterotypic comorbidity and continuity has done so. This enabled us to compare results to previously reported findings.

Chapter 3: Results

Descriptive Statistics

Descriptive statistics at study entry are reported by group in Table 1. As described in detail elsewhere (e.g., Vasilev et al., 2009), recruitment was effective in yielding groups with significant differences of large effect size across all measures of psychopathology, all Fs $(3,203) \geq 23.8$, all ps $<.001$, all $\eta^2 \geq .23$.

Growth in (1) depressive/dysthymic symptoms and (2) CD and ODD symptoms across Years 1-3 are reported in Tables 2 and 3, respectively. Table 2 includes mean symptom levels and percentages of those who met *DSM-IV* criteria for MDD and/or dysthymia at each assessment, and Table 3 includes mean levels of and percentages of those who met *DSM-IV* criteria for CD and at each assessment. Significant symptoms of both depression and CD persisted across time, as reported in detail below.

	Control (*n*=70)		Depressed (*n*=27)		CD (*n*=28)		Comorbid (*n*=81)	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age at Time 1	9.83	1.52	10.22	1.48	9.54	1.60	9.95	1.46
Child Symptom Inventory								
MDD symptom severity	0.70	1.01	6.56	3.43	2.82	2.82	10.22	4.92
MDD symptom count	0.03	0.17	1.56	1.53	0.21	0.79	2.72	2.16
DYS symptom severity	0.93	1.11	7.00	2.27	2.93	1.90	9.74	4.04
DYS symptom count	0.03	0.17	2.26	1.23	0.36	0.49	2.98	1.94
CD symptom severity	0.67	1.01	1.44	1.48	7.07	5.07	7.40	4.69
CD symptom count	0.03	0.17	0.15	0.36	1.86	1.90	1.80	1.91
ODD symptom severity	4.00	2.96	7.37	3.44	16.32	4.06	17.04	4.64
ODD symptom count	0.27	0.66	1.56	1.67	5.79	1.83	5.95	2.14
Child Behavior Checklist								
anxious/depressed (*T*)	52.80	3.61	74.37	7.47	66.75	8.61	81.56	8.34
aggression (*T*)	51.16	2.38	57.04	5.81	77.64	8.90	79.65	9.16

Table 1. Psychopathology Measures at Time 1 by Group

Notes. MDD=major depressive disorder; DYS=dysthymia; CD=conduct disorder; ODD=oppositional defiant disorder.

	Time 1			Time 2			Time 3		
	Severity			Severity			Severity		
Group	*M*	*SD*	% meeting criteria	*M*	*SD*	% meeting criteria	*M*	*SD*	% meeting criteria
Control	0.70	1.01	0.0%	9.96	1.54	23.5%	10.66	2.60	29.0%
Depressed	6.56	3.43	85.2%	12.81	3.25	68.0%	13.13	4.01	73.9%
Conduct	2.82	2.82	0.0%	12.81	3.59	76.9%	13.64	3.84	61.9%
Comorbid	10.22	4.92	79.0%	14.59	4.49	82.6%	16.13	4.99	73.7%

Table 2. Symptom Severity and Percentages of Participants Meeting Diagnostic Thresholds for Major Depression and/or Dysthymia by Group Over Time

Note. MDD and dysthymia are combined because symptoms are identical across disorders.

	Time 1			Time 2			Time 3		
	Severity			Severity			Severity		
Group	*M*	*SD*	% meeting criteria	*M*	*SD*	% meeting criteria	*M*	*SD*	% meeting criteria
Control	0.67	1.07	0.0%	0.43	0.94	4.4%	0.82	1.29	4.8%
Depressed	1.44	1.48	0.0%	0.97	1.45	20.0%	1.33	1.78	12.5%
Conduct	7.07	5.07	42.9%	4.12	3.55	42.9%	5.27	4.07	68.2%
Comorbid	7.40	4.69	38.3%	3.96	3.04	56.5%	4.93	3.73	64.9%

Table 3. Symptom Severity and Percentages of Participants Meeting Diagnostic Thresholds for Conduct Disorder by Group Over Time

In the first HLM model, age predicted Level-1 slopes in parent-reported depressive symptoms, without contrast codes entered. Thus, symptoms of depression increased over time for the sample as a whole, $b = 0.59$, $t(204) = 6.22$, $p < .001$. Interestingly, when entered as a Level 2 fixed effect, sex did not predict growth in depressive symptoms, $b = -0.04$, $t(200) = -1.30$, $p = .20$. This is not entirely surprising given that so many participants were recruited specifically for having high depression scores—regardless of sex.

Level 2 orthogonal contrasts comparing growth in depression across groups were evaluated next. The contrast comparing the control group to all three clinical groups (C1) indicated steeper growth in depressive symptoms among *controls* than among the three clinical groups, $b = -0.0003$, $t(200) = -2.58$, $p = .01$. Growth in depression for all groups is depicted in Figure 1. As this finding indicates, even children who were free from depression at study entry showed marked growth in symptoms from middle school to adolescence. However, their overall level of depression was lower than the other groups, as indicated by a significant mean-centered intercept for C1, $b = 0.003$, $t(201) = 10.44$, $p < .001$.

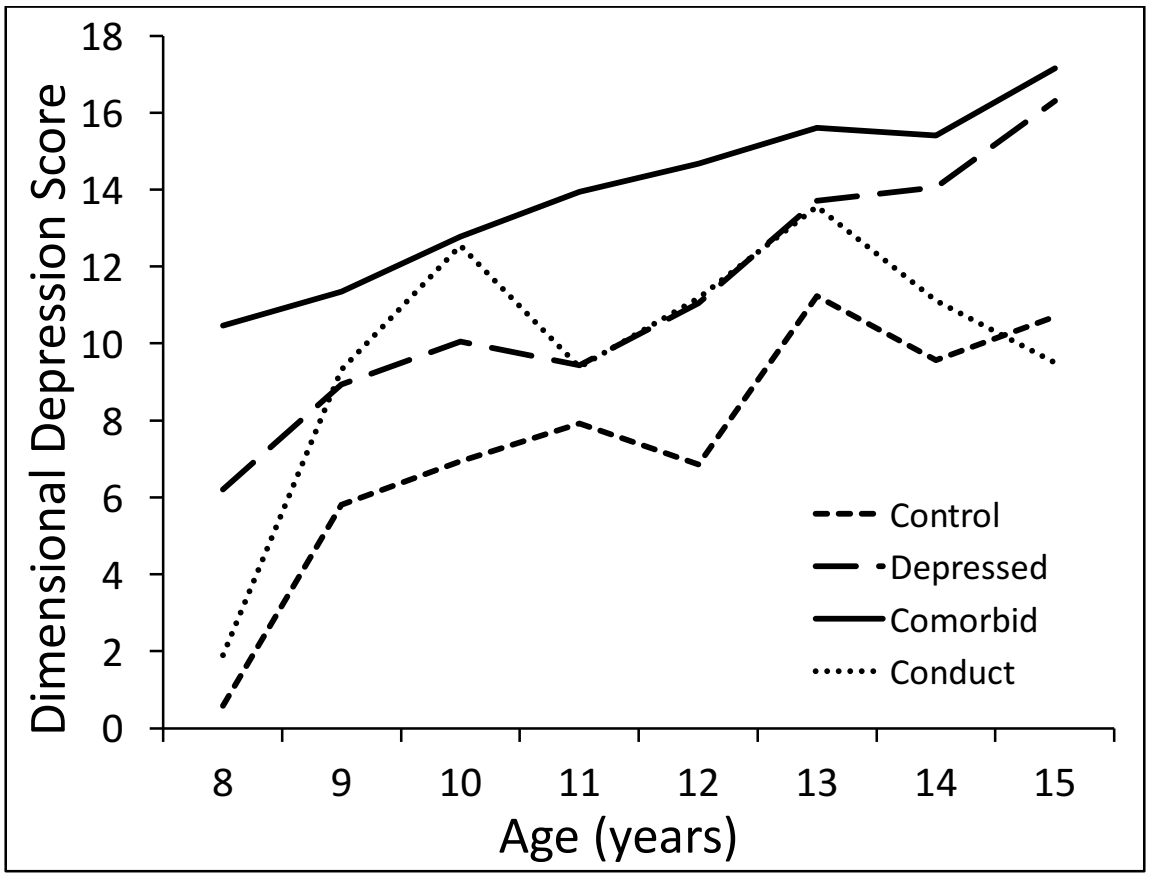

Figure 1. Growth in depressive symptoms by group from ages 8-15 years.

The next contrast, which compared the CMB group to the CP and DEP groups (C2), approached significance, $b = 0.0004$, $t(200) = 1.90$, $p = .06$. This indicates steeper growth in depressive symptoms among the CP and DEP groups than among the CMB group. As Figure 1 illustrates, this finding is almost certainly attributable to a ceiling effect, since CMB participants were the most symptomatic across the entire age range.

The final contrast (C3), which compared the CP and DEP groups, was not significant, $b = -0.001$, $t(200) = -1.19$, $p = .24$. Thus, there was no difference in growth in depression between children with CPs only at study entry vs. those with depression/dysthymia only.

Notably, however, both groups exhibited steep increases in depressive symptoms from ages 8-15 years[2].

Finally, to conform that CPs only were associated with development of depression, we evaluated the slope effect for the CPs only group. This analysis indicated significant growth in depression from ages 8 to 15 among those recruited for CPs only, $b = 0.80$, $t(26) = 3.62$, $p = .001$. Thus, CPs alone were associated with growth in depression that was indistinguishable from that observed in the depression only group.

Growth in Conduct Problems

Next, we assessed group differences in parent-reported CD symptom growth from ages 8-15 years. As with depressive symptoms, age predicted slopes in CD symptoms at Level 1 in a model without contrast codes. Thus, CD symptoms increased over time for the sample as a whole, $b = 0.39$, $t(205) = 7.55$, $p < 0.001$. When entered as a Level 2 fixed effect, sex did not predict growth in CD symptoms, $b = -0.20$, $t(200) = -1.19$, $p = .24$. As with depression, this is not entirely surprising given that many participants were recruited based on CD symptoms, regardless of sex.

The contrast comparing control participants to all clinical groups (C1) indicated steeper growth in CD symptoms among the control group versus the three clinical groups, $b = -0.002$, $t(200) = -2.93$, $p = .004$. Growth in CD symptoms for all groups is depicted in Figure 2. However, as depicted in Figure 2, CD symptoms were still lower overall among control participants than clinical groups, which was confirmed by a significant mean-

[2]We also assessed melancholic and non-melancholic symptoms of depression separately. In these analyses, the CSI-4 MDD subscale was partitioned into melancholic and non-melancholic symptoms according to *DSM-IV* criteria. No group differences in slopes were found for melancholic symptoms. In contrast, the non-melancholic model followed the same pattern of results reported herein for the full MDD model.

centered intercept of C1, b = -0.002, t(201) = -2.711, p = .008.

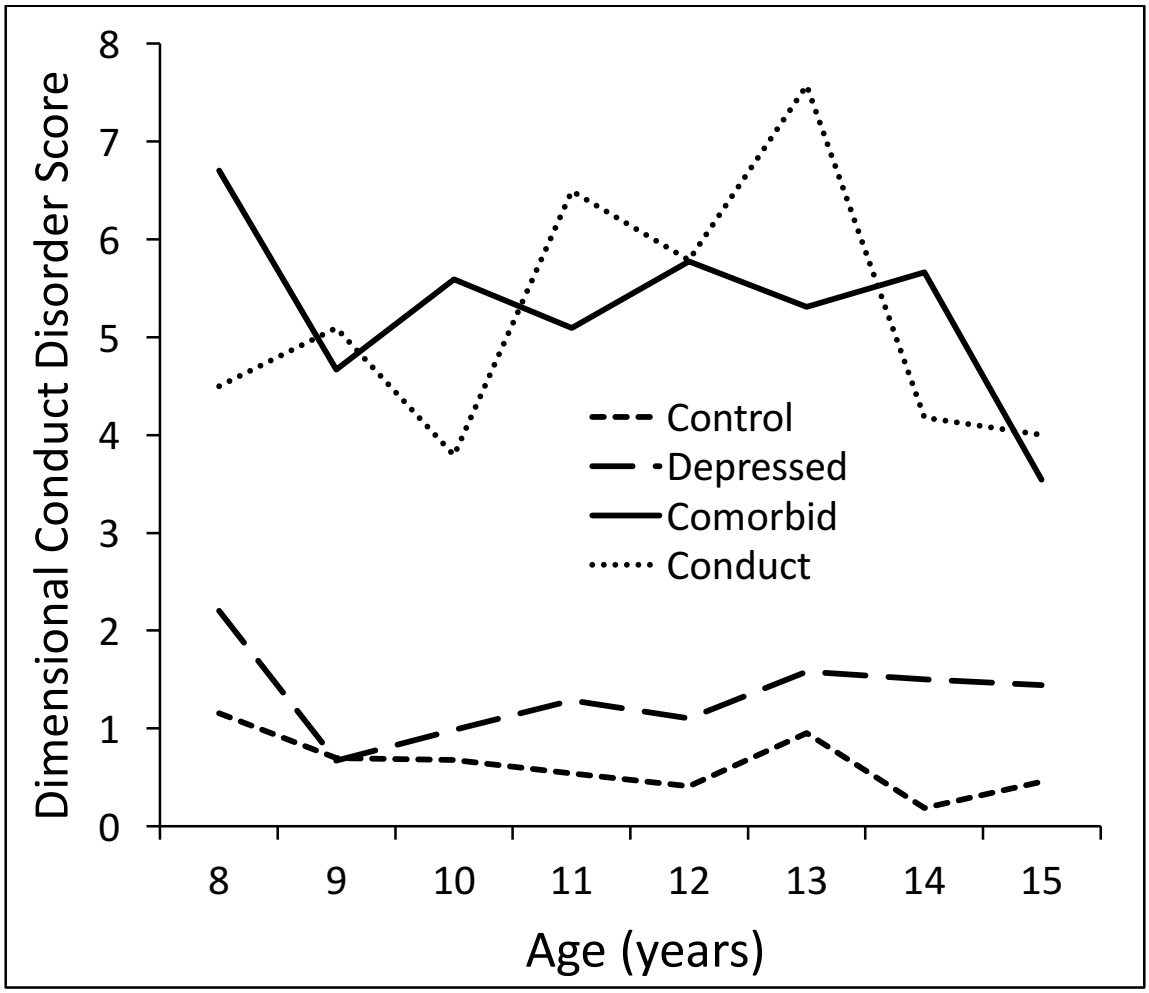

Figure 2. Growth in conduct disorder symptoms by group from ages 8-15 years.

The next contrast, which compared the CMB group to the CP and DEP groups (C2), was also significant, $b = 0.003$, $t(200) = 2.03$, $p = .04$. Participants in the CP and DEP groups showed steeper growth in CD symptoms than those in the CMB group (see Figure 2). The final contrast (C3), which compared the CP and DEP groups, was not significant, $b =$

0.007, $t(200) = 1.30$, $p = .20$, indicating similar patterns of growth in CD symptoms. However, the CPs group exhibited very high CD symptoms across the entire age range, whereas the DEP group exhibited very low CD symptoms across the entire age range (see Figure 2). This difference in overall levels of CD symptoms over time for the CP versus depressed groups was confirmed by a significant mean-centered intercept for C3, $b = -0.15$, $t(200) = -2.84$, $p = .006$.

Finally, to assess whether depression alone was associated with development of CPs, we evaluated the slope effect for the depression only group. This analysis indicated no growth in CPs from ages 8 to 15 years among those recruited for depression only, $b = -0.74$, $t(25) = -0.86$, $p = .40$**.** Thus, depression alone was not associated with growth in CPs. We discuss these findings in greater detail below.

Chapter 4: Discussion

In this study, we sought to disentangle—to the extent possible with parent-report data—whether early depression confers vulnerability to later CD, early CPs confer vulnerability to later depression, or both. Findings suggest that CPs alone confer vulnerability to later depression, but depression alone does not confer vulnerability to later CD. Most previous studies have addressed this question using cross-lag correlational designs with highly comorbid participants rather than relatively 'pure' CP and depressed groups. To our knowledge, ours is among the first studies to compare growth in depressive symptoms over this age range among children and adolescents with depressive disorders, CPs, heterotypic comorbidity, and no psychopathology, using explicit exclusion criteria to minimize comorbidity in the 'pure' groups. Use of an accelerated longitudinal design allowed us to compare groups on symptom growth from ages 8 to 15 in a study that lasted only three years. In addition, findings confirmed our hypotheses that all clinical groups would show growth in depression over time given secular norms, and that symptoms of CD would not show this same extent of growth.

In contrast to depressed only participants, who exhibited no growth in CD symptoms, heterotypically comorbid participants showed (1) persistently high rates of CD symptoms across elementary school to mid-adolescence, (2) growth in depression across the same time span, and (3) the highest rates of depressive symptoms at every age evaluated. These

children and adolescents therefore appear to be worse off than any of their peers—at least in terms of symptoms. This is consistent with the existing literature, which indicates that individuals with comorbid depression and CD show more severe symptoms of both disorders than individuals with either disorder alone (e.g. Ezpeleta, Domenech, & Angold, 2006; Marmorstein & Iaocono, 2003). In fact, comorbid internalizing symptoms predict better responses to behavioral treatments for CD (Beauchaine, Webster-Stratton, & Reid, 2005), as well as less physical aggression, better peer ratings, and fewer police contacts (Walker et al., 1991). Moreover, comorbid internalizing symptoms confer partial protection from structural compromises observed in the caudate, hippocampus, and anterior cingulate among those with CD (Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012). In contrast, both callous–unemotional (CU) and psychopathic traits—related constructs characterized by low trait anxiety—predict poorer concurrent and future functioning among children and adolescents with CD (e.g., Frick, Ray, Thornton, & Kahn, 2014; McMahon, Witkiewitz, & Kotler, 2010). Thus, even though our heterotypically comorbid group was the most symptomatic, the CD only group may be on a more pernicious long-term trajectory. Unfortunately, we did not collect data on either CU or psychopathic traits.

Taken together, our findings, depicted in Figures 1 and 2, help to clarify the existing literature on heterotypic comorbidity of and continuity in depression and CD from childhood to adolescence. To date, the literature has been mixed regarding the question of whether depression confers vulnerability to later CD, or CD confers vulnerability to later depression (e.g., Drabick et al., 2006; Gilliom & Shaw, 2004; Loth et al., 2014). In our

study, participants who were recruited for CPs only at study entry showed clear growth in depression, but participants who were recruited for depression only showed no growth in CD symptoms. Notably, we would not have been able to disentangle this question without relatively pure groups. Had we only recruited heterotypically comorbid participants, with high symptom counts for both depression and CPs, we would have been forced to evaluate cross-lagged partial correlations, which control for comorbidity statistically. As noted above, statistical partialling has significant limitations when used for such purposes (see Miller & Chapmen, 2001). We note, however, that both depression and CD are dimensional constructs in nature, so we had to impose relatively strict yet arbitrary cutoffs to create these "pure" groups.

Even control participants—who were recruited for clear absence of symptoms—showed steep increases in depression from ages 8-15. In fact, by the Year 3 assessment, 29% met criteria for dysthymia or depression based on parent reports. Although it might be tempting to explain these findings away as a result of biased parent reporting or some other artifact, sensitivity and specificity of the CSI-4 mood disorder scales are strong, and the observed rate of depression, although higher than that reported in the National Comorbidity Survey Replication Adolescent Supplement (Merikangas et al., 2010), is very close to that found in the National Longitudinal Study of Adolescent Health (Rushton et al., 2002). Regardless, growth in depressive symptoms among control participants is concerning.

Although CD symptoms expressed by comorbid and CP only participants seemed to decline at ages 14 and 15 (see Figure 2), we are reluctant to interpret these apparent

changes given that sample size in any accelerated longitudinal study is smallest at age extremes. Furthermore, previous research shows that (1) early-onset CPs are unlikely to abate by mid-adolescence (e.g., Moffitt, 1993), and (2) parents know less about their children's externalizing behaviors in adolescence than in middle school (see De Los Reyes & Kazdin, 2005). Unfortunately, this sample is no longer being followed so we cannot address this issue with more data.

Shared Neural Mechanisms of Conduct Problems and Depression?

Recently, common neural vulnerabilities have been identified that help to explain historically perplexing patterns of comorbidity between internalizing and externalizing disorders (see Beauchaine & Cicchetti, 2016). As reviewed recently by our research group (Beauchaine & Constantino, in press; Zisner & Beauchaine, 2016), overwhelming evidence now demonstrates striatal under-responding in anticipation of incentives in almost all externalizing spectrum disorders (see e.g., Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017; Beauchaine et al., 2017; Plichta & Scheres, 2014; Beauchaine, Zisner, & Sauder, 2017), in unipolar depression (see e.g., Forbes & Dahl, 2011; Luking, Pagliaccio, Luby, & Barch, 2016), and in non-suicidal self-injury (Sauder, Derbidge, & Beauchaine, 2016). The latter is of interest given associations between self-injury and both internalizing and externalizing psychopathology.

As outlined elsewhere, striatal under-responding in anticipation of incentives imbues a chronically anhedonic and irritable mood state, which characterizes both unipolar depressive and disruptive behavior disorders (Stringaris et al., 2015; Zisner & Beauchaine, 2016). This supposition follows from findings linking striatal activity and

reactivity to pleasurable affective states (e.g., Berridge, 2003; Smith & Berridge, 2007; Drevets et al., 2001), and from findings linking low striatal responding to both trait anhedonia and trait irritability (e.g., Laakso et al., 2003; Foti, Carlson, Sauder, & Proudfoot, 2014). This common neural substrate likely confers shared vulnerability to CD and depression, thereby contributing to high rates of observed comorbidity.

In contrast, CD and depression are differentiated by patterns of responding in other neural systems (e.g., Beauchaine et al., 2017; Stuber et al., 2011). For example, many children, adolescents, and adults with externalizing disorders show blunted amygdalar reactivity to threat (e.g., Jones, Laurens, Herba, Barker, & Viding, 2009), whereas those with depression show amygdalar hyper-reactivity to similar stimuli (e. g. Monk et al., 2008). As a result, depressed individuals are more avoidant of threat than those with pure CD—even though they share other behavioral/emotional traits. Thus, interrelations between CD and depression—including common and differentiating factors—can only be understood by embracing etiological complexity. Recent studies—as well as the RDoC initiative, suggest that comorbidities and continuities in psychopathology derive from functional interactions among multiple neural systems that shape and maintain behavior (e.g., Beauchaine, 2015; Zisner & Beauchaine, 2016).

Limitations

A primary limitation of this study is sole reliance on parent-report data using symptom checklists. As noted above, both the CSI and CBCL demonstrate strong reliability and validity. Nevertheless, structured clinical interviews would have strengthened our findings. Moreover, although parents become slightly poorer informants as their children

age (see above; De Los Reyes & Kazdin, 2005; Edelbrock, Costello, Dulcan, Kalas, & Conover, 1985), this effect would cause under-reporting of symptoms over time, and therefore cannot explain the increases in depression seen in all groups. We also relied on a single informant—an additional limitation.

In addition, with three time points, we could not assess non-linear trends in emerging CD or depression. Quadratic analyses may have been especially useful to assess patterns of growth in depression (see Figure 1). Furthermore, since we used an accelerated longitudinal design, there were relatively few participants at extreme ages range. We should be careful, for example, in making inferences about non-linear growth based on apparent leveling off of depression among the CD group (see Figure 1).

Conclusion

Depression and CD co-occur significantly more often than expected by chance, which may suggest shared etiology. In attempts to elucidate etiology and devise more effective treatments, several research groups have sought to determine which disorder precedes the other. To date, most analyses have evaluated lagged associations across time points in attempts to establish temporal precedence of CD versus depression via statistical control. As we note above however, statistical partialling has several limitations when disentangling comorbidity and continuity in psychopathology. In this study, we recruited relatively 'pure' groups who were vulnerable to CD, depression, or both based on high levels of symptoms. Our findings suggest that CPs alone portend vulnerability to later depression, but depression alone does not portend vulnerability to CPs. Notably, however, all groups showed steep growth in depressive symptoms from ages 8-15 years.

We hope future research continues to elucidate specific mechanisms of shared vulnerability to CPs and depression as we seek to develop more effective prevention and intervention programs.

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