

TEMPORAL DYNAMICS AND LONGITUDINAL CO-OCCURRENCE OF DEPRESSION
AND DIFFERENT ANXIETY SYNDROMES IN YOUTH: EVIDENCE FOR RECIPROCAL
PATTERNS IN A 3-YEAR PROSPECTIVE STUDY

BY

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THESIS

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ABSTRACT

Depression is highly comorbid with anxiety in youth. It is frequently reported that anxiety precedes depression; however, evidence surrounding the temporal precedence of anxiety over depression is mixed. Many studies of anxiety-depression co-occurrence lump distinct forms of anxiety, obscuring information regarding trajectories of specific anxiety syndromes. This study sought to more accurately describe the development of anxiety and depression over time by moving beyond the question of temporal precedence to investigate a developmentally dynamic model of anxiety-depression co-occurrence. A community sample of 665 youth ($M=11.8$, $SD=2.4$; 55% female) completed repeated self-report measures of depression and anxiety (social, physical, and separation anxiety) over a 3-year longitudinal study. Prospective associations between distinct syndromes of anxiety with depression were analyzed using an autoregressive cross-lagged path model over four time points. Physical symptoms and depression symptoms reciprocally predicted each other, above and beyond the stability of either domain. Social anxiety and depression symptoms similarly predicted each other in a systematic pattern. Our study is limited in its generalizability to other forms of anxiety, like worry. Additional research is needed to determine whether similar patterns exist in clinical populations, and whether these processes maintain symptoms once they reach diagnostic levels. The development of syndromes of depression, physical, and social anxiety during childhood and adolescence occurs in a predictable, systematic reciprocal pattern, rather than sequentially and unidirectionally (i.e., anxiety syndromes precede depression). Results are clinically useful for predicting risk for disorder, and demonstrate the necessity of tracking symptom levels across domains.

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CHAPTER 1: INTRODUCTION

It is well established that depression is highly comorbid with anxiety during childhood and adolescence (Brady & Kendall, 1992). Estimates suggest that half of depressed individuals have a comorbid anxiety disorder (Kessler et al., 2003). Comorbidity is associated with greater symptom and diagnostic severity, and worse social functioning (Queen & Ehrenreich-May, 2014). It has been frequently reported that anxiety precedes depression (e.g., Cole, Peeke, Martin, Truglio, & Seroczynski, 1998; Keenan, Feng, Hipwell, & Klostermann, 2009; Avenevoli, Stolar, Li, Dierker, & Merikangas, 2001).

However, there are significant, unresolved questions regarding the temporal and longitudinal relations between anxiety and depression. While it has been established that youth who experience symptoms of anxiety are at heightened risk for later experiencing symptoms of depression (Kessler et al., 2005; Merikangas et al., 2010; Rohde, Lewinsohn, & Seeley, 1991; Cole et al., 1998), other research shows that those who experience symptoms of depression are similarly at greater risk for later symptoms of anxiety (Moffitt et al., 2007; Pine, Cohen, Gurley, Brook, & Ma, 1998; Merikangas et al., 2003). To date, most research has focused on a “which comes first” question regarding diagnostic patterns of depression and anxiety comorbidity. More recently, researchers have suggested that the temporal ordering between anxiety and depression may not be as straightforward as has been commonly presumed (Cummings, Caporino, & Kendall, 2014; Moffitt et al., 2007). The present study sought to advance knowledge on the temporal patterning of different forms of anxiety and depression by moving beyond the question of mere temporal precedence (i.e., “which comes first”) to investigate a more developmentally dynamic model of anxiety-depression co-occurrence over time.

An important issue that may obscure meaningful findings in the study of anxiety-depression co-occurrence is the lumping together of distinct forms of anxiety. Anxiety is not a single, isomorphic class of symptoms and disorder. Rather, anxiety disorders and the core defining features of various anxiety syndromes (e.g., social anxiety, panic, separation anxiety) are heterogeneous in terms of age of onset, longitudinal trajectories (Copeland, Angold, Shanahan, & Costello, 2014; Kessler et al., 2005), and symptom expression (Weems & Costa, 2005). Moreover, the rate of co-occurrence of these heterogeneous forms of anxiety with depression and other psychopathologies varies (Hankin et al., 2016; Angold, Costello, & Erkanli, 1999).

The current study longitudinally examined the reciprocal associations of depressive symptoms with different forms of anxiety syndromes¹. Our main purpose was to investigate whether particular anxiety syndromes predict, and are predicted by, depression, in a systematic manner across time in youth. To explore this descriptive question, we assessed depression and different anxiety syndromes (social anxiety, panic, separation anxiety) using a multi-wave prospective design over a three-year follow-up across different age cohorts, with youth recruited from the community. This study aims to contribute to a more nuanced, accurate picture of anxiety-depression co-occurrence over time in childhood and adolescence than the study of temporal precedence alone. By establishing a descriptive pattern of how different forms of anxiety relate to depression across time among youth, this knowledge can be used to better

¹ In this paper, we discuss syndromes, or symptom clusters, of anxiety and depression. While much of the prior literature on anxiety and depression focuses on comorbidity at the disorder level, we focus on syndromes, as predictors of later disorders (Gerhardt, Compas, Connor, & Achenbach, 1999). Additionally, dimensionally examining symptoms allows for a more sensitive, fine-grained measure of how different forms of anxiety and depression relate to each other over time, as subthreshold fluctuations in symptom levels are captured that would not be represented using a diagnostic approach.

understand processes that may explain why particular anxiety syndromes predict, and are predicted by, depression over time in a systematic, organized manner.

Developmental Progression of Anxiety-Depression Co-Occurrence

A large body of research has investigated the temporal patterns of different forms of anxiety with depression (Cummings et al., 2014) with the goal of addressing the question of “which comes first.” Most prior work finds that anxiety, when broadly conceptualized and measured, predicts depression (e.g., Kouros, Quasem, & Garber, 2013; Kessler et al., 2005; Merikangas et al., 2010; Rohde et al., 1991; Cole et al., 1998). Much of this work combines multiple anxiety syndromes into a broad “anxiety symptoms” scale. However, this conclusion that anxiety precedes depression may depend on the specific anxiety syndromes examined as predictors of subsequent depression. We focus in the current study on the association of syndromes of social anxiety, panic, and separation anxiety with depression.

Social anxiety and depression are related during childhood and adolescence (Epkins & Heckler, 2011; Hamilton et al., 2016; Ranta, Kaltiala-Heino, Rantanen, & Marttunen, 2009); however, their temporal association has been debated. Cummings et al. (2014) proposed that social anxiety may predict depression, and vice versa, as impairment in one domain results in an increase in symptoms in the other domain. Many studies show that social anxiety predicts depression across the lifespan (e.g., Aune & Stiles, 2009; Last, Perrin, Hersen, & Kazdin, 1992; Beesdo et al., 2007). Others found that depression predicts social anxiety during adolescence, but that social anxiety did not predict depression (Hamilton et al., 2016). However, most of these studies have not repeatedly assessed social anxiety and depression with more than three time points. With three time points or fewer, it cannot be determined prediction from one symptom domain to another happened only once, or whether *both* temporal sequences exist as part of a

larger pattern of mutually reinforcing symptom escalation over time (i.e., social anxiety predicts, and is predicted by, depression across time). This possibility has yet to be examined empirically.

Studies of adults find that panic is a risk factor for later depression (Horn & Wuyek, 2010). However, National Comorbidity Survey data (Kessler et al., 1998) show of those individuals who reported experiencing both depressive episodes and panic attacks, 43.4% reported their first panic attack occurred before their first depressive episode, whereas 31.1% reported the reverse sequence. A review similarly found that panic precedes depression in one third of adults, depression precedes panic in another third, and panic and depression develop concurrently in the last third (Johnson & Lydiard, 1998). Thus, the precise temporal patterning between panic and depression symptoms across time is not well understood, especially among youth.

Most research has focused on separation anxiety as a risk factor for depression, and has found separation anxiety precedes depression (e.g., Lewinsohn, Zinbarg, Seeley, Lewinsohn, & Sack, 1997). The median age of onset of separation anxiety disorder is younger than that of social anxiety and panic disorders across samples (Kessler et al., 2005; Last et al. 1992). Therefore, the temporal patterning of separation anxiety and depression may differ from that of other forms of anxiety with depression, such that separation anxiety may be most likely to precede depression symptoms. The heterogeneous ages of onset for different anxiety syndromes, combined with different temporal patternings of particular anxiety manifestations with depression over time, support the use of an analytical approach that can parse the independent associations of specific forms of anxiety with depression over time.

Moderators of Anxiety-Depression Co-occurrence

Age and gender may moderate the association of anxiety and depression over time. Depression and anxiety are both more prevalent among girls than boys (Hankin et al., 1998; Costello et al., 1996; Axelson & Birmaher, 2001), and anxiety-depression co-occurrence is more common in girls (Cummings et al., 2014). Research finds greater heterotypic continuity from anxiety to depression, and vice-versa, for girls than for boys (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; McGee, Feehan, Williams, & Anderson, 1992). However, findings have been equivocal on whether gender moderates the development of anxiety and depression symptoms. Some studies have found evidence for stronger associations between anxiety and depression for girls over time (Merikangas et al., 2003), whereas others have not found evidence that gender moderates developmental trajectories of anxiety and depression (McLaughlin & King, 2015; Hamilton et al., 2016). Relatedly, there are well-established age differences in both depression and certain forms of anxiety (Kessler et al., 2005), which have been proposed to lead to different patterns of comorbidity by age (Cummings et al., 2014). Few studies have examined whether age moderates trajectories of anxiety and depression across time.

Methodological Considerations

Much of the existing research has been limited to two- or three-point prospective designs (e.g., Avenevoli et al., 2001; Keenan et al., 2008; Pine et al., 1998), or to retrospective studies relying on participants' recall of anxiety and depressive symptoms, which underestimate comorbidity rates (Angold et al., 1999; Moffitt et al., 2010). These designs were not structured to test for potential reciprocal associations in the developmental interplay of anxiety and depression. Accurate delineation of the descriptive patterning of the temporal associations between different anxiety syndromes and depression benefits from a minimum of four time

points with adequate spacing between follow-up assessments. This allows for change to occur in symptoms, and enables reliable prediction of co-occurring internalizing syndromes after controlling for the autoregressive stability of a particular internalizing syndrome (e.g., social anxiety) over time (Cole & Maxwell, 2003; Burt et al., 2008). The current study uses a multi-wave prospective design in which different anxiety syndromes and depression were assessed across three years, and the repeated measures data analyzed across four assessment waves.

The Current Research

The proposed study used data from a prospective longitudinal study of 3rd, 6th, and 9th graders recruited from the community to examine and more accurately describe the co-occurring temporal patternings and reciprocal effects of different anxiety syndromes and depression. We move beyond the question of “which came first” and examine the possibility of reciprocal effects in different anxiety syndromes and depression to investigate how different anxiety syndromes and depression temporally relate to each over time. Especially important to accurately delineating their longitudinal co-occurrence is distinguishing between syndromes of anxiety, given the established heterogeneity in anxiety. We also tested for moderation of the model by age and gender.

CHAPTER 2: METHOD

Participants

Youth were recruited at the University of Denver (DU) and Rutgers University (RU). Brief informational letters were sent home to families with a child in 3rd, 6th, or 9th grades in the participating school districts, around DU (broader Denver metropolitan area) and RU (central New Jersey area). Of the families to whom letters were sent, 1,108 parents called the laboratory for more information. Parent report established that the parent and child were fluent in English, the child did not have an autism spectrum disorder, psychotic disorder, or intellectual disability. Of the families who initially contacted the laboratory, 665 (60%) qualified as study participants. The remaining 498 (40%) were nonparticipants for the following reasons: 4 (1%) were excluded because the parents reported that their child had an autism spectrum disorder or low IQ; 13 (3%) were non-English speaking families; 330 (71%) declined after learning about the study's requirements; 113 (25%) were scheduled but did not arrive for assessment.

The final sample consisted of 665 youth from 7-17 years ($M = 11.8$, $SD = 2.4$). The sample was comparable to the community and school districts from which it was recruited. 62.2% of participants identified their race and ethnicity as white, 11.3% identified as African American, 7.5% as Hispanic, 9.6% as Asian or Pacific Islander, and 9.3% identified as another race or ethnicity. 18.3% of participants received free or reduced lunch at school. Median annual family income was \$86,500. For additional details about the sample, see Hankin et al. (2015).

Procedure

Parents visited the laboratory for the baseline assessment and provided informed written consent. Youth provided informed written assent. Youth completed questionnaires assessing

their depressive and anxious symptoms at baseline. Follow-up assessments evaluating child-reported symptoms of depression and anxiety occurred every 3 months after the baseline visit for the following three years, for a total of 13 assessments. The Institutional Review Boards at both sites approved all procedures. Youth were compensated monetarily for their participation.

Measures

Depressive symptoms. The Children's Depression Inventory (CDI; Kovacs, 1992) is a widely-used measure of depressive symptoms in children and adolescents that was administered to participants at baseline and at each 3-month assessment. A total score, ranging from 0 to 54, is generated by summing all items, with a higher score indicating higher levels of depressive symptoms. The CDI has sound psychometric properties, including good internal consistency and construct validity (Klein, Dougherty, & Olino, 2005). In the current sample, internal consistency (α) was between 0.79 and 0.90 across all assessments.

Anxious symptoms. The Multidimensional Anxiety Scale for Children (MASC; March, Parker, Sullivan, Stallings, & Conners, 1997), a widely-used measure of anxious symptoms in children and adolescents, was administered to participants at baseline and at each 3-month assessment. The MASC assesses physical symptoms of anxiety, harm avoidance, social anxiety, and separation anxiety, and shows good reliability and validity (March et al., 1997). Scores on the MASC are more strongly associated with scores on the Revised Children's Manifest Anxiety Scale than the CDI (March et al., 1997), and have been found to be clinically useful at differentiating anxiety from depression, as assessed by the CDI (Osman et al., 2009). The present study included the physical panic symptoms, social anxiety, and separation anxiety subscales, which are associated with risk for their specific disorders and demonstrate discriminant validity (van Gastel & Ferdinand, 2008; Wei et al., 2014; March et al., 1997). The harm avoidance

subscale was not used, as it has questionable validity, and is either uncorrelated or negatively correlated with the other subscales (Baldwin & Dadds, 2007; Grills-Taquechel, Ollendick, & Fisak, 2008; Snyder et al., 2015). Subscale scores for physical symptoms, social anxiety, and separation anxiety were created by computing a mean score of the items in each subscale. A higher score indicates higher levels of anxious symptoms. Internal consistency was adequate for all subscales across all time points in the present sample ($\alpha > .80$ for physical symptoms, $\alpha > .80$ for social anxiety, and $\alpha > .63$ for separation anxiety).

Data Analytic Plan

All analyses were conducted using Mplus (Muthén & Muthén, 2008). “Good fit” was defined as confirmatory fit index (CFI) $\geq .95$ and standardized root mean square residual (SRMR) $\leq .08$; “acceptable fit” was defined as CFI $\geq .90$ (Hu & Bentler, 1999). Hu and Bentler (1999) recommend using a combination of two relative fit indices (e.g., CFI and SRMR). Given several statisticians’ recommendations to treat these values as guidelines, rather than as strict cutoffs, we prioritized the convergence across these two fit indices over reliance on any one particular measure of fit (Kenny, 2015; Barrett, 2007).

We modeled the prospective associations between physical panic symptoms, social anxiety, and separation anxiety with depression symptoms in an autoregressive cross-lagged path model over four time points: T1, T2, T3, and T4. T1 was the sum of scores from participants’ 3, 6, and 9 month assessments; T2 was the sum of scores from 12, 15, and 18 months; T3 was 21, 24, and 27 months; T4 was 30, 33, and 36 months. We created our composites from the sum of 3 time points as it has been demonstrated that three or more assessments results in more reliable, sensitive longitudinal analyses (Little, 2013). Sum scores improve the reliability of the estimate of each construct and account for outliers (Little, 2013). Symptoms at baseline were excluded, as

meta-analytic work has found the first administration of repeated measures self-report data, particularly the CDI, is elevated (Twenge & Nolen-Hoeksema, 2002). This approach allowed us to test cross-prediction from one syndrome domain to another across 4 time points, with equal assessments contributing to each time point in analyses, with equal spacing across time, and making use of all the data collected.

The general model (Figure 1) included correlations between CDI score and individual MASC subscale scores at each of the four time points, and paths linking CDI score with subsequent MASC subscale scores, and MASC subscale scores with subsequent CDI scores and with each other. We allowed depressive symptoms to predict subsequent depressive symptoms, and each specific form of anxiety symptoms to predict itself at subsequent time points, to model the stability of depressive and anxious syndromes over time and enable prospective prediction of change in different internalizing syndromes (e.g., social anxiety to later depression). Therefore, the cross-lagged paths provide the incremental estimate of how much one internalizing syndrome (e.g., social anxiety) predicts future change in another internalizing syndrome (e.g., depression) after accounting for auto-regressive stabilities and earlier influences of all forms of internalizing syndromes included in the model. Finally, we explored moderation of pathways in the general autoregressive cross-lagged model by age and gender.

Data were missing completely at random across each of the four time points for the CDI, and across each of the four time points for the MASC subscales (Little's MCAR test; CDI: $\chi^2=31.96$, $df=27$, $p=0.23$; physical symptoms: $\chi^2=36.93$, $df=27$, $p=0.10$; social anxiety: $\chi^2=28.01$, $df=27$, $p=0.41$; separation anxiety: $\chi^2=16.77$, $df=27$, $p=0.94$). Missing data were addressed using full information maximum likelihood (FIML) estimation (Graham & Schafer, 2002).

CHAPTER 3: RESULTS

Descriptive Statistics

The means and standard deviations of each anxiety syndrome and depressive symptoms, separated by gender, are reported in Table 1. Mean levels of physical symptoms, social anxiety, separation anxiety, and depression symptoms were within the range typically observed in general community samples of youth of these ages. The pattern of gender differences in our sample was consistent with prior literature on symptom levels for girls and boys across development. Girls reported higher mean levels of depression symptoms than boys at each time point (Table 1).

Correlations within and across domains are reported in Table 2. Within time at T1, T2, T3, and T4, symptoms of depression were moderately to strongly correlated with physical and social anxiety symptoms. Symptoms of depression were weakly correlated with separation anxiety symptoms within each time point.

General autoregressive cross-lagged model results

Figure 2 shows the model and main findings. The model had good fit by SRMR and acceptable fit by CFI (SRMR=.07, CFI=.93; $\chi^2 = 475.65$, $df = 55$, $p < .001$).

Physical panic and depression. Levels of physical symptoms of anxiety at T1 predicted variance in symptoms of depression at T2 ($\beta = .085$, $p = .055$). Levels of depression at T2 predicted variance in physical symptoms at T3 ($\beta = .082$, $p = .045$). Physical symptoms at T3 predicted variance in symptoms of depression at T4 ($\beta = .130$, $p = .003$). A reciprocal relationship comprising T2, T3, and T4 was also found from physical symptoms to depression beginning with physical symptoms at T2. Although symptoms of depression at T1 did not predict physical symptoms T2 ($\beta = -.027$, $p = .495$), levels of physical symptoms at T2 predicted variance in

depression at T3 ($\beta=.105, p=.01$), and levels of depression at T3 predicted variance in physical symptoms at T4 ($\beta=.100, p=.08$).

Social anxiety and depression. Levels of social anxiety symptoms at T1 predicted variance in symptoms of depression at T2 ($\beta=.093, p=.036$). Levels of depression at T2 predicted variance in symptoms of social anxiety at T3 ($\beta=.080, p=.055$). Additionally, symptoms of social anxiety at T2 predicted variance in symptoms of depression at T3 ($\beta=.080, p=.04$). Levels of depression at T3 also predicted variance in symptoms of social anxiety at T4 ($\beta=.085, p=.033$).

Separation anxiety and depression. Levels of separation anxiety symptoms at T3 predicted variance in symptoms of depression at T4 ($\beta=.081, p=.03$). Separation anxiety and depression were not prospectively associated at any other time points above and beyond the stability of either syndrome from one time point to the next, and the prospective contributions of other syndromes.

Moderation by age or gender.

Age moderated the path from symptoms of depression at T2 to physical symptoms at T3 ($\beta=.465, p=.023$). Gender moderated the relation of physical symptoms at T1 to depression at T2 ($\beta=-.104, p=.033$); this pathway was stronger for girls than for boys. Neither age nor gender moderated any other pathways.

CHAPTER 4: DISCUSSION

The temporal patterning of the development of co-occurring syndromes of anxiety and depression during childhood and adolescence has long been a topic of debate. The current study found physical panic symptoms and depression symptoms, as well as social anxiety and depression symptoms, longitudinally and reciprocally predicted each other over the three-year prospective follow-up, above and beyond the stability of either domain from one time point to the next. The results of the current study suggest that the development of syndromes of depression, physical and social anxiety during childhood and adolescence occurs in a predictable and systematic reciprocal pattern, rather than strictly sequentially in a unidirectional manner (i.e., anxiety syndromes strictly precede depression). This is the first study, to our knowledge, to investigate temporal dynamics relating the unique contributions of multiple and specific anxiety syndromes to the development of depression over time. That is, by entering depression and all three syndromes of anxiety in our model simultaneously and across all four time points, we were able to describe and parse the degree to which each individual internalizing syndrome separately predicts prospectively unique variance of symptom levels across domains.

An extensive literature has examined the co-occurrence of syndromes of anxiety with depression (e.g. Conway, Zinbarg, Mineka, & Craske, 2017; Hamilton et al., 2016; McLaughlin & King, 2015). While the preponderance of evidence indicates that most forms of anxiety precede depression (Kessler et al., 2005; Merikangas et al., 2010; Rohde et al., 1991; Cole et al., 1998), another body of research suggests that depression may precede anxiety (Moffitt et al., 2007; Pine et al., 1998; Merikangas et al., 2003) or that the two may develop in parallel (Cummings et al., 2014). The results of the current study suggest that the traditional view that

anxiety precedes depression is an oversimplification of a more nuanced, dynamic process. The present work can help to explain these inconsistencies in the sequential comorbidity literature regarding the temporal precedence of anxiety relating to depression.

Our study benefits from the use of four time points assessed longitudinally over three years. Most previous work has used three time points to investigate the prospective associations of syndromes of anxiety with depression (e.g. McLaughlin & King, 2015; Avenevoli et al., 2001; Pine et al., 1998). However, with three time points or fewer, it is not clear whether an escalation from one symptom domain to another happened only once over time (e.g. social anxiety at T1 predicts depression at T2, without being able to see the opposite thread in the dynamic pattern), or whether the escalations were part of a larger pattern of mutually reinforcing escalations unfolding over time, as seen here.

The current study most directly builds upon recent work by McLaughlin & King (2015), who used an autoregressive cross-lagged panel model to examine trajectories of anxiety and depression co-occurrence over a 12-month period with three assessments. Their model provides important contributions to understanding anxiety and depression co-occurrence over time. However, their approach left particular questions unanswered, as separate models were created for each of the anxiety syndromes studied. Thus, as these separate models did not parse the covariance between anxiety syndromes, the relative contributions of each form of anxiety to symptoms of depression are unclear. The present work, in contrast, *simultaneously* modeled physical, social, and separation anxiety with depression, and parsed the unique variance in symptoms of depression prospectively predicted by each form of anxiety on its own. Such a distinction is crucial in identifying potential mechanisms via which these longitudinal bi-directional patterns develop and are maintained.

Separation anxiety symptoms were not predicted over time by depression, physical, or social anxiety symptoms. The only consistent predictor of symptoms of separation anxiety at a given time point was separation anxiety at the previous time point. Separation anxiety has a younger median age of onset than panic disorder and social anxiety, and is less common in older adolescents (Kessler et al., 2005). In a younger sample of children, symptoms of separation anxiety and depression may have predicted variance in each other over time. Separation anxiety and depression may also develop independently of one another over time across development via unique mechanisms. This provides additional evidence that lumping distinct forms of anxiety together obscures meaningful differences in the temporal sequencing of syndromes of depression and anxiety, as these patterns vary by symptom type.

The pattern of findings in the current study raises questions about potential mechanisms that may account for these relations. Peer and social mechanisms may help to explain the reciprocal association between symptoms of depression and social anxiety over time. Peer relationships become increasingly important and intimate during adolescence, and these relationships have a strong influence on depression and social anxiety symptoms during this time (Somerville, 2013). Individuals with higher levels of depression engage in behaviors that expose them to more interpersonal stressors, such as withdrawal from social relationships, excessive reassurance seeking, and irritability (Liu & Alloy, 2010; Hamilton et al., 2013; Hammen, 1991). Increased experience of interpersonal stress may reinforce symptoms of social anxiety, and anxiety-related behaviors (e.g. avoidance of interaction with others) may in turn lead to escalations in symptoms of depression as individuals withdraw further from their social networks (Caldwell, Rudolph, Troop-Gordon, & Kim, 2004). Similar mechanisms may account for the relationship between physical anxiety and depression symptoms. Physical symptoms of anxiety

are closely associated with panic disorder (van Gastel & Ferdinand, 2008; Wei, et al., 2014). Avoidance of situations that are associated with panic attacks is a key feature of panic disorder, particularly in panic disorder with agoraphobia (Craske, Sanderson, & Barlow, 1987). This avoidance may lead individuals to become isolated, which may lead to escalations in symptoms of depression. Further empirical study is necessary to explore these and other possibilities.

Exploratory analyses to examine age and gender as moderators of these longitudinal reciprocal patterns suggested that results applied similarly to both girls and boys, as well as to youth of different ages, almost without exception. Mean level differences in syndromes of anxiety and depression are well established between boys and girls and across development (Hankin & Abramson, 2001), which was reflected in this study. The lack of moderation by gender in our findings is consistent with prior work that did not find evidence for moderation of developmental trajectories of anxiety or depression (McLaughlin & King, 2015; Hamilton et al., 2016) or of cross-domain covariance (Conway et al., 2017) as a function of gender, suggesting that both boys and girls follow the same trajectories of symptom development.

These findings have several clinical implications. First, this model is clinically useful for predicting risk for disorder. CDI scores predict the onset of depression (Mattison, Handford, Kales, Goodman, & McLaughlin, 1990), and MASC subscale scores predict their respective disorders (van Gastel & Ferdinand, 2008; Wei, et al., 2014). As amplifications within these domains predicted cross-domain escalations over time, this suggests increased susceptibility to eventual disorder. Second, the current model demonstrates the necessity of tracking symptom levels across domains. If clinicians limit their assessment to an individual diagnostic category, they may miss important sub-clinical cross-domain symptom level changes. Finally, the developmental trajectories of syndromes of anxiety and depression occur in systematic and

predictable patterns of bi-directional effects over time. This supports a reconceptualization of assessments and interventions, which assume that for the majority of youth, anxiety simply precedes depression. For many children and adolescents, depression and anxiety may oscillate in symptom severity in predictable ways over the course of development. Clinicians can use this knowledge to more accurately and effectively conceptualize and treat anxiety and depression in youth.

The current study has several methodological strengths that help to further knowledge of the development of co-occurring syndromes of anxiety and depression in youth. Using a four time point prospective longitudinal design spanning three years provided a rigorous investigation of longitudinal patterns in symptom development. Furthermore, by controlling for the stability of each symptom domain over time in the autoregressive cross-lagged model, and entering all four syndromes into the model simultaneously at all time points, associations across symptom domains from one time point to the next are not due merely to the stability or intercorrelations of these syndromes over time. Finally, these results were found in a large, racially and ethnically representative community sample of girls and boys. Therefore, the results of this study likely generalize to other youth populations.

The strengths of this study must be considered in light of several limitations. Our analyses focused on self-reported symptoms of anxiety and depression, rather than on diagnoses of these disorders. Although both the MASC and the CDI have been shown to be reliable and valid measures of symptoms of anxiety and depression, respectively, in community samples (Baldwin & Dadds, 2007; Klein et al., 2005), and have also been shown to predict the later development of disorder (van Gastel & Ferdinand, 2008; Wei, et al., 2014; Klein et al., 2005), additional research is needed to determine whether similar developmental patterns exist in

syndromes of anxiety and depression at a diagnostic level. Research with a psychiatric sample would be necessary to establish whether these patterns also apply in more severe clinically symptomatic populations and whether these processes maintain levels of anxiety and depression once they reach diagnostic thresholds. Additionally, the current study is limited in its ability to generalize to other forms of anxiety, such as worry, that are not assessed by the MASC.

The present study expands extant understanding of the development of co-occurring depression with different forms of anxiety during childhood and adolescence by demonstrating that symptom development of some internalizing syndromes occurs in mutually reinforcing, reciprocal patterns across time. More specifically, physical symptoms and depression predict each other over time, above and beyond the stability of either syndrome over time, for boys and girls across all ages. Similarly, symptoms of social anxiety and depression are also mutually predictive over time, above and beyond the expected stability, for all ages and genders. The current study also emphasizes the importance of distinguishing between heterogeneous forms of anxiety in the study of anxiety-depression comorbidity, as separation anxiety and depression were not reciprocally associated over time. Taken together, these results suggest that, rather than framing the development of co-occurring syndromes of anxiety and depression as a question of “which came first”, it is more informative and accurate to conceptualize the co-development of these syndromes as occurring in a series of systematic, predictable bi-directional patterns over time.

CHAPTER 5: TABLES AND FIGURES

Table 1

Means and standard deviations of symptoms of anxiety and depression by gender

Variable	<u>Total Sample</u>		<u>Boys</u>		<u>Girls</u>		<u>Gender Difference</u>
	Mean	SD	Mean	SD	Mean	SD	t –value
T1							
DEP	14.36	12.43	13.26	10.98	15.25	13.44	-1.87
PH	24.37	15.01	22.97	14.34	25.51	15.47	-1.95
SO	26.66	14.25	24.17	14.16	28.72	14.01	-3.68***
SA	21.08	12.10	19.16	11.42	22.65	12.43	-3.36***
T2							
DEP	12.83	12.05	11.75	11.41	13.67	12.47	-1.83
PH	21.06	14.16	19.53	13.67	22.25	14.45	-2.17*
SO	23.72	14.26	20.55	12.87	26.23	14.81	-4.59***
SA	18.90	11.51	17.11	10.41	20.29	12.14	-3.17**
T3							
DEP	11.32	12.00	10.10	9.76	12.25	13.41	-1.98*
PH	20.83	15.25	18.59	13.54	22.46	16.22	-2.62**
SO	24.65	14.66	21.85	13.63	26.67	15.07	-3.36***
SA	17.12	10.33	15.76	9.44	18.11	10.85	-2.33*
T4							
DEP	12.45	12.78	10.62	9.99	13.82	14.38	-2.60**
PH	20.26	16.54	18.05	14.41	21.91	17.81	-2.49*
SO	23.75	15.67	20.48	14.45	26.18	16.13	-3.86***
SA	15.12	10.65	12.80	9.56	16.83	11.10	-4.05***

Note. Gender = *male* (1) or *female* (-1). DEP: depression; PH: physical symptoms; SO: social anxiety; SA: separation anxiety

Table 1 (cont.)

* - Significant at the .05 level, 2-sided independent samples t-test; ** - Significant at the .01 level, 2-sided independent samples t-test; *** - Significant at the .001 level, 2-sided independent samples t-test.

Table 2

Intercorrelations among primary study variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1.DEP_T1															
2.PH_T1	.58**														
3.SO_T1	.48**	.55**													
4.SA_T1	.12**	.43**	.44**												
5.DEP_T2	.71*	.46**	.45**	.05											
6.PH_T2	.43**	.76**	.50**	.35**	.53**										
7.SO_T2	.45**	.45**	.77**	.31**	.55**	.54**									
8.SA_T2	.10*	.36**	.35**	.81**	.10*	.43**	.36**								
9.DEP_T3	.57**	.43**	.45**	.12*	.78*	.50**	.51**	.10*							
10.PH_T3	.39**	.69**	.41**	.29**	.45**	.75**	.41**	.28**	.57**						
11.SO_T3	.41**	.42**	.67**	.26**	.50**	.47**	.74**	.24**	.61**	.58**					
12.SA_T3	.11*	.29**	.27**	.73**	.08	.32**	.24**	.78**	.13*	.35**	.27**				
13.DEP_T4	.53**	.41**	.38**	.09	.65**	.46**	.47**	.06	.76*	.51**	.51**	.03			
14.PH_T4	.37**	.65**	.41**	.22**	.42**	.71**	.40**	.26**	.51**	.81**	.48**	.24**	.62**		
15.SO_T4	.26**	.36**	.61**	.28**	.39**	.43**	.72**	.26**	.53**	.46**	.81**	.21**	.55**	.53**	
16.SA_T4	.02	.27**	.29**	.67**	.06	.31**	.23**	.76**	.13*	.25**	.23**	.79**	.13**	.35**	.362**

Note. DEP: depression; PH: physical symptoms; SO: social anxiety; SA: separation anxiety

** - Correlation is significant at the 0.01 level (2-tailed). * - Correlation is significant at the 0.05 level (2-tailed).

Figure 1. Autoregressive cross-lagged path model.

Note. All four symptom domains were allowed to correlate within time at all four time points; these paths are included in the figure at T1, but are omitted from the figure at T2, T3, and T4 for simplicity.

DEP: depression; PH: physical symptoms; SO: social anxiety; SA: separation anxiety.

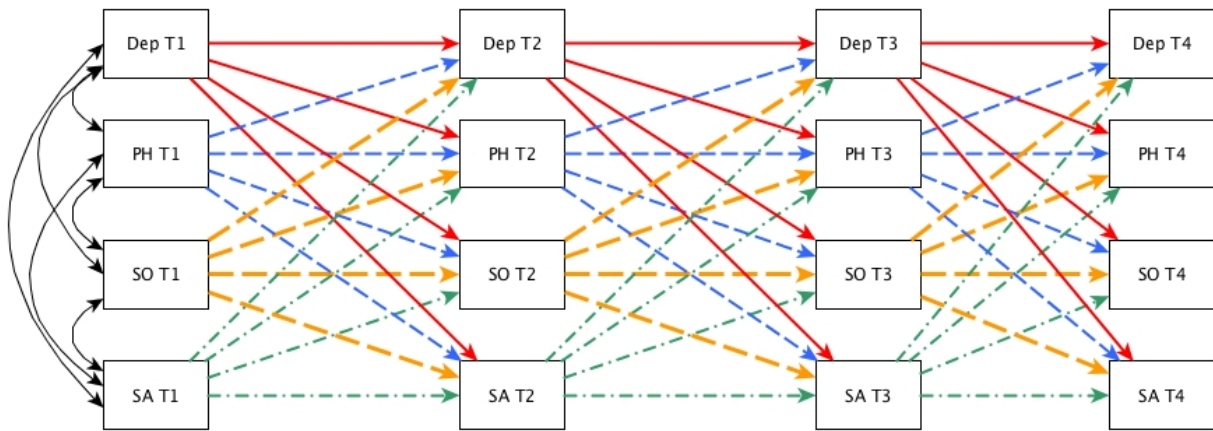
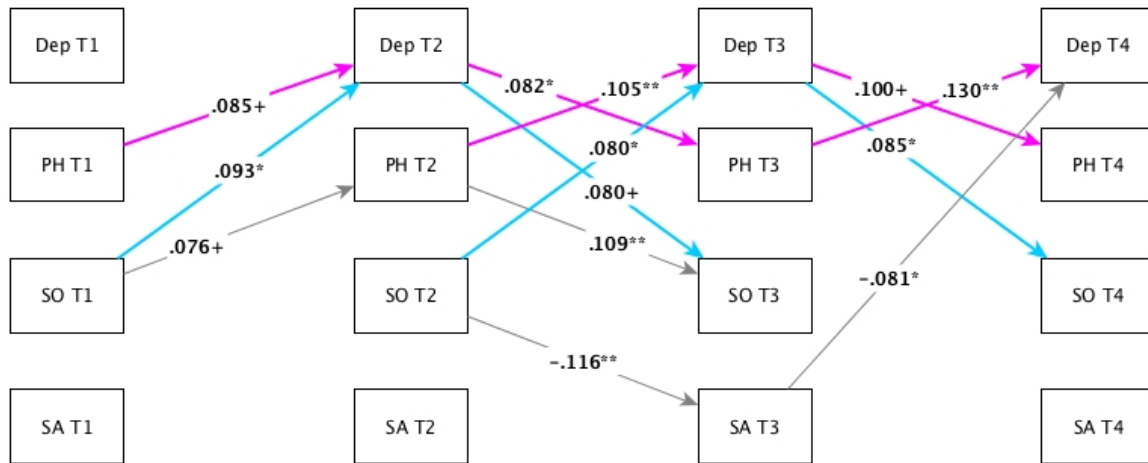


Figure 2. Significant pathways in the autoregressive cross-lagged path model.

Note. Autoregressive stability paths are not depicted in the figure for simplicity. All stability paths were significant, $p < .05$.

* Significant at $p < .05$; ** Significant at $p < .01$; + Significant at trend level, $p \leq .08$.

DEP: depression; PH: physical symptoms; SO: social anxiety; SA: separation anxiety.



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APPENDIX A: IRB LETTER

UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Office of the Vice Chancellor for Research

Office for the Protection of Research Subjects
805 W Pennsylvania Ave
Urbana, IL 61801



This letter supersedes the approval letter dated March 30, 2017. It has been modified to reflect expedited status and expiration date, which was previously listed as exempt.

April 4, 2017

Benjamin Hankin
Psychology
724 Psychology Bldg
603 E. Daniel

Champaign, IL 61820

RE: *Gene Environment and Mood Study*
IRB Protocol Number: 17605

Dear Dr. Hankin:

This letter authorizes the use of human subjects in your project entitled *Gene Environment and Mood Study*. The University of Illinois at Urbana-Champaign Institutional Review Board (IRB) approved, by expedited review, the protocol as described in your IRB application. The expiration date for this protocol, IRB number 17605, is 03/28/2018. The risk designation applied to your project is *no more than minimal risk*.

Copies of the attached date-stamped consent form(s) must be used in obtaining informed consent. If there is a need to revise or alter the consent form(s), please submit the revised form(s) for IRB review, approval, and date-stamping prior to use.

Under applicable regulations, no changes to procedures involving human subjects may be made without prior IRB review and approval. The regulations also require that you promptly notify the IRB of any problems involving human subjects, including unanticipated side effects, adverse reactions, and any injuries or complications that arise during the project.

If you have any questions about the IRB process, or if you need assistance at any time, please feel free to contact me at the OPRS office, or visit our website at <https://www.oprs.research.illinois.edu>.

Sincerely,

Ron Banks, MS, CIP

Human Subjects Research Coordinator, Office for the Protection of Research Subjects

Attachment(s): 4 Consent Forms