THE DISSERTATION COMMITTEE FOR PETER CUNNINGHAM CLASEN CERTIFIES THAT THIS IS THE APPROVED VERSION OF THE FOLLOWING DISSERTATION:

ELABORATIVE PROCESSING BIASES ASSOCIATED WITH VULNERABILITY AND MAINTENANCE OF DEPRESSION: EVIDENCE ACROSS LEVELS OF ANALYSIS

Committee:

Christopher G. Beevers, Supervisor

Robert A. Josephs

Jeanette A. Mumford

Stephanie S. Rude

David M. Schnyer

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by

PETER CUNNINGHAM CLASEN, BFA

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Dedication

For my parents.

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ELABORATIVE PROCESSING BIASES ASSOCIATED WITH VULNERABILITY AND MAINTENANCE OF DEPRESSION: EVIDENCE ACROSS LEVELS OF ANALYSIS

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Supervisor: Christopher G. Beevers

Abstract: Major depressive disorder (MDD) will soon represent the most costly and debilitating disorder in the world. Yet, a clear model of the mechanisms underlying MDD remains elusive. This lack of clarity obscures efforts to prevent and treat MDD more effectively. This dissertation seeks to advance an integrated model of the mechanisms underlying MDD across cognitive, neural, and genetic levels of analysis. Building on the empirical foundation of cognitive theories of MDD, the dissertation includes three studies that help address questions about the cognitive mechanisms underlying depression vulnerability and maintenance. Specifically, the three studies focus on identifying 1) how elaborative processing biases, including attentional biases and rumination, give rise to specific symptoms of MDD and 2) elucidating biological mechanisms that may give rise to these biases. Together, these studies help advance an integrated model of MDD that, ultimately, may help facilitate the prevention and treatment of this costly and debilitating disorder.

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INTRODUCTION

Major depressive disorder (MDD) is poised to become the world's leading public health problem in terms of disease burden (World Health Organization, n.d.). Managing the impact of MDD on individuals and societies requires effective interventions for prevention and treatment. A major barrier to the effectiveness of current interventions is the fact that a comprehensive model of depression remains elusive: We do not have a clear picture of the mechanisms underlying depression vulnerability and maintenance. As a result, we cannot predict, for example, who will become depressed or who will respond to a given treatment with any degree of certainty. This uncertainty obscures efforts by policy makers and health care providers to effectively allocate resources for prevention and treatment. Moreover, it obfuscates research efforts aimed at improving effectiveness of existing interventions and developing new individualized treatments.

Building an integrated model of the mechanisms underlying depression, therefore, represents a first step toward reducing the burden of MDD. The cognitive model of depression represents a compelling foundation on which to build such a model. This model postulates that biases in the way people process emotional and social information predispose them to the onset and maintenance of depression (e.g., Beck, 1967). Over the past 40 years, this model has gained increasing empirical support (Clasen, Disner, & Beevers, in Press; Gotlib & Joormann, 2010 for recent reviews). In the past 20 years, much of this support includes converging evidence that cuts across levels of analysis (e.g., behavioral, biological, environmental) (Disner, Beevers, Haigh, & Beck, 2011 for

recent review). This evidence helps link the cognitive model to underlying neural and genetic models of depression and helps specify who is most likely to develop depression in the context of environmental circumstances (e.g., early abuse and neglect, life stressors). This evidence suggests that the cognitive model of depression is uniquely placed at the nexus of biology, psychology, and the environment and, therefore, represents a powerful foundation for the development of an integrated model of MDD.

This dissertation is a contribution the development of this integrated model of MDD. Building from the theoretical postulates of the cognitive model of depression, the dissertation includes three studies aimed at providing support for the cognitive model of depression across levels of analysis, including behavioral, neural, and genetic levels. Collectively, these studies elucidate mechanisms underlying the causes and consequences of elaborative information processing biases associated with MDD. Individually, they 1) identify how these biases influence specific symptoms of depression, 2) elucidate the neural mechanisms that give rise to these vulnerabilities, and 3) examine how genetic variation predisposes individuals to the expression of these vulnerabilities in the context of life stress. Before defining the specific aims of the dissertation I provide a brief epidemiological description of MDD and overview of the cognitive model. I then outline the specific aims of the dissertation research and provide an overview of the three studies implemented to achieve these aims. The three studies are then presented as manuscripts that are currently published (studies 1 & 3) or in submission (study 2). Finally, I conclude with a general discussion of the findings and important future directions.

Description and Epidemiology of Depression

Major depressive disorder (MDD) is a common, recurrent, and impairing condition that predicts future suicide attempts, interpersonal problems, unemployment, substance abuse, and delinquency (Kessler & Walters, 1998). According to the World Health Organization, 121 million people are currently suffering from MDD and it is a leading cause of disability. The annual economic cost of MDD in the United States alone is also quite large—billions of dollars annually—due to medical expenditures, lost productivity, and other costs (Greenberg, Stiglin, Finkelstein, & Berndt, 1993; Wang, Simon, & Kessler, 2003). Further, MDD accounts for more than two-thirds of the 30,000 reported suicides each year (Beautrais et al., 1996).

The Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition) defines Major Depressive Disorder (MDD) as the presence of 5 (or more) of the following symptoms during the same two-week period (American Psychiatric Association, 2000):

(1) depressed mood most of the day, nearly every day.

(2) markedly diminished interest or pleasure in almost all activities (anhedonia).

(3) significant weight loss/gain or decrease/increase in appetite.

(4) insomnia or hypersomnia.

(5) psychomotor retardation or agitation.

(6) fatigue or loss of energy.

(7) feelings of worthlessness (or excessive or inappropriate guilt).

(8) diminished ability to concentrate or make decisions.

(9) recurrent thoughts of death.

Symptoms must be present most of the day, nearly every day and should represent a significant change from previous functioning. Importantly, one of the nine symptoms has to be either depressed mood or anhedonia. Significant weight loss or gain is typically defined as 5% or more change in body weight in a month when not dieting. These symptoms must cause significant distress or impairment in social, occupational, or other important areas of functioning. Finally, these symptoms should not be attributable to substances (e.g., drug abuse, medication changes), medical conditions (e.g., hypothyroidism), or the death of a loved one.

Recent epidemiological research indicates that the 12-month prevalence rate for MDD is 6.6% (95% CI, 5.9 – 7.3%) among adults residing in the United States. Lifetime prevalence for MDD is 16.2% (95% CI, 15.1 – 17.3%) (Kessler et al., 2003). Put differently, approximately 13.5 million Americans experienced MDD in the past year and 34 million adults have experienced MDD at some point in their life. Approximately 51% who experienced MDD in the past year received health care treatment for MDD, although treatment was considered adequate in only 21% of the cases (Beautrais et al., 1996). Thus, MDD is a prevalent and pervasive mental health disorder that is unfortunately not treated optimally in the United States.

Obtaining adequate treatment is important, as the course of MDD tends to be relatively prolonged. One of the largest studies of MDD recovery among individuals seeking treatment found that 50% of the sample recovered from MDD within 6 months,

70% within 12 months, and 81% within 24 months. Approximately 17% did not recover within the five year follow-up period (Keller et al., 1992). The first six months represents a particularly important time period for MDD recovery, as the rate of MDD recovery significantly slows after 6 months. Similarly, Kessler (2009) writes that time to recovery from MDD in non-treatment seeking populations "appears to be highly variable, although epidemiological evidence is slim" (pg. 29). One study found that 40% had recovered from MDD by 5 weeks and 90% had recovered within 12 months (McLeod, Kessler, & Landis, 1992). Another study reported that mean time to recovery was four months and that approximately 90% had recovered by 12 months (Kendler, Walters, & Kessler, 1997). Taken together, these data suggest that most participants from a community sample recover from MDD within twelve months.

Given this enormous impact at societal and individual levels, there is a clear need to better understand factors that contribute to the onset of MDD so that efficacious treatments for this disorder can be developed and disseminated. Although a range of theories have been proposed (e.g., Schildkraut, 1965; Beck, 1967; Ferster, 1973; Mayberg, 1997; Joiner & Coyne, 1999), cognitive theories of depression have significant empirical support.

Cognitive Theories of Depression

Cognitive models of depression provide a compelling explanation for who is likely to become depressed. For the most part, cognitive models of MDD are diathesis-stress models of psychopathology. These models posit that an underlying vulnerability

(diathesis) is necessary and sufficient to produce the disorder if and when the person encounters an activating event (stress). According to cognitive models, cognitive mechanisms play a key role in vulnerability for the onset and maintenance of MDD (e.g., Beck, 1967; Ingram, 1984; Teasdale, 1988; Abramson, Metalsky, & Alloy, 1989)

Perhaps the best known cognitive model of depression was developed by Beck (1967, 1976). Beck's model postulates that individuals who are vulnerable to MDD harbor depressotypic schemas, or internal knowledge structures (e.g., beliefs, attitudes, memories, etc.) that influence information processing operations, like selective attention and memory search (also see Segal & Shaw, 1986; Williams, Watts, MacLeod, & Mathews, 1997). For example, if an individual holds the belief that he is worthless, he may focus on internal explanations for a negative event (e.g., "It is all my fault I lost my job. I have nothing to offer this company") instead of examining other possible explanations (i.e., bad economy, poor management, etc.). This internal focus includes selective attention for and elaborative reflection on schema-congruent information, which exacerbates negative mood and further reinforces schematic beliefs.

Rationale and Aims for Dissertation Research

This tendency to preferentially elaborate on negative emotional information is thought to play a central role in vulnerability and maintenance of MDD (Ingram, 1984; Teasdale, 1988). Elaborative processing biases are thought to involve biased attention for salient emotional stimuli and rumination, or a tendency to persistently think about the causes and consequences of depressed mood (Joormann & Gotlib, 2010; S Nolen-

Hoeksema, Wisco, & Lyubomirsky, 2008a). Moreover, elaborative attentional bias and rumination are thought to reflect biases that are unique to depression and distinct from cognitive biases underlying other disorders, including anxiety disorders (e.g., Mogg & Bradley, 2005; Hong, 2007).

Despite a wealth of research linking biased attention and rumination to MDD, many questions remain about how these biases give rise to specific symptoms of depression and the biological factors that underlie expression of these biases. This dissertation has three specific aims: 1) Examine whether attentional biases for negative stimuli are associated with persistent sad mood, a hallmark symptom of MDD, 2) Explore differences in the brain systems underlying attentional control in a population that is at high risk for MDD (adolescent women with a parental history of depression), and 3) Elucidate genetic vulnerability for ruminative thinking in the context of stressful life events. Three studies are implemented to achieve these aims. Together, these studies seek to better describe how elaborative processing biases cause and maintain MDD.

More generally, this dissertation provides support for an integrated, translational model of the mechanisms underlying vulnerability and maintenance of MDD. This approach involves the use of various methodologies to elucidate a model of depression that includes support across biological, cognitive, and environmental levels of analysis. To this end, each study of this dissertation features a unique core level of analysis (e.g., behavioral, neural, genetic); however, each of level of analysis is used to provide support for the underlying cognitive model of depression. This integrated, translational approach

is in line with a central tenet of the National Institute of Mental Health's strategic plan to strengthen the public health impact of translational research (Insel, 2009) and, perhaps more importantly, should yield a fuller, more nuanced understanding of this complex disorder.

Overview of Dissertation Studies

Study 1 examines whether attentional biases for emotional information are associated with impaired mood recovery following a sad mood induction among individuals with and without major depressive disorder (MDD). Attentional biases are assessed with an exogenous cueing task using emotional facial expressions as cues among adults with (N = 48) and without (N = 224) current MDD. Mood reactivity and recovery are measured following a sad mood induction. We anticipated that attentional biases for negative stimuli (sad and fear) would be associated with impairments in mood recovery among individuals who react to the mood induction, but that bias for sad stimuli would correspond to unique disturbances in mood recovery among depressed individuals. We also hypothesized that impairments in mood recovery would be associated with greater depression severity among individuals with MDD. This prediction is consistent with the idea that impaired mood recovery contributes to a more severe and persistent episode of MDD.

Study 2 investigates functional connectivity within a brain network associated with attentional control among adolescent woment with (n = 11) and without (n = 13) a parental history of depression. We used a seed based approach to analyzing functional

connectivity within this network using a seed location (right inferior frontal gyrus, rIFG) from our previous study of attentional control in dysphoric adults (Beevers, Clasen, Stice, & Schnyer, 2010). We hypothesized that women at high-risk for depression, based on the fact that one of their parents reported a previous episode of MDD, would demonstrate decreased connectivity between this seed region and other key components of this putative functional neural network, including right middle frontal gyrus (rMFG) and right supramarginal gyrus (rSMG). We also explored whether individual differences in the parents worst episode of depression were associated with connectivity between within this network.

Study 3 examined whether polymorphisms in the serotonin transporter (SLC6A4, 5-HTTLPR) and brain derived neurotropic factor (BDNF Val66Met, rs6265) genes moderate the relationship between life stress and rumination. Participants included a large homogenous group of healthy, unmedicated, never depressed individuals with few current symptoms of depression (N = 273). We hypothesized that individuals with genotypes associated with stress sensitivity (S 5-HTTLPR carriers or Met BDNF homozygotes) would report higher levels of rumination than individuals without these genotypes (L 5-HTTLPR and Val BDNF homozygotes) when they experienced recent adverse events. Exploratory analyses investigated the aggregate effect of risk alleles across genes (i.e. S and Met alleles) on the relationship between life stress and rumination.

STUDY1: ATTENTIONAL BIASES AND THE PERSISTENCE OF SAD MOOD IN MAJOR DEPRESSIVE DISORDER[1]

Introduction

Major depressive disorder (MDD) is a common disorder affecting approximately 121 million people worldwide (World Health Organization, n.d.). MDD is characterized as an emotional disorder that influences an individual's mood, motivation, sleep, eating, concentration, self-worth, and productivity (American Psychiatric Association, 2000). These symptoms have a significant impact on people with MDD and the people around them, leading to greater interpersonal problems, unemployment, substance abuse, delinquency, and risk for suicide (Kessler & Walters, 1998). Given the enormous impact at individual and societal levels, there is a clear need to better understand factors that maintain this disorder.

While the clinical presentation of MDD varies between individuals, one hallmark symptom is a persistent sad mood. Persistent sad mood involves feeling sad, down, depressed, or blue most of the day, nearly every day for a period of two weeks or longer (American Psychiatric Association, 2000). This symptom plays a defining role in the disorder; however, the mechanisms underlying mood persistence in MDD remain poorly understood. This gap in our understanding of MDD could undermine efforts to improve

[1] This study appears in the *Journal of Abnormal Psychology* (Clasen, P.C., Wells, T.T., Ellis, A.J., & Beevers, C.G. (2012). Attentional biases and the persistence of sad mood in major depressive disorder. *Journal of Abnormal Psychology, 122*, 74-85.)

treatments aimed at interrupting persistent sad mood. In this paper, we focus on identifying cognitive mechanisms associated with the persistence of sad mood in MDD.

Cognitive theories of depression posit that biases in the way depressed people process emotional information help perpetuate depressive symptoms (e.g., Beck, 1967; Ingram, 1984; Teasdale, 1988). These biases include, for example, preferential attention towards mood congruent information in the environment (see also Segal & Shaw, 1986; Williams, Watts, MacLeod, & Mathews, 1997). According to cognitive theories, events that trigger sad mood interact with these biases to influence the generation of negative thoughts and feelings that, in turn, lead to more persistent sadness (e.g., Teasdale, 1988; Ingram, 1984). A growing body of research supports the idea the depressed individuals demonstrate cognitive biases for emotional information, including attentional biases (Gotlib & Joormann, 2010 for review). Although this research suggests that biased attention could maintain sad mood, few studies have tested this possibility directly.

To date, research on the role of attentional biases in MDD has focused on characterizing the nature of such biases. This work followed influential research on the nature of attention for emotional stimuli in anxiety disorders (MacLeod, Mathews, & Tata, 1986; Mogg, Bradley, & Williams, 1995). Broadly, anxiety is associated with the rapid orienting of attention towards threatening (or fearful) stimuli (MacLeod et al., 1986). These biases are typically evident even when these stimuli are presented briefly (e.g., < 500 ms) (e.g., Mogg, Bradley, de Bono, & Painter, 1997; Mogg, Mathews, & Eysenck, 1992).

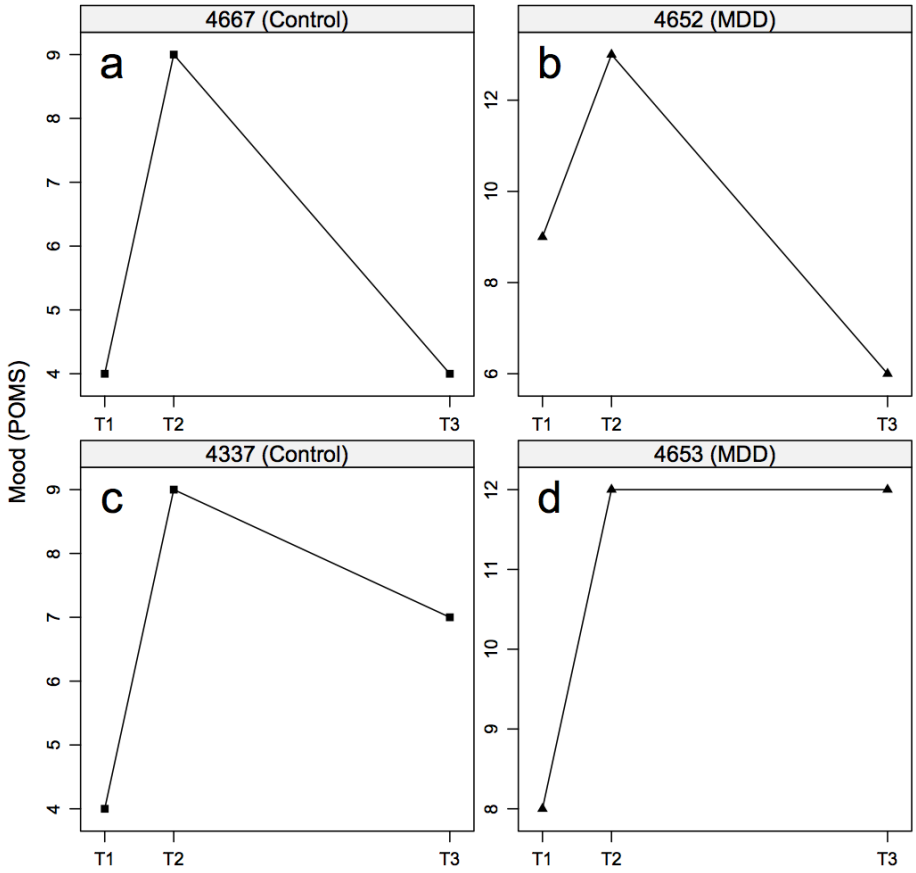
By contrast, depression is associated with elaborative attention towards mood congruent (or sad) stimuli (Mogg & Bradley, 2005; see also Mathews & MacLeod, 2005; Wisco, 2009). Depressed individuals do not automatically orient towards sad stimuli; however, they demonstrate preferential, sustained attention towards these stimuli once they enter awareness (e.g., > 1000 ms) (e.g., Bradley, Mogg, & Lee, 1997; Eizenman et al., 2003; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann, Talbot, & Gotlib, 2007; Kellough, Beevers, Ellis, & Wells, 2008; Leyman, De Raedt, Vaeyens, & Philippaerts, 2011; Siegle, Granholm, Ingram, & Matt, 2001).

But do these elaborative attentional biases help maintain depression, as posited by cognitive theories (e.g., Beck, 1967; Teasdale, 1988)? In this study, we employed a laboratory based mood induction procedure to examine whether attentional biases for negative information are associated with more persistent sad mood. Depressed and non-depressed participants underwent a standardized mood induction procedure and we measured sad mood before, immediately after the induction (i.e., reactivity), and twelve minutes later (i.e., recovery). This design allowed us to explore the relationship between attentional bias and mood in a well-controlled environment.

We were primarily interested in how participants recovered from the mood induction procedure, an index of mood persistence. It is important to note that participants can recover from the mood induction quite differently. To illustrate, Figure 1 shows mood reactivity and recovery profiles for four study participants. All reported significant reactivity to the mood induction procedure; however, each demonstrated

different levels of mood recovery. Panels (a) and (b) reflect "successful" levels of mood recovery for a non-depressed and depressed participant respectively. In each case, decrease in sad mood during recovery is equal to or greater than their initial mood reactivity. In contrast, panels (c) and (d) reflect "impaired" levels of mood recovery: Decrease in sad mood during recovery is less than their initial mood reactivity. Therefore, mood recovery depends, in part, on each individual's mood reactivity. However, these plots also illustrate that recovery can be quite variable across individuals. The current study examined whether attentional biases contribute to difficulty with mood recovery, particularly among individuals with MDD.

Figure 1. Pofiles of mood reactivity and recovery for four participants.



Note: T1 = POMS at baseline, T2 = POMS immediately after mood induction (~ T1 + 4 mins), T3 = POMS after 12 minutes of recovery (= T2 + 12 mins). Note the group (Control vs. MDD) differences in baseline mood. Panels (a) & (b) reflect "successful" mood recovery; Panels (c) & (d) reflect "impaired" mood recovery.

We anticipated that attentional biases for negative stimuli (sad and fear) would be associated with impairments in mood recovery among individuals who reacted to the mood induction, but that biases for sad stimuli would correspond to unique disturbances in mood recovery among depressed individuals. Recent experimental evidence demonstrates that inducing a negative attentional bias (using both sad and fear stimuli) in

healthy individuals leads to higher levels of sad mood following a laboratory stress-manipulation (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Further, biases for negative stimuli (sad and fear) are associated with neuroticism and introversion (e.g., Chan, Goodwin, & Harmer, 2007; Derryberry & Reed, 1994), two personality dimensions predicative of higher levels of negative affect, including sad mood, in the general population (Clark, Watson, & Mineka, 1994; Eysenck, 1998). Therefore, we hypothesized that a general negative bias, for sad or fear stimuli, would be associated with impaired mood recovery among all individuals who reacted to the mood induction procedure. However, we expected biases for sad stimuli to exhibit a stronger association with impaired mood recovery among depressed versus non-depressed individuals. This prediction is based on the idea that specific, mood congruent biases play an active role in maintaining MDD (cf. Ingram, 1984; Teasdale, 1988). Finally, we hypothesized that impairments in mood recovery would be associated with greater depression severity among individuals with MDD. This prediction is consistent with the idea that impaired mood recovery contributes to a more severe and persistent episode of MDD.

Method

Participants

Participants were recruited using internet, TV, and radio advertisement. The sample consisted of 291 community members from a large southwestern city in the United States who met the following inclusion and exclusion criteria: Inclusion criteria: 1) a DSM-IV diagnosis of major depressive disorder (MDD) or no current or past MDD

(Control); 2) between ages of 22 and 55; 3) normal or corrected to normal vision; 4) ability to speak, read, and understand English sufficiently well to complete the procedures of the study. Exclusion criteria: 1) current or past DSM-IV diagnosis of alcohol or drug abuse in past 6 months, 2) current or past DSM-IV diagnosis of substance or alcohol dependence, Bipolar Disorder, Psychotic Disorder, Obsessive-Compulsive Disorder, Social Phobia, Panic Disorder, PTSD, and Generalized Anxiety Disorder, 3) a history of epilepsy or head trauma.

Three individuals who qualified for the MDD group and fourteen individuals who qualified for the Control group were removed from this analysis due to incomplete or missing data. One individual who qualified for the control group was subsequently removed from this analysis because his or her estimates of attentional bias were considered outliers even after applying our data reduction procedures (see below): attentional bias score for sad stimuli was greater than 14 standard deviations from the sample mean and attentional bias score for fear stimuli was greater than 6.5 standard deviations from the sample mean. Excluding these individuals did not substantively change the findings reported below. After removing these participants the total sample size included in this analysis was 272 community members: 48 meeting criteria for the MDD group and 224 meeting criteria for the Control group. Demographic data about the sample is reported in the results section (below) and in Table 1.

Table 1. Participant demographics.

Demographics		Control	MDD	*Test*
Age (years)		28.14 (SD = 8.08)	33.06 (SD = 10.63)	*F(1, 270) = 13.01, p = 0.0004*
Gender	Male	83	12	$\chi^2 = 2.53, p = 0.112$
	Female	141	36	
Race	African American	15	8	
	Asian	49	4	*Fisher's exact, p = 0.077*
	White	119	29	
	Other*	51	7	
Hispanic	Yes	51	40	
	No	173	7	$\chi^2 = 1.43, p = 0.231$
	Unknown	0	1	
BDI-II		3.49 (SD = 4.64)	25.06 (SD = 9.37)	*F(1, 270) = 555.85, p < 0.0001*
BAI		3.25 (SD = 4.03)	13.00 (SD = 6.23)	*F(1, 270) = 186.51, p < 0.0001*
Psychiatric Medication	Yes	0	14	*Fisher's exact, p < 0.001*
	No	224	38	

* Includes American Indian, Native Hawaiian, Multiple races, and "none" (i.e., did not endorse a race).

Materials

Mini International Neuropsychiatric Interview (MINI). The electronic version of the MINI was used as a screening interview to determine whether participants provisionally met criteria for study entry. The MINI is a short, structured screening interview that was developed for the *Diagnostic and Statistical Manual of Mental*

Disorders, 4th edition (*DSM-IV*; American Psychiatric Association, 1994) and the International Classification of Diseases, 10th edition (ICD-10) psychiatric disorders (Sheehan et al., 1998). The MINI has been validated against the Structured Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 2002) diagnoses and against the Composite International Diagnostic Interview for ICD-10 (Lecrubier et al., 1997; Sheehan et al., 1998).

MINI interviewers were undergraduate research assistants who received at least 10 hours of training, wherein they learned interview skills, reviewed diagnostic criteria, and role-played interviews. Because this was a screening interview, brevity was important. Interviewers could terminate the interview as soon as the participant did not meet study criteria. Therefore, the full MINI was typically completed only for participants who met criteria for study entry. The average length of MINI screening interviews was approximately 15 minutes.

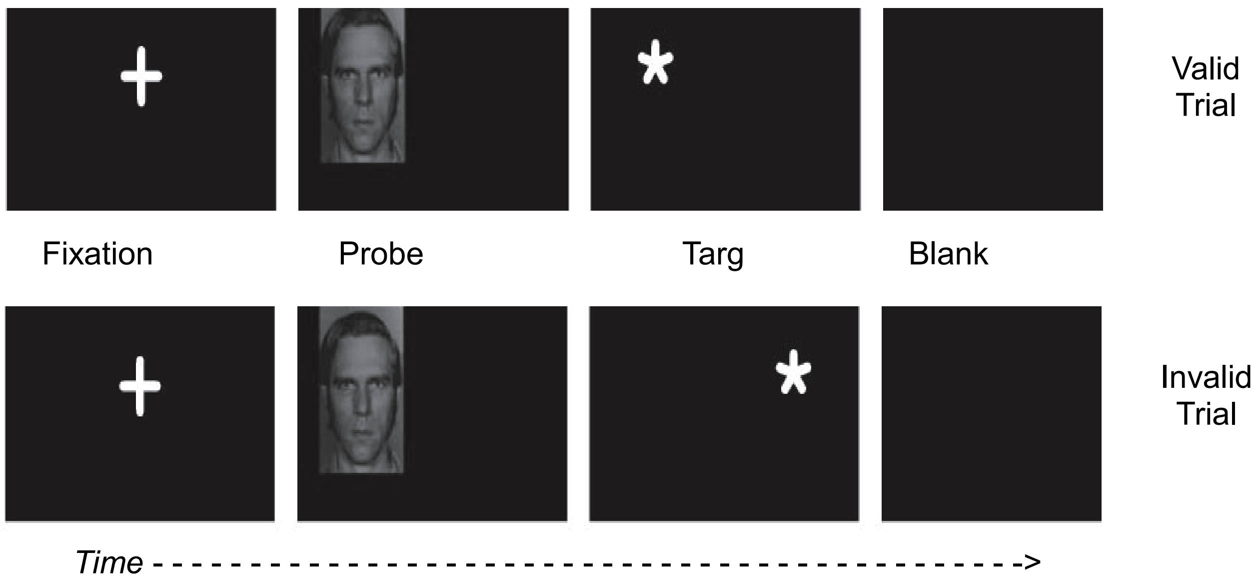
Structured Clinical Interview for DSM-IV (SCID). To confirm key inclusion/exclusion criteria from the screening interview, participants completed the patient version of the SCID (First et al., 2002) during an in-person interview at the time of study participation. Three assessors conducted all interviews. Two assessors were doctoral graduate students with at least two years of clinical training and assessment experience. The third assessor was a full time research assistant with a bachelor's degree in psychology. The third assessor participated in 15 hours of training and supervision led by graduate level assessors, wherein she learned interview sills, reviewed diagnostic

criteria for relevant *DSM-IV-TR* diagnoses (American Psychiatric Association, 2000), observed mock interviews, and role-played interviews. Twenty percent of all interviews were rated by an independent assessor who was a doctoral student in clinical psychology with at least two years of assessment experience. Agreement for MDD diagnosis between study interviewers and the independent assessor was excellent ($k = 1.00$, $p < 0.0001$).

Beck Depression Inventory-II (BDI-II). The BDI-II (Beck, Steer, & Brown, 1996) is a widely used self-report questionnaire that assesses depression severity. The BDI-II consists of 21 items and measures the presence and severity of cognitive, motivational, affective, and somatic symptoms of depression. Past reports have indicated test-retest reliability is adequate (Beck, Steer, & Carbin, 1988). The BDI-II has been found to be valid among psychiatric inpatient and outpatient samples (Beck et al., 1988).

Exogenous Cueing Task. The exogenous cuing task was developed by Posner (1980) and modified to incorporate emotional cues (e.g., Beevers, Wells, Ellis, & McGeary, 2009; Koster, De Raedt, Goeleven, Franck, & Crombez, 2005). Each trial sequence (shown in Figure 2) began by presenting a fixation cross in the center of the screen for 500ms. Then, a face cue was presented on either the left or the right side of the visual field for 1,500ms. After cue offset, a probe (either * or **) appeared immediately on the left or right side of visual field and remained on the screen until the participant responded.

Figure 2. Trial sequence for valid and invalid trials.



Note: Fixation cross, face stimulus, and probe are not to scale.

The participant's task was to identify probe type as quickly and accurately as possible. Participants pressed a corresponding button on a response box to indicate the type of probe that appeared. Reaction time (RT) for the participant to respond with a button press following the probe onset was logged for each trial. After the participant responded, the screen was black for 500ms before the next trail began. Seventy-five percent of probes appeared on the same side of visual field as the visual cue (a valid trial). Twenty-five percent of the probes appeared on the opposite side of visual field as

the cue (an invalid trial). Both valid and invalid trials had a fifty percent chance of having either the single- or double-asterisk probe.

Cue stimuli were images of faces were used, with permission, from the Pictures of Facial Affect (Ekman & Friesen, 1976) photo set. Human faces were selected because facial expressions receive special processing priority (Farah, Wilson, Drain, & Tanaka, 1998), and because human faces have been used extensively in behavioral and imaging studies, and are arguably more ecologically valid than written words. Twelve faces were selected from each of the following categories: happy, sad, fear, and neutral. All stimuli were presented on a black background on a 17-in. (43-cm) color monitor. Stimuli were approximately 10.5 x 17 cm when presented on the screen. Participants completed ten practice trials using neutral faces as cues. Anyone failing to respond accurately to at least eight of the ten trials repeated the practice trials until they had achieved eighty percent accuracy. Participants then completed a total of ninety-six trials. They viewed each of the forty-eight stimuli twice. Order of stimulus presentation was randomized for each participant, with the stipulation that each of the forty-eight stimuli were viewed once before stimuli were repeated.

As suggested by Mogg et al. (2008), a general measure of attentional bias can be derived from the exogenous cuing task using the following formula:

(1) Attentional bias score (ABS) = (mean RT invalid emotion cue – mean RT valid emotion cue) – (mean RT invalid neutral cue – mean RT valid neutral cue).

Positive values reflect an attentional bias for emotional cues relative to neutral cues. Negative values reflect an attentional bias for neutral cues relative to emotional cues. Bias scores were calculated for each emotional valence: sad, fear, and happy.

Data Reduction. Exogenous cueing task trials with incorrect responses (0.37%) were deleted and not used in analysis. Mean RTs were generated per individual, per condition (e.g., sad invalid, sad valid, happy valid, happy invalid, etc.). Trial-level RTs that were at least two standard deviations beyond the mean per individual, per condition were deleted (3.55% of total raw data) and a new mean RT was then calculated, per individual, per condition, and used in the analyses. Together, these procedures resulted in the exclusion of 3.92% of the raw data.

Mood induction. Participants were randomly assigned to receive one of two standardized mood inductions. One was a standardized film clip that has been shown to specifically elicit sadness (Gross & Levenson, 1995). The sad clip is 170 seconds and is taken from the film, *The Champ*, in which the father of a young boy dies after suffering a severe beating during a boxing match. A high-resolution digital version of the film clip was presented on a 20 inch LCD computer monitor. For the second mood induction participants listened to sad music while imagining a time in their life when they were very sad. The sad music (Samuel Barber's *Adagio for Strings*) effectively induced a sad mood in previous mood provocation research (Hunt & Forand, 2005). This type of sad mood induction in general is effective in eliciting a temporary sad mood (Van der Does,

2002). We used two mood inductions to ensure that results are not specific to a particular set of mood induction procedures.

Participants' mood was monitored throughout the study to ensure that it had returned to pre-experiment levels before being dismissed from the study. For those whose mood had not returned to baseline, a positive mood induction procedure was administered. An opportunity to talk with a doctoral level clinician was also offered to participants who continued to report sad mood following the positive mood induction. Treatment referrals were also offered to all participants in the study.

Profile of Mood States* (*POMS). Sad mood was measured at three time points: before, immediately after termination of the mood induction protocol, and twelve minutes after the mood induction, using four descriptors taken from the POMS (McNair, Lorr, & Droppleman, 1992). These included items with the best factor loadings for the depression mood scale: "sad," "worthless," "blue," and "hopeless." Participants rated how well each item described their current mood on a 5-point Likert scale ranging from *not at all* (0) to *very much* (4). Scores from these items were summed to create an index of sad mood at each time point.

Mood Variables. We created two variables to represent mood reactivity and mood recovery. Mood reactivity represents the difference between baseline mood and mood immediately after the mood induction: Higher scores reflect greater mood reactivity. Mood recovery represents the difference between mood immediately after the mood induction and mood twelve minutes later: Lower scores reflect greater mood recovery.

Procedure

Participants completed the MINI screening interview over the phone with a trained interviewer. Participants who passed the screening assessment were scheduled for a laboratory appointment. Upon arrival, participants were oriented to the lab, provided informed consent, and completed a demographic survey. They then completed the SCID interview to confirm presence of inclusion criteria and absence of exclusion criteria. Qualified participants then completed several self-report questionnaires, including the BDI-II. Next, they completed the exogenous cuing task and mood induction in a counter balanced order (half mood induction and recovery before exogenous cueing and half after). Mood induction type was also counter balanced across participants (music and video). Sad mood was measured using items from the POMS before, immediately after termination of the mood induction procedure, and after a twelve-minute delay. Upon completion of study procedures, participants were debriefed and paid $15 per hour (up to a maximum of $50) for their participation. The Internal Review Board at the University of Texas at Austin approved all study procedures.

Results

Statistical Analysis

All analyses were performed in R (http://www.r-project.org/) and STATA 11 (StataCorp: College Station, Texas, USA). The assumptions underlying repeated-measures analysis of variance and regression were tested and confirmed at each stage of analysis.

Sample Characteristics

Descriptive statistics for the sample are presented in Table 1. The mean age of participants was 29.01 (SD = 8.77), although the depressed group was significantly older than the non-depressed group. Participants were predominantly female and the distribution of gender did not differ across depression groups. The distribution of participants across racial groups approximated census estimates from the community (54.4% White, 8.5% African American, 19.5% Asian, and 17.6% other). The distribution of race across depression groups approached statistical significance. Across these racial groups, 21.4% of the sample was Hispanic. The number of Hispanic participants did not differ across depression groups. Given group differences, we controlled for age, gender, and race at each stage of the subsequent analyses.

Next, we examined depression group differences in depression severity, anxiety symptoms, and medication use (Table 1). MDD and Control groups differed in their levels of reported depression severity as indexed by the BDI-II. The average BDI-II score in the MDD group was in the moderate range (25.06) whereas the average score in the Control group was in the clinically insignificant range (3.49). MDD and Control groups also differed on reported levels of anxiety symptoms as measured by the BAI. The average BAI score in the MDD group was in the mild range, whereas the average score in the Control group was in the clinically insignificant range. Thus, we controlled for anxiety symptoms (BAI scores) at each stage of analysis. Finally, MDD and Control groups differed in use of psychotropic medication use (i.e., allowable medications as

specified by exclusion criteria). Thirteen depressed individuals (27.1%) were taking a psychotropic medication, whereas none of the Control individuals were taking psychotropic medications. For analyses limited to the MDD group, we also controlled for use of psychotropic medication.

Main Results

Mood induction. To confirm that the mood induction procedures successfully increased sad mood we performed a repeated measures analysis of variance (ANOVA) with mood as the dependent variable and time (before and immediately after the mood induction) as the within subjects factor. This model revealed a significant main effect for time, $F(1, 271) = 160.30$, $p < 0.0001$, *Cohen's d* = 1.54, indicating that the mood inductions did increase sad mood as expected. Change in sad mood did not vary as a function of depression status, $F(1, 270) = 0.12$, $p = 0.72$. MDD and Control participants reacted similarly to the mood induction procedure.

Next, we tested whether mood induction order (before or after exogenous cueing task) moderated these effects. The interaction term for order X time was significant, $F(1, 270) = 10.51$, $p = 0.0013$, *Cohen's d* = 0.40, suggesting that there were differences in mood reactivity based on the order in which the mood induction occurred. Simple effects testing indicated that while the mood induction produced significant changes in mood irrespective of the order in which it was administered, those who completed the attentional bias assessment before the mood induction reported greater reactivity to the mood induction, $F(1, 132) = 99.68$, $p < 0.0001$, *Cohen's d* = 1.74, compared to those who

completed the mood induction prior to the bias assessment, $F(1, 138) = 66.39$, $p < 0.0001$, *Cohen's d* = 1.39. Therefore, we have included mood induction order as a covariate in all subsequent analyses.

Finally, we tested whether mood induction type (music or movie) moderated the effect of time on mood. The interaction term for type X time was significant, $F(1, 270) = 17.39$, $p < 0.0001$, *Cohen's d* = 0.51, indicating that there were significant differences in mood reactivity based on type of mood induction. Simple effects testing indicates that while both induction types produced significant changes in mood, the music induction produced a stronger effect on mood, $F(1, 138) = 122.33$, $p < 0.0001$, *Cohen's d* = 1.88, than the movie induction, $F(1, 132) = 49.17$, $p < 0.0001$, *Cohen's d* = 1.22. Therefore, we have included mood induction type as a covariate in all subsequent analyses.

Mood variables. We then explored differences in baseline mood, mood reactivity, and mood recovery by depression group (see Table 2). As expected, depressed individuals reported significantly higher levels of baseline sad mood, $F(1, 259) = 53.24$, $p < 0.0001$, *Cohen's d* = 0.91. As reported in the repeated measures analysis, MDD and Control groups do not show significant differences in mood reactivity, $F(1, 259) = 0.27$, $p = 0.60$. Similarly, MDD and Control groups did not show significant differences in mood recovery, $F(1, 259) = 0.38$, $p = 0.54$. These results indicate that MDD and Control participants show similar patterns of mood reactivity and mood recovery despite baseline differences in sad mood. It is important to note, however, that there is a wide range of mood reactivity and recovery within each group (see Table 2).

Table 2. Summary of mood variables (baseline, reactivity, recovery) by depression group.

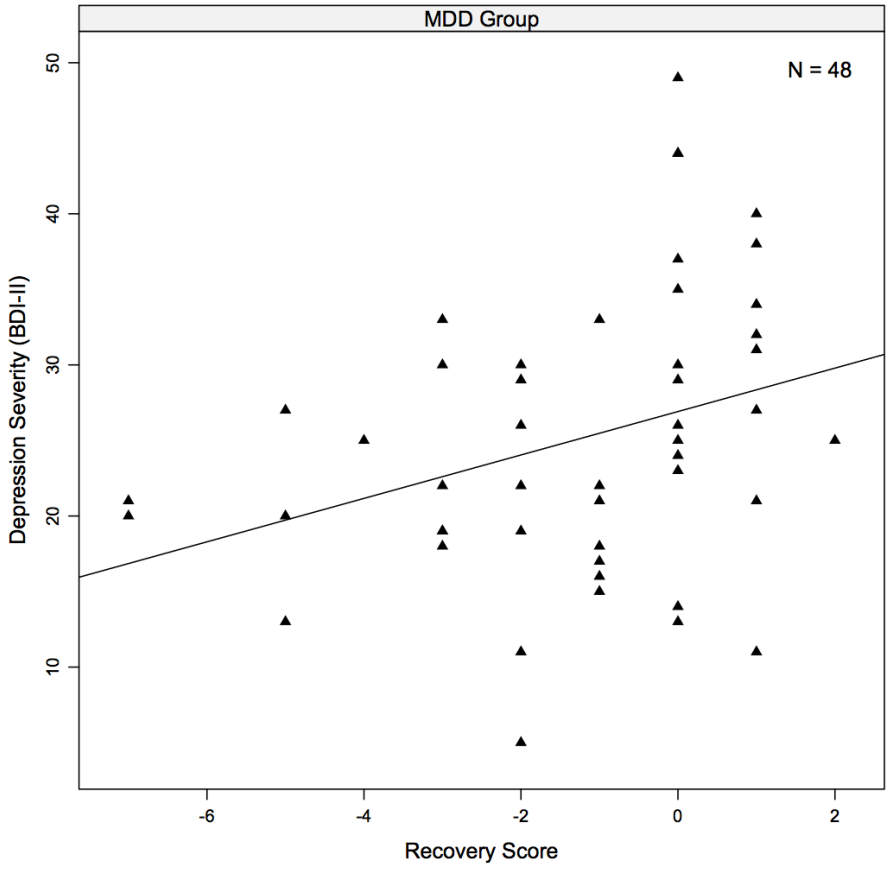
Mood	Control			MDD		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
Baseline	4.71	1.35	(4, 11)	8.46	3.42	(4, 16)
Reactivity	1.46	1.79	(-3, 11)	1.35	2.26	(-2, 7)
Recovery	-1.33	1.64	(-11, 3)	-1.29	2.11	(-7, 2)

Next, we explored the relationship between mood reactivity and recovery. We hypothesized a strong negative relationship between mood reactivity and mood recovery. Indeed, the correlation between these outcomes was strong and in the anticipated direction, $r = -0.80$, $p < 0.0001$ (after controlling for covariates, $t(259) = -20.59$, $p < 0.001$). The nature of this relationship did not differ as a function of depression status, $t(257) = 0.87$, $p = 0.38$. Although individuals experience differing levels of reactivity to a sad mood provocation they, on average, are able to recover from these moods within a relatively short period of time (i.e., return to baseline within twelve minutes).

Finally, we examined whether our estimates of mood reactivity and recovery were related to depression severity in the MDD group. Reactivity in the MDD group was not associated with depression severity ($r = -0.18$, $p = 0.22$; after controlling for covariates, $t(35) = -1.20$, $p = 0.24$). Thus, more severely depressed participants did not demonstrate reduced reactivity. In line with our predictions, mood recovery was positively associated with depression severity in the MDD group ($r = 0.32$, $p = 0.02$; after controlling for

covariates, t(35) = 2.74, p = 0.01) (Figure 3). Slower mood recovery was associated with increased depression severity. This finding indicates that impairments in mood recovery are associated with worse outcomes among depressed individuals. Mood reactivity and recovery were unrelated to depression severity in the Control group (reactivity: r = 0.04, p = 0.57; recovery: r = 0.01, p = 0.88).

Figure 3. Relationship between mood recovery and depression severity in MDD group.



Note: Line represents fitted regression (r = 0.32, p = 0.02). Two observations overlap.

Attentional bias score (ABS). A detailed summary of attentional bias scores by depression group is listed in Table 3. The reader will note substantial within-group variability among the three bias scores across depressed and non-depressed groups. We first examined whether there were differences in levels of attentional bias across MDD and Control groups. Contrary to previous findings, we did not discover a difference in ABS for sad stimuli, $F(1, 260) = 0.26$, $p = 0.61$, fear stimuli, $F(1, 260) = 1.44$, $p = 0.23$, or happy stimuli, $F(1, 260) = 0.27$, $p = 0.60$, based on depression group.

Table 3. Summary of attentional bias scores (sad, fear, happy) by depression group.

Bias	**Control**			**MDD**		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
Sad (ms)	0.15	115.69	(-320, 732)	2.87	114.36	(-208, 448)
Fear (ms)	7.15	97.96	(-390, 371)	38.81	106.95	(-202, 521)
Happy (ms)	8.53	116.79	(-505, 597)	13.08	77.35	(-127, 185)

It is important to note that the only group difference we observed in ABS was a main effect for gender: men and women differed in bias for sad, $F(1, 260) = 5.06$, $p = 0.03$, *Cohen's d* = 0.28, and fear stimuli, $F(1, 260) = 4.11$, $p = 0.04$, *Cohen's d* = 0.25, but not happy stimuli, $F(1, 260) = 1.67$, $p = 0.20$. Men showed significantly stronger bias for both sad ($Mean_{Men} = 25.71$ ms, $SD_{Men} = 145.27$ ms; $Mean_{Women} = -12.83$ ms, $SD_{Women} = 93.05$ ms) and fear stimuli ($Mean_{Men} = 30.02$ ms, $SD_{Men} = 116.66$ ms; $Mean_{Women} = 3.47$ ms, $SD_{Women} = 89.00$ ms).

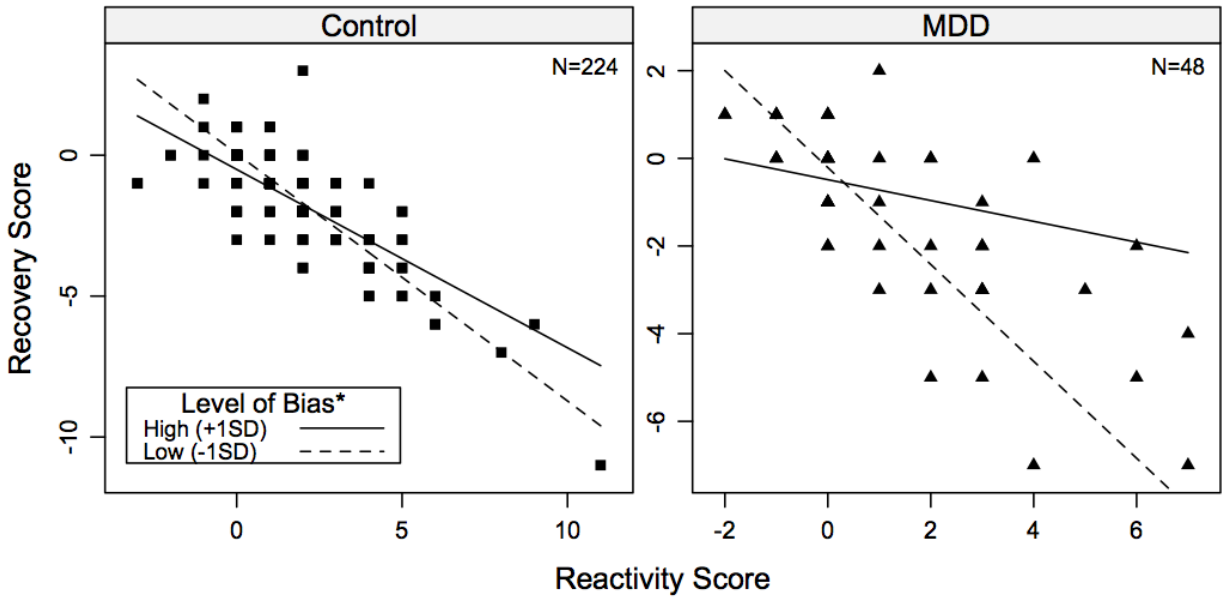
It is also important to note that there was no main effect of assessment order (before or after the mood induction) on ABS scores for sad, $F(1, 260) = 1.98$, $p = 0.16$, fear, $F(1, 260) = 0.16$, $p = 0.69$, and happy stimuli, $F(1, 260) = 0.06$, $p = 0.80$. Moreover, these results were not moderated by depression status across sad, $F(1, 259) = 0.44$, $p = 0.51$, fear, $F(1, 259) = 0.64$, $p = 0.42$, and happy stimuli, $F(1, 259) = 0.04$, $p = 0.84$. Engaging in the mood induction procedure either before or after the exogenous cueing task did not appear to substantively influence ABS scores for either depressed or non-depressed participants.

Next, we examined whether ABS for sad, fear, and happy stimuli were associated with mood reactivity. Furthermore, we tested two-way interactions to determine whether these relationships varied as a function of depression status. ABS was unrelated to mood reactivity across sad, $t(259) = -0.98$, $p = 0.33$, fear, $t(259) = -1.10$, $p = 0.27$, and happy stimuli, $t(259) = -1.21$, $p = 0.23$. This did not differ across depression groups (ABS sad X depression group: $t(257) = 0.09$, $p = 0.93$; ABS fear X depression group: $t(257) = 0.72$, $p = 0.48$; ABS happy X depression group: $t(257) = -0.79$, $p = 0.43$). These findings indicate that attentional biases are not associated with levels of mood reactivity.

Finally, we examined whether ABS for sad, fear, and happy stimuli moderated the relationship between mood reactivity and mood recovery. Furthermore, we tested three-way interactions to determine whether these relationships varied as a function of depression status.

Bias for sad stimuli. The two-way interaction between sad bias and mood reactivity predicting mood recovery was significant, t(257) = 4.00, p < 0.001, *effect size r* = 0.24. The three-way interaction between sad bias, mood reactivity, and depression status predicting mood recovery was also significant, t(253) = 2.65, p = 0.008, *effect size r* = 0.16. Simple effects testing of this three-way interaction indicated that while the two-way interaction between sad bias and mood reactivity was significant for both MDD, t(33) = 2.92, p = 0.006, *effect size r* = 0.45, and Control groups, t(209) = 2.54, p = 0.012, *effect size r* = 0.17, the effect is much stronger in the MDD group (see Figure 4).

Figure 4. Mood recovery as a function of mood reactivity and bias for sad stimuli (by depression group).



Note: * Legend applies to both plots. There are multiple overlapping observations on each plot.

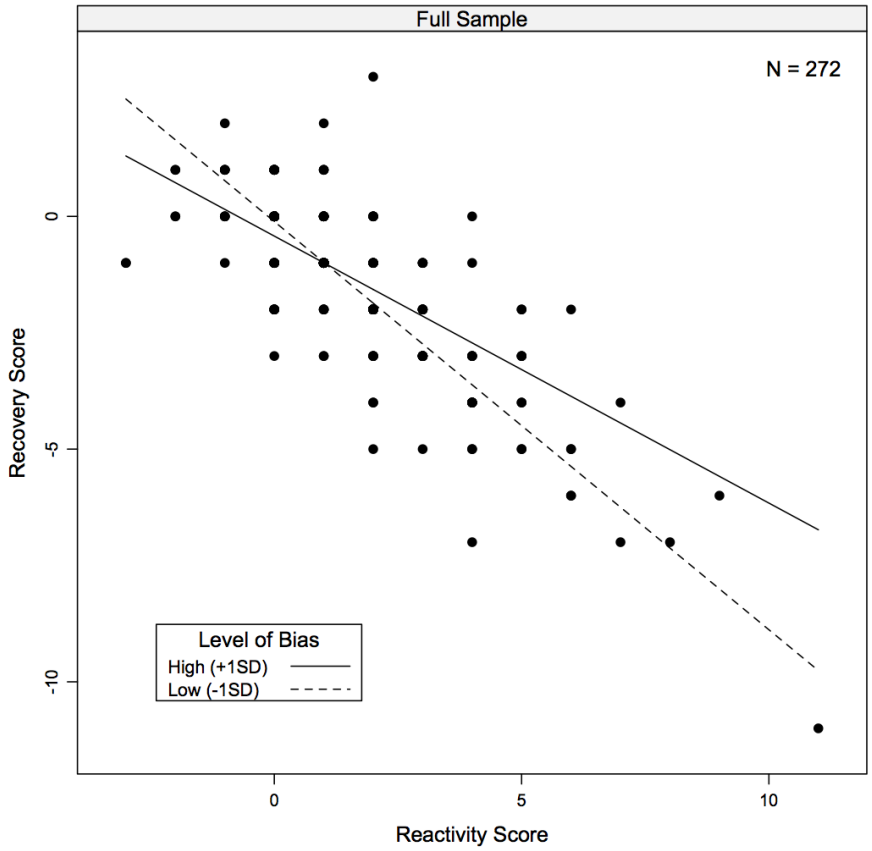
Individuals with stronger attentional bias for sad stimuli report greater impairments to mood recovery when they react to a mood-inducing event. This relationship is stronger among individuals with current MDD compared to healthy controls.

To further examine the nature of this effect in the MDD group, we examined simple slopes for the relationship between mood reactivity and mood recovery among depressed individuals with higher and lower attentional bias for sad stimuli (i.e., plus or minus one standard deviation, respectively). These simple slopes are plotted in the MDD panel of Figure 4. The simple slope for individuals with higher levels of sad bias was not significant, $t(44) = -1.48$, $p = 0.145$, indicating that as mood reactivity increases these individuals do not demonstrate a corresponding level of mood recovery. By contrast, the simple slope for individuals with lower levels of attentional bias for sad stimuli was significant, $t(44) = -7.16$, $p < 0.001$, suggesting that higher levels of mood reactivity is associated with greater mood recovery among individuals with lower levels of bias for sad stimuli. This analysis further supports the idea that depressed individuals with higher levels of attentional bias for sad stimuli experience impaired mood recovery, particularly when they react to a mood-inducing event.

Bias for fear stimuli. The two-way interaction between fear bias and mood reactivity predicting mood recovery was significant, $t(257) = 3.36$, $p = 0.001$, *effect size r* $= 0.21$. The three-way interaction between fear bias, mood reactivity, and depression status was not significant, $t(253) = 0.45$, $p = 0.65$. Individuals with stronger attentional

bias for fear stimuli report greater impairments to mood recovery when they react to a mood-inducing event (see Figure 5). This effect was consistent across as the full sample, as this relationship was not moderated by depression status.

Figure 5. Mood recovery as a function of mood reactivity and bias for fear stimuli.



Note: There are multiple overlapping observations.

Bias for happy stimuli. The two-way interaction between happy bias and mood reactivity predicting mood recovery was not significant, $t(257) = 0.72$, $p = 0.47$. The

three-way interaction between happy bias, mood reactivity, and depression status predicting mood recovery was not significant, $t(253) = 0.81$, $p = 0.42$. Biased attention for happy stimuli is not associated with differences in mood recovery when individuals react to a mood-inducing event.

Discussion

This study examined whether attentional biases for emotional stimuli are associated with the persistence of sad mood among individuals with and without MDD. Cognitive theories of depression implicate information processing biases, like biased attention, in the maintenance of depressive symptoms. Previous research suggests that depressed and dysphoric individuals harbor biased attention for emotional information (e.g., Bradley et al., 1997; Eizenman et al., 2003; Gotlib et al., 2004; Kellough et al., 2008); however, the consequences of these biases have not been examined. This study sought to link these biases to mood persistence, a hallmark symptom of depression.

Our results support the idea that negative attentional biases facilitate the persistence of sad mood. Depressed and non-depressed individuals who demonstrated more pronounced biases for negative stimuli and experienced greater reactivity to a mood-inducing event showed greater difficulty recovering from that event after twelve minutes. Biases for sad stimuli were particularly important for depressed individuals, as this bias was more strongly associated with impairments in mood recovery for depressed versus non-depressed participants. Further, impairments in mood recovery were positively associated with depression severity in the MDD group. Together, these

findings provide evidence that more severely depressed individuals show impairments in mood recovery that are associated with attentional biases, particularly when they experience greater mood reactivity.

While these findings have important implications for depression, they also speak to theories of emotional experience more generally. Our findings suggest that attentional biases for negative information also interfere with mood recovery among non-depressed individuals when they react to mood-inducing events. Thus, these biases appear to broadly influence emotional experience and may reflect individual differences in one's ability to manage emotional reactions. These findings are in line with experimental evidence demonstrating that inducing a general negative bias (using both sad and fear stimuli) leads to higher levels of sad mood following a laboratory stress-manipulation (MacLeod et al., 2002). Moreover, longitudinal studies suggest that negative processing biases predict future emotional and hormonal (i.e., cortisol) responses to stress (Fox, Cahill, & Zougkou, 2010) and vulnerability to negative mood states, such as depression and PTSD symptoms (Beevers, Lee, Wells, Ellis, & Telch, 2011). Thus, individuals with negatively biased attention (for sad and/or fear stimuli) without current psychopathology may be at increased risk for the development of negative mood states. More longitudinal research is needed to address this important question.

Research on the nature of emotion regulation processes (Gross, 1998; Ochsner & Gross, 2005) suggests that cognitive control processes, including mechanisms underlying attentional control, may mediate adaptive emotion regulation strategies that help

individuals manage distressing emotions (e.g., Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Therefore, one possibility is that the observed relationship between attentional bias and mood persistence is mediated by emotion regulation. Joormann (2004; 2006) has proposed that maladaptive emotion regulation strategies, including rumination, may mediate the relationship between inhibitory control deficits and depressive symptoms. Rumination represents the tendency to perseverate on the causes and consequences of depressed mood (Nolen-Hoeksema, 1991; Susan Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). While depressed individuals believe that rumination is helpful (Papageorgiou & Wells, 2001; Watkins & Baracaia, 2001; Papageorgiou & Wells, 2003), evidence suggests that ruminative thinking amplifies and maintains depression (e.g., Just & Alloy, 1997). Future work must explore whether the observed relationship between attention and mood persistence in this study is mediated by broader, maladaptive emotion regulation strategies (see also Joormann & Gotlib, 2010).

Another possibility is that these biases reflect stable differences in underlying personality dimensions associated with negative affect. Indeed, attentional biases for both sad and fear stimuli were associated with impaired mood recovery among depressed and non-depressed individuals. These findings suggest that independent of current psychopathology, a general bias towards aversive stimuli is associated with prolonged sad mood. This conclusion is supported by evidence that attentional biases for sad and fear stimuli are associated with neuroticism and introversion (Chan et al., 2007; Derryberry & Reed, 1994): stable personality dimensions that are highly predictive of

negative affect and, importantly, depression vulnerability (e.g., Clark et al., 1994). Therefore, biases for sad and fear stimuli may mediate the relationship between individual differences in stable personality dimensions (e.g., neuroticism) and prolonged episodes of negative affect. Future research is required to test this hypothesis.

Beside these theoretical implications, the current study highlights the value of taking an individual differences perspective when examining cognitive biases and mood in depression. This approach contrasts with previous research, which has primarily focused on comparing estimates of attentional bias between groups (e.g., depressed vs. non-depressed; dysphoric vs. non-dysphoric). That approach is useful to infer differences between groups; however, it largely ignores within group variability. For instance, some depressed individuals exhibit strong attentional biases for sad stimuli whereas others do not. Importantly, the current study indicates that these differences are meaningfully related to a hallmark symptom of depression. Thus, an individual differences approach may help identify mechanisms underlying variability (or stability) in symptom presentation both across individuals and within the same individual across time.

Our results point to two key areas of individual difference. First, attentional biases vary within a sample of MDD individuals. Indeed, many participants with MDD did not demonstrate negatively biased attention (e.g., Bradley et al., 1997; Gotlib et al., 2004). Importantly, these individuals show less persistent mood following an acute mood induction. Second, mood reactivity varies between individuals with MDD. While many individuals in our sample reacted strongly to the mood induction procedures, others did

not. This finding is consistent with previous studies using mood induction procedures (e.g., Larsen & Ketelaar, 1989; Martin, 1990; Rottenberg, Kasch, Gross, & Gotlib, 2002). Identifying factors that explain individual differences in attentional bias and mood reactivity in MDD will be an important future direction for this area of research (cf. Rottenberg, Gross, & Gotlib, 2005).

Overall, this pattern of individual differences within MDD is consistent with extant literature. Neural models of MDD largely implicate the interaction between hypo-active regions underlying cognitive control (e.g., dorsal lateral prefrontal cortex) and hyper-active regions underlying emotional reactivity (e.g., amygdala) (Drevets, 2001; Mayberg, 2003; Disner, Beevers, Haigh, & Beck, 2011). However, there is notable variability in this pattern of findings (e.g., Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Canli et al., 2004; Lawrence et al., 2004) that has been linked to differences in affective symptoms (e.g., anhedonia, anger) as well as significant etiological considerations (e.g., history of childhood maltreatment) (Dougherty et al., 2004; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011). Importantly, individual differences in pretreatment activity within these regions has also been shown to predict response to specific interventions (e.g., cognitive-behavioral therapy) (Siegle, Carter, & Thase, 2006; Siegle, Steinhauer, Friedman, Thompson, & Thase, 2011). This is an important avenue for future research and represents an exciting opportunity to integrate basic and applied research.

An important caveat is that this study was not designed to test the causal relationship between attentional bias and mood persistence. While we manipulated mood, we did not manipulate attentional bias. Therefore, the observed associations between negative attentional bias and mood recovery are correlational and, thus, it remains unclear whether attentional biases cause mood persistence in depressed and non-depressed people.

Cognitive bias modification (CBM) designs represent a growing class of experimental procedures aimed at testing causal predictions about putative cognitive biases associated with psychopathology (e.g., Mathews & Mackintosh, 2000; Wilson, MacLeod, Mathews, & Rutherford, 2006). These studies manipulate specific cognitive biases in a randomized, placebo-controlled design to test these predictions. Preliminary attention bias modification (ABM) research with dysphoric people suggests that manipulating attentional biases may help ameliorate mood persistence (Wells & Beevers, 2010), although this hypothesis has not been tested directly. Conversely, inducing negative attentional biases in non-depressed individuals appears to exacerbate emotional responses to adverse events (MacLeod et al., 2002). Together, these findings lend preliminary support to the idea that attentional biases play a causal role in the persistence of sad mood. However, future work using these methods is required to directly test this hypothesis.

Another important limitation of this study is that it represents a laboratory study of mood persistence. While this design provides experimental control of the mood

manipulation we were limited to examining mood persistence on the order of minutes, not weeks as the DSM-IV defines clinically significant persistent sad mood in MDD. Moreover, we examined mood persistence in response to a contrived laboratory-based mood induction procedure. This procedure represents a modest analogue to the types of real life events that induce sad mood (Martin, 1990). Further, outside of the laboratory, multiple mood inducing events likely interact in dynamic ways to predict mood reactivity and mood persistence. Future work is required to understand how cognitive biases influence the maintenance of mood over longer time intervals and during conditions of multiple, dynamic mood inducing events (cf. Peeters, Nicolson, Berkhof, Delespaul, & deVries, 2003).

Moreover, we only sampled mood once during the recovery period. Thus, we only have one index of mood persistence across time. Research suggests that mood persistence (or emotional lability, more generally) is a dynamic, non-linear process across time (e.g., Kuppens, Van Mechelen, Nezlek, Dossche, & Timmermans, 2007; Kuppens, Oravecz, & Tuerlinckx, 2010). Sampling mood with greater frequency during the recovery period would have allowed a more fine-grained analysis of mood persistence in MDD.

Finally, we used a brief assessment of attentional bias that was very similar to previously published work (Beevers et al., 2009). A brief assessment prevents fatigue for participants; however, it limits the number of trials included in indices of attentional bias, which may lower the reliability of these estimates. Future work should measure bias using more trials to address this potential limitation. Moreover, we relied on reaction time

estimates to compute attentional bias scores; future efforts may benefit from greater precision by using eye registration technology to generate estimates of attentional bias.

Despite these limitations this study is an important step towards understanding how attentional biases maintain depression. Results indicate that more severely depressed individuals show impairments in mood recovery that are associated with negative attentional biases when they respond to mood-inducing stimuli. Further, biases for sad stimuli may selectively impair efforts to regulate sad mood in MDD. These findings support cognitive theories of depression and provide a link between putative cognitive biases and a hallmark symptom of depression.

At the same time, these findings suggest that the adverse effects of negative attentional biases on mood recovery are not limited to MDD. Non-depressed individuals show similar, albeit less pronounced, impairments in mood recovery that are associated with biases for sad and fear stimuli. Therefore, these findings have implications for theories of emotion and emotion regulation more generally, and suggest that negative attentional biases interfere with efforts to resolve acute mood reactivity.

Taken together, these findings advance our understanding of how cognitive mechanisms maintain depressive symptoms. We believe this is an important step towards elucidating mechanisms that maintain MDD; a step that could ultimately help improve interventions aimed at preventing the onset of and promoting recovery from this common and debilitating psychiatric disorder.

STUDY 2: COGNITIVE CONTROL NETWORK CONNECTIVITY AMONG ADOLESCENT WOMEN WITH AND WITHOUT A PARENTAL HISTORY OF DEPRESSION[2]

Introduction

Adolescent women with a parental history of depression are at unusually high risk for major depressive disorder (MDD). Between the ages of 13 and 15, girls begin to experience depression at twice the rate as boys of the same age (Nolen-Hoeksema & Girgus, 1994; Hankin & Abramson, 2001; Hyde, Mezulis, & Abramson, 2008) These rates increase by 2- to 3-fold among girls who have a parental history of depression (Beardselee, Versage, & Giadstone, 1998; Weissman et al., 2006). Adolescent depression is particularly pernicious, as it is associated with increased risk for suicide (Birmaher et al., 1996) and frequently leads to chronic and recurrent MDD in adulthood (Lewinsohn, Rohde, Klein, & Seeley, 1999; Rao, Hammen, & Daley, 1999). Thus, there is a clear need to elucidate the mechanisms underlying depression vulnerability in this high-risk, adolescent population.

Neural models of depression broadly implicate deficits in the recruitment of regions associated with cognitive control, particularly control over mood congruent information (e.g., sad images) (Mayberg, 1997; Phillips, Drevets, Rauch, & Lane, 2003). These regions include ventral and dorsal lateral prefrontal cortex, anterior cingulate

[2] This study appears in *Developmental Cognitive Neuroscience* (Clasen, P.C., Beevers, C.G., Mumford, J.A., & Schnyer, D.M. (2014). Cognitive control network connectivity among adolescent women with and without a parental history of depression. *Developmental Cognitive Neuroscience, 7*, 13-22.)

cortex, and posterior parietal cortex (Disner et al., 2011). Recent work using resting state fMRI suggests that current depression is associated with abnormalities in the functional connectivity between these regions, which comprise key nodes of the so-called cognitive control network (CCN) (Schlösser et al., 2008; Vasic, Walter, Sambataro, & Wolf, 2009; Sheline, Price, Yan, & Mintun, 2010; Veer et al., 2010; Alexopoulos et al., 2012). Thus, a growing body of evidence supports the idea that CCN function is altered in depression. What remains unclear is whether differences in CCN network are due to current symptomatology or are evident prior to symptom onset. Alterations within the CCN network must predate onset of depression for CCN connectivity to be considered a viable risk factor for depression.

To investigate this possibility, we used seed-based, resting state functional connectivity analysis to explore differences in CCN connectivity among adolescent women with and without a parental history of depression. Our exploration focused specifically on a set of CCN regions implicated in attentional control. Cognitive models of depression posit that deficits in attentional control over emotional stimuli play a key role in depression vulnerability (Beck, 1967; Ingram, 1984; Teasdale, 1988). Behavioral studies suggest that these deficits predict the onset of depression in adults (Beevers & Carver, 2003; Beevers et al., 2011). Recent behavioral work also suggests that a parental history of depression predisposes adolescent women to deficits in attentional control for emotional stimuli (Joormann et al., 2007).

Importantly, difficulty with attentional control over emotional stimuli in depression appears to be associated with functional alterations within the CCN network. A recent imaging study examining attentional control over emotional information found that depression was associated with altered activity several key CCN regions, including right inferior frontal gyrus (rIFG), right middle frontal gyrus (rMFG), and right supramarginal gyrus (rSMG) (Beevers et al., 2010). The rIFG in particular is thought to play a key role in mediating the success of cognitive control over emotional stimuli (Ochsner & Gross, 2005; Wager et al., 2008). This region has been implicated in behavioral inhibition, suppression of unwanted thoughts, attention shifting, and efforts to reappraise emotional stimuli (Aron, Robbins, & Poldrack, 2004; Anderson et al., 2004; Hampshire & Owen, 2006; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010).

Given its important role in the cognitive control over emotion stimuli, we selected the rIFG region as a seed region for functional connectivity analyses in adolescent women with and without a parental history of depression. In addition to this whole brain approach, we performed a region of interest (ROI) analysis using the rMFG and rSMG locations identified in our previous study (Beevers et al., 2010). This analysis allowed us to explore the specificity of deficits in this previously defined network using an unbiased approach. We also supplemented group comparisons with analyses using severity of parents' worst episode of depression as a more continuous index of adolescent depression risk. This variable was then used to examine connectivity between the rIFG seed and rMFG/rSMG targets in the ROI analysis.

We are not aware of any studies examining functional connectivity within the CCN among adolescents at high risk for depression. Two recent studies suggest that adolescent depression is associated with decreased connectivity within putative resting state networks, including fronto-limbic and default mode networks (Bluhm et al., 2009; Cullen et al., 2009). Results in depressed adults are mixed; there is recent evidence of decreased (Veer et al., 2010; Alexopoulos et al., 2012) and increased connectivity within the CCN (Sheline et al., 2010).

Based on the adolescent and recent adult depression literature, we predicted that adolescent women at high-risk for MDD by virtue of parental history of depression would demonstrate decreased connectivity within the CCN. More specifically, we expected decreased connectivity between rMFG/rSMG targets and the rIFG seed. We also speculated that severity of parents' worst depressive episode would be associated with lower levels of connectivity between rMFG/rSMG targets and the rIFG seed.

Method

Sample. The sample included 27 adolescents and one of their adult parents (for 96% of the girls, this was their mother). One individual was removed from analysis due to excessive movement during imaging. Two other individuals were removed from the analysis because we could not confidently assign them to a group (parental history or no parental history) due to conflicting reports about depression history. In both cases, the parent who completed the study materials did not report a history of depression; however, their daughters reported a history of depression in the other parent (who did not

participate in the study) on a family history self-report questionnaire. In two cases we could not verify the daughter's self-report using standardized measures (i.e., attempts to have the other parent complete the depression history screening and questionnaire were unsuccessful); therefore, we removed these two individuals from the analysis. As a result, the final sample included 24 adolescent girls between the ages of 13 and 15. Girls were then assigned to high-risk (n = 11) and low-risk (n = 13) groups based on criteria used to classify their parents' history of depression (see below). There were no significant differences with respect to age and race across vulnerability groups (see Table 4 for demographic information).

Table 4. Demographics.

Demographic		**High-Risk**	**Low-Risk**
Age (mean (sd))		13.82 (.75)	13.54 (.88)
Race			
	African American	1	2
	Native American	1	0
	White	8	10
		2	1
	Multiple	1	1
Hispanic			
	Yes	2	0
	No	9	13

Note. All participants are female.

Measures.

Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). The Schedule for Affective Disorders and Schizophrenia for School-Age

Children (K-SADS) (Puig-Antich & Chambers, 1978) is a structured interview used to assess diagnostic symptoms of DSM-IV psychiatric disorders, including MDD, in children and adolescents. We used an adapted version of the K-SADS Present and Lifetime Version (K-SADS-PL), combining features of the epidemiological and the present episode versions, to screen for current and past MDD in the adolescent girls (Kaufman et al., 1997). K-SADS interviews were conducted as a prescreening measure over the phone and again in person on the day of the scanning procedure. Girls who met criteria for current or past history of MDD (i.e., 5 symptoms at a severity and duration consistent with DSM-IV criteria for MDD) either over the phone or during the laboratory visit were excluded from the study.

Demographic questionnaire. A demographic questionnaire was used to assess the age, gender, race, psychiatric history, treatment history, and history of psychiatric illness in immediate and extended family.

Structured Clinical Interview for DSM-IV (SCID). The Structured Clinical Interview for DSM-IV Disorders (First, Spitzer, Gibbon, & Williams, 2002) was used to assess current and past history of MDD in the parent of the adolescent participants. Two highly trained assessors conducted all interviews over the phone. Interviews were limited to current and past history of depression sections of the mood module. These sections allowed us to confirm the key inclusion/exclusion criteria in parents of prospective adolescent participants. Parents who reported a current history of depression were excluded from the study (along with their daughters). Daughters of parents who reported

a past history of depression on this measure were assigned to the high-risk group. Daughters of parents who reported no history of depression on this measure were assigned to the low-risk group.

Beck Depression Inventory-II (BDI-II). The Beck Depression Inventory-II (Beck et al., 1996) was used to verify that parents were not currently depressed on the day of the scanning procedure. The BDI-II is a widely used self-report questionnaire that assesses depression severity. It consists of 21 items and measures the presence and severity of cognitive, motivational, affective, and somatic symptoms of depression. The BDI-II is valid in both inpatient and outpatient samples and has demonstrated adequate test-retest reliability (Beck et al., 1988).

Patient Health Questionnaire-9 (PHQ-9). The Patient Health Questionnaire (PHQ) is a self-report measure used to assess common mental health disorders in primary care (Spitzer, Kroenke, & Williams, 1999). The PHQ-9 is the depression module of this questionnaire used to assess all 9 of the DSM-IV symptom criteria for depression using a "0" (not at all) to "3" (nearly every day) scale. It has demonstrated adequate internal and external validity and reliability (Kroenke, Spitzer, & Williams, 2001). This measure was administered to the same parent who completed to SCID interview on the day of scanning. It was used to assess the severity of the parent's worst lifetime depressive episode. The parent of one individual in the non-vulnerable group did not complete the PHQ-9. This individual was not included in the exploratory analysis of the relationship between parental depression severity and functional connectivity (see below).

MRI Scanning Acquisition. All MRI scans were acquired on a whole body 3T GE scanner with an 8-channel phase array head coil at the Imaging Research Center, University of Texas at Austin. The scanning protocol involved collection of a localizer followed by a high-resolution structural scan, a series of functional scans, a second high-resolution structural scan, and a diffusion tensor scan. The series of functional scans included both resting-state and task-based protocols. The resting state scan always occurred before the performance of any task-based scanning. This manuscript is limited to analysis of high-resolution structural scans and the resting-state scans.

The primary structural scans utilized 3D SPGR volume acquisitions with 1.4 mm thick sagittal slices for a total of 134 slices (Flip = 10 degrees, repetition time (TR) = 9.7 ms, echo time (TE) = 4 ms, inversion time (TI) = 20 ms, dwell time (TD) = 0 ms, field of view (FOV) = 25 cm, Matrix = 256 x 256, number of repetitions (NEX) = 1). Functional images were acquired using a GRAPPA parallel imaging EPI sequence that reduces typical EPI distortions and susceptibility artifacts. Images were collected utilizing whole head coverage with slice orientation to reduce artifact (approximately 20 degrees off the AC-PC plane and oriented for best whole head coverage, TR = 2000 ms, GRAPPA acceleration factor of two, TE = 30 ms, 31 axial slices, voxel size = 3.125 x 3.125 x 3 mm^3 with a .6 mm inter-slice gap). The first four EPI volumes were discarded to allow scans to reach equilibrium. Resting state scan instructions were presented utilizing a back projection screen located in the MR bore and viewed through a mirror mounted on the top of the head coil. Head motion was minimized with foam inserts.

Resting-state Scan Instructions. Prior to the acquisition of resting-state scans participants were instructed to remain awake and alert and keep their gaze on a fixation cross (+) presented approximately at the center of their field of view for the 6-minute duration of the scan.

Analysis Plan. Data were processed using FSL (Smith et al., 2004). Functional, blood oxygen level dependent (BOLD), volumetric time series were corrected for motion, spatially smoothed using a 6 mm Gaussian filter, and high pass filtered (100 hz). Seed-based functional connectivity analyses were then performed on the residual 4D volumes after motion parameters were modeled as a nuisance variable.

We took a conservative, unbiased approach to seed selection: The rIFG seed used in this study consisted of an 8 mm sphere centered on the peak location from a rIFG ROI identified in our whole brain analysis of attentional biases in dysphoric adults (Montreal Neurlogical Institute (MNI) coordinates [x = 52, y = 12, z = 8], see Figure 6 for seed location; (Beevers et al., 2010)). The seed was translated from MNI standard space to individual native space and the BOLD time series from this seed was extracted for each individual. The native space seed time series was then correlated against all other voxels within the brain to generate whole brain Pearson correlation coefficient (r) maps. These maps were then normalized using Fisher's r-to-z transform ($z = 0.5 \text{ Ln } [(1 + r)/(1 - r)]$) to correct for non-normality in the distribution of r-values within individual omnibus functional connectivity maps. Results were then translated to standard space (MNI) in preparation for group level hypothesis testing.

Group level contrasts involved the following steps. First, a full group connectivity map was generated as all correlations that survive a cluster corrected $p < .05$ threshold. Next, a priori contrasts were performed to explore group differences based on parental history of depression (low-risk vs. high-risk). These two-sample t-tests were only carried out in voxels that showed significant connectivity across the entire group and cluster corrected at a $p = 0.05$ level. Beyond these restricted whole brain contrasts, we examined differences in connectivity between the seed and a priori target locations in the rMFG and rSMG (MNI coordinate locations: rMFG [x = 44, y = 2, z = 34]; rSMG [x = 50, y -34, z = 42]). Again, these targets consisted of 8 mm spheres centered on peak locations from our previous study (see Figure 7 for ROI locations) (Beevers et al., 2010). Fisher z-transformed r-values were extracted from these locations for each individual from the full group connectivity map. Next, two-sample t-tests were performed on these values based on group assignment (low-risk vs. high-risk). Results were corrected for multiple comparisons using a Bonferronni correction. Finally, we performed an exploratory post-hoc analysis examining the relationship between parents' worst episode of depression and connectivity between the rIFG seed and rMFG/rSMG targets respectively. Fisher z-transformed r-values extracted from these target locations were regressed on parents' PHQ-9 scores. This analysis was conducted for all participants, irrespective of assignment to vulnerability groups. Results were corrected for multiple comparisons using a Bonferroni correction.

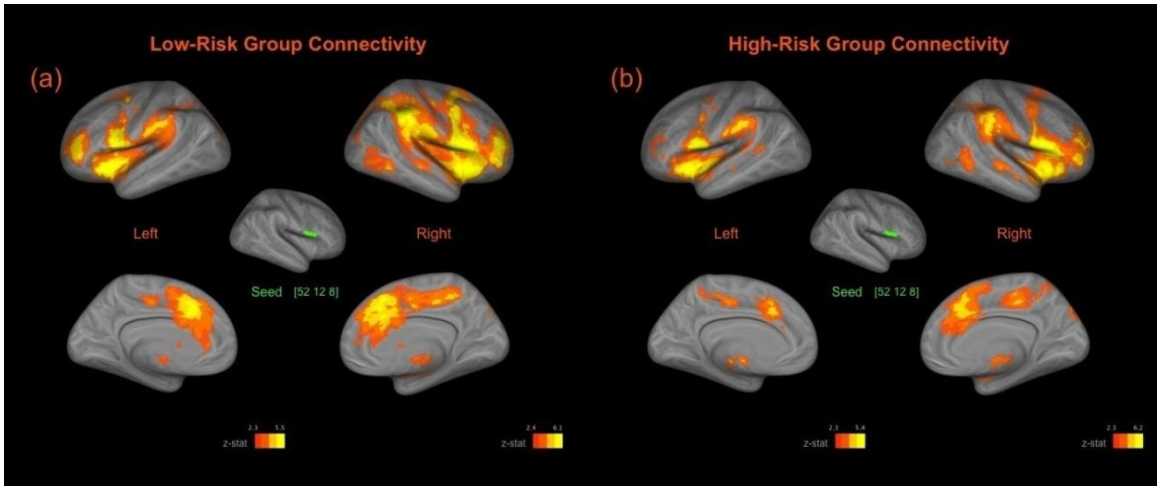
Procedure. Participants and their parent completed the phone-screening interview with a trained researcher to assess for 1) current or past history of depression in the adolescent, 2) current or past history of depression in the parent, 3) MRI contraindications in the adolescent. Participants and parents who met study criteria were invited to the Imaging Research Center at The University of Texas at Austin. After reviewing the consent form in detail, the participant's parent was asked to provide written informed consent and the participant was asked to provide written assent for participation. Next, participants completed the imaging protocol, including structural and functional scans. Then, participants completed a diagnostic interview and several questionnaires. Participants also provided a sample of saliva for genetic analysis; this will not be included in this manuscript. After completing all study protocols, participants were thanked for their time and compensated $100 per family.

Results

Seed connectivity whole-brain, by group. Whole-brain omnibus functional connectivity maps are plotted for each group (low and high risk) in Figure 6 (panels (a) and (b), respectively). The seed location is specified in the center of each panel and connectivity plots for left and right-hemispheres are arranged on each side. These maps demonstrate that, as expected, regions of the CCN – including bilateral dorsal lateral prefrontal cortex, anterior cingulate, and supramarginal gyrus – reveal significant connectivity with the rIFG seed location in both high-risk and low-risk groups. Visual inspection of these maps demonstrates the degree of similarity among regions showing

significant functional connectivity across groups. Next, we formally tested between group differences in functional connectivity.

Figure 6. Whole brain functional connectivity with right inferior frontal gyrus seed by group. Panel (a) reflects functional connectivity in the low-risk group. Panel (b) reflects functional connectivity in the high-risk group. Orange/Yellow overlays represent regions showing significant correlations with seed region (in green, at center of each panel) at cluster corrected $p < .05$ threshold projected onto inflated cortical surface renderings.



Group comparisons. Group contrast maps for the low-risk> high-risk comparison are plotted in Figure 7. This plot indicates higher levels of connectivity between the rIFG seed and regions of right dorsal lateral prefrontal cortex and left and right mesial prefrontal cortex in the low-risk group relative to the high-risk group. Peak location

coordinates, cluster sizes, and p-values are listed in Table 5. There were no significant differences for the high-risk > low-risk comparison. These findings support the hypothesis that adolescent women with a parental history of depression demonstrated lower levels of functional connectivity between nodes of the CCN that may underlie attentional control for emotional information.

Because recent work has shown that head movement can systematically influence estimates of resting state functional connectivity, particularly in between group comparisons (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), we examined the mean framewise displacement (FD) values for differences between groups. FD provides an index of instantaneous head movement for every volume (TR) of each participant's resting state time-series. There was no significant difference between the high-risk and low-risk groups on this measure, $t(22) = -0.74$, $p = 0.46$.

Figure 7. Whole brain group differences in connectivity with right inferior frontal gyrus seed (Low-Risk > High-Risk). Orange/Yellow overlays represent regions showing significant differences in connectivity with seed region by group (Low-Risk > High-Risk) at cluster corrected $p < .05$ threshold. Whole brain differences are shown on inflated cortical surface renderings (above) as well as axial slice renderings (below) for each hemisphere. Slice locations (z MNI coordinate) are noted in blue above each slice. Locations for Region of Interest (ROI) analysis are shown in blue in the Right Hemisphere panel. Areas of overlap between the whole brain group contrast and ROI locations are shown in purple.

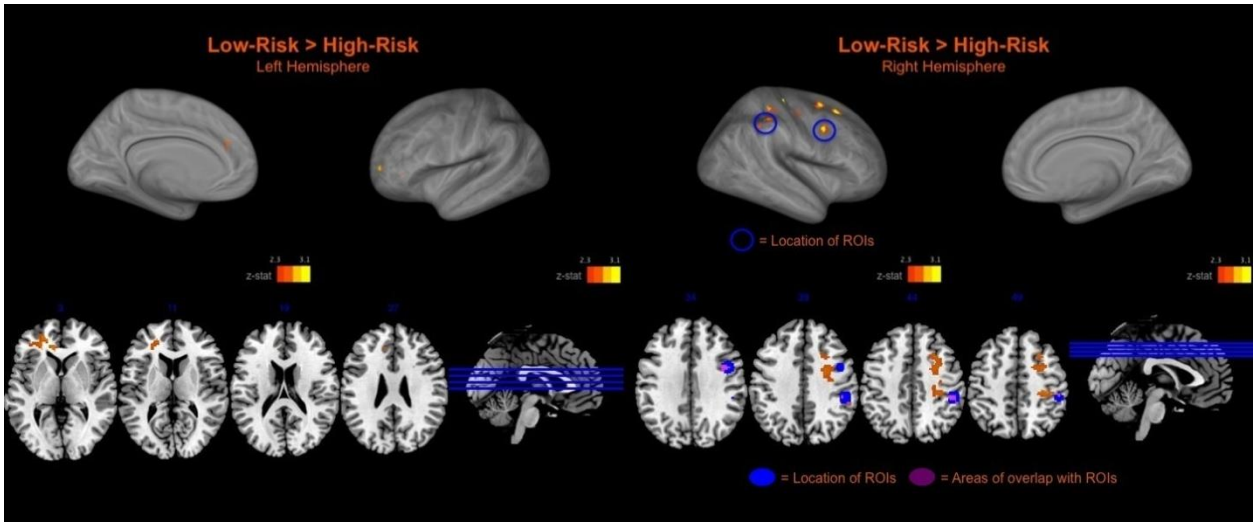
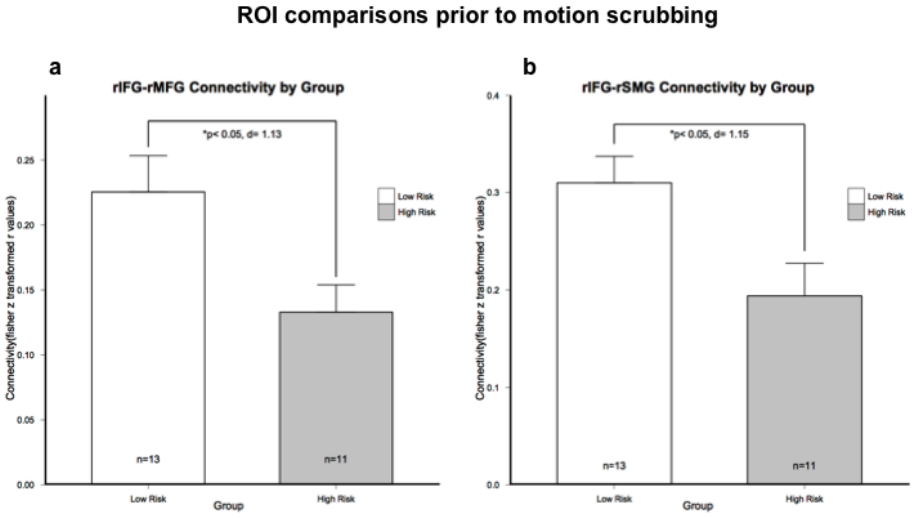


Table 5. Peak coordinate locations for whole brain group differences in connectivity with right inferior gyrus seed (Low-Risk > High-Risk). Region, number of voxels, Z-MAX, and MNI coordinates.

Location	Number of Voxels	Z-MAX	Z-MAX MNI Coordinates		
			X	Y	Z
Right – Middle Frontal Gyrus/Supramarginal Gyrus	618	3.39	26	-28	48
Left – Frontal Pole	302	3.54	-22	50	4
Left – Anterior Cingulate	16	2.77	-10	36	26

ROI analysis. Using a priori, unbiased ROIs in rMFG and rSMG we tested for differences between high-risk and low-risk groups. These ROIs overlap with locations from whole brain analysis and are indicated in Figure 7 (blue circles). Results of the ROI analysis are plotted in Figure 8. In both ROIs, connectivity was significantly greater for the low-risk than the high-risk groups: rIFG-rMFG connectivity X group, $t(22) = 2.64$, $p = 0.03$, *cohen's d* = 1.13 (Figure 8a); rIFG-rSMG connectivity X group, $t(22) = 2.69$, $p = 0.028$, *cohen's d* = 1.15 (Figure 8b).

Figure 8. Region of interest (ROI) analysis (prior to motion scrubbing (N=24)). Panel (a) represents group differences in connectivity between the right inferior frontal gyrus (rIFG) seed and the right middle frontal gyrus (rMFG) ROI. Panel (b) represents group differences in connectivity between the rIFG seed and the right supramarginal gyrus (rSMG) ROI.

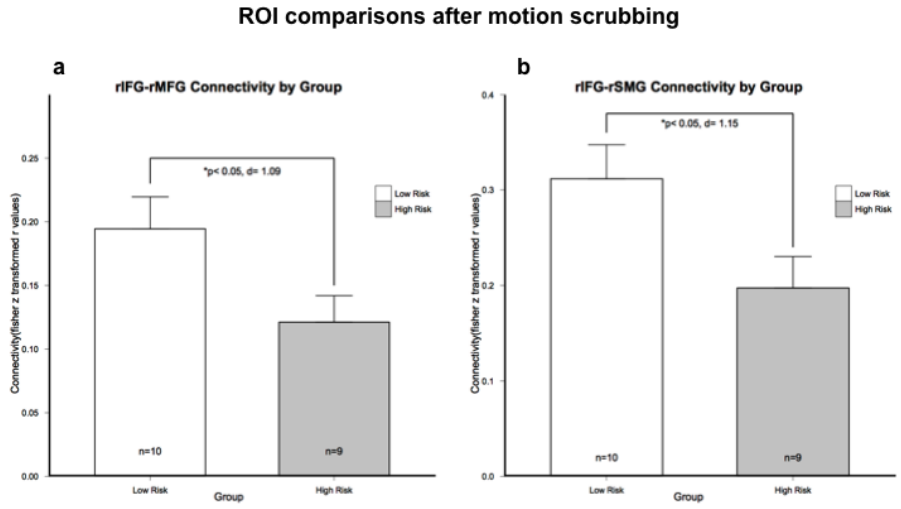


In order to further rule out that these results reflect differences in motion between groups we performed a "motion scrubbing" procedure, recommended by Power and colleagues (2012), to mitigate the influence of head motion on functional connectivity estimates. The first step of this procedure involves thresholding the time series to determine frames containing high motion for removal. A conservative FD threshold of 0.2mm was adopted based on visual inspection of the FD plots across participants.

Within each participant's time series, volumes that exceeded this threshold were flagged and removed. To accommodate temporal smoothing of BOLD data processing, the volume before and two volumes after each flagged volume were also removed. Participants with fewer than 100 volumes remaining following this "motion scrubbing" procedure were excluded from this follow up analysis. This led to the exclusion of 5 participants (2 high-risk, 3 low-risk).

Results of the ROI analysis performed after motion scrubbing (N=19) are plotted in Figure 9. Again, in both ROIs, connectivity was significantly greater for the low-risk than the high-risk group: rIFG-rMFG connectivity X group, $t(17) = 2.25$, $p = 0.04$, *cohen's d* = 1.09 (Figure 9a); rIFG-rSMG connectivity X group, $t(17) = 2.36$, $p = 0.03$, *cohen's d* = 1.15 (Figure 9b). These results suggest that despite the reduced power associated with significant data loss following motion scrubbing, the high-risk group continues to demonstrate a similar magnitude of greater connectivity between the rIFG seed and the a priori ROIs in rMFG and rSMG.

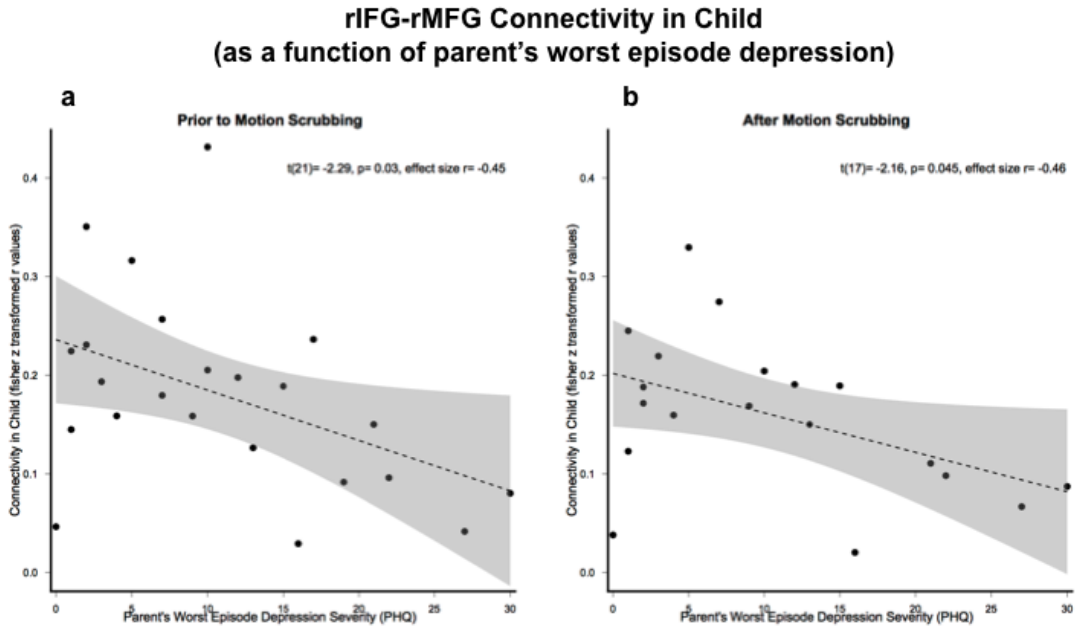
Figure 9. Region of interest (ROI) analysis (after motion scrubbing (N=19)). Panel (a) represents group differences in connectivity between the right inferior frontal gyrus (rIFG) seed and the right middle frontal gyrus (rMFG) ROI. Panel (b) represents group differences in connectivity between the rIFG seed and the right supramarginal gyrus (rSMG) ROI.



Parent's worst episode depression severity. Finally, we explored whether individual differences in the severity of the parents' worst lifetime episode of depression (across the whole group) predicted functional connectivity between our unbiased ROIs and the rIFG seed. Results from the analysis prior to motion scrubbing (N=24) are plotted in Figure 10a and indicate that more severe depression in parents correspond with lower levels of functional connectivity between nodes of the CCN, $t(21) = -2.28$, $p = 0.033$,

effect size r = -0.445. These findings suggest that individual differences in the severity of parents' depression history are associated with the development of neural networks underlying cognitive control for emotional information in their adolescent daughters. Results from the motions scrubbed data (N=19) further support this conclusion, t(17) = -2.16, p = 0.045, *effect size r* = -0.46 (see Figure 10b).

Figure 10. Relationship between severity of parents' worst episode of depression and connectivity between right inferior frontal gyrus seed and the right middle frontal gyrus target. Panel (a) represents this relationship prior to the application of the motion scrubbing procedure (N=24). Panel (b) represents this relationship after the application of the motion scrubbing procedure (N=19).



Discussion

This study aimed to identify differences in the neural systems underlying cognitive control for emotional information among adolescent women who are at risk for depression based on a parental history of MDD. Using functional connectivity analysis

within a circumscribed network of brain regions underlying cognitive control, we found that girls with a parental history of depression showed decreased connectivity between key brain regions implicated in attentional control for emotional information. Specifically, girls with a parental history of depression showed decreased connectivity between right inferior frontal gyrus (rIFG) and locations in right middle frontal gyrus (rMFG) and right supramarginal gyrus (rSMG). They also showed decreased connectivity between rIFG and regions of left frontal pole (lFP) and left anterior cigulate cortex (lACC). Exploratory analysis demonstrated that the severity of the parents' worst episode of depression was negatively associated with connectivity between right IFG and MFG locations. These findings support the hypothesis that daughters of parents with a depression history reveal an underdeveloped functional connectivity within neural systems underlying attentional control for emotional information. It is important to note that these findings cannot be attributed to between group differences in motion as they remain after a rigorous approach to removing the influence of head motion on resting state functional connectivity estimates.

To our knowledge, this study represents the first exploration of CCN connectivity in this high-risk population. Our findings are in line with a limited number of resting state functional connectivity analyses among individuals with adolescent depression. These studies did not examine CCN connectivity directly, however, they report a similar pattern of decreased connectivity in resting state networks that are similarly associated with adult depression (Bluhm et al., 2009; Cullen et al., 2009). Moreover, they are in line with

recent resting state functional connectivity analyses of the CCN in depressed adults (Veer et al., 2010; Alexopoulos et al., 2012), suggesting a pattern of decreased functional connectivity within this network. Our data extend this research in two important ways. First, they suggest that adolescent women who are high risk for depression, but have never been depressed, show a similar pattern of decreased connectivity within the CCN. Second, they highlight the possibility that the functional development of the CCN is a critical mechanism associated with depression vulnerability. Indeed, findings from the current study provide the first demonstration that CCN connectivity alterations predate the onset of depression.

These findings fit broadly into an integrated cognitive-neural model of depression. This model suggests that diminished recruitment of CCN regions influence depression vulnerability and maintenance via effects on cognitive control for emotional information (De Raedt & Koster, 2010; Disner et al., 2011). In other words, neural deficits are thought to underlie difficulties with basic cognitive control mechanisms (e.g., attentional control, inhibition, reappraisal) that support emotion regulation. These deficits may handicap the performance of this network and, therefore, negatively impact vulnerable individuals' ability to regulate negative information during a stage of development when this skill becomes increasingly important (Susan Nolen-Hoeksema, 1994; Cyranowski, Frank, Young, & Shear, 2000; Hankin & Abramson, 2001). Indeed, cognitive models of depression suggest that over time such difficulties may confer

vulnerability for the onset of depression, particularly in the context of stressful life events (Beevers et al., 2011).

These findings are also in line with evidence of behavioral deficits in cognitive control over emotional information in this population. Recent reaction time studies suggest that adolescent women with a parental history of depression demonstrate deficits in attentional control for mood congruent stimuli (Joormann et al., 2007; Gibb, Benas, Grassia, & McGeary, 2009). Our findings suggest that these behavioral deficits may correspond to abnormalities in CCN functional connectivity. Of course, the current study does not directly assess the relationship between differences in functional connectivity and behavioral deficits in attentional control in this population. This question remains an important area for future research.

Another exciting avenue for future research involves the potential to prevent depression in this high-risk population by enhancing CCN functional connectivity. Recent work using real-time neural feedback suggests that training people to modulate activity in a specific brain region can influence connectivity with regions in putative resting state networks (Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011). Our findings highlight a key region that may be targeted in similar paradigms (rIFG) as a means of modulating CCN connectivity. Future work is required to investigate the whether this intervention helps bolster cognitive control for emotional information among young women with a parental history of MDD and whether this, in turn, helps reduce depression vulnerability in this population.

Of course, our findings should be interpreted in the context of several important limitations. First, our sample size is relatively small. Efforts to replicate should consider enrolling a larger sample, although we note that this is the first study to examine CCN connectivity in adolescents at high-risk for depression. Second, the cross-sectional design did not involve follow-up with research participants. Therefore, we were not able to determine if differences in CCN connectivity predicted depression onset. Including longitudinal follow up is a critical feature of future research to directly assess the extent to which differences in connectivity predict depression onset, particularly in the context of life stress. Third, we only measured one parent's depression history. It is possible that some individuals in the non-vulnerable group, in fact, should have been assigned to the vulnerable group if their other parent had a history of depression. We used a self-report check to screen for this and successfully removed two participants, however, future work should consider measuring full inclusion/exclusion criteria in both parents.

Despite these limitations, we believe this study represents an important contribution to our understanding of the neural mechanisms underlying depression vulnerability in this high-risk population. Women with a parental history of depression are uniquely vulnerable for the onset of MDD, an onset that carries significant short and long-term consequences. This research is an important first step towards elucidating the neural mechanisms underlying this vulnerability; an effort that, ultimately, may facilitate interventions aimed at preventing the consequences of adolescent depression in this high-risk population.

STUDY 3: 5-HTTLPR AND BDNF VAL66MET POLYMORPHISMS MODERATE THE RELATIONSHIP BETWEEN LIFE STRESS AND RUMINATION[3]

Introduction

A polymorphism in the serotonin transporter gene (5-HTT, SLC6A4) has been associated with individual differences in response to stress. Individuals carrying one or two copies of the relatively low-expressing short (S) allele of the serotonin transporter linked polymorphic region (5-HTTLPR) demonstrate more aversive responses to stressful events in field and laboratory studies (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010) and are at greater risk for developing depression than long allele homozygotes (e.g., Karg, Burmeister, Shedden, & Sen, 2011; although see, Risch et al., 2009).

One way susceptibility to stress may increase vulnerability to depression is through intermediary phenotypes. Rumination, or the tendency to perseverate on problems and negative feelings, represents an important cognitive vulnerability for depression (S Nolen-Hoeksema, 2000; S Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008b). Ruminative thinking predicts the onset of depression, prolongs episodes of negative mood, hinders cognitive and behavioral efforts to improve mood, and is associated with diminished social support (e.g., Beevers, Rohde, Stice, & Nolen-

[3] This study appears in *Genes, Brain, and Behavior* (Clasen, P.C., Wells, T.T., Knopick, V.S., McGeary, J.E., & Beevers, C.G. (2011). *Genes, Brain, and Behavior, 10*, 740-6.)

Hoeksema, 2007; Just & Alloy, 1997; Lyubomirsky & Nolen-Hoeksema, 1993; Nolen-Hoeksema & Davis, 1999).

People who ruminate tend to believe that ruminative thinking helps them understand and solve problems (Papageorgiou & Wells, 2001; Papageorgiou & Wells, 2003). Thus, adverse events may provide the fodder for rumination and increases in adverse events are likely to increase rumination. In a small study (N = 21), Canli and colleagues (2006) found that S allele carriers reported higher levels of rumination than L allele homozygotes but only when they experienced current life stress (Canli et al., 2006). Similarly, individuals with two S alleles who experienced higher levels of emotional abuse in childhood report higher levels of rumination in adulthood than individuals carrying at least one copy of the high-expressing long (L) allele (Antypa & Van der Does, 2010). These findings are consistent with the idea that the 5-HTTLPR polymorphism moderates the effect of current life stress on rumination.

Variation in a gene regulating brain derived neruotropic factor (BDNF) may also influence the effect of current adverse events on rumination. Brain derived neurotropic factor (BDNF) is a protein involved in neuronal and synaptic development. An amino acid substitution (valine to methionine) at codon 66 (Val66Met, rs6265) of the BDNF gene results in two alleles: Val and Met. We recently reported that the Met allele was associated with increased levels of rumination in a sample of non-depressed adults (Beevers, Wells, & McGeary, 2009). Similar findings have been reported among women with adult onset depression (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007). It remains

unclear whether BDNF Val66Met variation interacts with life stress to predict differences in rumination, although a growing animal literature indicates that Met homozygotes display more aversive responses to stress than animals carrying at least one Val allele (e.g., Chen et al., 2006; Spencer, Waters, Milner, Lee, & McEwen, 2010; Yu et al., 2009).

In summary, we hypothesized that individuals with genotypes associated with stress sensitivity (S 5-HTTLPR carriers or Met BDNF homozygotes) would report higher levels of rumination than L 5-HTTLPR and Val BFND homozygotes when they experienced recent adverse events. Exploratory analyses investigated the aggregate effect of risk alleles across genes (i.e., S and Met alleles) on the relationship between life stress and rumination.

Method

Participants

Participants were 273 undergraduate students recruited from introductory psychology courses at the University of Texas at Austin (see Table 1 for demographic information). Participants were 57% Caucasian, 6% Black/African American, 15% Asian, 0.01% Hawaiian/Pacific Islander, 0.003% Native American/American Indian, 7% Multiple Ethnicities, and 15% did not endorse an ethnicity. Across these categories, 21% of the sample was Hispanic. Participants received one research credit for participating in this study. During the study, participants completed self-report measures of rumination, current adverse events, current depressive symptoms, past depressive episodes, current

psychiatric medication use, and demographic information. They also provided a sample of buccal cells used to extract DNA for genotyping. Inclusion criteria included no history of major depressive disorder and no current use of any psychiatric medications.

Materials

Genetic Sample. Genomic DNA was isolated from buccal cells using a modification of published methods (e.g., Freeman et al., 1997). The cheeks and gums are rubbed for 20 seconds with three sterile, cotton-tipped wooden swabs. The swabs are placed in a 50-ml capped polyethylene tube containing lysis bugger (500 µl of 1 *M* Tris-HCl; 200 mM disodium ethylene diaminetetracetic acid (EDTA), pH 8.0; 500 µl of 10% sodium dococyl sulfate; and 100 µl of 5 *M* sodium chloride). The subjects then rinse out the mouth vigorously with 10 ml of distilled water for 20 seconds and this was added to the 50-ml tube. The tubes were stored at 4°C until the DNA was extracted.

Serotonin transporter promoter region polymorphism (5-HTTLPR). The 5-HTTLPR gene, which maps to 17q11.1-17q12, contains a 43 bp insertion/deletion in the 5' regulatory region of the gene (Heils et al., 1996). This polymorphism in the promoter appears to be associated with variations in transcriptional activity: the long variant has approximately three times the basal activity of the shorter promoter with the deletion (Lesch et al., 1996). The assay is a modification of the method of Lesch and colleagues (1996). The primer sequences are: forward, 5′-GGCGTTGCCGCTCTGAATGC-3′ (fluorescently labeled), and reverse, 5′-GAGGGACTGAGCTGGACAACCAC-3′. These

primer sequences yield products of 484 or 528 bp. Allele sizes are scored by two investigators independently and inconsistencies were reviewed and rerun when necessary.

The 5-HTTLPR long allele (L) has two variants (L_A and L_G). The L_G variant mirrors the S allele in terms of transcriptional activity (Wendland, Martin, Kruse, Lesch, & Murphy, 2006): Two copies of the L_A variant are associated with significantly greater synaptic serotonin reuptake, compared to one or two copies of the S or L_G alleles (Hu et al., 2005; Lesch et al., 1996).To distinguish between the S, L_A, and L_G fragments, the PCR fragment was digested with M*sp*I according to the methods reported by Wigg and colleagues (2006). The resulting polymorphic fragments were separated using an ABI 3130xl DNA sequencer (S: 297, 127, 62 bp; L_A: 340, 127, 62 bp; L_G: 174, 166, 127, and 62 bp). Consistent with previous research, the low expressing S and L_G alleles were designated S' and the higher expressing L_A allele was designated L'. We therefore formed three groups: (1) S'S' (i.e., SS: n = 58; SL_G: n = 17; L_GL_G: n = 2); (2) S'L' (i.e., SL_A: n = 113; L_GL_A: n = 26); and (3) L'L' (i.e. L_AL_A: n = 52). Results of an exact test for Hardy Weinberg proportions using Markov chain–Monte Carlo implementation (Guo & Thompson, 1992) indicate that our observed genotype frequencies do not differ from Hardy Weinberg equilibrium (p= 0.525). We were unable to genotype 5-HTTLPR among three individuals for whom we had BDNF genotypes.

Brain derived neurotrophic factor (BDNF). The Val66Met polymorphism (rs6265) was genotyped using Taqman assay C___11592758_10 (Applied Biosystems) using an ABI 7900HT Real time PCR system. The frequency of the BDNF genotypes

(Val/Val, n = 161; Val/Met, n = 92; Met/Met, n = 20) did not differ from the Hardy-Weinberg equilibrium ($\chi^2 = 1.78$, $p = 0.18$).

Adverse Events Questionnaire (AEQ). The AEQ (Carver, 1998) was developed to measure current adverse events in the life of undergraduate students. Two items measure adverse events in the domains of academics and relationships, one item measures adverse events in any other domain, and one item measures the impact of accumulated minor negative events. Participants respond using a scale from 0 to 3 indicating the frequency of adverse events in each domain (i.e., *0 = No, 1 = Yes, this happened to me once, 2 = Yes, this happened to me twice, 3 = Yes, this happened to me more than twice*). This measure of life stress has previously been found to interact with a cognitive vulnerability in the prospective prediction of dysphoria (Beevers & Carver, 2003; Carver, 1998).

Ruminative Responses Scale (RRS). The RRS (Treynor, Gonzalez, & Nolen-Hoeksema, 2003) is a 10-item scale that measures an individual's tendency to ruminate, or repetitive and passive thinking about problems, negative events, and negative feelings. Participants respond using a scale from 1 (almost never) to 4 (almost always) indicating the frequency of with which they endorse rumination items. The RRS provides a measure of rumination that is not confounded with depression symptoms. Previous reports indicate good internal reliability and predictive validity (Treynor et al., 2003).

Beck Depression Inventory – II (BDI-II). The BDI-II (Beck et al., 1996) is commonly used in research and clinical settings to assess depression symptoms and their

severity. The inventory consists of 21 items sampling depressive symptoms across cognitive, motivational, affective and somatic domains. Previous reports indicate adequate test-retest reliability and validity among undergraduate student populations (Beck et al., 1996). BDI-II scores were included as a covariate in all analyses.

The Inventory for Diagnosing Depression – Lifetime Version (IDD-L). The IDD-L (Zimmerman & Coryell, 1987) is a self-report questionnaire used to diagnose lifetime major depressive disorder. It has been shown to have similar sensitivity and specificity as the Diagnostic Interview Schedule, and good construct validity and test-retest reliability (Zimmerman & Coryell, 1987). People who endorsed the presence of five of nine symptoms for a two week period or greater were classified as having a history of depression. Participants were required not to have a past history of depression to be included in this study.

Demographic Questionnaire. Participants completed a demographic questionnaire that included age, gender, race/ethnicity, and medication use (see Table 6). Participants were required to not be taking any psychiatric medications to be included in this study. To test moderating effects of ethnicity, we collapsed minority groups and created an ethnicity variable reflecting Caucasians vs. non-Caucasians (see Beevers et al., 2009).

Procedure

Participants were initially recruited based on having low scores on the short form of the Beck Depression Inventory, completed during a mass pre-testing session at the

beginning of the academic semester. We chose to examine study hypotheses in a sample of non-depressed healthy adults so that we could isolate genetic and environmental effects on rumination while simultaneously eliminating confounds like depression. For this reason, we also used a measure of rumination that is not confounded by depression symptoms (see above) and controlled for depressive symptoms in our sample at each stage of analysis (see below). Individuals with low scores (<4) were invited to participate in the current study. All participants provided informed consent, completed the self-report questionnaires described above, completed additional assessments not relevant to this research, and provided buccal cells via a cheek swab for genotyping. Upon completion of these procedures, participants were debriefed and assigned course credit for their participation. The institutional review board (IRB) at the University of Texas at Austin approved all study procedures.

Results

Sample Characteristics

Descriptive statistics for the sample are presented in Table 6 and organized by BDNF and 5-HTTLPR allele groups (Val/Val, Val/Met, Met/Met; L'L', S'L', S'S'). To test whether the distribution of allele groups differed based on ethnicity we collapsed all Non-Caucasian individuals into one group and compared this group to the Caucasian group. There were significantly different distributions of this reduced ethnicity variable (Caucasian/Non-Caucasian) across BDNF (*Fisher's exact* = 0.013) and 5-HTTLPR allele groups ($\chi^2 < 0.0001$). Therefore, we tested whether this reduced ethnicity variable

(hereafter called "ethnicity") moderated the interaction between genes and life events in all subsequent analysis. No other significant demographic differences were observed between groups.

Table 6. Demographics as a function of BDNF Val66Met and 5-HTTLPR allele group.

	5-HTTLPR			**BDNF Val66Met**		
	L'L' (n = 52)	L'S' (n = 139)	S'S' (n = 77)	Val/Val (n = 161)	Val/Met (n = 92)	Met/Met (n = 20)
Age (years)	18.96 (0.99)	18.80 (0.97)	19.01 (2.16)	18.84 (1.00)	18.87 (0.86)	19.55 (3.95)
% Gender (M/F)	54/46	54/46	52/48	55/45	46/54	75/25
% Caucasian/Other	67/33	64/36	35/65	60/40	58/42	25/75
Depressive Symptoms	3.30 (2.82)	3.46 (3.57)	3.64 (3.26)	3.72 (3.45)	2.96 (3.20)	3.86 (2.68)
Adverse Events	2.83 (1.42)	2.77 (1.64)	3.05 (1.73)	2.88 (1.65)	2.78 (1.60)	2.9 (1.52)
Rumination	9.89 (4.96)	9.29 (5.17)	9.44 (5.46)	8.86 (4.60)	10.26 (5.78)	9.95 (6.69)

Note: Within both BDNF Val66Met and 5-HTTLPR allele groups there were significantly different distributions for ethnicity (Caucasian/Non-Caucasian). Therefore, this variable was tested as a moderator for all genetic analysis. Rumination scores were significantly different between Val/Val and Val/Met groups. There were no other significant differences between allele groups.

Statistical Analysis

All analyses were preformed in STATA 11 (StataCorp: College Station, Texas, USA). RRS scores were linearly transformed with a square root transformation to help normalize the distribution and correct for heterscedasticity in the regression analyses. For each analysis we implemented multiple regression with a factors approach. This approach requires setting a reference group and then comparing groups of interest to this reference

group using a dummy code structure (e.g., two dummy codes are examined for the 5-HTTLPR variable: LL vs. SL, LL vs. SS). One advantage of this approach is that we can directly assess differences between specific genetic groups and their interaction with adverse events to the reference group in the initial model. Therefore, follow-up tests are unnecessary. We visually inspected residual plots at each stage of analysis to check for violations in the assumptions underlying linear regression.

5-HTTLPR

In order to test whether 5-HTTLPR genotype predicts rumination scores, while controlling for current depression symptoms, we performed a multiple regression analysis with 5-HTTLPR group (allele: L'L', S'L', and S'S') as the predictor variable, RRS scores as the dependent variable, and BDI-II scores as a covariate. We treated the L'L' genotype as a reference group in the analysis. Neither the S'L' group, $t(266) = -0.85$, $p = 0.40$, nor the S'S' group, $t(266) = -0.77$, $p = 0.44$, differed from the L'L' group. Consistent with our previous findings (Beevers et al., 2009), there was no 5-HTTLPR genotype main effect for the prediction of rumination. Ethnicity did not moderate these effects, S'L': $t(256) = 0.67$, $p = 0.50$; S'S': $t(256) = 0.59$, $p = 0.56$.

5-HTTLPR x Adverse Events

In order to test whether 5-HTTLPR genotype interacts with current adverse events to predict rumination we performed a multiple regression analysis with AEQ and 5-HTTLPR genotype as predictor variables and BDI-II as a covariate. High-expressing long allele homozygotes (LL) were treated as a reference group in the regression model.

Results indicate a significant S'S' x life stress interaction, t (263) = 2.11, p = 0.036, *effect size r* = 0.13 (see Figure 9a). The S'L' x life stress interaction fell just short of statistical significance, t (263) = 1.93, p = 0.054, *effect size r* = 0.12 (see Figure 9a). Relative to the L'L' group, S-carriers ruminated more as number of adverse events increased. Ethnicity did not moderate these effects, S'L' x AEQ x ethnicity, t (250) = 0.44, p = 0.66; S'S' x AEQ x ethnicity, t (250) = -0.31, p = 0.75.

BDNF Val66Met

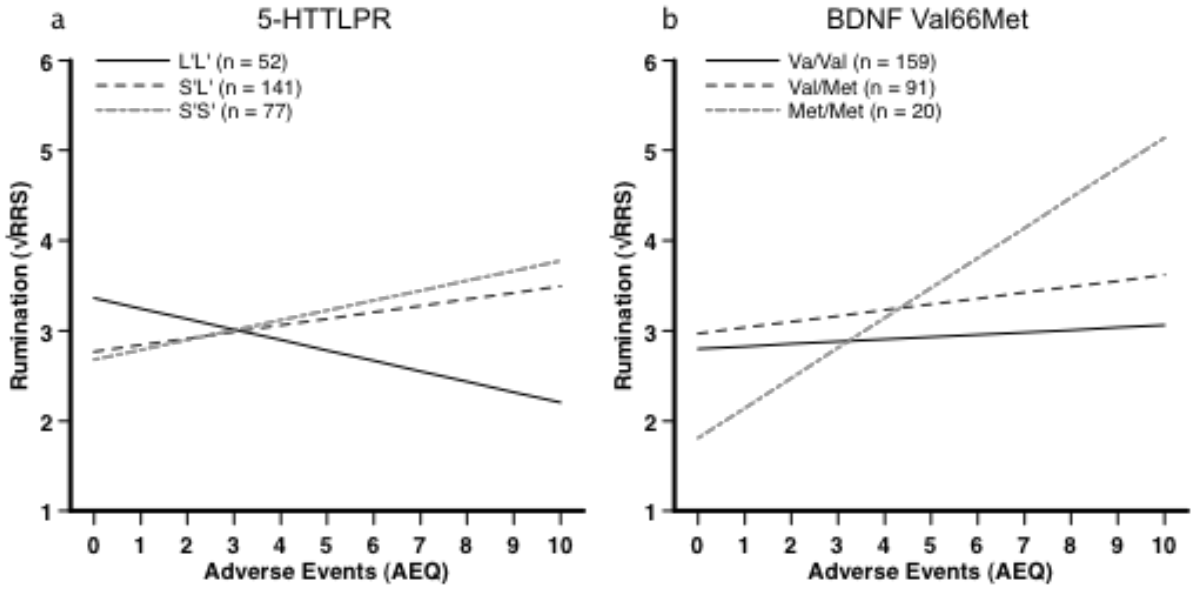
In order to test whether BDNF genotype predicts rumination scores, while controlling for depressive symptoms, we performed a multiple regression analysis with BDNF group (allele: Val/Val, Val/Met, and Met/Met) as the predictor variable, RRS scores as the outcome variable, and BDI-II scores as a covariate. The Val/Val group was treated as a reference group in the regression model. Results revealed a significant term for the Val/Met homozygote group, t (269) = 2.08, p = 0.039, *effect size r* = 0.13. Consistent with our previous findings, Val/Met individuals report higher levels of rumination than the Val/Val group (Beevers, Wells, & McGeary, 2009). Rumination for the Met homozygote group was not significantly different from the Val/Val group, t (269) = 0.41, p = 0.68 (see Table 1). Ethnicity did not moderate these effects, Val/Met x ethnicity, t (259) = 0.38, p = 0.70; Met/Met x ethnicity, t (259) = -0.22, p = 0.82.

BDNF Val66Met x Adverse Events

In order to test whether BDNF Val66Met genotype interacts with current adverse events to predict rumination we performed a multiple regression analysis with AEQ and

BDNF status as predictor variables and BDI-II as a covariate. The Val/Val group was treated as a reference group in the regression model. Results indicate a significant interaction term for Met/Met x AEQ, t (266) = 2.62, p = 0.009, *effect size r* = 0.16 (see Figure 9b), but not for Val/Met x AEQ, t (266) = 0.42, p = 0.68. Relative to Val homozygotes, Met homozygous individuals ruminate more as adverse events increase. The effect for adverse events on rumination did not differ for the Val/Met versus the Val/Val groups. Ethnicity did not moderate these effects, Val/Met x AEQ x ethnicity, t (253) = 0.76, p = 0.45; Met/Met x AEQ x ethnicity, t (253) = 0.33, p = 0.74.

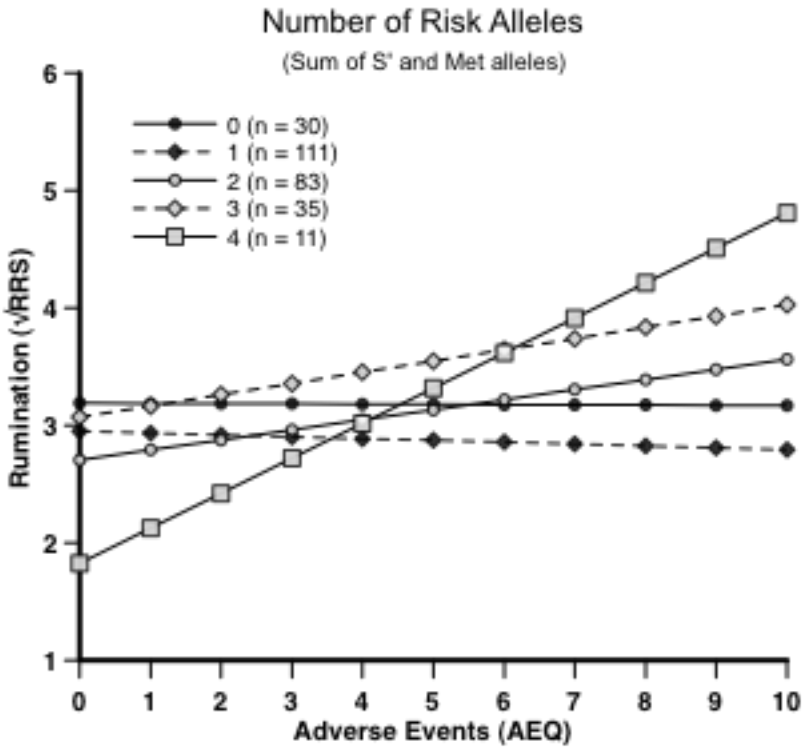
Figure 11. Rumination as a function of life stress and candidate gene (a - 5-HTTLPR, b - BDNF Val66Met).



Risk Alleles

In order to assess whether the current adverse events interact with number of risk alleles to predict rumination we conducted a regression analysis with AEQ and risk alleles as the predictor variables, RRS scores as the outcome variable, and BDI-II scores as a covariate. Given that we are examining two polymorphisms, number of risk alleles could range from 0 to 4 (M=1.57, SD=0.99). Number of risk alleles was used as a continuous variable, so there is no reference group for these analyses. The interaction term was significant, t (265) = 2.49, p = 0.013, *effect size r* = 0.15. The association between adverse events and rumination varied as a function of number of risk alleles across genes, with a higher number of risk alleles predicting a stronger association between adverse events and rumination (see Figure 10). Ethnicity did not moderate this effect, t (254) = -0.14, p = 0.89.

Figure 12. Rumination as a function of life stress and number of combined risk alleles.



Discussion

The goal of this study was to examine whether 5-HTT and BDNF genes moderate the relationship between life stress and rumination. We tested the hypothesis that individual differences in 5-HTTLPR and BDNF Val66Met polymorphisms predict differences in the relationship between adverse events and ruminative thinking. Results suggest that individuals with two S' alleles (5-HTTLPR) and individuals with two Met alleles (BDNF Val66Met) tend to ruminate more when they experience more adverse life events. Individuals with one S' allele showed a similar pattern (although this effect fell

just short of statistical significance, $p = 0.054$). Individuals with two L' 5-HTTLPR alleles and individuals with at least one Val BDNF allele do not show increased rumination in the context of life stress. These results support the hypothesis that 5-HTT and BDNF genes moderate the relationship between life stress and rumination.

These findings are consistent with a growing body of research that indicating that the 5-HTTLPR polymorphism is associated with susceptibility to the negative effects of stress (Caspi et al., 2010). They are also consistent with evidence that 5-HTTLPR variation moderates the relationship between early life stress and rumination (Antypa & Van der Does, 2010). Taken together, these results suggest individual differences in 5-HTTLPR genotype interact with life stress occurring across the life span to predict differences in ruminative thinking. Rumination represents an important cognitive vulnerability for depression (e.g., Nolen-Hoeksema et al., 2008); these results support the idea that rumination also represents an intermediary phenotype for depression vulnerability among S' allele homozygotes who experience life stress.

Moreover, these results provide the first evidence that the BDNF Val66Met polymorphism interacts with life stress to predict rumination. Previous studies showed that the Met allele is associated with direct differences in ruminative thinking (Beevers, Wells, & McGeary, 2009; Hilt et al., 2007); however, these studies did not (a) investigate the influence of life stress and (b) did not include Met homozygous individuals as a separate group in the analysis. A growing literature suggests that Met homozygotes exhibit susceptibility to the negative effects of life stress (e.g., Gatt et al., 2009; Schüle et

al., 2006; Vinberg et al., 2009). Results from this study are consistent with this evidence, as Met homozygotes were the only BDNF Val66Met genotype to demonstrate increased rumination when they experienced increased adverse events. These results highlight the importance of including this less common genotype in analyses, a demand that requires sampling a large number of participants in BDNF Val66Met association studies.

It is interesting to note that Val/Met individuals reported higher levels for rumination than Val homozygotes in this study, independent of the effects of life stress. This result is consistent with our previous research (Beevers, Wells, & McGeary, 2009). BDNF Val66Met variation, therefore, appears to influence rumination via two pathways: (1) moderating stable differences in the tendency to ruminate among Val/Met individuals and (2) moderating susceptibility to rumination under conditions of stress among Met homozygous individuals. More work is needed to replicate these initial findings. However, the notion that a gene can influence vulnerability for rumination via different mechanisms has important implications for understanding the etiology of rumination.

Consistent with this idea, future work should also examine whether these genotypes influence sensitivity to both positive and negative environmental contexts (Ellis & Boyce, 2008). This model, which is routed in evolutionary-developmental biology, suggests that selection pressures favor adaptive phenotypic plasticity—the capacity for a genotype to flexibly influence behavior depending on environmental context (Boyce & Ellis, 2005). The 5-HTTLPR appears to fit this model (Belsky & Pluess, 2009). In the current study, Met/Met carriers and individuals with 4 risk alleles

reported the lowest levels of rumination in the absence of life stress. This may be evidence for differential susceptibility to context—the BDNF genotypes may increase vulnerability to rumination in stressful environments but lead to lowered rumination in low stress (or more supportive) environments. Future should measure directly positive and negative environmental contexts to test this intriguing possibility.

Finally, our results suggest that susceptibility accumulates across polymorphisms associated with rumination. Previous research has documented evidence of epistatic interactions between 5-HTTLPR and BDNF Val66Met polymorphisms predicting differences in response to adversity (L. R. Dougherty, Klein, Congdon, Canli, & Hayden, 2010) and mood challenges (Wells, Beevers, & McGeary, 2010). This is the first study, to our knowledge, that shows that the accumulation of risk alleles (i.e., S' and Met alleles) across these polymorphisms is associated with greater susceptibility for ruminative thinking in the context of adverse events. These findings require replication; however, they suggest that susceptibility to stress is not only moderated by epistatic interactions, but can accumulate across combinations of risk alleles from different genes. Future work should consider including a larger number of SNPs that might influence rumination in the aggregate genetic risk score (e.g., De Jager et al., 2009). Doing so may increase the power of genetic models to predict individual differences in rumination.

There are two important limitations to this study. First, the correlational research design prevents conclusions about causal relationships. We assume that adverse events are capable of causing increases in rumination among individuals with certain genetic

profiles. Creating adverse events in the laboratory and measuring rumination across genetic profiles would allow us to better understand these relationships. Longitudinal studies would allow us to better explore the temporal relations between stress and rumination among different genetic profiles across the life span. This is particularly important given ambiguity about the nature of BDNF Val66Met associations with rumination at different stages of development (Hilt et al., 2007). Hilt and colleagues (2007) have reported that an association between the Val/Val genotype and rumination in daughters of women with adult onset depression; but among their mothers, there was an association between the Met allele and rumination. Future longitudinal research, including measures of life stress, may help to better characterize these associations across stages of development.

Second, this research does not identify mediating mechanisms. It is likely that genetic effects on biological systems underlying stress response, affect, and cognition mediate genetic influences on the relationship between life stress and rumination. There is growing evidence that both 5-HTTLPR and BDNF polymorphisms are associated with individual differences in stress reactivity, neural function, and brain development (e.g., Alexander et al., 2009; Canli et al., 2005; Dougherty, Klein, Congdon, Canli, & Hayden, 2010; Hariri & Holmes, 2006; Lau et al., 2010; Montag, Reuter, Newport, Elger, & Weber, 2008). Future work integrating functional and structural neuroimaging, for example, may help to identify mechanisms that mediate observed genetic differences in

the relationship between life stress and rumination (Canli et al., 2006; Canli & Lesch, 2007).

One of these mechanisms may include cognitive control. There is emerging evidence that 5-HTTLPR variation moderates inhibition of emotional stimuli following a laboratory stressor (Markus & De Raedt, 2011). Deficits in cognitive control have been associated with rumination (e.g., Joormann, 2006; De Lissnyder, Koster, Derakshan, & De Raedt, 2010; Koster, De Lissnyder, Derakshan, & De Raedt, 2011). Together, these results suggest that cognitive control represents an important mediating mechanism for the relationship between genes and rumination in the context of life stress. Future work is required to further examine this hypothesis and explore these relationships in other candidate genes (e.g., BDNF).

Despite these limitations, this research provides important insight into who is most likely to ruminate and when rumination is most likely to occur. Individual differences in the 5-HTT and BDNF genes moderate the relationship between adverse events and rumination among healthy adults. Individuals with two S' alleles of the 5-HTTLPR polymorphism or two Met alleles of the BDNF Val66Met polymorphism reported higher levels of rumination as adverse events increased. This susceptibility to rumination accumulates across genes, as individuals with the greatest number of summed risk alleles (i.e., S' and Met alleles) demonstrated the strongest relationship between adverse events and rumination. More work is needed to examine the causal nature of these relationships and to uncover mediating mechanisms that link genetic variation to

broad cognitive thinking styles like rumination. This work requires an integrated approach across levels of analyses (i.e., genetic, neural, cognitive, environmental) that will facilitate more comprehensive models of how genes confer susceptibility to the negative effects of stress.

GENERAL DISCUSSION

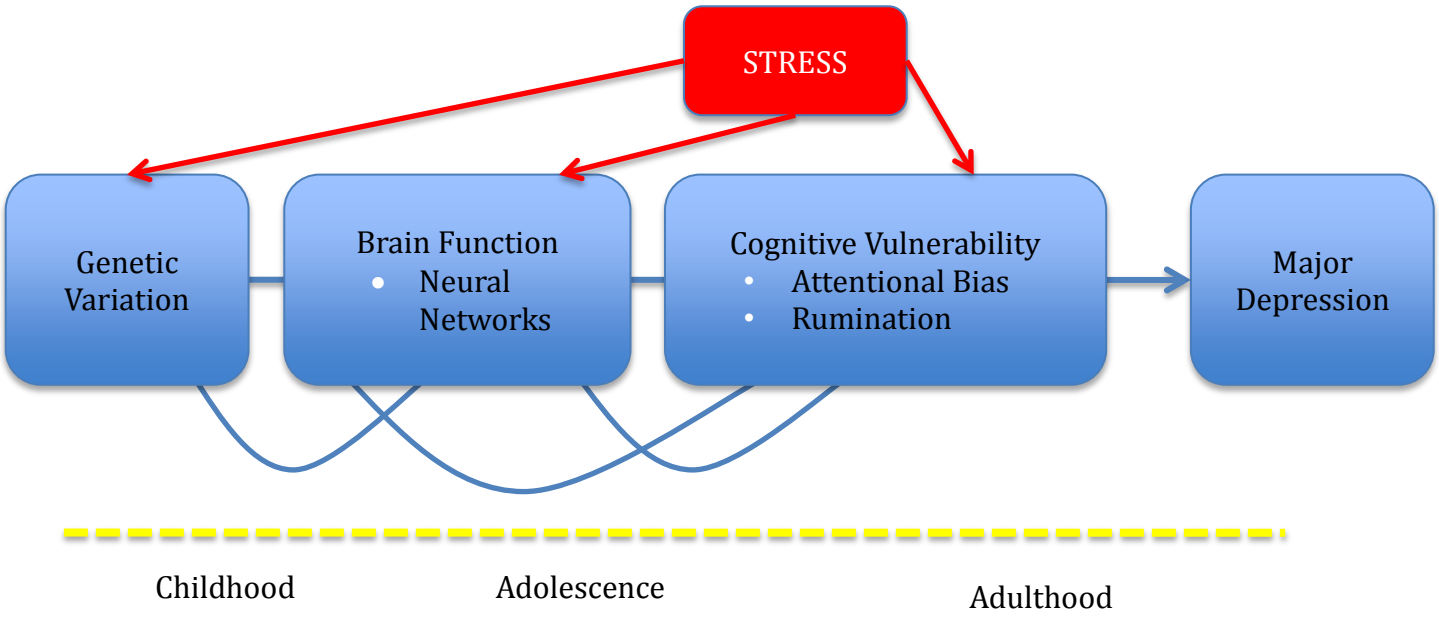
The three studies comprising this dissertation represent an effort to advance our understanding of elaborative processing biases associated with depression. The first study suggests that these biases maintain depression, in part, by facilitating the persistence of sad mood. Given this key role in depression maintenance, the second and third studies focused on elucidating biological factors that may give rise to elaborative processing biases. The second study suggests that depression risk may be associated with the development of neural networks underlying cognitive control. Indeed, adolescent women with a parental history of depression showed deficits within this network that may predispose them for elaborative processing biases and, thus, increase their risk for MDD. The third study indicates that genetic variation within two genes previously associated with susceptibility to stress (5-HTTLPR and BDNF Val66Met) is associated with elaborative processing bias in the context of life stress. Together, these studies provide evidence for mechanisms associated with the etiology of elaborative processing biases across neural and genetic levels of analysis.

This effort to characterize mechanisms associated with the etiology and maintenance of depression is necessary to build an integrated model of depression. Many of the specific future directions required to advance this model, with respect to the studies in this dissertation, have already been summarized in the individual discussion sections

above. Nevertheless, it is worth reflecting on two key themes that emerge when considering the future directions associated with all three studies.

The first theme involves careful integration of research across levels of analysis. Figure 13 represents a basic schematic of an integrated model of depression. This model suggests that genetic variation may predispose individuals, via effects at neural and then cognitive levels, for depression in the context of certain life events (e.g., stress). The three studies included in this dissertation help us understand some of the links between these levels of analysis. Future work must continue to explore these links, both in terms of how "downstream" factors (e.g., neural network function) influence "upstream" factors (e.g., elaborative processing biases), but also in terms of how "upstream" factors influence "downstream" factors over time (e.g., how chronic elaborative processing of negative stimuli might influence gene expression via epigenetic regulation). Careful consideration of the developmental context in which key mechanisms emerge and operate represents a vital component of this future research.

Figure 13. Schematic representation of integrated model of depression.



The second theme involves testing causal predictions. The three studies included in this dissertation highlight a number of intriguing relationships about the etiology of elaborative processing biases and their role in depression maintenance. However, none of these studies were designed to assess the causal nature of these relationships. Therefore, it remains unclear, for example, whether elaborative processing biases cause more persistent sad mood or, whether differences in neural networks underlying cognitive control cause elaborative processing biases and, in turn, increased risk for MDD in adolescent women.

Fortunately, many recently developed experimental procedures can be used to test these causal relationships. Cognitive bias modification (CBM) paradigms, for example, aim to manipulate (and subsequently ameliorate) elaborative processing biases and have been used to test causal hypotheses about the relationship between these biases and psychopathology (e.g., Mathews & Mackintosh, 2000; Wilson et al., 2006; Wells & Beevers, 2010). Moreover, trans-cranial magnetic stimulation (TMS) and real-time neural feedback using fMRI are two methods that are being used to manipulate neural network function and can easily be used to manipulate regions associated with cognitive control (e.g., Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2005; Hamilton et al., 2011). Using these tools to experimentally test causal predictions about the role of elaborative processing biases in depression represent critical next steps to build on the findings in this dissertation.

Major depressive disorder (MDD) is a common and debilitating disorder that is poised to become one of the world's leading public health problems. Improving efforts to prevent and treat MDD requires a clear understanding of the mechanisms underlying the etiology and maintenance of the disorder. This dissertation suggests that elaborative processing biases represent key mechanisms that maintain depression, in part, by facilitating the persistence of sad mood. Further, this dissertation elucidates biological factors that may give rise to elaborative processing biases. Future work is required to determine whether manipulating elaborative processing biases, or the biological mechanisms thought to underlie these biases, can help to prevent or treat MDD.

Nevertheless, these efforts promise to provide a clearer picture of how depression works that will ultimately help improve the prevention and treatment of major depression.

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