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Behavioral and Neural Mechanisms Underlying Cognitive Vulnerability Models of Depression

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Major depressive disorder significantly impacts the developmental trajectory of youth as well as adults, and cognitive vulnerability models of depression have contributed to our understanding of the onset, maintenance, and recurrence of depression. To date, the bulk of research has focused on three prominent theories: (a) Beck's cognitive model of depression, (b) hopelessness theory of depression, and (c) response styles theory. Although these etiological models have provided a wealth of information about how and why depression arises, less is known about the behavioral and neurobiological mechanisms that underlie these cognitive vulnerability factors. The article provides an overview of neural correlates for critical, but selective, cognitive vulnerability factors implicated in depression in youth and adults. Moreover, recommendations are provided for future research as it relates to etiology and treatment.

Keywords: depression, Beck's cognitive theory, hopelessness theory of depression, response styles theory, neurobiology, cognitive vulnerability

Major depressive disorder (MDD) is the leading cause of disability for individuals age five and older, and it is the second leading source of disease burden (Merikangas & Knight, 2009). The point prevalence of depression among adolescents is estimated between 3 and 8% (e.g., Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), and the lifetime prevalence is 14% among adolescents (Kessler & Walters, 1998) and 17% in adults (Kessler et al., 1997). In addition to the distress of depressive symptoms, depressive episodes are associated with a range of negative outcomes in adolescence (e.g., academic difficulties, impaired cognitive functioning, interpersonal discord, substance use) as

well as adulthood (e.g., lower income levels, greater marital conflict, higher incidence of substance abuse/dependence) (Avenevoli, Knight, Kessler, & Merikangas, 2008), and critically, approximately 40–70% of adolescents experience a recurrent episode in adulthood (Rutter, Kim-Cohen, & Maughan, 2006). In response to the alarming epidemiological data and the negative outcomes associated with MDD, cognitive theories of depression have sought to delineate the role that maladaptive cognitions and information processing biases play in shaping depressive symptoms and episodes (Ingram, Miranda, & Segal, 1992). Underlying cognitive vulnerability factors are thought to be relatively stable over time (Ingram et al., 1998), and critically, research indicates that cognitive processes, which are hypothesized to develop, in part, as a result of early life experiences, may play an important role in the onset, maintenance, and recurrence of depressive symptoms (Abela & Hankin, 2008).

To date, the preponderance of cognitive vulnerability research has centered on Beck's cognitive model of depression (BCM; Beck, 1967, 1983), hopelessness theory of depression (HTD; Abramson, Metalsky, & Alloy, 1989), and the response styles theory (RST; Nolen-Hoeksema, 1991). These prominent etiological theories provide an understanding of *how* cognitive vul-

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nerabilities confer vulnerability to depression, and each of these theories has received empirical support in children and adolescents (for review see Hankin et al., 2009; Lakdawalla, Hankin, & Mermelstein, 2007) and adults (Jormann, 2009). Overall, these models have provided a *conceptual roadmap* for predicting the onset, recurrence, and severity of depression; however, at present, there is a pressing need to understand the behavioral and neurobiological mechanisms that underlie core cognitive vulnerability factors. Identifying behavioral indicators and biomarkers may significantly improve our etiological understanding of depression, and importantly, may have important implications in the development of more efficacious, and perhaps efficient, interventions for this debilitating disorder.

In the current article, the goal is to review research examining BCM, HTD, and RST models of depression in youth. Over the last two decades there have been significant advancements with respect to our understanding of cognitive vulnerability and depression; however, presently the behavioral and neural mechanisms that underlie cognitive vulnerability in depression remain largely unknown, particularly among children and adolescents. Neurobiological research on cognitive vulnerability factors is an emerging field, and the current review is selective in including studies investigating central aspects of the BCM, HTD, and RST models rather than providing an exhaustive overview of neurobiological findings related to depression. The review is intended to be a first step summarizing this area of research, which to the authors' best knowledge, has not been attempted to date. In reviewing the literature, we note several challenges. First, the bulk of cognitive vulnerability research has relied on self-report measures. Although many of these measures have an increasing body of evidence supporting their reliability and validity, self-report assessments have a number of important limitations, including the fact that they rely on the participant's ability to access and report on processes underlying depression that may be at least in part outside of conscious awareness. Second, researchers have often used a number of methodological approaches (e.g., behavioral paradigms) to examine the same cognitive construct, and these tasks have implicated an array of brain regions, which has made it difficult to

integrate the specific behavioral and neurobiological processes to gain a more coherent view of cognitive vulnerability factors. Last, for many of the studies reviewed, it is unclear whether specific neurobiological abnormalities are causes, consequences, or mere correlates of cognitive vulnerability factors. To better address this key issue, multiwave prospective designs examining functional neural mechanisms, cognitive vulnerability, and MDD are needed.

Research examining neurobiological processes underlying cognitive vulnerability models of depression is a burgeoning area of research. Despite the inherent challenges, there is a need to integrate clinical psychology and neuroscience research, which may help identify behavioral indicators and biomarkers critically implicated in the onset and treatment of MDD. To this end, each section below provides a summary of key behavioral and neural findings postulated to underlie cognitive vulnerability for the three abovementioned theories. Further, given the relative paucity of research in youth, existing adult findings are presented as a framework for understanding and informing research on the neurobiological underpinnings of depression in youth.

Beck's Cognitive Model of Depression

The *cognitive model* of depression was originally formulated in the 1960s by Aaron T. Beck based on clinical observations and empirical findings (Beck, 1963, 1964, 1967; Beck, Rush, Shaw, & Emery, 1979; Beck & Alford, 2009). Broadly, the cognitive model highlights the role of depressogenic cognitive content and biased information processing in the etiology and maintenance of clinical depression. Importantly, the model also laid the foundation for the development of cognitive therapy (Beck et al., 1979), which has been shown to be effective at alleviating depressive symptoms, as well as reducing the risk of depression relapse (DeRu-beis, Webb, Tang & Beck, 2010).

The cognitive model refers to several overlapping and interacting cognitive constructs, including the *negative cognitive triad*, *negative automatic thoughts*, *cognitive errors*, *dysfunctional attitudes*, *schemas*, *core beliefs*, as well as maladaptive or biased attention, information processing and memory. Since its original formulation, a wealth of research has emerged

which has begun to shed light on the neurobiological underpinnings of the cognitive model. The bulk of studies investigating the neural correlates of Beck's cognitive model have focused on "lower" level components of the model, including biased attention, information processing, and memory (Disner, Beevers, Haigh, & Beck, 2011). These components likely have a reciprocal relationship with higher-order components, such as schemas and core beliefs. For example, the cognitive model posits that the activation of depressogenic schemas (e.g., via a stressful life event) drives negatively biased attention, preferential processing of schema-congruent information, and facilitated recall for such depressogenic information (Beck, 2008). Moreover, attentional, information processing and recall biases for schema-congruent material likely fuel and solidify depressogenic schemas. Given the scope of BCM and the challenges of examining the model as a whole, researchers have sought to examine distinct components of the theory as a way to better understand the mechanisms that underlie vulnerability to depression.

Research suggests that depressed individuals, relative to healthy controls, display biased attention toward negative emotional stimuli (e.g., sad images) and spend less time attending to positive emotional stimuli (e.g., pleasant images; Kellough, Beevers, Ellis, & Wells, 2008). Moreover, functional neuroimaging studies have reported increased amygdala activation in response to negative emotional stimuli in depressed individuals relative to healthy controls (Surguladze et al., 2005; Sheline et al., 2001; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Interestingly, Sheline et al. (2001) observed increased amygdala activation to fearful faces among depressed, relative to never-depressed, participants even when stimuli were presented *outside* of conscious awareness. In addition, studies have found that amygdala hyperarousal within depressed individuals persists even after the negative emotional stimuli are no longer present (Siegle et al., 2002; 2007). Taken together, these findings suggest that depressed individuals spend more time attending to depressogenic stimuli in their environment as well as "reacting" to negative stimuli outside of conscious awareness, a process that exacerbates negative affect and likely, maintains depressive

symptoms. Such attentional and information processing biases are central components of the cognitive model of depression, which likely fuel other higher-order components of the model (e.g., negative core beliefs about the self).

Interestingly, and also relevant to the cognitive model of depression, negative cognitions about the future have been linked to amygdala reactivity. Specifically, even the *expectation* of aversive stimuli elicits greater activation in sub-lenticular extended dorsal amygdala of depressed patients relative to controls (Abler, Erk, Herwig, & Walter, 2007). This finding may represent one of the neural underpinnings of pessimistic cognitions regarding the future described in the cognitive model of depression (e.g., in the negative cognitive triad). Indeed, and in contrast to earlier research on the "depressive realism" hypothesis (Alloy & Abramson, 1979), recent studies have found that depressed individuals exhibit particularly pessimistic expectations of future life events (see Strunk & Adler, 2009; Strunk, Lopez, & DeRu-beis, 2006), which is consistent with the cognitive model of depression.

Related findings on increased amygdala reactivity to negative emotional stimuli are studies reporting decreased activation in ventral striatal regions in response to positive stimuli in depression (e.g., Epstein et al., 2006; Surguladze et al., 2005). Similarly, studies using electroencephalography (EEG) have reported reduced feedback-related positivity (FRP)—a frontocentral waveform hypothesized to originate from dorsal anterior cingulate cortex (dACC) and striatal regions—in response to reward (Foti & Hajcak, 2009; Foti, Kotov, Klein, & Hajcak, 2011). The latter findings may reflect anhedonic processes and blunted responsivity to positive emotional stimuli, which are cardinal characteristics of depression described by BCM. In summary, neuroimaging research has provided support for the clinical observation that depressed individuals are not only more sensitive to negative stimuli (e.g., life stressors), but are also less responsive to positive stimuli (e.g., positive life events).

Hypoactivity in prefrontal cortex (PFC) regions, including the dorsolateral prefrontal (DLPFC), have also been linked to depressive symptoms (e.g., Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Mayberg et al., 1999; Siegle et al., 2007). Given their role in atten-

tional control (e.g., Bishop, Duncan, Brett & Lawrence, 2004), deficits in PFC regions may reflect the neural underpinnings of biased attention toward depressogenic stimuli in depression. That is, depressed individuals may struggle to avoid and disengage from negative emotional stimuli attributable, at least in part, to PFC deficits. In addition, PFC hypoactivity may help account for the relatively poor performance by depressed individuals in executive function tasks (Ottowitz, Dougherty, & Savage, 2002). As a result of deficits in PFC regions subserving executive control and emotion regulation, depressed individuals may have difficulties exerting top-down cognitive control over limbic emotional reactivity (Fales et al., 2008; Phillips, Drevets, Rauch, & Lane, 2003). Increased PFC functioning, as well as dampening of amygdala reactivity, may represent one of the mechanisms through which treatments for depression result in depressive symptom improvement. Although a variety of treatments for depression may ultimately affect both PFC and amygdala functioning, their proximal mechanisms of action may differ. For example, the cognitive skills emphasized in cognitive therapy may enhance patients' ability to exert inhibitory control over automatic negative emotional reactions. Whereas cognitive therapy may bolster prefrontal inhibitory control over automatic limbic emotional reactivity, antidepressants may more directly dampen limbic reactivity (rather than acting directly on prefrontal functioning; DeRubeis, Siegle, & Hollon, 2008; see Goldapple et al., 2004 for contrasting findings).

It should be noted that the above section focuses on Beck's *cognitive* model of depression. However, Beck also hypothesized *personality* predispositions to depression (Beck, 1983), including sociotropy and autonomy. These two constructs overlap with the personality characteristics of dependency and self-criticism described in detail throughout psychodynamic theory (see Blatt, 1974; Blatt & Zuroff, 1992). Although differences exist in conceptualizations, both the cognitive-behavioral and psychodynamic perspectives propose a personality predisposition focused on interpersonal (sociotropy or dependency) as well as achievement (autonomy or self-criticism) issues. Researchers have explored the extent to which these personality variables contribute to depressive symptoms and interact with domain-

congruent negative events (e.g., are sociotropic or dependent individuals especially vulnerable to depression following negative events within the interpersonal or achievement domains, respectively?; Abela, Webb, Wagner, Ho, & Adams, 2006). To our knowledge, research has not examined neural correlates of these personality predispositions. Nevertheless, given a growing body of promising research delineating the neural correlates of cognitive vulnerability to depression, research is examining the relationship between brain functioning and key personality predispositions may yield fruitful findings.

Hopelessness Theory of Depression

The hopelessness theory of depression (HTD; Abramson, Metalsky, & Alloy, 1989) posits that individuals with a tendency to attribute negative events to global and stable causes, anticipate negative consequences, and view the self as inherently flawed in response to stressors are more vulnerable to develop depression as compared with individuals who do not possess these depressogenic cognitive styles. For vulnerable individuals, the theory asserts that the interaction of negative cognitive styles and stress leads to the development of hopelessness, which is operationalized as (a) the expectation that negative events will occur and that positive events will not occur and (b) one is powerless to change this. In turn, hopelessness is believed to be a proximal sufficient vulnerability factor, and thus, once hopelessness develops, depression follows. To date, the HTD has received widespread support in children and adolescents (e.g., Hankin, Abramson, & Siler, 2001) as well as adults (e.g., Alloy, Abramson, Walshaw, & Neeren, 2006); however, the preponderance of research examining the HTD in youth has been conducted with self-report measures (for review see Abela & Hankin, 2008). Although these studies have significantly advanced our understanding of the applicability of the HTD in children and adolescents, the mechanisms that underlie hopelessness, and more generally, hopelessness depression remain unclear.

In earlier animal studies examining learned helplessness, a forerunner to the reformulated HTD, researchers identified promising neurobiological substrates that may underlie helplessness. For example, Lachman et al. (1992) posited that regulation of the NPY gene expression

may reduce vulnerability to develop learned helplessness. A number of other researchers noted that serotonergic pathway dysfunction, in particular deficits within the limbic-hypothalamic circuit, is associated with learned helplessness (e.g., Amat, Matus-Amat, Watkins, & Maier, 1998; Edwards, Kornich, Houtten, & Henn, 1992). Despite these promising findings, such seminal work has not been extended to HTD. Moreover, there remains a dearth of research examining the behavioral and neural mechanisms of HTD, particularly in youth.

More recent research has attempted to integrate the HTD (Abramson et al., 1989) and Davidson's (1994) approach-withdrawal model to incorporate cognitive and motivational components into a unified theory of depression. Whereas the HTD posits that negative cognitive styles lead to the development of depressive symptoms after stressful life events, Davidson's model examines underlying neural circuitry implicated in the approach motivation and the withdrawal systems. In particular, Davidson (1994) posits the left PFC is associated with approach motivation and the right PFC underpins withdrawal processes. Research has indicated that depressed individuals exhibit relatively reduced left frontal activation as compared to nondepressed individuals (for review see Davidson, Pizzagalli, & Nitschke, 2002). Importantly, left-sided frontal asymmetry has been shown to be a potential trait marker of MDD (Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990) as relative less left frontal asymmetry impairs the approach system and may, ultimately, contribute to subsequent MDD. In light of the conceptual overlap between approach motivation and hopelessness (i.e., hopelessness may lead to withdrawal symptoms), researchers have sought to determine whether these are shared or independent risk factors for depression. As a first step to examine the overlap between these etiological models, Haeffel and colleagues (2008) examined the integration of these theories using a 5-week prospective design with a sample of unselected university students. Results indicated that depressogenic cognitive styles interacted with stress to predict increases in hopelessness and subsequent decreases in goal-directed behavior. Critically, decreases in goal-directed behavior also predicted higher levels of depressive symptoms. Expanding on

these findings, Nusslock and colleagues (2011) sought to better examine the integration of these models by assessing frontal asymmetries in resting EEG activity. Forty university students were followed over the course of 3 years after completing self-report measures on depressogenic cognitive styles (i.e., hopelessness) and collecting a baseline EEG recordings. During the follow-up period, participants completed a diagnostic interview assessment every 4 months. Results indicated that at baseline, increased hopelessness was associated with decreased left frontal activity suggesting impairments in approach behavior. Further, although both hopelessness and relative left frontal asymmetry predicted the onset of future depressive episodes, the mechanisms represented a shared vulnerability as opposed to independent risk factors for MDD. As a whole, these findings are among the first to delineate the behavioral and neural mechanisms that underpin hopelessness and subsequent vulnerability to depression.

In our review, we located only two studies that have identified functional and structural correlates of HTD. Specifically, Zhong and colleagues (2011) completed an ambitious study that included MDD ($n = 29$), never depressed cognitively vulnerable (i.e., high levels of hopelessness on the Cognitive Style Questionnaire; CV $n = 26$), and healthy (HC; $n = 31$) adult participants. All participants received fMRI scans while completing an emotional faces matching paradigm (i.e., fearful or angry faces). Notably, in response to negative emotional faces MDD participants, compared with the CV individuals, showed greater right amygdala activation; however, relative to the HC participants, the CV and the MDD group exhibited greater activation in the amygdala and lower activation in the DLPFC. These findings suggest that self-reported hopelessness, even in the absence of MDD, is associated with decreased regulatory control and increased emotion reactivity. Expanding on these findings, Zhang and colleagues (2012) also compared MDD, CV, and HC groups using voxel-based morphometry to assess structural differences in the brain. Interestingly, relative to HC participants, CV individuals showed reduced gray matter volume in the precentral gyrus (BA 6; primary motor area). Critically, the findings also revealed that the CV and MDD group both had a significantly

smaller left precentral gyrus as compared to the HC group, and importantly, the volume of this area was negatively associated with a negative cognitive style (i.e., hopelessness). These findings are consistent with past research, which has found an association between the precentral gyrus and negative attributional bias, delineating a possible link between motor area dysfunction (i.e., tendency to withdraw and avoid) and negative cognitive styles (i.e., hopelessness) (Blackwood et al., 2000). As stated earlier, these pioneering studies have used innovative designs and yielded intriguing findings related to the behavioral and neurobiological mechanisms that may underlie HTD. Such research will improve our understanding of the etiology of MDD, and in time, may inform the development of more effective, and perhaps efficient, interventions aimed at alleviating and preventing depressive symptoms.

Response Styles Theory

Originally, the RST was conceptualized as a means of explaining the higher prevalence of depression in adult women as compared with men. Nolen-Hoeksema (1987) asserted that in response to negative affect, and in particular depressive symptoms, women were more inclined to ruminate whereas men were more likely to engage in distracting activities. In general, rumination involves focusing passively and repetitively on depressive symptoms, as well as the causes and consequences of such symptoms, which impedes one's capacity to proactively manage and/or address symptoms of depression. Despite the intention to enhance self-understanding, ultimately, rumination often exacerbates depressive symptomology (Abela, Aydin, & Auerbach, 2007). To date, the majority of research examining the RST has been conducted in adults (e.g., Nolen-Hoeksema & Morrow, 1991; Nolen-Hoeksema & Harrel, 2002); however, rumination is also a robust predictor of depressive symptoms in youth (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Although there is a vast body of RST research, there are relatively few studies investigating the behavioral and neural factors that may underlie ruminative processes, especially among adolescents.

Exploration of RST Among Adolescents

In a 2009 meta-analysis, Rood and colleagues reported that in both cross-sectional and prospective studies of nonclinical adolescent samples, rumination was significantly associated with depressive symptoms, with moderate to high mean effect sizes for cross-sectional studies and moderate mean effect sizes in longitudinal investigations. Despite robust findings using self-report instruments, relatively little behavioral and neurobiological research has examined rumination in adolescent populations. In a sample of healthy adolescents, Wilkinson and Goodyer (2006) did not find an association between trait rumination and performance in an attention-switching behavioral task hypothesized to underlie rumination. More recently, Rood and colleagues (2012) used a paradigm designed to induce rumination by instructing healthy adolescents to think about thoughts and feelings regarding a recent stressful event (e.g., fight and death of love one). Subsequently, participants were then given specific instructions about "how" to think about the past event using one of four conditions: rumination, distancing, positive reappraisal, and acceptance. Results within the rumination condition were mixed as participants initially reported increased negative affect; however, in the last 2 blocks of the experimental design there was a steep reduction in negative affect. In contrast to these studies, Park, Goodyer, and Teasdale (2004) used a paradigm in which depressed and nondepressed youth were instructed to focus on prompts designed to elicit thoughts about the self (rumination) or neutral external objects (distraction). Critically, induced rumination increased depressive symptom scores for both healthy and depressed adolescents, and moreover, compared with healthy individuals, depressed adolescents recalled autobiographical memories that were more negative and overgeneral than those recalled after distraction was induced. As a whole, these findings are promising, but further research is needed investigating putative behavioral and neural mechanisms underlying the RST among children and adolescents. Thus, the proceeding sections will examine such mechanisms among healthy, dysphoric, and depressed adults.

RST Research in Adult Samples Using Behavioral Paradigms

In comparison with youth, more experimental research examining the RST has been conducted with adults. For example, in a sample of undergraduates, [Bernblum and Mor \(2010\)](#) found that individuals reporting relatively elevated levels of brooding, a subtype of rumination, were more likely to focus on negative emotional (e.g., depression and emptiness) as opposed to neutral words. Research has also examined the impact of mood- or rumination-induced paradigms on task performance. Specifically, dysphoric undergraduates were instructed to spend 8 minutes thinking about emotion-, symptom-, and self-focused prompts (rumination induction) or neutral external objects and situations (distraction induction) before completing different tasks (e.g., reading a difficult passage, watching a lecture video, proofreading text). Relative to the distraction condition, participants randomized to the rumination induction completed the tasks more slowly, reported more difficulty concentrating, and performed more poorly ([Lyubomirsky, Kasri, & Zehm, 2003](#)). Similarly, in a study comparing healthy and dysphoric participants after a rumination induction, dysphoric individuals recalled more negatively biased autobiographical memories in both free and prompted recall ([Lyubomirsky, Caldwell, & Nolen-Hoeksema, 1998](#)). Further, when depressed and healthy individuals were randomized to a distraction or rumination induction and then instructed to list as many positive and negative events that they believe could occur over the next 10 years, depressed individuals in the rumination-versus the distraction-induced group listed a greater number of future negative events ([Lavender & Watkins, 2004](#)). Taken together, these findings strongly suggest that ruminative tendencies impair cognitive processing and behavioral performance. Moreover, it appears that rumination is a bottom-up process triggered via induction, which then compromises attention and performance.

Adult RST Neural Findings: Mood, Rumination, and Stress Induction Tasks

To examine neural mechanisms that underlie rumination, researchers have used a number of different approaches. For example, [Lo and colleagues \(2012\)](#) randomized subjects to either a

sad or neutral mood induction, and then an attention-switching task (i.e., neutral vs. affective stimuli) was completed while EEG data were collected. Results indicated that individuals with high trait rumination in the sad mood induction used more neuronal resources to redirect attention away from affective stimuli as measured by the late positive potential (time window: 480–820 ms) collected over the frontocentral midline on the scalp (electrodes: Fz, Cz, and Pz). Similarly, [Diener et al. \(2009\)](#) found that in an EEG study comparing healthy and depressed individuals, trait rumination was positively correlated with the magnitude of frontal postimperative negative variation (PINV), and moreover, they suggest that such neuronal allocation may contribute to biased information processing underlying rumination among depressed participants. Using fMRI with mood induction paradigms, researchers have found that medial prefrontal regions (e.g., amygdala, dACC, and rostral ACC) may be critically implicated in negative self-referential processing, and such dysfunction may potentiate ruminative processes that exacerbate negative affect (e.g., [Cooney et al., 2010](#); [Farb, Anderson, Bloch, & Segal, 2011](#); [Kross et al., 2009](#); [Ray et al., 2005](#)). Taken together, EEG and fMRI findings strongly suggest that neurobiological mechanisms associated with autonomic functioning, emotion, and attentional biases regarding the self and internal states may underpin ruminative processes.

Adult Neural Findings: Experimental Paradigms Without Mood or Rumination Induction

Research has also examined the relationship between rumination and neural activation without the use of mood or rumination induction, and importantly, these studies have also implicated medial prefrontal regions (e.g., [Berman et al., 2011](#)). For example, high, but not low, brooders demonstrated difficulty disengaging from negative material as indicated by an inability to inhibit a response to sad faces in an emotional go/no-go task. Further, higher levels of brooding were correlated with increased activity in the right DLPFC when participants were asked to disengage from negative information, suggesting that for brooders, effective emotion regulation requires increased recruit-

ment of areas implicated in cognitive control (Vanderhasselt, Kühn, & De Raedt, 2011). Rumination is also associated with differential patterns of neurobiological activation in response to affective stimuli in adults with remitted MDD. Specifically, rumination scores among these individuals were positively correlated with activity in the (a) right insula and midcingulate in response to the presentation of sad faces and (b) bilateral inferior frontal gyrus in response to fearful faces. Interestingly, for healthy adults, rumination scores were unrelated to neurobiological activation (Thomas et al., 2011). As a whole, these findings suggest that the tendency to ruminate is associated with increased emotional reactivity and decreased cognitive control, which reflect dysfunction in medial prefrontal regions.

RST: Resting and Functional Connectivity

More recent pioneering research has also begun to delineate the relationship between trait rumination and both resting and functional connectivity, and preliminary findings have also highlighted the role of prefrontal medial regions. In a sample of adult depressed outpatients, greater rumination was associated with a decreased alpha signal in the bilateral PFC during resting EEG (Putnam & McSweeney, 2008). Additionally, in depressed adults, functional connectivity between the subgenual cingulate, an area critically implicated in regulation of emotional states, and the posterior cingulate was correlated with rumination scores, and default-network connectivity with the subgenual cingulate was positively correlated with brooding (Berman, Peltier, Nee, Kross, Deldin, & Jonides, 2011). As compared with healthy adults, depressed participants also display increased functional connectivity in the anterior medial cortical regions (e.g., mPFC, ACC), and within the depressed group, increased connectivity was positively correlated with rumination scores (Zhu et al., 2012). Also, among depressed adults, greater depressive rumination and lower reflection scores were each associated with greater default mode network dominance over task-positive network dominance (Hamilton et al., 2011). While research has not examined these findings in youth, Cullen and colleagues (2009) found that depressed adolescents show decreased functional connectivity in a

subgenual ACC neural network (e.g., subgenual ACC, right mPFC), suggesting that findings in adults may, potentially, be extended to younger individuals.

Future Directions

Depression is a debilitating illness with profound developmental consequences. Research examining cognitive vulnerability has improved our understanding of the processes that trigger and maintain depressive symptoms. More recent research has also begun to bridge the divide between clinical psychology and neuroscience, and such an approach is consistent with the National Institute of Mental Health Strategic Plan, which emphasizes the critical need to investigate brain–behavior processes to provide for a more in-depth and comprehensive understanding of mental disorders. Along these lines, we believe there are three areas of potential growth that would strengthen an already broad and impressive body of research.

First, as the review above highlighted, the majority of studies examining behavioral and neural correlates of cognitive vulnerability factors have focused on adult samples. In light of significant developmental differences between youth and adults, greater attention is warranted to understand the behavioral and neural underpinnings of cognitive vulnerability in children and adolescents. Although comparatively less research has been conducted in youth, cognitive vulnerability research in adults has implicated key deficits in the PFC (e.g., Kross et al., 2009) and amygdala (e.g., Zhong et al., 2011). Moreover, it will be critical to examine whether such deficits contribute to the surge in depression rates and emergence of gender differences during the adolescence. Critical issues to consider will include the intersection of pubertal and brain development. Notably, the trajectory of brain development differs as a function of gender with girls' total brain volume peaking at 10.5 years versus 14.5 years for boys (Lenroot et al., 2007; Lenroot & Giedd, 2010; Sowell et al., 2007). Further, with respect to different patterns of brain development, boys exhibit greater cortical growth within the PFC and anterior cingulate cortex compared to girls, whereas girls display greater frontal gray matter (Gogtay et al., 2004). In light of key develop-

mental differences, adolescence may be an ideal time to examine how behavioral and neurobiological mechanisms associated with cognitive vulnerability contribute to the emergence of gender differences.

Second, theories regarding cognitive vulnerability to depression informed the initial development of, and refinements to, cognitive therapy. Treatment outcome research has found that cognitive therapy alleviates depressive symptoms in both youth and adults (e.g., DeRubeis, Siegle, & Hollon, 2008; Klein, Jacobs, & Reinecke, 2007; Reinecke, Ryan, & DuBois, 1998). However, the mechanisms through which cognitive therapy results in depressive symptom improvement are poorly understood. In other words, we know relatively little regarding how and why depressed patients improve in CBT and other treatments, and what role the above-mentioned cognitive vulnerability factors may play in mediating symptom change across various treatment modalities. At the same time, more recent research examining the pathophysiology of depression has implicated neural systems that may play an important role in predicting treatment response (e.g., Forbes et al., 2010; Pizzagalli, 2011; Siegle, Carter, & Thase, 2006). In light of these promising findings, research is warranted to better examine whether the behavioral and neurobiological deficits that underpin cognitive vulnerability play a role in mediating symptom improvement, as well as resistance to relapse.

Last, an exciting prospect is the development of targeted interventions informed by behavioral and neural findings. For example, a greater understanding of the neural and behavioral underpinnings of depression may inform the development of sophisticated, targeted interventions that increase cognitive control and/or reduce depressogenic attentional biases (e.g., Amir et al., 2009; Joormann, Hertel, LeMoult, & Gotlib, 2009). Interventions such as computerized cognitive bias modification (Macleod, 2012) or transcranial magnetic stimulation (Loo & Mitchell, 2005) may selectively target PFC regions (e.g., DLPFC) underlying depression, ultimately resulting in depressive symptom improvement, while perhaps at the same time being more cost-effective and less time-intensive than existing treatments.

Treatment of the Future

Given advancements in our understanding of the neural correlates underpinning cognitive vulnerability and major depressive disorder, it is exciting to contemplate what the future may hold for the treatment of depression. Specifically, in building a bridge between clinical psychology and neuroscience, a potential next step is learning to integrate these tools into every day clinical practice with regards to predicting and understanding the mechanisms underlying treatment response. Although there remains a considerable amount of knowledge and cost-effective technological advances before this is feasible, the case example below is offered as a means of underscoring the potential scope of translational research.

Case Example

T. R. is a 16-year-old female adolescent who has been experiencing clinically significant depressive symptoms for approximately 3.5 months. T. R.'s depressive episode had been marked by prominent anhedonic symptoms, as she has not been experiencing interest or pleasure in typically enjoyed activities including playing soccer, spending time with friends, and reading. During T. R.'s initial evaluation, she completed a diagnostic interview, and additionally, EEG data were collected regarding (a) resting state (i.e., task-free) and (b) event-related potentials (ERPs) while completing a probabilistic reward task probing anhedonic processes. Results from the initial assessment indicated that T.R. satisfied criteria for major depressive disorder, exhibited reduced left frontal activity (i.e., a marker of depression; see Thibodeau, Jorgensen, & Kim, 2006), and displayed greater feedback-related negativity (i.e., an ERP associated with dACC dysfunction). Moreover, the resting state data also indicated low subgenual ACC activity, suggesting that T.R. may be a strong candidate for CBT as compared with a pharmacological intervention (see Siegle et al., 2006). After 16 weeks of CBT, T. R. was administered the same battery of assessments (i.e., clinical interview and EEG). Results indicated that in addition to significant depressive symptom attenuation, the ERP data suggested improvement in feedback-related negativity and dACC functioning; sug-

gesting a lower likelihood of relapse. Critically, T.R. reported significant improvement in her hedonic capacity as she had begun engaging in, and deriving pleasure from, activities previously enjoyed.

As a whole, the clinical and neural assessment guided the case conceptualization (i.e., prominent anhedonic symptoms and reduced left frontal activity) and treatment selection (i.e., CBT vs. pharmacological regimen). While fictional, the case example is meant to demonstrate the promise of a day when such integration is possible and relatively cost-effective. Moreover, by bridging the divide between clinical psychology and neuroscience, it may ultimately improve the treatment course for patients in need by identifying the specific treatment as a function of individual biomarkers.

Summary

In sum, a substantial body of research has highlighted the role of cognitive theories of depression in the etiology of MDD. Moving forward, the integration of clinical psychology and neuroscience research through the use of sophisticated behavioral and neurobiological assessments will likely improve our understanding of the onset and course of MDD. Ultimately, such research may have important implications for the development and dissemination of more effective and efficient prevention and treatment approaches for this debilitating disorder.

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