Understanding Familial Risk for Depression: A 25-Year Perspective

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Abstract
Major depressive disorder (MDD) is among the most prevalent, debilitating, and costly of all illnesses worldwide. Investigators have made considerable progress in elucidating psychological and biological correlates of MDD; however, far less is known about factors that are implicated in risk for depression. Given the high risk for MDD associated with a family history of depression, investigators have worked to understand both the effects of parental depression on offspring and the mechanisms that might underlie familial risk for MDD. In this article, we describe the evolution of investigators' understanding of the psychobiological functioning of children of depressed parents, and we present recent findings concerning cognitive and neural aspects of risk for MDD using our high-risk sample as a context and foundation for this discussion. We integrate these data in a conceptualization of mechanisms underlying risk for depression, focusing on the constructs of emotion dysregulation and stress reactivity. Recognizing the 25-year anniversary of the Association for Psychological Science, we place this presentation in the context of the past 25 years of research on depression. We conclude by discussing the significance of emotion dysregulation and stress reactivity for studying risk for depression, for developing approaches to prevent MDD, and for moving theory and research in this field forward.

Keywords
depression, cognition, brain activation, risk, emotion regulation

Major depressive disorder (MDD) is among the most prevalent and debilitating of all psychiatric illnesses, with enormous personal, familial, and societal costs. Almost 20% of the U.S. population, or more than 30 million adults, will experience a clinically significant episode of depression at some point in their lives (Kessler & Wang, 2009). In fact, the prevalence of MDD is so high that the World Health Organization (2004) has projected that depression will be the single most burdensome disease in the world in terms of disability-adjusted years in the 21st century. This adverse impact of depression is due, in part, to the fact that MDD is frequently comorbid both with other mental disorders and with physical difficulties, cardiac problems, and smoking (e.g., Freedland & Carney, 2009). Depression also adversely affects the quality of interpersonal relationships and, in particular, relationships with spouses and children. Not only is the divorce rate higher among depressed than among nondepressed individuals (e.g., Wade & Cairney, 2000) but investigators have demonstrated that young children of depressed parents are at elevated risk for developing a depressive episode themselves (Joormann, Eugène, & Gotlib, 2008). Indeed, in general, first episodes of depression are occurring at increasingly younger ages (Kessler et al., 2003), and youths with early onset depression have pervasive dysfunction throughout their lives (Hill, Pickles, Rollinson, Davies, & Byatt, 2004). Finally, although there are effective treatments for depression, approximately 80% of depressed individuals will nevertheless experience recurrent episodes of MDD (Boland & Keller, 2009).

Given these alarming figures and trends, it is critical that investigators identify the factors and mechanisms that contribute to elevated risk for depression so that they can develop the most effective approaches to the treatment of this disorder and, perhaps more important, to the prevention of the first episode of MDD. During the past 25 years, there has been a growing literature...
focusing on risk for depression. Most of these studies involve assessing the offspring of depressed parents and documenting the magnitude of risk for depression in the children. Indeed, we know from this literature that the strongest and most reliable risk factor for the development of MDD is a family history of the disorder; having a parent with MDD has been found to be associated with a three- to five-fold increase in the risk for developing a depressive episode (Williamson, Birmaher, Axelson, Ryan, & Dahl, 2004). We also know that even before they develop an episode of depression, children are adversely affected by their mothers’ depression: Negative effects of maternal depression have been reported in children ranging in age from infancy through adolescence (see Hammen, 2009, for a review). However, far fewer investigations have been conducted in which specific mechanisms that are associated with this risk and that might play a role in the onset of MDD have been examined. Moreover, even in studies in which investigators have examined mechanisms that might underlie risk for depression, the researchers often included in their samples individuals who were currently experiencing depressive symptoms or who had recovered from depression, making it difficult to distinguish factors that increase risk for MDD from symptoms of depression or from consequences of having experienced the disorder. Finally, most researchers have focused on a single domain of risk for depression, such as negative cognitive biases, poor coping skills, or anomalous neural function or structure. Although the results of these studies are informative, it is becoming increasingly clear that the strongest advances in the understanding of risk for depression will come from investigators who integrate psychological and biological assessments in the study of the processes and mechanisms that are involved in the etiology of this disorder; such studies will contribute to the development of a broader and more comprehensive model of risk for MDD.

In the present article, we address these issues by describing and presenting results from a project in which we examined the psychobiological functioning of young girls who were at elevated risk for depression by virtue of having a mother who had experienced recurrent episodes of depression during the daughter's lifetime. We use these data, as well as results of other relevant studies when appropriate, as a foundation for a discussion of investigators' current knowledge concerning the nature of familial risk for the development of MDD. We draw on this body of research to present an initial integrative conceptualization aimed at (a) increasing the understanding of mechanisms that underlie the intergenerational transmission of risk for MDD and (b) helping to provide direction for the field in moving forward. Recognizing the 25-year anniversary of the Association for Psychological Science, we place this research in the context of the past 25 years of research on depression. Findings from this literature converge to underscore the importance of conceptualizing risk for depression in terms of emotion dysregulation and stress reactivity. In this context, therefore, we conclude by discussing the significance of these two constructs for studying risk for depression and for the development of approaches to the prevention of this disorder.

### The Stanford High-Risk Study

As we noted earlier, during the past several years, we have been assessing 10- to 14-year-old daughters of mothers who have experienced recurrent episodes of depression during the daughter's lifetime (high-risk girls) as well as an age-matched sample of daughters of mothers with no history of diagnosable psychopathology (low-risk girls) on a diverse range of psychological and biological characteristics. Given their family history of MDD, we estimated that at least half of the high-risk girls would go on to develop an episode of depression at some point during adolescence. We excluded from participation any daughter who had already experienced an *DSM* Axis I disorder. This criterion ensured that, at baseline, we were not assessing consequences of having experienced a depressive episode and that by following these girls, we were able to assess predictors of an initial onset of MDD.

In deciding which domains to assess in attempting to predict the onset of depression, we turned to findings of researchers who distinguished depressed from nondepressed adults most consistently on specific psychological and biological variables. We developed a protocol that would allow us to assess these two domains of functioning in the high-risk girls and to use our data to predict the subsequent onset of a first episode of MDD. Frankly, given that neither the low- nor the high-risk girls had experienced a significant episode of psychopathology and, not surprisingly, did not even have elevated levels of depressive symptoms, we did not expect the two groups of daughters to differ on measures of constructs in these domains at baseline; indeed, we assumed that we would have to wait to observe group differences until we collected follow-up data and used our baseline measures to predict onset of MDD within the high-risk group. We were wrong: Despite being asymptomatic and never having experienced an episode of MDD, the low- and high-risk girls differed at baseline on almost every construct we assessed. Moreover, as we hypothesized, we are beginning to find that initial functioning on most of these constructs also predicts the subsequent onset of an episode of depression. In the following sections, we describe the results of this project, and of other studies, in the context of investigators' current knowledge of psychobiological dysfunction in depression. We begin by
describing the cognitive functioning of depressed persons and of individuals at risk for developing depression, and then we turn to neural anomalies in MDD.

Cognitive Factors and Risk for Depression

One of the major approaches to understanding the etiology of MDD, the functioning of depressed individuals, and the vulnerability to this disorder involves the study of cognitive functioning in depression. Almost 50 years ago, Aaron Beck (1967) formulated the first cognitive theory of depression, positing that individuals who are vulnerable to developing depression have schemas, or expectancies, derived from early experiences that lead them to view their environment in more negative (or less positive) ways than do their nonvulnerable peers. For example, vulnerable and depressed individuals are posited to attend selectively to negative stimuli, filter out positive stimuli, perceive negative or neutral information as being more negative than is actually the case, and preferentially recall negative over positive information (see Kircanski, Joormann, & Gotlib, 2012, for a recent review). Beck postulated further that when individuals encounter a negative or stressful life event, these biases in cognitive processing are activated and give rise to negative automatic thoughts about the self, the world, and the future (the cognitive triad) as well as to negative mood. As in other diathesis-stress models, negative schemas are posited to be latent until individuals experience a stressful life event. Early interactions with their primary caregivers can lead children to develop “latent” dysfunctional schemas and negative cognitive styles that are activated by stressful events, by negative mood states, or by situations similar to those under which the schemas were acquired (e.g., being rejected by a significant other). Depressive affect activates the negative schemas and reinforces their activity. Thus, early life experiences are posited to play an important role in the formation of both adaptive and maladaptive cognitive schemas and, thereby, to increase depressive vulnerability.

In the following sections, we present an overview of empirical findings concerning cognitive aspects of depression in currently depressed and high-risk samples. We begin by discussing earlier research in which self-report measures were primarily used, and then we present the more recent use of tasks derived in experimental cognitive psychology.

Examining cognition in depression: From self-report to experimental tasks

During the past 25 years, researchers have worked diligently to assess cognitive aspects of depression, documenting the operation of depressive schemas and cognitive styles, negative biases in the processing of information, and difficulties in cognitive control in individuals diagnosed with MDD (for reviews, see Joormann, 2009; Kircanski et al., 2012). Because early studies in this area relied in large part on self-report measures of cognition, such as the Dysfunctional Attitudes Scale (A. Weissman & Beck, 1978), investigators’ knowledge of the cognitive functioning of a depressed person 25 years ago was based almost exclusively on self-report data. Investigators using these measures documented that, compared with their nondepressed peers, depressed adults reported more maladaptive schemas, higher levels of dysfunctional attitudes, hopelessness, and rumination and more negative attributional styles and automatic thoughts (see Alloy, Abramson, & Francis, 1999; Barnett & Gotlib, 1988).

Unfortunately, self-report measures do not permit the assessment of automatic cognitive processes in depression, including schema-driven functioning that is central to Beck’s (1967) theory. Moreover, self-report measures are particularly problematic in assessing cognitive functioning in children, who often have difficulty understanding the items and reporting on their internal states. Because of these concerns, investigators began to develop experimental tasks to examine cognitive processing in depression, most of which use reaction time as a dependent measure. Researchers have now used these experimental tasks to assess anomalies in perception, attention, interpretation, and memory as depressed individuals process and recall emotional material (for recent reviews, see Folland-Ross & Gotlib, 2012; Kircanski et al., 2012). As we describe briefly in the following paragraphs, findings of these studies indicate relatively consistently that depressed adults and children are characterized by negative biases in the processing of valenced stimuli and by deficits in cognitive control.

For example, in 1984, Gotlib and McCann modified the Stroop task and demonstrated that dysphoric adults exhibited difficulties ignoring or inhibiting the processing of negatively valenced stimuli. In more recent research, investigators have extended these findings, most often using the dot-probe task, which is used to assess the attentional capture of positive and negative stimuli. In this task, a pair of stimuli (words or faces) is presented simultaneously, either one above the other or one beside the other: One stimulus is neutral, and the other is emotional. Participants are asked to respond to a probe that replaces the neutral or the emotional stimulus (in its location). Allocation of attention to the spatial position of the stimuli is determined from response latencies to the probes. Results of these studies indicate that depressed adults are impaired in their ability to disengage from negatively valenced material (e.g., Gotlib et al., 2004; Sanchez, Vazquez, Marker, Lemoult, & Joormann, 2015).
Building on early self-report findings (e.g., Butler & Mathews, 1983), investigators have also used experimental tasks to assess biases in depressed individuals’ interpretation of information. For example, by using sentence completion tasks, researchers have found that depressed adults lack the positive bias exhibited by their nondepressed counterparts (Hindash & Amir, 2012; Moser, Huppert, Foa, & Simons, 2012; but see also Sears, Suzie Bisson, & Neilson, 2011). Perhaps most consistently, depressed adults have been found to demonstrate preferential recall of negative over positive stimuli and information, the opposite pattern of that typically observed in nondepressed persons (e.g., Koster, De Raedt, Leyman, & De Lissnyder, 2010; Ridout, Noreen, & Johal, 2009). Moreover, depressed adults also recall more generic, or overgeneral, memories than do their nondepressed counterparts, even when instructed to recall specific details (Williams et al., 2007). These findings are important counterparts, even when instructed to recall specific details (Williams et al., 2007). These findings are important in elucidating the nature of cognitive functioning in depression. Nevertheless, we cannot determine from results of these cross-sectional studies whether maladaptive cognitive processing is a symptom of MDD or, alternatively, plays a role in the onset of depression. To address this issue, investigators have examined cognitive functioning in samples of individuals at risk for developing MDD, sometimes prior to the onset of the first depressive episode. Because offspring of depressed parents are at high risk for developing depression themselves (e.g., Hammen, 2009), researchers interested in the functional role of cognitive difficulties in risk for the initial onset of MDD have assessed these constructs in this population. Twenty-five years ago, much of the knowledge about offspring of depressed parents came from high-risk studies of children of schizophrenic parents that included children of depressed parents as psychiatric controls (e.g., the Stony Brook High Risk Project; Neale & Weintraub, 1975). Of course, the constructs assessed in those studies were more relevant to schizophrenia than they were to depression.

In one of the first studies to focus explicitly on children of depressed parents, Jaenicke et al. (1987) administered questionnaires to assess attributional style in 8- to 16-year-old children of healthy mothers and of mothers diagnosed with MDD, bipolar disorder, or a physical medical illness. Children of mothers with MDD or bipolar disorder had significantly more depressotypic attributional styles than did children of medically ill or healthy mothers. Because many of the children in this study were symptomatic and had experienced past episodes of depression, however, it is possible that this negative attributional style was a consequence of depression. In a later study, children of unipolar depressed mothers were found to have more negative attributional styles than did children of never-depressed mothers, even after controlling statistically for children’s current levels of depressive symptoms (Garber & Robinson, 1997). Whereas Morris, Ciesla, and Garber (2008) found that cognitive style (i.e., a composite of attributional style, self-worth, and hopelessness) in high-risk children predicted an increase in depressive symptoms over time, Hammen et al. (1988) reported that attributional style alone did not predict symptoms of depression in offspring of depressed mothers. Dysfunctional attitudes have also been found to interact with daily hassles in children at familial risk for depression to predict an increase in depressive symptoms (Abela & Skitch, 2007; see Dunbar et al., 2013, for a similar finding).

Finally, Abela, Hankin, Sheshko, Fishman, and Stolow (2012) examined rumination in high-risk samples and found that rumination in offspring of depressed parents predicted a subsequent increase in depressive symptoms in response to negative events. This finding was stronger in girls than in boys and was not moderated by age. In a related study, brooding rumination was elevated in high-risk children, and this form of maladaptive rumination predicted onsets of new depressive episodes in a 20-month follow-up, even after controlling for initial depressive symptoms (Gibb, Grassia, Stone, Uhrlass, & McGearry, 2012). Moreover, high-risk children who ruminate have been found to be more likely to report increases in negative affect in response to greater negative affect in their mothers than are nonruminating high-risk children (Flancbaum et al., 2011). Neither gender nor mothers’ current clinical status moderated this effect.

Because attributional style is typically assessed with self-report questionnaires, this construct has been difficult to study in very young children. To address this issue, Murray, Woolgar, Cooper, and Hipwell (2001)
exposed 5-year-old children whose mothers had been depressed at least once since their birth to a mildly stressful situation (the threat of losing in a card game). These authors found that, compared with children whose mothers had never been depressed, children of mothers who had been depressed were more likely to express hopelessness and pessimism when losing a card deal. Thus, children as young as 5 years of age who have been exposed to maternal depression exhibit signs of a proposed cognitive vulnerability to depression.

**Findings from experimental tasks in high-risk samples**

More recently, investigators have utilized experimental designs to examine cognitive processes in high-risk children. For example, in emotion perception and categorization tasks, researchers have asked children to identify facial expressions of emotion using low-intensity or ambiguous stimuli. In one of the first such studies in high-risk children, Mannie, Bristow, Harmer, and Cowen (2007) found no evidence of a negative bias in young participants with a depressed biological parent. The authors did, however, find general impairments in emotion categorization in these individuals. We replicated this latter finding in our sample of daughters of depressed mothers using a morphed faces task, in which participants see a sequence of facial expressions with increasing intensity and have to press a key as soon as they can identify the emotional expression (Joormann, Gilbert, & Gotlib, 2010). Following a negative mood induction, the high-risk girls, compared with their low-risk peers, required greater intensity to accurately identify sad facial expressions and made significantly more errors identifying angry expressions. Collectively, these studies suggest that, even before the onset of a depressive episode, children at risk for depression are characterized by impaired emotion perception.

Using an emotion-faces dot-probe task, we also examined whether high-risk girls show evidence of the negative attentional biases that have been found to characterize depressed adults (Joormann, Talbot, & Gotlib, 2007). Following a negative mood induction, the high-risk girls, compared with their low-risk peers, required greater intensity to accurately identify sad facial expressions and made significantly more errors identifying angry expressions. Collectively, these studies suggest that, even before the onset of a depressive episode, children at risk for depression are characterized by impaired emotion perception.

Finally, several researchers have examined memory biases in high-risk children. In an early study in which valenced stimuli were used, Jaenicke et al. (1987) found that children of unipolar depressed mothers endorsed and recalled fewer positive self-descriptive adjectives than did children of control mothers. In an investigation in which a recall task was administered following a negative mood induction to 8- to 12-year-old children, Taylor and Ingram (1999) found that children whose mothers met diagnostic criteria for major depression or dysthymia at the time of the study recalled significantly more negative than neutral words; in contrast, control children did not exhibit this bias. It is important to note, however, that because these investigators did not assess children's prior history of depression, this recall bias could be a function of current symptomatology. More recently, young women at familial risk for depression have been found to show impaired recall and recognition on the Rey Auditory Verbal Learning Test (Mannie, Barnes, Bristow, Harmer, & Cowen, 2009). In our laboratory, high-risk girls had higher endorsement and better recall of negative words on a self-referent encoding task than did low-risk girls, and they lacked the positivity bias that was exhibited by the low-risk girls (Joormann et al., 2007). Finally, adolescent offspring of depressed parents have been found to
research in this area was limited by crude measurement techniques, small sample sizes, and diagnostic heterogeneity, often including mixed samples of unipolar and bipolar depressed patients.

During the past 25 years, researchers have made significant methodological advances in noninvasive neuroimaging technologies, and this progress has clearly increased the knowledge of anomalies in brain structure and function in MDD. Improvements in structural analytic methods, combined with the emergence of functional magnetic resonance imaging and diffusion tensor imaging (DTI) in the early 1990s, have been critical in establishing the utility of examining specific neural circuits to increase investigators’ understanding of the pathophysiology of MDD. In general, these circuits have been conceptualized as an emotion processing network that is modulated by serotonin neurotransmission and includes the amygdala, anterior cingulate cortex, and medial prefrontal cortex (Bertolino et al., 2005; Hariri et al., 2005; Heinz et al., 2007), and a reward network that is modulated by dopamine and includes the ventral striatum and orbital and medial prefrontal cortices (Surguladze et al., 2005). As we describe in the following sections, investigators have now documented consistent neural abnormalities in both function and structure in depressed individuals. Furthermore, as was the case with respect to cognitive functioning, although some of these neural abnormalities may be a symptom of depression or a consequence of having experienced this disorder, it is also possible that some anomalies reflect stable predisposing factors that place individuals at increased risk for the onset of MDD. In the following sections, we briefly describe aspects of neural function and structure that have been found to distinguish depressed individuals from their nondepressed counterparts. We then present findings from neuroimaging studies in which researchers have examined whether these depression-associated abnormalities in brain function and structure are also observable in offspring of depressed parents before they develop a first episode of depression.

Examining brain function in depression

On the basis of findings of negative biases in the processing of information and stimuli in MDD, most of the functional neuroimaging studies of depression have focused on elucidating the neural substrates of biased processing of emotional information. Indeed, in a recent voxel-wise meta-analysis of the functional neuroimaging literature of depressed adults, we found MDD to be associated reliably with increased activity in prominent nodes in the salience network during the processing of negative information (Hamilton et al., 2012). The salience network is a

**Summary**

Considered collectively, the results of these studies indicate that children and adolescents at high risk for depression because of a history of MDD in their parents, but who are not themselves depressed, are characterized by depressotypic cognitive styles and biases in attention to, interpretation of, and memory for emotional material. Thus, there is growing evidence of the operation of negative cognitive schemas and information processing biases in offspring of depressed parents, particularly as these children experience negative mood states. These findings support the formulation that the cognitive biases that have been documented in depressed adults have their origins in childhood, prior to the onset of MDD. It is critical to note, however, that there is currently little direct evidence that negative cognitive schemas play a role in the etiology of depression. As we describe in greater detail in the following sections, longitudinal studies are urgently needed to investigate whether these biases in cognitive functioning assessed in childhood predict the subsequent onset of MDD.

**Neural Factors and Risk for Depression**

The use of neuroimaging techniques has deepened the understanding of biological aspects of MDD. Twenty-five years ago, investigators were in the initial stages of using imaging technologies to examine anomalies in brain structure and function in neuropsychiatric disorders. In these early studies, in which computerized tomography and structural magnetic resonance imaging were used, investigators reported exciting associations between MDD and ventricular enlargement (e.g., Shima et al., 1984) and sulcal widening (e.g., Dolan, Calloway, Thacker, & Mann, 1986). Early optimism that these abnormalities would differentiate depression from other psychiatric populations and help to explain the etiology of MDD, however, was tempered by subsequent failures to replicate these findings (Nasrallah, Coffman, & Olson, 1989) and by reports of similar abnormalities in other psychiatric disorders, such as schizophrenia and bipolar disorder (e.g., Nasrallah et al., 1989). Similarly, early studies of brain function in MDD also yielded inconclusive findings; although the advent of positron emission tomography offered promise for the identification of depression-related anomalies in cerebral metabolism, research in this area was limited by crude measurement techniques, small sample sizes, and diagnostic heterogeneity, often including mixed samples of unipolar and bipolar depressed patients.
collection of structures that function to segregate the most relevant among internal and external stimuli to guide behavior, and it includes the amygdala, dorsal anterior cingulate cortex, and anterior insula. Furthermore, we found that compared with nondepressed controls, depressed adults exhibit higher baseline activity in the pulvinar—a nucleus of the thalamus that modulates attention and awareness to emotional stimuli (Pessoa & Adolphs, 2010) and that is directly connected with the same three regions in which we found elevated activation to negative stimuli in MDD (Jones & Burton, 1976; Mufson & Mesulam, 1984; Pessoa & Adolphs, 2010). Finally, across different studies involving the processing of negatively valenced stimuli, depressed individuals have been found to exhibit consistently reduced activation in the dorsolateral prefrontal cortex and dorsal striatum (i.e., caudate)—areas that suppress activation within nodes of the salience network and attenuate the adverse impact of negative stimuli (Lewis, Dove, Robbins, Barker, & Owen, 2004). Together, these findings support a neural model of depression in which activation in limbic regions of the salience network inhibits dorsal cortical activation, which in turn fails to inhibit limbic activation (e.g., Mayberg, 1997). Our meta-analytic findings also extend existing neural models of MDD by suggesting that high levels of baseline activity in the pulvinar in depressed individuals enhance responding of the brain's salience network to negative information.

Researchers examining neural aspects of emotional reactivity both in depressed children and in youths at risk for MDD have proposed a similar framework of potentiated limbic processing via diminished regulatory control of dorsal cortical regions. For example, studying preschool-onset depression, Luby and her colleagues have demonstrated that children with a history of preschool-onset MDD are characterized by elevated amygdala activation (Luking et al., 2011; Pagliaccio et al., 2012). Results of the few functional neuroimaging studies of individuals at familial risk for depression that have been reported to date are also generally consistent with the formulation that strong bottom-up neural responses in emotion-processing brain regions and circuits (such as the amygdala), coupled with hypo-responsivity in top-down regulatory regions (such as the dorsolateral prefrontal cortex), contribute to the negative information-processing biases we described earlier (Browning, Holmes, & Harmer, 2010; De Raedt, Koster, & Joormann, 2010; Monk et al., 2008).

**Brain function in emotional processing circuits.** Researchers are now beginning to use functional imaging to examine neural abnormalities involved in the regulation of emotion in MDD. Investigators have found that depressed adults are characterized by alterations in activation of the frontal lobe—including the medial (Beauregard, Paquette, & Lévesque, 2006), dorsal (Erk et al., 2010), and ventral (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007) subregions—as they utilize effortful emotion regulation strategies. Similar results have been reported in depressed children (Barch et al., 2012; Pagliaccio et al., 2012). In our laboratory, we have examined the extent to which these abnormalities in neural activation are present in offspring of depressed parents during the regulation of negative affect. We scanned the low- and high-risk girls as they recalled positive autobiographical memories following the induction and elaboration of a sad mood (Joormann, Cooney, Henry, & Gotlib, 2012). We found that during the elaboration of negative affect, the high-risk girls exhibited greater activations than did their low-risk counterparts in brain areas that have been implicated in the experience of negative emotion, including the amygdala and ventrolateral prefrontal cortex. Moreover, during the subsequent regulation of this negative affect through recall of a second positive memory, the high-risk girls exhibited less activation in dorsal cortical areas, such as the dorso-lateral prefrontal cortex and dorsal anterior cingulate cortex, as well as in the dorsal striatum. Thus, high-risk individuals are characterized by abnormalities in patterns of neural activation, both while experiencing and while repairing negative affect, in the same brain regions where anomalous activations have been found in depressed adults, indicating that neural functional anomalies involving the regulation of negative emotional experience precede the onset of a depressive episode and may be a marker of vulnerability for disorder.

**Brain function in reward processing circuits.** Given the diminished experience of pleasure and the high levels of anhedonia that often characterize individuals diagnosed with MDD (and that are cardinal symptoms of the disorder), investigators studying intergenerational risk for depression have also begun to examine whether functional anomalies associated with the processing of reward-related information are related to depression and to vulnerability to this disorder. Investigators have found attenuated striatal activity in response to reward information in both depressed adults (Kumar et al., 2008; Pizzagalli et al., 2009) and depressed adolescents (Forbes et al., 2009; Forbes, Shaw, & Dahl, 2007). Furthermore, whereas anhedonic symptoms usually improve with recovery from depression, anomalies in striatal function have been found to persist (McCabe, Cowen, & Harmer, 2009), indicating that abnormalities in the neural processes underpinning reward responsivity may represent a trait marker of vulnerability for depression. To examine whether anomalies in reward circuit function are present before the initial onset of MDD, we scanned our low- and high-risk girls as they performed a task designed to assess
anticipation and receipt of reward (Gotlib et al., 2010). Consistent with the findings obtained with currently depressed adults and adolescents, we found that the high-risk girls exhibited attenuated striatal response during both anticipation and receipt of reward. We also observed distinct patterns of reduced insula and anterior cingulate cortex activation during the anticipation and receipt of reward, respectively. Combined with conceptually similar findings reported by Monk et al. (2008) and McCabe, Woffindale, Harmer, and Cowen (2012), it appears that anomalies in reward circuit function represent stable and enduring vulnerability factors for the development of MDD. Because investigators have not systematically assessed behavioral aspects of anomalous reward processing in high-risk youths, elucidating the nature of the relation between behavioral and neural function is an important task for future research.

**Examining brain structure in depression**

Recent meta-analyses indicate that depressed adults are reliably characterized by abnormal gray matter volumes of several structures, including the hippocampus, amygdala, striatum, anterior cingulate cortex, and dorsal and ventral subregions of the prefrontal cortex (e.g., Hamilton, Siemer, & Gotlib, 2008; Kempton et al., 2011; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009). Although few investigators have yet demonstrated that these neural abnormalities can predict the onset of MDD, a number of reports have nevertheless been informative in identifying structural aberrations associated with elevated risk for depression.

**Subcortical gray matter structure.** One of the most frequently studied brain areas in major depression, the hippocampus, plays a critical role in both the regulation of mood (Eisenberger, Gable, & Lieberman, 2007; Fusar-Poli et al., 2009) and the modulation of neuroendocrine responses to stress (Herman et al., 1989; Mizoguchi, Ishige, Aburada, & Tabira, 2003). Meta-analyses consistently show that MDD in adults is associated with reduced gray matter volume of the hippocampus. Moreover, Suzuki et al. (2013) recently demonstrated in depressed children that smaller hippocampal volumes were associated with greater cortico-limbic activation to sad faces. In one of the first investigations of anomalies in brain structure in high-risk youths, we found that our high-risk girls had smaller hippocampal volumes than did their low-risk counterparts (Chen, Hamilton, & Gotlib, 2010), suggesting that reduced hippocampal volume precedes the onset of the disorder. This hippocampus finding was replicated in two subsequent studies of never-depressed adults at familial risk for depression by virtue of having a first- or second-degree relative with MDD (Amico et al., 2011; Baaré et al., 2010).

Adding to this work are findings showing that the magnitude of hippocampal volume loss in high-risk youths is similar to the magnitude of hippocampal volume loss that has been found in currently depressed youths (Rao, Chen, et al., 2010). It is important to note that in this study, stress experienced during childhood was significantly related to an increased likelihood of having smaller hippocampi. Furthermore, this association between stress and brain structure was present only in youths with a parental history of MDD. As we discuss later in this article, this pattern is intriguing in suggesting that familial risk for depression is associated with a heightened reactivity to stress and that this reactivity interacts with negative life events to influence the development of hippocampal gray matter. Thus, consistent with a diathesis-stress formulation, stress appears to interact with a heightened stress reactivity to predict a greater likelihood of developing depression, the onset of which may be predicted by anomalies in hippocampus structure.

Other investigators have documented associations between structural characteristics of the amygdala—a brain region that subserves functions related to the processing of emotional material—and familial risk for depression in children (Lupien et al., 2011). Specifically, it has been documented in prior work that gray matter volume in the amygdala of 10-year-old children is positively correlated with their mothers’ mean depression scores during the children’s lifespan. This indicates that neural anomalies associated with a heightened risk for depression may be influenced not only by the presence but also by the severity and duration of a parent’s depression.

**Cortical gray matter structure.** Investigators have found that risk for depression is also associated with structural abnormalities of cortical gray matter. For example, significant gray matter thinning across frontal, temporal, and parietal cortices has been found in high-risk children and adults (B. S. Peterson et al., 2009), and these reductions mediated deficits in attention and memory, suggesting that structural anomalies underlie risk-related deficits in cognitive functioning. Using a volumetric approach, Amico et al. (2011) reported similar structural deficits in the right dorsolateral prefrontal cortex of adults with a first- or second-degree relative diagnosed with MDD. Because these prior studies of cortical structure included adults who had a relative with depression, as well as individuals who had already experienced a depressive episode, we are examining more directly whether abnormalities in cortical structure are markers of vulnerability to depression by assessing cortical structure.
in our sample of young healthy girls at familial risk for the development of MDD (Foland-Ross et al., 2012). We are finding that, even before the onset of the first episode of MDD, never-disordered adolescent girls at familial risk for depression exhibit large expanses of cortical thinning, including thinning in gray matter of the anterior insula; anterior cingulate cortex; and superior frontal, parietal, and fusiform cortices. Furthermore, whereas low-risk girls exhibit normative declines in cortical thickness in several of these regions with increasing age, this pattern is absent in high-risk girls. Finally, combining neural and cognitive data, we are finding that thinning of fusiform gray matter in high-risk girls appears to be related to difficulties identifying negative emotional expressions, indicating again that structural anomalies of this face-processing region may contribute to impairment in the processing of emotional stimuli.

**White matter structure.** Finally, risk for depression has also been found to be associated with abnormalities in white matter structure. Using DTI, researchers have found impaired anatomical connectivity in depressed adults, including decreased fractional anisotropy (FA) in the temporal (e.g., Zhu et al., 2011) and occipital (e.g., Kieseppä et al., 2010) lobes and along midline structures (e.g., Kieseppä et al., 2010; Zhu et al., 2011). In fact, in a recent meta-analysis, lower FA of the superior longitudinal fasciculus—which connects large parts of the frontal cortex with portions of the parietal, temporal, and occipital lobes—was the most consistently reported abnormality across studies of white matter structure in depressed adults (Murphy & Frodl, 2011).

In the first study to use DTI to examine anomalies in white matter associated with risk for depression, never-disordered adolescent offspring of parents with recurrent depression were found to exhibit reduced FA in three tracts: the cingulum, which connects cingulate gray matter with that of the hippocampus and perihippocampus; the uncinate, which connects the amygdala and hippocampus to the inferior portions of the frontal lobe; and the superior longitudinal fasciculus (Huang, Fan, Williamson, & Rao, 2011). These findings were replicated in part in a more recent study by Whalley et al. (2013a), who found reduced FA in the superior longitudinal fasciculus in never-disordered young adults who were at increased risk for developing MDD by virtue of having a parent with bipolar disorder. Finally, adolescents with a significant history of early life stress who developed MDD at follow-up had significantly have been found to demonstrate lower FA values at baseline in the superior longitudinal fasciculus and right cingulum than did adolescents who remained well (Huang, Gundapuneedi, & Rao, 2012).

**Summary**

The neuroimaging literature on youths at familial risk for depression, considered with the well-documented findings of neural abnormalities in depressed adults and children, indicates that functional and structural anomalies in brain regions involving emotion and reward circuits are stable vulnerability markers for MDD that are present prior to the initial onset of illness. Although few researchers have attempted to predict onset of MDD from baseline neural characteristics, results of those that have indicate that abnormalities in both brain function (Whalley et al., 2013b) and brain structure (Huang et al., 2012; Rao, Chen, et al., 2010) may predict the development of depression in high-risk samples.

**Emotion Dysregulation and Stress Reactivity as Markers of Risk for Depression**

The findings we reviewed earlier indicate that a number of the anomalies in cognitive functioning and in neural activation and structure that have been found to characterize depressed adults are evident in young children and adolescents who are at familial risk for depression, even before the onset of an initial episode of MDD. Like depressed adults, high-risk youths have difficulties inhibiting the processing of negative stimuli. This enhanced processing of negative material may contribute to the better memory for negative than for positive information that has been documented in children at risk for depression. In addition, compared with their low-risk counterparts, high-risk children have also been found (a) to exhibit greater limbic reactivity as they experience and attempt to repair or regulate negative emotions and (b) to have smaller hippocampal volume.

None of this was known 25 years ago. In the late 1980s, investigators were just beginning to use questionnaires to assess cognitive functioning in offspring of depressed parents. In particular, Constance Hammen and her colleagues (e.g., Hammen et al., 1988; Jaenicke et al., 1987) had begun to examine attributional style in high-risk children as well as the ability of a dysfunctional attributional style in these offspring to predict the onset of depression. Of course, there were no studies of neural function or structure in children at familial risk for depression. Now, not only are investigators using more sophisticated methodologies adapted from contemporary experimental cognitive psychology to examine maladaptive cognitive functioning in high-risk offspring but, in addition, they are also beginning to assess neural aspects of risk for MDD and to integrate relevant findings across these, and other, domains.
These advances during the past 25 years are contributing to a more precise understanding of the nature of the risk experienced by children of depressed parents. Broadly, we posit that the findings from cognitive and neuroimaging studies described earlier converge to suggest that emotion dysregulation and increased stress reactivity play a central role in risk for the onset and maintenance of depression. Indeed, high-risk offspring have been found to be impaired in processes that are critical to the effective regulation of affective states. For example, difficulties inhibiting the processing of negative stimuli, enhanced memory for negative information, and poorer recall of positive material have been associated with both increased use of maladaptive emotion regulation strategies, such as rumination, and decreased implementation of effective strategies, such as reappraisal (Gotlib & Joormann, 2010). Amygdala hyper-reactivity to negative material has also been linked to difficulties in the regulation of negative affect (e.g., Erk et al., 2010). Thus, these risk factors, which likely increase children’s use of maladaptive emotion regulation strategies and hinder their implementation of effective strategies to deal with stressors and negative life events, may lead to a vicious cycle of sustained negative thinking and negative affect in the face of stressful events, resulting ultimately in a major depressive episode.

Although not yet tested explicitly, it is important to note that this formulation is supported by findings of research in related areas. For example, one of the best documented biological abnormalities in major depression is disturbed functioning of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is a major neuroendocrine system, composed of the hypothalamus and the pituitary and adrenal glands, that controls the body’s physiological reactions to stress. Studies of depressed adults have consistently reported abnormally elevated levels of cortisol—a glucocorticoid hormone that is released into systemic circulation by the HPA axis following awakening or exposure to an acute stressor (e.g., Knorr, Vinberg, Kessing, & Wetterslev, 2010; Stettler & Miller, 2011). Offspring of depressed parents have also been found to exhibit both increased basal (Lupien et al., 2011; E. A. Young, Vazquez, Jiang, & Pfeffer, 2006) and waking (Mannie, Harmer, & Cowen, 2007; Vreeburg et al., 2010) levels of cortisol. Moreover, both Goodyer, Tamplin, Herbert, and Altham (2000) and Adam et al. (2010) found higher levels of cortisol in adolescents who developed an episode of major depression during the following year than in adolescents who did not develop depression. Consistent with these findings, Rao et al. (2009) found that adolescents at familial risk for depression secreted higher levels of nocturnal urinary-free cortisol than did their low-risk counterparts and, further, that nocturnal urinary-free cortisol levels predicted the onset of MDD within the following 5 years.

The fact that not all children of depressed parents will go on to develop depression has led researchers to examine the role of genetic and environmental factors that may explain additional variance in risk-associated abnormalities biological measures. These investigations underscore the importance of stress reactivity and emotion dysregulation in contributing to risk for depression. For example, in a sample of adolescents at familial or psychosocial risk for depression, Goodyer et al. (2009) found that those who carried at least one copy of the short (s) allele in the promoter region of the serotonin transporter gene (5-HTTLPR) exhibited significantly higher levels of morning salivary cortisol. Moreover, prospective longitudinal analyses indicated that the interaction of carrying an s allele and having abnormally elevated levels of waking cortisol predicted the onset of MDD. Thus, genetic factors—in particular, allelic variation of the 5-HTTLPR gene—appear to influence HPA-axis function in the context of the risk for depression. Consistent with this formulation, we have documented in our own laboratory that girls who are homozygous for the s allele secrete higher levels of waking (but not afternoon or evening) cortisol than do their long-allele counterparts (Chen et al., 2010) as well as higher and more prolonged levels of cortisol in response to a psychosocial stressor (Gotlib, Joormann, Minor, & Hallmayer, 2008). Finally, it is noteworthy that glucocorticoid levels are well known to be modulated by areas of the brain that contain high concentrations of glucocorticoid receptors, such as the hippocampus and prefrontal cortex. As we have reviewed earlier, these are regions that have been found to be structurally or functionally aberrant both in depressed individuals and in offspring of depressed parents (e.g., Hamilton et al., 2008; Kempton et al., 2011; Koolschijn et al., 2009; Videbech & Ravnkilde, 2004). Thus, altered HPA-axis activity in depressed and high-risk individuals may be secondary to damage to hippocampal or prefrontal cortex gray matter. Future studies in which multiple measures across several time points are integrated are necessary to elucidate the temporal or causal nature of the relations among these neurobiological markers of risk for MDD.

**Concluding Comments**

It is clear from this review that investigators have made significant progress during the past 25 years in identifying factors that might increase the risk for the development of MDD in offspring of depressed parents. A critical direction for future researchers is (a) to examine more explicitly and systematically the nature of the relation
between cognitive dysfunction and neural abnormalities in high-risk children and (b) to determine whether and how impairments in cognitive function and anomalies in the function and structure of neural circuits that are important to the generation and regulation of negative affect might play a causal role in the onset of depression. There are already initial findings implicating these domains in the development of MDD. For example, Monk et al. (2008) found that offspring of depressed parents exhibited abnormally heightened activity in the amygdala as they viewed fearful faces. Because this pattern of anomalous response was present only during a passive viewing condition in which children’s attention to facial features was unconstrained, Monk et al. posited that heightened amygdala reactivity to negative stimuli is due to the attentional biases that have been documented in high-risk children (Joormann et al., 2007; Kujawa et al., 2011). Furthermore, in our own study, although we have not yet conducted follow-up assessments with all of the young high-risk girls, we are finding that attentional bias to negative stimuli, high levels of diurnal and stress-related cortisol secretion, and low hippocampal volume are predicting the onset of a first episode of depression in those high-risk girls who have developed MDD. These preliminary findings are important in adding to extant literature in which the initial associations among baseline anomalies in cortisol (Adam et al., 2010; Goodyer et al., 2000), brain function (Whalley et al., 2013b), and brain structure (Huang et al., 2012; Rao, Chen, et al., 2010) and the subsequent development of depression in high-risk youths has been documented.

A second important direction for future research involves the development of effective approaches to prevent the onset of depression in high-risk children. After 25 years of research, it is clear that developing effective intervention and prevention programs for depression requires a comprehensive and integrative understanding of the underlying mechanisms of risk. If the cognitive and neural anomalies that we described earlier in this article are found not only to characterize high-risk children but to also play a role in the onset of depression, then investigators might profitably focus on the constructs of emotion dysregulation and stress reactivity as potential targets in programs aimed at the prevention of MDD. Researchers have already demonstrated that cognitive bias modification methods, including attentional bias training and interpretation bias training, are effective in reducing depressive symptoms in adults (Baert, De Raedt, Schacht, & Koster, 2010; Tran, Hertel, & Joormann, 2011). Similarly, investigators have recently made exciting strides in using real-time neurofeedback training to teach individuals to alter patterns of neural activation (e.g., Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011; Linden et al., 2012). Extending these approaches to children at familial risk for depression has the promise of delaying or preventing the first onset of disorder. Although we have begun to study these approaches in our laboratory, much remains to be done. We urge investigators interested in risk for depression to conduct integrative assessments of biological and psychological aspects of emotion dysregulation and stress reactivity; it is only through such research that we will be able to develop effective prevention and intervention approaches for this debilitating disorder.

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