Neurobiological Markers of Familial Risk for Depression

Lara C. Foland-Ross, Michael G. Hardin and Ian H. Gotlib

Abstract Major depression is associated with a wide range of neurobiological disturbances, including anomalies in the structure and function of cortical and subcortical gray matter and dysregulation of the HPA axis. In this chapter, we review research demonstrating that many of these abnormalities are also present in never-depressed offspring of adults with recurrent depression and discuss how such findings might reflect dysfunctional neuroregulatory systems that precede the onset of this disorder. We also briefly discuss candidate genes and environmental factors that have been posited to be directly involved in the transmission of neural and HPA-axis abnormalities from depressed parents to their offspring, and we review how, by obtaining a better understanding of the neurobiological markers of depression risk, we can facilitate the development of targeted strategies for the prevention and treatment of major depression.

Keywords Depression · Risk · Neuroimaging · Cortisol · Hippocampus · DLPFC · Amygdala · Genetics

Contents

L. C. Foland-Ross · M. G. Hardin · I. H. Gotlib (✉)
Department of Psychology, Stanford University, Stanford, CA, USA
e-mail: ian.gotlib@stanford.edu

Curr Topics Behav Neurosci (2013) 14: 181–206
DOI: 10.1007/7854_2012_213

Published Online: 10 May 2012

Major depressive disorder (MDD) is among the most prevalent of all psychiatric disorders; almost 20 % of the American population (or more than 30 million adults) will experience a clinically significant episode of depression in their lifetime (Kessler and Wang 2009). Not surprisingly given this high prevalence, MDD is associated with disturbingly high societal costs; in fact, the World Health Organization has ranked MDD as the leading cause of years lived with disability and the single most burdensome disease in the world in terms of total disability-adjusted years among people in the middle years of life (Murray and Lobez 1996).

Given these alarming statistics, researchers have worked to understand factors that are involved in the onset and maintenance of MDD. In this context, scientists have described a complex interplay of genetic and environmental factors as playing an important role in contributing to vulnerability for the development of MDD. Indeed, the strongest and most reliable risk factor for the development of MDD is a family history of the disorder (Williamson et al. 2004): having a parent with MDD is associated with a three- to fivefold increase in the risk for developing a depressive episode (Beardslee et al. 1998; Williamson et al. 2004). Despite this fact, we know little about the mechanisms involved in this transmission of risk. Although investigators have identified a number of depression-related physiological and neural abnormalities, we do not know if these anomalies are epiphenomena of MDD, consequences of having been depressed, or familially transmitted aberrations that increase vulnerability to the disorder. By examining individuals who have not yet experienced MDD themselves, but who are at high risk for developing the disorder by virtue of having a family history of MDD, we can begin to elucidate these issues.

In this chapter, we describe research that has been conducted with individuals who are at familial risk for the development of depression, with a specific focus on neurobiological factors. We begin by reviewing findings from neuroimaging studies documenting abnormalities in brain structure and function in never-depressed offspring of parents with recurrent depression, and then review evidence implicating the specific involvement of hypothalamic–pituitary–adrenal (HPA) axis dysfunction in the intergenerational transmission of risk for depression. Finally, we present a brief discussion of specific genes and environmental factors that have been posited to be directly involved in the transmission of neural and HPA-axis abnormalities from depressed parents to their offspring.

1 Neuroimaging of Individuals at Familial Risk for Depression

Over the past 20 years, considerable advances in non-invasive neuroimaging technologies, particularly magnetic resonance imaging (MRI), have contributed significantly to our knowledge of anomalies in brain structure and function that are

associated with MDD. While some of these abnormalities may be a function of the depressive state at the time of assessment, other anomalies may reflect stable predisposing factors that place individuals at increased risk for the onset of depression. In the following section, we present findings from neuroimaging studies designed to identify structural and/or functional aberrations associated with an elevated risk for depression.

1.1 Structural Findings

Given that depression is primarily a disorder of the experience and regulation of emotion, it is perhaps not surprising that structural neuroimaging studies of this disorder have revealed volumetric abnormalities in brain regions that subserve the processing of emotional stimuli and information. Indeed, recent meta-analyses of depression-related structural neuroimaging studies indicate that depressed individuals reliably exhibit abnormal gray matter volumes of several structures, including the hippocampus, amygdala, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) (Videbech and Ravnkilde 2004; Hamilton et al. 2008; Koolschijn et al. 2009; Kempton et al. 2011). While it is possible that structural abnormalities in these regions are a consequence of major depression, it is also possible that these aberrations are present prior to the onset of the disorder and contribute to an individual's likelihood of developing MDD. To examine this issue, it is necessary that investigators determine whether neural abnormalities in depressed adults are also present in individuals who are at high risk for developing depression but have not yet experienced clinically significant symptoms. Although no structural neuroimaging studies have taken a prospective longitudinal approach to identifying whether neural abnormalities in never-depressed individuals at high risk for depression predict the eventual onset of MDD, over the past 5 years, a number of reports have indicated that abnormalities in brain structure that have previously been found to be associated with depression in adulthood are also present in younger, vulnerable individuals.

Given the involvement of the hippocampus in mood (Critchley et al. 2000; Eisenberger et al. 2007; Fusar-Poli et al. 2009) and physiological reactions (e.g., cortisol response) associated with psychosocial stress (Herman et al. 1989; Mizoguchi et al. 2003), several structural neuroimaging investigations of individuals at high familial risk for MDD have focused on this structure. For example, Chen et al. (2010) examined differences in hippocampal volume between never-depressed adolescent daughters of mothers with a history of MDD (high risk for depression) and never-depressed adolescent daughters of mothers with no history of psychopathology (low risk for depression). Results of this investigation revealed that high-risk girls had smaller hippocampal volumes than did their low-risk counterparts, suggesting that neuroanatomic anomalies of the hippocampus that are associated with depression (Videbech and Ravnkilde 2004; Koolschijn et al. 2009; Kempton et al. 2011) precede the onset of the disorder. This finding is

consistent with the results of two other studies that examined hippocampal abnormalities in never-depressed adults with a first-degree relative who was experiencing depression. In the first study, Baaré et al. (2010) found reduced hippocampal volume in never-depressed adult siblings of adults with recurrent depression compared to never-depressed siblings of never-depressed adults. In the second investigation, Amico et al. (2011) found that adults who had either a first- or a second-degree relative with depression had smaller hippocampal volumes than did both adults without a positive family history of depression and adults who were diagnosed with current MDD. This latter finding is particularly interesting in that it involves a comparison of hippocampal volumes between never-depressed high-risk individuals and diagnosed depressed persons. While it may, at first, seem counterintuitive that high-risk individuals had smaller hippocampal volume than did diagnosed depressed persons, it is important to note that this finding is consistent with a growing body of evidence indicating that hippocampal volume increases with pharmacological treatment of MDD (Santarelli et al. 2003; Vermetten et al. 2003; Lai et al. 2010), likely as a result of hippocampal neurogenesis (Malberg et al. 2000). In this context, therefore, Amico et al.'s findings not only point to reduced hippocampal volume as a risk factor for depression, but also suggest that depression-associated volumetric reductions of the hippocampus can be reversed with medication.

Adding to this body of work, Rao et al. (2010), like Chen et al. (2010), found adolescents at high familial risk for depression to exhibit volumetric decreases in the hippocampus compared to never-depressed adolescents with no family history of depression. Moreover, Rao et al. examined an additional group of adolescents with current depression and found these participants to exhibit deficits in hippocampal volume similar to those found in the high-risk group. Although this latter finding conflicts with the results of Amico et al. (2011), such a discrepancy may be due to effects of medication; whereas Amico et al. included mainly medicated participants in their depressed sample, Rao et al. assessed primarily medication-na individuals. Importantly, Rao et al.'s study of high-risk adolescents also extends previous findings obtained with high-risk populations by linking structural anomalies in the hippocampus to childhood stress. More specifically, using mediation analyses, Rao et al. found that early life adversity during childhood increased the likelihood of having smaller hippocampi at initial assessment, and that this association was present only in offspring of depressed parents, and not in children of never-depressed parents. These findings are intriguing in suggesting that depressed parents transmit a heightened sensitivity to stress to their offspring, and that this sensitivity directly influences hippocampal development. Alternatively, depressed parents may be more likely to select themselves, and therefore their children, into high-stress environments, and this form of chronic childhood stress may combine with other early life adversities to result in the volumetric reductions. Finally, Rao et al. followed their participants longitudinally and found that depressive symptoms at a follow-up assessment were partially mediated by smaller hippocampal volumes at initial assessment. Thus, a positive family history of depression in this study interacted with life stress to influence hippocampal

development, and these factors collectively contributed to a greater likelihood of developing depression. These findings are particularly notable because they are the first to suggest that abnormalities in brain structure, present in individuals at initial assessment, can predict which high-risk adolescents are most likely to develop depression.

Recent structural neuroimaging investigations of youths at high familial risk for depression suggest, in addition to the hippocampus, that volumetric abnormalities in other brain regions may also precede the onset of MDD. In the same study in which Amico et al. (2011) examined differences in hippocampal volume between adults at low and high familial risk for depression, group differences were also reported in the gray matter of the frontal lobe and striatum. More specifically, individuals at high familial risk for depression were found to exhibit volumetric reductions in the right DLPFC (rDLPFC) and putamen compared with low-risk individuals. These findings are particularly interesting given the respective roles of the rDLPFC and putamen in the processing of behavior and affect. For example, the rDLPFC has been implicated in cognitive and inhibitory control processes (e.g., Aron 2011; Ridderinkhoff et al. 2004), and is an integral component of a frontal system that is involved in the regulation of emotion through inhibitory control over limbic regions (e.g., Hariri et al. 2000; Beauregard et al. 2001). In turn, the putamen, as part of the striatum and the cortico-striatal-pallidal-thalamic (CSPT) loop (Alexander et al. 1986), has been posited to be involved in reward-seeking behavior (Kawagoe et al. 1998; Gold 2003). Volumetric reductions in each of these regions have also been reported in structural neuroimaging studies of depressed adults (see Kempton et al. 2011). Thus, Amico et al.'s finding of reduced volume of these structures in nondepressed individuals at familial risk for MDD suggests that these anomalies may precede the onset of depression.

Other investigators conducting structural and functional neuroimaging studies of depression have focused on the amygdala, given its critical involvement in the perception and memory of emotional information (Kensinger and Corkin 2004; Adolphs 2008; Pessoa and Adolphs 2010). Lupien et al. (2011) followed women with recurrent depression and never-depressed controls who had given birth to healthy offspring over a 10-year period and assessed their depressive symptoms at regular intervals. At the end of this 10-year period, the children were scanned to examine whether children of depressed mothers were characterized by structural abnormalities in subcortical limbic areas. Results of this study showed that children of depressed mothers had larger amygdala volumes than did their low-risk peers and, further, that these volumes were significantly positively correlated with the mothers' mean depressive scores assessed over the 10-year interval. These findings suggest that children's neural development is affected not only by whether their parent is depressed, but also by the severity and duration of the mother's depression during the child's lifetime. The authors compared their findings to results of studies that examined amygdala volume in children reared in orphanages—a model of early maternal separation (Mehta et al. 2009; Tottenham et al. 2010)—and interpreted the greater amygdala volume in the high-risk children to be a consequence of poor parental care caused by the mothers' depression. Indeed,

maternal depression has been found in other investigations to decrease the quality of maternal care (Field 1984, 1994; Murray and Cooper 2003); the influence of depression on parenting and the consequent effects on healthy neurobiological development in the child are topics that warrant discussion and are addressed in later sections of this chapter.

Finally, in a study examining structural abnormalities of cortical gray matter using measurements of cortical thickness, Peterson et al. (2009) found significant cortical thinning in never-depressed individuals with first- or second-degree relatives with depression in the right dorsal and inferior frontal gyri, somatosensory and motor cortices, dorsal and inferior regions of parietal cortex, and posterior regions of temporal cortex, compared to individuals who did not have a family history of depression. Follow-up correlational analyses of these data indicated that thinner cortical gray matter in these regions of high-risk individuals was associated with higher levels of inattention and poorer performance on tests measuring immediate and delayed visual memory. Risk-related cortical thinning in these brain regions may therefore directly underlie poor performance on measures of inattention and lead, in turn, to maladaptive emotion processing and subsequent difficulties in the ability to regulate emotional arousal, which may contribute to the onset of MDD. Indeed, mediator analyses confirmed that cortical thickness abnormalities mediated the association of familial risk with performance on cognitive tests. These findings both provide insight into how neurobiological abnormalities might mediate the intergenerational transmission of depression and highlight the need for future neuroimaging studies of samples at familial risk for depression to incorporate and integrate measures of behavior and cognition.

While the results of these studies suggest that structural differences within certain brain regions are involved in the intergenerational transmission of risk for depression, other research implicates the neural connections among brain regions in this process. For example, depression-related abnormalities have been documented in the white matter tracts that connect proximal and distal brain regions to facilitate complex behaviors (e.g. Sexton et al. 2009; Kieseppä et al. 2010). Using diffusion tensor imaging (DTI) to examine the possibility that these white matter abnormalities precede the onset of depression and represent a vulnerability marker for MDD, Huang et al. (2011) examined fractional anisotropy (FA, a measure that reflects aspects of membrane integrity and myelin thickness) in healthy adolescents who were at high or low familial risk for depression. Results of this investigation showed that high-risk adolescents exhibited reduced FA in the cingulum, which connects gray matter of the cingulate with that of the hippocampus and perihippocampus, as well as reduced FA in tracts that connect rostral portions of the temporal lobe (e.g., amygdala and hippocampus) with the inferior portions of the frontal lobe that have been posited to be involved in social and emotional regulation (Schmahmann et al. 2007; Sexton et al. 2009).

Taken together, these structural neuroimaging findings suggest that both subcortical and cortical gray matter structure, as well as FA of white matter, are aberrant in individuals who are at familial risk for depression but who have not yet experienced a depressive episode themselves. While the precise causes of these

structural anomalies are not yet known, genetic and/or environmental factors are likely to be involved. We will address the possible influence of a specific set of genes and environmental variables later in this chapter. It is also unclear how abnormalities in brain structure might affect function in overlapping and connected areas. Although we review findings below from studies examining brain function in individuals at familial risk for depression, experiments are required that address the direct consequences of changes in gray matter structure on brain function and behavior.

1.2 Functional Findings

Like the research described above examining risk-associated anomalies in brain structure, functional neuroimaging of individuals at familial risk for depression is still in its infancy. Given that depression is primarily a disorder of emotional processing, and that most neural functional abnormalities that have been found in depression are reported in emotion-related circuitry (Price and Drevets 2010), research conducted to date on populations at high risk for depression has focused almost entirely on neural activity associated with the processing of emotional stimuli. In support of such a focus, behavioral studies have demonstrated that, like depressed persons, never-depressed individuals at familial risk for depression are characterized by negatively biased processing of emotional information; high-risk individuals have been found behaviorally to exhibit negative biases in the interpretation (Dearing and Gotlib 2009) and identification (Joormann et al. 2010) of stimuli, in attentional processing (Joormann et al. 2007), and in the categorization of emotional information (Mannie et al. 2007a).

Results of the few emotion-related functional neuroimaging studies that have been conducted with individuals at high risk for MDD are generally consistent with findings from neuroimaging studies of depressed adults indicating that strong bottom-up neural responses in emotion-processing regions (such as the amygdala and limbic circuits), coupled with hypo-responsivity in top-down regulatory regions (such as the DLPFC), may contribute to these negatively based responses to emotional information (Browning et al. 2010; De Raedt et al. 2010). For example, compared to their low-risk peers, adolescents at high risk for MDD have been found to have a greater neural response in brain regions that mediate emotional reactivity to affective stimuli, such as the amygdala and insula, as they view negative emotion faces (Monk et al. 2008) or sad film clips (Lévesque et al. 2011; Joormann et al. 2012). High-risk young adults have also been found to have a smaller left DLPFC response than do their low-risk counterparts as they view negative emotion faces during an emotion-matching task (Mannie et al. 2011) or attempt to repair sad mood through recalling positive memories (Joormann et al. 2012). While these findings suggest that limbic and frontal functioning serve as markers for increased vulnerability to depression, it is clear that further investigation is warranted. For example, Monk et al. (2008) observed increased limbic

response by high-risk adolescents only when their attention was unconstrained, not in a constrained-attention condition, suggesting that attention-related processes mediate this effect. Similarly, Mannie et al. (2011) found no differences between young low- and high-risk adults in subcortical limbic response, highlighting the importance of considering the role of development in emotion processing.

Given the diminished experience of pleasure and the high levels of anhedonia that often characterize individuals diagnosed with MDD, investigators studying intergenerational risk for depression have also started to examine the possibility that functional anomalies related to the processing of reward information may serve as markers for increased vulnerability to MDD. Building on evidence that both depressed adults (Steele et al. 2007; Kumar et al. 2008; Pizzagalli et al. 2009) and adolescents (Forbes et al. 2007, 2009) show attenuated striatal activity in response to reward information, Gotlib et al. (2010) scanned low- and high-risk adolescent girls as they performed a task designed to study reward anticipation and consumption. These investigators found that high-risk adolescents demonstrated attenuated striatal response during the processing of reward, suggesting that reward-related neural function is a marker of increased risk for depression. While these data are encouraging, this is the only study to date to examine reward-related neural function in high-risk individuals. Therefore, it is critical that investigators extend this finding so that we can gain a better understanding of the role of reward-related processing in contributing to vulnerability for depression.

2 HPA-Axis Dysregulation in Individuals at Familial Risk for Depression

The observations that patients with Cushing's syndrome often experience severe depression (Gallagher et al. 2009) and that levels of cortisol increase in response to stress (Dickerson and Kemeny 2004) have contributed to the refinement of stress-diathesis hypotheses of depression (e.g., Monroe and Simons 1991), in which high levels of cortisol are posited to play a significant pathophysiologic role in the etiology of MDD. Indeed, one of the more consistently reported physiological abnormalities in major depression is abnormally elevated levels of cortisol (Burke et al. 2005; Knorr et al. 2010; Stetler and Miller 2011). This glucocorticoid hormone is released into systemic circulation by the HPA axis following awakening or during times of stress. More specifically, corticotropin-releasing hormone (CRH) is secreted from the hypothalamus, which causes the neighboring pituitary gland to secrete adrenocorticotropin hormone (ACTH). ACTH then acts on the adrenal glands to induce the release of cortisol, in addition to a number of other hormonal compounds, which help the body respond adaptively to awakening or to a stressful event by increasing heart rate, boosting vascular tone, and speeding reaction time. Elevated levels of cortisol also typically function through negative feedback mechanisms in the hippocampus to inhibit the further production and

secretion of cortisol by the HPA system (Sapolsky et al. 1986). Thus, in normal functioning, cortisol facilitates individuals' ability to adapt to, and recover from, stress.

Previous studies that have examined HPA responses to stress have typically used laboratory tasks that measure the temporal dynamics of cortisol release following exposure to a psychosocial stressor. Such a sampling approach typically consists of three phases: (1) a basal activity phase, involving baseline cortisol levels in the absence of a stressor; (2) a 'stress reactivity' phase, in which cortisol increases from baseline (i.e., pre-stressor) levels following the onset of a stressor; and (3) a 'stress recovery' phase, in which cortisol levels return to baseline following the offset of the stressor (McEwen 1998). Although reports of cortisol release in depressed individuals in response to a laboratory stressor are mixed (Gotthardt et al. 1995; Heim et al. 2000; Young et al. 2000), a recent meta-analysis showed that, controlling for baseline levels, elevations in cortisol in response to laboratory stressors are typically attenuated compared to levels in never-depressed control subjects (Burke et al. 2005). This meta-analysis also reported abnormalities during the stress recovery phase; across studies, depressed individuals generally take longer than do nondepressed individuals for their cortisol to return to baseline levels following the removal or termination of the stressor (Burke et al. 2005). Thus, whereas never-depressed individuals show reliable and dynamic patterns of neuroendocrine responses to laboratory stress, with greater stress reactivity and rapid recovery following stress, individuals diagnosed with MDD exhibit a relatively flat and unresponsive pattern of cortisol secretion. The meaning of this pattern in depression is unclear, although it has been posited that abnormal cortisol responses to stress may reflect difficulties in the ability of depressed individuals to adapt to, and recover from stressful events.

A second, more widely replicated finding in MDD concerns diurnal fluctuations in salivary cortisol. Typically, cortisol levels rise in the early morning, peaking approximately 30 min after awakening, and then diminish over the course of the day, reaching the lowest points in the evening (Posener et al. 1996). Although some investigators have reported a blunted cortisol awakening response in depression (Stetler and Miller 2005; Huber et al. 2006), most studies have documented abnormally high levels of morning salivary cortisol in MDD (Pruessner et al. 2003; Bhagwagar et al. 2005; Vreeburg et al. 2009). Consistent with this pattern of results, two recent meta-analyses concluded that morning salivary cortisol levels are higher in individuals diagnosed with MDD than they are in never-depressed participants (Knorr et al. 2010; Stetler and Miller 2011). Abnormally elevated levels of cortisol following awakening have also been found in studies of individuals who report chronic stress or worrying (Wust et al. 2000; Schlotz et al. 2004) and work overload (Steptoe et al. 2000). Thus, elevations in waking cortisol in depression could be a consequence of chronic stress, or could be related to the anticipation of more burdensome demands in daily life (Fries et al. 2009). Meta-analyses examining diurnal fluctuations of cortisol secretion in depression have also found, in addition to higher morning cortisol levels, that depressed individuals exhibit elevated cortisol levels before bedtime. This finding

provides empirical support for the suggestion that baseline levels of cortisol are chronically elevated in MDD, which may contribute to a ceiling effect observed in some laboratory studies of depressed individuals' cortisol response to stress.

Although anomalous functioning of the HPA axis could be the consequence, or "scar," of having a depressive illness, or of having experienced traumatic life events, it is also possible that dysregulation of the HPA-axis represents a vulnerability marker for depression. Indeed, investigators have found that depressed individuals who exhibit no change in HPA-axis activity following pharmacotherapy for MDD have poorer outcome than do depressed individuals who show medication-related normalization of the HPA axis (Heuser et al. 1994). Researchers have also found that alterations in HPA-axis activity can predict subsequent episodes of depression in remitted individuals, independent of the type of treatment they receive (Harris et al. 2000; Wust et al. 2000; Zobel et al. 2001).

Whether dysregulation of the HPA-axis might also predict the initial onset of MDD is a focus of ongoing research. Because, as we noted earlier, one of the strongest risk factors for depression is a family history of MDD, studies of young offspring of depressed parents are particularly promising in elucidating this issue. Interestingly, investigators who have examined HPA-axis function have found that children and adolescents who have a depressed parent demonstrate both increased basal (Lupien et al. 2000; Young et al. 2006; Lupien et al. 2011) and increased waking (Mannie et al. 2007b; Vreeburg et al. 2010) levels of salivary cortisol compared to offspring of never-depressed parents. These patterns are in striking overlap with findings of studies of currently depressed adults (Pruessner et al. 2003; Bhagwagar et al. 2005; Vreeburg et al. 2009; Knorr et al. 2010; Stetler and Miller 2011), and provide support for the formulation that aberrant HPA-axis function precedes the onset of MDD.

The gold-standard approach, however, to determining whether HPA-axis dysfunction precedes the onset of depression involves measuring cortisol secretion in participants prior to the onset of the first depressive episode and then following the same individuals longitudinally to determine whether anomalies in HPA-axis regulation predict higher rates of depression over time. Few studies have used this methodological approach. Of these few, however, there is a striking consistency in their findings. For example, Adam et al. (2010) found higher levels of morning salivary cortisol never-depressed adolescents who developed an episode of major depression over the following year than in adolescents who did not develop depression. Consistent with this finding, Rao et al (2009) examined nocturnal urinary-free cortisol (NUFC) excretion (i.e., basal levels of cortisol) in adolescents with or without a family history of depression. These investigators found that adolescents at familial risk for depression exhibited higher NUFC excretion than did their low-risk counterparts and, further, that levels of NUFC excretion were highest in those adolescents who developed MDD by a 5-year follow-up assessment. Goodyer et al. (2000) also followed adolescents who were at high risk for depression by virtue of either having a depressed parent or of experiencing psychosocial adversities. These adolescents were assessed at baseline for morning levels of salivary cortisol, and were assessed again for depressive symptoms 12

months later. Goodyer et al. found that high-risk adolescents who met diagnostic criteria for MDD at follow-up exhibited significantly higher morning cortisol levels at initial assessment a year earlier than did high-risk adolescents who did not develop depression. Interestingly, subsequent analyses of these data showed that the association between cortisol and risk for depression was moderated by genetic factors (Goodyer et al. 2009). More specifically, of the adolescents at familial or psychosocial risk for depression, those who carried at least one copy of the short (s) allele in the promoter region of the serotonin transporter gene (5-HTTLPR) exhibited significant higher levels of morning salivary cortisol than did high-risk individuals who were homozygous for the long (l) allele. Moreover, the risk for depression was highest in individuals who both were s-carriers and exhibited abnormally elevated waking cortisol levels at the initial assessment. Thus, genetic factors appear to influence both HPA-axis function and subsequent risk for depression. We discuss the role of genetic factors in the intergenerational transmission of neurobiological abnormalities below.

3 Mechanisms of Transmission of Neurobiological Abnormalities

One challenge facing researchers interested in elucidating intergenerational neurobiological markers of depression risk involves understanding the multiple pathways through which neurobiological abnormalities are transmitted from depressed parents to their children. Although several mechanisms have been proposed, in this section, we focus on the roles of genes and maternal environment.

3.1 Genetic Factors

Genetic factors are likely to contribute to associations that are observed between maternal depression and the emergence of depression-related neurobiological abnormalities in their children. One relatively straightforward first step in elucidating the specific genes that are involved in the intergenerational transmission of these anomalies is to study healthy individuals at genetic risk for depression to examine whether their brain structure and function resembles that of depressed persons. Although different genes have been proposed to moderate individuals' vulnerability to depression (Levinson 2006), investigators in this area have focused on two genes, in particular.

First, due in part to the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression, researchers have examined neural characteristics associated with functional polymorphisms of the serotonin transporter (5-HTT) gene. More specifically, the short (s) and long (l) alleles of the promoter

region of the serotonin transporter gene (5-HTTLPR) have been found to decrease and increase transcription rates of 5-HTT, respectively. Recent investigations of 5-HTTLPR suggest that functional polymorphisms of this gene contribute to the onset of depression by influencing individuals' sensitivity to stress. 5-HTTLPR s-allele carriers have been found to exhibit a greater number of, and more severe, depressive symptoms in response to stressful life events than do individuals who are homozygous for the long allele (Caspi et al. 2003; Kaufman et al. 2004). Evidence supporting this formulation comes from two studies reporting that increases in cortisol in response to stress are mediated by 5-HTTLPR polymorphisms, with s-allele homozygotes showing greater cortisol increases, as well as prolonged recovery from stress, compared to l-allele carriers (Gotlib et al. 2008; Way and Taylor 2010). Similarly, Chen et al. (2010) found that never-depressed girls who were s-allele carriers exhibited higher waking, but not afternoon or evening, cortisol levels than did l-allele homozygotes. Moreover, in a study we described earlier, Goodyer et al. (2009) found that s-allele carriers who were at familial or psychosocial risk for depression, but were not themselves depressed, exhibited both higher waking cortisol levels and higher rates of depression at a follow-up assessment than did high-risk individuals who were homozygous for the l-allele. Thus, a consistent picture is emerging across studies indicating that the s-allele genotype of 5-HTTLPR is associated with higher cortisol in response to awakening and psychosocial stress, and that this may serve to increase vulnerability for the development of depression.

Other investigators have focused on the involvement of 5-HTTLPR polymorphisms in the emergence of alterations in the structure and/or function of neural gray matter. In one study of never-depressed individuals, Hariri et al. (2005) found carriers of the s-allele to exhibit significantly greater activation in the amygdala during the performance of an affective faces task than did l-allele homozygotes. The association between amygdala response and s-allele carrier status has been replicated by other researchers (Dannlowski et al. 2010; Furman et al. 2010; von dem Hagen et al. 2011), adding support to the hypothesis that broad measures of neural system engagement are sensitive to alterations in serotonergic function influenced by 5-HTTLPR polymorphisms. Interestingly, the amygdala is well-known to provide positive feedback to the HPA axis (Feldman et al. 1982); therefore, 5-HTTLPR-related hyperreactivity of this region may contribute to the higher cortisol responses to stress that have been documented in s-allele carriers.

Researchers have also examined the effects of 5-HTTLPR polymorphisms on the structure of, and functional connectivity between, brain regions involved in the processing of emotional information. Pezawas et al. (2005) found that relative to l-allele homozygotes, s-allele homozygotes are characterized by reduced gray matter volume in, and abnormal functional connectivity between, the amygdala and the peri- and subgenual anterior cingulate cortices. Moreover, decreased cortical gray matter volume of the inferior frontal gyrus has been reported in s-allele carriers compared to l-allele homozygotes (Selvaraj et al. 2011). As we noted above, these areas have been implicated consistently in neuroimaging studies of depressed adults (Gotlib and Hamilton 2008; Koolschijn et al. 2009) and

their never-depressed offspring (Monk et al. 2008; Peterson et al. 2009). It is tempting to speculate, therefore, that depression-related abnormalities in brain structure and function (and, consequently, risk for MDD) may be transmitted directly from depressed parent to child through allelic variations in 5-HTTLPR.

Another gene that has been implicated in depression is one that encodes brain-derived neurotrophic factor (BDNF), a protein that aids in the survival and plasticity of neurons (Murer et al. 2001), the growth and differentiation of new neurons and synapses (especially in the hippocampus, e.g., Huang and Reichardt 2001), and the protection of neurons against stress-induced damage (Radecki et al. 2005). BDNF polymorphisms involving the substitution of Valine (Val) for Methionine (Met) at codon 66, result in an increase of activity-dependent secretion of BDNF (Egan et al. 2003). The amount of available BDNF protein, therefore, is significantly decreased in carriers of the Met allele.

Interestingly, recent research has documented that low levels of the BDNF protein are present in individuals with MDD (Karege et al. 2002), and that polymorphisms of the BDNF gene are associated with increased risk for depression (Schumacher et al. 2005). One hypothesis concerning the etiology of MDD is that lower levels of the BDNF protein decrease protection against stress-induced damage to neuronal gray matter (Duman and Monteggia 2006). Indeed, at least one study examining the association between MDD and the BDNF gene has supported this formulation. Frodl et al. (2007) found that currently depressed individuals exhibited reduced hippocampal volume compared with never-depressed individuals; interestingly, the greatest reductions were found in individuals who carried the BDNF Met allele. Importantly, however, this study, like others (Pezawas et al. 2004; Bueller et al. 2006) also found associations between BDNF and hippocampus volume in the nondepressed group, suggesting that the BDNF gene alone does not account for MDD-related abnormalities in brain structure. In this context, the results of more recent studies point to a better-defined role of BDNF polymorphisms in the pathogenesis of depression. For example, Gatt et al. (2009) found that the combination of Met-allele carrier status and exposure to childhood trauma predicted a reduction in gray matter in hippocampus and lateral prefrontal cortex and, in turn, higher rates of depression. Similarly, Gerritsen and colleagues (in press) reported that Met-allele carriers with a history of childhood trauma had significantly less gray matter volume in the subgenual ACC than did both Met-allele carriers without trauma and Val/Val homozygotes with trauma. Therefore, similar to the role of 5-HTTLPR in the emergence of depression and its related neurobiological abnormalities, the likelihood that neural markers for depression are transmitted from parent to child could also be a function of the interaction of the BDNF genotype and other personal or environmental factors.

Finally, a growing body of research suggests that interactions among various genes play a significant role in the development of both depression and depression-related abnormalities in neural structure and function. For example, in a study of healthy preschoolers, HPA-axis reactivity to a laboratory stressor was found to be higher in s-allele homozygotes who were also carriers of the BDNF Met-allele than it was in s-allele homozygotes who carried two copies of the BDNF Val allele

(Dougherty et al. 2010). This finding is consistent with the results of at least one study linking an interaction of the BDNF Met-allele and 5-HTTLPR s-allele with elevated levels of depressive symptoms in children (Kaufman et al. 2006), and extends prior suggestions of a protective effect of the BDNF Val-allele. However, the results of research examining the protective effects of the BDNF gene are equivocal. Pezawas et al. (2008), for example, found significant volume reductions in subgenual ACC in non-disordered individuals who were homozygous for the 5-HTTLPR s-allele compared to carriers of the l-allele, with the most severe deficits present in individuals who were also homozygous for the BDNF Val allele.

Indeed, a recurring difficulty in this field involves the non-replication of initially promising findings (e.g., see Scharinger et al. 2010 for a review). While this may be due in part to small sample sizes, another issue that serves to complicate matters is gene–environment correlations (rGE), which occur when specific genetic factors influence individuals' exposure to certain environments. It therefore remains possible for example, that reductions in neural function and structure of 5-HTTLPR s-allele homozygotes could be directly related to heritable increases in the exposure to high-risk environments. Indeed, relevant to the focus of this review, a growing body of research provides evidence to support the notion that environmental risk factors for depression, including aspects of the social environment, such as the experience of negative life events and negative parent–child relationships, are heritable (Thapar et al. 1998; Rice et al. 2003; Lau et al. 2006; Lau and Eley 2008; Wichers et al. 2008). These findings, taken in context with the knowledge that environmental factors have a profound effect on the development of depression and its neurobiological hallmarks (as we discuss in greater detail below), make it clear that additional studies are needed, with sample sizes large enough to be able to test the interaction of BDNF and 5-HTTLPR polymorphisms, to help clarify epistatic relations between these genes and their interaction with other neural and environmental risk markers for depression.

3.2 Environmental Factors

It is now well-documented that long periods of separation of neonatal rodents and non-human primates from their mothers elicit changes in HPA-axis function that persist into adulthood and that resemble characteristics of depressed adults (Sanchez et al. 2001). Paralleling these findings are reports showing that HPA-axis dysfunction (Heim et al. 2002, 2008) and volumetric reductions in cortical (Hanson et al. 2010; van Harmelen et al. 2010) and subcortical gray matter (Vythilingam et al. 2002) are present in individuals who have experienced childhood trauma.

Given these findings, researchers seeking to identify the factors that are involved in the intergenerational transmission of depression risk have also focused on whether environmental factors, such as depression-related alterations in parental care, might influence both risk for depression, and abnormal development of the HPA axis. For example, Halligan et al. (2004) found in a longitudinal study

that the presence of postnatal depression in mothers was significantly associated 13 years later with higher morning waking cortisol levels in their offspring, suggesting long-term associations between early exposure to maternal depression and HPA-axis dysfunction. Interestingly, subsequent analyses of these data indicated that cortisol abnormalities in these adolescent offspring were significantly associated with the quality of maternal care received during the first year of life, but not 5 years later when the majority of cases of mothers' depression had remitted (Murray et al. 2010). Additional data collected from this sample indicate that the level of cortisol abnormalities at age 13 significantly predicted the severity of depressive symptoms an average of 3 years later (Halligan et al. 2007). Thus, depression-related disturbances in maternal care may contribute to the risk for depressive disorder through long-term alterations of HPA-axis function in the first year of life.

Indeed, researchers are documenting that depression in mothers is associated with disturbed parenting processes, including a decreased sensitivity to infant needs and increased rates of withdrawn and disengaged behaviors (Field 1984, 1994; Murray and Cooper 2003). These types of behaviors may be particularly stressful to the child (Langrock et al. 2002), and researchers have suggested that this type of chronic stress mediates the association between maternal depression and depression in the offspring. For example, Hammen et al. (2003) found that whereas the onset of depression in offspring of depressed mothers was more frequently associated with chronic interpersonal stress (i.e., stress resulting from social interactions between the child/adolescent and others in his or her environment), the onset of depression in offspring of never depressed mothers was associated more frequently with an episodic stressor (i.e., a stressful life event). Moreover, although there are not yet studies similar to that conducted by Murray et al. (2010), who examined neuroendocrine systems while taking into account depression-related alterations in maternal care, it is becoming increasingly clear that poor maternal care is associated with alterations in structure of the amygdala (Caldji et al. 1998) and disturbances in HPA-axis function (Liu et al. 2000; Huot et al. 2004). Moreover, periods of maternal separation lasting as little as 24 hours have been documented in animal studies to lead to permanent reductions in hippocampal BDNF expression (Roceri et al. 2002). It is clear, therefore, that we need more investigations that integrate the construct of maternal care into models testing the mediating effects of this variable on the association between maternal depression and neurobiological abnormalities in the children.

Finally, maternal depression may contribute to neurobiological abnormalities in the child through prenatal exposure to biological factors present during pregnancy (see Goodman and Gotlib 1999, for a model and review). Although depression during pregnancy is at least as common as, if not more common than postnatal or lifetime depression (O'Hara et al. 1990; Evans et al. 2001), relatively few studies have examined this issue. Of these few however, women who experience depression during pregnancy have been found to demonstrate higher basal cortisol levels than do pregnant women who are not depressed (Lundy et al. 1999; Field et al. 2006a, b). Moreover, these elevations in cortisol have been linked with

higher levels of fetal (Glover 1997; Gitau et al. 2001) and newborn cortisol (Lundy et al. 1999; Diego et al. 2004). Newborns of mothers who were depressed during pregnancy also exhibit greater relative right frontal electroencephalography (EEG) asymmetries, as well as more negative and "withdrawal" emotions compared to newborns of mothers who were not depressed during pregnancy (Lundy et al. 1999; Diego et al. 2004). Thus, neurobiological abnormalities in offspring of depressed parents may emerge not only as a consequence of genetic factors and/or depression-related alterations in parental care, but may result from abnormal development of neural systems caused by exposure to aberrant biological factors in utero.

4 Conclusion and Future Directions

Major depression is associated with a wide range of neurobiological disturbances, including dysregulation of the HPA axis and disruptions in the structure and function of cortical and subcortical gray matter. In this chapter, we have reviewed research demonstrating that many of these same abnormalities are also present in the never-depressed offspring of adults with recurrent depression, suggesting that these aberrations are not necessarily correlates or consequences of the experience of depression and/or its treatment, but could reflect dysfunctional neuroregulatory systems that precede the onset of this disorder. Indeed, literature in this area has demonstrated that disruptions in the structure and/or function of the hippocampus, amygdala, prefrontal cortex, basal ganglia, and striatum are present in individuals who are at familial risk for MDD, as are abnormalities in the regulation of the HPA axis. Studies using a prospective approach have extended these findings to show that high-risk offspring who later go on to develop depression have more severe abnormalities in HPA-axis function and hippocampal structure than do individuals who do not develop depression. These findings indicate that anomalies in neurobiological functioning may be useful in predicting which high-risk individuals are at even greater risk for developing MDD. Whether neural function and structure of other brain regions may be similarly useful in predicting which individuals will develop depression is not known, and clearly is an important area for future research.

We also presented and discussed different mechanisms by which abnormalities in neural and neuroendocrine function may be transmitted from depressed parent to child. Genetic factors (e.g., 5-HTTLPR, BDNF) are likely to be important in explaining associations between maternal depression and neural anomalies in the offspring. In addition, environmental factors, particularly those involving stress and/or disruptions in prenatal, infant, or childhood surroundings, likely also influence the emergence of neurobiological markers of risk. It is imperative that researchers continue to try to understand how these and other factors may be involved in the transmission of neurobiological markers of risk; such studies will be critical to elucidating the mechanisms that underlie the intergenerational transmission of risk for depression. Complicating matters, however, are findings

that allelic variants of certain genes are correlated with environmental risk factors for depression (Lau and Eley 2008). Moreover, it is likely that there are several other variables that we did not discuss in this chapter but that are also involved in the intergenerational transmission of neurobiological abnormalities, and that these other variables interact with genetic and environmental risk factors for depression in complex ways, creating diverse pathways to MDD and depression-related patterns of neural anomaly.

In this context, future studies examining the intergenerational transmission of neural abnormalities should also elucidate the potential causal relations among different neurobiological markers of risk. The hippocampus and PFC, for example, both provide negative feedback to the HPA axis (Herman et al. 2005), and both are structurally and/or functionally abnormal in depressed individuals and their never-depressed offspring (Videbech and Ravnkilde 2004; Hamilton et al. 2008; Koolschijn et al. 2009; Kempton et al. 2011). Altered HPA-axis activity in depressed and high-risk individuals, therefore, could be secondary to damage to hippocampal or PFC gray matter. Chronically elevated levels of cortisol, however, can have adverse morphologic effects on gray matter (Sapolsky 2000), particularly in brain areas that contain a high density of cortisol receptors, such as the hippocampus and PFC (Chao et al. 1989; Sapolsky 2000; Furay et al. 2008). Thus, increased systemic levels of this hormone may cause the volumetric reductions that have been found in these brain regions. Future studies that integrate multiple measures across several time points would be helpful in determining whether and how these neurobiological markers of risk are causally related to each other in forming a vicious cycle of neurobiological abnormality.

Finally, although the research discussed in this chapter serves to increase our understanding of how depression in parents can influence neurobiological abnormalities in their never-depressed offspring, these findings could also contribute to the development of effective prevention strategies. Certainly, it is clear that there is still much to be learned about what leads to the development of neurobiological abnormalities in offspring of depressed parents; it is also clear that we do not yet understand precisely how these anomalies might mediate the appearance of depressive symptoms. Nevertheless, we are beginning to link the study of neurobiological anomalies with the elucidation of possibilities for prevention efforts. For example, Dozier et al. (2008) found that HPA-axis dysfunction becomes normalized in foster children, a population posited to share adversities similar to those of animals studied in early-separation paradigms, whose foster parents participate in behavior intervention paradigms that promote nurturing care and attachment security. These findings are consistent with "cross-fostering" experiments with animals, in which researchers have found that neurobiological changes associated with early life trauma can be altered by subsequent "optimal" caregiving experience (Maccari et al. 1995; Barbazanges et al. 1996). Other investigators have found that specific pharmacologic agents are capable of reversing neurobiological alterations caused by early life stress (Suomi 1991; Lopez et al. 1999). And, importantly, other classes of medications have been found to *prevent* abnormalities in neural structure (McEwen et al. 1997; Magariños et al. 1999)

that have been documented in previous studies to be caused by trauma or stress. Thus, pharmacologic agents and optimal caregiving environments may be useful in protecting against further neurobiological abnormality in individuals at familial risk for depression.

Findings from prevention and treatment studies are intriguing because they suggest that the results of these investigations, when combined with research examining aspects of parental depression that may contribute to the presence of neurobiological abnormalities in the children, could facilitate the development of targeted strategies for prevention and intervention, and thereby reduce the socio-economic burden of MDD. Moreover, by continuing to study and elucidate neurobiological abnormalities in individuals who are at high risk for depression but who have not yet developed depression themselves, we can begin to understand whether and how these abnormalities, once inherited, can influence the subsequent onset of clinically significant symptoms of MDD.

Acknowledgments Preparation of this chapter was facilitated by NIMH Grants MH59259 and MH74849 to Ian H. Gotlib and MH090617 to Lara Foland-Ross, and by a Hope for Depression Research Foundation Grant awarded to Ian H. Gotlib and Lara Foland-Ross.

References

Adam EK, Doane LD, Zinbarg RE, Mineka S, Craske MG, Griffith JW (2010) Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. Psychoneuroendocrinology 35(6):921–931

Adolphs R (2008) Fear, faces, and the human amygdala. Curr Opin Neurobiol 18(2):166–172

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381

Amico F, Meisenzahl E, Koutsouleris N, Reiser M, Moller HJ, Frodl T (2011) Structural MRI correlates for vulnerability and resilience to major depressive disorder. J Psychiatry Neurosci 36(1):15–22

Aron AR (2011) From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psychiatry 69(12):e55–e68

Baaré WF, Vinberg M, Knudsen GM, Paulson OB, Langkilde AR, Jernigan TL, Kessing LV (2010) Hippocampal volume changes in healthy subjects at risk of unipolar depression. J Psychiatr Res 44(10):655–662

Barbazanges A, Vallée M, Mayo W, Day J, Simon H, Le Moal M, Maccari S (1996) Early and later adoptions have different long-term effects on male rat offspring. J Neurosci 16(23):7783–7790

Beardslee WR, Versage EM, Gladstone TR (1998) Children of affectively ill parents: a review of the last 10 years. J Am Acad Child Adolesc Psychiatry 37(11):11134–11141

Beauregard M, Levesque J, Bourgouin P (2001) Neural correlates of conscious self-regulation of emotion. J Neurosci 21(18):RC165

Bhagwagar Z, Hafizi S, Cowen PJ (2005) Increased salivary cortisol after waking in depression. Psychopharmacologia 182(1):54–57

Browning M, Holmes EA, Harmer CJ (2010) The modification of attentional bias to emotional information: a review of the techniques, mechanisms, and relevance to emotional disorders. Cogn Affect Behav Neurosci 10(1):8–20

Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta JK (2006) BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. Biol Psychiatry 59(9):812–815

Burke HM, Davis MC, Otte C, Mohr DC (2005) Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 30(9):846–856

Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ (1998) Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. Proc Nat Acad Sci USA 95(9):5335–5340

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301(5631):386–389

Chen MC, Hamilton JP, Gotlib IH (2010) Decreased hippocampal volume in healthy girls at risk of depression. Arch Gen Psychiatry 67(3):270–276

Chao HM, Choo PH, McEwen BS (1989) Glucocorticoid and mineralocorticoid receptor mRNA expression in rat brain. Neuroendocrinology 50(4):365–371

Critchley H, Daly E, Phillips M, Brammer M, Bullmore E, Williams S, Van Amelsvoort T, Robertson D, David A, Murphy D (2000) Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. Hum Brain Mapp 9(2):93–105

Dannlowski U, Konrad C, Kugel H, Zwitserlood P, Domschke K, Schöning S, Ohrmann P, Bauer J, Pyka M, Hohoff C, Zhang W, Baune BT, Heindel W, Arolt V, Suslow T (2010) Emotion specific modulation of automatic amygdala responses by 5-HTTLPR genotype. Neuroimage 53(3):893–898

De Raedt R, Koster EH, Joormann J (2010) Attentional control in depression: a translational affective neuroscience approach. Cogn Affect Behav Neurosci 10(1):1–7

Dearing KF, Gotlib IH (2009) Interpretation of ambiguous information in girls at risk for depression. J Abnorm Child Psychol 37(1):79–91

Dickerson SS, Kemeny ME (2004) Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull 130(3):355–391

Diego MA, Field T, Hernandez-Reif M, Cullen C, Schanberg S, Kuhn C (2004) Prepartum, postpartum, and chronic depression effects on newborns. Psychiatry 67(1):63–80

Dougherty LR, Klein DN, Congdon E, Canli T, Hayden EP (2010) Interaction between 5-HTTLPR and BDNF Val66Met polymorphisms on HPA axis reactivity in preschoolers. Biol Psychiatry 83(2):93–100

Dozier M, Peloso E, Lewis E, Laurenceau JP, Levine S (2008) Effects of an attachment-based intervention on the cortisol production of infants and toddlers in foster care. Dev Psychopathol 20(3):845–859

Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59(12):1116–1127

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112(2):257–269

Eisenberger NI, Gable SL, Lieberman MD (2007) Functional magnetic resonance imaging responses relate to differences in real-world social experience. Emotion 7(4):745–754

Evans J, Heron J, Francomb H, Oke S, Golding J (2001) Cohort study of depressed mood during pregnancy and after childbirth. BMJ 323(7307):257–260

Feldman S, Conforti N, Siegel RA (1982) Adrenocortical responses following limbic stimulation in rats with hypothalamic deafferentations. Neuroendocrinology 35:205

Field T (1984) Early interactions between infants and their postpartum depressed mothers. Infant Behav Dev 7(4):537–540

Field T (1994) The effects of mother's physical and emotional unavailability on emotion regulation. The development of emotion regulation. N. A. Fox Chicago, University of Chicago Press

Field T, Diego M, Dieter J, Hernandez-Reif M, Schanberg S, Kuhn C, Yando R, Bendell D (2006a) Prenatal depression effects on the fetus and newborn: a review. Infant Behav Dev 29(3):445–455

Field T, Hernandez-Reif M, Diego M, Figueiredo B, Schanberg S, Kuhn C (2006b) Prenatal cortisol, prematurity and low birthweight. Infant Behav Dev 29(2):268–275

Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE (2009) Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry 166(1):64–73

Forbes EE, Shaw DS, Dahl RE (2007) Alterations in reward-related decision making in boys with recent and future depression. Biol Psychiatry 61(5):633–639

Fries E, Dettenborn L, Kirschbaum C (2009) The cortisol awakening response (CAR): facts and future directions. Int J Psychophysiol 72(1):67–73

Frodl T, Schüle C, Schmitt G, Born C, Baghai T, Zill P, Bottlender R, Rupprecht R, Bondy B, Reiser M, Möller HJ, Meisenzahl EM (2007) Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. Arch Gen Psychiatry 64(4):410–416

Furay AR, Bruestle AE, Herman JP (2008) The role of the forebrain glucocorticoid receptor in acute and chronic stress. Endocrinology 149(11):5482–5490

Furman DJ, Hamilton JP, Joormann J, Gotlib IH (2010) Altered timing of amygdala activation during sad mood elaboration as a function of 5-HTTLPR. Soc Cogn Affect Neurosci 6(3):270–276

Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P (2009) Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34(6):418–432

Gallagher P, Reid KS, Ferrier IN (2009) Neuropsychological functioning in health and mood disorder: modulation by glucocorticoids and their receptors. Psychoneuroendocrinology 34(Suppl 1):S196–S207

Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, Gordon E, Kemp AH, Williams LM (2009) Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry 14(7):681–695

Gerritsen L, Tendolkar I, Franke B, Vasquez AA, Kooijman S, Buitelaar J, Fernández G, Rijpkema M (in press) BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. Mol Psychiatry

Gitau R, Fisk NM, Teixeira JM, Cameron A, Glover V (2001) Fetal hypothalamic-pituitaryadrenal stress responses to invasive procedures are independent of maternal responses. J Clin Endocrinol Metab 86(1):104–109

Glover V (1997) Maternal stress or anxiety in pregnancy and emotional development of the child. Br J Psychiatry 171:105–106

Gold GI (2003) Linking reward expectation to behavior in the basal ganglia. Trends Neurosci 26(1):12–14

Goodman SH, Gotlib IH (1999) Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. Psychol Rev 106(3): 458–490

Goodyer IM, Bacon A, Ban M, Croudace T, Herbert J (2009) Serotonin transporter genotype, morning cortisol and subsequent depression in adolescents. Br J Psychiatry 195(1):39–45

Goodyer IM, Tamplin A, Herbert J, Altham PM (2000) Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. Br J Psychiatry 177:499–504

Gotlib IH, Hamilton JP (2008) Neuroimaging and depression: current status and unresolved issues. Curr Dir Psychol Sci 17(2):159–163

Gotlib IH, Hamilton JP, Cooney RE, Singh MK, Henry ML, Joormann J (2010) Neural processing of reward and loss in girls at risk for major depression. Arch Gen Psychiatry 67(4):380–387

Gotlib IH, Joormann J, Minor KL, Hallmayer J (2008) HPA-axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. Biol Psychiatry 63(9):847–851

Gotthardt U, Schweiger U, Fahrenberg J, Lauer CJ, Holsboer F, Heuser I (1995) Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. Am J Physiol 268(Pt 4):R865–R873

Halligan SL, Herbert J, Goodyer I, Murray L (2007) Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. Biol Psychiatry 62(1):40–46

Halligan SL, Herbert J, Goodyer IM, Murray L (2004) Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. Biol Psychiatry 55(4):376–381

Hamilton JP, Siemer M, Gotlib IH (2008) Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry 13(11):993–1000

Hammen C, Shih J, Altman T, Brennan PA (2003) Interpersonal impairment and the prediction of depressive symptoms in adolescent children of depressed and nondepressed mothers. J Am Acad Child Adolesc Psychiatry 42(5):571–577

Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ, Pollak SD (2010) Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. J Neurosci 30(22):7466–7472

Hariri AR, Bookheimer SY, Mazziotta JC (2000) Modulating emotional responses: effects of a neocortical network on the limbic system. NeuroReport 11(1):43–48

Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, Egan MF, Weinberger DR (2005) A susceptibility gene for affective disorders and the response of the human amygdala. Arch Gen Psychiatry 62(2):146–152

Harris TO, Borsanyi S, Messari S, Stanford K, Brown GW, Cleary SE, Shiers HM, Herbert J (2000) Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. Br J Psychiatry 177:505–510

Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB (2008) The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. Biol Psychiatry 63(4):398–405

Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB (2000) Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. J Am Med Assoc 284(5):592–597

Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB (2002) The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. Depress Anxiety 15(3):117–125

Herman JP, Ostrander MM, Mueller NK, Figueiredo H (2005) Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 29(8):1201–1213

Herman JP, Schäfer MK, Young EA, Thompson R, Douglass J, Akil H, Watson SJ (1989) Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo-pituitary-adrenocortical axis. J Neurosci 9(9):3072–3082

Heuser I, Yassouridis A, Holsboer F (1994) The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. J Psychiatr Res 28(4):341–356

Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677–736

Huang H, Fan X, Williamson DE, Rao U (2011) White matter changes in healthy adolescents at familial risk for unipolar depression: a diffusion tensor imaging study. Neuropsychopharmacology 36(3):684–691

Huber TJ, Issa K, Schik G, Wolf OT (2006) The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. Psychoneuroendocrinology 31(7):900–904

Huot RL, Gonzalez ME, Ladd CO, Thrivikraman KV, Plotsky PM (2004) Foster litters prevent hypothalamic-pituitary-adrenal axis sensitization mediated by neonatal maternal separation. Psychoneuroendocrinology 29(2):279–289

Joormann J, Cooney RE, Henry ML, Gotlib IH (2012) Neural correlates of automatic mood regulation in girls at high risk for depression. J Abnorm Psychol 121(1):61–72
Joormann J, Gilbert K, Gotlib IH (2010) Emotion identification in girls at high risk for depression. J Child Psychol Psychiatry 51(5):575–582
Joormann J, Talbot L, Gotlib IH (2007) Biased processing of emotional information in girls at risk for depression. J Abnorm Psychol 116(1):135–143
Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM (2002) Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatric Research 109(2):143–148
Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S, Krystal JH, Gelernter J (2006) Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry 59(8):673–680
Kaufman J, Yang BZ, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH, Gelernter J (2004) Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Nat Acad Sci USA 101(49):17316–17321
Kawagoe R, Takikawa Y, Hikosaka O (1998) Expectation of reward modulates cognitive signals in the basal ganglia. Nat Neurosci 1(5):411–416
Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, Williams SC (2011) Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 68(7):675–690
Kensinger EA, Corkin S (2004) Two routes to emotional memory: distinct neural processes for valence and arousal. Proc Nat Acad Sci USA 101(9):3310–3315
Kessler RC, Wang PS (2009) Epidemiology of depression. In: Gotlib IH, Hammen CL (eds) Handbook of depression, 2nd edn. Guilford, New York
Kieseppä T, Eerola M, Mäntylä R, Neuvonen T, Poutanen V, Luoma K, Tuulio-Henriksson A, Jylhä P, Mantere O, Melartin T, Rytsälä H, Vuorilehto M, Isometsä E (2010) Major depressive disorder and white matter abnormalities: a diffusion tensor imaging study with tract-based spatial statistics. J Affect Disord 120(1–3):240–244
Knorr U, Vinberg M, Kessing LV, Wetterslev J (2010) Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. Psychoneuroendocrinology 35(9):1275–1286
Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS (2009) Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp 30(11):3719–3735
Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD (2008) Abnormal temporal difference reward-learning signals in major depression. Brain 131(Pt 8):2084–2093
Lai CH, Hsu YY, Wu YT (2010) First episode drug-naive major depressive disorder with panic disorder: gray matter deficits in limbic and default network structures. Eur Neuropsychopharmacol 20(10):676–682
Langrock AM, Compas BE, Keller G, Merchant MJ, Copeland ME (2002) Coping with the stress of parental depression: parents' reports of children's coping, emotional, and behavioral problems. J Clin Child Adolesc Psychol 31(3):312–324
Lau JY, Eley TC (2008) Disentangling gene-environment correlations and interactions on adolescent depressive symptoms. J Child Adolesc Psychiatry 49(2):142–150
Lau JYF, Rijsdijk FV, Eley TC (2006) I think, therefore I am: a twin study of attributional style in adolescents. J Child Psychol Psychiatry 47:696–703
Lévesque ML, Beauregard M, Ottenhof KW, Fortier E, Tremblay RE, Brendgen M, Pérusse D, Dionne G, Robaey P, Vitaro F, Boivin M, Booij L (2011) Altered patterns of brain activity during transient sadness in children at familial risk for major depression. J Affect Disord 135(1–3):410–413
Levinson DF (2006) The genetics of depression: a review. Biol Psychiatry 60(2):84–92
Liu D, Diorio J, Day JC, Francis DD, Meaney MJ (2000) Maternal care, hippocampal synaptogenesis and cognitive development in rats. Nat Neurosci 3(8):799–806

Lopez JF, Akil H, Watson SJ (1999) Neural circuits mediating stress. Biol Psychiatry 46(11):1461–1471

Lundy BL, Jones NA, Field T, Nearing G, Davalos M, Pietro PA, Schanberg S, Kuhn C (1999) Prenatal depression effects on neonates. Infant Behav Dev 22(1):119–129

Lupien SJ, King S, Meaney MJ, McEwen BS (2000) Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. Biol Psychiatry 48(10):976–980

Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, Pruessner JC, Séguin JR (2011) Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc Nat Acad Sci USA 108(34):14324–14329

Maccari S, Piazza PV, Kabbaj M, Barbazanges A, Simon H, Le Moal M (1995) Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. J Neurosci 15(1):110–116

Magariños AM, Deslandes A, McEwen BS (1999) Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. Eur J Pharmacol 371(2–3):113–122

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110

Mannie ZN, Bristow GC, Harmer CJ, Cowen PJ (2007a) Impaired emotional categorisation in young people at increased familial risk of depression. Neuropsychologia 45(13):2975–2980

Mannie ZN, Harmer CJ, Cowen PJ (2007b) Increased waking salivary cortisol levels in young people at familial risk of depression. Am J Psychiatry 164(4):617–621

Mannie ZN, Taylor MJ, Harmer CJ, Cowen PJ, Norbury R (2011) Frontolimbic responses to emotional faces in young people at familial risk of depression. J Affect Disord 130(1–2): 127–132

McEwen BS (1998) Protective and damaging effects of stress mediators. N Engl J Med 338(3):171–179

McEwen BS, Conrad CD, Kuroda Y, Frankfurt M, Magarinos AM, McKittrick C (1997) Prevention of stress-induced morphological and cognitive consequences. Eur Neuropsychopharmacol 7(3):S323–S328

Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, Rutter M, Sonuga-Barke EJ (2009) Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian adoptees study pilot. J Child Psychol Psychiatry 50(8):943–951

Mizoguchi K, Ishige A, Aburada M, Tabira T (2003) Chronic stress attenuates glucocorticoid negative feedback: involvement of the prefrontal cortex and hippocampus. Neuroscience 119(3):887–897

Monk CS, Klein RG, Telzer EH, Schroth EA, Mannuzza S, Moulton JL III, Guardino M, Masten CL, McClure-Tone EB, Fromm S, Blair RJ, Pine DS, Ernst M (2008) Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. Am J Psychiatry 165(1):90–98

Monroe SM, Simons AD (1991) Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychol Bull 110(3):406–425

Murer MG, Yan Q, Raisman-Vozari R (2001) Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. Prog Neurobiol 63(1):71–124

Murray C, Lobez A (1996) The global burden of disease. Harvard School of Public Health, Cambridge

Murray L, Cooper P (2003) Intergenerational transmission of affective and cognitive processes asociated with depression: infancy and the pre-school years. Oxford University Press, Oxford

Murray L, Halligan SL, Goodyer I, Herbert J (2010) Disturbances in early parenting of depressed mothers and cortisol secretion in offspring: a preliminary study. J Affect Disord 122(3):218–223

O'Hara MW, Zekoski EM, Philipps LH, Wright EJ (1990) Controlled prospective study of postpartum mood disorders: comparison of childbearing and non childbearing women. J Abnorm Psychol 99(1):3–15

Pessoa L, Adolphs R (2010) Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat Rev Neurosci 11(11):773–783

Peterson BS, Warner V, Bansal R, Zhu H, Hao X, Liu J, Durkin K, Adams PB, Wickramaratne P, Weissman MM (2009) Cortical thinning in persons at increased familial risk for major depression. Proc Nat Acad Sci USA 106(15):6273–6278

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2005) 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8(6):828–834

Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2008) Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. Mol Psychiatry 13(7):709–716

Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, Egan MF, Meyer-Lindenberg A, Weinberger DR (2004) The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci 24(45):10099–10102

Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M (2009) Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry 166(6):702–710

Posener JA, Schildkraut JJ, Samson JA, Schatzberg AF (1996) Diurnal variation of plasma cortisol and homovanillic acid in healthy subjects. Psychoneuroendocrinology 21(1):33–38

Price JL, Drevets WC (2010) Neurocircuitry of mood disorders. Neuropsychopharmacology 35(1):192–216

Pruessner M, Hellhammer DH, Pruessner JC, Lupien SJ (2003) Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. Psychosom Med 65(1):92–99

Radecki DT, Brown LM, Martinez J, Teyler TJ (2005) BDNF protects against stress-induced impairments in spatial learning and memory and LTP. Hippocampus 15(2):246–253

Rao U, Chen LA, Bidesi AS, Shad MU, Thomas MA, Hammen CL (2010) Hippocampal changes associated with early-life adversity and vulnerability to depression. Biol Psychiatry 67(4):357–364

Rao U, Hammen CL, Poland RE (2009) Risk markers for depression in adolescents: sleep and HPA measures. Neuropsychopharmacology 34(8):1936–1945

Ridderinkhoff KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306(5695):443–447

Rice F, Harold GT, Thapar A (2003) Negative life events as an account of age-related differences in the genetic aetiology of depression in childhood and adolescence. J Child Psychol Psychiatry 44:977–987

Roceri M, Hendriks W, Racagni G, Ellenbroek BA, Riva MA (2002) Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. Mol Psychiatry 7(6):609–616

Sanchez MM, Ladd CO, Plotsky PM (2001) Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev Psychopathol 13(3):419–449

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301(5634):805–809

Sapolsky RM (2000) The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry 48(8):755–765

Sapolsky RM, Krey LC, McEwen BS (1986) The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev 7(3):284–301

Scharinger C, Rabl U, Sitte HH, Pezawas L (2010) Imaging genetics of mood disorders. Neuroimage 53(3):810–821

Schlotz W, Hellhammer J, Schulz P, Stone AA (2004) Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response. Psychosom Med 66(2):207–214

Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ (2007) Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain 130(3):630–653

Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, Schulze TG, Deschner M, Schmäl C, Höfels S, Zobel A, Illig T, Propping P, Holsboer F, Rietschel M, Nöthen MM, Cichon S (2005) Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. Biol Psychiatry 58(4):307–314

Selvaraj S, Godlewska BR, Norbury R, Bose S, Turkheimer F, Stokes P, Rhodes R, Howes O, Cowen PJ (2011) Decreased regional gray matter volume in S' allele carriers of the 5-HTTLPR triallelic polymorphism. Mol Psychiatry 16(5):472–473

Sexton CE, Mackay CE, Ebmeier KP (2009) A systematic review of diffusion tensor imaging studies in affective disorders. Biol Psychiatry 66(9):814–823

Steele JD, Kumar P, Ebmeier KP (2007) Blunted response to feedback information in depressive illness. Brain 130(Pt 9):2367–2374

Steptoe A, Cropley M, Griffith J, Kirschbaum C (2000) Job strain and anger expression predict early morning elevations in salivary cortisol. Psychosom Med 62(2):286–292

Stetler C, Miller GE (2005) Blunted cortisol response to awakening in mild to moderate depression: regulatory influences of sleep patterns and social contacts. J Abnorm Psychol 114(4):697–705

Stetler C, Miller GE (2011) Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 73(2):114–126

Suomi SJ (1991) Early stress and adult emotional reactivity in rhesus monkeys. Ciba Found Symp 156(171–183):183–188

Thapar A, Harold G, McGuffin P (1998) Life events and depressive symptoms in childhood-shared genes or shared adversity? A research note. J Child Psychol Psychiatry 39: 1153–1158

Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti IM, Thomas KM, Freed PJ, Booma ES, Gunnar MR, Altemus M, Aronson J, Casey BJ (2010) Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev Sci 13(1):46–61

van Harmelen AL, van Tol MJ, van der Wee NJ, Veltman DJ, Aleman A, Spinhoven P, van Buchem MA, Zitman FG, Penninx BW, Elzinga BM (2010) Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. Biol Psychiatry 68(9):832–838

Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD (2003) Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry 54(7):693–702

Videbech P, Ravnkilde B (2004) Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 161(11):1957–1966

von dem Hagen EA, Passamonti L, Nutland S, Sambrook J, Calder AJ (2011) The serotonin transporter gene polymorphism and the effect of baseline on amygdala response to emotional faces. Neuropsychologia 49(4):674–680

Vreeburg SA, Hartman CA, Hoogendijk WJ, van Dyck R, Zitman FG, Ormel J, Penninx BW (2010) Parental history of depression or anxiety and the cortisol awakening response. Br J Psychiatry 197(3):180–185

Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW (2009) Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry 66(6):617–626

Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD (2002) Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 159(12):2072–2080

Way BM, Taylor SE (2010) The serotonin transporter promoter polymorphism is associated with cortisol response to psychosocial stress. Biol Psychiatry 67(5):487–492

Wichers M, Kenis G, Jacobs N, Mengelers R, Derom C, Vlietinck R, van Os J (2008) The BDNF Val(66)Met x 5-HTTLPR x child adversity interaction and depressive symptoms: an attempt at replication. Am J Med Genet 147B(1):120–123

Williamson DE, Birmaher B, Axelson DA, Ryan ND, Dahl RE (2004) First episode of depression in children at low and high familial risk for depression. J Am Acad Child Adolesc Psychiatry 43(3):291–297

Wust S, Federenko I, Hellhammer DH, Kirschbaum C (2000) Genetic factors, perceived chronic stress, and the free cortisol response to awakening. Psychoneuroendocrinology 25(7):707–720

Young EA, Aggen SH, Prescott CA, Kendler KS (2000) Similarity in saliva cortisol measures in monozygotic twins and the influence of past major depression. Biol Psychiatry 48(1):70–74

Young EA, Vazquez D, Jiang H, Pfeffer CR (2006) Saliva cortisol and response to dexamethasone in children of depressed parents. Biol Psychiatry 60(8):831–836

Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M (2001) Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression: a prospective study. J Psychiatr Res 35(2):83–94