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Developmental Risk I: Depression and the Developing Brain

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SYNOPSIS

This article discusses recent findings on the neurobiology of pediatric depression as well as the interplay between genetic and environmental factors in determining the risk for the disorder. Utilizing data from both animal and human studies, the authors focus on the evolving understanding of the developmental neurobiology of emotional regulation, cognitive function and social behavior as it applies to the risk and clinical course of depression. Treatment implications and directions for future research are also discussed.

Keywords

Adolescent; Depression; Brain; Development; Neurobiology

INTRODUCTION

In the past three decades, public health recognition of depression in children and adolescents has increased significantly. The prevalence of pediatric depression is on the rise[1–4], and depression during this developmental period is associated with significant impairment in multiple social domains[5–8]. Furthermore, there is evidence that early depressive episodes persist and/or recur into adult life along with ongoing psychosocial difficulties[8,9]. A growing body of research has been identifying the neurobiological and psychological correlates[8,10,11]. In addition, recent studies have begun to identify specific genetic and experiential risk factors[12–15]. The aim of this article is to describe recent findings on the neurobiology of pediatric depression as well as the interplay between genetic and environmental factors in determining the risk for the disorder. In particular, utilizing data from both animal and human studies, we will focus on the evolving understanding of the developmental neurobiology of emotional regulation, cognitive function and social behavior

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as it applies to the risk and clinical course of depression. Treatment implications and directions for future research also will be discussed.

DELOPMENTAL INFLUENCES ON THE VULNERABILTY TO DEPRESSION

The risk for depression increases markedly during the transition from childhood to adolescence[1]. Adolescence is a crucial developmental stage marked by a confluence of physical, biological, psychological and social challenges[16–19]. There are significant physical maturational changes (e.g., the onset of puberty), social-cognitive advances (e.g., ability for more abstract thinking and generalizations across situations and time), interpersonal transitions (e.g., changes in social roles in family and peer relationships), and social-contextual changes (e.g., school transitions). Although these maturational transitions offer tremendous opportunities for youth, because the developing brain regions underlying emotional, cognitive and behavioral systems mature at different rates, and because these systems are under the control of both common and independent biological processes, this developmental period also is marked by heightened vulnerability[16,18,20–22]. The normative developmental transitions associated with adolescence might serve as sensitive periods for the activation of specific processes involved in the onset, persistence and recurrence of depressive episodes[23–25].

THE DEVELOPMENTAL NEUROBIOLOGY OF ADOLESCENCE

Adolescence is perhaps the greatest time of neural change and maturation since infancy[26,27]. Simultaneously, this period of brain maturation is marked by improvements in the ability to understand social and emotional cues, as well as an increase in the responsiveness to and importance of peer and other interpersonal relationships[28–31]. Also, there is a gradual increase in the capacity for cognitive control and executive function, including abstract thought, organization, decision-making and planning, and response-inhibition[16,30,32,33]. Until recently, there was limited research on the neurobiological changes that accompany the emotional and cognitive changes that occur during adolescence. The application of magnetic resonance imaging (MRI) techniques has enabled researchers to examine the specific areas and circuits within the brain that are involved in the development of emotional and cognitive abilities[31,34–36].

Although there is a minimal increase in brain size after early-school-age years, remodeling of grey and white matter occurs throughout adolescence and into early adulthood[34,37]. In the grey matter, these changes are non-linear and region-specific. The grey matter changes take the form of increased myelination of different cortical connections and/or synaptic pruning, with a net reduction in volume [26,37–40]. There is a simultaneous linear increase in white matter density associated with increases in the diameter and myelination of the axons forming the fiber tracts alongside increased neural size and proliferation of glia[27,39–42].

Myelination increases the speed of neural transmission[27,43]. Synaptic pruning is the process by which excess connections (synapses) between neurons are removed. Synapse elimination is believed to reduce the immature pattern of processing[44]. The elimination of this immature pattern of processing is adaptive in that in its immature state it requires greater metabolic activity and the recruitment of a wider array of structures[44]. Additionally, pruning appears to increase the efficiency of cognitive processing through the creation of dedicated neural networks[36]. For instance, synaptic overproduction followed by selective pruning allows for maximum efficiency in associative memory functions[45,46]. Disturbances in these developmental patterns can adversely affect behavioral, emotional and cognitive control[21,22].

Neural Circuits

Prominent developmental transformations are seen in prefrontal cortex (PFC) and limbic brain regions of adolescents across a variety of species[16,18]. The above-described emotional and cognitive processes and social behavior (i.e., self-regulation) appear to depend on the maturation of PFC and limbic system interconnectivity[47–51]. The limbic system consists of diverse neural structures, including the cingulate cortex, amygdala and hippocampus, and it regulates emotional experience and motivational learning[48,49,51–55]. Furthermore, maturation of connections between the PFC, basal ganglia and cerebellum also appear to be crucial for the development of higher cognitive functions[56].

The PFC mediates the highest cognitive capacities, including reasoning, planning and behavioral control[57,58]. This relatively large and complex associative brain region has been shown to develop along with other higher-order association regions as children mature from adolescence into adulthood[26,58]. Structural neuroimaging studies using growth mapping techniques suggest that the prefrontal cortex matures more slowly than other regions of the brain[26,59], and that its development parallels the improvements in cognitive control and behavioral inhibition that emerge during the adolescent transition into adulthood[60]. Frontal lobe maturation, particularly thinning of the cortical gray matter, has been associated with better performance on verbal memory tests in children aged 7–16 years[61], and PFC volume in healthy adolescents has been associated with greater ability to inhibit behavioral responses[62]. Using diffusion tensor imaging (DTI) technology, changes in white matter microstructure have been studied. These studies indicated that anisotropy, a measure that reflects myelin-related restriction of water diffusion across axons, was significantly lower in the frontal white matter in pediatric samples than in adults, suggesting less myelination[63,64].

Functional MRI (fMRI) studies indicate that core regions of the neural circuitry underlying cognitive control are on-line early in development[32]. However, age-related changes in localized processes across the brain, and in establishing long-range connections that support top-down (cortical-subcortical) modulation of behavior and more effective neural processing for optimal mature executive function, have been demonstrated[32,65–70]. With respect to affect regulation, adolescents seem to show a greater magnitude of amygdala activation in response to facial expressions of emotion compared to children and adults[71–73]. The exaggerated amygdala activation in response to emotional cues in adolescents might be related to their intense and variable emotional responses[74–76]. In contrast to the exaggerated amygdala responses to emotional cues, preliminary evidence indicates that the PFC is under-recruited in adolescents compared to adults[73,77].

Although some neuroscientists describe cognition and emotion as separable processes implemented by different regions of the brain, such as the amygdala for emotion and the PFC for cognition, functional interactions between the amygdala and PFC mediate emotional influences on cognitive processes and vice versa. These mental processes are inextricably linked and represented in dynamic neural networks composed of interconnected prefrontal and limbic brain structures[48,49,51]. During adolescence, social relationships take on a new importance and adolescents become adept at reading social and emotional cues, and modulating their affective responses[28,78]. Evidence suggests that children have difficulty managing interference from competing distractions and the level of difficulty seems to be correlated with the immaturity of posterior and frontal association cortices[70]. As children mature, they show an increased ability to attend to incoming information and control their behavior in a goal-directed manner[60,68,77,79]. This development seems to emerge in conjunction with a progressive “frontalization” of functional activity associated with inhibitory processing[32,66,70].

Neurotransmitter Systems

In addition to connective and structural changes in the central nervous system, adolescents undergo dramatic alterations in virtually all neurotransmitter systems, including innervation patterns, neurotransmitter levels and signaling mechanisms[18,80,81]. Developmental studies have shown that neurotransmitter systems generally follow a trajectory of overproduction and pruning, such that changes in expression typically peak during late childhood/early adolescence and are then reduced to reach adult levels. This pattern of overproduction and regressive elimination are believed to fine-tune the brain for efficiency but it also represents a state of vulnerability to exogenous influences[18,22,80].

Cholinergic neurons projecting from the basal forebrain innervate the cerebral cortex during critical periods of neural development[82]. Acetylcholine stimulation may help to promote a favorable environment for neuronal maturation and the refinement of cortical connectivity. Acetylcholine also is likely to play a critical role in neural plasticity. Nicotinic acetylcholine receptors (nAChRs) appear early during development and are expressed throughout the nervous system. They not only exist on neuronal cell bodies and dendrites but also are located on axon terminals and are involved in multiple neurotransmitter release, including acetylcholine, dopamine, 5-HT, gamma-aminobutyric acid (GABA), glutamate and norepinephrine[83]. Muscarinic receptors gradually appear in the postnatal cortex and may be more dependent on the presence of nAChRs[84]. The cholinergic receptors are expressed at high levels in the developing cortex but then decline progressively to a significant extent during adolescence, with the cholinergic innervation of the PFC reaching mature levels[18]. The timing of cholinergic cortical innervation is of primary importance for the normal development of cognitive functions as nAChRs are involved in attention, learning and memory[85].

The mesostriatal and mesocorticolimbic dopamine pathways are involved in processing natural rewards and reward-directed behavior[86,87]. The mesostriatal-mesocorticolimbic dopamine system includes reciprocal dopamine projections from the ventral tegmental area in the midbrain into the ventral striatum, the limbic structures (amygdala in particular), and the orbitofrontal cortex[88]. The temporal relationships among exposure to rewards, dopamine neuronal firing activity and extracellular dopamine concentrations suggest that ventral striatal dopamine release is involved in forming associations between salient contextual stimuli and internal rewarding events[86,89].

Adolescence is associated with substantial development of the dopaminergic system. There is an increase in dopaminergic input to the PFC indexed by an increase in the density of dopaminergic fibers and transporters[18], which is partially offset by developmental decline in dopamine synthesis and turnover after early adolescence[80]. Dopamine receptors are overproduced in early adolescence, followed by pruning that is more evident in subcortical than prefrontal regions[18,90]. The net effect of increased dopaminergic projection to the PFC, which shows less pronounced receptor pruning, is a shift in the relative balance between subcortical and cortical dopaminergic systems, with dominance of the mesocortical dopaminergic system. The development of the dopamine system during adolescence is likely to have an influence on the pruning of PFC neurons[18]. Dopaminergic input to the PFC, then, likely contributes to the coupling of salient cortico-cortical connections, and concomitantly to the pruning of connections that do not have significant salience, thereby influencing the important adolescent neurodevelopmental process of prefrontal pruning and myelination[24].

Serotonin (5-HT) is involved in neural plasticity, a process through which modification of the functional properties of neurons and their networks occurs based on experience[91]. It has been hypothesized that neural plasticity occurs through a reversal of neuronal maturation that reinstates neuronal functions lost during development[92]. Such a dynamic process may

involve a number of mechanisms, including neurite outgrowth, synaptogenesis, neurogenesis and cell survival during brain development and even in adulthood[91]. There is evidence of significant 5- HT synaptic pruning in the basal forebrain around puberty in rats[93], and 5-HT1A receptor binding appears to decrease most dramatically in humans during adolescence[94].

Serotonin inhibits and opposes dopamine activity, particularly in relation to dopamine's role in aggressive and impulsive behaviors[95–97]. By puberty, dopamine input to the PFC is up to 3 times greater than serotonin input[98], and PFC concentrations of dopamine precursor are much greater than those of 5-HT precursor in pubertal rhesus monkeys[99]. The relative imbalance in the dopamine-serotonin activity during adolescence might explain the enhanced sensitivity to appetitive (rewarding) situations, resulting in a higher prevalence of risky behaviors[18,100,101].

Maturational changes during adolescence also have been detected in glutaminergic and GABAergic systems. The behavioral effects of agonists for a specific glutamate receptor, the Nmethyl- D-aspartate (NMDA) receptor, appear to peak late in the pre-adolescent period in rats[102], and this coincides with greater NMDA agonist sensitivity[103]. Glutaminergic inputs to the PFC appear to decrease during adolescence[18]. GABA opposes the modulating excitatory effects of glutamate[104]. GABA receptors achieve maturity in adolescence[105], and GABAergic input to the PFC appears to decrease strongly through adolescence in humans[18].

In summary, there are significant developmental changes in the neural circuits involved in emotional and cognitive regulation from childhood through adolescence. The following sections will discuss how these maturational changes might be associated with increased vulnerability to depression during adolescence.

THE DEVELOPMENTAL NEUROBIOLOGY OF DEPRESSIVE DISORDER: THEORETICAL MODELS

Utilizing developmental, integrative and neuroscience frameworks, several theoretical models have been proposed for the increased vulnerability to depression during adolescence. Some of these models are described.

The Social Information Processing Model

Nelson and colleagues[106] have proposed that developmental changes in social behavior during adolescence are correlated with the maturation of a brain system referred to as the social information processing network. This network consists of three specific nodes: the detection node, the affective node, and the cognitive-regulatory node. They hypothesized that these nodes develop along different trajectories, such that the development of the affective node, approximately equivalent to the subcortical limbic system, outpaces maturation of the cortically-based cognitive-regulatory node. The mismatch is proposed to create a vulnerability in which strong emotional responses to social stimuli are not tempered by the yet-to-mature regulatory mechanisms.

The Triadic Model

Ernst and Korelitz[21] put forth a triadic model comprised of three primary systems, namely the affective system (which includes the amygdala), the reward system (which includes the ventral striatum), and the cognitive/response inhibition system (which includes the PFC). Each system/node has its own developmental trajectory, which creates a state of flux during adolescence. Final behavioral outcomes are likely to depend on the dominant node of a given stage or could result from a weakened node that fails to perform regulatory functions.

In its simplified form, the triadic model explains exaggerated reactivity to a number of emotional stimuli[74–76], changes in reward sensitivity[107,108], and the significant lag in cortical control and cognitive development.

The Dysregulated Positive Affect Model

A third model, proposed by Forbes and Dahl[109], focuses on the relationship between adolescent depression and the development of the reward system. They conceptualized depression as a reduction in positive affectivity (a factor that indexes active engagement with the environment). The approach system is a motivational system whose function is the pursuit of reward, and it is posited to include brain structures (e.g., the nucleus accumbens) that mediate processing of reward information. From this view, depression is associated with deficits in the approach system. They posited a link between the development of neural systems underlying reward processing, which may become vulnerable to dysregulation as a consequence of remodeling during adolescence, and a predisposition to depression, particularly in vulnerable youth with a temperamental characteristic of low positive affect.

Integration of the Theoretical Models

An integration of the various models suggests that the increased vulnerability to depression and other psychiatric disorders during adolescence may be due to an imbalance between the relative structural and functional maturity of brain systems critical to emotional and incentive-based behavior (subcortical regions such as the amygdala and ventral striatum) compared to brain systems mediating cognitive and impulse control (e.g., PFC), suggesting that the PFC exerts less regulatory control over subcortical regions relative to adults[16,20,21,101,106].

This framework provides a heuristic model for explaining the neurodevelopmental basis for the affective and behavioral changes observed in adolescence. By demonstrating how the development of regulatory mechanisms lag behind development of affective brain systems, the model seems particularly appropriate for explaining the increased rates of dysregulated behaviors, especially antisocial behaviors, that emerge during adolescence but decline during adulthood when regulatory brain systems have reached adult levels of maturity[110,111]. However, it is not able to explain the increased rates of depression that start in adolescence but persist through adulthood[9], by which time, presumably, the regulatory mechanisms whose delayed development putatively gave rise to affective dysregulation, have matured[26,40]. The theory also appears to hold that affective and motivational systems are primarily comprised of subcortical structures, whereas the regulatory systems are cortical. Recently, the concept that affect and affective regulation (or affect and cognition) can even be said to exist as separable processes has been questioned[112–115].

In contrast to the above-described models that implicated the delayed development of the PFC compared to limbic areas as being responsible for the increased vulnerability to depression in adolescence, Davey and colleagues[24] proposed that the maturation of the PFC itself might be responsible for the development and maintenance of depression. According to this model, there is a cost to the PFC's ability to make decisions in complex social environments that take into account the consequences of decisions into the future, resulting in a heightened vulnerability to depression when anticipated future rewards are not attained.

As described above, there is substantial remodeling and maturation of the dopaminergic reward system and PFC during adolescence, that coincides with the adolescent entering the complex world of adult peer and romantic relationships, where the rewards that can be obtained (such as group affiliation, romantic love, social status) are abstract and temporally distant from the proximal context. Development of the PFC makes it possible to pursue such

complex and distal rewards, which are, however, tenuous and more readily frustrated than the more immediate rewards. Davey and Colleagues[24] hypothesized that when these distant rewards are unattainable, they suppress the reward system. When such suppression is extensive and occurs for an extended period of time, it manifests as depressive disorder.

The functional significance of the dopaminergic system's more extensive integration with PFC during adolescence is that the nature of the represented rewards becomes more sophisticated. The net result is the ability of adolescents to be motivated by, and to respond to, rewards that are more distal and complex[86,89]. Serotonin interacts with the dopaminergic system to further shape reward function[116,117], possibly by reducing impulsive over-responding to proximal affective stimuli in favor of maintaining affective engagement with the long-term goals[96,118].

Davey and colleagues[24] proposed that the initial episodes of clinical depression during adolescence often result from the frustration, or omission, of a highly anticipated social reward(s). Abstract social rewards have a greater salience and are associated with an active state of arousal[119,120]. When an anticipated reward is omitted, it has the effect of transiently suppressing the neural reward system[86]. Omission of rewards that are extended in their representation into the more distant future will cause a correspondingly prolonged suppression of the reward system, resulting in depression.

THE DEVELOPMENTAL NEUROBIOLOGY OF DEPRESSIVE DISORDER: EMPIRICAL DATA

Structural Brain Changes

Hippocampus—The hippocampus has been a focal area of research in both animal and human studies because depression is recognized as a stress-sensitive illness and the hippocampus is highly sensitive to stress, particularly during the early developmental period[121–124]. The hippocampus also is involved in mood regulation and cognitive function[125]. In animal models, extreme or chronic psychosocial stress was associated with dendritic atrophy of hippocampal pyramidal neurons and impaired neurogenesis in the dentate gyrus[126–128]. In a recent investigation, adult female cynomolgus macaque monkeys which exhibited spontaneously occurring depressive behavior manifested reduced volume compared with non-depressed controls specifically in the anterior portion of the hippocampus [129]. This finding is notable in that this region of the hippocampus has been implicated in emotional functioning. In a developmental study, subjecting infant monkeys to early-life stress lead to reductions in glucocorticoid and mineralocorticoid receptors in the hippocampus during adolescence (compared to non-stressed controls[130]).

Human studies, including both pediatric and adult samples, also reported a reduction in hippocampal volume in association with depression[121,131]. In a recent study, reduced hippocampal volume was observed in healthy adolescents at high familial risk for depression, particularly in those who experienced high levels of adversity in childhood[132]. Among youth who experienced high levels of adversity, reduced hippocampal volume partly accounted for the increased vulnerability to depression during longitudinal follow-up[132]. In another investigation, adult patients with depression showed a greater decline in grey matter density of the hippocampus than controls after 3 years, particularly in those who failed to remit from the index depressive episode[133]. Although morphological changes in the hippocampus have been associated with depression, not all studies replicated these findings. The variability in findings might be attributed to sample size, developmental stage of the sample, number of depressive episodes, duration of illness, family history of depression,

history of early-life adversity, comorbid symptoms and methodology of the morphometric analysis[131,134].

Amygdala—The amygdala is of importance to depression research due to its posited role in stress responses, as well as emotional and mood processes. In human adult studies, there was significant variability in amygdala changes associated with depression[135]. The variability across studies was accounted for by medication status such that studies that included only medicated individuals showed increased amygdala volume, whereas studies with only unmedicated persons showed a decrease in amygdala volume[135]. In a pediatric sample of medication-naïve patients with depression, an increased ratio of the amygdala to hippocampal volume was observed compared to age- and gender-matched controls, but this difference was accounted for by the severity of associated anxiety symptoms[136]. In a separate investigation, depressed youngsters had significant reductions of left and right amygdala volumes compared with healthy subjects. No significant correlations were found between amygdala volumes and depressive symptom severity, age at onset of illness, or illness duration.

Frontal Lobes—In adult human studies, depressed patients showed large volume reductions in frontal regions, especially in the anterior cingulate and orbitofrontal cortex, and sub-genual region of the PFC[137,138]. Gender, medication status, stage of illness and family history appear to affect the nature of the findings in a region-specific manner. In a pediatric sample, patients with non-familial depression had significantly increased left PFC volume compared to patients with familial depression as well as with healthy controls[139]. Left PFC volume correlated with severity of depression in familial but not in non-familial patients with depression[139]. Taken together, decreased left PFC volume in familial depression in youth and adults might result from degeneration of the left PFC[139–141], whereas larger left PFC volume in pediatric patients with non-familial depression might be due to developmental alterations in PFC maturation.

Striatum—Several studies in depressed adults reported grey matter deficits in the striatum, especially in the caudate nucleus[137,142]. Reduced caudate volume also was observed in adolescents with depression (Rao et al., unpublished data).

Summary of Structural Brain Changes—Morphometric changes have been observed in a number of brain regions in association with depressive disorder, particularly those involving corticostriatal and corticolimbic networks, in adults[143,144]. Limited studies in pediatric samples showed similar patterns[145,146]. Several DTI studies reported reduced white matter integrity (fractional anisotropy) in adult patients with depression, particularly in the frontal and temporal regions[147–150]. Microstructural white matter abnormalities also were detected during the firstepisode of depression in young adult patients[151] as well as in depressed adolescents[152]. In a pilot study, we reported alterations in white matter tracts in healthy adolescents at high familial risk for depression, suggesting that it might be a vulnerability marker for depression[153]. Post- mortem studies in animals and adult humans revealed alterations in glial cells in these networks[154–156]. Glial cells not only protect neurons through the production of myelin, but they are also dynamic partners participating in brain metabolism and communication between neurons[156].

Functional Brain Changes

Consistent with structural brain changes associated with depressive disorder, functional imaging (fMRI) studies in adults also implicated impaired corticostriatal and corticolimbic circuits[51,143,157,158]. Most of this research has focused on resting state data[159,160], or the processing of negative or positive emotional stimuli[160,161]. A summary of these data

indicate that patients with depression show increased neural activity in response to negative cues and diminished neural activity in response to positive stimuli in emotion-related brain circuits (e.g., amygdala and ventral striatum). Some of these abnormalities in the processing of emotional information persist after symptom remission and they have also been found in healthy individuals who are at heightened risk for the development of mood disorders. Limited data in pediatric populations also reported similar deficits in these neural networks although the direction of change (i.e., increased versus decreased response) has not been consistent across pediatric studies or in comparison with adult data[146,162–167].

Biochemical studies utilizing magnetic resonance spectroscopy (MRS) reported alterations in N-acetyl aspartate, glutamate/glutamine/GABA, creatinine/phosphocreatinine, choline and myoinositol concentrations in specific regions of the corticostriatal and corticolimbic networks in adult patients with depression[160,168–170]. Modest amount of research in pediatric samples is consistent with the findings in adults, suggesting developmental continuities[146,170–172].

In summary, data from functional neuroimaging studies in youngsters and adults indicate alterations in corticolimbic and corticostriatal circuits, similar to structural brain changes.

Summary of Neuroimaging Findings in Pediatric Depression

Although a growing body of research in pediatric depression has identified structural and functional brain changes, it has raised more questions than answers. This is, in great part, due to the modest sample sizes with cross-sectional designs. For instance, it is not clear how the maturational changes across child, adolescent and adult development relate to the vulnerability and maintenance of depression. More information is needed on which neural changes are specific to depression and how family history, severity of illness, symptom patterns and comorbid conditions influence the findings[131]. Also, it is not known whether the neural changes are pre-existing and increase vulnerability to the disorder or if they are a consequence of the illness[132,153,165]. Further, it is not known with any certainty if the observed brain changes are temporary, state-like conditions which resolve without any sequalae, are temporary but still place an individual on a delayed trajectory towards normal development, or whether any disruption to the normal maturational process during this period permanently and deleteriously affects the neurobiological systems. The last of these possibilities may well be the most likely explanation based on data regarding the increased risk for recurrent depressive episodes[173,174]. The effect of disease course on the neurobiological substrate also has not been studied[133]. The utility of these neural markers in the diagnosis, treatment and prognosis of the disorder should be established, as well as neurobiological changes in response to treatment[175,176]. In the final section of this article, future research directions will be discussed to address these issues.

INDIVIDUAL DIFFERENCES IN DEVELOPMENT AND VULNERABILITY TO DEPRESSION

Although adolescence is associated with dramatic maturational changes in multiple domains and this developmental period is marked by vulnerability to depression, it is important to recognize that the behavioral and neurobiological responses are highly subject to individual differences and only a small subset develops the disorder. Such individual differences may take the form of heritable characteristics such as stable personality traits, differences in neurotransmitter profiles and biologically-governed changes in hormones or other effects of puberty. Environmental factors (e.g., the social context, such as one's social status among peers) also make a contribution to individual differences. Depression itself has a significant heritable component[177], but stress interacts with the genetic diathesis to determine the

clinical manifestation of the disorder[178–180]. In the following section, the moderating influence of genetic and environmental factors on the relationship between neurobiological markers and vulnerability to depressive illness will be described.

Gene-Environment Interactions in Determining the Risk for Depression

Research indicates that genetic factors account for anywhere between 24%–58% of the variance in depression[177]. The relative contribution of genetics to depression vulnerability seems to vary with age. Some studies reported that the genetic influence on depression appears to increase with age, such that depression in adolescents appears to be influenced more by genes than is depression in children[181,182]. Contrary to this finding, other investigators found that the influence of genes decreases as children grow into adolescence[183,184]. The genetic risk also may be moderated by gender. Eley and Stevenson[185] found that genetic factors made a greater contribution to depression in males but not females. Silberg and colleagues[186] reported the opposite finding, with genes playing a greater role in females as they matured into adolescence, but not with males. Clearly, more research is needed before any meaningful conclusions can be made with regard to the relationships among genetic factors, development, gender and depression vulnerability.

A growing body of research has indicated that the genetic vulnerability is modified by adverse environmental conditions, particularly during early development, to increase the risk for depression[178,187]. For instance, in a longitudinal study of a birth cohort, Caspi and colleagues[188] found that individuals with the short allele of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) were at elevated risk for developing a depressive episode in adult life only if they experienced severe maltreatment in childhood. On the other hand, another investigation showed that the presence of positive social support to be protective against depression in children with 5-HTTLPR short allele and a prior maltreatment history[189]. However, not all studies found a relationship between 5-HTTLPR polymorphism in determining the risk for depression[190]. In addition to methodological differences across studies, factors such as stress sensitivity might determine the contribution of environmental factors on vulnerability to depression. For instance, Wichers and colleagues[180] found that greater stress sensitivity required less environmental influence for the clinical manifestation of depression.

Another candidate gene that has received significant attention in depression research is the corticotropin-releasing hormone type 1 receptor (CRHR1) because it mediates the hormonal responses to stress[178,191]. In a large community study of adults, a single nucleoside polymorphism (rs110402) of the CRHR1 gene moderated the effects of childhood abuse on depressive symptoms in adult life in males only; females with childhood maltreatment were at elevated risk for depressive symptoms regardless of the genetic alleles[191]. Additionally, the presence of the rare allele (the A allele in the case of rs110402) was protective against depression in males exposed to childhood abuse.

Genetic variants of the Val66Met polymorphism of brain-derived neurotrophic factor (BDNF) gene also have been studies in relation to gene-environment interactions on depression risk[192]. In such studies, childhood adversity seems to have a greater impact on depressive symptoms in Met allele carriers of the BDNF gene than in the Val/Val group. BDNF is important for neural plasticity[193]. In animal models, depressive states were associated with reduced BDNF levels in the brain, and central administration of BDNF has been shown to reverse such depressive states. In an investigation of children with and without maltreatment, a three-way interaction was observed among BDNF genotype, 5-HTTLPR and maltreatment history in predicting depression[194]. Children with the Met allele of the BDNF gene and two short alleles of 5-HTTLPR had the highest depression scores, but

the vulnerability associated with these two genotypes was only evident in maltreated children. However, social support was protective against depression in the vulnerable group.

Taken together, these data support gene-environment interactions in the etiology of depression across the lifespan.

Genetic and Environmental Influences on Neurobiological Responses and Vulnerability to Depression

There is a growing interest in understanding genetic influences on the variability in brain structure and function[195–197]. For example, genetic variants of the 5-HTTLPR and BDNF polymorphisms were associated with amygdala, hippocampal and prefrontal volumes[195,197,198]. Moreover, individuals carrying the 5HTTLPR short (risk) allele or BDNF Met allele had smaller hippocampal and/or amygdala volumes when they had a history of childhood maltreatment compared with those who only had one risk factor (environmental or genetic). Independent of genetic risk, childhood stress predicted additional hippocampal white matter alterations[195,198]. Although depressed patients had reduced PFC volume, individuals carrying the non-risk (long) allele and who also experienced high levels of childhood stress had larger PFC volumes, suggesting a protective effect[198]. Structural brain changes due to stress represent part of the mechanism by which the illness risk and outcome might be genetically-mediated.

Genetic factors also influence neurobiological responses. In a meta-analysis, there was an association between the magnitude of amygdala activation in response to emotional cues and 5-HTTLPR[196]. To our knowledge, there are no data on the gene-environment interactions in brain responses in relation to depressive disorder. In the study described above, the A allele of CRHR1 gene was associated with a less robust hormonal response in men, possibly serving as a potential mediator of protection against depression[191].

Summary of Findings on the Associations among Genes, Neurobiology, Environment and Depression

Genetic polymorphisms modulate brain structure and function. The structural and functional brain changes might serve as intermediate phenotypes in determining the risk for depressive illness. Environmental insults can further exacerbate the neurobiological alterations in at-risk individuals and magnify the risk for the disorder. In a similar vein, enriched/supportive environment can ameliorate the risk in genetically-vulnerable persons. A better understanding of the gene-environment interactions, and the mechanisms (e.g., neurobiological changes) through which risk and resilience for the disorder occur, will be helpful in developing more specific and effective preventive and treatment interventions.

Treatment Implications for Depression

While there is still much to learn in terms of understanding the neurobiology of depressive illness across the lifespan in general and pediatric depression in particular, the available data offer potential options for intervention. Given that depression is associated with reduced hippocampal volume and possibly other structural brain changes, interventions that can potentially reverse these changes could be helpful. Potential therapies such as antidepressant agents, electroconvulsive therapy and exercise that have been shown to promote neurogenesis ought to be considered[199–201]. Lithium has been found to reverse the glial cell changes[202]. Anti-glucocorticoid agents and CRH antagonists can be helpful in reducing the toxic effects of hypercortisolemia[203]. Psychotherapeutic interventions also can induce brain changes[204].

Future Directions for Research

Perhaps the most obvious implication from the current chapter is the need for more prospective longitudinal research in youngsters. Investigators should identify clear structure/function hypotheses that utilize, but go beyond, the current diagnostic system in order to translate findings from clinical neuroscience research into a new classification system based on pathophysiology and etiological processes[205]. Such models also may be able to explain the high rates of comorbidity between depression and other psychiatric conditions. Studies of depressed children and adolescents have a number of advantages compared with studies of adults; confounding factors such as repeated episodes, long duration of illness, multiple medications and co-occurring medical problems are minimized. It is also important to include high-risk youth who have not yet developed a depressive episode in order to identify pre-morbid factors. Another focus of future research should center on evaluating the stability of biological abnormalities. Given that adolescence is a high risk period for the onset of depression, in a relatively short follow-up period, it is possible to identify both pre-existing and "scar" markers of the illness.

It is important to obtain functional neuroimaging measures before and after pharmacological or behavioral interventions. Results from such studies will shed light on the mechanisms through which treatments work and may provide new intervention targets for drug development[206,207]. In addition to identifying potential mediators of different treatments, it is important for neuroimaging studies to identify baseline predictors of treatment outcome (i.e., the moderators). The identification of mediators and moderators of treatment would help move the field towards more "personalized" care[208]. Exciting times lie ahead in our efforts to tackle the mechanisms involved in pediatric depression and its treatment response.

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