Stress, sensitive periods and maturational events in adolescent depression

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In this paper, we provide an overview of how the maturation of specific brain regions and stress exposure during windows of vulnerability initiate a series of events that render adolescents exceptionally susceptible to the development of depression. This stress-incubation/corticolimbic development cascade provides a means of understanding why depression emerges with such force and frequency in adolescence. The development of the prefrontal cortex, hippocampus, amygdala and ventral striatum is described from a translational perspective as they relate to stress exposure, onset, pathogenesis and gender differences in depression. Adolescent depression is a serious recurrent brain-based disorder. Understanding the genesis and neurobiological basis is important in the development of more effective intervention strategies to treat or prevent the disorder.

Introduction

The overriding issue of this review is to understand why depression emerges with such force and frequency in adolescence, particularly in young women. Conceivably, a host of psychosocial factors can render adolescents especially vulnerable, but our focus will be on neurobiological factors. In particular, we will examine the interplay of genetic, maturational and experiential factors affecting mood using a translational perspective that melds clinical and basic laboratory findings.

Basic epidemiology of adolescent depression

Major depression disorder is a common and serious disorder of adolescence [1]. Lifetime prevalence increases dramatically from 1% of the population under age 12 to ~17%–25% of the population by the end of adolescence [2]. The greatest surge in newly emergent cases occurs between 15 and 18 years [3].

Cross-sectional and prospective epidemiological studies indicate that anxiety disorders often precede the emergence of depression and identify children at risk for developing depression [4,5]. It is possible that early anxiety and later depression share a common genetic basis with a different developmental time course [5]. One study found that adolescent anxiety typically preceded onset of insomnia, whereas episodes of depression followed bouts of insomnia [6], suggesting that sleep disturbance might serve, in some instances, as a mediating link.

Adolescent major depression disorder typically follows a recurrent episodic course, with episodes averaging 7–9 months in those seeking treatment [1]. Adolescent onset is associated with a more chronic, severe and disabling form of depression, higher rates of family history and more suicide attempts than depression that first emerges in adulthood [7].

Children and adolescents are more likely to present with irritability without overt sadness than adults [1]. Depressed adolescents show more signs of anhedonia, hypersomnia, decreased ability to think and concentrate, melancholia and suicidality than depressed children [8] and greater disturbance in circadian rest–activity rhythms [9]. According to the National Center for Health Statistics, the incidence of suicide unfolds with age: suicide before the age of 10 is rare, increases 100-fold between 10 and 14 years, and rises an additional 10 times between the ages of 15 and 19.

Prevalence rates for depression are twice as high in females as males. This ratio is not apparent in childhood, but emerges by ~14 years of age [10]. Onset of depression is temporally linked to menarche [11], suggesting a hormonal mechanism. Females experience a marked increase in a subtype of depression associated with anxiety, sleep/appetite disturbances and fatigue [12]. They can also experience more body image dissatisfaction, feelings of failure, concentration problems and work difficulties [13]. By contrast, depressed boys are more anhedonic, and have greater diurnal variation in mood and energy [13].

Etiology of depression

Although the specific etiology of major depression remains unknown, both heredity and early experience are critical determinants. Further, maturational events might potentially increase prevalence or trigger episodes (see Box 1). It is important to distinguish between specific etiological factors (e.g. genetic polymorphisms, childhood adversity) that increase risk in selective recipients and universal phenomena (e.g. puberty) that exert moderating effects on the entire population.

Genes and adversity

Genetic factors accounted for 40.4% of the variance in risk of major depression in one study of adolescent female twins (n = 3416) [14]. Non-shared environmental effects accounted for the remaining 59.6%. Similarly, large-scale epidemiological studies indicate that exposure to early

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adversity (i.e. childhood abuse, parental loss or chaotic household) account for 54% of the population attributable risk for current depression and 67% of the risk for suicide attempts [15].

Most importantly, genes and early experience interact. Caspi et al. [16] found that exposure to severe childhood maltreatment (between 3 and 11 years of age) doubled the risk of major depression in individuals with two copies of the short allele promoter polymorphism of the gene encoding the serotonin transporter (5-HTT). By contrast, childhood maltreatment produced no increase in risk in individuals with two copies of the long allele polymorphism. In short, many cases of depression might arise from the confluence of genetic predisposition interacting with environmental experiences that occur during a specific window of vulnerability. This, in turn, sets up a cascade of events that unfold over the course of maturation.

Early stress exposure, however, is not specifically linked to the development of depression, but is also a predisposing factor that can lead to the emergence of posttraumatic stress disorder (PTSD), substance abuse, personality disorders and aggression. The outcome will likely depend on genetic factors, the severity, timing and nature of the exposure and the presence of moderating factors, such as degree of parental support or involvement.

**Maturational events**

Figure 1 provides a comparison of trajectories of gray matter development in key regions associated with depression from childhood through early adulthood. Three sets of developmental factors operate in the genesis of adolescent depression. The first are typical adolescent changes in brain maturation, including anatomical and functional rearrangements, sensitivity to gonadal and adrenal hormones, and increased psychosocial pressures. The second are early windows of vulnerability, or sensitive periods, when specific regions of the developing brain might be most susceptible to environmental influences that have the potential to increase risk for depression. The third are the key maturational changes taking place during adolescence that lead to the overt expression of the disorder in individuals with an underlying predisposition.

The developing brain undergoes a period of overproduction and pruning of synapses and signaling mechanisms between childhood, adolescence and young adulthood [17]. Windows of vulnerability potentially occur during periods of very rapid development, and synaptic pruning during adolescence might unmask underlying predispositions. Regional differences in the trajectory of synaptic development, programming of neurotrophic factor levels, connectivity between brain regions, rates of myelination and increased expression of glucocorticoid receptors potentially result in brain region-specific windows of vulnerability at different ages (Figure 2) and an overall increased sensitivity to depression onset during adolescence. The process is also sexually dimorphic, and males typically overproduce synapses and signaling mechanisms to a greater extent than females [18,19]. On average, gray matter density in the cortex peaks 1–2 years earlier in girls than boys (11.2 versus 12.6 years).

Fetal exposure to gonadal hormones exerts organizing effects responsible for sex differences in brain development [20]. Pubertal exposure activates hormones that modulate the development of the prefrontal cortex, amygdala and hypothalamus. Evidence for the role of gonadal hormones in this process in humans is still relatively sparse, but inferred from a finding in males with congenital adrenal hypoplasia (resulting in increased prenatal testosterone) and in individuals with XXY genotype [21]. Rodent studies suggest that estrogen suppresses neuronal overproduction in the female prefrontal cortex [22,23], whereas rising levels of testosterone aid in pruning of dendrites within the adolescent male amygdala [24]. Hence, adolescence is associated with sexually dimorphic pruning of synapses and signaling mechanisms in brain regions implicated in depression. The emergence of depression during adolescence might result, in part, from either insufficient overproduction [25] or enhanced pruning of these brain regions. Estrogenic effects might further exacerbate these processes.

Early studies that examined the role of pubertal hormones in depression failed to show a significant relationship between rising gonadal steroids and depressive

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**Box 1. Depression, anhedonia, reward and the dopamine system**

The mesolimbic system, composed of the dopaminergic cell bodies in the ventral tegmental area that project to the nucleus accumbens, plays a prominent role in reward processing of drugs of abuse and natural rewards, including food, sex and social interactions [78]. As reviewed elsewhere [78], the nucleus accumbens receives inputs from multiple brain regions, including the cortex, hypothalamus and amygdala. Reductions in dopamine neurotransmission within the ventral striatum (nucleus accumbens/extended amygdala) have been observed in depression [79]. These changes are likely to influence the primary symptoms of depression that are related to low positive affectivity: reduced energy, anhedonia, loss of libido, loss of appetite, social withdrawal and psychomotor retardation [59,78]. Treatment with antidepressants with some dopamine (and noradrenergic) activity, such as bupropion, restores lost positive affect.

The reduction in positive affectivity might be a normal process that occurs during adolescence [60]. To this end, extracellular levels of dopamine in the dorsal and ventral striatum are lower during adolescence relative to other ages [80]. By contrast, dopaminergic activity in the prefrontal cortex peaks during adolescence [81]. Here, dopamine within the adolescent cortex aids in the processing of contextual stimuli [76] and enhances responsiveness to stressful events [73]. As connections between the cortex and accumbens continue to mature [76], the prefrontal cortex increases its modulation of accumbens activity. Together, this might further render the adolescent uniquely vulnerable to contextual events. Whether increased cortical activity during adolescence is related to reduced accumbens activity through a direct or indirect pathway remains to be determined. On one hand, stimulation of the cortical D1 receptor enhances contextual salience through connections to the accumbens [76], as exemplified by increased drug-seeking to drug-associated environments. However, excessive D1 activation reduces cortical activity and ‘takes it off-line’ [82], possibly leading to reduced motivation and poor decision making. The majority of research on the adolescent dopamine system has focused on appetitive processes, with little emphasis on the relationship between dopamine and aversives. Although this remains a fruitful area of research, it is tangible that adolescent changes within the mesocorticollimbic dopamine system increase susceptibility to stress-related depression and anhedonia during this vulnerable period.
symptoms [26]. Recently, however, a population-based study demonstrated a linear relationship between depressive symptoms and estrogen (or estrogen + testosterone) in a representative sample of girls (n = 973) from 9 to 13 years of age. Gonadal hormones are likely to mediate their effects indirectly through GABA, 5-HT and/or dopamine systems (e.g. [27,28]), both of which are involved in depression and anxiety.

Stress-related hormones, the glucocorticoids (GC) and mineralocorticoids, play an important role in sculpting the adolescent brain (reviewed in Ref. [29]). They aid in programming adaptive function for survival through long-term potentiation and/or synaptic selection. This function might occur via epigenetic mechanisms or through the regulated expression of several genes, including that encoding BDNF. By contrast, glucocorticoids can adversely affect the brain in two major ways. Maladaptive secretion of these hormones can alter trajectories of development that are predisposing to the emergence of psychopathology. Abundant preclinical evidence shows that increased glucocorticoid secretion reduces neurogenesis and synaptogenesis, especially in the hippocampus. Further, glucocorticoids can directly affect brain function, provoking emotional lability [30]. Mood is regulated by interactions between cortical and limbic regions (Figure 2). As these pathways mature during adolescence, they are impacted by exposure to gonadal and adrenal hormones.

Episodes of melancholic depression are often associated with increased secretion of glucocorticoids that might potentially suppress hippocampal neurogenesis. Selective serotonin reuptake inhibitors (SSRIs) increase hippocampal neurogenesis in animal models of depression in parallel with symptom improvement [31]. These drugs also block progressive loss of hippocampal volume associated with duration of depression. However, whether increased glucocorticoid secretion causes or is the consequence of emotional dysregulation has been difficult to show [32]. Adolescents can be particularly vulnerable to stress as a consequence of heightened glucocorticoid receptor expression in the cortex [29] and more prolonged and exacerbated corticosterone response following acute stress [33]. Adolescent female rats have a greater corticosteroid response to acute stress than males [33], which might explain their increased susceptibility to learned helplessness following acute stress [34]. Increased vulnerability to stress might be a key factor in rising rates of depression during adolescence, as an acute stressor can precipitate the onset of depressive episodes in individuals primed to develop the disorder. Interestingly, male adolescent rats are particularly susceptible to repeated episodes of social stress [34]. This vulnerability appears to wane by adulthood (R. Romeo, personal communication).

Effects of early stress on brain development—evidence for sensitive periods

Early stress stemming from childhood adversity is a predisposing risk factor for the development of major depression [15], and depression is the most common adult sequela of early abuse [35]. Whether exposure to adversity leads to the eventual development of depression is likely to be determined by genetic susceptibilities [16], frequency, severity and multiplicity of the stressors [16,36], gender and timing of insult [37]. Exposure to physical or sexual abuse resulting in psychopathology has been associated with changes in brain structure (reviewed in Ref. [36]) that include attenuated left hemisphere maturation, dimin-
ished size of the corpus callosum, reduced hippocampal volume in adults (but not in children), alterations in gray matter volume (GMV), symmetry and neuronal integrity of the frontal cortex and reduced size of the anterior cingulate cortex and caudate nucleus [38]. Not surprisingly, many of these regions are involved in emotional regulation, and similar abnormalities have been observed in individuals with depression [39,40]. Notably, this is a relatively new area of inquiry. To date, more than a dozen cross-sectional studies have reported morphological differences, but they do not provide evidence for a cause-and-effect relationship. Only one small, longitudinal study (n = 15 subjects) shows that maltreatment-induced stress on cortisol levels and PTSD symptomatology correlates with changes in the trajectory of hippocampal development [41].

Here we emphasize structural changes that are associated with exposure to early stress. Several neurochemical and molecular changes likely accompany these morphometric differences and might serve to more directly tie early stress exposure to increased risk for depression.

The diagram shows the stress-vulnerable brain circuits involved in emotional processing. In this review, we highlight the role of the hippocampus, amygdala, prefrontal cortex and nucleus accumbens in mood regulation during adolescence. Connectivity between brain regions might also influence the emergence of adolescent depression as corticobasal and corticopontine circuits become functional. The green arrow shows the maturing connections between the amygdala and prefrontal cortex [72], whereas the blue arrow shows hippocampal-to-prefrontal cortex connections. The development of these connections is not well studied, nor are connections emanating from the prefrontal cortex to these regions (not shown), which are important for cognitive control over mood. Connections between the prefrontal cortex and nucleus accumbens (black) are still developing [76]. 

[Inset] The expression of glucocorticoid receptors changes across development in a regional-specific manner in the human hippocampus and frontal cortex (dorsolateral is shown here; adapted from Ref. [77]). Glucocorticoid receptors are abundant in the rat amygdala, but their density is not characterize in humans [29]. These receptors, along with gonadal steroids and genetic predisposition, play a role in the unique sensitive periods of vulnerability that exist for these regions.
Preclinical studies have shown that early stress is associated with enduring deficits in 5-HT turnover in the amygdala and nucleus accumbens [42], decreased density of dopamine transporters in the striatum and accumbens, alteration of GABA_A receptor subunit expression in the prefrontal cortex, hippocampus and amygdala, and α2 receptor changes in the locus coeruleus and nucleus tractus solitarius [43,44]. At this stage, however, human imaging studies have almost exclusively depended on morphometry to identify regional alterations associated with developmental stress.

Generally, early onset and longer duration of abuse are linked with greater morphological change [37], but this might be an oversimplification. An alternative hypothesis is that stress-susceptible brain regions have unique sensitive periods (or windows of vulnerability) to the effects of early stress [45]. Young adults who experienced childhood sexual abuse (CSA) between either 3–5 or 11–13 years of age demonstrate maximal reductions in hippocampal volume [46]. CSA between 9 and 10 years is associated with reduced corpus callosum size. By contrast, CSA between ages 14 and 16 years was associated with reduced frontal cortex GMV [46]. Preclinical studies in rats find parallel changes [25,47]. Taken together, mammalian brain regions have unique windows of vulnerability to the effects of stress (Figure 3).

These findings raise the possibility that different abuse-related syndromes might be associated with particular ages of abuse and regional brain changes. For example, current symptoms of depression were associated with abuse between 3 and 6 years of age. PTSD symptoms were associated with abuse that occurred between 9 and 10 years [46]. Early exposure to childhood adversity might initiate a cascade of consequences leading to hippocampal morphological abnormalities and clinical signs of depression.

**Maturation and onset of depression**

Depression is the most extensively documented outcome of exposure to CSA in adults but is not a common occurrence in children [35]. This suggests that a substantial time lag, or incubation period, occurs between early stress exposure and eventual development of depression. In a prospective study, rates of depression were increased by physical abuse or neglect (n = 676), which lead to an earlier emergence of depression relative to controls (n = 520) [48]. In a separate cohort exposed to CSA but no other forms of abuse, the mean survival time from onset of abuse to emergence of depression was 11.47 years overall. There was a delay of 9.2 ± 3.6 years in subjects who developed depression (62%). Notably, most first episodes of depression occurred between 12 and 15 years of age. These findings indicate that early stress not only increases risk of developing depression, it accelerates onset into early adolescence.

Depression in individuals not exposed to abuse or neglect often emerges later in adulthood. However, ~20% of these depressed individuals experienced their first episode in mid to late adolescence. Hence, the respective proportion of depressed individuals with early adversity would be maximal in childhood and early adolescence and begin to decline by mid to late adolescence. This is particularly important, as depressed individuals with a history of abuse or early loss can be less responsive to pharmacotherapy than depressed individuals without such histories [49].

**Delayed effects of early stress on the hippocampus**

The role of the hippocampus in adolescent depression is highly likely, given its susceptibility to the effects of stress.
Reduced hippocampal size has been observed in most studies of adults with major depression [39], and can vary as a function of episode number [39] or duration of time spent depressed but untreated [32]. We propose that the hippocampus contributes to the burden of depression by failing to provide an appropriate contextual response to affectively laden stimuli. This is consistent with findings of perturbed encoding of fearful faces in depressed children and adolescents [52]. Few studies have examined hippocampal volume in adolescents with depression. However, a substantial left > right reduction in hippocampal volume was observed in older adolescents (mean 16.7 years) with major depression (n = 17 depressed versus n = 17 controls) [53]. Increased amygdala:hippocampal ratios were also found in pediatric depression (mean age 14 years; n = 23) versus controls (n = 23), although this difference might be more directly associated with degree of comorbid anxiety [54].

The relationship between exposure to early maltreatment and hippocampal volume is intriguing. Five studies (total n = 209) have reported reduced hippocampal volume in adults with history of exposure to childhood abuse [46,55], whereas three studies (total n = 186) failed to observe reduced hippocampal volume in children with PTSD and comparable abuse histories [56,57]. Animal models can increase our understanding of this phenomenon, as they show that exposure to early stress results in a 34%–36% relative reduction in synaptic density in the hippocampus that emerged between puberty and early adulthood [25]. Thus, it is conceivable that exposure to early adversity during a window of vulnerability delays the expression of depression in susceptible individuals by setting into motion a series of events that affects processes regulating synaptic overproduction in the hippocampus.

**Late-maturing prefrontal cortex**

Multiple components of the prefrontal cortex (PFC) are involved in the emergence of depression as it matures during the periangeous period. A primary role of the PFC is to modulate activity of limbic structures. The PFC has a protracted postnatal ontogeny and does not attain adult volume until the early 20s [58]. The complexity of the region and its developmental time course render it vulnerable, especially to stress during adolescence [46]. PFC development is also affected by early pathology in other brain regions such as the hippocampus or striatum. As the functional properties of the PFC emerge sequentially throughout development, early PFC pathology might be silent until the PFC would normally subsume control of the affected abilities.

For these reasons, the PFC occupies a prominent place in theories of adolescent depression [59,60]. For example, the triadic model of Ernst et al. [60] postulates that adolescent depression emerges as limbic structures driving affect mature in advance of cortical structures providing regulatory control. However, this transient developmental mismatch does not account for the persistently elevated incidence of depression in adulthood.

Major depression most likely emerges in some individuals as a consequence of abnormalities in PFC development. This neuropathogenic view is compatible with adult observations of decreased orbitofrontal volume in patients with remitted major depression [61], and autopsy studies showing a marked reduction in the density and size of neurons and glia in dorsolateral and orbital PFC [62].

Although few morphometric or functional imaging studies have been conducted in depressed adolescents, the findings are generally consistent with those in adults. For example, reduced left subgenual cingulate volume was comparable between adolescents (n = 30) and middle-aged women (n = 18) with depression [63]. Similarly, reduced volume in right medial frontal gyrus and the anterior cingulate were observed in a preliminary analysis of depressed teens (total n = 16) [M.H.T. et al., unpublished]. Depressed adolescents had increased resting relative cerebral blood volume (rCBV) in left orbital and dorsolateral PFC and right subgenual cingulate (BA 25) using T2 relaxometry. Depressive symptoms correlated with diminished rCBV in left and elevated rCBV in right dorsolateral PFC. Despite similarities between depressed adolescents and adults, elevated indices of right subgenual cingulate rCBV parallel findings in treatment-refractory depressed adults [64]. This finding is consistent with the suboptimal response of depressed adolescents to many antidepressants (see Box 2).

Exposure to childhood stress might predispose to depression over a long incubation period by altering hippocampal development. By contrast, exposure to stress during adolescence might precipitate depression over a shorter incubation period by directly affecting the PFC. Exposure to a stressful event between 14 and 16 years activates the PFC and is associated with an 8% synaptic loss by young adulthood [46]. Synaptic loss was also

**Box 2. Efficacy of antidepressants and assessment tests**

Childhood and adolescent depression appear to be less responsive to antidepressant treatment than adult depression. Fewer drugs exert significantly better effects than placebo in pediatric depression, and beneficial drugs can produce a weaker response (e.g., 61% versus 50% drug:placebo response to SSRIs in children versus 78%:44% response in adults) [83]. All antidepressants now carry, in the USA, black-box warnings of treatment-emergent suicidality in children, adolescents and young adults. Treatment is often indicated, as depression causes great suffering and can markedly interfere with academic and social development. Suicide is a leading cause of death in teenagers. Clinicians must weigh the importance of acute treatment of symptoms against the potential for unknown long-term side effects.

Standard screening tests for antidepressant efficacy in animal models are inescapable stress and the forced swim test [84]. These tests are stress based and predicated on the learned helplessness model of Seligman and Maier [85]. Rats placed into inescapable stressful situations often show helplessness on subsequent exposure even when escape is possible. Antidepressants can reverse this effect. In adults, these tests have led to successful identification of antidepressant agents that have good clinical efficacy [84]. However, the use of these tests to identify new, effective agents for the treatment of child and adolescent depression is limited. There is a pressing need for antidepressant drugs with increased efficacy in children and adolescents. Specifically screening for novel agents with potential utility in pediatric depression might eventually be necessary, given the suboptimal response seen so far to drugs designed to target depression in adults.
observed in an adolescent model of social stress in rats, and depressive symptoms manifested immediately [47]. Depressive episodes in adolescents often occur within a year of exposure to one or more significantly stressful life events [65], and might be the result of stress-induced alterations in prefrontal development.

The amygdala: fear, irritability and anxiety

The amygdala has become an increasingly important component of theories of depression, based largely on imaging studies of mood regulation. The amygdala is over-responsive to fearful stimuli in depression [66], and insufficiently regulated by PFC controls [67]. This leads to an excessive and persistent degree of negative affectivity, which is a significant but nonspecific feature of depression. Alteration in the genes encoding 5-HTT and 5HT1 is associated with augmented amygdala response to emotional stimuli [68], which might underlie observed decreases in amygdala volume [69].

Onset of depression in adolescence is often preceded by social anxiety disorder [4], which might be related to overactivation of the amygdala. Interestingly, social anxiety is typically an early-onset adolescent disorder, with the rare new case occurring after age 25. Early emergence of social anxiety can result from immature integration of cortical and limbic components into expression of affective states [70]. With increasing maturation there is an enhanced degree of cortical involvement in processing response to fearful faces [71], which provides a potential means of checking or correcting an excessive amygdaloid response. This is supported by preclinical studies showing delayed development of connectivity between basolateral amygdala and medial PFC [72].

Conclusions

Recent studies have emphasized the importance of gene x environment in the genesis of depression. Time is another crucial factor, both in terms of windows of vulnerability when brain regions might be maximally sensitive to environmental influences and in the cascade of maturational events that lead to the unfolding of depression. The hippocampus and PFC can have early and late windows of vulnerability, and serve respectively as targets for the predisposing and precipitating effects of stress. Alterations in the amygdala and nucleus accumbens might contribute, in turn, to the negative and positive affectivity symptoms seen in depression. Together, this model provides a neurobiological framework that potentially accounts for the emergence of depression and gender differences during adolescence.

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