Review

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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0166-2236/$ – see front matter doi:10.1016/j.tins.2008.01.004 Available online 10 March 2008

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 mesocorticolimbic dopamine system increase susceptibility to stress-related depression and anhedonia during this vulnerable period.

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