

UC Irvine

UC Irvine Previously Published Works

Title

Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders

Permalink

<https://escholarship.org/uc/item/89g5q6f8>

Journal

Dialogues in Clinical Neuroscience, 11(1)

ISSN

1294-8322

Authors

Rao, Uma
Chen, Li-Ann

Publication Date

2009-03-31

DOI

10.31887/dcns.2009.11.1/urao

Peer reviewed

Clinical research

Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders

Uma Rao, MD; Li-Ann Chen, MA



Developmental psychopathology has identified the defining clinical and contextual features of depression in youngsters. In particular, empirical studies have characterized the longitudinal course of depressive illness and common patterns of co-occurring psychiatric conditions. The functional consequences of early-onset illness have also been documented. A growing body of research is identifying the neurobiological and psychological correlates. In addition, studies are beginning to identify specific genetic and experiential risk factors. In general, the core patterns of depressive disorders across the lifespan are emerging. This paper details the phenomenology, correlates, clinical course, and consequences of pediatric depression, highlighting the similarities and differences in the characteristics of depression among children, adolescents, and adults. A few caveats are warranted before

Depressive illness beginning early in life can have serious developmental and functional consequences. Therefore, understanding the disorder during this developmental stage is critical for determining its etiology and course, as well as for developing effective intervention strategies. This paper summarizes current knowledge regarding the etiology, phenomenology, correlates, natural course, and consequences of unipolar depression in children and adolescents. Using adult depression as a framework, the unique aspects of childhood and adolescence are considered in order to better understand depression within a developmental context. The data suggest that the clinical presentation, correlates, and natural course of depression are remarkably similar across the lifespan. There are, however, important developmental differences. Specifically, the familial and psychological context in which depression develops in youngsters is associated with variability in the frequency and nature of depressive symptoms and comorbid conditions among children and adolescents. Maturation differences have also been identified in the neurobiological correlates of depression. These developmental differences may be associated with the observed variability in clinical response to treatment and longitudinal course. Characterization of the developmental differences will be helpful in developing more specific and effective interventions for youngsters, thereby allowing them to reach their full potential as adults.

© 2009, LLS SAS

Dialogues Clin Neurosci. 2009;11:45-62.

Keywords: depression; phenomenology; comorbidity; clinical course; development; neurobiology; pediatric; risk factor; pathophysiology

Address for correspondence: Uma Rao, MD, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9101, USA (e-mail:uma.rao@utsouthwestern.edu)

Author affiliations: Department of Psychiatry, the University of Texas Southwestern Medical Center, Dallas, Texas, USA

Clinical research

proceeding to the following sections. The term “depression” refers to unipolar mood disorders only. Up to now, most of the research on pediatric depression was conducted in major depressive disorder, and therefore, the reported findings are primarily for this condition.

Historical context of depression in children and adolescents

Case reports of youngsters exhibiting symptoms resembling depressive disorders in adults were described as early as the 17th century. Nevertheless, early theories of depression discounted the validity of the disorder in youth, suggesting that the necessary psychological mechanisms were not yet present for the experience of depression, or that depression was “masked” in the form of other disorders. In particular, it was considered that children did not have a well-developed superego. In 1975, the National Institute of Mental Health convened a meeting to discuss the incidence and diagnosis of depression in children. When the existence of depression in children became acceptable and the basic diagnostic criteria were established,¹ research on childhood depression burgeoned, resulting in the growth of theoretical models as well as empirical databases, and depression is no longer considered “an adult disease.” Despite this burgeoning research, some obstacles remained with regard to the pursuit of knowledge on adolescent depression. The early “storm and stress” theories of development suggested that many of the problems associated with depression, such as sadness, irritable mood, self-doubt, and social withdrawal, were normative expressions of adolescent angst.² It is now established, however, that many youngsters do not go through such emotional distress, and that adolescent depression is a serious disorder, often heralding chronic or recurrent problems into adulthood.

A developmental framework in understanding childhood and adolescent depression

In the past three decades, depression research in children and adolescents has progressed from applying simple extensions of clinical descriptions and theories developed in adults to generating an increasingly sophisticated understanding of these disorders informed by the emerging field of developmental psychopathology. Research adopting this framework has taken into account the normative

developmental processes influencing differences in the etiology, phenomenology, correlates, and outcomes of depression in children, adolescents, and adults.^{3,7} It is important to note, however, that this new field of research often does not differentiate among particular stages of development through childhood and adolescence. Although some continuity is likely across childhood and adolescence in the experience and expression of depression, the underlying risk mechanisms and the consequences of depression, some differences are also plausible.

When applying a developmental perspective to psychopathology, one important issue to consider is the conceptualization of different life stages. For example, the transition from childhood to adolescence involves changes in multiple domains, including physical, sexual, cognitive, and social development, with a considerable range of individual differences in the age at which each of these changes occur. At present, there is no consensus on the clear boundaries in defining child and adolescent populations. Since gathering information on these multiple domains is complex, for pragmatic reasons, the majority of the studies have used chronological age to define these boundaries; children ≤ 12 years and adolescents between 13 and 18 years. In some cases, however, studies are reviewed in which these ages overlap (eg, some studies included 13-year-olds in the child samples, whereas others included 12-year-olds among adolescent samples, and still others reported findings according to grade level or physical/pubertal status).

Epidemiology of unipolar depression in children and adolescents

Prevalence and incidence

Prevalence estimates of unipolar depression vary with the time period of reference and method of assessment. The reported point prevalence rates (30-day or 1-year) of major depressive disorder in nonreferred samples range between 0.4% and 2.5% in children, and between 0.7% and 9.8% in adolescents.^{8,9} Elevated risk for the disorder begins in the early teens, and continues to rise in a linear fashion throughout adolescence, with lifetime rates estimated to range from 15% to 25% by late adolescence.¹⁰⁻¹² These prevalence estimates of adolescent depression are comparable to the lifetime rates reported in adults, suggesting that the rates of depression begin to plateau by early adult life.^{11,13} These data also indicate

that, for a substantial proportion of adult cases, the onset occurred during adolescence.¹⁴

The prevalence of depression in youngsters is even greater when minor depression and subsyndromal depressive symptoms are considered. In the National Comorbidity Study, the only nationally representative community study in the United States that included adolescents, the lifetime prevalence of minor depression in 15- to 18-year-olds was 11%.¹⁵ In a large sample of high-school students, up to 40% of adolescents exceeded the cutoff point for high symptom levels on self-reported depressive symptoms.¹⁶ Subsyndromal depression is associated with high levels of distress and impaired functioning,¹⁷ and prospective studies indicated that it is a strong predictor of major depressive disorder.^{18,19}

Secular trends

Retrospective data from successive cohorts born since World War II suggest that the diagnosis of unipolar depression may be becoming increasingly common and beginning earlier in life.^{20,21} Interpreting secular trends is complicated because of increased clinical awareness of early-onset depression and changing diagnostic practices. However, the recent replication results from the National Comorbidity Survey and some studies of pediatric clinical cohorts are very compelling, because adjusted lifetime hazard rates of depression are based on the same interview methods with participants across different age groups ascertained at the same time.^{13,22,23}

Gender differences

Epidemiological studies have consistently demonstrated that females are two to three times more likely than males to develop depression.²⁴ The female predominance in depression has been observed across many countries and cultures, as well as in cohorts across multiple generations.^{25,26} A developmental trend has been observed for sex differences in the prevalence of depression. Prior to adolescence, the rate of depressive disorders is about equal in boys and girls, or even higher among boys.^{8,27} During early to middle adolescence, the rate of depressive symptoms and disorders in girls rises by two to three times that of boys, a trend that continues through adult life.^{11-13,28} Explanations for this gender difference have included hormonal changes, increased stress, tendencies toward rumination and other maladaptive responses to

stress, and differences in interpersonal orientation and socialization experiences.^{7,29,30}

Effect of social status

The effect of social class on depression has been well-documented in adults.³¹ Studies in children and adolescents, using both symptom levels and diagnostic criteria, have linked depression to lower income and socioeconomic status.³²⁻³⁴ Lower socioeconomic status may be a marker of specific risk factors associated with depression, rather than exerting a direct influence. For example, low socioeconomic status is associated with high levels of chronic stress due to economic difficulties, adverse environmental conditions, and family disruption.

Ethnic and cultural differences

Among adults, ethnic/racial differences have been reported with regard to prevalence rates of depression, with ethnic minority groups having lower rates compared with non-Hispanic whites.^{35,36} Among child and adolescent samples, either no ethnic differences were detected in depression, or ethnic minority groups, Hispanics, in particular, had higher symptom levels.^{33,37-39} However, analysis of data from more nationally representative samples in the United States revealed complex relationships between ethnicity and depression. For example, one study found that African-American girls did not manifest the puberty-related increase in depressive symptoms that is commonly observed in non-Hispanic white girls.⁴⁰ It appears that both individual- and context-level characteristics exert effects on depressive symptomatology. For instance, African-American teens living within predominantly non-Hispanic white neighborhoods were at especially high risk for depressive symptoms.⁴¹ Similarly, adolescents of Mexican descent living in the United States, but not Mexican adolescents, had higher rates of depression compared with non-Hispanic white youth.³⁷ Future investigations should attempt to disentangle the effects of adverse conditions that might be associated with ethnic status as well as cultural expressions of depressive symptoms among different ethnic groups.^{41,42}

Functional consequences and socioeconomic burden

Depressive disorders in children and adolescents are associated with significant economic and social burden

Clinical research

on individuals, families, and societies.⁴³⁻⁴⁶ The functional consequences that characterize depressed youngsters suggest that the disorder can interfere with developmental milestones. For example, depression is frequently associated with problems in interpersonal relationships and school performance, as well as delays in social, emotional, and cognitive development.⁴⁷⁻⁵² It is not clear, however, whether these psychosocial disturbances are precursors or consequences of depression. Moreover, other factors frequently associated with depression, such as comorbid psychiatric disorders, poor family functioning, low socioeconomic status, and exposure to stressful life events, impact psychosocial functioning.⁵³⁻⁵⁵ Depression in children and adolescents is also associated with an increased frequency of suicidal behaviors, delinquency, and alcohol and drug use.^{50,53} Prospective studies found that after recovery, children and adolescents continue to manifest impaired psychosocial functioning in multiple domains.⁵⁶⁻⁵⁸ Moreover, children and adolescents with depression have persistent psychosocial problems in adult life, including criminal behavior, dysfunctional interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning, unemployment, and suicidal behavior.⁴⁶ Some studies also reported high rates of psychiatric hospitalization and mental health services compared with their counterparts without depression.⁴⁶ Data in adults suggest that depressed patients with early-onset illness have more impaired social and occupational functioning and poorer quality of life compared with patients whose episode(s) first started in adult life.⁵⁹

Clinical presentation of depression in children and adolescents

Developmental influences

The diagnosis of dysthymic disorder and major depressive disorder are based on similar criteria for children, adolescents, and adults, with two exceptions. First, the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition with text revisions; *DSM-IV-TR*) has allowed the substitution of irritability for depressed mood in children and adolescents.⁶⁰ Second, the duration criterion for dysthymic disorder in children and adolescents is 1 year instead of 2.⁶⁰ Empirical data also suggest that the clinical syndrome of depression is remarkably similar among children, adolescents, and adults.⁶¹⁻⁶³ There are some developmental differences, however.⁶⁴ Specifically, hypersomnia shows a devel-

opmental trend, with a higher prevalence in depressed adolescents than in children.⁶⁵⁻⁶⁸ Suicide attempts, particularly those involving high lethality, also increase with age.^{66,68} Melancholic and psychotic symptoms may occur less frequently in children, whereas somatic complaints and behavior problems are more common during this developmental period.^{64,67,69} Psychotic depression in children appears to be manifested by auditory hallucinations instead of delusions, as seen in adolescents and adults. Although the reasons for the developmental variations in depressive symptoms are not known, maturational effects on emotional and behavioral regulation and cognitive function might contribute to these differences.

Gender differences

Gender differences have also been documented with respect to the severity and symptom profiles of unipolar depression among children, adolescents, and adults although no compelling gender effects were found on the salient features.^{62,67,70-73} Among both adolescents and adults, females typically report higher levels of symptoms.^{70,74} With regard to symptom patterns, somatic symptoms, such as changes in appetite and weight, sleep problems, and psychomotor retardation are more common in females.^{73,75-78} Increased crying, feelings of failure, guilt, poor self-esteem, and other cognitive symptoms may also be more frequent in females.^{75-77,79-81} In contrast, depressed males more frequently report anhedonia, diurnal variation in mood and energy, social withdrawal, and work impairment.^{75,76,80} The reasons for gender differences in unipolar depression are not well understood. One model suggests that females are more prone to exhibit a cognitive style characterized by negative self-evaluation and rumination.^{82,83} Gender differences in brain function have also been postulated as one potential reason for the symptom variability.^{84,85}

Comorbidity

Both clinical and epidemiological studies have shown that up to 40% to 70% of children and adolescents with depression also suffer from another psychiatric disorder, and many youngsters have two or more comorbid diagnoses.⁸⁶⁻⁸⁸ Approximately 70% of children and adolescents with dysthymic disorder will eventually develop an episode of major depressive disorder, resulting in "double depression."^{89,90} Other frequent comorbid diagnoses include anxiety disorders, disruptive disorders, and sub-

stance use disorders. Although it is not clear whether these comorbid conditions represent a developmental sequence, shared genetic or environmental risk factors or a separate subtype of the disorder, it is likely that one or more of these factors contribute to comorbidity.^{86,91}

Age and gender can influence the patterns of comorbidity.^{88,92} Specifically, separation anxiety disorder and attention-deficit hyperactivity disorder are more common in children, whereas conduct disorder, panic disorder, and substance abuse are more common in adolescents.^{92,93} Similarly, disruptive and substance use disorders are less likely, and eating disorders are more likely, in girls than boys.^{102,188,92}

The presence of comorbidity has important clinical and functional implications.^{63,94} In particular, youth with comorbid dysthymia and major depression had more severe and longer depressive episodes, and higher frequency of suicidality and social impairment than those who had a single mood disorder.^{90,95,96} Similarly, comorbid anxiety disorder was associated with increased severity and duration of depressive symptoms, increased suicidality, poor response to psychotherapy, and elevated risk for addictive disorders.⁹⁷⁻¹⁰¹ In contrast, depressed youth with co-occurring disruptive disorders tended to have fewer melancholic symptoms, fewer recurrent episodes of depression, a lower frequency of familial mood disorders, a higher incidence of criminal behavior, and a higher response to placebo than patients with pure depressive illness.¹⁰²⁻¹⁰⁵ Comorbid substance abuse is associated with earlier onset and more severe substance-related problems, increased frequency of behavioral problems, more prolonged and recurrent depressive episodes, more severe impairment in family, school, and legal domains, higher risk for suicidal behavior, and increased utilization of health services and substantially higher treatment costs.⁵⁵ Examination of data in adults suggest that, compared with depressed patients whose first depressive episode occurs in adult life, patients with early-onset illness have increased rates of anxiety disorders and substance use disorders, as well as personality disorders, resulting in more chronicity and disability.^{59,106-109}

Developmental course and outcomes of childhood and adolescent depression

Episode duration

Considerable variations have been found in the duration of depressive episodes in nonreferred and clinical sam-

ples of youth. For example, in a large sample of high-school students, the duration of major depressive episode ranged from 2 weeks to 250 weeks, with a mean duration of 26 weeks.¹¹⁰ The probability of remission was 3 weeks in 25% of the sample, 8 weeks in 50%, and 24 weeks in 75% of the sample. Longer durations were reported in clinical samples, with a mean length of 6 to 9 months.^{46,111-113}

Up to 30% to 40% of patients can be expected to recover by 6 months and 70% to 80% by 12 months, and 5% to 10% of patients have a protracted episode, lasting longer than 2 years.^{46,113} Dysthymic episodes tend to be more protracted, with an average duration of 2.5 to 3.5 years.^{90,114} In a prospective study of a clinical sample, only 7% of youth with dysthymia showed evidence of recovery 2 years after the onset of a first episode.¹¹³ Overall, children and adolescents have similar recovery patterns,^{69,113} and these patterns also are comparable to the data in adults.¹¹⁵⁻¹¹⁹ Among the baseline demographic and clinical variables that were examined, none has yet been shown to consistently predict recovery from a depressive episode in youngsters. Age at onset of illness, greater severity, presence of comorbid disorders, and parental history of depression potentially influence the time to recovery.^{69,120} Among adults, greater severity, longer duration of episode at the time of recruitment, pre-existing dysthymic disorder, and co-occurring anxiety disorders and personality problems were associated with longer time to recovery.^{115,116,118,121,122}

Recurrence and continuity into adulthood

Longitudinal studies of both epidemiological and clinical samples consistently demonstrated that children and adolescents with depression tend to have recurrent episodes. The probability of recurrence following the recovery of a major depressive episode is approximately 40% by 2 years and 70% by 5 years.^{46,110,123} These rates are comparable to the rates of recurrence in adult samples.¹²⁴⁻¹²⁶

In addition to recurrent episodes during childhood and adolescence, longitudinal studies of depressed youngsters documented recurrent episodes in adult life.^{46,112,127} There also appears to be some specificity in the continuation of psychopathology in adult life, particularly with respect to adolescent-onset depression. Several studies of depressed adolescents documented increased risk for recurrent depressive episodes, but not other psychiatric disorders, when compared with their counterparts without depression.¹²⁷⁻¹³⁰ In contrast, there is some evidence that child-

Clinical research

hood-onset depression is not necessarily predictive of depression in adulthood, except for a subsample with symptoms characteristic of the adult disorder.^{128,130,131}

Among children, adolescents, and adults, few baseline demographic or clinical characteristics predict who will or will not experience a recurrent depressive episode. Some potential predictors of recurrence in adults include early onset, number of prior episodes, stressful experiences, cognitive vulnerability, negative family interaction patterns, comorbid personality disorders, and persistent biological dysregulation during recovery.^{59,132} Among youth, co-occurring personality problems, specifically borderline personality disorder symptoms, were associated with recurrence.^{125,133} There is disagreement regarding whether girls are at increased risk for recurrent depressive episodes than boys.^{69,111,112,133} although no gender differences were found in recurrence rates among adults.¹³⁴

Other psychiatric outcomes

Although recurrent unipolar depression is the primary outcome for depressed youth, development of other psychiatric disorders has also been documented. Longitudinal studies reported that 20% to 40% of children and adolescents with major depressive disorder developed bipolar disorder within a period of 5 years.^{48,129,135,136} The clinical characteristics associated with increased risk for bipolar disorder in youngsters and adults with depression include early-onset illness, mood lability, depressive episode accompanied by psychomotor retardation or psychotic features, atypical depression, protracted depressive episodes, family history of bipolar disorder or heavy familial loading for mood disorders, and pharmacologically induced hypomania.^{94,136-139} Depressed youngsters are also at risk for developing substance use disorders in adolescence and adulthood.^{62,88,101,140-142} Protracted depressive episodes, comorbid anxiety or conduct disorder, and hypothalamic-pituitary-adrenal (HPA) dysregulation may be associated with increased risk for substance abuse in depressed youth.^{101,103,142}

Risk factors for depression in children and adolescents

Developmental influences on vulnerability to depression

As described above, the risk for depression increases markedly during the transition from childhood to adoles-

cence.⁸ Adolescence is a crucial developmental stage, marked by a confluence of biological, psychological, and social challenges.¹⁴³⁻¹⁴⁶ There are significant physical maturational changes (eg, the onset of puberty), social-cognitive advances (eg, ability for more abstract thinking and generalizations across situations and time), interpersonal transitions (eg, changes in social roles in family and peer relationships), and social-contextual changes (eg, school transitions). Although these maturational transitions offer tremendous opportunities for youth, because the developing brain and behavioral and cognitive 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. 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.^{147,148}

Family-genetic factors

There is clear evidence of familial transmission of depression.¹⁴⁹⁻¹⁵¹ These data, however, cannot distinguish environmental from genetic causes of transmission. Family, twin, and adoption studies indicated effects of both genetic and environmental factors for unipolar depression.^{152,153} Based on epidemiological data, the proportion of variance attributed to genetic factors is between 24% and 58% for depressive illness.¹⁵⁴ Genetic influences have been found to vary with age and sex. Shared environmental influences may be more important in younger children, and these influences may be replaced by new genetic and unique environmental influences as children grow older.^{150,155} In one study, the increased heritability effect in adolescents was found only for girls, and not boys.¹⁵⁶ Research on behavioral genetics initially partitioned population variance into two components, one due to genetic factors and the second due to environmental influences. The implication was that the two were separate, and it was assumed that gene-environment interactions were usually of so little importance that they could be ignored. Theoretical considerations suggested that this was not likely to be true, and empirical findings are now accumulating on the interactions between identified common single genetic variants and environmentally-mediated risks.¹⁵⁷ Indeed, the important role of environmental factors in modulating vulnerability and their

interactions with genetic variants has been specifically demonstrated for depression.^{152,158,159}

Recent research on genetic liability for depression has begun to address the mode of inheritance, such as temperament characteristics associated with emotionality and emotional regulation, a tendency toward stress exposure and reactivity, and alterations in neurobiological regulation.¹⁶⁰⁻¹⁶² Molecular genetic effects related to early-onset depression have been observed on chromosome 11p14 that has been associated with brain-derived neurotrophic factor (BDNF).^{163,164} BDNF is a nerve growth factor involved in the regulation of cellular development, neuronal survival, synaptic plasticity, and resistance to stress.¹⁶⁵ A growing body of evidence has implicated BDNF-dependent processes in the pathophysiology of depressive disorders and the therapeutic action of anti-depressant agents.¹⁶⁶ Developmental and gender-related differences have been documented with respect to BDNF expression.^{167,168} These findings highlight the dynamic changes in neurobiological processes underlying depressive disorders that may be shaped by environmental inputs.

Neurobiology

In contrast to the wealth of information on the neurobiology of adult depression, there are relatively few studies in pediatric samples, although this is a burgeoning area of investigation. Most studies of childhood and adolescent depression have followed up the observations and methods used in adult studies, and they focused primarily on electrophysiological, neuroendocrine, and neuroimaging techniques.^{5,169,170} Aside from cross-sectional designs during the acute depressive episode, some studies applied these measures to at-risk youth, or employed longitudinal designs to examine their relation to the clinical course of depression. It is important to note, however, that the sample sizes in many of these studies are modest. Nevertheless, convergent patterns across studies are informative in determining developmental continuities and discontinuities with adult depression.

Electrophysiological studies

Baseline electroencephalographic (EEG) studies documented reduced left frontal electrical activity in infant and adolescent offspring of depressed mothers,¹⁷¹⁻¹⁷³ and in adolescents with major depressive disorder.^{174,175}

Decreased left frontal EEG activity presumably reflects an underactivation of the approach system and reduced positive emotional expression, which also may be a vulnerability marker for depression.¹⁷⁶ In a study of young adults with a history of childhood depression, frontal EEG asymmetry differed between men and women and varied in relation to longitudinal clinical course.⁸⁵ Men showed more decreased alpha power at all sites than women, and women with history of childhood depression had greater right frontal alpha suppression, whereas men with childhood depression had greater left frontal alpha suppression. Participants who developed bipolar disorder had the most extreme patterns of frontal EEG asymmetry. In the same sample, eye-blink responses to affective stimuli also were associated with variations in clinical outcome in adult life.¹⁷⁷ These electrophysiological measures were acquired in adult life, and, therefore, the observed changes might be “scar” markers of repeated depressive and/or manic episodes rather than premorbid markers.

EEG sleep measures have shown considerable variability with regard to group differences between depressed youngsters and matched controls.^{5,178} Age and gender have a significant influence on these measures,^{179,180} and depressed adolescents seem to have relatively more frequent disturbances in circadian rest-activity rhythms, sleep architecture, and EEG rhythms during sleep compared with depressed children.^{5,180,181} Among adolescents, the EEG sleep measures were remarkably stable when examined both during the acute depressive episode and during sustained remission, suggesting that these measures are trait-like.^{182,183} Changes in sleep architecture and sleep-related EEG rhythms also were documented in healthy adolescents at high risk for depression, and these changes were associated with vulnerability for depression during prospective follow-up.¹⁸⁴⁻¹⁸⁶ Additionally, baseline EEG sleep patterns differed between depressed adolescents who subsequently had a recurrent unipolar course versus those who developed bipolar illness; adolescents with unipolar course had predominantly rapid eye movement (REM) sleep changes while adolescents with bipolar course had non-REM sleep changes.¹⁸⁷ In the same study, adolescents who subsequently developed substance use disorders had relatively normal EEG sleep patterns.¹⁰¹

Although EEG sleep changes in pediatric depression, particularly the childhood-onset type, show discontinuities with findings in adult depression,^{188,189} it is important

Clinical research

to also emphasize the variability across studies of both children and adolescents.^{5,178} The observed variability in EEG sleep changes in depressed youngsters may reflect, at least in part, heterogeneity in the longitudinal clinical course of these disorders. For example, sleep data in adults suggest distinct biological substrates in unipolar and bipolar mood disorders. REM latency changes were observed less frequently in bipolar depression.^{190,191} Sleep loss can effectively trigger the onset of mania in patients with bipolar illness,^{192,193} but has minimal euphorogenic effect in unipolar depression. Therapeutic sleep deprivation also appears to have different clinical effects in unipolar and bipolar patients.¹⁹⁴ As described above, a substantial minority of youngsters initially identified as having unipolar depression subsequently develop bipolar disorder, and those with early-onset illness in particular.⁴⁸ Among children, studies that excluded depressed patients with family history of bipolar disorder were more likely to demonstrate EEG sleep changes compared with controls.^{180,195}

Neuroendocrine studies

There has been considerable interest in the HPA system, consistent with the possibility that depression is linked to altered responses to stress, and numerous studies have documented HPA dysregulation in adult depression.¹⁹⁶ HPA findings in depressed children and adolescents were inconsistent.^{5,170} In particular, depressed children did not display changes in 24-hour cortisol patterns. Few differences in basal cortisol secretion have been observed between depressed adolescents and controls, and when group differences were detected, they tend to be subtle alterations in normal diurnal patterns. These subtle changes, however, were relatively robust in predicting the longitudinal clinical course; higher cortisol secretion in the evening or during sleep, a time when the HPA axis is relatively quiescent, was associated with a longer time to recovery from the depressive episode,¹⁹⁷ a propensity for recurrence,^{185,198} and suicide attempts.¹⁹⁹ Higher cortisol secretion also was detected in at-risk youth who subsequently developed depression.^{186,200,201}

Another neuroendocrine marker possibly related to depression is growth hormone, which is secreted by the anterior pituitary and follows a circadian pattern with increased secretion during slow-wave sleep. Although the precise role of growth hormone secretion in depression is not known, it appears to be a marker of central

noradrenergic and serotonergic (5-HT) systems. Reduced growth hormone secretion during sleep has been observed in adult depression,²⁰² but findings in children and adolescents have been variable, with some studies showing no differences whereas others showing reduced or increased secretion.^{5,170} One study found that depressed children with stressful life events had increased growth hormone secretion compared with their counterparts who did not experience recent stress, suggesting that environmental factors have a moderating influence and also underscoring the need for integrative models in examining the pathophysiology of pediatric depression.²⁰³ In another study, depressed adolescents who subsequently made suicide attempts had increased growth hormone secretion during sleep, and when this group was separated, depressed adolescents manifested blunted growth hormone secretion compared with controls, again highlighting the value of neuroendocrine measures in predicting the longitudinal course in depressed youngsters.²⁰⁴ In contrast to the findings in basal secretion, pharmacological challenge studies documented blunted growth hormone response to a variety of pharmacological agents in depressed children, similar to those reported in depressed adults.²⁰⁵ In contrast, data in adolescents were predominantly negative. Although the sample sizes were modest in these adolescent studies, pubertal changes and gender might account for some variability among child, adolescent, and adult samples.^{5,170}

Neuroimaging studies

Studies using various neuroimaging techniques provided converging lines of evidence supporting prefrontal cortical-striatal and medial temporolimbic dysfunction in adult depression.^{206,207} There is a striking paucity of neuroimaging studies in pediatric depression, and existing studies are marked by small sample sizes and inconsistent findings.^{169,170,208} Within this context, volumetric studies documented reduced left frontal lobe volume, particularly in those with familial depression. Alterations in amygdala and hippocampal volumes also were found, although the effects appear to be moderated by anxiety and manic symptoms. In neurochemical studies, reduced glutamate and creatinine/phosphocreatinine concentrations in the anterior cingulate, and increased choline concentrations in the left dorsolateral prefrontal cortex, were documented in pediatric depression.

Summary

Neurobiological research in pediatric depression suggests that neurobiological factors change during the course of development, and developmentally influenced neurobiological processes may become disrupted during depressive episodes. Longitudinal studies that account for familial and clinical variability allude to this possibility, whereas cross-sectional studies that fail to account for developmental changes, gender differences, and family history produced inconsistent findings. These data also indicate that early-onset depressive disorders may not necessarily result from the same etiological processes, and the specific subtype with a recurrent unipolar course is associated with neurobiological changes typically observed in adult unipolar depression.

Temperament and personality

Temperament is thought to have a genetic/biological basis, although experience and learning, particularly within the social context, also can influence its development and expression.²⁰⁹ The trait that is associated with most emotional disorders has been given various labels by different theorists, including behavioral inhibition,²¹⁰ harm avoidance,²¹¹ negative affectivity,²¹² neurotism,²¹³ and trait anxiety,²¹⁴ although the conceptual and empirical overlap among these constructs far outweighs the differences. Negative affectivity is the propensity to experience negative emotions, and it reflects sensitivity to negative stimuli, increased wariness, vigilance, physiological arousal, and emotional distress. In contrast, positive affectivity is characterized by sensitivity to reward cues, sociability, and adventurousness.²¹² Depression is characterized by high levels of negative affectivity and low levels of positive affectivity,²¹⁵ and these features have also been found in depressed children.²¹⁶ Elevated levels of behavioral inhibition have been observed in laboratory tasks with young offspring of depressed parents.²¹⁷ Longitudinal studies have shown that children with inhibited, socially reticent, and easily upset temperament at age 3 had elevated rates of depressive disorders at age 21 than those who did not demonstrate these characteristics.²¹⁸ Similarly, physicians' ratings of behavioral apathy (ie, lack of alertness) at ages 6, 7, and 11 predicted adolescent mood disorders and chronic depression in middle adulthood.²¹⁹ Difficult temperament, characterized by inflexibility, low positive mood, withdrawal, and poor

concentration correlated with depressive symptoms both concurrently and prospectively in adolescents.²²⁰

The relation between temperament and depression may vary somewhat by age. In one study, neurotic-like symptoms predicted the first episode of depression in 31- to 41-year-old individuals, but this was not the case for 17- to 30-year-olds.²²¹ Similarly, adult participants who experienced a first episode of depression had exhibited elevated levels of dependent traits 2 to 3 years earlier.²²² However, no differences were found with regard to dependent traits between adolescents who later developed depression and those who did not develop the disorder.⁵⁸ Gender might also moderate the relationship between temperament and depression; while females with higher levels of chronic depression during young adulthood had been described as shy and withdrawn at 3 to 4 years of age, males with chronic depression exhibited higher levels of under-controlled behavior as young children.²²³

Cognitive vulnerability

Cognitive theories of depression assert that, when confronted with stressful experiences, individuals who have negative beliefs about the self, world, and future, and those who make global, stable, and internal attributions for negative events will appraise stressors and their consequences negatively, and therefore are more likely to become depressed than those who do not have such cognitive styles.^{224,225} Several types of cognitions have been proposed to be related to depression, including low self-esteem, negative automatic thoughts, dysfunctional attitudes, and cognitive distortions²²⁵; self-control²²⁶; control-related beliefs and self-efficacy²²⁷; negative attributional style²²⁴; and a ruminative response style.²²⁸ Cross-sectional studies with clinic and community samples of children and adolescents have consistently shown a strong correlation between a range of negative cognitions and depression.^{148,229} In prospective studies, negative cognitions predicted depression, often in interaction with negative life experiences.^{148,230,231}

Developmental theorists have suggested that negative cognitions emerge over time, and that their relationship with depression becomes stronger with development.^{56,232,233} Indeed, the association between negative cognitions and depression is less robust in younger children than in older children and adolescents.^{56,234} If negative cognitions contribute to the development of depression, then offspring of depressed individuals should be more

Clinical research

likely to exhibit cognitive vulnerability than children whose parents have not experienced depression. Indeed, children of depressed mothers reported lower perceived self-worth and greater negative attributional style than children of nondepressed mothers.²³⁵ Even though there is a concurrent and predictive relationship between negative cognitions and depression in youngsters, some have questioned whether negative cognitions are a concomitant or consequence of depression rather than part of a longitudinal chain.^{236,237} Future studies should examine the development of cognitive vulnerability over time, and whether it needs to be primed in children.²³⁸

Interpersonal relationships

Interpersonal theories of depression emphasize the importance of social environment and the development of secure attachment. Vulnerability to depression presumably arises in early family environments in which the children's needs for security, comfort, and acceptance are not met.²³⁹ Literature on the relationship between family environment and depression indicates that families of depressed individuals are characterized by problems with attachment, communication, conflict, cohesion, and support, as well as poor child-rearing practices.^{149,240} Additionally, perceived rejection by peers, family, and teachers predicts increases in depressive symptoms in children and adolescents.²⁴¹⁻²⁴³ Interpersonal theories of depression propose that depressed individuals both react and contribute to interpersonal problems.^{244,245} Depressive symptoms and associated behaviors are presumed to elicit negative reactions from others; these aversive interpersonal experiences then foster the persistence or exacerbation of depression.²⁴⁶ Consistent with interpersonal models, depressed youngsters demonstrate difficulties in many aspects of relationships with peers and family members.^{52,54,110,247-249} Longitudinal studies on the association between interpersonal relationships and depression indicate that social problems temporally precede depression, and that depression contributes to interpersonal difficulties.²⁴⁵

Stress and coping

Stress

Common to all definitions of stress is a focus on environmental conditions that threaten to harm the biological or psychological well-being.^{250,251} Stress may occur either as an

acute event or as chronic adversity, and as a major life event or as minor accumulated events. Stressful events may be normative (eg, school transitions) or pathological (eg, abuse), and may be independent of, or dependent on an individual's actions. Stress plays a prominent role in most theories of depression, and a clear empirical link exists between stress and depression in children and adolescents.^{230,250,252} Although no single or specific type of stressful event leads to depression, certain types of negative events consistently have been found to be associated with depression: child abuse/neglect, especially for women,^{253,254} socioeconomic disadvantage;^{34,250,255} personal disappointments, failures, and losses,^{197,256} and interpersonal problems.^{6,257} Early adversity may be a marker of continuing exposure to negative stressors, such that those with exposure to negative events and circumstances in childhood are more likely to continue to be exposed to stressful situations.²⁵⁸⁻²⁶¹

The relationship between stress and depression appears to be stronger in adolescents than in children, particularly in girls.²⁶²⁻²⁶⁴ The reasons for this are not entirely clear; hormonal effects, consolidation of cognitive styles, cumulative stress burden, and stress reactivity might have a potential role.^{7,264} One theory proposes that childhood adversity alters neurobiological and psychosocial processes, whereby individuals may be sensitized to the effects of recent stressful events, leading to depression at lower levels of stress,²⁶⁵ or with greater reactivity to the effects of stress.^{266,267} Another approach suggests that childhood stressors add to lifetime stress burden and independently predict depression along with recent stress.^{268,269}

Developmental models of psychopathology also suggest a transactional perspective in which stress exposure contributes to depressive symptoms and, in turn, depressed individuals contribute to negative events through their own behavior.²⁷⁰ Longitudinal studies have shown support for the stress-generation model, particularly with regard to interpersonal relationships.^{6,270,271} Factors that might contribute to the generation of stress include personality,^{272,273} lack of interpersonal competence,^{271,274} and comorbid psychopathology.^{6,275} The reciprocal model highlights the "vicious cycle" that can occur between stress and depression, and support for this reciprocal model has been found in a few studies of youngsters.^{270,275-277}

Response to stress

Although stress clearly plays a role in depression, individuals vary in their response to stress, and how they

respond to stress can affect their future adjustment and emotional well-being. Diathesis-stress models propose that depression results from the interaction between personal vulnerability and stressful events or circumstances. The majority of research testing diathesis-stress models of depression has construed vulnerability in terms of maladaptive appraisals of events. Several studies documented interactions between cognitive styles, such as negative attributional style and low perceived self-efficacy, and life stress in the prediction of depression in youngsters.²⁷⁸⁻²⁸⁰ Even further refining these theories, it has been speculated that a key determinant of depression may be the match between a particular cognitive vulnerability (eg, a tendency to base one's self-worth on success in interpersonal relationships) and the nature of the stress (eg, interpersonal conflict). Supporting this theory, diathesis-stress interactions seem to be most powerful when there is a match between the type of cognitive vulnerability and the type of stressful experience.²³⁴ Consistent with the theory that cognitive styles may not yet be consolidated in younger children, cognitive-stress interactions predicted depression in adolescents but not in children.^{234,281}

In addition to cognitive styles, other types of coping mechanisms, such as behavioral styles and problem-solving skills, have been examined in relation to pediatric depression.^{230,282,283} Earlier theories differentiated between problem-focused and emotion-focused coping. Problem-focused coping involves responses that act directly on the source of stress, whereas emotion-focused coping involves palliative measures to counter the negative emotions that arise from stressful situations. Recent models of coping proposed responses to stress that can be distinguished as voluntary or involuntary, and engaged or disengaged.²⁸² Coping involves volitional and intentional responses to stress. Involuntary or automatic reactions to stress are, in part, a reflection of individual differences in temperament. Engaged coping includes problem-solving, cognitive restructuring, positive reappraisal, and distraction. In contrast, disengagement responses include avoidance, self-blame, emotional reaction, and rumination. Studies in children and adolescents indicated that higher levels of engaged coping and problem-focused coping are associated with lower levels of depressive symptoms. In contrast, disengagement, involuntary and emotion-focused coping are related to higher levels of depressive symptoms under stressful circumstances.^{230,282,284,285} Most of the research on coping has been cross-sectional, thereby

limiting our ability to draw conclusions about the direction of the relationship between coping and depression.

Summary and future directions

In the past three decades, considerable advances have been made regarding our knowledge of the phenomenology and natural course of depression in children and adolescents. Basic epidemiologic and clinical research has also helped identify a number of risk factors associated with pediatric depression. There appears to be a complex interplay among genetic, neurobiological, cognitive, interpersonal, and environmental factors in concert with developmental challenges in the onset and maintenance of depression. Recent studies have emphasized the importance of gene-environment interactions 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. Other factors, such as temperament/personality traits, cognitive styles and coping repertoires, moderate responses to stressful situations and precipitate depressive episodes.

Depression is likely to further compromise development by interfering with the achievement of key developmental tasks (eg, academic achievement, negotiating changes in family relationships, and establishing peer networks), resulting in the generation of additional stress, and perhaps even contributing to compromised neurobiological development and sensitization to future stress, depression, and other psychopathology. These dynamic processes may account, in part, for why early-onset depression tends to be recurrent throughout the life span and is also accompanied by other psychiatric problems and significant disability. The challenge for the field is to integrate the disparate findings across domains and to develop testable hypotheses with respect to clinical presentation, biopsychosocial processes, and clinical interventions. Effective interventions early in the course of the disorder will likely interrupt the "vicious cycle" and allow these youngsters to reach their full potential as adults. □

Acknowledgments: This work was supported, in part, by grants from the National Institutes of Health (DA14037, DA15131, DA17804, DA17805, MH62464 and MH68391), and the Sarah M. and Charles E. Seay Endowed Chair in Child Psychiatry at UT Southwestern Medical Center.

Clinical research

Características, correlatos y evoluciones de los trastornos depresivos en niños y adolescentes

La enfermedad depresiva que aparece precozmente en la vida puede tener serias consecuencias funcionales y durante el desarrollo. Por lo tanto, la comprensión del trastorno durante esta etapa del desarrollo es crítica para determinar su etiología y su curso, como también para la generación de estrategias de intervención efectivas. Este artículo resume el conocimiento actual relacionado con la etiología, la fenomenología, los correlatos, el curso natural y las consecuencias de la depresión unipolar en niños y adolescentes. Utilizando la depresión del adulto como referente, los aspectos distintivos de la niñez y de la adolescencia son tomados en cuenta para una mejor comprensión de la depresión dentro del contexto del desarrollo. La información disponible sugiere que la presentación clínica, los correlatos y el curso natural de la depresión son notablemente similares a lo largo de la vida. Sin embargo, hay importantes diferencias durante el desarrollo. Específicamente, el contexto familiar y psicológico en que ocurre la depresión en los muchachos está asociado con la variabilidad en la frecuencia y en la naturaleza de los síntomas depresivos y en las condiciones comórbidas entre los niños y adolescentes. También se han identificado diferencias madurativas en los correlatos neurobiológicos de la depresión. Estas diferencias durante el desarrollo pueden estar asociadas con la variabilidad observada en la respuesta clínica al tratamiento y en el curso longitudinal. La caracterización de las diferencias durante el desarrollo será útil para generar intervenciones más específicas y efectivas para los muchachos, lo que les permitirá alcanzar su potencial total cuando adultos.

Caractéristiques, similitudes et évolution des troubles dépressifs dans l'enfance et l'adolescence

La maladie dépressive qui débute tôt dans la vie peut avoir des conséquences sérieuses fonctionnelles et développementales. C'est pourquoi comprendre le trouble à ce stade développemental est capital pour en déterminer l'étiologie et l'évolution, ainsi que pour développer des stratégies d'intervention efficaces. Cet article résume la connaissance actuelle sur la dépression unipolaire chez l'enfant et l'adolescent à propos de son étiologie, son évolution dans le temps, ses corrélats, son évolution naturelle et ses conséquences. La dépression adulte servant de référence, une meilleure compréhension de la dépression dans son aspect évolutif passe par les aspects particuliers liés à l'enfance et à l'adolescence. D'après les données, le tableau clinique, les facteurs corrélés et l'évolution naturelle de la dépression seraient tout à fait identiques tout au long de la vie, malgré d'importantes différences évolutives. En particulier, le contexte psychologique et familial dans lequel se développe la dépression chez les jeunes est associé à des variations de fréquence et de nature des symptômes dépressifs et de la comorbidité. Il existe aussi des différences de maturation dans les interactions neurobiologiques de la dépression, différences qui peuvent être associées aux variations de la réponse clinique au traitement et à son évolution dans le temps. Il faudra caractériser ces différences de développement pour intervenir de façon plus efficace et spécifique chez les jeunes, leur permettant ainsi d'atteindre leur plein potentiel à l'âge adulte.

REFERENCES

1. Shulterbrant JG, Ruskin A. *Depression in Childhood: Diagnosis, Treatment and Conceptual Models*. New York, NY: Raven Press; 1977.
2. Arnett JJ. Adolescent storm and stress, reconsidered. *Am Psychol*. 1999;54:317-326.
3. Cicchetti D, Rogosch FA, Toth SL. A developmental psychopathology perspective on depression in children and adolescents. In: Reynolds WM, Johnston HF, eds. *Handbook of Depression in Children and Adolescents (Issues in Clinical Child Psychology)*. New York, NY: Plenum Press; 1994:123-141.
4. Kaslow NJ, Adamson LB, Collins MH. A developmental psychopathology perspective on the cognitive components of child and adolescent depression. In: Sameroff AJ, Lewis M, Miller SM, eds. *Handbook of Developmental Psychopathology*. 2nd ed. New York, NY: Kluwer/Plenum Press; 2000:491-510.
5. Kaufman J, Martin A, King RA, Charney D. Are child-, adolescent-, and adult-onset depression one and the same disorder? *Biol Psychiatry*. 2001;49:980-1001.
6. Rudolph KD, Hammen C, Burge D, Lindberg N, Herzberg D, Daley SE. Toward an interpersonal life-stress model of depression: the developmental context of stress generation. *Dev Psychopathol*. 2000;12:215-234.

7. Zahn-Waxler C, Shirtcliff EA, Marceau K. Disorders of childhood and adolescence: gender and psychopathology. *Annu Rev Clin Psychol.* 2008;4:275-303.
8. Kessler RC, Avenevoli S, Ries-Merikangas K. Mood disorders in children and adolescents: an epidemiologic perspective. *Biol Psychiatry.* 2001;49:1002-1014.
9. Lewinsohn PM, Essau CA. Depression in adolescents. In: Gotlib IH, Hammen CL, eds. *Handbook of Depression.* New York, NY: Guilford Press; 2002:541-559.
10. Giaconia RM, Reinherz HZ, Silverman AB, Pakiz B, Frost AK, Cohen E. Ages of onset of psychiatric disorders in a community population of older adolescents. *J Am Acad Child Adolesc Psychiatry.* 1994;33:706-717.
11. Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE. Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *J Abnorm Psychol.* 1998;107:128-140.
12. Weissman MM, Warner V, Wickramaratne P, Moreau D, Olfson M. Offspring of depressed parents. 10 years later. *Arch Gen Psychiatry.* 1997;54:932-940.
13. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005;62:593-602.
14. Newman DL, Moffitt TE, Caspi A, Magdol L, Silva PA, Stanton WR. Psychiatric disorder in a birth cohort of young adults: prevalence, comorbidity, clinical significance, and new case incidence from ages 11 to 21. *J Consult Clin Psychol.* 1996;64:552-562.
15. Kessler RC, Walters EE. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the National Comorbidity Survey. *Depress Anxiety.* 1998;7:3-14.
16. Roberts RE, Lewinsohn PM, Seeley JR. Screening for adolescent depression: a comparison of depression scales. *J Am Acad Child Adolesc Psychiatry.* 1991;30:58-66.
17. Gotlib IH, Lewinsohn PM, Seeley JR. Symptoms versus a diagnosis of depression: Differences in psychosocial functioning. *J Consult Clin Psychol.* 1995;63:90-100.
18. Angst J, Sellaro R, Merikangas KR. Depressive spectrum diagnoses. *Compr Psychiatry.* 2000;41(2 suppl 1):39-47.
19. Pine DS, Cohen E, Cohen P, Brook J. Adolescent depressive symptoms as predictors of adult depression: moodiness or mood disorder? *Am J Psychiatry.* 1999;156:133-135.
20. Klerman GL, Lavori PW, Rice J, et al. Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. *Arch Gen Psychiatry.* 1985;42:689-693.
21. Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *J Abnorm Psychol.* 1993;102:133-144.
22. Kovacs M, Gatsonis C. Secular trends in age at onset of major depressive disorder in a clinical sample of children. *J Psychiatr Res.* 1994;28:319-329.
23. Ryan ND, Williamson DE, Iyengar S, et al. A secular increase in child and adolescent onset affective disorder. *J Am Acad Child Adolesc Psychiatry.* 1992;31:600-605.
24. Nolen-Hoeksema S. *Sex Differences in Depression.* Stanford, CA: Stanford University Press; 1990.
25. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994;51:8-19.
26. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA.* 1996;276:293-299.
27. Nolen-Hoeksema S. Sex differences in depression and explanatory style in children. *J Youth Adolesc.* 1991;20:233-245.
28. Wade TJ, Cairney J, Pevalin DJ. Emergence of gender differences in depression during adolescence: national panel results from three countries. *J Am Acad Child Adolesc Psychiatry.* 2002;41:190-198.
29. Nolen-Hoeksema S, Girgus JS. The emergence of gender differences in depression during adolescence. *Psychol Bull.* 1994;115:424-443.
30. Rao U. gender differences in depression during the transition to adulthood. *Trends Evidence-Based Neuropsychiatry.* 2002;4:46-53.
31. Turner RJ, Lloyd DA. The stress process and the social distribution of depression. *J Health Soc Behav.* 1999;40:374-404.
32. Bird HR, Canino G, Rubio-Stipec M, et al. Estimates of the prevalence of childhood maladjustment in a community survey in Puerto Rico. The use of combined measures. *Arch Gen Psychiatry.* 1988;45:1120-1126.
33. Costello EJ, Angold A, Burns BJ, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. *Arch Gen Psychiatry.* 1996;53:1129-1136.
34. Gore S, Aseltine RH, Jr, Colton ME. Social structure, life stress and depressive symptoms in a high school-aged population. *J Health Soc Behav.* 1992;33:97-113.
35. Breslau J, Aguilar-Gaxiola S, Kendler KS, Su M, Williams D, Kessler RC. Specifying race-ethnic differences in risk for psychiatric disorder in a USA national sample. *Psychol Med.* 2006;36:57-68.
36. Williams DR, Gonzalez HM, Neighbors H, et al. Prevalence and distribution of major depressive disorder in African Americans, Caribbean Blacks, and Non-Hispanic Whites: results from the National Survey of American Life. *Arch Gen Psychiatry.* 2007;64:305-315.
37. Roberts RE, Roberts CR, Chen YR. Ethnocultural differences in prevalence of adolescent depression. *Am J Community Psychol.* 1997;25:95-110.
38. Rushton JL, Forcier M, Schectman RM. Epidemiology of depressive symptoms in the National Longitudinal Study of Adolescent Health. *J Am Acad Child Adolesc Psychiatry.* 2002;41:199-205.
39. Saluja G, Iachan R, Scheidt PC, Overpeck MD, Sun W, Giedd JN. Prevalence of and risk factors for depressive symptoms among young adolescents. *Arch Pediatr Adolesc Med.* 2004;158:760-765.
40. Hayward C, Gotlib IH, Schraedley PK, Litt IF. Ethnic differences in the association between pubertal status and symptoms of depression in adolescent girls. *J Adolesc Health.* 1999;25:143-149.
41. Wight RG, Aneshensel CS, Botticello AL, Sepulveda JE. A multilevel analysis of ethnic variation in depressive symptoms among adolescents in the United States. *Soc Sci Med.* 2005;60:2073-2084.
42. Choi H, Gi Park C. Understanding adolescent depression in ethnocultural context: updated with empirical findings. *Adv Nurs Sci.* 2006;29:E1-12.
43. Lynch FL, Clarke GN. Estimating the economic burden of depression in children and adolescents. *Am J Prev Med.* 2006;31(6 suppl 1):S143-151.
44. Ma J, Lee KV, Stafford RS. Depression treatment during outpatient visits by U.S. children and adolescents. *J Adolesc Health.* 2005;37:434-442.
45. Patel V, Flisher AJ, Nikapota A, Malhotra S. Promoting child and adolescent mental health in low and middle income countries. *J Child Psychol Psychiatry.* 2008;49:313-334.
46. Rao U. Development and natural history of pediatric depression: treatment implications. *Clin Neuropsychiatry: J Treat Eval.* 2006;3:194-204.
47. Brumback RA, Weinberg WA. Pediatric behavioral neurology: an update on the neurologic aspects of depression, hyperactivity, and learning disabilities. *Neurol Clin.* 1990;8:677-703.
48. Geller B, Zimmerman B, Williams M, Bolhofner K, Craney JL. Adult psychosocial outcome of prepubertal major depressive disorder. *J Am Acad Child Adolesc Psychiatry.* 2001;40:673-677.
49. Kovacs M, Goldston D. Cognitive and social cognitive development of depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 1991;30:388-392.
50. Merry S, McDowell H, Hetrick S, Bir J, Muller N. Psychological and/or educational interventions for the prevention of depression in children and adolescents. *Cochrane Database Syst Rev.* 2004;CD003380.
51. Messer SC, Gross AM. Childhood depression and family interaction: A naturalistic observation study. *J Clin Child Psychol.* 1995;24:77.
52. Puig-Antich J, Lukens E, Davies M, Goetz D, Brennan-Quattrochio J, Todak G. Psychosocial functioning in prepubertal major depressive disorders. I. Interpersonal relationships during the depressive episode. *Arch Gen Psychiatry.* 1985;42:500-507.
53. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part I. *J Am Acad Child Adolesc Psychiatry.* 1996;35:1427-1439.
54. Hammen C, Rudolph K, Weisz J, Rao U, Burge D. The context of depression in clinic-referred youth: neglected areas in treatment. *J Am Acad Child Adolesc Psychiatry.* 1999;38:64-71.

Clinical research

55. Rao U, Chen L. Neurobiological and psychosocial processes associated with depressive and substance-related disorders in adolescents. *Current Drug Abuse Reviews*. 2008;1:68-80.
56. Nolen-Hoeksema S, Girgus JS, Seligman ME. Predictors and consequences of childhood depressive symptoms: a 5-year longitudinal study. *J Abnorm Psychol*. 1992;101:405-422.
57. Puig-Antich J, Lukens E, Davies M, Goetz D, Brennan-Quattrock J, Todak G. Psychosocial functioning in prepubertal major depressive disorders. II. Interpersonal relationships after sustained recovery from affective episode. *Arch Gen Psychiatry*. 1985;42:511-517.
58. Rohde P, Lewinsohn PM, Seeley JR. Are adolescents changed by an episode of major depression? *J Am Acad Child Adolesc Psychiatry*. 1994;33:1289-1298.
59. Zisook S, Lesser I, Stewart JW, et al. Effect of age at onset on the course of major depressive disorder. *Am J Psychiatry*. 2007;164:1539-1546.
60. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th (Text Revision) ed. Washington, DC: American Psychiatric Press; 2000.
61. Kovacs M. Presentation and course of major depressive disorder during childhood and later years of the life span. *J Am Acad Child Adolesc Psychiatry*. 1996;35:705-715.
62. Lewinsohn PM, Pettit JW, Joiner TE, Jr., Seeley JR. The symptomatic expression of major depressive disorder in adolescents and young adults. *J Abnorm Psychol*. 2003;112:244-252.
63. Ryan ND. Diagnosing pediatric depression. *Biol Psychiatry*. 2001;49:1050-1054.
64. Carlson GA, Kashani JH. Phenomenology of major depression from childhood through adulthood: analysis of three studies. *Am J Psychiatry*. 1988;145:1222-1225.
65. Mitchell J, McCauley E, Burke PM, Moss SJ. Phenomenology of depression in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1988;27:12-20.
66. Ryan ND, Puig-Antich J, Ambrosini P, et al. The clinical picture of major depression in children and adolescents. *Arch Gen Psychiatry*. 1987;44:854-861.
67. Sorensen MJ, Nissen JB, Mors O, Thomsen PH. Age and gender differences in depressive symptomatology and comorbidity: an incident sample of psychiatrically admitted children. *J Affect Disord*. 2005;84:85-91.
68. Yorbik O, Birmaher B, Axelson D, Williamson DE, Ryan ND. Clinical characteristics of depressive symptoms in children and adolescents with major depressive disorder. *J Clin Psychiatry*. 2004;65:1654-1659.
69. Birmaher B, Williamson DE, Dahl RE, et al. Clinical presentation and course of depression in youth: does onset in childhood differ from onset in adolescence? *J Am Acad Child Adolesc Psychiatry*. 2004;43:63-70.
70. Compas BE, Oppedisano G, Connor JK, et al. Gender differences in depressive symptoms in adolescence: comparison of national samples of clinically referred and nonreferred youths. *J Consult Clin Psychol*. 1997;65:617-626.
71. Kovacs M. Gender and the course of major depressive disorder through adolescence in clinically referred youngsters. *J Am Acad Child Adolesc Psychiatry*. 2001;40:1079-1085.
72. Masi G, Favilla L, Mucci M, Poli P, Romano R. Depressive symptoms in children and adolescents with dysthymic disorder. *Psychopathology*. 2001;34:29-35.
73. Young MA, Scheftner WA, Fawcett J, Klerman GL. Gender differences in the clinical features of unipolar major depressive disorder. *J Nerv Ment Dis*. 1990;178:200-203.
74. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571.
75. Baron P, Joly E. Sex-differences in the expression of depression in adolescents. *Sex Roles*. 1988;18:1-7.
76. Bennett DS, Ambrosini PJ, Kudes D, Metz C, Rabinovich H. Gender differences in adolescent depression: do symptoms differ for boys and girls? *J Affect Disord*. 2005;89:35-44.
77. Carter JD, Joyce PR, Mulder RT, Luty SE, McKenzie J. Gender differences in the presentation of depressed outpatients: a comparison of descriptive variables. *J Affect Disord*. 2000;61:59-67.
78. Silverstein B. Gender differences in the prevalence of somatic versus pure depression: a replication. *Am J Psychiatry*. 2002;159:1051-1052.
79. Angst J, Dobler-Mikola A. Do the diagnostic criteria determine the sex ratio in depression? *J Affect Disord*. 1984;7:189-198.
80. Vredenburg K, Krames L, Flett GL. Sex-differences in the clinical expression of depression. *Sex Roles*. 1986;14:37-49.
81. Wilhelm K, Roy K, Mitchell P, Brownhill S, Parker G. Gender differences in depression risk and coping factors in a clinical sample. *Acta Psychiatr Scand*. 2002;106:45-53.
82. Hankin BL, Abramson LY. Development of gender differences in depression: an elaborated cognitive vulnerability-transactional stress theory. *Psychol Bull*. 2001;127:773-796.
83. Nolen-Hoeksema S, Larson J, Grayson C. Explaining the gender difference in depressive symptoms. *J Pers Soc Psychol*. 1999;77:1061-1072.
84. Giedd JN, Clasen LS, Lenroot R, et al. Puberty-related influences on brain development. *Mol Cell Endocrinol*. 2006;254-255:154-162.
85. Miller A, Fox NA, Cohn JF, Forbes EE, Sherrill JT, Kovacs M. Regional patterns of brain activity in adults with a history of childhood-onset depression: gender differences and clinical variability. *Am J Psychiatry*. 2002;159:934-940.
86. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry*. 1999;40:57-87.
87. Essau CA. Comorbidity of depressive disorders among adolescents in community and clinical settings. *Psychiatry Res*. 2008;158:35-42.
88. Kovacs M, Obrosky DS, Sherrill J. Developmental changes in the phenomenology of depression in girls compared to boys from childhood onward. *J Affect Disord*. 2003;74:33-48.
89. Kovacs M, Akiskal HS, Gatsonis C, Parrone PL. Childhood-onset dysthymic disorder. Clinical features and prospective naturalistic outcome. *Arch Gen Psychiatry*. 1994;51:365-374.
90. Lewinsohn PM, Rohde P, Seeley JR, Hops H. Comorbidity of unipolar depression: I. Major depression with dysthymia. *J Abnorm Psychol*. 1991;100:205-213.
91. Avenevoli S, Stolar M, Li J, Dierker L, Ries Merikangas K. Comorbidity of depression in children and adolescents: models and evidence from a prospective high-risk family study. *Biol Psychiatry*. 2001;49:1071-1081.
92. Cohen P, Cohen J, Kasen S, et al. An epidemiological study of disorders in late childhood and adolescence—I. Age- and gender-specific prevalence. *J Child Psychol Psychiatry*. 1993;34:851-867.
93. Fleming JE, Offord DR. Epidemiology of childhood depressive disorders: a critical review. *J Am Acad Child Adolesc Psychiatry*. 1990;29:571-580.
94. Lewinsohn PM, Rohde P, Seeley JR. Adolescent psychopathology: III. The clinical consequences of comorbidity. *J Am Acad Child Adolesc Psychiatry*. 1995;34:510-519.
95. Ferro T, Carlson GA, Grayson P, Klein DN. Depressive disorders: distinctions in children. *J Am Acad Child Adolesc Psychiatry*. 1994;33:664-670.
96. Kovacs M, Feinberg TL, Crouse-Novak MA, Paulauskas SL, Finkelstein R. Depressive disorders in childhood. I. A longitudinal prospective study of characteristics and recovery. *Arch Gen Psychiatry*. 1984;41:229-237.
97. Brent DA, Perper JA, Goldstein CE, et al. Risk factors for adolescent suicide. A comparison of adolescent suicide victims with suicidal inpatients. *Arch Gen Psychiatry*. 1988;45:581-588.
98. Clarke G, Hops H, Lewinsohn PM, Andrews J, Seeley JR, Williams J. Cognitive-behavioral group treatment of adolescent depression - prediction of outcome. *Behavior Therapy*. 1992;23:341-354.
99. Kendall PC, Kortlander E, Chansky TE, Brady EU. Comorbidity of anxiety and depression in youth: treatment implications. *J Consult Clin Psychol*. 1992;60:869-880.
100. Kovacs M, Gatsonis C, Paulauskas SL, Richards C. Depressive disorders in childhood. IV. A longitudinal study of comorbidity with and risk for anxiety disorders. *Arch Gen Psychiatry*. 1989;46:776-782.
101. Rao U, Ryan ND, Dahl RE, et al. Factors associated with the development of substance use disorder in depressed adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999;38:1109-1117.
102. Biederman J, Rosenbaum JF, Bolduc EA, Faraone SV, Hirshfeld DR. A high risk study of young children of parents with panic disorder and agoraphobia with and without comorbid major depression. *Psychiatry Res*. 1991;37:333-348.
103. Harrington R, Fudge H, Rutter M, Pickles A, Hill J. Adult outcomes of childhood and adolescent depression: II. Links with antisocial disorders. *J Am Acad Child Adolesc Psychiatry*. 1991;30:434-439.

104. Harrington R, Rutter M, Weissman M, et al. Psychiatric disorders in the relatives of depressed probands. I. Comparison of prepubertal, adolescent and early adult onset cases. *J Affect Disord.* 1997;42:9-22.
105. Hughes CW, Preskorn SH, Weller E, Weller R, Hassanein R, Tucker S. The effect of concomitant disorders in childhood depression on predicting treatment response. *Psychopharmacol Bull.* 1990;26:235-238.
106. Alpert JE, Fava M, Uebelacker LA, et al. Patterns of axis I comorbidity in early-onset versus late-onset major depressive disorder. *Biol Psychiatry.* 1999;46:202-211.
107. Fava M, Alpert JE, Borus JS, Nierenberg AA, Pava JA, Rosenbaum JF. Patterns of personality disorder comorbidity in early-onset versus late-onset major depression. *Am J Psychiatry.* 1996;153:1308-1312.
108. Parker G, Roy K, Hadzi-Pavlovic D, Mitchell P, Wilhelm K. Distinguishing early and late onset non-melancholic unipolar depression. *J Affect Disord.* 2003;74:131-138.
109. Ramklint M, Ekselius L. Personality traits and personality disorders in early onset versus late onset major depression. *J Affect Disord.* 2003;75:35-42.
110. Lewinsohn PM, Clarke GN, Seeley JR, Rohde P. Major depression in community adolescents: age at onset, episode duration, and time to recurrence. *J Am Acad Child Adolesc Psychiatry.* 1994;33:809-818.
111. Birmaher B, Arbelaez C, Brent D. Course and outcome of child and adolescent major depressive disorder. *Child Adolesc Psychiatr Clin N Am.* 2002;11:619-637.
112. Dunn V, Goodyer IM. Longitudinal investigation into childhood- and adolescence-onset depression: psychiatric outcome in early adulthood. *Br J Psychiatry.* 2006;188:216-222.
113. Kovacs M, Obrosky DS, Gatsonis C, Richards C. First-episode major depressive and dysthymic disorder in childhood: clinical and sociodemographic factors in recovery. *J Am Acad Child Adolesc Psychiatry.* 1997;36:777-784.
114. Klein DN, Clark DC, Dansky L, Margolis ET. Dysthymia in the offspring of parents with primary unipolar affective disorder. *J Abnorm Psychol.* 1988;97:265-274.
115. Coryell W, Endicott J, Keller MB. Predictors of relapse into major depressive disorder in a nonclinical population. *Am J Psychiatry.* 1991;148:1353-1358.
116. Holma KM, Holma IA, Melartin TK, Rytasala HJ, Isometsa ET. Long-term outcome of major depressive disorder in psychiatric patients is variable. *J Clin Psychiatry.* 2008;69:196-205.
117. Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. *Am J Psychiatry.* 2006;163:872-880.
118. Melartin TK, Rytasala HJ, Leskela US, Lestela-Mielonen PS, Sokero TP, Isometsa ET. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. *J Clin Psychiatry.* 2004;65:810-819.
119. Posternak MA, Solomon DA, Leon AC, et al. The naturalistic course of unipolar major depression in the absence of somatic therapy. *J Nerv Ment Dis.* 2006;194:324-329.
120. Kaminski KM, Garber J. Depressive spectrum disorders in high-risk adolescents: episode duration and predictors of time to recovery. *J Am Acad Child Adolesc Psychiatry.* 2002;41:410-418.
121. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry.* 1992;49:809-816.
122. Viinamaki H, Hintikka J, Honkalampi K, et al. Cluster C personality disorder impedes alleviation of symptoms in major depression. *J Affect Disord.* 2002;71:35-41.
123. Avenevoli S, Steinberg L. The continuity of depression across the adolescent transition. *Adv Child Dev Behav.* 2001;28:139-173.
124. Coryell W, Akiskal HS, Leon AC, et al. The time course of nonchronic major depressive disorder. Uniformity across episodes and samples. National institute of mental health collaborative program on the psychobiology of depression—clinical studies. *Arch Gen Psychiatry.* 1994;51:405-410.
125. Hart AB, Craighead WE, Craighead LW. Predicting recurrence of major depressive disorder in young adults: a prospective study. *J Abnorm Psychol.* 2001;110:633-643.
126. Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. *Am J Psychiatry.* 2000;157:229-233.
127. Lewinsohn PM, Rohde P, Klein DN, Seeley JR. Natural course of adolescent major depressive disorder: I. Continuity into young adulthood. *J Am Acad Child Adolesc Psychiatry.* 1999;38:56-63.
128. Harrington R, Fudge H, Rutter M, Pickles A, Hill J. Adult outcomes of childhood and adolescent depression. I. Psychiatric status. *Arch Gen Psychiatry.* 1990;47:465-473.
129. Rao U, Ryan ND, Birmaher B, et al. Unipolar depression in adolescents: clinical outcome in adulthood. *J Am Acad Child Adolesc Psychiatry.* 1995;34:566-578.
130. Weissman MM, Wolk S, Goldstein RB, et al. Depressed adolescents grown up. *JAMA.* 1999;281:1707-1713.
131. Hofstra MB, Van der Ende J, Verhulst FC. Continuity and change of psychopathology from childhood into adulthood: a 14-year follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2000;39:850-858.
132. Belsher G, Costello CG. Relapse after recovery from unipolar depression: a critical review. *Psychol Bull.* 1988;104:84-96.
133. Lewinsohn PM, Rohde P, Seeley JR, Klein DN, Gotlib IH. Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. *Am J Psychiatry.* 2000;157:1584-1591.
134. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: lifetime prevalence, chronicity and recurrence. *J Affect Disord.* 1993;29:85-96.
135. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. *Arch Gen Psychiatry.* 1982;39:549-555.
136. Strober M, Lampert C, Schmidt S, Morrell W. The course of major depressive disorder in adolescents: I. recovery and risk of manic switching in a follow-up of psychotic and nonpsychotic subtypes. *J Am Acad Child Adolesc Psychiatry.* 1993;32:34-42.
137. Akiskal HS, Maser JD, Zeller PJ, et al. Switching from 'unipolar' to bipolar II. A 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry.* 1995;52:114-123.
138. Brent DA, Perper JA, Moritz G, et al. Psychiatric risk factors for adolescent suicide: a case-control study. *J Am Acad Child Adolesc Psychiatry.* 1993;32:521-529.
139. Geller B, Fox LW, Clark KA. Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *J Am Acad Child Adolesc Psychiatry.* 1994;33:461-468.
140. Deykin EY, Buka SL, Zeena TH. Depressive illness among chemically dependent adolescents. *Am J Psychiatry.* 1992;149:1341-1347.
141. Kandel DB, Davies M. Adult sequelae of adolescent depressive symptoms. *Arch Gen Psychiatry.* 1986;43:255-262.
142. Rao U, Hammen CL, Poland RE. Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: interactions between stress and HPA activity. *Am J Psychiatry.* In press.
143. Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. *Ann N Y Acad Sci.* 2004;1021:1-22.
144. Masten AS. Regulatory processes, risk, and resilience in adolescent development. *Ann N Y Acad Sci.* 2004;1021:310-319.
145. Paus T. Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci.* 2005;9:60-68.
146. Steinberg L. Cognitive and affective development in adolescence. *Trends Cogn Sci.* 2005;9:69-74.
147. Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. *Trends Neurosci.* 2008;31:183-191.
148. Rudolph KD, Hammen C, Daley SE. Mood disorders. In: Wolfe DA, Mash EJ, eds. *Behavioral and Emotional Disorders in Adolescents.* New York, NY: Guilford Press; 2006:300-342.
149. Beardslee WR, Versage EM, Gladstone TR. Children of affectively ill parents: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1998;37:1134-1141.
150. Rice F, Harold GT, Thapar A. Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry.* 2002;43:1039-1051.
151. Weissman MM. Recent advances in depression across the generations. *Epidemiol Psychiatr Soc.* 2006;15:16-19.
152. Rice F, Harold GT, Shelton KH, Thapar A. Family conflict interacts with genetic liability in predicting childhood and adolescent depression. *J Am Acad Child Adolesc Psychiatry.* 2006;45:841-848.

Clinical research

153. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry*. 2000;157:1552-1562.
154. Uhl GR, Grow RW. The burden of complex genetics in brain disorders. *Arch Gen Psychiatry*. 2004;61:223-229.
155. Scourfield J, Rice F, Thapar A, Harold GT, Martin N, McGuffin P. Depressive symptoms in children and adolescents: changing aetiological influences with development. *J Child Psychol Psychiatry*. 2003;44:968-976.
156. Silberg J, Pickles A, Rutter M, et al. The influence of genetic factors and life stress on depression among adolescent girls. *Arch Gen Psychiatry*. 1999;56:225-232.
157. Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatry*. 2006;47:226-261.
158. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301:386-389.
159. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A*. 2004;101:17316-17321.
160. Drabant EM, Hariri AR, Meyer-Lindenberg A, et al. Catechol O-methyltransferase val158met genotype and neural mechanisms related to affective arousal and regulation. *Arch Gen Psychiatry*. 2006;63:1396-1406.
161. Gonda X, Fountoulakis KN, Juhasz G, et al. Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. *Eur Arch Psychiatry Clin Neurosci*. In press.
162. Papaleo F, Crawley JN, Song J, et al. Genetic dissection of the role of catechol-O-methyltransferase in cognition and stress reactivity in mice. *J Neurosci*. 2008;28:8709-8723.
163. Strauss J, Barr CL, George CJ, et al. Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2004;131B:16-19.
164. Strauss J, Barr CL, George CJ, et al. Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample. *Mol Psychiatry*. 2005;10:861-867.
165. Thoenen H. Neurotrophins and neuronal plasticity. *Science*. 1995;270:593-598.
166. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry*. 2008;64:527-532.
167. Bland ST, Schmid MJ, Der-Avakian A, Watkins LR, Spencer RL, Maier SF. Expression of c-fos and BDNF mRNA in subregions of the prefrontal cortex of male and female rats after acute uncontrollable stress. *Brain Res*. 2005;1051:90-99.
168. Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci*. 2004;27:589-594.
169. Miller A. Social neuroscience of child and adolescent depression. *Brain Cogn*. 2007;65:47-68.
170. Zalsman G, Oquendo MA, Greenhill L, et al. Neurobiology of depression in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2006;15:843-868, vii-viii.
171. Dawson G, Klinger LG, Panagiotides H, Hill D, Spieker S. Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms. *Child Dev*. 1992;63:725-737.
172. Field T, Fox NA, Pickens J, Nawrocki T. Relative right frontal EEG activation in 3- to 6-month-old infants of "depressed" mothers. *Dev Psychol*. 1995;31:358-363.
173. Tomarken AJ, Dichter GS, Garber J, Simien C. Resting frontal brain activity: linkages to maternal depression and socio-economic status among adolescents. *Biol Psychol*. 2004;67:77-102.
174. Kentgen LM, Tenke CE, Pine DS, Fong R, Klein RG, Bruder GE. Electroencephalographic asymmetries in adolescents with major depression: influence of comorbidity with anxiety disorders. *J Abnorm Psychol*. 2000;109:797-802.
175. Tomarken AJ, Keener AD. Frontal brain asymmetry and depression: a self-regulatory perspective. *Cognition & Emotion*. London, UK: Psychology Press; 1998:387-420.
176. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annu Rev Psychol*. 2002;53:545-574.
177. Forbes EE, Miller A, Cohn JF, Fox NA, Kovacs M. Affect-modulated startle in adults with childhood-onset depression: relations to bipolar course and number of lifetime depressive episodes. *Psychiatry Res*. 2005;134:11-25.
178. Ivanenko A, Johnson K. Sleep disturbances in children with psychiatric disorders. *Semin Pediatr Neurol*. 2008;15:70-78.
179. Robert JJ, Hoffmann RF, Emslie GJ, et al. Sex and age differences in sleep macroarchitecture in childhood and adolescent depression. *Sleep*. 2006;29:351-358.
180. Armitage R, Emslie GJ, Hoffmann RF, et al. Ultradian rhythms and temporal coherence in sleep EEG in depressed children and adolescents. *Biol Psychiatry*. 2000;47:338-350.
181. Teicher MH, Glod CA, Harper D, et al. Locomotor activity in depressed children and adolescents: I. Circadian dysregulation. *J Am Acad Child Adolesc Psychiatry*. 1993;32:760-769.
182. Rao U, McCracken JT, Lutchmansingh P, Edwards C, Poland RE. Electroencephalographic sleep and urinary free cortisol in adolescent depression: a preliminary report of changes from episode to recovery. *Biol Psychiatry*. 1997;41:369-373.
183. Rao U, Poland RE. Electroencephalographic sleep and Hypothalamic-pituitary-adrenal changes from episode to recovery in depressed adolescents. *J Child Adolesc Psychopharmacol*. 2008;18:607-613.
184. Morehouse RL, Kusumakar V, Kutcher SP, LeBlanc J, Armitage R. Temporal coherence in ultradian sleep EEG rhythms in a never-depressed, high-risk cohort of female adolescents. *Biol Psychiatry*. 2002;51:446-456.
185. Rao U, Dahl RE, Ryan ND, et al. The relationship between longitudinal clinical course and sleep and cortisol changes in adolescent depression. *Biol Psychiatry*. 1996;40:474-484.
186. Rao U, Hammen CL, Poland RE. Risk markers for depression in adolescents: sleep and HPA measures. *Neuropsychopharmacology*. In press.
187. Rao U, Dahl RE, Ryan ND, et al. Heterogeneity in EEG sleep findings in adolescent depression: unipolar versus bipolar clinical course. *J Affect Disord*. 2002;70:273-280.
188. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49:651-668; discussion 669-670.
189. Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry*. 2005;66:1254-1269.
190. Giles DE, Rush AJ, Roffwarg HP. Sleep parameters in bipolar I, bipolar II, and unipolar depressions. *Biol Psychiatry*. 1986;21:1340-1343.
191. Thase ME, Himmelhoch JM, Mallinger AG, Jarrett DB, Kupfer DJ. Sleep EEG and DST findings in anergic bipolar depression. *Am J Psychiatry*. 1989;146:329-333.
192. Barbini B, Bertelli S, Colombo C, Smeraldi E. Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Res*. 1996;65:121-125.
193. Wehr TA, Sack DA, Rosenthal NE. Sleep reduction as a final common pathway in the genesis of mania. *Am J Psychiatry*. 1987;144:201-204.
194. Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E. The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Res*. 1998;79:43-50.
195. Emslie GJ, Rush AJ, Weinberg WA, Rintelmann JW, Roffwarg HP. Children with major depression show reduced rapid eye movement latencies. *Arch Gen Psychiatry*. 1990;47:119-124.
196. Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *J Affect Disord*. 2001;62:77-91.
197. Goodyer IM, Park RJ, Herbert J. Psychosocial and endocrine features of chronic first-episode major depression in 8-16 year olds. *Biol Psychiatry*. 2001;50:351-357.
198. Rao U, Hammen C, Poland R. Social factors and the psychobiology of adolescent depression: relations between life stress and HPA activity. *Biological Psychiatry*. 2003;53(suppl 1):S75.
199. Mathew SJ, Coplan JD, Goetz RR, et al. Differentiating depressed adolescent 24 h cortisol secretion in light of their adult clinical outcome. *Neuropsychopharmacology*. 2003;28:1336-1343.
200. Goodyer IM, Herbert J, Tamplin A, Altham PM. Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *Br J Psychiatry*. 2000;177:499-504.
201. Halligan SL, Herbert J, Goodyer I, Murray L. Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biol Psychiatry*. 2007;62:40-46.

202. Steiger A. Sleep and endocrine regulation. *Front Biosci.* 2003;8:s358-376.
203. Williamson DE, Birmaher B, Dahl RE, al-Shabbout M, Ryan ND. Stressful life events influence nocturnal growth hormone secretion in depressed children. *Biol Psychiatry.* 1996;40:1176-1180.
204. Coplan JD, Wolk SI, Goetz RR, et al. Nocturnal growth hormone secretion studies in adolescents with or without major depression re-examined: integration of adult clinical follow-up data. *Biol Psychiatry.* 2000;47:594-604.
205. Dinan TG. Psychoneuroendocrinology of depression. Growth hormone. *Psychiatr Clin North Am.* 1998;21:325-339.
206. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol.* 2001;11:240-249.
207. Mayberg HS. Defining the neural circuitry of depression: toward a new nosology with therapeutic implications. *Biol Psychiatry.* 2007;61:729-730.
208. Rosenberg DR, MacMaster FP, Mirza Y, Easter PC. Imaging and neurocircuitry of pediatric major depression. *Clin Neuropsychiatry: J Treat Eval.* 2006;3:219-229.
209. Rothbart MK, Ahadi SA, Evans DE. Temperament and personality: origins and outcomes. *J Pers Soc Psychol.* 2000;78:122-135.
210. Kagan J, Reznick JS, Snidman N. The physiology and psychology of behavioral inhibition in children. *Child Dev.* 1987;58:1459-1473.
211. Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry.* 1987;44:573-588.
212. Watson D, Clark LA. Negative affectivity: the disposition to experience aversive emotional states. *Psychol Bull.* 1984;96:465-490.
213. Eysenck HJ. *Dimensions of Personality.* London, UK: Kegan Paul; 1947.
214. Gray J. *The Neuropsychology of Anxiety: an Enquiry Into the Functions of the Septo-hippocampal System.* New York, NY: Oxford University Press; 1982.
215. Clark LA, Watson D. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J Abnorm Psychol.* 1991;100:316-336.
216. Chorpita BF. The tripartite model and dimensions of anxiety and depression: an examination of structure in a large school sample. *J Abnorm Child Psychol.* 2002;30:177-190.
217. Rosenbaum JF, Biederman J, Hirshfeld-Becker DR, et al. A controlled study of behavioral inhibition in children of parents with panic disorder and depression. *Am J Psychiatry.* 2000;157:2002-2010.
218. Caspi A, Moffitt TE, Newman DL, Silva PA. Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. *Arch Gen Psychiatry.* 1996;53:1033-1039.
219. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. *Arch Gen Psychiatry.* 1997;54:625-631.
220. Davies PT, Windle M. Interparental discord and adolescent adjustment trajectories: the potentiating and protective role of intrapersonal attributes. *Child Dev.* 2001;72:1163-1178.
221. Hirshfeld RM, Klerman GL, Lavori P, Keller MB, Griffith P, Coryell W. Premorbid personality assessments of first onset of major depression. *Arch Gen Psychiatry.* 1989;46:345-350.
222. Rohde P, Lewinsohn PM, Seeley JR. Are people changed by the experience of having an episode of depression - a further test of the scar hypothesis. *J Abnorm Psychol.* 1990;99:264-271.
223. Gjerde PF. Alternative pathways to chronic depressive symptoms in young adults: gender differences in developmental trajectories. *Child Dev.* 1995;66:1277-1300.
224. Abramson LY, Alloy LB, Metalsky GI. Hopelessness depression - a theory-based subtype of depression. *Psycho Rev.* 1989;96:358-372.
225. Beck A. *Depression: Clinical, Experiential, and Theoretical Aspects.* New York, NY: Harper and Row; 1967.
226. Rehm LP. Self-control model of depression. *Behav Ther.* 1977;8:787-804.
227. Bandura A. *Social Learning Theory.* Englewood Cliff, New Jersey: Prentice Hall; 1977.
228. Nolen-Hoeksema S. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *J Abnorm Psychol.* 2000;109:504-511.
229. Garber J, Hilsman R. Cognition, stress, and depression in children and adolescents. *Child Adol Psych Clin N Am.* 1992;1:129-167.
230. Garber J. Depression in children and adolescents: linking risk research and prevention. *Am J Prev Med.* 2006;31(6 suppl 1):S104-125.
231. Jacobs RH, Reinecke MA, Gollan JK, Kane P. Empirical evidence of cognitive vulnerability for depression among children and adolescents: a cognitive science and developmental perspective. *Clin Psychol Rev.* 2008;28:759-782.
232. Cole DA, Turner JE, Jr. Models of cognitive mediation and moderation in child depression. *J Abnorm Psychol.* 1993;102:271-281.
233. Weisz JR, Southam-Gerow MA, McCarty CA. Control-related beliefs and depressive symptoms in clinic-referred children and adolescents: developmental differences and model specificity. *J Abnorm Psychol.* 2001;110:97-109.
234. Turner JE, Jr., Cole DA. Developmental differences in cognitive diatheses for child depression. *J Abnorm Child Psychol.* 1994;22:15-32.
235. Garber J, Robinson NS. Cognitive vulnerability in children at risk for depression. *Cogn Emotions.* 1997;11:619-635.
236. Barnett PA, Gotlib IH. Psychosocial functioning and depression: distinguishing among antecedents, concomitants, and consequences. *Psychol Bull.* 1988;104:97-126.
237. Haaga DA, Dyck MJ, Ernst D. Empirical status of cognitive theory of depression. *Psychol Bull.* 1991;110:215-236.
238. Ingram R, Miranda J, Segal Z. *Cognitive Vulnerability to Depression.* New York, NY: Guilford Press; 1998.
239. Bowlby J. By ethology out of psycho-analysis: an experiment in interbreeding. *Anim Behav.* 1980;28:649-656.
240. Rapee RM. Potential role of childrearing practices in the development of anxiety and depression. *Clin Psychol Rev.* 1997;17:47-67.
241. Barber BK. Parental psychological control: revisiting a neglected construct. *Child Dev.* 1996;67:3296-3319.
242. Kistner J, Balthazor M, Risi S, Burton C. Predicting dysphoria in adolescence from actual and perceived peer acceptance in childhood. *J Clin Child Psychol.* 1999;28:94-104.
243. Nolan SA, Flynn C, Garber J. Prospective relations between rejection and depression in young adolescents. *J Pers Soc Psychol.* 2003;85:745-755.
244. Hammen C. Cognitive, life stress, and interpersonal approaches to a developmental psychopathology model of depression. *Dev Psychopathol.* 1992;4:191-208.
245. Joiner TE. *The Interpersonal, Cognitive, and Social Nature of Depression.* In: Brown JS, Kistner J, eds. Mahwah, NJ: Lawrence Erlbaum Associates; 2006.
246. Asarnow JR, Goldstein MJ, Tompson M, Guthrie D. One-year outcomes of depressive disorders in child psychiatric in-patients: evaluation of the prognostic power of a brief measure of expressed emotion. *J Child Psychol Psychiatry.* 1993;34:129-137.
247. Kobak R, Ferenzgillies R. Emotion regulation and depressive symptoms during adolescence - a functionalist perspective. *Dev Psychopathol.* 1995;7:183-192.
248. Puig-Antich J, Kaufman J, Ryan ND, et al. The psychosocial functioning and family environment of depressed adolescents. *J Am Acad Child Adolesc Psychiatry.* 1993;32:244-253.
249. Sheeber L, Sorensen E. Family relationships of depressed adolescents: a multimethod assessment. *J Clin Child Psychol.* 1998;27:268-277.
250. Grant KE, Compas BE, Thurm AE, McMahon SD, Gipson PY. Stressors and child and adolescent psychopathology: measurement issues and prospective effects. *J Clin Child Adolesc Psychol.* 2004;33:412-425.
251. Meyer SE, Chrousos GP, Gold PW. Major depression and the stress system: a life span perspective. *Dev Psychopathol.* 2001;13:565-580.
252. Hammen C. Stress and depression. *Annu Rev Clin Psychol.* 2005;1:293-319.
253. Bifulco A, Brown GW, Adler Z. Early sexual abuse and clinical depression in adult life. *Br J Psychiatry.* 1991;159:115-122.
254. Weiss EL, Longhurst JG, Mazure CM. Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. *Am J Psychiatry.* 1999;156:816-828.
255. McLoyd VC. Socioeconomic disadvantage and child development. *Am Psychol.* 1998;53:185-204.
256. Brown GW. Life events and affective disorder: replications and limitations. *Psychosom Med.* 1993;55:248-259.
257. Davis MC, Matthews KA, Twamley EW. Is life more difficult on Mars or Venus? A meta-analytic review of sex differences in major and minor life events. *Ann Behav Med.* 1999;21:83-97.
258. Cole DA, Nolen-Hoeksema S, Girgus J, Paul G. Stress exposure and stress generation in child and adolescent depression: a latent trait-state-error approach to longitudinal analyses. *J Abnorm Psychol.* 2006;115:40-51.

Clinical research

259. Pearlman LI. The sociological study of stress. *J Health Soc Behav.* 1989;30:241-256.
260. Turner RJ, Wheaton B, Lloyd DA. The epidemiology of social stress. *Am Sociol Rev.* 1995;60:104-125.
261. Turner HA, Turner RJ. Understanding variations in exposure to social stress. *Health.* 2005;9:209-240.
262. Ge X, Lorenz FO, Conger RD, Elder JGH, Simons RL. Trajectories of stressful life events and depressive symptoms during adolescence. *Dev Psychol.* 1994;30:467-483.
263. Larson R, Ham M. Stress and storm and stress in early adolescence - the relationship of negative events with dysphoric affect. *Dev Psychol.* 1993;29:130-140.
264. Rudolph KD, Hammen C. Age and gender as determinants of stress exposure, generation, and reactions in youngsters: a transactional perspective. *Child Dev.* 1999;70:660-677.
265. Hammen C, Henry R, Daley SE. Depression and sensitization to stressors among young women as a function of childhood adversity. *J Consult Clin Psychol.* 2000;68:782-787.
266. Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. *Depress Anxiety.* 2002;15:117-125.
267. Rao U, Hammen C, Ortiz LR, Chen LA, Poland RE. Effects of early and recent adverse experiences on adrenal response to psychosocial stress in depressed adolescents. *Biol Psychiatry.* 2008;64:521-526.
268. Turner RJ, Lloyd DA. Lifetime traumas and mental health: the significance of cumulative adversity. *J Health Soc Behav.* 1995;36:360-376.
269. Hazel NA, Hammen C, Brennan PA, Najman J. Early childhood adversity and adolescent depression: the mediating role of continued stress. *Psychol Med.* 2008;38:581-589.
270. Hammen C. Stress generation in depression: reflections on origins, research, and future directions. *J Clin Psychol.* 2006;62:1065-1082.
271. Davila J, Hammen C, Burge D, Paley B, Daley SE. Poor interpersonal problem solving as a mechanism of stress generation in depression among adolescent women. *J Abnorm Psychol.* 1995;104:592-600.
272. Daley SE, Hammen C, Davila J, Burge D. Axis II symptomatology, depression, and life stress during the transition from adolescence to adulthood. *J Consult Clin Psychol.* 1998;66:595-603.
273. Nelson DR, Hammen C, Daley SE, Burge D, Davila J. Sociotropic and autonomous personality styles: contributions to chronic life stress. *Cognit Ther Res.* 2001;25:61-76.
274. Herzberg DS, Hammen C, Burge D, Daley SE, Davila J, Lindberg N. Social competence as a predictor of chronic interpersonal stress. *Personal Relationships.* 1998;5:207-218.
275. Daley SE, Hammen C, Burge D, et al. Predictors of the generation of episodic stress: a longitudinal study of late adolescent women. *J Abnorm Psychol.* 1997;106:251-259.
276. Cohen LH, Burt CE, Bjorck JP. Life stress and adjustment - effects of life events experienced by young adolescents and their parents. *Dev Psychol.* 1987;23:583-592.
277. Kim KJ, Conger RD, Elder GH, Jr., Lorenz FO. Reciprocal influences between stressful life events and adolescent internalizing and externalizing problems. *Child Dev.* 2003;74:127-143.
278. Hilsman R, Garber J. A test of the cognitive diathesis-stress model of depression in children: academic stressors, attributional style, perceived competence, and control. *J Pers Soc Psychol.* 1995;69:370-380.
279. Lewinsohn PM, Joiner TE, Jr., Rohde P. Evaluation of cognitive diathesis-stress models in predicting major depressive disorder in adolescents. *J Abnorm Psychol.* 2001;110:203-215.
280. Robinson NS, Garber J, Hilsman R. Cognitions and stress: direct and moderating effects on depressive versus externalizing symptoms during the junior high school transition. *J Abnorm Psychol.* 1995;104:453-463.
281. Abela JR. The hopelessness theory of depression: a test of the diathesis-stress and causal mediation components in third and seventh grade children. *J Abnorm Child Psychol.* 2001;29:241-254.
282. Compas BE, Connor-Smith JK, Saltzman H, Thomsen AH, Wadsworth ME. Coping with stress during childhood and adolescence: problems, progress, and potential in theory and research. *Psychol Bull.* 2001;127:87-127.
283. Lazarus R, Folkman S. *Stress, Appraisal, and Coping.* New York, NY: Springer; 1984.
284. Spence SH, Sheffield J, Donovan C. Problem-solving orientation and attributional style: moderators of the impact of negative life events on the development of depressive symptoms in adolescence? *J Clin Child Adolesc Psychol.* 2002;31:219-229.
285. Gazelle H, Rudolph KD. Moving toward and away from the world: social approach and avoidance trajectories in anxious solitary youth. *Child Dev.* 2004;75:829-849.