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PRODROMAL SYMPTOMS AND ATYPICAL AFFECTIVITY AS PREDICTORS OF MAJOR DEPRESSION IN JUVENILES: IMPLICATIONS FOR PREVENTION

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Abstract

Background—Given the long-term morbidity of juvenile-onset major depressive disorder (MDD), it is timely to consider whether more effort should be dedicated to its primary and secondary prevention.

Methods—We reviewed studies of prodromal symptoms that may herald a first episode pediatric MDD and considered whether that literature has made an impact on secondary prevention (efforts to prevent progression from symptoms to full disorder). We also reviewed studies of children at familial risk for MDD that addressed atypical affectivity and the regulation of sad, dysphoric affect (mood repair) and related physiological systems, and considered whether research in those areas has made an impact on primary prevention of pediatric MDD (efforts to prevent the disorder).

Results—A compelling body of literature indicates that depressive symptoms in youngsters predict subsequent MDD across the juvenile (and early adult) years and that any combination of several symptoms for at least one week is informative in that regard. These findings are echoed in the case selection criteria used by many secondary prevention programs. Convergent findings also indicate that (compared to typical peers) young offspring at familial-risk for depression manifest low positive affectivity and compromised mood repair, along with signs of dysfunction in three intertwined physiological systems that contribute to affectivity and mood repair (the HPA axis, cerebral hemispheric asymmetry, and cardiac vagal control). While all these affect-related parameters are suitable for case selection and as intervention targets, they have not yet made an impact on primary prevention programs.

Conclusions—According to recent meta-analyses, attempts to prevent pediatric depression have not lived up to expectations. Based on our review, possible reasons for this include: (a) the use of case selection criteria that yield samples heterogeneous with regard to whether the symptoms are truly prodromal to an episode of MDD or are trait-like (which could affect response to the intervention), (b) failure to fully capitalize on the broad-ranging literature on vulnerability to pediatric MDD, as evidenced by the infrequent use of family history of depression (a robust index of vulnerability) or combined indices of vulnerability for case selection, and (c) lack of synchrony between dimensions of vulnerability and the content of the prevention program, as indicated by the overwhelming use of cognitive-behavioral interventions, irrespective of subjects' age, developmental readiness, and whether or not they evidenced the relevant cognitive vulnerability. Prevention trials of pediatric MDD could benefit from new approaches to case selection that combine various indeces of vulnerability, more effective use of existing findings, and new or modified interventions that are developmentally sensitive.

Keywords

Depression; developmental psychopathology; emotion regulation; prevention; psychophysiology; risk factors

Introduction

Using the context of secondary and primary prevention, we were asked to examine for this Annual Review "prodromal research" in pediatric depression as well as research on "developmental processes that may herald" full psychiatric syndromes. As a medical concept, a prodrome is a premonitory symptom of a disease (Dorland's, 1988) and signifies that the disease process has begun. Given that a prodrome is part of the natural clinical history of a disorder and designates a symptomatic but not-yet-diagnosable individual, prodromal research can facilitate case identification for secondary prevention programs. We focus in this article on prodromes of the initial episode of major depressive disorder (MDD) in youths. Accordingly, our first question is: "Are there particular psychopathological symptoms that reliably precede (herald) the first episode of major depression in juveniles, and how can that information facilitate early case identification and intervention?"

In contrast to secondary prevention, primary prevention of pediatric MDD requires that vulnerable youths be identified before they develop prodromal symptoms. Vulnerability can be defined in many different ways. We focus herein on two parameters of vulnerability: (a) having a familial history of depression and (b) atypical development of affectivity and mood repair (the self-regulation of sad, dysphoric affect) and physiological processes that are believed to undergird and influence them (specifically, the functioning of the HPA axis, brain hemispheric lateralization, and cardiac vagal control). Accordingly, our second question is: "Do youngsters at familial-risk for depression differ from low-risk peers with regard to the development of affectivity, mood repair, and related physiological processes, and how can that information facilitate prevention of MDD?"

We first address aspects of the literature on symptom prodromes and affective vulnerabilities related to pediatric depression, and then examine the interface of that literature with prevention trials. In discussing the current state of depression prevention research, we make recommendations about sample selection criteria, better use of existing information on dimensions of vulnerability, new intervention targets for children at familial-risk for depression, and also underscore the need for novel, developmentally sensitive prevention programs.

Prodromes and vulnerabilities

In the literature on pediatric depression, the search for prodromes, developmental precursors, personal vulnerabilities-diatheses, or risk factors reflects different although overlapping disciplinary perspectives on ways to identify that child or adolescent that is likely to become clinically depressed. In this article we distinguish between prodromes (early pre-diagnostic clinical features associated with a disorder), vulnerabilities (personal characteristics of individuals that increase the likelihood of a disorder), and traditional risk factors (i.e., aspects of the environment or context that also increase the odds of a given disorder).

Prodromes

Given the well-established morbidity of depression in the pre-adult years (Birmaher et al., 1996), its prevention has become a priority. Prodromal research can inform secondary

prevention by helping to identify children with early clinical indicators of the disorder. As we already noted, a "prodrome" is a medical term that signifies "a premonitory symptom or precursor; a symptom indicating the onset of a disease" (Dorland's, 1988). The prodromal symptom is connected to the disease via some (known or unknown) physiological pathway, signals its early phase (although it is generally not a salient or defining feature of the disorder or disease), and typically represents a change in the person's functioning. However, there is no single rule as to the time lag between prodromal symptoms and the full-blown disease. Finally, it is worth emphasizing that a prodrome "can be defined only retrospectively" (Eaton, Badawi, & Melton, 1995).

Much of prodromal research in psychiatry has had a clinical framework and focused mostly on schizophrenic and bipolar disorders (e.g., Jackson, Cavanagh & Scott, 2003), bipolar rather than unipolar depression, and depression in adults rather in youngsters (Fava & Kellner, 1991; Jackson et al., 2003). Along the way, the meaning of the word "prodrome" has become rather unclear. Psychiatric prodromes have been conceptualized not only as early symptoms and signs, but also as various indices of role impairment (Simon, Ferrero & Merlo, 2001), early expressions of core vulnerability or "risk factors" (Cornblatt et al., 2003), biological markers (Fava & Kellner, 1991), the manner of onset of symptoms including their rapidity and course (Fava, Grandi, Canestrari & Molnar, 1990), the period of "difficulties" before full diagnostic criteria for a disorder are met (Eaton et al., 1995), and both in connection with the onset of an episode and relapse into a prior episode (e.g., Cornblatt et al., 2003). Depression prodromes have been defined both as "symptoms and signs that *differ* from those of the acute clinical phase" [emphasis is ours] (Fava & Kellner, 1991) and as "subclinical symptoms," which are "*milder* than those of the full clinical syndrome [emphasis is ours] (Fava & Tossani, 2007).

The typical design of clinical prodromal research has involved retrospectively gathering from recovered patients (and/or relatives) reports about the early manifestations of the disorder, and then monitoring patients prospectively to detect re-emergence of the very same signs as indicative of relapse or recurrence. However, studies focusing on the prediction of pediatric depression have used epidemiological rather than clinical designs. The typical epidemiological "prodromal" research study has entailed identification of symptomatically depressed (but never diagnosable) cases and determining via follow-up the relative risk associated with those symptoms for incident MDD across a subsequent time interval (e.g., Murphy, et al., 1989). While such a prospective design is necessary to assess whether putative symptoms contribute to later disorder, strictly speaking, it is not prodromal research (which is retrospective by definition and uses affected cases). In any case, given the available literature, our examination of prodromes of pediatric MDD focuses on putative symptoms prior to the emergence of the full episode.

Vulnerabilities

Studies of vulnerability are particularly germane to prevention programs because they help to define which individuals should be targeted. Vulnerability (or diathesis) refers to a personal characteristic that increases the likelihood of an individual developing a particular disorder. In this article, we focus on two domains of vulnerability to depression, not including the cognitive domain (which we address in a later section of this article).

Having a family history of major depressive disorder is a well established diathesis (or vulnerability factor) for juvenile-onset depression (for reviews, see Kovacs & Devlin, 1998; Rice, Harold, & Thapar, 2002; Todd, Neuman, Geller, Fox, & Hickok, 1993). It is generally accepted that this index of vulnerability is likely to have multiple genetic components (e.g., Dempster et al., 2007; Strauss et al., 2005). While a juvenile's familial-risk for depression can be indexed by having a young sibling with a history of depression (e.g., Ryan et al.,

1992), the familial risk-status that has received almost exclusive attention is being the offspring of a depressed parent (reviewed by Avenevoli & Merikangas, 2006; Beardslee, Versage, & Gladstone, 1998). High-risk family studies concur that (compared to having a psychiatrically well or medically ill parent), parental depression poses to the offspring a more than three-fold increased risk of depressive disorder and also signals elevated rates of non-affective psychiatric disorders (e.g., Hammen et al., 1987, 1991, Hammen, 1997; Henin et al., 2005; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992; Weissman et al., 2006; Welner & Rice, 1988; Williamson, Birmaher, Axelson, Ryan, & Dahl, 2004). Juveniles at familial risk for depression are at singularly increased risk for major depressive disorder (MDD), with at least 50% affected by about the age of 20 years (Hammen, Burge, & Stansbury, 1990; Weissman, Fendrich, Warner, & Wickramaratne, 1992; Williamson et al., 2004), and they develop depression earlier than do control peers (Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Weissman et al., 1987, 2006; Williamson et al., 2004). While such youths also are at elevated risk for early-onset anxiety disorders (Biederman et al., 2006; Henin et al., 2005; McClellan, Rubert, Reichler, & Sylvester, 1990; Weissman et al., 1992, 1997, 2006) and possibly externalizing and substance-use related diagnoses (e.g., Grigoroiu-Serbanescu et al., 1991; Hirshfeld-Becker et al., 2008; McClellan et al., 1990), such non-affective disorders appear to reflect similar (comorbid) disorders in their parents (e.g., Biederman et al., 2001; Hirshfeld-Becker et al., 2008). All in all, the compelling relation of familial mood disorder and eventual clinical depression in young offspring indicates that high-risk juveniles provide a unique window on developmental aspects of vulnerability to MDD. Therefore, we focus on research with children at familial-risk for depression.

Using at-risk status as a general framework, the other domain of vulnerability central to this article is the atypical development of positive and negative affectivity, mood repair, and related physiological processes. Research on affectivity has underscored the importance and functional significance of emotion and mood in children's lives (e.g., Campos, Campos & Barrett, 1989). A construct closely related to affectivity is emotion regulation or affect regulation. Emotion regulation has been defined in various ways and at different levels of complexity (e.g., Cole, Martin, & Dennis, 2004; Davidson, Jackson, & Kalin, 2000; Eisenberg & Zhou, 2000; Goldsmith & Davidson, 2004; Gross, 1998; Thompson, 1994) and researchers have debated whether the generation and the regulation of emotion are separable processes (see for example, Campos, Frankel, & Camras, 2004; Cole et al., 2004; Goldsmith & Davidson, 2004).

In this article, the term "emotion regulation" or "affect regulation" refers to the (psychological, behavioral, and physiological) responses and processes set in motion after an affect has been activated that can alter its intensity and duration (Cole et al., 2004; Davidson, 1998; Thompson, 1994). While emotion regulation concerns the entire repertoire of human affect and includes attempts to increase or decrease affect intensity and duration, we focus on those responses that constitute "mood repair." *Mood repair* (Isen, 1985; Josephson, Singer, & Salovey, 1996; Morris & Reilly, 1987) refers to regulatory responses specifically to sadness and dysphoria **and** the explicit goal of recovering from it. In addressing this overall domain of functioning, we will use—whenever possible--the terms "affectivity" or "affect regulation" (rather than emotion and emotion regulation) in order to bypass often "arbitrary" and "ambiguous" distinctions between an emotion and a mood (Berkowitz & Harmon-Jones, 2004).

There is consensus in the field that emotions and emotional development have been fundamentally re-conceptualized in the 1970's and 1980's. Among other things, that re-conceptualization called attention to the primacy of emotion in the lives of children rather than as epiphenomena of cognition (Campos et al., 1989). How children and youth typically

experience, regulate, and display affect (their temperament) have also come to be regarded as a core feature that contributes to continuity of the self across development (Campos et al., 1989). Affectivity and its development also are very important for a better understanding of depressive disorders, which, by definition, reflect a serious problem in this domain of functioning. Notably, sadness/dysphoria and anhedonia were the affects of most interest to depression researchers in the past. But recent work has increasingly focused on the role of positive affect and its development in *vulnerability* to depressive disorder (e.g., Fareri, Martin, & Delgado, 2008), a proposition that has been succinctly articulated by Clark, Watson and Mineka (1994). Indeed, as we document, there is emerging evidence that aspects of affective development may be going awry as early as the toddler-years in offspring at familial-risk for depression.

Early identification of clinical depression

The symptoms that have been identified as prodromes of an impending episode of depression in adults include irritability, anxiety, sleep disturbance, and a sense of personal inadequacy (for reviews, see Fava & Tossani, 2007; Jackson et al., 2003). However, methodological differences across the historically early studies make it difficult to determine, which (if any) symptoms are more decisive than are others. Indeed, recent investigations of adults (many of which used community samples) indicate that any combination of a few depressive symptoms for at least 1-2 weeks (sometimes called sub-threshold syndromes or minor depression) predicts a later episode of major depression (reviewed by Cuijpers & Smit, 2004). Interestingly, studies of the predictive value of prior depressive symptoms for later unipolar depression in youngsters have yielded similar findings.

Do depressive symptoms predict subsequent major depression in juveniles?

Epidemiology has long been regarded as providing important tools for examining the natural history of mental disorders (Eaton et al., 1995; Murphy et al., 1989). More than two decades ago, Murphy and colleagues (1989) had reported that (adult) incident cases with a depressive disorder across a 16-year follow-up were highly likely to have had “premonitory symptoms” in the beginning of the study. Shortly thereafter, Horwath and collegues (1992) published their findings on the *relative* and *attributable* risks posed by depressive symptoms for first onset (incident) MDD in a multi-site epidemiological study of adults. Respondents who reported at least 2 depressive symptoms for 2 weeks anytime up to the initial (T1) assessment (but did not meet diagnostic criteria) were highly likely to have onset of new MDD (incident cases) across the following 12-months (odds ratio: 4.4), and about 55% of the new MDD cases had had T1 depressive symptoms (attributable risk). Interestingly, only 52% of the T1 symptomatic cases had a “mood” symptom (dysphoric mood or anhedonia) and its presence did not alter the predictability of MDD. The eventual recognition that depressive symptom clusters, which fail to meet diagnostic criteria (sub-threshold or sub-syndromal depressions) are common and impairing (e.g., Kessler, Zhao, Blazer, & Swartz, 1997) has kindled considerable interest in their subsequent course and predictive value.

The pediatric literature is remarkably consistent on the value of depressive symptoms to predict subsequent depressive disorders. Such findings have held up regardless of whether depressive symptoms were assessed by self-rating (e.g., Ialongo, Edelsohn, & Kellam, 2001) or semi-structured clinical interview (e.g., Georgiades, Lewinsohn, Monroe, & Seeley, 2006), when important variables were statistically controlled (e.g., Shankman et al., 2009), and appear to be specific to the prediction of depressive as compared to anxiety or substance use disorders (e.g., Shankman et al., 2009). Even more remarkably, the predictive value of pediatric depressive symptoms remains across follow-ups from childhood into middle adulthood!

Because our interest is in youngsters, we start with studies in which the outcomes were confined to the juvenile years. According to a pioneering follow-up of a community sample of 1st graders (n=1,030), self-rated depressive symptoms predicted a diagnosis of MDD during the 12-month period between the 7th and 8th grades, as determined in structured clinical assessments of the youth (Ialongo et al., 2001). For each one point increase in the depression inventory score (completed in the 1st grade), there was an about 4-fold increase in the odds of MDD between the 7th and 8th grades. Essentially similar findings were reported by a study of young girls, selected from a larger community-based sample, in which the initial depressive symptoms were determined by clinical interview (Keenan et al., 2008). Namely, child reported depressive symptoms at age 9 predicted DSM-IV major or minor depression at age 10 or 11. For each depressive symptom, the risk of later disorder increased about 2-fold, and this association was not affected by race, poverty, or pubertal status (Keenan et al., 2008).

Are certain depressive symptoms in youngsters more predictive than are others of eventual MDD? This question was explored in a one-year follow-up of 14- to 18-year-olds in a community sample (n=1,456) in the Oregon Adolescent Depression Project (OADP) (Georgiades et al., 2006). Depressive symptoms reported by the adolescents in the initial semi-structured clinical interviews predicted new onset MDD in the following 12 months. All but one (psychomotor disturbance) of 9 depressive symptoms predicted clinical depression, regardless of subject's sex and past depression history. However, in a summary model, only depressed mood (in the presence of other symptoms) was a unique contributor to future MDD. All in all, most of the risk for later depression derived from the co-occurrence of non-mood depressive symptoms (with depressed mood increasing the risk) and almost all (8 of 9) depressive symptoms specifically predicted MDD rather than later substance use/abuse disorder (Georgiades et al., 2006).

Data from the 14-year follow-up of OADP participants (around the age of 30 years) have yielded additional information about the predictive value of adolescent depressive symptoms. Further indicating homotypic continuity, sub-threshold depressions (at least 1 core and 2 further depressive symptoms with a one week duration) at (or prior to) age 16 heralded a full-syndrome MDD or dysthymic disorder across the following 14-years (Shankman, et al., 2009). This finding was specific (sub-threshold depression did not predict anxiety or externalizing disorders) and held even when comorbidity was controlled. Then, this research group examined predictors of escalation from sub-threshold to full-syndrome depression across the same follow-up interval (Klein, Shankman, Lewinsohn, & Seeley, 2009). Five variables in a multivariate model predicted escalation of age 16 depressive symptoms to later full depression: self-rated depression symptoms, medical conditions, lifetime suicidal ideation, lifetime anxiety disorder, and familial history of depression. An estimated 90% of the adolescents with sub-threshold depression and 3 or more risk factors eventually developed depressive disorders (MDD in all cases except one). Notably, no particular symptom cluster emerged as having predictive power (Klein et al., 2009).

Findings from other research groups reinforce the remarkable predictive value of adolescent depressive symptoms into *adulthood*, even when potential confounds are controlled. This conclusion is supported by study of more than 1,000 cases in a birth cohort, in which interview-based 12-month symptoms at age 18 predicted depressive disorders between ages 18-25 (Fergusson, Horwood, Ridder, & Beautrais, 2005) and an epidemiologic study of more than 700 cases, in which both age 14 and age 16 depressive symptoms (based on parent- and child-interviews) predicted MDD at the average age of 22 years, with especially high symptom counts increasing the odds 2- to 3-fold (Pine, Cohen, Cohen, & Brook, 1999). While in the Pine et al, (1999) study, no specific age-14 symptom was predictive, age-16

anhedonia and thoughts of death were predictive, but no symptoms of other disorders predicted adult MDD.

Can we conclude that the clustering of a few depressive symptoms for a brief time period mark *the early phase of a first episode MDD* in youngsters (that presumably could be prevented from progressing to a full blown MDD episode)? Unfortunately, several methodological issues preclude an affirmative answer. First, because this body of literature did not address the fact that a prodrome reflects a change from a pre-prodromal phase, the symptom endorsement of some youths may represent a long standing, trait-like characteristic. Second, much of this research concerns prediction from symptoms to full syndromes many years later. Indeed, given intervals as long as a decade (or more) between symptoms and eventual disorder, one wonders if the identified symptoms were uniformly premonitory of the target MDD episode. Finally, studies have not examined the continuity of the putative prodromal symptoms and the target episode within individuals.

Nonetheless, the literature does allow one clear conclusion: children and adolescents who experience as few as 2 depressive symptoms for at least a week are highly likely to have an eventual first episode MDD. The remarkable replicability of this finding across long time periods suggests that, at least for some portion of study samples, the symptoms probably are surrogates for a personal characteristic closely related to depressive disorders but are NOT prodromes to a given MDD episode. Findings by Klein et al., (2009) do indicate that sub threshold depressive symptoms may reflect an enduring vulnerability rather than a clinical prodrome. However, for some other portion of study samples, the symptom clusters are likely to be truly prodromal to an episode, while for still other cases, the symptoms may be passing phenomena. Thus, depression screens identify a population of youths heterogeneous with respect to the significance of sub-threshold depression in their lives (i.e., chronic symptoms, acute but circumscribed episode). This heterogeneity could impact on the likelihood of positive response to an intervention program.

Do anxiety symptoms predict subsequent major depression in juveniles?

Clinicians have long observed that, when patients present with a mixture of depression and anxiety, the anxiety is likely to have preceded the depression, rather than the other way around (Akiskal, 1990). The fact that anxiety frequently segues into depression has been thought to reflect a natural progression in the course of loss-induced depression (Akiskal, 1990). A similar temporal sequencing of anxiety and depressive disorders has been longitudinally verified in clinically referred depressed children (e.g., Kovacs, Gatsonis, Paulauskas, & Richards, 1989). While anxiety disorders do typically antedate depressive disorders in youngsters, we focus on the predictive value of anxiety symptoms because, by definition, only symptoms are considered to be premonitory (Dorland's 1988).

Do anxiety symptoms presage depressive disorders in youngsters (for reviews, see Seligman & Ollendick, 1998; Zahn-Waxler, Klimes-Dougan, & Slattery, 2000)? Emerging evidence suggests that symptoms of anxiety predict future depressive symptoms. In a study of the association between self-rated anxiety and depressive symptoms, 11- to 14-year-old students (n=113) were assessed at 2 time points approximately 12 months apart (Chaplin, Gilham & Seligman, 2009). Physiological anxiety symptoms endorsed at Time 1 predicted depressive symptoms at Time 2 for all youths; total anxiety symptoms and the worry and oversensitivity symptom cluster predicted later depression for girls but not boys, while the social concern, concentration problem cluster was not a significant predictor of Time 2 depressive symptoms. A three-year longitudinal study of 3rd and 6th grade students also reported that anxiety and depressive symptoms were related across time (Cole, Peeke, Martin, Truglio, & Seroczynski, 1998); whether by child self-report or parental report, high

levels of anxiety at any given point predicted high levels of depressive symptoms at subsequent assessments, even after controlling for prior depressive symptoms.

Do anxiety symptoms predict pediatric depressive disorders? Using parent rated questionnaires, onset of major or minor depressive disorder between the ages of 11 and 13 was examined in a large (n = 2,451) community sample of girls (Keenan, Feng, Hipwell, & Klostermann, 2009). Symptoms associated with generalized anxiety syndromes at ages 8, 9, and 10 predicted onset of later depression, with each further symptom signaling a 1.4-fold rise in the risk of depression onset. Separation anxiety symptoms at age 9 also predicted depression onset, with each symptom increasing 1.4-fold the odds of developing a depressive disorder. In another epidemiological study of youths (n=776) and their parents, structured interviews at the mean ages of 13.7, 16.4, and 22.1 years served to explore whether overall level of fears and fear of the dark predicted later major depression (Pine, Cohen, & Brook, 2001). Controlling for potential confounds (e.g., prior depression), both anxiety variables predicted later major depression but the associations varied depending on the type of anxiety rating (overall fear vs. fear of the dark), the informant (child vs. parent) and the timing of MDD (age 16 vs. age 22). For example, only overall level of fear at age 13.7 predicted MDD at age 16 (but not later), suggesting that the relations of early fears to later depression may be developmentally mediated.

A study of the predictive utility of pediatric anxiety *symptoms* into adulthood found that self-rated anxiety symptoms of community based adolescents (n=354) predicted major depression across ages 18 to 26 (Reinherz, Paradis, Giaconia, Stashwick, & Fitzmaurice, 2003). While studies of mixed anxiety-depression symptoms, or “internalizing” symptom composites, generally report that such presentations predict mood (but not anxiety) disorders by young adulthood (Lewinsohn, Gotlib, & Seeley, 1995; Roza, Hofstra, van der Ende, & Verhulst, 2003; Rueter, Scaramella, Wallace, & Conger, 1999), they did not examine whether the initial anxiety or depression symptoms were more decisive.

Overall, are symptoms of anxiety prodromal to pediatric major depression? Would information about anxiety symptoms improve the prediction of impending MDD and provide a better way to identify cases for early intervention? While symptoms of anxiety appear to predict symptoms of depression, the literature is scant and inconclusive on the link between anxiety symptoms and eventual MDD. Further, even supportive findings can not be considered replicative because different studies have examined different anxiety symptoms as predictors. As well, there are indications that the predictive value of symptoms may differ as a function of the child’s age and the particular symptom under consideration. Thus, a developmental dimension may be crucial to understanding the relations of specific anxiety symptoms and pediatric MDD and should be addressed in future research.

All in all, information about symptoms that signal heightened risk of an MDD episode can be valuable in the selection of cases for early intervention when the goal is to forestall a full depressive episode. However, if the goal is primary prevention of pediatric MDD, then vulnerable children have to be identified before they ever become symptomatic. We now turn to that issue.

Vulnerability to clinical depression: Selected dimensions

One challenge in primary prevention of mental disorders is to specify the vulnerability parameters that will define the target population. We focus in this article on selected aspects of affectivity and affective development as key dimensions of vulnerability. Atypical affective functioning, particularly in children at familial-risk for depression, is likely to be proximally related to developing MDD (which, by definition, is an “affective disorder”) and therefore can facilitate case detection as well as point the way to plausible targets of

intervention. In the following sections, we provide effect sizes for comparisons of at-risk offspring versus controls if that information had been included in the cited articles (or could be computed).

Positive and negative affectivity in typical and at-risk youngsters

Clinically depressed youngsters (and adults) are notable for their sadness and dysphoria, and in many cases, a markedly diminished ability to experience pleasure or positive affect. This is certainly not surprising because depressed mood or anhedonia is one of the required symptoms for the diagnosis of MDD (American Psychiatric Association, 1994). It has been proposed, however, that the tendency to heightened dysphoric affect and reduced positive affect not only are salient features of clinical depression but also may be possible substrates or precursors of it (for overviews, see Durbin, Klein, Hayden, Buckley, & Moerk, 2005; Forbes & Dahl, 2005). An informative test of this proposition would require a suitably large, pediatric, high-risk, not–yet-disordered sample (and controls), and repeated longitudinal assessments of multiple aspects of affective development up to late- adolescence (the first high risk period for incident MDD). In the absence of such a study, we now consider whether at-risk and typically developing children differ in positive and negative affectivity, and if such differences can be linked to later depression.

But first, we wish to note that in much of the (adult) literature on the association of depression to positive and negative affectivity (e.g., Watson, Clark, & Carey, 1988), the two affect constructs are defined quite broadly. For example, a commonly used adult self-report measure of negative affectivity queries about being overly sensitive, irritable, easily upset, nervous, scared, as well as feeling sad, discouraged, angry, guilty, or ashamed (Watson et al., 1988).In contrast, studies of children typically assess *observable affect displays* based either on parent report or in laboratory settings and tend to focus on the specific affects of sadness, anger, fearfulness, and joy/happiness.

What do we know about the developmental unfolding of positive and negative affectivity in typical children? An increase in positive affectivity (e.g., smiling, laughing, playing) is one aspect of normative emotional development from infancy up to at least late childhood, a pattern that has been observed already in the first year of life (Denham & Lehman, 1995; Gaertner, Spinrad, & Eisenberg, 2008; Mathiesen & Tambs, 1999; Rothbart & Bates, 2006). This trend was evident in repeated maternal ratings of their developing infants from the age of 6 weeks up to the age of 30 months (Denham & Lehman, 1995) and in observational ratings of facial, vocal, and bodily affect displays across ten structured laboratory tasks in a sample of 206 offspring, aged 36 to 83 months (Dr. Emily Durbin, personal communication, September 23, 2009). In the latter study, displays of positive affect/happiness were significantly related to chronological age (r=.30). Observational ratings in various laboratory situations also revealed a trend of gradually increasing positive affectivity in a longitudinal study of 1- to 9-year old offspring of normal control parents (Olino et al., 2009).

In contrast to the normative increase in positive affectivity, negative affect displays generally decrease from infancy up to about late childhood, although there is some variability by specific affect across the youngest ages. In an observational study of more than 200 toddlers, global negative affect (reflecting frustration, sadness, and fear) declined from 18– to 30-months of age (Gaertner et al., 2008). In contrast, according to repeated maternal ratings of young (6 weeks to 30 months old) offspring, that age span was associated with a linear increase in fear and a U-shaped trajectory for anger (Denham & Lehman, 1995). Maternal ratings also revealed a linear increase in overall negative emotionality among 18- to 50-month-olds (Mathiesen & Tambs, 1999). But subsequent to the toddler years, findings are quite consistent regarding declining negative affect displays. Such a developmental trend was reported across 7- to 11-year olds, based on a parent-rated

composite index of negative affects (Murphy, Eisenberg, Fabes, Shepard, & Guthrie, 1999); across 3- to 7-year old children, based on observational ratings of fearfulness and sadness (Dr. Durbin, cited above); and across toddlers, pre-schoolers, and early school-age children, based on parent reported anger and fear (with a peak at ages 4-5) (Rothbart, Ahadi, Hershey, & Fisher, 2001). It also appears that the intensity of NA declines from the early school-age years up to early adolescence (Sallquist et al., 2009).

What do we know about the development of affectivity in young children at familial-risk for depression? It is unclear whether at-risk children and control peers differ in the extent or frequency of NA displays. In contrast, however, several independent research groups have found that low positive affectivity characterizes offspring at familial-risk for depression. In the studies noted below, young subjects' at-risk status was based on having a first degree relative (typically a mother) with a history of diagnosed depressive disorder (MDD in almost all instances). Comparison peers typically were age-matched offspring of parents with no history of MDD or other diagnosable major mental disorder.

Once again, the findings are somewhat variable in studies of very young offspring. For example, among 3-month-olds (n=50) and their parents, high-risk offspring displayed significantly less PA and more NA in a distress inducing protocol than did offspring of non-depressed parents (Forbes, Cohn, Allen, & Lewinsohn, 2004), although these across-group differences were no longer significant by the age of 6 months. On the other hand, observations of 69 mother-child pairs during affect eliciting tasks revealed that, while at-risk and control children had similar NA and PA displays at ages 2-3, at-risk children displayed significantly more NA about two years later (ES=.40; Feng, Shaw, Skuban, & Lane, 2007).

More consistent results have been reported by studies of somewhat older children and of samples with a wider age range. According to laboratory assessments of 3- to 4-year olds (n=100), low levels of positive affectivity (but not high levels of negative affectivity) were related to maternal (but not paternal) history of depression (r=−.26), particularly if mothers had early-onset and/or chronic/recurrent depression (Durbin et al., 2005). Low offspring PA was not explained by parental psychiatric comorbidity, concurrent maternal behavior, or depressive symptoms. Another study compared 8- to 17-year old depressed patients, their age-mates at familial-risk for depression, and low risk controls (Dietz et al., 2008), using observational ratings of a mother-child interaction task. High-risk children displayed significantly lower levels of positive affect than did controls (ES= 1), but were similar to their depressed peers (while depressed cases displayed higher levels of negative affectivity than did the other 2 groups). Likewise, according to observational ratings of 1- to 8-year olds (mean=3.8 years) in various play situations, high-risk offspring displayed significantly lower levels of positive affect than did normal control offspring (ES= .30; Shaw et al., 2006).

In one of the few longitudinal studies of the developmental trajectories of PA and NA (observed yearly during laboratory tasks) children with parental histories of mood disorder (high-risk) and those with no such parental histories (low-risk) were compared across the ages of 1 to 9 years (Olino et al., 2009). On average, both offspring groups showed the expected normative developmental changes from infancy through middle and late childhood, namely, decreasing negative affect displays and increasing positive affect displays. The two groups did not differ in their NA trajectories. However, offspring at familial risk for depression displayed consistently and significantly lower levels of PA across the years than did controls (average ES=.20).

Therefore, attenuated capacity for PA may be one source of vulnerability for clinical depression (rather than heightened NA or a developmental failure to attenuate negative

affect displays with age). This possibility is supported by two recent neuroimaging studies of at-risk youths that reported reduced neural activation in brain regions associated with positive affect and reward processing. In one study, when 10- to 18-year-old, high-risk offspring were presented with happy faces, they showed less neural activation in the nucleus accumbens (a region in the ventral striatum) than did controls (Monk et al., 2008). The other study examined reward processing in 10- to 14-year-old never-ill daughters of mothers with histories of recurrent depression (and controls); it also found that high risk daughters exhibited markedly blunted or attenuated neural responding (i.e., reduced ventral striatal activation) both during the anticipation and actual receipt of reward (Gotlib et al., in press). High-risk daughters also failed recruit various sub-regions of the anterior cingulate cortex during reward, suggesting a possibly general reduction of sensitivity to reward.

As Durbin et al., (2005) cogently noted, low positive emotionality may increase the risk of eventual depression by attenuating reactivity to external reinforcers or rewarding experiences. As they further remarked, low levels of PA also may fail to provide the positive (and protective) cognitive bias that is characteristic of typical youths. We propose that low PA also can contribute to depression via a different mechanism, namely, by compromising the ability to effectively "repair" dysphoric mood. Thus, we now turn to this area.

Affect regulation and mood repair in typical and at-risk youngsters

Clinically depressed individuals are clearly not able to attenuate their sadness and dysphoria. Although the nature of this impairment has not been fully elucidated, one component undoubtedly is the person's responses to his or her own affect or mood. As far back as two decades ago, Teasdale (1988) was quite specific about the importance of affect self regulation in depression. He stated that people who are likely to become clinically depressed, and those who recover from an episode of sadness, do not differ in the *initial* experience of dysphoria but in how they *respond to it*, with depression prone people likely to respond in ways that impede "natural recovery."

Not surprisingly, research has confirmed that depression and problems in mood repair go hand in hand. For example, symptomatically depressed children are not as adept as are non-depressed peers at self-regulating negative affect (Garber, Braafladt, & Weiss, 1995), college students who had recovered from an episode of MDD still evidence affect regulation difficulties and are more likely to use dysfunctional regulatory strategies than control peers (Ehring, Fischer, Schnulle, Bosterling, & Tuschen-Caffier, 2008), and the mood repair repertoires of 7- to 14-year-old patients with MDD entail a significantly greater number of "upregulating" dysfunctional responses than that of normal controls (Tamas et al., 2007). Further, mood repair strategies that are ineffective or exacerbate the dysphoria (e.g., behavioral passivity, rumination) are associated with higher levels of self-rated depression; this was confirmed in an experience sampling study of 12- to 17-year-old students (Silk, Steinberg, & Morris, 2003), in a very large survey of 12- to 18-year-old students (Garnefski & Kraaij, 2006), and among several hundred young outpatients with MDD (Tamas et al., 2007). Parental reports of their children's dysfunctional mood repair responses also are significantly related to independent clinical ratings of offspring's depressive symptoms (Gentzler, Santucci, Kovacs, & Fox, 2009).

What do we know about mood repair in typically developing youngsters? Studies of infants, toddlers, and young children have shown that the self-regulation of sadness/dysphoria is a developmentally mediated process (for a brief overview, see Kovacs, Joormann, & Gotlib, 2008). This process unfolds in a social context via multiple learning mechanisms (e.g., operant conditioning, differential reinforcement, role modeling), is both potentiated and constrained by various neural and other physiological maturational processes (e.g., Fox, 1994), and embraces both automatic and voluntary responses and processes, including

responses that can attenuate and those that can (unwittingly) exacerbate dysphoric affect (Gross, 1998, 1999; Kovacs et al., 2008).

Although even infants are capable of rudimentary regulatory responses such as self-soothing (Kopp, 1989), most regulatory attempts early in life are initiated by care-givers. Thus, one developmental feature of emotion regulation is the transition from care-giver initiated to self-initiated responding, which occurs across the ages of 2- to 3-years (Grolnick, Bridges & Connell, 1996; Kopp, 1989; Spinrad, Stifter, Donelan-McCall & Turner, 2004). Normative development also entails the acquisition of increasingly effective and sophisticated mood repair responses. Responses that can attenuate distress and restore some degree of emotional homeostasis eventually encompass (but are not restricted to) various forms of self-soothing and self-comforting, including "consumption based self-indulgence"; visual orienting, distraction, and the strategic use of attention; seeking physical or emotional proximity, comfort, support, or help from others; active task-oriented behaviors including play activity, behavioral problem solving, forms of rewarding activity, reading, listening to music, or altering aspects of the environment; physical activity or exercise; a variety of cognitive strategies such as information seeking or problem solving, re-framing one's experience, positive reappraisal, positive re-focusing, cognitive restructuring, or acceptance (e.g., Calkins & Johnson, 1998; Fichman, Koestner, Zuroff, & Gordon, 1999; Garnefski & Kraaij, 2006; Grolnick, Kurowski, McMenamy, Rivkin, & Bridges, 1998; Kopp, 1989; Kovacs et al., 2008; Parkinson & Totterdell, 1999; Reijntjes, Stegge, Terwogt, Kamphuis, & Telch, 2006; Spinrad et al., 2004). Responses to dysphoria/distress that maintain (or exacerbate) it include behavioral inaction, disengagement, or passivity; rumination, negative cognitions, and suppression/denial of affect; as well as venting, aggressive acting-out, and impulsive action (Calkins & Johnson, 1998; Garnefski & Kraaij, 2006; Silk et al., 2003).

However, the efficacy of relatively few responses has been empirically studied and even fewer studies have focused on children. Correlational studies, using laboratory observations of very young children, have reported that the ability to re-orient attention is associated with lower levels of distress (e.g., Calkins & Johnson, 1998; Grolnick et al., 1996) as are attempts at behavioral problem solving and recruiting the care giver (Calkins & Johnson, 1998). Other findings on typically developing youngsters indicate that distraction or attention re-focusing facilitates mood repair. As early as 3- to 6-month of age, diverting the attention of distressed infants (via visual and auditory distracters) is associated with reduced distress as long as the distracter is present (Harman, Rothbart, & Posner, 1997). The utility of distracting activities also was documented among 10- to 13-year olds, who were subjected to a peer rejection scenario and then were observed in the laboratory that provided opportunities for mood repair. Children who engaged in "behavioral distraction" (listened to music CDs, read funny comic books) after in vivo peer rejection showed significant mood improvement (Reijntjes et al., 2006). Given the scant data on children, it is worth noting that in laboratory studies of adults, cognitive distraction or attention re-focusing has been shown to ameliorate experimentally induced dysphoria (Joormann, Siemer, & Gotlib, 2007; Trask & Sigmon, 1999). There also is some experimental evidence that being physically-motorically active (rather than passive) can facilitate mood repair in adults (Erber & Erber, 2000; Morrow & Nolen-Hoeksema, 1990).

What do we know about the self-regulation of distress in at-risk offspring? One of the earliest studies reported that adolescent and pre-adolescent children of depressed mothers (vs. children of control mothers) generated fewer strategies to manage negative emotions in hypothetical scenarios, which were deemed by independent judges to be of "significantly worse" quality than those generated by controls (Garber, Braafladt, & Zeman, 1991). At-risk offspring also rated their own strategies as less effective than did controls. In an observational study, dysphoric affect was experimentally induced by denying 4- to 7-year-

old children immediate access to a desired (and visible) object (Silk, Shaw, Skuban, Oland, & Kovacs, 2006). Silk et al. (2006) reported that at-risk offspring were more likely (than were control offspring) to focus on the desired object (ES=.53), but sex effects also were noted: compared to control girls, at-risk girls were particularly likely to display passive waiting (ES=.62) and less likely to actively distract themselves (ES= .87). In an overlapping sample (n=65) of 5- to 13-year-olds (Gentzler et al., 2009), parental ratings revealed that at-risk children were more likely to deploy dysfunctional mood repair responses in daily life (ES=.66; responses that upregulate dysphoria) and less likely to use functional responses (ES=.70; those that attenuate dysphoria) than were control peers. Thus, different assessment methods are yielding convergent findings: youngsters at familial risk for depression appear to show subtle signs of dysfunctional mood repair.

What specific factors may account for the mood repair difficulties of at-risk youngsters? As already discussed, at-risk children appear to have an attenuated capacity for PA (evident fairly early in development); this could be one contributor to mood repair problems. An attenuated capacity for PA puts children at a mood repair disadvantage because *activation of positive affect* is central to a range of effective regulatory responses. Mood repair attempts that capitalize on hedonic capacity include turning to various play activities, looking at the comics or reading a humorous book, watching a funny movie, going to the amusement park, as well as finding positive meaning in one's dysphoric experience, thinking about pleasant matters, or focusing on happy memories (Garnefski & Kraaij, 2006; Parkinson & Totterdell, 1999; Thayer et al., 1994). Laboratory studies of adults have confirmed that hedonic capacity can be harnessed for mood repair in various ways, including conjuring up happy personal memories (Cooney, Joormann, Atlas, Eugene & Gotlib, 2007; Joormann et al., 2007) or reading jokes and puns (Strick, Holland, van Baaren & van Knippenberg, 2009). Indeed, positive affect has been shown to "undo" the adverse physiological effects of negative emotions (Fredrickson, Tugade, Waugh, & Larkin, 2003). Interestingly, while adults who have remitted from their depression appear to be capable of implementing responses with positive affective content, such responses fail to repair mood among them (Joormann et al., 2007).

Impaired attention deployment during distress could be another contributor to the mood-repair difficulties of at-risk youngsters. More specifically, while re-focusing of attention away from the sense of distress can be a discreet mood repair response (e.g., "I try to keep my mind busy with things"), it also appears to be central to a variety of effective ways of attenuating sadness. Mood repair attempts that are probably effective because they require re-focusing of attention include a diverse set of responses such as organizing one's room, reading a book, fixing a broken toy, doing chores, or seeking the presence of parents or peers (Erber & Erber, 2000). Focusing on an involving task engages working memory, which is believed to constrain ongoing processing of negative-mood related information (Erber & Tesser, 1992). Indeed, complex and difficult tasks, which make notable demands on working memory, are the most effective in improving experimentally induced dysphoria (van Dillen & Koole, 2007)

As already noted, studies of adults have documented that cognitive responses involving refocusing attention away from experimentally induced dysphoria are effective in mood repair. While the *effectiveness* (or lack thereof) of attention refocusing for mood repair by at-risk children is yet to be thoroughly studied, this mechanism may be compromised quite early. In an important recent study with clinically depressed and non-depressed mothers, their 5-month-old offspring were observed during a paradigm involving maternal display of aversive facial expressions (modified still-face paradigm)(Manian & Bornstein, 2009). While the 2 groups of infants did not differ in averting their gaze from and focusing on objects other than the maternal face, these responses were not effective in reducing distress

in the at-risk group but did have salutary effects in the control group. The authors commented that at risk infants did not evidence the "appropriate attentional regulatory capacities" that were observed in controls, and that they used more often "self-soothing" which can be considered to represent a somewhat "primitive" regulatory response (Manian & Bornstein, 2009). Importantly, maternal behavior was similar across the two groups and therefore did not affect the results. In one of the previously cited studies (Silk et al., 2006), at-risk offspring also were less likely to disengage their attention from a distressing stimulus, or to get involved in distracting activities, than were control peers. In a related psychophysiological study, such offspring demonstrated subtle deficits in selective attention when emotionally challenged, which led them to recruit more anterior brain processing resources than did control peers (Perez-Edgar, Fox, Cohn, & Kovacs, 2006).

Taken together, the findings suggest that children at familial risk for depression evidence subtle problems in affectivity and mood repair early in development. Thereby, such youngsters may be less well equipped than typical peers to meet the mood repair challenges that become more numerous as they become older, enter school, and have to function in a wider social context. The possible extent of this vulnerability is of some concern given that different neural circuits are implicated in the two important mechanisms that we identified, namely, harnessing positive affect and deploying effortful attention in the service of mood repair. Attempts to self-induce positive affect probably recruit brain reward circuits, which are distinct from neural (e.g., prefrontal) circuits involved in abstract thinking and attention deployment (Nestler & Carlezon, 2006). Compromised mood repair also is likely to reflect perturbations in related physiological processes, an area to which we now turn.

Physiological substrates of affectivity and mood repair

From among various physiological domains that can plausibly be linked in the pre-adult years to affectivity and depression (and thereby mood repair), we focus on hypothalamic-pituitary-adrenal (HPA) axis functioning, brain hemispheric asymmetry, and cardiac vagal control (CVC). Converging evidence implicate these physiological substrates in the experience, expression, and regulation of affect states (e.g., Fox & Davidson, 1988; Korte, 2001; Porges, 1997) and their contribution to the development of emotion regulation in youngsters is well accepted (e.g., Zeman, Cassano, Perry-Parrish, & Stegall, 2006).

Further, the structural and functional physiology of these domains has been reasonably well delineated, suggesting points of interconnection that are of particular relevance to a coordinated, affectively-driven response system. For example, aspects of HPA functioning in response to stress are under the control of the right cerebral hemisphere: there are elevations in cortisol production when aversive stimuli are presented (via the contralateral visual field) to the right but not the left hemisphere (Wittling & Genzel, 1995). Greater right than left prefrontal cerebral activation (both in human and non-human subjects) are associated with greater cortisol secretion prior to and during stress, compared to peers that do not have such asymmetry patterns (e.g., Kalin, Larson, Shelton, & Davidson, 1998; Field, Pickens, Fox, & Nawrocki, 1995; see Lopez-Duran, Vazquez, Felt, & Olson, 2009 for a review). The magnitude of cortisol response to laboratory stress also has been associated with cardiac vagal control: adults who have lower cardiac vagal control show elevated cortisol responses to stress (Pico-Alfonso et al., 2007). Finally, there is some evidence that anomalies within these physiological systems are present prior to the onset of MDD, and in offspring at familial-risk for depression, which may adversely impact on affectivity and its regulation.

Hypothalamic pituitary adrenal-axis (HPA) functioning—Given that the HPA axis is involved in responding to stress, its functioning has long been of interest to depression

researchers. HPA axis functioning has been studied mostly in terms of subjects' cortisol ("stress hormone") response to biological or psychological probes or challenges. It also has been studied by assessing basal cortisol levels (typically using salivary cortisol) at specific times of day, within the framework of the normal diurnal variation in cortisol secretion. Contrary to findings on depressed adults, earlier evidence had suggested that depressed youngsters have typical HPA-axis functioning (Birmaher & Heydl, 2001). However, a recent and more comprehensive meta-analysis revealed a significant relationship between endocrine dysregulation and pediatric depression (Lopez-Duran, Kovacs, & George, 2009). Compared to non-depressed peers, depressed youth show a dysregulated HPA-axis negative feedback mechanism, higher baseline cortisol, and atypical recovery after exposure to psychological stressors. There also is preliminary evidence that endocrine dysregulation precedes the onset of pediatric MDD. Specifically, one study reported that children and adolescents with cortisol 'peaks' at 8 am (>80 percentile from the group mean) were significantly more likely to develop MDD 12 months later than were subjects who did not show such peaks (Goodyer, Herbert, Tamplin, & Altham, 2000). Likewise, elevated levels of cortisol awakening response were associated with increased risk of MDD across the subsequent 12 month period among adolescents at risk for depression by virtue of high neuroticism scores (Adam et al., in press).

There also are indications that HPA-axis dysregulation is present in young offspring at familial risk for depression, although there is variability in the type of dysfunction that has been observed. For example, several studies have found higher HPA-axis *reactivity* among at-risk children as compared to their low-risk peers. In a parent-offspring interaction task, infants of depressed mothers displayed significantly higher cortisol levels than did infants of non-depressed mothers (Field et al., 1988). Compared to controls, adolescents and young adults with a parental history of depression had significantly higher levels of cortisol awakening response, which is another index of HPA-axis stress reactivity (ES = .63; Mannie, Harmer, & Cowen, 2007). Other studies have reported elevated *baseline* cortisol levels suggestive of hypercortisolemia. For example, 7- to 8-year-olds with high levels of internalizing symptoms and maternal history of depression had significantly higher baseline cortisol levels than did control peers, although the groups did not differ in cortisol levels after laboratory tasks (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002). In another study, children of parents with a history of depression who were also concurrently depressed had significantly higher baseline cortisol and an atypical (blunted) response to the dexamethasone suppression test (Young et al., 2006). Furthermore, according to a study of temperament and risk for depression among 3- to 5-year olds, maternal history of melancholic depression was associated with higher morning (but not evening) cortisol levels in the children (Dougherty et al., 2009). Likewise, elevated morning, but not evening, cortisol was observed among adolescents whose mothers had experienced post-partum depression (Halligan et al, 2004).

What are the potential mechanisms whereby HPA-axis dysregulation may render these children vulnerable to affective difficulties and increase the risk of depressive disorders? First, elevated basal cortisol levels may lower the threshold at which the stress response is activated and thus confer heightened stress reactivity and affective sensitivity (see Lopez-Duran et al., 2009). Research indeed has shown that high levels of basal cortisol are associated with greater affective reactivity to social stressors in some children (see Davis, Donzella, Krueger, & Gunnar, 1999; Donzella, Gunnar, Krueger, & Alwin, 2000). Second, an overactive HPA-axis response to aversive stimuli could contribute to a chronically high level of physiological arousal, which may interfere with successful mood repair. Indeed, experimental laboratory work has implicated stress hormones in the modulation of behavioral responses to stress (reviewed by Smagin, Heinrichs, & Dunn, 2001). Finally, it is known that exposure to corticoids can have negative effects on the developing brain,

possibly resulting in adverse changes to the HPA-axis and memory and affective responses (see Gunnar & Vazquez, 2006 for a review). Exposure to cortisol during various developmental stages appears to potentiate the ability to remember emotionally relevant events (Korte, 2001), and cortisol infusion produces a recall bias for emotional information in humans (e.g., Buchanan & Lovallo, 2001). Therefore, dysregulation of the HPA-axis may compromise effective mood repair by reducing the stress threshold, increasing affective reactivity to a stressor, and facilitating a memory bias towards emotionally salient (negative) stimuli.

Cerebral hemispheric asymmetry as indexed by EEG—Electroencephalographic (EEG) measures of frontal brain regions have long been used as indexes of brain activity that can mirror affective and motivational states and/or traits (for a brief overview, see Light, Coan, Frye, Goldsmith, & Davidson, 2009). Such measures are taken from the surface of the scalp, have a high temporal resolution, and have been particularly favored in studies of youngsters because they are non-invasive and easy to implement. A substantial body of EEG findings has shown that the left and right frontal brain regions are differentially associated with various affects and related behavior tendencies. While the relation of cerebral asymmetry and *affective valence* continues to be debated (e.g., Harmon-Jones, 2003), it is generally accepted that greater left than right hemispheric activation (left frontal asymmetry) is associated with a tendency towards approach behaviors and approach motivation, while the reverse (right frontal asymmetry) is associated with withdrawal motivation and related behaviors (for overviews, see Coan & Allen, 2004; Davidson et al., 2000). Further, right posterior asymmetry (greater right than left activation in the parietal-temporal areas) has been associated with reduced physiological arousal as observed in anhedonia, while left posterior asymmetry has been linked to anxious arousal (see Bruder et al., 1997; Heller, Etienne, & Miller, 1995; Kentgen et al., 2000; Reid, Duke, & Allen, 1998). Studies of the relations of hemispheric asymmetry and depression have generally found that, compared to non-depressed peers, depressed individuals have right frontal asymmetry (relatively greater right than left frontal activation) (see Thibodeau, Jorgensen, & Kim, 2006 for a recent meta-analysis) and left posterior asymmetry (relatively greater left than right activation in parietal-temporal areas) (Bruder et al., 1997; Kentgen et al., 2000; Reid et al., 1998), but the latter finding is limited to those without co-morbid anxiety.

Do children at familial risk for depression have a characteristic frontal asymmetry pattern? Studies of infants of currently depressed mothers generally concluded that such offspring manifest greater *right* frontal asymmetry than do infants of non-depressed mothers (e.g., Dawson, Frey, Panagiotides, Osterling, & Hessl, 1997; Field, Pickens, Fox, & Nawrocki, 1995; Jones, Field, Fox, Lundy, & Davalos, 1997; Jones, Field, & Almeida, 2009; Jones, Field, & Davalos, 2000; Jones, Field, Davalos, & Pickens, 1997). However, findings have been equivocal from studies of older children whose mothers had a history of depression (but were not necessarily symptomatic at the time of study participation). According to one study of 3- to 9-year-olds, those at familial-risk for depression did not significantly differ from comparison peers in frontal asymmetry during a resting condition (Forbes, Fox, Cohn, Galles, & Kovacs, 2006). But interestingly, among these at-risk children, resting right frontal asymmetry correlated with their mothers' concurrent and increasing depressive symptoms across a year-long follow up (Forbes et al., 2008). Finally, in a sample of adolescents, those at familial-risk for depression displayed higher baseline right frontal asymmetry than did control peers, but concurrent maternal depression was not controlled (ES=.58; Tomarken et al., 2004). Overall, the findings could indicate that right frontal asymmetry may be limited to those at-risk children whose mothers have high levels of current depressive symptoms.

There also is preliminary evidence linking *left posterior* cerebral asymmetry and familial risk for depression in at-risk children and adults. Bruder et al. (2005) reported that, irrespective of the presence or absence of a prior history of major depression, adult at-risk offspring had relatively left posterior asymmetry (greater left than right activation) in parieto-temporal areas compared to low-risk controls. In a subsequent study with the same sample, children who had both a parent and a grandparent with a history of depression also displayed left posterior asymmetry in parietal regions (Bruder, Tenke, Warner, & Weissman, 2007).

How does right frontal and left posterior asymmetry translate into increased risk for affective difficulties and later depression? Left frontal circuitry has been associated with approach behaviors and generally positive affect during “pre-goal attainment” (i.e., as the individual moves towards a goal). It is possible that in the context of high levels of environmental stress, which is common in the lives of at-risk children, left frontal asymmetry facilitates successful coping owing to its association with approach related behaviors. Indeed, in a study of 6- to 13-year-old at-risk children and control peers, left-frontal asymmetry blunted the adverse effects of prior life stressors and protected against internalizing symptoms (Lopez-Duran, Nusslock, Kovacs, & George, 2009). On the other hand, because right posterior (parietal-temporal) cerebral regions are involved in emotional arousal and the processing of emotional stimuli (see Moratti, Rubio, Campo, Keil, & Ortiz, 2008), hypoactivity in these regions may signal reduced arousal in response to positive affective stimuli or chronically low levels of positive emotionality. This possibility is supported by a study of pre-school age children who were identified (via laboratory observations) as displaying relatively low or high positive and negative affectivity and then received EEG evaluations 2- to 3-years later (Shankman et al., 2005). Children who had displayed low positive emotionality initially were found to have left posterior asymmetry on follow up. Because high negative emotionality was not associated with later cerebral asymmetry, the authors concluded that left posterior asymmetry may reflect reduced responses to positive stimuli. This interpretation is in line with our arguments presented earlier that vulnerability to depression includes reduced hedonic capacity, which then compromises the likelihood of engaging in pleasurable activities for mood repair.

Cardiac vagal control—Cardiac vagal control (CVC) is one index of the functioning of the parasympathetic nervous system (a branch of the autonomic nervous system). Measures of CVC quantify the influence of vagal nerve activity on oscillations in heart rate, typically assessed indirectly from an electrocardiogram (ECG). We use the term “cardiac vagal control” to describe the vagal contribution to heart rate variability, which also has been referred to as respiratory sinus arrhythmia, high-frequency heart rate variability, or cardiac vagal tone (Beauchaine, 2001). During rest, CVC reflects the inhibitory function of the vagal nerve on the sympathetic nervous system in order to limit energy expenditure (e.g., by reducing heart rate); during conditions of environmental demands or stress, CVC is reduced (e.g., resulting in increased heart rate). Porges (1997) has regarded CVC as a key physiological process that contributes to the regulation of complex behaviors and emotion, especially in response to environmental demands. Further, CVC is an increasingly accepted window on emotion regulation in youngsters, at least in laboratory settings (Vasilev, Crowell, Beauchaine, Mead & Gatzke-Kopp, 2009). Studies of adults (which dominate the field) have suggested that depressed people may have lower resting CVC than non-depressed controls (see Rottenberg, 2007 for a recent meta-analysis) and show less of a change back to baseline levels (i.e., are less likely to recover) after the termination of a stressor (Rottenberg, Salomon, Gross, & Gotlib, 2005).

Do offspring at familial risk for depression evidence compromised CVC? Along with early work on cerebral hemispheric lateralization (summarized above), initial studies in this area

also had focused on infants of actively depressed mothers (rather than mothers with a history of depression). Overall, the findings indicate that infants of depressed mothers generally display lower levels of CVC than do control offspring. Lower CVC was detected among 3- to-6–month-old at-risk infants during parent-child interaction tasks (Field et al. 1988), among 6-month-olds during rest (Field et al., 1995), and among newborns during rest (Jones et al., 1998). Further, high risk infants failed to show a developmental increase in CVC from 3- to 6-months of age while control infants did (Field et al., 1995). However, some studies reported that at-risk and comparison infants did not differ in CVC (e.g., Dawson et al., 2001).

Studies of CVC among older offspring at familial risk for depression have yielded equivocal findings. In one study of 3- to 9-year-olds, at-risk children and typical comparison peers were experimentally subjected to a disappointment (Forbes et al., 2006). While changes in CVC from baseline to the disappointment experience were comparable in the two groups (both showed reduced CVC), at-risk children failed to recover (return to their baseline levels of CVC). In a study of 6-year-olds at high and low familial risk for depression, the findings were counter-intuitive: children whose mothers had chronic depression displayed higher CVC reactivity (reduced CVC) during the presentation of emotion-eliciting films than did children of mothers with stable mild symptoms (Ashman et al., 2008). Unfortunately, the authors did not report post-stimulus (recovery) levels of CVC. In further studies with the same overall sample as the one described by Forbes et al. (2006), offspring at-risk for depression and comparison children did not significantly differ in CVC reactivity during the presentation of a sad film (Gentzler et al., 2009) or a delay of gratification task (Santucci et al., 2008), but post-task CVC recovery was not examined.

Although the overall findings are equivocal about the CVC characteristics of depression-prone children, there is strong evidence that appropriate CVC in response and subsequent to various stressors is associated with better affect regulation. For example, in one study, CVC (baseline and reactivity) of normal 4- 5-year olds during stressful laboratory interactions with their parents predicted parent-rated emotion regulation skills at age 8 (Gottman & Katz, 2002). Among 5- to 13-year-olds, greater CVC suppression during presentation of a sad film was associated with more adaptive mood repair responses as reported by parents, regardless of the children's depression-risk status (Gentzler et al., 2009). Greater CVC suppression during a delay of gratification task in one protocol also was associated with more adaptive regulatory responses (distraction) in a separate protocol, also regardless of children's depression-risk status (Santucci et al., 2008). Conversely, children who displayed reduced CVC recovery after experimental disappointment were less likely to be able to disengage their attention from the object of disappointment (Forbes et al., 2006), indicating a suboptimal emotion regulatory response.

Through its sympathetic and parasympathetic arms, the autonomic nervous system is the "first-responder" to stress experiences (Ulrich-Lai & Herman, 2009). CVC provides one window on this intricate system and its relations to affectivity, affect regulation, and adaptive responses to environmental demands. Findings on CVC and depression-risk status in young offspring hint at the possibility that some aspect of CVC may be impaired in such youths (e.g., post-task recovery to baseline levels), but the results are far from conclusive. And yet, there is strong evidence that children whose CVC functioning is appropriate to their context (i.e., high CVC during rest, attenuation of CVC during psychosocial challenge, return to baseline levels post-challenge) are better able to self-regulate distress and dysphoria than are peers whose CVC functioning is less optimal. Such findings have useful implications for prevention, the area to which we now turn.

Prodromes, vulnerabilities, and the prevention of clinical depression in youngsters

Recent quantitative and qualitative reviews of the prevention of pediatric depression testify to the importance of this topical area (Cuijpers, vanStraten, Smits, & Smit, 2006; Gladstone & Beardslee, 2009; Merry & Spence, 2007; Spence & Shortt, 2007; Stice, Shaw, Bohon, Marti, & Rohde, 2009; Horowitz & Garber, 2006). Accordingly, in the beginning of this article, we posed two questions relevant to the prevention of first episode MDD in youngsters. One question focused on studies of depression prodromes that potentially can inform secondary prevention trials by helping to identify symptomatic cases. The other question focused on vulnerability research that may serve to identify cases before they become symptomatic and also can point to targets for intervention. How has prodromal and vulnerability research on pediatric MDD affected intervention efforts?

Prodromal research and indicated prevention

Our review has revealed that depressive symptoms in children and adolescents (that never had a diagnosable episode) are robust predictors of eventual MDD and, that apparently any combination of several symptoms (rather than a single decisive symptom) is informative in that regard. Whether the index depressive symptoms were assessed by self-rating or clinical interview, studies typically required that the symptoms be present for at least one week, within a time frame that was frequently restricted to the 12 month period just prior to the initial assessment. Does the clustering of a few depressive symptoms for a brief time period therefore mark the early phase of a first episode pediatric MDD? Unfortunately, the literature provides few clues about the *temporal continuity* of symptom clusters and the target depressive episodes that they presumably herald (which would mark a prodrome).

If we assume that the attributable risk posed by children's depressive symptoms for later MDD is comparable to the figure for adults reported by Horwath et al. (1992), then only about 50% of youths with first episode MDD can be expected to have symptom prodromes 12 (or more) months earlier. Conversely, although depressive symptom clusters are associated with significant odds of a new MDD episode, a notable portion of symptomatic youths do not progress to MDD. Thus, to render the relevant literature more useful for depression prevention trials, we need to find the point of divergence between "truly" prodromal and other symptoms. Further, it is important to recognize that when initial (index) symptoms are assessed by traditional self-rated depression scales, it is not possible to determine if the complaints mirror an acute change in functioning or a long standing, trait-like personal characteristic. If a person's symptom endorsement is a surrogate for some personal trait, then those symptoms can **not** be considered prodromes because prodromes refer to the natural history of the disorder (rather than the history of the person). This distinction is likely to be important because treating symptoms and treating personality traits probably call for different interventions. All in all, the use of self-rated depression symptom scales for case detection in secondary prevention trials will identify a population *heterogeneous* with respect to what the symptoms signify.

Indeed, such a heterogeneity could be one contributor to the lower than expected success of *indicated prevention* trials of pediatric depression. Indicated prevention programs mirror a prodromal approach to case identification because they target children and adolescents who show clinical symptoms, but do not meet diagnostic criteria for a depressive disorder (e.g., Stice, Rohde, Seeley, & Gau, 2008). In such trials, cases have been typically ascertained by using either predetermined or sample-based cut-off scores on self-rated depression symptom scales (e.g., Roberts, Kane, Thomson, Bishop, & Hart, 2003; Stice et al., 2008). Recent reviews and meta-analyses of the literature on the prevention of childhood depression have

concurred that, although there is promising evidence for the effectiveness of *indicated prevention* programs, the effect sizes are relatively modest (Gladstone & Beardslee, 2009; Merry & Spence, 2007; Stice et al., 2009; Horowitz & Garber, 2006). For example (using Cohen's D as the index of effect size), Horowitz and Garber (2006) reported an overall effect size of .23 at the end of prevention programs with symptomatically depressed youths, which increased to .31 at follow up; both of these effect sizes signify very mild effects.

Can research on symptom predictors of pediatric depression contribute to more effective indicated prevention programs? The answer is "yes" in so far as a better understanding of the relations of symptoms and episode-onset can help to select more homogeneous samples. For example, following the approach of Horwath et al. (1992), existing data sets could be used to estimate the relative and attributable risk that depressive symptom clusters pose for new onset pediatric MDD. Depending on the extent and nature of available clinical data, cases could be classified according to temporal continuity of symptoms and MDD outcomes, and the various groups could then be compared with regard to potentially informative characteristics. Characteristics that distinguish truly prodromal cases from the rest may then be used as selection criteria in prevention studies. To further improve the clinical predictive value of early symptoms, it also would be informative to see more analyses along the lines reported by Klein et al., (2009) regarding predictors of escalation from sub-syndromal to full syndrome depression, but across a shorter time interval. One other way to further refine case selection is to combine criteria used in *indicated* programs and *selective* programs (e.g., Clarke et al., 2001).

Vulnerability research and selective prevention

Selective prevention programs typically focus on groups with hypothesized or documented characteristics that signal increased probability of the disorder of interest (Horowitz & Garber, 2006). In general, such programs target youths who do not yet have depressive symptoms. Instead, selective prevention trials of pediatric depression have focused on youngsters with *personal vulnerabilities* such as being the offspring of depressed parents (Beardslee, Gladstone, Wright, & Cooper, 2003) or being an adolescent girl (Bearman, Stice, & Chase, 2003), as well as youths that have been exposed to contextual *risk factors* for depression such as the death of a parent (Sandler et al., 1992), parental divorce (Gwynn & Brantley, 1987), or placement in a juvenile detention facility (Miller, 1999). However, some other extensively documented risk factors, such as dysfunctional family processes including problematic attachment (Restifo & Bogels, 2009), have received scant attention. Recent reviews concur that, while selective interventions for the prevention of pediatric depression are promising, their effect sizes have been very modest (Gladstone & Beardslee, 2009; Horowitz & Garber, 2006; Merry & Spence, 2007; Stice et al., 2009).

One contributor to the disappointing performance of selective intervention trials could be the case identification criteria that were used. More specifically, much of the information on proximal variables that render children susceptible to MDD have received limited attention in case identification. For example, there is compelling evidence that a familial history of depression greatly raises the odds of a youth developing depression (rendering him/her an ideal candidate for primary prevention). And yet, relatively few studies have used family history as a selection criterion either solely (Beardslee et al., 2003) or in combination with clinical characteristics or other indices of vulnerability (Beardslee et al., 2003; Clarke et al., 2001; Garber et al., 2009). As we noted, there also are indications that at-risk but not yet depressed youngsters display vulnerabilities deriving from atypical affectivity and compromised mood repair (and associated physiological dysfunctions). But, to the best of our knowledge, no prevention study has targeted cases based on these affect-related dimensions. Even more surprising is that dimensions of cognitive vulnerability have been infrequently used to identify cases for selective prevention trials.

Although we did not address in this article cognitive vulnerability for depression, partly because it has been extensively reviewed by others (see the references cited below), we do acknowledge its importance. Inspired by various models of (adult) depression, a large literature has accumulated on the relations of cognitive vulnerability and depressive symptoms or disorders in youngsters. Cognitive vulnerability has been variously defined as dysfunctional attitudes or negative cognitive schemata, a depressogenic attributional style, and ruminative ways of responding to depressed affect and, more recently, as biased processing of affective information. Studies of children and adolescents have indeed linked depressive symptoms and the various cognitive vulnerabilities (reviewed by Gladstone & Kaslow, 1995; Joiner & Wagner, 1995; Jacobs, Reinecke, Gollan & Kane, 2008; Lakdawalla, Hankin, & Mermelstein, 2007), specifically: negative attributional style (e.g., Abela, 2001; Abela & Payne, 2003), dysfunctional attitudes (e.g., Abela & Skitch, 2007; Abela & Sullivan, 2003), negative self-perception (e.g., Cole, Jacquez, & Maschman, 2001; Hoffman, Cole, Martin, Tram, & Seroczynski, 2000), as well as ruminative ways of responding to sad affect (e.g., Abela & Sarin, 2002; Abela, Aydin, & Auerbach, 2007).

But while the vast literature on the relations of dysfunctional cognitive processes and depression has not appreciably influenced case selection, it has made a singular impact on the *content* of prevention programs. It has been estimated that more than 75% of all prevention trials of youths have employed cognitive-behavior therapy and related interventions (Calear & Christensen, 2009). At the same time, 59% of the programs failed to reduce depressive symptoms, while 77% failed to lower the risk of a depressive episode (Stice et al., 2009). While Stice et al. (2009) as well as Calear and Christensen (2009) have concluded that the content of prevention programs did not affect overall outcomes, the results also suggest that cognitive interventions may not be optimal for depression prevention in youths.

We suspect that the less than stellar performance of depression prevention programs therefore also could reflect a poor match between the (probably cognitive-behavioral) intervention and youngsters' actual vulnerabilities. Further, findings that prevention efforts are more effective with adolescents than with children (Horowitz & Garber, 2006; Stice et al., 2009) could signify that current cognitively oriented programs are not developmentally suitable for pre-adolescent or early adolescent age groups. The latter interpretation is quite plausible in light of emerging understanding of the developing brain, and findings that, on a neural level, various maturational processes presumably relevant to abstract thinking and efficient problem solving are still ongoing in early adolescence (Casey, Tottenham, Liston & Durston, 2005; Durston et al., 2006).

Ways to improve prevention programs for pediatric depression

Primary prevention trials of pediatric MDD have to specify the population to which the interventions should be delivered, identify the vulnerability parameters the interventions should target, and establish some degree of "match" between vulnerability parameters and the content of a given intervention. As already suggested earlier in this article, more precise case selection criteria can reduce unwanted heterogeneity in the target samples and thereby facilitate more favorable response to interventions. Case selection also can be improved by using multiple indeces of vulnerability, or combinations of clinical predictors and indices of vulnerability. Notable strides already are being made in such directions. For example, recent prevention trials have identified their targets as youths at familial risk for depression that *also* had symptoms of depression (Clarke et al., 2001; Garber et al., 2009).

Prevention programs also may benefit from exploring developmentally more appropriate indices of vulnerability for case selection, and matching the content or focus of an intervention with the presumed (and preferably measured) vulnerabilities. We have proposed

that reduced positive affectivity, problematic mood repair, and associated physiological dysfunctions in offspring at familial risk for depression are promising both as case selection criteria and intervention targets. In arguing for the importance of low positive emotionality as a vulnerability factor for clinical depression among at-risk youths, we emphasized characteristics which not only distinguish them from typically developing peers, but ones they share to some extent with age-mates who already are depressed. While we acknowledge the lack of longitudinal data linking low positive affectivity with clinical depression in at-risk juveniles, several follow up studies of school- or community-based samples support our tenet that low PA is a vulnerability factor for depression. Namely, low positive emotionality at age 3 predicted children's depressive symptoms by the time they were 10 years old, but not earlier (Dougherty, Klein, Durbin, Hayden & Olino, in press), contributed to elevated anhedonic depression symptoms across a five-month period among 6^{th} to 10^{th} grade students (Wetter & Hankin, 2009), and also predicted overall depressive symptoms at 7-month follow up in a study of 4^{th} to 11^{th} graders (Lonigan, Phillips, & Hooe, 2003). Further, low positive emotionality (established by laboratory observation) at age 3 was found to predict a tendency to right-sided EEG asymmetry at ages 5-6, the latter being a frequent correlate of depression (Shankman et al., 2005).

We proposed that impaired mood repair also is a vulnerability factor for eventual depression among at-risk youngsters and that low positive emotionality is one contributor to impaired mood repair. However, manifestations of impairment are likely to differ across different ages because mood repair skills and responses are developmentally mediated. The impact of development on mood repair responses across the school-age years is most evident with regard to responses requiring abstract cognitive skills. For example, young adolescents (aged 12- to 15-years) report significantly less usage of cognitive emotion regulation strategies than do older adolescents (aged 16- to 18-years), and older adolescents, in turn, report generally lower usage than do adults (Garnefski & Kraaij, 2006). Not surprisingly, in the experience sampling study of 12- to 15-year-olds previously cited, Silk et al. (2003) were not able to confirm the hypotheses that cognitive responses to dysphoria (e.g., problem solving, cognitive restructuring) have salutary regulatory consequences. Likewise, a recent 2-year follow-up of the normative development of emotion regulation strategies in 9- to 15-year-olds also failed to confirm a significant increase in cognitive responses (reappraisal) as a function of age (Gullone, Hughes, King, & Tonge, 2009). Therefore, pediatric depression prevention programs that select mood repair as a dimension of vulnerability and an intervention target should have developmentally balanced curricula that highlight a variety of age-appropriate behavioral and interpersonal regulatory responses instead of primarily focusing on cognitive skills.

We also proposed that HPA axis function, cerebral hemispheric asymmetry, and cardiac vagal control undergird or contribute to different but related aspects of the experience and regulation of affect, and that atypical functioning in these areas should be considered both as selection criteria and as intervention targets in depression prevention trials. HPA-axis dysregulation may hamper mood repair by increasing reactivity to aversive events, prolonging the resultant physiological and emotional responses, and facilitating memory biases towards particular affective stimuli. Right frontal and left posterior cerebral hemispheric asymmetry may contribute to motivational and affective biases that promote lack of goal directed action and attenuated arousal to positive stimuli, both of which may compromise the adequacy of children's mood repair repertoires. Inflexible CVC during stress exposure is likely to index problems in adaptive physiological regulatory responses. Admittedly, however, some ingenuity will be required to translate available findings into operational definitions of independent or dependent variables. In the absence of population based normative data on positive affectivity, mood repair, and the just noted physiological systems, sample-specific performance distributions or score cut-offs may provide ways to

select cases that manifest vulnerabilities (or strengths) in these domains, as compared to controls. See, for example, the study by Goodyer et al. (2000) that addressed HPA functioning, and a recent investigation of the relations of overt joy and changes in EEG asymmetry in normal children (Light et al., 2009).

Preliminary evidence suggests that the affective and physiological processes under consideration are malleable, and therefore pertinent change techniques could be incorporated into prevention programs. We suspect that this sentiment may not be widely shared particularly with regard to affectivity, which has been regarded as a component of (biologically based) temperament. However, as Stiles (2009) has cogently argued, recent work on brain development has revealed that contemporary psychological models of biological "innateness" are outdated. Thus, the main challenge for interventions is to identify optimal approaches to bring about change. For example, according to research with infants, the best way to foster positive affectivity at very young ages is to promote it in the parents (for a relevant discussion, see Forbes et al., 2004). Among adults, psychological and pharmacological approaches have been explored to increase or maintain positive affect (Harmer, Hill, Taylor, Cowen, & Goodwin, 2003; Nutt et al., 2007; Sheldon & Lyubomirsky, 2006). Given the feasibility of a mood-repair focused psychotherapy for young depressed children (Kovacs et al., 2006), a similar, developmentally sensitive preventive intervention would be an appropriate alternative to CBT especially among preadolescents. There also are indications that both CVC (Hatch, Borcherding, & German, 1992) and HPA functioning (e.g., DeGood & Redgate, 1982) can be altered via biofeedback procedures. Preliminary evidence also suggests that biofeedback can help to improve symptoms of depressed patients as well (Karavidas et al., 2007). EEG neurofeedback, which seeks to teach individuals to alter brain electrical asymmetry, has recently emerged as a potential intervention for mood disorders and depression, although the information is based mostly on case reports (see Hammond, 2005; Hirshberg, Chiu, & Frazier, 2005; Robbins, 2000). While substantially more research is needed before such techniques and approaches can be considered to be evidence-based, they have considerable promise to move the field in new directions and facilitate prevention of pediatric MDD.

Summary and conclusions

Given the documented morbidity of pediatric MDD (Birmaher et al., 1996), further development of effective primary and secondary prevention programs should be research priorities. As indicated by recent reviews (e.g., Horowitz & Garber, 2006; Stice et al., 2009), universal prevention of pediatric depression has not been effective and should no longer be pursued. New analyses of extant data on prodromal features or symptom precursors of MDD in children may help to refine clinical criteria for case selection. Both primary and secondary prevention efforts could benefit from using multiple vulnerability parameters to select cases at greatest risk for developing MDD. The effectiveness of existing prevention programs could be improved by matching the content of the intervention to particular vulnerabilities. Reflecting the tenets of developmental psychopathology (Cicchetti & Toth, 2009), there is a need for intervention approaches that are developmentally sensitive and also address vulnerabilities that are proximal to and undergird increased risk of depression in children with a family history of this condition. Affectivity, mood repair, and related physiologic processes are ideal candidates both for case selection and as intervention targets because they are developmentally important, can be assessed with relative ease, and are modifiable.

Key points

- What do we know about predictors of major depressive disorder (MDD) in children that could inform primary and secondary prevention? This is an

important question because attempts to prevent pediatric depression have not lived up to expectations according to recent meta-analyses.

- To answer the above noted question, we focused our review on studies of prodromal symptoms that may herald a first episode of pediatric MDD, and studies of affectivity, regulation of dysphoric affect, and related physiological parameters in not-yet-disordered youngsters at familial risk for MDD.
- The pediatric literature is remarkably consistent that the presence of any combination of several depressive symptoms for at least one week (in the context of no prior episodes) is one of the best predictors of subsequent first episode MDD. These findings have already been reflected in the selection criteria of several programs aimed at secondary prevention.
- According to studies of young offspring at familial risk for MDD, such youngsters are characterized by generally low levels of positive affectivity (compared to typical peers), emerging difficulties with mood repair (the appropriate attenuation of sad, dysphoric affect), and signs of atypical functioning in 3 intertwined physiological systems (HPA axis, cerebral hemispheric asymmetry, and cardiac vagal control) that are implicated in affectivity and mood repair. However, primary prevention programs rarely have used familial history of depression as a selection criterion and none (to date) has utilized findings on affectivity and its physiological correlates for case selection.
- Our review suggests that the disappointing outcomes of attempts to prevent pediatric depression may be partly due to non-optimal case selection criteria, failure to fully capitalize on the available literature on vulnerability, and lack of synchrony between dimensions of vulnerability and intervention targets.
- We conclude with recommendations that call for the use of multifaceted case selection approaches, more critical use of existing findings from various disciplines, and developmentally more sensitive depression prevention programs.

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