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In Search of HPA Axis Dysregulation in Child and Adolescent Depression

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Abstract Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis in adults with major depressive disorder is among the most consistent and robust biological findings in psychiatry. Given the importance of the adolescent transition to the development and recurrence of depressive phenomena over the lifespan, it is important to have an integrative perspective on research investigating the various components of HPA axis functioning among depressed young people. The present narrative review synthesizes evidence from the following five categories of studies conducted with children and adolescents: (1) those examining the HPA system's response to the dexamethasone suppression test (DST); (2) those assessing basal HPA axis functioning; (3) those administering corticotropin-releasing hormone (CRH) challenge; (4) those incorporating psychological probes of the HPA axis; and (5) those examining HPA axis functioning in children of depressed mothers. Evidence is generally consistent with models of developmental psychopathology that hypothesize that atypical HPA axis functioning precedes the emergence of clinical levels of depression and that the HPA axis becomes increasingly dysregulated from child to adult manifestations of depression. Multidisciplinary approaches and longitudinal research designs that extend across development are needed to more clearly and usefully elucidate the role of the HPA axis in depression.

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Pediatric depression is being increasingly recognized as a major mental health issue. Although it has a complex and multifaceted etiology, evidence is accumulating that disruptions to key neurobiological systems characterize at least some children and youth with depression. This narrative review aims to provide a summary and analysis of the current state of research investigating the functioning of the hypothalamic–pituitary–adrenal (HPA) axis among depressed children and adolescents. By applying a developmental psychopathology perspective, we seek to identify the empirical consistencies across multiple lines of research and, as importantly, to highlight the gaps in the existing literature in order to identify some key aspects needed in future research agendas.

The Problem of Child and Adolescent Depression

Depression is among the most prevalent of psychological disorders. It has been referred to as the "common cold" of psychopathology (Gotlib and Hammen 2002), a designation that belies its seriousness. After taking into account the natural course, mental suffering, and medical morbidity associated with major depression, the World Health Organization declared it the leading cause of disability and the fourth leading cause of premature death worldwide (Murray and Lopez 1996). One of the primary reasons that depression stands out as a major public health problem, with singular costs to individuals and to society, is that this disorder is often chronic, recurrent, and increasingly

harmful over time (Judd 1997). In particular, when depression strikes during adolescence the condition is far more likely to be associated with a persistent, pernicious course over the lifespan (e.g., Lewinsohn et al. 1999). For example, as many as 84% of depressed youths will relapse (Harrington et al. 1996) and these individuals are at particularly high risk for developing a wide range of psychiatric and physical health problems in later adulthood (e.g., Achenbach et al. 1995a, b; Fleming et al. 1993; Kandel and Davies 1986; Puig-Antich et al. 1993; Rao et al. 1995). Given that childhood and adolescence together constitute a watershed period of simultaneous, reciprocally influenced biological, psychological, cognitive, social, and emotional development, it is unsurprising that pervasive disruptions related to juvenile depression have myriad implications and long-term consequences.

Compounding its impact, the prevalence of depression in young people increases over development, particularly during adolescence. Whereas approximately 2% of 13-year-olds experience depression, this rate rises over eightfold to 17% among 18-year-olds and then remains at high levels throughout much of adulthood (Abela and Hankin 2008; Angold et al. 2002; Hankin et al. 1998; Lewinsohn et al. 1994; Wade et al. 2002). Data from recent birth cohorts indicate that adolescence has become one of the most common periods for the onset of first depression (e.g., Andrade et al. 2003; Kessler et al. 2003; Lewinsohn et al. 1999).

The Importance of a Developmental Perspective

These facts underscore the vital importance of conducting research aimed at elucidating the nature, etiology, course, and treatment of depression in young people. Accordingly, scientific interest in these areas has proliferated dramatically in the last decade (Nolen-Hoeksema and Hilt 2009). However, despite an imperative to view depression from a developmental psychopathology perspective (Cicchetti and Schneider-Rosen 1984; Cicchetti and Toth 1998), much of the knowledge on vulnerability to the disorder continues to be framed by a simple and likely simplistic downward extension of adult theories. As such, there is a need for research in the area of child and adolescent depression to more explicitly address two central principles of a developmental psychopathology framework: (1) The clear articulation and examination of transactional models that combine the roles of biological and environmental influences and (2) the careful formulation of theories that take into account how factors at various stages of development operate within these models to shape pathways to affective illness. Rather than simply characterizing how individuals with and without depression differ on a given factor,

a developmental psychopathology perspective considers ontology and trajectory: What is the origin of this association and how does it unfold over time?

The Roles of Stress and the HPA Axis: Conceptual Frameworks

One of the most fruitful and commonly cited lines of inquiry from the adult depression literature comes from the robust and often causal association between depression and stress. Stress generation models have proven useful in revealing the bidirectional, mutually perpetuating relationship between stress and depression (Hammen 1991, 1992). Briefly, these models have highlighted the ways in which depressed individuals may themselves contribute to the generation or exacerbation of certain "dependent" stressors, particularly those occurring within the interpersonal context, as opposed to "independent" or more apparently random events (e.g., a sudden loss or death in the family). Additionally, a much larger and longer-standing body of work has provided compelling evidence that most episodes of major depression are temporally *preceded* by stressful life events (e.g., Hammen 2005; Kessler et al. 1997; Mazure 1998; Monroe and Hadjiyannakis 2002; Tennant 2002). For example, Mazure (1998) summarized across empirical findings and concluded that acute stressors were 2.5 times more likely to have been experienced by depressed patients when compared with controls, and 80% of depressive episodes among community samples developed subsequent to a major life event. Other studies have underscored the possible distinctive importance of more chronic stress or ongoing "daily hassles" as risk factors for depression, and some have argued that this class of stressors represents even stronger predictors (or drivers) of depressive symptoms than do acute stressors (e.g., McGonagle and Kessler 1990).

An individual's pattern of psychological and biological reactions to stressors is often of equal or greater relevance to the development of depression than are the stressors' objective intensity or chronicity. Paralleling the research demonstrating that depressed individuals report stronger reactions to various stressors, decades of work investigating the pathophysiology of depression has revealed that many depressed adults exhibit abnormal patterns of acute responsiveness and/or chronic functioning in their stress physiology (e.g., see Hankin and Abela 2005; Southwick et al. 2005). Much of this work has focused on the hypothalamic–pituitary–adrenal (HPA) axis, which, alongside the sympathetic-adrenal-medullary (SAM) axis, is one of the major biological stress response systems in humans. Many of the hallmark symptoms of depression reflect processes indicative of hypothalamic dysfunction, such

as disturbances of mood, appetite, sleep, sex drive, and motivation. Further still, the same neurotransmitters implicated in the pathogenesis of depression (i.e., serotonin and norepinephrine) are known to regulate the functioning of the HPA axis (e.g., Feldman and Weidenfeld 1998; Klee and Garfinkel 1984).

There have been many studies of the role played by the HPA axis in the link between stress and depression. Over the past 40 years, the literature has revealed that abnormal HPA axis activity in adults with major depressive disorder is among the most consistent and robust biological finding in psychiatry to date (e.g., Halbreich et al. 1985; Rubin et al. 1987; Stokes et al. 1984; see Chrousos and Gold 1992; Ehlert et al. 2001, for reviews). Adults with depression disproportionately show chronic HPA axis hyperactivity and an inability for this system to return to normal functioning following a stressor (e.g., Young and Korzun 1998). Indeed, at least 50% of depressed adults show evidence of dysregulated HPA axis functioning (American Psychiatric Association 1987; Nestler et al. 2002). Prolonged elevation in circulating cortisol levels can result in exhaustion and irritability, which are classic physiological symptoms of depression (Gurguis et al. 1990), and adults with the most severe depression also tend to have the highest cortisol levels (Pruessner et al. 2003). Thus, although not all individuals with elevated cortisol levels are depressed, and not all depressed adults show elevated cortisol, patterns of chronically dysregulated HPA activity are highly over-represented in depressed populations.

Less clear from the adult research is whether HPA axis dysregulation is a consequence of stress experiences or a pre-existing vulnerability. The former perspective is reflective of models proposing that the activity of the HPA axis changes in response to extreme and/or chronic stress and that these changes might be part of the causal mechanisms by which environmental stress contributes to the development of depression, the persistence of symptoms, and the recurrence of the disorder (e.g., Nemeroff 1996; Southwick et al. 2005). The latter hypothesis is that pre-existing differences in HPA axis functioning may make certain individuals more susceptible to the depressogenic effects of stress (Holsboer 2000; van Rossum et al. 2006). Both of these hypotheses implicitly highlight the importance of bringing a developmental perspective to study of the role of adrenocortical regulation in depression.

Examining the developmental pathogenesis of childhood and adolescent depression would serve to broaden understanding of depression across the lifespan. Given this, it is somewhat surprising that there has been far less work investigating the neurobiological correlates of depression in young people (Kaufman et al. 2001). Indeed, until the past decade, our understanding of the potential role of the HPA axis in depression has been informed primarily by research conducted on animals and adult humans. The relative dearth of work conducted with children and adolescents may be partially explained by an earlier reliance on invasive procedures to assess HPA axis functioning (e.g., blood draws through repeated venipunctures), but the recent development of highly sensitive immunoassay techniques has allowed for the accurate measurement of cortisol from salivary samples. Such progress has facilitated the study of HPA axis functioning in a broader range of populations (Klimes-Dougan et al. 2001).

There is a particular research imperative to begin mapping possible changes in HPA axis functioning among depressed individuals at the transition to adolescence. When compared with childhood, it has been well established that adolescence is marked by significant and relatively abrupt increases in stressful life events (Ge et al. 1994; Larson and Ham 1993), particularly within the interpersonal context (Rudolph and Hammen 1999). Further, it has been found that adolescent girls are exposed to both a higher number of interpersonal stressors and report greater distress in response to them, when compared with younger children and adolescent boys (Rudolph 2002; Rudolph and Hammen 1999; Hankin et al. 2007). The timing and nature of these dramatic rises in stressors coincides with that of the equally alarming increases in depressive symptomatology during adolescence, particularly for girls; adolescence marks the period which initiates the increasingly greater prevalence in the rates of depression in girls versus boys (e.g., Hankin et al. 1998; Twenge and Nolen-Hoeksema 2002).

If HPA axis functioning plays a mechanistic role in depression, it might be that pre-existing dysregulation makes some youths vulnerable to the depressogenic effects of stress or that the increase in stress disrupts HPA regulation in some youths, which in turn initiates the progression of depressive symptoms. Early empirical examinations of these proposals—chiefly conducted in the 1990s and involving the examination of cortisol response to various biological and psychological probes or the assessment of basal cortisol levels—led some to conclude that the association between HPA axis dysregulation and pediatric depression is weak or inconclusive at best (Birmaher et al. 1996a, b; Birmaher and Heydl 2001). More recent research, however, has led some to the more nuanced conclusion that the association appears to be stronger or weaker depending upon which index of HPA functioning is examined and at what age depression is manifested (Lopez-Duran et al. 2009; Kaufman et al. 2001).

With the explicit goal of applying a novel theoretical perspective to the extant literature on the functioning of various components of the HPA axis in depressed children and adolescents, the sections below will correspond to the

four categories of studies outlined in Lopez-Duran and colleagues (2009) meta-analysis: (1) those examining the HPA system's response to the dexamethasone suppression test (DST); (2) those assessing basal HPA axis functioning; (3) those administering corticotropin-releasing hormone (CRH) challenge; and (4) those incorporating psychological probes of the HPA axis. In addition, attention will be given to a fifth category of studies: examinations of HPA axis functioning in the offspring of parents with depression. As much as possible within the constraints of available data, a particular effort has been made to contextualize these findings within a developmental psychopathology framework. Principally, this necessitated the characterization and comparison of both atypical and normative developmental variations in HPA stress response across the pubertal/adolescent transition (Cicchetti and Rogosch 2002). Accordingly, in addition to analyzing for methodological variations between studies that may be obscuring potentially consistent findings, careful attention was paid to possible differences in HPA system functioning between depressed versus non-depressed samples and to the relative degree and nature of these deviations across developmental periods.

Overview of the HPA Axis

The HPA axis functions through the coordinated activity of a series of organs within and outside the brain that produces a cascade of hormones resulting in the release of cortisol from the adrenal glands (Chrousos and Gold 1992; Kaltas and Chrousos 2007). Upstream is the hypothalamus, wherein neurons in the paraventricular nuclei (PVN) secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). When these reach the anterior pituitary, they stimulate the corticotrophic cells to release adrenocorticotropic hormone (ACTH). Blood-borne ACTH circulates out of the central nervous system and reaches the adrenal glands, located above the kidneys. There, ACTH triggers the adrenal cortex to release corticosteroids, including cortisol and dehydroepiandrosterone (DHEA), into the circulatory system, where they are carried by the blood to targets throughout the body to produce a variety of effects.

One effect of cortisol is on the HPA axis itself. The HPA axis is also a self-regulating system that decreases activity through a negative feedback loop. Cortisol crosses the blood–brain barrier and signals the hypothalamus to reduce CRH production in the PVN. As less CRH is produced, the pituitary gland decreases its production of ACTH, such that the adrenal glands lose the signal to produce cortisol and DHEA. This self-regulation is a critically adaptive feature of the HPA axis that protects tissue from prolonged exposure to elevated cortisol. Cortisol is a multifunctional steroid that in the short-term supports coping with immediate challenges and threats, but persistently elevated cortisol levels—a condition called *hypercortisolism*—can lead to a variety of harmful immunological, metabolic, and psychological side effects.

The HPA axis is constantly active, to greater or lesser degrees. Over the circadian cycle of day and night, or waking and sleeping, normative cortisol production follows a predictable pattern (Lovallo and Thomas 2000). The normative pattern is for cortisol levels to be fairly high by the end of the sleeping period and to continue increasing until it peaks 30–40 min after awakening, called the cortisol awakening response (CAR) (Adam et al. 2008; Chida and Steptoe 2009). It is thought that the CAR evolved to aid in preparing the body for rapid transition from nighttime quiescence to daytime activity. Circulating cortisol levels then drop rapidly over the morning, drop more slowly through the afternoon, and are at their lowest in the evening (with temporary increases after eating meals, Lovallo and Thomas 2000). Thus, over the waking (daytime or diurnal) period, the change in cortisol levels is characterized by a negative slope. Cortisol levels then increase again during sleep, until the waking level is reached in the morning hours. The diurnal rhythm constitutes "baseline" or "basal" HPA activity, representing the amounts of cortisol that would be expected to be circulating through the blood at a given time of day, all other things being equal. Remarkably, this diurnal rhythm becomes evident very early in development and can be detected in infants a few months after birth (Gunnar and Quevedo 2007). Yet there clearly are developmental changes in HPA axis function, as it has been established that basal cortisol levels rise over childhood and adolescence (Gunnar et al. 2009a). Still, because there have been few basic, descriptive studies of normative HPA axis functioning in children, there is limited information on age differences in typical levels of cortisol over the day (Rosmalen et al. 2005).

Healthy HPA functioning also supports appropriate responses to acute or discrete stressors by changing its level of activity. The HPA axis triggers an increase in circulating cortisol levels when a challenging or threatening event occurs. Once the HPA axis begins ramping up its response to a stressful event, it typically takes about 20 min to reach peak levels of circulating cortisol (Gunnar and Talge 2006; Kudielka et al. 2004). Depending on the intensity and duration of the stressful event, it can take longer for circulating cortisol to return to the baseline expected for the time of day. Counterintuitively, whereas the diurnal rhythm of cortisol is consistent across development, there appears to be a curvilinear relation between age and cortisol reactivity. The periods of preschool and

childhood have been characterized as a time of *hypore-sponsivity* of the HPA axis (Gunnar and Quevedo 2007; Lupien et al. 2009). Compared with infants, adolescents, and adults, children have been found to show much weaker changes in cortisol production in response to psychosocial stressors. It remains uncertain whether this reflects an actual period of biological protection from the effects of stress, possibly due to external regulation by parental care (Lupien et al. 2009), or simply a methodological artifact of researchers' lack of success in designing and implementing appropriate stressors to induce acute HPA axis responses in children (Gunnar et al. 2009a). Either way, it is noteworthy that the normative development of HPA axis activity results in both higher basal cortisol levels and stronger HPA axis responses to stressful events in adolescence, when the frequency of life stressors and the prevalence of depression also increase markedly.

The response of the HPA axis to chronic or pervasive stressors, like poverty or family violence, is quite different than its reactions to acute stressors. Stressful life conditions seem to induce hypercortisolism. For example, children living in socioeconomically impoverished homes have been found to have higher cortisol levels in their basal diurnal cycles (Lupien et al. 2000). Cortisol elevations that are unusually prolonged can become deleterious (Kaltas and Chrousos 2007; Lovallo and Thomas 2000), leading to tissue catabolism, decreased immune function, and such neuropsychological effects as lethargy and disrupted emotional functioning. In fact, many of the side effects of hypercortisolism are strikingly parallel to symptoms of depression (Gurguis et al. 1990).

With this primer on the functioning of the HPA axis system complete, we will now consider the evidence for associations between HPA activity and depression in children and adolescents.

The Dexamethasone Suppression Test

As a potent synthetic glucocorticoid, dexamethasone functions to suppress the production of CRH by the hypothalamus, as well as ACTH by the pituitary gland. Hence, cortisol levels following the administration of dexamethasone represent the sum of two opposing agents acting on the HPA axis to modulate adrenal production of the hormone: one to suppress cortisol's secretion (e.g., endogeneous cortisol and exogenous dexamethasone) and the other to stimulate it (e.g., exogenous stressors; Dahl et al. 1992). Assuming the level of exogenous stress remains constant, a normative response to orally administered dexamethasone the night before leads to a profound decrease in cortisol levels during the next day, while incomplete levels of suppression or early escape from

suppression indicate dysregulation within the HPA axis's negative feedback mechanism (e.g., Burke et al. 2005; Nicolson 2008). Such dysregulation appears to reflect tonic HPA axis arousal and is usually considered an indication of hypercortisolemia (Lopez-Duran et al. 2009).

The dexamethasone suppression test (DST) was originally applied in the late 1960s as a laboratory diagnostic tool for major depression in adults (Carroll 1982; Carroll et al. 1981). In the decades since, the DST has become the most extensively studied biological parameter of depression in adult (Casat et al. 1989), as well as in child and adolescent samples (Kaufman et al. 2001; Weller and Weller 1988). In reviews of the use of the DST in adults, it has been estimated that between 50 and 60% of depressed inpatients and approximately 40% of outpatients have abnormally high levels of cortisol (reflecting blunted suppression) following the DST (APA 1987; Carroll 1982). Although the diagnostic utility of the DST has been questioned more recently due to its lower specificity in inpatient samples (e.g., Dahl et al. 1989; Luby et al. 2003; Pfeffer et al. 1989; Puig-Antich et al. 1989), its cumulatively high sensitivity led the American Psychiatric Association Task Force on Laboratory Tests in Psychiatry (1987) to conclude that the test may add to diagnostic reliability in adult patients suspected of having major depressive disorder. Moreover, it has been argued that the lack of specificity of the DST does not negate its clinical relevance. Given that adult studies have consistently demonstrated that heightened cortisol response to the DST is associated with more severe depressive symptomatology, it may serve as an index of clinical severity (e.g., Steingard et al. 1990).

Approximately 30 studies to date have examined the DST within samples of depressed children and adolescents (see Table 1, an update and expansion of data previously compiled by Kaufman et al. 2001). This still nascent and heterogeneous literature can be summarized as follows. First, about equal numbers of studies utilized samples of prepubertal children and adolescents, and the majority of these studies (77%) were conducted with psychiatric inpatients. The remaining studies, which recruited depressed participants referred either to outpatient evaluation or to treatment, were mostly composed of children. Only two studies by Birmaher et al. (1992b) and Dahl et al. (1992) have conducted the DST with outpatient adolescents. Second, the majority of studies utilized non-depressed control groups which were nonetheless composed of individuals who met criteria for other psychiatric conditions. Only six studies included normative control samples (Birmaher et al. 1992a, b; Dahl et al. 1992; Fristad et al. 1988; Weller et al. 1985; Young et al. 2006). Third, the vast majority of studies used a standardized experimental protocol, namely the oral administration of dexamethasone

Table 1 Dexamethasone suppression test studies with children and adolecents

Study	MDD	Control	MDD measure	Dose	Collection method/time	Non-suppressors	Sensitivity (%)	Specificity (%)
Inpatient children								
Livingston et al. (1984)	3 MDD (1 pure, 2 comorbid with DD, CD, etc.)	12 PC	Dx assigned at clinical case conference	0.5 mg @ 11 pm	Venipuncture @ 4 p.m. next day	2/3 MDD 4/6 ANX 1/1 SZ-S 0/3 CD 0/2 MISC	67	58
Petty et al. (1985)	7 MDD (3 pure, remainder comorbid with CD, aggressive behavior, etc.)	23 PC	"Consensus dx" assigned using DSM-III criteria; KSADS-E administered for 60% across all groups	0.5 mg @ 11 pm	Venipuncture @ 4 pm next day, 2/3 of all patients also had 11 pm venipuncture	6/7 MDD 4/5 DD 5/6 SZ-S 1/3 CD 2/3 ANX 1/6 MISC	86	43
Casat et al. (1994)	11 MDD (unknown comorbidity status)	9 PC	Dx assigned by K-SADS-E using DSM-III-R criteria	2 trials: 0.5 mg @ 11 pm on Days 1 and 6	Venipuncture @ 8 am and 4 pm on Days 2 and 7	**Day 2:** 3/11 MDD 5/9 PC **Day 7:** 2/11 MDD 3/9 PC	27/18	44/66
Pfeffer et al. (1989)	20 MDD (unknown comorbidity status)	31 PC	Dx assigned by 2 independent parent and child K-SADS-P, consensus dx made using DSM-III criteria	0.5 mg @ 11 pm	Venipuncture @ 8 am, 4, and 11 pm next day	11/20 MDD 4/31 PC	55	87
Pfeffer et al. (1989)	19 MDD (unknown comorbidity status)	As above	As above	1 mg @ 11 pm	As above	2/19 MDD 1/31 PC	11	97
Fristad et al. (1988)	63 MDD (unknown comorbidity status)	14 PC 21 NC	DICA, CDI administered w/child and parents	0.5 mg @ 11 pm	Venipuncture next day @ 8 am and 4 pm	Either time: 42/63 MDD 1/14 PC 2/21 NC	67	91
Naylor et al. (1990)	14 MDD (unknown comorbidity status), 11 DD	48 PC	"Consensus dx" assigned after 2 weeks of hospitalization based on DSM-III criteria	0.5 mg @ 11 pm if < 36 kg 1 mg @ 11 pm if > 36 kg	Venipuncture @ 4 pm next day	7/25 MDD + DD 11/48 PC	28	77
Doherty et al. (1986)	59 MDD (19 pure, remainder comorbid)	34 PC	Dx assigned by DSM-III criteria following "Standard clinical assessment"	1 mg @ 11 pm	Venipuncture next day @ 8 am, 4 pm, and 11 pm	15/34 MDD 4/19 DD 2/6 ADDM 1/15 ANX 0/4 CD 0/8 SZ-S 0/7 MISC	44	88
Weller et al. (1984)	20 MDD (unknown comorbidity status)	N/A	Unknown	0.5 mg @ 11 pm	Venipuncture next day @ 8 am and 4 pm	14/20 MDD	70	N/A
Freeman et al. (1985)	5 MDD (comorbid w/SZ-S)	N/A	Child, parent KSADS	0.5 mg @ 11 pm	Venipuncture next day @ 4 pm	4/5 MDD	80	N/A
Weller et al. (1985)	50 MDD (unknown comorbiditystatus)	18 PC 18 NC	DICA, DSM-III	0.5 mg @ 11 pm	Venipuncture next day @ 8 am and 4 pm	41/50 MDD 5/18 BD 2/18 NC	82	72 PC 89 NC

Table 1 continued

Study	MDD	Control	MDD measure	Dose	Collection method/time	Non-suppressors	Sensitivity (%)	Specificity (%)
Livingston and Martin-Cannici (1987)	8 MDD (significant comorbid ANX)	12 ANX 12 BD	Child, parent DICA	0.5 mg @ 11 pm	Venipuncture next day @ 4 pm	8/8 MDD 8/12 ANX 1/12 BD	100	63
Outpatient children								
Young et al. (2006)	3 MDD; Due to low N only conducted analyses with grouped Dxs (3 MDD, 4 ANX, 3 ODD, 1 ADHD)	32 NC	K-SADS	2 trials, randomly assigned: 0.5 mg @ "bedtime" 1 mg @ "bedtime"	Saliva sample next day w/in 45 min of awakening, 4 pm, and "bedtime"	Not reported	Unknown	Unknown
Steingard et al. (1990)	27 MDD (comorbidity status unknown), 29 MDD + ADHD	5 PC	Clinical interviews conducted with child/parent, all dx based on DSM-III criteria	Weight corrected 17 µg/kg @ 11 pm	Venipuncture next day @ 4 pm	8/27 MDD 11/29 MDD + ADHD 5/22 ADHD 0/5 PC	34	81
Birmaher et al. (1992a)	26 MDD (comorbidity status unknown)	10 PC 8 NC	2 independent child and parent KSADS-P, MDD Dx assigned by RDC criteria, control dx by DSM-III	0.25 mg @ 9 pm	Indwelling catheter: 24 hourly samples	11/26 MDD 2/10 PC 6/8 NC	42	55 overall 80 PC 25 NC
Birmaher et al. (1992a)	23 MDD (comorbidity status unknown)	13 PC 9 NC	As above	0.5 mg @ 9 pm	As above	4/23 MDD 0/15 PC 5/8 NC	17	78 overall 100 PC 38 NC
Poznanski et al. (1982)	9 MDD (comorbidity status unknown)	9 PC	Dx assigned by "case conference consensus" after parent and child KSADS	0.5 mg @ 11 pm	Venipuncture next day @ 4 pm	5/9 MDD 1/9 PC	56	89
Geller et al. (1983)	14 MDD (9 comorbid for antisocial behavior or ANX)	N/A	KSADS-P according to RCD and DSM-III	Weight corrected 20 µg/kg @ 11:30 pm	Venipuncture next day @ 4 pm	2/14 MDD	14	N/A
Inpatient adolescents								
Extein et al. (1982)	15 MDD (all "pure")	12 PC	Semistructured interviews, Dx assigned by DSM-III criteria for MDD	1 mg @ 12 am	Venipuncture next day @ 8 am, noon, 4 pm, and midnight	8/15 MDD 1/12 PC	53	92
Hsu et al. (1983)	14 MDD (unknown comorbidity status)	79 PC	Semistructured, standardized intake interview, chart review according to DSM-III criteria	1 mg @ 11 pm	Venipuncture next day @ 4 pm and 11 pm	9/14 MDD 2/6 ADDM 0/2 DD 4/26 CD 2/8 SZ-S 6/10 ED	64	68

Table 1 continued

Study	MDD	Control	MDD measure	Dose	Collection method/time	Non-suppressors	Sensitivity (%)	Specificity (%)
Robbins et al. (1983)	16 MDD (unknown comorbidity status)	12 PC	"Consensus dx" according to RDC criteria based on K-SADS, Hamilton Rating Scale	1 mg @ 11 pm	Venipuncture next day @ 8 am, 4 pm, 11 pm	4/16 MDD 0/12 PC	25	100
Ha et al. (1984)	26 (22 MDD, 4 w/ "minor depressive d/o")	16 PC	Adolescent and parent KSADS	1 mg @ 11:30 pm	Venipuncture next day @ 4 pm and 11 pm	7/22 MDD 2/4 DD 3/16 PC	32	75
Targum and Capodanno (1983)	17 MDD (unknown comorbidity status)	103 PC	Dx assigned according to DSM-III criteria using clinical interview	1 mg @ 11:30 pm	Venipuncture next day @ 4 pm @ 11:30 pm	7/17 MDD 7/38 DD 7/47 CD 4/15 SZ-S	41	82
Robbins et al. (1982)	4 MDD	5 PC	2 independent KSADS, consensus dx according to RCD criteria	1 mg @ 11:30 pm	Venipuncture next day @ 8 am, 4 pm, 11 pm	2/4 MDD 0/5 PC	50	100
Klee and Garfinkel (1984)	20 MDD (unknown comorbidity status)	13 PC	KSADS dx according to RDC criteria	1 mg @ 11 pm	Venipuncture next day @ 8 am, 4 pm, 11 pm	8/20 MDD 1/13 PC	40	92
Emslie et al. (1987)	33 MDD (predominantly comorbid)	18 DD 35 PC	Dx assigned according to DSM-III criteria using semistructured interview w/patients and parents	0.5 mg for children (< Tanner 3), 1 mg for adolescents	Venipuncture next day @ 4 pm	18/33 MDD 4/18 DD 4/35 PC	55	89 (PC)
Woodside et al. (1987)	10 MDD (unknown comorbidity status)	18 CD 2 BP	Consensus diagnosis according to DSM-III	1 mg @ 11 pm	Venipuncture next day @ 4 pm and 11 pm	8/10 MDD 2/18 CD 2/2 BP	80	80
Khan (1987)	33 MDD (predominantly comorbid)	22 CD 6 DD 5 ADHD	Semistructured interview according to DSM-III	1 mg @ 11 pm	Venipuncture next day @ 4 pm and 11 pm	23/33 MDD 3/22 CD 1/6 DD 1/5 ADHD	70	85
Evans et al. (1987)	20 MDD (unknown comorbidity)	32 PC	Semi-/un-structured interview with patient and family members according to DSM-III criteria	1 mg @ 11 pm	Venipuncture next day @ 4 pm and 11 pm	8/20 MDD 5/32 PC	40	84
Appelboom-Fondu and Kerkhofs (1988)	8 MDD (comorbid with bipolar)	12 PC	KSADS according to RDC criteria	1 mg @ 9 pm	Venipuncture next day @ 2 and 9 pm	4/8 MDD 0/12 PC	50	100

Table 1 continued

Study	MDD	Control	MDD measure	Dose	Collection method/time	Non-suppressors	Sensitivity (%)	Specificity (%)
Outpatient adolescents								
Birmaher et al. (1992b)	44 MDD (Unknown comorbidity status)	38 NC	2 independent K-SADS administered, HAM-D, According to RDC criteria for MDD	1.0 mg @ 11 pm	Indwelling catheter: hourly samples next day from 8 am - 11 pm	6/44 MDD 1/38 NC	14	97
Dahl et al. (1992)	27 MDD (significant comorbidity)	34 NC	2 independent parent and child KSADS-P, dx based on RDC, DSM-III criteria	1 mg @ 11 pm	Indwelling catheter: hourly samples next day from 8 am - 11 pm	4/27 MDD 3/34 NC	15	91

ADDM adjustment disorder with depressed mood, *ADHD* attention-deficit/hyperactivity disorder, *ANX* anxiety disorders, *BD* behavior disorders (oppositional defiant disorder, ADHD with hyperactivity, conduct disorder), *BP* bipolar disorder, *CD* conduct disorder, *DD* dysthymic disorder, *ED* eating disorders, *MDD* major depressive disorder, *MISC* miscellaneous diagnoses, *NC* normative controls, *ODD* oppositional defiant disorder, *PC* psychiatric controls, *SZ-S* schizophrenia spectrum

to depressed participants and non-depressed controls at or around 11 p.m., and cortisol levels were measured with single or repeated blood draws at various times during the subsequent day. Fourth, almost without exception, cortisol "non-suppression" (i.e., an abnormal DST result) was defined according to the categorical adult criterion recommended by Carroll and colleagues (1968; i.e., an unbound plasma cortisol level ≥ 5 μg/dl at any time during the first day post-dexamethasone administration).

A wide range of variability in DST results was found across individual studies, likely due to the large number of studies using small samples sizes. Indeed, approximately half of these published reports included only 15 or fewer depressed children or adolescents and a comparably small number of non-depressed control participants. Important trends are apparent, however, when considering these findings in aggregate. Most salient and consistent with the overall meta-analytic finding based on the smaller set of studies reported by Lopez-Duran et al. (2009), depressed children and adolescents demonstrated greater cortisol production (or less suppression) after the DST when compared with non-depressed controls. In averaging across all studies, approximately 45% of depressed children and adolescents and only 18% of non-depressed control participants had positive DST results. This overall rate of cortisol non-suppression among juvenile depressed samples (compiled of results from child, adolescent, as well as from inpatient and outpatient samples) is comparable to that reported in samples of depressed adults (APA 1987). Thus, these data suggest that abnormal HPA axis functioning as measured by cortisol non-suppression following the DST is associated with at least some forms of child and adolescent depression. Further,

given the psychobiological mechanisms purportedly measured by the DST, this dysregulation supports the hypothesis that the HPA axis of some young people with depression is hyperactive due to either insensitivity to or early escape from the system of hormonal "brakes" that, in normative populations, has evolved to return the HPA stress system to homeostasis following a stressful precipitant.

Also consistent with a robust finding from the adult DST literature, the rates of cortisol non-suppression in inpatient depressed children and adolescents were approximately double those found in outpatient samples. This pattern is unsurprising. Assuming that inpatients as a group tend to be individuals with more serious forms of psychopathology, dysfunction, and impairment than their outpatient counterparts, it is intuitive that greater HPA axis dysregulation might be present among more severely depressed young people. As noted above, parallel evidence for this contention can be found in the adult data; severe MDD patients showed greater post-DST non-suppression than did those with less symptomatology (APA 1987). Unfortunately, this hypothesis cannot be directly examined within individual studies conducted with child and adolescent samples, much less between samples of inpatients and outpatients. Most DST studies conducted with young people relied on assessment methods that assigned a simple categorical diagnosis of depression based on clinician-administered, semistructured interviews. Only Birmaher et al. (1992a, b) conducted analyses of supplementary, continuous data related to the severity of depression among their sample of adolescent outpatients. However, these investigators reported unexpected results; adolescents who scored higher on the self-reported Hamilton Rating Scale

for Depression (HAM-D; Hamilton 1960) had a lower rate of non-suppression following the DST (Birmaher et al. 1992a, b).

Of more direct relevance to viewing the association between depression and HPA axis dysregulation through a developmental psychopathology perspective, the available DST data allow for a preliminary comparison of the rates of cortisol non-suppression among children versus adolescents. Ostensibly contrary to the expectations of theoretical models proposing progressive HPA axis dysfunction across development consequent to recurrent stress exposure (e.g., Southwick et al. 2005), the rates of non-suppression were observed to be somewhat higher among children than among adolescents. An estimated 50–70% of depressed children and 40–60% of depressed adolescents were found to have abnormally high levels of cortisol subsequent to the DST (Kaufman et al. 2001).

However, a potentially confounding methodological factor must be considered in the interpretation of these unexpected data. Critically, the dose of dexamethasone most frequently used in studies with children was 0.5 milligrams, while the standard, adult dose of 1.0 milligrams was used in all studies with adolescents. It is possible, as some have argued (e.g., Dahl et al. 1992; Pfeffer et al. 1989), that it is unwarranted and misleading to use the 1-mg, adult-equivalent dose of dexamethasone with adolescents. Administering dexamethasone to adolescents at double the milligrams of the typical child dose might not be proportionate to the increase in body mass and/or metabolism expected across this period of development. One possible result of an overly high dose of dexamethasone could be the uniform suppression of cortisol regardless of diagnostic status.

Pfeffer et al. (1989) found compelling empirical support for the importance of using the "appropriate" dose of dexamethasone among preadolescents. In conducting the DST with children at the threshold of adolescence, these investigators found that the 0.5-mg dose was more sensitive (i.e., correctly identified a greater proportion of depressed individuals) than the 1-mg dose. Accordingly, the pattern of slightly higher rates of non-suppression observed among child relative to adolescent samples may reflect a systematic difference in the dose of dexamethasone used between age groups, rather than any developmental differences in HPA axis functioning. Future work comparing child and adolescent response to the DST would benefit from the consistent (or, best, physically proportionate) application of dexamethasone dose. Naylor et al. (1990), for example, suggested that dosage might be better calculated as a proportion of body surface area.

A final and considerable limitation of the extant literature examining the DST among pediatric samples pertains to the generally ambiguous diagnostic classification of

participants. Many studies reportedly utilized rigorous diagnostic procedures such as repeated, multi-informant, semistructured clinical interviews to diagnose MDD based on DSM or RDC criteria (e.g., Birmaher et al. 1992a, b; Dahl et al. 1992; Pfeffer et al. 1989; Robbins et al. 1982). However, the majority of studies either made no explicit attempt to characterize (let alone control for) the possible comorbid status of depressed participants, or—when comorbidities were determined—simply defaulted to major depression as the primary diagnosis. Thus, as has been argued in the adult DST literature (Zimmerman et al. 1986), DST studies conducted with children and adolescents are seriously limited by a failure to account for the diagnostic heterogeneity of depressed participants.

Basal Cortisol Functioning and Diurnal Variation

As mentioned above, studies conducted with depressed adults have consistently demonstrated that a substantial proportion of these adults hypersecrete cortisol across various measured indices of basal HPA axis functioning. For example, when compared with non-depressed controls, depressed adults tend to exhibit higher mean 24-h plasma levels of cortisol, increased frequency of cortisol secretion episodes, greater magnitudes of cortisol released during each pulse, an earlier time of cortisol rise during sleep, and an overall loss of the usual circadian rhythm (Christensen et al. 1985; Halbreich et al. 1985; Jarrett et al. 1983; Linkowski et al. 1985; Mortola et al. 1987; Pfohl et al. 1985, b; Rubin et al. 1987; Sachar et al. 1973; Stokes et al. 1984; for reviews see Stokes and Sikes 1991; Barden 2004).

As with the body of work investigating the DST, basal cortisol secretion and diurnal rhythms associated with child and adolescent depression are similarly incomplete. The 20 studies conducted to date in this area are summarized in Table 2, which is an adaptation and expansion of data previously presented by Lopez-Duran et al. (2009). Here again, approximately equal numbers of published reports utilized child and adolescent samples. The average sample size in studies of diurnal cortisol is larger than that of studies of response to DST, but about half the studies included fewer than 40 patients with depression and a comparable number of control participants. In contrast to the DST literature, all but four studies of child and adolescent basal HPA axis functioning included normative control samples. A synthesis of findings across this preliminary research is difficult due to the wide array of basal cortisol measures that have been indexed (e.g., mean 24-h composite, overall peak/nadir, time of nocturnal rise, individual samples collected at different predetermined times during the day) and the disparate biological samples that were assayed (e.g., blood, saliva, urine). For example,

Table 2 Studies of basal cortisol functioning in children and adolescents

Study	Sample	MDD	Control	MDD measure	Collection method/time	Nighttime cortisol	Daytime and/or total cortisol
Pfeffer et al. 1989	Inpatient children	20 MDD (unknown comorbidities)	19 DD 9 SZ-S 3 Neither	Dx assigned according to DSM-III criteria based on 2 independent K-SADS-P with parents and children	Venipuncture @ 8 am, 4, and 11 pm	Equivalent	Equivalent
Casat et al. (1994)	Inpatient children	11 MDD (unknown comorbidities)	9 PC	Dx assigned according to DSM-III criteria based on K-SADS-E	Venipuncture @ 8 AM on two separate days	N/A	Lower
Birmaher et al. (1996)	Both inpatient and outpatient children	34 MDD (unknown comorbidities)	22 NC	Dx assigned according to RDC based on parent and child K-SADS-P and K-SADS-E	Indwelling venous catheter; samples taken 30, 15, 0 min before 9 am CRH infusion	N/A	Equivalent
Kaufman et al. (1997b)	Both inpatient and outpatient children	13 MDD abused 13 MDD non	13 NC	Dx assigned according to RDC based on 2 independent K-SADS	Indwelling venous catheter: samples taken at 30, 15, and 0 min pre- CRH infusion	N/A	Equivalent
Birmaher et al. (1992b)	Outpatient children	23 MDD (15 endogenous, 6 psychotic, 18 suicidal)	13 PC 9 NC	Dx assigned according to DSM-III (PC) or RDC criteria (MDD) based on 2 independent parent and child KSADS-P	Indwelling catheter: 24 hourly samples beginning 9 PM	Equivalent	Equivalent
Feder et al. (2004)	Outpatient children	76 MDD (unknown comorbidities)	31 ANX 17 NC	Dx assigned according to RDC criteria based on 2 independent K-SADS-P	Indwelling venous catheter: hourly blood samples collected over 24-hr period	Equivalent	Equivalent
Luby et al. (2003)	Outpatient preschoolers	55 MDD (unknown comorbidities)	43 PC 57 NC	Parent DISC (modified to be developmentally appropriate)	Saliva samples collected on 3 consecutive nights	Equivalent	N/A
Forbes et al. (2006)	Outpatient children and adolescents	116 MDD (unknown comorbidities)	32 ANX 76 NC	Dx assigned by case conference consensus based on K-SADS-PL	Indwelling venous catheter: daytime = 40, 20, and 0 min before CRH infusion; nighttime = every 20 min beginning 2 h before individual bedtime	Higher than NC	N/A
Puig-Antich et al. (1989)	Outpatient children	45 MDD (unknown comorbidities)	20 PC 8 NC	Dx assigned according to RDC criteria based on 2 independent K-SADS-Ps	Indwelling venous catheter: samples every 20 min for 24 h	Equivalent	Equivalent

Table 2 continued

Study	Sample	MDD	Control	MDD measure	Collection method/time	Nighttime cortisol	Daytime and/or total cortisol
Doherty et al. (1986)	Inpatient children and adolescents	43 MDD (significant comorbidity)	29 PC	Dx assigned according to DSM-III criteria following "Standard clinical assessment"	Venipuncture @ 8 am and 11 pm.	Equivalent	Equivalent
Goodyer et al. (1996)	Outpatient children and adolescents	82 MDD (unknown comorbidities)	11 PC 40 NC	Dx assigned according to DSM-III-R criteria based on K-SADS-P	Salivary cortisol samples at 8 AM, 12 PM, 8 PM over 2 consecutive days	Higher than both PC, NC	Equivalent
Extein et al. (1982)	Inpatient adolescents	15 MDD (unknown comorbidities)	12 PC	Dx assigned according to DSM-III criteria based on semistructured interviews	Venipuncture @ 4 pm, midnight, and 8 am.	Equivalent	Equivalent
Kutcher et al. (1991)	Inpatients adolescents	12 MDD (unknown comorbidities)	12 NC	Dx assigned according to DSM-III-R criteria based on K-SADS	Indwelling venous catheter: samples at 10 PM, 12 AM, 1, 2, 3, 4, and 6 AM	Equivalent	Equivalent
Dahl et al. (1991)	Inpatient and outpatient adolescents	27 MDD ("significant comorbidity")	32 NC	Dx assigned according to adult RDC criteria based on 2 independent K-SADS-Ps	Indwelling venous catheter: blood draws every 20 min for 24 h (starting 8:30 AM)	Higher	Equivalent
Rao et al. (2008)	Outpatient adolescents	30 MDD (unknown comorbidities)	25 NC	Dx assigned according to DSM-IV criteria based on adolescent and parent K-SADS-PL	Saliva samples collected at 30 min intervals for 2 h (i.e., 5 samples)	N/A	Equivalent
Dahl et al. (1989)	Outpatient adolescents	48 MDD (unknown comorbidities)	40 NC	Dx assigned according to adult RDC criteria based on 2 independent K-SADS-Ps	Indwelling venous catheter: blood samples every 20 min for 24 h	Equivalent	Equivalent
Rao and Poland (2008)	Outpatient adolescents	16 MDD (unknown comorbidities)	16 NC	Dx assigned according to DSM-IV criteria based on adolescent and parent K-SADS-PL	Nocturnal urinary free cortisol (10:30 pm and 7 am samples)	Higher	N/A
Mathew et al. (2003)[a]	Outpatient adolescents, in 10 year follow-up study	48 MDD at Time 1; 56 MDD at Time 2 (15 with comorbid anxiety disorder)	21 NC	Dx assigned according to SADS-LA according to best estimate procedure	Indwelling venous catheter; blood samples every 20 min for 24 h (starting in the A.M.)	Equivalent, but LOWER in subsequently suicidal outpatients	Equivalent, but HIGHER in subsequently suicidal outpatients

Table 2 continued

Study	Sample	MDD	Control	MDD measure	Collection method/ time	Nighttime cortisol	Daytime and/or total cortisol
Goodyer et al. (2003)[b]	Outpatient adolescents, in 2 year follow-up study	30 MDD (19 RMD, 11 PMD)	30 NC (high risk, never depressed)	Dx assigned according to DSM-IV criteria based on the Kiddie-SADs patient version	Salivary cortisol samples at 8 A.M. and 8 P.M. over 4 consecutive days	Equivalent	Equivalent, but higher morning cortisol:DHEA ratio in PMD
Adam et al. (2010)[c]	Outpatient adolescents, in 1 year follow-up study	40 past MDD and 16 current MDD at Time 1; 18 MDD at Time 2 (9 recurrences, 9 new cases); 20 with subclinical MDD at Time 2.	192 NC (over-sampled for high neuroticism)	Dx assigned according to the DSM-IV (SCID)	Salivary cortisol samples gathered 6 times per day over 3 consecutive weekdays: at wake-up, 40 min after waking, at 3, 8, and 12 h post-awakening, and at bedtime.	Equivalent	Higher (Car)

ANX anxiety disorders, *DD* dysthymic disorder, *MDD* major depressive disorder, *NC* normal controls, *PC* psychiatric controls, *SZ-S* schizophrenia spectrum disorders, *RMD* remitted major depression, *PMD* persistent major depression, *CAR* cortisol awakening response

[a] Groups were further split into: MDD T1 Suicide (attempts prior to T1), MDD T10 Suicide (attempts between T1 and follow up), and MDD No Suicide. MDD T10 showed elevated cortisol levels prior to sleep onset (afternoon, evening, night). MDD T10 also showed elevated cortisol levels 100 min prior and 100 min after sleep onset, but lower levels of cortisol secretion 2-4 h after sleep onset

[b] Youths with MDD that persisted over 24 months had higher cortisol:DHEA ratios in morning saliva samples than at-risk youths without depression, and at-risk youths who had MDD at 12 months follow-up but remitted by 24 months

[c] Study also used CAR (cortisol awakening response) information as predictor of later onset of MDD, and found that individuals who had higher levels of cortisol in their CAR were more likely to become MDD by follow-up. For these purposes, the 56 baseline MDD participants were excluded from that part of the study

nine studies employed the use of an indwelling venous catheter to collect unbound plasma cortisol samples from blood at various, unstandardized times throughout the day, whereas seven studies collected samples either from repeated venipuncture or from saliva. Assays of saliva samples assess only the levels of unbound (active) cortisol, whereas assays of serum assess both unbound and bound (inactive) cortisol. However, there is high correspondence between serum and saliva assays of cortisol in children (Bober et al. 1988; Burke et al. 1985; Schwartz et al. 1998), and results of studies using the two procedures are generally convergent.

Further complicating a systematic comparison of results between depressed and non-depressed children and adolescents across studies is the well-known and substantial inter- and intra-personal variability in daily cortisol production due to a number of variables. For instance, not only are basal levels thought to represent individual differences in temperamental or trait dimensions (e.g., Stansbury and Gunnar 1994), but particular diurnal patterns of cortisol secretion vary as a function of an individual's usual circadian sleep–wake cycle (e.g., Nicolson 2008). Likewise, given that sleep disruption is a criterial symptom of the diagnosis of major depression, it is certainly possible that systematic group differences exist in the sleep-wake cycles

of depressed versus non-depressed young people. Thus, to control for these group and individual differences and enable meaningful comparison of data between depressed and non-depressed samples, it is arguably necessary to analyze diurnal cortisol trajectories aligned by time of sleep onset rather than by objective clock times (e.g., Klimes-Dougan et al. 2001). Seven of the studies presented in Table 2 (Adam et al. 2010; Dahl et al. 1989, 1991; Forbes et al. 2006; Goodyer et al. 2003; Mathew et al. 2003; Puig-Antich et al. 1989) accounted for these possible confounders. It may be important to note, at least anecdotally, that of the eight studies from Table 2 that found any evidence for differences in basal cortisol levels between depressed patients and controls, four (Adam et al. 2010; Dahl et al. 1991; Forbes et al. 2006; Mathew et al. 2003) took additional steps to conduct analyses that accounted for time of sleep onset.

Methodological and biological heterogeneity notwithstanding, several important patterns emerge from results found across studies of HPA basal functioning. First, the majority of published reports failed to detect statistically significant differences between depressed and control youths on any measure of basal cortisol secretion. More specifically, and contrary to reliable findings in the adult data, none of the studies conducted with children and

adolescents found significant differences between groups of depressed and control youths on any of the following basal cortisol summary variables: 24-h mean level, overall peak, daytime mean, pulse frequency, or pulse amplitude.

It is interesting to note, however, that overall non-significant trends of cortisol hypersecretion were often found among samples of depressed young people. It is certainly plausible that the aforementioned small samples sizes typically utilized throughout this literature seriously limited the power of any individual study to detect more subtle deviations from normative diurnal pattern of cortisol production. Indeed, significant basal elevations appeared to be more often reported by those studies with larger samples sizes (i.e., Dahl et al. 1991; Forbes et al. 2006; Goodyer et al. 1996). This argument is further strengthened by the positive result of a recent meta-analysis that revealed a statistically significant tendency for depressed children and adolescents to have higher basal cortisol levels relative to non-depressed controls (Lopez-Duran et al. 2009). Intriguingly, Lopez-Duran et al. (2009) also found that age did not moderate this association; cortisol levels were similarly elevated in depressed prepubertal children and depressed adolescents. This is somewhat surprising, given that the association between dysregulation of basal cortisol secretion and depression appears to be more robust in adults. It is worth noting, though, that one of the few studies to directly and carefully compare the HPA axis activity of depressed children and adolescents found that only depressed adolescents had elevated cortisol levels in the period preceding sleep onset (Forbes et al. 2006). Thus, there may be a pattern in which pediatric depression becomes increasingly linked to basal HPA axis dysfunction with advancing age.

Interestingly, Casat et al. (1994) conducted the only study that found evidence for *reduced* cortisol secretion among depressed children. However, there are certain distinguishing characteristics of this study that may account for these divergent results. These investigators utilized a methodology distinct from the majority of other studies of basal cortisol levels and patterns, and they included the smallest number of depressed participants (i.e., $n = 11$) of any study examining basal HPA axis functioning in this age group. Taken together, these limitations raise the possibility that these aberrant results are spurious.

Perhaps most revealing, though, are the three longitudinal studies on the relations between HPA axis function and adolescent depression (Adam et al. 2010; Goodyer et al. 2003; Mathew et al. 2003). All three involved the measurement of cortisol levels in adolescents with and without depression and the prediction of youths' subsequent mental health one to 10 years later. Goodyer et al.

(2003) compared morning and evening salivary cortisol and DHEA levels in 60 adolescents at high risk for developing MDD but who had not manifested any disorder. They conducted diagnostic interviews at two follow-ups, 12 and 24 months later. Of note, these investigators examined youths' cortisol:DHEA ratios; because DHEA has neuroprotective properties and is an antagonist to the actions of cortisol, this ratio provides an indicator of *functional hypercortisolism*. Goodyer and colleagues found that having higher cortisol: DHEA ratios predicted youths' development of persistent MDD, present at both 12- and 24-month follow-ups, compared with youths who did not develop MDD and youths with MDD at 12 months that subsequently remitted.

Mathew et al. (2003) used continuous blood sampling to study 24-h cortisol cycles in 42 adolescents with MDD and 35 without and examined these youths again 10 years later with the goal of predicting suicide attempts. Although cortisol levels had not distinguished the youths with and without depression in concurrent analyses (Dahl et al. 1989), cortisol rhythms predicted trajectories toward suicidality. Compared with all other young adults, the 13 youths with lifetime diagnoses of MDD who attempted suicide in the subsequent 10 years had elevated cortisol levels in the 6 h before sleep onset, from late afternoon through evening. They also had lower cortisol levels 2–4 h after sleep onset when, normatively, the HPA axis would be expected to increase cortisol production. Thus, a systemic dysregulation of diurnal HPA axis activity predicted subsequent suicidal behavior in young people with depression.

Finally, Adam et al. (2010) assessed depression symptoms and collected saliva samples to measure the CAR in 230 17-year-old youths, many of whom had high levels of *neuroticism*, a risk factor for depression (Kendler et al. 2004), and again measured symptoms of depression one year later. Those young adults who had highly elevated CAR a year earlier were three times more likely to have developed MDD, compared to average. Earlier high CAR predicted subsequent MDD even after the researchers took account of the youths' original symptoms of depression and anxiety, their experiences of stressful life events, and other potentially confounding factors.

Together, these three studies offer strong evidence that dysregulated basal HPA activity precedes and predicts the development of depression and associated behaviors in adolescence and early adulthood. As suggested in the meta-analysis by Lopez-Duran et al. (2009), this does not appear to be due to dysregulation at any specific part of the diurnal rhythm. Rather, exaggerated CAR, elevated morning and evening cortisol, and lower cortisol after sleep onset all appear to characterize youths who are at greater risk for developing depression.

CRH Infusion Studies

The chain of physiological activation of the HPA axis begins far upstream in the hypothalamus with the release of CRH, ultimately leading to the release of cortisol and DHEA (for review, see Sapolsky et al. 2000). Given the central role of CRH as the driver for this sequence of activation, some investigators have hypothesized that the cortisol-related abnormalities observed among depressed adults may be due to enhanced secretion of CRH (Gold et al. 1986; Plotsky et al. 1998). This led to several investigations examining patients' ACTH and cortisol responses to the administration of exogenous CRH in a laboratory setting. This research, which has almost exclusively relied on adult samples, has repeatedly demonstrated that depressed individuals tend to have elevated cortisol and blunted ACTH secretion in response to CRH infusion, relative to normal controls (see Birmaher et al. 1996b, for a review). ACTH secretion is hypothesized to be attenuated due to a gradual downregulation of pituitary CRH receptors over time in response to chronically increased hypothalamic CRH secretion and/or the loss of fast feedback regulation in the hypothalamus or hippocampus (Ronsaville et al. 2006). Accordingly, a normal cortisol response to blunted ACTH secretion is evidence of HPA axis dysregulation in the form of a hyper-responsive adrenal cortex (see Gold et al. 1995).

Surprisingly, only four studies have compared cortisol and ACTH responses between samples of depressed and non-depressed children and adolescents following CRH challenge (Birmaher et al. 1996b; Dorn et al. 1996; Kaufman et al. 1997a, b; Ronsaville et al. 2006). In contrast to the adult data, none of these studies found significant differences in overall cortisol or ACTH secretion between depressed and non-depressed groups of children (Birmaher et al. 1996b; Kaufman et al. 1997a, b; Ronsaville et al. 2006) or adolescents (Dorn et al. 1996). With the exception of the study conducted by Ronsaville et al. (2006), which reported results based on only six actively depressed children, null findings across the remainder of CRH studies were reported despite sample sizes which included 20 or more depressed children or adolescents and a comparable number of non-depressed control participants.

Nonetheless, a closer examination of the scarce literature on CRH in the young suggests important directions for further investigation. If these replicated the albeit limited historical data, they would establish continuities with the adult data. For example, Birmaher et al. (1996b) found that depressed inpatient children exhibited significantly lower total ACTH secretion after CRH infusion relative to depressed outpatients, while still maintaining comparable cortisol reactivity. Similar to the findings in adults, it is possible that some depressed young people may manifest

HPA axis dysregulation through adrenal cortex hyper-responsivity. Such evidence, however preliminary, is also in accord with a salient pattern found in DST studies, namely the pronounced differences in HPA axis functioning between inpatients and outpatients. Birmaher et al. (1996b) hypothesized explanations for group differences in total ACTH secretion following CRH infusion also parallel DST findings. First, their suggestion that the depressed inpatients in their sample may have been more severely depressed than the outpatient subgroup was not supported by secondary analyses that revealed no significant group differences between inpatients and outpatients on either the Hamilton Depression Rating Scale or the depression module from the K-SADS-P. Therefore, the explanation for the observed group differences in total ACTH secretion was considered to lie in increased (but unmeasured) levels of exposure to and/or perception of stress experienced by inpatients before and during the first days of hospitalization. Such hypotheses remain speculative and significant questions remain as to how to account for possible group differences in CRH studies between inpatient and outpatient samples of depressed young people. It may be that inpatient status serves as a proxy for greater stress exposure, more severe depressive symptomatology, chronicity of the disorder, and/or some combination of these factors.

Likewise, the study conducted by Kaufman et al. (1997a, b) allowed for interesting analyses of subgroup data with possible developmental implications. These investigators examined the results of CRH challenge among samples of depressed abused and depressed non-abused outpatient children, as well as age-matched normal controls. Although no differences in cortisol secretion were found post-CRH infusion between groups, one group of children differed significantly—and in the unexpected direction—with regard to their subsequent ACTH levels. When compared with depressed children without a history of abuse and control children, depressed abused children had significantly *higher* peak, total, and net ACTH secretion post-CRH challenge. Exploratory analyses of this disparity revealed that increased ACTH secretion was only observed in depressed abused children who were experiencing *ongoing* chronic adversity (e.g., marital violence, emotional abuse, poverty, insufficient social supports).

Taking a developmental psychopathology perspective, although Kaufman et al. (1997a, b) make no explicit mention of whether depressed participants were experiencing either first- or recurrent-onset major depression, we may assume from the young mean age of participants (M = 9.5; range 7–13 years) that they had experienced few previous episodes of depression. To the extent that the attenuation of ACTH secretion commonly observed in depressed adults can be accounted for by downregulation of CRH receptors in response to these individuals'

chronically increased hypothalamic CRH levels, young people experiencing their first depressive episodes likely have not yet undergone this downregulation. Thus, it might be expected that the combination of early-onset disease status (that would impact on normally abundant/sensitive CRH receptors) and chronic, ongoing adversity (that would drive overproduction of CRH) would lead to the augmented ACTH secretion found in these vulnerable children. This hypothesis of progressive HPA axis dysregulation in response to chronic stress exposure parallels the pattern reported in animal studies (e.g., LeMevel et al. 1979; Vernikos et al. 1982).

Psychological Challenge Studies

While hypothalamic CRH represents the *physiological* trigger for activation of the HPA system, *psychological* activation of this system begins upstream with affective information processed in the limbic system. The limbic system, in turn, stimulates CRH-releasing neurons in the hypothalamus (e.g., Adam et al. 2008). Since the limbic system serves as the primary conduit between cognitively processed exogenous stressors and endogenous physiological signals, psychological stressors represent important probes of the higher-order functioning of the HPA axis. Surprisingly, there has been little research in this area. As discussed previously in the introductory sections, although both depression and the transition to adolescence are associated with increases in exposure to psychological stressors, a paucity of studies has addressed HPA axis response to this class of stimuli among depressed children and adolescents.

Recall that in normative populations, childhood has been hypothesized to be a period of hyporesponsivity to psychological stressors, relative to adolescence (Gunnar et al. 2009b; Lupien et al. 2009). For example, Stroud et al. (2009) examined the neuroendocrine (salivary cortisol), sympathetic-adrenomedullary (salivary alpha amylase), and cardiovascular responses of typically developing children and adolescents to several performance-related tasks (e.g., public speaking, mental arithmetic recitation) and to an ecologically valid peer rejection paradigm (The Yale Interpersonal Stressor; Stroud et al. 2000). These investigators found that adolescents exhibited significantly greater reactivity across several physiological indices relative to children for both tasks. The authors argued that while "heightened reactivity to psychological stressors in typically developing adolescents may facilitate adaptation to new challenges of adolescence and adulthood…in high-risk adolescents, this normative shift may tip the balance toward stress response dysregulation associated with depression and other psychopathology" (Stroud et al. 2009, p. 47).

Until very recently, however, no studies had explicitly compared the HPA axis response patterns to psychological challenge between pediatric samples of depressed and "typically developing" control participants. Only four such reports have been published (Hankin et al. 2010; Luby et al. 2003, 2004; Rao et al. 2008), and two of these publications utilized data from the same sample (Luby et al. 2003, 2004). Although these few published data reflect the smallest body of literature examining pediatric HPA axis dysregulation associated with early-onset depression, it is intriguing to note that the patterns of findings are by far the most consistent. All four studies reported significant findings related to cortisol hypersecretion of depressed juveniles in response to acute, laboratory-induced psychological stress relative to non-depressed psychiatric controls or normative volunteers. Given the small number of published reports, a brief review of each is provided below.

The two studies by Luby et al. (2003, 2004) examined HPA reactivity to experimentally induced psychosocial stress among the same sample of preschool-aged children. The evidence from these studies suggests continuities of HPA axis dysfunction in depressive disorders across early development and into adulthood. Both studies drew upon data from a relatively large sample of depressed preschoolers together with age-matched psychiatric and normative comparison groups. The investigators collected multiple salivary samples before and after stressors that involved separation from parents and frustrating tasks (e.g., not being able to unlock a transparent box with a desirable toy inside).

The 2003 study revealed that whereas all groups of children displayed heightened cortisol response to frustrating tasks relative to baseline, depressed preschoolers were the only group to show significantly augmented cortisol levels in response to a separation stressor, as well as an overall pattern of increasing mean cortisol secretion throughout the 2-h assessment. Importantly, in comparison with both control groups, depressed children displayed higher cortisol levels subsequent to their arrival at the laboratory, perhaps indicating heightened emotional reactivity to the novel experimental paradigm or chronically elevated basal cortisol levels. Additional subgroup analyses of these data presented in the 2004 study indicated that depressed preschoolers experiencing significant symptoms of anhedonia tended to exhibit the greatest cortisol reactivity to acute psychological stress. The authors argued that, as with adults, anhedonia in children may represent a marker of a more severe, biologically, and genetically based depressive subtype. This pattern of more consistent and pronounced patterns of HPA hyperactivity corresponding to more severe depressive symptomatology parallels findings from studies using DST and CRH probes.

Rao and colleagues ([2008]) study of adolescents utilized the Trier Social Stress Test (TSST), a standardized and validated psychosocial stress protocol that has been shown to reliably induce HPA activity in adolescents and adults (Gunnar et al. [2009a]; Kirschbaum et al. [1993]). The TSST is an interpersonal stressor that involves the participant being challenged to perform well on evaluative tasks by an unsupportive examiner. The TSST was administered to 30 depressed adolescents and 25 healthy volunteers and systematically measured both baseline and post-TSST samples of salivary cortisol. Consistent with their hypothesis, the authors found that although both groups of adolescents exhibited significantly elevated cortisol response to the TSST relative to their respective baseline levels, depressed participants showed significantly higher and more prolonged cortisol secretion following psychosocial stress induction when compared with control subjects.

Parallel findings were reported by Hankin et al. ([2010]). They used an interpersonal psychosocial stress procedure to examine cortisol reactivity in a small sample of depressed children and youths, aged 8–15 years, compared with a larger, age-matched sample with no evidence of depression or dysphoria. Prepubertal children with current MDD had higher initial cortisol levels, but they did not differ from comparison children in reactivity (20-min post-stress) or recovery (40-min post-stress) saliva samples. Conversely, post-pubertal youths with current MDD evidenced stronger reactivity to the task than did comparison youths. Intriguingly, in a parallel analysis of children and youths with remitted MDD, no differences from the comparison groups were noted.

Given the limited literature on response to psychological stressors in depressed children and adolescents, perspective is gained from examining studies of cortisol reactivity in children and adolescents with subclinical levels of depression (Gunnar et al. [2009b]; Hankin et al. [2010]; Klimes-Dougan et al. [2001]; Natsuaki et al. [2009]). HPA reactivity to TSST procedures was examined by Klimes-Dougan et al. ([2001]; Natsuaki et al. [2009]) with a large sample of 11- to 16-year-old youths with elevated internalizing and externalizing problems and by Gunnar et al. ([2009b]) with unselected participants aged 9–13 years. In the former study, older adolescent boys showed the strongest reactivity to the task, but it was only for adolescent girls that having a stronger reaction to the TSST (larger increase in cortisol from pre-task to 20-min post-task samples) was associated with having more internalizing problems (Klimes-Dougan et al. [2001]). In subsequent analyses, youths with early pubertal maturation were found to have more internalizing problems, and again for girls only, stronger HPA reactivity to the TSST mediated the association between early pubertal maturation and internalizing problems (Natsuaki et al. [2009]). Thus, adolescent girls, and particularly early-maturing girls, appear to show heightened physiological reactivity to interpersonal stressors that might increase their risk for developing depression-related problems.

Analogous findings were reported by Gunnar et al. ([2009b]), who noted a developmental increase in cortisol reactivity to psychosocial stress from childhood to adolescence and found that girls with greater post-TSST cortisol reactivity had more anxious and depressive symptoms. Together, these findings of gender differences in the links between HPA axis response to psychological stressors and severity of affective problems echo other literature that has hypothesized that HPA dysregulation might function as one mechanism underlying sex differences in depression (Stroud et al. [2000], [2002], [2004], [2009]; Zhan-Waxler et al. [2008]).

Finally, in addition to studying pediatric depression, Hankin et al. ([2010]) examined HPA reactivity to interpersonal psychosocial stressors in a large sample of children in preschool, third grade, sixth grade, and ninth grade with elevated, but non-clinical, dysphoria. They distinguished subclinical dysphoric children from children with low negative affect, measured temperament and recent stressful life events and, in the three older groups, assessed pubertal maturation. The dysphoric preschoolers and third-graders did not show cortisol increases to the stressors, whereas the non-dysphoric children had significant cortisol elevations. No group differences were evident for sixth-graders, but the dysphoric youths in ninth grade showed stronger cortisol elevations than did the non-dysphoric youths. Group differences in temperament and life stressors could not account for these findings, but pubertal maturation explained the age effects. Regardless of puberty, non-dysphoric children and youth showed the expected pattern of moderate HPA reactivity, whereas prepubertal dysphoric children were relatively hyporesponsive and post-pubertal dysphoric children were relatively hyper-reactive.

Studies of Children of Depressed Parents

Studies have provided consistent evidence that the offspring of depressed parents are themselves at increased risk for developing depression (Beardslee et al. [1993]; Downey and Coyne [1990]; Nomura et al. [2002]; Weissman et al. [1986]). This possibly reflects a genetic component of susceptibility to depression, alterations to the fetal environment (such as more cortisol crossing the placental barrier in depressed mothers), and in the postnatal period, deviations from appropriate and effective child-rearing by depressed parents that interfere with children's healthy emotional development. All of these mechanisms also could affect children's HPA regulation, and researchers have begun to

examine HPA axis activity in children of depressed mothers. Should the children of depressed parents demonstrate adrenocortical dysregulation prior to evidencing their own depressive symptoms, this could be taken as further evidence that atypical HPA axis activity is a precursor of, and possibly contributing factor to, pediatric depression.

There have been 13 papers that specifically examined the relations between parental depression and cortisol levels in offspring, with children ranging in age from neonates through young adults (Ashman et al. 2002; Brennan et al. 2008; Diego et al. 2004; Dougherty et al. 2009; Essex et al. 2002; Feldman et al. 2009; Field et al. 2004, 2010; Halligan et al. 2004, 2007; Lundy et al. 1999; Mannie et al. 2007; Young et al. 2006). Most studies included only depressed mothers, although some included both depressed mothers and depressed fathers. All of the papers included non-depressed comparison families and, strikingly, all of the investigations identified elevated cortisol levels in one or more measures of HPA axis activity in the offspring of depressed parents.

For example, in several reports, Field and her colleagues (2004, 2010; Diego et al. 2004; Lundy et al. 1999) have found that young infants of mothers with pre- or postpartum depression have elevated urinary cortisol levels, relative to infants of anxious mothers or mothers without psychopathology. Similarly, Brennan et al. (2008) examined salivary cortisol levels at baseline and in reaction to psychosocial stressors in 6-month-old infants of mothers who had depression before they were pregnant, during pregnancy, or in the postnatal period. They found that, relative to infants of mothers without depression, there were elevated basal cortisol levels in the infants of mothers with perinatal or postnatal depression. Infants of mothers who had experienced depression only prior to conception did not differ from infants of non-depressed mothers, suggesting that genetic transference of risk for depression alone cannot account for the elevated cortisol levels in offspring. Although Brennan et al. (2008) did not find differences for HPA reactivity, Feldman et al. (2009) did. They reported that 9-month-old infants of depressed mothers had greater elevations in cortisol in response to a fear-induction paradigm than did infants of mothers without psychopathology.

Several of the studies of children and youths included measurements of family functioning, stressful life events, temperament or personality, and similar factors to determine whether these accounted for differences in cortisol levels between depressed and non-depressed groups. For example, Halligan et al. (2004) examined morning and evening cortisol levels in 13-year-old children of mothers with postnatal depression. These children had higher and more variable morning cortisol levels over 10 days, compared with children of mothers without depression. This could not be accounted for by mothers' concurrent depression, marital conflict, life events, and numerous other factors. When these youths were seen again 3 years later, Halligan et al. (2007) found that elevated and variable morning cortisol levels at 13 years predicted more symptoms of depression in the youths at 16 years. Their earlier cortisol levels also mediated the association between maternal postnatal depression and youths' depression, suggesting that adverse effects of maternal depression in infancy on the development of HPA regulation might be a mechanism for the intergenerational transmission of depression.

It is not clear that disruptions to the diurnal rhythm of basal HPA activity in the children of depressed parents are specific to the morning period, however. As did Halligan et al. (2004), Dougherty et al. (2009) found that preschool-aged children of mothers with melancholic depression had elevated morning, but not evening, cortisol levels. Mannie et al. (2007) similarly found that young adults with depressed parents had higher waking cortisol levels than young adults without depressed parents; cortisol levels were not related to the offsprings' own mental states. Essex et al. (2002), however, found that preschoolers with mothers who had both postnatal and concurrent depression had higher afternoon basal cortisol levels than children of mothers without depression or only with concurrent depression. Young et al. (2006) also found that children of depressed parents had higher cortisol levels at bedtime, but not earlier in the day, compared with children of parents without depression. The children of depressed parents also were less responsive to the DST, evidencing higher waking and afternoon cortisol levels the day after receiving dexamethasone.

Conversely, maternal depression during infancy was unrelated to morning, evening, or reactive cortisol levels in 7- to 8-year-old children in a study by Ashman et al. (2002). This was despite the authors' finding that at an earlier assessment, when children were 3 years old, there was an association between maternal depression and children's basal cortisol levels (Hessl et al. 1996, as reported in Ashman et al. 2002). At the school-age assessment, though, the children of depressed mothers had higher pre-stress baseline cortisol levels, and both their baseline and reactive cortisol levels were associated with the children's internalizing problems.

Considered together, these studies present singularly consistent evidence that parental depression, and particularly maternal depression in the prenatal and postnatal periods, is associated with atypical HPA axis functioning in offspring. This is evidenced across developmental periods and principally in disruptions to basal cortisol levels. Other factors associated with parental depression, such as

stressful life events, do not appear to account for the effects, and the offsprings' elevated cortisol levels are apparent prior to there being evidence that they are experiencing depression. Yet in the two samples that were followed longitudinally (Ashman et al. 2002; Halligan et al. 2007), HPA dysregulation appeared to set the stage for the emergence of mental health problems in the offspring of depressed parents.

Synthesis and Conclusions

Important, if preliminary, observations can be offered from this review of the emerging body of literature examining various components of HPA axis functioning among depressed children and adolescents. The principal conclusion, drawing from a number of experimental approaches and findings, is that there is good evidence that HPA dysfunction plays a role in depressive syndromes in populations of young people. First, this conclusion derives from the broad similarity of findings from studies in young populations with the results observed in research with adults. Studies of the dexamethasone suppression test (DST) in pediatric depressed samples have revealed robust rates of cortisol non-suppression that are comparable to those found in studies of depressed adults. These data suggest that at least some forms of child and adolescent depression are characterized by abnormal stress system functioning (i.e., cortisol hypersecretion) through inadequate responsiveness of the HPA axis to physiological negative feedback. Moreover, the pediatric DST data appear to mirror adult findings of greater HPA axis dysregulation associated with inpatient when compared with outpatient status. It is likely that inpatient status serves as a proxy for more serious depressive symptomatology, heightened stress exposure, or a combination of both factors. Second, early evidence for a similar symptom and/or stress dose–response pattern has been found in investigations examining cortisol response to corticotropin-releasing hormone (CRH) challenge among depressed young people. Careful research is needed to disentangle these associations by systematically controlling for the severity of depression and/or the environmental context of stress.

Third, results from research assessing basal HPA axis functioning and diurnal variation among child and adolescent samples show some continuity with corresponding work in adults. On the whole, the evidence supports a developmental pattern in which basal HPA axis dysfunction becomes increasingly associated with pediatric depression with advancing age. Further, emerging longitudinal research provides strong evidence that overall dysregulated basal HPA activity precedes and predicts the development of depression in adolescence and early

adulthood. Consistent with the conclusion made by Lopez-Duran et al. (2009), this does not appear to be due to dysregulation at any specific part of the diurnal rhythm. Rather, depressed children and youth manifest slightly elevated circulating cortisol levels across the diurnal cycle. Nonetheless, future work with depressed young people will gain power from the collection of larger samples sizes, which may allow for the detection of more subtle changes across various indices of basal and/or diurnal variation during this developmental period.

Fourth, initial evidence supports the observation that depressed children and adolescents demonstrate increasing cortisol hyper-reactivity with age in response to developmentally appropriate psychological stressors. Indeed, relative to non-depressed controls, all of the germane studies reported significantly elevated cortisol levels subsequent to acute psychosocial stress induction in depressed children and adolescents. These results may also point to the primary importance of abnormalities in the functions of brain regions involved in processing or evaluating stressful events and affective information (i.e., prefrontal cortex, limbic system). Such abnormalities suggest a neuropathological mechanism of initial stress system dysregulation among at least some depressed young people. This still untapped area represents an important direction for future multidisciplinary research with depressed children and adolescents.

Fifth, studies that have examined HPA axis functioning in asymptomatic children and adolescents of depressed parents provide consistent evidence that parental depression, and particularly maternal depression, is associated with elevated HPA axis functioning in offspring. This finding has been observed across developmental periods and appears to be principally manifested by disruptions to basal cortisol functioning, which might precede the onset of symptoms of depression. Interestingly, this HPA dysregulation in offspring tends to be associated with maternal depression occurring during the prenatal and postnatal periods rather than with a history of maternal depression prior to conception. This pattern of results, together with the scarce longitudinal data available, suggests that genetic risk for depression alone cannot account for the elevated cortisol levels in offspring and provides further evidence that HPA axis dysregulation precedes and predicts the development of depression in young people.

The second principal conclusion that can be drawn from investigations of HPA axis functioning in pediatric depression is the centrality of a developmental perspective. Children and adolescents are not just small adults. The findings of the reviewed studies of the functions of young subjects' HPA axis diverge in important ways and/or degrees from those conducted with depressed adults. For instance, relative to their adult counterparts, depressed

young people appear to have somewhat lower rates of cortisol non-suppression following the DST. Additionally, in contrast to the adult data, there were generally smaller differences between depressed children and adolescents and control participants on such HPA indices as overall basal cortisol secretion and natural diurnal variation, as well as cortisol and ACTH secretion following the administration of the CRH challenge. This normative cortisol response to CRH infusion among depressed young people suggests intact hypothalamic and/or adrenal sensitivity to CRH. This could suggest that any HPA axis dysregulation among depressed young people may be due to "upstream" factors that affect production of CRH by the hypothalamus. Above all, there is a pressing need for research aimed at identifying these and other possible mechanisms of HPA axis dysfunction among depressed young people.

Two broad conclusions emerge from developmentally oriented research examining HPA axis irregularities associated with child and adolescent depression. First, the differences in HPA axis functioning that exist among depressed young people relative to non-depressed individuals appear to be smaller in scale than those found between their adult counterparts, but these disruptions to normative HPA axis functioning might emerge prior to evidence of symptoms of depression. Second, differences in HPA axis functioning are found most consistently and prominently in the context of increased exposure to psychological stress, whether that is a brief, acute stress (e.g., laboratory-based stress induction) or a chronic and pervasive stress (e.g., being raised in the context of maternal depression).

The ostensible discontinuities between the data on the HPA axis in pediatric populations and those more consistent and pronounced findings from adult depression literature may reflect important developmentally associated patterns. Rather than a simple dichotomous transition from absence to presence of HPA axis dysregulation when one compares child versus adult manifestations of depression, the consideration of longitudinal data across developmental periods suggests more subtle, progressive changes in HPA axis functioning. Indeed, research conducted with depressed adults has found a positive correlation between age and basal cortisol hypersecretion (Asnis et al. 1981; Halbreich et al. 1984). Other cross-sectional studies—which have included samples of participants ranging from infancy to adulthood— have also supported the possibility of a developmental increase in cortisol levels over the pubertal and especially post-pubertal periods in adolescence (Kenny et al. 1966; Kiess et al. 1995). Although longitudinal evidence is exceedingly scarce, Shirtcliff et al. (2005) found that yearly increases in cortisol in a sample of 6- to 13-year-olds predicted increases in internalizing symptoms over this time period.

There is a pressing need for more prospective, longitudinal research to determine whether developmental changes in HPA functioning could account in part for the dramatic increases in the rates of depression from childhood to adolescence. As well, by more firmly establishing the temporal aspects of HPA axis/stress system dysfunction, it may be determined whether this vulnerability can be better characterized at various times throughout development as a correlate, cause, or consequence of depression. In other words, it needs to be more clearly explicated whether, when, and how the HPA axis dysregulation associated with depression may serve as (1) a "trait marker" (i.e., a pre-existing biological vulnerability to the development of depression that remains present regardless of disease status); (2) a "state marker" (i.e., a transient, disease-specific biological change that occurs concurrently or as a consequence of depression); or (3) a "scar marker" (i.e., a potentially longstanding pathophysiological consequence of the disorder, not evident before first onset of a depressive episode; Dahl and Ryan 1996).

Regrettably, a salient omission from the extant pediatric literature is information related to stage of illness (i.e., number of depressive episodes, total duration of illness). It is possible that the observed differences from adult studies may be primarily attributable to systematically differences in the proportion of depressed patients experiencing recurrent as opposed to first-onset episodes of the disorder. Accordingly, it will be critical for future work to consider the relative contribution of developmental changes in neurobiology (e.g., altered neurotransmitter activity and connectivity, onset of pubertal hormones), as well as the recurrence of disorder in accounting for the progressive HPA axis dysregulation associated with depression across the lifespan.

Finally, given the robust and troubling gender differences in the rates of depression that also emerge in the context of the transition from childhood to adolescence, it will be essential to further examine gender differences in stress system functioning. It is reasonable to hypothesize that patterns of hyper-reactive HPA axis functioning are more pronounced and/or have qualitatively different psychosocial triggers for adolescent girls than those for boys (e.g., Stroud et al. 2009). This notion is supported by the emerging empirical work indicating that adolescent girls, and particularly early-maturing girls, without a history of depression exhibit heightened HPA axis reactivity to interpersonal stressors. Although this research requires replication, these findings closely parallel earlier work using subjective measures of stress response. For example, it has been suggested that the greater prevalence of depression in adolescent girls when compared with boys may be at least partially explained by girls' more frequent exposure and heightened self-reported reactivity to

interpersonally themed stressors (e.g., Hankin et al. 2007; Rudolph 2002). Similarly, there is a critical need for additional investigations that utilize a developmental psychopathology perspective to determine whether and how aberrant physiological stress system reactions may interact with other, possibly gender-specific sources of physiological, psychological, cognitive, and social vulnerabilities.

Multidisciplinary, methodologically rigorous (particularly with respect to subject selection, power, and the nature and timing of biological sampling) and longitudinal research designs are needed to further elucidate the role of the HPA axis in depression, as well as likely transactions between biological and psychological stress system functioning across development. For example, future prospective research might benefit from the examination of possible HPA axis changes associated with certain cognitive vulnerabilities to depression (e.g., a depressogenic attributional style for negative life events) in high-risk individuals. Another future avenue of investigation might utilize an epidemiological approach incorporating psychological, neurological, and endocrinological measures in depressed, high-risk, and control samples.

There are four salient conclusions from the present review. First, the extant research clearly supports the presence of HPA dysregulation in pediatric depression, and it appears this association strengthens with age. Second, based on studies examining the DST among depressed samples of children and adolescents, pediatric depression may involve particular disruption to higher regulatory (inhibitory) autofeedback. Third, available data suggest that HPA dysregulation may precede and predict the onset of depression in individuals, regardless of age. Fourth and finally, HPA dysregulation is evident in acute stress responses and might result from exposure to chronic early stressors or perturbations to normal infant care experiences. Although adopting a developmental psychopathology perspective has helped to shed light on the ontogenesis of the relation between HPA axis function and depression, continued child clinical research is needed to further this understanding with the aim of informing diagnosis, prognostication, and intervention.

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