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Developmental influences on stress response systems: Implications for psychopathology vulnerability in adolescence

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ABSTRACT

The adolescent transition is marked by increases in stress exposure and significant maturation of neural and hormonal stress processing systems. Variability in the development of these systems during adolescence may influence the risk for stress-related psychopathology. This paper aims to review the developmental maturation of the HPA axis and related stress regulation systems, and demonstrate how interference in this adaptive developmental process may increase the risk for negative outcomes. We argue that the developmental maturation of the HPA axis aims to improve the regulatory capacity of the axis in order to more adaptively respond to these increases in stress reactivity. Additionally, we review evidence that sex differences in the development of the HPA and related axes may contribute to sex differences in the risk for stress-related psychopathology. Finally, we discuss how contextual factors, such as early trauma and obesity may alter the development of HPA axis during the adolescence transition and how alterations of normative development increase the risk for stress-related disorders.

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1. Introduction

The adolescent transition involves complex developmental changes in neural and hormonal stress processing systems [1,2]. The period is also characterized by significant increases in stress [3] as a function of increased academic [4,5], social, and family demands [6]. Most adolescents are able to cope with these stressors, and "survive" this transition without developing any major mental health disorders [7]. Therefore, changes in stress regulation systems during this developmental period are likely adaptive to facilitate stress coping [8]. However, there is also an acceleration of the incidence of stress-related psychopathology during adolescence [9], which suggests that many adolescents are at elevated risk. Here, we explore how risk for stress-related disorders in some adolescents may emerge as the result of atypical development of stress processing systems. To this end, we review findings related to developmental changes in key neuroendocrine networks during adolescence, including the Hypothalamus-Pituitary-Adrenal axis (HPA axis) and the Hypothalamus-Pituitary-Gonadal axis (HPG axis), the contextual factors that may alter normal development (e.g., stress), and how deviation from typical development may influence risk for stress-related psychopathology.

2. The HPA axis

Given that the adolescent period is associated with increased stress exposure, individual differences in stress coping may contribute to the elevated risk for psychopathology observed in some adolescents. As the body's primary stress processing system, the HPA axis is responsible for a number of adaptive biological responses to stressors, including the mobilization of energy stores, increasing cardiovascular tone, and temporarily inhibiting non-essential functions such as growth, immune function, and reproduction [8,10]. Activation of the HPA axis also leads to enhanced cognition and metabolism, promoting the fight or flight response and the formation of memories that shape future behavioral and physiological responses to stressors [2,10]. Although the HPA axis activates to a number of stressors such as pain [11], exercise [12], and restraint [13,14], the most reliable stressors are those that are perceived as uncontrollable and a threat to one's physical or social self (i.e., socially-evaluative threat; [15]). These types of psychosocial stressors are also strongly related to increased risk for psychopathology [16–18] and thus the HPA axis response to psychosocial stressors has been a key focus of study for researchers interested in neuroendocrine functioning in stress-related psychopathology. Therefore, unless otherwise specified, conclusions about 'stress' in this review refer to the psychosocial stressors rather than physical stressors.

Activation and recovery of the HPA axis are regulated by a complex interplay of neural and hormonal processes that follow a well-characterized developmental trajectory. The HPA axis response begins with excitatory signals from cortical and deep brain regions [19] that stimulate neurons within the paraventricular nucleus (PVN) of the

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hypothalamus [10]. The PVN then releases corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) which act on receptors within the anterior pituitary to release adrenocorticotropin hormone (ACTH; [20,21]). ACTH then travels through the blood-brain barrier and bloodstream and binds to receptors within the *zona fasciculata* of the adrenal cortex, leading to the synthesis and release of cortisol. In response to stress, cortisol levels increase rapidly, peaking generally about 20–40 min after stressor onset, and then decrease back to basal levels [15] although peak latency may vary as a function of age [22], sex [23], and other psychosocial factors [24–26].

Cortisol contributes to its own regulation by binding to mineralocorticoid (MR) and glucocorticoid receptors (GR) throughout the hypothalamus, pituitary, medial prefrontal cortex, and hippocampus, which either up or down-regulates the subsequent production of glucocorticoids [21,27]. MRs demonstrate high sensitivity for cortisol and thus are activated by low levels of cortisol observed in non-stressful situations (i.e., basal levels) and are saturated when cortisol levels increase in response to stress or during the post-awakening response. In contrast, GRs exhibit lower sensitivity to cortisol and are activated when MR receptors are saturated and thus play a key role in down regulation of the HPA axis stress response [2,27]. Activation of GR and MR result in positively or negatively regulating gene transcription [27,28]. This negative feedback mechanism is central to maintaining homeostatic balance during both basal and stress-responsive conditions [10]. Recent research suggests that negative feedback occurs rapidly, within minutes, highlighting the need for fast acting, non-genomic mechanisms in HPA axis regulation [29]. Non-genomic down-regulation occurs at the level of the CNS when glucocorticoids bind to receptors on PVN CRH neurons, leading to the production of endocannabinoids [30]. The release of endocannabinoids appears to inhibit glutamate release and reduce the activity of the parvocellular neurons, inhibiting the HPA axis response [27]. This fast-acting negative feedback mechanism permits the rapid down-regulation of the HPA axis and return to homeostasis after stress exposure.

Finally, cortisol levels also vary according to a diurnal pattern, implicating both time of day and context as important factors for consideration when investigating cortisol levels. Over the course of the day, cortisol levels peak during the first 30–45 min post-awakening, known as the cortisol awakening response (CAR: [31,32]), and then decrease gradually over the course of the day, reaching their lowest point in the afternoon and evenings [33,34]. CAR and diurnal cortisol levels show significant sex differences. Studies in adults suggest that men exhibit flatter CAR [35] and women demonstrate a more sustained CAR [36]. Cortisol levels also appear to vary as a function of age, with younger children and early adolescents exhibiting smaller CAR compared to adults. Adolescent females demonstrate greater CAR [37,38], mid-day, and afternoon [39,40] cortisol levels compared to adolescent males but not greater evening levels [38]. In conclusion, the HPA axis utilizes a complex interplay of neural and hormonal systems in order to release cortisol and respond to the demands of the environment. Interference at any point within this complex system may lead to deficits in stress coping that may impact an individual's risk for stress-related psychopathology.

2.1. Adolescent development and the HPA axis

The HPA axis undergoes significant changes during the adolescent transition that may serve to protect the individual from increases in environmental demands and stress [8]. In general, studies suggest that adolescents demonstrate greater HPA axis activity compared to younger children. For example, older adolescents tend to have a greater CAR [37] and higher overall cortisol levels throughout the day [41–43]. Regarding stress reactivity to laboratory task, there is some variability in findings with some studies finding an age effect only in anticipation of the stressor [44], while other studies observed greater cortisol levels during both activation and recovery to stressors [41,45–48].

Research suggests that adolescence begins around age 10 and ends around age 18 [49], although some literature proposes that adolescence may last until age 26 [50]. However, developmental changes in HPA axis reactivity appear to be better predicted by pubertal status rather than age [48]. Pubertal maturation has been shown to be positively associated with increases in cortisol secretion following a corticotropic releasing hormone challenge [47], a psychosocial stress task [41], and in response to a novel social setting [51]. Females enter puberty 1–2 years prior to adolescent males [52,53], therefore developmental changes to stress processing systems may occur earlier for females. In support of this claim, developmental increases in HPA axis stress reactivity were observed for females between ages 11 and 13 years, whereas parallel increases in males began during ages 13 to 15 years [41].

Sex differences in HPA axis activity appear to emerge during puberty [41,54–56], indicating that sex may moderate the association between pubertal status and HPA axis reactivity. While some studies suggest that adolescent boys may show greater HPA axis reactivity to stressors compared to adolescent girls [39,57], others support higher reactivity for girls [41,45,55]. Some researchers propose that the observed developmental increase in cortisol stress reactivity may be specific to males [245]. Overall, studies in post-pubertal adolescents support greater stress reactive cortisol levels for males compared to females (for review see [54]). These findings are in line with the adult literature in which males exhibit greater stress reactivity than females [23,58]. Variable findings may reflect differences in stress processing and coping among men and women. Men perceive intellectual and performance failures as more stressful and are more likely to exhibit a more traditional 'fight or flight' reaction [59]. In contrast, women perceive social rejection as more threatening [60] and tend to respond to stress with a 'tend and befriend' response that includes nurturing and creating social networks [61,62]. Therefore, females may exhibit greater negative affect and perceive social stressors as more threatening, possibly leading to greater cortisol reactivity to socially evaluative stressors [60]. A meta-analysis by Ordaz & Luna [54] concluded that adolescent females respond to social stressors with more negative affect and greater neural reactivity than males, however, this greater subjective response did not predict greater HPA axis reactivity compared to males. It is possible that sex differences may be better explained by differences in the availability of sex hormones that regulate HPA axis functioning, as will be proposed later in this review.

This developmental increase in HPA axis functioning has been interpreted as reflecting greater sensitivity of the axis given the increased demands of adolescence [46,48]. However, it is possible that these findings do not reflect a sensitization of the axis but instead reflect expected increases in HPA activation due to changes in important contextual stressors. First, most laboratory stressors finding greater stress responses in adolescents have used the Trier Social Stress Task [63], which utilizes social evaluation as its main trigger for the HPA axis response. Although the TSST has been shown to be effective in children [64], there are well established developmental differences in the influence of peers and social evaluation, such that fear of peer evaluation increases significantly during the adolescence transition [48,65]. Thus, the observed increases in cortisol responses to stressors may not be due to developmental changes in the HPA axis but to changes in social evaluation that may make laboratory stressors more stressful during the adolescent period. Furthermore, adolescence is marked by increases in social and academic demands that may lead to more chronic activation of the axis, which may explain the observed elevation in afternoon and evening samples [46]. Finally, on-going development of cortical-limbic attentional and emotion processing systems may contribute to the heightened self-perceptions of stress during the TSST reported by children transitioning into adolescence compared to younger children [47,48,66–68]. Taken together, research suggesting increased reactivity of the HPA axis in adolescence likely reflects a heightened sensitivity to the social evaluative components of the stress task and more chronic activation of the axis as a function of increased stress exposure.

From an evolutionary perspective, increasing sensitivity of the HPA axis during a time of increased stressors would not be adaptive as this could lead to chronic hyper-responsivity that might have significant negative consequences given our understanding of the detrimental effects of excess cortisol exposure [69,70]. Instead, the more adaptive pattern would be a down-regulation of the axis during adolescence to adapt to the increased stressors associated with this developmental transition. Data from animal models support this hypothesis. Across a variety of stressors, pre-pubertal rats display a more prolonged HPA axis response when compared to post-pubertal rats [71], suggesting improved recovery of the HPA axis post-puberty. In addition, adult rats show greater habituation to repeated stressors whereas pre-pubertal animals demonstrate sensitized ACTH and corticosterone responses when repeatedly confronted with the same stressor [72,73]. It has been suggested that the prolonged release of corticosterone prepuberty may reflect the incomplete maturation of negative feedback systems [74–76]. Prolific neural development occurs during puberty and adolescence. In animals, prefrontal cortical regions demonstrate significant development during adolescence [77,78]. Studies of both humans and animals, have identified increases in hippocampal and amygdala volume during the early stages of puberty (see [79] for review). In longitudinal studies, frontal and cortical volume increases from childhood to the onset of puberty and then decreases through adolescence and young adulthood as a result of synaptic pruning and programmed cell death [1,79]. While the nature of this cortical thinning is unclear [80], it has been suggested that these alterations may be associated with adolescent-related adaptive changes in psychological, emotional, and cognitive functioning [81,82].

This pruning may also lead to maturation of brain regions that have inhibitory projections to the HPA axis, including the hippocampus, prefrontal cortex (PFC), medial amygdala, and lateral septum [2]. Rather than acting directly on the PVN of the hypothalamus, these systems project to the bed nucleus of the stria terminalis (BnST), which have direct GABAergic input to the PVN [83,84]. For example, lesion studies have demonstrated the projections from the BnST inhibit CRH mRNA levels and corticosterone responses to stress [85,86]. This suggests that increased regulatory capacity of the HPA axis during adolescence is not only due to increase GR-mediated negative feedback, but to maturation of neural systems that play an inhibitory role on the HPA axis.

Developmental changes have also been observed in the dorsal raphe nucleus and ventral tegmental areas, regions that modulate stress sensitivity by projecting to the PFC and nucleus accumbens [1]. Within these regions, CRH mRNA expression increases across childhood development peaking in early adolescence [87]. Adolescent females demonstrate significantly greater CRH receptor expression, potentially underlying sex differences in stress reactivity observed in adolescence [1,54]. Therefore, maturation of neural systems during the adolescent transition differs between males and females, contributing to sex differences in stress responsivity.

In conclusion, the HPA axis system acts on neural and peripheral systems to mobilize energy resources and prepare the body to cope with the demands of the environment. During adolescence and puberty, extensive maturation of neural networks improves HPA axis negative feedback loops, leading to shorter duration of HPA axis responses and improved stress response habituation during late adolescence and adulthood. This view of a *better regulated HPA axis* in adolescence is contrary to findings comparing children and teens. Yet, we argue that such elevations in cortisol observed in adolescence reflect increased stress exposure and sensitivity to social evaluation, and thus occur despite, not because, the developmental changes that make the axis more restrained in its response to stress.

3. DHEA

While the majority of research on stress processing has focused on cortisol, the most abundant hormones regulated by the HPA axis are dehydroepiandrosterone (DHEA) and its sulfate form, dehydroepiandrosterone sulfate (DHEA-S). DHEA has significant anti-glucocorticoid properties and therefore play important roles in stress processing, obesity, and immunity [88–90]. DHEA also serves as a precursor for sex hormones and regulates luteinizing hormones, suggesting that it plays an important role in pubertal development and reproduction [91,92]. Not surprisingly, there are marked age and sex differences in DHEA levels, highlighting the importance of considering the effect of these hormones when studying the adolescent transition [8]. The availability of DHEA-S serves as reservoir for DHEA and has a long half-life and slower clearance rate [93]. Given that DHEA is only biologically active in its unsulfated form [89], the current review focuses solely on DHEA (for more information on DHEA-S see [89,91,94,95] among others).

DHEA is primarily released from the adrenal in response to ACTH after HPA axis activation and thus DHEA increases in response to stress in parallel with cortisol [89,91]. Unlike cortisol however, which is released upon stimulation of the *zona fasciculata* of the adrenal, DHEA is released by the *zona reticularis* [8]. Upon release, DHEA has strong regulatory influence on the HPA through multiple pathways. DHEA appears to have direct down-regulatory impact on corticoid receptors [88,89] and emotion regulation neurocircuitry (e.g., amygdala connectivity, [96]), and facilitates behavioral activation associated with stress coping [97]. In addition, DHEA has strong neuroprotective effects. For example, exogenous administration of DHEA to laboratory animals decreased the neurotoxic effects of cortisol on the hippocampus [98,99]. In humans, DHEA attenuated the negative impact of high cortisol on episodic memory in older and young adult males [100,101] and greater stress reactive DHEA levels were associated with improved decision-making competence [102]. In a study of depressed adults prescribed SSRIs, high levels of circulating DHEA prior to beginning the medication predicted greater likelihood for remission 8 weeks later [103]. Finally, attenuated DHEA levels in response to the TSST were associated with greater depression severity [93]. Thus, individual differences in DHEA availability during the adolescent transition may contribute to the variability in adaptive stress responding and associated risk for stress-related disorders observed during this time.

3.1. Adolescent development and DHEA

During adrenarche, ages 6–7 years for females or 8–9 years for males, the androgen-producing *zona reticularis* expands, leading to an increase in the production of DHEA [92,104–106]. This surge in DHEA levels marks the first sign of puberty and continues to rise throughout adolescence, reaching a peak at 25–30 years of age [89,107,108]. Coupling, or the parallel release of DHEA and cortisol, was found to increase from age 11 to age 15 [109]. Older adolescents displayed tighter coupling of cortisol and DHEA in response to psychosocial stressors and these findings were greater in boys compared to girls [110]. This increase in coupling was influenced by age, but not pubertal maturation, suggesting that alternative developmental markers, such as social changes or brain maturation as a result of the adolescent transition may offer a better explanation for this shift than pubertal development [110]. This coupling is primarily a function of increased sensitivity of the *zona reticularis* to ACTH, leading to increased DHEA release in response to stress. This could contribute to the improved HPA regulation observed in post-pubertal animals [71,72]. This expansion of the *zona reticularis*, and the developmental changes in gonadal steroids discussed below, can also result in progressively increasing DHEA to cortisol ratios as children undergo puberty and beyond. All in all, the developmental pattern observed in DHEA is consistent with a picture of a progressively more mature HPA axis as individuals enter and transition through adolescence, highlighting that in typical development, changes in DHEA and HPA axis serve as a protective rather than a putative factor to stress-related psychopathology.

3.2. DHEA/cortisol ratios

Given their shared stimulation by ACTH, secreted levels of cortisol and DHEA should be proportionate in the context of normative axis

functioning. There is likely an adaptive balance of the proportion of DHEA to cortisol release in response to stress and atypical variation from such adaptive balance may signal dysfunction within the axis. For example, low DHEA to cortisol ratios may signal low availability of DHEA to counteract the negative effects of cortisol [8] and thus may be an indication of risk. Accordingly, low DHEA/CORT ratios have been linked to worse prognosis in depressed adults [111] and elevated risk for depression onset in adolescents [112]. Alternatively, low ratios may signal poor adrenal sensitivity to ACTH in the *zona fasciculata* resulting in low cortisol production that may also lead to increased risk. In fact, higher DHEA/CORT ratios reflecting blunted cortisol have been found in females with PTSD [113]. To the extent that DHEA and cortisol have different developmental trajectories, then the examination of DHEA/CORT ratios during the adolescence transition can provide another window into the adaptive changes of the HPA axis throughout development.

4. The HPG-axis

The Hypothalamus-Pituitary-Gonadal (HPG axis) regulates sex hormone production and release, therefore playing a major role in maturation, puberty, reproduction, immune function, and social behaviors including approach, dominance, leadership, and aggression [114–116]. Within the HPG axis, developmental changes associated with puberty result in gonadal maturation and sex-specific functions. For instance, testosterone secretion leads to increased sexual motivation and copulatory behaviors [117–119], promoting typical male reproductive behaviors. On the other hand, estradiol and progesterone release in females signal readiness to mate and the likelihood of becoming pregnant by increasing proceptive and receptive behaviors [120–122]. However, the HPG axis also has strong interconnections with the HPA axis and plays an important role in facilitating the organism's adaptation to stressful situations, especially during the pubertal transition and adolescence [123].

Activation of the HPG axis begins with innervation of gonadotropin-releasing hormone (GnRH), a decapeptide produced by specialized neurons from nerve terminals in the median eminence of the basal hypothalamus [124]. GnRH acts on gonadotropes of the anterior pituitary to stimulate the release of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH; [10]). Circulating LH stimulates the gonads to secrete steroid hormones. LH and FSH act on cells within the testes and ovaries to drive production of sperm and eggs and secrete testosterone and estrogen [10,124]. Testosterone and estrogen, in turn, regulate GnRH secretion at the level of the brain by binding to gonadal steroid receptors and contributing to negative feedback loops [124].

Testosterone is also believed to have an inhibitory impact on HPA functioning as evidenced by increases in HPA basal and stress responsivity after gonadectomy [10,125]. In humans, males appear to show greater ACTH responses to the Trier Social Stress Test [126,127]. There is evidence that sex differences in HPA stress response are highly sensitive to the type of stressor with males reacting stronger to achievement stressors while females reacting more to social rejection [60]. However, in studies directly probing the HPA using exogenous ovine CRH, adolescent males show elevated ACTH response [128], but surprisingly, this effect is reversed in older samples [129].

The higher ACTH response but similar plasma cortisol in males compared to females suggests increased hypothalamic drive in males (leading to more ACTH) but potentially reduced adrenal sensitivity (leading to equal cortisol). This is consistent with a proposed dual but opposite effect of testosterone at various levels of the HPA axis. Specifically, estradiol has been consistently found to have an excitatory effect on the central drive of the HPA [123]. In males, testosterone is first converted to estradiol prior to exerting a neuroactive role in the brain [130]. The greater availability of testosterone in males would result in greater excitatory impact of estradiol on the brain. However, there is evidence that testosterone also has a blunting effect at the level of the adrenal [131], which would explain the reduced cortisol production in response to DHEA. Despite this dual role, the effect of gonadectomy [125,132,133] suggests that the overall combined effect of testosterone in *inhibitory* because the complete absence of testosterone increases HPA activity.

4.1. Adolescent development and the HPG axis

The influence of gonadal hormones on puberty originates during a sensitive period in early life. In late prenatal and early postnatal life, periodic activation of the HPG axis results in increased circulating gonadal steroids, which influence sexual differentiation and other critical nervous system programming [124]. After this initial increase in early life, GnRH pulse frequency slows to discharge only once every few hours and continues in this fashion throughout the pre-pubertal stage [124]. Puberty officially begins in response to a number of permissive signals that lead to significant increases in GnRH secretion and marked elevations in testosterone and estrogen [124,134,135]. Increases in sex hormones continue past the pubertal period and into adolescence contributing to a number of sex-specific behaviors across a variety of domains including reproduction, social affiliation, competition and dominance [136,137]. Testosterone specifically increases dramatically during the pubertal transition in both males and females and peaks in the teen years, coinciding with traditional conceptualizations of adolescence [138].

Given the inhibitory impact of testosterone on the HPA axis, drastic increases in testosterone during the pubertal and adolescent transition would also lead to an increase in the regulatory capacity of the axis despite potentially greater ACTH release [128]. This would be consistent with our view of adolescence as a time of improved HPA axis regulation. Further, sex differences in estradiol and testosterone during this period could also explain observed sex differences in regulatory capacity. For example, early pubertal timing has been associated with increased cortisol reactivity in girls and this enhanced reactivity, in turn, explained increases in internalizing symptoms [139]. Increased exposure to estradiol among early developing girls could contribute to this enhanced reactivity effect. In contrast, late pubertal timing has been linked with greater cortisol reactivity and conduct problems in boys [56], which could be partially a function of low testosterone exposure.

The menstrual cycle has significant effects on cortisol levels in females. During the follicular phase, the period prior to ovulation, estrogen levels are low and progesterone levels are high, comparable to levels observed in men [246]. In contrast, the luteal phase is characterized by high levels of estrogen and low levels of progesterone. As would be expected due to the excitatory impact of greater estrogen levels on cortisol production [140], women in the luteal phase of the menstrual cycle display greater cortisol responses than women in the follicular phase [57,59,126]. Therefore, studies that suggest women demonstrate greater cortisol stress reactivity than may include more women in the luteal compared to the follicular phase of the menstrual cycle. This possibility highlights the importance of controlling for menstrual timing when investigating sex differences in HPA axis functioning. In contrast, menstrual timing does not appear to influence cortisol responses to awakening [57]. Oral contraceptives have also been shown to impact HPA axis activity. Studies have associated oral contraceptives use with lower basal cortisol levels [126,141], lower peak stress reactive cortisol levels [23,57], and flattened CAR [57] compared to free-cycling women. In conclusion, menstrual timing and oral contraceptives impact HPA axis activity via differences in the availability of progesterone and estrogen, offering another possible explanation for variable findings regarding sex differences in HPA axis stress reactivity.

In sum, DHEA and testosterone appear to have an inhibitory effect on the HPA axis while estradiol has an excitatory effect. We propose that developmental trajectory of these hormones, as well as cortical changes associated with adolescence, result in more “regulated” HPA axis and this improved regulatory profile may be stronger in boys

than girls. It is also likely that the emerging sex differences in gonadal and adrenal steroid functioning during the adolescent period play a role in the increased risk for stress-related disorders observed in adolescent girls.

5. Contextual factors impacting development of stress processing systems in adolescence

The normative development of the HPA and HPG axes may be influenced by various contextual factors. For instance, exposure to stress, trauma, and obesity may interfere with normative development of these systems in adolescence. Such atypical development may, in turn, reduce an individual's developmentally expected capacity to respond to stress leading to increased risk for a variety of stress-related disorders. This section explores the impact of developmental contexts on HPA and HPG axis functioning during adolescence.

5.1. Stress exposure and sensitization of the HPA axis

The adolescent transition is associated with maturation of stress processing systems, including improvement of neural negative feedback systems regulating the HPA axis. Exposure to stressors during this period may have deleterious effects on the development of metabolic, hormonal, neural, and immune systems due to the negative effects of prolonged cortisol exposure [10,70]. The glucocorticoid cascade hypothesis states that damage to the neural structures regulating HPA axis activity results in a feed-forward circuit in which ongoing stressors drive overproduction of glucocorticoids indefinitely [142,143]. This overproduction of glucocorticoids as a result of chronic stress may damage key brain structures, such as the hippocampus, imperative for HPA axis and HPG axis regulation [70,144]. This damage would also lead to a dysregulation in HPA axis feedback mechanisms, resulting in glucocorticoid overproduction that can contribute directly to many of the adverse behavioral and physiological outcomes associated with chronic stress [69,70]. In animal models, administration of exogenous glucocorticoids produced hippocampal degeneration [145] and lifetime cumulative exposure to glucocorticoids was associated with the degree of hippocampal cell death [146–149].

The impact of glucocorticoid exposure on the hippocampus appears to focus on alteration of GR and MR receptors. For example, a study by Sapolsky et al. [150] administered cortisol at levels equivalent to those achieved after stress induction for 3 months. After this administration of cortisol, hippocampal GR and MR binding sites were downregulated by 50% and this receptor depletion showed no recovery 4 months after exposure, suggesting a long-lasting effect of cortisol on GR and MR receptor density [150]. This decreased availability of receptors limits their ability to downregulate the axis resulting in increased activity. Additionally, the hippocampus plays an important role in the negative feedback inhibition of the HPA axis response. In animal models, destruction of the hippocampus results in hypersecretion of corticosterone in response to a stressor [151–153] and attenuation of the suppressive effects of dexamethasone on the stress response [154]. Corticosterone administration results in both a downregulation of MR and GR in the rat hippocampus as well as reduced sensitivity to feedback inhibition by glucocorticoids, exhibited by cortisol hypersecretion in response to stressors [155].

We argued earlier that the natural development of the axis during adolescence is towards a more adaptive and regulated response to stressors, and that this effect makes evolutionary sense given the increase of potentially deadly stressors associated with the transition to adulthood. It is possible that if excessive exposure to stressors occurs during the time when the axis is down-regulating (the pubertal transition), that the developmental process may be arrested limiting the individual's capacity to respond to stressors during the adolescence period. Unfortunately, most studies examining the timing of stress exposure and its impact on the HPA axis have focused on early infancy and early childhood stress [156]. However, a few studies with peripubertal and post-pubertal youth are consistent with this hypothesis. In 8 to 14-year-old children, exposure to a high number of stressful events during the last 12 months was associated greater cortisol output during a typical day, which suggests a sensitization of the axis. Notably, this sensitization effect was eliminated for those who experienced early life trauma [157]. Likewise, in adolescent females ages 15–19, exposure to episodic stressors in the context of high chronic stress led to increased cortisol release, both upon awakening and overall daily output, and reduced GR mRNA [158]. Another study of adolescent females found that greater self-reported interpersonal and acute stress in the past year was associated with greater latent trait cortisol, a profile reflecting trait HPA axis reactivity patterns generated based on waking cortisol samples across 3 days [159].

Taken together, these studies suggest that excessive exposure to glucocorticoids as a result of chronic stress during the pubertal period and beyond may lead to the sensitization of the HPA axis, resulting in greater cortisol production, degenerative loss of glucocorticoid receptor neurons in the hippocampus, and impaired negative feedback. In the context of adolescence, this sensitization may, in turn, contribute to the increased risk for some types of stress-related disorders observed during this period.

5.2. Stress exposure and blunting of the HPA axis

Exposure to stress may also result in long-term downregulation or blunting of the HPA axis through the upregulation of regulatory systems. For example, blunted HPA axis functioning, i.e., lower activation than expected as compared to non-affected peers, has been found among adolescents maltreated or exposed to harsh parenting as children [160–162], combat-exposed individuals [163], sexual abuse survivors [164,165], survivors of natural disasters [166], and survivors of motor vehicle accidents [167]. Early abuse has also been linked to flattened diurnal variations in cortisol [168]. Thus, this blunting effect may be specific to some types of traumatic events or potentially unique to individuals at higher risk for PTSD [169].

The attenuation theory proposes that since chronic exposure to elevated cortisol levels are damaging to neural systems, the HPA axis downregulates resulting in lower cortisol levels [170]. This downregulation may be mediated by GR availability given that the density of GR within the brain regulates the negative feedback of the HPA-axis and enhanced negative feedback may lead to blunting of the HPA-axis response. Studies of patients with PTSD observed greater GR expression which correlated with younger age at trauma exposure [171]. Increased GR may reflect developmental processes by which early life trauma increases GR expression, in turn facilitating negative feedback and contributing to blunting of the axis [170,172]. Likewise, there is evidence that blunting of cortisol in plasma and brain tissue may be a compensatory process for increased cortisol in the kidney and liver due to decreased levels of 11-β-dehydrogenase isozyme 2 (11β-HSD2), an enzyme that converts cortisol to inactive corticosterone in peripheral tissues. PTSD patients show evidence of reduced 11β-HSD2 and this effect is greatest in individuals who were the youngest at the time of exposure [173]. This developmental effect may be related to the role that 11β-HSD2 play in facilitating survival. In the context of early life adversity, particularly lack of access to food or key nutrients, decreases in 11β-HSD2 allows cortisol to persist and activate renal MR, increasing sodium retention to prevent dietary deficiencies. Increased cortisol levels in the liver and kidney would then be complemented by lower levels of plasma cortisol in the brain and muscles to protect against the deleterious catabolic effects of glucocorticoids, promoting longer-term survival [171].

Yet, the literature linking childhood trauma or deprivation to variability in HPA axis functioning is complex and often contradictory with some studies finding hyper-reactivity in the HPA axis among adults, adolescents, and children exposed to trauma or early life stress

[174–177], others finding hypo-reactivity [159,178–182], and others findings no effect at all [168,183,184]. A possible explanation for this variability is the timing of the stressor [159]. For instance, sexually abused girls demonstrated higher cortisol levels compared to non-abused girls at younger ages and closer to the time of the abuse [165]. However, at older ages and further from the time of the abuse, these girls exhibited blunted levels. Therefore, there appears to be a switch from HPA axis hyper-reactivity to hypo-reactivity over time, a change potentially mediated by downregulation of glucocorticoid receptors within neural networks regulating HPA axis activity.

In addition to variability based on timing of the stressor, there may also be an additional developmental effect. During the first week of the rat's life, the HPA axis ceases to respond to most mild stressors due to a time-limited period of adrenal insensitivity to ACTH [142,143]. In older rats and humans, the presence of the dam or maternal figure appears to buffer cortisol stress reactivity [68,185]. This is likely an adaptive process that protects the brain from excessive cortisol exposure during a time of significant plasticity. However, severe stress during this period can break through this blunting effect leading to strong HPA axis responses to stress [186]. Additionally, infants who exhibit disorganized or insecure attachment to their caregivers demonstrate increases in cortisol after stressors [187]. It is possible that in response to the renewed HPA axis responsivity due to high stress exposure or poor maternal attachment, the organism responds by further upregulating the negative feedback system in order to downregulate HPA axis activity. Therefore, exposure to stress during this sensitive period may be more likely to lead to blunting of the HPA axis as opposed to exposure during the peri-pubertal or post-pubertal period. In support of this conclusion, early adversity better explained a blunted latent trait cortisol profile compared to chronic stress exposure during adolescence [159]. One of largest examinations of the impact of childhood abuse on HPA axis functioning – and one of the few that has examined the timing of abuse to a high level of specificity – found that children who experienced physical or sexual abuse during the preschool years and display high levels of internalizing symptoms during early adolescence, also displayed lower cortisol levels throughout the day when compared those who experienced abuse after the preschool period [168].

A notable aspect of Cicchetti et al.'s [168] seminal finding is that the atypical HPA axis profile was observed only among those who also experienced internalizing symptoms in late childhood and early adolescence. This finding is in line with other studies identifying blunted diurnal cortisol slopes among depressed adolescents who experienced trauma in childhood [183,188]. Although it is possible that the blunted profile is a byproduct of having both early trauma and internalizing symptoms, it is also possible that the blunting made these individuals at higher risk for such symptoms [181]. There is growing evidence that blunting of the HPA axis is associated with future risk for PTSD [171] and that proper activation of the HPA axis is necessary for adaptive responding to stressful situations [189]. Thus, we suggest that blunting of the axis due to stress exposure during the preschool years may be compounded by the naturalistic, and otherwise adaptive, down-regulation that occur during the pubertal transition to create an atypically blunted profile that makes these adolescents unable to mount a proper stress response and thus become at high risk for developing stress-related disorder.

Beyond the timing of the stress exposure and developmental effects of stress exposure during sensitive periods, the severity of the stressor experienced may also help explain variable findings. Severity of maltreatment moderated the association between blunted HPA axis stress reactivity in young adolescents and childhood maltreatment in that blunting was more pronounced for adolescents who experienced more severe maltreatment, such as physical and sexual abuse [162]. Finally, mental health comorbidities in the samples may also help explain discrepant results [190]. Harkness et al. [175] observed hyper-reactivity to stressors in among maltreated youth who were mild or moderately depressed at the time. In contrast, moderate and severe depression was associated with blunted HPA axis stress reactivity among both depressed and healthy youth [175]. Therefore, both the severity of the traumatic experience and comorbid mental health symptoms should be considered when assessing HPA axis functioning.

In contrast, recent evidence suggests that CAR may not follow the same profile in response to early trauma. Early life institutionalization was associated with blunted CAR measured in pre- and early-puberty whereas no impact on CAR was observed in late puberty [191]. Similarly, in a community sample, King et al. [192] found that early life stress exposure was associated with blunted CAR in earlier puberty but at later stages of puberty, early life stress exposure was associated with greater CAR. This suggests that the pubertal transition may result in a re-programing of CAR and exposure to early life adversity may not impact CAR to the same degree as other HPA axis systems. Interestingly, these findings were specific to CAR and did not extend to diurnal variations [192]. However, this re-programming has not been consistently found. A study by Kumsta et al. [193] observed blunted or even absent CAR in adults adopted from Romanian orphanages who experienced more than 6 months of deprivation in early childhood. CAR has been suggested to reflect both response to awakening and measures of circadian regulation and to be relatively distinct from daily cortisol levels [32]. Elevated CAR in later adolescence has been linked to first onset of anxiety disorders [194]. In conclusion, exposure to early life adversity may have differential or limited impacts on the re-programming of CAR during the adolescent transition compared to other indices of HPA reactivity.

5.3. Early obesity & the pubertal transition

The development and maturation of neuroendocrine systems are also impacted by nutrition during early childhood. Most of this research has focused on examining the impact of obesity on pubertal timing and HPG axis development (see [195]). However, there is evidence that this effect may expand beyond sexual maturation to influence HPA axis changes that have a direct influence on an individual ability to cope with stress [196].

High Body Mass Index (BMI) and general over-nutrition during early childhood have consistently been associated with an acceleration of pubertal timing, especially in girls [197]. The main mechanism for this effect is believed to be leptin, a hormone predominantly produced by adipose tissue [198]. Leptin's primary purpose is to decrease appetite by inhibiting hunger peptides produced in the hypothalamus [199]. However, leptin's impact on the hypothalamus also results in increased production of luteinizing hormone (LH) by the pituitary [198]. LH has critical roles in sexual development and reproduction by serving a permissive metabolic gate that signal readiness for the initiation of puberty [200,201]. Therefore, obesity during childhood can lead to a leptin-mediated acceleration of pubertal timing, which is in turn associated with increased risk for internalizing symptoms in females and externalizing problems in males [202].

Beyond puberty, obesity is also associated with alterations of HPA axis functioning. Exposure to excess cortisol has been extensively associated with weight gain and increased visceral fat deposits [203,204]. However, there is also evidence that obesity leads to disruption of various HPA axis processes. Obesity has been linked to poor catecholaminergic regulation of CRH production [205] and reduced cortisone to cortisol reactivation in adipose tissue that may lead to a compensatory response by the HPA axis to increase cortisol secretion [206]. In fact, obesity is associated with higher cortisol production rates [207] and recent studies using hair cortisol measurement, which facilitates the assessment of long-term cortisol exposure, show increased total cortisol exposure in obese adults [208] and children [209]. Furthermore, weight loss results in reductions in circulating cortisol in pre-pubertal obese children [210] and adults [211].

Although there is debate regarding whether such hypercortisolism is observed after controlling for total body mass (see [212]), net elevations of cortisol in early childhood may still result in long-lasting adaptations

of the HPA axis given that brain tissue and related GR and MR receptors do not increase in size linearly with body mass. In experimental models with animals, forced fat diet during the pre-pubertal period leads to increased plasma corticosterone and reduced GR levels in the hypothalamus at puberty, but only in females [213]. Prolonged exposure to corticosteroids can eventually lead to a downregulation of the axis including blunted stress responsivity that can limit the organism ability to cope with stress. In fact, in animals, a high-fat diet during early development can lead to decreased basal cortisol levels in adulthood, increased anxiety behaviors, and high MR and GR receptor expression in the amygdala, but primarily for females [196]. This suggests that high levels of adipose tissue during the pre-pubertal period can lead to a process of initial chronic hyper-activation of the HPA axis that is followed by a downregulation of the axis after the pubertal transition. The pattern observed by Sasaki et al. [196] of blunted basal HPA axis activation in females is identical to the HPA profile often observed in female trauma survivors with post-traumatic stress disorder [164].

The impact of childhood obesity on later functioning of the HPA axis and risk for stress-related disorder in humans is surprisingly understudied. There is consistent evidence that obesity in early childhood affects HPA axis functioning and pubertal timing, as well as evidence from animal models that early obesity can lead to long-term adaptations of the HPA axis similar to those experienced by trauma survivors that increases risk for later mental health problems. Likewise, early puberty is also associated with increased risk for psychological problems during adolescence, especially among girls [214]. Biobehavioral models have focused on the hormonal changes that occur during the pubertal transition, but these efforts primarily explore the impact of changing sex hormones in mood and behavior [215], and on brain reorganization [216]. We argue that the evidence suggests a potential obesity-mediated effect on both pubertal timing and HPA axis functioning that may contribute to increased mental health difficulties associated with early puberty and obesity during adolescence.

6. Implications for mental health

Given increases in academic and social demands that adolescents endure, it is not surprising that during the adolescent period there are significant increases in the rate of stress-related disorders, including depression, PTSD, and some forms of anxiety [7,217,218]. However, despite these increases, the vast majority of adolescents are able to successfully cope with these demands and transition this period without developing health problems [219]. We argue that the typical development of the HPA axis and related networks towards a more effective stress regulation system contributes to this resilience. Increases in risk, therefore, would emerge at least partially when the typical development of the stress regulation system is altered.

Rates of depression increase significantly during the adolescent transition [220]. Additionally, significant gender differences in depression prevalence emerge during this period, with adolescent females showing higher rates of MDD compared to males [220,221]. Increased cortisol secretion represents one of the most common findings in studies of adult MDD (see [222] for review). Studies of adolescents show a similar pattern, in that depressed adolescents demonstrate higher basal cortisol levels and greater cortisol production after the dexamethasone suppression test [24]. Adolescents with MDD were also found to exhibit elevated and prolonged cortisol secretion in response to the TSST, a well-validated psychosocial stress task [25,223].

Although blunted HPA axis functioning has also been found in some depressed adolescents [109,175,224,225], the typical profile is one of hyper-reactivity. For instance, depressed adolescents demonstrate elevated and prolonged cortisol responses in response to social stressors [25,223] and higher and flatter diurnal patterns [226]. Additionally, higher basal levels of morning cortisol predict the onset of MDD in adolescence [227–230]. In contrast, Keenan et al. [225] found that increases in daily cortisol output from age 10 to 12 years predicted fewer depressive symptoms at age 12, whereas decreases in daily cortisol output was associated with stable or slightly increasing depressive symptoms. Therefore, blunted cortisol profiles may be associated with risk for MDD in younger children and early adolescence whereas later adolescence shows an opposite pattern in that hyper-reactivity of the HPA axis increases risk for MDD.

Findings using laboratory tasks suggest that HPA axis hyper-reactivity in depressed adolescents is not just a reflection of increased stress exposure. It is possible that this hyper-reactivity reflects an immature HPA axis due to deviation of its typical developmental trajectory. The risk for atypical development of the axis may be higher in girls than boys, which could contribute to the observed differences in depression. For example, developmental changes in the adrenal lead to increased DHEA release during the adolescence transition [89,91] and this increase can provide added neuroprotection and downregulation of the HPA axis. There are important sex differences in DHEA synthesis in that after puberty, most DHEA for females is produced in the adrenal but in males, up to 25% of DHEA is produced in the testes [89,91]. Consequently, any delays or alteration in the adrenal development could impact females more than males. Furthermore, although both males and females would experience increases in estradiol-mediated excitatory influence on the axis as they get older, males may benefit from greater testosterone-mediated regulation [123]. Thus, an alteration of androgen production during development could also negatively impact females preferentially due to their lower androgen base levels.

Atypical development of the HPA can also involve severe blunting of the response. This blunted profile would prevent the individual from mounting an adaptive response to stressors leading to increased risk and this effect may also be stronger in females. As explained earlier in this review, exposure to chronic or early life stress may also lead to down-regulation of the HPA-axis and decreased exposure to cortisol. For instance, children exposed to early life trauma or abuse [165,182] or those raised in long-term foster or institutionalized care [231,232] show relatively blunted cortisol levels. Blunted cortisol levels have been associated with PTSD diagnosis and risk in both adults [189] and adolescents [233,234] with the stronger effect being found in females [235]. Likewise, early puberty, especially in the context of obesity, leads to early hypersecretion of cortisol followed by a downregulation that can increase risk. Notably, early puberty has been associated with increased risk for internalizing disorders [236]. Although some studies suggest the link between early puberty and internalizing psychopathology is stronger in females [139], a more recent meta-analysis failed to find significant sex differences in this association [236].

Variable findings may also reflect the impact of previous depressive episodes on HPA axis functioning. For instance, one study found greater cortisol reactivity to a psychosocial stressor was associated with a past year depressive diagnosis in 16-year-old adolescents, whereas individuals who experienced chronic depressive symptoms from ages 11 to 16 demonstrated blunted cortisol reactivity [237]. It's also possible that this profile reflects a certain subtype of depression given that research in adults have shown differences in HPA axis reactivity based on depression subtype [238]. In adolescents, low diurnal cortisol output has been associated with co-occurring depressed mood, perceived stress, fatigue, and pain [225,239,240]. Associations between cortisol reactivity and depression subtypes also appear to vary as a function of age. Adolescents with dysthymia under the age of 12 demonstrated hypo-reactivity to a laboratory stressor, whereas dysthymic adolescents older than age 12 exhibited hyper-reactivity [241]. Finally, the association between risk for MDD and HPA axis reactivity appears to vary as a function of pubertal status. In fact, pubertal stage appears to be a better predictor of depression onset than age [242]. Colich et al. [243] observed that girls at early pubertal stages who demonstrated blunted cortisol reactivity to a social stress task were more likely to develop MDD. In contrast, at more advanced pubertal stages, increased risk for MDD was observed for girls who exhibited greater cortisol reactivity to the stress task [243]. Therefore, blunted cortisol reactivity patterns may be more

common during early pubertal stages and among individuals with a history of trauma and more chronic forms of depression. However, at later pubertal stages and in the absence of early life or chronic stress exposure, risk for depression may be predicted by cortisol hyper-reactivity. These findings underscore the importance of assessing pubertal status in addition to age and sex differences when investigating the association between HPA axis reactivity and risk for depression.

7. Conclusion

The adolescent transition involves complex developmental changes in neural and hormonal stress processing systems. This period is marked by increases in social and academic stressors, and maturation of the HPA axis during this transition aims to improve the capacity of the HPA axis to cope with these increases in stress. Animal models support this hypothesis by demonstrating that post-pubertal rats display a less prolonged HPA axis response compared to pre-pubertal rats [71], indicating improved negative feedback. Adolescence also involves maturation of brain regions that have inhibitory projections to the HPA axis [2], providing a neural explanation for enhanced negative feedback during this time. Therefore, we argue that elevations in cortisol observed in adolescence reflect increased stress exposure and changes in the threat intensity of common laboratory stressors, and occur despite, not because of, the developmental changes that make the axis more restrained in its response to stress.

We also reviewed findings that suggest that sex differences in the normative development of the HPA axis and related systems may contribute to the observed sex differences in risk for stress-related disorders that emerge during adolescence. Regulation of the HPA axis is influenced by DHEA and sex hormones of the HPG axis. DHEA is neuroprotective [88] and individual differences in DHEA availability during the adolescent transition may also contribute to the variability in adaptive stress responding. Significant sex differences in DHEA production arise during adolescence [104] and the production of additional DHEA in the testes may provide males greater protection against the effects of stress compared to females. Testosterone also inhibits HPA axis responsivity, further contributing to the increase in regulatory capacity of the HPA axis as a result of the adolescent transition [128]. In contrast, estradiol has an excitatory effect on HPA axis activity [123]. Therefore, increasing sex differences in hormones that inhibit the HPA axis during adolescence, including testosterone and DHEA, may contribute to greater HPA axis reactivity in adolescent females compared to males and greater risk for internalizing psychopathology.

Finally, we reviewed contextual factors also influence the HPA axis development during the adolescent transition. Excessive exposure to stressors during the pubertal transition may interfere with the adaptive down-regulation of the axis, resulting in glucocorticoid overproduction that can contribute directly to many of the adverse behavioral and physiological outcomes associated with chronic stress [70], including risk for depression [244]. In contrast, exposure to trauma and chronic stress in early life may lead to down-regulation of GR within the brain and blunting of the HPA axis [171]. There is growing evidence that blunting of the HPA axis is associated with future risk for PTSD [171] and that proper activation of the HPA axis is necessary for adaptive responding to stressful situations [189]. Thus, we suggest that blunting of the axis due to stress exposure during the preschool years may interact with the naturalistic and adaptive downregulation that occurs during the pubertal transition. This atypically blunted profile makes these adolescents unable to mount a proper stress response, increasing the risk of developing stress-related disorders.

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