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Sex differences in physiological reactivity to acute psychosocial stress in adolescence

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Summary

Females begin to demonstrate greater negative affective responses to stress than males in adolescence. This may reflect the concurrent emergence of underlying differences in physiological response systems, including corticolimbic circuitries, the hypothalamic—pituitary—adrenal axis (HPAA), and the autonomic nervous system (ANS). This review examines when sex differences in physiological reactivity to acute psychosocial stress emerge and the directionality of these differences over development. Indeed, the literature indicates that sex differences emerge during adolescence and persist into adulthood for all three physiological response systems. However, the directionality of the differences varies by system. The emerging corti-colimbic reactivity literature suggests greater female reactivity, particularly in limbic regions densely innervated by gonadal hormone receptors. In contrast, males generally show higher levels of HPAA and ANS reactivity. We argue that the contrasting directionality of corticolimbic and peripheral physiological responses may reflect specific effects of gonadal hormones on distinct systems and also sex differences in evolved behavioral responses that demand different levels of peripheral physiological activation. Studies that examine both subjective reports of negative affect and physiological responses indicate that beginning in adolescence, females respond to acute stressors with more intense negative affect than males despite their comparatively lower peripheral physiological responses. This dissociation is not clearly explained by sex differences in the strength of the relationship between physiological and subjective responses. We suggest that females' greater subjective responsivity may instead arise from a greater activity in brain regions that translate stress responses to subjective awareness in adolescence. Future research directions include investigations of the role of pubertal hormones in physiological reactivity across all systems, examining the relationship of corticolimbic reactivity and negative affect, and sex differences in emotion regulation processes.

Keywords

Adolescent; Autonomic nervous system; Corticolimbic system; Hypothalamic—pituitary—adrenal axis; Sex differences; Psychosocial stress

1. Introduction

Adolescence is a transitional phase defined as the period spanning the onset of puberty to the beginning of self-sufficiency (Dahl and Hariri, 2005)¹ and is marked by ongoing structural brain maturation and by hormonal changes of puberty. It is also characterized by the emergence of sex differences in *negative affect*, the subjective experience and behavioral expression of negative emotion, in response to acute psychosocial stress. Beginning in early adolescence, females respond to stressors with stronger negative affect (Stapley and Haviland, 1989; Petersen et al., 1991; Ge et al., 1994; Garber et al., 2002). These differences persist into adulthood, as women report feeling upset and angry more frequently and with greater intensity than men in reaction to stress (Fischer and Manstead, 2000; Kelly et al., 2008), and women also express these feelings more frequently (Schwartz et al., 1980; Kring and Gordon, 1998; Hall et al., 2000; Kring, 2000). However, it is not clear whether the sex differences in negative affective responses to stress that emerge in adolescence are driven by parallel sex differences in underlying biological reactivity processes that are thought to be associated with puberty and brain development. The possible association between sex differences in brain development is now acknowledged by The Institute of Medicine, which has urged an exploration of the functional impact of brain structural sex differences (IOM, 2011) because of its implications for understanding differential susceptibility for, prevalence, course, and progression of psychiatric disease. This may have implications for understanding why rates of depression skyrocket among females in adolescence, shifting an equal prevalence of the disorder in childhood to a 2:1 female to male ratio (Hankin et al., 1998; Holsen et al., 2000).

Sex differences in the nature and timing of puberty may have differential effects on brain development affecting behavior. Females begin the pubertal process of gonadarche one to two years earlier than males (Marshall and Tanner, 1969, 1970; Dorn et al., 2006) and estrogen and testosterone levels vary by sex (Elmlinger et al., 2002, 2005; Dorn et al., 2006). Females also begin cortical thinning and maturation of white matter integrity prior to males and brain volumes differ by sex even after accounting for differences in body size (Asato et al., 2010; Lenroot and Giedd, 2010). In addition, sex differences in limbic volumes that are already present in childhood (Caviness et al., 1996) are amplified in adolescence, with greater amygdala growth among males (Giedd et al., 1997; Bramen et al., 2010). Further, amygdala volumes are associated with pubertal status and gonadal hormone levels in adolescence (Neufang et al., 2009) in a sex-specific manner (Bramen et al., 2010). Despite this evidence for sexual differentiation associated with puberty and brain morphometry, it is not clear how sex differences influence the *functioning* of affective networks and the downstream autonomic and neuroendocrine physiological systems they activate.

The goal of this review is to generate hypotheses regarding whether and how the unique biological events of adolescence may contribute to the emergence of sex differences in negative affective responses at this time. To this end, this review will examine the plausible mechanism of *physiological reactivity* to acute psychosocial stressors. Physiological functioning includes activity in corticolimbic brain circuits, the hypothalamic—pituitary—adrenal axis (HPAA), and the autonomic nervous system (ANS). This set of biological phenotypes is likely impacted by the biological events of adolescence and has potential implications for negative affect. *Acute* stressors (or threats; these terms will be used interchangeably) probe the functional integrity of various systems, and *psychosocial* rather than physical stressors engage cognitive processes to index responses potentially relevant

¹Adolescence will be defined to include the range of ages spanning 11—17 years. This conservative lower age limit (11 rather than 13) will allow for the inclusion of individuals who are at relatively early stages of puberty across both genders, as puberty is a key developmental event of this period.

negative affective responses. The review will characterize the directionality and timing/developmental emergence of sex differences from childhood to adulthood, with a focus on adolescence. Findings will be used to evaluate the application of theories developed for adults to adolescents as adult-oriented theories may provide additional guidance regarding mechanisms contributing to any sex differences which may exist.

1.1. Implications of physiological responses for subjective experience

As physiological changes follow a threatening stimulus in the environment and motivate a behavioral readiness response, some have proposed that the physiological changes are emotional in nature and may therefore be related to changes in subjective experience (Lang et al., 1993; Levenson, 2003). This has been supported by evidence of positive associations between physiological responses and ratings of negative affective responses to stressors (Ekman et al., 1983; Lang et al., 1993). As such, understanding sex differences in *physiological* responses to psychosocial stress has been argued to have implications for understanding females' greater subjective negative affective responses to stress in adolescence (Kelly et al., 2008; Stroud et al., 2009; Spear, 2010;).

1.2. Examining the role of hormones in sex differences

One theory has suggested that sex differences in physiological reactivity reflect the influence of gonadal hormones on the basis of evidence that sex differences disappear at menopause and evidence that women's reactivity changes during different stages of pregnancy and the menstrual cycle. Kajantie and Phillips (2006) proposed that estrogen may suppress women's physiological reactivity during the child-bearing years as a result of evolutionary pressures to protect a fetus from the detrimental impact of elevated cortisol and autonomic activation. This theory was informed by studies of peripheral physiology and took a broader lifespan perspective, so we seek to re-evaluate this theory with a focus on changes in sex differences at puberty and with an added examination of corticolimbic findings.

1.3. Examining the role of stressor type

Psychological stressors that have been used to elicit acute physiological reactivity with adolescents can be classified as interpersonal or achievement stressors. Interpersonal paradigms include talking about oneself before a panel of critical judges or being socially rejected. These are tasks with strong social-evaluative characteristics, meaning they threaten a person's social esteem or status, and this involves placing individuals in a situation where there is potential to demonstrate the lack of a valued quality (e.g., intelligence, social capability) in front of other people who may judge them (Stroud et al., 2002; Dickerson and Kemeny, 2004). Achievement stressors include cognitive tasks that are frustratingly difficult. These include tasks where participants are required to replicate a design while only looking at its mirror image and a computer beeps when the tracing deviates from the correct response (Matthews and Stoney, 1988). Interpersonal challenges are thought to pose a greater threat to females and achievement challenges a greater threat to males, based on evidence that females' sense of self is more interpersonally oriented whereas males' is more achievement oriented (Cross and Madson, 1997). In the adult literature, there is some empirical support for women to show greater physiological reactivity to social threats than males, but for men to show greater reactivity to achievement threats (Frankenhaeuser, 1978; Stroud et al., 2002). To examine whether this may influence patterns of sex differences in adolescence, findings will be organized according to stressor type. If sex differences vary by stressor type, this would suggest that the perception of threat contributes to changes measured at the biological level.

1.4. Physiological reactivity

Physiological reactivity will be quantified through changes in levels of activity in corticolimbic, neuroendocrine (HPAA), and autonomic (ANS) systems following exposure to stressors. The HPAA and ANS pathways are distinct and initiated via different brain structures. Yet activation in corticolimbic structures such as the amygdala can also stimulate both the HPAA and ANS pathways. Therefore, understanding similarities in patterns of findings among multiple physiological domains can inform us about basic central nervous system processes supporting affect while differences can highlight system-specific patterns of biological responses. In order to understand potential linkages between the brain and peripheral responses, we examine activity in areas of the brain that can initiate peripheral responses. To further our goal of understanding the relationship of sex differences in physiological changes and sex differences in subjective affect, we also seek to examine brain activity in regions of the brain involved in phenomenological experience and regulatory control.

Human fMRI and animal studies indicate a corticolimbic basis for affect and its regulation (Dalglish, 2004; Quirk and Beer, 2006). A network of regions are involved in the perception of threat, organization of a peripheral stress response, awareness of current interoceptive and emotional states, and regulation of activity in threat responsive regions. Central to this network is the *amygdala*, an area implicated in processing threat and uncertainty (LeDoux, 2007; Lee and Hoaken, 2007) and which integrates and distributes salient affective information via its dense interconnections with subcortical and cortical regions (Young et al., 1994; Pessoa and Adolphs, 2010). The *hypothalamus* receives outputs from the amygdala and initiates neuroendocrine and autonomic responses (Dalglish, 2004). The *insula* and *subACC* are involved in reconciling visceral, attentional, and sensory information to generate subjective awareness of the response state (Dalglish, 2004; Vogt, 2005; Craig, 2009). The *orbitofrontal cortex* (OFC), *ventromedial prefrontal cortex* (vmPFC), *ventrolateral pre-frontal cortex* (vlPFC), and the *dorsolateral prefrontal cortex* (dlPFC) are regulatory regions engaged during the processing of stressful stimuli, regardless of explicit regulation of emotions (Hariri et al., 2000; Eisenberger et al., 2003; Meyer-Lindenberg et al., 2005; Quirk and Beer, 2006; Fuster, 2008). Greater engagement of regulatory regions is associated with less self-reported distress in response to threat stimuli (Hariri et al., 2003; Hare et al., 2008) and enhanced connectivity with the amygdala is associated with lower levels of distress or anxiety (Simpson et al., 2001; Kim et al., 2003, 2010). Indeed, the relationship between prefrontal activity and distress/anxiety is mediated by lower activity in regions associated with monitoring internal and external cues (Eisenberger et al., 2003). Among prefrontal regions, the dlPFC is thought to initiate regulatory activity via the vmPFC and OFC, which have bidirectional connections to the amygdala (Hariri et al., 2000; Sah et al., 2003). An understanding of sex differences in the recruitment of regions within this network may provide insight into whether there are sex differences in brain processes that engender, monitor, evaluate, and regulate peripheral physiological reactions (Critchley, 2005, 2009).

The HPAA is a slow-acting neuroendocrine system that acts via chemical signaling in the bloodstream to regulate the release of the steroid hormone cortisol. The ANS, by contrast, produces immediate changes across a number of physiological systems, including elevated heart rate, increased blood pressure, and decreased heart rate variability in the cardiovascular system. Changes in these measures are the result of complex interactions between two independent systems that compose the ANS, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). Despite their distinct time courses and response characteristics, the HPAA and ANS generally coactivate. Both can be activated by the amygdala; outputs from this region signal the paraventricular nucleus of the hypothalamus to activate the HPAA and signal the locus coeruleus to generate an ANS

response. The HPAA and ANS also modulate each other via bidirectional connections of the paraventricular nucleus of the hypothalamus and the locus coeruleus within the brain and noradrenergic signaling in the periphery (Habib et al., 2001; Ulrich-Lai and Herman, 2009). Consistent with HPAA and ANS activation by common central and peripheral processes and mutual modulation, there is evidence for correlations among the HPAA and ANS responses (Pasquali et al., 1996; Root et al., 2009), and for correlations between responses in these systems and corticolimbic responses (Critchley et al., 2000, 2005; Urry et al., 2006; Gianaros and Sheu, 2009; Root et al., 2009; Pruessner et al., 2010). There is, however, also evidence for dissociations among system responses (Pacak et al., 1995; Young et al., 2005), suggesting that corticolimbic, HPAA, and ANS responses reflect more than just a common underlying process. Therefore, patterns of sex differences may not be similar across systems (Marsland et al., 1995; Pacak et al., 1995; Young et al., 2005).

2. Methods

A PubMed search was completed with a limitation of human studies and using the MeSH headings “sex factors” AND (“Affect/physiology” OR “Anger/physiology”). References from papers including adolescents and older children were searched to obtain any additional studies not covered by this search. Adolescence is broadly defined as ages 12–17, though studies that included participants within this age range were classified as studies of adolescents. Only studies explicitly comparing healthy males and females were included.

Each domain-specific section will begin with a brief review of adult sex differences to provide a developmental context for interpreting the sex differences reported by the child and adolescent literatures. We will focus on examining the developmental emergence (“timing”) of the sex differences and their directionality, particularly during adolescence. Based on this characterization of sex differences and an evaluation of convergences and divergences in sex difference findings across systems, we will propose potential mechanisms for these findings, discuss implications for understanding physiological and negative affective responses, and suggest future directions for research.

3. Sex differences in physiological reactivity

Tables 1–3 summarize adolescent studies examining sex differences in corticolimbic, HPAA, and ANS reactivity, respectively. Each table notes findings as well as consequential differences in ages of participants, paradigm features, sample size, and statistical power. Two-tailed sensitivity analyses indicating the magnitude of the effect size a study comparison was powered to detect on the basis of sample size, $\alpha = 0.05$, and $\beta = 0.80$ (Faul et al., 2007). The tables are subdivided according to stressor type (interpersonal or achievement) to highlight whether results segregate on the basis of this task characteristic. Each stressor is rated with regard to the degree of social-evaluative threat and uncontrollability present in accordance with Dickerson and Kemeny's (2004) criteria. Such ratings are parametrically associated with the magnitude of the stress response in adults (Dickerson and Kemeny, 2004) and therefore provide a meaningful metric by which to compare stressors. Though the criteria were developed for and evaluated among adults, they are useful quantitative indices for comparing the literature in youth.

3.1. Corticolimbic systems

Adult sex difference findings are concisely summarized by a meta-analysis of 65 functional neuroimaging studies examining sex differences in corticolimbic responses to salient visual stimuli that similarly elicit fear, anger, and anxiety (Wager et al., 2003). This provides the most relevant context for understanding results of child and adolescent social-evaluative studies. The meta-analysis revealed sex differences were evident in the insula and the

subACC, regions that have both been implicated in the construction of subjective awareness vis-a-vis processing internal states and reconciling them with the ongoing situation (Vogt, 2005; Drevets et al., 2008; Craig, 2009; Singer et al., 2009). Women showed greater reactivity than men in the subACC, a region specifically associated with the subjective awareness and experience of emotion and mood (Vogt, 2005; Drevets et al., 2008; Hamilton et al., 2011). Men, by comparison, showed greater activity in the insula, a region specifically associated with representation and awareness of interoceptive states (Critchley et al., 2004; Craig, 2009). There were no consistent sex differences in the recruitment of other corticolimbic regions (the amygdala, mPFC, and OFC were examined). Instead, these findings indicate males and females differ in *how* internal and external cues are translated into subjective awareness, with women recruiting regions supporting mood to a greater extent while men engage regions supporting interoception.

To our knowledge, no child studies examining sex differences in corticolimbic reactivity to interpersonal or achievement stressors exist, and adolescent functional imaging studies (summarized in Table 1) are limited to studies using interpersonal stressors. The fMRI-compatible interpersonal stressor paradigms have consisted of computerized paradigms whereby participants are deceived into believing avatars with whom they interact are peers also participating in the experiment. These include being gradually excluded from an online ball-tossing game (Masten et al., 2009) or rating how much peers they wanted to befriend were reciprocally interested in chatting with them (Guyer et al., 2009). Superficially, adolescent studies reveal no sex differences in the subACC or insula, or any other regions activated by interpersonal stress (hypothalamus, hippocampus, vIPFC). Closer examination suggests that sex differences may not be present in early adolescence, but emerge gradually over the course of this period. Among 12–13 year-olds, there were no sex differences evident in the insula and subACC, regions whose activity was positively correlated with ratings of subjective distress during the task, consistent with their role in reconciling and interpreting internal and external emotional states. There were also no sex differences in the vIPFC, a regulatory area demonstrating activity inversely related to insula and subACC activity and to reports of subjective distress (Masten et al., 2009). These findings suggest that in early adolescence the sexes do not differ in their recruitment of the circuitry supporting integrative and evaluative affective processes or in the regulation of affect. Among 9–17 year-olds, there were no sex differences in the insula, hypothalamus, and hippocampus to interpersonal stress when collapsing across this eight year age range. However, sex did modulate age-related changes (Guyer et al., 2009). Females showed developmental increases in activity in all three regions, while males' activity decreased in the insula and was unchanged in the hypothalamus and hippocampus (Fig. 1). Insula findings suggest that subjective awareness of internal physiological states may be enhanced over adolescence in females and diminished in males, though sex differences in the subACC, which is more directly implicated in mood-generating processes, were not examined in this study. As the hypothalamus and hippocampus are involved in visceral awareness, memory, and motivational processes, these findings suggest that females but not males may become more sensitive to peer evaluations as they progress through adolescence.

Taken together, the research suggests sex differences are not present early in adolescence, but females uniquely show increased activity across various regions over this period. Studies examining how sex modulates change from childhood to adulthood are also needed to sort out the important inconsistency that women demonstrate less insula activity than men but developmental changes in adolescence predict that women should demonstrate greater insula activity than men. As the insula is involved in interoceptive awareness and the subACC in mood generation, studies clarifying developmental patterns in reactivity in these regions will be necessary to clarify our initial developmental hypothesis. That is, sex differences in corticolimbic reactivity to interpersonal stress emerge during adolescence, and this may

contribute to females and males differentially relying on key regions involved in conscious awareness of experiential responses.

The amygdala is a region with a central role in reacting to and initiating peripheral physiological responses to threat (LeDoux, 2000), yet computerized interpersonal tasks do not elicit amygdala activity in adolescents (Guyer et al., 2009; Masten et al., 2009; Sebastian et al., 2010a) or adults (Eisenberger et al., 2003; Sebastian et al., 2010b). Sex differences in amygdala reactivity across development warrant specific discussion because of evidence for sex differences in morphometry across development (Caviness et al., 1996; Bramen et al., 2010), continued structural (Giedd et al., 1996) and functional (Baird et al., 1999) changes in adolescence, and the amygdala's capacity to initiate both ANS and HPA axis cascades. Presentation of facial expressions of threat can probe amygdala reactivity and also elicit associated regulatory activity. Importantly, these paradigms reliably elicit amygdala activity across childhood, adolescence, and adulthood (Baird et al., 1999; Thomas et al., 2001; Monk et al., 2003b), enabling interpretation of sex differences within a developmental context.

Studies of adults reveal that women demonstrate greater amygdala reactivity than men to *angry* facial expressions (contrasted with fearful or neutral expressions) (McClure et al., 2004). Yet both sexes show equal reactivity to expressions of *fear* (contrasted with neutral expressions or fixation baseline) (Guyer et al., 2008). As angry expressions are direct signals of threat, while fearful expressions are ambiguous, indirect cues signaling potential threat in the environment (Whalen, 2007), these findings suggest that women are uniquely responsive to direct interpersonal threat cues. Connectivity analyses from these data indicate that OFC activity is positively associated with amygdala activity and supports its regulation (Guyer et al., 2008); consistent with this, sex differences in OFC activity mirror those for the amygdala, as women show greater OFC responses specifically to angry faces (McClure et al., 2004) but not fearful faces (Guyer et al., 2008). Thus, women not only demonstrate more reactivity to direct signals of interpersonal threat but also engage in more regulatory processes.

Adolescent findings generally indicate no sex differences in the amygdala and the OFC, likely because they rely on samples spanning a wide age range (at least six years; see Table 1). The null amygdala and OFC findings apply to both angry and fearful facial expressions (Baird et al., 1999; McClure et al., 2004; Guyer et al., 2008) and persist despite variation in task instructions and contrast comparison. The lack of differences in amygdala function across studies is not explained by sex differences in attention to particular aspects of facial stimuli as determined by eye-gaze patterns (Guyer et al., 2008). The studies that include both adolescents and adults indicate that what develops between the late teen years and early 20s is a relative increase in female amygdala and associated regulatory (OFC) responsivity to angry facial expressions but not fearful facial expressions (McClure et al., 2004; Guyer et al., 2008). Thus, over development only females increasingly engage an emotion circuitry involved in both processing and regulating unambiguous interpersonal threat.

Despite consistent evidence for no changes when comparing male and female adolescents spanning a wide age range, one study suggests subtle changes occur over the 9–17 year age range. One study that only investigated responses to fearful faces found that females show age-related declines in amygdala responses and increases in regulatory dlPFC relative to amygdala reactivity over the course of adolescence (Killgore et al., 2001). However, studies directly examining developmental changes in patterns of functional connectivity between regulatory regions and the amygdala are needed in order to understand how time courses of reactivity may be linked. Combined with the findings of the Guyer et al. (2008) study, these results suggest that sex differences in response to fearful facial expressions diminish with age — however, studies of how sex differences to angry facial expressions change over the

course of adolescence are needed to understand how sex differences to angry faces emerge over development. Ideally, studies must examine how age and pubertal development modulate reactivity to both angry and fearful faces in order to clarify specificity of sex differences to particular domains of affect processing.

Taken together, studies using both interpersonal stressors and facial expressions do indicate different developmental trajectories by sex in a variety of limbic regions including the insula, hypothalamus, and amygdala, and these findings are particularly notable given the low power of such studies to detect effects. Yet these fMRI studies reveal no sex differences in any regions of the affective processing network when collapsing across the full range of adolescence, regardless of stressor type. Such findings are not surprising, as the variable timing of pubertal changes causes adolescents to be a particularly heterogeneous group. Future studies would benefit from including a wide age range where age can be considered as a continuous variable to characterize sex differences in developmental trajectories. The few studies that did investigate this indicated that females showed increased activity in these regions to various social stimuli with age whereas males did not. These studies suggest that females may in later adolescence and early adulthood “grow” into greater sensitivity to stress cues that have interpersonal significance. Females may also increasingly engage prefrontal affect regulatory processes with age, but whether this is sufficient to counteract potentially increased amygdala activity is unclear. Importantly, what may actually prove to be the most interesting and relevant to emotion are the developmental changes in regions implicated in self-awareness such as the subACC and insula.

3.2. Hypothalamic—pituitary—adrenal axis

Cortisol levels provide the most direct measure of HPA axis functioning and can be determined by blood serum or salivary assays. The latter compose the vast majority of developmental sex difference studies and will be the focus of this review. The salivary metric is also advantageous because it uniquely reflects bioavailable cortisol that is available to exert physiological effects because it is not bound to other proteins (Vining et al., 1983). Comparisons of cortisol levels across studies will not be made because variability in sampling times across studies are confounded by diurnal influences.

The HPA axis literature has consistently relied on interpersonal stressors and specifically public speaking tasks based on the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993). In the TSST, a participant is informed upon arrival to the laboratory that he/she must make a speech about him/herself that will be judged by an audience. After a short period for preparation, the participant delivers the speech and then completes a difficult mental arithmetic task during which he/she is interrupted and badgered by judges whenever he/she makes an error. The TSST task is effective in eliciting HPA axis reactivity in adults because it incorporates both social-evaluative and uncontrollable elements (Dickerson and Kemeny, 2004). However, it is challenging to implement these elements when designing an effective but ethically appropriate paradigm for youth (see Gunnar et al., 2009a for detailed discussion). The youth-adapted TSST (TSST-C) (Buske-Kirschbaum et al., 1997) and its variants reduce social evaluation by requiring participants to complete a story rather than speak about themselves. Yet the TSST-C reliably elicits a cortisol response in children and adolescents, suggesting sufficient threats to the social self remain (Jansen et al., 2000).

The majority of adult studies indicate that males show greater increases in salivary cortisol than females to social stressors despite a lack of baseline differences (for reviews, see Kudielka and Kirschbaum, 2005; Otte et al., 2005; Kajantie and Phillips, 2006). In fact, findings reveal magnitudes are up to *twice* as high in men and persist an hour after the stressor (Kirschbaum et al., 1992), suggesting a robust difference in initial responses and subsequent regulation. Such findings also extend to young adults, as a study of 18–25 year

olds demonstrated that young adult males had higher pre-task anticipatory cortisol levels and reactivity to the task after accounting for baseline levels than females (Fig. 2a) (Yim et al., 2010b).

Studies of youth, which use the TSST-C and variants, suggest that this greater male reactivity to social-evaluative stressors emerges in late adolescence. Children ages 9–12 show no sex differences in cortisol reactivity (Gunnar et al., 2009a) (Yim et al., 2010b). Three different studies of young adolescents ages 9–15 similarly report no sex differences in baseline levels, amplitudes of the cortisol response, or time course of reactivity (Buske-Kirschbaum et al., 1997; Kudielka et al., 2004b; Gunnar et al., 2009b). One study that included both younger (11–13 years) and older (14–16 years) adolescent age groups revealed that sex differences were not present in the younger adolescents, but were present in the older adolescents, with males showing greater cortisol reactivity despite no baseline differences (Klimes-Dougan et al., 2001). Consistent with the latter finding, a study of 15–17 year-olds revealed males showed greater elevations in cortisol levels despite no sex differences in baseline cortisol (Bouma et al., 2009). Sensitivity power analyses indicating older adolescent comparisons were only powered to detect large effects suggest a substantial sex difference among older adolescents, whereas younger adolescent studies powered to detect medium effects suggest small, if any, sex differences among young adolescents. Taken together, these studies converge to indicate that greater male cortisol reactivity emerges around age 14 or 15. This, in turn, fits with the directionality of adult findings indicating that men show greater amplitudes of cortisol reactivity to stress.

As these differences across development are relative, it is essential to note findings reflect a uniquely male developmental increase in cortisol reactivity. The Klimes-Dougan et al. (2001) study that included both younger and older adolescents revealed that older adolescent boys show greater stress reactivity than older adolescent girls, younger adolescent girls, and younger adolescent boys, who do not differ from each other (Fig. 2b). Another study using a specially modified TSST task explored how sex modulates change from late childhood (ages 9–12) to young adulthood (ages 18–25). Pre-task anticipatory responses were higher in adult males than adult females and youth of both sexes, whose pre-task levels did not differ (Fig. 2a) (Yim et al., 2010b). Adult males also demonstrated larger magnitudes of cortisol responses relative to baseline than the other three groups. By contrast, the adult female response to the stressor itself was blunted as compared to all groups (Yim et al., 2010b). The adult findings fit with a series of thorough studies of young adults and older adolescents showing greater anticipatory and task responses to the TSST among males (Kirschbaum et al., 1992). Taken together, these studies suggest an adult-like pattern emerges in mid-adolescence, whereby male responses are enhanced and female responses are equal if not somewhat diminished.

Based on the mid-adolescent timing of the emergence of sex differences, pubertal processes may contribute the differentiation of male and female HPAA responses. A follow-up analysis of sex differences within 9, 11, 13, and 15 year-olds by Gunnar et al. (2009b) indicated that developmental increases in cortisol reactivity increase in tandem with the timing of pubertal onset for each sex, with females first (between ages 11 and 13) and males following two years later (between ages 13 and 15). The greatest sex difference in cortisol reactivity existed at the age (13 years) with the greatest difference in self-reported pubertal status. Future studies are needed to explicitly examine how age-related and pubertal status-related changes are moderated by sex and to clarify the extent of increases in reactivity among males and any decreases in activity in females. It warrants note that one study has examined this across the adolescent period (Sumter et al., 2010) and found no sex by age or sex by pubertal status interactions despite power to detect small to medium interaction effects. However, it is difficult to reconcile these results with the rest of the literature

because they used a much milder variant of the TSST-C task (Westenberg et al., 2009) in which participants prepared the speech in the familiar surroundings of their home, completed only one of two stressors, and the task involved fewer social-evaluative and uncontrollable components (see Table 2). Consistent with this, cortisol reactivity was far lower than in other studies, with mean differences between peak response and recovery around 2 nmol/L versus 6–8 nmol/L as reported in other studies using the same measurement unit (Kirschbaum et al., 1992; Yim et al., 2010a,b).

Thus, it remains unclear whether pubertal changes initiate these sex differences. Future studies must be designed to examine puberty by sex and age by sex interactions independently of each other. Additionally, the reviewed studies also indicate that sex differences may only be evident at relatively higher levels of stress. Future studies comparing tasks with varying demands could clarify the effects of age and pubertal influences on sex differences within adolescence.

3.3. Autonomic nervous system

The vast majority of developmental studies examining sex differences in ANS reactivity to stressors have used cardiovascular measures including blood pressure and heart rate. This review will focus on systolic blood pressure (SBP), the pressure when the heart is contracting, rather than diastolic blood pressure, the pressure when the heart is filling, because SBP reactivity is more directly related to the central nervous system influences on the heart whereas the latter is associated more strongly with peripheral influences on the vasculature (Berntson et al., 2007). For reference, adolescent diastolic blood pressure findings are included in Table 3 and generally reveal no sex differences, consistent with the adult literature (Kudielka et al., 2004a). Heart rate accelerations reflect the influence of both sympathetic and parasympathetic innervations and can arise from sympathetic activation, parasympathetic withdrawal, sympathetic activation paired with a parasympathetic withdrawal, para-sympathetically dominated co-withdrawal, or sympathetically dominated co-activation (Berntson et al., 2007). Due to this complexity, pre-ejection period (PEP) and vagal tone are valuable indices reflecting unique sympathetic and para-sympathetic influences on heart rate, respectively (Berntson et al., 2007). PEP is the length of the interval that begins when the heart receives the electrical signal to contract and ends when blood is pumped out of the heart. Vagal tone can be determined in various ways, but all index respiratory influences on variability in interbeat intervals that is driven by the vagal nerve. Sex differences in these metrics have not been studied extensively, but findings that do exist will be used to clarify the heart rate and blood pressure findings.

Studies examining sex differences in adults generally indicate that findings vary as a function of cardiovascular index. An early meta-analysis of adult studies concluded that men show greater SBP responses, even after accounting for their higher baseline SBP (Stoney et al., 1987). There was also a trend for women to show greater heart rate increases than men, despite women's higher baseline heart rates. A more recent compilation of five independent studies strengthened these conclusions with evidence that men systematically show greater SBP reactivity while women show greater heart rate reactivity (Kudielka et al., 2004a) (Fig. 3a), even after accounting for sex differences in body mass index and baseline levels. A few studies, however, have failed to find sex differences in heart rate reactivity (Kelly et al., 2008; Neumann et al., 2010; Strahler et al., 2010), indicating that this effect may not be as robust as the SBP effects in adults. In fact, evidence suggests that the inconsistencies in heart rate studies may reflect the moderating influence of polymorphisms in the serotonin transporter gene-linked polymorphic region (5-HTTLPR). The short/short 5-HTTLPR genotype is associated with reduced serotonergic responsivity and lower serotonin turnover, which in turn generates greater sympathetic reactivity (Williams et al., 2001). Estrogen and progesterone also reduce 5-HTTLPR transcription (Pecins-Thompson et al., 1998), so it fits

that adult women who carry the “risk” short/short genotype have greater SNS reactivity and higher heart rate acceleration than men with this genotype, and all other individuals with the heterozygous or long/long genotype, who do not differ from each other (Fig. 3c) (McCaffery et al., 2003; Way and Taylor, 2011). Therefore, a subset of women with a “risk” genotype may drive sex differences in cardiac acceleration, and differential distributions of these individuals across studies may account for the mixed findings.

Adolescent ANS studies are summarized in Table 3, which highlights that sample sizes are generally large, and almost all studies have the sensitivity to detect small to medium effects.

3.3.1. Systolic blood pressure—A series of three studies by the same group measured SBP responses to achievement stress among youth spanning a wide age range. These included a study of 10–18 year-olds (McCann and Matthews, 1988), an overlapping but larger study of 7–18 year-olds (Matthews and Stoney, 1988), and a longitudinal follow-up of these subjects when they were 11–22 year-olds (Matthews et al., 1990). Achievement stressors included: (1) a mental arithmetic task under time constraints requiring participants to perform a difficult yet age-appropriate subtraction task aloud and (2) a mirror tracing task in which participants traced the outline of a star while only looking at a mirror image, and a computer beeped whenever the tracing deviated from the model shape to frustrate the participant. Comparisons involving 7–11 year-olds indicated no sex differences in older children's SBP responses to achievement stressors. Males demonstrated higher SBP responses than females in all but one of six comparisons across three studies and both cognitive tasks that included adolescents. However, since many of the comparisons also included children or adults, it merits note that males still consistently evidence greater SBP reactivity in adolescent-limited samples of 14–18 year-olds (Matthews and Stoney, 1988), 12–18 year-olds (Fig. 3b) (Syme et al., 2009), and 15–17 year-olds (Ewart and Kolodner, 1991; Allen and Matthews, 1997) across a heterogeneous set of cognitive stressors that tax spatial, verbal, and mathematical abilities. These robust findings persist even after accounting for males' greater SBP at baseline and the confounding sex difference in body mass index (Matthews and Stoney, 1988; Matthews et al., 1990), which is positively associated with elevated blood pressure across development (Gerber and Stern, 1999; Syme et al., 2009).

Studies of adolescent sex differences in SBP reactivity to interpersonal stressors have used the Social Competence Interview (Ewart and Kolodner, 1991), a task requiring participants to describe a recurring source of emotional distress while an interviewer probes the participant to reconstruct the event in detail. It is designed to elicit the same physiological, affective, and cognitive responses in the laboratory as are elicited in the situation itself. Two studies of older adolescents (15–17 years) (Ewart and Kolodner, 1991; Allen and Matthews, 1997) reported greater male SBP responses, even after baseline and body mass corrections. Overall, these consistent findings provide compelling evidence that SBP reactivity is greater among males regardless of stressor type. It is also remarkable that these results are so robust even though the tasks used to assess SBP are less stressful compared to those used in the HPAA literature, as indexed by the strength of social-evaluative and uncontrollability components rated in Tables 2 and 3.

3.3.2. Heart rate—One study of children (3–6 years) did not find significant sex differences in heart rate elevations to a variety of achievement and interpersonal stressors (Quas et al., 2000), and a study of 7–11 year-olds similarly reported no such sex differences (Matthews and Stoney, 1988). Adolescent studies, however, begin to reveal sex differences, but these are inconsistent and do not depend upon age. One large study revealed greater female heart rate acceleration to a serial subtraction task in 7–18 year olds (Matthews and Stoney, 1988), which was no longer present four years later at ages 11–22,

(Matthews et al., 1990). Yet another study of older adolescents using a more limited range (15–16 years) did reveal sex differences, with females showing more elevated heart rate responses to the serial subtraction task (Ewart and Kolodner, 1991). Studies using the mirror tracing task also do not report consistent sex differences in adolescent heart rate reactivity, as there were no sex differences among 7–18 year olds (Matthews and Stoney, 1988), but the 11–22 year-olds demonstrated greater female heart rate acceleration (Matthews et al., 1990). Two studies limited to narrower, older adolescent age ranges were also inconsistent, as one reported no sex differences among 15–17 year olds (Allen and Matthews, 1997) but another (14–15 years) reported that females displayed greater heart rate acceleration (Ewart and Kolodner, 1991). Importantly, even though females make more mistakes on the unjudged mental arithmetic while males perform worse on mirror tracing, task difficulty did not seem to influence reactivity findings.

Interpersonal challenges are theorized to be more threatening to females, but these tasks still do not elicit more consistent findings. Two studies investigated how 9–15 year old participants responded to the standard TSST-C protocol described in the previous section (Gunnar et al., 2009b; Kudielka et al., 2004a). One study reported greater heart rate reactivity after accounting for baseline levels (Kudielka et al., 2004a), but the other did not (Gunnar et al., 2009b), and contradictory findings are not attributable to study differences in sensitivity to detect effects (see Table 3). Two studies of older adolescents (15–17 years) used the same paradigm (Social Competence Interview), but also diverged in their findings, with one reporting no significant sex differences in heart rate acceleration (Allen and Matthews, 1997), while another reported larger heart rate acceleration in females (Ewart and Kolodner, 1991).

Taken together, these studies suggest that sex alone is not a robust predictor of heart rate reactivity among adolescents. Consistent with the adult literature, only a subset of heart rate studies reveal sex differences, and those reporting differences are not unique with regard to study power, ages of samples, or stressor type. What is clear is that the directionality of the sex difference, when evident, is for females to show greater heart rate reactivity. Importantly, this inconsistent pattern emerges in adolescence and persists into adulthood. Elevated heart rate reactivity may emerge among a subset of females with the short/short 5HTTLPR genotype females when estrogen and progesterone levels increase during puberty.

3.3.3. SNS and PNS tone—Measures that isolate SNS or PNS inputs to the heart have the potential to clarify the inconsistencies in the heart rate findings, but unfortunately the literature examining sex differences is still too small to provide a clear picture of developmental change. A study exploring sympathetic influences on the heart among 8–10 year olds found no sex differences on achievement stress (reaction time and mirror tracing tasks) but girls exhibited higher sympathetic arousal than boys to interpersonal stress (Allen and Matthews, 1997). Adolescent females have been shown to respond with greater sympathetic activation to stress at ages 9–15 (Gunnar et al., 2009b) and 15–17 (Allen and Matthews, 1997), regardless of stressor type. The parasympathetic findings, however, have been mixed. Studies using achievement stressors alternately report less female parasympathetic activity among 9–15 year-olds completing a variety of tasks (Allen and Matthews, 1997) or no sex differences among 12–18 year-olds completing a mental arithmetic task (Syme et al., 2008). Studies using interpersonal stressors are similarly inconsistent regarding parasympathetic tone despite consistencies in the age group studied (9–15 year-olds). Gunnar et al. (2009b) reported no sex differences in response to the TSST-C, while Allen and Matthews (1997) reported females demonstrated less parasympathetic activity in response to the Social Competence Interview. More research in samples spanning childhood to adulthood are needed to clarify how sex differences in SNS and PNS

responsivity change with development, though the current literature does suggest greater female sympathetic reactivity present as early as childhood.

4. Conclusions

A crucial finding regards *timing*: the sex differences in reactivity seem to emerge in adolescence and these differences persist into adulthood. A careful review of the literature within peripheral physiological response domains reveals that even though many adolescent studies using wide age ranges find no sex differences, those that utilize participants within narrow, mid- to late-adolescent age ranges reveal differences. That is, sex differences exist across domains by the second half of adolescence, and the directionality aligns with adult patterns within each domain. The latter half of adolescence is when the majority of adolescents have already begun puberty, and specifically gonadarche, the phase of puberty characterized by the sex-specific increase in estrogen and testosterone levels (Dorn, 2006). Taken together, the *timing* of the emergence of HPAA and ANS reactivity to psychological stress coincides with pubertal changes and may specifically reflect the influence of gonadal hormones on physiological markers of affective responses to threat, which will be discussed in the following section. The corticolimbic research has limited capacity to examine this, but there is some evidence that developmental change varies by sex in hormone-sensitive corticolimbic areas.

To understand the *directionality* of sex differences which emerge at this time, results were segregated by response domain (corticolimbic systems, cortisol, SBP, heart rate). This helped to clarify *how* adolescent males and females differ in physiological reactivity. Neuroimaging findings point to the emergence of greater reactivity and regulatory activity in females and also show that, in adulthood, females rely more on a region that promotes awareness of mood states while males rely on a region involved in interoceptive awareness. In multiple peripheral physiological domains, including the HPAA and blood pressure, males demonstrate greater physiological reactivity starting in adolescence and continuing in adulthood. The only exception is heart rate, which women sometimes show greater reactivity.

5. Discussion

We will use the framework presented in the introduction to evaluate the following questions raised by this review. First, what are potential mechanisms for the adolescent emergence of sex differences and their directionality? Second, how can we understand reactivity in the context of studies showing greater female negative affect in adolescence and adulthood? We propose that rising levels of gonadal hormones associated with puberty initiate greater female reactivity in the brain and greater male reactivity in the periphery in adolescence. We also suggest that adolescent-emerging sex differences in interoceptive processes may contribute to discrepancies in subjective emotional responses. A proposed model representing developmental changes in sex differences of physiological reactivity to acute psychosocial stress over development and summarizing the proposed relationship of these changes to pubertal changes and development changes in sex differences of negative affect are represented in Fig. 4. We conclude by suggesting future avenues of research that can fill in research gaps and test these hypotheses.

5.1. Role of stressor type

A crucial finding was the lack of evidence for differential directionality of sex differences according to stressor type, at least within the autonomic domains in which variability in study stressors allowed for this to be investigated. That is, sex difference findings did not differ according to the type of stressor used. This was surprising in light of evidence that

adult females are more physiologically responsive to interpersonal stressors while men are more responsive to achievement-oriented threats (Stroud et al., 2002). Behavioral studies of attentional biases and self-reports confirm that adolescent females are more responsive to social cues than males (McClure, 2000) and more interpersonally sensitive (Rose and Rudolph, 2006), but our review indicates that adolescent females do not show stronger physiological responses to such cues than males. Indeed, stressors that were hypothesized to be gender biased (interpersonal threats for females and achievement threats for males) do not elicit greater physiological reactivity among that sex. Rather, any sex differences seemingly reflect the sex-specific sensitivity of the physiological domain rather than the type of stressor which elicited the response. These results suggest that sex differences in physiological reactivity to a stressor do not primarily reflect cognitive perceptions about how one's gender should perform according to gender-socialization pressures (Matthews et al., 1991). Instead, they seem to be influenced more by sex-specific predispositions of the physiological response domain being examined, suggesting the important role played by biological factors. As these findings are based solely on findings from peripheral autonomic systems, future studies must examine whether this is also true in the HPA axis and corticolimbic areas, as effects reflecting cognitive interpretation may be stronger for metrics of brain activity.

5.2. Role of gonadal hormones

The timing of sex differences emerging in adolescence across multiple systems suggests that they may reflect the emergence of gonadal hormones at puberty. That females show greater reactivity in some systems but males in others fits with evidence from animal studies that gonadal hormones act differently on different body systems and that estrogen and testosterone tend to have opposite effects (Walker et al., 1996; Spear, 2000; McEwen and Gianaros, 2010).

The uniquely female elevation in corticolimbic reactivity over adolescence may reflect the effects of increasing estrogen, as the regions showing developmental modulation by sex (the hypothalamus and hippocampus and the insula to a lesser extent) are unique in their high densities of estrogen receptors (Shansky, 2009; Ter Horst et al., 2009). Findings fit with the animal research showing that estrogen enhances hypothalamic responses to cognitive stress (Resnick et al., 1998). Estrogen has also been shown to promote stress sensitivity in the mPFC-amygdala pathway by facilitating stress-induced hypertrophy of dendritic spine density (Shansky, 2009; Shansky et al., 2010), which aligns with our evidence for increased amygdala and OFC activity. Studies of human adolescents are needed to validate whether pubertally driven increases in estrogen levels contribute to enhanced reactivity in the hypothalamus, amygdala-mPFC pathway, and in other regulatory pathways. Much less is known about the influence of testosterone on corticolimbic stress responses, and more research is needed.

In the HPA axis, estrogen reduces bioavailable cortisol by facilitating production of corticosteroid binding globulin, a molecule that binds to cortisol, making it unavailable for receptor binding (Chrousos et al., 1998). Estrogen also decreases cortisol release by enhancing oxytocin release from the hypothalamus in response to stress, which inhibits CRH's effects on the anterior pituitary (Taylor et al., 2000). In contrast, animal studies suggest that testosterone potentiates male HPA axis responses to acute stress during puberty, as post-pubertal male mice show greater HPA axis responsivity than pre-pubertal mice (McCormick and Matthews, 2007). However, timing of hormones also matters — simply treating pre-pubertal mice with adult levels of circulating testosterone cannot induce a post-pubertal-like HPA axis response (Romeo et al., 2004). This indicates that increased testosterone must co-occur with other adolescence-specific events to produce adult-like HPA axis responses. Indeed, it has been proposed that increasing gonadal hormone levels may

re-organize the plastic, developing brain at puberty (Sisk and Zehr, 2005). Human studies that explicitly explore the role of age and testosterone levels can confirm how these factors independently and interactively contribute to the emergence of greater male reactivity.

In the ANS, gonadal hormones can explain greater male blood pressure responses and, to a lesser extent, greater female heart rate responses. Estrogen and testosterone act via multiple mechanisms to diminish and enhance blood pressure responses, respectively. First, estrogen stimulates growth of endothelial cells, which reduces the turbulence of blood flow and enables blood to be pumped further with less resistance (Kauser and Rubanyi, 1995; Kauser et al., 1998). Second, estrogen reduces muscle signaling to inhibit smooth muscle cell contraction, which results in vasodilation (Orshal and Khalil, 2004). Third, estrogen acts on the renin—angiotensin—aldosterone system that regulates blood pressure and fluid balance by inhibiting renin release and enzyme activity to keep blood vessels dilated (Takeda-Matsubara et al., 2002). Testosterone acts on these three systems via opposing mechanisms to generate increased blood pressure (Reckelhoff et al., 2000; Reckelhoff, 2001; Orshal and Khalil, 2004; Yanes et al., 2008). Human studies examining natural variations in estrogen levels indicate that pregnancy-induced estrogen level increases are associated with diminished blood pressure reactivity to stress (Matthews and Rodin, 1992), while menopause-induced estrogen level declines are associated with enhanced blood pressure reactivity (Spary et al., 2009). Consistent with estrogen's attenuation of blood pressure, hormone replacement therapy diminishes the enhanced reactivity of menopause (Huikuri et al., 1996).

The effects of gonadal hormones on heart rate responses are less clear. As noted earlier, gonadal hormones estrogen and progesterone may interact with serotonin transporter genotype to produce elevations in heart rate via enhanced SNS tone. However, animal studies of estrogen's effects on neuronal signaling pathways suggest that females in general will actually show less SNS reactivity and greater PNS reactivity (Saleh et al., 2000; Saleh and Connell, 2003), and estrogen may further decrease SNS activity by facilitating the release of oxytocin (Taylor et al., 2000). Further, studies of variability in cardioacceleration across phases of the menstrual cycle suggests that estrogen may attenuate heart rate reactivity (for review, see Kajantie and Phillips, 2006). Future studies examining sex differences in SNS and PNS reactivity via PEP and vagal tone, the contribution of gonadal hormones to these differences, and 5HTTLPR genotype are needed to highlight the complex relationship between genetics, hormones, and the various inputs contributing to cardioacceleration.

Adrenergic influences in the cardiovascular system are mediated by α - and β 2-adrenergic receptors on the vasculature, and by β 1-adrenergic receptors on the heart (Berntson et al., 2007). Therefore, another explanation for domain specific patterns of sex differences is differential sensitivity and density of α - and β -adrenergic receptors. That is, males' greater SBP reactivity could reflect enhanced sensitivity of α - or β 2-adrenergic receptors, a greater density of these receptors, or both. This is supported by pharmacologic evidence showing that β 2-adrenergic agonists cause more forearm vasoconstriction in men than women (Kneale et al., 2000). The effect may be mediated or moderated by gonadal hormones, but this research is needed. Further studies of the effects of α - and β 1-adrenergic agonists on blood pressure and heart rate responses in both sexes can establish differential effects across cardiovascular systems. Differential effects may also be mediated by differences in sympathetic neural outflow to the vasculature that would produce increased SBP mediated by norepinephrine acting via α receptors and cardioacceleration mediated by activation of β 1 receptors. Additionally, this would cause the adrenal medulla to release circulating epinephrine, enhancing cardiovascular responses. There may also be an impact of decreased

or increased parasympathetic (vagal) outflow to the heart. Assessment of heart rate variability with spectral analysis may be helpful in assessing such effects.

In sum, we hypothesize estrogen generally enhances stress reactivity in specific threat-processing circuits of the brain but generally minimizes stress reactivity in peripheral physiological systems. Testosterone enhances blood pressure responses but further research is needed to examine its influence on corticolimbic systems and the HPA axis in order to understand whether it has differential effects across physiological systems. Studies of human adolescents are needed to examine whether increased gonadal hormone levels at puberty generate predicted alterations and to examine how mechanisms may differ in the context of concurrent brain development.

5.3. “Tend and befriend” in females and “fight or flight” in males

The seemingly contradictory finding that females' cortisol and blood pressure responses are lower than males' in spite of their relatively higher corticolimbic brain responses can also be explained in the context of a theory that females have evolved a different behavioral response to stress than males. The stress response has traditionally been characterized as “fight or flight,” in which increased circulating cortisol and enhanced blood flow to the periphery support muscular movements supporting aggressive behavior or escape. While this may promote survival among males, Taylor et al. (2000) argues this is not the adaptive response for females who seek to protect their offspring from threat. Fleeing or fighting behaviors leave the offspring vulnerable, whereas maternal soothing and soliciting assistance from a larger social group provide safe hiding from predators. This theory is supported by evidence that when female primates and humans are stressed, they soothe their offspring more and demonstrate enhanced affiliative behavior (Taylor et al., 2000). Importantly, this theory proposes that females differ in the behaviors generated by the perception of threat, so it would predict diminished sex differences in peripheral responses, but not necessarily the brain. Taylor et al. (2000) document that among females, the perception of threat is associated with a more pronounced release of oxytocin, a posterior pituitary hormone that is associated with parasympathetic activation (Uvnas-Moberg, 1997), and attenuated cortisol and blood pressure responses to acute psychosocial stress (for review, see Taylor et al., 2000). Oxytocin's effects are further enhanced by estrogen but suppressed by testosterone (Jezova et al., 1996). Ensuing predictions are consistent with our review indicating that females show lower cortisol and blood pressure responses despite generally greater corticolimbic responses than males.

5.4. Implications for understanding subjective emotional experience

Physiological reactivity to stressors has been shown to correspond to negative affective states across the sexes in adolescence, implying that the physiological response has an associated emotional basis. Elevated cortisol responses have been shown to correspond to feeling less “relaxed” (Granger et al., 2006) and more aroused (“freaked out”) (Gunnar et al., 2009b). In the autonomic domain, cardioacceleration is linked to increased negative affect (Steiner et al., 2002), while increased SNS tone estimated via PEP is associated with feeling more aroused (Gunnar et al., 2009b). In addition, limbic responses to threatening stimuli are associated with higher ratings of arousal (Monk et al., 2003a). However, this review revealed sex differences findings in physiological measures do not parallel sex differences in subjective reports of state affect in adolescence and adulthood. Understanding this paradox is pertinent to understanding why females begin to experience more subjective negative affect in day-to-day experiences than males in adolescence. One possible contributor to the paradoxical findings is that females may demonstrate a stronger association between subjective experience and physiological reactivity. If present, the implication would be that males and females process physiological reactivity differently

resulting in distinct affective experiences. One study of 9–15 year olds completing a TSST-C task found no sex differences in the association of baseline-corrected cortisol reactivity and visual analogue scale ratings of feeling “freaked out” (Gunnar et al., 2009b). The same study of young adolescents also reported no sex differences in the relationship between increased SNS tone and arousal ratings (Gunnar et al., 2009b). By contrast, Steiner et al. (2002) reported that the relationship between affective state and increased heart rate in response to stress-inducing speech tasks was significant in older adolescent (14–18 years) females but not males. Correlations between heart rates and reports of negative affect were significant in females because their subjective reports were sensitive to small changes in heart rate even in spite of a high baseline heart rate. By contrast, males' heart rate changed more drastically over the 5 min experiment, but reported changes in negative affect were minimal. This suggests females may translate cardiovascular responses to affective experience more sensitively than males, in keeping fits with the neuroimaging literature showing that females rely more on brain regions involving the generation and awareness of emotional feeling states. Overall, however, the initial findings, however, are equivocal. As one set of results relied on a sample of young adolescents who show fewer physiological sex differences and who may also have less-developed interoceptive abilities, more studies are needed in samples spanning early and late adolescence.

Additionally, negative affect encompasses a broad array of emotions; in response to these stressors, some individuals may feel aroused and stressed, while others feel over-whelmed and hopeless, and others feel angry. Examining facial expression responses to threat provides another perspective into the relationship between physiological reactivity and subjective affective experience. Such responses are physiological by nature of reflecting muscular changes but have also been shown to be associated with emotional experiences, so some have argued that it lies on a continuum between physiology and subjective responses (Lang et al., 1993; Levenson, 2003). Studies of adults reveal women are more emotionally expressive than males across a number of emotions, including sadness, disgust, fear, and anger (reviewed by Kring and Gordon, 1998). In response to threatening images, women demonstrate more intense negative expressions than men (Buck et al., 1974; Kring and Gordon, 1998; Brody and Hall, 2000). Concurrent measurements of physiological responses reveal that these expressions do not match with physiological differences, as men show higher levels of peripheral physiological arousal than women. In fact, when individuals were categorized according to a pattern of expressive and physiological responses, most men were “internalizing” responders who show higher levels of physiological arousal with lower levels of negative emotional expressions, while women tended to be “externalizers” who show lower levels of physiological arousal and higher levels of overt negative emotional expressions (Buck et al., 1974; Kring and Gordon, 1998; Brody and Hall, 2000). Thus, when considering multiple response types to threat, males seem to only manifest the differences internally in peripheral physiological responses. Dissociations between physiological and emotional expression responses have also been shown in children (Quas et al., 2000), but sex difference findings warrant replication in younger age groups.

Understanding how a threat is translated into a pattern of physiological, expressive, and subjective emotional responses also requires consideration of how the threat is interpreted. In fact, facial expressions may be particularly informative when the type of negatively valenced response (e.g., anger versus fear) is considered rather than the magnitudes of responses that are all considered to be negatively valenced. There is evidence that different types of unpleasant facial expression responses are associated with different physiological responses (Zuckerman et al., 1981; Levenson et al., 1990). Further, a study administering the TSST with adults reported that, facial expressions of fear were associated with *increased* peripheral physiological reactivity (cortisol, SBP, HR), but anger was associated with *decreased* reactivity (Lerner et al., 2007). In addition to showing that specific expressive

responses are characterized by a unique physiological profile, these results underscore that the type of emotional response differs across individuals. Research is needed to examine whether sex differences in physiological responses reflect different types of emotional responses, which in turn may reflect different interpretations of events.

Overall, there appears to be a recurrent theme of males showing increased peripheral physiological reactivity while females show increased subjective awareness of affect. One explanation is that peripheral physiological responses do not contribute to subjective awareness as much as corticolimbic systems. And it may be the particular regions within the corticolimbic system that matter. Sex differences in the regions recruited by men and women for processing of emotional experiences (subACC for women and insula for men) suggest that the nature of interoceptive processes may differ by sex. The subACC is associated with awareness of affective state while the insula may be associated with awareness of physiological body states in males. More research is needed to examine whether this also applies to adolescents and what are the implications of recruiting these different regions on subjective experience.

5.5. Current challenges and future directions

This review reveals research needs that will facilitate a comprehensive understanding of the nature and timing of sex differences in adolescent physiological reactivity and the mechanisms that support it, particularly pubertal factors and brain maturation. As some literatures are still small, future research must begin with some clarifications. Studies characterizing how sex modulates developmental trajectories in samples spanning childhood to adulthood are needed to precisely estimate when sex differences in physiological reactivity emerge for each domain. Our review suggests that that HPA axis reactivity may emerge in mid-adolescence, but the timing of the adolescent-emergent ANS and corticolimbic differences remains unclear. Specific examination of the timing, let alone the directionality, of SNS and PNS sex differences across development is also needed. Sorting this out can refine our understanding of relationships among systems. Second, examining the role of puberty in physiological reactivity can test the proposed mechanisms supporting the emergence of physiological sex differences. Studies can maximize the capacity to investigate the role of puberty independent of age by sampling limited, sex-specific age ranges of maximal pubertal change. Given the focus on estrogen- and testosterone-mediated mechanisms in the theories proposed, such assessments should include indices of these circulating gonadal hormone levels. Third, developmental neuroimaging studies are needed to expand our understanding of sex differences in age-related changes in limbic and regulatory corticolimbic areas, and also to specify developmental change in activity in the subACC and insula, regions responsible for producing awareness of subjective emotional and physiological responses to threat. Specifically, more powerful studies with larger sample sizes can expand the current literature by facilitating direct testing of sex by age interactions and by collecting circulating hormone levels to test gonadal mechanisms. Such studies must also examine developmental change in the functional connectivity of affective, regulatory, and phenomenological networks, as these may reveal processes underlying sex differences in regional recruitment including top-down regulation of affect and the process supporting the construction of subjective experience. Fourth, studies must explore associations between brain activity, indices of peripheral ANS and HPA axis activity, and reports of negative affect to understand relationships across systems. Such studies will benefit from examining how different types of negative emotional responses (that may follow different interpretations) relate to different patterns of physiological experience. In addition, incorporating examination of behavioral indices of emotional expression can enrich this study of sex differences in the relationship of physiological responses to negative affect. Finally, future research investigating sex differences in executive regulation of affect through development

may also help clarify sex differences in both physiological reactivity and affect awareness. Female adults and adolescents may also respond to stress by engaging more regulatory regions that temper stress-related physiological responses. Relatedly, neuroimaging studies that assess cognitive/attention circuitry in addition to affect processes may reveal neurobiological bases for sex differences in the association between physiology and experience. This area of investigation can subsequently have important translational significance informing the known emergence of sex differences in psychopathology in adolescence.

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Figure 1.

Taken from Guyer et al. (2009). Results indicate age-related increases in activation among females in the insula (INS), hypothalamus (HThal), and hippocampus (Hip). In contrast, males show decreases in activity with age (insula) or no age-related changes (hypothalamus and hippocampus).

Figure 2.

(a) Sex differences in HPA reactivity in childhood (left) and adulthood (right) in response to a modified TSST comparable in social-evaluative demands to the TSST-C and TSST (taken from Yim et al., 2010b). Sex differences are not present in childhood for magnitude or time to recovery in the cortisol response whereas males clearly show greater magnitudes of responses in adulthood. (b) Adolescent sex differences in salivary cortisol responses ($\mu\text{g/dL}$) to a social performance stressor in Klimes-Dougan et al. (2001). Results indicate older adolescent males show greater reactivity than similarly aged females, and that sex differences in cortisol reactivity are not present in early adulthood.

Figure 3.

(a) Early adolescent and adult sex differences in heart rate responses to a public speaking paradigm (TSST) in Kudielka et al. (2004b). Results indicate that both young adolescent (left) and adult (right) females show greater heart rate increases over pre-test and post-task baselines as well as significantly greater areas under the response curve. (b). Adolescent (ages 12–18) sex differences in SBP (left) and HR (right) responses to a mental arithmetic test in Syme et al. (2009). In response to the math test, males show greater SBP responses while females show greater HR responses that reflect consistent differences across pre-test, testing, and recovery. (c) Among adults, variation in 5-HTTLPR genotype moderates sex differences in heart rate reactivity to a psychosocial stressor (McCaffery et al., 2003). Only in the “risk” s/s genotype group were sex differences evident.

Figure 4.

Model representing sex differences in developmental changes in physiological reactivity to acute psychosocial stress from childhood to early adulthood, their proposed relationships to negative affect, and the proposed influence of puberty. Thickness of arrows representing relationships between physiological reactivity and negative affect reflect proposed differences in their strengths.

Corticolimbic system studies — adolescent results.

Table 1

Reference	N(%F)	Effect size powered to detect ^a	Within-sex developmental effects powered to detect ^b	Ages	Amygdala — main effect of sex	Age-related change within adolescence	fMRI design	ROIs or voxel-based	Paradigm	Stressor	Comparison	Attention
<i>Interpersonal stressors</i>												
Masten et al. (2009)	23 (61%)	Large; $d = 1.26$	N/A	12.5—13.5	No main effect of condition	N/A	Block (2 blocks within each of 2 runs)	Voxel-based (10 voxel cluster)	UCLA cyberball	Cyberball—original	Social inclusion	Press button to pass ball
Guyet et al. (2009)	34 (47%)	Large; $d = 0.99$	F: large ($d = 0.60$), M: large ($d = 0.58$)	9—17	No main effect of condition	Hypothal: F↑ w/age, M n.s.; Insular: F↑ w/age, M↓ w/age; Hippo: F↑ w/age, M n.s.	Rapid event-related	ROIs	NIMH chatroom paradigm	Rate others' desire to interact	Peers rated as high versus low interest	Rate others' desire for future interaction
<i>Facial expressions of threat</i>												
Baird et al. (1999)	12 (58%)	Large; $d = 1.82$	N/A	12—17	T: n.s., A: n.s.	N/A	Block (5 blocks)	ROIs	McLean paradigm	Fearful faces	Nonsense grayscale figures	Label expressions of faces
Guyet et al. (2008)	31 (43%)	Large; $d = 1.06$	N/A	9—17	T: n.s., A: n.s., T: n.s., A: n.s.	N/A	Mixed event-related (4 blocks)	ROIs	NIMH faces paradigm	Fearful faces	Fixation Neutral faces	Passive viewing
McClure et al. (2004)	17 (47%)	Large; $d = 1.46$	N/A	9—17	T: n.s., A: F> T: n.s., A: F>	N/A	Mixed event-related (4 blocks)	ROIs	NIMH faces paradigm	Angry faces	Neutral faces	How hostile is this face?
Killgore et al. (2001)	19 (53%)	Large; $d = 1.37$	F: large ($d = 0.74$), M: large ($d = 0.71$)	9—17	N/A	L Amyg: F↓ w/age, M n.s.; L DLPFC: F n.s., M↓ w/age	Block (2 blocks)	ROIs	McLean paradigm	Fearful faces	Fearful faces Fixation	Passive viewing

^aBased on two-tailed sensitivity analyses where $\alpha = 0.05$, $1 - \beta = 0.80$. Cohen's conventions for interpreting effect sizes: 0.20 = small, 0.50 = medium, 0.80 = large.

^bBased on two-tailed sensitivity analyses where $\alpha = 0.05$, $1 - \beta = 0.80$. Cohen's conventions for interpreting effect sizes: | r |, 0.10 = small, 0.30 = medium, 0.50 = large.

Table 2

Hypothalamic—pituitary—adrenal axis studies — adolescent results.

Reference	N (% F)	Effect size powered to detect ^d	Ages	Main effect of sex	Task	Stressor type ^a	Social-evaluative rating ^b	Uncontrollability rating ^c	Audience
<i>Interpersonal stressors</i>									
Gunnar et al. (2009b)	82 (52%); (13yo; N = 22, 45%)	Medium; $d = 0.62$ (13yo; $d = 1.26$)	9—15	n.s.; (13yo: F >)	TSST-C	PS/CT	1	1	Y
Buske-Kirschbaum et al. (1997)	16 (44%)	Large; $d = 1.52$	9—14	n.s.	TSST-C	PS/CT	3	1	Y
Kudielka et al. (2004a)	31 (48%)	Large; $d = 1.04$	9—15	n.s.	TSST-C	PS/CT	1	1	Y
Bouma et al. (2009)	644 (45%)	Small; $d = 0.22$	15—17	M >	GSST (different in that must talk about themselves)	PS/CT	2	1	Y
Klimes-Dougan et al. (2001)	33 (48%)	Large; $d = 1.01$	14—16	M >	Social Performance Paradigm (TSST-like + talk with curt confederate)	PS(+VI)	2	1	Y
Klimes-Dougan et al. (2001)	38 (53%)	Large; $d = 0.94$	11—13	n.s.	Social Performance Paradigm (TSST-like + talk with curt confederate)	PS(+VI)	2	1	Y
Sumter et al. (2010)	295 (49%)	Small to medium; $d = 0.33$	9—17	n.s.	Leiden Public Speaking Task (visit lab 1 wk prior; talk re types of movies they like)	PS	1	0	N

^aPS = public speaking task; CT = cognitive task; VI = verbal interaction.^bSocial ratings indicate the level of threat (0—3; 3 is worst); Used ratings as outlined in Dickerson and Kemeny (2004).^cUncontrollability ratings — based on degree that behavioral responses do not affect outcomes (0—4; 4 is worst); used ratings as outlined in Dickerson and Kemeny (2004).^dBased on two-tailed sensitivity analyses where $\alpha = 0.05$, $1 - \beta = 0.80$; according to Cohen's conventions for interpreting effect sizes, 0.20 = small, 0.50 = medium, 0.80 = large.

Table 3

Autonomic nervous system studies — adolescent results.

Reference	N(% F)	Effect size powered to detect ^a	Ages	Main effect of sex			Task	Stressor type ^b	Social-evaluative rating ^c	Uncontrollability rating ^d	Audience?
				SBP	DBP	HR					
Achievement stressors											
McCann and Mathews (1988)	171(58%)	Medium; <i>d</i> = 0.44	10—18	M>	n.s.	n.s.	Mental arithmetic	CT	1	1	N
Mathews and Stoney (1988)	217(56%)	Small to medium; <i>d</i> = 0.38	7—18	n.s.	n.s.	F>	Mental arithmetic	CT	1	1	N
Mathews et al. (1990)	132(58%)	Medium; <i>d</i> = 0.50	11—22	M>	M>	n.s.	Mental arithmetic	CT	1	1	N
Ewart and Kolodner (1991)	260(52%)	Small to medium; <i>d</i> = 0.35	15—16	M>	n.s.	F>	Mental arithmetic	CT	1	1	N
Syme et al. (2009)	425(53%)	Small; <i>d</i> = 0.27	12—18	M>	M>	F>	Mental arithmetic	CT	0	1	N
McCann and Mathews (1988)	171(58%)	Medium; <i>d</i> = 0.44	10—18	M>	n.s.	n.s.	Mirror tracing (frustration)	CT	0	0	N
Mathews and Stoney (1988)	217(56%)	Small to medium; <i>d</i> = 0.38	7—18	M>	n.s.	n.s.	Mirror tracing (frustration)	CT	0	0	N
Mathews et al. (1990)	132(58%)	Medium; <i>d</i> = 0.50	11—22	M>	n.s.	F>	Mirror tracing (frustration)	CT	0	0	N
Ewart and Kolodner (1991)	260(52%)	Small to medium; <i>d</i> = 0.35	15—16	M>	n.s.	F>	Mirror tracing (frustration)	CT	0	0	N
Allen and Mathews (1997)	157(50%)	Medium; <i>d</i> = 0.45	15—17	M>	—	n.s.	Mirror tracing (frustration)	CT	0	0	N
Interpersonal stressors											
Ewart and Kolodner (1991)	260(52%)	Small; <i>d</i> = 0.35	15—16	M>	n.s.	F>	Social competence interview	PS	1	0	N

Reference	N(% F)	Effect size powered to detect ^a	Ages	Main effect of sex			Task	Stressor type ^b	Social-evaluative rating ^c	Uncontrollability rating ^d	Audience?
				SBP	DBP	HR					
Allen and Matthews (1997)	157(50%)	Medium; $d = 0.45$	15–17	M>	—	n.s.	Social competence interview	PS	1	0	N
Steiner et al. (2002)	133(55%)	Medium; $d = 0.49$	14–18	—	—	n.s.	Free association speech about any topic	PS	1	0	N
Steiner et al. (2002)	133(55%)	Medium; $d = 0.49$	14–18	—	—	M>	Stress-Inducing Speech T ask about stressful life event	PS	1	0	N
Gunnar et al. (2009b)	82(52%)	Medium to large; $d = 0.63$	9–15	—	—	n.s.	TSST — prep, free speech, mental arithmetic	PS/CT	1	1	Y
Kudielka et al. (2004b)	28(50%)	Large; $d = 1.10$	9–15	—	—	F>	TSST — prep, free speech, mental arithmetic	PS/CT	1	1	Y

^aBased on two-tailed sensitivity analyses where $\alpha = 0.05$, $1 - \beta = 0.80$; According to Cohen's conventions for interpreting effect sizes, 0.20 = small, 0.50 = medium, 0.80 = large.

^bPS = public speaking task; CT = cognitive task; VI = verbal interaction.

^cSocial-evaluative ratings indicate level of threat (1–3; 3 is worst); details in Dickerson and Kemeny (2004).

^dUncontrollability ratings (0–4; 4 is worst); details in Dickerson and Kemeny (2004).