Published in final edited form as:
J Clin Child Adolesc Psychol. 2013 ; 42(4): 564–575. doi:10.1080/15374416.2013.804387.

Future Directions in the Study of Social Relationships as Regulators of the HPA Axis across Development

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Abstract

Many promising findings support the notion that social relationships can dampen HPA axis stress responses and protect individuals from maladaptive psychological and physical disease states. Despite the public health relevance of this topic, little is known about developmental changes in the social regulation of the HPA system, with most prior research having focused on early childhood and adulthood. This gap is particularly striking with regards to adolescence, an age period when it seems likely that reliance on parents as sources of stress-buffering decreases, even as the security of friends and relationship partners as stress buffers may not yet be certain. Furthermore, we speculate that early life stress or abnormal social experiences may impact the propensity to draw mental and physical health benefits from social relationships, but more empirical support for these ideas is needed. Lastly, research linking social support to cumulative life stress has mostly relied on self-report measures of stress, making it difficult to show that social support impacts the type of chronic stress exposure that is associated with increased allostatic load or "wear and tear" on the body and on psychological functioning. Recent advancements in methodology (e.g., assessing hair cortisol levels) as well as composite measures of allostatic load using biomarkers that capture the activity of multiple neuroendocrine, cardiovascular, immune, and metabolic systems will allow us to ask new questions about the extent to which social relationships can impact cumulative life stress and health.

Social relationships have been widely recognized as protective factors for psychological well-being (Taylor, 2011) and physical health (Cohen, 2004; Uchino, 2006). With respect to mental illness, higher levels of social support are associated with lower prevalence, milder manifestations, or better treatment outcomes for a number of psychiatric conditions (Kessler, Price, & Wortman, 1985). Two broad sets of mechanisms are believed to underlie these beneficial effects: stress-buffering effects and main effects (Cohen, 2004; Thoits, 2011). First, social support networks can promote positive outcomes by buffering (i.e., reducing or blocking) the impact of stressful life experiences (Cobb, 1976; Cohen & Wills, 1985). Stressful life events are important risk factors in the development and maintenance of psychopathology (Grant et al., 2003), whereas social relationships have been shown to serve as coping resources (Taylor & Stanton, 2007), which are known to impact individuals' affective, cognitive, and neurobiological stress responses. Secondly, main effect models suggest that relationships are important regulators of psychological well-being and of many

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physiological functions (Gunnar & Donzella, 2002; Reis, Collins, & Berscheid, 2000) and, critically, that loss or lack of relationships is stressful and can increase risk for mental illness (e.g., Monroe, Rohde, Seeley, & Lewinsohn, 1999; Tyrka et al., 2008). Much of this work has been conducted with adults, and relatively little is known about these types of mechanisms in children and adolescents. We briefly review extant work in this area focusing primarily on stress-buffering effects, then describe some of the myriad questions that still remain and argue that in order to fully understand the processes through which relationships impact stress regulation, we need to adopt a developmental perspective. We focus primarily on the hypothalamic-pituitary-adrenocortical (HPA) axis as a stress-mediating biological system, but the important role of the autonomic nervous system and its interaction with the HPA axis are undeniable and should continue to be explored in this area of research.

Brief Overview of the HPA Axis

Stress can be defined as a "real or interpreted threat to the physiological or psychological integrity of an individual which results in physiological and/or behavioral responses" (McEwen, 2000, p. 508). These threats or challenges can be psychological (e.g., social evaluation) or physical (infection, cold, etc.), but both types of stressors place demands on the organism that require mobilization of energy to restore homeostasis. The HPA axis is an important mediator of these stress responses in mammals. The activation of the axis occurs via cortico-limbic circuits relaying information to neurons in the medial parvocellular region of the paraventricular nuclei of the hypothalamus, which secrete corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system, traveling to the anterior pituitary and causing the release of adrenocorticotropic hormone (ACTH) into the general circulation (Cone, Low, Elmquist, & Cameron, 2003). ACTH subsequently binds to its receptors in the cortex of the adrenal glands, leading to the release of glucocorticoids (cortisol in humans). Activating the HPA axis ultimately results in the mobilization of energy to muscles, enhanced cardiovascular tone, inhibition of reproductive physiology, decreased feeding and appetite, sharpened cognition, and increased local cerebral glucose utilization (Sapolsky, Romero, & Munck, 2000).

The acute stress response is only one aspect of HPA axis function, the other important dimension being its basal diurnal function. Glucocorticoids are released in pulses across the day following a circadian clock, with typically higher levels (i.e., larger amplitude pulses) in the morning for humans that reach peak levels approximately 30 minutes after wake-up (this is the cortisol awakening response and it has been associated with numerous physical and mental health outcomes; Fries, Dettenborn & Kirschbaum, 2009) and production declines throughout the day, reaching minimum levels approximately 30 minutes after the onset of nighttime sleep. Both elevated and low, blunted cortisol patterns have been associated with psychiatric and physical symptoms (Miller, Chen, & Zhou, 2007). The HPA axis has internal regulatory mechanisms, such that chronically elevated levels of the hormone can, over time, lead to down-regulation of the system and lower than normal levels of glucocorticoids, a phenomenon that has been termed "hypocortisolism" and is associated with numerous physical and psychological symptoms (Fries, Hesse, Hellhammer & Hellhammer, 2005; Gunnar & Vazquez, 2001). This is important to note as studies

investigating correlates of chronic life stress grapple with the challenge of noting either hyper- or hypocortisolism in high-risk samples.

Developmental Shaping of the HPA System by Caregiving

Experimental studies in rodents and primates have shown that maternal care is a powerful regulator of HPA stress responses early in development (Coe, Franklin, Smith, & Levine, 1982; Coe, Mendoza, Smotherman, & Levine, 1978; Levine, 2001; Stanton & Levine, 1990). Both high-quality maternal care (e.g., high levels of licking and grooming in rodents) and maternal separation, neglect or abuse have long-lasting effects on the developing brain and the functioning of stress systems (Meaney, 2010). For instance, rat pups reared by dams that are high in licking and grooming behavior exhibit lower endocrine and cardiovascular stress responses later in life and exhibit less fearful behavioral phenotypes compared to animals reared by dams that exhibit lower levels of these caregiving behaviors (Caldji et al., 1998; Francis, Diorio, Liu, & Meaney, 1999). Importantly, cross-fostering of rat pups and random assignment to maternal caregiving phenotypes have demonstrated the experiential basis for these alterations in brain and behavior (Francis et al., 1999). The animal literature has recognized a rich set of inputs that are embedded in maternal care that serve to regulate offspring's physiology and behavior, inputs that have been termed "hidden regulators" (Hofer, 1984) and include tactile stimulation, feeding, temperature regulation, etc.. However, it must be noted that the sheer presence of an anesthetized mother can also be enough to dampen cortisol stress responses in rat pups (Stanton & Levine, 1990).

Our goal is not to review this extensive animal work here, but merely to highlight the gaps in our understanding of similar developmental effects in humans. To understand the social regulation of the HPA, we review some of the known associations between aspects of social relationships and basal, acute response, or recovery patterns in the activity of the HPA axis. When social relationships are able to diminish or block acute responses to stressors, we will refer to these effects as "social buffering" in line with prior literature in humans and animals indicating a dampening of stress reactivity with the presence or assistance of conspecifics. When information on reactivity and social buffering is not available, we will review the main effects of relationships on basal functioning of the HPA, as it is likely that repeated buffering –or lack thereof- leads to alterations in diurnal rhythms and perhaps the set points of the axis.

There is a wealth of studies showing associations between adverse or disrupted childhood relationships and alterations in the functioning of the HPA axis in adulthood, whether predicting reactivity (Carpenter et al., 2007; Fisher, Kim, Bruce, & Pears, 2012; Goldman-Mellor, Hamer, & Steptoe, 2012; Gump et al., 2009; Heim et al., 2000) or basal circadian secretion of cortisol (Nicolson, 2004; Trickett et al., 2010; van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). Many previous studies have used retrospective measures of early life stress or have understandably focused on high-risk populations, such as children experiencing maltreatment or orphanage care, while the full spectrum of variations in caregiving has often been neglected in relation to observed adult stress reactivity. A recent study has aimed to answer this question, reporting that parental responsivity to the child at age 4 as observed in a home visit predicted adolescent cortisol

reactivity to the Trier Social Stress Test (TSST) 11–14 years later, such that lower parental responsivity predicted diminished or blunted patterns of reactivity in this sample of 55 African American participants (Hackman et al., 2013). More prospective longitudinal studies are needed to link observed and objectively measured natural variations in early caregiving –with information being especially needed before age 4- with measures of HPA axis reactivity across adolescence and into adulthood. This gap in the literature is understandable since there are very few longitudinal studies that span a sufficient timescale for testing this hypothesis. It will be important for longitudinal studies that have collected prospective data on early caregiving (e.g., the Minnesota Longitudinal Study of Parents and Children, Sroufe, Egeland, Carlson, & Collins, 2005) to assess the functioning of stress systems in adulthood. Additionally, many studies focus on broad time windows of child adversity (e.g., before age 5 or before age 16 in some studies), making it difficult to study possible sensitive or critical periods during which the HPA axis may undergo developmental programming by caregiving, to parallel the specificity of effects noted in animal models.

Short-term longitudinal studies would also be very informative, as there are also very few studies addressing the question of how caregiving is prospectively associated with later stress reactivity. For instance, one study reported that self-reported parenting style, in particular low level of structure (i.e., organization and consistency) measured between the ages of 6–13 predicted higher stress reactivity to the TSST in adolescents around the age of 16 (Ellenbogen & Hodgins, 2009). Turning to examinations of diurnal cortisol rhythms, one prospective longitudinal study found that maternal or paternal depression and family expressed anger measured when the child was 1, 4 or 12 months old predicted diurnal cortisol levels and slopes between the ages of 9 and 15, with children who experienced higher levels of these family risk factors exhibiting flatter diurnal slopes and elevated morning cortisol at age 9 and decreasing morning levels with abnormally flattened slopes by age 15 (Essex et al., 2011). Furthermore, children experiencing this particular familial risk exhibited more variable HPA levels. This study is consistent with other findings showing that maternal postnatal depression is associated with higher and more variable salivary morning cortisol in 13-year old children, patterns which are predictive of depressive symptoms at age 16 (Halligan, Herbert, Goodyer, & Murray, 2007). However, these findings presume low quality of early caregiving without objective measurement and also face interpretation challenges due to potentially shared genetic vulnerability. Studies of objectively documented child maltreatment are important in showing dysregulated patterns of HPA axis activity in children with these histories –e.g., experiencing physical and sexual abuse in the first five years of life is associated with higher levels of internalizing symptoms, as well as flatter diurnal cortisol slopes when children are school-aged (Cicchetti, Rogosch, Gunnar, & Toth, 2010) and into adolescence and young adulthood (Trickett et al., 2010). However, maltreatment is often a chronic, ongoing stressor and these patterns of results may not necessarily generalize well to time-delimited or milder stressors experienced early in development, and future studies will need to address these gaps in the literature. Both severity and chronicity of stressors are known to impact the basal activity of the HPA axis. Animal models (e.g., Houshyar, Galigniana, Pratt, & Woods, 2001) and meta-analyses of human studies (Miller, Chen, & Zhou, 2007) suggest that stressors lead to acute elevations in basal cortisol levels soon after stressor onset, but with time and chronicity hormonal

output is reduced. In particular, traumatic, uncontrollable or life-threatening stressors that are chronic in nature tend to elicit a flat pattern of cortisol production across the day, with lower morning and greater evening concentrations, sometimes leading to higher levels of total cortisol output across the day (Miller, Chen, & Zhou, 2007). These outcomes are likely due to the previously described self-rectifying feedback mechanisms of the HPA axis, which can shut down its own production to suppress morning levels subsequent to elevated evening levels. In contrast to the upregulation observed with severe acute stressors and downregulation that occurs with chronicity, mild stressors might have radically different effects on the functioning of the HPA axis, with some evidence that exposure to mild, manageable stressors may actually be beneficial and result in less fearful or less stress-reactive phenotypes, a phenomenon that has been termed “stress inoculation” (Lyons, Parker, Katz, & Schatzberg, 2009). Consistent with this notion, there is also some developmental evidence that moderate versus severe life stress has differentiable consequences for the functioning of the HPA axis in children adopted internationally (Gunnar, Frenn, Wewerka, & van Ryzin, 2009).

Many of these studies exploring links between the quality of early caregiving and later stress system functioning in humans are correlational, thus it will become especially important in future studies to use experimental designs and study the regulation of stress reactivity by caregivers in controlled laboratory settings. For instance, studies in adults have shown that social support from a romantic partner can dampen HPA axis reactivity (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995) to laboratory stressors. This process has yet to be studied comprehensively in children and adolescents, since much of the experimental developmental work in this area has focused on infancy and toddlerhood. We briefly review some of these findings next before highlighting gaps and future directions in this area.

The Social Buffering of the HPA Axis in Early Childhood

In infancy, maternal tactile stimulation seems to dampen cortisol stress responses to a still-face paradigm (a distressing event for most infants in which the mother abruptly presents a neutral, still face) compared to infants who are not touched during the procedure (Feldman, Singer & Zagoory, 2010). Maternal behavior is also associated with cortisol recovery after minor daily stressors such as being removed from a bath (Albers, Riksen-Walraven, Sweep, & De Weerth, 2008). Later in development, 18-month-olds who were scared by potentially frightening events (i.e., a live clown) but were securely attached to the parent who was with them did not show any elevation in cortisol, as compared to those who were insecurely attached to the accompanying parent (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). A similar marked buffering of the cortisol response was found with the presence of the parent in secure relationships for a clinic exam-inoculation visit and the Strange Situation procedure (Gunnar, Brodersen, Nachmias, Buss & Rigatuso, 1996). However, during the infancy and toddler period secure attachment does not prevent elevations in cortisol to stressors when the parent is not available to support the child (e.g., Ahnert, Gunnar, Lamb, & Barthel, 2004). Thus it is the presence of the attachment figure in combination with the security of the relationship that provides this type of potent buffering

of the adrenal response for fearful children (although, see also Roque, Veríssimo, Fernandes, & Rebelo, 2013).

Previous research has identified behaviorally inhibited temperament in childhood as a risk factor for the later development of anxiety disorders (Fox, Henderson, Nichols, Marshall, & Ghera, 2005; Lahat, Hong, & Fox, 2011). Furthermore, research shows that caregiving modulates the emergence, developmental continuity, and severity of behavioral inhibition. For instance, preschoolers who are shy will exhibit more social withdrawal at age 7 if their mothers exhibit negative behaviors such as intrusiveness and hostility (Hane, Cheah, Rubin, & Fox, 2008), while maternal anxiety and overinvolvement at age 4 predicts increased behavioral inhibition at age 6 (Hudson, Dodd, Lyneham, & Bovopoulous, 2011) and maternal punishment is associated with elevated cortisol reactivity in preschoolers meeting an adult stranger (Hastings et al., 2011). However, studies have not directly examined whether chronic activation of fear and stress biology mediates these effects of parental intrusiveness and hostility on maintaining and perhaps enhancing this fearful phenotype. Given the experimental findings from Nachmias et al. (1996) and Gunnar et al. (1996), this is a plausible model. Future studies should address this important gap in the literature in order to provide a biologically plausible model for how anxiety symptoms are maintained over time and become amplified to culminate in disorder.

Much of the work in this area has focused on the stress-buffering role of parents, however little is known about the roles of other care providers or siblings. One study found that being separated from the mother elicits an increase in salivary cortisol in 9-month old infants, but being randomly assigned to a babysitter who was experimentally programmed to be sensitive and responsive to the infant during this time dampened reactivity compared to being assigned to one who was experimentally instructed to only respond to the infant if she fussed and cried (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992). When separation lasts hours, for instance during the first two weeks of child care, even highly supportive caregivers are not able to prevent elevations in cortisol for young children; however, increases in cortisol from morning to afternoon are lower in settings with more supportive, less intrusive caregivers (Gunnar, Kryzer, van Ryzin, & Phillips, 2010). Furthermore, when preschoolers have been in child care for at least one month and are in high-quality settings, they show decreasing levels of cortisol across the day if they are securely attached to their parents, but this is not observed in moderate-quality care settings (Badanes, Dmitrieva, & Watamura, 2012). Furthermore, children who have been in child care for more than a month and are securely attached to their teachers show decreasing levels of cortisol across the day (Badanes, Dmitrieva, & Watamura, 2012). This finding suggests that it would be important to examine the extent to which non-parental caregivers or secondary attachment figures can serve as stress buffers across development, since this could form the basis for interventions with children who do not have access to supportive parents. However, currently there are many unknowns in this area. Furthermore, one can only speculate about the degree of familiarity or the duration needed to obtain a buffering effect from a social partner.

Another major gap that should be filled by future studies concerns the effect of early caregiving or early life stress more generally on the likelihood of experiencing a stress-buffering effect. It seems theoretically plausible that children who experience neglect or

maltreatment would show reduced anti-stress effects with social support, but this has not yet been empirically tested. A hint of support for this hypothesis comes from a study of post-institutionalized 4–5-year-old children who had been internationally adopted from orphanages who showed elevations in cortisol after playing a social game with their adopted mothers, while this was not observed for the non-adopted, comparison children (Wismer Fries, Shirtcliff, & Pollak, 2008). However, this particular instance of early social deprivation is not necessarily easy to extrapolate to children who form attachments to abusive caregivers or children experiencing intermittent parental neglect. More research is needed to examine the extent to which these high-risk populations show any buffering of stress responses by social partners. Furthermore, it is currently not known how abnormalities in the functioning of the HPA axis due to early life stress would interact with normative social developmental processes to impact the ability to draw upon social support in times of stress across development.

The major challenge in studying the social buffering of the HPA axis in children or youth who have experienced chronic stress would be that they show atypical patterns of reactivity to standard laboratory stressors. As described above, chronic stress can lead to blunted reactivity to acute stressors due to downregulation effects. For instance, parentally bereaved youth do not show the expected increase in cortisol to a laboratory stressor conducted 5 years after the loss of their parent, but they instead present with high and flat levels of cortisol across the session (Dietz et al., 2013). One could be baffled by the fact that diminished reactivity is also what would be expected in a normative context when youth are buffered by a supportive figure; however, this becomes easier to interpret when considering the functional significance of acute cortisol peaks, which help mobilize energy to cope with perceived threats or stressors. In the study just described, youth whose parents were still alive could mount a short-lived cortisol response to a public speaking task and quickly contain the response, returning to baseline in 20 minutes. One could imagine that if they had a supportive parent present, they might not even mount this response, perhaps because the task is perceived as less threatening or as not exceeding the youth's capacity to cope. In contrast, bereaved youth (who are known to show higher than average rates of depression) were not able to mount a stress response, but instead presented with persistently high cortisol levels, suggesting that their ability to contain or reduce stress responses may be impaired. In fact, one would predict that in chronically-stressed populations, buffering by social support or other therapeutic interventions might take a different form than a reduction in reactivity –namely, perhaps the effect of social support would be to normalize basal cortisol levels, restore the dynamics of HPA acute reactivity and the ability to recover from these peaks. In summary, associations with behavior or emotional symptoms could help our inferences regarding the beneficial or deleterious nature of observed cortisol patterns, whereas a thorough analysis of all dimensions of activity (basal circadian levels, acute responses, and recovery) could help differentiate adaptive from maladaptive forms of diminished reactivity.

Few studies have examined the social buffering of stress reactivity in middle/late childhood or adolescence, thus little is known about the developmental course of this phenomenon. As an exception, a study by Seltzer, Ziegler and Pollak (2010) showed that 7–12 year old girls who had either direct contact or a phone conversation with their mothers after the TSST

exhibited lower salivary cortisol levels post-stressor, and also higher levels of urinary oxytocin. However, this study did not examine the process in boys and also seems to have tested a buffering effect of recovery from the stressor, which is a different aspect of the process compared to the pre-stressor support paradigm used in adult studies showing diminished reactivity to a subsequent stressor. We do not know which paradigm provides more potent regulation of the HPA axis, but one advantage of the Seltzer et al. (2010) paradigm is that we do not need to question whether instrumental help partially explains any stress buffering that was observed. In another study that used correlational methods, 10–11-year-olds reported daily events using diaries and negative events were associated with lower levels of cortisol if children reported being with their best friend at the time of the event (Adams, Santos, & Bukowski, 2011). Replicating this study in the laboratory with experimentally-controlled stressors would be an important future direction to better characterize this phenomenon.

Puberty, Stress Buffering, and Psychopathology

Children's social relations undergo significant changes from childhood to adolescence. Parents, while still important in children's lives, begin to share their salience with same-sex peers, and later with romantic partners (Harris, 1995; Hartup, 1996; Hunter & Youniss, 1982). Across adolescence, participants report decreasing levels of support from parents, especially when the quality of the parent-child relationship was poor before this transitional period (Laursen, DeLay, & Adams, 2010). Activity of the HPA axis increases between childhood and adolescence and it has been hypothesized that this increases children's vulnerability to psychopathology (Spear, 2000). Because girls begin to exhibit markedly more depression than boys at around 13–14 years (Nolen-Hoeksema & Girgus, 1994) and because abnormalities in the activity of the HPA axis have been associated with depression (Herbert, 2013), there is a strong expectation that puberty in girls results in a more hyper-responsive HPA axis and that this is one of the factors that underlies their increased vulnerability to depression (Spear, 2000; Stroud, Papandonatos, Williamson & Dahl, 2011). It is also possible, based on some of the available evidence, that gender moderates the association between HPA axis reactivity and internalizing symptoms (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Klimes-Dougan, Hastings, Granger, Usher & Zahn-Waxler, 2001; Natsuaki et al., 2009), such that stronger reactivity may be more tightly coupled with psychopathology in girls than boys, irrespective of gender differences in reactivity. There are many pieces to this argument and our goal here is not to thoroughly evaluate it. Rather, it is to note that we may gain more traction in understanding the HPA axis and the vulnerability of young girls to depression if we at the same time considered developmental changes and gender differentiation in the role of relationships in stress activation and buffering as children transition from childhood to adolescence.

There is considerable evidence that basal cortisol levels increase from childhood to early adolescence (for review, see Gunnar & Vazquez, 2006, but see also Rosmalen et al., 2005). There is also evidence that by the end of puberty, but not before puberty, basal levels are higher among girls than boys (e.g., Netherton, Goodyer, Tamplin & Herbert, 2004; Stroud et al., 2011). The evidence for a greater increase in cortisol *reactivity* with puberty for girls than boys is mixed. When the adrenal is stimulated through pharmacological challenge (e.g.,

CRH infusion), puberty has been associated with an increase in cortisol response in girls but not boys (Stroud et al., 2011). When the adrenal is stimulated psychologically, this has not been found. Indeed, while puberty is associated with increased cortisol reactivity to both public speaking and peer rejection stressors (Gunnar et al., 2009; Stroud et al., 2009), sex differences have not been noted, even to the peer rejection stressor that, among adults, produces larger cortisol increases in women than men (Stroud, Salovey, & Epel, 2002). Furthermore, when a sex difference has been noted in response to public speaking-type stressors, pubertal boys have been found to show larger cortisol responses than pubertal girls and younger children of either sex (Klimes-Dougan et al., 2001). This is also the pattern reported for performance stressors among adults (Kudielka & Kirschbaum, 2005). Thus the idea that the HPA axis becomes hyper-responsive among girls during puberty, contributing to their greater vulnerability to depression is clearly overly simplistic and future research needs to take additional factors into consideration.

We have only begun to explore the possibility that it is not simply the reactivity of the HPA axis, but its sensitivity to social regulation that becomes more gender-differentiated with puberty. It has been argued that women rely more on “tend-and-befriend” strategies to cope with stress, while men rely more on “fight-or-flight” strategies (Taylor et al., 2000). This may mean that women either exhibit stronger stress-buffering effects with social support, or that both genders can have their stress responses regulated by social stimuli but women may be more likely to seek and utilize social coping mechanisms, whereas men might resort to other coping strategies before they turn to social support. If any of these theoretical predictions hold true, we might expect these differences in coping strategies to emerge over the course of adolescence, as children shift from a reliance on parental attachment and adult-child protective relations to regulate stress biology to coping methods that allow them to leave the natal group. To our knowledge, there are hardly any data in the literature to test this prediction in adolescence.

In a previously mentioned social buffering experiment in adults (Kirschbaum et al., 1995), the presence of a significant other for men (typically a female partner) during preparation for a public speaking task was a potent buffer of cortisol responses to the task, whereas the presence of a significant other for women (typically a male partner) was not effective. Even though this seems opposite to the “tend-and-befriend” hypothesis it is not, as the hypothesis suggests that women tend and befriend typically with other women. Nevertheless, this model provides one way to examine the potency of social relationships as stress regulators. This type of experimental paradigm would be very useful to employ in examining whether relationships become more or less potent as stress regulators over the course of adolescence, whether changes are related to puberty or age, whether relationships remain potent but reliance shifts from parent-child relationships to peer relationships, and whether gender differences emerge in the effectiveness of social support either with regards to the gender of the individual who is exposed to the stressor and/or to the gender of the individual providing social support. Even though we know from correlational studies that self-reported characteristics of the family environment and of peer relations are associated with cortisol levels in adolescence (e.g., Dorn et al., 2009), experimental studies in this arena will be needed.

It is also possible that puberty and gender may interact to shape the types of events that are stressful for males versus females. There are likely developmental changes in the types of stressors that activate the HPA axis and these stressors may also change status or salience with puberty. One such stressor that has the potential for differential effects by gender is social rejection by peers, given the growing importance of peer relationships in adolescence. We know that peer victimization is associated with alterations in the activity of the HPA axis in children and teenagers (Knack, Jensen-Campbell, & Baum, 2011; Ouellet-Morin et al., 2011; Vaillancourt et al., 2008), with gender moderating these links such that males show higher and females lower cortisol levels with occasional victimization (Vaillancourt et al., 2008). This may be because females are more likely to become depressed due to bullying, since one longitudinal examination reported that victimization predicted depression symptoms, which in turn predicted lower cortisol levels at a subsequent assessment (Vaillancourt et al., 2011). Thus, even though boys and girls show different patterns of HPA axis alterations, there is little evidence currently that peer rejection is more stressful for girls than boys, although such evidence exists in adulthood (Stroud et al., 2011). We might expect, though, that social support would be more important in moderating the impact of rejection than it is when performance (e.g. public speaking) is the threat that triggers activation of the HPA axis. There is some evidence that having at least one friend is an important buffer of the impact of peer rejection on the HPA axis in children (Peters, Riksen-Walraven, Cillessen, & de Weerth, 2011). Whereas puberty appears to increase responses to peer rejection (Stroud et al., 2009) we do not know whether the role of friends as buffers of rejection stress changes as we move from childhood to adolescence, nor whether sex differences in the potential of friends to serve as stress buffers begins to emerge. It is possible that the type of rejection and victimization experienced matters. We might expect that since boys tend to be more exposed to physical victimization, having at least one male friend might become highly important, especially as such a friend might provide a source of instrumental support under fight/flight conditions and thus reduce the threat of physical harm. In contrast, as girls tend to be more exposed to relational victimization, the stress-buffering role of having at least one friend may be more complex. The friend could become a weapon or tool for those who are victimizing the girl or might be the source of relational aggression, and thus unless the friendship was completely secure it might not be an effective buffer.

This last point relates to a yet unexplored aspect of peer relations as sources of stress buffering. As noted earlier, the security of the parent-child attachment relationship is an important moderator of the power of the parent's presence and availability to buffer reactivity of the HPA axis (Gunnar et al., 1996, Nachmias et al., 1996). Among adult couples, there is also some evidence that attachment security moderates the effect of social support on psychological stress, but one study failed to find a significant moderation effect on cortisol reactivity (Ditzen et al., 2008); however, this study only used a self-report measure of attachment security. Importantly, individuals in secure dating relationships exhibit lower cortisol stress responses to an experimental relationship conflict negotiation task compared to individuals who have avoidant or anxious adult attachment patterns (Powers, Pietromonaco, Gunlicks, & Sayer, 2006). Based on some of these preliminary findings in infants and adults, we might well expect that when and if peers begin to be

capable of buffering reactivity of the HPA axis to stressors, the quality of the relationship will moderate the stress-buffering effectiveness of the peer's presence.

Parenting Interventions Affect Children's Stress System Function

The findings regarding the social buffering of stress described above would have important clinical implications if they could serve as a foundation for interventions that would minimize the burden of stress and decrease risk for psychopathology across development. Since some of the studies mentioned are correlational, the argument could be made that children with sensitive parents could exhibit reduced stress responses to various challenges due to shared genetic factors that lead to similarly well-regulated phenotypes in parents and children. Experimental studies described could also be criticized for using laboratory stressors, raising concerns regarding the generalizability of these buffering effects to naturalistic situations. For these reasons, parenting interventions provide important evidence that changes in parenting are associated with alterations in stress system function, often normalizing dysregulated patterns of activity. These interventions have largely been conducted with high-risk populations. For instance, maltreated children are known to show dysregulated HPA axis patterns (Cicchetti et al., 2010), but one intervention with 13-month olds from maltreating families aimed to shift HPA axis function by randomly assigning mothers to receive either child-parent psychotherapy, psychoeducational parenting, or be in a control group receiving standard community services (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011). Infants of mothers from the control group showed decreasing levels of cortisol over time (up to one year post-intervention), suggesting blunted cortisol patterns, whereas infants from the two active interventions showed cortisol patterns that were indistinguishable from a non-maltreated control group. Infants and preschoolers in foster care show similar abnormalities in diurnal cortisol rhythm as those observed in maltreated samples. For instance, Dozier et al. (2006a) reported dysregulated basal cortisol rhythms in up to 65% of infants in foster care, with many of these children exhibiting abnormally low or blunted morning levels. Additionally, preschoolers entering a new foster placement have been shown to exhibit similar patterns, with review of their records showing that the severity of experienced neglect predicts this atypical diurnal pattern (Bruce, Fisher, Pears, & Levine, 2009). Importantly, for infants and toddlers in foster care, interventions that focus on improving foster parenting appear to either normalize cortisol levels (Dozier et al., 2006b) or prevent the development of atypical diurnal patterns (Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Future studies should incorporate physiological measures of stress reactivity, not just diurnal cortisol and should also test similar effects in other populations, as it would be useful to know whether they generalize outside of these high-risk, chronically stressful environments.

Social Support and Cumulative Measures of Life Stress

It is becoming increasingly evident that chronic stress and allostatic load (the cumulative "wear and tear" on the body due to long-term activation of stress-mediating systems) are the major risk factors predicting adult mental and physical illness (McEwen, 2008; McEwen & Gianaros, 2011). Previous studies have mostly linked social support to cumulative measures of stress derived from self-report questionnaires (Cohen & Wills, 1985), which can be

problematic due to memory and bias problems inherent in these measures. On the other hand, physiological measures of stress reactivity often capture only acute aspects of HPA system function through measurement of momentary hormone levels in blood plasma, urine, and more non-invasively in saliva. However, recently developed techniques may help overcome this problem as they allow measurement of cortisol levels in the hair of humans and other animals (Meyer & Novak, 2012). It is thought that cortisol is incorporated into the growing hair shaft from the vascular supply to the follicular cells that generate the hair shaft, as well as through diffusion from nearby tissue, but the exact mechanisms remain to be fully characterized. Hair cortisol reflects cumulative cortisol levels over long periods of time (weeks and months), whereas traditional measures from saliva or plasma capture momentary concentrations of stress hormones that are heavily impacted by the time in the diurnal cycle when the sample is collected (approximately 70% of variance, Adam, 2012) and also by contextual variation. Even though the latter methods have been very useful in measuring reactivity to controlled laboratory stressors (e.g., Gunnar et al., 2009) or day-to-day dynamics (e.g., Adam, 2006), hair cortisol measures promise to reveal a new dimension of HPA axis activity. Indeed, recent reviews of this emerging area of research suggest that hair cortisol correlates well with measures of life stress across a variety of contexts and samples (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2012). Such a cumulative measure will be important in our psychobiological toolkit and will allow us to test whether the availability of social support tracks well with these cumulative measures of stress exposure. Future studies should incorporate both momentary and cumulative measures of stress hormones in their design in order to gain a more comprehensive characterization of the interplay between social relationships and stress system regulation over time and especially during developmental periods known to exhibit heightened vulnerability for psychopathology such as adolescence.

Another emerging approach to assessing allostatic load has been to create multi-index composites across several biological systems, including biomarkers capturing neuroendocrine, immune/inflammatory, metabolic, and/or cardiovascular functioning (e.g., Chen, Miller, Lachman, Gruenewald, & Seeman, 2012; Doan & Evans, 2011; Hickson et al., 2012; Juster et al., 2013; Rogosch, Dackis & Cicchetti, 2011). Some of these studies have begun to show that social relationships can attenuate the impact of allostatic load on development –e.g., maternal responsiveness acts as a moderator for links between allostatic load at ages 9 and 13 and later adolescent working memory at age 17 for youth who had been living in low socioeconomic conditions (Doan & Evans, 2011). Maternal nurturance also seems to buffer against metabolic risk factors (Miller et al., 2011) and inflammatory states (Chen, Miller, Kobor, & Cole, 2011) associated with low childhood SES and with heightened risk of affliction with chronic diseases of aging. Future research should examine whether these protective effects are direct effects of social support on immune and metabolic function or are, at least in part, mediated by reductions in stress load.

Conclusions

Many exciting findings support the notion that relationships can dampen stress responses and protect individuals from maladaptive psychological and physical disease states. Nevertheless, relationships also have a “dark side” (Thoits, 2011) in that their destructive

forms (e.g., abusive parenting) also impact stress physiology and may establish patterns of activity that set the stage for later psychiatric or physical illnesses. Despite the public health relevance of understanding relationships as stress buffers and as factors critical to vulnerability and resilience, little is known about the developmental course of these social buffering effects, with most prior research having focused on early childhood and adulthood. This gap is particularly jarring during adolescence, a period that has been intensely studied with regards to emerging psychopathologies. The field will also need to gather more knowledge about the factors that determine who in one's social network can serve as a stress buffer, and how this may change across development. Furthermore, we speculate that early life stress or abnormal social experiences will impact the propensity to be able to use conspecifics to buffer stress, but more empirical support for these ideas will be needed. Recent advancements in methodology (e.g., assessment of hair cortisol levels) and in study designs which collect and combine multiple biological indices of physiological arousal and allostatic load will also allow us to ask new questions about the ability of social relationships to impact these measures of cumulative life stress. This future avenue is particularly important since it is the chronic, cumulative aspects of stress that have been linked to increased allostatic load or "wear and tear" on the body and on psychological functioning (McEwen, 2008).

Acknowledgments

This work was supported by the Eva O. Miller Fellowship to Camelia E. Hostinar and by National Institutes of Health Grant MH078105 to Megan R. Gunnar.

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