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High levels of life adversity are implicated in depression and may increase risk through altered physiological reactivity. Prior work has examined the role of life adversity in hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system (SNS) responses to lab-based stress, but few studies have examined specific dimensions of depression-relevant adversity (severity, interpersonal nature, timing [recent versus distal]—applicable only to episodic adversity here). In a sample of healthy, non-depressed adults, I examined how these dimensions influenced HPA and SNS reactivity. In session 1, participants completed the UCLA Life Stress Interview and in session 2, completed either a negative evaluative version of the Trier Social Stress Test (n=67) or a control condition (n=66). Extending evidence for the impact of life adversity on depression, I predicted that major severity, interpersonal, recent events (i.e., past 3 months), and chronic interpersonal stress would predict HPA and SNS dysregulation. The results provided no support for a role of major, interpersonal, recent life events or for chronic interpersonal stress. However, exploratory analyses suggested value in examining specific chronic domains; financial stress was associated with blunted cortisol reactivity in the challenge condition. Because the current study was as similarly powered as recent investigations, and the only supportive findings were exploratory, results cast doubt on the notion that objectively measured “depressogenic” stress exposure, on average, alters HPA and SNS reactivity in an unselected adult sample. Potentially, such relationships may hold only for those with prior vulnerability, or those exposed to stressors uncommon in this sample (e.g., trauma).

CRITICAL FORMS OF LIFE ADVERSITY AND MULTIMODAL INDICATORS OF LAB-BASED STRESS REACTIVITY

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CHAPTER I: INTODUCTION

Major depressive disorder affects around 17% of people in the United States in their lifetime (Kessler et al., 2005), results in major economic loss (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015), and negatively affects physical health (Moussavi et al., 2007). Life adversity is a critical predictor of the onset of depression (Brown & Harris, 1989; Kessler, 1997; Monroe & Depue, 1991) and may in part exert its effects by dysregulating stress responsive systems (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Two key physiological stress reactivity systems are the hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system (SNS). The goal of the current work was to test whether life adversity is associated with dysregulated stress responding in non-depressed young adults. Evidence suggests that certain types of life adversity such as major life adversity—sometimes referred to as "severe" adversity (Brown & Harris, 1978), recent adversity (Kendler & Gardner, 2017), and interpersonal adversity (McLeod, Weisz, & Wood, 2007; Vrshek-Schallhorn et al., 2015; Whisman, 2001) may increase risk for depression more so than their counterparts, i.e., non-severe, distal, and noninterpersonal adversity; thus, they may play a role in dysregulating physiological stress responding as well. Furthermore, life adversity is often conceptualized separately as chronic (ongoing, non-acute stressors) versus episodic (acute events), and though evidence is somewhat more robust for a relationship between episodic events (as compared to chronic stress) and depression, both are thought to contribute to depression risk (Vrshek-Schallhorn et al., 2015). Here, I predicted that depressogenic life adversity would also predict dysregulated lab-based stress reactivity in the HPA and SNS systems. Within episodic stress, I examined how severity, recency and interpersonal status predicted reactivity. For past-year chronic stress—rated dimensionally on severity—I examined how severity and interpersonal status predicted reactivity.

Stress Reactivity Systems

SNS

The SNS and the HPA-axis are the two key components of the physiological stress response. Mobilization of both systems can be adaptive in the short term in response to genuinely threatening circumstances. In response to an acute stressor, the SNS responds within seconds to facilitate the "fight or flight" response (Cannon, 1914; Christensen, 1991). Hypothalamic signals

stimulate sympathetic nerve fibers from the locus coeruleus to signal organ systems directly allowing for quick response. One such target is the adrenal medulla, which when stimulated, releases catecholamines such as epinephrine and norepinephrine. These hormones in turn help to increase heart rate, breathing rate, blood flow, blood glucose, and reduce "rest" functions such as digestion (Cannon, 1929). This "fight or flight" response is then attenuated through parasympathetic nervous system mediated mechanisms (e.g., vagal nerve influences on cardiac tissue; Quigley, 2010). SNS reactivity is typically measured through salivary alpha-amylase (sAA), systolic blood pressure, diastolic blood pressure, catecholamine release, and skin conductance (Cannon, 1929; Grassi & Esler, 1999). Additionally, heart rate reactivity in often used in the stress reactivity literature as an SNS indicator though it is more accurately a general indicator of overall arousal (Kamarck & Lovallo, 2003; Nater & Rohleder, 2009). In the present study, I excluded heart rate data from analyses and instead, utilized sAA because of the feasibility of collecting this index and its utility as an indicator of SNS function (Nater & Rohleder, 2009); in addition, systolic and diastolic blood pressure were only available for a subset of participants and thus, were not included in the present study.

HPA-axis

Relative to the SNS, the HPA-axis facilitates a relatively longer-term stress response, unfolding over minutes rather than seconds. Neurons in the paraventricular nucleus of the hypothalamus release corticotropic releasing hormone, which then binds to receptors on the anterior pituitary gland, resulting in the release of adrenocorticotropic hormone (ACTH). This hormone in turn results in generation and release of glucocorticoids (e.g., cortisol in humans; Smith & Vale 2006). Cortisol is then released by the adrenal gland to facilitate energy mobilization; specifically gluconeogenesis (i.e., breakdown of proteins and lipids into glucose), to suppress energy storage, and to reduce bodily functions not essential for survival such as reproduction (McEwen & Wingfield, 2003; Sapolsky, Romero, & Munck, 2000). Circulating cortisol then binds to low affinity (i.e., requiring high levels to activate) glucocorticoid receptors in brain regions such as the paraventricular nucleus and the hippocampus, signaling a negative feedback mechanism to downregulate the HPA axis response (Smith & Vale, 2006). The primary indicator of HPA reactivity in the human literature is cortisol reactivity.

In addition to energy facilitation effects of individual stress reactivity systems, evidence indicates that both the HPA and SNS stress responses work synergistically to help the organism respond to adversity. Indeed, both systems share anatomic structures such as the hypothalamus (Stratakis & Chrousos, 1995) and can modulate the other's response. For example, cortisol may modulate sympathetic activity function by sensitizing cardiac muscles to the effects of catecholamines (Sapolsky et al., 2000). Physiological actions of both systems possess similarities. Both catecholamines and cortisol increase glucose levels (Cannon 1929; Sapolsky et al. 2000), work together to facilitate immune response to fight infection (Dhabhar & McEwen, 1999), and heighten memory during adverse situations through SNS-mediated epinephrine and HPA-mediated cortisol release, serving an adaptive function for remembering details important for survival or success in future similar situations. Thus, understanding stress reactivity to life adversity in both systems is important for a more complete understanding of the stress response.

Allostasis

The functions and responses of the HPA-axis and the SNS are consistent with theories of homeostasis and allostasis. The concept of homeostasis refers to the tendency for an organism's physiology to maintain a pattern of stability of action through regulatory mechanisms (Cannon 1929). Adversity is one external stimulus that may disrupt homeostasis. While homeostasis emphasizes the notion of a maintained level of stability, allostasis emphasizes continual adaptation. Allostasis refers to the mechanism by which the individual achieves homeostasis in response to constantly changing environments (McEwen & Wingfield, 2003). For example, temporary elevations in cortisol may indicate the organism's attempt to maintain homeostasis in response to a threatening or demanding situation (Kirschbaum & Hellhammer, 1999). Allostatic load refers specifically to the "side effects" of physiological efforts to maintain homeostasis, which are cumulative "wear and tear" effects over time. Thus, though allostasis in response to adversity may be adaptive, factors such as severity of the adversity may result in excessive and prolonged allostatic states, increasing risk for disorders such as depression. Indicators of allostatic load include overactivation, prolonged atypical activation, and insufficient response in one or multiple physiological systems (McEwen, 1998).

"Maladaptive" stress responding

Indeed, repeated activation or overactivation of the HPA-axis and SNS may result in damage to hippocampal neurons (McEwen, 1999; Sousa, Lukoyanov, Madeira, Almeida, & Paula-Barbosa, 2000) and inhibition of neurogenesis (McEwen, 1999). These alterations in the hippocampus may affect regulatory mechanisms that are responsible for preventing chronic activation of physiological stress response systems (Jacobson & Sapolsky, 1991). Additionally, under activation in the HPA axis and/or the SNS, in addition to signaling an inadequate mobilization of physiological resources to meet the demands at hand, may also result in maladaptive elevations in other biological systems to compensate (e.g., elevated inflammatory cytokines; McEwen 1998), that increase risk of disease and cause excessive burden to other allostatic systems.

The role of lab-based stress inductions

Understanding adaptive and dysfunctional responding in both systems will provide insight into maladaptive physiological responding and depression risk. Lab-based stress inductions serve a necessary role in assessing the functioning of physiological stress responsive systems. This approach facilitates studying groups of individuals with a consistent level of challenge to provide an understanding of factors affecting differences in stress responding. A commonly used approach to lab-based stress induction is the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) in which participants prepare and give an extemporaneous speech to neutral confederate judges followed by a serial subtraction task performed out loud. Negative evaluative adaptations of the TSST (e.g., Way & Taylor, 2010) direct confederate judges to respond in a bored, dissatisfied manner to the participant's performance, may be more relevant to depression risk, and have been shown to provoke greater cortisol reactivity than their neutral counterparts (Vrshek-Schallhorn, Avery, Ditcheva, & Sapuram, 2018). Though not without limitations, lab-based stressors provide an important snapshot into the processes that occur during naturalistic life stress and provide insight into the allostatic state of the HPA-axis and SNS.

What is Life Adversity?

"Stress" is a multifaceted construct that various researchers have defined in different ways. One perspective considers stress to be the objective level of environmental pressure,

demand, or challenge placed upon the organism (Dohrenwend, 2000; Monroe & Roberts, 1990). Another perspective considers stress as the physiological or subjective response to environmental challenges or "stressors" (Selye, 1936, 1956). And yet others consider stress to involve *both* the environmental pressure placed on the organism as well as the organism's reaction (Lazarus, Folkman, 1984). Critically, though both the objective environmental pressure on the individual (i.e., stress exposure) and the individual's subjective reaction to the experience (i.e., stress response) are important to understand the effects of adversity, differentiating the exposure and response is important to understand the unique effects of each (Harkness & Monroe, 2016; Monroe & Roberts, 1990). Though each individual's subjective experience of a stressor is important in understanding how they will be affected by the stressor, individual differences in subjective response cannot be understood without clarifying and separating out the objective environmental circumstances.

Measuring life adversity

Any measurement of life adversity that fails to differentiate between objective and subjective components of stress, or that examines only subjective stress, may confound illness risk with stressor occurrence and severity. For example, research attempting to understand the relationship between subjective (i.e., perceived) stress and depression may conclude that adversity is associated with depression risk; however, this conclusion may be driven by individuals higher in Neuroticism (a personality trait associated with depression risk; Kendler, Neale, Kessler, Heath, & Eaves, 1993) who may appraise stressors to be more severe and have elevated behavioral or emotional reactions to the stressor (Bolger & Schilling, 1991; Schneider, 2004). Indeed, a prior study found an association between internalizing psychopathology symptoms and overappraisal of stressor severity (relative to researcher rated stressor severity) in adolescents and in young adults (Conway, Starr, Espejo, Brennan, & Hammen, 2016). Failure to differentiate (to the extent possible) between objective and subjective stress may result in spurious correlations between life adversity and risk for depression (Monroe, 2008; Monroe & Kelley, 1995). Thus, in the present study, I utilized the UCLA Life Stress Interview (LSI; Rudolph & Hammen, 1999), one of several "gold-standard" measures of recent adversity, involving blind rating of the "long-term" contextual threat (i.e,. extent to which the stressor has negative impact or threat at a point one week following the onset of the event) according to what a typical person would experience in the exact same context (discussed further in the Methods

section). Naturally, such interview measures are not *perfectly* objective, but represent substantially greater objectivity as compared to self-report measures that often include items measuring perceived stress. Furthermore, such interview measures of adversity are generally considered more valid than self-report measures (Harkness & Monroe, 2016).

Life Adversity and Depression Risk

Life adversity shows a robust association with depression risk (Kendler, Karkowski, & Prescott, 1999; Kessler, 1997). A meta-analysis of twin studies indicated that unshared environmental factors (e.g., stress) accounted for approximately 63% of variance in risk for depression (Sullivan, Neale, & Kendler, 2000). Moreover, some types of adversity appear to be more depressogenic than others (Brown & Harris, 1978) and thus, may be more likely to predict dysregulation in physiological systems under laboratory examination. Despite the clear association between adversity and depression, a meta-analysis by Chida and Hamer (2008) did not find an association between general life stress on either HPA or SNS reactivity to lab-based stress. Notably, their meta-analysis did not distinguish between key types of life adversity associated with depression risk. Likely, fine-grained analyses of key types of life adversity are needed to better understand the relationship between adversity and physiological reactivity. Potential dimensions critical to understanding this relationship are reviewed below.

Severity

In their influential work on adversity and depression, Brown and Harris (1978) operationalized severity as the level of long-term contextual threat conferred by an event 7 days after its occurrence given the context of the event. To broaden this definition to a wider array of stressful experiences (e.g., chronic adversity), I define severity as the level of negative impact or threat conferred by the adverse *experience* for the average individual in the same context. That is, higher severity adversity (i.e., major life adversity) is characterized by higher levels of threat or difficulty that likely result in long-term threat or challenge and may include traumatic events, the death of a close friend, the experience of an abusive relationship, or a divorce in a long-standing marriage involving significant legal battles. Lower severity adversity (i.e., minor life adversity) may include experiences that do not result in significant, long term impact such as a brief argument among a group of friends or a minor illness for which the individual has coping resources and support.

Major life adversity demonstrates a more robust relationship with depression than lower severity adversity (Brown & Harris, 1978; Monroe, 2008; Vrshek-Schallhorn et al., 2015). Notably, minor life adversity is thought to potentially play a role in the occurrence of depressive episodes particularly among those with a prior history of depression but may contribute less to an initial depressive episode (i.e., kindling; Monroe & Harkness, 2005; Post, 1992). Thus, it appears likely that major adversity ought to play a greater role in the development of depression risk, and that it thus might also influence physiological stress responding more robustly than minor stressors.

Indeed, several studies demonstrated a significant relationship between relatively major life adversity and HPA-axis and SNS reactivity. These studies measured stress exposure including traumatic events (Elzinga et al., 2008; Jaffee et al., 2015) and interview-measured stressful life event severity (Lawler & Schmied, 1987). However, many of the studies examining major life adversity examined maltreatment history in childhood (Harkness, Bruce, & Lumley, 2006; Leitzke, Hilt, & Pollak, 2015; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014). Indeed, few studies examined the role of *recent* major and minor life adversity.

Furthermore, not all studies examining major life adversity found significant effects on physiological reactivity. For example, Murali and Chen (2005) failed to find an effect of violence exposure on cortisol reactivity in $n=115$ high school children—possibly due to a relatively mild lab-stressor task in which the adolescent participant engaged in a debate and then instructed the experimenter in a puzzle task. Similarly, other studies assessed an amalgam of major and minor severity life adversity and did not specifically differentiate between higher and lower severity adversity (Mazurka, Wynne-Edwards, & Harkness, 2016; Pike et al., 1997). This potentially may have diluted results and made it unclear whether major life adversity plays a greater role than minor life adversity. Similarly, other studies that did not differentiate between major and minor life adversity and found significant effects on HPA and SNS dysregulation are unable to determine whether this was driven by major life adversity or minor life adversity (Boyce & Chesterman, 1990; Musante et al., 2000; Ouellet-Morin et al., 2011; Pagliaccio et al., 2014).

Examinations of different levels of severity within study related to physiological dysregulation has been largely lacking and are often limited by methodological factors. A

notable exception includes Rao, Hammen, Ortiz, Chen, and Poland (2008), examining the severity of past 6-month chronic and episodic adversity. Researchers found an effect of past 6 month chronic but not episodic adversity—however results are limited by small sample size (N=55), which is particularly noteworthy given that episodic events that meet the threshold are somewhat infrequent and may have further hampered power (e.g., Mazurka et al., 2016). Another limitation to the prior literature is that measures intended to examine relatively major life adversity such as the Childhood Trauma Questionnaire (Bernstein et al., 1994) and its short-form (Bernstein et al., 2003) may actually capture milder forms of adversity, depending on the exposure level of the sample. Several items on the CTQ and the CTQ short form likely measure high severity adversity such as, "I got hit so hard by someone in my family that I had to see a doctor or go to the hospital," and, "Someone threatened to hurt me or tell lies about me unless I did something sexual with them." However, other items are relatively more ambiguous such as "I felt loved" (reverse scored) and "I thought that my parents wished I had never been born." Notably, these latter items are not necessarily insignificant markers of adversity but are less concrete and more subjective. Further, it is possible that on average, these items, grouped into the same scales as the "severe" items, may be endorsed more frequently in some samples (e.g., low risk samples), which would give the impression of high levels of adversity, but which may not be qualitatively similar to substantiated cases of neglect or abuse. Thus, the CTQ potentially captures both severe abuse and perhaps milder experiences as well. Thus, in the present study, to clarify whether major life adversity results in greater dysregulation relative to milder severity, I measured and analyzed severity dimensionally and planned to examined differences between levels of severity while also addressing a convention in the adversity and depression literature to separately analyze relatively minor and relatively major severity events.

Timing of Adversity

As noted above, recency of adversity also plays a role in whether the adversity will be more or less depressogenic. For example, in a large sample of middle-aged women from a twin study, 70% of the variability of environmental factors (versus genetic factors) contributing to depression was accounted for by past year environmental factors whereas environmental factors occurring prior to the last year accounted for only 13% of variance (Kendler & Gardner, 2017). Further, research that appropriately measured timing of adversity has shown that most stressful events that predict depressive episode onset occur within the past 9 weeks before the episode

(Brown & Harris, 1978). Additional work has provided estimates of the how long adverse events are likely to predict depression onset. These estimates converge on a brief window of time between approximately one month (Kendler, Karkowski, & Prescott, 1998) to 13 weeks (Surtees & Wainwright, 1999). To compromise between using a long enough time-span to maximize variation from events which are not particularly common (e.g., 1 month) and using too long of a period which would dilute the impact of events on physiological dysregulation (e.g., 1 year), I operationalized "recent" adverse events as those occurring within the past 3 months—reflecting the upper end of the short window in which adverse events predict depression onset (Surtees & Wainwright, 1999).

Because the recency of adversity is important for depression risk (e.g., Kendler & Gardner, 2017), in the present study, I examined only adverse experiences within the past year. However, it is worth noting that many prior studies have examined the role of early childhood adversity—thought to contribute to depression risk in adulthood as well (Bernet & Stein, 1999). Notably, this effect of childhood adversity on depression risk appears to be indirect, through sensitization to future adversity or stress generation processes. This is consistent with research that found those with a history of maltreatment reported less major life adversity prior to a depressive episode onset relative to those with no history of maltreatment who reported more major life adversity prior (Harkness et al., 2006). Potentially, one source of this sensitization may be through alterations in physiological stress responsive systems (Van Voorhees & Scarpa, 2004). Additionally, early adversity may be associated with greater levels of later adversity (putatively through continued environmental threat; e.g., very low socioeconomic status). Indeed, several studies suggested that the association between early life adversity and depression was mediated by recent adversity (Hazel, Hammen, Brennan, & Najman, 2008; Kessler & Magee, 1994; Turner & Butler, 2003; Vrshek-Schallhorn et al., 2015).

Although childhood adversity data are not available to test in the sample for the present study (drawn from a larger dataset), I planned to examine the relative roles of recent versus past-year life adversity in regard to episodic life adversity. This will further clarify the growing body of work that indicates that recent life adversity is particularly important to depression onset, by elucidating whether or not a similar relationship exists for physiological dysregulation. In sum, because adversity is multifaceted—each experience of adversity varies on several dimensions—

work that can disentangle relationships between severity, interpersonal nature, and timing of adversity, is needed to understand the relationship between life adversity and dysregulation in physiological stress reactivity systems.

Chronic versus Episodic Stress

Within past-year adversity, gold-standard measures have examined two types of stress—episodic and chronic stress. "Episodic" adversity refers to discrete/acute stressful life events, delimited in the time they occur, but not necessarily in the duration of their long-term consequence or impact (e.g., death of a loved one). Additionally, episodic adversity has the potential to be sudden or unexpected. Although there are several conceptualizations and operationalizations of chronic adversity in the extant literature, they share in common that they capture ongoing strain or environmental burden (e.g., tumultuous or abusive romantic relationships, childhood neglect, or poverty). One commonly used approach—the LSI—further operationalizes chronic adversity as a dimension of quality of life, ranging from positive (low scores) to worst circumstances (high scores). In prior work, both episodic (i.e., short, time-limited events) and chronic (i.e., more prolonged, ongoing) adversity resulted in statistically unique increases in risk for developing depression (Vrshek-Schallhorn et al., 2015) and thus, both ought to affect physiological stress responsive systems.

However, other evidence suggests that chronic adversity may play a more robust role in physiological dysregulation than episodic adversity. In their review of 19 studies examining "ongoing" adversity, researchers noted that the majority of such studies found dysregulated SNS reactivity—except when studies utilized life event measures. Authors explained this as possibly due to the fact that life event measures included many items representing "resolved" adversity, thus diluting the effects of ongoing stressors. However, an alternative explanation may be that ongoing adversity appears to be chronic whereas the life event measures are episodic (Gump & Matthews, 1999). Thus, these results may also be interpreted as demonstrating a more potent role of chronic adversity. However, further research is needed to disentangle whether effects were found due to the recency of the ongoing stressors or whether or not the stressor was chronic or episodic in nature. Furthermore, other work demonstrated that only adverse experiences lasting longer than 9 months affect current SNS reactivity (Lepore, Miles, & Levy, 1997). These results

are consistent with the notion that repetitive adversity is likely to lead to dysregulation in allostatic systems (McEwen & Wingfield, 2003).

Additionally, many studies examining episodic adversity failed to find a relationship between adversity and SNS or HPA dysregulation. Notably, many of these studies utilized lifetime measures of episodic adversity (Alexander et al., 2009; Mueller et al., 2011) or non-severe measures of episodic life adversity such as general stressful life events (Carroll, Phillips, Ring, Der, & Hunt, 2005; Roy, Steptoe, & Kirschbaum, 1998). In contrast, episodic adversity studies that examined major life adversity such as traumatic events (Heim et al., 2002; Jaffee et al., 2015) and exposure to violent events (Peckins, Dockray, Eckenrode, Heaton, & Susman, 2012) found significant effects on HPA reactivity. Similarly, the SNS literature, studies examining recent episodic adversity generally found significant effects on dysregulation (Gump, Reihman, Stewart, Lonky, & Darvill, 2005; Liang et al., 1995; Murali & Chen, 2005). Thus, it appears that adversity that is both recent and major is most likely to produce effects. It is possible that in some prior work, effects of episodic adversity on physiological reactivity would have been observed when using recent and/or severe measures of life adversity. However, this has yet to be empirically tested.

Interpersonal status

Interpersonal adversity (i.e., adversity that is characterized by effects on one's relationships with other people) is particularly relevant for depression risk (Joiner & Timmons, 2002; Whisman, 2001). In two samples of emerging adults, interpersonal adversity was associated with a unique increase in risk for developing depression over and above other forms of stress, whereas non-interpersonal adversity did not consistently contribute unique variance to depression risk (Vrshek-Schallhorn et al., 2015). Additionally, in this study, secondary analyses in one sample using deviance tests revealed that both chronic and episodic interpersonal adversity showed more robust effects than chronic and episodic non-interpersonal adversity respectively. The relationship between interpersonal forms of adversity and depression is further supported by meta-analyses indicating relationships between specific examples of interpersonal adversity (e.g., marital discord, parental rejection) and depression (McLeod et al., 2007; Whisman, 2001). Despite the relevance of interpersonal status of adversity to depression etiological research, overall, studies examining the association between life adversity and

physiological reactivity to lab-based stress do not distinguish between interpersonal and non-interpersonal adversity. For example, studies that look at job-stress do not measure and examine differences between reduction in salary (primarily non-interpersonal) versus arguments with managers (primarily interpersonal; e.g., Johannes Siegrist & Klein, 1990). Such research is necessary to understand how an important precipitant of depression—interpersonal adversity—relates to physiological risk pathways.

Theories of Life Adversity and Physiological Reactivity

Augmented responding

There are relatively disparate ideas about how life adversity ought to affect stress-responsive systems and how to interpret evidence. One model predicts augmented stress reactivity after exposure to life adversity and thus, elevated risk for depression (Hammen, Henry, & Daley, 2000; Heim et al., 2002; Monroe & Harkness, 2005; Post, 1992). Specifically, in terms of physiology, augmented responding models generally posit heightened physiological reactivity (e.g., greater increases in cortisol or SNS indicators in response to lab-based stress) even in response to future milder stressors (e.g., a lab-based stressor). For example, in one study, traumatic events experienced in adulthood (as measured by the Trauma Assessment Interview for Adults; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993) were associated with greater HPA-reactivity to lab-based stress (Heim et al., 2002). In another study, women experiencing more questionnaire assessed stressful life events in the last year showed greater increases in systolic blood pressure (SBP) in response to a mental arithmetic and vigilance task than those who had experienced fewer stressful life events (Lawler & Schmied, 1987). Similarly, several other studies demonstrated relationships between various types of adversity such as crowded living conditions (Baum, Davidson, Rectanus, & McArdle, 1987), caregiver stress (Cacioppo et al., 1998; Roepke et al., 2008), familial adversity (Ouellet-Morin et al., 2008) and elevated physiological reactivity. However, the crux of the augmented responding perspective is that vulnerability to stress is observable in *dysregulated* physiological stress responding, which others have demonstrated is not necessarily reflected exclusively in larger responses, but in some cases also in *blunted* responses.

Blunted responding

Indeed, numerous studies demonstrate an *inverse* relationship between adversity and physiological reactivity (Carpenter et al., 2007; Murali & Chen, 2005; Siegrist & Klein, 1990). Some have pointed to the possibility of down-regulation following major life adversity; for example, stress reactivity systems may show reduced reactivity through enhanced glucocorticoid and mineralocorticoid receptor negative feedback; Boyce & Chesterman, 1990; Cole et al., 2000; Grissom & Bhatnagar, 2009) possibly to protect the organism from chronic levels of heightened reactivity. Additionally, blunting in stress responsive systems may reflect insufficient activation and inadequate mobilization of physiological resources in response to environmental demand. Indeed this notion of the potential for blunting responses is consistent with allostatic damage reflecting both heightened and *insufficient* physiological responses (McEwen, 1998). Furthermore, evidence linking maladaptive states (e.g., social and behavioral problems; Ouellet-Morin, Odgers, et al., 2011, depression; Burke, Davis, Otte, & Mohr, 2005) with blunted reactivity support the notion that blunted physiological reactivity may reflect a maladaptive physiological state.

Notably, these studies found results seemingly "opposite" to expected hyper-reactivity using similar indicators of adversity and physiological reactivity. For example, both Heim et al. (2002) and Carpenter et al. (2007) examined self-report childhood trauma and abuse on ACTH and cortisol reactivity in adults, though where Heim et al. (2002) found evidence of hyperreactivity, Carpenter et al. (2007) demonstrated blunted ACTH and cortisol reactivity to the TSST in participants with a history of maltreatment versus those without.

Cortisol Reactivity Threshold Model

To explain the seemingly opposite hypo- and hyperreactivity results in the stress reactivity literature, one model examines variations in the objective level of threat in lab-based stressor tasks. The cortisol reactivity threshold model posits a systematic individual difference in the level of objective stressor severity that elicits a person's maximum cortisol response. It further predicts elevated cortisol reactivity to moderate stressor tasks in those at higher levels of depressive risk than those at lower risk, but in response to a more robust stressor task, it predicts that high depression-risk individuals will show blunted response relative to low risk individuals. This model has been tested using trait rumination as a depression risk factor in response to a

modified TSST utilizing three conditions of different levels of objective threat (Vrshek-Schallhorn et al., 2018). This model was motivated by discrepancies in results in prior work in which HPA hyperreactivity in those with heightened genetic risk for depression occurred under a mild lab-based stressor (Brummett et al., 2012) but opposite (i.e., hypo-reactivity) under a more robust lab-based stressor (Avery & Vrshek-Schallhorn, 2015). This effect may be due to those at high depression-risk appraising mild to moderate stressor tasks as relatively more severe than low-risk individuals resulting in greater reactivity, and by high depression-risk individuals appraising robust stressor tasks as severe, reaching a threshold of severity, resulting in a change in strategy to facilitate withdrawal and conservation of energy. Although results for trait rumination and cortisol reactivity were consistent with this model, evidence for this cognitive mechanism has yet to be tested. Thus, the cortisol reactivity threshold model suggests that both types of physiological reactions may occur within the same individual dependent on the level of threat encountered. In sum, the cortisol reactivity threshold model provides the theoretical basis by which I hypothesized the relationship between life adversity (i.e., a depression risk factor) and blunted HPA reactivity to a negative-evaluative TSST.

Asymmetry

An additional model seeks to understand how both the HPA and SNS respond to stress concurrently. The asymmetry hypothesis suggests that optimal stress responding is reflected by positive relationships between the HPA and SNS response (e.g., heightened activation to stress in both systems, lower activation to stress in both systems), whereas a disjointed relationship (i.e., asymmetry) reflects dysfunction and risk (e.g., heightened HPA but blunted SNS to stress, heightened SNS and blunted HPA to stress, or an uncorrelated response; Bauer, Quas, & Boyce, 2002; Gordis, Granger, Susman, & Trickett, 2008). Indeed, preliminary work that has integrated HPA and SNS reactivity markers has demonstrated that asymmetrical stress responses across the HPA axis and SNS showed stronger associations with current depressive symptoms than reactivity in individual systems alone (Ali & Pruessner, 2012).

Thus, in the present study, based on the cortisol reactivity threshold model, I expected blunted cortisol reactivity under lab-based stress in those experiencing depressogenic life adversity in response to a relatively robust lab-based stressor. Furthermore, based on the asymmetry model (Bauer et al., 2002), among those who have experienced more depressogenic

life adversity, I expected disjointed HPA-SNS responding to stress—I expected SNS hyper-reactivity in response to the relatively robust lab-based stressor relative to blunted cortisol responding.

Goals and Hypotheses

To-date, although research has examined how severity of adversity affects physiological dysregulation, this work has a number of drawbacks. These include utilization of a variety of life adversity measurement—many of which, rely on less valid self-report questionnaires, lab-stress inductions that are insufficiently robust to provoke an HPA response, and examination of severity largely categorically. Furthermore, few studies appropriately measure and examine other key dimensions of interpersonal nature and timing related to physiological dysregulation as well as the confluence of these dimensions. Work that examines these dimensions while distinguishing between chronic and episodic adversity is important for obtaining a more authoritative understanding of the types of adversity that alter stress reactivity systems, critical to the etiology of depression. Thus, in the present study, I examined the relationship between past life adversity and current lab-based physiological reactivity across the HPA and SNS systems. Extrapolating from the stress and depression literature, for episodic events, I hypothesized that major severity, recent, interpersonal event burden would significantly predict physiological dysregulation to lab-based stress versus a control protocol, whereas I did not hypothesize such an effect for other episodic indices. For chronic stress, I hypothesized that higher scores on a dimensional measure of interpersonal chronic stress (indicating higher severity) would predict physiological dysregulation, whereas I did not hypothesize such an effect for non-interpersonal chronic stress (See Figure 1 for graphic depiction of hypotheses).

CHAPTER II: METHOD

Participants

The present study examined healthy young adults aged 18 to 30 (N = 133; negative evaluative TSST n= 67; Control n= 66) drawn from a larger study examining genetics, lab-based stress, and stress responding. Participants were recruited through the University of North Carolina at Greensboro undergraduate student population. Individuals who reported current use of hormonal contraceptives, nicotine, corticosteroids, psychoactive medications, stimulant medications, or were experiencing a chronic health condition (all contraindications for cortisol and/or cardiovascular testing) in a screening were excluded from participation. Furthermore, data were collected in two phases to maximize the number of cognitive tests that could be examined for aims outside the scope of the present work. Participants with a current depressive episode as determined by the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002) at Session 1 did not complete the negative evaluative TSST given findings that current depression predicted blunted cortisol reactivity in a meta-analysis (Burke et al., 2005). These individuals were instead diverted to the control condition and are excluded from the present analyses due to non-randomization.

Additional exclusion criteria relevant to cognitive tests not discussed here include self-reported head trauma history, uncorrected hearing/visual deficits, learning disabilities, and colorblindness. Additionally, for the second phase of the study, capturing approximately half of participants, at a screening on arrival to Session 1 and prior to consent, individuals meeting with hypertensive blood pressure (i.e., either a systolic blood pressure above 160 and/or a diastolic blood pressure above 100, the American Heart Association cutoff in place at the time of data collection) were excluded. Participants received course credit or $30 for study completion, and all participants received $5 as an incentive for an additional cognitive task not described here.

Materials

LSI

Past 12-month naturalistic life adversity was assessed using the UCLA Life Stress Interview (Hammen et al., 1987). All interviewers completed extensive training, including

matching internal "gold-standard" ratings, and passing a mock administration with the larger study's principal investigator.

Episodic

To measure episodic adversity, the interviewer collected information regarding event including the duration, context (e.g., coping resources available, expectedness, prior exposure to similar events, mitigating factors), start date of event, and impact. Interviewers then presented an account of each event to a team of raters blind to the participant's diagnosis (i.e., depressive symptoms) and subjective response to the event. The team then assigned a interpersonal status score of 0 (primarily non-interpersonal) or 1 (primarily interpersonal), and a nominal numeral from a list of 77 descriptors to label the event (Paykel, 1997). Interpersonal adversity reflected events with effects primarily on one's relationships with other people.

The severity score scale included half-point increments and was rated based on the expected negative impact of the event for the average person in the same context. Events with a severity rating of 2.5 or greater were categorized as "major" stressful life events and those below 2.5 were categorized as "minor" life events in keeping with prior work (Uliaszek et al., 2012; Vrshek-Schallhorn et al., 2013). All events retained a dimensional severity rating (i.e., major life event between 2.5-5 severity). This allowed use of categories with distinct impact on depression risk, (i.e., "major" and "minor"; Brown & Harris, 1978) while retaining dimensional severity within each category (For examples of each dimension of episodic adversity, see Table 1).

Additionally, the LSI provides ratings for independence versus dependence of episodic stress (i.e., the extent to which the event was due to the individual's behavior). However, prior work suggests that this domain is not particularly critical to depression risk and demonstrates mixed effects on depression onset (Hammen, Mayol, DeMayo, & Marks, 1986; Kendler et al., 1999; Monroe et al., 2006; Shrout et al., 1989). Indeed, one study that explicitly tested the relative risk due to independent versus dependent adversity on depression onset failed to find a difference (Vrshek-Schallhorn et al., 2015). Thus, I did not examine this dimension here.

To assess the impact of relatively recent adversity, recorded start dates of events were used to calculate a recent episodic adversity score from past 3-month adversity given the importance of this period to depression risk (Brown & Harris, 1978). Additionally, a past "distal"

composite was calculated from events with a start date 3 and 12 months from the date of the interview.

To assess the impact of interpersonal nature, the team-assigned interpersonal status score was utilized to calculate separate interpersonal and non-interpersonal indices for each participant.

Calculation of episodic indices

Events with a severity score of 1 (i.e., non-event) were not included in analyses consistent with the LSI user manual. Thus, to place scores on a continuous scale, severity scores were re-coded by subtracting 1 from events rated with a severity between 1 and 5 resulting in a severity scale that could range from 0 – 4, where 0 reflected no events, and the lowest event was valued at 0.5. To compute the sum of severity index for each type of episodic stressor (e.g. Minor Interpersonal Recent stress), I obtained the sum of the severity scores of all relevant events per participant.

Episodic reliability

To calculate inter-rater reliability (inter-class correlations; ICCs) of episodic severity ratings and interpersonal versus noninterpersonal categorization, I listened to a sample of 20 participants' LSI interviewer audio recordings detailing the circumstances of their stressful life events. I was blind to the original ratings and did not select from recordings for which I was the original interviewer. I chose tapes to rate quasi-randomly to ensure I rated at least 25 major and minor events. In total, I rated 96 stressful life events, 25 of which were major life events. For episodic severity, inter-rater reliability was good: The average measure ICC was .892. For categorization of interpersonal versus noninterpersonal, inter-rater reliability was excellent: kappa = .934, $p<.001$.

Chronic

To assess chronic life adversity, interviewers assessed quality of life in 10 domains (best friend relationship, peer social circle, romantic relationships, family relationships, academics, work, finances, neighborhood conditions, physical health, family health) using semi-structured questions. Interviewers rated the level of chronic adversity in each domain distinct from other domains (i.e., avoiding a halo effect), on a 1 (excellent/ optimal circumstances) to 5 (very bad circumstances) with half-point increments. An interview manual provides suggested qualitative

descriptions for each whole point to anchor the ratings. Interviewers provided a single rating for the full 12-month period in each domain queried—precluding analyses of the role of timing within chronic adversity. Prior studies with the LSI have generated interpersonal and non-interpersonal chronic stress composite scores (e.g., Vrshek-Schallhorn et al., 2015). The interpersonal chronic adversity composite was composed of the mean of the best friend relationship, peer social circle, romantic relationships, and family relationships domains. The non-interpersonal chronic adversity composite was composed of the mean of the academics, work, finances, neighborhood conditions, self-health, and family-health domains.

Chronic reliabilities

To calculate inter-rater reliability (inter-class correlations; ICCs) of chronic severity ratings, I and another graduate student randomly selected 25 original LSI interview recordings to listen and rate. We were blind to the original ratings and did not rate recordings for which we were the original interviewers. Inter-rater reliability was good for both chronic interpersonal and chronic noninterpersonal composites. Average measures ICC for the chronic interpersonal stress and chronic noninterpersonal stress composites was .895 and .789 respectively.

Overlap between chronic and episodic stress

Notably, per LSI guidelines, when the interviewer detected events occurring in succession such as a major argument in a romantic relationship immediately followed by a break-up, the second event was considered sequelae and included when rating the severity of the original event. Additionally, in keeping with scoring conventions for the LSI, when events occurred frequently with consistent severity (e.g., repeated arguments with a friend), these were not included as episodic adversity but rather, were included in the chronic stress rating of that domain. However, within repeated events, if one event was characterized by a spike in severity (e.g., a serious altercation occurring within the context of a generally tumultuous relationship), these were then scored as episodic stressors—to account for the unexpected and marked change due to the event.

Socioeconomic status

Socioeconomic status was calculated using the Hollingshead index composed of parental education and occupation, providing a scale ranging from 8-66 (Hollingshead, 1975).

Manipulation checks

After completing the TSST or control protocol during Session 2, participants were asked to what extent they felt evaluated, and if they endorsed feeling evaluated to any extent, to what extent the evaluation was positive, and to what extent it was negative.

Stress reactivity

Salivary cortisol

Participants provided saliva samples via passive drool into sterile cryogenic vials 5 times during the second session, 4 of which were planned for use in assessing cortisol reactivity. One sample was collected five minutes after the baseline sample to ensure that changes in sAA were not overlooked, as it has the potential to change more rapidly than does cortisol. After collection, saliva samples were stored in a freezer at -80°C. After data collection was completed, samples were shipped to Trier, Germany, for duplicate assay by time-resolved fluorescent-detection immunoassay (DELFIA; Dressendorfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). Cortisol (and sAA) values at each time point were windsorized to 3 standard deviations to reduce influence of any potential univariate outliers, which is a common practice in the cortisol literature (Tukey, 1977). I then calculated area under the curve with respect to increase, a technique that has been used to index cortisol reactivity compared to a baseline level (AUC_I; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003), across 4 time points. AUC_I provides a notable advantage over other methods such as pre-post change scores as it utilizes more time points and thus captures greater variation in reactivity over time.

Salivary Alpha Amylase

sAA was collected through the same saliva samples used for cortisol collection. I similarly computed an AUC_I to index sAA reactivity. Notably, the timing of samples used for sAA differ slightly from those used for cortisol analyses with an additional saliva collection immediately before the TSST (as noted above) and exclusion of the saliva collection following debriefing and rest.

Procedure

Participants were pseudo-randomly assigned to either the control or TSST condition. That is, participants were blind to the study condition scheduled for their selected timeslot, often

signed up via an online system without interacting with study staff, and in cases in which they did sign up via study staff, the study coordinator did not know the identity of the participants when scheduling. In most cases, participants completed two sessions 1 day apart at the same time of the day. All sessions were completed between 1 and 5:30 P.M. to reduce the influence of diurnal variation in cortisol (Dickerson & Kemeny, 2004).

During Session 1, participants first provided salivary DNA, completed questions including health variables (e.g., caffeine use, exercise, and allergies) and then completed the Life Stress Interview (LSI) regarding stressful life experiences in the past 12 months. Participants then completed the depressive episode sections of the Structured Clinical Interview for DSM-IV Disorders, Non-Patient Edition (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002). If the interviewer preliminarily diagnosed a current major depressive episode, the participant was placed in the control condition (for Session 2) and was excluded from the present analyses due to violation of pseudo-randomization and effects of depression on cortisol reactivity (Burke et al., 2005).

During Session 2, participants underwent a negative-evaluative Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993; Way & Taylor, 2010) or a non-evaluative control procedure. During the TSST or control, participants provided salivary cortisol and sAA. Cortisol data was derived from 4 time points: immediately prior to the TSST (baseline), +20 minutes (following the TSST), +45 minutes, and +65 minutes (following debriefing and rest). Based on inspection of a subset of mean data, sAA data was derived from 4 time points: immediately prior to the TSST (baseline), +5 minutes (before the TSST), +20 minutes (following the TSST), and +45 minutes (after the TSST) when average levels have returned to baseline. Use of +45 as the last data point for sAA is further consistent with prior evidence that sAA will both peak and recover more quickly than cortisol (Maruyama et al., 2012). Self-reported affect was collected but not examined in the present study. Immediately after the TSST or control protocol, participants completed questionnaire manipulation checks.

Trier Social Stress Test (TSST)

Both experimental conditions shared several common elements and were developed based on commonly used protocols (Kirschbaum et al., 1993; Way & Taylor, 2010). In both

conditions, participants were told they would be video-recorded and instructed to face the camera. They had 5 minutes to prepare for a 5-minute speech. Following the preparation and speech, they completed a serial subtraction arithmetic task counting backwards from 2,017 by 13's. If they made a mistake, they were instructed to start back from 2,017 again. In addition, the conditions had several differences. The negative evaluative TSST represents a modification designed to be overtly negative (Way & Taylor, 2010) compared to the more neutral original TSST (Kirschbaum et al., 1993). In the TSST condition, participants were told that they would be evaluated by two judges (1 male, 1 female confederate). Throughout the speech and arithmetic tasks, confederate judges reminded participants to face the camera; they followed a behavioral script during the speech task to appear bored and dissatisfied (See Appendix A) and provided stern feedback during the arithmetic task. Additionally, the speech topic differed by condition despite efforts to make it appear that each participant randomly selected a topic: in the TSST, participants were assigned to speak about why their peers should select them for a student leadership position, whereas in the control condition, participants spoke about tips others could follow for living a healthy lifestyle. In the control condition, no confederates were present, their speech topic was less evaluative, and they received neutral, polite feedback from the experimenter, who pretended to prepare for future sessions in the same small room but out of the participants' line of sight during the tasks. In prior work, these experimental conditions produced the expected differences in cortisol reactivity and in perceived global, negative, and positive evaluation (Avery & Vrshek-Schallhorn, 2015).

Analytic Plan

Preliminary Analyses

Stressful Life Events

I examined the number of stressful life events for each dimension of life adversity to ensure adequate frequency of life events. Next, I conducted independent samples *t*-tests to test whether the average number of stressful life events in each category differed between participants in the control and challenge conditions.

Chronic Life Adversity

I additionally examined the variability of chronic interpersonal and chronic noninterpersonal adversity to ensure appropriate distribution of adversity within each of these domains.

Group Equivalence and Manipulation Checks

As a manipulation check, I conducted a one-way ANOVA to assess the difference between the degree to which participants felt evaluated in the stress and control groups.

Multivariate Outliers

To identify outliers, I inspected scatterplots of the data for each analysis, separated by stress condition. I ran analyses with and without data points that appeared to be overly influential and have noted the outcome throughout.

Primary Analyses

I examined the role of life adversity on physiological reactivity through separate linear regressions conducted in IBM SPSS Statistics version 23 (IBM, 2016). I considered results be statistically significant if the *p*-value $\leq$.05. I also noted when non-significant effects had *p*-values between .05 and .10, a common practice for this literature, and listed the non-significant *p*-values. In all analyses, I covaried depression history and variables known to affect stress reactivity including gender (Kirschbaum, Wust, & Hellhammer, 1992), socioeconomic status (Hackman, Betancourt, Brodsky, Hurt, & Farah, 2012), caffeine use (Lovallo, Farag, Vincent, Thomas, & Wilson, 2006), regular exercise (Klaperski, Dawans, Heinrichs, & Fuchs, 2014), and allergies (Buske-Kirschbaum, Ebrecht, & Hellhammer, 2010). I also covaried these variables and their interaction with 1) stress condition and 2) life adversity to partial out their effects on the hypothesized life adversity by stress condition interactions (Keller, 2014).

Separate linear regressions were completed for each dependent variable (cortisol AUC_I and sAA AUC_I) and for each form of life adversity. Continuous variables were examined for normality, then centered for calculation of interaction effects. In each regression, AUC_I reactivity was regressed on life adversity, stress condition (i.e., control or challenge), and their interaction. In all cases, the final model step with all variables was reported and interpreted. I planned to follow any significant Life Adversity x Stress Condition interactions with simple slopes analyses

and regions of significance analyses (Preacher, Curran, & Bauer, 2003) to determine at which levels of life adversity does the effect of stress condition on physiological reactivity differ.

Additionally, if multiple predictors were significant, I planned to conduct a follow-up test placing all significant predictors in a model simultaneously to evaluate whether each remained significant (i.e., a unique predictor).

Power Considerations

Prior work examining the role of life adversity on physiological reactivity has found significant effects utilizing relatively small sample sizes. In one study, SNS differences between a high chronic life adversity group and a low chronic life adversity group observed differences in SNS reactivity with 24 participants (Pike et al., 1997). Similarly, another study demonstrated differences in HPA reactivity between participants with high and low childhood trauma with 50 participants in response to the TSST (Carpenter et al., 2007). Thus, in the present study, I expected power to be sufficient given a relatively larger sample of N=133 (TSST n= 67; Control n= 66), robust measurement of life adversity, and a well-validated, robust lab-stressor paradigm (Kirschbaum, Wust, & Hellhammer, 1992; Way & Taylor, 2010). Additionally, I expected sufficient power to detect significant interactions, given prior work examining a Maltreatment x sAA interaction to predict cortisol reactivity using N=84 participants. Finally, from the first phase of this dataset, prior work has detected a significant interaction of trait rumination and stress condition on cortisol reactivity (Vrshek-Schallhorn et al., 2018)—further suggestive of sufficient power.

CHAPTER III: RESULTS

Preliminary Analyses

Stressful Life Events

Major events were observed infrequently; examination of the frequencies of stressful life events in each category revealed that major noninterpersonal recent and distal stressful events had 0 and 4 stressful life events recorded respectively. These categories were thus not analyzed given low frequency of stressful life events. Major interpersonal recent stress (count: 8) and major interpersonal distal stress (count: 31) were collapsed across the dimension of timing given relatively fewer events in these categories to calculate a "major interpersonal" category. All other stressor variables included markedly greater frequencies of stressful life events (at least 54 events), suggesting suitability for analyses (See Table 2 for breakdown of life event frequencies and Table 3 for zero-order correlations of all relevant predictor and outcome variables). Independent samples *t*-tests suggested that the average number of stressful life events did not differ between participants in the control and challenge conditions (*ps*>.173).

Chronic Life Adversity

The variability of the chronic noninterpersonal stress scores (*M*=2.203, *SD*=.327, Range: 1.25 – 3.0) was relatively similar to yet slightly more constrained than the spread of the chronic interpersonal stress data (*M*=2.256, *SD*=.458, Range: 1.25 – 3.50). Overall, the data suggested a range of chronic stress from "excellent" conditions to "somewhat bad or poor".

Manipulation Checks

Subjective evaluation

A one-way ANOVA supported the expected effect of the TSST challenge condition on the extent to which participants felt evaluated during the TSST ($F(1,131) = 19.879$, $p<.001$) with participants in the challenge condition (*M*=3.391, *SD*=.833) perceiving greater overall evaluation than participants in the control condition (*M*=2.676, *SD*=1.009). Similarly, a one-way ANOVA ($F(1,117) = 46.615$, $p<.001$) suggested that the challenge condition elicited greater *negative* evaluation (*M*=2.937, *SD*=.914) than the control condition (*M*= 1.9107, *SD*=.695).

Cortisol

Cortisol reactivity (i.e., AUC_I) differed as expected between conditions ($F(1,131) = 36.224$, $p<.001$): Participants in the challenge condition showed elevated cortisol AUC_I (M=121.069, SD=182.046) relative to participants in the control condition (M=-42.303, SD=125.276).

sAA

Similarly, sAA reactivity (i.e., AUC_I) differed as expected between conditions ($F(1,131) = 6.283$, p=.013): Participants in the challenge condition showed elevated sAA AUC_I (M=1357.210, SD=2126.435) relative to participants in the control condition (M=474.869, SD=1926.613).

Multivariate Outliers

In each analysis, a maximum of two data points were considered outliers. One participant's data was considered an outlier across all analyses. Planned analyses were conducted with outliers excluded. Moreover, when outliers were reintegrated, the overall pattern of results did not vary; results presented exclude these multivariate outliers. Cook's distances from full models were inspected to further verify that removed outliers were indeed overly influential. Only removed outliers showed Cook's distance values >.03 indicative of heightened influence (Cook, 1977).

Primary Analyses

Cortisol

Multiple regression analyses were run to examine the effect of Life Adversity x Stress Condition for each type of life adversity examined. Full results are available in Table 4. Covariates, as well as Covariate x Stress Condition, and Covariate x Life Adversity interaction effects (Keller, 2014) were included in presented analyses but not displayed in Tables for succinctness. Across all life adversity indices, none of the interaction terms of Life Adversity x Stress Condition emerged as significant ($-53.317 < b\text{s} < 100.898$, $.098 < p\text{s} < .960$). A non-significant interaction of Minor Noninterpersonal Distal Adversity x Stress Condition emerged (b=100.898, SE(b)=60.373, p=.098) such that at higher levels of minor noninterpersonal distal adversity, participants in the challenge condition showed *greater* cortisol AUC_I, whereas

participants in the control condition showed lower AUC_I. No simple main effects of life adversity emerged (-169.048 < *b*s < 82.491; .384 < *p*s < .895).

sAA

Multiple regression analyses were run to examine the effect of Life Adversity x Stress Condition for each type of life adversity examined. Full results are available in Table 5. Across all life adversity indices, no significant interaction terms (-267.216 < *b*s < 1630.245; .218 < *p*s <.994) nor simple main effects of life adversity (-1815.682 < *b*s < 1023.3; .217 < *p*s < .983) emerged. Significant main effects of stress condition on sAA AUC_I evident in manipulation checks contrasted with the non-significant *simple* main effects of stress condition (-2168.766 < *b*s < 4026.677; .087 < *p*s < .363) in regression analyses including the interaction of stress condition and prior life stress. The simple main effect of stress condition reflects its point estimate where life adversity equals zero (i.e., its mean, due to centering), because the interaction effect of these two variables is partialed out, and thus may differ from a traditional main effect estimated with no interaction in the model.

Exploratory Analyses of Chronic Domains

I did not observe significant effects of chronic interpersonal or noninterpersonal adversity or an array of episodic forms of stress on either cortisol or sAA AUC_I; however, analyses for chronic stress utilized composite indices, whereas episodic variables were already considered as "fine grained" as possible. Thus, to better understand the lack of significant findings, in exploratory analyses, I tested whether any of the individual domains of chronic stress predicted cortisol or sAA AUC_I in interaction with stress condition.

Chronic Stress and Cortisol

To test whether particular domains of chronic noninterpersonal stress were influential to cortisol reactivity, finances, neighborhood, education, self-health, family-health and work were separately entered in six models to predict cortisol reactivity. Of these, only the effect of Finances x Stress Condition emerged as a significant predictor (*b*=-62.896, SE(*b*)=27.694, *t*=-2.271, *p*=.025; See Table 6 for results of the full model). Simple slopes analyses indicated that in the challenge condition, participants with higher levels of financial stress showed blunted AUC_I (*t*=-3.141, *p*=.021); no relationship emerged in the control condition (*t*=-.0262, *p*=.9792) (See

Figure 2). A regions of significance analysis (Preacher, Curran, & Bauer, 2003) determined that the detection of significant differences between slopes occurred below financial stress values of approximately +1SD, representing chronic stress values of <2.7 (i.e., ranging from modest financial strain (2.7) to excellent (1) level of financial resources). There was not a significant simple main effect of financial stress (b=168.801, SE(b)=118.399, t=1.426, p=.157).

School, neighborhood, work, self-health, family-health and their interaction terms with stress condition did not emerge as significant predictors. Of these, the effect of Self-Health x Stress Condition emerged as a non-significant predictor (b=-50.665, SE(b)=29.323, t=-1.728, p=.087) such that participants in the challenge condition showed lower cortisol AUC_I in response to greater self-health strain, with no relationship in the control condition. I did not detect a simple main effect of self-health (b=-55.320, SE(b)=114.945, t=-.481, p=.631).

To test whether particular domains of chronic interpersonal stress were influential to cortisol reactivity, the four chronic interpersonal domains—romantic relationships, close friendships, social life, and family—were examined separately. I did not observe significant effects of any of the individual Chronic Interpersonal Domains x Stress Condition (-46.684 < bs < 46.055, .127 < ps < .696) or simple main effects of chronic interpersonal domains (-33.690 < bs < 90.139, .415 < ps < .956).

Chronic Stress and sAA

No Chronic Noninterpersonal Adversity Domains x Stress Condition effects (-379.309< bs <149.441, .281< ps <.900) nor simple main effects (-2372.352< bs < 2581.744, .065 < ps <.331) emerged as significant predictors of sAA. A non-significant simple main effect of family health emerged (b=2581.744, SE(b)=1385.823, t=1.863, p=.065) such that higher levels of family health stress were associated with higher AUC_I in the control condition (Stress Condition = 0). The interaction of Family Health x Stress Condition was not significant (b=44.513, SE(b)=354.479, t=.126, p=.900) suggesting this non-significant relationship between greater family health stress and greater sAA output did not differ for participants in the challenge condition.

Similarly, no Chronic Interpersonal Domains x Stress Condition effects (-155.268< *b*s < 231.897, .551 < *p*s < .794) nor simple main effects of chronic interpersonal domains (-1777.557< *b*s < 457.269, .182 < *p*s <.781) emerged as significant predictors of sAA.

CHAPTER IV: DISCUSSION

The present study aimed to examine the relationship between prior life adversity and current lab-based physiological reactivity across the HPA and SNS. Based upon the stress and depression literature, I hypothesized that major severity, recent, interpersonal event burden would predict HPA and SNS dysregulation to the TSST and did not hypothesize an effect for other episodic indices. For chronic life adversity, I hypothesized that higher interpersonal chronic stress would predict HPA and SNS dysregulation, whereas I did not hypothesize such an effect for noninterpersonal chronic stress. Based on the cortisol reactivity threshold model and the asymmetry model, I hypothesized significant interactions between life adversity and stress condition such that dimensions of life adversity would confer blunted cortisol reactivity and augmented sAA reactivity to the challenge condition of the TSST. Despite that the TSST manipulation performed as expected based on evidence of greater cortisol and sAA AUC_I, perceived overall evaluation, and perceived negative evaluation, the primary results of planned analyses did not support the hypotheses; no significant Life Adversity x Stress Condition interaction emerged for either cortisol or sAA reactivity. In exploratory analyses of individual domains of chronic adversity, I observed a significant Financial Stress x Stress Condition effect such that in the challenge condition, greater financial stress was associated with lower cortisol AUC_I, a blunting effect. Here, I discuss potential explanations for this pattern of results, limitations of the present study, and implications for future directions.

No Significant Life Adversity x Stress Condition Effects in Primary Analyses

Despite indications of sufficient power and use of high-quality, researcher-rated adversity measurement, contrary to hypotheses, no significant Life Adversity x Stress Condition effects emerged across either cortisol or sAA in the primary analyses of episodic and chronic adversity. In the episodic domain, the lack of significant findings contrasts with prior work that has examined major severity life adversity on HPA/SNS reactivity and depression risk. Several studies have demonstrated significant effects of traumatic events on HPA reactivity (Elzinga et al., 2008; Jaffee et al., 2015), researcher-rated severe, stressful life events on SNS reactivity (Lawler & Schmied, 1987), and maltreatment history on HPA (Harkness et al., 2006; Leitzke et al., 2015; Sumner et al., 2014) and SNS reactivity (Gooding, Milliren, Austin, Sheridan, & McLaughlin, 2015; McLaughlin, Sheridan, Alves, & Mendes, 2014). Other work has also shown

the importance of major life adversity to depression onset (Brown & Harris, 1978; Monroe, 2008; Vrshek-Schallhorn et al., 2015). In the chronic domain, although prior work on HPA and SNS outcomes had not distinguished between chronic interpersonal and noninterpersonal adversity, the current lack of overall effect of chronic interpersonal stress on HPA and SNS reactivity was inconsistent with the expectation that chronic interpersonal stress would be particularly salient based on its relationship to increased depression risk (Vrshek-Schallhorn et al., 2015). Below, I discuss several potential explanations for the pattern of results observed.

Sample characteristics and limited distribution of adverse experiences in the present study

There are several reasons to speculate that sample characteristics contributed to largely null findings and thus, null findings may not be generalizable to all samples or all types of adversity. The lack of support for hypotheses may have been driven by the relatively low frequency of moderate to severe prior-year life adversity in the present sample of healthy, non-depressed, college students. Indeed, on the LSI chronic stress scale of 1 (best possible quality of life) to 5 (worst possible quality of life), participants' chronic interpersonal composite stress was rated M=2.35 (reflecting a "normative" overall quality of interpersonal life), SD=.437 with a range between 1.2 to 3.7 reflecting "excellent" to "somewhat bad or poor" quality of life. Thus, few participants likely experienced very poor quality of life in interpersonal domains (e.g., abusive romantic or family relationships, extreme social isolation). Indeed, prior work showing significant effects of putatively chronic interpersonal experiences on lab-based HPA and SNS reactivity have examined full-time caregiving for a spouse with Alzheimer's (Aschbacher et al., 2013; Cacioppo et al., 1998, 2000). This caregiving relationship likely captures a higher level of severity than commonly experienced in the present sample.

Similarly, on the re-coded LSI event severity scale from 0 (no events) to 4 (highest severity), event severity ranged from .5 to 2.5 with a mean of .746 and a standard deviation of .401, reflecting the predominance of lower severity events and potential restriction of the range of severity. Though I created the dimensional recent severity index to maximize power, higher scores on the recent severity index likely represented numerous minor severity events rather than high severity events. Similarly, although I collapsed major interpersonal recent and distal episodic adversity, the somewhat limited frequency of major interpersonal *recent* events (i.e., the

type of episodic life adversity with the stronger depression associations; Brown & Harris, 1978), may have prevented detecting support for episodic indices.

The somewhat limited frequency of major events is likely attributable to the natural, low prevalence of severe life stress in this population. Indeed, a prior study using the LSI in two samples detected an average of 2.67 (Sample 1) and 3.26 (Sample 2) major life events per participant across 5 successive 1-year interview periods (Vrshek-Schallhorn et al., 2015). Additionally, participants in the present study were enrolled in an undergraduate institution, likely associated with adaptive functioning and resources compared to their counterparts who did not go on to universities, possibly diminishing the occurrence of major severity adversity (e.g., major financial change, severe illness onset). Finally, participants with current depressive episodes were excluded from the stress induction protocol as previously discussed. This may have further reduced frequency of major severity events; participants excluded on the basis of current depression may have been more likely to have recently experienced major interpersonal events (i.e., the events that likely contributed to depression onset; Vrshek-Schallhorn et al., 2015) than their non-depressed counterparts in the study, but were excluded from biomarker analyses. Taken together, there are several reasons for the low prevalence of major severity life adversity in this sample of healthy, non-depressed college students.

Possibility of no association between depressogenic adversity and HPA and SNS reactivity

Indeed, past-year or recent adversity of the sort typically experienced by the healthy, non-depressed, college population may not significantly influence HPA or SNS reactivity. The lack of significant findings parallels a meta-analysis that did not detect an overall effect of life adversity on HPA or SNS reactivity (Chida & Hamer, 2008). Associations between major interpersonal episodic and chronic interpersonal adversity and HPA and SNS reactivity were hypothesized based on the depression literature (Brown & Harris, 1978; Monroe, 2008; Vrshek-Schallhorn et al., 2015). However, based on the observed lack of significant findings in the present study, what is known about the characteristics of adversity in relationship to depression may not also generalize to prior adversity's relationship to HPA and SNS reactivity. That is, the present study does not support the implied path between depressogenic life adversity and depression risk through alterations in HPA and/or SNS dysregulation.

However, several studies have found associations between the more "depressogenic" types of life adversity and HPA/SNS reactivity. Notably, many of these studies do not screen out or account for (e.g., covary or reanalyze without) participants with current depression in their sample (e.g., Lawler & Schmied, 1987; Leitzke et al., 2015; Sumner et al., 2014). Thus, significant associations between "depressogenic" life adversity and HPA or SNS reactivity may have been driven by participants with current depressive symptoms and diagnoses in past studies. Putatively, these participants would likely have higher frequencies of depressogenic adverse experiences *and* may have disrupted HPA or SNS reactivity associated with their depressive symptoms (e.g., Burke et al., 2005), thus leading to a spurious correlation between depressogenic life adversity and HPA or SNS reactivity.

A role for other risk factors

Another alternative explanation for the lack of association between life adversity and HPA and SNS reactivity is that the association between life adversity and HPA and SNS reactivity may be moderated by other factors in a way that masks an interaction of prior adversity and experimental condition alone. Thus, rather than a broadly applicable effect of life adversity on HPA and SNS reactivity in interaction with condition, specific trait-like vulnerability factors may predispose individuals to dysregulated HPA or SNS reactivity in the presence of life adversity. For example, several risk factors have been found to affect response to life stress including trait rumination (Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013) and trait neuroticism (Evans et al., 2016), decreased emotion regulation capacity (McLaughlin, Borkovec, & Sibrava, 2007), and low positive affect/behavioral drive (Nikolova, Bogdan, Brigidi, & Hariri, 2012).

Additionally, though not a trait per se, prior life adversity (e.g., childhood maltreatment) may serve as another vulnerability factor, sensitizing HPA and SNS systems to demonstrate dysregulation in the face of later life adversity. This is consistent with the notion that life adversity may lead to alterations in stress response systems during particular sensitive periods in development (Heim & Nemeroff, 2001; Heim et al., 2002). Indeed, one study showed that an interaction of recent adversity and early childhood maltreatment was a stronger predictor of cortisol reactivity over and above recent adversity alone in a sample of 55 adolescents, when controlling for current depressive symptoms (Rao et al., 2008), supporting a Pre-existing

Vulnerability x Life Adversity model. Potentially, these factors are important to understand why some people may be more affected by life adversity than others. The potential for such an alternative model, however, also comes with additional concerns about multiple testing and power for interactive effects. In the present study, I did not examine the role of personality vulnerability factors or early childhood maltreatment.

Exploratory Analyses

As episodic analyses were already considered "fine grained", I conducted exploratory analyses in chronic composites only to probe negative findings. I tested whether individual domains of chronic interpersonal and noninterpersonal adversity were significant predictors of cortisol and sAA AUC_I, potentially masked by overall non-significant effects of both chronic adversity composites. A significant effect of Finances x Stress Condition emerged, such that heightened chronic financial stress was associated with *blunted* cortisol AUC_I in the challenge condition but not in the control condition. Regions of significance analyses suggested that the slopes of the control and challenge statistically differed for participants with financial quality ranging from excellent conditions to modest financial strain. Though this may appear to suggest that results were driven by participants with better financial conditions, the pattern of reactivity among those with high levels of financial stress is revealing. Conceptually, participants with greater financial stress showed a blunting response in the challenge condition that was more similar to the response of participants in the control condition (See Figure 2). Given cortisol's role as a resource-mobilizing hormone (Sapolsky et al., 2000), a "control" pattern of cortisol output to a robust lab-based stressor is likely maladaptive reflecting a failure to rise to a demanding occasion physiologically. Indeed, this blunting pattern of responding to a robust lab-based stressor was detected in prior work amongst participants with high trait rumination (Vrshek-Schallhorn et al., 2018) and in C-allele carriers of the *HTR2C* gene (implicated in depression risk (Loo, Hale, & D'haenen, 2002) and stress responding (Heisler, Zhou, Bajwa, Hsu, & Tecott, 2007)). Thus, this pattern of reactivity may represent lowered physiological capacity to adaptively respond to a robust lab-based stressor task amongst those with a background of greater financial strain.

Additionally, when both blunted and augmented reactivity are viewed as dysregulated, this finding could be considered consistent with prior work in African American male

adolescents of low SES experiencing heightened cortisol reactivity to a modified-TSST (Hackman et al., 2012) and consistent with a study of South African adolescents in which a history of low SES was associated with blunted cortisol reactivity to the TSST (Fearon et al., 2017). Consistent with the expectations of the cortisol reactivity threshold model (Vrshek-Schallhorn et al., 2018), the former study, associated with an augmenting cortisol response, utilized a potentially less robust TSST manipulation than the latter study which was associated with a blunted cortisol response.

Additionally, in prior work, financial strain (measured by debt-to-income ratio) showed a robust association with depression over and above income (Zimmerman & Katon, 2005). Thus, the observed effect of financial stress on cortisol reactivity may have been due to depressogenic effects of financial strain. Other work has shown that in college students, financial strain may be particularly damaging to depression risk, potentially through associations with decreased academic engagement and increased academic stressors (Joo, Durband, & Grable, 2008), although in the present study, academic chronic stress did not significantly interact with experimental condition. However, prospective clinical data is needed to determine whether the observed pattern of reactivity predicted by chronic financial stress would be associated with depression risk. Ultimately, these results point to a role of financial strain on HPA axis reactivity, and potential benefit of more fine-grained analysis by examining specific domains of chronic adversity. However, exploratory analyses were post-hoc and increased the overall number of tests (18 primary analyses, 20 exploratory analyses of individual chronic domains), increasing the probability of a Type I error. Thus, the effect of financial strain on HPA axis reactivity should be interpreted with caution.

Limitations and Future Directions

Though the present study had several strengths including utilizing a lab-controlled stress induction with both challenge and control conditions, use of an expert-rated, relatively objective measurement of life adversity, and examination of reactivity to life adversity across both the HPA and SNS systems, there were some limitations. Examination of adversity in a healthy, non-depressed college sample may have somewhat restricted the severity of adversity. Most notably, the low frequency of major life events in this college sample of emerging adults precluded attempts to examine the major interpersonal recent (past 3 month) adversity index and may have

contributed to the lack of effects of episodic life adversity. Indeed, this raises a larger issue for the examination of recent life stress: It is a methodological challenge to collect data in real time on participants who have experienced relatively rare, major severity events in the last few months. Such investigation would require vulnerable populations such as patients in emergency rooms, victims of natural disasters, and those who have recently lost loved ones. The poor feasibility of recruiting participants during a time in which their lives are maximally disrupted may preclude data collection. Indeed, this conundrum likely has led to the observed pattern in the literature of utilizing retrospective lifetime adversity to examine severe but distal adversity (e.g., maltreatment) without assessing recent life stress. Though labor-intensive, one approach to manage this challenge is to utilize larger sample sizes. Another approach may be to identify individuals at higher risk of greater overall life adversity (e.g., participants of very low SES; Kristenson, Eriksen, Sluiter, Starke, & Ursin, 2004) or participants managing major medical conditions (Wu & Andersen, 2010) that may be prone to experience more adverse experiences, though, reactivity patterns in these specific populations may not necessarily generalize to the overall population.

Another limitation of the present study is the lack of prospective clinical data to better understand whether the observed pattern of blunted cortisol reactivity in response to financial stress is truly maladaptive and linked with heightened incidence of depression. Longitudinal studies examining the pathway between life adversity, stress reactivity and depression onset are limited but needed to clarify the role of physiological reactivity in risk for depression.

A third limitation is the relatively limited snapshot conferred by lab-based stress reactivity as an indicator of overall physiological system health. Though lab-based stress reactivity is a useful indicator of the health of a stress reactivity system, data on other aspects of the health of the HPA (e.g., diurnal rhythm, cortisol awakening response) and SNS systems (e.g., pre-ejection period) may provide a more thorough perspective on physiological stress systems.

Conclusions

The present study aimed to address a gap in the literature regarding whether the mixed findings in the life adversity and stress reactivity literature could be clarified by utilizing high quality adversity measurement and by taking a theory-driven approach. Overall, I did not find the

expected interaction of life adversity and stress condition, the effect of episodic life adversity indices, or of chronic interpersonal stress. Exploratory analyses revealed a significant Financial Stress x Stress Condition effect such that greater financial stress was associated with blunted cortisol reactivity in the challenge condition; however, given the exploratory nature of this significant interaction effect, replication will be particularly critical. Ultimately, the lack of significant hypothesized effects suggests the possibility that there may not be large, systematic effects of life adversity on average, that is, without taking account other factors such as early life adversity, or trait risk factors such as trait rumination or neuroticism. Additionally, the difficulties in collecting elevated adversity data in the present study reveal both challenges for the life adversity literature and insights into the feasibility of better understanding the role of nuanced types of life adversity.

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APPENDIX A: TABLES AND FIGURES

Table 1. Definitions and Examples of Episodic Adversity Dimensions

Severity	
Major Severity	**Minor Severity**
Definition: An event with moderate to severe expected negative impact for the average person in the same context. On the LSI, a severity rating of 2.5 or higher	**Definition**: An event with less than moderate impact for the average person in the same context. On the LSI, a severity rating below 2.5
Examples: Death of a partner, close friend or close family member, assault, receiving life-threatening medical diagnosis	**Examples**: Argument with friend that lasts a few days, car accident with no long term financial or health consequences
Interpersonal Nature	
Interpersonal	**Noninterpersonal**
Definition: Events with effects primarily on one's relationships with other people	**Definition**: Events with effects primarily outside one's relationships with other people
Examples: Ending romantic relationship, close friend moving away and reducing contact	**Examples**: Job demotion, academic probation, acute injury
Timing	
Recent	**Distal**
Definition: Events with a start date within the 3 months preceding the interview date	**Definition**: Events with a start date between 3 - 12 months preceding the interview date
Example: Losing job 1 month ago	**Example**: Ending romantic relationship 4 months ago (regardless of whether there is continued strain)

Table 2. Frequencies of Stressful Life Events

	Total	**Control**	**Challenge**
Major Interpersonal	39	18	21
Minor Interpersonal Recent	88	52	36
Minor Interpersonal Distal	166	80	86
Minor Noninterpersonal Recent	54	23	31
Minor Noninterpersonal Distal	99	53	46
Recent Severity	152	80	72
Distal Severity	300	149	151

Table 3. Zero-Order Correlation Table

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Cortisol AUC_I																		
2. sAA AUC_I	0.080																	
3. Stress Condition	.459*	.197*																
4. Gender (m=1, f=0)	0.041	-.037	.018															
5. SES	-0.117	-.080	-.123	.067														
6. Caffeine Use	-0.117	.155	.029	-.027	-.076													
7. Allergies	-0.016	.022	.063	.032	-.104	-.035												
8. Exercise	-0.107	.087	-.167	-.292*	-.073	.008	-.022											
9. Past Depression	-.178*	-.182*	-.062	-.025	.073	-.005	.035	-.081										
10. Chronic Interpersonal (1-5)	-.137	.145	-.064	-.094	-.135	.103	-.079	.062	.053									
11. Chronic Noninterpersonal (1-5)	-.143	.134	-.095	-.134	-.327*	.001	-.072	.134	-.076	.444*								
12. Major Interpersonal	-.015	-.092	.047	.032	.117	.112	-.218*	-.078	.036	.157	.062							
13. Minor Interpersonal Recent	-.055	-.035	-.108	-.030	-.024	.089	.001	.070	-.047	.036	-.006	-.064						
14. Minor Interpersonal Distal	-.048	-.07	.010	-.118	-.069	-.040	-.037	.076	.114	.193*	.074	.076	.120					
15. Minor Noninterpersonal Recent	-.089	.143	.109	-.021	.089	.007	-.176*	-.079	-.018	.060	.186*	-.096	-.097	.089				
16. Minor Noninterpersonal Distal	-.077	-.018	-.083	-.026	.188*	.029	.010	.201*	.112	.069	-.015	-.057	-.008	.056	-.009			
17. Recent	-.108	.002	-.010	-.084	.148	.096	-.222*	-.065	.038	.036	.049	.256*	.524*	.114	.526*	-.062		
18. Distal	-.037	-.109	.007	-.042	.068	.024	-.134	.106	.110	.284*	.136	.594*	.054	.661*	-.056	.390*	.028	
M	43.499	976.482	.510	.4091	43.756	1.550	1.780	1.390	.230	2.258	2.203	.496	.398	.701	.224	.424	.724	1.572
SD	172.089	1969.808	.502	.49354	13.141	.499	.416	.490	.426	0.456	.327	1.062	.512	.833	.420	.537	.747	1.429

* $p < .05$

Table 4. Full Results of Cortisol Primary Analyses

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	482.539	188.513	2.560	0.012
Major Interpersonal Stress	8.802	66.612	0.132	0.895
Major Interpersonal Stress x Stress Condition	-22.393	31.435	-0.712	0.478

Cortisol AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	421.273	187.155	2.251	0.026
Minor Interpersonal Recent Stress	-45.532	132.238	-0.344	0.731
Minor Interpersonal Recent Stress x Stress Condition	86.904	61.644	1.410	0.161

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	511.195	180.349	2.834	0.005
Minor Interpersonal Distal Stress	-48.281	72.425	-0.667	0.506
Minor Interpersonal Distal Stress x Stress Condition	32.299	41.141	0.785	0.434

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	522.133	192.256	2.716	0.008
Minor Noninterpersonal Recent Stress	-169.048	205.531	-0.822	0.413
Minor Noninterpersonal Recent x Stress Condition	-37.965	106.112	-0.358	0.721

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	492.179	185.24	2.657	0.009
Minor Noninterpersonal Distal Stress	82.491	119.125	0.692	0.490
Minor Noninterpersonal Distal x Stress Condition	100.896	60.373	1.671	0.098

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	504.089	192.283	2.622	0.010
Recent Stress	-15.251	73.152	-0.208	0.835
Recent Stress x Stress Condition	23.403	42.863	0.546	0.586

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	462.181	185.473	2.492	0.014
Distal Stress	7.558	33.85	0.223	0.824
Distal Stress x Stress Condition	7.773	21.582	0.360	0.719

Cortisol AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	461.249	182.189	2.532	0.013
Chronic Interpersonal Stress	-35.777	60.12	-0.595	0.553
Chronic Interpersonal x Stress Condition	-31.616	49.613	-0.637	0.525

Cortisol AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	522.579	185.025	2.824	0.006
Chronic Noninterpersonal Stress	60.781	84.303	0.721	0.472
Chronic Noninterpersonal x Stress Condition	-66.295	54.669	-1.213	0.228

**Note. Covariate, Covariate x Life Adversity, and Covariate x Stress Condition terms are included in the above analyses but not reported for conciseness. In all analyses, the interaction terms of Caffeine Use x Stress Condition (-169.625 < b < -131.759; .004 < p < .020) were significant.*

Table 5. Full Results of sAA Primary Analyses

sAA AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	4026.677	2332.822	1.726	0.087
Major Interpersonal Stress	1023.3	824.317	1.241	0.217
Major Interpersonal Stress x Stress Condition	-267.216	389.004	-0.687	0.494

sAA AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2181.726	2387.331	0.914	0.363
Minor Interpersonal Recent Stress	-722.358	1686.058	-0.428	0.669
Minor Interpersonal Recent Stress x Stress Condition	302.079	749.078	0.403	0.688

sAA AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2947.142	2193.926	1.343	0.182
Minor Interpersonal Distal Stress	-74.99	881.212	-0.085	0.932
Minor Interpersonal Distal Stress x Stress Condition	-61.649	500.458	-0.123	0.902

sAA AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2519.192	2383.711	1.057	0.293
Minor Noninterpersonal Recent Stress	-633.729	2548.301	-0.249	0.804
Minor Noninterpersonal Recent x Stress Condition	1630.245	1315.643	1.239	0.218

sAA AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2913.834	2285.105	1.275	0.205
Minor Noninterpersonal Distal Stress	-754.908	1474.408	-0.512	0.61
Minor Noninterpersonal Distal x Stress Condition	440.892	749.69	0.588	0.558

sAA AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2573.602	2328.35	1.105	0.271
Recent Stress	-19.135	885.841	-0.022	0.983
Recent Stress x Stress Condition	459.172	519.111	0.885	0.378

sAA AUCi (n = 132)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	3510.101	2126.02	1.651	0.102
Distal Stress	-112.382	388.018	-0.29	0.773

Distal Stress x Stress Condition	-168.256	247.419	-0.68	0.498

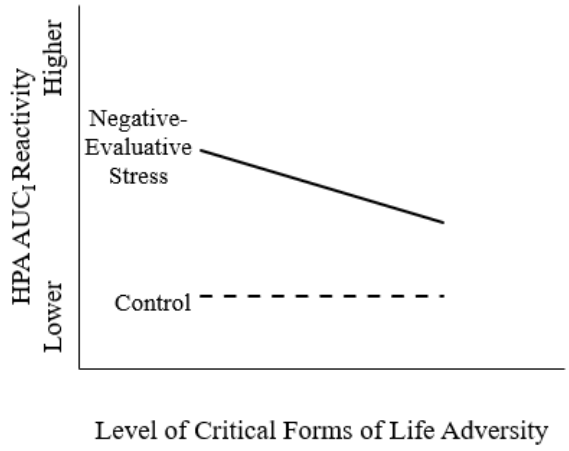
sAA AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2902.175	2230.566	1.301	0.196
Chronic Interpersonal Stress	209.815	740.000	0.284	0.777
Chronic Interpersonal x Stress Condition	46.775	608.17	0.077	0.939

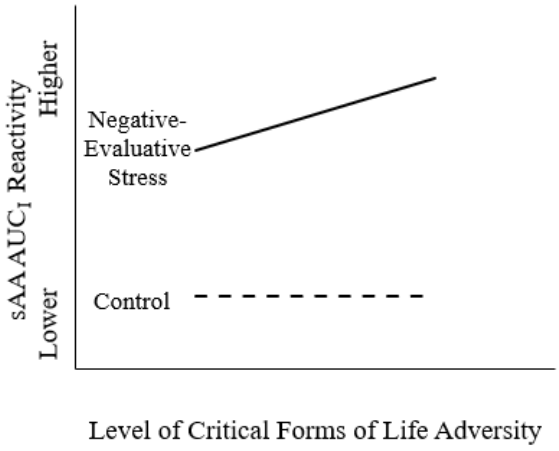
sAA AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Stress Condition	2168.766	2231.96	0.972	0.333
Chronic Noninterpersonal Stress	-476.319	1037.352	-0.459	0.647
Chronic Noninterpersonal x Stress Condition	-261.841	671.311	-0.39	0.697

**Note. Covariate, Covariate x Life Adversity, and Covariate x Stress Condition terms are included in the above analyses but not reported for conciseness. In all models, depression history was significant except in the model examining minor noninterpersonal recent stress (-1344.891 < b < 1148.886; .001 < p < .066).*

Table 6. Chronic Financial Stress and Cortisol Reactivity

Cortisol AUCi (n = 131)	***b***	**SE(*b*)**	***t***	***p*-value**
Gender	-3.814	38.055	-0.1	0.920
SES	-0.671	1.471	-0.456	0.649
Allergies	-14.434	41.481	-0.348	0.729
Caffeine Use	29.881	35.458	0.843	0.401
Exercise	-8.934	37.302	-0.239	0.811
Past Depression	-28.019	39.877	-0.703	0.484
Stress Condition	441.987	172.112	2.568	0.012
Financial Stress	168.801	118.399	1.426	0.157
Gender x Stress Condition	7.586	54.943	0.138	0.890
SES x Stress Condition	-1.749	2.054	-0.852	0.396
Allergies x Stress Condition	-13.801	62.875	-0.219	0.827
Caffeine Use x Stress Condition	-141.292	51.587	-2.739	0.007
Exercise x Stress Condition	-39.401	55.464	-0.71	0.479
Past Depression x Stress Condition	-68.774	61.112	-1.125	0.263
Gender x Financial Stress	-3.445	31.091	-0.111	0.912
SES x Financial Stress	-3.181	1.045	-3.044	0.003
Allergies x Financial Stress	21.97	33.114	0.663	0.508
Caffeine Use x Financial Stress	-4.608	29.551	-0.156	0.876
Exercise x Financial Stress	-31.863	32.026	-0.995	0.322
Past Depression x Financial Stress	-14.612	40.889	-0.357	0.722
Financial Stress x Stress Condition	-62.896	27.694	-2.271	0.025





A **B**

Figure 1. Hypothesized relationship between life adversity exposure and stress reactivity in control and stress conditions. Figure 1A hypothesizes that under stress conditions, those who have experienced more depressogenic life adversity will show a blunted cortisol response relative to those who have less depressogenic life adversity. I did not expect differences in the control condition. Figure 1B hypothesizes that under stress conditions, those who have experienced more depressogenic life adversity will show elevated SNS responding relative to those who have experienced less depressogenic life adversity. I did not expect differences in the control condition.

C

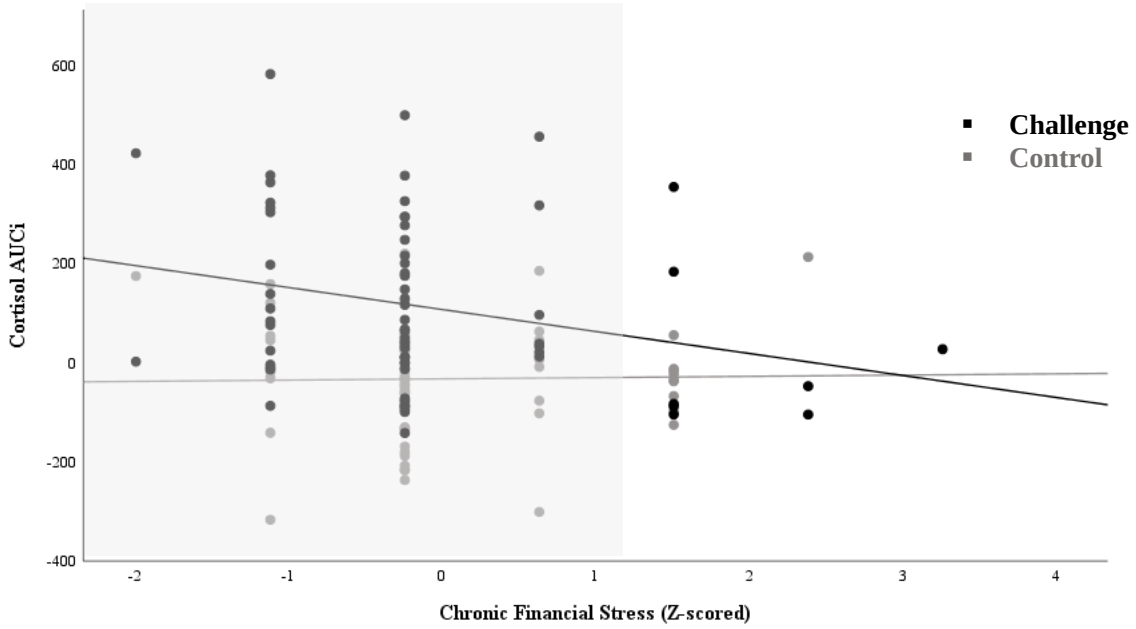


Figure 2. Bivariate correlation plots of chronic financial stress (z-scored) and cortisol AUC_I (residualized by covariates) by stress condition. Higher z-scores on chronic financial stress are associated with greater stress. A significant interaction was detected such that in the challenge condition, at higher levels of chronic financial stress, cortisol AUC_I was lower, whereas no relationship between was detected in the control condition. Chronic financial stress predicted <.001% of the variability in the control condition and 6.5% of the variability in the challenge condition. Regions of significance analyses suggested that slopes differed at values of <+1SD (area shaded in grey).

APPENDIX B: CHALLENGE CONDITION EXAMPLE BEHAVIORAL SCRIPT

Speech portion: Both confederates begin with a mildly pleasant facial expression and neutral to interested body language, e.g., sit up and slightly lean forward in your chair. Administer all directions with a firm, stern tone of voice.

Possible timing in speech	**Confederate 1 (dissatisfied)**	**Confederate 2 (bored)**
0:00	Scribble notes on your paper	Slump shoulders & posture
0:30	Furrow brow with slightly confused look	Quiet sigh of fatigue
1:00	Continue scribbling	Stare into space
1:30	Look more confused	Play with hair
2:00	Shuffle papers	Slight eye roll
2:30	Look at other confederate and shrug shoulders as if to ask "what do you think?"	Look at other confederate and slightly shake head "no"
3:00	Subtle grimace; rub the bridge of your nose	Cross arms, squirm
3:30	Make a conspicuous X mark on your papers	Look at your watch briefly
4:00	Glance at your phone then put it away	Widen eyes and breathe in and out deeply
4:30	Exchange dissatisfied glance with other confederate	Exchange dissatisfied glance with other confederate
5:00	Tap fingers on table	Fidget with finger nails

Arithmetic portion: Conspicuously make tally marks on your paperwork for errors/restarts. Maintain dissatisfied or bored body language and stern tone of voice.