DIFFERENCES IN STRESS BIOMARKERS IN WOMEN WITH HIGH AND LOW STRESS APPRAISAL

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Abstract

Measures of physiological biomarkers have been widely used in the field of stress research to explain how stress negatively impacts health outcomes. Women in particular have been shown to be more at risk for developing physiological and psychological stress-induced conditions (e.g., hypertension, depression) due to hormonal differences (Kirschbaum et al., 1992), but more importantly, because of their appraisal of stressful events (Schamus et al., 2008). Few studies however have examined whether women's stress appraisal is predictive of stress reactivity, as measured by stress biomarkers, during stressful events. The goal of this study was to examine whether stress appraisal predicted stress biomarker activity level. The Appraisal of Challenge or Threat Scale (ACTS; Tomaka et al., 2002) was used to select college-age females for inclusion in one of two mutually exclusive groups including High Stress-Low Coping subjects (Group 1, N = 24) who perceived trigger events as very threatening and their ability to cope as low, and Low Stress-High Coping subjects (Group 2, N = 24) who perceived trigger events as challenging rather than threatening and their ability to cope as high. All subjects (N = 48) completed a standardized stress-induction procedure (Trier Social Stress Test, TSST) that included two stress inducing tasks. Heart rate was continuously measured and saliva samples were collected to determine alpha-amylase stress biomarker levels at 3 time points, including prior to the stress induction, after the completion of the first stress task, and after completion of the second stress task. It was hypothesized that as compared to women with low stress-high coping appraisal, women with high stress-low coping appraisal would have significantly greater reactivity (higher biomarker levels) following stress induction.

A 3 x 2 mixed model ANOVA with time as the within subjects factor and group as the between subjects factor was used for the analyses. The findings showed that there was a main effect of stress induction on sAA ($F_{(2,45)} = 15.09$, $p = .00$) and HR ($F_{(2,45)} = 68.99$, $p = .00$) levels. Post-hoc analyses showed that significant differences in sAA and HR levels occurred only between baseline and the speech task indicating that the speech task and not the arithmetic task

induced a physiological stress response. With regard to the central hypothesis, stress appraisal did not predict stress reactivity (biomarker levels) during stress induction. There was no effect of group on sAA ($F_{(1,46)} = 1.42$, $p = .24$) or HR ($F_{(1,46)} = .00$, $p = .95$). Furthermore, no significant interaction was seen between group and sAA ($F_{(2,45)} = .71$, $p = .49$) or between group and HR ($F_{(2,45)} = .61$, $p = .55$), suggesting that high stress-low coping women did not experience different amounts of sAA or HR changes as compared with low stress-high coping women. When pre- and post-test mood state (PSM-9) scores were compared by group, findings showed no significant interaction ($F(_{1,46}) = 2.48$, $p = 0.12$), however there was a significant group effect indicating that groups differed overall for PSM scores. Paradoxically, high stress-low coping individuals had significantly lower scores before and after the TSST procedure as compared to low stress-high coping individuals ($F(_{1,46}) = 3.99$, $p = .05$).

The current findings provided valuable additional evidence that sAA is a sensitive biomarker of psychological stress. Importantly, the findings suggested that self-reported stress is not an indicator of biological stress reactivity and that self-reported stress should not be used by health care workers to determine whether subjects are at risk of stress-related disease. Furthermore, the findings suggested that high stress-low coping subjects may be vulnerable to emotional blunting. The results require replication.

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Chapter 1: Introduction

Stress is a multifaceted concept that includes environmental, cognitive, affective, behavioral, and physiological components. Over the years, various definitions of stress have emphasized one or more of these different facets (Lumsden, 1981). Today, most researchers define stress according to the effects that are produced when individuals are faced with situations or events that exceed their coping abilities.

It is important to study stress, and in particular, biomarkers of the stress response because it is well established that stress negatively impacts health outcomes. Identifying biomarkers of the stress response could provide a means to identify at-risk individuals long before adverse health outcomes have occurred. In order to understand which biomarkers may be most valuable for identifying individuals who experience high levels of stress, it is important to know the physiological underpinnings of the stress response.

The stress response is founded in the activation of the autonomic nervous system, which includes two components, the sympathetic (SNS) and parasympathetic (PNS) nervous systems. The SNS and PNS systems work together to maintain the body's homeostatic state (Tsigos and Chrousos, 2002). While the sympathetic nervous system initiates the fight or flight responses, the parasympathetic nervous system governs "rest and digest states" (Tsigos and Chrousos, 2002) including regaining homeostasis following fight or flight reactions and initiating salivation, tear production, defecation, digestion, and/or urination. In these ways, the sympathetic and parasympathetic systems are complimentary. For example, while SNS increases pulse rate and blood pressure levels in response to stress, the PNS attempts to bring levels back to a homeostatic norm (Tsigos and Chrousos, 2002).

These complementary processes are associated with the production of key biomarkers. Two components of the SNS, the sympathetic adrenal medullary (SAM) axis and the hypothalamic pituitary adrenal (HPA) axis, are responsible for changes in levels of enzymes, hormones and/or heart rate. The SAM axis is responsible for biophysiological responses to the fight or flight response and stimulates increase of circulating epinephrine (i.e., adrenaline), which then increases heart rate and redirects blood away from the periphery and towards the lungs and large muscle beds in the legs and arms. In turn, the SAM axis increases muscular efficiency, releases energy storage, and increases arterial blood pressure and muscle blood flow. Blood flow is controlled via vasodilation within internal organs and vasoconstriction; these mechanisms allow an organism to become mobile and cope with the stressor.

The second component of the SNS system, the HPA axis, stimulates the pituitary gland, which is responsible for secreting adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal glands to produce corticosteroid, a hormone that allows the body to stabilize blood sugar. Maintaining steady supplies of blood sugar facilitates the return of the body to a normal state. The HPA axis system also stimulates the release of other hormones and enzymes that contribute to the return of a physiologically homeostatic state.

As a result of these processes, the SAM and HPA axes activate the release of various chemicals and proteins. These are valuable biomarkers of stress and measuring these can allow researchers to reliably quantify an individual's reactions to stressful situations.

Alpha-amylase, a well-established stress biomarker is an enzyme governed by HPA axis reactivity. Alpha-amylase is found in saliva and is responsible for the digestion of carbohydrates and starches. Interestingly, it has also been shown that psychological stress results in marked changes of salivary alpha-amylase levels (Rohleder, 2004). Another valuable biomarker used in

stress research is heart rate. Heart rate changes are under the influence of the SAM axis and reflect the body's automatic fight or flight response.

Although stress responses were selected through evolution to ensure greater odds of survival (Cannon, 1932) they can cause bodily damage when activated chronically in response to recurrent psychological stress. The SAM axis is involved in acute stress, while the HPA axis is involved in longer-term reactivity to both acute and chronic stress, remaining active long after the stress is no longer present. Prolonged stress reactivity and long-term elevation of cortisol levels, for example, have been shown to produce a wide range of psychological and physiological symptoms including decreased memory, decreased thyroid function, and accumulation of abdominal fat, which contributes to additional cardiovascular health risks (Blascovich and Katkin, 1993). Also, chronic cortisol release causes immune, digestive, and endocrine systems to down-regulate in response to sustained energy release. This in turn, generally compromises the organism's healthful state (Tsigos and Chrousos, 2002).

When considering possible effects of the stress response systems on physiological health, research has shown marked differences in reactivity in males and females. As compared with men, women report greater levels of chronic stress (McDonough and Walters, 2001; Turner et al., 1995; Nolen-Hoeksema et al., 1999). Furthermore, males and females have marked differences in their perceptions of whether a situation is stressful (Barnett et al., 1987). As compared with men, women perceive greater numbers of stressors in their daily lives and studies have shown that as compared with men, women more often report being in stressful circumstances (Almeida and Kessler, 1998; McDonough and Walters, 2001). Research has also suggested that males and females differ with regard to their coping resources during stressful events. Importantly, gender and specifically the hormonal differences associated with being

male or female, are likely to alter the effects of stress on health (Kirschbaum et al., 1992). Because studies have suggested that women are both more psychologically and physiologically reactive to stress than men (Schamus et al., 2008), this study will focus exclusively on biomarker reactivity in females with differing levels of stress appraisal.

In order to fully assess differences in perceived stress, Tomaka et al. (2012) developed a unique stress appraisal scale using a theoretical framework suggested by Lazarus and Folkman (1984). The ACTS is a 24-item scale that describes potentially stressful life events in six content domains – conflict situations, unexpected events, public speaking, transportation, social anxiety, and financial concerns. Unlike other scales, the ACTS separately quantifies the perception of threat, that is, the extent to which a given trigger event is perceived as threatening, and one's perceived ability to cope with the given trigger event. The measure has been shown to have good factor structure, reliability, and validity (Tomaka et al., 2012).

Studies have not yet examined the extent to which individuals who differ with regard to their cognitive appraisals of threat as measured by the ACTS, differ with regard to their stress biomarker reactivity following a stressful event. Determining whether stress appraisal patterns predict biomarker reactivity following a stressful state could additionally guide our understanding in determining the extent to which an individual's perception influences physiological health risks.

It was hypothesized that alpha-amylase levels and heart rate, would differ in individuals according to their perceptions of situational demands as threatening or challenging. The ACTS was used to select women for inclusion in one of the two mutually exclusive groups; two groups of subjects included High Stress-Low Coping subjects (Group 1) who perceive trigger events as very threatening and their ability to cope as low and Low Stress-High Coping (Group 2) who

perceive trigger events as challenging rather than threatening and their ability to cope as high. Informed consents were completed and salivary samples and heart rate were measured to assess baseline biomarker levels of alpha-amylase and heart rate upon arrival. Subjects completed a widely-used laboratory stress test (Kirschbaum et al., 2010) that involved two stress-inducing activities (e.g., speech and arithmetic task). Biomarker samples were collected upon arrival and at the completion of the first and second stress task (e.g., speech and arithmetic task).

Chapter 2: Review of the Literature

2.1 A History of Stress Concepts

The concept of stress has a long history. In the 14th century, stress was most commonly used to describe the experience of hardship and adversity, for example, incidents involving the death of a loved one or the diagnosis of a chronic illness (Lumsden, 1981). In the 17th century, the term "stress" was used in the context of the physical sciences. "Load" was defined as an external force, "stress" was that which created the load, and "strain" was used to describe the distortion that resulted from load and stress (Hinkle, 1977). It was not until the 19th century that stress was first used to describe a source of ill health. During the 20th century, researchers such as Cannon, Wolff, and Selye (Cannon, 1914, 1932; Wolff, 1953; Selye, 1956, 1964, 1974, 1976) would continue to refine the health-related aspects of stress.

Walter Cannon (1914) was the first researcher to equate stress with emergency, and elaborated its effect by coining the term, "fight or flight response." He was also the first to use the term "homeostasis" which referred to the ability to maintain a stable, constant condition of the body's internal environment such as temperature, pH level, and blood sugar level. His conception of "fight or flight" included the view that stress was a necessity for overcoming threatening events and situations. Cannon believed that stress could be induced by stimuli that were either physiologically or emotionally challenging or threatening to one's survival (Cannon, 1932).

Along with physiologist Philip Bard, Cannon developed the Cannon-Bard Theory (Bard, 1934), which explains why emotions were experienced before a physiological reaction occurred. Specifically, he proposed that the thalamus received a signal via the autonomic nervous system

to the amygdala, which then caused physiological reactions such as muscle tension and sweating. His most notable work (1932) focused on the effect of frequent acute stress on an individual's health and showed that frequent acute stress increased the risk of developing heart conditions and disrupted levels of insulin, triglycerides, cholesterol, and other hormones.

Cannon's groundbreaking findings led other scientists such as Harold Wolff, to use his work as a platform for conducting research. Wolff used a different approach to define and conceptualize stress and as a result introduced the concept of medicine in stress research by describing it as a state of the body (Wolff, 1953). Wolff's research focused on demonstrating the relationship between stressful environments such as domestic difficulties, strenuous working conditions, and unforeseen medical diagnoses; and cardiovascular disorders such as coronary heart disease, hypertension, and atrial fibrillation. He believed that because the cardiovascular system maintained the body's reactions and its state of well-being, anything that disrupted that rhythm caused the organism to undergo disturbances, which could eventually lead to diminished health and/or disease. His research revealed that stress responses such as, tension, frustration, conflict, anxiety, and depression affected the cardiovascular system by inducing irregular heart rates, contractions, and a decrease in the heart's potential to respond. He also suggested that stress experienced in day-to-day living eventually compromised the body's health depending on its frequency and duration.

Like Wolff, Hans Selye used Cannon's work to explain his notions of stress. Specifically, Selye (1956) incorporated Cannon's concept of "homeostasis." Selye was the first to define stress as the effects and symptoms seen and experienced by living organisms when presented with environmental challenges. He explained that stress followed a general pattern of responses, regardless of the type of stimulus. He subcategorized the pattern into three stages –

alarm reaction, resistance, and exhaustion, and referred to this sequence of stages as the General Adaptation Syndrome or GAS (1956). In his model, stress-induced responses activated the sympathetic nervous system and released hormones including cortisol and adrenaline into the bloodstream. This led to a coping response that caused large amounts of energy to be expelled so that a homeostatic state could be obtained. If stress was persistent and caused energy reservoirs to become depleted, a state of exhaustion was reached. This was considered highly detrimental to the health of the organism because tissue damage was probable and in severe cases could result in death. In addition to the GAS model, Selye's work prompted later investigations that helped to explain the progression of physiological stress responses, more specifically, the development from acute to chronic stress.

Adding to his research findings, Selye also distinguished between good and bad stress, otherwise referred to as eustress and distress. Both lead to the activation of the General Adaptation Syndrome (Selye, 1964) and are not defined by the type of stressor, but rather how the stressor was perceived, that is, as a threat versus a challenge. For example, eustress was defined as a positive stress when the psychological demand is perceived as a positive challenge and therefore led to a healthy outlook. In contrast, distress was the negative form of stress. Distress tends to have a negative effect because the situation from which it arose is unresolvable, for example, the death of a loved one, losing one's job, or injury. Thus, distress can be chronic and debilitating if unresolvable situations occur frequently and/or the associated distress persists. Importantly, Selye (1964) demonstrated that the stress response can be lessened or eliminated depending on how it is perceived and dealt with which led him to study the appraisal of stress and its effect on the activation and release of physiological biomarkers (e.g., corticosteroids) (Selye, 1975a, 1975b).

Prior to the 1960s, stress was largely a physiological concept and little to no attention was paid to the role of perception in the stress response. This focus shifted when Magda Arnold developed a cognitive theory of stress (1960). Arnold's theory was based on the idea that all emotions, including stress, resulted from the cognitive appraisal of a situation. For the first time, Arnold suggested that cognitive appraisal was the initial cause of psychological changes and subjective emotional experiences (Arnold, 1960). Interestingly, this theory was poorly received because many believed that the study of cognitive processes was fundamentally unscientific, and that such an approach was too general to explain emotional experience and behavior. It was not until later that her theories gained approval and provided insight for stress research.

Shortly after Arnold's theories were rejected by the scientific community, Richard Lazarus and his colleagues conducted a series of laboratory studies to test a "scientific" approach for measuring stress appraisal. They attempted to experimentally manipulate how subjects would appraise or interpret a potentially stressful situation (Lazarus, 1966, 1991, 1993; Lazarus and Folkman, 1984; Lazarus and Launier, 1978). For example, some of their studies were designed to create psychological stress in the laboratory (e.g., watching stressful films, anticipating an electric shock), allowing them to measure autonomic nervous system activity (e.g., heart rate and skin conductance). Findings showed that appraisal and coping processes shaped the stress reaction and were influenced by environmental stimuli (Lazarus, 1993). Also, their studies showed the potential impact of appraisal in the stress process by explaining the dynamics of taxing experiences. They explained that the way in which a stressful demand is perceived affects coping abilities and physiological responses. In other words, a taxing experience can either be perceived as a challenge or threat, depending on coping abilities/resources. A demand appraised as challenging suggests that an individual feels capable

of coping with a stressful situation; whereas a threat suggests that there is an inability to cope.

Advances in stress research have continued to the present time. For example, "allostasis" was introduced by Sterling and Eyer (1998) to describe the body's ability to adjust and adapt to environmental changes that do not necessarily challenge survival. In order to describe the effects of the loss of allostasis, McEwen and colleagues (McEwen et al., 1998) conceptualized the notions of "allostatic load" and "allostatic overload." Allostatic load described the effects the body endured from stress and allostatic overload was the period in which the body endured persistent stress or the inability to cope (2003). McEwen further delineated four different types of situations that could create allostatic overload. These included, 1) brief exposure to one or more environmental demands; 2) failure to adjust physiologically due to repeated stressful demands; 3) delay of physiological recovery even if the frequency or magnitude of the stress is normal; and 4) inability to cope and respond to the stress due to a state of poor well-being. Their research on animal models revealed that allostatic overload, regardless of the type, had potential to cause tissue damage if frequently experienced (McEwen and Stellar, 1993).

In summary, the concept of stress is centuries old. Throughout its long history stress has been recognized as a phenomenon that adversely impacts human functioning and health depending on its frequency, chronicity, and or how it is coped with. Particularly important for the proposed studies, modern researchers have shown that the perception of stress significantly alter its effects on humans.

2.2 Transactional Model of Stress

The stress model proposed by Lazarus and colleagues (1984) is particularly valuable for understanding the cognitive processes involved in stress appraisal. The model of Lazarus et al.

was referred to as the "transactional model" of stress because it viewed the stress response as the result of the relationship of a person to her environment. It has become one of the most widely used models in research on psychological coping (Lazarus and Folkman, 1984; Duhachek and Kelting, 2009).

Cognitive-relational stress theory (Lazarus and Folkman, 1987) defined appraisals as the process of categorizing situations based on their significance for well-being. In the transactional model of stress, both primary and secondary appraisals together determine the emotional, physiological, and behavioral responses to stress.

2.2.1 Primary Stress Appraisal

According to Lazarus and Folkman's model (1984), primary appraisals are judgments about the importance or significance of a particular "transaction" with respect to the well-being of the individual, referred to as a "person-environment transaction." There are three categories of primary appraisals of a "person-environment transaction" including, 1) irrelevant; 2) benign-positive; 3) stressful (Lazarus and Folkman, 1984). Events or transactions appraised as irrelevant occur when the individual has no stake or investment in the encounter (i.e., nothing can be gained or lost in the person-environment transaction). Transactions appraised as benign-positive or stressful have greater weight and are more likely to elicit an emotional response. (For the purpose of this study, irrelevant and benign-positive appraisals will not be discussed further because of their inability to affect or produce significant stress-inducing responses. Instead, primary appraisals of stress that carry threat and/or challenge will be discussed.)

The transactional model of stress suggested that an encounter began with the evaluation of a situation/event followed by the perception of its demands as threatening and/or challenging,

as illustrated in Figure 2.1. For example, if an individual appraised an encounter or situation as threatening, he or she anticipates that the outcome will produce negative feelings and a potential for loss. Appraisals of threat are associated with emotions such as fear, anger, and sadness.

While threat appraisals have negative implications, appraisals of challenge, reflect a potential for gain. Challenge appraisals are also anticipatory in nature but produce feelings of eagerness, motivation, and excitement. When an encounter is perceived as challenging, it poses an opportunity for growth and development (Lazarus and Folkman, 1984).

2.2.2 Secondary Stress Appraisal

Once a situation/event has been appraised as threatening, challenging, or irrelevant, coping resources, constraints, and options are assessed to determine the prospects for successful coping (Lazarus and Folkman, 1984). When evaluating coping options, the individual chooses those that he or she believes will accomplish a particular goal or those that provide the most effective outcome. Furthermore, an individuals' perception of coping abilities lead to experiencing positive stress (e.g., eustress) or negative stress (e.g., distress). Both positive and negative stress is determined according to whether or not the individual feels that they possess the necessary resources to cope with the stressor.

Considered together, primary and secondary appraisal processes shape the degree of stress and the strength of the emotional reaction. Both appraisal processes are integrated within Lazarus and Folkman's transactional model of stress and lead to emotional and behavioral outcomes and produce action tendencies that awaken the emotional system.