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Sex differences in salivary cortisol in response to acute stressors among healthy participants, in recreational or pathological gamblers, and in those with posttraumatic stress disorder

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Abstract

Sex differences in incidence and severity of some stress-related, neuropsychiatric disorders are often reported to favor men, suggesting that women may be more vulnerable to aberrant hypothalamic-pituitary-adrenal (HPA) axis responses to stress. In this review, we discuss several investigations that we, and others, have conducted assessing salivary cortisol as a measure of HPA function. We have examined basal cortisol among healthy men and women and also following acute exposure to stressors. Among healthy participants, men had higher basal cortisol levels than did women. In response to acute stressors, such as carbon dioxide or noise, respectively, cortisol levels were comparable between men and women or higher among women. We have also examined cortisol levels among those with problem eating, gambling, or post traumatic stress disorder (PTSD). Women with restrained eating habits have higher basal cortisol levels than do women without restrained eating habits. Pathological gamblers have more aberrant stress response to gambling stimuli than do recreational gamblers, and these effects are more prominent among men than women. Men who have motor-vehicle accident related PTSD, demonstrate more aberrant cortisol function, than do their female counterparts. Although these sex differences in cortisol seem to vary with type of stress exposure and/or pathophysiological status of the individual, other hormones may influence cortisol response. To address this, cortisol levels among boys and girls with different stress-related experiences, will be the subject of future investigation.

Keywords

Cortisol; Gender Differences; Hypothalamic-Pituitary-Adrenal Axis; Hypothalamic-Pituitary-Gonadal Axis; Panic Attack

Introduction

Individuals respond to stressors in a variety of ways. Understanding how factors such as sex and/or hormone status mitigates stress response may shed light on how these factors can influence pathophysiological states. First, neuropsychiatric disorders, such as anxiety, depression, and posttraumatic stress disorder (PTSD), are stress-related and influenced by sex and gonadal hormones (Arborelius et al., 1999; Boyer, 2000; Cameron and Nesse, 1988; Esch et al., 2002; Gold and Chrousos, 2002; Kasckow et al., 2001; McEwen, 2002; Rasmusson et al., 2001; Steckler et al., 1999; Young, 1998). Second, stress also modulates engagement in, and effects of, rewarding and/or addictive behavior, and there are salient sex biases associated with these behaviors (Koob and Le Moal, 2008; Lynch, 2006; Lynch et al., 2002; Pendergast, 1994; Sinha, 2001, 2008; van Etten et al., 1999, 2001). In particular, males tend to be more susceptible to engagement in drug abuse whereas females tend to be more labile with greater peaks in abuse behavior. Understanding these pathophysiological states is not only important for revealing the etiology of the disorders but is also crucial for elucidating possible mechanisms of the normative state, which may be influenced by interactions between adrenal and gonadal hormones. Research to identify the extent to which sex- and/or adrenal-hormones can influence response to acute, chronic, and/or pathophysiological stressors is a critical step in understanding treatment and prevention of health risks associated with various types of stress.

Although the extant literature examines how experiential factors, such as the history of stress-related disorder, may influence stress reactivity, here we consider how sex may contribute to stress responses across a variety of healthy and/or pathophysiological states. Our laboratory has investigated sex and/or hormonal differences in various behaviors using animal models, and has worked to elucidate the role that neurosteroids may play in mitigating these effects. We, and others, have found that one mechanism that precipitates neurosteroid biosynthesis to levels that exert effects on behavior is the activation of the hypothalamic-pituitary-adrenal (HPA) stress axis. We have been collaborating with clinical investigators to assess the role that HPA activation may play in healthy, subclinical, and clinical human samples and the following review summarizes a decade of this work.

Salivary Cortisol as a Research Approach to Investigate Sex Differences

Sex differences in vulnerability to stress are dependent on many factors including the type of stressor utilized as well as the endogenous hormonal status of the individuals examined. While some studies indicate that differences in neurobiological stress response favor men (Gallucci et al., 1993; Jezova et al., 1996), there have been many reports demonstrating the opposite effect (Kajante and Philips, 2006; Kudielka et al., 2009), and some reporting no differences between the sexes (Earle et al., 1999; Owens et al., 1993). Unlike, investigations of people, studies using rodent models typically find females to have increased stress axis activity compared to males (Critchlow et al., 1963; Handa et al., 1994; Kitay, 1961). Thus, activation of the HPA stress axis is a sexually-divergent trait but this relationship may be more difficult to parse out in humans. As depicted in Figure 1, stress elicits production of corticotropin releasing hormone (CRH) from paraventricular hypothalamus, which acts to mediate pulsatile release of adrenocorticotrophic hormone (ACTH) from anterior pituitary into circulation. Actions of ACTH at adrenal glands promote release of glucocorticoids (primarily cortisol in humans and corticosterone in most rodents) which can act in the brain to produce some of the psychological effects that are associated with stress (such as enhanced memory consolidation and perception of arousal; Abercrombie et al., 2005; Buchanan and Lovallo, 2001; Roozendaal, 2000) and attenuate CRH/ACTH production in a negative feedback loop. The hippocampus is included in this depiction of the HPA, as stress hormones can have profound effects on physiological, behavioral, and neuroendocrine

responses associated with this and other limbic regions (Conrad 2005, 2006; Herman et al., 2005; Weinstock, 2008). Cortisol levels in plasma have been shown to correlate well with cortisol concentrations in saliva among infants (Calixto et al., 2002), children (Schwartz et al., 1998), and adults (Aardal and Holm, 1995; Cadore et al., 2008; Kahn et al., 1988). In the following investigations we have used salivary cortisol as a biomarker for HPA function.

Acute vs. Chronic Activation of the Hypothalamic-Pituitary-Adrenal Axis

Acute stressors typically produce rapid enhancement in glucocorticoid levels and do not affect the basal (non-stress) activity of the HPA axis (Assenmacher et al., 1995). This glucocorticoid response to an acute stressor is typically considered “adaptive”. Acute increases in glucocorticoids enhance arousal and energy mobilization (the brain stimulates neurotransmitter release, the muscles increase protein metabolism, the adipose tissue mobilizes lipids, and the liver increases glycogen synthesis) so that “fight-or-flight” behavioral responses can be subserved (Axelrod and Reisine, 1984; Sie and Fishman, 1964; Munck et al., 1984). Acute release of adrenal steroids also enhances memory consolidation of stressful events, which may facilitate similar “adaptive” responses in future situations (Buchanan and Lovallo, 2001; McEwen, 2007; Roozendaal, 2000). The physiological, psychological, and behavioral consequences of acute stress are, thus, likely to be adaptive to an individual in the short run. However, sex differences in response to acute stress may influence responding to chronic or unrelenting stress. One aspect of this review will focus on the role that sex and environment may play on acute stress response and implications for pathological states associated with acute and chronic stress, such as panic attack.

Ongoing (chronic) stressors are characterized by overactivation of the HPA axis (compared to acute stress; Chrousos and Gold, 1992; Gold et al., 1988). There may not be differences in the basal levels of glucocorticoids, but stress-induced increases in glucocorticoids may occur with a less robust stimulus, be greater, and persist for a longer time than occurs with acute stressors. This dysfunctional state of the HPA axis can result in persistently decreased basal glucocorticoid levels, as can be seen in PTSD and atypical depression (Ehlert et al., 2001; Mason, 1986; Stratakis and Chrousos, 1995; Yehuda et al, 1990, 1991, 1993, 1995ab) or basal glucocorticoid levels can be elevated in response to HPA dysregulation, as can be observed in melancholic depression, obesity, and panic and anxiety disorders (Arborelius et al., 1999; Bjorntorp, 1995; Bjorntrop et al., 2000; Bjorntorp and Rosmond, 2000; Board et al., 1957; Gold et al., 1988; Stratakis and Chrousos, 1995). The factors that may promote one HPA response (hypo- or hyperactivity) when confronted with pathological stress are not well-understood but are likely complex and dependent on interactions between organizational, activational, and epigenetic effects (McEwen, 2002, 2007). Chronic stress can dysregulate a variety of normal, peripheral, physiological functions, including cardiovascular, hepatic, immune, and digestive processes in addition to promoting central reductions in neurogenesis and neuron efficiency (McEwen, 2007). The type of stressors that are generally considered pathophysiological may be initially similar to chronic or traumatic stress, but then become pathophysiological because the stress response (HPA activity) and psychological recurrences of trauma are altered and unremitting even when the source of the stressor is removed (Sapolsky, 1992). Stress influences so many physiological systems (central, immune, metabolic, and cardiovascular) that chronic HPA reactivity can have profound negative effects on health. Chronic stress contributes to neurodegeneration of the hippocampus, development of cognitive and affective disorders, cardiovascular disease, immune deficiency and/or autoimmune disorders (Chorot and Sandin, 1994; McEwen, 2000; Torpy and Chrousos, 1996; Young, 1998). Contributors associated with the shift from adaptive responses to acute stress to maladaptive responses to chronic stress are not well-understood. Thus, the latter half of this review will address pathological states associated

with more moderate and chronic HPA arousal such as that observed in addiction and posttraumatic stress disorder (PTSD), respectively.

Acute Stress in Men and Women by Induction of Panic Attack Symptoms

Panic attacks, which occur in both nonclinical and clinically-anxious populations, are time-limited, highly aversive, abrupt neurobiological events. They are often accompanied by wide-ranging negative physiological, psychological, behavioral, and health-related consequences (Barlow, 2001; Gater et al., 1998; Kessler et al., 1994; Lewinsohn et al., 1998; Patel et al. 1999; Pearson 1995). A model of acute stress/panic is exposure to carbon dioxide (CO₂)-enriched air, which produces autonomic and psychological effects that are analogous to panic attacks (Forsyth et al., 2000ab). In this acute stress paradigm, men and women with no known history of psychopathology are exposed to a single 20 second inhalation of 20% CO₂-enriched air or normal room air (control condition). This CO₂ exposure paradigm has been used successfully in the past to evoke, in both fear learning and biological challenge contexts, psychological and behavioral responses analogous to panicogenic arousal (Forsyth et al., 2000ab). This procedure is capable of supporting aversive fear learning to exteroceptive and interoceptive cues (Acheson et al., 2007). CO₂ inhalation results in refractory elevations in plasma cortisol (Argyropoulos et al., 2002; Coplan et al., 2002; Sasaki et al., 1996) with no acute or long-term health risk or subsequent vulnerability for later panic attacks or anxiety (Harrington et al., 1996; Prenoveau et al., 2006). CO₂ exposure is an effective paradigm to examine acute stress-induced changes in nonclinical and clinical populations without inducing actual panic attack (Beck et al., 1996; Bouton et al., 2001; Forsyth and Eifert, 1998; Forsyth et al., 2000a; Fyer et al., 1987; Griez, and van den Hout, 1986; Lejuez et al., 1998; Rapee et al., 1992; Schmidt et al., 1996; van den Hout and Griez, 1984; Zvolensky et al., 1999). We and others have seen that exposure to CO₂ increases salivary cortisol (Bandelow et al., 2000; Belgorodsky et al., 2005; van Duinen et al., 2005) but diurnal rhythmicity remains with a 3-fold increase in the morning (0800 h) compared to mid-day (1400 h) exposure, and a 1-fold decrease in the afternoon (1600 h) compared to mid-day exposure (Fig. 2; Murray et al., 1999).

Women are affected more often by panic than are men (Barlow, 2001; Gater et al., 1998; Kessler et al., 1994; Lewinsohn et al., 1998; Patel et al., 1999; Pearson, 1999). However, sex differences in cortisol response to a psychological or physical stressor are not always reported to discriminate between males and females, despite sex differences in self-reported stress, emotional response, and/or discomfort (Kelly et al., 2008; van Stegeren et al., 2008). Our collaborator, Dr. John Forsyth, has found that following CO₂ exposure, women consistently report a greater frequency (Fig. 3, top) and greater severity (Fig. 3, middle) of panic symptoms relative to their male counterparts. These women also report a greater distress rating following CO₂ compared to men (Fig. 3, bottom). However, it must be noted that both men and women reported panic attack symptoms, but no participants in either group had an experience meeting diagnostic criteria for panic attack. In addition to these findings, we have observed that men (n=19) who were given instruction to elicit a coping response had decreased salivary cortisol compared to women (n=29) or those not given any instructions to counter CO₂ when tested in the afternoon (approximately 12:00 h; Murray et al., 1999). Together, these data support the notion that a sex-specific perception, and/or coping skill-set, may be important in the neuroendocrine response to acute stress (see also Kelly and Forsyth, 2007). While, women demonstrated a greater stress response than men in this study, there are many investigations utilizing validated stressors that report the opposite effect (reviewed in Kudielka et al., 2009). It remains an open and interesting question if this paradigm, which induces panic-like symptoms, is sex-biased, as others have discussed in reference to pharmacological stressors (Kudielka et al., 2009).

Investigations such as this begin to elucidate the behavioral and physiological aspects of stress that may be mitigated by sex under experimental conditions. It is rare to have the opportunity to investigate how sex may influence these factors in the native environment under non-experimental conditions. We have also examined acute stress responses in individuals that are not in an experimental setting.

Stress Response Among Laboratory Workers in the Native Environment

Our laboratory is situated in a new Life Sciences Research Building on The University at Albany-SUNY campus and infrequent construction is still necessary to conduct at times. Given the impact that auditory stimuli can have on behavioral outcomes of people and animals under laboratory conditions, routine construction is coordinated so as not to occur when experiments are being conducted. However, we have recently experienced an unanticipated situation wherein workers (6 male and 9 female observations) in our behavioral laboratory were exposed to an unexpected, intermittent construction noise every 2-4 minutes for a period of approximately 4 hours from 09:00 to 13:00 h. Other workers in our group (3 male and 7 female observations) were in the biochemistry laboratory and were not exposed to this spontaneous, noise stimulus. All workers, in the behavior and biochemistry laboratories, were administered the Spielberger's State-Trait Anxiety Inventory (STAI) at 12:00, 15:00, and 18:00 h, and saliva samples were collected at each of these timepoints. As depicted in Figure 4 (top), mean State anxiety scores were significantly higher among workers exposed to the unpredictable construction noise compared to those who were not. In both groups, women had greater State anxiety scores. No differences were observed in Trait anxiety scores (data not shown). Further, salivary cortisol concentrations appeared to be affected by sex and noise exposure, albeit these differences were not significant (Fig. 4, bottom). Men had higher salivary cortisol than women in the control condition (as we and others have observed is the case at basal concentrations in healthy populations). Among the noise-exposed group, women had a much greater salivary cortisol response than did men. These are consistent with our observations that healthy women may be more responsive to an acute stressor, such as CO₂-exposure, than healthy men, and extend them to illustrate that sex differences in response to acute stress can be seen in a native, non-experimental situation. Thus, sex differences observed under these circumstances may be mitigated by environmental conditions associated with testing. The extent to which these factors may influence (sub)clinical disorders that are known to be associated with HPA dysfunction is also of interest.

Salivary Cortisol and Restrained Eating in the Native Environment

A common, sex-biased, stress-related disorder among college students is disordered eating, or aberrant eating/dieting behavior. With our collaborator, Dr. Drew Anderson, we have found that among non-obese, undergraduate college women, those identified by questionnaires (Herman and Polivy, 1980) as demonstrating restrained eating (n=50; characterized by chronic, unsuccessful dieting and fluctuating weight; Anderson et al., 2002; Gorman and Allison 1995; Heatherton et al., 1988) had significantly higher salivary cortisol levels (0.39 ± 0.02 $\mu\text{g}/\text{dl}$) than did non-afflicted college women (n=24) when assessed between 09:00 and 11:00 h (0.17 ± 0.01 $\mu\text{g}/\text{dl}$; see also Anderson et al., 2002). We have also observed that women who exhibit disordered eating or alcohol abuse demonstrate similarly high degrees of impulsivity and attitudes permissive of social deviance (Benjamin and Wulfert, 2005). As well, this impulsivity can be associated with involvement in illicit substance use and poor academic performance (Wulfert et al., 2002). Given these implications, the extent to which HPA dysregulation is associated with sex-differences in addictive behavior was of interest. We assessed HPA response in pathological gambling, as

this presents a situation wherein physiological responses to addiction can be studied independent of a drug stimulus that can have confounding psychoactive effects.

HPA Activation in Recreational and Pathological Gamblers in the Laboratory Setting

Neuroendocrine factors appear to play a role in impulsivity associated with motivated behavior. Pathological gamblers can exhibit levels of impulsivity that exceed those observed in non-gambling controls, recreational gamblers, and individuals with substance use addictions that include alcohol and cocaine (Blaszczynski et al., 1997; Castellani and Rugle, 1995; Steel and Blaszczynski, 1998). Moreover, impulsivity has been related to severity of gambling as measured by the South Oaks Gambling Screen (SOGS) among gambling men (Steel and Blaszczynski, 1998; Vitaro et al., 1997) but some studies do not report a clear relationship with HPA function (Krueger et al., 2005). Other investigations have found that plasma cortisol and heart rate are significantly increased among male blackjack players at the onset of engaging in blackjack gambling in a casino when playing with their own money compared to a control condition when they were playing for non-monetary points (Krueger et al., 2005; Meyer et al., 2000). In these studies, both plasma cortisol and heart rate remained elevated for the duration of 60 or 90 minutes of play. As well, investigation in an aboriginal community in which everyone gambles following receipt of weekly pay, demonstrated that urinary cortisol is greater on days when gambling is most intense compared to days when it is minimized, and this effect was more prominent among men than among women (Schmitt et al., 1998). These data suggest a role for HPA arousal in response to gambling when in the casino environment.

In experimental settings, strong evidence support the involvement of prefrontal processes in decision-making that could lead to the addiction process (Bechara et al., 2000ab; Cavedini et al., 2002; Clarke, 2004). The extent to which HPA status is a causative factor in such behavior or the result of engagement in addictive behavior remains unclear. We have observed that the magnitude of reduction in pathological gambling symptoms with therapeutic intervention is positively correlated with reduction in heart rate to gambling cues (Freidenberg et al., 2002) suggesting a role for autonomic arousal in the addiction process.

To begin to elucidate the role of HPA and sex on pathological gambling in a laboratory setting, we compared salivary cortisol levels of men and women who were recreational or pathological gamblers following exposure to gambling cues (Paris et al., 2009). It is notable that brief exposure to drug cues can readily reinstate craving for an addiction among human addicts and can reinstate a previously extinguished addiction among animals. Saliva samples were collected at baseline, following visual scenes that depicted engagement in gambling, and after a visual scene that depicted a neutral, stimulating event (a rollercoaster ride). We anticipated that pathological gamblers would have an attenuated HPA response following exposure to gambling cues compared to recreational gamblers. Participants each viewed gambling scenes depicting a gambling win and a gambling loss (in a counterbalanced manner). Whereas no differences emerged in basal levels of salivary cortisol among recreational or pathological gamblers, following the gambling stimuli, recreational gamblers had significantly elevated cortisol levels compared to pathological gamblers, who did not demonstrate a significant cortisol response to the stimuli. Moreover, pathological gambling men demonstrated a depression in cortisol concentrations from baseline after exposure to gambling footage, whereas all other groups demonstrated an elevation (Fig. 5). These data suggest that hypo-arousal of the HPA axis is associated with pathological gambling and that men may be particularly vulnerable. Similarly, others have found that lower concentrations of salivary cortisol were associated with riskier choices and monetary loss in the Iowa gambling task, whereas higher salivary cortisol indicated less risky choices and monetary

gain (van Honk et al., 2003). As observed in some chronic stress-related pathologies, repeated exposure to the stressor may be associated with dysregulation of the stress response, wherein the stimuli no longer elicits HPA activation. In animal models, cortisol administration is rewarding. Thus, pathological-gamblers may have a hypocortisolemic response to gambling stimuli in the laboratory environment and this may play a role in the addiction process as the stimuli no longer elicits the prior degree of rewarding stress-related arousal.

Stress Response and Engagement in Gambling Behavior in the Native Environment

We have observed that HPA arousal is attenuated among pathological gamblers in a laboratory setting when exposed to gambling cues, but whether engaging in gambling in the native environment would differentially influence HPA function was of interest. Engagement in motivated behaviors in the native situation presents a unique circumstance under which HPA-related effects on behavior can be observed. A reciprocal relationship between pharmacological addiction and HPA activation may exist, such that stress and HPA activation promote the likelihood of use (Goeders 1997, 2002ab), and use alters HPA arousal. Indeed, research in animal models indicates that early stress experiences alter HPA response throughout life such that HPA hormones can be down-regulated while ligand targets can be upregulated and these effects are sex-dependent with males attenuating and females hyper-activating HPA response (Bosch et al., 2007; Mabandla et al., 2007; Orдын and Pivina, 2004). As well, reinforcing properties of hedonic stimuli can be enhanced by early stress (Kippin et al., 2007). Similarly, human research indicates that negative life events in adolescence (such as loss of a parent, parental divorce, abuse, etc.), trauma, and certain socio-cultural stressors are all associated with increased vulnerability to engagement in addictive processes (reviewed in Sinha, 2008) and enhancement of cortisol can promote pharmacological addiction (Elman et al., 2003; Sinha et al., 2000). Some of these effects may be related to glucocorticoid actions to enhance central dopamine secretion (Barrot et al., 2001). These data support the notion that HPA activation can influence addiction.

The environment may provide salient cues to elicit HPA response that may be associated with motivated and addictive processes. To investigate the role of HPA involvement on sex differences and gambling in the native environment, we assessed salivary cortisol in men and women gamblers at an off-track-betting (OTB) establishment (Franco et al., 2009). All participants engaged in gambling at the OTB at least twice per week. Participants placed a \$2 bet of their own money on a horse-race to win and had saliva sampled before the race, immediately following the race, 10-min post-race, and 20-min post-race. Among OTB bettors, we found that men had significantly higher salivary cortisol concentrations at all sampling times compared to women. By 20 minutes post-race salivary cortisol was resolving among both men and women (Fig. 6). Absolute values of salivary cortisol were also significantly higher among men compared to women (Franco et al., 2009). Thus, among OTB bettors engaging in gambling in the natural environment, men have a greater and more sustained HPA response to gambling than do women. These data support the notion that gambling men may have an increased cortisol response when gambling in the native environment that is not as readily observed among women. However, it is a notable drawback that non-gambling controls were not included in either gambling experiment as men have been found to demonstrate a greater anticipatory stress response than women (Kirschbaum et al., 1992; Kudielka et al., 2009). Future experiments will seek to assess the role that anticipatory appraisal plays in the observed findings.

These data may be important for addictive processes apart from gambling. There is evidence that sex differences exist in problem and pathological gambling as in pharmacological

addiction wherein men may be more vulnerable (Wilson et al., 2006; Blanco et al., 2006; Westermeyer and Boedicker, 2000). Pathological gambling and substance abuse are often co-morbid (Lesieur et al., 1986) and share many characteristics in pathology. In support, assessments of personality are similar among pathological gamblers and substance abusers (McCormick et al., 1987; Ramirez et al., 1988). Engaging in gambling activates substrates that are also associated with natural or drug-induced reward (Bechara, 2001; Kalenscher et al., 2006; Goodman, 2008; Reuter et al., 2005). In addition, therapeutics with efficacy treating substance addictions can reduce pathological gambling (Kim et al., 2001; Grant et al., 2006ab, 2008). Engaging in gambling also elicits similar physiological responses as drugs of abuse. For instance, as is observed in drug use, there are autonomic effects of gambling. Autonomic arousal, measured by elevation in heart rate, has been demonstrated in response to many types of gambling stimuli including blackjack (Anderson and Brown 1984; Krueger et al., 2005; Meyer et al., 2000), poker machines (Coulombe et al., 1992; Dickerson et al., 1992; Leary and Dickerson 1985), slot machines (Carroll and Huxley 1994; Griffiths 1993), and horse race betting (Coventry and Norman 1997). Further, greater stakes elicit a greater autonomic response (Anderson and Brown 1984). These autonomic responses are indicative of HPA arousal. Thus, stress factors may underlie aspects of the general addiction process.

Chronic Stress in Posttraumatic Stress Disorder

We have found that, among healthy individuals in the described studies, HPA activity is greater among women than men in response to acute stressors. When considering a pathological state, such as gambling addiction, this sex difference may be reversed and this reflects the behavioral phenotype wherein men may be more vulnerable to pathology. It is also important to understand the influence that sex may have in cases of extreme pathology caused by stress.

Stress is a cause of PTSD, which results in impaired daily and HPA function (Aardal-Eriksson et al., 2001; Vanitallie, 2002). It has been observed that people with PTSD for 20+ years have lower basal urinary cortisol compared to controls (Mason et al., 1986; Yehuda et al., 1990, 1991, 1993, 1995ab). Levels of urinary or serum cortisol, proximate to a motor vehicle accident (MVA), are lower among people with intrusive thoughts of the MVA, or that are later diagnosed with PTSD, than are those without such symptomology (Delahanty et al., 2000; McFarlane et al., 1997). These results suggest that altered HPA axis activity associated with extreme stress may lead to the development of “overconsolidation” of memories and thereby contribute to the development of PTSD (Pitman, 1989; Pitman et al., 1991). Van der Vegt et al. (2009) report a bifurcated effect of traumatic stress on cortisol among individuals maltreated during childhood such that individuals with histories of severe maltreatment exhibited lower cortisol levels and a flatter diurnal variation, whereas individuals who had experienced moderate maltreatment had higher levels and a steeper diurnal pattern.

More women than men are diagnosed with PTSD (Aardal-Eriksson et al., 2001; Breslau et al., 1997; Vanitallie, 2002). Examinations of sex effects on development of PTSD reveal that the majority of those diagnosed with PTSD are women (Breslau et al., 1991, 1997, 1998, 2004). However, when considering the influence of sex on pathophysiological state, investigations of PTSD have suffered inherent sex-specific confounds. That is, sex differences in stress-related pathologies are often subject to *a priori* categorization related to trauma experiences that are more prevalent in men vs. women (e.g., combat vs. sexual assault). These trauma experiences have different characteristic consequences (Buck and Walker, 1982; Frayne et al., 1999; Hofmann et al., 2003; Lang et al., 2003) and may also be superimposed on characteristics of traumatized individuals that confound apparent gender

effects. We have examined men and women suffering from PTSD as a result of MVA-related trauma as this is a more gender-neutral stimulus.

Our collaborator, Dr. Edward Blanchard, has shown that PTSD can occur following an MVA (Barton et al., 1996; Blanchard et al., 1994, 1995ab, 1996). Those with acute stress disorder due to an MVA are at high risk (60 to 80%) for converting to PTSD within 6 months (Harvey and Bryant, 1998). In our study, men and women who were referred by medical professionals or recruited by local media coverage and advertising were invited to The Center for Stress and Anxiety Disorders at The University at Albany-SUNY for an assessment of PTSD. Participants were diagnosed with PTSD via the Clinician Administered Post-Traumatic Stress Disorder Scale (Blake et al., 1998; Weathers et al., 2001; Weathers and Litz 1994). Within a week of the assessment, participants underwent re-exposure therapy for their MVA and saliva samples were collected at 14:00, 18:00, and 22:00 h.

Among men and women with MVA-related PTSD, men had higher levels of salivary cortisol than did women and demonstrated atypical diurnal variation whereas women still demonstrated some reduction in cortisol concentrations across testing times, albeit these were not typical (Fig. 7; Freidenberg et al., 2009). However, compared to reference values from non-afflicted controls, both men and women with MVA-related PTSD were hypocortisolemic. These data support the notion that men and women with PTSD may present with perturbation of the HPA axis, and that men, compared to women, may have a more aberrant response when suffering from MVA-related PTSD. Past and recent investigations have also found that among men and women with MVA-related PTSD, cortisol levels are depressed (Delahanty et al., 2000) and males may have greater HPA arousal than women (Hawk et al., 2000; Shalev et al., 2008). Furthermore, examinations of MVA-related PTSD in children and adolescents have demonstrated that urinary cortisol predicts the degree of PTSD, with a larger effect among boys (Delahanty et al., 2005). These data support the notion that hormonally-mediated organizational sex differences may underlie some of the observed effects in HPA aberration associated with MVA-related PTSD.

Role of Hypothalamic-Pituitary-Gonadal Axis

An important question is what processes may underlie these sex differences in cortisol response. Sexual differentiation is initiated by early organizational effects of androgens and estrogens in humans and animals. Throughout life, production of steroids (primarily androgens from the testes of males and estrogens/progestogens from the ovaries of females) will have activational effects to alter physiological and psychological processes. Secretion of gonadotropin releasing hormone from hypothalamus acts on anterior pituitary to secrete lutenizing hormone and follicle stimulating hormone into circulation. Gonadotropins mediate gonadal release of sex steroids which can alter stress response in the HPA axis (Fig. 1). For example, in rats, estrous cycle differences can alter stress response. During the proestrous phase of the rat estrous cycle, when estradiol (E_2) levels peak, female rats have increased stress responsiveness compared to females in other stages of the estrous cycle (Audrain et al., 1978; Carey et al., 1995; Critchlow et al., 1963; Shors et al., 1998; Viau and Meaney, 1991). Removal of the ovaries, the primary source of E_2 , attenuates elevated stress response among female rats (Audrain et al., 1978; Kitay, 1961) and replacement with E_2 and/or progestogens to ovariectomized rats reinstates this (Burgess and Handa, 1992; Dayas et al., 2000; Kitay, 1961; Patchev and Almeida, 1996; Viau and Meaney, 1991). Evidence for such effects are observed in women wherein salivary cortisol is observed to fluctuate across the menstrual cycle with greatest levels occurring during the menstrual phase (days 1-5 of the cycle), when endogenous estrogens and progestogens are at nadir (McCormick and

Teillon, 2001). Further, progesterone elevations in the menstrual cycle have been associated with enhancement of plasma cortisol in response to a physical stressor (Roca et al., 2003). When considering sex differences, we must consider both the “organizing” effects of gonadal hormones during development (usually defined as sex), as well as the “activating” effects of gonadal hormones on behavior and physiology (typically defined as diurnal phase, time of day, in males and cycle phase in females) of the hypothalamic-pituitary-gonadal (HPG) axis. One of our goals is to examine the physiological and behavioral response to stressors as a function of both the organizational and activational effects of gonadal hormones. Throughout many of the aforementioned investigations, we were not able to control for cyclical variations in women's menstrual cycles. The extent to which observed sex differences are attributable to activational vs. organizational effects of sex hormones remains unknown.

To begin to address this, one situation that can be considered is whether there are sex differences in stress responses among boys and girls. Our collaborator, Dr. Elana Gordis, has assessed salivary cortisol in maltreated and comparison male and female youth (age 9-14). In a pilot sub-sample selected from the larger study sample, youth provided 2 saliva samples before and 4 saliva samples after a psychological stressor (a modified version of the Trier Social Stress Test; Kirschbaum et al., 1993). Results suggest that maltreated youth overall demonstrated a hypocortisolemic response compared to age-matched control youth (Gordis et al., 2008), and that HPA aberration in combination with lower adrenergic responses may predict parent-reported aggressive behavior (Gordis et al., 2006). Preliminary analyses with the full sample of 454 youths (Trickett et al., 2006) indicate effects of cortisol response to the acute stressor, in addition to the main effects of maltreatment, with females showing lower overall levels but greater percent change from baseline in response to the stressor. Together, these data suggest that there are effects of maltreatment on cortisol response, but also that sex differences in cortisol response to stress may be present in youth as well as adulthood. These data may have important implications for development of cortico-limbic and/or executive functioning processes. Figure 8 displays the percent change from baseline salivary cortisol for male (n=201) and female (n=235) youth across the 6 samples. Following stressor, females have a consistent, albeit non-significant elevation in cortisol compared to males. This difference may be mediated by organizational as opposed to activational factors.

Conclusion

Together our data and the findings of others reveal that HPA function can influence, and be influenced by, pathophysiological state and this may have implications for neuropsychiatric disorders (such as panic attack, disordered eating, and PTSD) as well as development of pathological engagement in reward behavior such as drug use and gambling. Further, these data elucidate the nature of sex differences when observing situations wherein sex biases are minimized or are atypical. The sex-specific neuroendocrine factors that mediate HPA responsiveness in these situations will be the target of future investigation. As well, work in animal models will be aimed to elucidate the extent to which sex-differences in stress-response are due to genetics, organizational hormone effects, or epigenetic phenomena.

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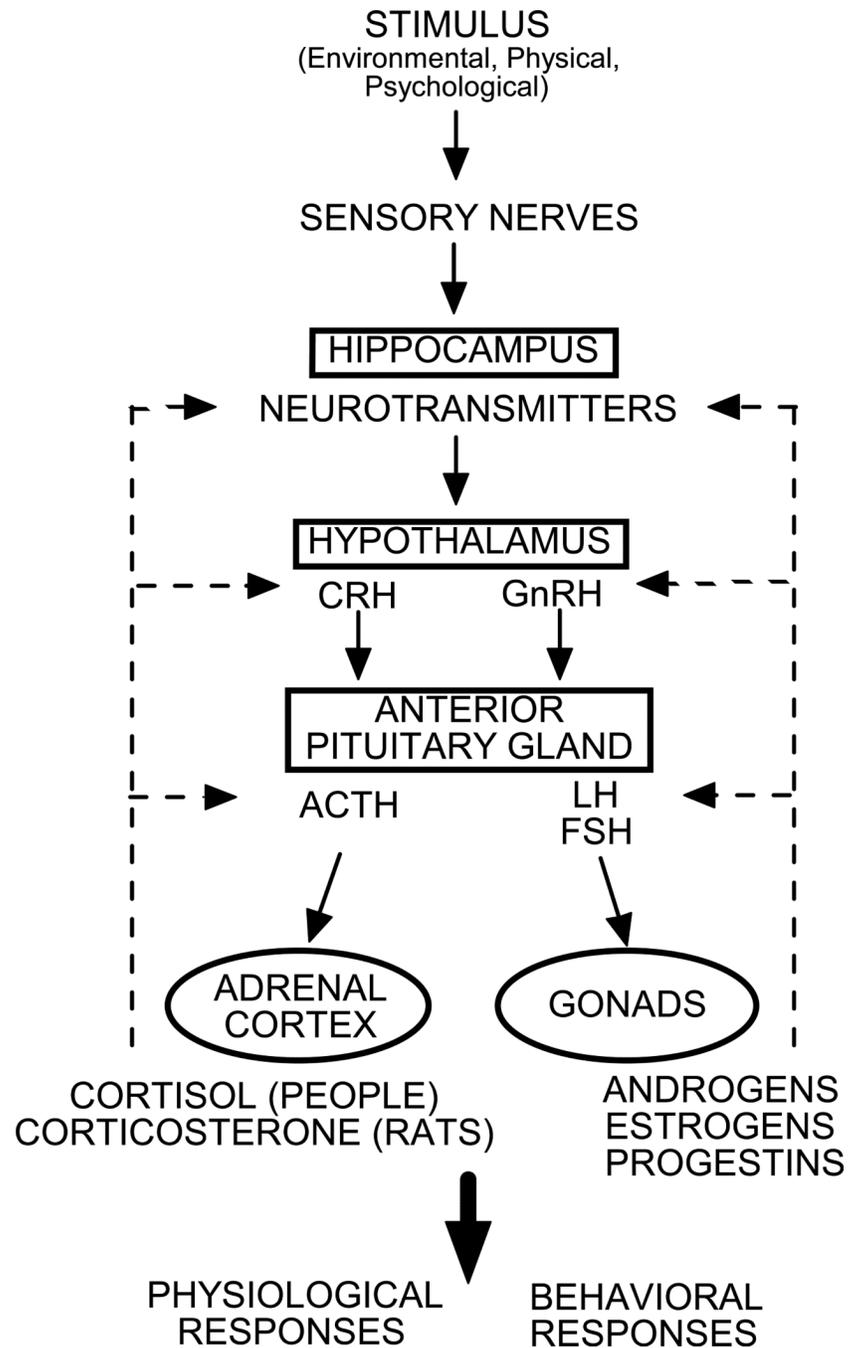


Figure 1. Depicts hypothalamic-pituitary-adrenal/gonadal axes. ACTH = adrenocorticotrophic hormone; CRH = corticotropin releasing hormone; FSH = follicle stimulating hormone; GnRH = gonadotropin releasing hormone; LH = lutenizing hormone.

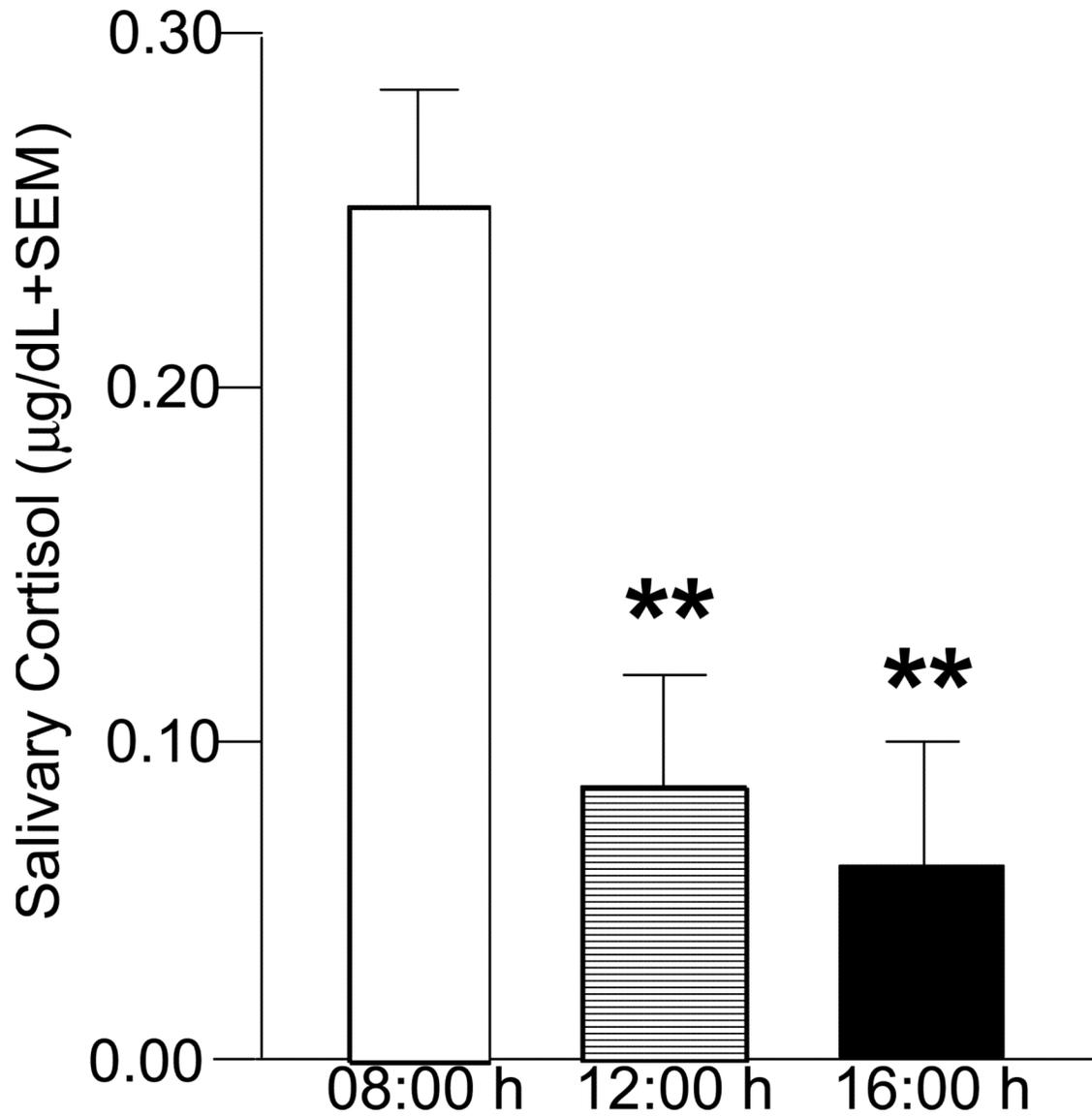


Figure 2. Depicts salivary cortisol levels of laboratory personnel (4 males and 7 females) following 20% CO₂-exposure at 08:00, 14:00, and 16:00 h. * indicates significantly different from 08:00 h sampling, $p < 0.05$.

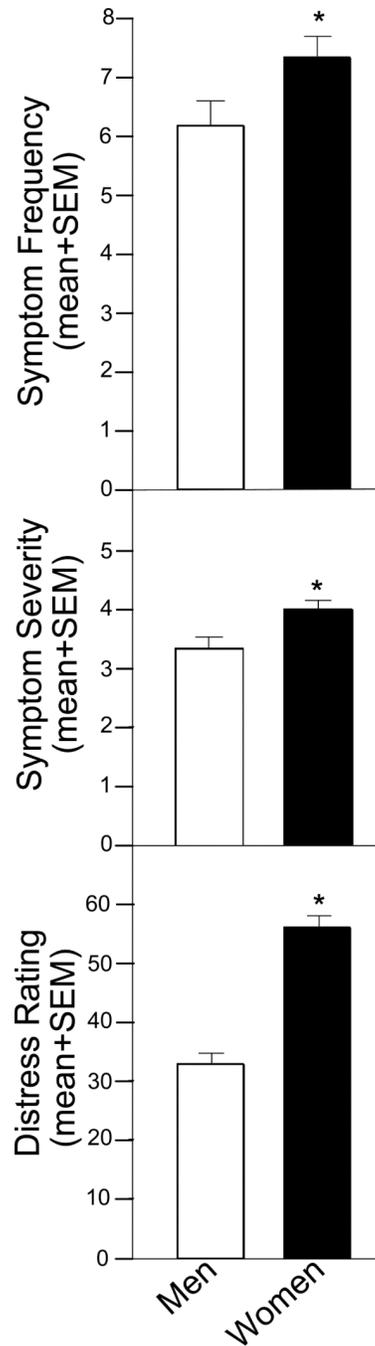


Figure 3.

Undergraduate women (n=19) exposed to 20% CO₂ report increased frequency (top) and severity (middle) of panic attack symptoms and report more distress (bottom) than do undergraduate men (n=29) exposed to 20% CO₂. * indicates significant difference, $p < 0.05$.

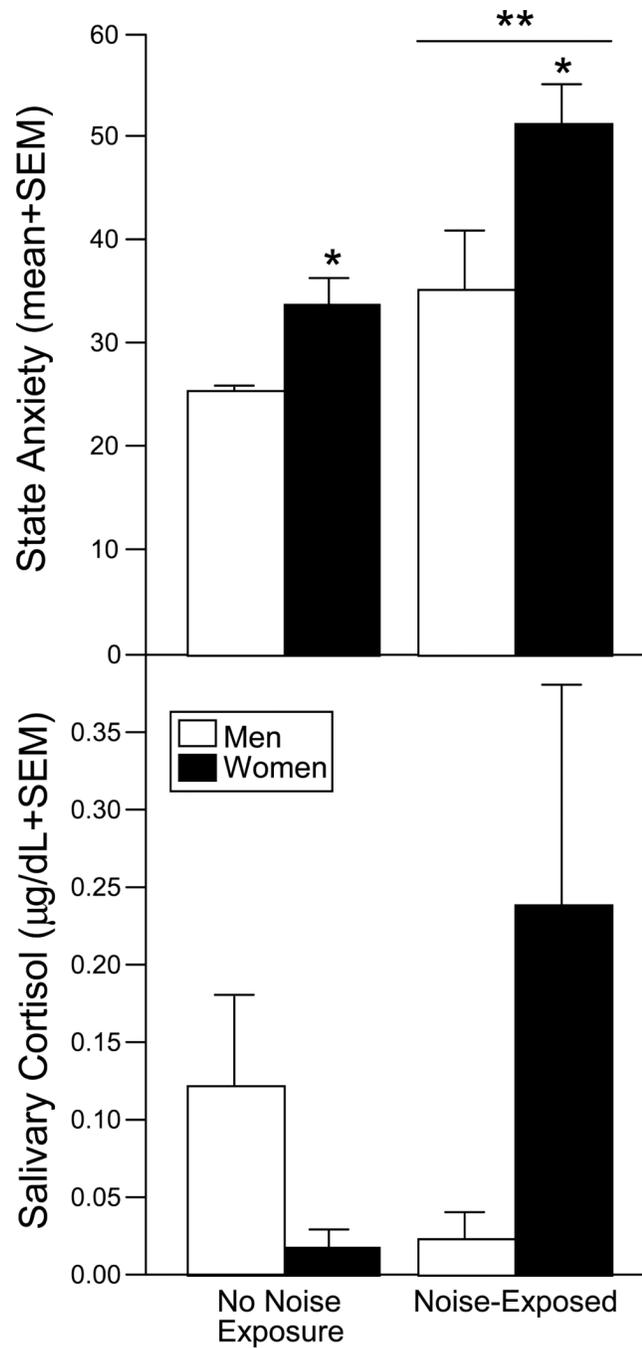


Figure 4.

Depicts State Anxiety on the Spielberger State-Trait Anxiety Inventory (top) and salivary cortisol (bottom) among male and female laboratory workers that were exposed to intermittent construction noise (6 males and 9 females) or not (3 males and 7 females). * indicates significant main effect for women to score higher than men; ** indicates significant main effect for noise-exposed group to score higher than non-exposed group, $p < 0.05$.

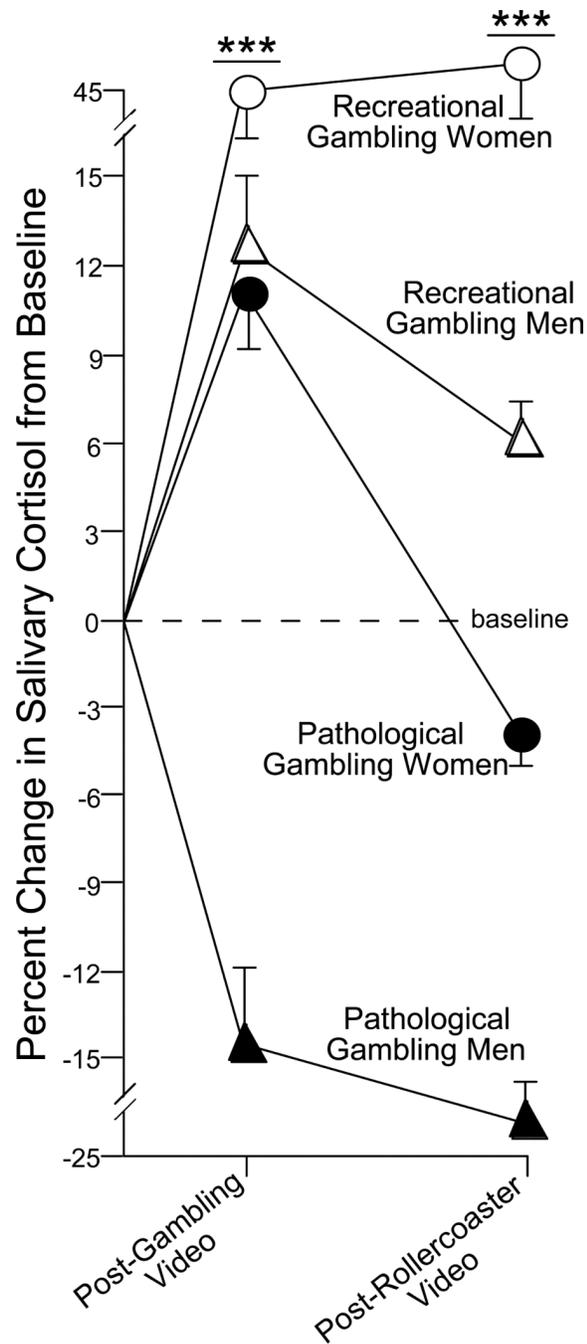


Figure 5.

Men ($n=15$ /group) and women ($n=6$ /group) with gambling pathology demonstrate significantly attenuated salivary cortisol in response to gambling cues compared to recreational gamblers. As well, pathological gambling men demonstrate a hypocortisolemic response to gambling cues that is greater than all other groups (adapted from Paris et al., 2009). *** indicates significant interaction wherein pathological gamblers are different from recreational gamblers at all timepoints and pathological gambling men are different from all other groups, $p < 0.05$.

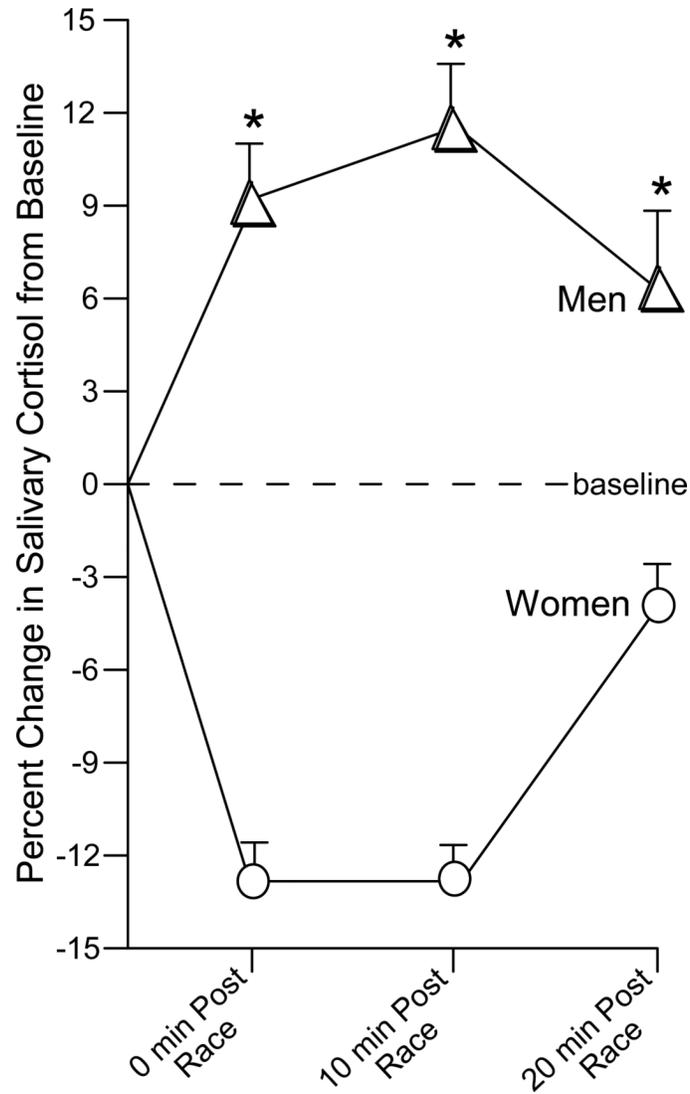


Figure 6. Off-track betting men ($n=21$) demonstrate a significantly greater cortisol response to gambling on a horse race than do off-track betting women ($n=11$; adapted from Franco et al., 2009). * indicates significant main effect of sex, $p < 0.05$.

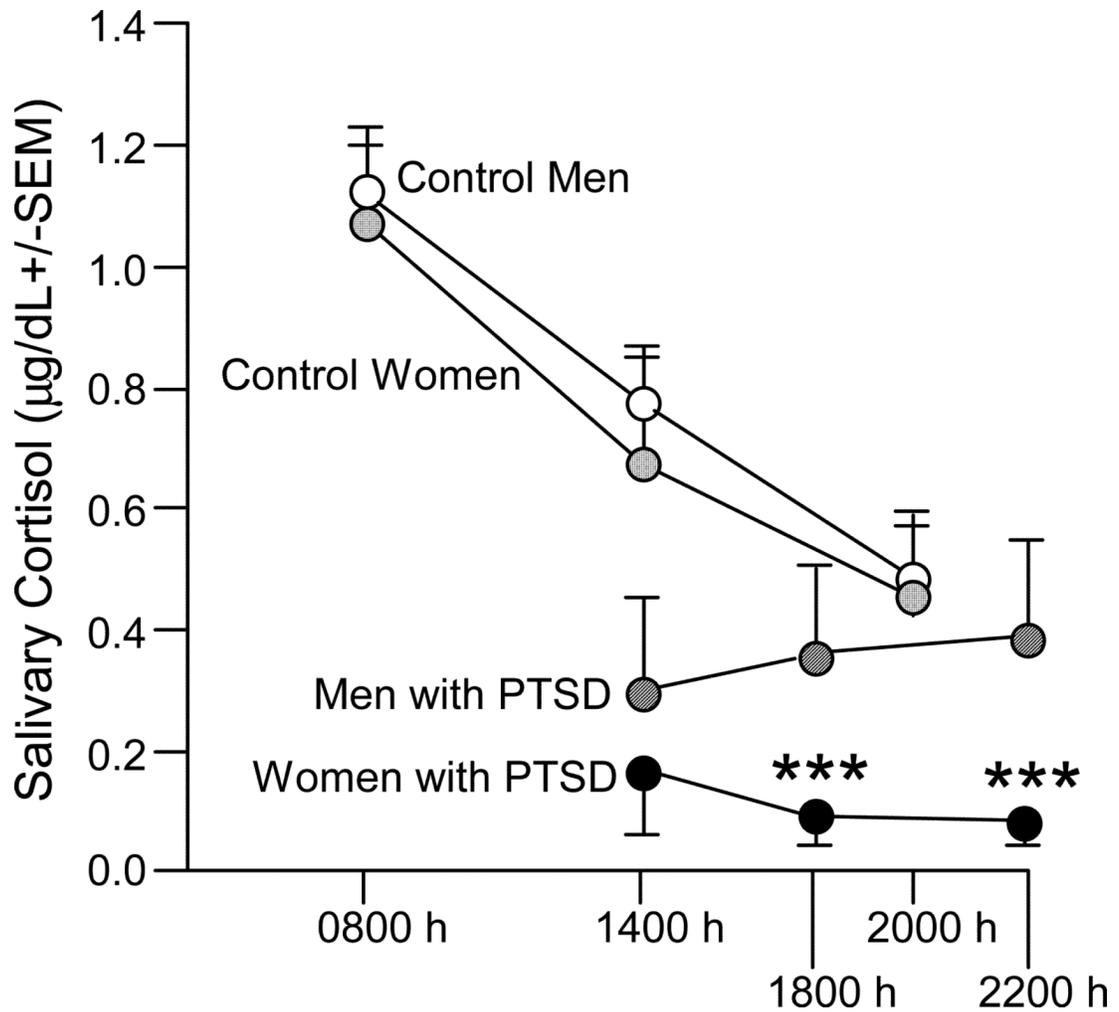


Figure 7. Men (n=3) and women (n=6) with posttraumatic stress disorder (PTSD) from exposure to motor vehicle accidents (MVA) have lower salivary cortisol than do non-afflicted historical controls (11 males and 13 females). As well, diurnal cortisol rhythmicity is attenuated among those with MVA-PTSD (adapted from Freidenberg et al., 2009). *** indicates significant interaction wherein women with PTSD have lower cortisol at 18:00 and 22:00 h, but not at 14:00 h, than do men with PTSD, $p < 0.05$.

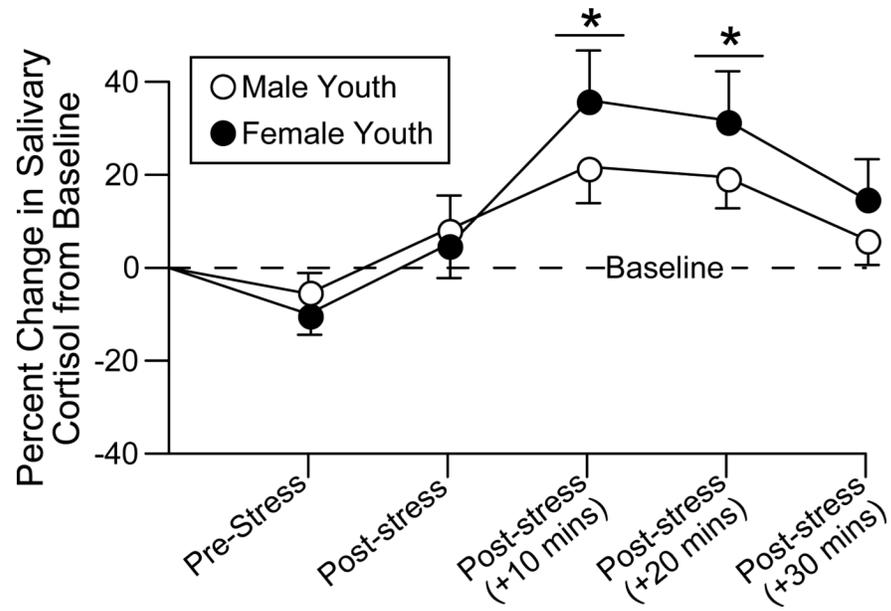


Figure 8. Female youth ($n=235$) have a greater and more sustained salivary cortisol response to a psychological stressor than do male youth ($n=201$). * indicates significant main effect for cortisol to be greater compared to baseline, $p < 0.05$.