University of Alberta

Violence Against Women:
Impacts on Psychological Health and Stress Hormones

by

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For all the women who resist the darkness
and create the light.

ABSTRACT

This thesis contributes to the growing body of gender-specific health research by integrating both psychological and neuroendocrine data to assess the impacts of stress and violence on women's health.

Women seeking support for intimate partner violence (IPV) were compared with women seeking support for non-interpersonal stressors (stress associated with immigration). Psychological measures included perceived stress and entrapment and mental defeat (EMD) scores as well as assessment of Axis I disorders. Neuroendocrine measures included basal levels of salivary cortisol and percent suppression of cortisol after the low-dose dexamethasone suppression test (DST).

Positive relationships were found between experiences of IPV and perceived stress, EMD and Axis I diagnosis. The neuroendocrine measures did not differentiate IPV from non-interpersonal stressors and both groups showed hypersuppression of cortisol after the DST.

IPV influences women's perceptions about EMD and perceived stress. By integrating neuroendocrine and psychological measures, further development of gender-specific stress models may occur.

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LIST OF ABBREVIATIONS

3-H	Tritium
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
ACTH	Adrenocorticotropic Hormone
BSA	Bovine Serum Albumin
CBG	Cortisol Binding Globulin
CMS	Chronic Mild Stress
CRH	Corticotropin Releasing Hormone
CSC	Chronic Subordinate Colony
CTQ	Childhood Trauma Questionnaire
CTS1	Conflict Tactics Scale 1
DCC	Dextran Coated Charcoal
dL	Decilitre
DEX	Dexamethasone
DNA	Deoxyribonucleic Acid
DSM-III	Diagnostic and Statistical Manual of Psychiatric Disorders, 3rd Edition
DSM-IV	Diagnostic and Statistical Manual of Psychiatric Disorders, 4th Edition
DST	Dexamethasone Suppression Test
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay

EMD	Entrapment and Mental Defeat
g	Gram
GAS	General Adaptation Syndrome
GR	Glucocorticoid Receptor
HPA	Hypothalamic-Pituitary-Adrenal
HPG	Hypothalamic-Pituitary-Gonadal
HPT	Hypothalamic-Pituitary-Thyroid
IES	Impact of Events Scale
IPV	Intimate Partner Violence
K_d	Dissociation Constant
KHA	Koltushi High-Avoidance
KLA	Koltushi Low-Avoidance
MDD	Major Depressive Disorder
mg	Milligram
MINI	Mini International Neuropsychiatric Interview
mL	Millilitre
Mol/L	Moles per Litre
MR	Mineralocorticoid Receptor
ng	Nanogram
nm	Nanometre
nM	Nanomolar
OT	Oxytocin
PBS	Phosphate Buffered Saline

PID	Pelvic Inflammatory Disease
PSS	Perceived Stress Scale
PTSD	Posttraumatic Stress Disorder
RIA	Radioimmunoassay
rpm	Revolutions Per Minute
SAM	Sympathetic-Adrenal-Medullary
SCID	Structured Clinical Interview for DSM-IV
SPSS	Statistical Package for Social Sciences
STI	Sexually Transmitted Infections
TSST	Trier social stress test
µCi	Microcurie
µg	Microgram
µL	Microlitre

CHAPTER 1: INTRODUCTION

1. SUMMARY OF THE PROBLEM

The silence on violence against women was broken at the United Nations World Conference on Human Rights in 1993 when the pandemic of violence against women was officially recognized as a violation of human rights. Intimate partner violence (IPV) is characterized by frequent psychological and physical attacks or injury of a person by their intimate partner. The term IPV is meant to include all types of intimate relationships; however this gender-based crime disproportionately affects women. Females continue to be the most likely victims of police-reported spousal violence, accounting for 83% of victims. This holds true for every province and territory across Canada (Statistics Canada, 2008). Partner violence is the leading cause of injuries to women between the ages of 15 and 44, and is the second leading cause of injuries to women of all ages (Barrier, 1998). This violence has devastating impacts on women and their families and represents huge economic costs to health care, social services, employment and justice systems. Women who experience the stress of IPV can endure a wide range of significant and complex physical and mental health impacts.

Studies that have focused on the neurobiology of stress have grouped populations by various categories, for example, single psychiatric diagnosis, occupation, specific type of stressor or traumatic event experienced. Research into neuroendocrine stress responses often focuses on discrete psychiatric diagnostic categories, despite frequent symptom overlap and high levels of

comorbidity. Additionally, the stress of IPV experiences may activate stress response systems even in the absence of formal Axis I psychiatric disorders, with potential physical and mental health consequences. There is evidence that the type of stressor plays a role in health outcomes, however the type, acuity and duration of the stressor, and potential gender differences, are often not well described in the literature. This presents challenges in integrating findings between studies and has left gaps in understanding of stress responses and the subsequent myriad of health outcomes.

Animal models of stress have focused on the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis as key stress response systems responsible for fight-or-flight behaviours to perceived threat and fear. The fight-or-flight behavioural response is generally regarded as the prototypic response to stress with sympathetic nervous system activation resulting in release of catecholamines. The HPA axis is also activated, causing a hormonal cascade resulting in release of glucocorticoids. In states of chronic stress, changes have been reported at each level of the HPA axis. One of the markers of dysregulation is altered feedback control of the HPA axis. The dexamethasone (DEX) suppression test (DST) is used to assess the strength of negative feedback inhibition of the HPA axis and has been used extensively in studies of psychiatric disorders (Ehlert, Gaab, & Heinrichs, 2001; Yehuda, 2006). The DST may also be used to further understand neuroendocrine changes in women who have experienced IPV.

It is widely recognized that gender is a powerful determinant of health and for this reason national and international health-serving organizations have called for more gender-specific health research. Despite the prevalence of IPV and the links between stress and risk of stress disorders in women, few studies have looked at the biological impact of IPV. There is strong evidence that sex (as a biological distinction) and gender (as a sociocultural construct) affects the perceptions and experiences of stress. However, little attention has been paid in the neuroendocrine literature to sex and gender differences in stress responses. Work to develop gender-specific models of behavioral responses to stress has been limited. Recently it has been postulated that in addition to basic physiological fight-or-flight responses observed in all humans, females' behavioural responses to stress may be marked by nurturing activities (tending) and creating and maintaining social networks (befriending) (Taylor et al., 2000). This conceptualization of behavioural stress responses as "tend-and-befriend" may be of particular interest in women experiencing IPV because social support and networking is often restricted within abusive relationships as part of a general pattern of power and control.

Despite negative health impacts, many women remain in intimate relationships characterized by violence. The reasons for this are complex and varied, but one component may be reflected in analogous behaviors observed in animal models of chronic stress. In particular, under chronic and inescapable stress paradigms, animals display blocked or arrested adaptive defenses and decreased resistance to the stressful condition. This reflects a state of learned

helplessness. Gilbert and Allen used the term Entrapment and Mental Defeat (EMD) for analogous behaviours in humans that reflect learned helplessness in animals (Gilbert & Allan, 1998). This tool has been used in clinical populations of people with depression (MDD) and anxiety and high-stress mothers; however measures of EMD have not been used in relation to women that have experienced IPV. Entrapment and defeat scores have received relatively little attention in neuropsychiatric literature; however this measure may be especially relevant to women experiencing IPV, as isolation and entrapment are characteristic of partner violence.

Simultaneous investigations of psychological factors (measures of perceived stress and EMD) and biological stress response systems (peak cortisol levels and levels following the DST) may lead to an integrated approach to investigate the impacts of IPV. There have been connections made in the psychological literature suggesting that IPV is a chronic, severe stressor in some women's lives. There is less evidence from neurobiological studies that examine the fit between animal models of chronic severe stress, and the neuroendocrine responses of women experiencing IPV. By analyzing both psychological and neuroendocrine data, the feasibility of using IPV as a gender-specific model of chronic, severe stress can be examined.

2. OBJECTIVE AND RESEARCH QUESTIONS

The broad goal of this thesis is to contribute to the growing body of knowledge regarding the impact of IPV on women's health and to examine the

relationships among psychiatric diagnoses, psychological parameters and patterns of HPA axis activity.

The specific aim is to investigate the impact of IPV on HPA axis activity and how patterns of HPA axis activity relate to women's neuroendocrine activity and emotional health. There is evidence that interpersonal stress leads to poorer health outcomes than non-interpersonal stress. Psychological and neuroendocrine parameters of women experiencing IPV may show different or more profound changes compared to women experiencing other types of stressors. Understanding the changes that may occur in the HPA axis in response to the stress of IPV may fill gaps in the literature on gender-specific stress research. By investigating the impacts of IPV, it may be possible to determine if IPV is different in nature from other types of stressors such that IPV can serve as a model for chronic, severe stress in women.

The research question guiding this study is: In women who have experienced IPV, do perceived stress and entrapment and mental defeat scores relate to changes in basal salivary cortisol levels and percent suppression of cortisol levels following dexamethasone? There are four specific objectives related to this research question:

(1) To compare the scores on psychological measures of entrapment, mental defeat and perceived stress when women are grouped by their experiences (IPV or other types of stressors) or by stress-related psychiatric disorder (MDD or posttraumatic stress disorder [PTSD])

(2) To compare salivary cortisol levels at awakening and 30 minutes after awakening between women when grouped by experience or by stress-related psychiatric disorder

(3) To compare percent suppression of cortisol after ingestion of dexamethasone between

women grouped by experience or by stress-related psychiatric disorder

(4) To examine the relationships between neuroendocrine measures of morning cortisol levels and percent suppression of cortisol with psychological measures of entrapment, mental defeat and perceived stress

CHAPTER 2: LITERATURE REVIEW

1. INTIMATE PARTNER VIOLENCE

1.1. Background

Intimate partner violence (IPV) is one of the most common, preventable threats to women's health. In a review of 48 population-based surveys from around the world it was found that between 10% and 69% of women report experiencing IPV at some point in their lives (Heise, Ellsberg, & Gottemoeller, 1999). These surveys only collected data on physical assault, however physical violence in intimate relationships is often accompanied by psychological and sexual abuse as part of a general pattern of power and control. The wide variances in prevalence rates reported between countries are likely due to methodological differences between the studies and not reflective of a real difference in prevalence rates (Krug, Dahlberg, Mercy, Zwi & Lozano, 2002). Additionally, estimates of IPV are highly sensitive to the particular definitions of IPV used, the manner in which the questions are asked, the degree of privacy in the interview and the nature of the population being studied (Ellsberg, Heise, Peña, Agurto, & Winkvist, 2001). There is currently no consensus on the definition of IPV, also referred to as domestic violence, spousal abuse, wife battering and wife beating (Tjaden & Thoennes, 2000).

Overall, approximately one in every four women will be impacted by IPV as it occurs with a lifetime prevalence rate of 27% and is present in all countries,

irrespective of economic, religious or cultural association (Krug, Dahlberg, Mercy, Zwi & Lozano, 2002). Further, there is wide agreement that the rates of reported assaults are representative of only a fraction of the actual number of women who experience IPV and that this violence is universally underreported (Krug, Dahlberg, Mercy, Zwi & Lozano, 2002).

In addition to directly impacting women's health, IPV has a significant economic impact. Research estimates the economic cost of all types of violence against women in Canada ranges from $385 million to $15 billion annually (Johnson, 2006). Included in these analyses were costs associated with direct medical care, lost productivity, criminal justice, shelters and social services. These estimates also include lifetime earnings lost from intimate partner homicide. Data from Canada, Australia, Israel, the United States and South Africa indicate that 40% to 70% of murdered females were killed by intimate partners, often in the context of an abusive relationship (Krug, Dahlberg, Mercy, Zwi & Lozano, 2002).

The term IPV can be divided into two distinct categories: "situational couple violence" and "intimate partner terrorism." Although the distinction between situational couple violence and intimate partner terrorism can have important implications for research design, theory development, design of educational and intervention programs and public policy, the different forms of IPV are not necessarily mutually exclusive. Situational couple violence is characterized by a pattern of escalating verbal and physical violence for both partners. Situational couple violence is more common in cohabiting relationships,

is less gender biased and less associated with controlling behaviour than intimate partner terrorism (Johnson, 2000; MacMillan, Ross, & Gartner, 99). Intimate partner terrorism is characterized by (a) gender biased violence with a higher prevalence of women victims, (b) frequent physical attacks and injury, (c) persistence and (d) PTSD symptoms in victims (Johnson, 1995; Johnson, 2000). Intimate partner terrorism is also characterized by physical and sexual violence embedded in a general pattern of controlling behaviours.

For the current study, the term IPV refers to intimate partner terrorism and is defined as the actual or threatened physical, sexual, psychological, economic, or spiritual abuse of an individual by someone with whom they have or had an intimate relationship (Coker, 2005). Figure 2.1 shows the Duluth Power and Control Wheel, summarizing the many forms of abuse that may be experienced with IPV. The Duluth Wheel was devised by the Duluth Domestic Abuse Intervention Project as the core of a perpetrator program to help men convicted of domestic assault to modify their behaviour away from violence and towards mutual co-operation with their partners (Domestic Abuse Intervention Programs, 2008). The wheel divides violence into eight sectors: coercion and threats; intimidation; economic abuse; gender-privilege; isolation; using children; minimizing, denying and blaming. In relationships characterized by IPV, some or all of these behaviours may be seen.

Figure 2.1: The Duluth Power and Control Wheel

(Source: Domestic Abuse Intervention Programs, 2008)

The Duluth Power and Control Wheel outlines the variety of abusive behaviours that may be used by perpetrators of IPV. These behaviours are embedded within a general pattern of physical and sexual violence.

Women living in a relationship characterized by IPV live under the constant threat of violence and are vulnerable to their partners' abruptly changing moods and behaviours (Langford, 1996). IPV is associated with a lack of control in victims resulting from a significant power differential within the relationship (Lasiuk et al., 2008). While it is not possible for women to control the threat of violence, many women develop knowledge about and response patterns to their partners' violent behaviours. Langford termed this knowledge "predicting unpredictability" from a study of 30 women (Langford, 1996). Some women have a sense of perceived control over their partner's violence by responding with strategies of avoidance, engagement, fleeing and help-seeking to avert or delay episodes of violence (Langford, 1996). Women engaged in these strategies despite knowing that their actions did not have any effect on reducing the violence; however, it highlights their strength in interacting within the constraints of dangerous environments. Often their strategies are aimed at controlling the potential physical, psychological and emotional damage from violence (Lempert, 1996). These strategies may include rationalization, minimization and self-blame. Women who attribute blame for the abuse to themselves may feel they are more able to control the abuse than those who attribute blame to the abuser (Haggerty, Kelly, Hawkins, Pearce, & Kearney, 2001). Not all women experiencing violence have perceived control over their experiences. Arias and Pape noted that women recently admitted to shelters saw themselves as having little control over their partners' violence, though women in this study had entered shelters within the

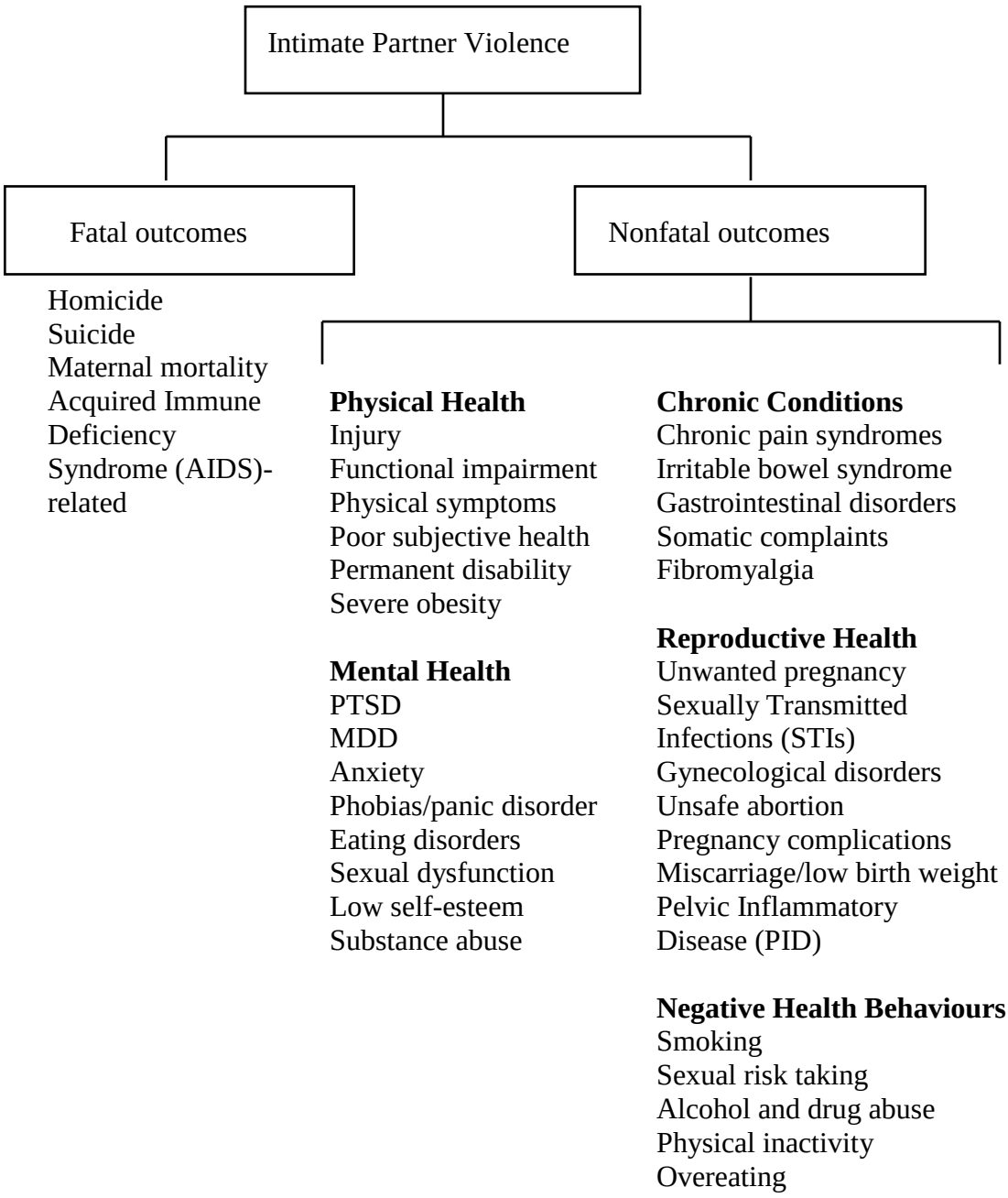
preceding 2 weeks, which may have reflected their immediate situation (Arias & Pape, 1999).

The effects of violence can be wide-ranging and can vary as a function of a number of victim-specific, trauma-related and sociocultural variables (Briere & Jordan, 2004). Recent studies have shown that women who are exposed to IPV report significantly more physical and mental health problems, putting IPV into the foreground as a serious health problem for women (Coker et al., 2002; Klymchuk, Cooper, & Pacey, 2002; Kramer, Lorenzon, & Mueller, 2004; Pottie Bunge, 2002). While some effects of violence are relatively common (MDD, PTSD, anxiety), the clinical presentation of women experiencing IPV is often complex and often cannot be summarized by discrete physical sequelae or by discrete diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 2000; Briere & Jordan, 2004). Often women present with multiple nonspecific somatic complaints with symptoms that change over time (Sutherland, Bybee, & Sullivan, 2002). Survivors of interpersonal trauma may be in contact with health care services for chronic health effects that persist well after the original injury sustained during the traumatic event and long after the abuse has ended (Johnson, Zlotnick, & Perez, 2008; Schnurr & Green, 2004).

Despite the prevalence of IPV and the links between stress and risk of stress disorders in women, few studies have looked at the neuroendocrine impact of IPV. Ignoring violence as a factor in women's health and wellbeing disregards the pervasive and long term personal and social consequences of violence. There

is widespread recognition that relationships exist among stress, illness and disease. The influence of abuse on health can persist long after the abuse itself has stopped (Statistics Canada, 2008). Figure 2.2 summarizes some possible health outcomes of violence against women.

Figure 2.2: Health Outcomes of Violence Against Women



(Source: Adapted from Krug, Dahlberg, Mercy, Zwi & Lozano, 2002)

Ranging from physical to emotional abuse, IPV affects the welfare of millions of women and their families worldwide, regardless of socioeconomic status, race, sexual orientation, age, ethnicity, health status and presence or absence of a current partner.

1.2. Physical Health Outcomes

Population-based studies suggest that 40-72% of all women who experience IPV suffer a physical injury as a result of this violence at some point in their life (Statistics Canada, 2008). The immediate physical consequences of IPV include, but are not limited to, scratches, bruises, sprains and strains, broken bones, concussions, STIs, central nervous system injuries and death (Tjaden & Thoennes, 2000). Women experiencing IPV also show increased rates of chronic somatic symptoms such as headaches, muscle tension, weight gain or weight loss, fatigue, chronic joint pain, and abdominal pain. In a study of women in domestic violence shelters, the most common chronic physical symptom was neck or back pain (Campbell et al., 2002). Another population-based study found that of women reporting both IPV and a serious health problem, 60% had back or neck problems, or a bone or joint injury (Hathaway et al., 2000). Risk for these injuries may be a result of direct trauma, stress, or a combination of factors relating to the violence they experience.

Research with both men and women has shown relationships between cardiovascular disease, stress, and negative affect (Grippo & Johnson, 2009). Cardiovascular problems such as chest pain and hypertension have been found in women who experience IPV (Koss & Heslet, 1992). There are also strong associations between IPV and gastrointestinal disorders including vomiting, diarrhea, constipation, irritable bowel syndrome and spastic colon (Campbell et al., 2002). One study found that women who were sexually abused were 2.8 times more likely to have a bowel disorder than those who had not experienced

this violence (Talley, Fett, Zinsmeister, & Melton, 1994). Women also report gynecological problems such as dysmenorrhea, chronic pelvic pain, PID, and dyspareunia (Coker et al., 2002; Henningsen, Zimmermann, & Sattel, 2003; Koss & Heslet, 1992; Kramer et al., 2004; Walker, 1984; Woods & Wineman, 2004).

Although these physical problems can be partly explained by behavioural and lifestyle factors (e.g. smoking, substance abuse and poor nutrition), there is increasing recognition that chronic stress contributes to physical disease and illness (Campbell & Soeken, 1999). These impacts are not solely from physical violence experienced, as psychological abuse has also been found to contribute to pain and poorer physical health (Dutton et al., 2006).

1.3. Psychological Health Outcomes

Interpersonal violence disrupts one's sense of identity, basic trust in other people, and trust in the world as a safe, predictable place. Interpersonal trauma, particularly violence occurring early in life, is a major contributor to the development of psychiatric illness (Hegadoren, Lasiuk, & Coupland, 2006). Women who are abused by their partners suffer more depression, anxiety and phobias than non-abused women, according to studies in Australia, Nicaragua, Pakistan and the United States (Statistics Canada, 2008). They report more anger, nightmares, shame, low self-esteem, addictions, dissociation or dissociative symptoms, and impaired work and social functioning than women who have not experienced partner violence, and these effects can linger even after the relationship has ended.

Women experiencing IPV have lower levels of perceived social support and higher levels of entrapment compared to women experiencing other types of psychological stress (Lasiuk et al., 2008). A review of mental health problems among women with a history of IPV in the United States reported that women experiencing IPV had a three to five times greater likelihood of MDD, PTSD, substance abuse and suicidality than women not experiencing this stressor (Golding, 1999). A broad spectrum of psychiatric conditions may result from IPV; however MDD and PTSD are the most common mental health outcomes associated with these experiences (Campbell & Soeken, 1999).

1.3.1. Depression

The most common psychiatric disorder in women who experience IPV is MDD, with rates ranging from 66-80% (Follingstad, Wright, Lloyd, & Sebastian, 1991; Gelles, 1989; Goodman, Koss, Fitzgerald, Russo, & Keita, 1993). The prevalence of MDD is twice as high in women as it is in men in both community samples and clinical populations (Campbell et al., 2002; Campbell, 2002). There is a significant body of literature that links depressive symptoms with a lack of perceived control, particularly relevant to women experiencing the stress of IPV (Muris, Schouten, Meesters, & Gijsbers, 2003; Weisz & Stipek, 1982). Gilbert and colleagues suggested that MDD might be considered as a state of chronic stress in which adaptive defenses (e.g. fight, flight or help-seeking) are blocked, arrested or ineffective (Gilbert, Gilbert, & Irons, 2004). They equate these conditions, which they term entrapment, to preclinical inescapable stress models

and the resulting state of defeat to learned helplessness (Brown, Harris, & Hepworth, 1995; Gilbert, Allan, Brough, Melley, & Miles, 2002; Haatainen et al., 2003; Kendler, Hettema, Butera, Gardner, & Prescott, 2003; Papakostas et al., 2003; Presson & Benassi, 2003). Greater severity of partner violence and experiences of sexual violence were associated with higher levels of depression (Dutton et al., 2006).

1.3.2. Posttraumatic Stress Disorder

PTSD is a psychiatric condition that can occur after people experience traumatic events and is commonly associated with IPV (Yehuda, 1997). PTSD was originally defined in the DSM-III in 1980, after observations of trauma reactions in male combat veterans of the Vietnam conflict. The recognition of PTSD as a psychiatric condition endorsed the notion that people have reciprocal interactions with their environment, viewing disorders as embodied in human experiences (Lasiuk & Hegadoren, 2006). According to the DSM-IV, PTSD involves three main symptom clusters: re-experiencing the traumatic event; avoidance of trauma cues or reminders; and hyperarousal. These symptoms persist for at least one month and cause significant impairment. The chronic autonomic over-reactivity observed with PTSD may lead to sleep disturbance, irritability, poor concentration, increased heart rate, and exaggerated startle responses (Brunello et al., 2001; Coupland, Bell, Potokar, Dorkins, & Nutt, 2000; Morgan, Grillon, Southwick, Davis, & Charney, 1996; Orr S.P., Lasko, Shalev, & Pitman, 1995; Shalev, 2000). Perceived helplessness and lower perceived control

have also been identified as predictors of PTSD severity (Brewen & Homes, 2003; Frazier, 2003). PTSD is associated with severe morbidity and psychosocial impairment (Johnson et al., 2008).

Lifetime prevalence of PTSD is 7-12%, and community rates of lifetime exposure to trauma are estimated to be 40-80% (Cortina & Kubiak, 2006). In a meta-analysis of 11 studies, Golding reported that 31% to 84.4% of women who experienced IPV met PTSD criteria (Golding, 1999). Through the United States National Comorbidity Survey it was found that women are twice as likely as men to develop PTSD following exposure to a traumatic event (10.4% vs. 5.0%) (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The differences in prevalence rates of PTSD between men and women could be a result of many factors including the number and severity of past traumas, revictimization, other life events and chronic stressors such as poverty, immigration and discrimination (Glass, Perrin, Campbell, & Soeken, 2007). Despite lower frequency of exposure to trauma, women may be more susceptible to PTSD as a consequence of greater exposure to specific types of trauma with the highest probability of PTSD (Olff, Langeland, Draijer, & Gersons, 2007). While males are more likely to experience violence in general through combat, accidents and physical attacks, females are more frequently exposed to sexual assault and molestation (Shalev et al., 1998). Sexual trauma history was found to be the greatest risk factor for lifetime PTSD (Perkonigg, Kessler, Storz, & Wittchen, 2000). In one study of women who had been abused, 66% still experienced PTSD symptoms 9 years after leaving the violent relationship, as measured by the IES (Impact of Events

Scale), a self-report measure that assesses posttraumatic intrusive and avoidant symptoms related to a stressful event (N=52) (Woods, 2000). In a recent study of 177 battered women living in shelters, when controlling for severity of IPV, PTSD severity was associated with psychiatric and social morbidity and significantly mediated the relationships between IPV severity, psychiatric severity and loss of personal and social resources (Johnson et al., 2008). In a culture where sexism remains a significant phenomenon, the tendency to blame or devalue women for their victimization may also contribute to their greater levels of post-assault distress relative to men (Briere & Jordan, 2004).

1.3.3. Comorbid Depression and Posttraumatic Stress Disorder

PTSD seldom occurs independent of other psychiatric sequelae and women who experience IPV often develop comorbid MDD and PTSD (Dutton et al., 2006). The National Comorbidity Study reported comorbidities of MDD and PTSD in 49% of women. Only 21% of women had PTSD as their sole psychiatric diagnosis (Kessler et al., 1995). Comorbidity has negative impacts on prognosis and course of illness. Individuals with comorbid MDD and PTSD have higher levels of impairment and greater severity of symptoms than those with a single psychiatric diagnosis of MDD or PTSD, as assessed by the Global Assessment of Functioning Scale from the Structured Clinical Interview for DSM-IV (SCID) (Shalev et al., 1998).

In addition to full diagnoses of MDD or PTSD, subthreshold symptoms are also associated with considerable functional impairment (Cuijpers & Smit,

2003; Lewinsohn, Shankman, Gau, & Klein, 2004; Rucci et al., 2003; Zlotnick, Franklin, & Zimmerman, 2002). Being a victim of violence can be regarded as a risk factor for a variety of diseases and conditions. Psychological and physiological illness is inextricably linked. For example, general population studies have linked the severity of depressive symptoms to the risk for death after myocardial infarction, even after controlling for standard medical risk factors (Frasure-Smith et al., 2000). There is growing evidence that MDD is an important psychological predictor of cardiovascular disease. MDD is also associated with insulin resistance and Type II diabetes, as well as osteoporosis (Michelson et al., 1996; Okamura et al., 2000). Relationships among stress, depression and immune function may contribute to the increased prevalence rates of autoimmune disorders such as chronic fatigue syndrome and chronic fibromyalgia in women. Physiological alterations in response to chronic stress, such as increased levels of circulating stress hormones (glucocorticoids) and pro-inflammatory mediators (interleukin-1, interleukin-6), may be factors in these associations between chronic stress and disease. Changes in both the HPA axis and the SAM system have been documented in response to chronic stress (Dutton et al., 2006; Ehlert et al., 2001).

2. STRESS

2.1. Early Conceptualization of Stress

The term "stress" is difficult to characterize and is often loosely defined. It has been used to describe a stimulus, a process, a response and a state, leading to confusion and ambiguity (Le Moal, 2007). The concept of stress has been around for centuries, but only recently has it been systematically conceptualized and become a subject of research (Lazarus & Folkman, 1984; Le Moal, 2007).

In 1865, Claude Bernard, the founder of experimental medicine, described the concept of the "milieu interne", stating that "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment" (Cannon, 1929). He based this concept on the discovery of sugar-storing functions of the liver and that stability of the internal environment is vital for life to occur (Goldstein & Kopin, 2007). This idea of an essential internal environment was taken up by Walter Cannon. Cannon used this concept to develop the idea of homeostasis, published in 1926. He described all living parts of an organism to be in contact with a fluid matrix which protects the functional parts from changes. Cannon describes this as coordinated physiological reactions, which act to maintain steady states in the body and to keep internal conditions constant and within narrow normal limits (Cannon, 1929). Cannon demonstrated that the SAM system acted to maintain homeostasis of the internal environment (Le Moal, 2007). He first coined the term "fight or flight" in 1915 to describe an animal's response to threats through the activation of this SAM system, producing a hormonal cascade resulting in the

secretion of catecholamines (Cannon, 1953). Together, Bernard and Cannon laid the groundwork for regulatory physiology and concepts of adaptation.

Hans Selye followed shortly after, shifting research focus to maladaptation and the pathology of stress. In 1936, Selye introduced the idea that all organisms respond to stress in a nonspecific biological pattern that is the same regardless of the cause or type of the stressor (Selye, 1951). He proposed the existence of a biological stress syndrome which he called the General Adaptation Syndrome (GAS) (Selye, 1974). This three stage syndrome occurs in response to adverse events. The first stage is the Alarm Reaction, analogous to Cannon's "fight or flight" response to stress. Here, complex physiological changes take place to mobilize energy and allow the organism to react to the stressor. The second stage of the GAS is the Resistance Stage. During resistance, the organism maintains arousal while the body works to defend against and adapt to the stressor, and maintain homeostasis. Should the stressors continue for an extended period, organisms use up their finite ability to adapt and enter a third stage of the adaptation syndrome, called Exhaustion. This is a pathological state where organisms will start showing negative physiological impacts of long term stress and may eventually result in death. Selye's doctrine of nonspecificity has been criticized and the understanding of stress has greatly evolved since this time to acknowledge that responses to stress can vary greatly with the type, duration and perception of the stressor. However, Selye was pivotal in furthering understanding of both the short and long term impacts of stress and was the first

to emphasize the role of the pituitary-adrenal axis in the pathology of stress (Le Moal, 2007).

At this point, two systems for stress were proposed: the SAM system for behavioural "fight-or-flight" reactions to stress and immediate adaptation, and the pituitary-adrenal axis for maintaining homeostasis. The SAM system activates and sustains the physiological stress response by mediating an increase in epinephrine and increasing glucose uptake in skeletal muscles, mobilizing energy needed to respond to the stressor (Ennis, Kelly, & Lambert, 2001). The pituitary-adrenal axis was extended to the hypothalamic-pituitary-adrenal (HPA) axis and described mediation of a bidirectional brain-body communication during physiological and psychological stress (see Figure 2.3). This axis promotes the return of systems to a stable set-point, called homeostasis, allowing the organism to adapt to threatening or stressful situations (Engelmann, Landgraf, & Wotjak, 2004; Onaka, 2004). The HPA axis plays a key regulatory function in the body, and is controlled in part by negative feedback inhibition to effect changes in the neural, endocrine, immune and metabolic systems (Brunello et al., 2001).

Bruce McEwen expanded the concept of homeostasis and described the term allostasis, or changes in physiological set points (McEwen, 1998a). Through allostasis, organisms are readied to respond and adapt to stressors, but changing physiological set points and maintaining a state of readiness has energy cost. This cost is called allostatic load (McEwen, 1998a). McEwen described that when this load becomes too great, the stress response moves from adaptation to pathology.

2.2. Perceptions of Stress

In addition to physiological models of stress and stress responses that were being developed during this period, there were also developments in cognitive models of stress. The GAS and fight-or-flight responses to stress did not explicitly take into account perceptions and appraisals of stress in humans. The relationship between the person and the environment became a focus of research. The role of perception and appraisal in the stress response is integral in the framework of stress proposed by Richard Lazarus (Lazarus & Folkman, 1984). In Lazarus' theory, cognitive appraisal plays a major role in a person's ability to identify coping strategies to attempt to adjust to the stressful situation (Lazarus & Folkman, 1984). He describes two aspects of appraisal: primary appraisal, assessing the demands of the stressor; and secondary appraisal, assessing one's resources to cope with the stressor and manage the internal and external demands of the stressor. In this way, stress is not just based on the reality of the stressor, but also on how a person perceives the stressor and the strength of their own resources. Here, the person and the environment are dynamic and mutually reciprocal with a bidirectional relationship and feedback (Folkman, Lazarus, Gruen, & DeLongis, 1986). Women and men may experience different types of stressors, or perceive stressors in different ways, and thus would likely have different responses to that same stressor. This recognition introduced gender as an important determinant of behavioural responses to a significant stressor. Gender differences may be conceptualized as an interaction between biologically

based sex differences and an individual's social context (Kimerling, Ouimette, & Wolfe, 2002).

Michael Meaney further contributed to the conceptualization of stress and stress responses by demonstrating that prenatal environments can permanently change how an individual responds to stress (Buss et al., 2007; Meaney, 2001). Early-life physiological programming may explain the associations between prenatal environment, altered fetal development and pathophysiology later in life (Seckl, 2004). For example, while glucocorticoids are commonly used to treat human fetuses at risk of preterm delivery, prenatal glucocorticoid administration may be a mechanism of programming for cardiovascular disease and diabetes later in life (Fowden, Li, & Forhead, 1998; Newnham, 2001; Seckl, 2004). Prenatal exposure to glucocorticoids in rodent models can impact fetal development and lead to a range of tissue-specific pathophysiologies (Seckl & Meaney, 2006). Repeated prenatal DEX exposure in humans has been linked to up to 4% lower birth weight and head-circumference reduction by 9% (Newnham, 2001). The clinical use of DEX to enhance lung maturation has saved the lives of many children born preterm, however the use of this treatment may contribute to disease later in life. As such, other glucocorticoids with different pharmacokinetic and pharmacodynamic properties have been investigated (Baud et al., 1999). The new understanding that many diseases of adult life may have origins in the prenatal environment has been a milestone in the understanding of stress and pathophysiology.

In addition to environmental impacts before birth, Meaney also identified that postnatal environments and early childhood experiences can influence health throughout life (Meaney et al., 1993; Meaney & Szyf, 2005). This is environmental programming where exposure to an event during development can change phenotypes in adulthood. Gene expression can be turned on and off by certain environmental conditions and dysregulation in stress response systems that is acquired early in life may be transmitted across generations (Meaney, 2001; Ogren & Lombroso, 2008). Epigenetics is the study of how offspring can inherit changes in gene function and express new traits from their parents through a process of deoxyribonucleic acid (DNA) methylation, without changes in the base structure of DNA itself (Ogren & Lombroso, 2008). In DNA methylation, a methyl group is transferred from the coenzyme S-adenosyl methionine to a carbon atom in DNA via DNA methyltransferases. This type of epigenetic programming is responsive to changing environments (Szyf, McGowan, & Meaney, 2008). Developmental studies provide evidence of active DNA methylation driven by maternal care and social interactions (Meaney & Szyf, 2005; Ogren & Lombroso, 2008). In humans, relationships between socioeconomic status and physical health may be partly explained by the concept that the social environment may change the phenotype by modifying the epigenome (Szyf et al., 2008).

Individual differences affect perceptions of stress based on gender, allostatic load, coping resources, comorbidities and previous vulnerabilities and experiences. For example, childhood sexual abuse (CSA) may increase risk for stress disorders throughout the life span, because abuse experiences alter

biological and psychological responses to stress (Nolen-Hoeksema & Girgus, 1994). Perception and appraisals of stress may differ between men and women, which may account for some of the gender-specific responses to stress. Women have less power and status than men in most societies, experience certain types of interpersonal trauma and chronic stress more often than men, are more likely to be sexually harassed, and also fulfill social roles that carry a number of chronic strains, such as performing most of the childcare and domestic work of the home (Nolen-Hoeksema & Girgus, 1994). Females seek and give social support at levels that are significantly different from the levels of social support given or received by males, which also may alter the secondary appraisal of resources (Taylor & Stanton, 2007). When men and women experience similar stressors, women are more likely to develop MDD due to sex and gender differences in biological and psychological responses to stressors, as well as sociopolitical factors (Nolen-Hoeksema & Girgus, 1994). This increased vulnerability has also been demonstrated in the 2:1 female bias in prevalence rates of PTSD (Gill & Theriault, 2005). The cognitive theories of stress take into account differences in perception and coping resources between males and females.

2.3. Gender Differences in Stress Responses

Various endogenous products have been associated with stress response and stress disorders. The focus of stress physiology has prominently been on the SAM system and the HPA axis, which are activated during stress to prepare an organism to respond to the stressor. Shelley Taylor and colleagues have

suggested that summarizing the stress response as "fight-or-flight" has been founded on decades of stress research which have been disproportionately based on studies of male animals or male human subjects. Instead, they have proposed a gender-specific response to stress and suggest that female responses to stress may not be fully characterized by fight-or-flight, but also by a behavioural pattern of "tend-and-befriend" (Taylor et al., 2000). In this model, females respond to stress by nurturing and protecting offspring (tend), and by affiliating with social groups (befriend).

Oxytocin (OT) is a nine amino acid neuropeptide released from the pituitary. It is the peripheral actions of OT that are most well-known, particularly those associated with female reproduction such as milk let-down, uterine contraction and maternal care (Bakos et al., 2007). It was previously considered that these were the primary functions of OT; however recent research has indicated that OT also has central actions. Oxytocinergic pathways are distributed throughout the central nervous system and OT acts at receptors in a variety of brain areas including limbic areas such as the hippocampus, amygdala, bed nucleus of stria terminalis, lateral septum, ventrolateral septum, caudate and the anterior olfactory nucleus (Bell, Nicholson, Mulder, Luty, & Joyce, 2006; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Onaka, 2004; Windle et al., 2004). In both human and animal studies, central OT has been associated with stress attenuation and decreases in anxiety (Neumann, Kromer, Toschi, & Ebner, 2000). Given its dual roles in social attachment and stress-modulation, OT has

been theorized to be at the core of the "tend-and-befriend" behavioural stress response.

Despite methodological problems in quantifying plasma OT levels and understanding relationships between levels of OT in plasma and in the brain, studies of OT do support a role for OT in stress responses. Central administration of OT in rats causes a decrease in blood pressure, attenuates pain sensitivity and decreases corticosteroid levels, opposite to the traditional fight-or-flight stress response and suggesting a role in anxiolysis (Taylor et al., 2000). Infusion of synthetic OT into the lateral ventricle of ovariectomized rats lowered anxiety-related behaviours and decreased corticosterone response to noise, also evidence of a decreased response of the HPA axis to stress (Neumann et al., 2000; Windle et al., 2004). Conversely, central infusion of an OT antagonist caused an increase in plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone in virgin female rats under stress through forced swim, repeated air puffs, or placement in an elevated plus maze (Amico, Mantella, Vollmer, & Li, 2004; Neumann et al., 2000). Mice who were administered an OT antagonist displayed more behaviours of anxiety (Amico et al., 2004).

Stress and glucocorticoids cause an upregulation of OT receptors in the hippocampus, an important brain area involved in memory and a region that is rich in glucocorticoids (Neumann et al., 2000; Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000; Windle et al., 2004). This may be evidence of OT receptor modulation mediating some of the long term effects of stress on memory (Young et al., 1997). OT levels are elevated in response to chronic stress. In a

study of older women experiencing chronic problems in their social relationships or unrewarding relationships, plasma levels of OT were significantly elevated (Taylor et al., 2006). This is consistent with other findings which demonstrated that young women in relationship distress also had elevated OT plasma levels (Turner, Altemus, Enos, Cooper, & McGuinness, 1999). Thus, across different samples of women, a correlation was found between OT levels and relationship strain. Higher OT levels have also been associated with faster HPA axis recovery in women after an acute stress laboratory challenge (Olff et al., 2007). Lower OT levels may therefore be a risk factor for stress-related disorders.

Although there has been much research linking peptides with particular behaviours (i.e. OT and mother-infant bonding), it is more complex than this with integrated activity across several physiological systems (Nair, Gutman, Davis, & Young, 2005). Studying the properties of the oxytocinergic system in relation to complex affiliative behaviours and its role in stress attenuation will be an informative next step toward understanding the role that OT may play in the unique and complex stress responses in women.

It is widely recognized that gender affects health and the expression of illness and that males and females may respond to stress in different ways. With differentiation of stress responses by gender and by sex, researchers can start to examine some of the mechanisms and potential underlying processes that account for the observed differences in how males and females respond to stress. One challenge is to identify the sex differences and gender differences in response to stress. In this way, 'gender' is a social science construct, linked to economic and

social status. Gender is culturally specific and implies a hierarchy or other differentials between men and women. Alternatively, 'sex' is a biological construct that encompasses genes, hormones, anatomy and physiology. Sex is often presented as a binary (male/female) and affects trajectories, prevalence and treatment of health conditions and diseases. It may be that human females are more likely to 'tend and befriend' because they are encouraged throughout their development to maintain close social networks and engage in nurturing activities, which are not as supported throughout male development. Nurturing behaviours are strongly influenced by previous experiences and by culture (Denmark, Russo, Frieze, & Sechzer, 1988). Although some differences are biologically determined, others may be more accurately accounted for as socialized gender differences, or as interactions of biological and sociological variables (Denmark et al., 1988). The impact of gender differences in economic power, social support, social roles, life stress and characteristic ways of coping cannot be neglected in gendered stress research (Palanza, 2001). Interpretation of data regarding innate differences must take into account the biological mechanisms behind these differences, many of which have not yet been determined. The field of epigenetics is emerging as an important way to facilitate this dialogue around sex and gender differences and better understand how the genetic code is shaped by history and experience.

3. STRESS RESPONSE SYSTEMS

Stress is perceived when an individual needs to respond to a situation where they believe they do not have the available resources, and the consequences of not responding are important (Averill, 1973). A behavioural stress response occurs when a person appraises a situation as a stressful encounter and has a sense of inadequate options for coping with this encounter (Folkman et al., 1986). Within seconds of the perception of a threat, cascades of hormones and neurotransmitters are released in the body. When the danger subsides, the body signals stress response systems to shut off, causing a return of these hormones and neurotransmitters to basal levels. The focus of stress physiology has prominently been on the SAM axis and the HPA axis. These systems mediate bidirectional brain-body communication during physiological (i.e. hunger, fever, infection) and psychological stress and are activated to promote homeostasis and to adapt to threatening or stressful situations (Engelmann et al., 2004; Onaka, 2004). These two axes have significant interplay and together, these systems regulate energy utilization and metabolic activity throughout the body.

3.1. Sympathetic-Adrenal-Medullary Axis

Activation of the SAM axis due to a stressful situation initiates physiological processes that promote rapid response to the threat. In this response, norepinepherine is released from brainstem nuclei, which activates the adrenal gland medulla to release epinephrine. Epinephrine stimulates the

sympathetic ganglia, increasing sympathetic nervous system tone. This is a rapid, short-lived response to stress that promotes increased heart rate and blood pressure, bronchodilation, glucose mobilization and decreased peripheral blood flow and gastrointestinal activity (Engelmann et al., 2004; Ennis et al., 2001). In addition, this increase in norepinephrine enhances cognitive function in the prefrontal cortex and motivation in the nucleus accumbens of the mesolimbic areas.

3.2. Hypothalamic-Pituitary-Adrenal Axis

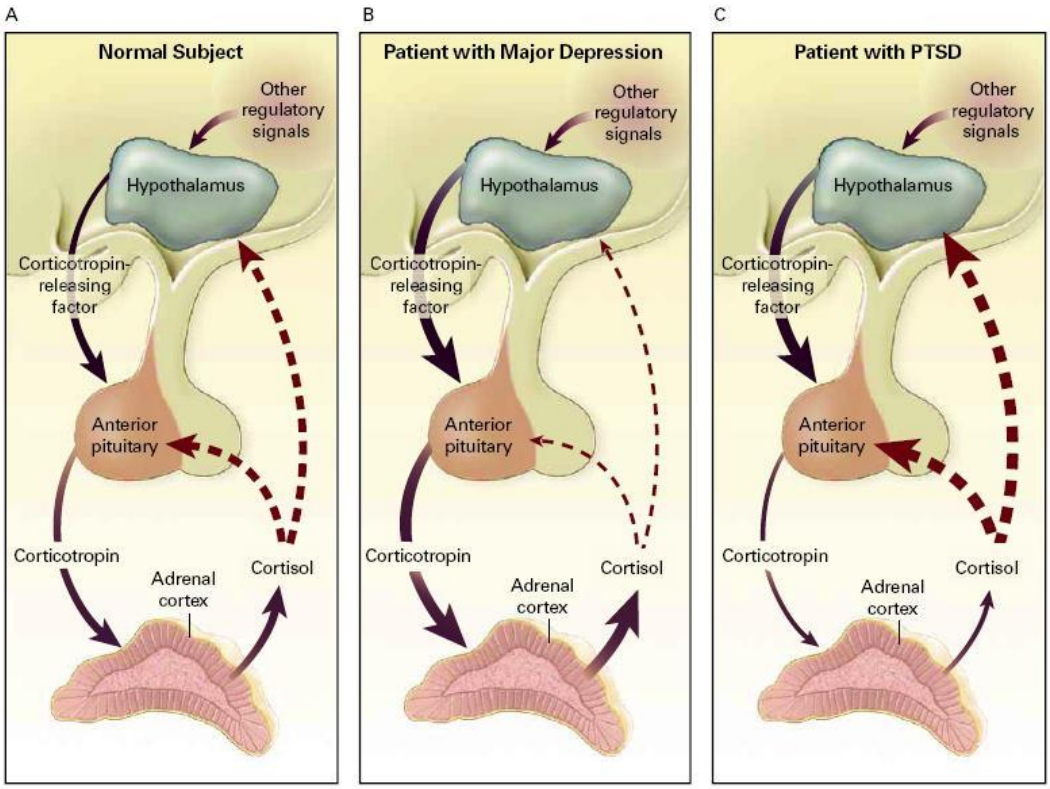
3.2.1. Description of Axis

Activation of HPA axis is slower than the SAM system, but the effects are longer lasting. The SAM and HPA systems are anatomically and functionally interconnected and there is considerable interplay between these systems. Mobilization of the SAM system activates the HPA axis through norepinepherine-mediated corticotropin releasing hormone (CRH) release. Together, these systems regulate energy utilization and metabolic activity. The hypothalamus plays a critical role in transducing neural input to neuroendocrine output. When activated by stress, the hypothalamus releases CRH which stimulates release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. This in turn stimulates the synthesis and release of glucocorticoids from the adrenal cortex. Once activated, appropriate feedback mechanisms are in place to ensure HPA axis functioning returns to basal levels after the stressor has ended. This system is controlled via negative feedback inhibition of cortisol at the level of the

pituitary and hypothalamus to reduce synthesis and release of ACTH and CRH and limit the amount and duration of increased cortisol levels (see Figure 2.3). Regulation of the HPA axis is critical and imbalances in this cascade and feedback have been associated with many disease processes. The HPA axis is important in supporting physiological and psychological coping with a stressor and plays a role in moderating the effects of stress on health, mood, behaviour and the development of stress related diseases. The glucocorticoid cortisol is the predominant output of the HPA axis in humans and a key stress hormone in the body. Glucocorticoids have widespread effects because they influence the function of most cells in the body and between 10% and 20% of expressed genes are regulated by glucocorticoids (Chrousos, 2007). Cortisol has numerous influences on metabolic, physiological and psychological processes. Cortisol increases glucose availability to skeletal muscles, limits memory processing during highly stressful events, and augments the epinephrine-related increases in heart rate and blood pressure. Cortisol also affects immune function, growth and metabolic homeostasis. Chronic activation of the HPA axis is linked to cardiovascular, endocrine and autoimmune disorders including hypertension, obesity, type II diabetes and affective disorders. For example, some women with a history of MDD have decreased bone mineral density, due to the allostatic load of chronically elevated cortisol concentration (Michelson et al., 1996). Chronic stress is also linked to risk of myocardial infarction through increased reactivity of the fibrinogen system platelets (McEwen, 1998b).

Additionally, when one system does not respond adequately to a stressor, other systems compensate. For example, inflammatory cytokines are counterregulated by cortisol, so if cortisol levels do not increase appropriately in response to stress, these inflammatory cytokines may, leading to autoimmune and inflammatory disturbances. The hippocampus is a key link between the HPA axis and cognition. According to the "glucocorticoids-cascade hypothesis," wear and tear on the hippocampus leads to HPA axis dysregulation and cognitive impairments (McEwen, 1998b). Normalization of the acute cortisol response after a stressful event is imperative to protect against these negative impacts. Cortisol secretion is tightly regulated by the central nervous system and this regulation is sensitive to negative feedback inhibition by circulating cortisol and exogenous glucocorticoids.

Figure 2.3: The Hypothalamic-Pituitary-Adrenal Axis



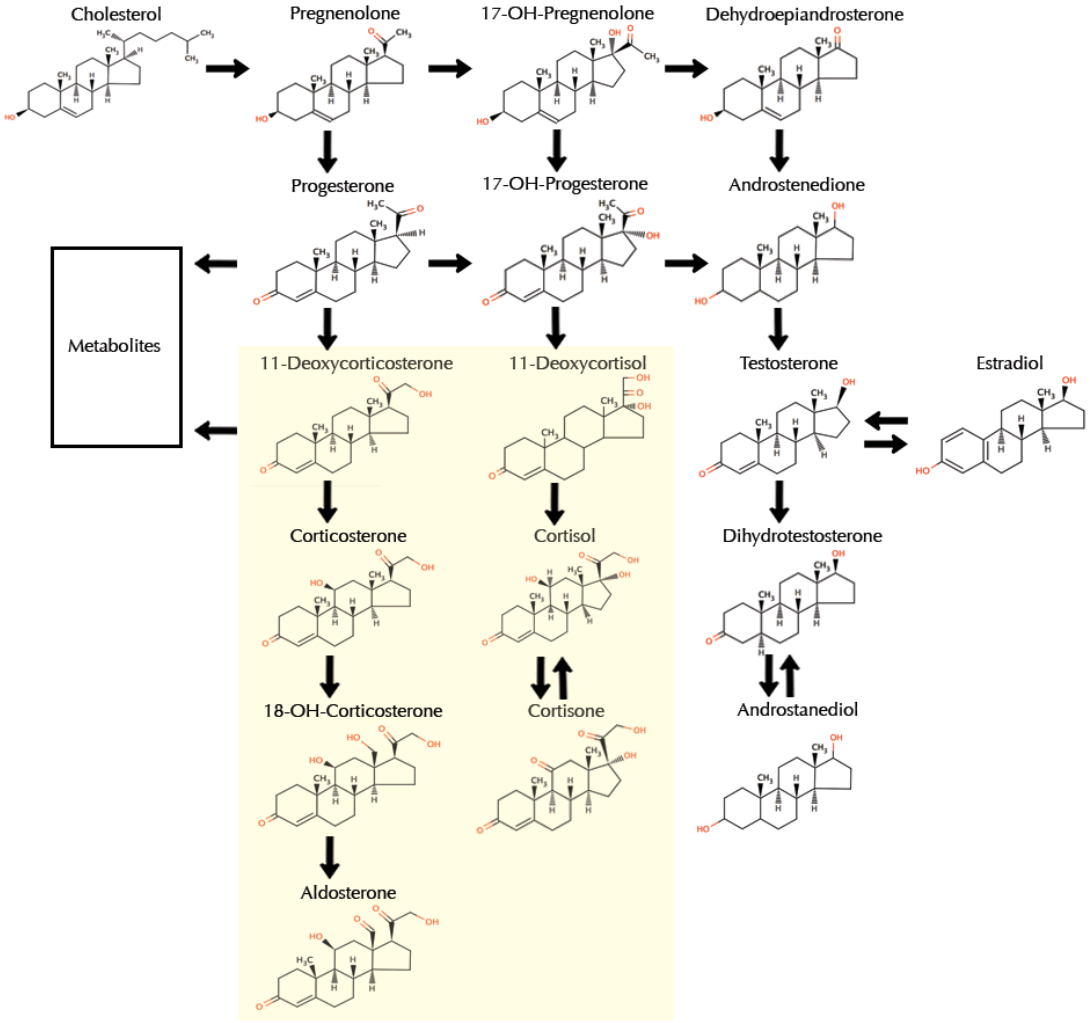
(Source: Yehuda, 2002)

The HPA axis is shown under normal conditions in Panel A. When activated by stress or other regulatory signals, the hypothalamus releases corticotropin releasing factor, which stimulates the release of adrenocorticotropic hormone from the anterior pituitary gland, as indicated by the solid arrows. This stimulates the release of glucocorticoids from the adrenal cortex. This system is controlled by negative feedback inhibition of cortisol at the level of the pituitary and the hypothalamus, as indicated by the dashed arrows. In each panel, the thickness of the interconnecting arrows indicates the magnitude of the biological response. In about 50% of patients with MDD (Panel B), basal cortisol hypersecretion is observed. Additionally, feedback inhibition is impaired in approximately 50% of people with MDD. Panel C shows decreased basal cortisol levels in patients with PTSD, however, this finding is equivocal. People with PTSD also show enhanced negative feedback inhibition through increased feedback sensitivity.

3.2.2. Cortisol Pharmacology

In the normal adult, in the absence of stress, corticosteroids are made and secreted in the adrenal cortex at a rate of about 10 to 25 milligrams (mg) per day, with cortisol representing 85-90% of total corticosteroid production in humans. Cholesterol is the basic substrate for all steroid compounds and is synthesized in the liver, skin and intestinal mucosa. Corticosteroid biosynthesis from cholesterol is depicted in Figure 2.4. Biosynthesis of cortisol is rapid and corticosteroids appear in peripheral circulation less than 2 minutes after stimulation by ACTH (Carpenter & Gruen, 1982). The adrenal gland does not store significant quantities of corticosteroids so regulating the rate of synthesis controls release of cortisol. The secreted cortisol travels back to the hypothalamus and pituitary to exert negative feedback on CRH and ACTH secretion, preventing overproduction of cortisol.

Figure 2.4: Corticosteroid Biosynthesis



(Source: Centre for Bioenvironmental Research, 2009)

Corticosteroids are synthesized from cholesterol within the zona fasciculata of the adrenal cortex. ACTH is released from the anterior pituitary and stimulates the biosynthesis of cortisol by stimulating the conversion of cholesterol to pregnenolone.

Due to the lipophilic properties of free steroid molecules, they are often in conjugated form (e.g. as a sulfate or glucuronide derivative), or non-covalently bound to carrier proteins. Steroid hormones in plasma are either free or bound to

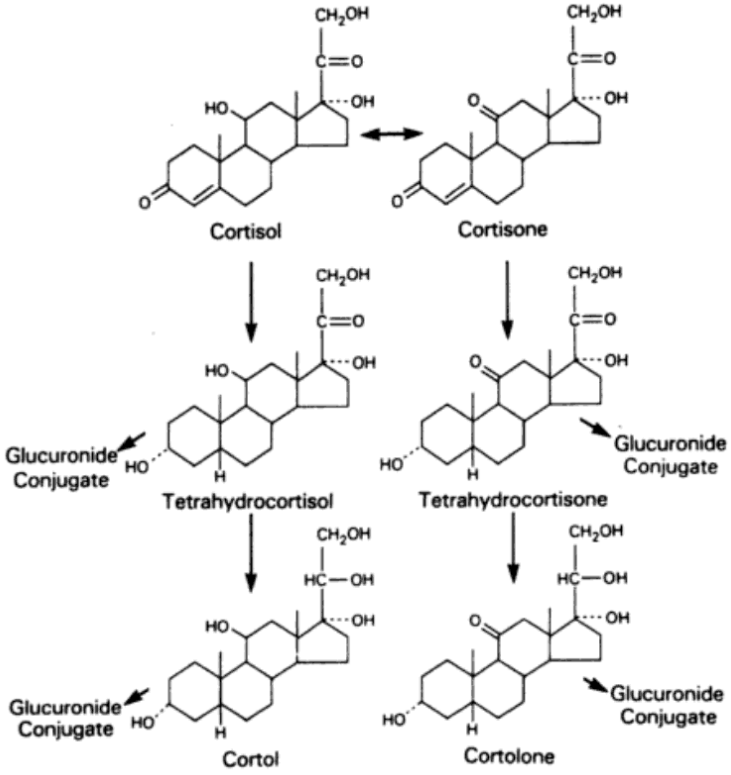
various plasma proteins. The free concentration of a particular steroid hormone is dependent on the affinity and binding capacity of the binding proteins in plasma (Quissell, 1993). 90% of cortisol is bound to cortisol binding globulin (CBG) in plasma and is not physiologically active (Dhillo et al., 2002). Approximately 5% of cortisol is loosely bound to albumin, and the final 5% is unbound. Albumin has a low affinity for cortisol, so albumin-bound cortisol is considered free cortisol. When plasma cortisol levels exceed 20-30 micrograms per decilitre (μg/dL), CBG is saturated and the concentration of free cortisol rises rapidly (Chrousos, 2007). Unbound, free cortisol is physiologically active. About 40% of the variance in cortisol concentration may be attributed to the changes in concentration of CBG between individuals and are regulated by hormones and other factors (Bright, 1995). CBG concentrations have been shown to be negatively regulated by insulin and interleukin-6 (Fernandez-Real et al., 2002). Estrogens impact CBG levels so pregnancy, oral contraceptives and hormone replacement therapy can elevate concentrations of plasma CBG. CBG is decreased by hypothyroidism, genetic defects in synthesis and protein deficiency states. Elevated CBG levels occur in diabetes, chronic active hepatitis, and some hematologic and liver disorders (Felig & Frohman, 2001).

Cortisol secretion is released in episodic bursts (about 10 per day) and follows a circadian rhythm. This pattern of release is regulated by the suprachiasmatic nucleus of the hypothalamus. Peak plasma concentrations of cortisol occur approximately 30 minutes after awakening (Edwards, Evans, Hucklebridge, & Clow, 2001). Cortisol concentration declines throughout the day

and reaches minimal concentrations between midnight and 0200 hours (Carpenter & Gruen, 1982; Weitzman et al., 1971). When measuring cortisol levels, different time points are chosen to reflect different points of the diurnal pattern of cortisol release.

The liver and the kidney are the principal organs involved in clearing steroid hormones from circulation. Cortisol has a half-life of 60 to 100 minutes and is converted to tetrahydrocortisone in the liver, decreasing biological activity and increasing water solubility. The kidney is the major site of conversion of cortisol to cortisone, whereas the conversion of cortisone to cortisol occurs in the liver (Morineau et al., 1997). In adult humans, plasma cortisol is ten times greater than plasma cortisone (Morineau et al., 1997). Only 1% of cortisol is excreted unchanged in the urine as free cortisol. Approximately 20% of cortisol is converted to cortisone in the kidney and other tissues before reaching the liver. At least 90% of cortisol and cortisone is metabolized in the liver and excreted in urine as water soluble glucuronide conjugates. The metabolism of cortisol is shown in Figure 2.5.

Figure 2.5: Major Metabolic Pathways of Cortisol



(Source: James, 1992)

Within the kidneys, 11ß-hydroxysteroid dehydrogenase catalyses the conversion of cortisol to cortisone (the inactive metabolite of cortisol). Most of cortisol and cortisone is metabolized in the liver and excreted in urine as water soluble conjugates.

3.2.3. Control of Axis Output

Within the HPA axis, glucocorticoids are the key regulatory signals. Feedback regulation of the HPA axis by cortisol is maintained by two intracellular receptors that act as gene transcription factors (de Kloet, Oitzl, & Joels, 1993). These receptors are called the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The MR and GR share considerable structural and functional homology and cloning of these receptors revealed that they are 56% identical in the steroid binding domain (Pippal & Fuller, 2008). As such, glucocorticoids can bind to both receptors.

GRs are widely distributed in the brain and periphery and play a major role in stress responsiveness. GR concentrations are high in the limbic system (hippocampus, septum) and in the parvocellular neurons of the hypothalamus, where CRH is synthesized (de Kloet et al., 1993). GRs are also present in the brainstem and thalamic nuclei. MRs are present in classic target tissues for mineralocorticoids, such as the kidneys, where aldosterone binds. MRs also act in areas which are not targets for aldosterone, such as the neurons of the limbic brain, particularly in the hippocampus, lateral septum, medial and central amygdale and olfactory nucleus (de Kloet et al., 1993). In most hippocampal neurons, GRs and MRs are highly colocalized (de Kloet et al., 1993; Nishi & Kawata, 2007).

MR- and GR-mediated effects can be coordinated or antagonistic. For example, in the hippocampus, MR activation maintains excitability and regulates behavioural reactivity and response selection; while GR occupancy decreases

behavioural reactivity and facilitates memory storage (de Kloet et al., 1993). Additionally, both MRs and GRs interact with cortisol, but this signal may have different effects in different areas of the body. For example, cortisol can act as a MR agonist in the kidney and colon, but as a MR antagonist in the heart and areas of the central nervous system, though this tissue specific dichotomy is not yet understood (Pippal & Fuller, 2008). The two corticosteroid receptors are dynamic and interactive. For example, in the hippocampus, chronic GR activation downregulates density of GRs but increases MR density (de Kloet et al., 1993).

Even at high levels of glucocorticoids, there are many unoccupied GRs (Young, Lopez, Murphy-Weinberg, Watson, & Akil, 1998). MRs have about a ten-fold higher affinity for glucocorticoids and are saturated at lower concentrations of cortisol (Nishi & Kawata, 2007; E. A. Young et al., 1998). De Kloet found that GR affinity to corticosterone [K_d = 5.0 nanomolars (nM)] was about one order of magnitude higher than that of MR (K_d = 0.5 nM). In the hippocampus, MRs are 70% saturated during the circadian trough, while only 10% of GR are occupied (de Kloet et al., 1993; Young et al., 1998). Substantial GR occupation occurs only during stress and at the circadian peak (de Kloet et al., 1993). MR occupancy varies between 70% and 90%, while GR occupancy varies from 10% to 90% due to circadian variation or stress-induced changes. For example, a chronic mild stress paradigm in rats (handling during the early postnatal period) leads to increased GR binding in the hippocampus and is associated with enhanced negative feedback control over the HPA axis function (Meaney et al., 1993).

Once in the bloodstream, cortisol participates in a number of physiological processes that enable the body to cope with both acute and chronic stressors. In times of acute stress, cortisol stimulates gluconeogenesis and the entry of glucose into cells. During states of chronic stress, cortisol inhibits growth, reproductive, and immunological processes, allowing resources to be diverted into processes that facilitate longer-term coping. If the stress response persists, for example in relationships characterized by IPV, repeated cortisol release could desensitize or disinhibit the HPA axis. In this way, the protective negative feedback that normally occurs after repeated stress is dysregulated and chronic hypercortisolism may occur. Prolonged exposure to excess cortisol produces marked changes in carbohydrate and protein metabolism and abnormal cortisol levels are associated with many common health problems. Hypercortisolism may increase susceptibility to chronic inflammatory disease, autoimmune disease and other diseases of inflammation or could result in hippocampal damage. There are two prominent effects of chronic stress on the HPA axis. With repeated exposure to chronic stress, habituation may occur, with adaptation to that stressor. For example, in response to the stress of a public speaking challenge, most people experience activation of the HPA axis. After repeated challenges however, most people habituate and their cortisol secretion does not increase with the challenge (Kirschbaum et al., 1995). For some, this habituation is not seen. Alternatively, chronic stress experiences may induce facilitation of HPA axis activity. The mechanisms by which habituation and facilitation occur may have important implications in the pathophysiology of stress disorders.

3.2.4. Measurement of Cortisol

Cortisol levels increase during stress. Thus, ideally sample collection should be stress-free. To measure cortisol, saliva collection has become frequently used. It is a practical, reliable and non-invasive approach that provides quantitative data regarding biologically active cortisol levels. Collection is painless, less stressful, easy, economical and has a high rate of compliance.

Cortisol is not converted to its water-soluble metabolites by the salivary glands, in contrast to substances excreted by the kidneys, so saliva is often preferable to urine as a noninvasive measure of steroid levels (Groschl, 2008). Salivary flow has little or no effect on salivary cortisol levels as steroids enter the saliva by rapid diffusions through the acinar cells (Lewis, 2006). As opposed to plasma measures of cortisol, salivary cortisol is less influenced by variations in CBG and by drugs that may compete with cortisol with its binding sites. Cortisol in saliva is 100% unbound and biologically active. However, plasma, urinary and salivary cortisol measures are highly intercorrelated (Lewis, 2006). Since the earliest reports, there is evidence that salivary cortisol levels are correlated with the levels of free cortisol in plasma (Umeda et al., 1981). The proportion of salivary cortisol to plasma cortisol is approximately 8-9% (Hellhammer, Wüst & Kudielka, 2009). Ultra sensitive enzyme-linked immunosorbent assays (ELISA) allow for easy quantification of salivary cortisol.

Cortisol is converted to the biologically inactive cortisone in the salivary glands, which must be considered in salivary measurements of cortisol. This conversion may explain some of the discrepancies in cortisol concentrations

reported in the literature and depending on the cross-reactivity of antibodies used in immunoassays, data may reflect concentrations of both cortisol and cortisone, falsely inflating the results (Groschl, 2008).

3.3. Animal Models used in Stress Research

Stress underlies both anxiety disorders and MDD due to chronic arousal and impaired functioning of the HPA axis (Kalueff, Wheaton, & Murphy, 2007). One in five people experience depression or anxiety of clinical severity (Nesse, 1999). The DSM-IV outlines six anxiety disorders including generalized anxiety, panic, social and separation anxiety, agoraphobia, PTSD and obsessive-compulsive disorders. The tripartite model has been used to define the behavioural dimensions shared by MDD and anxiety disorders. In this model, three independent factors were derived, accounting for differences as well as similarities between MDD and anxiety disorders. These three factors are negative affect (common to both MDD and anxiety), positive affect (inhibited in MDD, distinguishing it from anxiety disorders) and physiologic hyperarousal (more commonly seen in anxiety disorders than in MDD) (Clark & Watson, 1991; Frazer & Morilak, 2005). Only about half of patients diagnosed with MDD or an anxiety disorder have pure syndromes of one type or the other, and self reported anxiety and MDD scales correlate between 0.4 and 0.7 across a wide range of clinical and non-clinical samples (Lovibond & Lovibond, 1995). Evolutionary approaches suggest connections between anxiety, stress and depression (Nesse, 1999). Anxiety and depression are multi-faceted psychiatric illnesses, and both

demonstrate marked overlap and co-occurrence (Kalueff et al., 2007). Stress, anxiety and depression are interrelated phenomena and animal models of these conditions have been key in furthering the understanding of the impacts of stress (Palanza, 2001).

It is as yet not possible to adequately model the complex etiology and expression of clinical and subclinical human psychiatric disorders in animals (Siegmund & Wotjak, 2006). Many psychiatric disorders and health consequences of stress are multifaceted and extremely difficult to replicate in a comparative animal model. There are many factors that contribute to a stress response, which would be very difficult to replicate in any one model (see Table 2.1). Even so, animal models in research have been invaluable in understanding the mechanisms behind many biological and psychological disorders, as well as in identifying possible treatment targets (Willner, 1997). Animal models are used to investigate the cellular and intracellular changes that are difficult or not feasible to study in humans. Rodents have been used for studies in behavior since the turn of the century and are major experimental animals in all fields of biomedical research and technology.

Table 2.1: Factors Influencing the Stress Response

Stressor type
Processive (neurogenic or psychogenic)
Systemic (immune insults)
Stressor characteristics
Controllability
Predictability
Ambiguity/uncertainty
Chronicity
Intermittence
Organismic variables
Species
Strain
Age
Sex
Experiential variables
Previous stressor experiences (sensitization)
Early life events (maternal factors, trauma)
Resource characteristics
Personal characteristics
Coping skills
Self-esteem
Self-efficacy
Personality (hardiness, optimism, neuroticism)
Social characteristics
Social support (perceptions)
Attachment (bonding)

(Source: Adapted from Anisman & Matheson, 2005)

Experiences and perceptions of stress are influenced by a variety of factors, either related to the stressor itself, or to organismic variables. Each of these variables needs to be considered in a broad view of the stress response.

When animals are exposed to unfamiliar situations, psychological and biological stress responses are observed, including inhibition of exploratory behavior, increased heart rate and increase in plasma corticosterone levels, similar to human responses to stress (Palanza, 2001). Animals also display withdrawal, difficulties in social functioning and lack of active coping, analogous to humans (Palanza, 2001). Traditional animal models of anxiety are based on the exploration of novel environments, such as in an open-field, elevated plus maze, light-dark box, mirrored chamber or social interaction tests (Kalueff et al., 2007; Palanza, 2001). Traditional animal models of depression are based on despair paradigms through chronic mild stress (CMS).

3.3.1. Chronic Mild Stress

The CMS model has been a valuable tool for drug discovery and development, and has provided insight into the pathophysiology of depression and dysthymia (Anisman & Matheson, 2005; Willner, 1997). In the CMS paradigm, rats or mice are exposed to a variety of mild, unpredictable stressful events, such as restraint stress, exposure to cold, tail pinch or forced swim tests. For example, in the forced swim test, rodents are placed in a cylinder of water at a depth where their feet and tail cannot touch the bottom (Frazer & Morilak, 2005). The rodents try to escape by swimming, but over several exposures, stop struggling and float quietly. Here, swimming is an adaptive escape response, while floating is considered a pathological depressed response. Exposure to a few minutes of a moderate uncontrollable stressor distributed over the course of several hours

results in deficits in behavioural coping, associative learning and emotional expression (Overmier, 2002). Additionally, after the stressor, there are performance deficits in response to pleasant events, such as consumption of a sweet solution, and brain stimulation or drug rewards (Willner, 1997). This is considered indicative of anhedonia in these animals, a central feature of all forms of depression (Anisman & Matheson, 2005; Palanza, 2001). While the CMS paradigm was initially developed to model MDD, it may more closely model dysthymia (chronic mild depression) (Anisman & Matheson, 2005).

Learned helplessness is an outcome of the CMS paradigm. It is based on the observation that exposure to inescapable stress produces performance deficits in subsequent learning tasks. In initial experiments of learned helplessness, animals were exposed to either escapable or inescapable stressful events (shocks while confined in a shuttlebox) (Seligman & Maier, 1967). The animals were then tested on a new task, where they are able to escape the stressor. The animals that experienced uncontrollable stress learn that the result is independent of their responses, and past experiences of uncontrollable shock interfered with escape and avoidance responses in the new task (Seligman & Maier, 1967). With learned helplessness, animals stop trying to escape from a setting where they have initially found escape impossible and show more passive coping strategies during subsequent stressors (Nesse, 1999; Singewald, Nguyen, Neumann, Singewald, & Reber, 2009). The question remains as to how this unnatural setting of a shuttlebox can be generalized to real life experiences. The behaviour of learned

helplessness in animal models has been equated with a sense of giving up, experienced by humans with MDD.

In the CMS paradigm, animals learn over the course of chronic exposure to uncontrollable stressful events that their responses are ineffective. As such, the learned helplessness model has been proposed to explain the emotional numbing and maladaptive passivity sometimes seen following victimization (Peterson & Seligman, 1983). While there are many problems in over-generalizing this model, previous experiences of helplessness in the context of IPV may contribute to current feelings of inescapability that some women may experience.

A key criticism of the learned helplessness model is the lack of reliability in humans and lack of evidence that it characterizes people with MDD (Palanza, 2001). Additionally, the vast majority of studies using CMS paradigms have been conducted in male rats. Recently Dalla and colleagues showed that female rats may not express learned helplessness in the same way that male rats do (Dalla, Edgecomb, Whetstone, & Shors, 2008). In this study, most male rats exposed to uncontrollable stress demonstrated learned helplessness, while most female rats did not (Dalla et al., 2008). This was independent of sex hormones, raising the question of the validity of the learned helplessness model for depressive behaviour in women, at least in the form that was used in this study.

3.3.2. Social Stress

Stress paradigms in the lab such as restraint stress, exposure to cold, tail pinch or forced swim tests are unlike conditions experienced in natural

environments. As such, rodent and non-human primate models of social stress have been developed to better mimic natural conditions. Social stress is a chronic factor in the lives of nearly all higher animal species (Blanchard, McKittrick, & Blanchard, 2001). Social stress in animal groups commonly results from competition for access to reproductive partners, space, food, water and other resources (Tamashiro, Nguyen, & Sakai, 2005).

Common models for social stress in rodent animals are defeat in aggressive encounters, isolation and crowding (Palanza, 2001). For example, in the resident-intruder paradigm, a resident male rodent is exposed to an unfamiliar male intruder, causing stress in the resident male while the rodent defends its territory (Tamashiro et al., 2005). A similar model of social stress is through chronic subordinate colony (CSC) housing (Singewald et al., 2009). In non-human primates, dominance hierarchy models are also used to understand the impacts of stress in animals. Groups of social animals often form dominance hierarchies and an animal's rank within this hierarchy can dramatically influence quality of life (Sapolsky, 2005). In animals, psychosocial stress and the lack of control over one's social environment can lead to chronically elevated HPA axis activity (DeVries, Glasper, & Detillion, 2003).

Animals that are more socially stressed in the dominance hierarchy have higher basal glucocorticoid levels and impaired sensitivity of the HPA axis to negative feedback regulation. Chronic activation of stress responses systems by social stressors can increase risk of disease and conditions such as hypertension, elevated heart rate, decreased body weight, elevated levels of low density

lipoprotein, atherosclerosis, and reproductive impairment (McEwen, 1998a; Sapolsky, 2005; Singewald et al., 2009; Tamashiro et al., 2005). Psychosocial stress in non-human primates has been shown to suppress cellular immune function, and relationships have been found between social status and infection susceptibility (Cohen et al., 1997).

Among male rodents and primates, social stress can suppress fertility and is associated with suppression of the hypothalamic-pituitary-gonadal (HPG) axis and lowered testosterone levels (Sapolsky, 2005). Neurobiological changes are also seen in primates socially stressed by the dominance hierarchy. These changes include inhibition of neurogenesis, impaired synaptic plasticity of the hippocampus and dendritic atrophy (Sapolsky, 2005). In animal models, social stress leads to behavioural changes involving emotionality-linked behaviours such as anxiety, defensiveness and substance self-administration, as well as neuronal changes in structure and neurotransmission (Blanchard et al., 2001). Chronic exposure to glucocorticoids and catecholamines impair cognitive function and promote damage to brain structures such as the hippocampus (McEwen, 2000).

The prevalence, etiology and treatment response to psychiatric disorders is gender-specific, though there is a lack of animal models addressing this issue (Stam, 2007). Until the last quarter of the 20th century, sex and gender were not recognized as variables in health research (Uhl, Parekh, & Kweder, 2007). Both the CMS paradigm and social defeat models have been validated behaviourally, physiologically and pharmacologically as models of anxiety and depression in male rats, but this validation has not been carried out for female rats (Palanza,

2001). Sensitivity to the CMS paradigm varies between sex and strains of rats used (Willner, 1997). Animal models of social defeat almost exclusively use male subjects and it is difficult to apply some models to female subjects (Bjorkqvist, 2001). For example, female rodents have low defensive scores as compared to male rodents and it is difficult to obtain strong dominance relationships or highly aggressive females in the laboratory, so it is difficult to apply the resident-intruder model of social stress (Palanza, 2001; Tamashiro et al., 2005).

Pragmatically, it can be difficult to use female animals in studies. Inclusion of female animals in research increases sample heterogeneity and raises issues of impacts of hormonal changes throughout oestrus cycles. To avoid this, many female animals are ovariectomized and then hormones are artificially injected. However, this may invalidate results when generalizing to naturally cycling female animals.

There are close interactions between the HPA axis, the HPG axis and the hypothalamic-pituitary-thyroid (HPT) axis (Rasgon, Kenna, Wong, Whybrow, & Bauer, 2007). Thus, stress responses are affected by sex hormones, leading to differences by premenstrual period, in the ante- and postpartum period, during the transition phase to the menopause and during the use of oral contraceptives (Swaab, Bao, & Lucassen, 2005). Thyroid gland disorders are associated with affective disorders (Rasgon, Kenna, Wong, Whybrow, & Bauer, 2007). However, most animal studies focus on a single hypothalamic-pituitary-end organ system and largely ignore the greater body-context in which these systems act.

It is impossible to adequately model the complex etiology and expression of human psychiatric disorders in animal models. Certain features of human behaviour and cognition are not reproducible in animals. Animal studies often model simple behavioural, neurophysiological, biochemical, anatomical or endocrine systems, and not complex behavioural syndromes (such as MDD) that are impacted by all of these systems (Kalueff et al., 2007). Animal paradigms often fail to model the multi-syndromal human experiences of affective disorders (Kalueff et al., 2007). MDD is a diagnostic construct that is comorbid with many other psychiatric illnesses and medical diseases (Frazer & Morilak, 2005). Presently, animal models do not account for the considerable symptom overlap between MDD and anxiety disorders and fail to determine the complex intersection between gender, health and violence.

3.4. Human Models used in Stress Research

Much of our knowledge of the neurobiology of stress has been obtained through animal models. This has resulted in an increased understanding of which neurochemicals and neuroanatomical pathways are involved in stress responses, but an incomplete understanding of how they may result in psychopathology in humans. Results from animal studies provide the basis for studies of neuronal mechanisms after chronic psychosocial stress in humans. Animal models are very useful in assessing organismic variables and to a certain extent, experiential variables, however, they cannot be readily used to assess the moderating role of personal and social characteristics (Anisman & Matheson, 2005). Social stress is a

chronic recurring stressor in the lives of nearly all higher animal species and it is generally acknowledged that the main source of stress stimuli in humans is social in nature (Blanchard et al., 2001; Palanza, 2001).

Data from animal models in dominance hierarchy and social defeat situations have been used to further understand the chronic stress experienced by humans. For example, bullying has parallels with animal models of social defeat and a body of literature exists around bullying in schools and work places. Victims of bullying have been found to have higher rates of MDD, lower self-esteem, submissiveness, social withdrawal, and higher anxiety and are dissatisfied with their peer relations (Bjorkqvist, 2001).

Experimentally, psychosocial stress has also been measured with the Trier Social Stress Test (TSST). This test enables researchers to investigate psychological and physiological response to social stress in humans in a controlled laboratory environment. The TSST is 20 minutes long. It consists of a 10 minute anticipation period, 5 minutes of public speaking and 5 minutes of mental arithmetic performed in front of a panel of evaluators (Kirschbaum, Pirke, & Hellhammer, 1993). Physiological and psychological markers of the stress response are then recorded. The TSST has reliably been shown to induce psychological, neuroendocrine and cardiovascular changes due to SAM and HPA axis activation. Occupational stress also models social stress in humans. Working conditions often constitute prolonged stressors. Correlations have been found between hypercortisolemia and working conditions in samples of traffic

controllers, pilots, ambulance personnel, as well as in people who are anticipating unemployment (Ehlert et al., 2001).

Much of the initial research surrounding the diagnostic criteria, epidemiology, biology and treatment of PTSD focused on data obtained from male Vietnam War veterans, whose experiences of trauma are qualitatively different from that of women who experience IPV (Lilly & Graham-Bermann, 2009). While the combat-survivor population surely models chronic severe stress, many studies have not systematically included gender across these trauma studies. This has left gaps in the literature of a full understanding of the different patterns of health and illness between men and women. While many of the above models are good investigations of stress in humans, none of them adequately model the chronic severe stress experienced by women living in relationships characterized by IPV. Only limited neurobiological studies of IPV are available.

3.4.1. Basal Cortisol Levels

Despite the significance of IPV as a serious public health issue, neuroendocrine study of this severe stress in a gender-specific manner is scarce (Griffin, Resick, & Yehuda, 2005). As one of the major stress response systems, the integrity of the HPA axis has often been examined in psychiatric illnesses related to stress. In addition to providing information about the functioning of the HPA axis, basal cortisol levels may help differentiate among stress and illness.

Initial observations that the HPA axis was affected in individuals with MDD was shown when elevated basal plasma cortisol levels were observed in

patients with depression (Gibbons & McHugh, 1962). Additional links were made between the HPA axis and MDD with studies of Cushing's disease, an endocrine disorder in which the pituitary gland overproduces ACTH. Individuals with Cushing's disease have elevated glucocorticoid levels and often experience depression (Kelly, Kelly, & Faragher, 1996; van Rossum & Lamberts, 2006). Neuroendocrine studies of people with MDD often show basal cortisol hypersecretion (Claes, 2004; Steckler, Holsboer, & Reul, 1999). In addition to disturbances in basal cortisol levels, changes have been seen in the pattern of cortisol secretion such as flattened circadian curve, earlier and/or elevated nadir, and changes in duration, amplitude and frequency of pulsatile cortisol release (Peeters, Nicolson, & Berkhof, 2004). Not all studies have reported hypercortisolism in people with MDD, particularly studies of outpatient or community populations (Peeters et al., 2004). Although HPA axis dysfunction is often considered a core feature of MDD, only about 50% of inpatients exhibit hypercortisolism (see Figure 2.3, Panel B) (Peeters et al., 2004).

Because of the strong association between cortisol levels and stress, and because high cortisol levels were observed in MDD, it was initially thought that cortisol levels would also be increased in PTSD (Yehuda, 1997). However, studies of basal cortisol levels in individuals with PTSD had equivocal results (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Yehuda, 2006). Depressed basal levels of cortisol have been reported in individuals with PTSD in some studies (Golier, Schmeidler, Legge, & Yehuda, 2006; Griffin, Resick, & Yehuda, 2005; Yehuda et al., 1993), and initial investigations of cortisol levels in PTSD

showed a decreased 24-hour urinary cortisol excretion in Vietnam veterans suffering from PTSD as compared to healthy controls (Heim et al., 2001). However, not all studies showed hypocortisolism in PTSD (Orr et al., 1995). One study showed hypercortisolism in women with childhood abuse-related PTSD (Lemieux & Coe, 1995). In many studies, cortisol levels in individuals with PTSD are within the normal neuroendocrine range (Ehlert et al., 2001; Yehuda, 2006).

Further clarifications of the neuroendocrine differences between MDD and PTSD are needed, as well as how this relates to neuroendocrine changes in people who have experienced chronic severe stress. In response to the variability observed in basal cortisol levels in MDD and PTSD, research shifted to examine changes in cortisol levels after various neuroendocrine challenge tests to further assess negative feedback systems and HPA axis reactivity. The sensitivity of the HPA axis glucocorticoid feedback system may be a better predictor than baseline cortisol concentrations in terms of behavioural arousal to stress (Kalin et al., 1981).

3.4.2. Hormone Challenge Tests

Hormone challenge tests provoke biological systems under controlled conditions, which allows for assessment of the responsiveness of stress systems. The dexamethasone (DEX; a glucocorticoid agonist) suppression test (DST) is one such test (Carroll, 1982). The DST is used to assess the negative feedback control of the HPA axis by increasing the total circulating levels of

glucocorticoids (Ehlert et al., 2001; Yehuda, 2006). This neuroendocrine test consists of the administration of a specific dose of DEX (ranging from 0.25 mg to 1.5 mg) at 2300 hours and then measurement of cortisol levels at one or more time points on the following day. DEX is an exogenous steroid that binds to glucocorticoid receptors and tests the effects of receptor activation on ACTH secretion (Cole, Kim, Kalman, & Spencer, 2000). Through interactions at GRs in the pituitary, DEX administration results in a suppression of ACTH and cortisol from the pituitary and adrenal gland respectively (Carroll, 1982; Cole et al., 2000; Miller et al., 1992). If HPA feedback regulation is functioning normally, cortisol secretion will be decreased or suppressed the next morning in response to the DEX.

The DST has been applied to animal models to better understand the impacts of stress on the HPA axis. In 1988, the DST was first applied with the learned helplessness model in animals to test the role of psychological stress in feedback inhibition of the HPA axis. In this study, rats that were exposed to inescapable shock showed less suppression of corticosterone in response to the DST than rats who could escape from shock. As learned helplessness is a model of depression, this supported the hypothesis that HPA resistance to DEX suppression is enhanced by the distress associated with ineffective behavioural coping resources (Haracz, Minor, Wilkins, & Zimmermann, 1988). HPA axis reactivity following aversive stimuli was found to depend on an interaction between genotype and stressor controllability in a study applying the DST to male rats of Koltushi high- (KHA) and low-avoidance (KLA) strains (Zhukov, 1993).

It was found that DST non-suppression of corticosterone after inescapable stress only occurred in KHA rats. In studies with the social defeat model of chronic stress in rats, corticosterone non-suppression was seen following DEX, similar to a MDD profile in humans (Stam, 2007).

There is compelling evidence for important links between HPA axis abnormalities and the pathophysiology of mood disorders (Kunugi et al., 2006). If there is dysregulation of the HPA feedback and cortisol levels are not decreased the following morning, the response is referred to as non-suppression. About 50% of people with MDD show non-suppression after the DST (Arana, Baldessarini, & Ornsteen, 1985). It is suggested that cortisol non-suppression by DEX is a marker of impaired feedback regulation and HPA axis hyperactivity (see Figure 2.3, Panel B). No relationships have been found between the type, duration or severity of depressive symptoms and suppressor or non-suppressor status, though people who show non-suppression after the DST have a higher risk of MDD relapse after successful treatment.

The DST has also been used to assess HPA axis integrity in individuals with PTSD. In contrast to non-suppression results in some patients with MDD, many studies have demonstrated exaggerated suppression of cortisol in response to DST in PTSD, called hypersuppression (Griffin et al., 2005). The low dose DST (0.5 mg) was introduced in population studies with PTSD, as it results in a more modest suppression of cortisol, allowing for differentiation between normal suppression and hypersuppression by decreasing the risk of a ceiling effect (Kosten, Wahby, Giller, & Mason, 1990; Yehuda et al., 1993). This

hypersuppression of cortisol in individuals with PTSD has been attributed to enhanced negative feedback inhibition of the HPA axis (see Figure 2.3, Panel C). This is likely due to an increased responsiveness of the central or peripheral glucocorticoid receptors (Yehuda, 2006). Cortisol hypersuppression in individuals with PTSD seems to be unaffected by the type of trauma, medication status or comorbid psychiatric conditions. Neuroendocrine function in rats stressed with shock or a prolonged stress paradigm show low to normal basal activity of corticosterone, but increased feedback sensitivity of the HPA axis, similar to neuroendocrine findings in humans (Stam, 2007). Three recent studies reported enhanced cortisol or ACTH suppression after the low-dose DST in veterans with and without PTSD (Golier et al., 2006; de Kloet et al., 2007; de Kloet et al., 2008). This suggests that the neuroendocrine dysregulation seen is based on experiences of trauma exposure, rather than discrete diagnosis of PTSD.

A major drawback of the DST is its modest sensitivity (Kunugi et al., 2006). In the DST, non-suppression is 50% sensitive for MDD. A significant improvement was achieved by Heuser and colleagues who combined the DST with CRH stimulation (Heuser, Yassouridis, & Holsboer, 1994). In the DEX/CRH challenge, DEX is used as a pretreatment to lower cortisol levels before acute administration of CRH. The DEX/CRH challenge is more closely associated with the activity of HPA axis than the standard DST in both healthy and depressed subjects (Kunugi et al., 2006). The combined administration of the DST and the CRH test is used to examine HPA activity under the condition of suppressed glucocorticoid feedback (Ehlert et al., 2001). The DEX/CRH test is

more sensitive for MDD (up to 80%) with findings of enhanced secretion of ACTH and cortisol after the DEX/CRH challenge in individuals with MDD (Heuser et al., 1994; Kunugi et al., 2006).

As the DEX/CRH test is a more sensitive test to assess HPA axis dysregulation in MDD, it has recently been used to investigate HPA axis regulation in individuals with PTSD. Based on the hypothesis that GR sensitivity is enhanced in PTSD, an attenuated ACTH and cortisol response is expected in patients with PTSD as compared to trauma controls. However, in a study of male veteran with and without PTSD, it was found that the DEX/CRH test did not show HPA axis abnormalities in PTSD patients as compared to controls (de Kloet et al., 2008). Subgroup analysis of individuals with and without comorbid MDD showed a lower ACTH and cortisol response to the DEX/CRH challenge in PTSD patients with comorbid MDD (de Kloet et al., 2008).

Neuroendocrine changes have been observed in animal studies of acute and chronic stress and in studies of stress disorders in humans. However, gaps exist in terms of the role of gender and type of stressor in the direction and magnitude of neuroendocrine changes. Women who have experienced IPV may serve as an exemplar to study the impact of a chronic interpersonal stressor on HPA axis activity.

By investigating the impact of IPV on HPA axis activity and how patterns of HPA axis activity relate to women's health, the relationships among psychiatric diagnoses, psychological parameters and neuroendocrine patterns may be elucidated. To this aim, psychological measures of entrapment, mental defeat and

perceived stress scores were examined with basal and challenged cortisol levels to better understand the impacts of stress and violence on women's health.

CHAPTER 3: METHODS

1. RECRUITMENT

This study was approved by the Health Research Ethics Board, Biomedical Panel, at the University of Alberta. Women, aged 18-65, were recruited from Changing Together: A Centre for Immigrant Women, in Edmonton, Alberta, Canada. This non-governmental, community agency offers services to women who face personal and systemic barriers following their immigration to Canada.

Each participant received an information sheet (see Appendix A) and signed a letter of informed consent (see Appendix B). Every woman was assigned a confidential code that was maintained by the project coordinator. The primary investigator completed the interviews in a private office at a time chosen by the participant. Interview questions included information about demographics, current mental health status, past trauma histories, current medication status and other current medical conditions. Inclusion and exclusion criteria for participants are listed in Appendix C.

2. DIAGNOSTIC AND PSYCHOLOGICAL ASSESSMENT TOOLS

General demographic data and lifestyle questions were collected (see Appendix D). Information about current menstrual status, hormonal contraceptives and hormone replacement therapy were included. The following assessment tools were used:

2.1. Mini International Neuropsychiatric Interview (MINI)

The MINI is the most widely used psychiatric structured diagnostic interview instrument in the world (Medical Outcome Systems Inc., 2006). It is a short, structured diagnostic interview, and has been validated against the much longer SCID (Sheehan et al., 1998). The MINI, version 5.0.0 was used to identify the presence of Axis I disorders, specifically MDD and PTSD (Sheehan et al., 1998).

2.2. Conflict Tactics Scale, CTS1, Form R, 1985 (Appendix E)

The CTS is a 15-item instrument designed to measure the tactics of reasoning, verbal aggression and violence in resolving conflict (Straus, 1979). The CTS is a six-point scale (0 = never, 1 = once that year, 2 = two or three times, 3 = often, but less than once a month, 4 = about once a month, 5 = more than once a month) (Straus & Gelles, 1990). In this study, only verbal aggression and physical aggression items were used to assess IPV experiences. For inclusion of participants experiencing IPV, women had to score their partners' behaviours as at least a "3" on six of the nine verbal or physical tactic items (items F through N). Women experiencing situational couple violence alone are excluded from this study, assessed by the women rating themselves at least a "2" on three of the six physical tactic items (items I through N).

2.3. Entrapment and Mental Defeat Scale (Appendix F)

The EMD scale is a two-part survey that asks about feelings and perceptions over the last seven days. Part I measures level of entrapment and is sixteen items long, each on a 5-point Likert scale (0 = not at all like me, 1 = a bit like me, 2 = moderately like me, 3 = quite a bit like me, 4 = extremely like me). Part II measures thoughts and feelings of defeat. It is also sixteen items on a five-point scale (0 = never, 1 = rarely, 2 = sometimes, 3 = mostly, 4 = always/all the time). The EMD scale measures have been found to significantly correlate with depression (Gilbert & Allan, 1998).

2.4. Perceived Stress Scale (PSS) (Appendix G)

The PSS is a widely used psychological instrument for measuring the degree to which situations are appraised as stressful (Silver, McAllister, & Yudofsky, 2005). It is a ten-item instrument with a five-point scale (0=never, 1= almost never, 2 = sometimes, 3 = fairly often, 4 = very often). It is designed to identify feelings and thoughts of stress during the last month (Cohen & Williamson, 1988). Items are designed to identify feelings of predictability and controllability of stress.

2.5. Childhood Trauma Questionnaire (CTQ) (Appendix H)

The CTQ is a twenty-eight-item self-report questionnaire that screens for histories of abuse and neglect (Bernstein & Fink, 1997). It has questions

regarding five broad types of maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect (Bernstein et al., 1994). This scale also includes three minimization/denial questions to detect false-negative trauma reports. Factor analyses of this scale show strong content validity (Wright et al., 2001). The five questions related to sexual abuse were used in this study to screen for CSA.

3. NEUROENDOCRINE MEASUREMENTS

3.1 Saliva Collection

Participants collected saliva in their homes using cotton rolls in plastic collection devices called Salivettes (Sarstedt, Inc., Newton, NC). In this simple, non-invasive procedure, each participant was given six pre-labeled Salivettes. Participants were instructed to remove the cotton roll from the tube, put it in their mouths, chew on it for 60 seconds, and return the roll to the collection tube. A form was provided to track time of sample collection (see Appendix I). Sample 1 was collected immediately upon awakening. Sample 2 was collected 30 minutes after awakening. Sample 3 was collected at 1 hour after awakening, after which participants were able to eat breakfast. Sample 4 was collected 4 hours after awakening. At 2200 hours, participants ingested a 0.5 mg tablet of DEX with water. Sample 5 was collected 30 minutes after DEX ingestion. Sample 6 was collected 30 minutes after awakening the following morning. It was requested that participants not eat, drink, smoke or brush their teeth before providing the morning saliva samples and to not eat or drink 30 minutes prior to collecting

samples. Participants mailed the six saliva samples and the record sheet to the Research Coordinator, using an addressed, pre-paid envelope, which was provided with the saliva collection kit.

Once samples were returned, they were centrifuged at 2000 revolutions per minute (rpm) for 5 minutes at 4°C, transferred to microcentrifuge tubes in duplicate, and stored at -80°C until time of analysis.

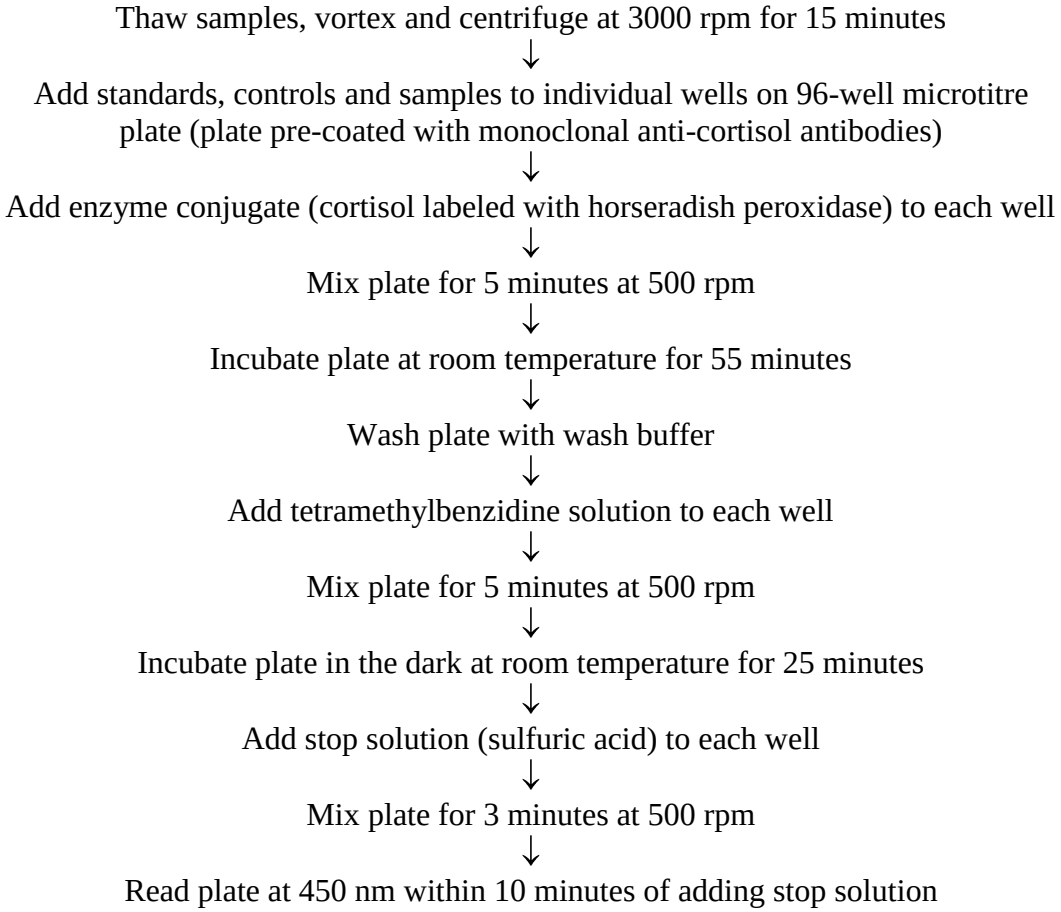
3.2. Cortisol Measurements

Cortisol is stable in saliva for five to seven days at 4°C, so using salivettes to collect samples away from the study site is appropriate (Vedhara et al., 2003). Cortisol is stable in centrifuged saliva and is unaffected by two freeze-thaw cycles (Lewis, 2006). A variety of factors may influence cortisol levels including menstrual phase. Menstrual phase was controlled for by matching women into two groups based on luteal or follicular phase, as determined by date of last menstrual period.

Salivary cortisol levels were determined using an Expanded Range High Sensitivity salivary cortisol Enzyme Immunoassay (EIA) kit (Salimetrics LLC) based on a competitive binding technique, according to the procedure described in the assay protocol. This protocol is summarized in Figure 3.1. Microtitre plates were read at 450 nanometers (nm) and with a Power Wave X plate reader spectrophotometer (Bio-tek Instruments Inc.) using KC4 software (version 2.7). The minimal concentration of cortisol that can be distinguished from 0 was reported as <0.003 ug/dL.

Percent suppression of cortisol following the DST was calculated using the formula [(Salivary cortisol level 30 minutes post-awakening Day 1) – (Salivary cortisol level 30 minutes post-awakening Day 2)] / (Salivary cortisol level 30 minutes post-awakening Day 1) x 100. Conventionally, nonsuppression is defined as post-DEX cortisol levels greater than 5.0 ug/dL; however, this value is used when measuring plasma cortisol and after a 1.0 mg dose of DEX. There is as yet no defined measure of hypersuppression in the literature, despite common use of the term in many studies. For this study, nonsuppression was defined as suppression less than 25%. Hypersuppression was defined as suppression greater than 75%. Any percent suppression between 25% and 75% was coded as 'normal' suppression.

Figure 3.1: Summary of Expanded Range High Sensitivity Salivary Cortisol EIA Protocol



3.3. Dexamethasone Measurement

To confirm that participants ingested the DEX tablet, a DEX Radioimmunoassay (RIA) was used and DEX levels were quantified. Saliva sample #5 (30 minutes post-DEX ingestion) was assayed to determine DEX levels. Before the start of the assay, all necessary solutions were prepared. Table 3.1 outlines the solutions required for the DEX assay.

Table 3.1: Solutions used in Dexamethasone Radioimmunossay

Solution	**Method**
0.01 mol/L Phosphate Buffered Saline (PBS)	8.00 grams (g) of NaCl, 0.20 g of KCl, 1.15 g of Na2HPO4 7H20 and 0.20 g of KH2PO4 was dissolved into 1000 millilitre (mL) of ultrapure water. This solution was mixed well
RIA Buffer	1.00 g of Bovine Serum Albumin (BSA) was added into 1 L of PBS buffer and mixed well
Antiserum	Rabbit anti-dexamethasone serum (IgG-DEX-1, IgG Corporation, TN) was used, diluted 200x with RIA buffer and stored in 75 microlitre (uL) aliquots at -80°C until use
(^{3}H)-DEX	A stock solution of tritium labeled DEX was made at a concentration of 0.005 microcurie per microlitre (uCi/uL) in RIA buffer. The amount needed for each assay was taken from this stock and diluted 200 times further in RIA buffer to a final concentration of 0.025 uCi/mL (a total dilution of 40 000 times from initial concentration)
DEX standards	A stock solution of 1 mg/mL DEX was prepared with 1 mg of DEX (powder, ≥97%, Sigma-Aldrich) in 1 mL of absolute methanol. Standards were prepared in RIA buffer at concentrations of 10 nanograms per milliliter (ng/mL), 5 ng/mL, 1ng/mL, 0.5 ng/mL, 0.1 ng/mL and 0.05 ng/mL
Dextran-Coated Charcoal (DCC)	50 mg of DCC was suspended in 20 mL of 0.01 moles per litre (mol/L) PBS. The solution was stirred for 30 minutes at 4°C before use to ensure suspension of DCC

PBS and RIA buffer were kept at 4°C for two weeks. DEX standards and DCC were remade on each new day of DEX RIA assay.

All samples and standards were run in triplicate. After thawing and vortexing the stored saliva samples, 4 mL of ethyl acetate was added to 100 uL of sample. Samples were shaken at 1000 rpm for 10 minutes. The tubes were then centrifuged at 3000 rpm for 10 minutes at 4°C. The top 3.8 mL of supernatant was removed and dried on the SpeedVac.

After drying, each sample was reconstituted with 200 uL of RIA buffer and vortexed well. 200 uL of antiserum and 200 uL of (^{3}H)-DEX was added to each tube, mixing well and incubating overnight at 4°C. The following morning, 0.5 mL of DCC suspension was added to each sample and standard and the tubes were incubated for 30 minutes at 4°C. The tubes were then centrifuged at 2000 g/minute for 10 minutes at 4°C.

The supernatant was transferred into counting vials and 10 mL of liquid scintillation fluid [CytoScint ES, MP Biomedicals (ICN)] was added to each vial. Vials were vortexed and counted on a liquid scintillation counter for 5 minutes (Beckman LS 6000 Scintillation Counter). The amount of DEX in the unknown samples was calculated by comparing the percentage of binding in the samples with the percentages of binding obtained from the known standards.

4. MENSTRUAL PHASE DETERMINATION

The date of start of last menstrual period and the length of usual menstrual cycle was collected by self report. This information was used to determine menstrual phase at time of saliva sample collection.

5. STATISTICAL METHODS

The Statistical Package for Social Sciences (SPSS) student version 17.0 was used to summarize the data and run the planned descriptive and inferential statistics (SPSS Inc., 2008). Initial descriptive analyses of the variables were performed with frequency, percentage and range used to summarize discrete data and median ± interquartile range to summarize continuous data. The Chi-squared procedure was used to compare groups on categorical data. The Mann-Whitney *U* and the Kruskal-Wallis procedures were used to make group comparisons on continuous variables.

The first objective was to compare scores on psychological measures of entrapment, mental defeat and perceived stress between women who experience IPV and women who experience other types of stressors. Group comparisons were made with the Mann-Whitney *U* test, the non-parametric analogue of the two-sample *t* test. When women were grouped by Axis I diagnosis, the Kruskal-Wallis test was used. This is a non-parametric analogue of the one-way ANOVA procedure. These non-parametric tests were used as the groups are small and do not meet assumptions of normality for parametric statistical procedures as assessed by the Two-Sample Kolmogorov-Smirnov test.

The second objective was to compare salivary cortisol levels at awakening and 30 minutes after awakening between women when grouped by experience or by stress-related psychiatric disorder. Group comparisons of salivary cortisol levels were made using the Mann-Whitney *U* test and the Kruskal-Wallis test.

The third objective was to compare percent suppression of cortisol after ingestion of dexamethasone between women grouped by experience or by stress-related psychiatric disorder. Group comparisons of percent suppression were made using the Mann-Whitney *U* test and the Kruskal-Wallis test.

The final objective was to examine the relationships between neuroendocrine measures of morning cortisol levels and percent suppression of cortisol, and psychological measures of entrapment, mental defeat and perceived stress. The analysis was completed using the Spearman's rank order correlation coefficient and the Chi-squared test.

6. ETHICAL CONSIDERATIONS

Experiences of IPV can put women at serious risk. Safety issues were addressed in this study by having the researcher complete the interview and self-report components of the study within the community agency where the women felt safe. Childcare was provided within Changing Together, when necessary. The preferred methods of contact were discussed with each woman. Women with significant depression or trauma related symptoms were provided with information about mental health resources and about community resources for physical health problems. Honoraria were paid for the women's time ($30.00 for interview and completion of questionnaire, in addition to funds to cover travel and parking expenses).

Written informed consent was obtained from the subjects prior to their participation in the study. Each woman was informed that they were free to

withdraw from the study at any time without consequence. Each woman was assigned a code number and confidentiality was strictly maintained. The consent forms and questionnaires were kept in a locked office of the project coordinator.

CHAPTER 4: ANALYSIS

1. DEMOGRAPHIC DATA AND SAMPLE CHARACTERISTICS

Sample characteristics for each group are summarized in Table 4.1. No statistically significant differences in age, body mass index, hormone status or use of oral contraceptives were noted between the groups.

In total, 33 women fit the inclusion criteria for the control group in this study. Women who were found to be pregnant or were currently taking medications known to affect the HPA axis were excluded from the study.

The control group in this study was unique relative to most other studies, as the women in this group would not be considered typical 'healthy controls'. All of the women were seeking support for a variety of stressors in their lives. These women were immigrants to Canada and faced many challenges including struggling with learning a new language, unemployment or underemployment, financial stressors, and isolation from family and friends back in their home country. Additionally, some women in this group had experienced severe stressors in their home countries. As such, some women in the control group suffered from stress related disorders such as MDD, PTSD, generalized anxiety disorder and social anxiety disorder and many either met criteria for comorbid stress related disorders or had subthreshold disorders.

The women in the IPV group faced similar challenges as the women in the control group in terms of their immigration to Canada; however, they had the added stressor of living with IPV. While some women in the IPV group were not

currently living with their abusive partner, their lives were controlled in many ways by their partner by interactions with shared children, immigration or visa issues, or financial dependency. In total, 30 women met the inclusion criteria for the IPV group.

The variety of experiences and of psychiatric history in both the IPV and the control groups resulted in a unique and diverse study sample. This allowed different strategies to be employed when grouping women for analysis. Primarily, analyses were carried out by grouping women into two groups based on their experiences (control or IPV). However, psychiatric diagnosis has a significant impact on the functioning of the HPA axis. Many women in both the control and the IPV group met criteria for MDD, PTSD, or other stress-related disorder. As such, two separate sets of analyses were completed. The first set grouped the women by their experiences: 1) control, n = 33, 2) IPV, n = 30. The second set grouped the women by diagnosis: 1) no MDD, no PTSD (-MDD/-PTSD, n = 34), 2) MDD only (+MDD/-PTSD, n = 8), 3) PTSD only (-MDD/+PTSD, n = 8), 4) comorbid MDD and PTSD (+MDD/+PTSD, n = 13).

Table 4.1 Summaries of Sample Characteristics

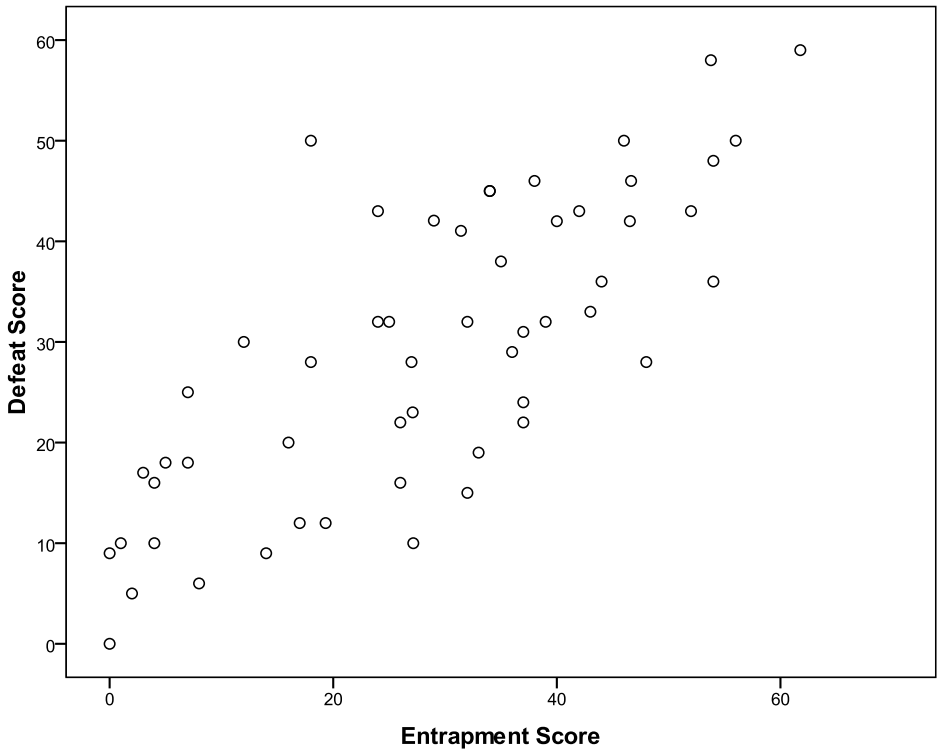
	Control (n=33)	IPV (n=30)	P value
Age (age ± S.D.)	37.3 + 8.1	37.5 + 8.3	0.700
Body Mass Index (mean ± S.D.)	25.8 +5.2	24.6 + 4.5	0.468
Menstrual Phase Status (for those women completing neuroendocrine measures, n = 36)			
Follicular	50.0% (8)	75.0% (15)	0.390
Luteal	31.3% (5)	10.0% (2)	
Unknown	6.3% (1)	5.0% (1)	
Menopausal	12.5% (2)	10.0% (2)	
Use of Oral Hormones			
None	78.8% (26)	93.3% (28)	0.299
Oral Contraceptive, HRT	18.2% (6)	6.7% (2)	
Unknown	3.0% (1)	0.0% (0)	
Groups by Diagnosis (MINI)			
-MDD/-PTSD	72.7% (24)	33.3% (10)	0.002
+MDD/-PTSD	15.2% (5)	10.0% (3)	
-MDD/+PTSD	6.1% (2)	20.0% (6)	
+MDD/+PTSD	6.1% (2)	36.7% (11)	
Other Psychiatric History (MINI)			
Generalized Anxiety Disorder	30.3% (10)	16.7% (5)	0.990
Agoraphobia	0.0% (0)	3.3% (1)	
Dysthymia	0.0% (0)	3.3% (1)	
Obsessive Compulsive Disorder	0.0% (0)	3.3% (1)	
Panic Disorder	0.0% (0)	10.0% (3)	
Social Anxiety Disorder	6.1% (2)	3.3% (1)	

2. ENTRAPMENT AND MENTAL DEFEAT

A total of 55 women completed the entrapment scale and 54 women completed the defeat scale. The Two-Sample Kolmogorov-Smirnov test was used

to assess normality and showed that the scores on both the entrapment and the defeat scales displayed non-normal distributions. Therefore, non-parametric tests were used to analyze the data. Correlation between scores on entrapment and scores on mental defeat are shown in Figure 4.1. There was a significant positive correlation between scores on the entrapment scale and scores on the defeat scale ($\rho = 0.771$, $p < 0.0001$).

Figure 4.1: Correlation between Entrapment Score and Defeat Score

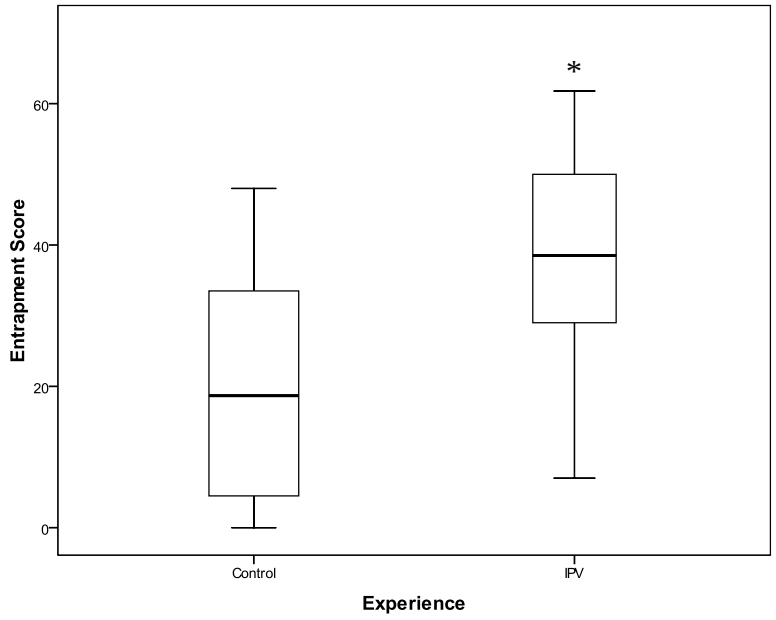


$\rho = 0.771$, $p < 0.0001$

2.1. EMD Scores Grouped by Experience

As seen in Figure 4.2, the IPV group (Md = 38.5, n = 26) had significantly higher entrapment scores than the control group (Md = 19.3, n = 29), revealed by the Mann-Whitney *U* test ($p < 0.0001$).

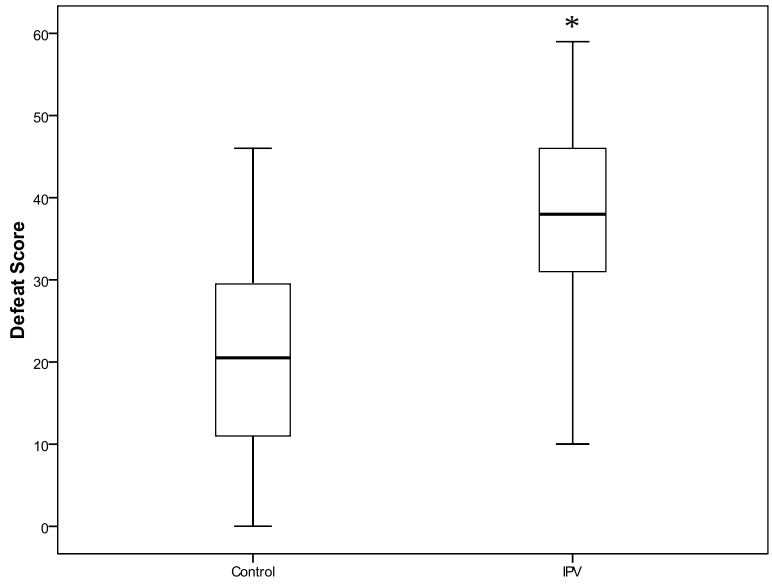
Figure 4.2: Entrapment Scores Grouped by Experience



*$p < 0.0001$

The Mann-Whitney *U* test also revealed significant differences in defeat scores of the control group (Md = 22.0, n = 29) and the IPV group (Md = 38, n = 25), $p < 0.0001$ as shown in Figure 4.3.

Figure 4.3: Defeat Scores Grouped by Experience



*p < 0.0001

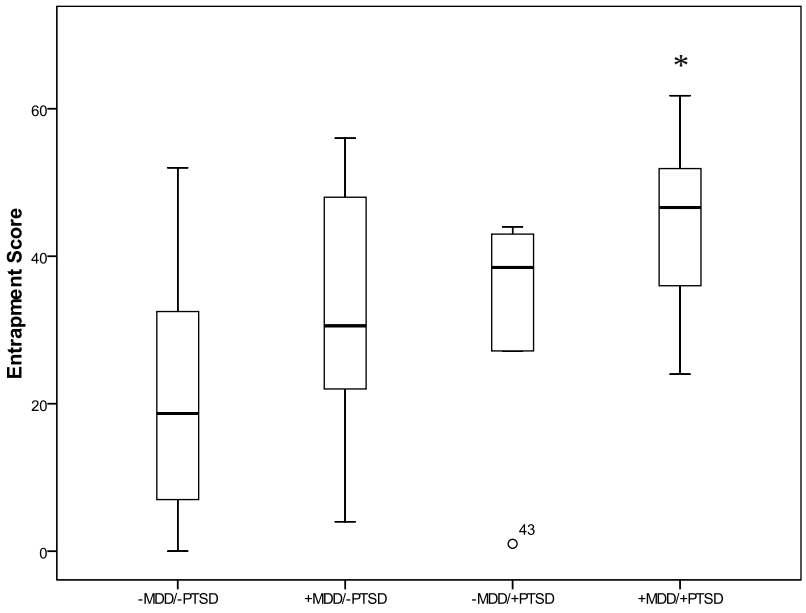
2.2. EMD Scores Grouped by Diagnosis

A Kruskal-Wallis test revealed a statistically significant difference for entrapment scores when the women were arranged by diagnostic group (-MDD/-PTSD, n = 29; +MDD/-PTSD, n = 8; -MDD/+PTSD, n = 6; +MDD/+PTSD, n = 12), $\chi 2$ (3, 55) = 16.496, p = 0.001. As seen in Figure 4.4, one woman had an entrapment score greater than 1.5 times the interquartile range below the median and is marked as an outlier. All of the outliers in the study were still included in the statistical analysis. The Mann-Whitney *U* test revealed significant differences in entrapment scores of the -MDD/-PTSD group (Md = 19.3) and the +MDD/+PTSD group (Md = 46.6), p < 0.0001.

One woman did not complete the defeat scale; therefore only 11 women were included in the +MDD/+PTSD group for this measure. With the Kruskal-

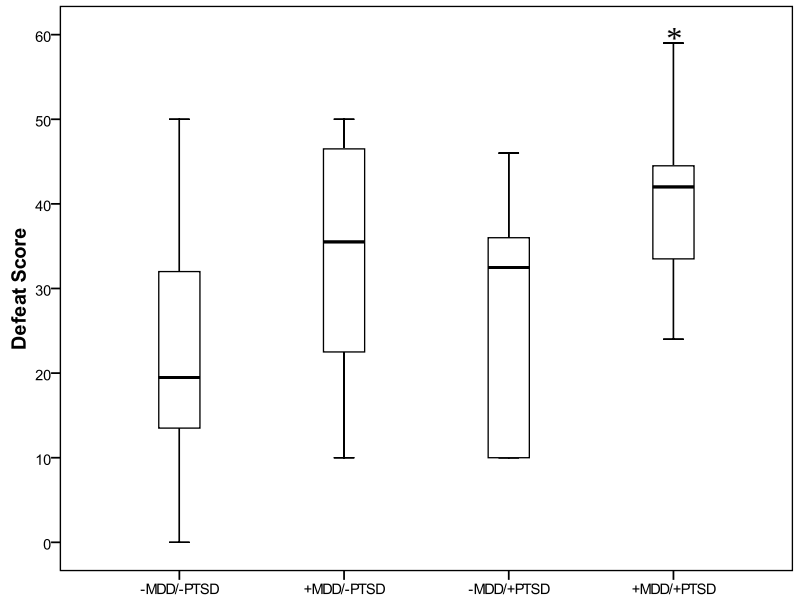
Wallis test, significant differences were found between the four groups on measures of defeat [$\chi 2$ (3, n = 54) = 10.194, p = 0.017]. This statistically significant difference was localized between the defeat scores of the -MDD/-PTSD group (Md = 20.0) and the +MDD/+PTSD group (Md = 42.0), p = 0.002, as seen in Figure 4.5.

Figure 4.4: Entrapment Scores Grouped by Diagnosis



*p = 0.001

Figure 4.5: Defeat Scores Grouped by Diagnosis



*p = 0.017

3. PERCEIVED STRESS SCALE

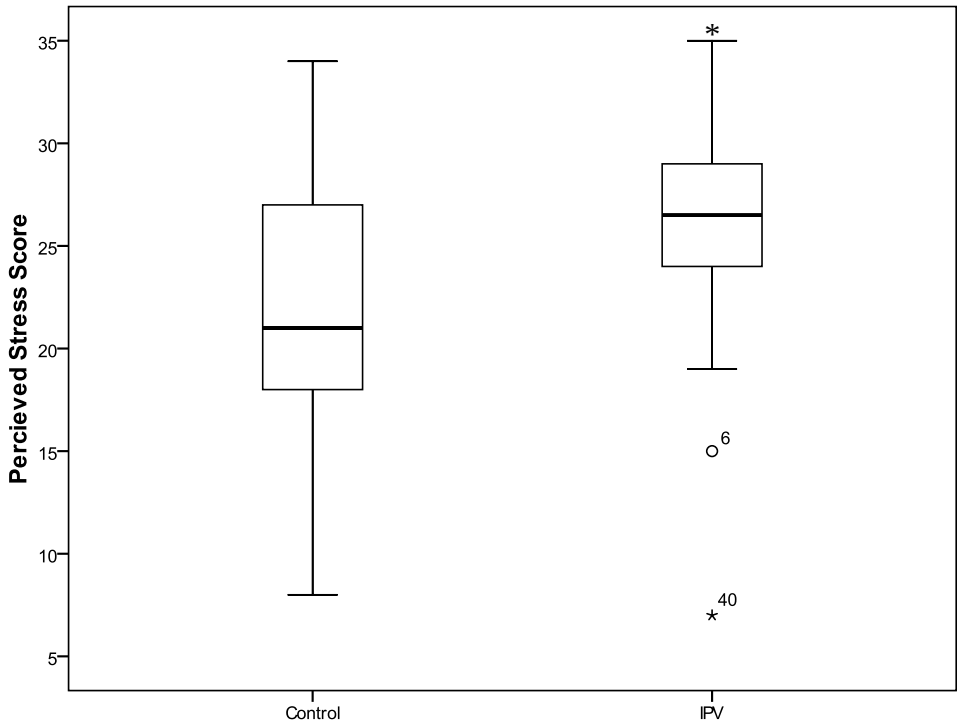
In total, 56 women completed the perceived stress scale. The Two-Sample Kolmogorov-Smirnov test showed that perceived stress scores were not normally distributed, so non-parametric statistical analyses were completed.

3.1. PSS Scores Grouped by Experience

The Mann-Whitney *U* test revealed significant differences in perceived stress scores of the control group (Md = 22.00, n = 30) and the IPV group (Md = 26.50, n = 26), p = 0.043. Perceived stress scores are summarized in Figure 4.6.

One woman in the IPV group is marked as an outlier and one is marked as an extreme outlier.

Figure 4.6: Perceived Stress Scores Grouped by Experience



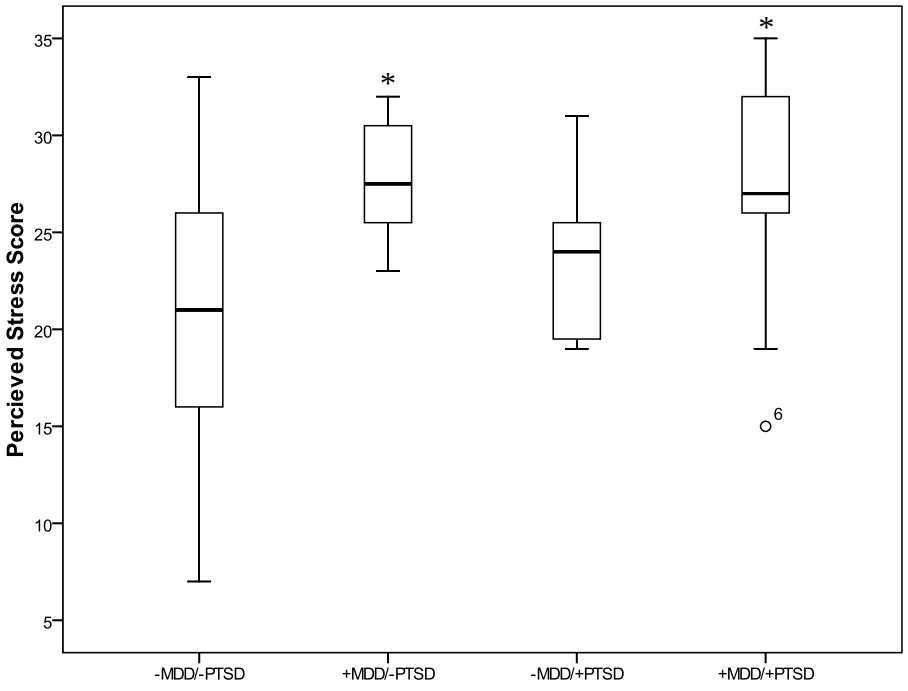
*p = 0.043

3.2. PSS Scores Grouped by Diagnosis

A Kruskal-Wallis test revealed a statistically significant difference in perceived stress scores across the four diagnostic groups (-MDD/-PTSD, n = 29; +MDD/-PTSD, n = 8; -MDD/+PTSD, n = 7; +MDD/+PTSD, n = 12), $\chi 2$ (3, 56) = 12.288, p = 0.006. Women with MDD had the highest median score (Md = 27.5)

of the four groups. Mann-Whitney U test revealed significant differences in perceived stress scores when women without MDD or PTSD (Md = 21.0, n = 29) were compared with women with MDD (Md = 27.5, n = 8,) and women with comorbid MDD and PTSD (Md = 27.0, n = 12), p = 0.006. One woman in the +MDD/+PTSD group had a score that was more than 1.5 times the interquartile range and is marked as an outlier in Figure 4.7.

Figure 4.7: Perceived Stress Scores Grouped by Diagnosis



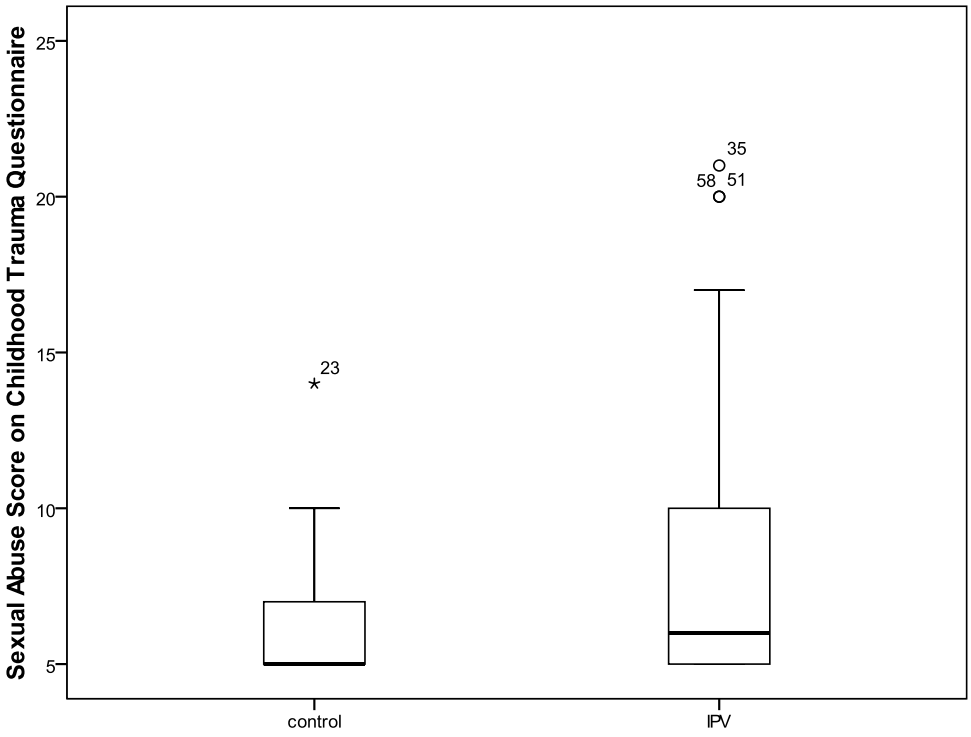
*p = 0.006

4. CHILDHOOD TRAUMA QUESTIONNAIRE

To screen for experiences of CSA, the five items on the CTQ relating to sexual abuse were used, as were disclosures during the study intake interview. In

total, twenty-two women (34.9%) disclosed histories of CSA. No significant differences were seen between the control and the IPV groups in reported CSA severity, although there was a trend towards increased severity in the IPV group, as seen in Figure 4.8.

Figure 4.8: Childhood Trauma Questionnaire Scores Grouped by Experience



p = 0.085

Responses on the CTQ were then converted into a yes/no dichotomous variable. Significant differences were seen between the IPV and the control groups on frequency of reported CSA, with 16 women in the IPV group disclosing CSA as compared to 7 in the control group (p = 0.038).

5. CORTISOL MEASUREMENTS

Cortisol levels were measured with a commercially available EIA kit (Salimetrics LLC). The interassay coefficient of variability for the high control was 1.16% and for the low control was 2.50%, which were within the acceptable variance as provided by the manufacturer (high control: 1.000 ± 0.251 µg/dL; low control: 0.100 ± 0.026 µg/dL). The range for the high control was 0.924 – 1.199 µg/dL and was 0.095 – 0.169 µg/dL for the low control. The commercially available assay was designed to capture the full range of salivary cortisol levels (0.003 -3.000 µg/dL) and nearly all of the samples in this study fell within that range. After the DST, two women had cortisol levels below the level of detection. The cortisol curve was graphed with a 4-parameter sigmoid minus curve fit according to the commercial software program attached to the spectrophotometer (KC4, version 2.7).

Only a subset of women (57%) completed the DST and provided saliva samples for analysis. Of those women that provided neuroendocrine data, two women were excluded from the analysis because they only provided a partial set of saliva samples and therefore circadian pattern and percent suppression were not able to be determined. In total, 36 women were included in the analysis of salivary cortisol and percent suppression, 20 in the IPV group and 16 in the control group.

Through Kruskal-Wallace and Chi-Square tests, no statistically significant differences in awakening cortisol levels, 30 minute post-awakening cortisol levels or percent suppression of cortisol after the DST were found when women were

grouped by menstrual phase status or use of oral hormones. However, the lack of significant difference may reflect small sample sizes in some of the groupings. Previous studies have found that basal cortisol levels do not differ significantly in the follicular and luteal phases of the menstrual cycle (Altemus et al., 1997). Although significant differences have been reported between percent suppression of cortisol after the DST in these phases (Altemus et al., 1997), in the current study, the majority of women had percent suppression far exceeding 50% (see Chapter 4, Section 6).

5.1. Circadian Rhythm

Circadian rhythm of cortisol was analyzed using the first three salivary collection time points: (1) awakening, (2) 30 minutes post awakening, and (3) 60 minutes post awakening. The four-hour time point was not included as many women had a cortisol peak at this time point, which may reflect a stressor that occurred on the day of saliva collection, rather than a shifted circadian pattern. The circadian pattern was defined as normal if the cortisol peak was at 30 minutes. The pattern was defined as flattened if there was less than a 30% change in cortisol levels between the three time points. The pattern was defined as shifted if the cortisol peak was at awakening or at 60 minutes, rather than the expected peak at 30 minutes post-awakening. Figures 4.9, 4.10 and 4.11 show the cortisol patterns of three women in the study, reflecting these three rhythms. No differences were found between the IPV and the control groups in the pattern of cortisol ($p = 0.900$). This data is summarized in Table 4.2.

The flattened and shifted peak groups were then collapsed to one group and coded as 'altered pattern' to compare normal vs. altered cortisol patterns as shown in Table 4.3. Using the Mann-Whitney *U* test, no statistically significant differences were seen between the normal cortisol pattern group and the abnormal cortisol pattern group (p = 0.749)

Figure 4.9: Normal Cortisol Pattern

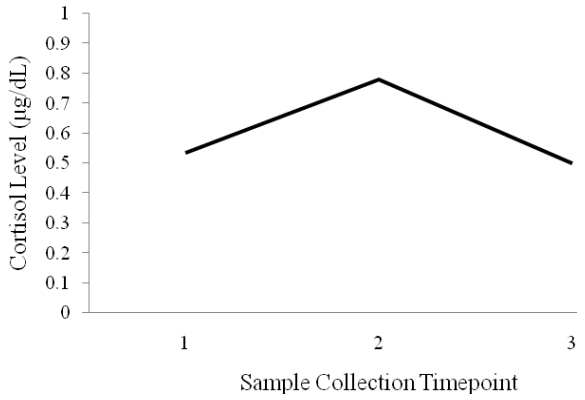


Figure 4.10: Flattened Cortisol Pattern

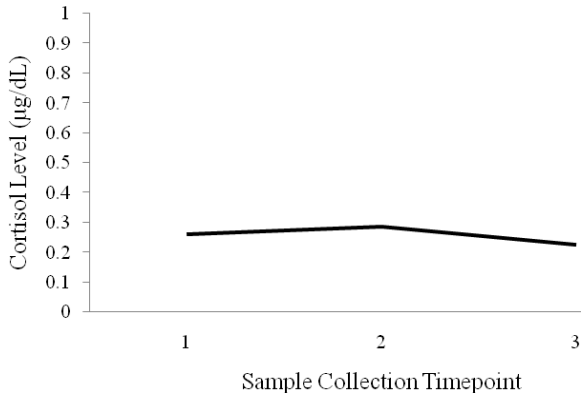


Figure 4.11: Shifted Cortisol Pattern

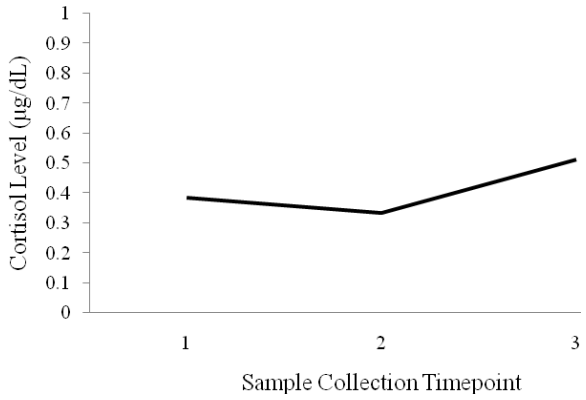


Table 4.2: Cortisol Pattern in Three Groups

	Control (n = 16)	IPV (n = 20)
Normal	56.3% (9)	50.0% (10)
Flattened	6.3% (1)	5.0% (1)
Shifted Peak	37.5% (6)	45.0% (9)

Table 4.3: Cortisol Pattern in Two Groups

	Control (n = 16)	IPV (n = 20)
Normal	56.3% (9)	50.0% (10)
Altered	43.8% (7)	50.0% (10)

5.2 Basal Cortisol Grouped by Experience

With the Mann-Whitney *U* test, there were no statistically significant differences in awakening cortisol values between the control group (Md = 0.335 µg/dL, n = 16) and the IPV group (Md = 0.368 µg/dL, n = 20), p = 0.504. Likewise, no significant differences in cortisol levels 30 minutes post-awakening were found between the two groups (control group: Md = 0.365, IPV group: Md = 0.444), p = 0.975. These data are shown in Figures 4.12 and 4.13.

Figure 4.12: Awakening Salivary Cortisol Levels Grouped by Experience

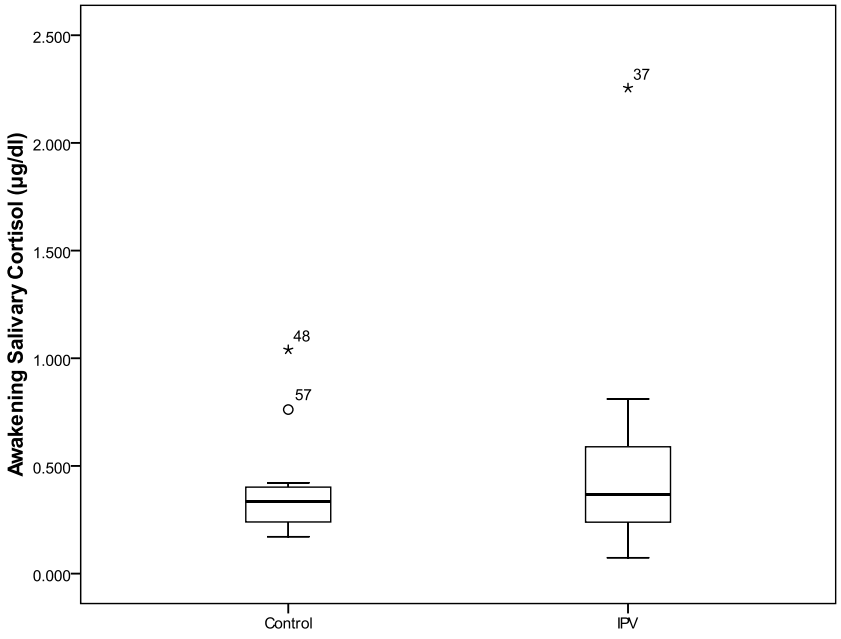
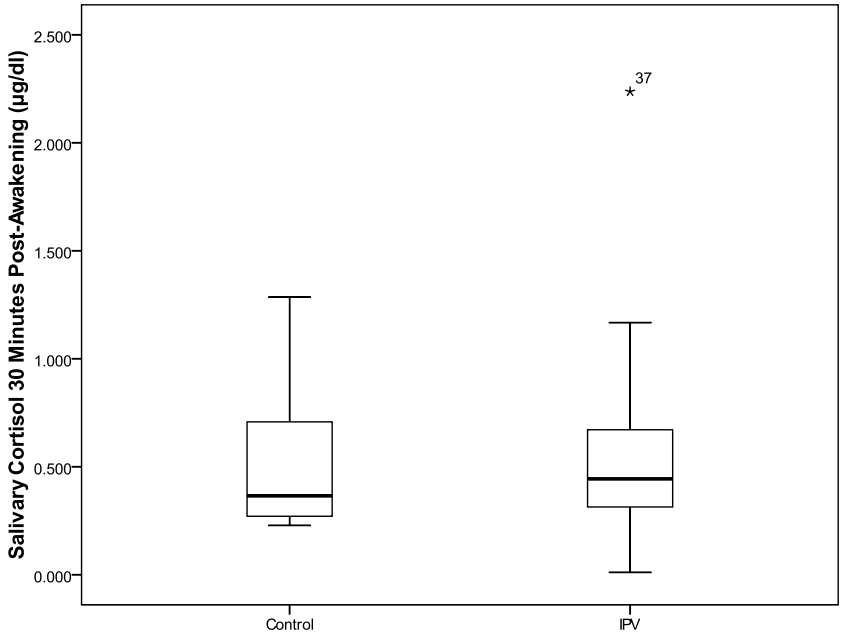


Figure 4.13: 30 Minutes Post-Awakening Salivary Cortisol Levels Grouped by Experience



5.3. Basal Cortisol Grouped by Diagnosis

When the women were arranged by diagnosis, no statistical differences were identified in awakening salivary cortisol values [$\chi 2$ (3, 36) = 4.376, p = 0.224]. Additionally, no differences were found between the groups at the 30 minutes post-awakening time point [$\chi 2$ (3, 36) = 4.478, p = 0.214]. These data are summarized in Figures 4.14 and 4.15.

Figure 4.14: Awakening Salivary Cortisol Levels Grouped by Diagnosis

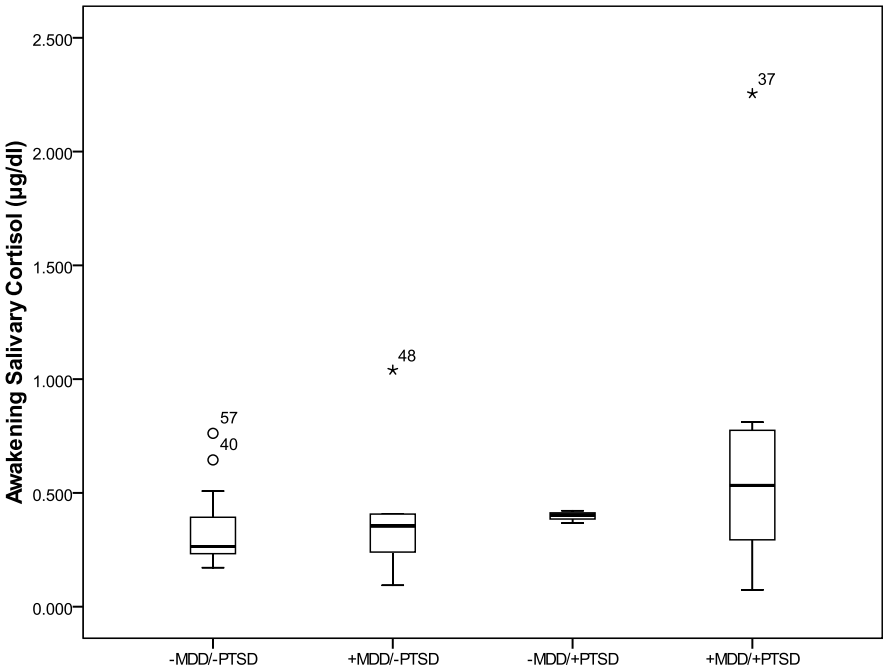
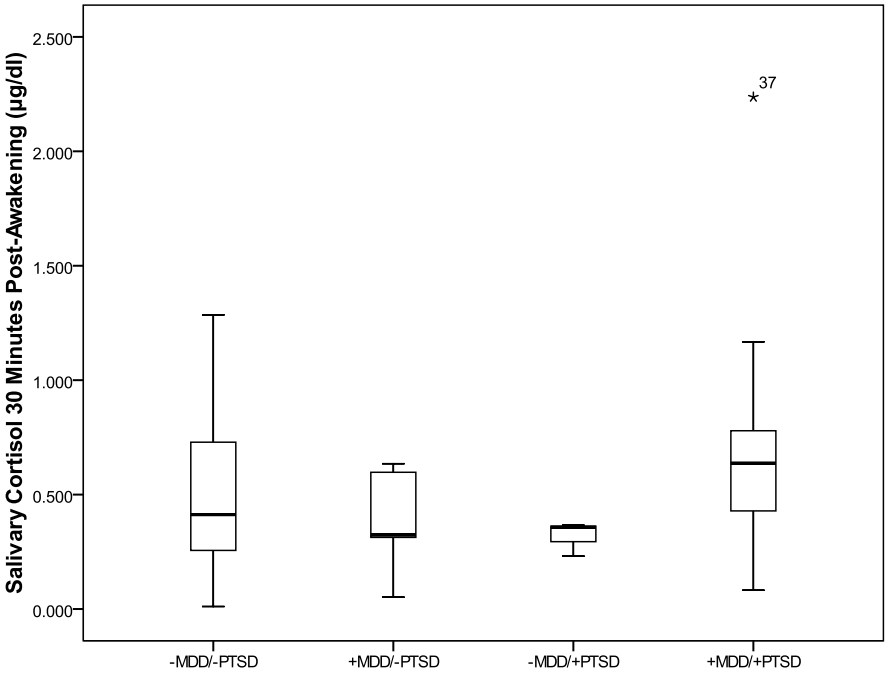


Figure 4.15: 30 Minutes Post-Awakening Salivary Cortisol Levels Grouped by Diagnosis



6. DEXAMETHASONE MEASUREMENTS

DEX levels were measured in saliva 30 minutes after ingestion of DEX. This was done by adapting the Dexamethasone Radioimmunoassay Protocol with IgG-DEX-1 from the IgG Corporation. The assay analyses of DEX concentrations were used to confirm that DEX was ingested. As a secondary goal, DEX levels were quantified to see if the levels in saliva had an effect on the degree of cortisol suppression. In total, DEX levels of 15 women in the control group and 18 women in the IPV group were quantified and included in the final analysis. Two women in the IPV group and one woman in the control group had DEX levels that were too high to quantify and were excluded from further analysis. None of the woman had levels that were below the limit of detection. With the Mann-Whitney *U* test, no statistically significant differences in DEX levels were found between the IPV and the control group ($p = 0.329$) or when women were grouped by diagnosis ($p = 0.606$) as seen in Figures 4.16 and 4.17.

To calculate the interassay coefficients of variability, 5.0 ng/mL was used for the high control and 0.5 ng/mL was used for the low control. These values fall on the linear range of the DEX curve. The interassay coefficient of variability for the high control is 17.39% and for the low control is 11.76%. The intraassay coefficient of variability for the high control is 1.27% and for the low control is 3.02%. The range for the high control is 2.98 – 8.42 ng/mL and is 0.350 – 0.547 ng/mL for the low control. The range of the assay was 0.05 ng/mL – 10 ng/mL. Of the 36 women who completed saliva samples, 7 fell outside of this linear range and 3 were far too high to quantify. The DEX curve was graphed with a 4-

parameter sigmoid minus curve fit using Prism Statistics, Version 4.0 (GraphPad Software Inc.).

Figure 4.16: Dexamethasone Levels Grouped by Experience

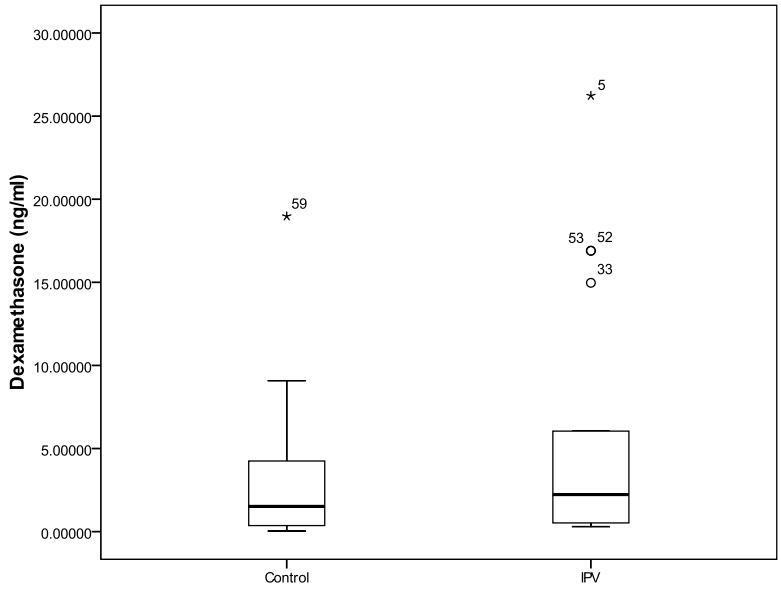
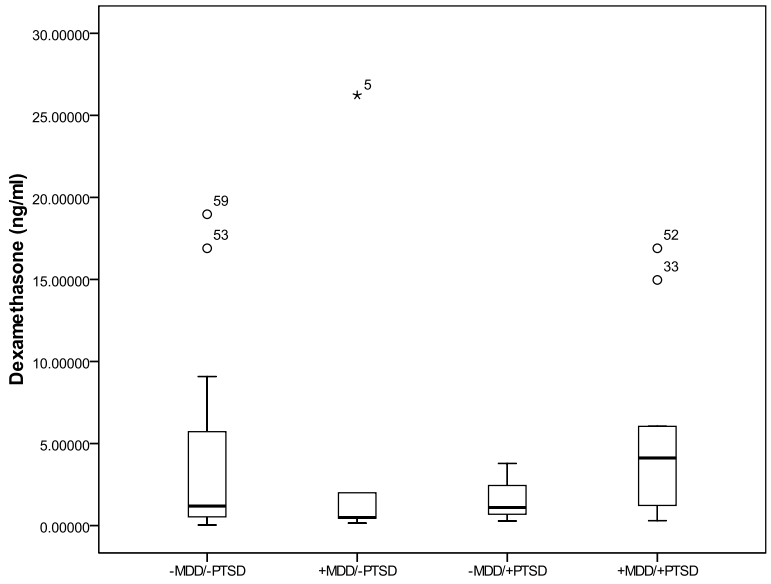


Figure 4.17: Dexamethasone Levels Grouped by Diagnosis



7. PERCENT SUPPRESSION OF CORTISOL FOLLOWING THE DST

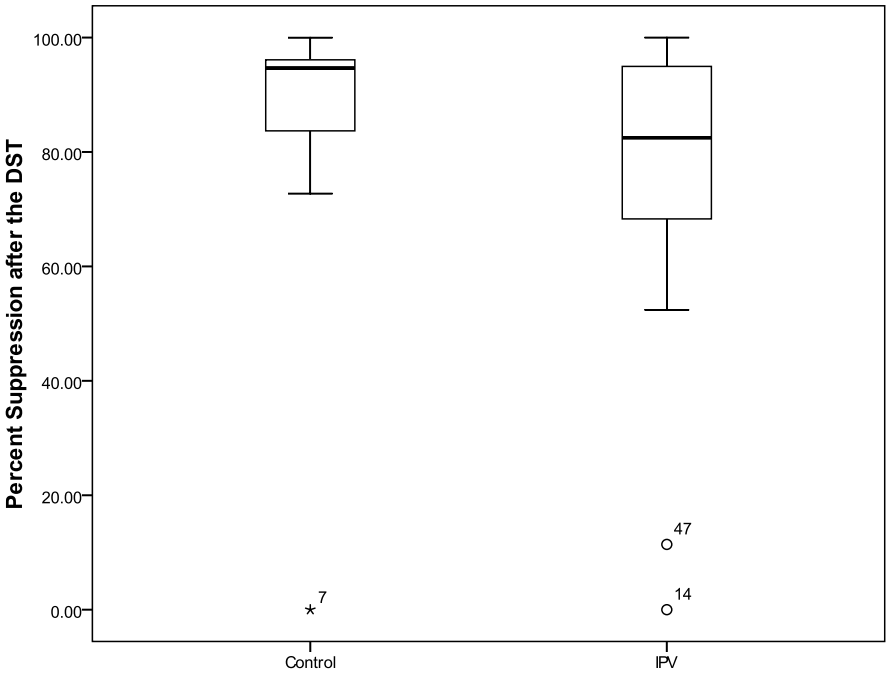
Women took 0.5 mg of DEX at 2200 hours on Day 1. Percent suppression was calculated by comparing salivary cortisol levels 30 minutes post-awakening on Day 1 with levels 30 minutes post-awakening on Day 2. Percent suppression was calculated for 16 women in the control group and for 20 women in the IPV group. Unexpectedly, almost all women in the study showed enhanced suppression, regardless of experience or diagnostic group. Two women had a Day 2 30 minutes post-awakening sample with cortisol below the level of detection and as such were 100% suppressed. Two women had 30 minutes post-awakening values of cortisol higher on Day 2 than on Day 1, leading to percent suppression of -40.2% and -900.0%. In the analysis, these women were coded as 0.0% suppressed.

Table 4.4: Patterns of Suppression Grouped by Experience

	Control (n = 16)	IPV (n = 20)
Nonsuppression	6.3% (1)	10.0% (2)
Normal suppression	0.0% (0)	10.0% (2)
Hypersuppression	93.8% (15)	80.0% (16)

There are no significant differences between the groups based on percent suppression [$\chi 2$ (2, 36) = 1.945, p = 0.378]. The data is summarized in Table 4.4 and Figure 4.18.

Figure 4.18: Percent Suppression Grouped by Experience

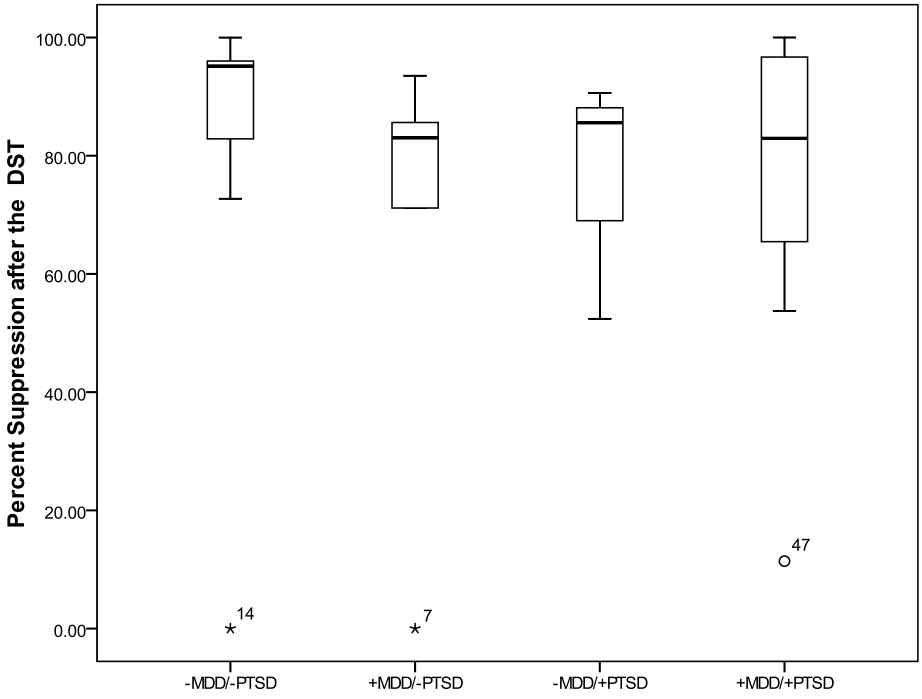


Additionally, there are no significant differences in percent suppression between the groups based on psychiatric diagnosis [$\chi 2$ (6, 36) = 7.355, p = 0.289]. These data are summarized in Table 4.5 and Figure 4.19.

Table 4.5: Patterns of Suppression Grouped by Diagnosis

	-MDD/-PTSD (n = 18)	+MDD/-PTSD (n = 6)	-MDD/+PTSD (n = 3)	+MDD/+PTSD (n = 9)
Nonsuppression	1	1	0	1
Normal suppression	0	0	1	1
Hypersuppression	17	5	2	7

Figure 4.19: Percent Suppression Grouped by Diagnosis



8. INTEGRATION OF PSYCHOLOGICAL AND NEUROENDOCRINE DATA

It is difficult to find correlations between the sets of neuroendocrine and psychological data. Correlations were determined using the non-parametric Spearman's rank order correlation coefficient. As nearly all women showed enhanced suppression of cortisol following the DST, a ceiling effect occurred and no relationships were evident between percent suppression and cortisol levels at awakening; DEX level 30 minutes after DEX ingestion; scores on entrapment and mental defeat scale; and scores on the perceived stress scale (see Table 4.6). Additionally, no significant relationships were found between cortisol levels at awakening with entrapment, mental defeat or perceived stress scores (see Table 4.7).

Table 4.6: Correlations between Percent Suppression and Neuroendocrine and Psychological Data

		Awakening Cortisol Levels	DEX Levels	Entrapment Score	Defeat Score	Perceived Stress Score
Percent Suppression	ρ	-0.178	0.093	-0.204	-0.121	-0.175
	p	0.300	0.605	0.289	0.533	0.365

Table 4.7: Correlations between Salivary Cortisol Levels at Awakening and Psychological Data

		Entrapment Score	Defeat Score	Perceived Stress Score
Salivary Cortisol Levels at Awakening	ρ	0.141	0.164	0.183
	p	0.467	0.396	0.341

CHAPTER 5: DISCUSSION

1. DEMOGRAPHIC DATA AND SAMPLE CHARACTERISTICS

All women were recruited from Changing Together: A Centre for Immigrant Women, between May 2005 and June 2009. While a total of 86 women were recruited and interviewed for this study, only 63 were included in the final analysis. Some women did not fully complete the psychological data or provide saliva samples for analysis. Where possible, women were contacted to obtain missing data; however, due to the long recruitment duration and sensitive subject nature of this study; some women were lost to follow-up. Women that did not complete the psychological questionnaires and the DST were not included in the final analysis. In efforts to maintain as large a dataset as possible, women that provided data for at least one of the psychological questionnaires or provided saliva samples remained in the analysis, and were excluded on a test-by-test basis for the missing data. One woman withdrew from the study and was excluded from data analysis.

As described in the literature review, experiences of IPV can lead to a number of physical and mental health sequelae. Recent studies have indicated that women who experience IPV report significantly more mental health problems (Coker et al., 2002; Klymchuk, Cooper, & Pacey, 2002; Kramer, Lorenzon, & Mueller, 2004; Pottie Bunge, 2002). This finding was supported in the current study and as seen in Table 4.1, there was a significant difference between women in the control and the IPV group on measures of MDD and PTSD. Surprisingly,

there were no significant differences in other psychiatric history, with 11 women in each group living with another stress related Axis I disorder, as identified by the MINI. The women in this study were not a homogenous group, which allowed for definition of two unique groups for analysis. One analysis arranged women into groups based on their experiences of partner abuse (control group and IPV group), and the other by arranging women based on psychiatric diagnosis (-MDD/-PTSD, +MDD/-PTSD, -MDD/+PTSD, +MDD/+PTSD). All women recruited for this study are immigrants to Canada, increasing the diversity of the groups. While all of the women in this study have the shared experience of being immigrants, each woman also had her own unique background, challenges and reasons for immigrating, all of which could contribute to current measures of entrapment and mental defeat, perceived stress or neuroendocrine dysregulation. However, EMD and perceived stress scores appeared to be more sensitive to the specific psychosocial impact of IPV.

The diversity of experiences for women in both the control and the IPV group before their immigration was considerable. Some women spoke about stressors of living through natural disasters including hurricanes, earthquakes, floods and tsunamis. Others discussed the social or political unrest in their countries, and had either witnessed or personally experienced threats of violence, particularly in countries where drug wars were salient. Some women spoke of their experiences living in war zones, refugee camps or under threats of terrorism. These women witnessed daily violence or intense human suffering with

experiences of having family, close friends, or community members murdered or missing.

Certainly not all of the women in this study immigrated to Canada after experiencing such profound events. Even so, the process of immigration itself can be a difficult and traumatic experience. Many women have left behind their community and extended family support networks and face challenges of acculturation, discrimination, and language barriers. Some women came to Canada drawn by economic opportunities but many face the current stress of unemployment or underemployment and still support their families back home. Many women spoke of stressors including feeling socially isolated, burdened by care of their children and the stress of caring for older relatives.

Immigrant women who have the added burden of living in the context of IPV may face unique challenges that can include cultural beliefs and practices that may provide rationalizations used to excuse or deny the existence of IPV in their communities. Woman abuse or IPV is not defined as a crime in many communities. Some cultures have beliefs, norms and social institutions that can legitimize and therefore perpetuate violence against women (Heise, Ellsberg, & Gottemoeller, 1999). Abusers of immigrant women often use immigration-related threats to assert power and control over their partners. Immigrant women experiencing IPV may be hesitant to seek help from community agencies or official institutions based on real or expected negative experiences with similar institutions in their home country or within Canada. Help-seeking may be inhibited by institutional barriers such as location, professional background of the

staff, ethnicity and language skills of the staff and confidentiality concerns. Ultimately, cultural, economic, practical and legal barriers exist in help-seeking for immigrant women. Despite these complex stressors shared by all the women in this study, it was hypothesized that IPV constituted a unique, chronic, serious stressor and this would be reflected in differences on psychosocial and neuroendocrine measures.

2. PSYCHOLOGICAL MEASURES

2.1. Entrapment and Mental Defeat

Gilbert and Allen used the term entrapment and mental defeat for behaviours in humans that are analogous to learned helplessness in animals (Gilbert & Allan, 1998). They suggested that MDD may be a state of felt entrapment, which results in learned helplessness, which they term "defeat" (Gilbert, Gilbert, & Irons, 2004; Gilbert, Allan, Brough, Melley, & Miles, 2002). While this tool has been used in other populations, to the best of our knowledge, it has not yet been used in relation to immigrant women or women experiencing IPV. Significant differences between the groups were found on measures of EMD, which can be expected as isolation and entrapment are characteristic of partner violence. Statistically significant differences were found between the control and the IPV group on measures of both entrapment and mental defeat, though slightly higher EMD scores were seen in the control group than has been reported in other community-based 'healthy control' populations. For example, in a study of measures of EMD using a healthy control population of college

students, the mean entrapment score was 14.7 and the mean defeat score was 17.2, lower than the control group in the current study, which had entrapment scores of 19.3 and defeat scores of 22.0 (Gilbert & Allen, 1998).

When grouped by diagnosis, women experiencing MDD did not have scores of entrapment or mental defeat that were significantly higher than the groups without MDD; however, significant differences in both entrapment and mental defeat were uncovered between the -MDD/-PTSD and +MDD/+PTSD group. In this population, the added burden of PTSD in the +MDD/+PTSD group contributed to a significant difference in EMD scores. It may be that the sample sizes of these groups were not large enough to detect these differences with adequate power. As seen in Figure 4.4, there was one outlier in the -MDD/+PTSD group, with an entrapment score of 1. While this woman has PTSD, this diagnosis is unrelated to experiences of IPV, as she is in the control group. While she is experiencing other extreme stressors, her score may be low in entrapment because she is not experiencing the unique stress of IPV.

Using EMD measures as an analogue in humans to learned helplessness in animal models, our findings suggest that experiences of IPV significantly contribute to feelings of learned helplessness. Women living in the context of IPV do not have control in their relationship and live under constant threat of unpredictable violence. Findings of significantly higher entrapment and mental defeat scores in the IPV group indicate that perceived lack of control contributes to the chronic stress of IPV and suggests that IPV is different in nature from other stressors.

EMD measures may be a useful tool to understand the unique stress that IPV contributes and may better characterize the experiences of women living in the context of IPV and to better address the needs of women who are experiencing violence.

2.2. Perceived Stress

As seen in Figure 4.6, measures of perceived stress were also able to discriminate between the control and the IPV group. When grouped by experience, two outliers were found. One woman in the IPV group had a score that was greater than 1.5 times the interquartile range below the lower quartile. This woman had comorbid MDD and PTSD. She also had a comorbid diagnosis of panic disorder. It is unknown why her score is so low on this scale, though it may reflect part of an adaptive coping mechanism of minimizing or denying perceived stress. While measures were not included in this study, she may have had an exceptional support system or other factors that support resiliency and lead to this lowered score. Another woman was an extreme outlier on the measure of perceived stress. This woman (40) did not have any psychiatric diagnoses, although she was experiencing the stress of IPV; the low score in perceived stress may be reflective of the lack of burden from psychiatric diagnoses, unlike many other women in this group.

When grouped by diagnosis, statistically significant differences were seen between women without MDD or PTSD and women with MDD, or with

comorbid MDD and PTSD. As MDD has been considered a stress disorder, this result is expected, with perceived stress increasing with the added burden of MDD or comorbid MDD and PTSD. The outlier from the IPV group seen in Figure 4.6 is also seen as an outlier in Figure 4.7 in the +MDD/+PTSD group. The mean PSS score reported in a study of women in a community sample was 25.6 (Cohen, Kamarack & Mermelstein, 1983). In the current study, women in the control group and the -MDD/-PTSD group had scores on the PSS comparable to other community samples (22.0 and 21.0 respectively). These results indicate that the stress of IPV contributes a significant difference to perceived stress measures and may be used clinically to assess the unique impact of the stress of IPV as opposed to other stressors.

3. CORTISOL

Despite the significance of IPV as a serious public health issue, neuroendocrine studies of this severe stress in a gender-specific manner are scarce (Griffin, Resick, & Yehuda, 2005). This study therefore contributes to the growing number of neuroendocrine studies on women experiencing violence. Only 36 (57%) women completed the DST and provided saliva samples for cortisol analysis. While the questionnaires were completed at Changing Together: A Centre for Immigrant Women, the saliva collection was completed at home. Cortisol levels increase with stress, so ideally sample collection done at home should be less stressful or stress free. For many people, sampling in a naturalistic environment increases compliance and ease of testing; however, for

this vulnerable population of women, it may not have been safe to complete this test at home. This may have contributed in part to the smaller sample size for the neuroendocrine data. Additionally, some women had fear of the health impact of ingesting DEX. While the DST was fully explained to all women, lingering concerns may have inhibited some women from participating in this part of the study. Overall, the feasibility of using an at-home self-administered DST was confirmed and it represented a novel method to obtain neuroendocrine data in a convenient and lower stress manner.

3.1. Circadian Rhythm

Cortisol levels at the first 3 time points for all of the women in this study were graphed and analyzed to determine cortisol pattern and peak. Peak concentrations of cortisol occur approximately 30 minutes after awakening and curves that followed this pattern were defined as "normal cortisol pattern" (see Figure 4.9) (Edwards, Evans, Hucklebridge, & Clow, 2001). Initially, all 4 time points (awakening, 30 minutes post-awakening, 1 hour post awakening, and 4 hours post awakening) were to be used. However, many women had a cortisol peak at 4 hours, rather than the typical consistent decline seen over the afternoon and evening. As all women in this study were experiencing stress from immigration related issues, and half of the women in this study were experiencing stress from IPV, this late cortisol peak may have been a result of an acute stressor impacting the HPA axis, and not a shifted cortisol circadian pattern. As such, only the first three time points were used to determine cortisol rhythm. No

significant differences were found in cortisol patterns between the control and the IPV groups, with about half of the women showing a shifted cortisol peak. Previous studies of women with MDD have demonstrated similar changes in the pattern of cortisol secretion (Peeters, Nicolson, & Berkhof, 2004). Studies of basal cortisol levels in individuals with PTSD had equivocal results (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Yehuda, 2006). Interestingly, many women in this study had an altered cortisol pattern, independent of psychiatric diagnosis. The sample size was too small to further analyze whether the cortisol peak was shifted earlier, or later.

3.2. Basal Cortisol Levels

In addition to providing information about the functioning of the HPA axis, basal cortisol levels may help differentiate among stress and illness. The current study found no differences in levels of awakening or 30 minute post-awakening salivary cortisol between women experiencing IPV and those experiencing other types of stressors, not interpersonal in nature. Additionally, while slightly elevated, the medians for both groups are within normal range of expected cortisol levels. Three women had outlying values of awakening salivary cortisol levels, as seen in Figure 4.12. The woman in the IPV group (37) had comorbid MDD and PTSD, as well as generalized anxiety disorder. In the control group, the extreme outlier (48) also has MDD, which may have contributed to the increased basal cortisol levels at awakening. Neuroendocrine studies of people with MDD indicate that approximately 50% of people with MDD show elevated

basal cortisol levels, so this may be a contributing factor (Claes, 2004; Steckler, Holsboer, & Reul, 1999; Peeters et al., 2004). Interestingly, the other outlier (57) did not have any Axis I disorders, however, had reported experiences of spousal violence, though not meeting the criteria for IPV. It may be that living in the context of milder intimate partner stress or situational couple violence is a stressor which causes elevated cortisol release.

Additionally, no differences in basal salivary cortisol levels were seen when women were grouped by psychiatric diagnosis (see Figures 4.14 and 4.15). This is contrary to other studies that have seen elevated basal plasma cortisol levels in clinical patients with MDD though these studies are not specific to women (Gibbons & McHugh, 1962; Claes, 2004; Steckler, Holsboer, & Reul, 1999). Other studies have not shown this hypersecretion of cortisol in MDD when studying outpatient or community populations (Peeters et al., 2004). This may be a more relevant comparison population for the current study than research using clinical populations. Previous studies have demonstrated basal cortisol hyposecretion in individuals with PTSD, however many of these studies are not gender-specific and involve populations of Vietnam veterans who have been suffering with PTSD for many years (Yehuda et al., 1993; Heim et al., 2001). Not all studies have demonstrated hypocortisolism in PTSD (Orr et al., 1995), as was the case in the current study.

A further contributor to the results was the sample size for each of the diagnostic groupings, which may have been too small to reliably identify differences. While 18 women were in the -MDD/-PTSD group, only 9 had

comorbid MDD and PTSD, 6 had MDD only, and just 3 had a sole diagnosis of PTSD. While not statistically significant, the +MDD/+PTSD group had a higher median score than the other groups in both awakening salivary cortisol levels and in salivary cortisol levels at 30 minutes post-awakening. Again, outliers were seen when dividing groups by diagnosis. The woman labeled as 37 in Figure 4.14 remained an extreme outlier in Figure 4.15. Again, this may be due to the added burden of many comorbid Axis I disorders. This woman also scored quite high on EMD measures. She was also the only outlier on cortisol levels at 30 minutes post-awakening (see Figure 4.15). The other extreme outlier in awakening salivary cortisol levels was the woman coded as 48 in Figure 4.14. She also had a comorbid Axis I disorder, which may have contributed to this elevated level. Also seen in Figure 4.14, there were two outliers in the -MDD/-PTSD group in awakening salivary cortisol. The woman coded as 57 was also an outlier when grouped by experience and is discussed above. The other outlier (40) had experienced IPV and disclosed sexual abuse, physical abuse and spousal violence. While she did not have any Axis I disorders and had relatively low scores on perceived stress measures and entrapment and mental defeat, her experiences of violence may have contributed to the elevated cortisol levels.

These findings contribute to the growing body of literature around basal cortisol levels and chronic stress in women; although current published literature is equivocal and further clarifications of the neuroendocrine differences between psychiatric diagnostic groups are needed. As cortisol samples were taken during the period of one day, the results may not be indicative of typical cortisol patterns

for these women. Additionally, these data fail to take into account the salient environmental stressors that may have been occurring for these women on the day of sampling, which may impact cortisol levels.

These results challenge the validity of comparing community samples to clinical or inpatient psychiatric populations. As all women in this study were within a normal neuroendocrine range of cortisol levels, it may be that basal salivary cortisol measures are not a sensitive benchmark of neuroendocrine dysregulation in community samples of women, and that measures following a neuroendocrine challenge may be more appropriate. The sensitivity of the HPA axis glucocorticoid feedback system may be a better indicator of neuroendocrine responses to stress than basal cortisol concentrations (Kalin et al., 1981). As such, the DST was used to further explore regulation of the HPA axis in this population of stressed women.

4. DEXAMETHASONE

Hormone challenge tests provoke biological systems under controlled conditions, which allows for assessment of the responsiveness of those systems. For the DST, a low dose of 0.5 mg of DEX was used in order to avoid a ceiling effect in cortisol suppression. This was based upon previous research suggesting that in individuals with PTSD, hypersuppression of cortisol may be expected (Griffin, Resick, & Yehuda, 2005; Yehuda et al., 1993).

As the DST was completed with a novel take-home kit, the primary goal of quantifying DEX with an RIA was to confirm that the women ingested it. The

RIA in this study was adapted from a method from the IgG Corporation. The original assay was designed to measure plasma DEX using ^{3}H-DEX as a tracer. This assay was modified for salivary DEX by increasing the incubation times with the first and second antibodies. As levels of DEX in saliva are approximately 5-10% of those in plasma, by increasing the incubation period, the amount of time available for the antibody-antigen complex to form is optimized (Gillson & Zava, 2002). Using this novel method, DEX levels were analyzed to confirm that the women in the study ingested the DEX from their take-home DST kit. Of the 36 women that provided saliva samples, DEX was quantified for 33 women, as three people had DEX levels that were too high to measure even after repeated attempts at dilution. For these three women, something else may be masking the DEX signal. As such, it is not possible to be completely certain that they took the DEX; however, all three of these women had rates of cortisol suppression greater than 80%, reflecting a strong likelihood that they had indeed ingested DEX the night before.

As expected, there were no differences between levels of DEX 30 minutes after DEX ingestion when women were grouped by experience or by diagnosis. However, it is noted that there are many outliers (Figures 4.16 and 4.17), which highlights the wide range of DEX levels observed. There was no identifiable trend in DEX levels and DEX concentration ranged from 0.03 ng/mL to 26.22 ng/mL. The women in this study come from diverse ethnic and cultural backgrounds. Differential pharmacokinetics of DEX have been found between ethnic groups and this may have contributed to the wide range in DEX values

(Escobar, 1985; Shiah, Ko, & Lu, 1998). DEX comes in tablet form and is orally ingested. While some of the extremely high values of DEX may be due to another signal masking the DEX concentration, it may also be due to residue from the tablet left in the mouth when the saliva sample was taken. It is possible that other medical conditions may have falsely elevated DEX concentrations. Some women may have gastroesophageal or laryngopharyngeal reflux disease, which may cause DEX to be regurgitated into the mouth. Other sources of DEX contamination are also possible, though repeated retests were completed on the extremely high values.

5. PERCENT SUPPRESSION OF CORTISOL FOLLOWING THE DST

DEX ingestion was confirmed for all women. Percent suppression was then calculated. The current study did not observe any differences between the groups in percent suppression of cortisol following the DST (see Figure 4.18). This is a new finding as previous studies have shown increased suppression in individuals with PTSD (Griffin et al., 2005; Yehuda et al., 1993; Yehuda, 2006) and non-suppression in 50% of people with MDD (Arana, Baldessarini, & Ornsteen 1985).

Following convention, cortisol nonsuppression is defined as any post-DEX cortisol concentration that is greater than 5 ug/dL (Carroll, 1982). However, this is after a 1 mg dose of DEX. Some studies defined nonsuppression and hypersuppression as more than 1 standard deviation away from the mean cortisol concentration of the control group. In the current study, the control group also

showed enhanced suppression, so this was not an appropriate method to employ. There is no standard cut-off value for hypersuppression, and this is as yet undefined in the literature. It is difficult to make comparisons between studies, as definitions of percent suppression are vague or undefined. Even though the low dose DST was used in this study to allow for differentiation between normal suppression and hypersuppression, nearly all women in this study showed enhanced suppression of cortisol in response to the DST. As discussed in the literature review, recent evidence suggests that hypersuppression from the DST may be based on trauma exposure, rather than a discrete diagnosis of PTSD (Golier et al., 2006; de Kloet et al., 2007; de Kloet et al., 2008). This was reflected in the sample population for this study, as nearly all women showed enhanced suppression, even in the absence of formal Axis I disorders. Only three women showed non-suppression, and all three of these women had a shifted cortisol peak. As cortisol levels at 30 minutes post-awakening were used for all calculations of percent suppression, it may be that percent suppression is not accurately reflected in these women.

Additionally, no significant differences in percent suppression were seen when women were grouped by diagnosis (Figure 4.19). Though all women in this study are experiencing stressors related to immigration, the neuroendocrine impact of these stressors has not previously been studied. It is surprising that these stressors lead to neuroendocrine impacts, even in the absence of formal Axis I disorders. This may indicate the far-reaching impacts of chronic stress on health.

As all women in this study are immigrant women dealing with significant stressors in their lives, it may be that the stress of immigration results in neuroendocrine changes and the additional stress of IPV does not add any further neuroendocrine dysregulation. It may also be that the DST is not a sensitive enough neuroendocrine measure to differentiate between the stress of immigration and the experience of IPV. Gaps continue to exist in terms of the role of gender and type of stressor in the direction and magnitude of neuroendocrine changes. As the DST has modest sensitivity, a ceiling effect was reached in this study and nearly all women showed enhanced suppression of cortisol (Kunugi et al., 2006). The DEX/CRH challenge is a more sensitive measure of the negative feedback of the HPA axis than the standard DST in both healthy and depressed individuals, and may be an important next step in further understanding neuroendocrine dysregulation that can occur in this stressed population of women (Kunugi et al., 2006).

Future studies using more sensitive neuroendocrine measures may allow for further integration of neuroendocrine and psychological data. This study attempted to compare the neuroendocrine and the psychological data, however as the majority of women showed enhanced suppression of cortisol, even with a dose of 0.5 mg DEX, a ceiling effect was observed and correlations were not able to be determined. This finding does suggest that immigration stress alone does have significant neuroendocrine impacts, which is important knowledge to share with immigrant women and community agencies. Through this knowledge, support

can be provided to all immigrant women, irrespective of screening for IPV or psychiatric diagnosis.

While it is important for community agencies to recognize that IPV can have an impact on biological systems, psychosocial measures may also be used to identify those who feel the most powerless and are at greatest risk of negative health outcomes. By identifying women with high scores on scales such as the EMD and the PSS, help can be provided to support these women in regaining a sense of control. These findings support the need for a broad assessment across multiple health and psychosocial domains to understand the comprehensive and unique nature of the impact that IPV contributes to women's health and wellbeing.

6. CHILDHOOD SEXUAL ABUSE

Childhood sexual abuse contributes to effects of cumulative trauma and can impact the physical and mental health of adult survivors. Thus, subjects with both IPV and a history of childhood trauma may have more severe psychological and neurobiological sequelae. Screening questions were involved in the interviews completed by the primary investigator, as well as by self-report using the CTQ to assess for experiences of CSA. In initial screenings by the primary investigator, only 3 women disclosed experiences of childhood abuse. However, data from the CTQ reflected much higher numbers; therefore secondary analyses including CSA experiences were completed.

In a recent review, prevalence of CSA in community samples in the United States was found to be between 12% and 35% for females (Putnam, 2003). While women in the current study are immigrant women from outside of North America, international data indicates prevalence rates of CSA around the world to be comparable to those in the United States. In a review of studies from 19 countries, CSA rates were found to be between 7% and 36% for women (Finkelhor, 1994). The wide range of prevalence rates may be due to the definitions of CSA used and the method by which the history is obtained (Putnam, 2003). Of the women included in the final analysis for the current study, twenty-two (34.9%) disclosed experiences of CSA, which is in the high range as reported in other studies. The disclosure of CSA differed widely in this study depending on method of investigation (interview versus self report questionnaire), a trend observed in other studies. People are more likely to respond affirmatively to questions that describe abuse experiences (e.g. "When I was growing up, someone tried to touch me in a sexual way, or tried to make me touch them") rather than direct questions that may have stigmatizing labels such as "abuse" or "neglect" (Medrano, Brzyski, Bernstein, Ross, & Hyatt-Santos, 2004). In some circumstances, self-report instruments of childhood trauma are more likely to elicit truthful responses than clinical interviews (Savitz, van der Merwe, Stein, Solms, & Ramesar, 2007)

As childhood adversity is a predictor for risk of psychiatric illness in adulthood, the scores on the CTQ as well as disclosures in the interview were compared between the control and the IPV group. There was no statistically

significant difference between the groups in reported CSA severity using the CTQ ($p = 0.085$). However, significant differences were seen between the IPV and the control groups in frequency of CSA ($p = 0.038$). Interestingly, when stratifying the control and the IPV groups by experiences of CSA, the statistically significant associations between IPV and increased comorbidity of Axis I disorders, higher EMD scores and higher scores of the PSS were lost. Within the IPV group, no differences were seen between women who had experienced CSA and those who hadn't on measures of EMD and PSS. Additionally, within the control group no statistically significant differences in these measures were seen between women who had experienced CSA and those who hadn't. This suggests that it is the current experiences of violence that contribute to measures of EMD, PSS and increased Axis I comorbidity, rather than CSA experiences. Conclusions are limited by the small sample size of women who had experienced CSA; however, in future studies with a greater sample size, the independent contributions that IPV and CSA make to these psychological measures may be further elucidated.

7. STUDY STRENGTHS, LIMITATIONS AND FUTURE DIRECTIONS

The unique strength of this study is that it integrates data on the psychological and neuroendocrine impacts of stress in a gender-specific way. By comparing two groups of women, both experiencing a great deal of stress, the unique impact that IPV contributes to women's health can be identified. The sample of women in this study is novel, in that most previous research on the impact of IPV is based on populations from clinics or women living in shelters.

The sample recruited for this study was based on convenience sampling of women attending a community resource centre that offers a variety of support. As such, women with a broad range of experiences and symptom clusters were included in this study.

It is vitally important to study the effects of IPV to gain a more complete picture of the impact of violence on health; however, there are challenges and limitations in studying subjects of this nature and recruiting this vulnerable population. Definitions of IPV and methods of inquiry vary widely among published research, making it difficult to directly compare findings between studies. The phenomenology of violence is subject to ethnic variation and IPV in different cultures may have different personal meanings, occur for different reasons or have unique political or social significance. Women from various cultural backgrounds may differ in how they define, react to and cope with violence in ways that influence the health impacts of IPV.

Of the 63 women included in the final analysis, only 29 provided complete biological and psychological data. As the recruitment period continued for over 5 years, it was not possible in many cases to contact women for missing data. By including more women and increasing the sample size in each diagnostic group, subtle changes in basal and neuroendocrine measures may be identified. It appears that the DST is not sensitive enough to test the neuroendocrine function in this population of stressed women. Future studies could employ more sensitive HPA axis challenges such as the DEX/CRH test or the ACTH challenge, or use

the DST with a 0.25 mg dose of DEX, which may uncover statistically significant differences between the groups.

The women in this study are a diverse group, so controlling for variables to examine potential markers of neuroendocrine dysfunction poses a challenge. Potential confounding variables when examining measures of the HPA axis in women who have experienced violence include psychiatric diagnosis; duration and severity of IPV; age at which trauma occurred; relationship between victim and perpetrator; the number of perpetrators; frequency of the violence; the number of IPV experiences across the lifespan; comorbid physical conditions; and use of medications, among others. In future studies it would be informative to include a third group of women who have experienced IPV in the past, to determine if health impacts of IPV linger despite the woman having left the abusive relationship. Several protective factors such as personal resources, coping styles and social support were not assessed at this point. In future studies, including resiliency and protective measures may better identify support networks and resources to optimize care for these women.

Women experiencing IPV with resulting psychiatric symptoms often do not fit into the discrete diagnostic categories described in the DSM-IV. Future research can go beyond categorical outcome measures to include continuous dimensions using a symptoms-based approach to the pathophysiology of stress disorders. This method would take into account the diverse psychiatric history and subclinical psychiatric symptoms that are seen in some of these women. It is important to employ prospective studies to identify psychological, biological and

environmental factors and how they relate to the emergence of MDD, PTSD and/or other stress related disorders. By examining the longitudinal course of the effects of IPV, the emergence of psychiatric symptom clusters and their biological correlates, women in greatest need of support can be identified.

8. SUMMARY OF KEY FINDINGS

There is a relative lack of neuroscience research on chronic traumatic stress in adult women. Studies that have focused on the neuroendocrine impacts of stress often group populations by various discrete categories. By focusing on clinical diagnoses, studies neglect to recognize that stress responses are dynamic and include individuals in interaction with their environments. The goal of the current study was to determine if the stress of IPV had different psychological or neuroendocrine impacts than other chronic stressors, which are not interpersonal in nature, contributing to the growing body of gender-specific health research.

The key findings of this study are as follows:

- Gender-specific health research is important to gain a broader understanding of psychological and neuroendocrine impacts of violence and to integrate both experience and diagnosis in the prediction of outcomes
- Immigration-related stressors pose challenges for women and can have psychological and neuroendocrine impacts

- Measures of EMD and PSS were sensitive to IPV. Diagnostic classification provides some clinical direction, but is insufficient in terms of reflecting the broad impact of immigration and IPV on women's health
- At-home self administered saliva collection and DST proved feasible. By providing clear instructions, salivettes, an oral dose of DEX and an addressed, stamped envelope, women may complete the DST in their own homes and mail saliva samples to the lab for analysis. This suggests that clinicians and researchers may routinely use at-home DST kits in their investigations.
- Through a novel RIA, DEX levels could be measured in saliva 30 minutes after DEX ingestion. This enables confirmation of DEX ingestion, as well as specific quantification of salivary DEX levels
- Basal and challenged cortisol levels were not sensitive enough measures of the HPA axis to elucidate any significant neuroendocrine differences between women experiencing IPV and women who experience other types of stressors. The vast majority of women in this study showed hypersuppression in response to the DST, irrespective of their experience or psychiatric diagnosis

9. CONCLUSION

The current study has contributed to the growing body of gender-specific health literature and has knit together both psychological and neuroendocrine data in this stressed population of women. Simultaneous investigation of psychological factors and biological stress response systems allows for an integrated approach to investigate the impacts of IPV.

The current findings support the need for broad assessment across multiple health domains to understand the full and unique impact of IPV on women's health and wellbeing. Additionally, these findings have implications for service providers who are supporting immigrant women and their families, to recognize the severe stress that this life change presents and the risks it contributes to women's health.

By disseminating these findings with community agencies and organizations working with immigrant women and women experiencing violence, health care practitioners can better appreciate impacts of stress and violence on the whole body within the context of past and current environments. Women rarely volunteer information about trauma and healthcare providers rarely inquire about these experiences (Medrano et al., 2004). Health care providers who only screen for IPV when women present with a physical injury will miss many women who may be experiencing other health problems as a consequence of violence. By recognizing the profound impacts that IPV can have on health and by identifying individuals who may be at greater risk, health practitioners may formulate more effective interventions and treatment strategies.

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APPENDIX A: PARTICIPANT INFORMATION SHEET

INFORMATION SHEET

Impact of Partner Violence on Women's Health

Researchers: Dr. Kathy Hegadoren, Dr. Nicholas Coupland, Dr. Colleen Norris, Dr. Ruth Lanius (University of Western Ontario)

Purpose of the Study: Intimate partner violence (IPV; also called domestic violence, where your husband or male partner hurts you emotionally, physically or sexually) can have long term effects on mental and physical health. It is important to understand how IPV affects women's health, in order to provide the best help. You are being asked to take part in a *research* study. The study seeks to learn how emotions and stress *hormones* affect the impact of IPV on women's health. *Stress* hormones are chemicals that our bodies produce when we are *stressed*.

Schedule: The study has **two parts** and the schedule will be…

IPV Study Schedule

Part 1: First you will need to go through a screening form with Rosa or Nasim to decide whether you will fit in to the study criteria.
Schedule an appointment for the interview
Take home package for spit testing
Come to Changing Together for an interview with Kathy. This will be done in a quiet room. You will fill out some forms and answer some questions.

Part 2: We need to do two stress hormone tests. This means that we will check your spit and your blood.

Spit: The first test will be done by you at home. You will need to chew on a cotton ball when you wake up in the morning, again in 30 minutes, and 1 and 4 hours later. Later that day, you will take a pill with hormone (*dexamethasone*) in it – this hormone is like the hormone that your own body makes. The next morning you will chew on a cotton ball again. Once you have chewed on a cotton ball, you will need to put it inside a plastic tube. The tubes with the cotton balls in them need to be put in the mail.

Blood: This test will be done at the University at Kathy's office. You will relax in a chair when you arrive while a nurse takes some blood from your arm. The nurse will put an *IV* into your arm so that she can put a hormone (ACTH) into your blood – this hormone is like the hormone that your own body makes. After the hormone is put into your blood, the nurse will watch your heart beat and temperature and take more blood. The nurse will also ask you some questions about how you are feeling during the test.

Risks of taking part:
This study asks questions about stressful events, we know it can be upsetting to talk about these. You do not have to answer every single question, or tell us anything that you choose to keep private.

Benefits: Taking part in research does not help you directly. The study may help nurses and doctors understand how intimate partner violence affects women's health. You will be offered information about mental health support.

Right of withdrawal:
Taking part in the study is your choice. You can decide not to take part at any time. This will not affect the community services that are offered to you.

Expense Reimbursement: In addition to covering your parking and childcare expenses (if required), an honorarium will be given after the interview and again after the hormone test. Someone will go with you from Changing Together to the research center, if you wish. Bus tickets will be provided for the trip back and forth to the research center for the second test, if needed.

Privacy: Personal records relating to this study will be kept very private. Real names will not be put in any report published on this study.

Other information:
If you have any questions about the study, you are free to ask them anytime. You can call the researchers at the numbers listed.

Dr. Kathy Hegadoren, RN PhD, Tel: 492-4591
Women's Health Research Unit Tel: 492-9046
Or
Rosa or Nasim at Changing Together; Tel: 421-0175

Glossary of Terms

***Research*:** looking at how and why things happen in the body. Careful study to understand events, behaviours, the way the body works.

Hormones: substances in the body that send messages from one part of the body to another.

Stress: a physical or mental event that causes a change in the body.

IV: (Intravenous Line) a tube that is put into the blood vessel to let the nurse take blood out of the body or, put things into the body.

APPENDIX B: CONSENT FORM

CONSENT FORM

TITLE: *Impact of Partner Violence on Women's Health*

RESEARCH TEAM:

Dr. Kathy Hegadoren	Telephone: 492-4591
Dr. Nicholas Coupland	Telephone: 407-3369
Dr. Colleen Norris	Telephone: 492-0644

Do you understand that you have been asked to be in a research study?	Yes	No
Have you read and received a copy of the attached Information Sheet?	Yes	No
Do you understand the benefits and risks involved in taking part in this research study?	Yes	No
Have you had an opportunity to ask questions and discuss this study?	Yes	No
Do you understand that you are free to refuse to participate or withdraw from the study at any time? You do not have to give a reason and it will not affect the community services offered to you.	Yes	No
Has the issue of confidentiality been exlained to you? Do you understand who will have access to your records?	Yes	No

This study was explained to me by: _____

I agree to take part in this study.

_____	_____	_____
Signature of Research Participant	Date	Witness
_____		_____
Printed Name		Printed Name

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

_____	_____	_____
Signature of the Investigator or Designee	Date	Printed Name

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

APPENDIX C: SCREENING FORM

"IMPACT OF PARTNER VIOLENCE ON WOMEN'S HEALTH" STUDY

Participants Initials | | | |

Date Screened: _____/ _____/ _____/ dd mm yyyy **Age: _____ Years**

A. Participant's with IPV history

INCLUSION: ***MUST HAVE*** ALL OF THE FOLLOWING CRITERIA:

YES	NO	Criteria
		Currently or within the ***last 4 months*** residing with a male partner who is rated as at least a 3 on 6 of the 9 verbal or physical tactic items

		Never	Once that Year	2 or 3 times	Often, < 1x/month	About 1x/month	> 1x/month
F.	Yelled and/or insulted.	0	1	2	3	4	5
G.	Sulked and/or refused to talk about it.	0	1	2	3	4	5
H.	Stomped out of the room.	0	1	2	3	4	5
I.	Threw (but not at the other) or smashed something.	0	1	2	3	4	5
J.	Threatened to hit or throw something at the other.	0	1	2	3	4	5
K.	Threw something *at the other*.	0	1	2	3	4	5
L.	Pushed, grabbed or shoved the other.	0	1	2	3	4	5
M	Hit (or tried to hit) the other person but not with anything.	0	1	2	3	4	5
N.	Hit (or tried to hit) the other person with something hard.	0	1	2	3	4	5

Total: ____ (total score ≥ 18 = **Yes**)

		Fluent English speaker
		18 years of age or older

A. Continued

EXCLUSION: ***MAY NOT*** HAVE ANY OF THE FOLLOWING CRITERIA:

<table>
<tr><th>YES</th><th>NO</th><th>Criteria</th></tr>
<tr><td></td><td></td><td>Experienced situational couple violence alone, assessed by the women’s rating herself at least a 2 on 3 out of the 6 physical tactic items
<table>
<tr><th></th><th></th><th>Never</th><th>Once that Year</th><th>2 or 3 times</th><th>Often, < 1x/month About 1x/month</th><th></th><th>> 1x/month</th></tr>
<tr><td>I.</td><td>Threw (but not at the other) or smashed something.</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>J.</td><td>Threatened to hit or throw something at the other.</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>K.</td><td>Threw something at the other.</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>L.</td><td>Pushed, grabbed or shoved the other.</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>M</td><td>Hit (or tried to hit) the other person but not with anything.</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td>N.</td><td>Hit (or tried to hit) the other person with something hard.</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
</table>
Total: ____ (total score ≥ 6 = Yes)</td></tr>
<tr><td></td><td></td><td>Daily use of psychotropic medications: antidepressants, anxiolytics, antipsychotics, anticonvulsants/mood stabilizers ● See Table for a list</td></tr>
<tr><td></td><td></td><td>Pregnant, breastfeeding, or within 6 months of childbirth</td></tr>
<tr><td></td><td></td><td>Medical conditions with a known impact on stress response systems (e.g. Asthmatics being treated with a corticosteroid, Diabetics, those being treated for High blood pressure, conditions) ● See Table for a list</td></tr>
</table>

B. Participants in the Control Group

INCLUSION: ***MUST HAVE*** ALL OF THE FOLLOWING CRITERIA:

YES	NO	Criteria
		Fluent English speaker
		18 years of age or older

EXCLUSION: ***MAY NOT*** HAVE ANY OF THE FOLLOWING CRITERIA:

YES	NO	Criteria

		A History of intimate partner violence
		Daily use of psychotropic medications: antidepressants, anxiolytics, antipsychotics, anticonvulsants/mood stabilizers ● See Table for a list
		Pregnant, breastfeeding, or within 6 months of childbirth
		Medical conditions with a known impact on stress response systems ● See Table for a list

ELIGIBILITY: Is this person eligible for the study? ❒ Yes ❒ No

If yes, date consent obtained: _____/ _____/ _____
dd mm yyyy

APPOINTMENT: Date available for Interview: _____/ _____/ _____ Time: ____:____ am/pm
dd mm yyyy

CHECKLIST:

❒ Can participant be reached by phone?

If yes, does participant wish to have messages left? ❒ Yes ❒ No

If no, how would participant like to be contacted? _____

❒ Participant's contact information

Name: _____
Home: _____
Work: _____
Cell: _____
Email: _____
Convenient time to contact: _____

❒ Does the participant require Childcare? ❒ Yes ❒ No

❒ Information letter and Consent form given to participant.

❒ Screening sheet stored in IPV folders

❒ Notified Research Staff

Contact Information:

Monday to Friday: 492-9046. After hours, please leave a detailed message.

Form completed by _____ Signature _____
Date ___/___/_____
(please print name) dd mm yyyy

APPENDIX D: DEMOGRAPHIC INFORMATION FORM

"IMPACT OF PARTNER VIOLENCE ON WOMEN'S HEALTH" STUDY
DEMOGRAPHIC FORM

Patient Information:

Initials (F-M-L):	Date (dd/mm/yyyy): ____/____/200__
Age:	
Height: ____ Ft. ____ in. (Patient self-report only)	Weight: _____ lbs or _____ kg (Patient self-report only)

LIFESTYLE QUESTIONS

Alcohol and Caffeine Intake:	
How often do you consume any type of alcohol? (check the appropriate answer):	
	Never
	Occasionally
	Daily
If occasionally or daily:	
How many alcoholic drinks have you had this past week? _____	
Has this been a typical week for alcohol intake? □ Yes □ No If not, what is the typical number of drinks per week you have? _____	
How many cups of coffee (or cola products) do you drink on average per day? _____	

Current marital status (check the appropriate answer):	
	Single (never married)
	Currently married
	Common-law
	Separated/divorced
	Widowed

Educational background (check the appropriate answer):	
	Did not complete grade 12
	High school diploma
	Some college or university courses
	Completed college or university degree
	Graduate degree

Are you currently working outside your home? (check the appropriate answer):	
	No
	Full time
	Part time
What type of work are you doing at this time?	

MEDICAL HISTORY

1a. **What is your height?** b. **What is your weight?** c. **What is your age?**

2a. **Do you have a physician/clinic that you see regularly to receive medical care, physical examinations, etc.?** **YES ____ NO ____**

b. **Are you currently being treated for any physical disease or condition?** **YES ____ NO ____**

If YES, specify:

_____

3a. **When was your last physical exam?**

_____

b. **What were the results of this exam?**

_____

4a. **Have you ever had to be hospitalized for a physical problem?** **YES ____ NO ____**

Date	Hospital/Doctor	Reason	Comments/Complications
_____	_____	_____	_____
_____	_____	_____	_____

b. **Have you ever had surgery, or been advised to have surgery?** **YES ____ NO ____**

Date	Hospital/Doctor	Reason	Comments/Complications
_____	_____	_____	_____
_____	_____	_____	_____

c. **Have you ever had a concussion or any head injury?**

YES ____ NO ____

Date	Hospital/Doctor	Reason	Comments/Complications
_____	_____	_____	_____
_____	_____	_____	_____

5. **Have you ever been diagnosed with any of the following?**

	Yes	No	Date	Comments
a. Diabetes	___	___	_____	_____
b. Heart problems	___	___	_____	_____
c. High/low blood pressure	___	___	_____	_____
d. Epilepsy	___	___	_____	_____
e. Cancer	___	___	_____	_____
f. Thyroid disease	___	___	_____	_____
g. Other hormonal problem	___	___	_____	_____
h. Asthma	___	___	_____	_____
i. Other respiratory problem	___	___	_____	_____
j. Migraines	___	___	_____	_____
k. Stroke	___	___	_____	_____
l. Ulcers/GI problems	___	___	_____	_____
m. Blood disorders	___	___	_____	_____
n. HIV/AIDS	___	___	_____	_____
o. Eczema	___	___	_____	_____
p. **Any other diseases?**	___	___	_____	_____

q. **Is there a family history (e.g., Father, mother, siblings) of any of these problems (e.g., hypertension, heart disease, cancer)?**

YES ____ NO ____

If yes, specify:

_____

6. **Do you have any allergies (hay fever, penicillin, medications, etc.)?**

YES ____ NO ____

If yes, specify:

_____

7. **Smoking History (check the appropriate answer):**

Current smoker	YES ____ NO ____
Former smoker	YES ____ NO ____
Never smoked	YES ____ NO ____

If YES, Packs/day? _____ How many years? _____

8. **Have you had any of the following tests in the last five years? Did these tests indicate any abnormalities?**

	Yes	No	Date	Results
a. Electrocardiogram (EKG)	___	___	_____	_____
b. EEG, brain scan, EMI	___	___	_____	_____
c. CT scan or similar	___	___	_____	_____
d. Chest X-ray	___	___	_____	_____
e. Blood test	___	___	_____	_____
f. Urine test	___	___	_____	_____

8a. **Are you still experiencing menstrual periods? YES ____ NO ____**

b. **Date last menstrual period began:** ___/___/_____
Length of usual cycle (Days) ____ dd mm yyyy

c. **Any reason to believe you may be pregnant? YES _____ NO _____**

d. **Are your periods changing (peri-menopausal)? YES _____ NO _____**
(Changes in your pattern of cycling – e.g. skipping periods sometimes or having shorter cycles, increased or decreased flow, but you are still having periods)

e. **Are currently on any type of female hormone (oral contraceptives, hormone replacement)? YES _____ NO _____**

f. **History of any gynecological problems, miscarriages, etc.?**
YES _____ NO _____
If YES, specify: _____

Daily medications:
(Including over the counter medicines if taken daily such as pain medications, cold preparations, wake-up pills, herbal products or pills from health food or natural products stores).

For each one, write down how long you have been taking it. ☐ **N/A**

Medication:	Use:	Length of time taken:

APPENDIX E: CONFLICT TACTICS SCALE

Conflict Tactics Scale

(CTS1, Form R, 1985)

Here is a list of things that you and your partner might have done when having a conflict. During the last year, take all the *disagreements* you and your partner had into account (not just the most serious one). How often did you do the things listed at any time?

0=Never
1=Once that year
2=Two or three times
3=Often, but less than once month
4=About once a month
5=More than once a month

		Partner	Self
A.	*Tried* to discuss the issue relatively calmly.	0 1 2 3 4 5	0 1 2 3 4 5
B.	*Did* discuss the issue relatively calmly.	0 1 2 3 4 5	0 1 2 3 4 5
C.	Got information to back up his/her side of things.	0 1 2 3 4 5	0 1 2 3 4 5
D.	Brought in someone else to help settle thing (or tried to).	0 1 2 3 4 5	0 1 2 3 4 5
E.	Argued heatedly but short of yelling.	0 1 2 3 4 5	0 1 2 3 4 5
F.	Yelled and/or insulted.	0 1 2 3 4 5	0 1 2 3 4 5
G.	Sulked and/or refused to talk about it.	0 1 2 3 4 5	0 1 2 3 4 5
H.	Stomped out of the room.	0 1 2 3 4 5	0 1 2 3 4 5
I.	Threw (but not at the other) or smashed something.	0 1 2 3 4 5	0 1 2 3 4 5
J.	Threatened to hit or throw something at the other.	0 1 2 3 4 5	0 1 2 3 4 5
K.	Threw something *at the other*.	0 1 2 3 4 5	0 1 2 3 4 5
L.	Pushed, grabbed or shoved the other.	0 1 2 3 4 5	0 1 2 3 4 5
M	Hit (or tried to hit) the other person but not with anything.	0 1 2 3 4 5	0 1 2 3 4 5
N.	Hit (or tried to hit) the other person with something hard.	0 1 2 3 4 5	0 1 2 3 4 5
O.	Other: Please describe:	0 1 2 3 4 5	0 1 2 3 4 5

Description: A 15-item instrument designed to measure three tactics in resolving conflict between family members – reasoning, verbal aggression, and violence.

Scoring: Reasoning scores are in items: A though E, verbal aggression scores are the sum of items F through J, and physical aggression consists of items K through O. Scores for each person are tallied separately and range from 0 to 15 for each subscale. Higher scores indicated more use of the particular tactic.

Authour: Murray A. Straus.

APPENDIX F: ENTRAPMENT AND MENTAL DEFEAT SCALE

Entrapment and Defeat Scale

(Gilbert P and Allan S, 1998)

PART I:

Instructions: Please circle the number that you feel best answers your thoughts and feelings about the statements below.

0= Not at all like me
1=A bit like me
2=Moderately like me
3=Quite a bit like me
4=Extremely like me

1.	I want to get away from myself.	0	1	2	3	4
2.	I feel powerless to change myself.	0	1	2	3	4
3.	I would like to escape from my thoughts and feelings.	0	1	2	3	4
4.	I feel trapped inside myself.	0	1	2	3	4
5.	I would like to get away from who I am and start again.	0	1	2	3	4
6.	I feel I'm in a deep hole I can't get out of.	0	1	2	3	4
7.	I am in a situation I feel trapped in.	0	1	2	3	4
8.	I have a strong desire to escape from things in my life.	0	1	2	3	4
9.	I am in a relationship I can't get out of.	0	1	2	3	4
10.	I often have the feeling that I would just like to run away.	0	1	2	3	4
11.	I feel powerless to change things.	0	1	2	3	4
12.	I feel trapped by my obligations.	0	1	2	3	4
13.	I can see no way out of my current situation.	0	1	2	3	4
14.	I would like to get away from other more powerful people in my life.	0	1	2	3	4
15.	I have a strong desire to get away and stay away from where I am now.	0	1	2	3	4
16.	I feel trapped by other people.	0	1	2	3	4

PART II:

Instructions: *Thinking about the last 7 days* please circle the number that you feel best corresponds to your thoughts and feelings about the statements below.

0=Never
1=Rarely
2=Sometimes
3=Mostly
4=Always/All the time

17.	I feel that I have not made it in life.	0	1	2	3	4
18.	I feel that I am a successful person.(R)	0	1	2	3	4
19.	I feel defeated by life.	0	1	2	3	4
20.	I feel that I am basically a winner. (R)	0	1	2	3	4
21.	I feel that I have lost my standing in the world.	0	1	2	3	4
22.	I feel that life has treated me like a punching bag.	0	1	2	3	4
23.	I feel powerless.	0	1	2	3	4
24.	I feel that my confidence has been knocked out of me.	0	1	2	3	4
25.	I feel able to deal with whatever life throws at me (R)	0	1	2	3	4
26.	I feel that I have sunk to the bottom of the ladder.	0	1	2	3	4
27	I feel completely knocked out of action.	0	1	2	3	4
28.	I feel that I am one of life's losers.	0	1	2	3	4
29.	I feel that I have given up.	0	1	2	3	4
30.	I feel down and out.	0	1	2	3	4
31.	I feel I have lost important battles in life.	0	1	2	3	4
32.	I feel that there is no fight left in me.	0	1	2	3	4

Reference: Gilbert P. and Allan S. 1998. The role of defeat and entrapment (arrested flight) in depression: an exploration of an evolutionary view. *Psychological Medicine.* 28; 585-598.

APPENDIX G: PERCEIVED STRESS SCALE

Perceived Stress Scale

(Cohen S, 1983)

PSS

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

Name: _____ Date: _____

Age: _____ Gender (circle): M F Other: _____

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1.	How often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	How often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3.	How often have you felt nervous, or "stressed?"	0	1	2	3	4
4.	How often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5.	How often have you felt that things were going your way?	0	1	2	3	4
6.	How often have you found that you could not cope with all the things you had to do?	0	1	2	3	4
7.	How often have you been able to control irritations in your life?	0	1	2	3	4
8.	How often have you felt that you were on top of things?	0	1	2	3	4
9.	How often have you been angered because of things that were outside of your control?	0	1	2	3	4
10.	How often have you felt difficulties were piling up so high you could not overcome them?	0	1	2	3	4

APPENDIX H: CHILDHOOD TRAUMA QUESTIONNAIRE

CTQ

Childhood Trauma Questionnaire

INSTRUCTIONS

These questions ask about some of your experiences growing up as a child and a teenager. Although these questions are of a personal nature, please try to answer as honestly as you can. For each question, circle the number under the response that best describes how you feel. If you wish to change your response, put an X through it and circle your new choice.

Example of corrected response:

Original Response

Never True	Rarely True	Some-times True	Often True	Very Often True
(1)	2	3	4	5

Changed Response

Never True	Rarely True	Some-times True	Often True	Very Often True
~~(1)~~	2	(3)	4	5

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CTQ

Childhood Trauma Questionnaire

Name: _____ Age: _____ Sex: _____

When I Was Growing up….	Never True	Rarely True	Some-times True	Often True	Very Often True
1. I didn't have enough to eat.	1	2	3	4	5
2. I knew that there was someone to take care of me and protect me.	1	2	3	4	5
3. People in my family called me things like "stupid," "lazy" or "ugly."	1	2	3	4	5
4. My parents were too drunk or high to take care of the family	1	2	3	4	5
5. There was someone in my family that helped me feel important or special.	1	2	3	4	5
6. I had dirty clothes to wear.	1	2	3	4	5
7. I felt loved.	1	2	3	4	5
8. I thought that my parents wished that I had never been born.	1	2	3	4	5
9. I got hit so hard by someone in my family that I had to go see a doctor or go to the hospital.	1	2	3	4	5
10. There was nothing that I wanted to change about my family.	1	2	3	4	5
11. People in my family hit me so hard that it left me with bruises or marks.	1	2	3	4	5
12. I was punished with a belt, a board, a cord, or some other hard object.	1	2	3	4	5
13. People in my family looked out for each other.	1	2	3	4	5
14. People in my family said hurtful or insulting things to me.	1	2	3	4	5
15. I believe that I was physically abused.	1	2	3	4	5
16. I had the perfect childhood.	1	2	3	4	5
17. I got hit or beaten so badly that it got noticed by someone like a teacher, neighbor, or doctor.	1	2	3	4	5
18. I felt that someone in my family hated me.	1	2	3	4	5
19. People in my family felt close to each other.	1	2	3	4	5
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	1	2	3	4	5
21. Someone threatened to hurt me or tell lies about me, unless I did something sexual with them.	1	2	3	4	5
22. I had the best family in the world.	1	2	3	4	5
23. Someone tried to make me do sexual things or watch sexual things.	1	2	3	4	5
24. Someone molested me.	1	2	3	4	5

25. I believe that I was emotionally abused.	1	2	3	4	5
26. There was someone to take me to the doctor, if I needed it.	1	2	3	4	5
27. I believe that I was sexually abused.	1	2	3	4	5
28. My family was a source of strength and support.	1	2	3	4	5

APPENDIX I: SALIVA COLLECTION INSTRUCTION AND RECORD SHEET

COLLECTION OF SALIVA SAMPLES

Each saliva sample needs to be collected at a SET TIME

Step 1: ***Write your name and address on the return address box on the envelope***.

Step 2: Collect the saliva samples in the tubes according to the instructions below. Fill in the Record Sheet as you go along. Keep samples in the envelope until you are ready to mail them back to us. Please mail the envelope back either the same day the samples are collected, or the next day at the latest.

HOW TO COLLECT SALIVA

- Take the cotton roll from the tube, put it in your mouth, swirl it around and chew on it for **ONE MINUTE (i.e. for a full 60 seconds).** It is important that the cotton roll gets very wet. Then spit it back into the tube and put the cap back on.

- If it helps you to remember, put the tube for collecting the WAKE sample next to your bedside so you see it when you wake up.

- ***PLEASE COLLECT THE MORNING SAMPLES BEFORE BRUSHING YOUR TEETH, SMOKING, EATING (ANYTHING), OR DRINKING JUICE, COFFEE OR TEA. YOU MAY DRINK A FEW SIPS OF PLAIN WATER.***

Sample 1: WAKE – 0 Minutes

- Collect the WAKE sample AS SOON AS YOU WAKE UP. Record the time you wake up on the recording sheet and then check the time for 30 minutes later.

Sample 2: 30 Minutes after Wake Up

- Collect the next sample, and then check the time for another 30 minutes.

Sample 3: 60 Minutes after Wake Up

- Collect the next sample and then check the time for 3 hours later.

You may now enjoy your breakfast! ☺

Sample 4: 4 Hours after Wake Up

- ***DO NOT EAT OR DRINK TEA OR COFFEE for 30 minutes prior*** *to collecting this sample*.

DEXAMETHASONE

- At 10:00 PM the same day, take the DEX Tablet with water. (or 30 minutes before bedtime)
- Do not eat anything between taking the DEX and collecting the next sample.

Sample 5: 30 Minutes after taking the Dexamethasone

- Collect a saliva sample the same as the previous samples.

Sample 6: 30 Minutes after Wake UP - Day 2

- Collect a sample 30 minutes after you wake up the next morning, before eating or drinking anything, following the same procedure.

Step 3: When ready to mail, seal the envelope, which should contain **6 saliva tubes and the record sheet**.

Step 4: Mail the envelope in any mail box, ***on the same day or the next day***. No postage is needed.

RECORD SHEET

Please record the times of your samples on this sheet. This will remind you when to do the samples. It is **very important** for our study that the **WAKE** time is recorded on this form.

DATE:
INITIALS (F-M-L):

Sample	TUBE	✓	TIME	EXAMPLE
1	WAKE (Record time)			7:00 AM
2	30 Minutes after wake up			7:30 AM
3	60 Minutes after wake up			8:00 AM
4	4 Hours after wake up			11:00 AM
	DEX at **10:00 PM**			10:00 PM
5	DEX sample at **10:30 PM**			10:30 PM
	Refrigerate samples with Record Sheet			
6	**Day 2** 30 Minutes after wake up			7:30 AM
	Seal Envelope and Mail the Same or Next Day			

Please record the date of your last menstrual period or as close as you can remember:

____ ___ ___
yyyy mm dd

PLEASE RETURN THIS FORM WITH YOUR SAMPLES IN THE XPRESSPOST© ENVELOPE PROVIDED.

Thank You!