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The Role of Cortisol in the Cycle of Violence

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Child abuse and neglect are universal risk factors for delinquency, violence and aggression; this phenomenon is known as the cycle of violence. Despite a wide body of research demonstrating this phenomenon, the processes which mediate this relationship remain largely unknown. One potentially relevant result of abuse and neglect may be disruptions in the development of the body's stress response, specifically the function of the Hypothalamic-Pituitary-Adrenal (HPA) axis. The HPA-axis, and its end-product, cortisol, may play a role in regulating aggressive behavior, but this function may be disrupted following abuse and neglect. Another risk factor for aggression, psychopathy, may mediate the cycle of violence or independently contribute to aggressive behavior. This study examined the relationship between child abuse and neglect, HPA-axis function, psychopathy and aggression. History of abuse was measured using a self-report questionnaire, the Childhood Trauma Questionnaire. Using a within-subject, placebo-controlled, counter-balanced dosing design, 67 adults were given an acute dose of 20mg cortisol as a challenge to the HPA-axis. Following dosing, measures of cortisol response were obtained through saliva samples, and state-aggressive behavior was measured by a laboratory task, the Point-Subtraction Aggression Paradigm (PSAP). Basal measures of cortisol were obtained prior to dosing. Psychopathy and a trait-measure of aggression were assessed through self-report questionnaires. PSAP data and trait-aggression scores were normalized and summed for an overall aggression score. Linear regression analyses indicated that a history of abuse and neglect robustly predicted aggression, supporting the cycle of violence hypothesis. Further, abuse and neglect predicted a diminished HPA-axis response to the cortisol challenge. Although a diminished HPA-axis response significantly predicted increased aggression, mediation analysis revealed that HPA-axis reactivity did not mediate a significant portion of the effect of abuse and neglect on aggression. However, HPA-axis reactivity did mediate part of the effect, indicating that HPA-axis function may be a factor in the cycle of violence. Psychopathy robustly predicted increased aggression. Although the results indicate that cortisol, psychopathy and HPA-axis function are involved in the cycle of violence, further research is required to better understand the complex interaction of these factors.

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Introduction

"Peace cannot be achieved through violence; it can only be attained through understanding."
-Ralph Waldo Emerson

In Easson and Steinhilber's 1961 case report, they quote the father of a 13-year old patient as saying "I am sure he is going to kill someone and end up in the penitentiary." The boy had recently attempted to stab the father with a knife following an argument. The patient reported "My mother will not stay in the house with me." Easson and Steinhilber (1961) concluded that the family had rejected the boy, treated him with hostility and expected him to become violent; further, they allowed him to keep a supply of knives and the father had recently given him a gun as a gift. According to the US Department of Health and Human Services' definition (2001), the lack of appropriate supervision and emotional support exhibited by the parents constitutes neglect. The cycle of violence—when a mistreated child grows up to become criminally aggressive—has become the "premier hypothesis" in the field of child abuse and neglect (Widom, 1989a).

Since this hypothesis was first articulated, researchers have demonstrated that a cycle of violence does exist—abused children are at increased risk to become violent adults (Widom, 1989a). However, many questions remain. An effect exists, but we don't know why. The question of greatest concern to this dissertation is what causes abused children to have an increased risk for violence as adults. The literature has provided several clues that will serve as starting points for this study.

One of the leading models for the developmental pathway from abuse and neglect to adult psychopathology highlights the role of the body's stress response (De Bellis, 2005). Being born is the first of many stressful experiences an individual experiences during life, and to respond to stress the human body, like all vertebrates, has a system designed to restore balance (Sapolsky et al., 2000). However, extensive, repeated or enduring stressful situations, such as abuse and neglect, may overload the stress response and result in lasting, detrimental changes (De Bellis, 2005). Among these changes, these individuals may become more likely to engage in aggressive behavior (Veenema, 2009).

Some of the central topics include the neurobiological control of aggression and the potential changes in the brain and body which may result from adverse experiences such as abuse and neglect. Although a number of studies have examined the cycle of violence, none of them have applied laboratory-measures of aggression to assess the effects of a

history of child abuse and neglect on aggressive responding. Laboratory measures allow for the examination of variables that are impossible to study using other methods of aggression research, such as observing behavior in real-time in a controlled setting. Further, subjects can be tested in multiple conditions, including a challenge to the stress system by acute administration of drugs. In this study, subjects received cortisol and placebo capsules to determine if cortisol differentially alters aggressive responding in subjects with a history of abuse and neglect compared to those who do not. Cortisol is the end-product of the hypothalamic-pituitary-adrenal (HPA) axis, part of the body's stress response system (Sapolsky et al., 2000).

Subjects' basal levels of cortisol were measured using saliva samples to determine if any differences existed between subjects with a history of abuse or neglect and, further, if these basal levels predicted aggressive responding. Subjects' heart rate and blood pressure were also examined. Finally, subjects were given questionnaires to assess their trait levels of aggressive behavior and the presence of psychopathy. Psychopathy is a construct which may provide a disparate pathway to aggression, and hence is important in terms of explaining variance in aggressive responding (Hawes et al., 2009).

The goal of this dissertation is to further the understanding of the processes involved in the cycle of violence.

Background

Chapter 1. The Cycle of Violence

Overview

The idea that early experiences can shape adult behaviors and abilities has been a recurring theme for many developmental models. Freud suggested that our first years of life shaped our adult personalities and desires. Konrad Lorenz showed that imprinting—the sights and sounds it experiences soon after hatching—help define a bird's preferences throughout its lifetime. Developmental neuroscience research has focused on critical or sensitive periods; for example, if an animal does not receive visual input from its eyes soon after birth, its brain may begin reorganizing and the animal may never learn to see. In the same way, the relationship between a child, its parents and peers may influence the child's social behavior as an adult.

Being abused or neglected as a child presents a universal risk factor for developing criminal and aggressive tendencies later in life; this phenomenon is commonly known as the cycle of violence (Caspi et al., 2002). Violence is defined by the American Psychological Association as an extreme form of physical aggression such as assault, rape or murder (APA Psychology Topics: Violence, 2011). In its simplest form, the cycle of violence suggests that if parents or guardians, who may be criminals themselves, abuse their children, this causes their children to become violent criminals. The second generation of criminals will then become abusive when they grow up, ensuring that the following generation will suffer at their hands, thus continuing the cycle *ad infinitum* (or *ad nauseum* depending on how disturbing one finds the idea).

At its core, the cycle of violence offers an explanation for why some individuals become violent, whereas most humans rarely engage in violent behavior, if they do at all. One possible explanation for why someone becomes a criminal is that they experienced something traumatizing during their youth, such as child abuse, and this experience set the occasion for later violence.

While this theory provides a plausible explanation for violent behavior and has become an accepted idea in popular psychology and criminology, many questions remain (Widom, 1989a). First, do we have evidence that the effect is real? The possibility remains that these abused individuals may have become violent even if they weren't abused or mistreated. Second, do all abused children become violent, or is it just some vulnerable individuals? Third, if the cycle of violence is real, by how much does it increase the risk for

violence? Finally, if a relationship exists, what mechanism mediates it? Abused children may learn to behave violently because they are modeling their parents (Bandura, 1962) or they may undergo a psychological or biological change following abuse which alters their behavior (De Bellis, 2005). Understanding why the cycle of violence exists may help to both illuminate it and offer a more complete explanation of what causes it and what factors may protect against it.

Historical Perspective

Although violence has long been a part of human culture, it wasn't until 1879 that criminology became an independent academic field (Garland, 1988). At this time, criminal study took on more complex questions, looking into the type, severity, causes, and control of criminal behavior in both the individual and society.

Looking beyond the immediate emotional motives behind violence, criminologists also wanted to know which people are most likely to murder, and why. Still heavily influenced by Freudian concepts, criminologists and psychologists sometimes framed the problem relative to a person's psyche, for example by citing an Oedipus complex, where a child develops jealousy toward their opposite-sex parent (Bender and Curran, 1940). In one of the earliest case report looking at children and adolescents who had committed murder, Bender and Curran noted that these children came from abusive and neglectful homes (some of the children presented signs of physical abuse, e.g. "cauliflower ears"). They went on to described five factors that motivated young people's violence (1940). Their five factors included 1) severe sibling rivalry, 2) coming from an unloving home, 3) an inferiority complex, 4) educational difficulties, and 5) coming from an aggressive or violent home.

Expanding on this idea, Easson and Steinhilber (1961) documented eight adolescents who attempted murder and speculate on the cause. Replacing Freudian explanations, they suggest that murder occurs in a psychotic state that may result from a troubled childhood (Easson and Steinhilber, 1961). They place greater importance on the aggressive and brutal behavior of the parents, leading the dogma in the direction of the cycle of violence.

Not long after, Curtis (1963) distilled the ideas presented in the aforementioned case studies and formed a succinct hypothesis, expressing the concern that abused and neglected children may "become tomorrow's murderers and perpetrators of other crimes of violence, if they survive."

The idea of violence breeding future violence had both theoretical and anecdotal support (Curtis, 1963). Termed the 'battered child syndrome,' abused children may develop hostility towards their parents because of the suffering they endured and this hostility may lead to anger, aggression and violence. Also, if children learn proper behavior from their parents, they may adopt abusive tendencies because they grow up to mimic their parents' habits. Many vignettes of violent children found that they came from abusive or neglectful home situations, such as growing up in foster families that did not provide enough love or in families with extreme rivalry and discord. Professionals inferred that abuse may play a causative role in anti-social behavior. In the same way that parents might teach their children to mend their socks, they may also pass on violent tendencies (Bandura, 1962).

Although in the 1960s it became the leading hypothesis for the development of violence, an 'intergenerational transmission of violence' served as anecdotal speculation. No scientific studies had examined the phenomenon to rule out other possible explanatory factors. Although the literature had produced provocative accounts by astute observers, without controlled experiments, it would be impossible to prove that being abused propelled children to become abusive. At this point, the evidence was hindered by small sample sizes, weak sampling techniques, questionable accuracy of information and the lack of appropriate comparison groups (Widom, 1989a).

Empirical Evidence for the Cycle of Violence

Animal Models

To what extent does being the victim of abuse as a child contribute to the likelihood of becoming violent as an adult? Despite the popular acceptance of the theory of the intergenerational transmission of violence, it requires empirical support to definitively conclude that experiencing violence leads to becoming violent. Further, child abuse may involve a range of behaviors and experiences, but they may not all contribute equally to violent behavior.

Some evidence for the cycle of violence comes from other species. Reflecting the challenge of finding empirical support for the cycle of violence, only one study has found evidence for it in the wild (Muller et al., 2011). Muller et al. (2011) followed a generation of Nazca Boobies (*Sula Granti*), a bird native to the Galápagos Islands and one of the few species where physical and sexual abuse by non-related adults towards young animals can be consistently observed. Adult boobies demonstrate attraction to young boobies and regularly behave aggressively towards them, both physically and sexually, when parents

leave the chicks unattended while they hunt food. Muller et al. (2011) found a positive relationship between the amount of abuse chicks experienced and their likelihood to abuse other chicks when they grew up. Since the abusive adults were not genetically related to the chicks, the increased likelihood for the chicks to become abusive cannot be due to genetic effects, and may be due to the cycle of violence.

In captivity and laboratory settings, non-human primates have been used to model the effects of child abuse, neglect, and early-life stress on aggression. Most non-human primates are social animals that live in large groups with established and consistent matriarchal dominance hierarchies (Veenema, 2009). Mothers care for their young for a considerable period of time, and this care, in addition to providing food, warmth and shelter, is essential to the social development and maturation of the infant. When mothers do not provide adequate rearing, infants may fail to develop proper social skills (Veenema, 2009).

Providing a close model for human child abuse, 5-10% of macaque mothers living in captivity physically abuse or neglect their infants (Maestripieri, 1999). In an experiment exploring whether abusive parenting resulted from genetics or experience, a group of macaque mothers, some abusive and some non-abusive, raised either their biological infant or a foster infant (Maestripieri, 2005). Over half of the abused monkeys went on to become abusive parents, whereas none of the non-abused monkeys did, suggesting that the intergenerational transmission of abuse results from experience, not genes (Maestripieri, 2005). Although this model offers close resemblance to human abuse, no studies have looked at how child abuse affects aggression in adult male macaques, so it remains unknown how strongly abuse affects adult male aggression.

In the most commonly used model for early-life stress in primates, infants are separated from their mothers and, sometimes, from their peers. The infant's age and extent of isolation influences the severity of its social and emotional deficits (Suomi, 1991). Developed by Harlow and colleagues during the late 1950s and early 1960s, the initial model isolated infant macaques, either partially or completely, and found that it devastatingly altered normal development (Harlow et al., 1965). Release from isolation was usually followed by severe emotional shock characterized by 'autistic self-clutching and rocking;' one of the six monkeys isolated for three months refused to eat upon release and died within five days (Harlow et al., 1965). Monkeys isolated for 6 months or more showed permanent deficits in socialization and tended to remain isolated for life (Harlow and Suomi, 1971). In another group, infants were reared normally for the first six months and then isolated for the next six months. Although the isolation-first groups displayed both decreased aggression

and social interaction compared to controls, the isolation-second group showed increased aggression (Harlow et al., 1965).

Adapted non-human primate models currently use either periodic tactile isolation from mothers and peers for up to a year after birth or peer-only rearing from birth onwards. After 6-12 months of peer-rearing or isolation, the monkeys are housed with naturally raised monkeys (maternally-raised and socialized with peers) for comparison. Compared to naturally raised monkeys, peer-reared monkeys display less affiliative behaviors and more aggressive behaviors, such as wrestling and pursuit (Winslow et al., 2003). Rhesus monkeys that were reared by their mother other, without any peer social exposure, displayed increased submission behavior compared to monkeys raised in a natural setting and they showed more inappropriate and incompetent social behavior (Kempes et al., 2008). The isolated monkeys, whether raised in the absence of a mother or age-similar peers, moved towards the bottom of social-dominance hierarchies and remained there (Suomi, 1997). Disruptions in typical rearing patterns early in life, such as lacking a mother or peers, may permanently alter social behavior and dispose these deprived individuals to increased aggression (Suomi, 1997).

In addition to primates, rodents have been used extensively to examine the effects of early-life experiences on long-term behavioral and developmental outcomes (Veenema, 2009). During early development, pups require a great deal of maternal nurture for food, warmth and safety. As they begin to mature, they require interaction with peers to learn socially appropriate behaviors. Manipulating mother-pup or pup-peer interactions can alter development.

The most widely used rodent model of early life stress, maternal-separation paradigms can take several different forms. Litters may be separated from the dam for a single 24 hour period, for 3 hour periods on consecutive days, or individuals may be separated from both their litter and dam for several hours on consecutive days. Regardless of which paradigm has been used, rats that underwent maternal-separation as pups all exhibit increased fear and anxiety as adults, as evident from lack of exploration in a new environment and increased time freezing following a loud noise (Kalinichev et al., 2002). In male Wistar rats, daily 3 hour maternal-separation during the first two weeks after birth led to increased fighting behavior as adolescents (Veenema et al., 2006). Further, maternally-separated rats bit an opponent more often than controls and directed twice and many attacks at the nape of the opponent's neck (Veenema and Neumann, 2009).

Some studies have isolated rats immediately after weaning from the mother and housed them in individual cages for 4-8 weeks; the post-weaning period is when rats typically

learn appropriate social behaviors through interactions with peers and older adults (Veenema, 2009). This type of isolation has been considered a model of human neglect (Veenema, 2009). Social isolation results in heightened fear and anxiety as adults, in addition to increased alcohol intake (Fone and Porkess, 2008). Additionally, social-isolation induces heightened and abnormal aggressive behavior as adults, with an increase in attacks against peers with fewer warnings (i.e. threats), and an increase in attacks at vulnerable body parts such as the head, throat and belly (Toth et al., 2011; Veenema, 2009).

Finally, social defeat is a natural stressor in rats and most social animals (Veenema, 2009). Social defeat has been commonly used as a model to understand the effect of single episodes or repeated exposure to stressful situations such as bullying and abuse. In the social defeat stress model, juvenile male rats (post-weaning) are placed in the cage of an aggressive adult male for 30 minutes, during which the adult acts aggressively toward the juvenile, establishing dominance. Following this social-defeat the juvenile rats become more aggressive; they attack other rats more frequently and with less provocation and they are less likely to exhibit submissive behavior, even when paired with a larger rat (Veenema, 2009; Cunningham and McGinnis, 2008). In contrast, adult rats exposed to social defeat actually display decreased levels of aggression and increased submission (Raab et al., 1986), highlighting the importance of critical developmental periods in the expression of appropriate (or dysfunctional) social behavior patterns.

Based on the findings across several species, scientists have found copious evidence that early-life experience can alter adult social behavior. Neglect, isolation and abuse disrupt emotional processing, particularly increasing fear and anxiety, positive social interactions such as bonding and cooperation and, of primary concern for this dissertation, aggressive behavior. Numerous studies across species demonstrate that abuse creates abusers, providing evidence for a non-genetic, intergenerational transmission of violence. These studies model human behavior and development, but non-human models may not always parallel phenomena as complex as human social development and aggression. Further, once ideas are established in animal models, it is important to validate them in humans.

Human Studies of the Cycle of Violence

Researchers, professionals and writers have used the term ‘cycle of violence’ to refer to a range of situations and outcomes related to hypothesized effects of abuse and victimization. On one side, some refer to the cycle of violence as exclusively pertaining to abused children growing up to become abusers, but some refer to it more loosely as the

potential for abused children to commit delinquents, criminal or violent behaviors (Widom, 1989a).

Of the hypothesized outcomes of child abuse, the idea that abused children will become child abusers as adults has received some empirical support (Widom, 1989b). Yet, Kaufman and Zigler (1987) suggest that unqualified acceptance of the cycle of abuse hypothesis is unsubstantiated because the majority of abused children do not become abusers, whereas some individuals who lack a history of abuse will become child abusers. Further, many of the studies which demonstrate this pattern of abuse between generations are methodologically unsound because they rely on self-report and retrospective data, do not adequately document abuse and seldom use baseline measures or control groups. The method of assessing the rate of the transmission of abuse can affect the outcome; the lowest estimate is 18 percent, while the highest estimate is 70 percent (Kaufman and Zigler, 1987; Widom, 1989a). According to Kaufman and Zigler (1987), the best estimate is that 30 ± 5 percent of abused individuals go on to abuse their own children.

In addition to the abuser-leads-to-abusers aspect of the cycle of violence, another part of the hypothesis is that child abuse and neglect will lead to delinquency, such as crimes against property, teen pregnancy and not completing secondary education. Although early studies found rates of delinquency ranging from 10-30 percent, the fact that they lack appropriate control groups prevents inference into whether or not that differs from typical rates of delinquency, so the results were ambiguous (Widom, 1989a).

In the largest and most definitive assessment of the cycle of violence hypothesis, Widom (1989a; Maxfield and Widom, 1996) improved upon the methods of prior investigators by using clearly-defined criteria for abuse and neglect, a large sample to allow for sub-group comparisons, an age-, sex- and socioeconomic class-matched control group, and finally by looking at long-term consequences of abuse and neglect beyond adolescence and into adulthood. The abuse and neglect samples included all cases of physical and sexual abuse and neglect that went through a Midwestern county's court system between 1967 and 1971, with a final sample size of 908 individuals. 667 controls were matched using the county's birth records and elementary school records. Abused and neglected children had a higher rate of arrests for violence than did controls (11 versus 8 %; Widom, 1989a). Additionally, abused and neglected children had a higher mean number of offenses (2.4 versus 1.4; Widom, 1989a).

In subgroup analyses, males were more likely to have a criminal record than females, but both males and females who were abused or neglected had significantly higher rates of crime compared to controls (Widom, 1989a). Blacks were statistically more likely to have an

arrest record than whites, but both groups showed increases in criminal behavior following child abuse or neglect. For whites, there was no significant increase in violent crime (WIdom, 1989a).

Among the subjects who had a juvenile record, abused and neglected individuals were as likely as controls to have an adult criminal record (53 versus 50%). Similarly, among those with a violent record as a juvenile, abused and neglected individuals were as likely as controls to have violent criminal records as adults (34 versus 36 %; Widom, 1989a). Hence, abused and neglected individuals are more likely to commit violent and non-violence crimes in the first place, but once a person has committed a crime they are just as likely to do it again whether or not they were abused. Beyond adolescence, the best predictor of future behavior is past behavior.

Widom (1989a) found that 15.8 percent of physically abused children had been arrested for a violent offense, compared to 12.5 percent of neglected children, but only 7.9 percent of controls. In a review, Maas et al. (2008) concluded that physical abuse is the most consistent predictor of youth violence. However, according to Widom (1989a), neglect is the second strongest predictor of violence.

Recently, a prospective longitudinal study followed 574 children from age 5 to 24 and examined whether early abuse (before age 5) led to higher rates of delinquency and violence (Lansford et al., 2007). At the time of enrollment in kindergarten (age 5), 69 children (12% of the sample) were classified as abused based on interviews with the child's parents, a rate consistent with national samples (Straus and Gelles, 1990). The study found that abused individuals were significantly more likely to have been arrested for violent (12 versus 4 percent) and non-violent crimes (22 versus 9 percent) as determined by court records, and they were also more likely to have committed domestic violence (10 versus 28 percent), have lost their job in the past year (7 versus 26 percent) and to have dropped out of high school without completing their degree (38 versus 13 percent; Lansford et al., 2007).

In addition to the small-sample clinical accounts which prompted the idea and the retrospective studies which gave the first statistical analysis, prospective studies also bear evidence confirming the cycle of violence hypothesis. Hence, we have good reason to answer the question that Curtis posed in the title of his 1963 clinical note "Violence Breeds Violence—Perhaps?" that indeed, violence does breed violence.

Synthesis: Understanding the Cycle of Violence

The evidence presented above provides a framework for the etiology of violence, but the story remains incomplete. For example, although numerous studies demonstrate support for the cycle of violence hypothesis, they fail to explain why the effect exists. Similarly, although genetics clearly play a role in violence and aggression, identical twin studies reveal that genes do not solely determine behavior; they account for approximately half of the likelihood. A combination of nature and nurture interact to determine the risk for violence.

Further, describing the cycle of violence gives the impression that all abused children are destined to become violent. In fact, the majority of abused children will never be arrested for violent crimes or abuse their own children (Widom, 1989a; Maxfield and Widom, 1996; Lansford et al., 2007). Around 70 percent will have no legal troubles (Widom, 1989a; Lansford et al., 2007). These individuals may be protected by factors that prevent the intergenerational transmission of violence, such as biological traits, positive experiences, disposition or environmental conditions (Widom, 1989).

Also, the cycle of violence may not be a direct cause-and-effect relationship. Instead, violence and aggression may result from some other changes which take place in certain susceptible individuals following abuse or neglect. The following sections will examine some possible biological and psychological explanations for the cycle of violence to help better understand this complex phenomenon.

Chapter 2. Lasting Effects of Child Abuse and Neglect

Overview

When Curtis (1963) worried that today's abused children might become tomorrow's murderers, if they survive, his concern was not exaggerated. In 2006 alone, nearly one million children were victims of child abuse (US Department of Health and Human Services, 2008a). Some abused children will never reach adulthood because they will be killed by their parents or guardians. According to the Center for Disease Control's (CDC) Morbidity and Mortality Weekly Report, 4±1 children die each day from child abuse. Those that do survive may be scarred physically or emotionally, which can have long-term effects on their health and functioning. This section will explore the consequences of child abuse and neglect.

Although child abuse typically occurs within the home, its costs burden the entire society. First of all, the means for investigation and prevention of child abuse cost the US $24 billion annually (Prevent Child Abuse America, 2001). The direct cost of combating child abuse is high, but Prevent Child Abuse America estimates the indirect cost as even higher. Society pays as much as $69 billion annually in terms of lost productivity and the burden on the criminal justice system caused by the increased rate of delinquency among victims of abuse and neglect (2001).

First, to understand the effects of child abuse and neglect, we must know what we're talking about. One of the problems many early studies of child abuse and neglect faced was that—having no agreed-upon and accepted definition of abuse and neglect—not all researchers and professionals were discussing the same issue. Further, child abuse and neglect are broad categories containing a wide range of situations. Threatening a child's safety differs from failing to provide a child's needs, and the consequences of these situations may differ according to the type of suffering the child endures.

The Federal Child Abuse Prevention and Treatment Act (CAPTA) defines child abuse and neglect as "any recent act or failure to act on the part of a parent or caretaker which results in death, serious physical or emotional harm, sexual abuse or exploitation; or an act or failure to act which presents an imminent risk of serious harm" (US Department of Health and Human Services, 2008b). The rate of substantiated child abuse cases is about 10 children out of every 1,000, or 1 percent (US Department of Health and Human Services, 2001). In table 1, the types of child abuse and neglect are defined and their prevalence is listed.

Type of abuse	*Definition*	*Prevalence*
Physical Abuse	Any incident of non-accidental physical injury to the child inflicted by the caregiver, e.g. hitting, burning or choking the child	17.8 %
Emotional Abuse	A pattern of behavior that impairs a child's emotional development or sense of self-worth, e.g. constant criticism, threats, or rejection, as well as withholding love, support, or guidance	7.6 %
Sexual Abuse	The use or coercion of any child to engage in, or assist any other person to engage in, any sexually explicit conduct, e.g. fondling a child's genitals, incest, rape, indecent exposure, and exploitation through prostitution	9.5%
Physical Neglect	Failure to provide necessary food, shelter, or medical or mental health treatment; the lack of appropriate supervision	78.3%
Emotional Neglect	Inattention to a child's emotional needs, failure to provide psychological care, or permitting the child to use alcohol or other drugs	12%

Table 1. Types and prevalence of abuse and neglect. Prevalence is the percent of abused and neglected children who fall into each category. Percentages add up to more than 100 because most abused children fall into more than one category and are counted accordingly (US Department of Health and Human Services, 2001).

Psychological Outcomes

The short-term emotional distress of abuse and neglect, such as isolation, fear and pain, can generate long-term psychological problems. Cohen et al. (2001) found that abused and neglected children developed a wide range of psychiatric disorders—depression, anxiety, substance abuse, personality disorders—at twice the rate of non-abused and neglected peers.

At age 13, over 70 percent of abused children had a cluster A personality disorder (often characterized by mistrust of others, lack of social interest), and the increased morbidity of abused and neglected children persisted from adolescence through adulthood (Cohen et

al., 2001). Abused children also had higher rates of suicidal thoughts and attempts (Silverman et al., 1996). A longitudinal study also found that abused children had lower grades in school and had more difficulty fitting in with peers and adapting to the social pressures of school (Zolotor et al., 1999). Abuse and neglect put children at risk for poorer emotional and cognitive health throughout their lives.

Behavioral Outcomes

As examined in Chapter 1, abuse and neglect both lead to an increase in delinquency, crime and violence. These problems can develop at a young age. Jaffee et al. (2004) found that children who experienced abuse displayed significantly more antisocial behavior by the age of 5, and the extent of their antisocial behavior corresponded to the amount they were abused. If abuse continued, the differences were magnified by age 7 and the abused children scored even higher than their non-abused peers (Jaffee et al., 2004).

Abused and neglected children have higher rates of behavioral problems throughout life. They are also more likely to engage in un-safe sex practices, increasing the chance that they will contract sexually transmitted diseases (Johnson et al., 2006). Further, as many as two-thirds of patients seeking treatment for substance abuse and dependence reported being abused or neglected as children (Swan et al., 1998). Also, as mentioned in Chapter 1, roughly 30 percent of abused and neglected children will abuse their own children (Kaufman and Zigler, 1987).

Physical Health Outcomes

Child abuse and neglect can have both immediate and lasting effects on a child's health. Of course, physical abuse can cause bodily injury, but a study of children who experienced adversity, such as abuse, early in life found that they were more likely to suffer from poor health throughout childhood (Flaherty et al., 2006). Experiencing one adverse event doubled a child's risk for serious medical issues, and experiencing four or more events tripled a child's risk (Flaherty et al., 2006). These effects persisted into adulthood. A longitudinal study found that adults who had a history of child abuse or neglect were more likely that non-abused peers to suffer from a range of medical problems, such as arthritis, bronchitis, asthma, high blood pressure and ulcers (Springer et al., 2007).

Importantly, abuse and neglect have been associated with slowed brain development and maturity (De Bellis and Thomas, 2003). These changes in brain development and formation may impact an individual's social, psychological and educational abilities and may explain some of the aforementioned problems associated with abuse and neglect (De Bellis,

2005). As the possible changes in brain structure and function represent an important part of this dissertation, it is important to examine the neurobiological effects of child abuse and neglect in greater detail.

Neurobiological and Endocrinological Effects of Child Abuse and Neglect: Hypothalamic-Pituitary-Adrenal Axis

Important to the primary goals of this project, child abuse and neglect can have a lasting adverse impact on the body and the brain (De Bellis, 2005). Particularly, the Hypothalamic-Pituitary-Adrenal (HPA) axis may be disturbed as a result of maltreatment, and this disruption may be associated with many of the other negative outcomes associated with maltreatment (De Bellis, 2005).

The hypothalamus, pituitary and adrenal glands that make up the HPA axis work as a group by making use of feedback loops, where each has some direct or indirect regulatory control over the others (Reichlin, 1992). For example, the hypothalamus releases corticotropin releasing hormone (CRH), which stimulates the pituitary to release adrenocorticotropic hormone (ACTH). ACTH then stimulates the adrenal gland to release cortisol. Cortisol, in turn, dampens both the hypothalamus and pituitary, preventing the further release of stimulating hormones (Reichlin, 1992). The HPA axis mobilizes the body's response to stress, and regulates many bodily functions, such as digestion, the immune response and energy storage and expenditure. Further, it mediates the body's response to mood, emotions and sexuality (Reichlin, 1992).

The end product of the HPA axis, cortisol (also known as hydrocortisone), is the primary human glucocorticoid (Reichlin, 1992). Physiologically, cortisol stimulates the release of glucose into the bloodstream through gluconeogenesis and suppresses the immune system (Reichlin, 1992). Although most cortisol (approximately 90%) circulating in the body is associated with binding proteins, such as corticosteroid-binding globulin or transcortin, free cortisol mediates most of the physiological effects (Reichlin, 1992). Free cortisol can cross cell membranes and bind to either glucocorticoid or mineralocorticoid receptors, through which it mediates its effect on cells. For example, when cortisol binds to the glucocorticoid receptor, it can form a dimer that then enters the cell nucleus and regulates DNA transcription via the glucocorticoid response element (Reichlin, 1992).

Cortisol release follows a circadian rhythm, where levels are highest soon after waking and fall throughout the day, reaching a nadir in the late evening (Reichlin, 1992). Events throughout the day also affect HPA axis function and cortisol release. For example, cortisol levels rise after eating to aid in digestion and metabolism and, germane to the

dissertation, acute stressors can cause the release of cortisol (Reichlin, 1992; Lopez-Duran, 2009). Cortisol levels follow a homeostasis in the body, where excessive or insufficient amounts can be pathological, resulting in disorders such as Cushing's syndrome or Addison's disease (Reichlin, 1992). Furthermore, the shape of the diurnal cortisol curve can indicate pathology, where a peak and trough are normal, but a flattened curve—usually characterized by a blunted peak—is associated with mental health disorders such as Post-Traumatic Stress Disorder (PTSD) and depression (Thorn, 2011).

Clearly, a well-functioning HPA axis is important to general health and well-being. Yet, rat studies show that pups separated from their mother exhibit both acutely elevated cortisol levels and long-term changes in HPA axis function (Veenema, 2009). Rhesus monkeys with abusive mothers have elevated basal morning cortisol levels during the first month of infancy (McCormack et al., 2003). Similarly, maltreated children often have higher HPA axis and cortisol activity compared to non-maltreated children (De Bellis, 2005). In one study, Romanian orphans who lived in an orphanage for over 8 months of their life had significantly elevated cortisol levels (2 SD above mean) as adolescents compared both to orphans who were adopted within 8 months or to non-orphaned children (Gunnar et al., 2001). Further, the longer the children remained in the orphanage, the higher their cortisol levels as adolescents (Gunnar et al., 2001). These changes in HPA axis function and cortisol activity are hypothesized to play a role in the adverse outcomes associated with child abuse and neglect. Accordingly, this hypothesis features prominently in the study rationale.

Heightened HPA axis activity and cortisol levels are related to atrophy in vulnerable brain regions, such as the hippocampus (Sapolsky, 2000). Repeated administration of corticosteroids during pregnancy led to deficits in nerve myelination in sheep, suggesting that glucocorticoids may impair the formation and development of the central nervous system (CNS; Dunlop et al., 1997). In tree shrews, repeated exposure to stressors prevented the growth and proliferation of granule cells in the hippocampus (Gould et al., 1998). Deficits in brain structure and development relate to impaired cognitive function, such as decreased short-term memory capacity (Bremner, 1997). Clearly, experiencing stress—such as physical or sexual abuse—during development can not only alter HPA axis function and cortisol patterns, but lead to altered brain structure and function (Bremner et al., 1997). One of the hypotheses of this project is that abuse and neglect induce changes in the HPA axis function that are associated with altered brain function and control of aggressive behavior.

Resilience

Finally, it is important to understand that some abused and neglected children, through protective factors, demonstrate resilience—that is, they do not suffer from lifelong pathologies. Despite the increased risk they face, not all abused and neglected children will experience long-term consequences. In fact, the majority of abused children will never have a criminal record, will not abuse their own children, will graduate high school and will become physically and psychologically healthy adults (Widom, 1989; Kaufman and Zigler, 1987; Lansford et al., 2007, Cohen et al., 2001). McGloin and Widom (2001) found that 22 percent of abused and neglected children met their criteria for resilience (versus 41 percent of demographically matched-controls), satisfying at least six of the following eight domains of success: employment, homelessness, education, social activity, psychiatric disorder, substance abuse, arrest record and self-reports of violence. It should be noted that during their assessment, only 20 percent of maltreated individuals and 30 percent of controls were employed (McGloin and Widom, 2001).

The outcomes of childhood maltreatment vary widely by individual and are affected by a combination of factors. As suggested by Harlow's research (1965) and by studies of orphans, the age when abuse or neglect occurs affects the likelihood and severity of negative outcomes (Nelson et al., 2007). The type of maltreatment also plays a role in the potential outcomes (Widom, 1989; Cohen et al., 2001).

Individual differences, such as optimism, intelligence, and social support may also buffer children from the adverse effects of maltreatment (Fraser and Terzian, 2005). Environmental differences such as neighborhood stability, access to safe schools and health care also play a protective role (Fraser and Terzian, 2005).

Further, differences in biology alter the risk for adverse outcomes following maltreatment. For example, certain genotypes are less likely to result in violence and psychopathology even if the individual was abused (Caspi et al., 2002). These biological differences in likelihood for aggression will be discussed in Chapter 4, but the next section will examine aggression as a phenomenon and some of the relevant factors that affect its likelihood.

Chapter 3. Study of Aggressive Behavior

Overview

When a clownfish swims too far into the territory of another clownfish, the resident will normally threaten or attack the intruder until it has chased it away; this is an illustrative example of aggressive behavior (Lorenz, 1966). Aggression is a highly conserved behavior, present in nearly all animals, indicating its importance for both the immediate survival of an individual animal and—from an evolutionary perspective—the preservation of species as a whole (Lorenz, 1966).

Despite its clear value, aggression can also cause destruction, as in war and murder. From a scientific standpoint, aggression is interesting as an explanation and exploration of behavior, but from a societal standpoint, the general public stands to gain by better understanding aggression in the hopes that some of it may be prevented. Violence decreases the quality of life for a society through several means, including direct injury, subsequent mental and emotional health issues, and the vast cost of repairing the damage. The Center for Disease Control (2003) estimates that intimate partner violence alone costs society over $5 billion annually due to medical expenses, psychological treatment and loss of productivity. Yet crime rates vary by year and location; the crime rate in New York City in 1995 not only differs from the crime rate in London in 1995, but also from New York City in 2003 (Uniform Crime Reports FBI, 2006). This fact alone suggests that all aggression is not inevitable, but a behavior that can vary in frequency and intensity.

Defining Aggression

To accurately understand aggression or any behavioral phenomenon, it is important to have an operational definition. A broad array of behaviors may qualify as aggression: territorial defense, responding to a threat, rape, murder, warfare and intimate partner violence. To this list, one could also add insulting a neighbor or making a rude gesture, such as raising your middle finger at someone. Colloquially, people may characterize a daring skier or a relentless salesperson as aggressive. Do all of these acts qualify as aggressive?

Studying aggression would be greatly simplified by knowing, categorically, which acts meet the criteria for aggression and which do not. Yet, historically, defining aggression has been a challenging issue. Similar to U.S. Supreme Court Justice Potter Stewart's test for pornography in 1964, we may feel we "know it when we see it," but cannot circumscribe every action which would satisfy it. Aggression encompasses too broad a range of behaviors to accurately list them all, and as skeptic and British foreign secretary Sir Austen

Chamberlain said, trying to define aggression by the acts which satisfy it would create a "trap for the innocent and a signpost for the guilty." Such limits would seem to permit all activity that lay outside the limits. A good definition, then, would describe the heart of the behavior rather than specifying a set of actions.

In 1994, Baron and Richardson defined aggression as "any form of behavior directed toward the goal of harming another living being who is motivated to avoid such treatment." If we look back at the clownfish defending its territory, we may "know it when we see it," but additionally, Baron and Richardson provide specific criteria we can use to determine if the behavior is truly aggressive. Aggression is a behavior, such as when the clownfish attacks. The behavior has a goal; the resident clownfish wants the intruder to flee. The motivation is to harm and the clownfish's attack—which often takes the form of biting—would cause physical harm to the intruder. The behavior must be directed at another living being, so biting a grain of sand would not qualify, but biting an intruder would. Finally, the other being must be motivated to avoid the treatment. We know the intruder clownfish does not want to be attacked; that is why it flees.

Following from Baron and Richardson's definition, this dissertation will define aggression according to the following criteria:

A) a social behavior that involves the interaction of at least two people
B) it is intended to harm another person
C) the other person finds the harm aversive and would act to avoid it

This has served as the operational definition of aggression for many previous studies from this laboratory, and is the basis for which the Point-Subtraction Aggression Paradigm (explained below), the primary tool used to study aggression here, was designed (Cherek, 1992; Cherek and Lane, 1999).

Types of Aggression

Our definition broadly defines aggression, but it offers no way to distinguish between acts that qualify as aggressive. Both insulting a neighbor and committing murder count as aggressive, but they scarcely resemble one another. Now that we have a general definition, we can begin to parse the behavior into categories. The definition itself offers a starting point. There are many behaviors which can harm, but they do not all harm uniformly. There are many possible motivations for harming, and these intentions may affect both the way the action is performed and perceived.

Scholars of human aggression generally divide the behavior into two broad categories, proactive and reactive (Dodge and Coie, 1987; Bushman and Anderson, 2001). Poulin and Boivin (2000) described the difference between the two as follows:

> *Reactive aggressive behavior is a hostile act displayed in response to a perceived threat or provocation. This behavior is generally impulsive and typically occurs with hostile facial expressions and a strong negative affect. A proactive aggressive behavior is a nonprovoked aversive act aimed at influencing others. This behavior could attempt to gain a resource (i.e., an object, a privilege, or a territory) or could be directed towards a person with the purpose of intimidation or domination (pg 115).*

Evidence exists that aggressive acts can be divided into proactive versus reactive, with some individuals consistently engaging in proactive and others consistently engaging in reactive aggression (Dodge and Coie, 1987). A recent study demonstrated that grouping children by teacher ratings of their aggressive tendencies into proactive, reactive, proactive-reactive mix, or nonaggressive predicted how they would respond to a stressful situation; children in the reactive and proactive-reactive mix groups had significantly higher cortisol levels following stress (Lopez-Duran et al., 2007). Such studies corroborate the notion that proactive and reactive forms of aggression are discrete and their constructs have utility when studying aggression.

However, Bushman and Anderson (2001) suggest that nearly all aggressive behavior contains at least some elements of both proactive and reactive aggression. They argue that although the proactive-reactive distinction does capture some important elements of aggressive behavior, by dichotomizing aggression, it fails to consider aggressive acts with multiple motives; dichotomizing aggression will delay further advances in understanding and controlling human aggression (Bushman and Anderson, 2001). Although their argument has merit, a detailed consideration is beyond the scope of this dissertation and subsequent references to proactive and reactive aggression will ascribe to Poulin and Boivin's (2000) definition above.

History of Aggression Research

Some of the earliest research into the causes of aggression focused on crime statistics (Lombroso, 1911). For example, criminal records in France, England and Italy all demonstrated that crime varied with temperature, showing that more rape, murder and riots occurred during the hottest months (Lombroso, 1911). For over a hundred years,

criminologists have recognized that to understand crime, you must consider a multitude of factors, including “the man's heredity, the man's physical and moral make-up, his emotional temperament, the surroundings of his youth, his present home, and other conditions” (Lombroso, 1911). One of the constant problems facing researchers is that aggression is a rare occurrence in man in natural surroundings, so early studies were limited to crime statistics and case studies of criminals (Lombroso, 1911).

Similarly, most early animal research studied aggressive behavior in natural settings (Lorenz, 1966). Observing animals natural behavioral patterns allowed early researchers to better understand the conditions in which animals may behave aggressively, and for what purpose (Bernstein, 1976).

Animal Studies

Animal studies have led to crucial and significant advancements in the understanding of aggression, especially regarding questions which would be impossible to address in humans for safety and ethical reasons. For instance, animal studies have enhanced the precision with which we can study the involvement of specific brain regions, neurotransmitters and hormones in aggression (examined in chapter 4; Miczek et al., 2002). Further, animal studies allow scientists to manipulate environmental conditions and isolate variables that would be impossible to isolate in humans, such as the type, amount and extent of stress endured early in life (Veenema, 2009).

For example, whereas it would be impossible to control the early environment of a cohort of children, exposing some of them to child abuse and some not, this model is feasible in rodents (Veenema, 2009). Controlled experiments in the laboratory have provide valuable evidence for biological changes accompanying aggression, such as the fact that rats separated from their mothers early in life release more cortisol in response to social encounters with novel rats compared to controls; these rats are also more aggressive in social encounters (Veenema et al., 2009).

In non-human primates, monkeys who are raised in a peer-housing environment without a mother or surrogate primary caregiver tend to develop abnormal social behaviors (Suomi, 1997). For example, they are more fearful of novel objects and engage in abnormal play, characterized by impulsive, excessive and inappropriate aggression towards other members of their group (Suomi, 1997).

Animal studies allow for assessment of changes in the brain following aggression as well, including neurotransmitters, genetic expression and structural changes not observable in humans. Czeh et al. (2010) found that exposing rats to repeated experiences of social

defeat, where they faced a larger opponent who attacked and defeated them, caused a decrease in capillaries in the hippocampus.

Assessment of Human Aggression Research

Methods of studying aggression vary on a continuum that includes external and internal validity. External validity refers to the extent that a given study allows for wider inferences into universal truths (Mitchell and Jolley, 2001). Internal validity refers to the extent that measurements variables are carefully controlled, external sources of variance are minimized, and as a result one can infer causality (Mitchell and Jolley, 2001).

Epidemiological Studies

Epidemiology looks at health events and patterns in a society. In terms of aggression research, it may observe the prevalence of a behavior in a population and look at which factors predict its likelihood. An example would be the twin studies looking at violent crime convictions among MZ and DZ twins (Cloninger et al., 1987). In this study, the authors concluded that having an MZ twin who committed a violent crime presents a greater risk for an individual to also commit a violent crime compared to having a violent DZ twin (Cloninger et al., 1987).

Widom's (1989) study of victims of substantiated cases of child abuse or neglect versus matched controls found that victims had an increased risk of committing a violent crime. Specifically, victims of abuse and neglect (11.2%) had a higher rate of violent crime compared to controls (7.9%), meaning that their relative risk was 1.41, with a 95% confidence interval (95%CI) of 1.03 to 1.94 (Widom, 1989). Thus, abused and neglected children are 1.4 times more likely to commit a violent crime compared to non-abused and neglected children.

The advantage of epidemiological studies is that they allow for a behavior or event to occur in a natural environment. Given sound methods, the results have high external validity and can be generalized to a larger population. On the other hand, the disadvantage of epidemiological studies is that they do not allow for the observation of a behavior in determine causal relationships. Further, the types of questions that can be addressed are limited to behaviors that occur relatively frequently and observably in a natural environment.

Psychiatric and Prison Studies

Samples of psychiatric patients or prisoners have also been used to study aggression. For example, Sarchiapone et al. (2009) found that prisoners with higher self-

reported histories of child abuse and neglect scored higher on a questionnaire that measured lifetime history of aggression. Furthermore, when prisoners were grouped into a high versus low abuse and neglect group, there was a significant group difference on rates of violent infractions during incarceration: the high abuse/neglect group committed more violent infractions than the low abuse/neglect group during their time in prison (Sachiapone et al., 2009). An estimate from the US Department of Justice suggests that 14 percent of men and 36 percent of women in prison were abused or neglected as children (Harlow, 1999).

In a study of psychiatric patients who had both a history of aggressive behavior and a DSM-IV-defined personality disorder, treatment with the GABA-modulating, anti-convulsant medication divalproex decreased the incidence rate of impulsive aggression over a twelve-week period (Hollander et al., 2003). Here, the dependent variable was self-reported and observed verbal aggression and assault against objects (Hollander et al., 2003).

The advantage of prison and psychiatric studies is that they allow for external validity because the behavior of interest occurs in a natural context. Prisoners and individuals with substance use disorders or anti-social personality disorder represent the populations most likely to commit crimes related to aggression, such as assault (Coid et al., 2006). Further, prison and psychiatric studies allow for manipulation of key variables to provide internal validity, such as administering a drug or changing the environment to observe how the behavior changes as a result.

Conversely, a disadvantage of some prison and psychiatric studies is that they do not allow for the observation of a behavior in real-time. Also, participants and researchers may be in risk of harm because sometimes the variable being measured is frequency of aggression. Also, external validity may be limited because the subjects do not represent the general population. Also, the context in which the behavior takes place, such as a prison or psychiatric inpatient unit, may differ from the world that the general population inhabits, limiting external validity.

Self-Report and Laboratory Studies

Self-report and laboratory studies provide another method of addressing questions about aggression. Self-report methods can include interviews and questionnaires related to a participant's history of aggressive behavior, including verbal fights, physical fights and crimes. Laboratory studies are designed to quantify aggressive behavior and measure it in real-time. For example, subjects may be given a task that allows for the expression of an operationally-defined aggressive behavior, such as administering an electric shock to an opponent.

In a study using both self-report and laboratory measures of aggression, Miller et al. (2009) found that individuals with high levels of trait aggression were more likely to use the highest aggressive response option in the Taylor Aggression Paradigm (TAP) after alcohol administration. The TAP is a reaction-time task where participants compete with a fictitious opponent to respond faster to a stimulus (Taylor, 1967). The winner administers a shock to the loser and can set the level of the shock from mild to severe. The participant is provoked by receiving severe shocks from the fictitious opponent; provocation is an important precursor to aggression because although most people rarely initiate aggression, they may respond aggressively to provocation (Baron and Richardson, 1994). The study measured trait aggression using the Buss-Perry Aggression Questionnaire, a 29-item survey that assesses physical aggression, verbal aggression, anger and hostility (Buss and Perry, 1992).

A similar laboratory method, the Point-Subtraction Aggression Paradigm (PSAP; Cherek, 1992) places subjects in a chamber with a computer where they are given the opportunity to earn points that can later be exchanged for money. Via a computer network, the subject interacts with a fictitious opponent that periodically provokes the subject by subtracting the subject's earnings; the subject has the option of subtracting the opponent's points throughout the task. Subtracting points meets the operational definition of aggression because it involves the interaction of at least two people (the subject believes they are subtracting money from another person), the subject intends to harm the opponent (taking their money) and the opponent find the harm aversive (they would rather keep the money). The subject may subtract the opponent's points proactively, without provocation, or reactively as retaliation for a loss. Whereas the TAP measures the intensity of the aggressive response (the level of shock), the PSAP measures the frequency. For example, in one study Cherek et al. (1996) found that parolees with a history of violent crime used the aggressive response more than twice as often parolees without a history of violent crime.

Another self-report assessment of aggression is the Impulsive/Premeditated Aggression Scale (IPAS; Stanford et al., 2003). This instrument dichotomizes aggression into proactive, pre-meditated acts versus reactive, impulsive acts and seeks to classify individuals as higher on one of the two scales. In a study of 113 males convicted of intimate partner violence in a court-ordered intervention program, males who scored higher on premeditated aggression were more resistant to treatment, whereas males who scored higher on impulsive aggression were more likely to have psychiatric disorders (Stanford et al., 2008).

Among the advantages of laboratory measures of aggression, researchers can manipulate key variables such as the level of provocation, the environment and the time of

day that the behavior occurs. Aggression can be observed in real-time, but without putting participants at risk of any serious harm. Repeated-measures are also possible to see how aggressive behavior changes across time and conditions. These advantages allow for a high level of internal validity.

Some potential disadvantages are that the behavior is not the same as the real-world behavior of interest, so some external validity is compromised. Researchers do not observe participants in the act of assault, but instead they see a proxy for aggressive behavior. However, with the use of self-report, researchers can obtain a reliable measure of trait aggression and aggressive history to compare to laboratory measures to bolster the interpretation of the results.

For the present study, laboratory and self-report methods of assessing aggression were chosen to allow for testing across multiple conditions and times of day. Further, unlike other measures, the frequency of aggressive responding is free to vary in the PSAP and is not constrained to a single trial or option (see Cherek, Lane and Pietras, 2003). One innovative feature of this project is the laboratory measurement of aggression in subjects with a history of child abuse and neglect. Finally, as cortisol and the stress-response are hypothesized to play a role in aggression as a result of child abuse and neglect, the PSAP allows for the observation of changes in aggressive responding following the manipulation of cortisol levels in the body. To better understand how cortisol may affect aggression aggression, the next chapter will explore the biological underpinnings of aggression.

Chapter 4. Hormones and the Neurobiology of Aggression

Overview

In 1848, a group of railroad workers were packing blasting powder when an accidental explosion propelled an iron tamping rod up through the skull of the foreman, Phinneas Gage (Harlow, 1868). According to his physician's account, the brain damage forever changed Gage's behavior, providing early evidence that brain regions may play a specific role in the regulation of behavior (Harlow, 1868). Gage was described as a composed man before the injury, but after a portion of his prefrontal cortex was destroyed his temperament changed and his newfound temper produced bouts of rage (Harlow, 1868). In the intervening years, neuroscientists have elucidated the role of brain structures, neurotransmitters and hormones in the regulation of aggression.

As described in a review by Siever (2008), aggression may be "grounded in an underlying neurological susceptibility" resulting from the "failure of 'top-down' control systems to modulate aggressive acts triggered by anger," a hyper-responsive amygdala and other limbic regions involved in affect. As an overly simplistic metaphor to serve heuristic purposes, aggression can result from an imbalance in the brain between the drive, which spurs on aggression, and the brakes, which slows it down.

An in depth review of the current understanding of the neurobiological regulation of aggression is beyond the scope of this dissertation, so instead this chapter will focus on summarizing important findings and exploring the topics most relevant to the current project.

Structures Involved in Aggression

Among early experimental findings, Hess (1943) demonstrated that surgically removing sections of a cat's hypothalamus could invoke rage-like behavior. Similarly, using an electrode to stimulate regions of the hypothalamus could invoke hissing and threatening postures, but when the stimulation ceased, the cat would go to sleep (Hess, 1943). Two case studies in humans indicated that tumor-induced hypothalamic lesions corresponded to heightened aggressive behavior (Tonkonogy and Geller, 1992). Similarly, a PET imaging study in humans showed that perpetrators of domestic violence had decreased metabolism in the right hypothalamus (George et al., 2004). Important to this study, these findings indicate the involvement of the hypothalamus, the brain structure involved in the HPA axis. One of the hypotheses of this project is that the HPA axis is disrupted following child abuse and neglect.

In the heuristic model of the neurobiological regulation of aggression, the amygdala is typically viewed as a region involved in the initiation of aggressive behavior (Siever, 2008). Potegal et al. (1996) found that electrically stimulating the corticomedial amygdala of male Syrian Golden Hamsters led to increased attack behaviors. A functional PET imaging study of aggression found that subjects with Borderline Personality Disorder (BPD) responded more aggressively using the PSAP and also showed increased metabolism in the amygdala compared to healthy controls (New et al., 2009). Structural imaging studies in humans have linked Conduct Disorder (CD) with reduced volume of the amygdala (Fairchild et al., 2011). Germane to this study, the authors suggested that because the amygdala contributes to the initiation of the HPA axis stress-response, reduced volume in the amygdala could account for previous findings of a blunted stress response in individuals with CD (Fairchild et al., 2011).

Contrary to the amygdala, regions of the prefrontal cortex (PFC) are generally thought to be involved in regulatory control of behaviors, including aggression, providing inhibitory control (Siever, 2008). For example, in a study comparing murderers and healthy controls, Raine et al. (1998) found that murderers either had decreased glucose metabolism in the PFC during an attention task or increased subcortical activity, including amygdala activation. A study of Vietnam veterans found that men with lesions in the prefrontal cortex reported more aggressive and violent behavior than men with lesions in other brain areas (Grafman et al., 1996). When a group of healthy controls were asked to imagine engaging in aggressive behavior, Pietrini et al. (2000) saw a reduction in ventromedial PFC (VMPFC) activity, suggesting a release of top-down regulation (Siever, 2008). Using a PET version of the PSAP, New et al. (2009) found that healthy controls displayed less aggressive behavior than BPD subjects and had increased activity in the anterior, medial and dorsolateral PFC, suggesting that they had greater regulatory behavioral control. Notably, Tomoda et al. (2009) found reduced PFC volume in subjects who had been victims of physical child abuse relative to healthy controls, suggesting that one of the lasting effects of abuse may be contraction of brain regions involved in regulatory control of behavior.

The anterior cingulate cortex (ACC) has been implicated in a number of cognitive and emotional processes (Bush et al., 2000). Ducharme et al. (2011) found a negative correlation between ACC volume and a history of aggressive behavior in adolescents. A functional imaging study found that acute tryptophan depletion led to a decrease in connectivity between the amygdala and the ACC when viewing angry versus neutral faces, suggesting a potential loss of regulatory control of the amygdala's response to fear (Passamonti et al., 2011).

Although the neurological structures involved in the regulation of aggression are not entirely understood, research shows support for the heuristic model of top-down control and sub-cortical involvement in aggressive behavior (Siever, 2008). By modulating transmission in these structures, neurochemicals also play a role in aggressive behavior.

Neurotransmitters and Aggression

Neurotransmitters play a role in the regulation of aggressive behavior. Human studies of the metabolite 5-Hydroxy Indolacetic Acid (5-HIAA), an indicator of serotonin (5-HT) levels, consistently show that lower systemic levels of 5-HIAA correspond to increased aggressive behavior (Moore et al., 2002). A meta-analysis found a moderate effect size of -.45 in the direction that aggressive individuals had nearly half a standard deviation less 5-HIAA compared to controls (Moore et al., 2002). Although the studies in the meta-analysis measured 5-HT metabolites in the cerebrospinal fluid, precluding any indication of where in the brain the differences occur, the results support a model where individuals with lower 5-HT have less inhibitory control of their behavior (Moore et al., 2002). Studies have shown that drugs which generally increase 5-HT levels reduce aggressive responding on the PSAP (Cherek and Lane, 1999; Cherek and Lane, 2001). Preclinical models have indicated that 5-HT_1 and $_2$ receptor families play a significant role in the regulation of aggression, particularly 5-HT receptors in the PFC of rodents (de Almeida et al., 2005). In humans, the 5-$HT_{1B/D}$ agonist zolmitriptan reduced alcohol-related aggressive responding on the PSAP (Gowin et al., 2010). Importantly, abnormalities in the HPA axis stress-response are associated with disruptions in 5-HT function; this relationship may play a mechanistic function in altered aggressive behavior (Pompili et al., 2010).

In psychiatric inpatient settings, one of the most enduring pharmacotherapeutic interventions for aggression and violence is the administration of dopamine antagonists such as haloperidol (Kraus et al., 2005; Fitzgerald, 1999). Evidence from cat studies suggests that dopamine receptor D_2 antagonism—via injections of haloperidol into the medial preoptic area and anterior hypothalamus—decreases hissing and reactive defense behavior (Sweidan et al., 1991). However, pharmacologic dopamine increases can also be associated with increases in aggression in some conditions (de Almeida et al., 2005). For example, amphetamines can increase aggression indirectly by preventing fatigue during extended fights (Winslow and Miczek, 1983).

Another important neurotransmitter related to aggression, γ-amino butyric acid (GABA) has demonstrated a consistent, but complex, relationship with aggression (de Almeida et al., 2005). Postmortem studies found decreased levels of GABA in the striatum

and olfactory bulbs of aggressive mice and rats (Clement et al., 1987). Similarly, Bjork et al. (2001) found low GABA levels corresponded to increased levels of aggression in humans with a family-history of depression. These studies provide evidence suggesting that GABA, the primary inhibitory neurotransmitter in the CNS, plays a similar inhibitory role in aggression (Kandel et al., 2000). Consistent with this model, tiagabine, a drug which increases extracellular GABA levels, caused both acute and sustained decreases in human aggressive behavior on the PSAP (Gowin et al., 2011; Lieving et al., 2008). Contrariwise, drugs which positively modulate GABA receptor A, such as benzodiazepines and alcohol, have been shown to enhance aggressive behavior (de Almeida et al., 2005).

In addition to neurotransmitters themselves, two enzymes which regulate neurotransmitters—catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAOA)—have demonstrated a role in aggressive behavior (de Almeida et al., 2005). COMT and MAOA both catabolize catecholamines (dopamine, epinephrine and norepinephrine) in the CNS, inactivating them, and MAOA also catabolizes 5-HT (Kandel et al., 2000). According to de Almeida et al. (2005), "If aggressive behavior is enhanced by catecholaminergic activity, then the lower activity of COMT and MAOA (resulting in slower inactivation of catecholamines) should indirectly enhance aggression." Mice with either the COMT or MAOA gene knocked out displayed increased aggressive behavior (Gogos et al., 1998; Cases et al., 1995).

Germane to this project, evidence from MAOA genetic polymorphisms in humans provide some of the most direct evidence for a gene by environment interaction with respect to aggressive behavior (Ferrari et al., 2005). For instance, in a Dutch family with a rare mutation in the MAOA gene, males exhibited excessive bouts of aggression and violence, but these instances typically followed stressful events in their lives (Brunner et al., 1993). In a longitudinal study looking at the interaction between genotype (high versus low expression of MAOA) and child abuse and neglect, Caspi et al. (2002) found that individuals with high levels of MAOA were less likely to develop antisocial behavior following childhood maltreatment. This interaction effect may explain why only some abused and neglected children will develop antisocial behavior (Caspi et al., 2002).

Hormones and Aggression

Like neurotransmitters, hormones do not produce a behavior *in vacuo*, but rather increase or decrease the behavior's probability (Pfaff et al., 2004). The sensitivity to a particular hormonal trigger of aggression depends on a variety of factors, including hormone exposures early in development (Pfaff et al., 2004). As an example of the possible role of

hormones on aggression, between 1974 and 1992 the homicide rate in Canada rises sharply as males reach puberty and hormonal changes occur (prepubertal homicide rates are 2 murders/million people/year, post-pubertal [age 15-19] rates are 55 murders/million people/year), and the rate declines over the course of decades until, around age 60, they approximate pre-pubertal levels again (Pfaff et al., 2004). Of course, many other factors may contribute to this relationship, but hormones certainly demonstrate a relationship.

One prominent role of hormones is to initiate the "fight or flight" response, which includes elevated heart rate, energy mobilization (increased blood glucose), a "shift of attention towards socially relevant stimuli, decrease in pain sensitivity, and the enhancement of memory (an aggressive encounter is very relevant for the future of the animal)" (Haller et al., 1998).

Testosterone has long been considered important in aggression for the reason that males display more aggressive behavior in most species, including humans, and males have higher levels of testosterone (Pfaff et al., 2004). Testosterone, being a steroid, readily crosses the blood-brain barrier, where it can activate receptors in the amygdala, hypothalamus and limbic system (Pfaff et al., 2004). Testosterone also increases norepinephrine production, the neurotransmitter most responsible for the "fight or flight" response (Kandel et al., 2000). In rats, males castrated at birth fight less than do males castrated at weaning age or intact rats (Conner and Levine, 1969). Although the males castrated at weaning can be induced to fight at levels comparable to intact rats, males castrated at birth remain less aggressive. Conner and Levine (1969) concluded from this finding that the neural substrates affected by testosterone are permanently altered by early castration, corroborating the idea that hormonal effects on aggression depend on timing and concentration.

Oxytocin generally increases trust and bonding in mammals, including humans (Insel and Young, 2001; Kosfeld et al., 2005). It plays a role in inducing pair-bonding in adults and mother-offspring bonding after birth (Insel and Young, 2001). However, oxytocin can also produce increases in aggression in specific circumstances, notably maternal aggression when a mother feels her offspring is threatened (Caughey et al., 2011).

Like oxytocin, vasopressin helps regulate emotional and social behaviors such as anxiety, social attachment, social recognition and aggression (Veenema, 2009). Vasopressin levels in adults, as with cortisol, are impacted by early life experiences; for example orphaned children have lower vasopressin levels as adults compared to family-reared children (Fries et al. 2005). Coccaro et al. (1998) found that higher levels of vasopressin corresponded to greater life-histories of aggression in humans with personality

disorders. Thompson et al. (2004) found that intranasal administration of vasopressin led to reductions in subjects' perception of happy or neutral faces, but an increase in their perception of angry faces. Hence, vasopressin may increase an individual's perception of threat, which may indirectly increase aggressive behavior (Veenema, 2009).

An important part of the neuroendocrine system, the HPA axis and its end product, cortisol, also play a role in aggression and a wide range of social behaviors. As it comprises a central part of this project, cortisol's effects on behavior, aggression and the brain will be explored in depth in the next chapter.

Chapter 5. Neurobiological and Behavioral Effects of Cortisol

Overview

Harlow's social isolation model of monkeys, along with subsequent studies in rodents, indicate that lack of bonding with a mother early in life can be stressful to an infant and cause elevations in cortisol (Suomi, 1997; Veenema, 2009). In humans, a group of Romanian children placed in an orphanage for an extended period (over 8 months) during infancy displayed altered cortisol levels in adolescence, indicating a persisting change in cortisol levels (Gunnar et al., 2001). Although this is an oversimplified hypothesis, elevated cortisol levels resulting from lack of bonding early in life may, in part, contribute to deleterious outcomes associated with child abuse and neglect (De Bellis, 2005).

As discussed earlier, cortisol is the end product of the HPA axis in humans, released from the adrenal gland. Like many hormones, especially ones regulated by the hypothalamus, cortisol follows a circadian rhythm (Reichlin, 1992). It peaks early in the morning and falls throughout the day; cortisol levels just before waking are 3-fold higher than levels at the nadir, in the evening, so individuals are exposed to a wide range of concentrations (Reichlin, 1992). Cortisol has an optimum range, and levels above or below that range are often associated with pathology (Reichlin, 1992). Further, the diurnal cortisol curve has an optimum shape, and deviation from it can indicate pathology. A flattened curve, without a pronounced peak early in the morning, can indicate mood disorders (Thorn, 2011). Further, cortisol levels are affected by stressors; they rise by approximately an order of magnitude in response to a stressor, although the exact level varies by individual and the severity of the stressor (Sorrells et al., 2009).

Cortisol has a wide range of effects, but their direction (positive or negative) and magnitude depend on when, how much and for how long levels are altered. One of the ideas examined in this project relates to the General Adaptation Syndrome (GAS) model of the stress response as proposed in the 1930s by Hans Selye, who discovered many fundamental aspects of glucocorticoid physiology (Sapolsky et al., 2000). In Selye's model, the response to a stressor can be adaptive and produce resistance to and protection from the stressor in the short term. However, when the stress response remains chronically activated, it produces exhaustion from the constant state of arousal, and the hormonal response, including cortisol, can become toxic, producing ulcers, cardiovascular problems, and deterioration of the brain (Sapolsky et al., 2000). Although subsequent findings have led to a revision of Selye's GAS model, it provides a heuristic approach and a framework within

which to place relevant findings. This section will explore some findings of the acute and long-term effects of cortisol.

Acute Effects

The extant literature suggests that acute of effects of cortisol are complex and affect a variety of functions. Effects vary by a number of factors, including past experiences and circumstances. Because acute effects occur in less than an hour, the time course indicates that the effect is not related to genetic transcription or protein production, but to an effect that occurs on a shorter time scale, such as indirectly altering levels of neurotransmitters or directly acting at a receptor, although the exact mechanism is not known (Putman and Roelofs, 2010).

Some studies have found that acute doses of cortisol protected against negative mood effects associated with a stress task (reviewed by Putnam and Roelofs, 2011). Putnam and Roelofs (2011) suggest that cortisol may facilitate effective coping in response to an acute stressor. Conversely, in a group of healthy volunteers, acute cortisol administration increased anxiety in a dose dependent fashion, where placebo showed no increase from baseline, but 20mg and 60mg doses showed linear increases for an anxiety-potentiated startle reflex (Grillon et al., 2011). However, Grillon et al. (2011) found no difference in subjective mood or self-report of anxiety, so their focus on anxiety as measured by a startle response as opposed to self-report could explain the disparity in findings compared to other studies. The mood-protective or anxiogenic effects of cortisol may be related to the genesis of aggression.

Compared to healthy controls, subjects with PTSD demonstrated greater decreases in performance on a declarative and working memory task following the acute administration of cortisol (Grossman et al., 2006). There was a significant negative correlation between concentration of glucocorticoid receptors and working memory score for both controls and PTSD subjects, suggesting that subjects with PTSD may have greater sensitivity to the effects of cortisol which influences their memory performance (Grossman et al., 2006).

Bohnke et al (2010a) found that acute 20mg doses of cortisol caused females, but not males, to use louder and longer unpleasant sound on their opponent in the TAP. Bohnke et al. (2010a) provide the first evidence that cortisol can acutely affect the expression of aggressive behavior in a laboratory-model. In a different study from the same group, Bohnke et al. (2010b) found a negative relationship between waking cortisol levels and aggressive responding on the TAP, where the subjects with the lowest waking cortisol were most aggressive. A follow-up study found that acute cortisol administration led to faster reaction

times for emotional facial expressions, suggesting that cortisol may function by altering the evaluation of social information (Bertsch et al., 2011).

In a study looking at the cortisol response to an acute stressor, Lopez-Duran et al. (2009) found that children labeled by teachers as reactive-aggressive had significantly higher levels of cortisol after the stressor compared to either non-aggressive children or proactive-aggressive children. Proactive-aggressive did not differ from non-aggressive children regarding cortisol levels in response to a stressor (Lopez-Duran et al., 2009). This finding suggests that the cortisol response to a stressor may be related to patterns of aggressive behavior.

In a group of adolescent females who had been abused or neglected and a healthy comparison group, the control group showed a significant spike in free cortisol levels following a stress task, whereas the abused and neglected group showed a blunted response to the stressor (MacMillan et al., 2009). In contrast, a subsequent study found that maltreated adolescents without depression showed an enhanced cortisol response, whereas adolescents who were currently depressed showed a blunted cortisol response regardless of history of maltreatment (Harkness et al., 2011). Hence, the response to cortisol may depend on prior exposure to cortisol, group differences, and mood outcomes between maltreated versus non-maltreated individuals.

Long-term Effects

Hayden-Hixson and Ferris (1991) found that chronic cortisol administration in the hypothalamus affected aggression in male hamsters, but the direction of the effect depended dose, context and on which nucleus in the hypothalamus was targeted. For example, cortisol administration in medial hypothalamic regions increased submission behavior during encounters with another male, but administration in anterior hypothalamic regions increased aggression (Hayden-Hixson and Ferris, 1991).

A series of experiments in adrenalectomized rats—thereby chronically and systemically lowering cortisol levels—found that these rats developed heightened aggressive behavior and social deficits (Kim and Haller, 2007). The cortisol deficient rats showed an increase in activity in the amygdala following aggressive behavior, and aimed more of their attacks at vulnerable body parts (Halasz et al., 2002). A study looking at the interaction between 5-HT and cortisol found that in control rats, there was a negative relationship between 5-HT and aggression, whereas in adrenalectomized rats there was no relationship (Haller et al., 2005). This suggests that deficiencies in cortisol disrupt 5-HT's anti-aggressive effects, or alternatively that 5-HT's anti-aggressive effects may be mediated in part by

cortisol. The interaction between 5-HT and cortisol may be important for the regulation of aggression (Kim and Haller, 2007).

Relatedly, van Bokhoven et al. (2005) followed a group of boys with Conduct Disorder (CD) and a control group from early childhood through adolescence. They found that boys with CD had higher levels of cortisol compared to controls, and furthermore that CD boys who expressed greater amounts of aggression had higher cortisol levels than CD boys who only had internalizing problems such as anxiety, depression or social withdrawal (van Bokhoven et al., 2005).

In a review, Hawes et al. (2009) suggest that there may be two pathways to antisocial behavior, including aggression, related to chronic cortisol levels and HPA axis function. They suggest that individuals with hyperactivity of the HPA axis and cortisol may be prone to antisocial behavior following childhood maltreatment, but that in individuals with callous-unemotional traits, a marker of psychopathy, chronic hypoactivity of the HPA axis characterizes a severe risk for antisocial behavior (Hawes et al., 2009).

In agreement with Hawes et al.'s model, Cima et al. (2008) found that, by comparing psychopathic prisoners, non-psychopathic prisoners and healthy controls, both prisoner groups were more aggressive than controls; the psychopathic group had lower daily cortisol levels whereas the non-psychopathic group had higher daily cortisol levels compared to controls. Both prisoner groups had higher scores on the Childhood Trauma Questionnaire (CTQ) compared to controls. However, their study found that while both controls and non-psychopathic prisoners showed a positive relationship between aggressive behavior and CTQ scores, psychopathic prisoners did not show a relationship between CTQ and aggression (Cima et al., 2008).

Cortisol and Neural Changes

According to Selye's GAS model, a chronically active stress response can become deleterious (Sapolsky et al., 2000). Cortisol can damage tissue throughout the body, or prevent its repair, if present for long durations or in large quantities (Sapolsky et al., 2000). The reason for these negative effects is not entirely known, but some of the mechanisms involved in the mediation of cortisol effects may offer some explanation. Cortisol can bind to either mineralocorticoid receptors (MR) or glucocorticoid receptors (GR), but have a ten-fold higher affinity for MRs, so at low concentrations most cortisol binds there (Sorrells et al., 2009). When cortisol concentrations saturate MRs, cortisol binds to GRs (Sorrells et al., 2009). Thus, cortisol effects can have an inverse U-shape, where low concentrations produce a certain effect, but higher concentrations produce the opposite. For example, in

the nervous system, basal and low stress levels of cortisol enhance glucose utilization and hippocampal synaptic excitability, but higher cortisol levels have the opposite effect (Sorrells et al., 2009).

Chronic stress has been shown to cause damage and premature aging to the brain (Sapolsky et al., 1990). Some brain regions, such as the hippocampus and PFC, are more sensitive to cortisol effects due to high receptor concentrations (Sorrells et al., 2009). To determine if cortisol directly damaged CNS tissue, Sapolsky et al., (1990) implanted cortisol capsules into the right hippocampi of four vervet monkeys and cholesterol capsules into the left hippocampus. One year later, the cortisol-treated side had severe cellular atrophy, irregularity, shrinkage, or cell-nucleus damage (Sapolsky et al., 1990).

A number of human psychiatric disorders associated with stress have been linked to decreased cortical volume (Tischler et al., 2006). For example, patients with have smaller hippocampi compared to control subjects who experienced similar stressful experiences but did not develop PTSD (Tischler et al., 2006). This decreased volume may relate to disrupted cortisol release (Sapolsky et al., 1990).

Similarly, child abuse and neglect may alter brain structure, and these alterations may be due to enduring exposure to stress and cortisol. Tomoda et al. (2009) used structural MRI to compare brain size between 23 subjects (aged 18-25) who had experienced physical abuse and 22 matched controls that did not. The abused subjects had reduced volume in the left DLPFC (14.5% less), right medial PFC (19% less) and right ACC (16.9% less) compared to controls (Tomoda et al., 2009). The affected regions of the PFC and ACC are related to control of aggressive behavior (Siever, 2008), which suggests that abused children may have disruptions in the brain regions responsible for control of aggressive behavior. In a follow up study looking at individuals who had experienced verbal, but not physical, abuse, Tomoda et al. (2011) found that the verbally abused individuals have increased volume in the left superior temporal gyrus compared to controls. Although the effects on brain structure and volume provide evidence that child abuse can alter the brain, replication in a larger sample size would be required to make specific conclusions about the implication of these results. Nonetheless, they provide evidence that child abuse is associated with significant alterations in brain development. One hypothesis is that these alterations may be due to neurotoxic effects of cortisol (De Bellis, 2005).

Chapter 6. A Model for the Cycle of Violence

Recapitulation of Background

Since Curtis (1963) first expressed concern that abused and neglected children might become tomorrow's murderers, numerous studies have demonstrated the validity of the cycle of violence (Widom, 1989a; Lansford et al., 2007; review by Maas et al., 2008). Yet, despite the increased risk that abused and neglected children face, the fact remains that most maltreated children will not become violent. For example, in Widom's (1989a) sample, 26-percent of maltreated children committed a juvenile criminal offense, but 74-percent did not. Yet as Widom (1989a) concludes:

> *The scientific issue should not be the 'box score' (the magnitude of the association between childhood victimization and later delinquent or criminal behavior), but rather the goal should be further knowledge of the processes involved. Research should be directed at understanding how these early experiences relate to later violent behavior, recognizing the likelihood of multiple pathways, and noting how possible protective factors act to buffer some children from the long-term negative effects of these early childhood experiences.*

In keeping with Widom's idea, the purpose of this project is to further the understanding of the processes involved in actualizing the cycle of violence. One of the most fully developed models for the effects of child maltreatment towards creating a cycle of violence highlights the impact on the HPA axis (De Bellis, 2005). De Bellis (2005) suggests that the HPA axis may be disrupted or dysregulated following early adverse experiences such as abuse and neglect, and these changes can impact mood and behavior. For example, orphans who are not adopted soon after being placed in an institution face greater risk of infection, possibly a result of increased release of cortisol, the end-product of the HPA axis, part of the body's stress response and an immunosuppressant (Bakwin, 1942). The changes in HPA axis function linger long after these children are eventually adopted; a study of Romanian orphans who spent over 8 months in institutional care demonstrated that as adolescents they still had elevated levels of cortisol (Gunnar et al., 2001).

The dysregulation of the HPA axis could affect aggressive behavior directly or indirectly. Some evidence in humans suggests that acute increases in cortisol may directly increase aggressive behavior (Bohnke et al., 2010a). Similar evidence in hamsters suggests that cortisol may directly affect aggressive behavior (Hayden-Hixson and Ferris, 1991).

Cortisol's effect on aggression may relate to altered emotion and perceptions of threat (Putman and Roelofs, 2010).

Alternatively, the dysregulation of the HPA axis may affect CNS 5-HT function. For example, the end product of the HPA axis, cortisol, acts on the brain at multiple sites and may affect stress and behavior via 5-HT_{1A} receptors; this HPA-5-HT interaction may play a role in aggression (Pompili et al., 2010). 5-HT, as much as any neurotransmitter, has been implicated in aggression (de Almeida et al., 2005).

Cortisol also has neurotoxic effects if levels are chronically elevated (Sapolsky et al., 1990). Brain regions with higher concentrations of glucocorticoid receptors, such as the hippocampus and areas of the PFC, are most susceptible to these effects (Sapolsky et al., 1990). Damage to the brain regions responsible for the regulation of aggression may diminish the ability to control aggressive tendencies.

An important distinction may be made between chronically over-activated and under-activated cortisol levels. As Hawes et al. (2009) suggest, two divergent pathways may lead to increased aggression: hypercortisol or hypocortisol. Excess cortisol may suggest an overactive stress system that sensitizes the individual to the effects of stress and increases the likelihood of aggression in response to provocation; conversely, low cortisol levels may indicate psychopathic tendencies, such as callousness, which also increases the likelihood of aggression (Hawes et al., 2009). A study of prisoners found that only non-psychopathic criminals demonstrated a relationship between experiences of childhood maltreatment and aggression (Cima et al., 2008). Corroborating Hawes et al.'s (2009) hypothesis, the non-psychopathic criminals had elevated cortisol levels compared to controls, whereas the psychopathic criminals had diminished cortisol levels (Cima et al., 2008).

Unanswered Questions

Nearly 50 years after the cycle of violence hypothesis was proposed (Curtis, 1963) and 20 years after the most definitive evidence confirming it (Widom, 1989a), many questions remain concerning why the cycle of violence exists and the processes that mediate it. Therefore, the specific aim of this dissertation is to examine the relationship between child abuse and neglect, HPA axis function at rest and during a challenge, and the effects of these factors on state and trait aggression. A visual representation of the hypotheses can be seen in figure 1. The following specific aims and hypotheses will be examined:

Specific Aims and Hypotheses

Specific aim 1. Child abuse and neglect predicts aggression.

Hypothesis 1. Among adults age 18-55 with a range of histories of child abuse and neglect, higher levels of abuse and neglect as measured by the Childhood Trauma Questionnaire (CTQ) will predict higher levels of aggression as measured by the Point-Subtraction Aggression Paradigm (PSAP) and Buss-Perry Aggression Questionnaire (BPAQ).

Specific aim 2. Psychopathy predicts aggression.

Hypothesis 2. Among adults age 18-55 with a range of psychopathic traits, higher levels of psychopathy as measured by the Self-Report Psychopathy scale III (SRP-III) will predict higher levels of aggression as measured by the PSAP and BPAQ.

Specific aim 3. Child abuse and neglect predicts basal cortisol levels.

Hypothesis 3. Among adults age 18-55 with a range of histories of child abuse and neglect, higher levels of abuse and neglect as measured by the CTQ will predict higher levels of basal cortisol as measured by the area under the curve (AUC) of saliva samples taken between 8 am and 10 am.

Specific aim 4. Psychopathy predicts basal cortisol levels.

Hypothesis 4. Among adults age 18-55 with a range of psychopathic traits, higher levels of psychopathy as measured by the SRP-III will predict lower levels of basal cortisol as measured by the AUC of saliva samples taken between 8 am and 10 am.

Specific aim 5. Basal cortisol levels predict aggression.

Hypothesis 5. Among adults age 18-55, basal cortisol levels as measured by the AUC of saliva samples taken between 8 am and 10 am will predict aggression as measured by the PSAP and BPAQ. Specifically, both low and high levels of basal cortisol will predict higher levels of aggression compared to mid-levels of basal cortisol, reflecting the differential influence of both psychopathy (lower basal cortisol) and child abuse/neglect (higher basal cortisol) on aggression.

Specific aim 6. Child abuse and neglect predicts HPA-axis reactivity.

Hypothesis 6. Among adults age 18-55 with a range of histories of child abuse and neglect, higher levels of abuse and neglect as measured by the CTQ will predict higher levels of HPA-axis reactivity as measured by the increase from baseline of cortisol present in saliva following the acute administration of 20mg cortisol capsules.

Specific aim 7. HPA-axis reactivity predicts aggression.

Hypothesis 7. Among adults age 18-55, HPA-axis reactivity as measured by the increase from baseline of cortisol present in saliva following the acute administration of 20mg cortisol capsules will predict higher levels of aggression as measured by the PSAP.

Specific aim 8. Impulsivity predicts aggression.

Hypothesis 8. Among adults age 18-55 with a range of impulsivity, higher levels of impulsivity as measured by the Barratt Impulsivity Scale 11 (BIS-11) will predict higher levels of aggression as measured by the PSAP and BPAQ.

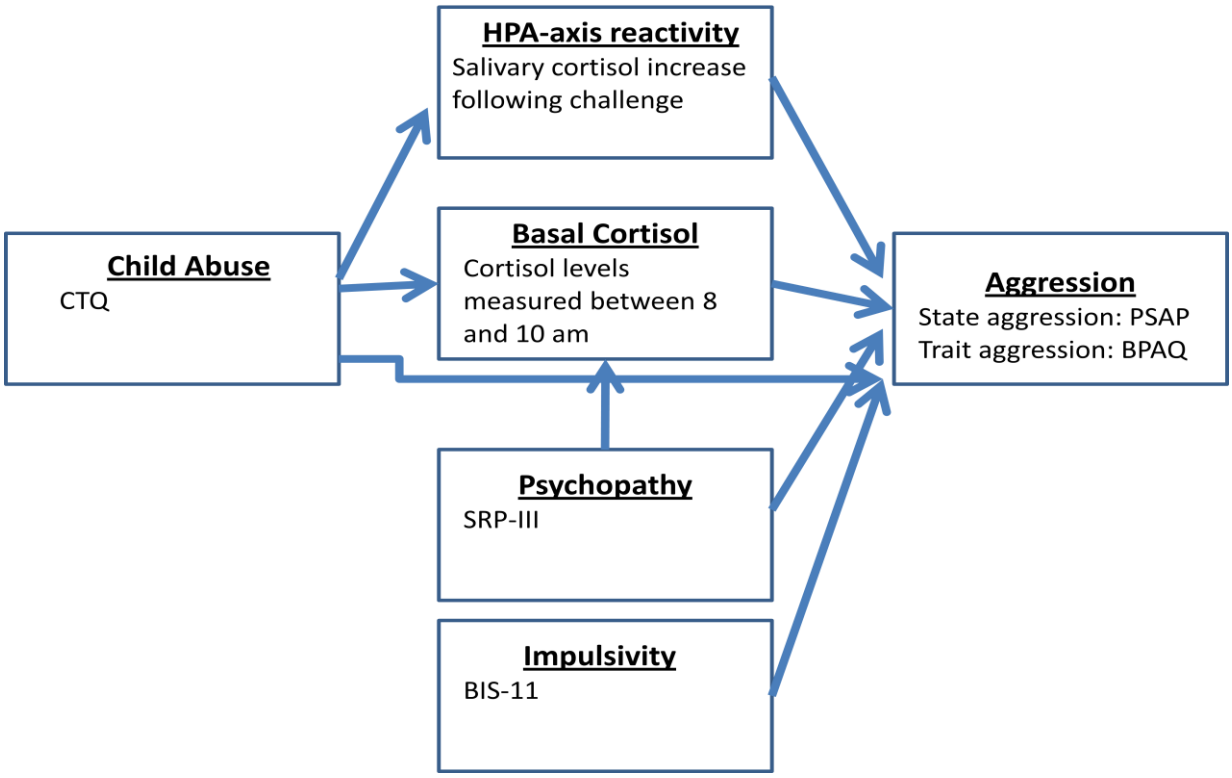

Figure 1. A visual representation, or model, of the hypotheses to be addressed in this dissertation. Each arrow corresponds to one of the hypotheses.

Methods

This study was approved the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. All procedures complied with the Declaration of Helsinki.

Subjects

Recruitment: Subjects were recruited through local newspaper advertisements seeking either controls or individuals on parole or probation. The advertisement can be found in the appendix. Subjects then called a screening line for an initial phone interview to assess eligibility based on drug use, medical and psychiatric history. Eligible subjects were scheduled for an intake procedure. During the intake procedure, subjects came to the clinic, consented to provide information on personal history and to be evaluated on both a psychiatric and physiological exam. Each day the subject came to the laboratory, the subject provided a urine sample to test for drug use and a breath sample to test for alcohol use. The physiological exam was conducted by a qualified medical professional and included a complete health history, an electrocardiogram and blood tests. The psychiatric exam diagnosed subjects based on the Structured Clinical Interview for the DSM-IV; including axis I and II disorders (SCID; First et al., 2002).

Exclusion Criteria: Subjects were excluded on the basis of age, criminal record, medical history, current prescription medication use, smoking habit, drug use history and psychiatric diagnosis. Specifically, subjects under the age of 18 or over the age of 55 were excluded. Subjects with criminal charges related to sexual assault were excluded. Subjects with a history of cancer, tuberculosis, HIV, AIDS, diabetes, heart problems, liver problems, seizures, or loss of consciousness lasting longer than 30 minutes were excluded due to the possibility of neurological complications, which may confound results. Subjects diagnosed with DSM-IV mood disorders or psychotic disorders were excluded. Subjects currently taking psychoactive prescription or non-prescription medications were excluded due to possible interaction effects with the study drug. Subjects who smoked more than 10 cigarettes per day were excluded due to possible withdrawal effects from abstaining for the time in the laboratory. Subjects who provided positive urine samples or breath-alcohol samples on more than one occasion were excluded. Drug use was monitored using the One Step Drug Screen Test Card (Inovacon, San Diego, CA), which tests for amphetamines, cocaine, benzodiazepines, marijuana and opiates. Alcohol use was monitored using and Alcosensor III breathalyzer.

Inclusion Criteria: Eligible subjects included males and females between the ages of 18 and 55. Subjects were either healthy controls or parolees or probationers. Acceptable criminal charges included drug charges, theft, forgery, burglary, assault, domestic violence or attempted murder. For safety reasons, eligible subjects had no contraindications for study procedures as assessed by a qualified medical professional. An example of a contraindication would be high blood pressure, which may be a risk factor when taking doses of cortisol. Eligible subjects may have had no psychiatric diagnoses, or may have had substance use disorders (SUD), anxiety disorders or personality disorders. Anxiety disorders were included because the literature suggested that victims of child abuse have a high risk for post-traumatic stress disorder (De Bellis, 2005). Subjects with substance use disorders were included because they represent a significant proportion of the violent criminal population (Arsenault et al., 2000).

Demographics: 74 subjects were recruited for this study. Of those, 67 completed the study. The seven participants who did not finish dropped out or were removed for various reasons, as follows. Four got another job or stopped showing up without notice. One refused to comply with procedures once admitted into the study. One could not swallow the capsule containing the dose. One was removed after they realized the laboratory task was a deception, invalidating the results. A summary of the demographics can be seen in Table 2. The final sample was 77% male, 82% African American, 8% Hispanic, 8% Caucasian, and 2% Asian. The sample was 31.5±9.6 years old with 13.1±1.9 years of education. 66% were on parole or probation, 62% had a SUD, and 18% were diagnosed with antisocial personality disorder (ASPD). 1 subject had PTSD. The mean Shipley score of intellectual aptitude was 200.4 ± 24.7, with a range of 147 to 246. A score of 200 is the mean for the general population, so this sample was of normal intelligence.

Enrolled	*Completed*	*Age*	*Education (Years)*	*Shipley*	*ASPD*	*Parole/Probation*	*PTSD*	*SUD*
N=74	N=67	31.5(9.6)	13.1(1.9)	200.4(24.7)	N=13	N=45	N=1	N=42

Table 2. Enrolled is the total number of subjects who signed the initial consent. Completed is the final sample size. All of the other variables refer exclusively to the final sample. Shipley is an intellectual aptitude scale. Parentheses contain standard deviations. ASPD is Anti-Social Personality Disorder. PTSD is Post-Traumatic Stress Disorder. SUD is Substance Use Disorder.

Procedures

Study Design: Subjects who had been screened and deemed eligible according to the inclusion criteria were invited to participate in the study. After consenting, subjects were introduced to the aggression task, the PSAP. On day 1, subjects participated in two PSAP sessions to ensure that they understood the instructions and to establish a baseline measurement of aggressive responding. Subjects also completed the Childhood Trauma Questionnaire on day 1.

On days 2 and 3, subjects came to the laboratory at 8 a.m. and provided breath and urine samples which had to be clean (0) to ensure that no extraneous drug or alcohol use would confound behavioral results. At 6 time points throughout the day, subjects provided saliva samples to measure cortisol levels, and also had their blood pressure and heart rate measured. Subjects were administered a capsule at 9:30 a.m. that contained either placebo or 20mg of cortisol. Dosing order was counter-balanced. Both the subject and the capsule administrator (research assistant) were blind to the dose contents. Following dosing, subjects completed three sessions on the PSAP and then were released at 1 p.m.

On Day 4, subjects filled out psychometric questionnaires. In order to measure basal cortisol level in the absence of an external stressor (PSAP), subjects continued to provide physiologic measures and saliva samples at the same time as on dosing days, they did not receive a dose or participate in any PSAP sessions. Both the daily schedule and an outline of the experimental design are provided below.

Experimental Design

Day 1: consent, childhood trauma, PSAP baseline

Day 2: PSAP with dose/placebo, cortisol collection

Day 3: PSAP with dose/placebo, cortisol collection

Day 4: exit questionnaires, cortisol collection

Daily Schedule on Dosing Days

8:30 am: Collection of BAC, CO, cortisol and urine samples, blood pressure and heart rate

9:00 am: Blood pressure, heart rate, cortisol

9:30 am: Placebo / cortisol administration

9:50 am: Blood pressure, heart rate, cortisol

10:00 am: Test session #1: PSAP

10:30 am: Blood pressure, heart rate, cortisol

11:00 am: Test session #2: PSAP

11:30 am: Blood pressure, heart rate, cortisol

12:00 am Test session #3: PSAP

12:30 am: Blood pressure, heart rate, cortisol

12:30 pm: Lunch

12:40 pm: Social interaction questionnaire

12:45 pm: Evaluation for impairment

1:00 pm: Subject payment and release from laboratory

Dosing: A dose of 20 mg was selected based on previous research which found significant effects on laboratory-measured aggression at this dose (Bohnke et al., 2010) and because FDA and manufacturer recommendations suggested this dose would be safe.

All dosing was conducted in an unoccupied room. Subjects received a small envelope labeled with the date, their subject number and first name. The envelope contained a dark blue, #00 capsule containing either a 20mg tablet of cortisol and filled with corn starch, or a capsule containing corn starch only. Capsules were prepared by a licensed pharmacist. Subjects were also provided a glass of water. A research assistant watched the subject place the capsule into his/her own mouth and swallow it. When the subject had swallowed the capsule, the research verified that it had been swallowed by asking the subject to open their mouth and lift their tongue.

Counter-balancing of dose order was performed to prevent dose-order effects on behavioral responding. Subjects were randomized to receive either placebo first or cortisol first using urn-randomization software that controlled for gender and history of child maltreatment. The software was obtained from the University of Connecticut Health Center's Project MATCH (Project MATCH Research Group, 1993).

Subject Payment: During the initial interview subjects were given a memorandum of understanding explaining the payment contingencies for the study. Subjects were paid according to the payoff contingencies scheduled on the experimental tasks. Three experimental sessions were conducted each experimental day. Typically, earnings range from $20 - $30 per day. Subjects also earned daily bonuses for each clean urine and breath sample, and on-time attendance ($20/day for each). On the last day of the study, subjects received a completion bonus of $40.00.

Point Subtraction Aggression Paradigm (PSAP): PSAP (Cherek, 1992) sessions took place in a small room (2m x 2m) with a desk, computer monitor and response panel. The response panel had four buttons (red, blue, yellow and green), only three of which were active during the task (blue, yellow and green). When the subject entered the room, the monitor read "Start Session," and they were told that the session would begin momentarily when the person they were paired with was situated. The research assistant started the task after letting the subject wait between 30 seconds and 2 minutes.

When the session began, the monitor displayed a monetary counter set at $00.00 and the letters A, B and C. The letters corresponded to the blue, yellow and green colored buttons, respectively, on the subjects' response panel. Through instructional deception, the subjects were told that they were paired with another person through a computer network and they would interact with the other person during the task. Males were always paired with males and females with females.

The subjects' task was to earn as much money as possible in the experimental session. Non-aggressive, monetary reinforced responding could be achieved by pushing the blue button on the panel, corresponding to letter A, 100 consecutive times (fixed ratio, FR 100). The A response was continuously available to the subject throughout the session, and a completed A ratio of 100 presses added 15 cents to the subject's counter.

The aggressive response option was also continuously available during the session. Subjects were instructed that pushing the yellow button, corresponding to letter B, 10 consecutive times (FR 10) would result in the subtraction of money (15 cents) from another person paired with them during that particular session. Subjects received no money when choosing B, and thus did not receive any direct monetary reinforcement for their aggressive responses.

Human aggression may be operationally defined as (a) a social behavior that involves the interaction of at least two people; (b) is intended to proximally harm (present an aversive stimulus to) another person who (c) finds this harm aversive and would act to avoid it (Baron

and Richardson, 1994). Thus, the B option on the PSAP, the ostensible subtraction of money from another person, is the aggressive option. This meets the operational definition because the subject believes they are subtracting money from another person, which is considered an aversive stimulus that the other person would choose to avoid. The frequency of pressing button B is the measure of aggressive responding, unlike the other aggression laboratory procedures that focus on intensity while not allowing frequency of aggressive responses to vary (Taylor, 1967).

Aggression is generally a rare behavior that does not occur without provocation. To induce aggressive responding in the PSAP, the subject was provoked periodically. Subtractions were scheduled on average every 125 seconds. Money was subtracted from the subject's earnings and these subtractions were attributed to the person paired with the subject during the session. Subtractions were signaled by the subjects' monetary counter doubling in size, flashing for a few seconds. Following the flashing signal, the subjects' earnings were reduced by 15 cents and the counter returned to the normal size.

To establish a motive for the provocations, subjects were told that money subtracted from them would be added to the earnings of the other person. Through instructional deception, subjects were told that two conditions existed, one where the B option both earned money while subtracting it from the other person, and a second where the B option only subtracted money from the other person. The subject was always told that the conditions were determined randomly, by the toss of a coin, and that they were in the second condition, where they could not gain money by choosing B.

In addition to the A and B responses, subjects also had an escape response. By pressing the green button, corresponding to letter C, the subject could prevent some of the subtractions from the person they were paired with. The escape response was added to the PSAP to provide a non-aggressive response option maintained by the same schedule (FR 10) and the same consequence as the aggressive response (described below).

These two response options, aggressive B and escape C, allow a direct comparison of the effects of drugs on two similar responses, which vary only by instructions. The consequences of aggressive and escape responding are provocation-free intervals (PFI) where subtractions of money, or provocations, are not presented. The PFI serves to maintain the responding by temporarily removing an aversive stimulus (provocation) following B or C responding. Typically, subjects choose the aggressive response in retaliation after the fictitious paired-person provokes the subject with a subtraction. When the subject chooses the aggressive response, a PFI is initiated. The subjects' aggressive

responding is maintained in part by the PFI. However, subjects are not informed about this contingency. The PFI was 125±30 seconds.

Escape responding was maintained by the same consequence, i.e. the initiation of a PFI. Subjects were explicitly informed that the C response would prevent some of their subtractions. Hence, although both B and C produced a PFI, subjects were only informed about the protection obtained from C responding. They may attribute the PFI following B responding to the other person's altered responding. That is, the subject may believe that the other person stopped subtracting their money because he/she feared retaliation.

The PFI is initiated by whichever response option (button B or C) is completed first. These intervals are not initiated unless at least one provocation has been presented to the subject, so that subjects cannot avoid provocations entirely and are periodically provoked across the session. Once the PFI has elapsed, provocations are again presented until more aggressive or escape responding initiates another PFI.

The three response options are available as non-reversible options. Before the subject makes a choice all three letters are displayed on the computer screen. The first response on any one of the three buttons (A, B, or C) removes the other two options. The subject must then complete the response requirement (FR 10 or FR 100) for the selected option before the other options are again available.

Prior to the first session, subjects were given a set of printed instructions (shown in Appendix I) describing the response requirements for all three response options and the immediate consequence (A earns 15 cents, B subtracts from another person, C protects their earnings). Aggression is not mentioned.

Evaluation of the validity of the social deception: The integrity of the social deception in the PSAP was evaluated following the last experimental session of each day. Subjects completed a four-item questionnaire to assess their strategy and assessment of their opponent (see appendix). Any report that indicated the subject did not believe the social deception, i.e., "I was not paired with anyone" or "I think it was a computer" resulted in the removal of the subject from the study. One subject was removed for this reason. Subjects responses indicated that the social deception was effective, as subjects' answers on the questionnaire were consistent with (a) the presence of other players, and (b) were generally sensitive to their session earnings. For example, decreases from the prior session typically corresponded to less favorable ratings of the other player.

Measures

1. Aggressive Responding: The PSAP quantifies the frequency of aggressive responding. Aggression can be measured as total aggressive responses or the number of aggressive responses per provocation. This study used aggressive responses per provocation as the outcome measure of state-dependent aggressive responding. As aggressive responding occurs in response to a provocation, it is considered a measure of reactive aggression.

Physiological Measures

1. Cortisol: Salivary cortisol samples were chosen because they are minimally invasive, but allow for measurement of free circulating cortisol. Cortisol, as the end-product of the HPA-axis, serves as a proxy for the stress response.

Subjects provided saliva samples in salivette tubes at six time points throughout the day. Salivette tubes were then stored at -80˚C and shipped to a collaborator for analysis. At the time of writing, only 62 out of 67 samples had been analyzed. Cortisol concentrations that were too low (below 0.5 nmol/L) or high (above 85 nmol/L) were removed as invalid. A single inadequate or missing sample was interpolated by imputation, but subjects with three or more adjacent missing samples were excluded from cortisol analyses. One issue with administering cortisol orally and then measuring cortisol through saliva is the potential for contamination of the saliva, which would result in salivary cortisol concentrations above 85 nmol/L. For the cortisol administration day, 20 subjects had contaminated samples. Thus, only 42 subjects were analyzed with regard to HPA-axis reactivity.

From the cortisol measures at each time point, a curve can be drawn to represent changing cortisol levels across time. The area under the curve with respect to ground, or zero, (AUC_G) represents the total output of cortisol across a given time. A widely accepted procedure for deriving the AUC_G of cortisol is to add the values of two adjacent time points, multiply it by the duration of time between them and divide by two (Pruessner et al., 2003). After doing this for each interval, the values are added up and the sum is the AUC_G for the entire time period of interest. For example, if there are three time points, the below equation would be used with m_i being the value of cortisol at a given time and time t_i being the interval between measurements.

$$AUC_G = \frac{(m_2 + m_1) * t_1}{2} + \frac{(m_3 + m_2) * t_2}{2}$$

2. Heart Rate/Blood Pressure: Heart rate and blood pressure were measured using a sphygmometer (BpTru Vital Signs Monitor, Coquitlam, Canada) at six time points throughout the day. The sphygmometer cycled through six times per reading and computed the mean of the last five cycles. Heart rate and blood pressure served as an indication of autonomic nervous system arousal.

Questionnaires

1. The Childhood Trauma Questionnaire (CTQ; Bernstein and Fink, 1998) is a 28-item, likert-rated scale (never true–often true) of history of abuse and neglect during childhood. It asks questions such as “People in my family called me things like “stupid” or “lazy” or “ugly.” Or “I didn’t have enough to eat.” It has five subscales: physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect. It was designed to capture, through self-report, the pertinent information that would otherwise have to be obtained through a lengthy interview with a trained professional. Further, it provides a metric to quantify severity.

2. Buss Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992) is a 29-item true-false rating scale of trait aggression. It provides scores on four subscales: physical aggression, verbal aggression, anger, and hostility. The total score from this instrument has been correlated with behavior in laboratory measures of aggression (Cherek et al., 1997).

3. The Impulsive-Premeditated Aggression Scale (IPAS; Stanford et al., 2003) is a 30-item self-report measure looking at aggressive behavior over past six months. Using a 1-5 likert rating scale, it distinguishes between impulsive and pre-meditated aggression, which are orthogonal measures.

4. The 65-item Self-Report Psychopathy Scale III (SRP-III; Paulhus et al., 2009) was used to measure psychopathy. Subjects rate their level of agreement with statements such as “I think I could beat a lie detector” on a 1-5 likert scale. The SRP-III sub-categorizes into callous affect, erratic lifestyle, criminal tendencies and interpersonal manipulation. Either the sub-scales or the total score can be used as measures of psychopathic traits.

5. The Shipley II (Shipley Boyle, 1967) is a test of general intellectual aptitude that includes a 40-item vocabulary test and a 20-item abstraction test. Shipley score estimates of WAIS IQ correlate highly (0.76-0.87) with actual WAIS IQ scores (Zachary et al., 1985).

6. The Barratt-Impulsivity Scale 11 (BIS 11; Barratt, 1997) is a 30-item self-report measure of impulsivity. It provides a continuous measure of impulsive traits, and can be

used as a total score or broken down into three sub-scales: non-planning, attentional and motor impulsivity.

Power Analysis

To estimate an appropriate sample size prior to collecting data, a power analysis was performed based on a linear regression model. The power analysis was performed using GPower 3, a free software program designed specifically for power estimates. Estimates of the effect sizes of child abuse (Cohen's d=0.7) and cortisol administration (Cohen's d=0.07) were derived from scientific literature (Widom, 1989; Alink et al., 2008). A power analysis, with α=.05 and 1-β=.8 suggested that a sample of 66.7 would be sufficient to produce a significant result (F=2.08) with 7 predictors.

Statistical Analysis

The effect of day (20mg cortisol vs. placebo vs. questionnaires) on salivary cortisol (AUCg), blood pressure and heart rate (mean across each day) was analyzed using a one-way ANOVA, and post-hoc tests were done using the Sidak method. Linear regression analysis was used to test the significance of the predictive variables on the outcomes variables. The sum of the CTQ served as the score for child abuse. For basal cortisol, the AUCg (Pruessner et al., 2003) for the first 30 minutes after the subject arrived was used, and this value represented the peak of the diurnal cortisol curve (Bohnke et al., 2010). For HPA-axis reactivity, the difference between AUCg across the day on the placebo and the cortisol day was calculated and used as a single score. For psychopathy, the total score on the SRP-III was used. For impulsivity, the total score on the BIS-11 was used. For aggression, a single score was calculated based on aggressive responding during PSAP sessions and the BPAQ. Aggressive responses per provocation for the placebo day were z-scored, as were BPAQ scores, and these standardized scores were summed to create a single aggression score per subject that represented both state and trait aggression.

If diagnostic tests of the linear regression models suggested the possibility of a non-linear relationship, median-spline analysis was conducted. Median-spline analysis is a non-linear model that consists of piecewise cubic polynomials between adjacent knots (i.e. locations where the magnitude of the slope changes). The knots can be evenly spaced throughout the x-variable, or placed based on observation. Once the knots are determined, a program in the statistical program STATA can predict the residuals within each knot (Dupont and Plummer, 2009). Once these residuals are predicted, a multiple linear

regression analysis can determine the predictive value of the model, as well as the predictive value of each of the residuals within each knot.

Regression models were also used to test for the effect of mediation (Baron and Kenny, 1986). Baron and Kenny's four steps were tested for mediation analysis (Baron and Kenny, 1986). The four steps are as follows:

1. Show that the initial variable, X, is correlated with the outcome, Y. A significant outcome in this regression establishes that there is an effect that may be mediated.
2. Show that X is correlated with the mediator, M. This evaluates path a.
3. Show that M affects the Y, after controlling for X. This evaluates path b.
4. If M completely mediates the X-Y relationship, the effect of X on Y controlling for M, or path c', should be zero.

The mediation model can be seen in figure 2. The model tests the direct effect of X on Y controlling for mediating variable M, and tests the indirect effect of X on Y. The indirect effect is the portion of the total effect that is mediated. As the Baron-Kenny steps do not assess the significance of mediation, a Sobel test was used to test significance (Sobel, 1982). A significant outcome on the Sobel test suggests that the null hypothesis can be rejected and the alternative hypothesis—that a mediation effect exists—can be accepted (Baron and Kenny, 1986). The Sobel approach also allows for the evaluation of the percent of the total effect that is mediated, the indirect effect, and the percent that results from the independent variable, the direct effect.

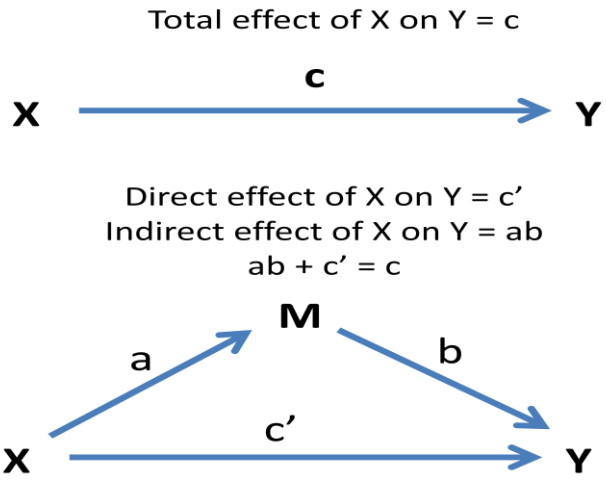

Figure 2. Diagram of the statistical model for mediation. Adapted from Baron and Kenny, 1986.

Mediation analysis focused on the likelihood that HPA-axis reactivity mediated the effect of physical-contact abuse or non-physical abuse and neglect on aggression score. As this analysis was part of a larger model of aggression, including measures of impulsivity and psychopathy, the residuals were calculated after a multiple linear regression of aggression score using only psychopathy and impulsivity as predictors. The residuals were used as the outcome variable in the mediation analysis. Thus, the mediation analysis explored the effect of physical-contact abuse and non-physical abuse and neglect on the remaining variance, the portion not explained by psychopathy and impulsivity.

Finally, a multiple linear regression model was used to examine the total predictive value of the model (fig. 1) for explaining the variance of the aggression score.

Results

Descriptive Statistics

There are a total of 67 observations, but only 42 observations of HPA-axis reactivity and 62 observations of basal cortisol (see Methods for detail). Measures of central tendency, variance and estimates of normality can be seen in table 3. Aggressive responding on the PSAP was not normally distributed and positively skewed. Many participants used the aggressive response sparingly or not at all. Similarly, scores on the BPAQ were not normal and showed a trend toward positive skewness, with many subjects reporting low levels of aggression. Abuse and neglect scores were not normal and were kurtotic and positively skewed, as many subjects reported low or no abuse. SRP-III scores were normally distributed. HPA-reactivity was normally distributed. This reflects the normal distribution of the AUCg on the cortisol day, because AUCg for the entire placebo day was not normally distributed. Similarly, AUCg for the peak levels of cortisol release was not normally distributed. BIS-11 scores passed the normality test, but were positively skewed.

Analysis of Variance (ANOVA)

Salivary Cortisol

One-way ANOVA of AUCg for cortisol across the day revealed a significant main effect of day on AUCg ($F_{2, 162} = 385.8$, $p<.001$). Due to contamination of twenty subjects' saliva samples on the cortisol day, only 42 samples were reported. For placebo and questionnaire days, 62 samples were reported. Sidak post-hoc tests revealed that the cortisol day was significantly different than both the placebo day ($p<.001$) and the questionnaire day ($P<.001$). There was no significant difference between the placebo and questionnaire days ($p=.99$). Measures of central tendency and variance can be seen in table 4.

Physiological Response

One-way ANOVA revealed that there was no effect of day for heart rate ($F_{2, 198} =.22$, $p=.804$), systolic ($F_{2, 198} =.16$, $p=.852$), or diastolic blood pressure ($F_{2, 198} =.01$, $p=.995$). The null hypothesis, that no difference exists between the questionnaire, cortisol and placebo days, can be accepted. Measures of central tendency and variance can be seen in table 4. More detailed descriptive statistics can be found in the appendix.

	N	*Mean (SD)*	*Range*	*Normal (probability)*	*Skewness (probability)*	*Kurtosis (probability)*
Aggressive Responding	67	30.7 (31.4)	0, 157.0	0.000	0.000	0.000
BPAQ	67	65.1 (18.6)	32, 112	0.047	0.057	0.696
Aggression Score	67	0 (1.55)	-2.4, 4.3	0.009	0.064	0.381
Abuse and Neglect	67	38.5 (11.2)	25, 77	0.000	0.000	0.03
SRP-III	67	157.7 (30.4)	93, 230	0.794	0.391	0.757
HPA-Reactivity	42	86.1 (31.7)	22.4, 166.0	0.631	0.533	0.740
AUCg	62	3.4 (1.3)	1.5, 7.0	0.000	0.000	0.370
BIS-11	67	57.4 (10.1)	37, 83	0.091	0.042	0.733

Table 3. Summary of descriptive statistics for the primary variables in the analyses. Aggressive responding is the average number of aggressive responses per provocation in the PSAP on the placebo day. BPAQ is the Buss-Perry Aggression Questionnaire. Aggression Score is the sum of the z-scored aggressive responding on placebo day and the z-scored BPAQ score. Physical abuse is the sum of physical and sexual abuse on the CTQ. Emotional abuse is the sum of emotional abuse, physical neglect and emotional neglect on the CTQ. HPA-reactivity is the difference between AUCg cortisol and AUCg placebo. AUCg is the peak cortisol detected in saliva in the first hour after arriving in the laboratory.

	Cortisol (SD)	*Heart Rate (SD)*	*Systolic BP (SD)*	*Diastolic BP (SD)*
Placebo	18.9 (9.4)	63.9 (8.6)	112.9 (9.4)	72.6 (7.2)
Cortisol	104.4 (32.0)	64.8 (8.7)	112.4 (9.1)	72.5 (7.2)
Questionnaire	18.0 (7.3)	64.6 (8.4)	112.0 (9.2)	72.5 (7.5)

Table 4. Placebo, Cortisol and Questionnaire represent the day of the study. All of the variables report mean and standard deviation (in parentheses). Cortisol is the AUCg across the day. The physiological measures are means across the day.

Linear Regression Analysis

Child Abuse and Neglect and Aggression

Linear regression analysis showed that child abuse and neglect was a significant predictor of aggression score ($t=5.11$, $p<0.001$) with $\beta = 0.074 \pm 0.01$ (95% CI 0.05, 0.10) such that higher self-reported physical contact abuse corresponded to higher aggression. A pairwise correlation indicated that child abuse and neglect had a large effect size on aggression score ($r = .536$). Abuse and neglect accounted for 29 percent of the variance in aggression score ($R^2=.287$).

Child Abuse and Neglect and HPA-axis Reactivity

Linear regression analysis showed that, in a sample of 42 subjects, child abuse and neglect was a significant predictor of HPA-axis reactivity ($t= -2.12$, $p = .040$) with $\beta = -1.01 \pm .48$ (95% CI -1.98, -0.05) such that higher self-reported abuse and neglect corresponded to lower HPA-axis reactivity. A pairwise correlation indicated that abuse and neglect had a medium effect size on HPA-axis reactivity ($r = -.318$). Abuse and neglect accounted for 10 percent of the variance in HPA-axis reactivity ($R^2=.101$).

Child Abuse and Neglect and Basal Cortisol

Linear regression analysis showed that, in a sample of 62 subjects, child abuse and neglect was not a significant predictor of basal cortisol ($t=-.1$, $p=0.923$).

Psychopathy and Basal Cortisol

Linear regression analysis showed that psychopathy had a non-significant trend towards being a predictor of basal cortisol ($t=1.74$, $p=0.087$) with $\beta = 0.009 \pm 0.005$ (95% CI -0.001, 0.019) such that higher psychopathy corresponded to higher basal cortisol. Psychopathy explained 5 percent of the variance of basal cortisol using a linear model ($R^2=.048$). A pairwise correlation indicated that psychopathy had a small effect size on basal cortisol ($r = .219$). A scatter plot of basal cortisol and psychopathy revealed the possibility of a non-linear relationship. An augmented component plus residual plot provided further evidence for a non-linear relationship. A Breusch-Pagan test for homoskedasticity indicated that the null hypothesis of constant variance can be rejected ($\chi^2(1)=4.65$, $p=.03$). A Shapiro-Wilks test of the residuals suggested a non-normal distribution ($p=.01$). A non-linear median spline analysis with four knots at 2.3, 3.5, 4.5 and 5.2 nmol/L for basal cortisol produced a better fit of the relationship between basal cortisol and psychopathy as determined by an increase in the percent of the variance explained ($R^2=.127$). Based on multiple linear

regression, the spline model of basal cortisol has significant predictive value of psychopathy ($F_{3, 58}$ =2.3, p=.047) and a large effect size (r= .356).

Psychopathy and Aggression

Linear regression analysis showed that psychopathy was a significant predictor of aggression score (t=5.87, p<.001) with β = 0.029±0.005 (95% CI 0.019, 0.04) such that higher psychopathy corresponded to higher aggression score. A pairwise correlation indicated that psychopathy had a large effect size on aggression score (r = .589) and accounted for 35-percent of the variance in aggression (R^2=.347).

HPA-axis Reactivity and Aggression

Linear regression analysis showed that HPA-axis reactivity was a significant predictor of aggression score (t=-2.13, p=0.04) with β = -0.014±0.006 (95% CI -0.027, -0.001) such that lower HPA-axis reactivity corresponded to higher aggression. HPA-axis reactivity accounted for 10-percent of the variance in aggression (R^2=.102). A pairwise correlation indicated that HPA-axis reactivity had a medium effect size on aggression score (r = -.319).

Basal Cortisol and Aggression

Linear regression analysis showed that basal cortisol was not a significant predictor of aggression score (t=.29, p=0.773).

Impulsivity and Aggression

Linear regression analysis showed that impulsivity had a trend toward being a predictor of aggression score (t=1.72, p=0.09) with β = 0.03±0.02 (95% CI -0.01, 0.069) such that higher impulsivity corresponded to higher aggression. Impulsivity accounted for 4.3-percent of the variance in aggression (R^2=.044). A pairwise correlation indicated that impulsivity had a small effect size on aggression score (r = .209).

Mediation Analysis

Since mediation requires that the causal variable is related to the mediating variable, mediation analysis was not performed for basal cortisol as the regression analyses did not indicate an effect of child abuse and neglect on basal cortisol (p=.923). Instead, mediation analysis focused on HPA-axis reactivity.

Effect	*Path*	*Step*	*β (Std. Error)*	*95% CI*	*z-score*	*p*
Total effect	C	1	.052 (.01)	.02 to .08	3.66	.000
	A	2	-1.01 (.477)	-1.98 to -.049	-2.12	.034
	B	3	-.002 (.005)	-.012 to .007	-.471	.638
Direct effect	c'	4	.049 (.015)	.018 to .080	3.28	.001
Indirect effect	a*b		.008 (.040)	-.005 to .011	.459	.646

Table 5. Summary of the mediation analysis for abuse and neglect on aggression score with HPA-axis reactivity as a mediator.

HPA-axis Reactivity Mediates the Child Abuse and Neglect-Aggression Relationship

The results of the mediation analysis (Baron and Kenny, 1986) are summarized in Table 5. The mediation analysis model can be seen in Figure 2. The total effect of abuse and neglect on aggression score (path c) controlling for psychopathy and impulsivity, was significant (z=3.66, p<.001), with β = 0.05±0.01 (95% CI 0.02, 0.08) and a large effect size (r=.506). The total effect explained 25 percent of the variance in aggression score not accounted for by psychopathy and impulsivity (R^2 = .250). Step 1 was passed. The effect of abuse and neglect on HPA-axis reactivity (path a) was significant (z=-2.12, p=.033), with β = -1.01±.477 (95% CI -1.98, -0.049) and a medium effect size (-.318). Step 2 was passed. The effect of HPA-axis reactivity on aggression score controlling for abuse and neglect, psychopathy and impulsivity (path b) was not significant (z=-0.471, p=.638). Step 3 was failed. The direct effect of abuse and neglect on aggression score controlling for HPA-axis reactivity, psychopathy and impulsivity (path c') is significant (z=3.28, p=.001), with β = .049±.015 (95% CI .018, .080) and a large effect size (r=.441). A Sobel test indicated that the indirect effect of abuse and neglect on aggression score, or path a*b, was not significantly different from zero (z=.459, p=.646). The indirect effect had a very small effect size (r*r = .017). 4.3 percent of the total effect of abuse and neglect on aggression score was mediated by HPA-axis reactivity. The direct effect and indirect effect combined to explain 25.5 percent of the variance of aggression score not accounted for by psychopathy or impulsivity (R^2=.255).

Multiple Linear Regression Analysis

Based on a multiple linear regression analysis, the model of abuse and neglect, psychopathy, basal cortisol, impulsivity and HPA-axis reactivity has significant predictive value of aggression score ($F_{5, 36}$= 11.57, p<.001). This model accounts for 62 percent of the variance in aggression score (R^2=.616). Psychopathy (t=4.98, p<.001) and abuse and

neglect (t=3.25, p=.002) were significant predictors in the model, with β=.025 ± .005 (95% CI .015, .036) and β=.052 ± .016 (95% CI .019, .085) respectively. None of the other variables have significant predictive value when adjusting for other predictors.

Discussion

Summary of Findings

In a sample of 67 adults, a history of child abuse predicted higher levels of aggression, supporting the cycle of violence hypothesis. Higher levels of psychopathy also predicted increased aggression. Abuse and neglect predicted altered HPA-axis reactivity in the direction that more abuse corresponded to diminished HPA-axis reactivity. HPA-axis reactivity, in turn, predicted aggression, such that lower HPA-axis reactivity predicted higher levels of aggression. Although abuse predicted HPA-axis reactivity and HPA-axis reactivity predicted aggression, HPA-axis reactivity did not mediate a significant portion of the effect of child abuse on aggression. However, it did carry some of the effect, which may have reached significance with a larger sample size. The effects of abuse on HPA-axis reactivity and aggression fit with animal models of early life stress on both HPA-axis function and aggressive behavior. Basal cortisol was not related to abuse or aggression.

This project featured four novel contributions. 1) While other studies have looked at the effects of abuse on basal cortisol, this is one of the first studies to look at the effects of abuse on HPA-axis response. Another study looked at the effects of abuse on HPA-axis response following a stress-task in females (Shenk et al., 2010), but this study expanded on Shenk et al. (2010) by examining the abuse-HPA-axis interaction in both genders and by using a pharmacological rather than a psychological challenge. This study provided evidence for a blunted HPA-axis response in both abused and neglected males and females following a cortisol challenge. 2) While other studies have used acute cortisol dosing in humans to examine aggression, none have looked at the interaction between abuse and acute cortisol dosing on aggression in humans. 3) Another novel aspect of this study was the use of a combined state-trait measure of aggression. Many studies of aggression employ state measures, such as laboratory paradigms, or trait measures, such as questionnaires, but by combining state and trait into a unitary measure of aggression, it may be possible to capture a more complete picture of an individual's true aggressive profile. Specifically, an aggressive individual may score high on a state measure but low on a trait measure, or vice versa, depending on the time and context of testing. Employing both state and trait measures for each individual may better capture his or her underlying attribute, aggression. 4) The cycle of violence is most likely mediated by multiple pathways. This study attempted to examine the relative contributions of several pathways (psychopathy, impulsivity, and changes to HPA-axis function) which may be related to or independent from the cycle of violence thus expanding on the number of factors examined within the same

experiment. This represents the first combined examination of these variables and their predictive value with regards to aggression.

Using a multiple regression model with five predictors (abuse/neglect, psychopathy, impulsivity, basal cortisol and HPA-axis reactivity), 62-percent of the variance in aggression was explained in the present sample. Most of the variance was accounted for by two of the predictors, psychopathy and history of child abuse and neglect. Importantly, few studies have examined the role of these two factors with regard to understanding human aggression. These two predictors may represent unique pathways leading to a single outcome, heightened aggressive behavior. Child abuse represents a developmental trajectory influenced primarily by environment (or gene-by-environment interaction), whereas psychopathy may be more heavily influenced by genetics (or a gene-by-environment interaction; Fontaine et al., 2011). Nonetheless, the five-factor model predicted over half the variance in aggression, indicating that the pathways represented in the model have a large effect size and comprise a significant portion of the risk factors for aggression and violence.

Evaluation of Specific Aims and Hypotheses

Specific aim 1. Child abuse and neglect predicts aggression.

Hypothesis 1. Among adults age 18-55 with a range of histories of child abuse and neglect, higher levels of abuse and neglect as measured by the Childhood Trauma Questionnaire (CTQ) will predict higher levels of aggression as measured by the Point-Subtraction Aggression Paradigm (PSAP) and Buss-Perry Aggression Questionnaire (BPAQ).

In a sample of 67 adults with a range of histories of abuse and neglect, those with higher levels of abuse and neglect had significantly higher levels of aggression as measured by the PSAP and BPAQ. Although the cycle of violence has been well-demonstrated in the literature (Widom, 1989; Lansford et al., 2007), this is the first study to evaluate the cycle of violence hypothesis using a laboratory aggression paradigm. It potentially provides a novel inroad for studying the processes that mediate the cycle of violence because aggression can be measured in real-time, which allows researchers to manipulate key variables which may relate to aggression-heightening aspects of abuse. This study provided new evidence confirming that child abuse is a significant risk factor for aggression.

Although the CTQ is a retrospective self-report measure, and thus subject to measurement error, the findings were robust and agree with the extant literature (Widom,

1989a; Caspi et al., 2002; Lansford et al., 2007). The CTQ may have several advantages over prospective longitudinal studies as a research tool because the time it saves compensates for noisier data. Further, it allows for a continuous measure of abuse and neglect rather than a dichotomous one, which provides measurement advantages.

Specific aim 2. Psychopathy predicts aggression.

Hypothesis 2. Among adults age 18-55 with a range of psychopathic traits, higher levels of psychopathy as measured by the Self-Report Psychopathy scale III (SRP-III) will predict higher levels of aggression as measured by the PSAP and BPAQ.

Psychopathy was a robust predictor of aggression. This may relate to inherited traits such as callous affect and fearlessness. Such traits comprise a principal component of psychopathy and may be present from birth (Viding et al., 2008). Thus, at least part of the predictive value of psychopathic traits on aggression remains even in the absence of adverse childhood experiences. Psychopathy, then, may represent a distinct pathway to aggression, independent of abuse. However, child abuse and a chaotic home environment during early development (age 4) can be a predictor of psychopathic traits, including callous-unemotional affect and criminal tendencies (Fontaine et al., 2011). Whether psychopathy results from abuse or from other independent factors, it was a significant predictor of aggression.

Specific aim 3. Child abuse and neglect predicts basal cortisol levels.

Hypothesis 3. Among adults age 18-55 with a range of histories of child abuse and neglect, higher levels of abuse and neglect as measured by the CTQ will predict higher levels of basal cortisol as measured by the area under the curve (AUC).

In a sample of 62 adults, child abuse and neglect did not significantly predict basal cortisol levels. This may have been due to several factors, including time of measurement for basal cortisol (see Limitations) or confounding variables that were not detected. It may also indicate that abuse and neglect do not have a significant effect on basal cortisol levels in healthy adults.

Specific aim 4. Psychopathy predicts basal cortisol levels.

Hypothesis 4. Among adults age 18-55 with a range of psychopathic traits, higher levels of psychopathy as measured by the SRP-III will predict lower levels of basal cortisol as measured by the AUC of saliva samples taken between 8 am and 10 am.

One of the most intriguing findings in the data was the relationship between psychopathy and basal cortisol. The data indicated a non-linear relationship between psychopathy and basal cortisol, such that both high and low levels of cortisol corresponded to high levels of psychopathy, whereas medium levels of cortisol corresponded to low levels of psychopathy. Whereas the hypothesis stated that individuals with high psychopathy would have low basal cortisol, the results showed that individuals with high psychopathy had either low or high levels of basal cortisol, but not medium levels. This suggests the possibility that levels of basal cortisol outside of the normal range may indicate psychopathy whether levels are low are high. Other studies suggest that psychopaths have low levels of basal cortisol (Cima et al., 2008). However, a recent study by Vaillancourt and Sunderani (2011) found that, in women only, lower cortisol predicted higher levels of callous affect and interpersonal manipulation, two factors comprising a dimension of psychopathy, whereas higher cortisol predicted higher levels of erratic lifestyle and criminal tendencies, factors comprising a separate dimension of psychopathy.

Specific aim 5. Basal cortisol levels predict aggression.

Hypothesis 5. Among adults age 18-55, basal cortisol levels as measured by the AUC of saliva samples taken between 8 am and 10 am will predict aggression as measured by the PSAP and BPAQ. Specifically, both low and high levels of basal cortisol will predict higher levels of aggression compared to mid-levels of basal cortisol, reflecting the differential influence of both psychopathy (lower basal cortisol) and child abuse/neglect (higher basal cortisol) on aggression.

In a sample of 62 adults, basal cortisol was not a significant predictor of aggression. This provides evidence contrary to findings in several studies, which found a relationship between basal cortisol and aggression (Bohnke et al., 2010b; Cima et al., 2008). Bohnke et al. (2010) found that basal cortisol, measured 30, 45 and 60 minutes after waking, explained over two-thirds of the variance in aggressive behavior on a laboratory paradigm. The lack of an effect in this study may have been due to several factors, including time of measurement for basal cortisol or confounding variables that were not detected (see Limitations).

Contrarily, it could indicate that abuse and neglect do not modulate basal cortisol levels in healthy adults.

Specific aim 6. Child abuse and neglect predicts HPA-axis reactivity.

Hypothesis 6. Among adults age 18-55 with a range of histories of child abuse and neglect, higher levels of abuse and neglect as measured by the CTQ will predict higher levels of HPA-axis reactivity as measured by the increase in salivary cortisol following the acute administration of 20mg cortisol capsules compared to salivary cortisol after placebo.

In a sample of 42 adults, abuse and neglect were significant predictors of HPA-axis reactivity. This finding may represent the first examination in humans of the relationship between abuse and cortisol response to an acute cortisol challenge. This measure of HPA-axis reactivity provides further supporting evidence for biological change resulting from experiences of child abuse and neglect (Veenema, 2009; De Bellis, 2005). Hormonal responses vary by age, context, and past exposure to hormones. One possible explanation for this finding is that experiencing abuse and neglect disrupted normal HPA-axis development for these individuals during a critical developmental period. This hypothesis is supported by non-human studies (Veenema et al., 2009). The resulting release of cortisol, above normal quantity and duration, may have altered the body's response to biological and environmental stressors. For example, the HPA-axis, a negative feedback loop that reduces output in response to cortisol, may change its sensitivity following abuse and neglect. In abused individuals, cortisol may promote shutting down of the HPA-axis, producing a flatter response—absence of a large peak observed in individuals with less history of abuse—to the cortisol challenge in this study (see Fig. 3).

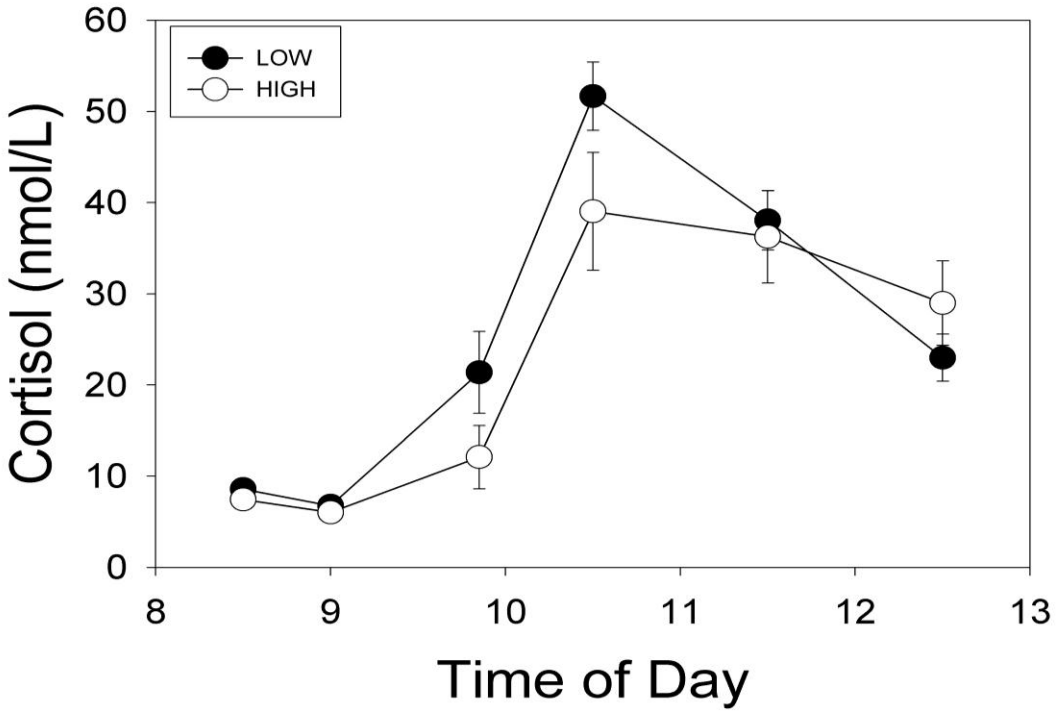

Figure 3. High includes all individuals with CTQ scores ≥ 43 (N=11). Low includes all individuals with CTQ scores ≤ 42 (N=31).

A study by Shenk et al. (2010) provided similar evidence that abuse leads to blunted HPA-axis reactivity. In Shenk et al.'s (2010) study, a group of sexually-abused females and healthy control females were administered a stress-task at age 18, and the abused females demonstrated a blunted release of cortisol compared to the controls. A follow-up 6 years later, when the subjects were 24, revealed that a blunted cortisol response predicted antisocial behavior and aggression (Shenk et al., 2010). The findings from Shenk et al. (2010) corroborate the results of the present study, in that abuse predicted a blunted HPA-axis reactivity in response to a biological challenge as measured by cortisol release, and HPA-reactivity in turn predicted aggression. Further, it supports the model put forth in the hypotheses of this dissertation which suggested that child abuse puts individuals at risk for aggression and antisocial behavior related in part to alterations in the HPA-axis.

Specific aim 7. HPA-axis reactivity predicts aggression.

Hypothesis 7. As measured by the increase from in salivary cortisol from baseline following the acute administration of 20mg cortisol, HPA-axis reactivity will predict higher levels of aggression as measured by the PSAP.

In a sample of 42 adults, HPA-axis reactivity was a significant predictor of aggression. Conversely, it remains possible that aggression predicts HPA-axis reactivity. This possibility, while noteworthy, is less likely. First, abuse and neglect typically precede aggression in the temporal sequence of development. Abuse and neglect also necessarily precede the changes in HPA-axis reactivity. Because of the significant relationship between abuse and HPA-axis reactivity, and the order of events, it seems likely that abuse and neglect cause changes in the HPA-axis response to a stressor (e.g. cortisol challenge). Second, as HPA-activity predicted aggression, it seems likely that the temporal sequence begins with abuse and neglect, followed by changes in HPA-axis reactivity, followed by changes in aggression. This corresponds to the findings of Shenk et al. (2010), which sequentially measured abuse and neglect, then HPA-axis reactivity, then aggression and found a predictive, sequential relationship.

Specific aim 8. Impulsivity predicts aggression.

Hypothesis 8. Higher levels of impulsivity as measured by the Barratt Impulsivity Scale 11 (BIS-11) will predict higher levels of aggression as measured by the PSAP and BPAQ.

Impulsivity did not significantly add to the predictive value of the model in terms of aggression. It was not predictive of aggression as an individual variable in a linear regression model nor as a predictor in a multiple linear regression model. However, it showed a trend toward being a significant independent predictor ($p=.09$) with a small effect size ($r=.209$). If the effect size in this sample is the true effect size, then a larger sample would produce significant results. In a longitudinal study looking at factors which predicted sexual aggression, Yeater et al. (2011) found that impulsivity was related to aggression, but was not a significant predictor in a multiple regression model. Further, research by Swann et al. (2009) found that impulsivity is highly correlated with antisocial personality disorder, a disorder characterized by heightened risk for aggression and violence. Yet, research examining the relationship between impulsivity and laboratory-measured aggression produced mixed findings (Dougherty et al., 1999; Bjork et al., 1998). Similar to the present

study, impulsivity may have predictive value towards aggression, but its effect size appears modest. Impulsivity underlies a wide range of maladaptive behaviors and may feed into aggression indirectly or through other factors, such as likelihood to develop substance use disorders, which have a relatively larger effect on aggression.

Similarly, a recent review of the literature relating aggression, impulsivity and suicidality found that all of these traits are related, and while both impulsivity and aggression predict suicidal behavior, the relationship between impulsivity and aggression remains less clear.

Another explanation is that aggression may comprise both impulsive and premeditated forms (Stanford et al., 2003; Swann, 2003). The measure of aggression in this study, a combination of the Buss-Perry Aggression Questionnaire (BPAQ) and PSAP responding, may have been influenced more heavily on premeditated aggression due to the sample and the measurement via the BPAQ. Impulsivity as measured by the Barratt Impulsivity Scale-11 (BIS-11) had significant predictive value on impulsive aggression as measured by the Impulsive-Premeditated Aggression Scale (see appendix). Further, as the BIS-11 rates impulsivity on three factors, it is possible that only some of the factors of impulsivity predict aggression rather than the total score.

Evaluation of the Model

The results of the present study suggested that some parts of the proposed model were supported, whereas others were not. Abuse and neglect were significant predictors of aggression, as was psychopathy. Abuse and neglect predicted HPA-axis reactivity, but not basal cortisol. Psychopathy was related to basal cortisol, but basal cortisol had no significant predictive value for aggression. However, HPA-axis reactivity predicted aggression. Impulsivity showed a trend toward being a significant predictor of aggression. In sum, the predicted model was supported except for the effects of abuse on basal cortisol and basal cortisol on aggression. An amended model is presented in figure 4.

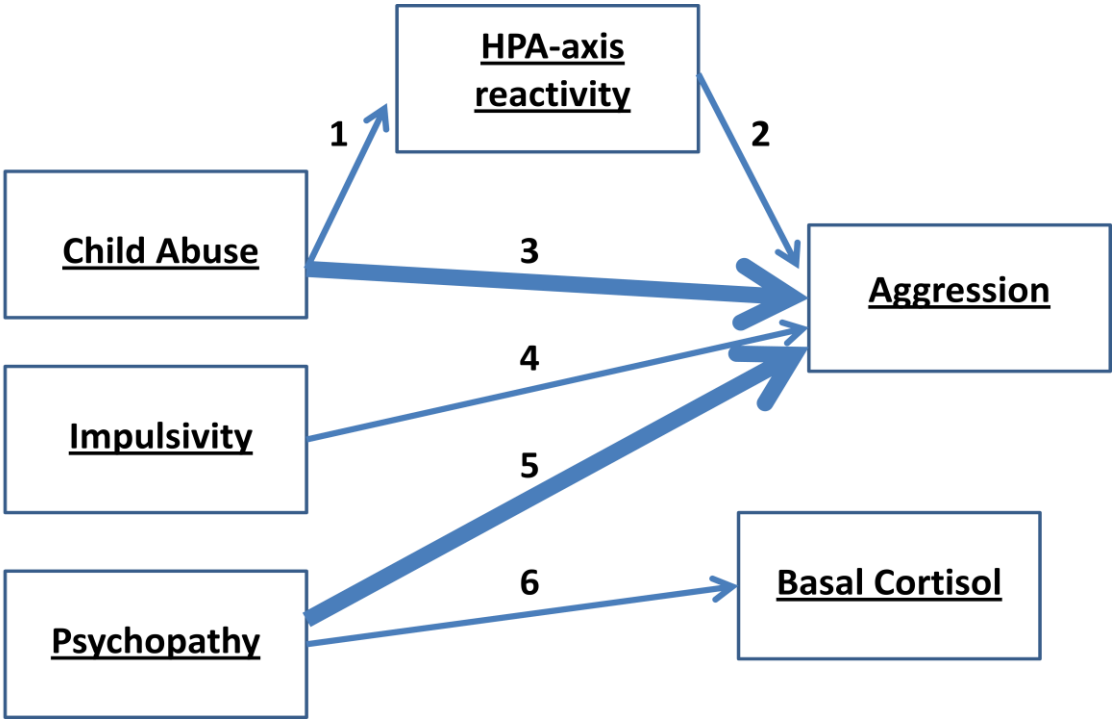

Figure 4. A revised version of the proposed model, amended according to the results. The thin lines represent relationships that approached significance ($p<0.1$) or were significant ($p<.05$). The thick lines represent robust relationships ($p\leq0.01$). The amount of variance explained by each relationship is as follows: 1) $R^2=.101$, 2) $R^2=.101$, 3) $R^2=.287$, 4) $R^2=.044$, 5) $R^2=.347$, 6) $R^2=.127$.

Limitations

One of the primary limitations of this dissertation was the high rate of contamination of saliva data on the day when subjects were administered cortisol. The problem stemmed from subjects ingesting cortisol orally and also providing samples orally, via saliva. Thus, if the capsules had any cortisol on them when being swallowed, there was a risk that it could remain in the saliva. The #00 capsules contained a single 20mg cortisol pill, but the pill was too large to place in the capsule whole. To make it fit, the pill was broken in half and then placed in the capsule. Cortisol, being a steroid, has a high affinity for lipids and is difficult to remove with water due to its hydrophobia. When the pill was broken in half, some of the cortisol may have contacted the pharmacist's gloves and then those gloves may have touched the outside of the #00 capsule once the pill was inside. The contaminated capsule was swallowed by the subject, but the cortisol on the capsule's exterior may have then mixed with the subject's saliva and produced samples with cortisol levels outside of the normal

range for human function, invalidating the results of the reading. Indeed, 32-percent of the samples were outside the range of normal human values (range ≤ 85 nmol/L). Future studies may circumvent this problem by using larger capsules that can contain a whole cortisol tablet without breaking it in two.

As the contamination was due to methodological problems, not due to characteristics of the subjects who had contaminated samples, contamination can be considered a random event that does not invalidate the rest of the sample. The subjects who had contaminated samples must be removed from measures of HPA-axis reactivity, but they were retained in the overall sample.

Salivary measures of cortisol provide a non-invasive, albeit indirect, way to measure HPA-axis function. One potential limitation of this study was that the first sample was taken at 8:30am. Peak levels of cortisol are typically present immediately after waking, and by measuring at 8:30am, this study may have missed that window.

No relationship was observed between abuse/neglect and basal cortisol. Most of the research in humans suggesting altered basal cortisol comes from adolescent populations, but these differences may disappear as individuals move into adulthood. Studies in rodents and non-human primates indicate that effects of abuse on basal cortisol can vary across developmental stages (Veenema, 2009).

Alternatively, the methodology employed in this study may not have been sufficiently robust to accurately detect differences in basal cortisol. For example, cortisol peaks soon after awakening and descends throughout the day. The optimal time to measure basal cortisol is immediately—within a few minutes—after waking. However, due to methodological constraints and compliance, we chose to obtain the first saliva sample of the day when the subject arrived in the laboratory, around 8:30 am. Subjects may have awakened at different times and still arrived in the laboratory at 8am. The first sample, our measure of basal cortisol, may have been obtained as much as 2 hours after awakening. We chose to obtain samples in the laboratory for this study because it allowed control of timing and guaranteed compliance. Nonetheless, this may have limited the ability to detect differences in basal cortisol.

Some of the relationships observed in this study that had a trend toward significance may prove significant in a larger sample. For example, the effects of impulsivity on aggression and the portion of the mediating effect of HPA-axis reactivity between abuse and aggression demonstrated small to moderate effect sizes, but were not significant in the present sample.

Further, males and females may have differential HPA-axis response to abuse and neglect (De Bellis, 2005), reflecting unique physiology, but the present sample was not large enough, and specifically didn't have enough females to explore these potential differences.

Future DIrections

Aside from abuse and neglect, there are likely other environmental factors that influence aggression not accounted for in this study. Similarly, there are likely other genetic influences that influence aggression not accounted for in this study. For example, several studies have linked variations in the MAO-A gene to aggressive behavior (Ferrari et al., 2005), particularly demonstrating that MAO-A genotype moderates the risk for development of aggression following abuse and neglect during childhood (Caspi et al., 2002). Despite several studies showing that the low-functioning MAO-O genotype confers an increased risk for antisocial behavior following abuse (Caspi et al., 2002; Kim-Cohen et al., 2006; Fergusson et al., 2011), it remains unclear why this is so. MAO-A was not examined in the present study, but it may be that MAO-A genotype interacts with HPA-axis function, and altered HPA-axis function would indicate a potential mechanism by which the low-functioning variant of MAO-A increases the risk for antisocial behavior following abuse.

Another potentially important genetic variation that has not been examined regarding abuse and neglect outcomes on aggression is the corticotrophin-releasing hormone (CRH) receptor, part of the HPA-axis known to be related to aggression (Takahashi et al., 2011). Gene x environment interaction studies have indicated that genetic variants of the CRH receptor 1 may moderate the risk for alcohol-use disorders in rodents Hannson et al., 2006) and in humans (Treutlein et al., 2006). Variants of the CRH receptor 1 may play an important role in the risk for aggression and violent behavior following abuse and neglect.

Cortisol dosing represents a tool to study the effects of abuse and neglect on the HPA-axis and the stress response. Looking at larger or smaller doses of cortisol may illuminate its effect on aggression and HPA-axis responding. Further, while this study examined the HPA-axis via cortisol manipulation, it did not specifically evaluate CRH-receptor activity. Specific CRH-receptor modulators may illuminate the specific role of this receptor in the altered HPA-axis response following abuse and neglect.

Psychopathy had an intriguing relationship with basal cortisol, such that psychopathy corresponded both to high and low levels of basal cortisol, but not medium levels. Work by Vaillancourt and Sunderani (2011) suggests low levels of basal cortisol may only predict psychopathy in women. Cima et al. (2008) found that psychopaths have lower basal cortisol.

Hence, this finding requires replication and further examination of the complex relationships among abuse, psychopathy, cortisol and gender.

Additionally, much of the previous literature regarding the HPA-axis effects of abuse and neglect has focused on adolescents. This population may provide information not present or observable in adults. A subsequent study of adolescents may provide different results or provide unique information on how HPA-axis reactivity changes across development.

Finally, to explore gender differences in HPA-axis development following abuse and neglect, future research could recruit a larger sample of females to compare to the mostly male sample in this study.

Conclusions

The results of this study suggest that abuse and neglect present a significant risk factor for aggressive behavior, and that part of this risk may be conferred by changes in HPA-axis reactivity. Further, psychopathy presents a risk factor for aggression that may occur independently from, or in concert with abuse and neglect. These findings should encourage further research into the processes involved in the cycle of violence, especially as it relates to the stress response and HPA-axis function. Research using different methodologies will hopefully provide further understanding of the cycle of violence, and this understanding may translate into successful prevention and treatment strategies for abused and neglected youth.

Appendix

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER - HOUSTON
Effect of Hydrocortisone on Computer-Based Social Interaction
INFORMED CONSENT FOR RESEARCH STUDY

INVITATION TO TAKE PART

You are invited to take part in a research project called, "Effect of Hydrocortisone on Computer-Based Social Interaction," conducted by Joshua Gowin and Dr. Scott Lane of the University of Texas Health Science Center Houston. For this research project, Joshua Gowin will be called the Principal Investigator.

Your decision to take part is voluntary and you may refuse to take part, or choose to stop taking part, at any time. A decision not to take part or to stop being a part of the research project will not change the services available to you from your doctor, or the University of Texas Health Science Center.

You may refuse to answer any questions asked or written on any forms.

This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston as HSC-MS-10-0178.

DESCRIPTION OF RESEARCH PURPOSE

The purpose of this research is to examine how the medication, Hydrocortisone, affects people's mood, and the way that people interact with each other during a computer task. This is a local study in Houston, Texas. The study will enroll a total of 200 people. The National Institute of Health is paying for this study to be completed.

PROCEDURES

During the study, you will receive a physical exam, mental health exam, and questions about drug use and medical history**.** Today you will be interviewed about your mental health. On your next visit you will be given a physical exam. If you meet the health requirements for the study, you will begin the experimental portion of this study. On the two experimental days, you will be given a pill containing either the drug Hydrocortisone or a placebo. Placebo is a capsule with no Hydrocortisone. Over the two days, you will receive both conditions. After taking the pill, you will work on a task where you will interact with other people through a computer. Every day you visit the medical center, you will be asked to provide a urine sample to test for recent drug use and (for females) pregnancy. You will also be asked to provide a breath sample to test for recent alcohol use. The results of these tests will determine if you can take part in the study on that day.

You will be asked to come into the laboratory for about 4-5 hours each day. You will arrive in the morning at 8:00 a.m. At 9:30am you will be given a medication called Hydrocortisone or a placebo (a capsule filled with cornstarch). During testing you will be in a room with a computer monitor screen and a response panel with three buttons. The task will require that you push the buttons to earn money. You will be paired with other people through the computer during the test session. The way you interact with these other people may affect the

amount of money you earn. The sessions will be about 25 minutes each, and there will be a break in between test sessions.

At the end of each day, you will be paid the amount of money earned during each session. At the end of the study, you will be asked to answer a series questions given on paper and pencil tests. The questions will ask you about your mood, previous things you have done, and what kinds of things you typically do in certain situations.

You are asked to not use alcohol or any other drug during the entire study. You are asked not to drink tea, coffee, or colas, smoke cigarettes, or eat food from outside during the test days. These requirements are very important to the study.

Hydrocortisone

First, you will receive a physical exam by a medical professional. This is a routine physical exam where the medical professional will listen to your heart, lungs and abdomen. The exam will include a personal history of health to ensure that you will have no complications with Hydrocortisone.

Then you will learn the computer task. Then, during all visits you will be asked to provide saliva samples to detect levels of Hydrocortisone in your spit.

After the pill, you will take part in three computer test sessions (described above).

We will measure the size of your pupil for effects on the nervous system.

At the end of the day, you will be tested for signs of any Hydrocortisone effects. Then you will be released from the medical center.

TIME COMMITMENT

You will be asked to come into the laboratory for 5 days, approximately 4-5 hours each day. Your total time in the study should be about 1 week.

BENEFITS:

The benefit you can expect to receive as a result of taking part in this study is information regarding your physical and mental health status obtained during the screening procedures. You will be provided a referral service if one is available that might benefit you.

RISKS AND DISCOMFORTS

Taking part in this study involves the following risks:

1. Hydrocortisone is a medication approved by the FDA for the treatment of a number of conditions, such as asthma, allergic disorders and arthritis. A single dose of Hydrocortisone is not expected to cause any serious changes to your health. The most common side effects of Hydrocortisone reported by the manufacturer compared to placebo are headache, high blood pressure, dizziness or nausea. Hydrocortisone should not be taken if you have a fungal infection in your body or if you allergic to Hydrocortisone. Due to this fact you will not be able to take part in this study in you have a history of allergic reactions to Hydrocortisone, or if you have diabetes, chronic high blood pressure, glaucoma, or a thyroid disorder.

2. Some of the questions asked of you will cover sensitive topics. You may be asked to recall difficult or traumatic experiences from your past.

ALTERNATIVES:

The only alternative is not to take part in this study.

STUDY WITHDRAWAL:

You may withdraw at any time without any penalty or unfair outcomes should you choose to stop taking part in this study. You may be asked to leave the study for the following reasons:

1. If alcohol is detected on your breath and/or drugs are found in your urine sample.

2. You fail to show up for three scheduled appointments at the laboratory, and do not contact the laboratory.

3. For females, if you become pregnant.

4. You experience side effects of Hydrocortisone that are considered to be unsafe for you to continue.

IN CASE OF INJURY

If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you, just as they are to the community in general. You should report any injury to Scott Lane at 713-486-2535 and to the Committee for the Protection of Human Subjects at (713) 500-7943. You will not give up any of your legal rights by signing this consent form. **COSTS, REIMBURSEMENT, AND COMPENSATION** Parking or bus tokens and lunch will be provided. You can expect to earn about $8-10 per hour. It will not cost you anything to join this study. If you should receive a bill that you believe is related to your taking part in this research project, please contact, the Principal Investigator, Joshua Gowin at 713-486-2613. You wll be paid for taking part in this project in the following amounts:

1. On experimental days, you will earn about $5-7 per testing session, based on your performance.
2. You will earn $20 each day that you arrive on time for scheduled appointment and your breath alcohol level and urine sample are free from drugs and alcohol.
3. Upon completion of the experiment (on the last day), you will earn a completion bonus of $10 for each day that you took part (e.g., 5 days = $50).
4. You will receive $8/hour for your time today, for the physical examination, and for the final day when you fill out questionnaires.

CONFIDENTIALITY

Please understand that representatives of the National Institute of Health (NIH) and the Committee for the Protection of Human Subjects may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. There is a separate authorization form that you will be asked to sign which details the use and disclosure of your protected health information.

QUESTIONS:

The Principal Investigator, Joshua Gowin and his research staff will be glad to answer any questions regarding the study at any time. The staff may be reached at 713-486-2794.

SIGNATURES:

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of Subject _____
Signature of Subject _____
Date / Time _____
Printed Name of Individual Obtaining Consent _____
Signature of Individual Obtaining Consent _____
Date / Time _____

CPHS STATEMENT:

This study (HSC-MS-10-0178) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

IRB NUMBER: HSC-MS-10-0178 IRB APPROVAL DATE: 2/18/2011 IRB EXPIRATION DATE: 1/31/2012

PSAP 3 option Instructions

This computer task examines mood, motor responses (button pressing), and interaction with other people. Each session will last approximately 25 minutes.

During the session you will be able to earn money by working at a response panel. This is a drawing of the response panel. As the drawing shows, the response panel has three buttons marked A, B, and C; a monitor, which will display the letters A, B, and C; and a money counter. When you press a button, the letter corresponding to that button will remain on the screen and the other letters will go off the screen. So when you press the A button, the letters B and C will disappear. Pressing button B removes the letters A and C, and pressing button C removes letters A and B. When one only one letter is showing on the screen, the other buttons will not work. So, you can only change from one button to another button when all three letters are displayed on the screen.

Your response panel is linked by a network to one of several other panels just like it. Other people like you will be seated at the same kind of panel. The panels are located in different locations. The other person will always be a (man/woman), as we pair people by the same gender in this task.

When the session starts, the letters A, B, and C will be displayed and the money counter will begin at zero. If you press button A, letters B and C letter will disappear. Pressing button A approximately 100 times will add 15 cents to your counter (you don't need to count presses, the computer program will do it for you). Then the A, B, and C letters will come back on the screen, and you can continue to press button A or switch to buttons B or C.

During the session, you may see the counter increase in size and start flashing off and on. Then 15 cents will then be subtracted from your counter, and the counter will return to its normal size. This means that the other person – whose computer in linked to yours – has subtracted 15 cents from your counter and added it to his counter by pressing button B on his response panel 10 times. So the other person can take 15 cents of your money and add it to his money by pressing B ten times, instead of pressing A 100 times.

If YOU press button B, the A and C letters will disappear. Then pressing button B ten times will subtract 15 cents from the counter of the person who is connected to your panel. When the A, B, and C letters reappear, you can continue to press button B or switch to button A or C. However, if you subtract money from the other person, it will not be added to your counter – the money is just removed from the other person's counter. There are two conditions in the task. In condition 1, the person keeps the money that s/he subtracts. In condition 2, the money that is taken from the other person is simply gone. The conditions are determined randomly by the toss of a coin and you ended up in the condition 2 in which you do not keep the money you subtract.

If you press button C, the A and B letters will disappear. Pressing button C until the letter C goes off the screen (approximately 10 times) will protect your counter from subtractions for a short period of time (about 2 minutes). When the A, B, and C letters reappear, you may continue to press button C or switch to button A or B.

You will be paid the money showing on your counter at the end of each test session. This money will be paid at the end of the day, after you have completed your last session. How much you earn depends mostly on how fast you press the A button. As a general rule, the faster you press button A the more money you can earn.

Please remain in the testing room until you see a message on the computer screen that reads “Session Over”

PSAP data :

A responses / second

Descriptive Statistics:

stats	Placebo	Cortisol
N	67	67
mean	4.297	4.400
sd	.895	.783
max	5.86	5.84
min	1.37	2.28

Inferential Statistics: A paired t-test comparing the mean A responding on the placebo day versus the cortisol day revealed no effect of dose (t= -0.69, p= 0.48). Linear regression analysis revealed no effect of abuse and neglect (CTQ total score) on A responses/minute (t= -0.48, p=0.64).

C responses / minute

Descriptive Statistics:

stats	Placebo	Cortisol
N	67	67
mean	11.4	11.0
sd	12.6	12.9
min	0	0
max	53.5	63.1

Inferential Statistics: A paired t-test comparing the mean C responding on the placebo day versus the cortisol day revealed no effect of dose (t= 0.193, p= 0.85). Linear regression analysis revealed a significant effect of abuse and neglect (CTQ total score) on C responses/minute (t=2.21, p=.031). Abuse and neglect had a coefficient of .299, such that an increase of 1 point on the CTQ corresponded to an increase in 0.299 ±0.14 C responses per minute (95% CI 0.03, 0.57).

Cardiovascular Data

Descriptive Statistics:

Systolic Blood Pressure

stats	Placebo	Cortisol	Questionnaires
N	67	67	67
mean	112.9	112.4	112.0
sd	9.4	9.0	9.2
max	152.3	138.8	133.2
min	93.7	96.7	93

Diastolic Blood Pressure

stats	Placebo	Cortisol	Questionnaires
N	67	67	67
mean	72.6	72.5	72.5
sd	7.2	7.2	7.5
max	89	93.2	88.7
min	53.7	55.2	53.6

Heart Rate

stats	Placebo	Cortisol	Questionnaires
N	67	67	67
mean	63.9	64.8	64.6
sd	8.6	8.7	8.4
max	82.2	84.8	84.2
min	44.3	44.2	48

Impulsive / Premeditated Aggression Scale

Descriptive Statistics:

stats	Impulsive	Premeditated
N	67	67
mean	27.6	21.6
sd	6.43	5.80
max	42	36
min	10	8

Inferential Statistics:

Abuse predicts impulsive/premeditated aggression. Linear regression analysis revealed a significant effect of abuse and neglect (CTQ total score) on impulsive aggression as measured by the IAPS (t= 2.13, p=0.037). Abuse and neglect had a coefficient of 0.146 ±0.069, such that an increase of 1 point on the CTQ corresponded to an increase of 0.146 on the impulsive aggression scale (95% CI 0.009, 0.283). Similarly, linear regression analysis revealed a significant effect of abuse and neglect on premeditated aggression (t= 2.13, p=0.037). Abuse and neglect had a coefficient of 0.132 ±0.062, such that an increase of 1 point on the CTQ corresponded to an increase of 0.132 on the premeditated aggression scale (95% CI 0.008, 0.256).

Impulsive/premeditated aggression predicts total aggression. Linear regression analysis revealed a significant effect of impulsive aggression on total aggression score (PSAP data and Buss-Perry) (t= 2.76, p=0.007). Impulsive aggression had a coefficient of 0.078 ±0.028, such that an increase of 1 point on the impulsive scale corresponded to an increase of 0.078 on the aggression score (95% CI 0.02, 0.13). Similarly, linear regression analysis revealed a significant effect of premeditated aggression on total aggression score (t= 4.61, p<0.001). Premeditated aggression had a coefficient of 0.132 ±0.029, such that an increase of 1 point on the premeditated scale corresponded to an increase of 0.132 on the premeditated aggression scale (95% CI 0.075, 0.19).

Multiple Regression model. A multiple regression model of total aggression score, with abuse/neglect, impulsive and premeditated aggression scores as predictors, revealed a significant overall model ($F_{3, 63} = 15.94$, p<.001) that explained 43-percent of the total variance on aggression score (R^2=.43). Controlling for impulsive and premeditated aggression, abuse and neglect were significant predictors of aggression (t=4.23, p<.001). Controlling for abuse/neglect and impulsive aggression, premeditated aggression was a

significant predictor of total aggression (t=3.44, p=0.001). Impulsive aggression was not a significant predictor of total aggression when controlling for abuse/neglect and premeditated aggression (t=0.84, p=0.406).

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Vita

Joshua Leigh Gowin was born in Fort Collins, Colorado on May 3, 1983, the son of Sheila Ann and Frank Houser Gowin. After completing the International Baccalaureate program and graduating from Greeley West High School, Greeley, Colorado in 2001, he entered The University of Colorado-Boulder (CU). He received the degree of Bachelor of Arts with a major in Psychology and a minor in Mathematics from CU, with distinction, in December, 2004. For the next year, he worked as an English teacher in France and Moscow, Russia. In August of 2006 he entered The Graduate School of Biomedical Sciences at The University of Texas Health Science Center at Houston (UTHSC-Houston). He earned a Master's of Science in May of 2009 for his work examining the potential of a migraine medication, zolmitriptan, to reduce alcohol-heightened aggression. In the same year, he interned at a magazine, *Psychology Today*, in New York City, where he currently maintains a neuroscience-themed blog entitled *You, Illuminated*. In June, 2009, immediately following completion of his Master's degree, he began work on his doctorate at UTHSC-Houston. Upon completion of his Ph.D., he plans to accept a post-doctoral research fellowship at the University of California, San Diego.