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Sex Differences in Physiological Predictors of Aggression in a Highly Traumatized, Inner-city Population of Men and Women

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Sex Differences in Physiological Predictors of Aggression in a Highly Traumatized, Inner-city Population of Men and Women

By

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B.S.
Georgia Institute of Technology
2009

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Abstract

Sex Differences in Physiological Predictors of Aggression in a Highly Traumatized, Inner-city Population of Men and Women

By Elicia Skelton

Violence is a serious public health concern with devastating physical, mental, social, and economic repercussions. In order to develop appropriate preventive and interventional strategies, risk factors associated with violence and aggression must be identified. Many of the previously studied predictors of aggression are subjective and often difficult to quantify, making risk-stratification difficult and necessitating the need to establish objective indices. The goal of this thesis is to identify whether the following physiological correlates of autonomic nervous system (ANS) activity – fear-potentiated startle response, respiratory sinus arrhythmia (RSA) in response to a negative stimulus (i.e. delivery of loud acoustic startle probes), and resting heart rate (HR)– are predictive of aggression in both men and women. Physiological data were collected between May 2008 and January 2011 from a population of 309 highly traumatized, at-risk, primarily African American civilians seeking primary care at Grady Memorial Hospital in Atlanta, GA. After excluding all individuals with missing self-reported aggression data, 251 remained. In men, fear-potentiated startle response to a cue that was previously paired with an airblast (*danger cue,* CS+) and startle RSA were positively associated with aggression ($R=0.26$, $R^2=0.07$, $p<0.05$ and $R=0.32$, $R^2=0.10$, $p<0.05$, respectively) and resting HR was negatively associated with aggression ($R= -0.26$, $R^2=0.07$, $p=0.042$). In women, only resting HR was significantly negatively associated with aggression

(R= -0.24 R^2=0.06, p<0.01). This study demonstrates that among men aggression is associated with dysregulation of ANS activity both at rest and in response to stressors, while among women aggression may only be associated with components of the ANS involved in resting HR. The associations between each of these physiological predictors and aggression in addition to the sex differences between each of these associations may provide further insight into the etiology of aggression. Such findings may eventually help in the development of measures targeted at identification of individuals prone to aggression and violence.

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Background

Over the past century, the incidence of mass public shootings committed throughout the United States has significantly increased [1]. In many of these cases such as the elementary school shooting in Newton, CT, the theater massacre in Aurora, CO, the college shooting in Santa Monica, CA., and the Navy yard shooting in Washington DC, the alleged perpetrator was a male with a known history of psychological illness. It has been speculated in the popular media that over half of the mass shootings that have occurred in the US over the past century were committed by individuals with known mental illness [2]. Each of these tragedies has repeatedly drawn attention to the link between mental illness and violence and has reinforced society's perception that mental illness is synonymous with violence. While in reality the overwhelming majority of individuals with psychiatric disorders are not violent, there is an increased association with some mental illnesses and violence. Studies have shown that individuals with serious mental illness or substance use disorders are at higher odds for committing violent acts (OR: 1.60, 95%CI: 1.17-2.20) compared with those who do not have mental illness or substance use disorders [3]. Equally as concerning is the increased risk of victimization in those who suffer from mental illness. In a study by Brekke and colleagues, individuals with schizophrenia or schizoaffective disorder were found to be 14 times more likely to be victims of violence than to be arrested for violent acts [4].

Sex is another well-studied correlate of aggression, with males at much higher risk for committing aggressive acts than females worldwide [5]. In the past century, over 90% of the mass murders in America were committed by men [1]. Nevertheless, there

are few studies of violence in females, and a poor understanding of how sex differences in violent behavior may relate to differences in autonomic physiology.

In addition to the obvious physical threats, an array of social, economic, and physical health consequences are associated with violence. Victims of violence are at increased risk for a variety of negative outcomes including psychological disorders, alcohol abuse, reproductive health problems and sexually transmitted infections [6]. Victims of adulthood violence also have increased odds of becoming perpetrators themselves (OR: 6.1, 95%CI: 54.0-9.1) [7]. Perpetrators, especially those with psychological comorbidities, often end up homeless or incarcerated, have prolonged hospital stays, and have higher incidence of psychiatric admissions compared with similar individuals without violent tendencies [8]. The ability to identify individuals who are at high risk of committing violent acts, particularly among males with a history of psychiatric disorders, could have tremendous implications from a public health standpoint and may allow us to develop appropriate interventions and preventive therapy.

Currently, our ability to risk-stratify the likelihood of violence is limited. This is at least partially due to the complex etiology of aggressive thoughts and behavior. Elucidation of the underlying physiology and neurobiology is needed to understand the causal pathways leading to violent behavior. Various psychophysiological measures have been considered as possible correlates of aggressive tendencies. Studies have shown that poor impulse control, non-adherence to medication and psychological therapies, presence of positive symptoms, and substance and alcohol misuse among those with psychosis are all associated with higher likelihood of violence and aggression [7]. However, the

subjective nature of many of these measures leads to variations in interpretation and makes their application as tools for risk stratification difficult.

Studies investigating biological and neurophysiological measures indicate a significant association between aggression and autonomic nervous system (ANS) activity. The ANS is comprised of both the parasympathetic and sympathetic nervous systems and is controlled by pathways within the limbic network. The ANS plays a crucial role in regulating multiple organ systems, including vascular smooth muscle and cardiac activity [9] [10] [11] [12]. The ANS has also been implicated in emotion regulation [13]. Animal studies, for example, have linked ANS-mediated neurotransmitters, such as α_2 adrenergic receptors, to aggression, startle response, stress sensitivity, and multiple neuropsychiatric disorders [14]. Human studies have long recognized the important link between ANS activity and aggression, conduct disorders, and other related behavioral problems [12] [15] [16] [17].

Physiological measures such as heart rate (HR), heart rate variability (HRV - defined as variations in intervals between successive heart beats, also known as the RR interval), and acoustic startle response can and have been used as a proxy for ANS activity. HR is a reflection of both sympathetic (HR acceleration) and parasympathetic (HR deceleration) activity [9] [18]. Respiratory Sinus Arrhythmia (RSA, defined as HRV within a single respiratory cycle), which is measured by high-frequency heart rate variability (HF-HRV), reflects parasympathetic cardiac control by the vagus nerve [19] [20] [21] [22] [23]. Vagal tone, in particular, is strongly associated with emotion regulation, hostility, and aggression [24] [25, 26]. Although RSA is not a perfect indicator of vagal tone, it is a widely used and currently accepted estimate [23] [26].

Acoustic startle response, which is modulated by structures within the limbic system, provides a broad measure of autonomic activity [27] [28] [29].

Finding robust measures of autonomic activity may be a promising direction in the development of objective tools for risk stratification of aggression. Studies exploring aggression among children, adolescents, and adults have consistently found higher levels of aggression to be associated with lower resting heart rate [12] [16] [30] [31] [32]. Studies on autonomic activity in the presence of interpersonal stressors have found increased autonomic reactivity among individuals who have higher tendency for aggression [31] [33]. Studies on HRV and aggression are inconsistent. One study by Scarpa *et al.* found a significant relationship between aggression and elevated resting RSA [34]. However, the majority of studies among children and adolescents have found aggression to be associated with lower resting RSA [11] [25] [26]. Studies on aggression and RSA in the presence of stressful stimuli and mentally challenging tasks have found an increase in RSA during stressors in children who have aggressive tendencies compared to those who do not [31] [35].

Previous research on startle response and aggression is more limited. However, studies conducted on startle response in psychopathic persons (typically defined by an individual's score on the Hare Psychopathy Checklist or the Hare Psychopathy Checklist-Revised [36] [37]) have found that these individuals have decreased startle response when compared to controls [38] [39]). A meta-analysis conducted in 2008 by C. J. Patrick found differences in autonomic reactivity between aggressive individuals versus adult psychopaths, with aggressive individuals demonstrating higher autonomic reactivity

to stressful stimuli and psychopathic individuals demonstrating lower reactivity compared with non-psychopathic, non-aggressive controls [31].

As in aggression, startle response, HR, and HRV have all been shown to be sex-dependent. Studies have repeatedly demonstrated differences in both HR and HRV between males and females [40] [41]. Studies have also found sex-related differences in acoustic startle response, which is speculated to be the result of two sexually differentiated structures within the limbic network – the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala [42] [43]. These areas help regulate social behaviors, reproductive behaviors, hormonal variations, and autonomic function. Several human and animal studies have also shown the importance of these areas in the modulation of aggressive behavior [44] [45] [46]. By studying the association between these autonomic correlates and aggression in men and women separately, we may be able to better understand the biological and neurological pathways involved in aggression.

While there are a number of studies investigating the association between aggression and physiological measures of autonomic activity in children and adolescents, the research within the adult population is relatively limited. This is particularly true among highly traumatized adult civilian populations with a high proportion of women, such as the one found in this study. Therefore, this paper provides a unique opportunity to explore startle parameters, HR, and HRV as physiological predictor variables for aggression among adult males and females with high levels of trauma exposure.

The goal of this thesis is to perform analyses on physiological indices, namely startle parameters, heart rate, and heart rate variability as primary predictor variables for indices of aggression as measured by the behavioral questionnaire (BQ) and to examine the sex differences between these associations. A secondary goal of this study is to determine how aggression is associated with the following social, demographic, and psychological factors: age, race, education, income, current employment, trauma history (both adult and child), and current or lifetime history of depression, PTSD, bipolar disorder, psychosis, schizophrenia, substance abuse/dependence, and alcohol abuse/dependence.

Given the current data on aggression, fear-potentiated startle, HR, and HRV we hypothesize that lower resting HR, heightened fear-potentiated startle response, and increased HRV during startle probe delivery will be associated with higher levels of aggression in all individuals. We also hypothesize that these findings will be different between men and women. Furthermore, we believe these associations will be exaggerated in those individuals with comorbid psychiatric disorders and high levels of trauma exposure.

Methods

Study Population:

Participants for this study were recruited between May 2008 through January 2011 from a larger study investigating the genetic and environmental factors that contribute to the development of PTSD in a civilian population seeking primary care at Grady Memorial Hospital in Atlanta, Georgia [47]. A total of 309 participants were selected for the study. Of these individuals, 251 completed the entire BQ (149 of whom had both startle response and HRV data collected, 61 who had startle response data collected alone, and 41 who had HRV data collected alone) (Figure 1). Exclusion criteria included prominent and active suicidal ideation, active psychotic symptoms, pregnancy (measured by urine pregnancy test), and major medical illnesses including uncontrolled hypertension and cardiovascular disease. All participants provided written informed consent approved by the Emory University Institutional Review Board.

Social and demographic information including sex, age, race, education, employment status, and income were obtained. Dichotomous variables were created for employment status (employed or unemployed), sex (male or female), and race (African American or other). Education was split into 4 levels (below 12th grade graduate, high school graduate or GED, some college or technical school, or college graduate or graduate school). Monthly income was categorized into 5 levels ($0 to $249, $250 to $499, $500 to $999, $1,000 to $2,000, or greater than $2,000).

Psychological assessments were conducted during initial screening interview and during follow-up visits. The Structured Clinical Interview for DSM-IV (SCID) [48] and

the Mini-International Neuropsychiatric Interview (MINI) [49] were used in combination to assess certain Axis I mood disorders, primary psychosis, substance abuse/dependence, and alcohol abuse/dependence within our study population. The modified PTSD Symptom Scale (PSS) [50] [51] was used to determine current PTSD symptoms and the MINI in conjunction with the Clinician Administered PTSD Scale (CAPS) [52] were used to determine lifetime PTSD diagnosis. The Beck Depression Inventory (BDI) [53] was used to define major depressive disorder (MDD) (i.e. score of 15 or higher on the BDI). Additionally, the Childhood Trauma Questionnaire (CTQ) [54] was used to assess traumatic events before the age of 19 years and the Traumatic Events Inventory (TEI) was used to assess adverse events during both childhood and adulthood (see Appendix for further details) [55].

Aggression

Aggression level was assessed for each participant using the Behavior Questionnaire (BQ). The BQ is a 16 item self-report behavior questionnaire assessing for frequency of lifetime participation in violent acts (Ex: hitting, choking, stabbing, shooting another human). Internal consistency of the BQ was assessed using Cronbach's coefficient alpha (α=0.874) [56]. The BQ is a truncated version of the Aggressive Behavior Questionnaire (ABQ), a 48-item self-report questionnaire designed by Dr. Bekh Bradley and Dr. Mark Evces to assess physical aggression, verbal aggression, and criminal activity [57].

Aggression scores were summarized for analysis in the following ways: (1) Each question on the BQ was assessed individually. Scoring for each question was based on lifetime frequency of each violent behavior, with scores of 0, 1, 2, 3, and 4 corresponding

to the answers “never,” “once,” “several times,” “many times,” and “more than I can count,” respectively. (2) A total BQ score was calculated by summing up the total points for all questions.

Startle Procedure

All of the physiological measurements in this study were collected as part of a startle protocol (see Appendix, Figures A.1 and A.2, for schematic of startle procedure).

Startle testing was conducted in a sound-attenuated booth on the first follow up visit. Each participant was screened for auditory impairment using an audiometer (Grason-Stadler Model GS1710). Subjects were required to be able to detect tones at 30 dB A-weighted (A) sound pressure level (SPL) at a range of frequencies from 250 to 4,000 Hz. Startle response data were acquired via electromyography (EMG) recordings using BIOPAC MP150 for Windows (BIOPAC Systems Inc., Aero Camino, CA). Specifically, the startle response was measured by EMG recordings of the right orbicularis oculi muscle. The muscular contractions were measured with two disposable 5-mm Ag/AgCl electrodes filled with electrolyte gel (BIOPAC, EL504). Electrodes were positioned both 1 cm inferior to the pupil of the right eye and 1 cm inferior to the lateral canthus. A ground electrode was placed over the mastoid behind the right ear. Impedance levels were less than 6KΩ for each participant (as measured by the Checktrode impedence meter, 1089 MKIII, UFI, Morro Bay, CA). All data were sampled at 1,000 Hz and amplified with a gain of 5,000 using the EMG module of the BIOPAC system. The acquired data were filtered, rectified, and smoothed using MindWare software (MindWare Technologies Ltd., Gahanna, OH). The EMG signal was filtered with low- and high-frequency cutoffs at 28 and 500 Hz, respectively.

The aversive unconditioned stimulus (US) was an airblast (intensity=140 psi) directed at the participant's larynx. The airblast lasted 250 ms and was administered via a compressed air tank attached to polyethylene tubing and controlled by a solenoid switch.

The acoustic startle probe was a 108-db (A) SPL burst of noise lasting 40 ms delivered binaurally via headphones (Model TDH-39-P, Maico, Minneapolis, MN). Startle magnitude was measured by analyzing the maximum amplitude of the eyeblink contraction 20 to 200 ms after the presentation of the acoustic startle probe.

Participants initially underwent a 2-minute acclimation period where they were exposed to the conditions of the sound-attenuated startle booth in the absence of any startle stimuli. The protocol for assessing fear-potentiated startle was developed by our group [58] and involved a fear acquisition phase followed by an extinction phase. Fear acquisition began with a series of six startle probes where the noise was presented alone (baseline or noise alone, NA, trials) followed by a habituation process in which the startle probe and the conditioned stimuli (CS) were presented without the aversive US. The conditioned stimuli consisted of different colored shapes (one shape representing the *danger cue* that was eventually paired with the aversive airblast during the conditioning phase and another shape representing the *safety cue* that was not paired with the airblast*)* presented for 6 seconds on a computer monitor. Following habituation was the conditioning phase, where the magnitudes of the acoustic startle reflex were obtained in the following situations: (1) in the presence of the startle probe alone (NA), (2) in the presence of a reinforced conditioned stimulus (CS+) paired with an aversive US (i.e. airblast), (3) in the presence of a non-reinforced conditioned stimulus (CS-) not paired

with the aversive US. The conditioning phase involved 36 total trials – 3 blocks with 12 trails per block (4 CS+, 4 CS-, 4 NA). The interval between each trial was randomized and occurred every 9 to 22 seconds. The extinction phase involved 6 blocks with 12 trials per block in which the startle probe and the conditioned stimuli (CS) were presented without the aversive US.

HR and HRV

Heart rate (HR) data were collected during the acclimation trials, which were before exposure to the acoustic startle probe or other stimuli, and startle (NA) trials. The HR data collected during acclimation was used to approximate resting HR. HR data collected during startle (NA) trials were only used in preliminary analyses (see Results and Discussion sections for more details).

Data on respiratory sinus arrhythmia (RSA), which is a measure of high-frequency heart rate variability (HF-HRV), were collected during the acclimation and startle (NA) trials. In this study, RSA data collected during the startle (NA) trials were considered to be a measurement of HRV in the presence of stressful stimuli (i.e. startle probe). This variable was referred to as startle RSA. RSA data collected during the acclimation phase were only used in preliminary analyses (see Results and Discussion sections for more details).

HR and HRV data were collected using the protocol described by Kamkwalala *et al.* [28]. HR data were acquired using an electrocardiogram (ECG) and via respiration modules within the BIOPAC system. The ECG signal was amplified by a gain of 1,000 and filtered using a Hamming windowing function with a 60-Hz notch filter. ECG measurements were obtained using two disposable Ag/AgCl electrodes placed on the

right torso 1 cm below the clavicle and on the inside of the left wrist. Respirations, in breaths per minute, were monitored using a chest band transducer. RSA and HR data were measured over single one-minute time intervals during both the acclimation and startle trials. During the acclimation trials, data were collected during the second minute in order to allow participants to get settled and to best simulate a "resting" condition. During the startle trials, data were obtained in the first minute in order to collect data before the participants began habituating to the startle probe. RSA data were analyzed by the fast Fourier transform spectral analyses of the time-sampled interbeat interval series using the guidelines published by the Society for Psychophysiological Research Committee on HRV [23]. The high frequency cutoff range used in this study was between 0.12 Hz and 0.40 Hz and the data were transformed using natural log.

Statistical Analyses

Analyses were conducted using IBM SPSS Statistics for Mac, Version 22.0 (IBM Corp., Armonk, NY). Fear-potentiated startle response to the danger (CS+) and safety (CS-) cues were calculated by subtracting the acoustic startle magnitude obtained during the baseline startle NA trials from the startle magnitude obtained during the CS+ trails and CS- trials, respectively.

Descriptive statistics for each study variable were obtained. Categorical variables were expressed as numbers and percentages. Normally distributed continuous variables were reported as mean (SD) values, while non-normally distributed variables were reported as median (IQR) values. Normality was determined using the Kolmogorov-Smirnov test for normality (Massey Jr., 1951 [59]). Frequency (N and percentage) of answers to each BQ question were analyzed and reported.

One-way ANOVA was used to explore associations between total BQ score and categorical variables with more than two categories (i.e. education and monthly household income). Simple linear regression models were constructed to examine bivariate associations between total BQ score and continuous or dichotomous covariates.

Simple linear regression models were also constructed to examine bivariate associations between total BQ score and the physiological predictor variables. Based on previous studies which have found sex differences in fear-potentiated startle response, HR, and HRV, the decision was made to analyze the association between these physiological variables and aggression in males and females separately [60] [40] [41] [42] [43]. Linearity assumptions were examined by reviewing residual plots for each model. Independence was assumed on the basis of sampling protocol. The residual plots of all significant linear regression models showed effects of zero-inflation. The histograms and the Kolmogorov-Smirnov tests of total BQ score indicated that this variable was not normally distributed. Particularly in females, the data were positively skewed due to zero-inflation. Transformation of the data using $\log(X_i+1)$ did not correct the skewness (see appendix, Figure A.3 and Table A.3), therefore we decided to continue using non-transformed total BQ score data in our analyses. We also considered an additional way to characterize aggression, which involved measuring aggression by individual BQ question. While we recognize that this is not ideal, the fact that the results in the analyses using total BQ score were similar to those results in the analyses using individual BQ question is reassuring.

The Spearman correlation method was used to determine correlation coefficients between each individual BQ question and the physiological predictor variables for both males and females.

Correlations between predictor variables were analyzed using Pearson correlation coefficients. Multiple linear regression models were constructed using the backwards elimination method to explore the relationship between aggression and the correlated physiological predictor variables and covariates for males. Given that each of these three physiological variables, fear-potentiated startle to the *danger cue*, acclimation HR, and startle RSA, is an indicator of ANS activity during different contexts, it would not be appropriate for these variables to be added to the same model. Therefore, three separate regression analyses were performed for each of the physiological predictors. In addition to the physiological variables, the following covariates were initially added into each of the three models: total trauma score, lifetime MDD, lifetime PTSD, and lifetime alcohol and/or substance abuse/dependence. Given that both childhood trauma score and adult trauma score are included in the total trauma score variable and alcohol abuse/dependence and substance abuse/dependence are included in alcohol and/or substance abuse/dependence variable, these separate predictors were not included in the regression models.

Statistical significance is determined by p values less than 0.05. All reported p values are two-sided.

Results

Participant Characteristics

Demographics, social characteristics, and psychological characteristics for each of the 251 subjects with any BQ data are described in Table 1. The average participant age was 40.3 years (SD=12.3). The majority of participants were female (66.1%) and were of African American race (93.6%). Most participants were either high school graduates (or GED test equivalent) (48.2%) or had not completed 12th grade (21.9%). The majority of participants were unemployed (80.9%) and had a monthly income of less than $1,000 (70.6%). A large proportion of individuals had a lifetime prevalence of depression (41.0%), PTSD (41.4%), alcohol abuse and/or dependence (35.9%), and drug abuse and/or dependence (39.4%). While a smaller proportion of individuals had a lifetime prevalence of psychosis not related to a medical condition (17.1%) and bipolar disorder (5.6%) (Table 1).

Physiological Predictors of Aggression

Descriptive Statistics for the Physiological Variables: Startle, HR, and HRV

The median fear-potentiated startle responses to the danger and *safety cues* were 15.1μV (IQR: 0.2 μV to 60.3 μV) and 5.3 μV (IQR: -3.9 μV to 27.0 μV), respectively. Negative values result when the startle magnitude obtained during the CS+ trails and CS- trials are less than the startle magnitude obtained during the baseline startle NA trials. The mean acclimation and startle HR's were 75.9 beats per minute (bpm) (SD: 13.0) and 74.4 bpm (SD: 12.7) and the mean acclimation and startle RSA's were 5.3 (SD: 1.9) and 5.5 (SD: 1.8), respectively (Table 2).

Aggression by Total BQ Score

As shown in Figure 2, the total BQ score for all 251 individuals was positively skewed with a high proportion of individuals having total BQ scores of 0 [Skewness 0.78 (SE: ±0.15); Kurtosis, -0.03 (SE: ±0.31)]. Histograms of total BQ score for men and women separately indicate that the positive skewness due to zero-inflation is more pronounced in women [Skewness 0.83 (SE: ±0.19)] than in men [Skewness 0.66 (SE: ±0.26)]. Total BQ scores ranged from 0 to 38 with a mean sore of 10.75. The mean total BQ score in men was higher than in women [Mean: 13.08 (SD: 9.51) versus 9.55 (SD: 8.42), respectively]

Simple linear regression models were used to determine the relationship between total BQ score and the physiological variables in both sexes (Table 3).

In men, fear-potentiated startle response to the *danger cue* (CS+) was positively associated with total BQ score ($R=0.259$ $R^2=0.067$, $p=0.021$). Total BQ score was not significantly associated with safety response to startle cue. In addition to startle magnitude, heart rate variables were also collected. Startle RSA (collected during the acquisition phase of the startle paradigm when the startle probe alone was the stimulus) was positively associated with total BQ score ($R=0.316$, $R^2=0.100$, $p=0.011$). Acclimation RSA (collected earlier during acclimation to the sound booth without the startle probe) was not significant but followed a similar trend ($R=0.215$, $R^2=0.046$, $p=0.089$). Both acclimation and startle HR were negatively associated with total BQ score ($R= -0.254$, $R^2=0.065$, $p=0.042$ and $R= -0.308$, $R^2=0.095$, $p=0.013$, respectively).

Likewise, in women both acclimation HR and startle HR were negatively associated with BQ score (R= -0.237 R^2=0.056, p=0.008 and R= -0.238 R^2=0.057, p=0.007, respectively). However, fear-potentiated startle response to the *danger cue* (CS+), acclimation RSA, and baseline startle RSA were not significantly associated with total BQ score (R= 0.127, R^2=0.016, p=0.149; R=0.053, R^2=0.003, p=0.557; and R=0.057, R^2=0.003, p=0.528, respectively). Total BQ score was also not significantly associated with safety response to startle cue. (Table 3).

As presented in Tables 2 and 3, the HR and RSA obtained during acclimation and startle probe delivery were very similar. The average HR during acclimation versus startle decreased by 1.5 beats per minute and the average RSA during acclimation versus startle increased by 0.2 ln(HF-HRV). In relation to aggression, acclimation and startle HR were significantly negatively associated with total BQ score in both men and women. In men, startle RSA was significantly positively associated with total BQ score and acclimation RSA was trending towards a significant positive association with total BQ score, while in women neither acclimation RSA nor startle RSA were significantly associated with total BQ score. Given the following: (1) the HR and RSA data collected during both acclimation and startle did not seem to differ substantially from one another, (2) acclimation HR is a better measure of resting HR than startle HR, and (3) startle RSA is a better indicator of RSA in the presence of stressful stimuli compared with acclimation RSA, the decision was made to use acclimation HR and startle RSA as the only two HR and HRV variables for further analysis.

Scatter plots and residual plots for each of these associations indicated no violations of linearity, however homoscedasticity may be violated due to zero-inflation of the total BQ scores. No overt outliers were observed (Figures 3-6).

Aggression Measured by Individual BQ Questions

Frequency of answers to each BQ question can be found in the appendix (Table A.1). Correlation analyses were conducted between answers to each separate BQ question and each of the physiological variables for both men and women (Table 4).

In men, fear-potentiated startle response to the *danger cue* was significantly ($\alpha<0.05$) positively correlated with the following questions:

> *Have you ever done the following in your lifetime:* (a) thrown something at someone that could hurt? (b) twisted someone's arm or hair? (c) pushed or shoved someone? (d) slammed someone against a wall? (e) grabbed someone by the neck, collar, clothes, or some part of their body in anger?

Fear-potentiated startle response to the *safety cue* was positively correlated with the following questions:

> *Have you ever done the following in your lifetime:* (a) punched or hit someone with something that could hurt? (b) destroyed something belonging to someone on purpose? (c) hit an adult you lived with?

And negatively correlated with the following question:

> *Have you ever done the following in your lifetime:* became so angry with a child that you hit them (other than events you already told me about)?

Acclimation HR was negatively correlated with the following questions:

> *Have you ever done the following in your lifetime: (*a) pushed or shoved someone? (b) destroyed something belonging to someone on purpose? (c) slammed someone against a wall? (d) grabbed someone by the neck, collar, clothes, or some part of their body in anger?

Startle RSA was positively correlated with the following questions:

> *Have you ever done the following in your lifetime: (*a) twisted someone's arm or hair? (b) pushed or shoved someone? (c) punched or hit someone with something that could hurt? (d) choked someone (e) slammed someone against a wall? (f) beat someone up?

In women, fear-potentiated startle to the *danger cue* was negatively associated with the following BQ questions:

> *Have you ever done the following in your lifetime*: (a) became so angry with a child that you attacked them with a weapon or with the idea of seriously hurting them? (b) became so angry with a child that you hit them (other than events you already told me about)?

Fear-potentiated startle response to the *safety cue* was negatively associated with the following BQ question:

> *Have you ever done the following in your lifetime*: thrown something at someone that could hurt?

Acclimation HR was negatively associated with the following BQ questions:

> *Have you ever done the following in your lifetime*: (a) stabbed or shot at someone? (b) choked someone? (c) grabbed someone by the neck, collar, clothes, or some part of their body in anger? (d) attacked an adult you've lived with with a weapon or with the idea of seriously hurting or killing them? (e) hit an adult you lived with?

There were no associations between BQ question and startle RSA in women.

Multivariate Analyses and Other Predictors of Aggression

Simple linear regression was used to assess the correlation between each of the continuous and dichotomous covariates and total BQ score (Table 5). One-way ANOVA models were used to compare the mean total BQ scores between the categorical covariates with more than two categories (Table 6). Sex (R=-0.187, R^2=0.035, p<0.01), total trauma history (R=0.437, R^2=0.191, p<0.001), adult trauma history (R= 0.423, R^2=0.179, p<0.001), childhood trauma history (R=0.205, R^2=0.042, p<0.01), lifetime history of MDD (R=0.188, R^2=0.035, p<0.01), lifetime history of PTSD (R=0.263, R^2=0.069, p<0.001), substance or drug abuse/dependence (R=0.381, R^2=0.145, *p<0.001*), alcohol abuse/dependence (R=0.286, R^2=0.082 p<0.001), and alcohol and/or substance abuse/dependence (R=0.352, R^2=0.124, p<0.001) were all significantly associated with total BQ scores (Table 5).

Histograms showing categorical distribution of total BQ score were created the each of the categorical variables associated with aggression (Figures 7 through 12). Figure 8, for example, displays the distribution of total BQ score split by those without

MDD (blue) and those with MDD (green). Among those individuals without depression, the majority scored 0 on the BQ while among those with depression, the majority scored 12 on the BQ. Pearson correlations between each of these predictor variables were assessed. Total trauma score was very strongly correlated with adult trauma score (R=0.969= , $p<0.01$) and moderately correlated with childhood trauma scores (R=0.515 , $p<0.01$). Alcohol and/or substance abuse/dependence was strongly correlated with both alcohol abuse/dependence (R=0.743, $p<0.01$) and substance abuse/dependence (R=0.810, $p<0.01$) and moderately correlated with total trauma (R=0.416, $p<0.01$) and adult trauma (R=0.441, $p<0.01$). Moderate correlations also existed between acclimation HR and startle RSA (R= -0.528, $p<0.01$), substance abuse/dependence and alcohol abuse/dependence (R=0.493, $p<0.01$), substance abuse/dependence and total trauma (R=0.464, $p<0.01$), and substance abuse/dependence and adult trauma (R=0.477, $p<0.01$) (Table A.4).

Multivariate Regression Models of Aggression Predictors in Men

Given that men showed a consistent association of aggression with fear-potentiated startle to the *danger cue*, acclimation HR, and startle RSA in our unadjusted regression models, we further examined this association in models adjusted for covariates.

Three multivariate regression models were constructed using the backwards elimination method to explore the relative contribution of different predictors of aggression in men. The predictor variables initially added to each regression model included the covariates determined to be significantly associated with total BQ score (see *Statistical Analyses* in Methods section and Table 5) and one of the following

physiological predictors: fear-potentiated startle to the *danger cue* (model 1), acclimation HR (model 2), and startle RSA (model 3).

The overall model for the first multivariate regression analysis contained fear-potentiated startle to the *danger cue*, total trauma score, and alcohol and/or substance abuse/dependence. Overall, 27% of the variability in total BQ score for men can be explained by these three predictor variables (R^2=0.27 F=7.74*, p<0.01*). The slope associated with fear-potentiated startle to danger was 0.24 (p<0.05), meaning that among men, for every one standard deviation increase in fear-potentiated startle to the *danger cue*, the standard deviation of total BQ score increased by 0.24, controlling for total trauma and alcohol and/or substance abuse/dependence (Table 7).

The overall model for the second multivariate regression analysis contained acclimation HR and total trauma score. Overall, 37% of the variability in total BQ score for men can be explained by these two predictor variables (R^2=0.37 F=13.08*, p<0.001*). The slope associated with acclimation HR was -0.24 (p<0.05) meaning that, among men, for every one standard deviation increase in heart beat per minute during acclimation trials the standard deviation of total BQ score decreased by 0.24, controlling for total trauma (Table 8).

The overall model for the third multivariate regression analysis contained startle RSA and total trauma score. Overall, 35% of the variability in total BQ score for men can be explained by these two predictor variables (R^2=0.35 F=13.15*, p<0.001*). The slope associated with baseline startle RSA was 0.25 (p<0.05) meaning that, among men, for every one standard deviation increase in ln(HF-HRV) during startle probe delivery the

standard deviation of total BQ score increased by 0.25, controlling for total trauma (Table 9).

A histogram, normal P-P plots, residual plots, and partial regression plots for each of the final models from the MLR analyses can be found in the appendix (Figures A.4 through A.9).

Discussion

ANS activity is increasingly being recognized to play an important role in emotion and emotion regulation [13]. In this study, we examined how three different indices of ANS activity – fear-potentiated startle, HR, and HRV – predict aggression in a highly traumatized adult civilian population. By studying each of these physiological variables in men and women separately, we aimed to gain further insight into the association between ANS response and aggression. We hypothesized that lower acclimation heart rate, heightened fear-potentiated startle response to a *danger cue* (CS+), and increased startle RSA during moderately stressful startle probe delivery would be associated with higher levels of aggression in all individuals and that there would be sex-dependent differences in the strength of associations between each of these variables [12] [26] [31]. A secondary goal of this study was to identify additional social, economic, and psychological risk factors that may help predict aggression in the study population.

The results from the current study suggest that despite whether aggression is measured via self-reported answers to incidence of specific aggressive behaviors (Ex: *have you ever done the following in your lifetime*: stabbed or shot at someone?) or total score for all the BQ questions, fear-potentiated startle response to the *danger cue* (CS+), acclimation HR, and startle RSA were significantly associated with aggression in males only. In females, acclimation HR was the only physiological variable significantly associated with aggression. Additionally, simple linear regression models indicate that aggression, as measured by total BQ score, was linearly associated with the following covariates: sex, total trauma history, adult trauma history, childhood trauma history,

lifetime history of MDD, lifetime history of PTSD, substance or drug abuse/dependence, alcohol abuse/dependence, and alcohol and/or substance abuse/dependence.

There are multiple findings in this study that merit further discussion.

Startle

Startle response to a *danger cue* (i.e. fear-potentiated startle in the presence of the CS+ paired with the aversive airblast) was used as an indirect indicator for ANS reactivity in the presence of "threatening or noxious stimuli." By studying fear-potentiated startle response we also hoped to develop deeper understanding for the anatomical regions involved in aggression.

This study showed that males with higher self-reported aggression, as measured by the total BQ score, were found to have higher fear-potentiated startle response and thus have greater ANS reactivity [27] [28] [29] in the presence of a *danger cue* (i.e. CS+) signaling the impending delivery of an aversive stimuli (i.e. airblast). Among females, there was no association between fear-potentiated startle response to the *danger cue* and aggression. For both men and women, there was no significant association between total BQ score and startle response in the presence of the *safety cue* (CS-). However, when aggression was measured using answers to each individual BQ question some different trends emerged. In men, startle responses to both the *danger* and *safety cues* were positively correlated with multiple questions. Startle response to the *safety cue* was also negatively correlated with one question involving frequency of an aggressive act towards a child. In women, startle response to danger was negatively correlated with two questions (both of which involved aggressive acts towards a child) and startle response to safety was negatively correlated with one question.

To our knowledge, this is the first study of its kind to investigate the association between fear-potentiated startle response and aggression in adults. However, a handful of studies have been conducted investigating fear-potentiated startle response in psychopathic individuals versus control populations. These studies have found that psychopathic individuals had a significantly *decreased* startle response compared with non-psychopathic individuals [39] [61] [62]. A somewhat similar study conducted in 1993 looked at differences in startle response to pictures of pleasant and unpleasant stimuli in a psychopathic/sociopathic criminal population versus non-psychopathic/sociopathic population. This study found that in the presence of unpleasant pictures, psychopathic individuals had a significantly decreased startle response compared with non-psychopathic individuals [38]. These studies emphasize an important distinction between the individuals in the former study, psychopathic individuals, versus the individuals in the current study, those who score highly on an aggression questionnaire. While psychopathy and aggression are related in that they often result in violent acts, psychopathy is distinguished from aggression alone in that it involves such traits as lack of remorse, lack of empathy, manipulation, pathological lying, and grandiosity [63]. There are also clear physiological distinctions between psychopathy and aggression. Aggressive individuals show enhanced autonomic reactivity in response to stressful or aversive events while psychopathic individuals do not demonstrate enhanced reactivity [11] [31]. Thus, using startle as an indirect indicator for ANS reactivity, the results in this study concur with conclusions made in previous studies, which used electrodermal activity and cardiovascular measurements as indicators for autonomic reactivity.

It is also important to mention the sex-related differences between the association of startle and aggression found in the current study. The data in this study suggest that when aggression is measured using a combination of different techniques (i.e. total BQ score and individual BQ questions), greater fear-potentiated startle during both *safety* and *danger cues* may be predictive of higher aggression in men, while lower fear-potentiated startle may be predictive of higher aggression in women. However, we are reluctant to make these conclusions based on this current study alone, especially given the following limitations. First, when measuring aggression by individual BQ question, only two questions were significantly correlated with fear-potentiated startle response to danger in women. Both of these questions, in addition to a third question asked in the BQ, involved acts of violence towards a child. Together, these three questions raise suspicion because they repeatedly show different associations with the physiological variables relative to the other questions. For example, all significant correlations between fear-potentiated startle response to the *safety cue* and BQ questions in men are positive except for one question, which involves aggression towards children. A similar example is seen in the associations between fear-potentiated startle response to the *danger cue* for men and BQ question. Among men, all the correlation coefficients between BQ question and fear-potentiated startle response to danger are positive or very weakly negative (i.e. correlation coefficient > -0.01) except for two questions, both of which are trending towards a negative correlation and both of which are related to aggression towards children. These discrepancies call into question both the significance and validity of these particular questions. As we will discuss later, all participants provided written informed consent that stated researchers were legally obligated to report any participant

answer that involved knowledge of or participation in *current* child abuse. Therefore, it is plausible that many participants did not answer questions involving aggression towards a child truthfully. Those who did answer this question positively may have a particular trait in common that may also make them more likely to have a decreased startle response to a *danger cue*. For example, it is possible that individuals who answered positively to these questions do not fear or are insensitive to the potential for punishment, a trait found in psychopathy [64]. Alternatively, it is possible that those who answered positively to these questions have the most extreme aggressive tendencies and that the answers to these questions are actually more indicative of aggression than the other BQ questions. Second, while most of the Spearman correlations between individual BQ question and startle response to danger and *safety cue* for women did not reach significance, nearly all of the correlation coefficients were negative. From these findings, it is difficult to conclude whether fear-potentiated startle response is negatively associated with aggression in women or whether it is not at all associated with fear-potentiated startle in women.

Despite these issues, the data clearly indicate that there is a sex-dependent difference in the relationship between fear-potentiated startle response to *danger cues* and aggression within our study population. While gender-related factors in the psychosocial milieu likely play some role, our findings could also be indicative of neuroanatomical differences between males and females. The BNST and the amydala, two sexually-differentiated regions known to play a part in aggression, startle, and ANS activity, may account for at least some of the differences in aggression seen between the two sexes. One study looking at sex differences in the volume of the darkly staining region of the

posteromedial BNST found that the volume in male brains was nearly 2.5 times that of females [65]. It is possible that these brain structures play a significant role in aggressive tendencies in males but not in females, thereby indicating different etiologies for aggression between men and women. Or it is possible that because these structures are more developed in males than in females, the differences between aggression-related fear-potentiated startle are only significant enough to be measured in males. Regardless, because this study is one of the first of this kind to investigate fear-potentiated startle and aggression, it is difficult to draw any concrete conclusions from this study alone. Further research on startle and aggression must be conducted to see whether the current findings can be replicated.

HRV

RSA, which was estimated using measurements of HF-HRV, was used in this study as a proxy for parasympathetic inputs of the ANS (i.e. vagal tone). We found RSA to be positively associated with aggression in men but not in women. Among the male participants, total BQ score in addition to several BQ questions were associated with increased startle RSA during the startle probe delivery.

These findings point to several important issues. First, the relationship between RSA and aggression is not simple. In a meta-analysis by Kibler and colleagues, the researchers found higher RSA during mental challenges to be associated with misconduct among children and adolescents [66]. A longitudinal study by Calkins *et al*. found that children with behavioral problems who were at higher risk for externalizing problems had less vagal withdrawal (and higher RSA) during multiple challenging tasks compared with both control children without behavioral problems and children with behavioral problems

who internalize and externalize problems [35]. However, other studies involving the relationship between aggression and baseline RSA have consistently demonstrated the association between high aggression and lower baseline RSA [11] [25] [26]. While the findings in our study may appear to conflict with these latter studies, it is important to note that in the current study we explore the association between aggression and *RSA in response to a stressor*. As discussed previously in the results and as we will discuss further in the strengths/weakness section that follows, although RSA was initially obtained both during acclimation and startle trials, we decided to exclusively use the startle RSA data to assess RSA in response to a stressor. Therefore, the results in our study cannot be directly compared with studies looking at resting RSA.

Taken together, the results of this study along with the results of studies analyzing the association between startle RSA and aggression suggest that vagal tone and reactivity among individuals who have difficulties regulating anger and aggression may be reversed compared with emotionally healthy individuals. According to the literature in healthy individuals, vagal tone should be suppressed (and thus HF-HRV should decrease) in the presence of threatening stimuli allowing for sympathetic nervous system inputs to dominate. This allows for fight or flight response to take over and the organism to react appropriately in a stressful situation [67] [68]. However, results in this study suggest the opposite to be true among men who scored highly on the BQ. Although further research in this area is necessary, prior research in conjunction with the results in this thesis suggest that aggression is associated with dysregulated vagal tone at both baseline and in the presence of negative stimuli.

It is also possible that the RSA is strongly influenced by the type of stimuli presented to the individuals, which in the case of this study was acoustic startle. Studies on cardiac activity have demonstrated that changes are dependent on the type and presentation of the stimuli [69]. Perceptions of chronic emotional stress [70], acute laboratory stress [9], and increasing difficulty of memory tasks were all associated with decreased HF-HRV [71]. Another study looking at RSA in response to different pictures found visualization of fear-evoking pictures (i.e. angry faces) to be associated with higher RSA than non fear-evoking pictures (i.e. happy faces) [72]. While another study looking at RSA during different mental tasks found decreases in RSA during arithmetic tasks and increases in RSA during visual illusion tasks [73]. These mixed results suggest comparing HRV to stimuli between studies may be very difficult, resulting in a variety of conflicting results. Nevertheless, since all our participants were responding to the same stimuli, our findings concerning the positive correlation of RSA and aggression remain valid.

Another noteworthy issue involves the sex-related differences in the startle RSA. Studies on sex and HRV alone are inconsistent, but most studies have found baseline RSA to be greater in women than in men [74] [75]. Women also tend to have higher RSA during various stress evoking tasks [76]. With regards to sex differences in RSA and aggression, one study looking at sex differences in autonomic indices of behavior disorders and aggression found lower baseline RSA to be associated with higher aggression (as measured by the Child Behavior Checklist Aggression subscale) for boys but not girls [77]. These findings along with the results of our study support the belief that there is at least a distinction between parasympathetic activity among aggressive men

versus aggressive women. These findings also help support the theory that sex differences in aggression are at least partially due to differences in underlying biological mechanisms that increase the propensity for aggression in men compared with women.

HR

Resting HR—which was obtained by measuring HR during the acclimation trial – was used in this study to reflect both parasympathetic and sympathetic inputs of the ANS. Our results reveal that lower acclimation HR was associated with higher levels of self-reported aggression in both men and women. These findings agree with previous studies which have consistently shown lower resting HR to be predictive of higher levels of current aggression [12] [32] and higher levels of aggression years later [78]. These findings also emphasize the concept that aggression is associated with ANS dysfunction.

However, while the association between HR and aggression in men was stronger than the association in women, HR was the only physiological variable analyzed in this study that did not differ substantially between sexes. These findings seemingly contradict the other findings in the present study, which suggest that the underlying etiology of aggression may different between sexes. It is unclear as to why this is or what this signifies. However, it is important to note that the regulation of HR involves complex interactions between the parasympathetic and sympathetic nervous systems. Therefore, it is possible that the sympathetic inputs of the ANS may be less sexually-differentiated than the parasympathetic inputs, resulting in a sex-dependent difference in RSA but not in HR.

Overall, it is difficult to explain each of the associations seen between aggression and the three physiological correlates of ANS activity studied in this paper using one

straightforward, overarching description of autonomic activity. The apparent inconsistencies seen within this study (Ex: association between aggression in men and the following: (1) elevated fear-potentiated startle response, indicating increased sympathetic activity and autonomic reactivity, (2) elevated RSA during acoustic startle, indicating increased parasympathetic activity, and (3) decreased resting HR, indicating decreased overall ANS activity) and the lack of consensus between related studies on this topic argue that the interactions between the parasympathetic and sympathetic systems are complex and are dependent on a variety of factors. It is possible that these discrepancies may involve a situation-dependent uncoupling between the parasympathetic and sympathetic branches of the ANS, which are typically regarded as inversely related. However, more studies on this topic must be conducted before any valid conclusions can be drawn.

CoVariates

Finally, secondary analysis in the current study involved investigating additional covariates that may be predictive of aggression. As expected, trauma history (both in childhood and adulthood) was highly predictive of aggression. Substance and/or alcohol abuse/dependence, history of MDD, and PTSD were also strongly associated with aggression. Psychosis, as measured in this study was not significantly associated with aggression. This finding is particularly surprising given the broad consensus in the literature that psychosis increases the risk for aggression [3] [8]. In this study, psychosis was classified using the SCID [48] and was defined as individuals who endorsed current and/or lifetime psychosis not associated with a mood disorder (i.e. when psychotic features are not exclusively confined to periods when mood disorder is active), substance

abuse, or general medical condition. The lack of positive findings in this study is unclear, though they may reflect the uncertainty in the literature concerning the relative contribution of substance abuse, situational factors, social context, and medication history in the supposed increased rates of aggression in persons with psychosis. It is possible that the number of individuals with psychosis was too small to detect a significant difference. Or it is possible that within the population investigated, psychosis is not significantly associated with aggression.

Strengths & Weaknesses

To our knowledge, the present study is the first of its kind to examine the physiological variables of fear-potentiated startle response, HR, and HRV in a highly traumatized civilian population. This study also had a higher proportion of women relative to men, which is unique to this area of research where the majority of research participants are men. The higher number of female participants compared to prior studies allowed us to explore sex differences in each of the physiological predictor variables. Our sample was also comprised mainly of African American individuals and showed a wide age range (18-77 years).

However, this study has several limitations. The most serious issue involves the measurement of our primary outcome, aggression. In this study, aggression was measured using a self-report questionnaire, which consisted of 16 questions that each involved different acts of aggression. Participants were asked to answer each question based on the lifetime frequency for each act. This self-report measure of aggression is subject to multiple biases. Given that the BQ was administered during the initial

interview, which was conducted in public waiting areas, it is conceivable that participants may have under-reported aggression as a result of these social constraints. Additionally, participants were told that all answers they provided during the interview would remain confidential with a few exceptions. One of these exceptions involved revealing any information regarding the current abuse of an elderly individual or a minor (under the age of 18 years). This may explain why the three BQ questions involving aggression towards children had a lower negative response rate than any of the other BQ questions. This may also explain why the correlations between these questions and the physiological variables did not follow many of the trends seen for the other BQ question. As we discussed previously, it is possible that individuals who are more likely to answer positively to these questions may also possess some physiological trait or factor that would lead them to display different patterns of autonomic activity during the situations studied. Some of these issues may have been alleviated by interviewing participants in a private area, obtaining collateral reports from friends and family, and/or obtaining objective data including police records and background checks.

Another weakness in the BQ is difficulty in scoring the questionnaire. Simply using a total score for all the questions may not have accurately portrayed the severity of aggression. For example, if individual A admitted to purposefully destroying something that belonged to another individual and pushing someone once in life (for a total score of 2) and individual B admitted to stabbing someone several times (also a total score of 2), their scores would be identical although it is clear that these two individuals are not equally aggressive. In order to mitigate this issue we used two separate methods for scoring aggression including exploring each question individually and calculating a total

score based on answers to each question. While this does not eliminate all problems involved with classification, it is at least reassuring that many of the physiological variables were consistently associated with aggression, despite the method used for quantifying aggression.

Another limitation in this study involves the circumstances in which "resting HR" data were collected. In our study, the "resting HR" was actually measured during the acclimation process wherein HR for each individual was measured shortly after the participants were exposed to and entered the small sound-attenuated booth. This scenario may conceivably be stress-invoking for some individuals and may not be a truly accurate representation of the resting HR but may instead include an element of HR reactivity in response to a negative stimulus. This issue is somewhat reduced by not including the first minute of the acclimation period in the analysis of resting HR, so that the participants had an opportunity to relax before the measurement was taken. Previous studies conducted on HR reactivity to negative stimuli have found increased HR reactivity among aggressive adults [12]. Therefore, this bias would only cause the association between aggression and resting HR seen in this study to trend towards the null hypothesis.

A similar issue occurred when measuring RSA. Initially, RSA was measured during both the acclimation phase and during the baseline phase of the startle session (when the startle probes were initially delivered). Since both can conceivably be stress-invoking situations, the RSA data collected did not allow accurate conclusions to be drawn regarding aggression and true baseline RSA. However, the data could provide information on the association between aggression and RSA in the presence of a stressor.

Since the conditions during the baseline startle trials involved both the potential stress evoked by the startle booth environment alone in addition to the stress evoked during acoustic startle, RSA during the startle trials was a more accurate assessment of RSA in the presence of negative stimuli than was acclimation RSA. Thus, in the majority of the analyses, startle RSA was the only HRV variable analyzed.

Finally, the external validity and thus generalizability of our findings may be limited to populations similar to those in the current study. There could be some selection bias for individuals willing to participate in the physiological measures and complete the BQ questionnaire. For example, those who declined to participate may be more concerned or paranoid about answering questions with perceived legal consequences or could be more avoidant of conditions used in the physiological assessments.

This study explores the outcome in a highly traumatized, primarily African American population of low socioeconomic status. Given this specific population, the findings in this study may not be applicable to a population more representative of the larger population. However, the characteristics of this population are common to other large urban areas with low socioeconomic status and high rates of trauma, which are typically understudied. Therefore, the knowledge gained in the current study may significantly inform research on aggression in similar environments.

Future Directions

In conclusion, we found that enhanced fear-potentiated startle response to the *danger cue*, along with decreased resting heart rate, and higher RSA in response to stressful stimuli were associated with higher levels of aggression among men. On the other hand, we found that higher levels of aggression in women were only associated with decreased resting heart rate. These sex-related differences in physiological predictors of aggression reinforce the understanding that aggression is at least partially autonomically regulated and involves sexually dependent neurological pathways. This study also demonstrated that ANS activity in aggressive individuals differs from that in less aggressive individuals. However, this study also revealed that the role of the ANS in aggression is complex and does not follow a simple pattern (Ex: decreased ANS activity was not consistently associated with higher levels of aggression). We recommend that future studies be directed towards exploring autonomic reactivity in both the presence and absence of stressful stimuli. We also recommend that future studies investigate autonomic reactivity in the presence of a variety of stressful stimuli including emotional stress, interpersonal stress, and physical stress. Additionally, we suggest that future efforts be geared towards elucidating how well these physiological measures correlate with objective and documented acts of aggression. Finally, we suggest that future studies incorporate a larger and more ethnically diverse patient population to determine if the results seen in this study may be applicable to a different population.

While some of the associations between ANS activity and aggression in this study were highly statistically significant, the R^2 values did not suggest these associations were sufficiently robust to be used in risk stratification. However, this study does shed new

light on physiological variables that may be considered and used in the future development of preventive and interventional measures to help attenuate the prevalence of violence.

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Figure 1: Flowchart Showing Inclusion and Exclusion of Participants with Complete BQ Data

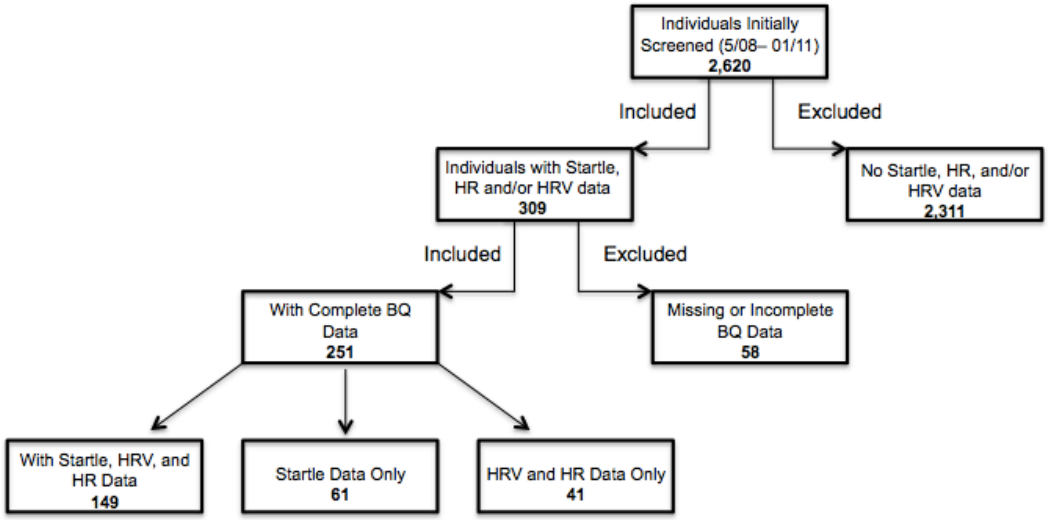


Table 1: Demographics, Social, and Psychological Characteristics of all Study Participants with Complete BQ

Demographics	**Mean or n (N=251)**	**SD or %**	**Range**
Age in years	40.3	12.3	18 to 77
Sex			
Female	166	66.1%	--
Male	85	33.9%	--
Race			
African American	235	93.6%	--
Other	16	6.4%	--
Education			
Below 12th grade graduate	55	21.9%	--
Highschool graduate or GED	121	48.2%	--
Some college or technical school	48	19.1%	--
College, technical or graduate school graduate	27	10.8%	--
Income per month			
$0-$249	73	29.1%	--
$250-$499	29	11.6%	--
$500-$999	75	29.9%	--
$1,000-$2,000	48	19.1%	--
>$2,000	17	6.8%	--
Missing	9	3.6%	--
Current Employment			
Yes	48	19.1%	--
No	203	80.9%	--
Trauma History			
Total Trauma Score[a]	5.1	3.4	0 to 19
Missing	1	0.4%	--
Adult Trauma Score[a]	4.3	2.9	0 to 16
Missing	1	0.4%	--
Child Trauma,[b] median, IQR	36.0	29.0 to 51.0	25 to 119
Missing	1	0.4%	--
Psychological Assessment			
Depression[c]			
Yes	103	41.0%	--
No	108	43.0%	--
Missing	40	15.9%	--
PTSD[d]			
Yes	104	41.4%	--
No	107	42.6%	--
Missing	40	15.9%	--
Bipolar[e] n (%)			
Yes	14	5.6%	--
No	198	78.9%	--
Missing	39	15.5%	--
Psychosis[f] n (%)			
Yes	43	17.1%	--
No	168	66.9%	--
Missing	40	15.9%	--
Substance or Drug Abuse/Dependence[g]			
Yes	99	39.4%	--

No	111	44.2%	--
Missing	41	16.3%	--
Alcohol Abuse/Dependence[g]			
Yes	90	35.9%	--
No	120	47.8%	--
Missing	41	16.3%	--
Alcohol and/or Substance Abuse/Dependence[g]			
Yes	121	48.2%	--
No	89	35.5%	--
Missing	41	16.3%	--

[a] Trauma score as measured by the TEI
[b]Childhood trauma score as measured by the CTQ
[c] Lifetime Major Depressive Disorder as measured by the SCID.
[d]Lifetime PTSD as measured by the CAPS and the MINI.
[e]Lifetime presence of bipolar type I disorder as measured by the SCID.
[f]Lifetime presence of primary psychotic symptoms (not part of a mood disorder) as measured by the SCID.
[g]Lifetime substance, drug, or alcohol abuse/dependence as measured by the SCID and the MINI

Table 2: Descriptive Statistics for Startle, HR, and HRV

(N=251)

Predictor Variables	N	Range	Median	IQR	Skewness (S.E.)	Kurtosis (S.E.)
Fear-potentiated Startle[a], μV						
Danger Cue (CS+)	210	-87.9 to 358.6	15.1	0.2 to 60.3	2.15 (0.17)	6.39 (0.33)
Safety Cue (CS-)	210	-92.6 to 257.7	5.3	-3.9 to 27.0	2.03 (0.17)	7.43 (0.33)

Predictor Variables	N	Range	Mean	Std Deviation	Skewness (S.E.)	Kurtosis (S.E.)
HR, BPM						
Acclimation[b] HR	190	51.7 to 112.1	75.9	13.0	0.42 (0.18)	-0.26 (0.35)
Startle[c] HR	190	48.3 to 111.9	74.4	12.7	0.54 (0.18)	-0.06 (0.35)
HRV, lnHF-HRV						
Acclimation[b] RSA	190	0.7 to 9.3	5.3	1.9	-0.12 (0.18)	-0.23 (0.35)
Startle[c] RSA	190	0.4 to 9.5	5.5	1.8	-0.18 (0.18)	-0.01 (0.35)

μV = microvolts; CS+=in the presence of the Conditioned Stimulus; CS-=in the absence of the Conditioned Stimulus; HR=Heart Rate; BPM=Beats per minute, RSA=Respiratory Sinus Arrhythmia; lnHF-HRV=natural log of High Frequency Heart Rate Variability; HRV=Heart Rate Variability.

[a]Fear-potentiated startle response to the danger (CS+) and safety (CS-) cues were calculated by subtracting the acoustic startle magnitude obtained during the noise alone trials, where only the acoustic startle probes were delivered, from the startle magnitude obtained during the CS+ trials and the CS- trials.

[b]Acclimation refers to data collected in the sound-attenuated startle booth, before exposure to the startle probe or other stimuli.

[c]Startle RSA refers to data collected during the delivery of the startle probes during the baseline phase of the startle session, prior to the fear-potentiated startle experiment.

Table 3: Statistics for Simple Linear Regression Models Exploring Relationship Between Total BQ score and Startle, HR, and HRV, Split by Sex.

(N=251)

Outcome Variable	Predictors	N	R	R^2	F	Significance
	FPS to Danger Cue (CS+)[a]					
Total BQ score	Total	210	0.020	0.000	0.082	0.775
	Males	79	0.259*	0.067*	5.535	0.021
	Females	131	0.127	0.016	2.105	0.149
	FPS to Safety (CS-)[a]					
	Total	210	0.051	0.003	0.539	0.464
	Males	79	0.020	0.000	0.030	0.863
	Females	131	0.057	0.003	0.426	0.515
	Acclimation[b] HR					
	Total	190	-0.260*	0.068*	13.656	0.000
	Males	64	-0.254*	0.065*	4.291	0.042
	Females	126	-0.237*	0.056*	7.384	0.008
	Startle[c] HR					
	Total	190	-0.278*	0.077*	15.737	0.000
	Males	64	-0.308*	0.095*	6.492	0.013
	Females	126	-0.238*	0.057*	7.434	0.007
	Acclimation[b] RSA					
	Total	190	0.100	0.010	1.884	0.171
	Males	64	0.215	0.046	2.993	0.089
	Females	126	0.053	0.003	0.347	0.557
	Startle[c] RSA					
	Total	190	0.141	0.020	3.816	0.052
	Males	64	0.316*	0.100*	6.866	0.011
	Females	126	0.057	0.003	0.400	0.528

BQ=Behavioral Questionnaire; HR=Heart Rate; RSA=Respiratory Sinus Arrhythmia; HRV=Heart Rate Variability; FPS =Fear-potentiated Startle; CS+=In the presence of the Conditioned Stimulus; CS- =In the absence of the Conditioned Stimulus. *Significant $p<0.05$.

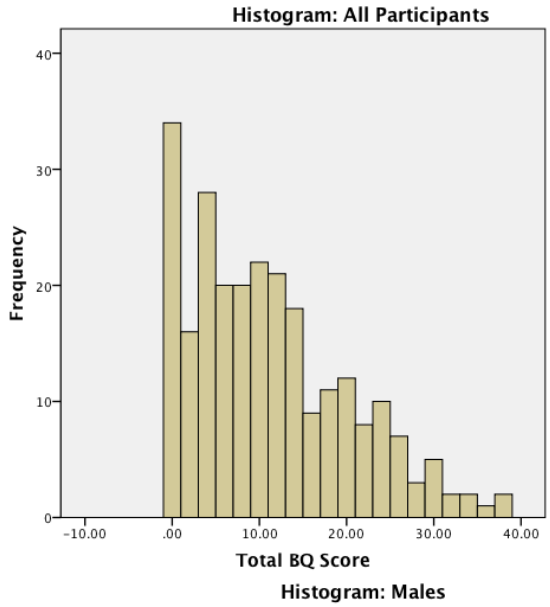
[a]Fear-potentiated startle response to the danger (CS+) and safety (CS-) cues were calculated by subtracting the acoustic startle magnitude obtained during the noise alone trials, where only the acoustic startle probes were delivered, from the startle magnitude obtained during the CS+ trials and the CS- trials.

[b]Acclimation refers to data collected in the sound-attenuated startle booth, before exposure to the startle probe or other stimuli.

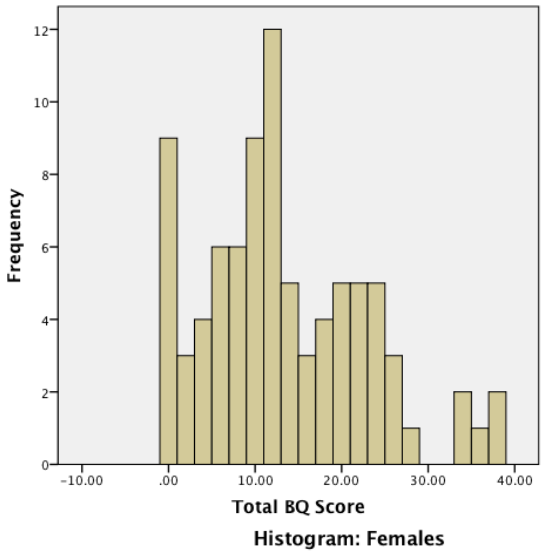
[c]Startle RSA refers to data collected during the delivery of the startle probes during the baseline phase of the startle session, prior to the fear-potentiated startle experiment.

This table depicts the correlation between aggression score (as measured by the total BQ score) and startle response, heart rate, and heart rate variability. As seen above, in men, for every one μV increase in startle magnitude to the danger cue, the total BQ score increases by 0.259 and for every one unit increase in the ln(HF-HRV) during startle trials, the total BQ score increases by 0.316. Conversely, for every one beat increase in heartbeats per minute during acclimation trials, the total BQ score decreases by 0.254 and for every one beat increase in heartbeats per minute during startle trials, the total BQ score decreases by 0.308. In women, for every one beat increase in heartbeats per minute during acclimation trials, the total BQ score decreases by 0.237 and for every one beat increase in heartbeats per minute during baseline startle trials, the total BQ score decreases by 0.238.

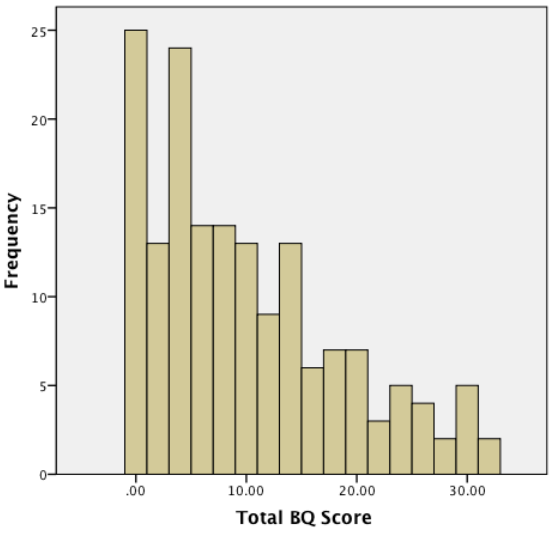
***Figure 2*:** Distribution of Aggression Scores for All Participants, Males Participants, and Female Participants



Skewness = 0.78 (SE: ±0.15)
Kurtosis = -0.03(SE: ±0.31)
Range = 0.0 to 38.0

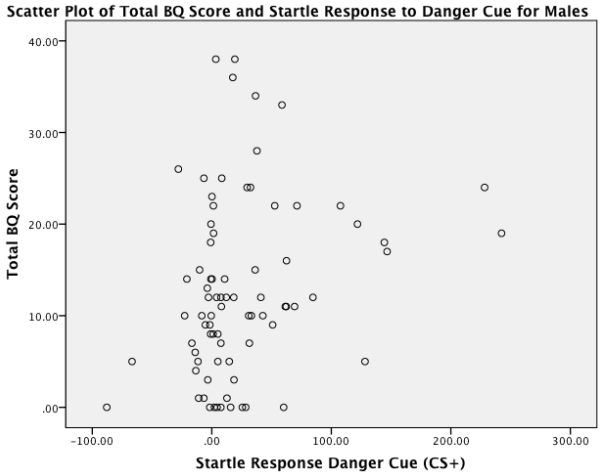


Skewness = 0.66 (SE: ±0.26)
Kurtosis = 0.04(SE: ±0.52)
Range = 0.0 to 38.0



Skewness = 0.83 (SE: ±0.19)
Kurtosis = -0.20(SE: ±0.38)
Range = 0.0 to 31.0

Figure 3: Scatter Plots and Residual Plots for Total BQ Score with Fear-potentiated Startle Response to Danger Cue for Males



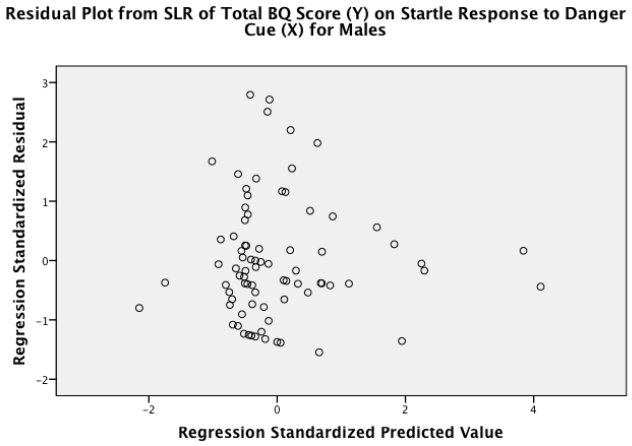
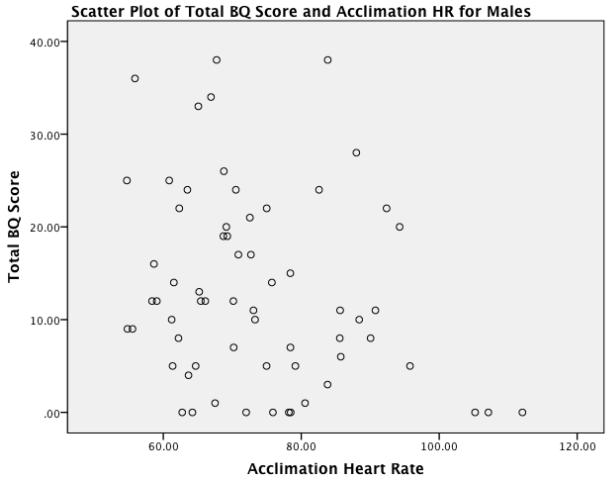


Figure 4: Scatter Plots and Residual Plots for Total BQ Score with Acclimation HR for Males



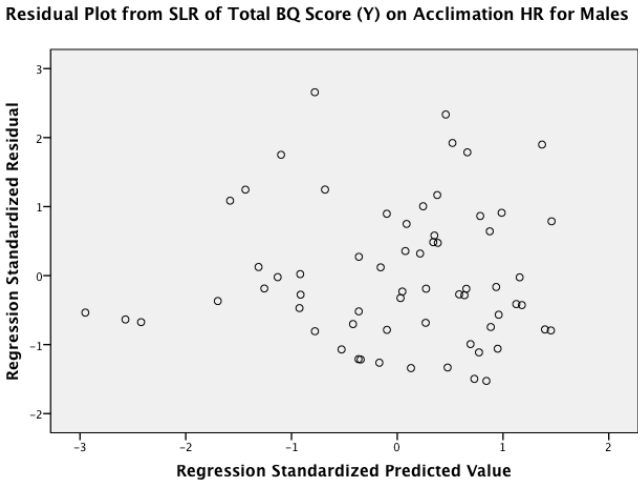
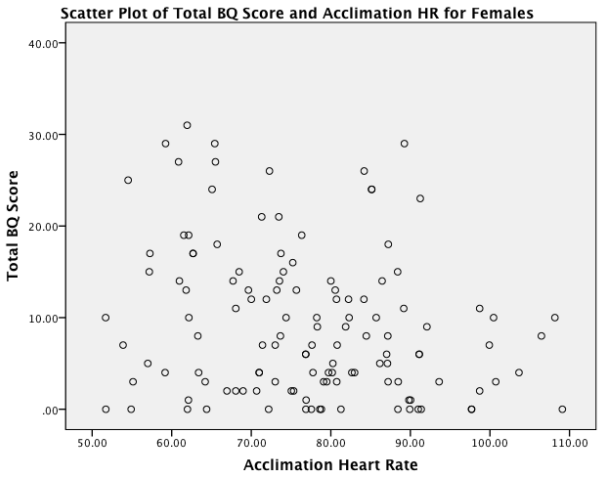


Figure 5: Scatter Plots and Residual Plots for Total BQ Score with Acclimation HR for Females



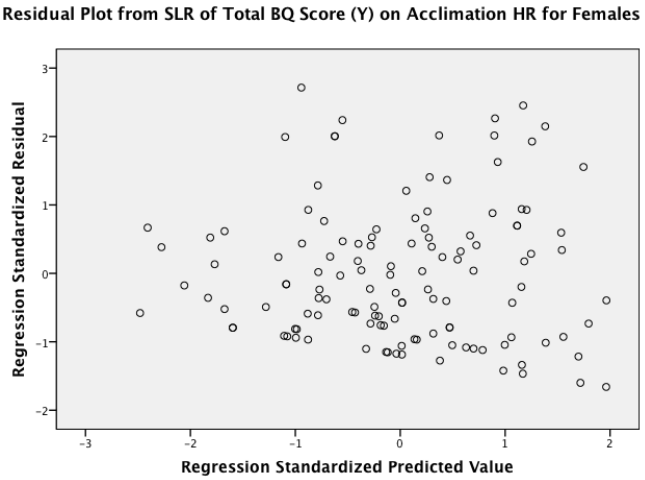
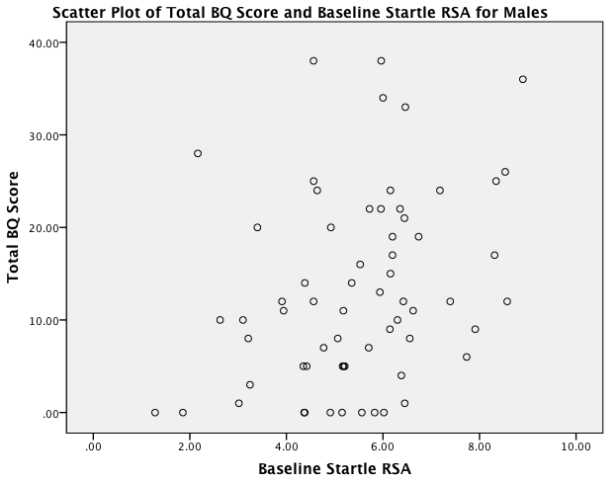


Figure 6: Scatter Plots and Residual Plots for Total BQ Score with Startle RSA for Males



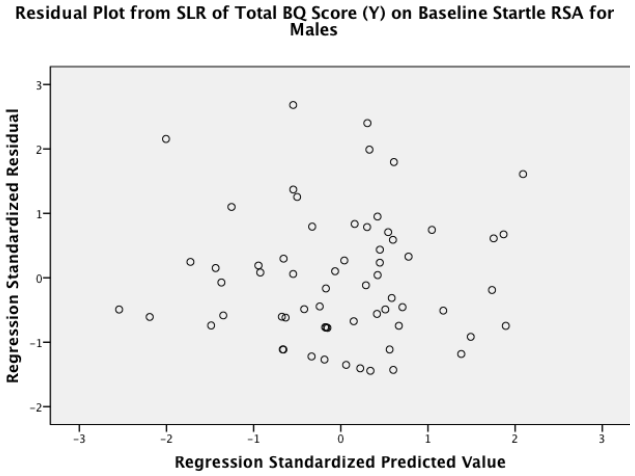


Table 4: Pearson Correlation Coefficients Between Separate BQ Questions and Physiological Predictor Variables Split by Sex

BQ Question	FPS to Danger Cue (CS+)[a]		FPS to Safety Cue (CS-)[a]		Acclimation[b] HR		Startle[c] RSA	
	Spearman ρ, p		Spearman ρ, p		Spearman ρ, p		Spearman ρ, p	
Thrown something at someone that could hurt?								
Males	0.304*	0.006	0.157	0.167	-0.023	0.858	0.067	0.598
Females	-0.123	0.163	-0.178*	0.042	0.043	0.635	-0.027	0.766
Twisted someone's arm or hair?								
Males	0.224*	0.047	0.046	0.689	-0.011	0.930	0.264*	0.035
Females	0.068	0.439	-0.050	0.568	-0.215	0.016	0.090	0.319
Pushed or shoved someone?								
Males	0.262*	0.020	0.149	0.190	-0.264*	0.035	0.267*	0.033
Females	-0.041	0.639	-0.066	0.453	-0.148	0.098	0.102	0.257
Pulled a knife or gun on someone (but didn't stab them or pull the trigger)?								
Males	0.031	0.783	0.039	0.734	-0.015	0.909	0.106	0.404
Females	-0.012	0.893	0.078	0.373	-0.167	0.062	0.022	0.805
Stabbed or shot at someone?								
Males	-0.004	0.973	0.111	0.331	-0.080	0.529	0.084	0.511
Females	-0.103	0.240	0.001	0.988	-0.201*	0.024	0.110	0.219
Punched or hit someone with something that could hurt?								
Males	0.175	0.123	0.234*	0.038	-0.136	0.282	0.294*	0.019
Females	-0.151	0.084	-0.042	0.632	-0.148	0.098	0.069	0.441
Destroyed something belonging to someone on purpose?								
Males	0.191	0.091	0.225*	0.046	-0.280*	0.025	0.232	0.065
Females	-0.133	0.131	-0.032	0.713	0.075	0.405	-0.109	0.225
Choked someone?								
Males	0.167	0.140	-0.038	0.736	-0.149	0.241	0.358*	0.004
Females	-0.143	0.102	-0.026	0.768	-0.215*	0.016	0.091	0.313
Slammed someone against a wall?								
Males	0.271*	0.016	-0.023	0.843	-0.251*	0.045	0.315*	0.011
Females	-0.022	0.807	-0.048	0.590	-0.078	0.385	-0.071	0.430
Beat someone up?								
Males	0.197	0.081	-0.008	0.944	-0.218	0.083	0.279*	0.026
Females	-0.169	0.054	0.019	0.825	-0.173	0.053	-0.092	0.306
Grabbed someone by the neck, collar, clothes, or some part of their body in anger?								
Males	0.250*	0.027	0.038	0.742	-0.311*	0.012	0.192	0.129
Females	-0.052	0.558	0.031	0.727	-0.183*	0.040	-0.015	0.870
Became so angry with a child that you attacked them with a weapon or with the idea of seriously hurting them?								
Males	-0.040	0.728	-0.144	0.205	-0.051	0.688	0.038	0.769
Females	-0.205*	0.019	-0.071	0.421	-0.155	0.084	0.126	0.159
Became so angry with a child that you attacked them with something really hard or painful like a belt, chair, etc?								
Males	0.055	0.630	-0.111	0.330	-0.071	0.576	-0.144	0.258
Females	-0.062	0.485	-0.120	0.172	-0.033	0.713	-0.053	0.553
Became so angry with a child that you hit them (other than events you just told me about)?								
Males	-0.195	0.085	-0.227*	0.044	-0.010	0.940	0.151	0.234
Females	-0.183*	0.036	-0.083	0.346	-0.125	0.164	-0.049	0.583
Attacked an adult you've lived with with weapon or with the idea of seriously hurting or killing them?								
Males	0.014	0.901	0.099	0.386	-0.142	0.264	0.216	0.087
Females	-0.072	0.412	-0.025	0.775	-0.242*	0.006	0.008	0.929
Hit an adult you lived with?								
Males	0.169	0.136	0.269*	0.017	-0.201	0.112	0.233	0.064
Females	-0.094	0.287	-0.079	0.367	-0.273*	0.002	0.099	0.272

BQ=Behavioral Questionnaire; HR=Heart Rate; RSA=Respiratory Sinus Arrhythmia; HRV=Heart Rate Variability; FPS=Fear-potentiated Startle; CS+=In the presence of the Conditioned Stimulus; CS-=In the absence of the Conditioned Stimulus. *.Significant $p<0.05$.

[a]Fear-potentiated startle response to the danger (CS+) and safety (CS-) cues were calculated by subtracting the acoustic startle magnitude obtained during the noise alone trials, where only the acoustic startle probes were delivered, from the startle magnitude obtained during the CS+ trials and the CS- trials.

[b]Acclimation refers to data collected in the sound-attenuated startle booth, before exposure to the startle probe or other stimuli.

[c]Startle RSA refers to data collected during the delivery of the startle probes during the baseline phase of the startle session, prior to the fear-potentiated startle experiment.

Table 5: Simple Linear Regression of Covariates with Total BQ score

(N=251)

Dependent	Independent	N	*β*	R^2	F	P value
Total BQ score	Age	251	-0.097	0.009	2.358	0.126
	Sex (1=female; 0=male)	251	-0.187*	0.035*	9.068	0.003
	Race (1=African American; 0=other)	**251**	**-0.064**	**0.004**	**1.019**	**0.314**
	Current Employment	251	0.020	0.000	0.095	0.758
	Trauma History, Total [a]	250	0.437*	0.191*	58.625	0.000
	Adult Trauma	250	0.423*	0.179*	53.987	0.000
	Child Trauma[b]	250	0.205*	0.042*	10.881	0.001
	Depression[c] (1=MDD; 0=No MDD)	211	0.188*	0.035*	7.624	0.006
	PTSD[d] (1=PTSD; 0=No PTSD)	211	0.263*	0.069*	15.567	0.000
	Bipolar[e] (1=Bipolar; 0=No Bipolar)	212	0.057	0.003	0.681	0.410
	Psychosis[f] (1=psychosis; 0=No psychosis)	211	0.102	0.010	2.177	0.142
	Substance or Drug Abuse/Dependence[g] (1=Yes; 0=No)	210	0.381*	0.145*	35.377	0.000
	Alcohol Abuse/Dependence[g] (1=Yes; 0=No)	210	0.286*	0.082*	18.497	0.000
	Alcohol and/or Substance Abuse/Dependence[g] (1=Yes; 0=No)	210	0.352*	0.124*	29.341	0.000

*Significant at $p \leq 0.05$.

[a] Trauma score as measured by the TEI

[b] Childhood trauma score as measured by the CTQ

[c] Lifetime Major Depressive Disorder as measured by the SCID.

[d] Lifetime PTSD as measured by the CAPS and the MINI.

[e] Lifetime presence of bipolar type I disorder as measured by the SCID.

[f] Lifetime presence of primary psychotic symptoms (not part of a mood disorder) as measured by the SCID.

[g] Lifetime substance, drug, or alcohol abuse/dependence as measured by the SCID and the MINI.

Table 6: One-Way ANOVA of Categorical Covariates with Total BQ score

(N=251)

Dependent	Independent	N	df	F	P value
Total BQ score	**Education**	**251**	**3, 247**	**0.539**	**0.656**
	Income	242	4, 237	0.400	0.808

Figure 7: Aggression Scores for Male vs. Female Participants

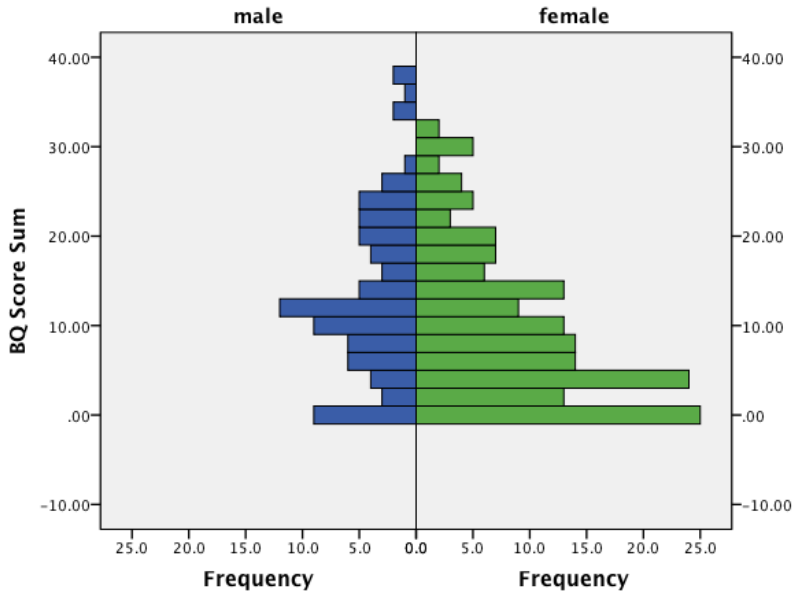


Figure 8*:* Aggression Scores for Participants With vs. Without Lifetime Major Depressive Disorder (MDD)

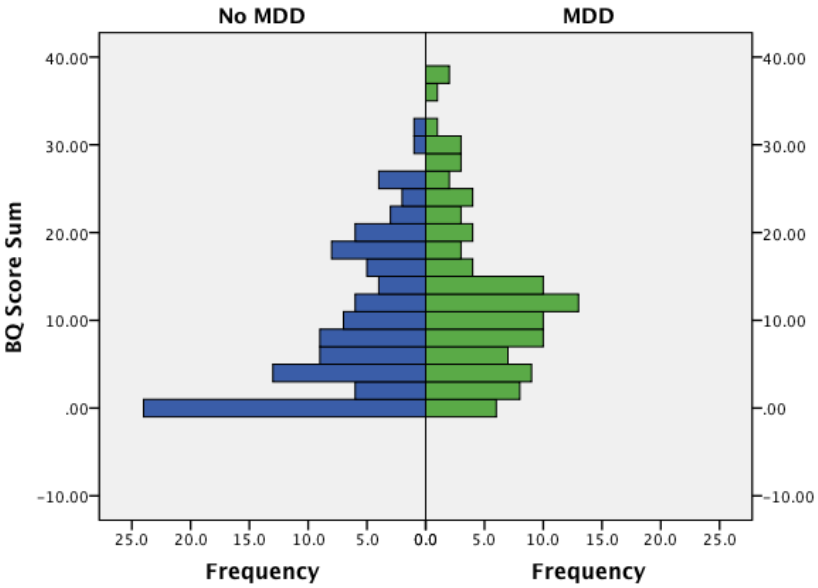


Figure 9: Aggression Scores for Participants With vs. Without Lifetime Post Traumatic Stress Disorder (PTSD)

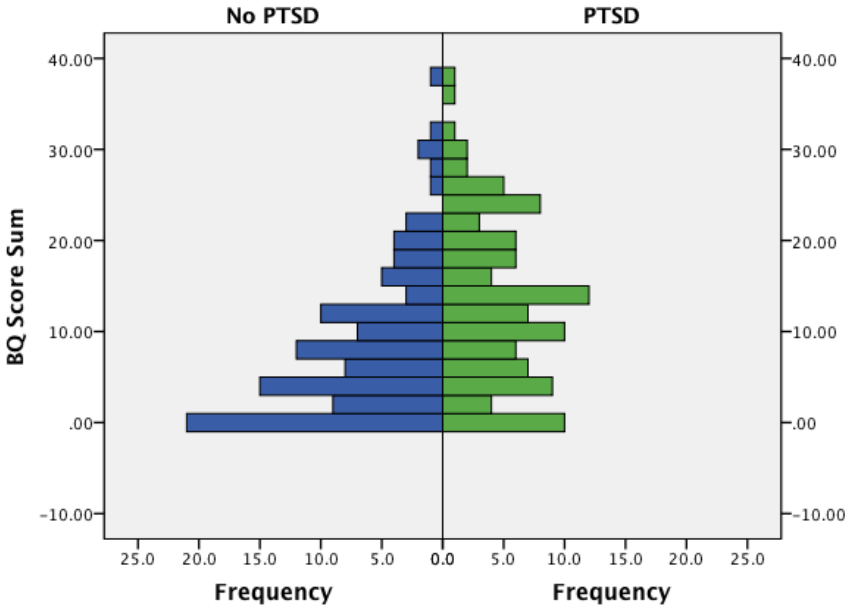


Figure 10: Aggression Scores for Participants With vs. Without Lifetime Alcohol Abuse

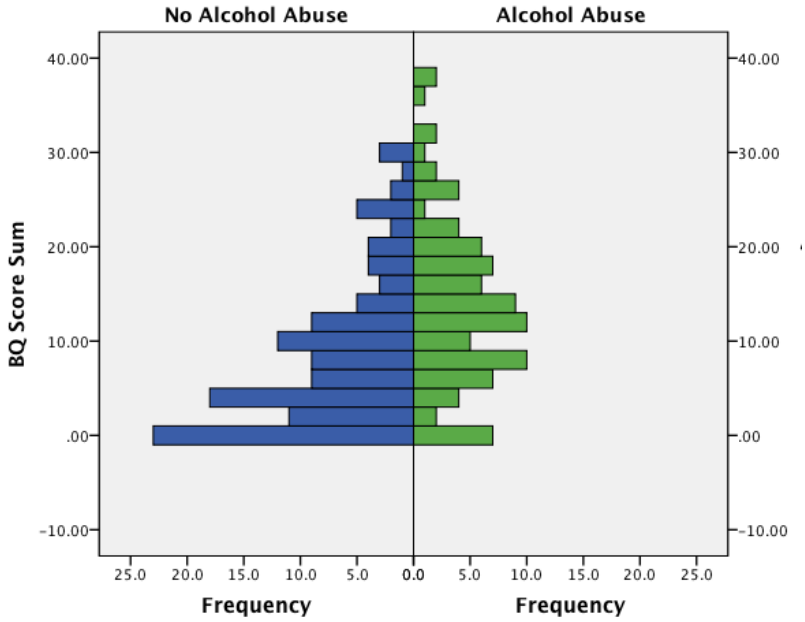


***Figure 11**:* Aggression Scores for Participants With vs. Without Drug Abuse

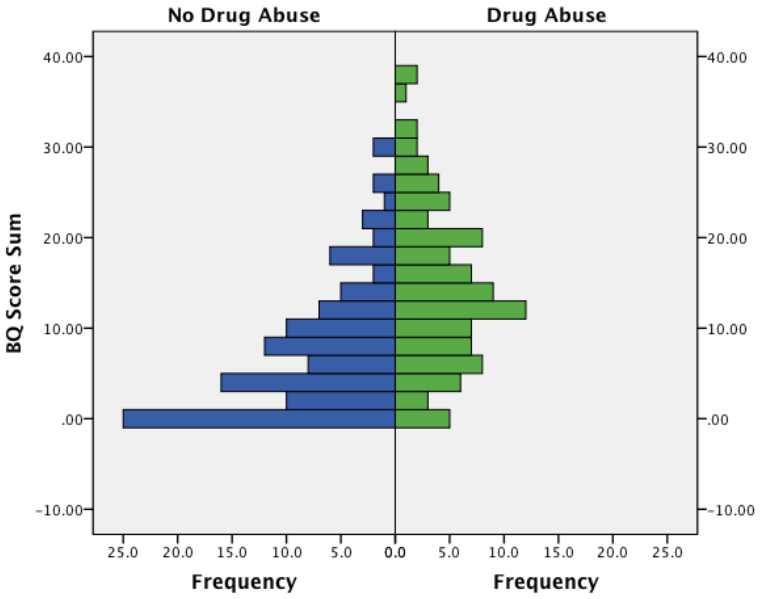


***Figure 12**:* Aggression Scores for Participants With vs. Without Drug and/or Alcohol Abuse

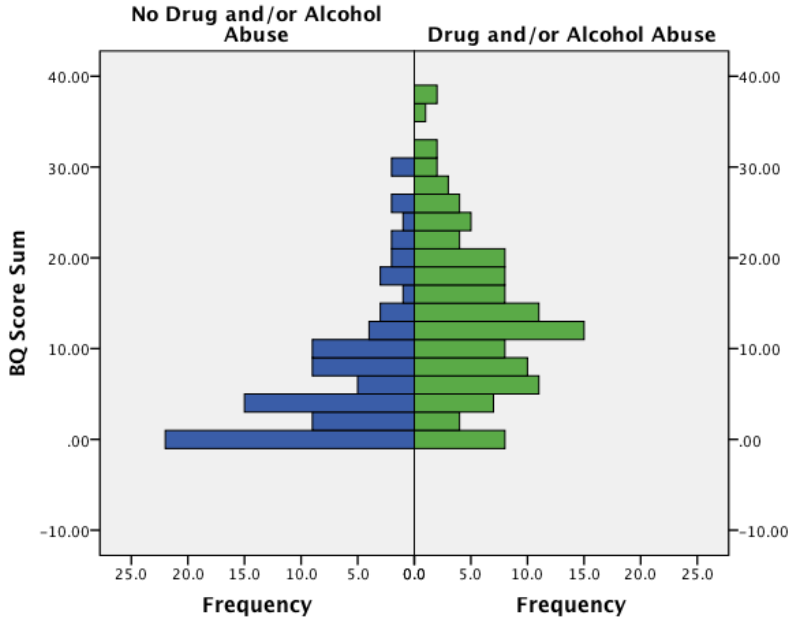


Table 7: Backwards Elimination Multiple Regression Models Predicting Aggression with Fear-potentiated Startle Response to *Danger Cue* and Other Covariates in Men **(N=66)**

	Model 1		Model 2		Model 3	
	B (SE B)	*β*	B (SE B)	*β*	B (SE B)	*β*
DV: Total BQ Score						
FPS to Startle Danger Cue[a]	0.04 (0.02)	.23*	0.04 (0.02)	.24*	0.04 (0.02)	.24*
Total Trauma Score[b]	0.85 (0.32)	.35*	0.88 (0.30)	.36**	0.91 (0.29)	.37**
Alcohol and/or Substance Abuse/Dependence[c]	5.19 (3.05)	.21	5.36 (2.97)	.22	5.31 (2.95)	.21
Depression[d]	0.74 (2.12)	.04	.89 (2.05)	0.05		
PTSD[e]	0.71 (2.38)	.04				
Adjusted R^2	0.22		0.23		0.24	
R^2	0.28		0.28		0.27	
F model	4.57**		5.77**		7.74**	

FPS=Fear-potentiated Startle

Note. B = Unstandardized regression coefficient; β = Standardized regression coefficient

*$p < .05$ ** $p < .01$ *** $p < .001$

[a]Fear-potentiated startle response to the danger (CS+) and safety (CS-) cues were calculated by subtracting the acoustic startle magnitude obtained during the noise alone trials, where only the acoustic startle probes were delivered, from the startle magnitude obtained during the CS+ trials and the CS- trials.

[b]Trauma score as measured by the TEI.

[c]Lifetime substance, drug, or alcohol abuse/dependence as measured by the SCID and the MINI.

[d]Lifetime Major Depressive Disorder as measured by the SCID.

[e]Lifetime PTSD as measured by the CAPS and the MINI.

Table 8: Backwards Elimination Multiple Regression Models Predicting Aggression with Acclimation HR and Other Covariates in Men **(N=51)**

	Model 1		Model 2		Model 3		Model 4	
	B (*SE B*)	*β*	*B* (*SE B*)	*β*	*B* (*SE B*)	*β*	*B* (*SE B*)	*β*
DV: Total BQ Score								
Acclimation HR[a]	-0.18 (0.10)	-.23	-0.18 (0.09)	-.23	-0.19 (0.09)	-.24	-0.19 (0.09)	-.24*
Total Trauma Score[b]	1.36 (0.37)	.50**	1.36 (0.36)	.50**	1.38 (0.34)	.51***	1.46 (.31)	.54***
Alcohol and/or Substance Abuse/Dependence[c]	2.20 (3.52)	.08	2.20 (3.47)	.08	2.24 (3.43)	.08		
PTSD[d]	0.55 (2.92)	.03	.55 (2.60)	0.03				
Depression[e]	-0.01 (2.82)	.00						
Adjusted R^2	0.29		0.30		0.32		0.33	
R^2	0.36		0.36		0.36		0.37	
F model	5.04**		6.45***		8.76***		13.08***	

HR=Heart Rate

Note. B = Unstandardized regression coefficient; β = Standardized regression coefficient

*$p < .05$ ** $p < .01$ *** $p < .001$

[a]Acclimation refers to data collected in the sound-attenuated startle booth, before exposure to the startle probe or other stimuli.

[b]Trauma score as measured by the TEI.

[c]Lifetime substance, drug, or alcohol abuse/dependence as measured by the SCID and the MINI.

[d]Lifetime PTSD as measured by the CAPS and the MINI.

[e]Lifetime Major Depressive Disorder as measured by the SCID.

Table 9: Backwards Elimination Multiple Regression Models Predicting Aggression with Startle RSA and Other Covariates in Men **(N=51)**

	Model 1		Model 2		Model 3		Model 4	
	B (*SE B*)	*β*	*B* (*SE B*)	*β*	*B* (*SE B*)	*β*	*B* (*SE B*)	*β*
DV: Total BQ Score								
Startle RSA[a]	1.47 (0.75)	.24	1.49 (0.74)	.24	1.48 (0.74)	.24	1.54 (0.73)	.25*
Total Trauma Score[b]	1.26 (0.37)	.47**	1.25 (0.36)	.46**	1.31 (0.34)	.49**	1.38 (0.32)	.51**
Alcohol and/or Substance Abuse/Dependence[c]	1.96 (3.52)	.07	1.86 (3.48)	.07	1.98 (3.44)	.07		
PTSD[d]	1.82 (2.82)	.09	1.33 (2.57)	.07				
Depression[e]	-1.20 (2.70)	-.06						
Adjusted R^2	0.29		0.31		0.32		0.33	
R^2	0.37		0.36		0.36		0.35	
F model	5.17**		6.53***		8.75***		13.15***	

RSA=Respiratory Sinus Arrhythmia

Note. B = Unstandardized regression coefficient; β = Standardized regression coefficient

*$p < .05$ ** $p < .01$ *** $p < .001$

[a]Startle RSA refers to data collected during the delivery of the startle probes during the baseline phase of the startle session, prior to the fear-potentiated startle experiment.

[b]Trauma score as measured by the TEI

[c]Lifetime substance, drug, or alcohol abuse/dependence as measured by the SCID and the MINI.

[d]Lifetime PTSD as measured by the CAPS and the MINI.

[e]Lifetime Major Depressive Disorder as measured by the SCID.

Appendix

Explanation of Psychological Assessments

Psychological assessments were conducted during initial screening interview and during follow-up visits via administration of the Structured Clinical Interview for DSM-IV (SCID), the Mini-International Neuropsychiatric Interview (MINI), the modified PTSD Symptom Scale (PSS), and the Beck Depression Inventory (BDI). Additionally, the Childhood Trauma Questionnaire (CTQ) was used to assess traumatic events before the age of 19 years and the Traumatic Events Inventory (TEI) was used to assess adverse events in adulthood.

The Structured Clinical Interview for DSM-IV – The SCID is a validated interview assessment of DSM-IV disorders [48].

Mini-International Neuropsychiatric Interview – The MINI is a brief interview designed to analyze major Axis I disorders (according to the DSM-IV) [49].

The SCID and the MINI were used in combination to assess certain mood disorders, substance abuse/dependence, and alcohol abuse/dependence within our study population.

Modified PTSD Symptom Scale –The modified PSS is a 17-item self-report questionnaire, which assesses PTSD symptoms over a period of 2 weeks prior to rating [50]. The PSS has been validated with the Clinician Administered PTSD Scale (CAPS), which is a widely used form of PTSD measurement [52]. The definition of PTSD used in this study was established based on the DSM-IV A-E criterion responses to the PSS questionnaire (A-presence of trauma; B-presence of at least 1 intrusive symptom; C- presence of at least 3 avoidance/numbing symptoms; D-presence of at least 2 hyper-arousal symptoms; E-symptoms present for at least 1 month).

Beck Depression Inventory – The BDI is a 21-item questionnaire, which measures the severity and presence of depressive symptoms (ranked on a scale from 0 to 3). Major depressive

disorder (MDD) was defined as a score of 15 or higher on the BDI [53]. Current diagnosis of MDD was also confirmed by the SCID. The BDI interview was conducted at least 1 week prior to the startle session.

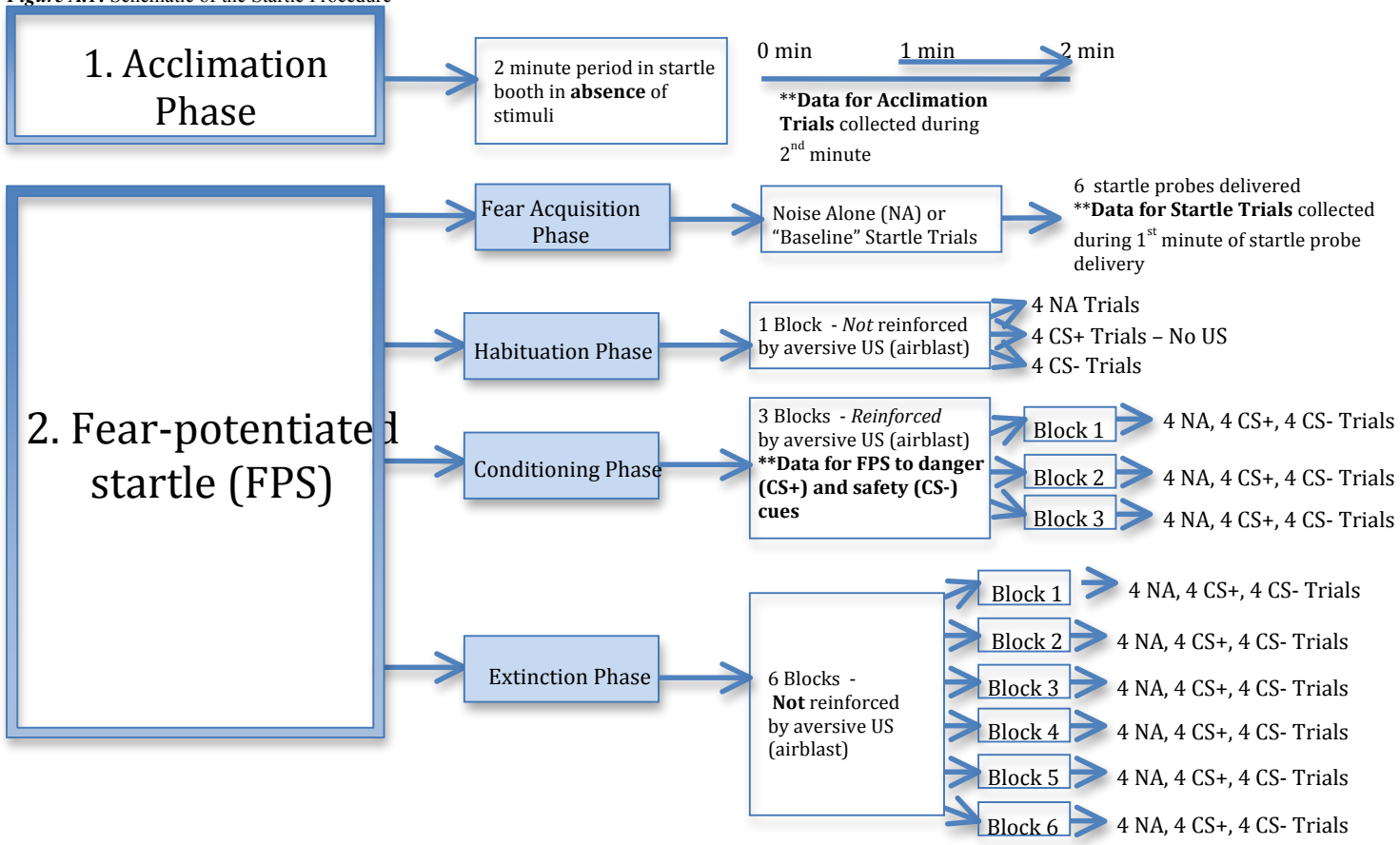
Childhood Trauma Questionnaire - The CTQ is a 28 question self-report inventory assessing childhood physical, emotional, and sexual abuse. The internal consistency and criterion validity of both the original 70-item CTQ and the current "brief version" have been established by multiple studies [54]. The CTQ provides a total score as well as a subscale score for each type of childhood abuse. Participants were split into the following 2 groups depending on their CTQ score ranges: (1) none to mild (2) moderate and severe. Participants were further divided into the following 3 groups based on the number of types of childhood abuse they had in the moderate and severe range: (1) no abuse in the moderate and severe range (2) 1 type of abuse in the moderate and severe range (3) 2 or more types of abuse in the moderate and severe range.

Traumatic Events Inventory – The TEI assesses 13 separate categories of trauma (including both type of experience and frequency) in addition to feelings of terror, horror, and helplessness associated with these events. The TEI assesses lifetime history of trauma exposure by measuring both child abuse and non-child abuse trauma [55].

Non-childhood abuse trauma was determined using the TEI and screening out all participants who had childhood trauma. Participants were then divided into the following 3 groups based on the number of types of traumatic exposures: (1) none (2) 1 (3) 2 or more.

Appendix – Tables and Figures

Figure A.1: Schematic of the Startle Procedure

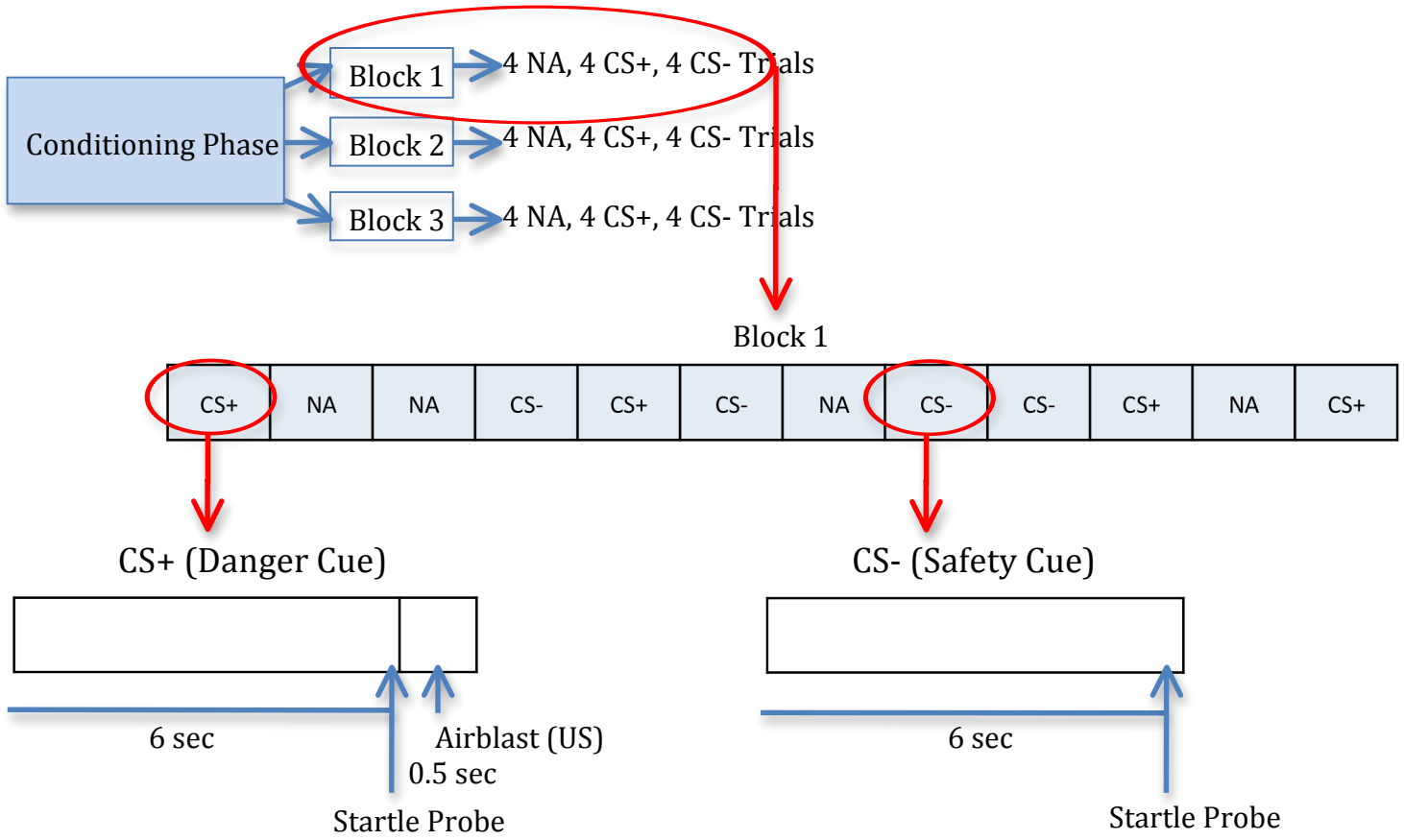


Startle was broken up into acclimation and fear-potentiated startle. Acclimation involved a two-minute period where individuals were exposed to the conditions of the sound-attenuated startle booth in the absence of any startle stimuli. Fear-potentiated startle involved the three following phases:

1. Fear acquisition phase where a series of six startle probes were presented alone (baseline or noise alone, NA, trials), in the absence of any stimuli.
2. Habituation phase where the startle probe and the conditioned stimuli (CS) were presented without the aversive US.
3. Conditioning phase where the magnitudes of the acoustic startle reflex were obtained in the presence of the startle probe alone (NA), in the presence of a reinforced conditioned stimulus (CS+) paired with an aversive US (i.e. airblast), and in the presence of a non-reinforced conditioned stimulus (CS-) not paired with the aversive US. The conditioning phase involved 36 total trials – 3 blocks with 12 trails per block (4 CS+, 4 CS-, 4 NA). The interval between each trial was randomized and occurred every 9 to 22 seconds.
4. Extinction phase where the startle probe and the conditioned stimuli (CS) were presented without the aversive US. The extinction phase involved 6 blocks with 12 trials per block.

All acclimation-related resting data were collected during the acclimation phase, all startle or baseline related data were collected during the fear acquisition phase, and all fear-potentiated startle data were caollected during the conditioning phase.

***Figure A.2*:** Schematic of the Conditioning Phase



The conditioning phase involved 36 total trials – 3 blocks with 12 trails per block (4 CS+, 4 CS-, 4 NA). Depicted above is an example of one block during the conditioning phase. The intervals between each of the 12 trials were randomized and occurred every 9 to 22 seconds. The conditioned stimuli used in this study were different colored shapes indicating either danger (CS+) or safety (CS-). The CS+ trials, depicted above, involved the initial presentation of a danger cue (CS+), followed by the presentation of a startle probe after six seconds, followed by the delivery of an aversive airblast (US). The CS- trials, also depicted above, involved the initial presentation of a safety cue (CS-), followed by the presentation of a startle probe after six seconds, The blink response was measured 21 to 120 ms after the acoustic startle probe was presented. Fear-potentiated startle response to the danger and safety cues were calculated by subtracting the magnitude of the blink response obtained during the noise alone (NA) startle trials from the startle magnitude obtained during the CS+ and CS- trials, respectively.

Appendix - Tables and Figures

Table A.1: Frequencies of Answers to Each Question on the BQ

BQ Question (N=251)	Never, N(%)	Once, N(%)	Several times, N(%)	Many times, N(%)	More than I can count, N(%)
Thrown something at someone that could hurt?	97 (38.6%)	46 (18.3%)	75 (29.9%)	22 (8.8%)	11 (4.4%)
Twisted someone's arm or hair?	178 (70.9%)	14 (5.6%)	45 (17.9%)	11 (4.4%)	3 (1.2%)
Pushed or shoved someone?	84 (33.5%)	27 (10.8%)	97 (38.6%)	29 (11.6%)	14 (5.6%)
Pulled a knife or gun on someone (but didn't stab them or pull the trigger)?	183 (72.9%)	33 (13.1%)	30 (12.0%)	3 (1.2%)	2 (0.8%)
Stabbed or shot at someone?	204 (81.3%)	23 (9.2%)	19 (7.6%)	4 (1.6%)	1 (0.4%)
Punched or hit someone with something that could hurt?	128 (51.0%)	25 (10.0%)	71 (28.3%)	18 (7.2%)	9 (3.6%)
Destroyed something belonging to someone on purpose?	157 (62.5%)	37 (14.7%)	40 (15.9%)	13 (5.2%)	4 (1.6%)
Choked someone?	193 (76.9%)	25 (10.0%)	27 (10.8%)	5 (2.0%)	1 (0.4%)
Slammed someone against a wall?	176 (70.1%)	29 (11.6%)	35 (13.9%)	10 (4.0%)	1 (0.4%)
Beat someone up?	114 (45.4%)	31 (12.4%)	75 (29.9%)	19 (7.6%)	12 (4.8%)
Grabbed someone by the neck, collar, clothes, or some part of their body in anger?	127 (50.6%)	30 (12.0%)	72 (28.7%)	15 (6.0%)	7 (2.8%)
Became so angry with a child that you attacked them with a weapon or with the idea of seriously hurting them?	245 (97.6%)	2 (0.8%)	4 (1.6%)	0 (0.0%)	0 (0.0%)
Became so angry with a child that you attacked them with something really hard or painful like a belt, chair, etc?	235 (93.6%)	4 (1.6%)	8 (3.2%)	2 (0.8%)	2 (0.8%)
Became so angry with a child that you hit them (other than events you just told me about)?	213 (84.9%)	13 (5.2%)	21 (8.4%)	1 (0.4%)	3 (1.2%)
Attacked an adult you've lived with with weapon or with the idea of seriously hurting or killing them?	195 (77.7%)	29 (11.6%)	22 (8.8%)	4 (1.6%)	1 (0.4%)
Hit an adult you lived with?	102 (40.6%)	33 (13.1%)	93 (37.1%)	16 (6.4%)	7 (2.8%)

BQ=Behavioral Questionnaire.

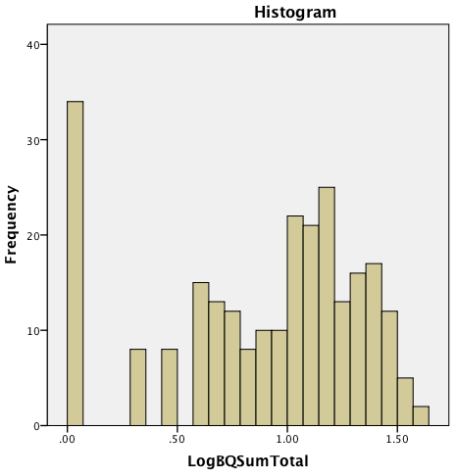
***Table A.3*:** Kolmogorov-Smirnov Tests of Normality for the Log Transformation of (Total BQ Score +1) in All Participants, Males, and Females

Dependent Variable:	Participants	Kolmogorov-Smirnov Statistic	df	P value
Log(TotalBQScore+1)				
	Total (N=251)	0.127	251	0.000
	Males (N=85	0.177	85	0.000
	Females (N=166)	0.117	166	0.000

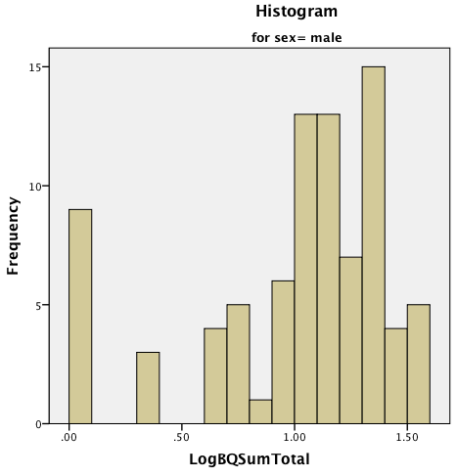
Table A.2: Kolmogorov-Smirnov Tests of Normality for the Dependent Variable, Total BQ Score, in All Participants, Males, and Females

Dependent Variable:	Participants	Kolmogorov-Smirnov Statistic	df	P value
Total BQ Score				
	Total (N=251)	0.115	251	0.000
	Males (N=85	0.122	85	0.002
	Females (N=166)	0.128	166	0.000

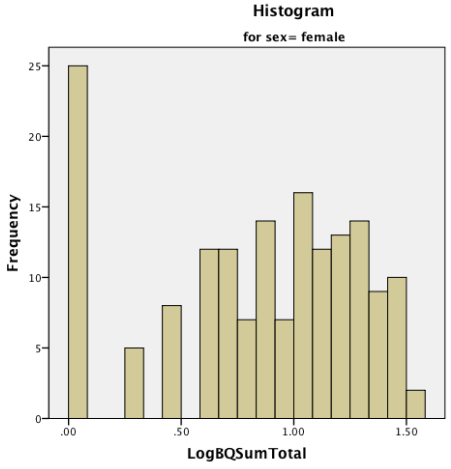
***Figure A.3*:** Distribution of Aggression Scores for All Participants, Males Participants, and Female Participants Using Log Transformation for Total BQ Score



Mean = 0.89
Std. Dev. = 0.46
N = 251
Skewness = -0.74 (SE: ±0.15)
Kurtosis = -0.47(SE: ±0.31)
Range = 0.0 to 1.59



Mean = 1.00
Std. Dev. = 0.44
N = 85
Skewness = -1.15 (SE: ±0.26)
Kurtosis = 0.50(SE: ±0.52)
Range = 0.0 to 1.59



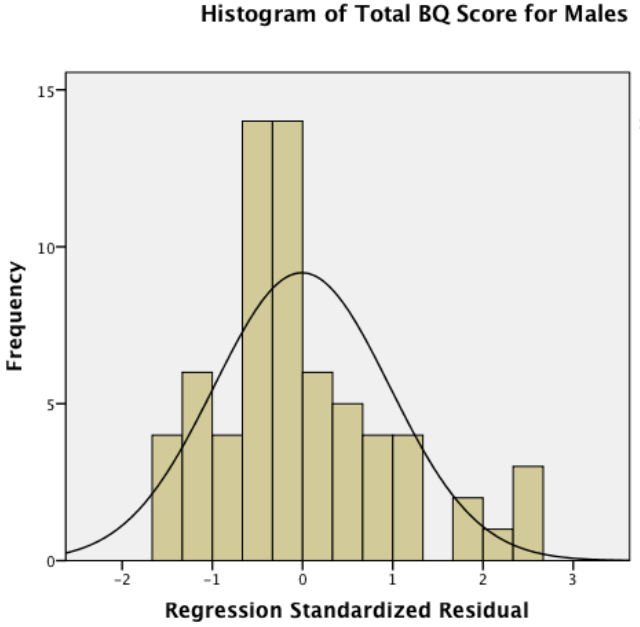
Mean = 0.84
Std. Dev. = 0.46
N = 166
Skewness = -0.59 (SE: ±0.19)
Kurtosis = -0.70(SE: ±0.38)
Range = 0.0 to 1.51

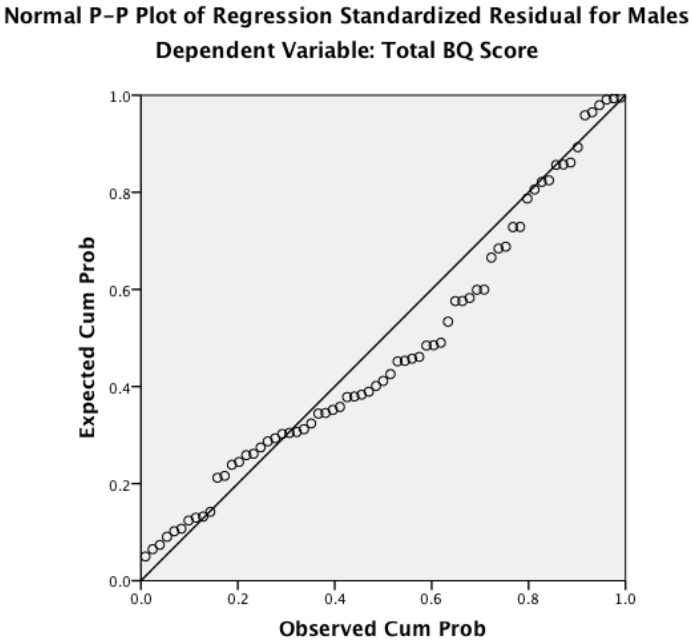
Table A.4*:* Correlations between Predictor Variables

Variable	*n*	1 – CS+	2 -HR	3 - RSA	4 - S	5 - TT	6 - AT	7 - CT	8 - P	9 - D	10 - AA	11 - SA
1. FPS to Danger Cue (CS+)	210	-										
2. Acclimation HR (HR)	190	0.150	-									
3. Startle RSA (RSA)	190	-0.029	-0.528**	-								
4. Sex (S)	251	0.143*	0.123	0.011	-							
5. Total Trauma Score (TT)	250	-0.065	-0.130	0.067	-0.154*	-						
6. Adult Trauma Score (AT)	250	-0.044	-0.130	0.054	-0.212**	0.969**	-					
7. Childhood Trauma Score (CT)	250	-0.102	-0.085	0.003	0.158*	0.515**	0.389**	-				
8. PTSD (P)	211	0.031	-0.115	0.112	0.090	0.366**	0.315**	0.334**	-			
9. MDD (D)	211	0.032	-0.004	0.068	0.013	0.215**	0.201**	0.231**	0.303**	-		
10. Alcohol Abuse/Dependence (AA)	210	-0.097	-0.110	0.086	-0.337**	0.368**	0.397**	0.153*	0.174*	0.121	-	
11. Substance or drug Abuse/Dependence (SA)	210	-0.174*	-0.186*	0.044	-0.333**	0.464**	0.477**	0.182**	0.224**	0.151*	0.493**	-
12. Alcohol and/or Substance Abuse/Dependence	210	-0.144	-0.135	0.054	-0.369**	0.416**	0.441**	0.165*	0.193**	0.159*	0.743**	0.810**

Note. CTQ = Childhood Trauma Questionnaire; BDI = Beck Depression Inventory; EDS = Emotion Dysregulation Scale; FPS=Fear-potentiated Startle
*$p<0.05$ **$p<0.01$

Figure A.4*:* Fit Diagnostics for Frequency of Total BQ Score for Males in MLR model (See Table 7) of Total BQ Score on Total Trauma, Fear-potentiated Startle Response to Danger Cue, and Alcohol and/or Substance Abuse/Dependence





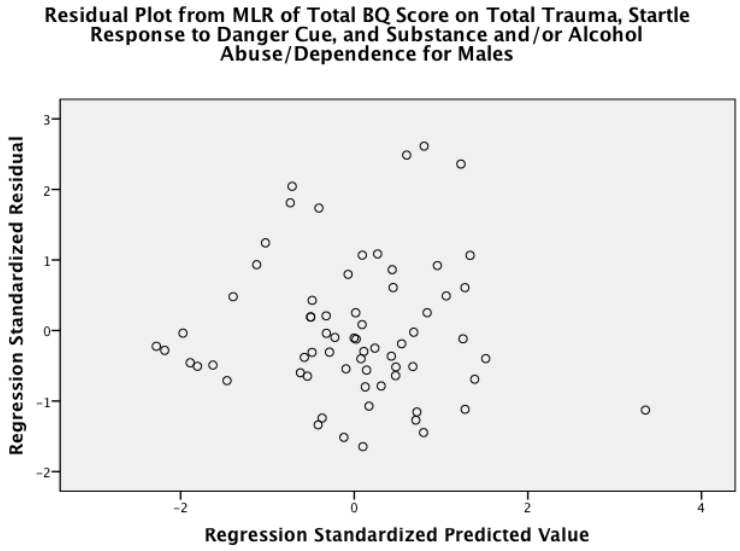
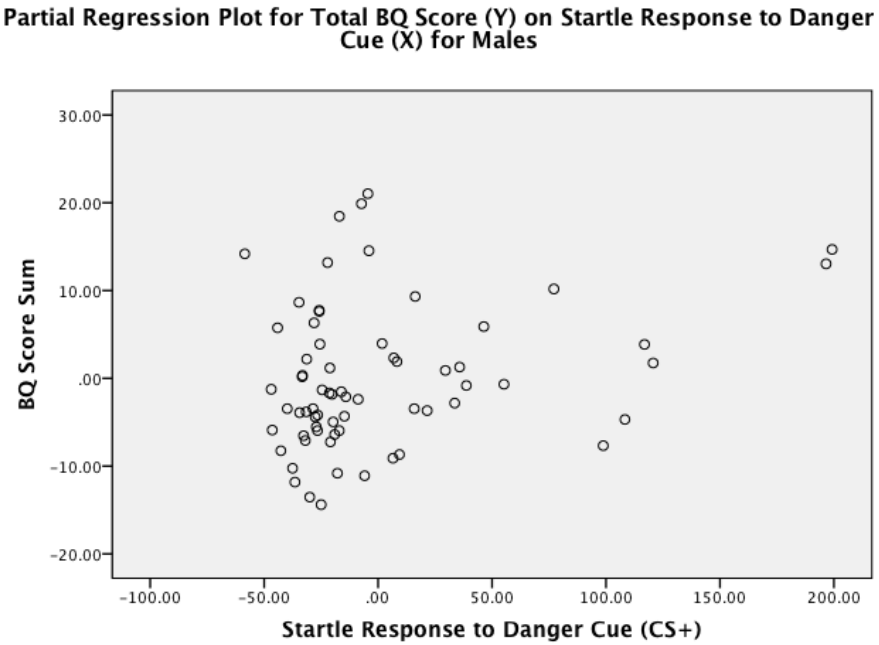
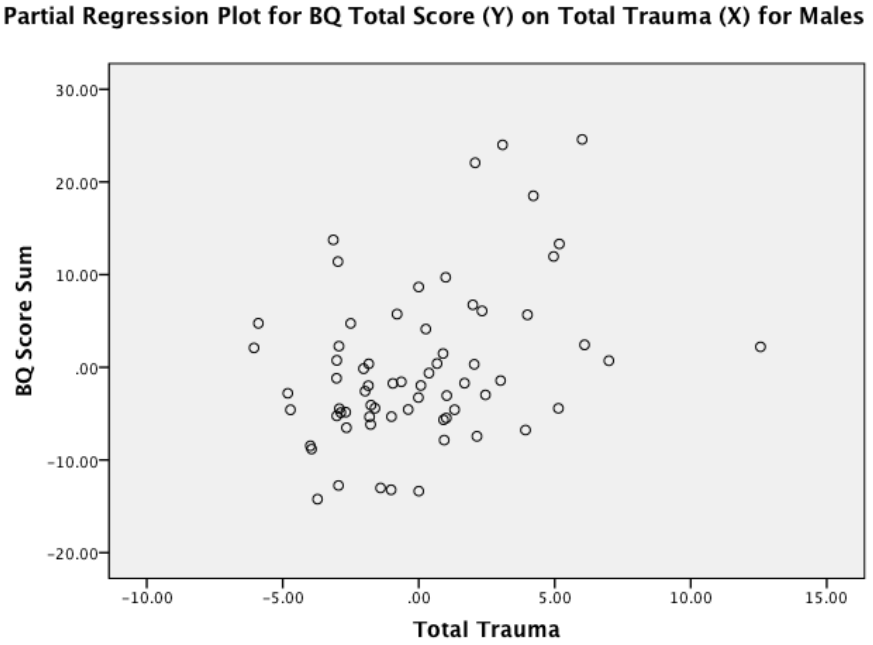


***Figure A.5*:** Partial Regression Plots from MLR Model (See Table 7) with the Predictor Variables Total Trauma, Fear-potentiated Startle Response to Danger Cue, and Alcohol and/or Substance Abuse/Dependence





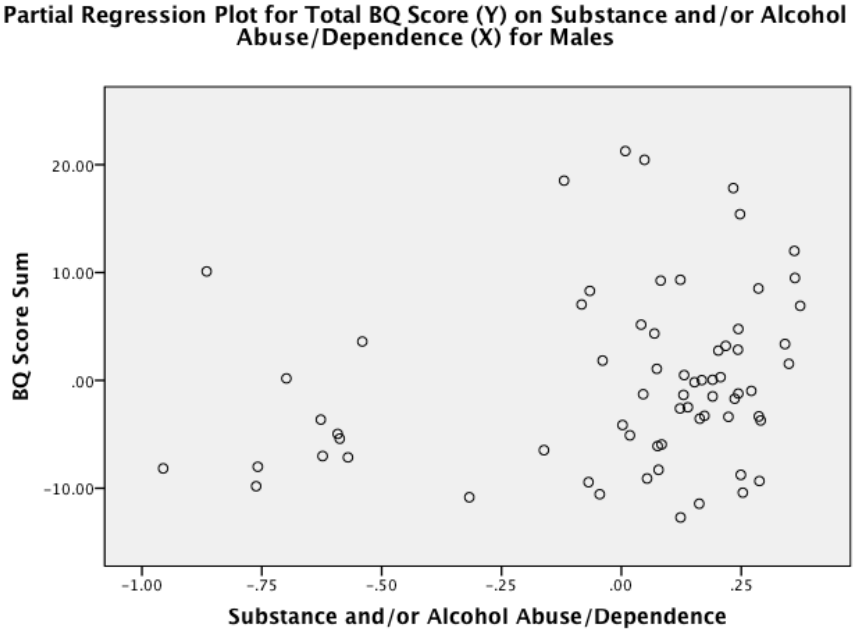
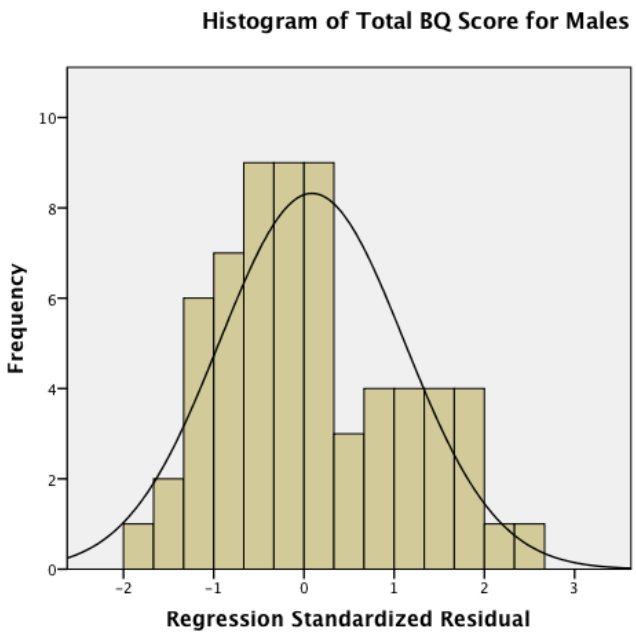
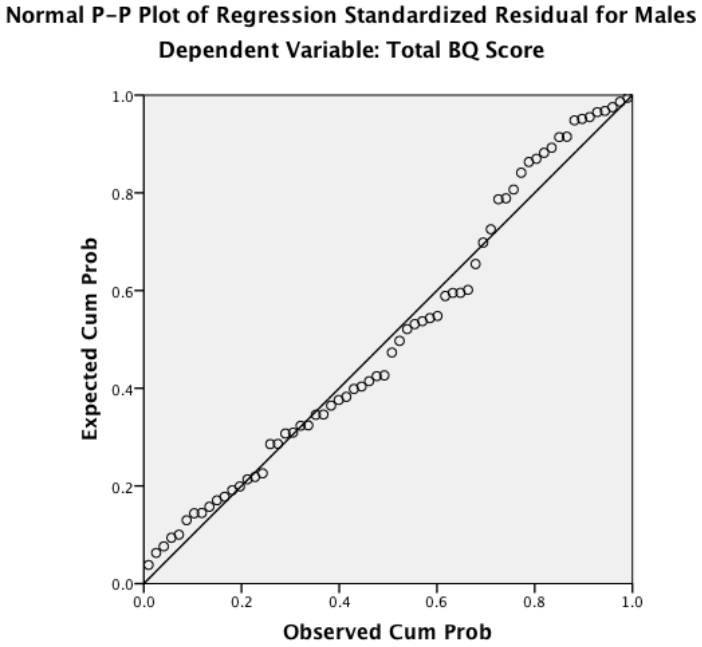


Figure A.6*:* Fit Diagnostics for Frequency of Total BQ Score for Males in MLR model (See Table 8) of Total BQ Score on Total Trauma and Acclimation HR





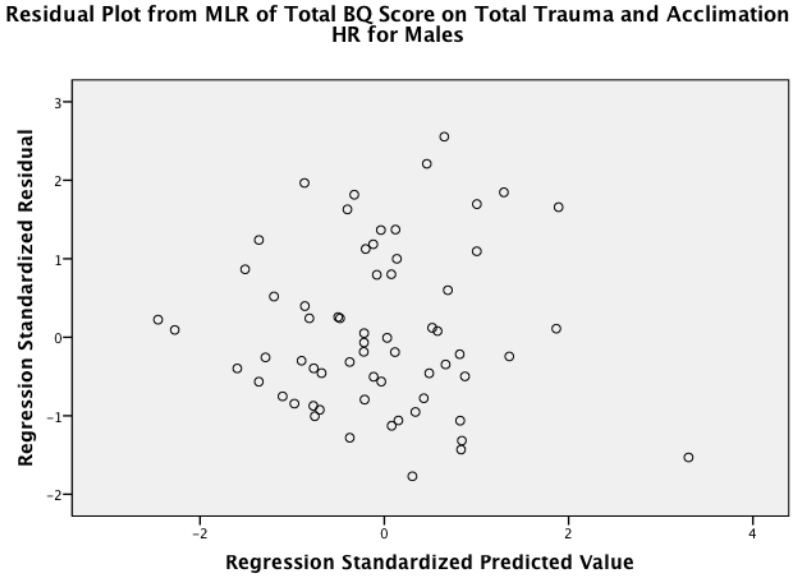
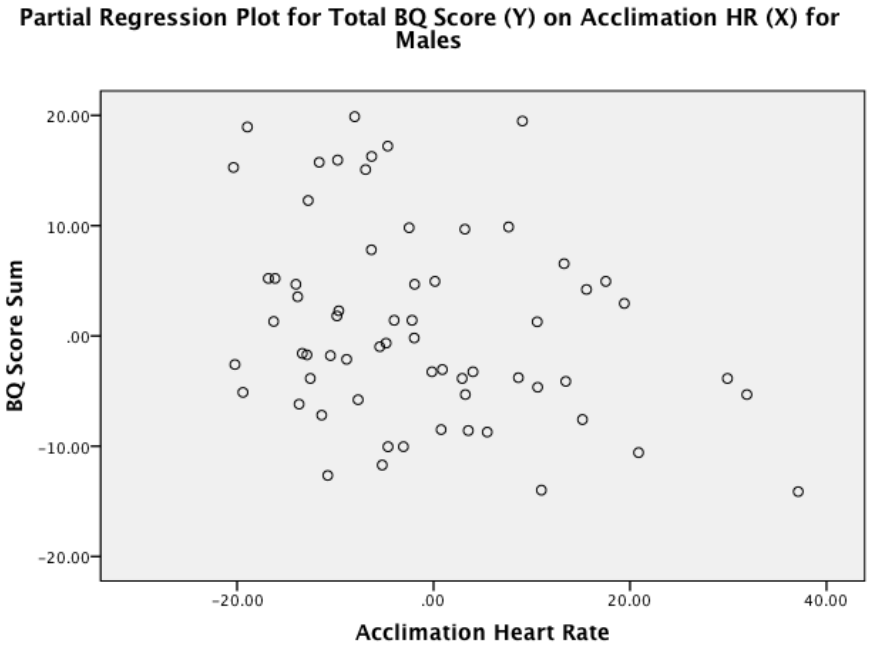


***Figure A.7*:** Partial Regression Plots from MLR Model (See Table 8) with the Predictor Variables Total Trauma and Acclimation HR



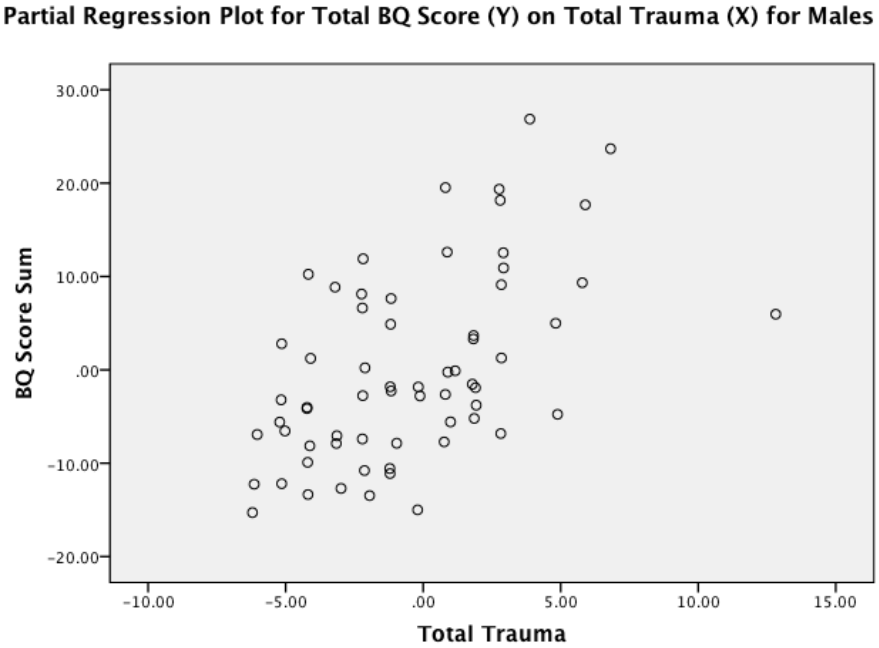
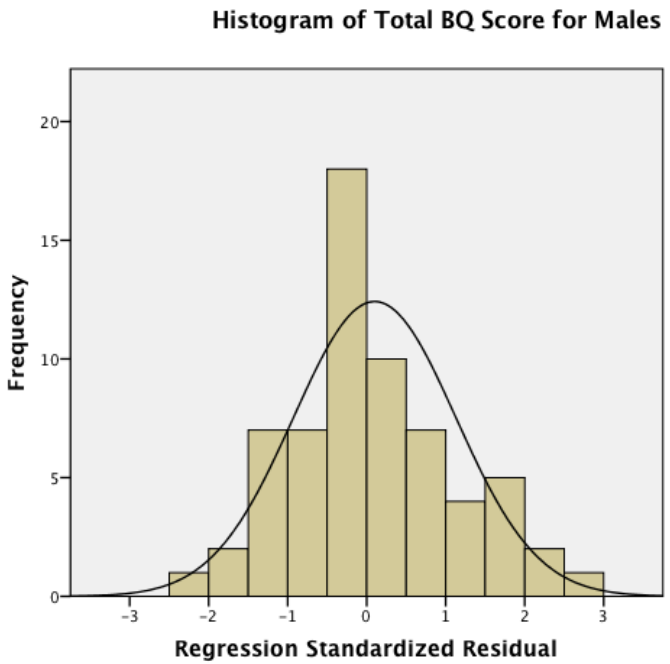
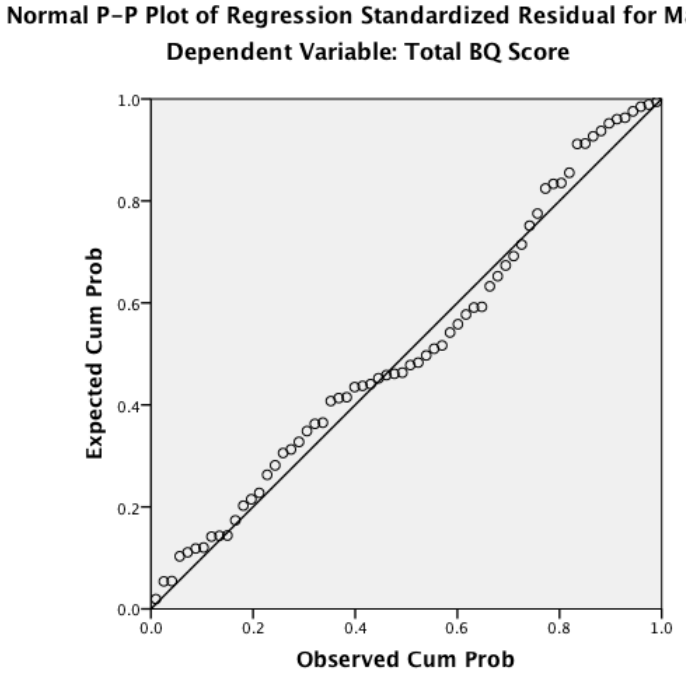


Figure A.8: Fit Diagnostics for Frequency of Total BQ Score for Males in MLR model (See Table 9) of Total BQ Score on Total Trauma and Startle RSA





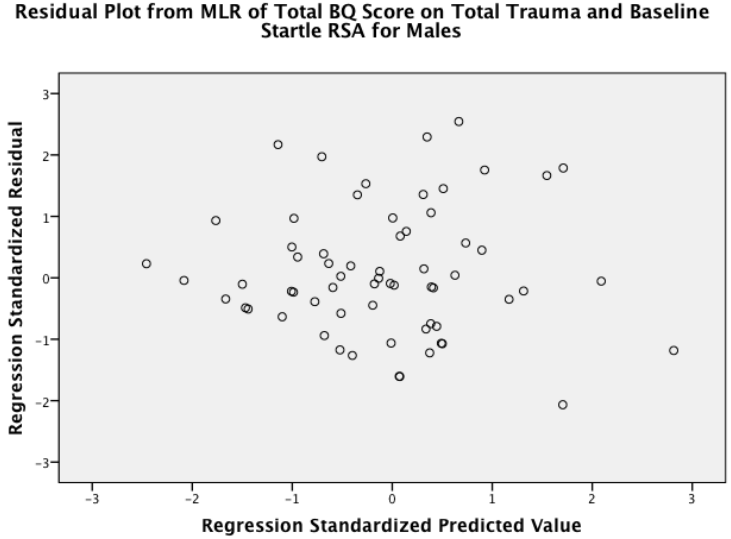


***Figure A.9*:** Partial Regression Plots from MLR Model (See Table 9) with the Predictor Variables Total Trauma and Startle RSA