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Investigating Heterogeneous Associations in Fear Responses Among PTSD Patients Using Quantile Regression

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Abstract

Investigating Heterogeneous Associations in Fear Responses Among PTSD Patients Using Quantile Regression

By Hanna Mar

Post traumatic stress disorder (PTSD) is a heterogeneous disorder with characteristics including a heightened fear response or a reduced ability to inhibit fear in safe situations. The mechanisms that lead to this response are not fully understood. Fear Potentiated Startle (FPS) is a tool often used to study fear response by exposing patients to visual cues that are associated with safety and danger, and measuring their startle responses (Jovanovic et al., 2005). This thesis will use quantile regression to conduct a secondary analysis of fear responses to better understand the heterogeneous associations between potential covariates and heightened startle response. Study participants were recruited at a large hospital in Atlanta, GA, and were predominately from a low-income, urban area. Participants were asked to complete questionnaires to assess past trauma and current PTSD symptoms before undergoing fear potentiated startle experiments. Startle response measurements were recorded in response to the safety and danger cues during fear acquisition, and for early, mid, and late fear extinction.

Gender and reexperiencing symptoms were found to influence the distribution of startle response to the safety cue at higher quantiles, but not at the lower or middle quantiles. At the 75^{th} quantile females experienced a 27.31 ($p = 0.004$) point increase in startle response compared to males, and a one point increase in reexperiencing symptoms was associated with a 2.39 ($p = 0.049$) point increase in startle response to the safety cue. The effect of childhood trauma on the 75^{th} quantile of the safety cue was also significant ($p = 0.036$). No covariates were found to be significantly different from zero at lower or middle quantiles of the startle response to the danger cue. At the 75^{th} quantile, gender was associated with a 30.53 ($p = 0.003$) point increase in startle response to the danger cue. A one point increase in reexperiencing symptom severity was associated with a 4.27 ($p = 0.003$) point increase in startle response to the danger cue, while a one point increase in hyperarousal symptom severity was associated with and 3.03 ($p = 0.028$) point decrease in startle response to the danger cue. These results demonstrate that gender and reexperiencing symptoms play an important role in influencing the startle response to the safety and danger cues for patients with high startle responses. Subjects with high startle responses to the danger cue may also be differentiated by hyperarousal symptom severity. Future studies on subjects who have high startle responses may help to further understand the heterogeneity of PTSD.

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1 Introduction

Posttraumatic Stress Disorder (PTSD) is an anxiety disorder which may develop after a person witnesses or experiences a traumatic event. Populations with high risk of exposure to trauma, such as military veterans (Hoge et al., 2004) and low-income, urban areas, (Gillespie et al., 2009) experience heightened rates of PTSD (*Diagnostic and statistical manual of mental disorders*, 1994; Kessler et al., 1995). PTSD is characterized by three symptom categories which include reexperiencing the trauma, avoiding reminders, and increased arousal. All three types of symptoms must be present for at least one month for an individual to be diagnosed with PTSD (*Diagnostic and statistical manual of mental disorders*, 1994). In chronic cases of PTSD, symptoms may persist for much longer, and in cases of delayed onset, symptoms may not appear for six months after trauma (Breslau et al., 1998).

PTSD is a complex disorder that is not well understood. The symptoms experienced and their duration can vary by individual, and although some individuals recover completely, others experience symptoms that temporarily dissipate and return (*Diagnostic and statistical manual of mental disorders*, 1994). While it was estimated that 60.7% of men and 51.2% of women will experience a traumatic event in their lifetime, the prevalence of PTSD in the general population is 7.8% (Kessler et al., 1995). It is unclear why some individuals develop PTSD after experiencing a traumatic event and some don't (B. van Der Kolk, 2000). In addition, PTSD patients are at higher risk for secondary disorders, such as mood or anxiety disorders, and are more likely to attempt suicide. They may struggle with simple everyday activities (B. van Der Kolk, 2000), be less productive at work, or have trouble in the workforce because of the stress involved (Kessler, 2000).

PTSD is one of several disorders that cause exaggerated fear responses and an inability to suppress fear under safe conditions (Jovanovic et al., 2005). The study of fear response is motivated by the need to further understand the mechanisms that influence heightened fear response and the role that trauma plays. The use of fear conditioning helps inform about the differences in fear processing between healthy individuals, and anxiety and PTSD patients (Duits et al., 2015).

Studies looking at fear expression have utilized different methods to measure fear including eye blink contraction, heart rate and skin conductance (Norrholm et al., 2011; Metzger et al., 1999; Glover et al., 2011; Jovanovic et al., 2013). To elicit a fear response, studies have used a small electric shock (Guthrie & Bryant, 2006) or an air blast to the throat (Jovanovic, Norrholm, et al., 2009).

Fear Potentiated Startle is a useful tool to study fear response (Jovanovic et al., 2005). It involves a conditioning procedure where participants are exposed to two visual cues that correspond to danger and safety. The danger cue is followed by an air blast to the throat while the safety cue is not (Norrholm et al., 2011). Patient's fear expression is assessed by measuring the startle response through the muscle contraction of participants' eye blink (Jovanovic et al., 2005). Regardless of the method, all studies have sought to identify predictors that are associated with an increase in fear expression or a reduced ability to inhibit fear under safe circumstances. While there has been a recent surge in the number of studies using fear potentiated startle (Duits et al., 2015), results are varied and have identified prior traumatic experiences, including child abuse (Jovanovic, Blanding, et al., 2009), and PTSD symptom severity (Norrholm et al., 2011) as contributing to heightened fear expression.

A recent meta-analysis consisting of studies of all anxiety disorders found that fear responses to the safety cue differed by the severity of anxiety symptoms (Duits et al., 2015). A study of Vietnam veterans and PTSD symptom severity found it to be associated with startle response, specifically how effectively patients were differentiating between the danger and safety cues (Jovanovic, Norrholm, et al., 2009). Another study cited childhood trauma as being associated with a heightened startle response (Jovanovic, Blanding, et al., 2009). When considering PTSD symptom categories separately, a study revealed that the type of symptom was associated with startle responses (Norrholm et al., 2011).

In fear potentiated startle, interest lies in the examination of heightened fear expression, such as an increased fear response to the visual cue, or continuing to have a fearful response when the situation becomes safe. Previous work has focused on factors that influence the mean of the fear response (Duits et al., 2016; Jovanovic, Blanding, et al., 2009; Jovanovic, Norrholm, et al., 2009; Norrholm et al., 2011). This thesis will provide a secondary analysis of fear potentiated startle using a more flexible method called quantile regression. This will allow us to examine how patient characteristics are associated with different segments of the distribution of startle response. For instance, it is plausible that a covariate may be associated with the fear response at high quantiles, but not at low quantiles.

The objective of this thesis is reanalyze fear potentiated startle responses using quantile regression. This analysis will provide further insight into the investigation of factors that are responsible for variations in fear outcomes among subjects who have low, middle, or high startle responses.

2 Methods

2.1 Participants

Data were collected as part of a larger cross-sectional study on genetics and environment factors and their relation to PTSD in a predominately African American and low income civilian population. Study participants were approached in the primary care and obstetrics and gynecology waiting rooms of a large hospital in Atlanta, GA (*The*

Grady Trauma Project, n.d.). Patients provided demographic information and completed the self-administered PTSD Symptom Scale (PSS) and the Traumatic Events Inventory (TEI). Some participants continued to the second round of assessments, at which point they underwent the fear potentiated startle assessment (Norrholm et al., 2011).

2.2 Clinical Assessments

The following scales were administered to patients to assess previous adult and childhood traumatic experiences and PTSD symptoms.

2.2.1 Traumatic Events Inventory (TEI)

The Traumatic Events Inventory (TEI) consists of 13 items assessing prior experience of traumatic events. Individuals respond yes or no to each item indicating whether they have experienced the traumatic event. Two items are specific to childhood, while the remaining eleven relate to traumatic events experienced during adulthood (Schwartz et al., 2005).

2.2.2 PTSD Symptom Scale (PSS)

The PTSD Symptom Scale (PSS) is a 17 item questionnaire measuring the presence of PTSD symptoms in the past two weeks. Each item is scored on a four point scale (0 - 3), and the 17 items are summed for the total score. PTSD diagnoses are based on PSS scores (Breslau, Peterson, Kessler, & Schultz, 1999). Symptoms are categorized into three groups: Reexperiencing includes intrusive thoughts and reexperiencing the traumatic event. Avoidance symptoms consist of avoiding or numbing against reminders of the trauma. Hyperarousal includes increased arousal or hyper vigilance. The scores of the questions addressing each category are summed to get a total score for the symptom subcategory. Reexperiencing and hyperarousal symptoms pertain to five questions each, for a total score ranging from 0 - 15. Seven questions address avoidance for a total score between 0 - 21.

2.3 Fear Potentiated Startle

Patients with PTSD experience heightened fear expression and a reduced ability to inhibit fear, even in safe situations, but a full understanding of the mechanisms contributing to these responses is not yet known (Briscione, Jovanovic, & Norrholm, 2014). Fear Potentiated Startle (FPS) is used to assess an individual's startle response to visual cues and provides a useful tool for studying PTSD (Norrholm et al., 2014). Startle response is measured by placing sensors below participants' eyes that capture the muscle contraction of their eye blink (Jovanovic et al., 2005).

FPS takes place in two stages. During the first stage, called fear acquisition, participants are presented with two visual cues or conditioned stimuli (CS). The danger cue, CS+, is paired with a blast of air to the throat. Over a series of trials, participants learn to expect the air blast after seeing the CS+ and will exhibit a stronger startle response. The safety cue, CS-, is presented without the air blast. There are three fear acquisition blocks, and during each block the CS+, CS-, and NA are presented four times each. The NA is an auditory startle probe presented without any visual cues that acts as a baseline startle response. The second stage is fear extinction. Fear extinction consists of three blocks (early, mid, and late) during which participants are presented with the same cues as before. The difference is that the danger cue is no longer followed by the air blast. Over a series of trials, the fear associated with the CS+ is extinguished and the startle response decreases as participants learn that the CS+ no longer signals danger (Norrholm et al., 2011).

The recorded startle reactions are used to calculate a difference score. The score is calculated for both conditioning stimuli cues during the final block of acquisition, referred to as late acquisition, and the danger cue (which is no longer dangerous) for early, mid, and late extinction. The average of the NA trials is subtracted from the average of the responses to the conditioning stimuli creating a total of five startle response variables (startle responses to the danger and safety cues during fear acquisition and to the newly safe danger cue during early, mid, and late fear extinction) (Norrholm et al., 2011). These five variables are used to assess patients' fear expression. Each variable is continuous, and since the baseline startle reaction was subtracted, can take on all values.

2.4 Quantile Regression

In multiple linear regression (MLR), it is often of interest to model how the expected value of the mean of the response variable, y, changes depending on the value of the predictor variables, x. Such a model takes the form

$$y = \beta_0 + \beta_1 x_1 + ... + \beta_n x_n + \epsilon_i, \tag{1}$$

where ϵ_i represents the error term and $\epsilon_i \sim$ N(0, σ^2). Inference for the β_i's are developed with maximum likelihood methods or least squares theory. This approach assumes the effect of the β_i's are the same across all quantiles. The ordinary least squares method is attractive for many reasons. For one, it is relatively easy computationally. Additionally, the resulting linear model has a nice interpretation making it a popular choice for regression analysis. Use of maximum likelihood methods in Equation 1 requires that certain distributional assumptions be met, mainly that the error term, ϵ_i be homoscedastic. That is, the variance of ϵ_i should not differ according to values of $\mathbf{x}$.

Ordinary least squares is limited by distributional assumptions and by its ability to only provide inference about the conditional mean of the response variable. Quantile regression differs from linear regression because it does not focus on the mean of y, but rather on the quantiles of y. The τ^{th} quantile of a random variable Y is defined by $\mathrm{F}^{-1}(\tau) = inf\{y|F(y) \geq \tau\}$ where F(y) is the cumulative distribution function of y and $0 < \tau < 1$. For instance, when $\tau = 0.5$, $\mathrm{F}^{-1}(0.5)$ is the median (Koenker, 2005). In situations where the assumptions of ordinary least squares are not met due to a heterogeneous outcome, or if interest lies in a parameter other than the mean, quantile regression provides an alternative. Not only does it enable examination of an upper or lower quantile, it does not require distributional assumptions. In this way, quantile regression can provide a robust and comprehensive examination of the association structure between covariates and response.

Instead of considering $E(y|\mathbf{x})$ as in least squares, quantile regression considers the quantiles of the response variable conditioned on covariates $\mathbf{x}$. A linear quantile regression model at the τ^{th} quantile may take the form,

$$Q_y(\tau|\mathbf{x}) = \mathbf{x}^T\beta(\tau). \tag{2}$$

The estimated regression coefficients, $\hat{\beta}(\tau)$ can be found through optimizing

$$\min_{\beta\in\mathbb{R}^p} \sum_{i=1}^{n} \rho_\tau(y_i - x_i^T\beta), \tag{3}$$

where $\rho_\tau(u) = u(\tau - I(u < 0))$, which is a piecewise linear function called the "check function" (Koenker, 2006; Koenker & Hallock, 2005). The objective function in Equation 3 is piecewise linear, but not differentiable at zero. For a given τ, the solution to Equation 3 gives the estimated covariate effects on the τ^{th} conditional quantile of y. When $\tau = 0.5$, Equation 2 corresponds to median regression. Note that the effect of the predictor variables may not have the same effect across quantiles. Examining different quantile levels provides a sweeping view of the response distribution, rather than the snapshot view from ordinary least squares. As a result, quantile regression can provide a more robust assessment of covariate effects than linear regression. Taken together, these qualities make quantile regression an appealing alternative in the presence of heterogeneous associations (Koenker, 2005).

2.5 Statistical Analysis

The 13-item TEI Questionnaire was broken down into two variables, one for questions pertaining to adult trauma, and the other childhood trauma. The adult trauma variable was collapsed into a categorical variable consisting of four groups: no trauma experienced, only interpersonal trauma experienced (such as being attacked by another person with or without a weapon), only non-interpersonal trauma experienced (including experiencing an accident or the murder of a family member), and both types of trauma experienced. The childhood trauma questions asked whether patients were sexually or physically abused. These two questions were collapsed into a three group categorical variable with levels corresponding to no childhood trauma, one childhood trauma (either sexually or physically abused), and two childhood trauma (both sexually and physically abused).

We summarized each demographic and clinical variable, as well as the five startle outcomes by the mean and standard deviation if continuous, or the count and percentage if categorical. We also compared them by PTSD diagnosis to determine whether there were differences between the PTSD and non-PTSD groups. Two-sample t-tests were used for continuous variables and, χ^2 tests for categorical variables.

Additional tests were conducted to assess the univariate association between each of the explanatory variables and the five outcome variables. For categorical variables with two levels, the Wilcoxon Rank Sum Test was used, while the Kruskal-Wallis Test was used for categorical variables with three or more levels. Correlation was tested for the continuous variables, and for variables not meeting the normal assumption, the Spearman Rank Correlation Coefficient, a non-parametric analogue to the Pearson Correlation Coefficient, was used.

2.5.1 Univariate Quantile Regression

In the preliminary step of univariate quantile regression, each of the five fear variables were treated as separate outcomes and models were fit with each demographic and clinical variables as an individual predictor. The 25^{th}, 50^{th}, and 75^{th} quantiles were chosen for all models. For each of the quantile regression models, separate parameter estimates were calculated, such that every model had three parameter estimates and standard errors, one for each quantile. The standard error was calculated using a bootstrap resampling method (Davino, Furno, & Vistocco, 2014). This method was chosen because it does not require any distributional assumptions to be made and has been shown to robustly estimate the standard error, provided the sample size is reasonably large.

2.5.2 Multivariate Quantile Regression

While the univariate models describe the marginal relationships between the predictors and fear outcomes, it is of interest to investigate how multiple covariates jointly influence the outcome distribution. It is possible that the effects of predictors may change across different quantiles of the outcome. Consequently, the set of significant predictors may vary across quantiles. PTSD symptom categories and adult and childhood trauma had previously been identified as variables of particular interest. First, a big model was fit with all predictors for the 25^{th}, 50^{th}, and 75^{th} quantiles. This model was used to identify important predictors at each quantile. Then individual models were fit for the three quantiles and all outcomes. The goal was to fit a meaningful model at each quantile and outcome.

2.5.3 Model Fitting and Variable Selection Process

It was decided to adjust for age and gender in all models leaving five possible predictors to add. Models with each combination of the five predictors (reexperiencing, avoidance, and hyperarousal symptoms, and adult and childhood trauma) were fit. The results from each model were examined to see if the additional predictors contributed to a model that better explained the variability of the fear outcome. Once candidate models were identified, the larger model was compared to the reduced model to determine if the additional covariates were necessary. Models needed to be nested, and the quantiles in the two models must be the same. A Wald test similar to ANOVA was used (Koenker & Bassett, 1982; Koenker, 2016; Davino et al., 2014). An F statistic compared whether the smaller model fit as well as the full model. Under H_0: All additional β's $= 0$ vs H_1: At least 1 of the additional β's $\neq 0$, with a statistically significant p-value indicating the additional predictors in the full model were necessary and that model was chosen. Otherwise, the reduced model was selected. For a given outcome, the models for the three quantiles were allowed to have different sets of predictors as the goal was to determine if a predictor was important across quantiles, and if so, to gain inference into how the effect of a predictor varied across quantiles. Finally, a multiple linear regression model was fit for each outcome to compare the results to those from the quantile regression models.

Statistical analysis was performed using R version 3.3.2 (R Core Team, 2016). The quantreg package version 5.29 was used to conduct quantile regression (Koenker, 2016).

3 Results

A total of 190 patients were included in the final dataset. Full Baseline Characteristics are displayed in Table 1. The mean age was 40.6 years (range 18-66 years old), and patients with PTSD were slightly older (41.1 years, SD = 11.1) on average than patients without PTSD (40.2 years, SE = 12.3). There were more females in the total sample (65.8%), with the PTSD group having a higher proportion of females (70.3%) than the group without PTSD (62.9%). A total of 74 patients met criteria for PTSD diagnosis. Adult trauma was associated with PTSD diagnosis ($p = 0.04$), as was childhood trauma ($p < .0001$). The mean score for reexperiencing, avoidance, and hyperarousal symptoms differed by PTSD diagnosis ($p < .0001$ for all).

Table 2 shows the mean startle response for each of the five fear outcomes by PTSD group, as well as results of the two sample t-tests. Figures 1 - 5 show scatter plots of PSS Total Scores with each fear outcome. For all fear outcomes, high startle responses are displayed by both PTSD and non-PTSD patients. The upper quantiles of the startle responses have larger variability than the middle quantiles showing the heterogeneous variance of startle responses across quantiles. Within the PTSD and non-PTSD groups, there was large variability for all of the fear outcomes. No difference in the mean startle response between PTSD and non-PTSD groups was found for any of the five fear outcomes (Danger Cue: p = 0.95, Safety Cue: p = 0.56, Early Extinction: p=0.72, Mid Extinction: p = 0.06, Late Extinction: p = 0.37).

3.1 Univariate Quantile Regression

The univariate quantile regression models displayed in Table 3 show the association between individual predictors and the startle response to the safety cue during fear acquisition. Without adjusting for any other covariates, gender was not associated with startle response at the 25^{th} quantile (p = .91). However, females exhibited a 6.84 (p = 0.02) point increase at the 50^{th} quantile, and a 26.42 (p = 0.004) point increase at the 75^{th} quantile compared to males. Additionally, while no association was found for the effect of reexperiencing symptoms at the 25^{th} (p = 0.85) or 50^{th} (p = 0.63) quantiles, at the 75^{th} quantile, higher symptoms were associated with a 2.63 (p = 0.02) point increase. In both cases, these results suggest that the association of gender and reexperiencing symptoms change across quantiles. Neither avoidance, hyperarousal or adult or childhood trauma were associated with startle response to the safety cue on their own.

Presented in Table 4 are results from the univariate quantile regression where the outcome was startle response to the danger cue during fear acquisition. The effect of gender was not significant at the 25^{th} (p = 0.21) and 50^{th} (p = 0.09) quantiles. At the 75^{th} quantile, the estimated gender difference increased to 33.32 (p = 0.002). All of the trauma and PTSD symptoms were non-significant at the 25^{th}, 50^{th}, and 75^{th} quantiles.

3.2 Multivariate Quantile Regression

3.2.1 Safety Cue

Parameter estimates for the parsimonious models are presented in Table 5. Figure 6 visually shows the value of the coefficient estimates as the quantiles change. Quantile regression produces an estimate for each parameter at each quantile, and by plotting them, we can see how these estimates are changing across quantiles. In Figure 6, the dots represent the parameter estimate at the 1^{st} through 99^{th} quantiles. The shaded area is the 95% confidence interval for that estimate. When the shaded area crosses the horizontal line, the estimate is not significantly different from 0 at that quantile. Each covariate included in the model has its own plot. For example, the estimates for gender are plotted in Figure 6a. At the lower quantiles, the coefficient estimates hug the horizontal line indicating that gender is not associated with startle response to the safety cue. However, the parameter estimates appear to increase as the quantile increases. At some quantiles, especially at and above the 75^{th} quantile, the shaded area is completely above 0, indicating that the startle response for females is significantly higher than males.

Parsimonious models for the safety cue did not find that additional predictors were meaningful at the 25^{th} or 50^{th} quantiles. However, for the 75^{th} quantile, reexperiencing and childhood trauma were added to age and gender, and all three models are shown in Table 5. Gender was not significantly different from 0 at the lower (p = 0.41) or middle (p = 0.06) quantiles, but it did increase to 27.31 (p=0.004) at the 75^{th} quantile. Figure 6a shows that the coefficient estimate for gender continues to increase above the 75^{th} quantile. Reexperiencing also demonstrates an increase at higher quantiles. Similar to gender, the plot for reexperiencing in Figure 6b shows that it is not significantly associated with startle response to the safety cue at low and middle quantiles. However, at the 75^{th} quantile, a one point increase in reexperiencing score is associated with a 2.39 ($p = 0.049$) point increase in the 75^{th} quantile of the safety cue. The absence of reexperiencing and childhood trauma in the model at the 25^{th} and 50^{th} quantiles suggests that the effect of these variables changes across quantiles. Even though gender was always kept in the model, Figure 6a demonstrates its pronounced increase with quantile level, τ.

The Type III test for the three-level categorical variable representing childhood trauma was significant ($p = 0.036$), indicating that not all coefficients for childhood trauma were equal to 0. However, pairwise tests were not significant. Patients who had experienced one type of trauma during childhood did not have a startle score that was significantly different from patients who had not experienced trauma during childhood ($p = 0.13$). This was also the case when comparing patients who had experienced two types of trauma with those who had experienced none ($p = 0.11$).

3.2.2 Danger Cue

Table 6 and Figure 7 contain parameter estimates and coefficient plots for the multivariate quantile regression models for the danger cue. Childhood trauma was the only additional predictor added to the 25^{th} quantile. No additional predictors were added to the 50^{th} quantile, and reexperiencing and hyperarousal were both added to the 75^{th} quantile. At the 25^{th} quantile, the overall test for childhood trauma was significant ($p = 0.048$), although the pairwise tests were not. Gender was not significant at lower ($p = 0.22$) or middle ($p = 0.10$) quantiles. It did have a strong effect at the 75^{th} quantile where females were found to have a difference score that was 30.53 ($p = 0.003$) points higher than males. Reexperiencing symptoms were not present in the model at lower and middle quantiles. From Figure 7c, the increase in the effect of reexperiencing is evident, and there was a strong effect of reexperiencing at upper quantiles. Also included at the 75^{th} quantile was hyperarousal symptoms where a one point increase in hyperarousal symptom severity was associated with a 3.03 (p = 0.028) decrease in difference score. Figure 7 displays the noticeable change in the effect of gender, reexperiencing, and hyperarousal. None of these variables were significantly different from zero at lower and middle quantiles. However, the association changed at the higher quantiles.

The results from multiple linear regression models are displayed in Tables 7 and 8. For the safety cue, the multiple linear regression model contained the same covariates as the quantile regression model for the 75^{th} quantile. What's noticeable is the difference in magnitude of the parameter estimates between the two models. MLR estimated that the effect of gender on the mean startle response to the safety cue was 15.87 (p = 0.014). The quantile regression model estimated a much larger effect (27.31, p = 0.004) for females at the 75^{th} quantile.

When looking at the two models for the danger cue, (Tables 6 and 8) its important to note the absence of hyperarousal from the MLR model. From the coefficient plot for hyperarousal in Figure 7d, it is evident that the effect of hyperarousal was minimal until the upper quantiles. Therefore, it is not surprising that hyperarousal would be absent from a linear regression model as it is unlikely to exert any effect on the mean startle reaction. In this instance, quantile regression was able to pick up on the effect of hyperarousal by taking into account the covariate effects on the 75^{th} quantile of the outcome.

4 Discussion

Previous studies have noted that PTSD patients showed a heightened fear response to the safety cue in addition to the danger cue, as demonstrated in a study of veterans (Grillon & Morgan, 1999). In a study of civilians where PTSD symptoms were categorized as high or low, patients exhibiting low symptoms responded similarly to controls, while high symptom patients had fear responses to the safety cue that were not significantly different from their responses to the danger cue (Norrholm et al., 2011). The findings in this analysis add credence to prior results, especially the effect of reexperiencing symptoms which was highlighted by Norrholm et al., 2011. The use of quantile regression in this thesis enabled us to detect and demonstrate the varying effect of covariates. At upper quantiles, the magnitude of the effect of gender and reexperiencing symptoms was greatest. This goes beyond the multiple linear regression analysis which is limited to evaluating covariate effects on the mean outcome.

Interestingly, the effect of childhood abuse on the safety cue, and avoidance on the danger cue were negative. This seems counter intuitive as one would think that experiencing child abuse, or having higher PTSD symptoms would cause startle response to increase. It is not completely understood why this effect may be present. A previous study found childhood abuse was associated with an increase in startle response (Jovanovic, Blanding, et al., 2009). In a study focusing on environmental factors that contribute to PTSD, childhood and adult trauma were both identified as contributing to an increase in the overall PSS Total Score (Gillespie et al., 2009). As the number of childhood or adult trauma experienced increased, the PSS Total Score also increased. However, exposure to more traumatic events also incurs more stress on the body. In the case of PTSD, reminders of the event, such as visual cues, can turn innocuous situations into stressful events. The body handles these situations by producing hormones such as cortisol, but the constant stress and necessity for the body to combat new situations can lead the body to react differently causing a blunting of the stress response (B. A. van Der Kolk & Saporta, 1991). The decrease in the difference in startle reaction could be a product of this blunting effect.

Also of note is the negative effect of higher avoidance symptoms. Higher avoidance symptom severity is associated with a decrease in the difference score for the danger cue at the 75^{th} quantile. The startle responses are calculated as a difference score by subtracting the mean of the baseline scores from the mean of the scores for the conditioned stimuli. Because of this, baseline scores and fear responses to each cue are not explicitly known. Therefore, a larger difference score doesn't necessarily mean that the fear expression was greater, simply that there was a greater difference between the fear response to the baseline and conditioned stimuli. While it is possible that patients with higher hyperarousal symptom scores had lower fear potentiation scores, it is also possible that it wasn't their fear response to the conditioned stimuli that was high, but rather their response to the baseline noise only probe. It is also a possibility that patients with higher hyperarousal scores had fear responses equivalent to those without heightened hyperarousal symptoms. In this situation, if hyperarousal was associated with increased baseline scores, then the estimated effect of hyperarousal symptoms would be negative and it would appear that hyperarousal was protective. This example does not capture what effect hyperarousal symptoms have on patient's fear responses to the danger cue, but it is illustrative that the difference score does not provide any information on the patient's baseline score, or the score in response to the conditioned stimuli.

As previously mentioned, a limitation of this study was the inability to specifically know the baseline and visual cue startle response. In addition, the cross-sectional study design makes it impossible to know whether the startle response precedes or follows the traumatic experience or PTSD diagnosis. Furthermore, while the the TEI and PSS assessments are widely used, they were all self reported and contingent on how patients perceived their own experiences. Finally, this analysis treated each fear variable as an individual outcome. As measurements were taking on the same individual over a series of trials, the fear responses are correlated. A future analysis could build on this one by using a statistical method that takes the correlated fear responses into account.

5 Conclusion

Our analysis using quantile regression revealed that gender and reexperiencing symptoms had a heterogeneous association with the startle response to the danger and safety cues. While gender and reexperiencing symptoms have been previously identified as important to the study of fear potentiated startle, this analysis demonstrated that the effect of these covariates on startle response to the safety and danger cues becomes more prominent at the higher quantiles. Future studies may consider focusing on patients with high startle responses to the danger and safety cues.

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Table 1: Baseline Characteristics of Subjects

Variable	Total (n = 190)	PTSD (n = 74)	Non-PTSD (n = 116)	Test Statistic (p-value)
Age [a]	40.6 (11.8)	41.1 (11.1)	40.2 (12.3)	-0.5 (0.63)
Gender (Female) [b]	125 (65.8%)	52 (70.3%)	73 (62.9%)	1.1 (0.3)
Adult Trauma [b]				8.5 (0.04)
None	16 (8.4%)	3 (4.1%)	13 (11.2%)	
Non-Interpersonal	16 (8.4%)	3 (4.1%)	13 (11.2%)	
Interpersonal Only	10 (5.3%)	1 (1.4%)	9 (7.8%)	
Both	83 (43.7%)	39 (52.7%)	44 (37.9%)	
Childhood Trauma [b]				24.9 (< .0001)
0 Types of Childhood Trauma	110 (57.9%)	27 (36.5%)	83 (71.6%)	
1 Type of Childhood Trauma	56 (29.5%)	30 (40.5%)	26 (22.4%)	
2 Types of Childhood Trauma	24 (12.6%)	17 (23%)	7 (6%)	
PTSD Symptoms				
Reexperiencing [a]	3.8 (3.9)	6.8 (3.6)	1.9 (2.6)	-9.9 (< .0001)
Avoidance [a]	6.2 (5.6)	11.3 (4.4)	3 (3.6)	-13.6 (< .0001)
Hyperarousal [a]	5.4 (4.6)	9.2 (3.6)	3 (3.3)	-12.1 (< .0001)

[a] Mean (SD) Two-sample t-test, [b] Frequency (%) χ^2 test

Table 2: Fear Outcomes by PTSD Group

Variable	Total (n = 190)	PTSD (n = 74)	Non-PTSD (n = 116)	Test Statistic (p)
Fear Acquisition				
Danger Cue	36.9 (60.9)	37.2 (65.1)	36.6 (58.3)	-0.1 (0.95)
Safety Cue	16.7 (41.7)	18.9 (41.3)	15.3 (42.1)	-0.6 (0.56)
Fear Extinction				
Early	44.5 (60.2)	46.4 (60.2)	43.2 (60.4)	-0.4 (0.72)
Mid	18.4 (39.7)	25.7 (45.3)	13.8 (35.1)	-1.9 (0.06)
Late	1.7 (27.3)	3.9 (26.2)	0.3 (28)	-0.9 (0.37)

Mean (SD) Two-sample t-test

Table 3: Univariate Models for Safety Cue using Quantile Regression

Variable	Quantile 25% Estimate (SE)	p	Quantile 50% Estimate (SE)	p	Quantile 75% Estimate (SE)	p
Age	0.01 (0.12)	0.93	-0.22 (0.13)	0.07	-0.4 (0.39)	0.27
Gender Female (vs Male)	0.3 (2.73)	0.91	6.84 (2.58)	0.02	26.42 (8.13)	0.004
Adult Trauma						
None (Reference Group)	-	-	-	-	-	-
Non-Interpersonal Only	7.84 (5.63)	0.33	5.99 (5.4)	0.41	12.52 (21.91)	0.64
Interpersonal Only	-4.01 (10.53)	0.7	5.59 (11.6)	0.56	5.36 (25.98)	0.84
Both	5.76 (5.95)	0.42	0.82 (5.79)	0.9	3.08 (21.43)	0.89
Childhood Trauma						
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-
1 Type of Childhood Trauma	-4.19 (4.09)	0.25	-4.78 (3.74)	0.2	-3.02 (11.23)	0.79
2 Types of Childhood Trauma	-1.06 (4.29)	0.77	-1.96 (5.43)	0.74	-0.34 (14.77)	0.98
PTSD Symptoms						
Reexperiencing	0.06 (0.31)	0.85	0.28 (0.54)	0.63	2.63 (1.17)	0.02
Avoidance	-0.12 (0.2)	0.57	-0.29 (0.3)	0.33	1.14 (0.66)	0.15
Hyperarousal	0.17 (0.27)	0.57	0.25 (0.49)	0.64	1.19 (0.67)	0.1

Univariate Quantile Regression Models were fit with the Safety Cue as the outcome for each predictor at the 25^{th}, 50^{th}, and 75^{th} quantiles.

Table 4: Univariate Models for the Danger Cue using Quantile Regression

Variable	Quantile					
	25%		50%		75%	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Age	-0.21 (0.16)	0.17	-0.66 (0.2)	0.002	-0.49 (0.67)	0.42
Gender Female (vs Male)	3.22 (2.32)	0.21	14.13 (7.67)	0.09	33.32 (9.44)	0.002
Adult Trauma						
None (Reference Group)	-	-	-	-	-	-
Non-Interpersonal Trauma Only	-2.3 (5.3)	0.62	8.43 (20.28)	0.7	-0.28 (29.1)	0.99
Interpersonal Trauma Only	-10.33 (16.79)	0.6	4.9 (25.52)	0.84	-23.95 (27.97)	0.4
Both	-4.93 (6.23)	0.37	1.76 (17.94)	0.93	-11.36 (27.14)	0.68
Childhood Trauma						
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-
1 Type of Childhood Trauma	-4.14 (2.38)	0.21	-10.51 (10.4)	0.28	-3.59 (18.76)	0.84
2 Types of Childhood Trauma	-2.48 (4.79)	0.68	-10.65 (9.47)	0.21	-17.76 (23.99)	0.48
PTSD Symptom Categories						
Reexperiencing	0.04 (0.4)	0.92	2.28 (1.5)	0.11	2.58 (1.95)	0.13
Avoidance	-0.23 (0.23)	0.3	-0.22 (0.76)	0.75	0.76 (1.19)	0.56
Hyperarousal	-0.35 (0.29)	0.27	-0.31 (0.74)	0.65	1.02 (1.64)	0.51

Univariate Quantile Regression Models were fit with the Danger Cue as the outcome for each predictor at the 25^{th}, 50^{th}, and 75^{th} quantiles.

Table 5: Multivariate Models for the Safety Cue using Quantile Regression

Covariates	Quantile 0.25 Estimate	0.25 SE	0.25 p	0.5 Estimate	0.5 SE	0.5 p	0.75 Estimate	0.75 SE	0.75 p
Age	-0.092	0.133	0.491	-0.195	0.161	0.229	-0.046	0.292	0.874
Gender Female (vs Male)	2.232	2.675	0.405	6.206	3.236	0.057	27.305	9.327	0.004
Reexperiencing	-	-	-	-	-	-	2.394	1.207	0.049
Childhood Trauma*									
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-	-	-	-
1 Type of Childhood Trauma	-	-	-	-	-	-	-12.198	7.919	0.125
2 Types of Childhood Trauma	-	-	-	-	-	-	-21.136	12.989	0.105

Multivariate Quantile Regression Models were fit individually for the 25^{th}, 50^{th}, and 75^{th} quantiles. A dash (-) indicates that a particular variable was not included in the model at that quantile.

$Q_{0.25} = -0.092 * age + 2.232 * gender$

$Q_{0.5} = -0.195 * age + 6.206 * gender$

$Q_{0.75} = -0.046 * age + 27.305 * gender + 2.394 * Reexperiencing - 12.198*$(1 Type of Childhood Trauma Experienced)$-21.136*$(2 Types of Childhood Trauma Experienced)

* The p-value for the Type III test comparing the current model to a model without childhood trauma was 0.036. This test was used to determine if the two coefficients for the childhood trauma groups in the larger model were jointly equal to 0. Additional pairwise tests were conducted against the reference group of no childhood trauma and are included in the table.

Table 6: Multivariate Models for the Danger Cue using Quantile Regression

Covariates	Quantile								
	0.25			0.5			0.75		
	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Age	-0.221	0.172	0.201	-0.720	0.243	0.003	-0.756	0.396	0.058
Gender Female (vs Male)	3.704	2.979	0.215	10.970	6.629	0.100	30.525	9.959	0.003
Reexperiencing	-	-	-	-	-	-	4.265	1.540	0.006
Hyperarousal	-	-	-	-	-	-	-3.025	1.362	0.028
Childhood Trauma*									
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-	-	-	-
1 Type of Childhood Trauma	-5.148	4.022	0.202	-	-	-	-	-	-
2 Types of Childhood Trauma	-10.110	6.991	0.150	-	-	-	-	-	-

Multivariate Quantile Regression Models were fit individually for the 25^{th}, 50^{th}, and 75^{th} quantiles. A dash (-) indicates that a particular variable was not included in the model at that quantile.

$Q_{0.25} = -0.221 * age + 3.704 * gender - 5.148 *$(1 Type of Childhood Trauma Experienced)$-10.110*$(2 Types of Childhood Trauma Experienced)

$Q_{0.5} = -0.720 * age + 10.970 * gender$

$Q_{0.75} = -0.756 * age + 30.525 * gender + 4.265 * Reexperiencing - 3.025 * Hyperarousal$

* The p-value corresponding to the Type III test comparing the current model to a smaller model without childhood trauma was 0.048. This test was used to determine if the two coefficients for the childhood trauma groups in the larger model were jointly equal to 0. Additional pairwise tests were conducted against the reference group of no childhood trauma and are included in the table.

Table 7: Multiple Linear Regression Model for the Safety Cue

Covariates	Estimate	SE	p
Age	0.025	0.254	0.923
Gender Female (vs Male)	15.856	6.377	0.014
Reexperiencing	1.670	0.807	0.040
Childhood Trauma*			
0 Types of Childhood Trauma (Reference Group)	-	-	-
1 Type of Childhood Trauma	-15.542	6.830	0.024
2 Types of Childhood Trauma	-12.897	9.649	0.183

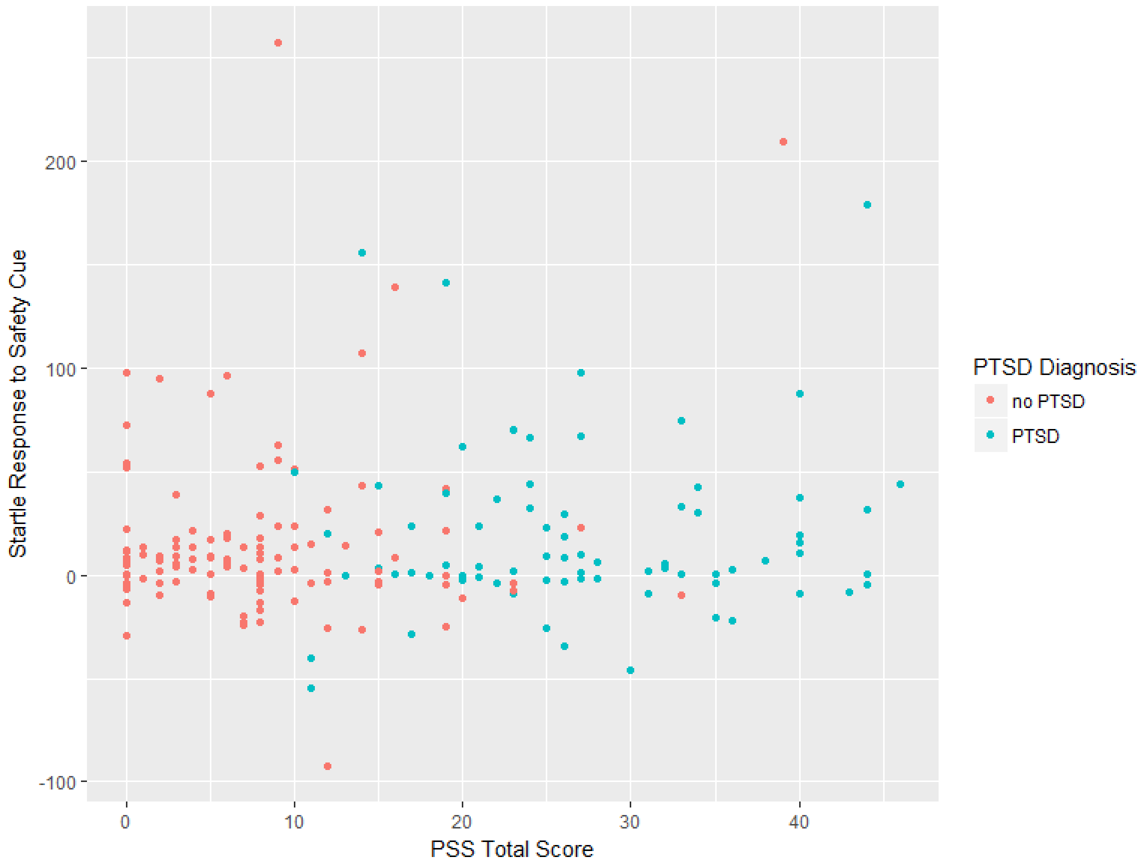
Multiple Linear Regression Model for the Safety Cue Outcome during Fear Acquisition.
$E(y) = 0.025 * Age + 15.856 * Gender + 1.670 * Reexperiencing - 15.542*$(1 Type of Childhood Trauma Experienced)$-12.897*$(2 Types of Childhood Trauma Experienced)
* The p-value corresponding to an ANOVA test comparing nested models with and without childhood trauma is 0.060

Table 8: Multiple Linear Regression Model for the Danger Cue

Covariates	Estimate	SE	p
Age	-0.438	0.373	0.242
Gender Female (vs Male)	16.889	9.353	0.073
Reexperiencing	2.447	1.183	0.040
Childhood Trauma *			
0 Types of Childhood Trauma (Reference Group)	-	-	-
1 Type of Childhood Trauma	-16.529	10.018	0.101
2 Types of Childhood Trauma	-27.378	14.153	0.055

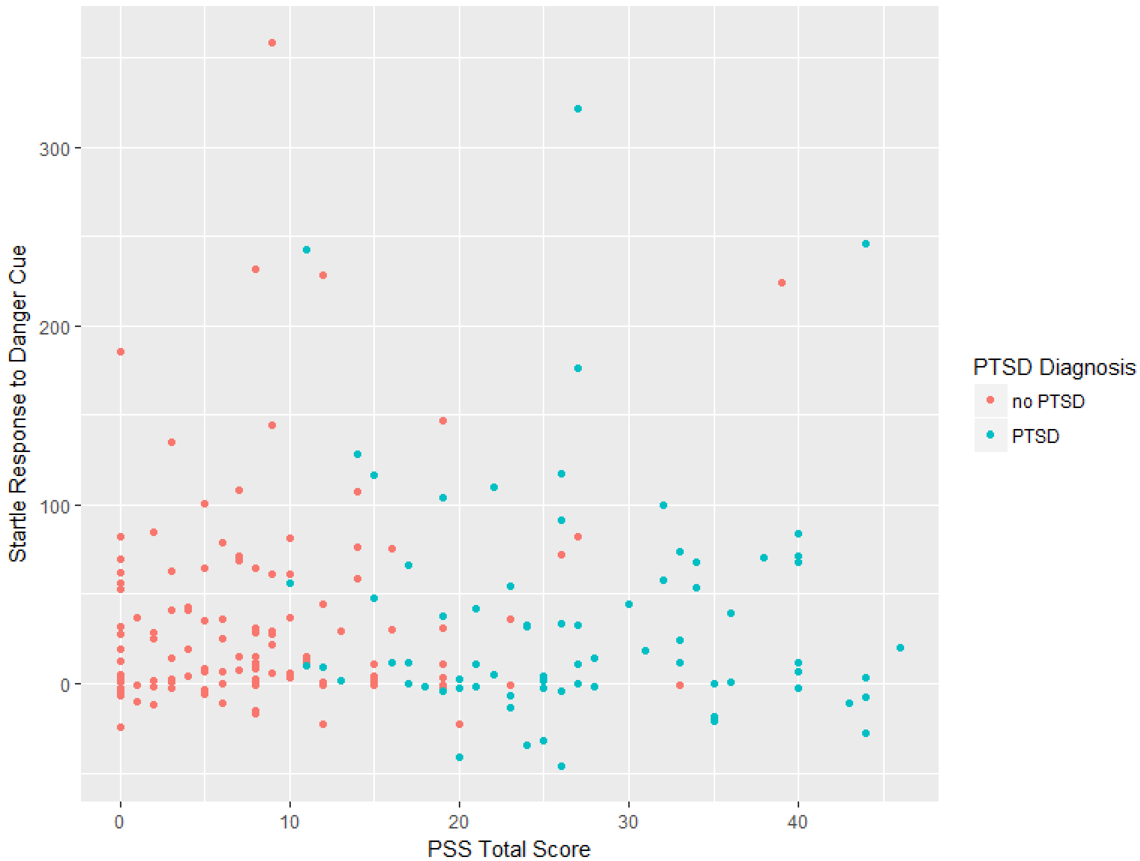
Multiple Linear Regression Model for the Danger Cue Outcome during Fear Acquisition.
$E(y) = -0.438 * Age + 16.889 * Gender + 2.447 * Reexperiencing - 16.529*$(1 Type of Childhood Trauma Experienced)$-27.378*$(2 Types of Childhood Trauma Experienced)
* The p-value corresponding to an ANOVA test comparing nested models with and without childhood trauma is 0.082.

Figure 1: Scatter Plot of PSS Score and Startle Response to the Safety Cue



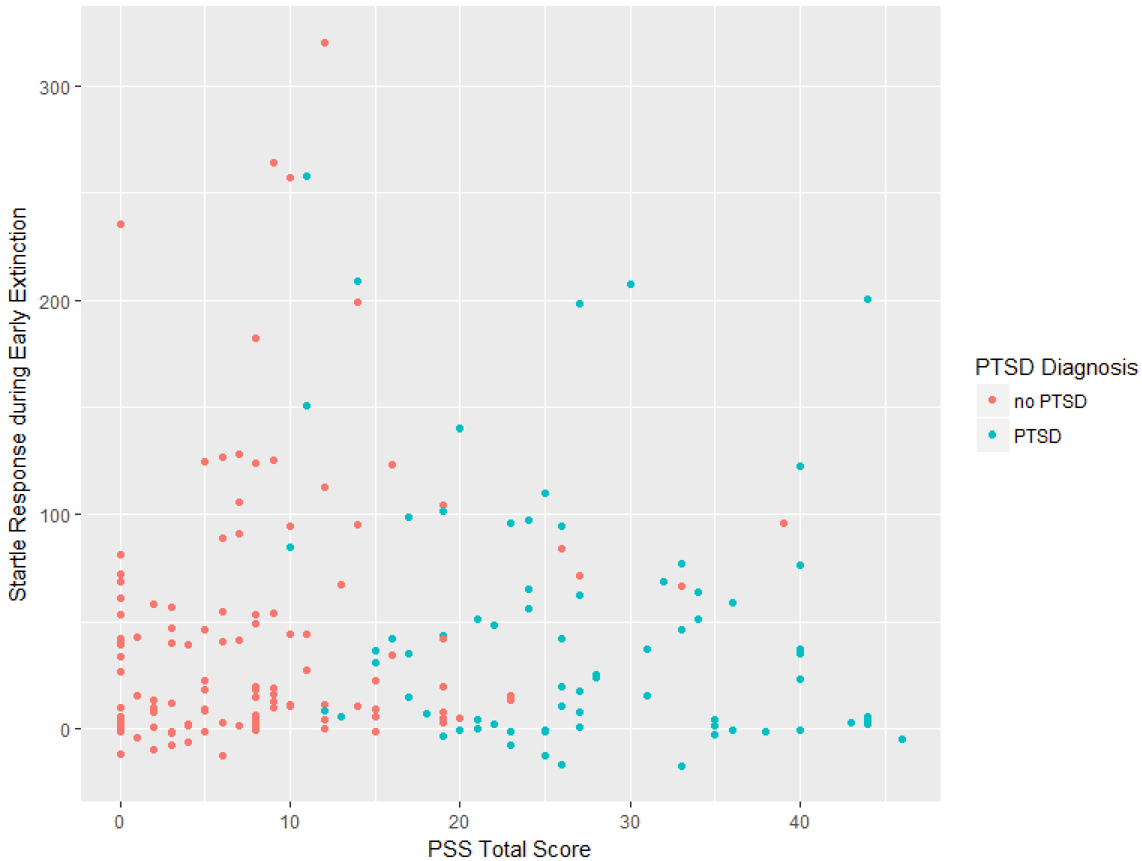
Plot of the distribution of startle responses to the Safety Cue by PSS Total Score. PTSD diagnosis is based on the PSS score, so patients with PTSD have higher PSS scores. However, high startle responses are exhibited by patients in both groups.

Figure 2: Scatter Plot of PSS Score and Startle Response to the Danger Cue



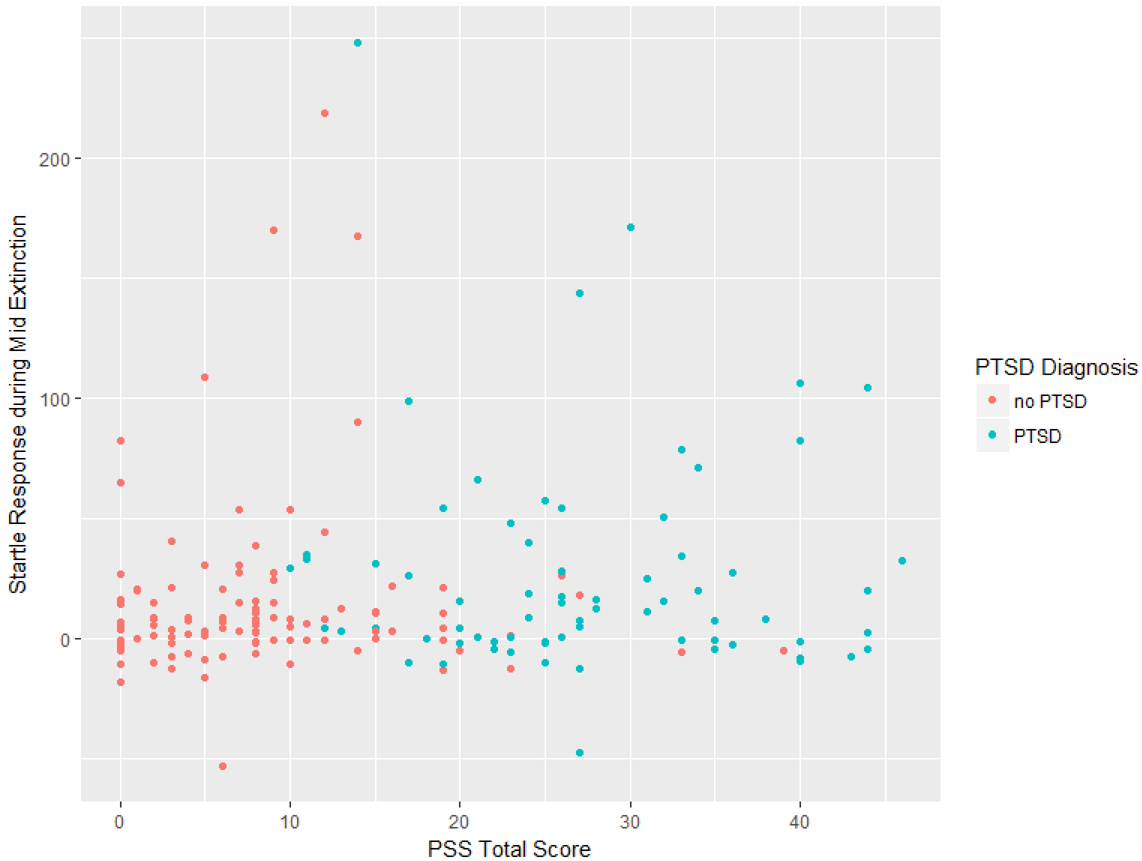
Plot of the distribution of startle responses to the Danger Cue by PSS Total Score. PTSD diagnosis is based on the PSS score, so patients with PTSD have higher PSS scores. However, high startle responses are exhibited by patients in both groups.

Figure 3: Scatter Plot of PSS Score and Startle Response during Early Extinction



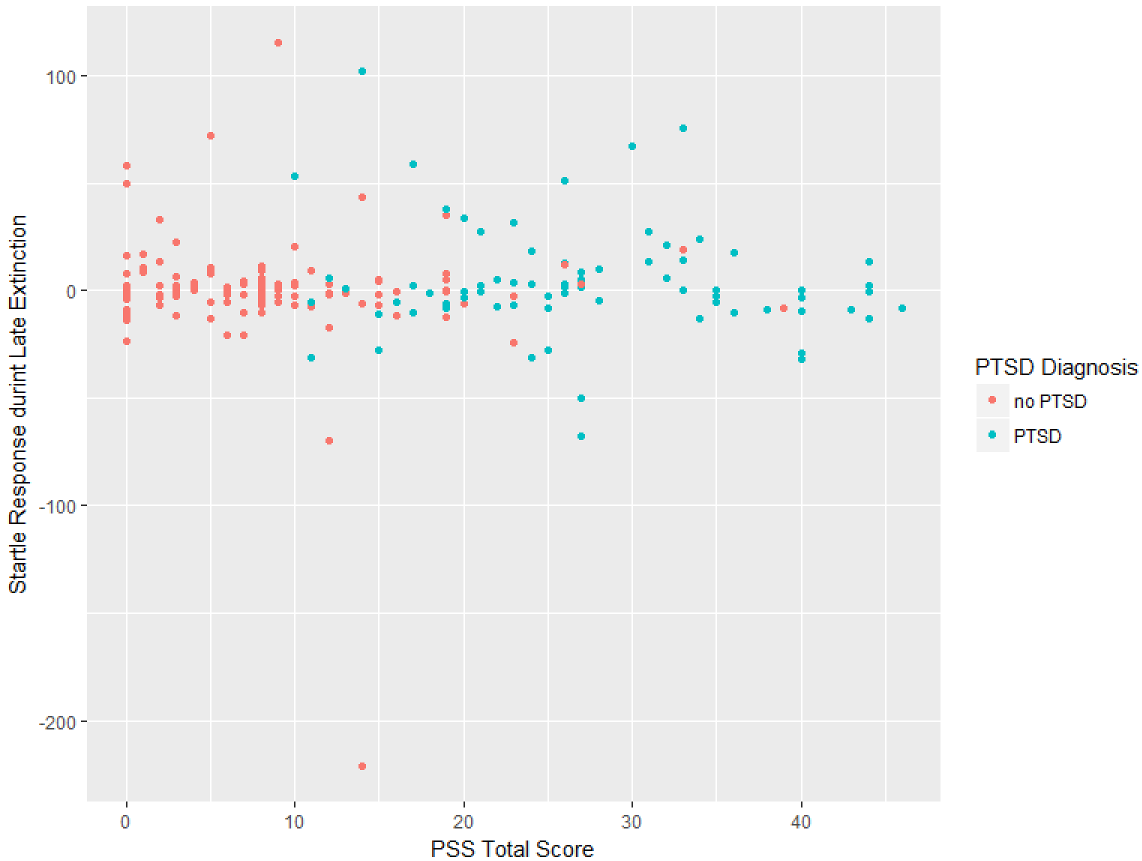
Plot of the distribution of startle responses during Early Extinction by PSS Total Score. PTSD diagnosis is based on the PSS score, so patients with PTSD have higher PSS scores. However, high startle responses are exhibited by patients in both groups.

Figure 4: Scatter Plot of PSS Score and Startle Response during Mid Extinction



Plot of the distribution of startle responses during Mid Extinction by PSS Total Score. PTSD diagnosis is based on the PSS score, so patients with PTSD have higher PSS scores. However, high startle responses are exhibited by patients in both groups.

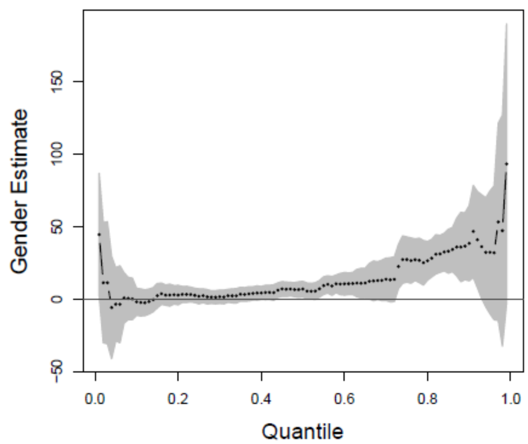
Figure 5: Scatter Plot of PSS Score and Startle Response during Late Extinction



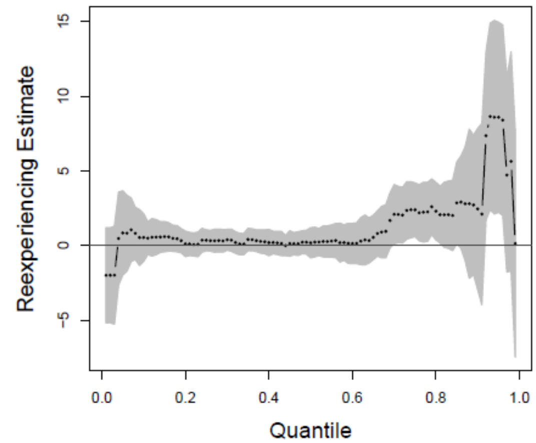
Plot of the distribution of startle responses during Late Extinction by PSS Total Score. PTSD diagnosis is based on the PSS score, so patients with PTSD have higher PSS scores. However, in both groups, most patients have extinguished fear.

Figure 6: Plot of Coefficient Estimates for a Quantile Regression Model for the Safety Cue

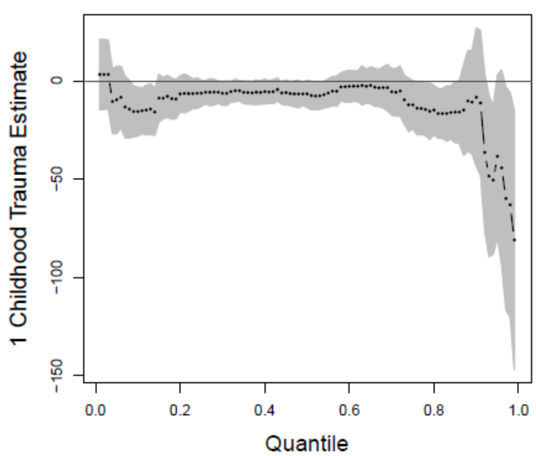
(a) Gender (Female)



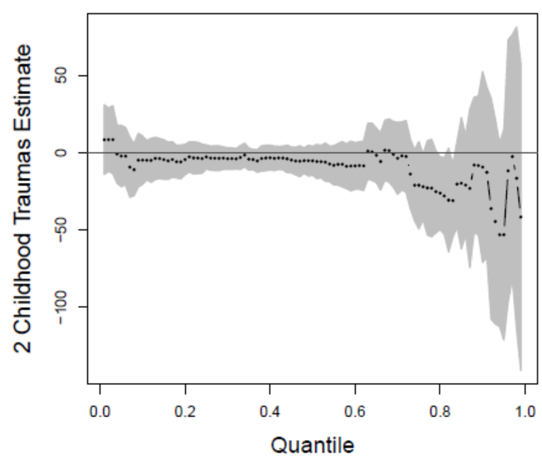
(b) Reexperiencing Symptoms



(c) 1 Type of Childhood Trauma Experienced*



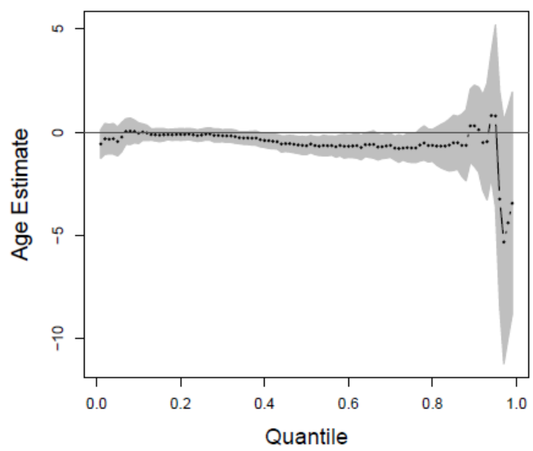
(d) 2 Types of Childhood Trauma Experienced*



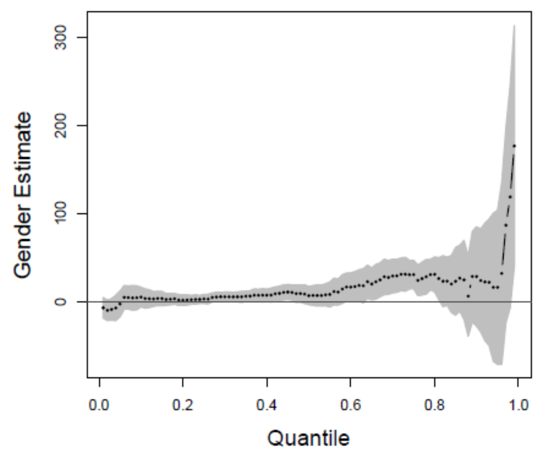
Plots of the coefficient estimates and 95% Confidence Intervals for each covariate in the Multivariate Quantile Regression Model show how the effects of covariates are changing across quantiles. Parameter Estimates and Standard Errors were calculated for each of the 1^{st} through 99^{th} quantile. The black dots correspond to estimates and the shaded gray area represents the 95% CI. For example, 6a shows the estimates for gender. At the lower quantiles, gender is not significantly different from zero as evident by the confidence intervals crossing zero. As the quantiles increase, the effect of gender also increases and at quantiles where the shaded area is entirely above zero, the effect of gender is statistically significant.
*Childhood Trauma is a 3-level categorical variable. The reference group is 0 types of childhood trauma experienced. The plots displayed in Figures 6c and 6d are coefficient estimates for the pairwise comparisons to the reference group.
Age was also included in the model but is not displayed here.

Figure 7: Plot of Coefficient Estimates for a Quantile Regression Model for the Danger Cue

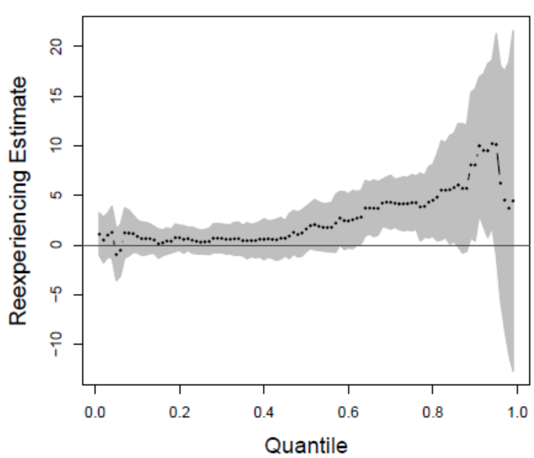
(a) Age



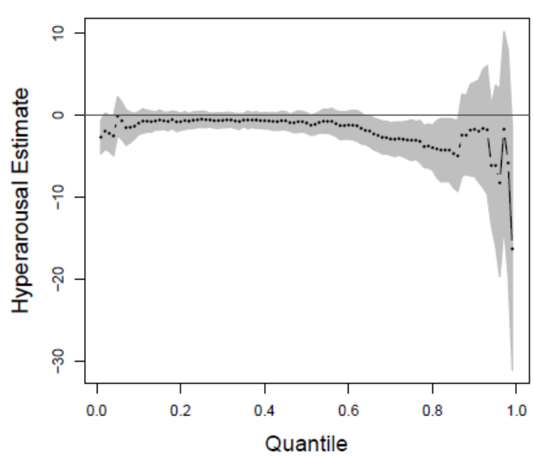
(b) Gender (Female)



(c) Reexperiencing Symptoms



(d) Hyperarousal Symptoms



Plots of the coefficient estimates and 95% Confidence Intervals for each covariate in the Multivariate Quantile Regression Model show how the effects of covariates are changing across quantiles. Parameter Estimates and Standard Errors were calculated for each of the 1^{st} through 99^{th} quantile. The black dots correspond to estimates and the shaded gray area represents the 95% CI. For example, 7c shows the estimates for reexperiencing symptoms. At the lower quantiles, reexperiencing is not significantly different from zero as evident by the confidence intervals crossing zero. As the quantiles increase, the effect of reexperiencing also increases and at quantiles where the shaded area is entirely above zero, the effect of reexperiencing is statistically significant.

Appendix

Table 9: Univariate Association with Fear Outcomes

	Fear Acquisition		Fear Extinction		
Variable	Safety Cue	Danger Cue	Early	Mid	Late
Age [a]	-0.11 (0.12)	-0.17 (0.02)	-0.2 (0.01)	-0.09 (0.21)	0.08 (0.3)
Gender (Female) [b]	3127 (0.01)	3201 (0.02)	3078 (0.01)	3544 (0.15)	4118 (0.88)
Adult Trauma [c]	3.86 (0.28)	2.66 (0.45)	6.44 (0.09)	1.69 (0.64)	5.14 (0.16)
Childhood Trauma [c]	3.41 (0.18)	4.15 (0.13)	0.72 (0.7)	1.5 (0.47)	0.01 (0.99)
PTSD Symptoms					
Reexperiencing [a]	0.08 (0.25)	0.11 (0.12)	0.15 (0.04)	0.18 (0.01)	-0.02 (0.8)
Avoidance [a]	-0.01 (0.94)	-0.02 (0.75)	0.03 (0.67)	0.07 (0.31)	-0.01 (0.84)
Hyperarousal [a]	0.08 (0.26)	-0.03 (0.66)	-0.002 (0.98)	0.06 (0.4)	-0.06 (0.44)

[a] - Spearman Rank Correlation Coefficient (p), [b] - Wilcoxon Rank Sum (p), [c] - Kruskal-Wallis Rank Sum (p)

Table 10: Univariate Models for Early Fear Extinction using Quantile Regression

Variable	Quantile 25% Estimate (SE)	p	50% Estimate (SE)	p	75% Estimate (SE)	p
Age	-0.32 (0.1)	0.008	-0.93 (0.33)	0.002	-0.71 (0.47)	0.13
Gender (Female)	5.83 (2.32)	0.01	27.08 (8.81)	0.0003	26.67 (16.37)	0.07
Adult Trauma						
None (Reference Group)	-	-	-	-	-	-
Non-Interpersonal Trauma Only	-4.42 (7.19)	0.52	-5.98 (18.27)	0.75	6.3 (28.45)	0.84
Interpersonal Trauma Only	2.83 (20.9)	0.89	1.44 (36.29)	0.97	63.07 (46.84)	0.23
Both	-7.71 (5.43)	0.26	-27.88 (19.12)	0.11	-18.68 (28.35)	0.52
Childhood Trauma						
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-
1 Type of Childhood Trauma	2.94 (3.11)	0.38	3.89 (10.47)	0.75	7.75 (18.04)	0.66
2 Types of Childhood Trauma	-0.53 (4.42)	0.91	5.06 (14.5)	0.71	-9.48 (17.54)	0.65
PTSD Symptoms						
Reexperiencing	0.2 (0.57)	0.74	3.2 (1.45)	0.03	1.78 (1.1)	0.15
Avoidance	-0.11 (0.16)	0.47	0.24 (1.2)	0.84	1.05 (1.56)	0.51
Hyperarousal	-0.08 (0.24)	0.77	0.36 (1.11)	0.74	0.71 (1.2)	0.59

Parameter Estimates for each covariate based on estimates from Univariate Quantile Regression models for Early Fear Extinction at the 25^{th}, 50^{th}, and 75^{th} quantiles

Table 11: Univariate Models for Mid Fear Extinction using Quantile Regression

Variable	Quantile					
	25%		50%		75%	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Age	-0.02 (0.05)	0.65	-0.15 (0.13)	0.26	-0.3 (0.3)	0.35
Gender (Female)	0.75 (1.23)	0.52	3.71 (2.96)	0.17	11.75 (5.39)	0.02
Adult Trauma						
None (Reference Group)	-	-	-	-	-	-
Non-Interpersonal Trauma Only	0.08 (3.56)	0.98	1.94 (7.22)	0.76	5.21 (12.77)	0.65
Interpersonal Trauma Only	1.36 (6.45)	0.85	0.92 (7.99)	0.92	-5.66 (14.5)	0.69
Both	0.07 (3.24)	0.99	-2.5 (5.38)	0.69	-0.42 (13.58)	0.97
Childhood Trauma						
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-
1 Type of Childhood Trauma	0.17 (1.33)	0.91	1.7 (3.34)	0.56	4.55 (7.78)	0.6
2 Types of Childhood Trauma	-3.63 (2.09)	0.12	1.78 (5.36)	0.75	-6.06 (6.8)	0.41
PTSD Symptoms						
Reexperiencing	-0.02 (0.24)	0.93	1.12 (0.67)	0.1	2.82 (1.4)	0.04
Avoidance	-0.04 (0.14)	0.76	0.16 (0.38)	0.65	0.66 (1.03)	0.58
Hyperarousal	-0.03 (0.16)	0.86	0.38 (0.39)	0.36	1.16 (0.71)	0.08

Parameter Estimates for each covariate based on estimates from Univariate Quantile Regression models for Mid Fear Extinction at the 25^{th}, 50^{th}, and 75^{th} quantiles

Table 12: Univariate Models for Late Fear Extinction using Quantile Regression

Variable	Quantile					
	25%		50%		75%	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Age	0.09 (0.08)	0.24	-0.01 (0.07)	0.81	-0.01 (0.13)	0.95
Gender (Female)	-1.35 (2.03)	0.47	-0.72 (1.19)	0.52	2.73 (3.19)	0.41
Adult Trauma						
None (Reference Group)	-	-	-	-	-	-
Non-Interpersonal Trauma Only	-0.14 (3.28)	0.96	0.18 (3.71)	0.96	5.52 (6)	0.61
Interpersonal Trauma Only	-5.46 (6.16)	0.34	1.79 (6.35)	0.79	-3.23 (10.11)	0.73
Both	-0.92 (3.24)	0.76	-1.23 (3.46)	0.73	-5.44 (7.86)	0.39
Childhood Trauma						
0 Types of Childhood Trauma (Reference Group)	-	-	-	-	-	-
1 Type of Childhood Trauma	0.31 (2.59)	0.88	0.72 (1.54)	0.65	0.15 (3.08)	0.96
2 Types of Chidhood Trauma	-1.68 (2.85)	0.55	-0.82 (3)	0.8	8.17 (7.05)	0.28
PTSD Symptoms						
Reexperiencing	-0.37 (0.22)	0.19	-0.03 (0.2)	0.89	0.71 (0.52)	0.16
Avoidance	-0.23 (0.12)	0.06	-0.11 (0.13)	0.41	0.31 (0.42)	0.48
Hyperarousal	-0.31 (0.2)	0.16	-0.08 (0.17)	0.6	0.31 (0.48)	0.54

Parameter Estimates for each covariate based on estimates from Univariate Quantile Regression models for Late Fear Extinction at the 25^{th}, 50^{th}, and 75^{th} quantiles

Table 13: Multivariate Models for Early Fear Extinction using Quantile Regression

Covariates	Quantile								
	0.25			0.5			0.75		
	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Age	-0.215	0.107	0.047	-0.806	0.289	0.006	-0.630	0.546	0.250
Gender Female (vs Male)	3.694	2.958	0.213	20.899	6.425	0.001	27.931	15.584	0.075

Multivariate Regression Models were fit individually for the 25^{th}, 50^{th}, and 75^{th} quantiles.

$Q_{0.25} = -0.215 * age + 3.694 * gender$

$Q_{0.5} = -0.806 * age + 20.899 * gender$

$Q_{0.75} = -0.630 * age + 27.931 * gender$

Table 14: Multivariate Models for Mid Fear Extinction using Quantile Regression

Covariates	Quantile								
	0.25			0.5			0.75		
	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Age	-0.011	0.063	0.862	-0.206	0.138	0.138	-0.466	0.260	0.075
Gender Female (vs Male)	0.669	1.286	0.604	4.452	3.079	0.150	3.687	6.444	0.568
Reexperiencing	-	-	-	-	-	-	2.735	1.596	0.088

Multivariate Regression Models were fit individually for the 25^{th}, 50^{th}, and 75^{th} quantiles. A dash (-) indicates that a particular variable was not included in the model at that quantile.

$Q_{0.25} = -0.011 * age + 0.669 * gender$

$Q_{0.5} = -0.206 * age + 4.452 * gender$

$Q_{0.75} = -0.466 * age + 3.687 * gender + 2.735 * Reexperiencing$

Table 15: Multivariate Models for Late Fear Extinction using Quantile Regression

Covariates	Quantile 0.25 Estimate	SE	p	0.5 Estimate	SE	p	0.75 Estimate	SE	p
Age	0.139	0.071	0.053	-0.012	0.068	0.861	-0.012	0.145	0.936
Gender Female (vs Male)	-0.278	1.671	0.868	-0.735	1.369	0.592	2.743	3.429	0.425
Avoidance	-0.340	0.133	0.011	-	-	-	-	-	-

Multivariate Regression Models were fit individually for the 25^{th}, 50^{th}, and 75^{th} quantiles. A dash (-) indicates that a particular variable was not included in the model at that quantile.

$Q_{0.25} = 0.139 * age - 0.278 * gender - 0.340 * Avoidance$

$Q_{0.5} = -0.012 * age - 0.735 * gender$

$Q_{0.75} = -0.012 * age + 2.743 * gender$