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Startle Response in Women with the FMR1 Premutation and Risk for Anxiety Disorders

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STARTLE RESPONSE IN WOMEN WITH THE *FMR1* PREMUTATION AND RISK FOR ANXIETY DISORDERS

By

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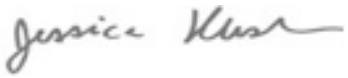

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Abstract:

Background: The *FMR1* premutation, which occurs when there is an expansion of 55 - 200 repeats of the CGG trinucleotide on the *FMR1* gene, is associated with an increased risk for anxiety disorders. Indices of autonomic regulation may prove to be useful biomarkers for psychopathological risk, including stress and anxiety. In the general population, diminished habituation to a startle response is linked to a variety of psychological disorders, including anxiety, yet little is known about this relationship in those with the *FMR1* premutation. Given the increased risk for anxiety in those with the *FMR1* premutation, the present study aims to examine the relationship between the startle response and psychiatric vulnerability. Research Questions: (1) Is there a difference among women the *FMR1* premutation and control women regarding habituation when taking into account various cardiac indicators? (2) Are any of the cardiac indicators of the initial startle probe associated with the severity of generalized anxiety symptoms in women with the *FMR1* premutation? Methods: Participants included 31 women with the *FMR1* premutation and 16 neurotypical control women aged 35-75 years. Participants completed a startle probe task in which they were exposed to 10 pure tone auditory probes through headphones. Participant's heart activity was recorded for the duration of the task. Participants also filled out the Beck Anxiety Inventory, which is a self-reported questionnaire that indicates current anxiety symptoms. Results: Parasympathetic reactivation was found to be significant with a main effect of group (F [1, 34] = 5.47, p = 0.025), in which the control had higher parasympathetic reactivation. Additionally, it was observed that severity of anxiety symptoms increased as parasympathetic reactivation increased at the initial startle for

the premutation group (F [1, 22] = 4.66, p = 0.043, R^2 = .18). Conclusion: The premutation group had a blunted response during the parasympathetic reactivation which indicates autonomic dysregulation. Additionally, habituation did not occur in either group to the reoccurring startles when the heart rate was used as the measure. Lastly, as the severity of anxiety symptoms increased, the parasympathetic reactivation increased. Future studies could investigate the initial startle to look at the initial cardiac reactivity in the premutation group.

Introduction

The *FMR1* premutation occurs when there is an expansion of 55-200 repeats of the trinucleotide CGG sequence on the 5' untranslated region on the *FMR1* gene. The *FMR1* premutation has the likelihood of being passed on to offspring and can expand further upon transmission causing fragile X syndrome. Fragile X syndrome can occur when a carrier, a mother with the *FMR1* premutation, passes off their gene which may expand further to over 200 repeats of the CGG trinucleotide on the *FMR1* gene. The *FMR1* premutation affects approximately 1 in 151 women (Seltzer et al., 2012). Research suggests that there are physical, cognitive and mental health risks associated with the *FMR1* premutation including but not limited to thyroid disease, hypertension, and psychiatric disorders (Wheeler et al., 2014). Although the *FMR1* premutation affects a great part of the population, a phenotype that characterizes the full range of features associated with the premutation has not yet been fully delineated.

However, some features have been well-documented, including the characterization of mental health problems in those with the *FMR1* premutation. About 41% of women with the *FMR1* premutation population display elevated rates of psychiatric disorders (Roberts et al., 2008). Anxiety disorders, in general, have shown to debilitate a person's adaptation skills to stressors, so studying anxiety in the premutation group may further shed light on the pathophysiological phenotype (Roberts et al., 2008). Currently, it is unclear whether psychological vulnerability is associated with atypical physiological responses in the *FMR1* premutation. Biomarkers (i.e. measurable traits that are specific to certain disorders) have been used to better understand psychiatric disorders, such as anxiety (Beauchaine, 2009). Identifying

biomarkers for anxiety disorders will help recognize personalized risk factors to then curate more patient centered therapies (Beauchaine & Thayer, 2015). This is especially important for the *FMR1* premutation population since there is not a clear pathophysiological phenotype established. By studying the biomarkers coinciding with anxiety and the premutation, we will be able to better understand the phenotype by curating targeted treatments, understanding the expression of the phenotype, and whether mechanisms behind anxiety in this group present similarly to patterns as compared to the general population.

One method to observe the physiological biomarkers for psychological vulnerability is through examination of the startle response, which can be elicited through a startle probe task (Chen et al., 2014). In this task, the participant is exposed to a series of loud auditory startle probes at random intervals and heart activity, in response to the startle, is recorded and analyzed off-line. The startle response is an unconscious reflex that occurs due to a sudden stimulus and is mediated by the autonomic nervous system, which is a physiological stress regulation system that plays a key role in regulating bodily responses to environmental stressors. The integrity of the autonomic response can be measured through the analysis of heart activity data (Sztajzel et al., 2004). This can be denoted in a three-part change in the heart rate. Initially, after a stressor is delivered, there will be an increase in heart rate post-startle, which is the parasympathetic inhibition. This will be followed by a rapid decrease in heart rate, which is the parasympathetic reactivation. Lastly, there will be a delayed increase in heart rate to the stressor (Chen et al., 2014 & Vila et al., 2007).

The analysis of responses to repeated startle probes can also lend insight into the habituation response. The habituation response is a form of non-associative learning in which change occurs due to subsequent stimuli being delivered (Ardiel et al., 2017). Repeated exposure to a startle probe will result in reduced reactivity over time as the individuals becomes accustomed to the probe (Kamkwalala et al., 2013). Deficits in the habituation response have been studied in patients with anxiety disorders, meaning that their heart rate variability (HRV), which is the variation between heart rate over time, will be heightened during all of the startles as opposed to gradually decreasing (Akdag et al., 2013; Schmidt et al., 2013). Furthermore, low resting HRV has been linked to anxiety and other psychiatric disorders (Chalmers et al., 2014). Additionally, the greater risk for anxiety exhibited by a patient, the greater the deficiency in the habituation response (Campbell et al., 2014).

The purpose of the current study is to examine startle habituation as a potential biomarker for anxiety disorders among women with the *FMR1* premutation. Emerging evidence suggest that resting respiratory sinus arrhythmia, an index of parasympathetic tone that is measured via the analysis of heart activity patterns, is reduced in women with the *FMR1* premutation (Klusek et al., 2017). Thus, autonomically-mediated cardiac responses to a startle probe task may be impaired as well. Understanding physiological biomarkers associated with anxiety in those with the *FMR1* premutation can help to inform targeted medications and treatments for those affected. In this study we tested differences in the physiological habituation responses of women with the *FMR1* premutation compared to neurotypical control women and examine the association between startle responses and anxiety symptoms.

Research questions

1. Is there a difference among women the *FMR1* premutation and control women regarding habituation when taking into account various cardiac indicators?
2. Are any of the cardiac indicators of the initial startle probe associated with the severity of generalized anxiety symptoms in women with the *FMR1* premutation?

Methods

Participants

The participants included 31 women who are carriers of the *FMR1* premutation and 16 control women, aged between 35-75 years old. The *FMR1* premutation group was characterized as women with 55-200 CGG repeats on *FMR1*, as confirmed by genetic testing conducted as part of the larger study from which the participants were drawn. Control women had no family history of fragile X syndrome and were mothers to typically developing children. All participants spoke fluent English. The mean in age of the groups differed (p=0.050), with the premutation group averaging 53 years and the controls 46 years. Age was covaried in the statistical models because heart activity can be influenced by age (Sztajzel, 2004).

Procedures

This study took place in a research laboratory the University of South Carolina. The anxiety questionnaire was completed one to two weeks prior to the participant assessment when the startle probe task was administered. Heart rate was measured during the duration of the startle probe task. The procedures and recruitment process

for this study were all approved by the Institutional Review Board of the University of South Carolina and participants provided informed consent.

Measures

Startle Probe Task

At the beginning of the task, participants were asked to listen to the audio file. They were instructed not to speak and to listen to the whole file in its entirety. Participants listened to the audio file on a laptop while wearing noise cancelling headphones. Ten pure tone startles were delivered at 95 dB at 1000 Hz with intervals between the startle probe varying from 30-50 seconds. The task lasted for about ten minutes.

Cardiac Autonomic Activity

Cardiac activity was recorded during the startle probe task using the Actiwave Cardio Monitor (CamNtech Ltd., Cambridge, UK). Two electrodes which were placed on the participant's chest and an ECG signal was recorded at a rate of 1024 Hz. The files were edited in CardioEdit software (Brain-Body Center, University of Illinois at Chicago) to clean any artifacts. Fortunately, no files were excluded since none of the files needed editing on more than 5% of the beats. Seven individual IBI points were analyzed after each startle for each participant. Three cardiac indices were computed: (1) Parasympathetic inhibition, which reflects an increase in heart rate post-startle. Parasympathetic inhibition was calculated by taking an average of three IBI pre-startle and taking an average of two IBIs post startle to determine the change score. (2)

Parasympathetic reactivation, which is characterized by a rapid decrease in heart rate post-startle. Parasympathetic reactivation was computed by taking the difference of the average of the 5^{th} to the 7^{th} IBI post startle and average of the 2 IBIs post startle. (3) RMSSD which provides an index for the heart variance presented. RMSSD was quantified by taking the difference between the RMSSD of 7 IBI post-startles and the RMSSD of 7 IBI pre-startle. To examine the association between the first startle and generalized anxiety symptoms in women with the premutation, we calculated the parasympathetic inhibition, the parasympathetic reactivation, and RMSSD change score of the first startle and plotted it against the severity of anxiety symptoms.

Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) (Beck et al.,1996) was used to index current anxiety symptoms. This questionnaire was used due to its high internal consistency and reliability (Fydrich et al.,1992). The BAI contains 21 symptoms of anxiety in which the participants self-report each symptom based on whether it has bothered them within the past week. The results from this is a severity score, with a score of 0-9 indicating no or low anxiety, 10-18 indicating moderate anxiety, 19-29 is moderate to severe while a score of 36 and above indicating clinically significant levels of anxiety (Julian, 2011).

Data Analysis

Analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). A series of mixed effects linear models were fit to test group differences in the parasympathetic inhibition, parasympathetic reactivation, and RMSSD change scores

across trials. Trial was specific as a random effect, nested within participant. Group, trial, and their interaction were included as predictors for each model. Age was added into each model as a covariate. The distribution of the residuals was examined for each model and found to be normality distributed. Next, a series of linear regressions were conducted to examine the association between parasympathetic inhibition, parasympathetic reactivation, RMSSD change score of the first startle and anxiety symptoms.

Results

Group Differences in Parasympathetic Inhibition

A linear mixed model was performed to analyze group differences of parasympathetic inhibition across trials. After controlling for age, there was no main effect of trial ($p = 0.095$), group ($p = 0.147$), or the interaction between trial and group ($p = 0.143$).

Group Differences in Parasympathetic Reactivation

A linear mixed model was performed to analyze the parasympathetic reactivation during the startle task, covarying for age. The model showed a significant main effect of group (F [1, 34] = 5.47, $p = 0.025$). The control group showed higher parasympathetic reactivation than that of the premutation group across the repeated startles (Figure 1). There was no main effect of trial number ($p = 0.406$) or the interaction between group and trial ($p = 0.166$).

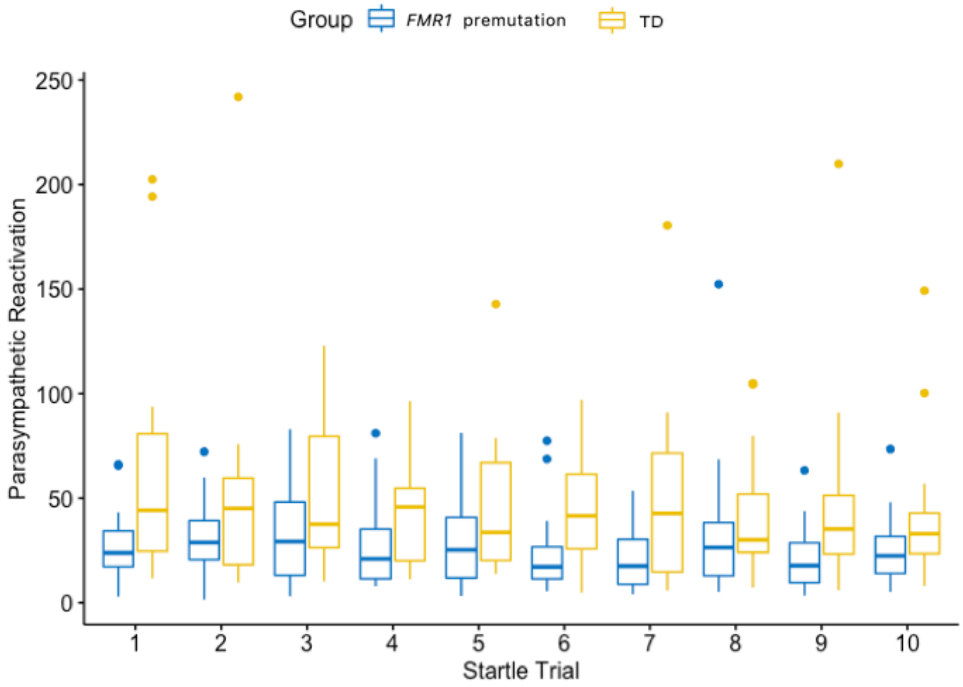

Figure 1. Parasympathetic reactivation is blunted in the FMR1 premutation group.

Group Differences in RMSSD

A linear mixed model was conducted to test group differences in RMSSD, controlling for age. Group ($p = 0.494$), trial ($p = 0.433$), and the interaction between group and trial ($p = 0.507$) did not prove to be significant.

Associations Between Anxiety Symptoms and Physiological Responses

Linear regressions were investigated to see if there was an association between anxiety symptoms and parasympathetic reactivation, parasympathetic inhibition and the RMSSD change score in the *FMR1* premutation group. Parasympathetic inhibition ($p = 0.062$) and RMSSD change score ($p = 0.908$) were not significant models overall. Anxiety severity was a significant predictor of parasympathetic reactivation, (F [1, 22] =

4.66, p = 0.043, R^2 = .18), with anxiety symptom severity increasing as parasympathetic reactivation increases (see Figure 2).

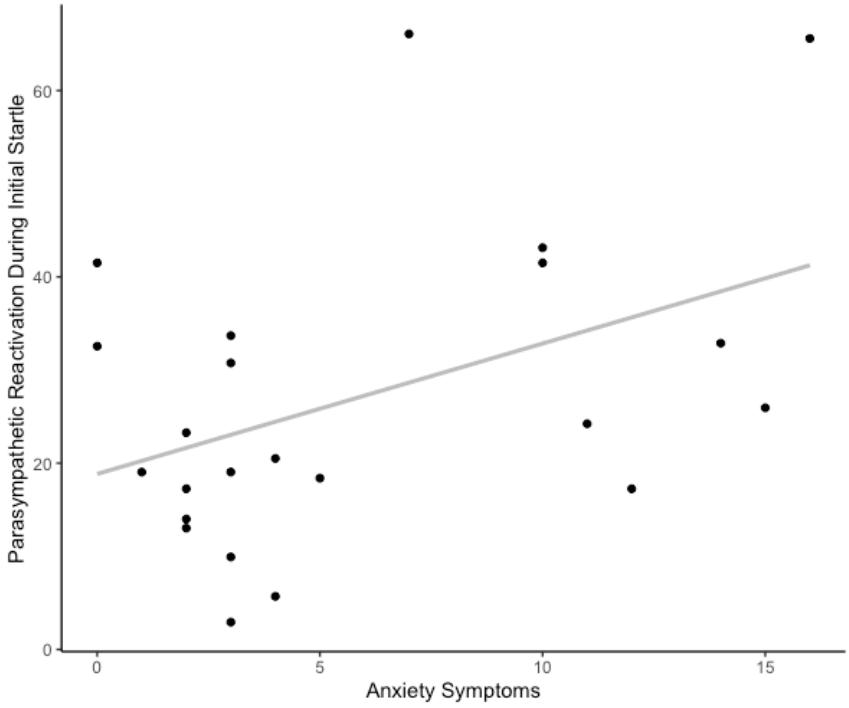

Figure 2 Significant association between anxiety symptoms and parasympathetic reactivation

Discussion

Women with the *FMR1* premutation are a big portion of the population, yet no targeted treatments or medications have been developed to alleviate the symptoms associated with this phenotype. In this study, we investigated whether startle responses could be used as a biomarker for anxiety in women with *FMR1* premutation. This was done by focusing on autonomic regulation in response to auditory startle probes through the analysis of heart rate indices. It was observed that mothers with the *FMR1* premutation had blunted parasympathetic reactivation as compared to the controls

when reoccurring startles were delivered. Additionally, anxiety symptoms were associated with only parasympathetic reactivation but not any of the other cardiac indicators.

The women with the *FMR1* premutation were shown to have blunted parasympathetic reactivation to the startles, indicating that this group had greater trouble recovering physiologically following the startles. This finding aligns well with previous studies showing reduced heart rate variability and autonomic dysregulation in those with the *FMR1* premutation (Klusek et al., 2017). The parasympathetic system represents “rest and digest” and is responsible for the unconscious regulation of the body, such as regulation the heart function (Gordon et al., 2015). With the premutation group having a blunted response, this shows that this group exhibits subpar physiological control.

A relationship between anxiety and *FMR1*-associated physiological measures in the *FMR1* premutation has not been documented extensively. Individuals with the premutation are an at-risk group for anxiety, specifically social anxiety (Roberts et al., 2008). In this study we investigated whether there was an association between anxiety symptoms and physiological response to the first startle. Only parasympathetic reactivation was discovered to be an indicator for anxiety symptoms, while parasympathetic inhibition and RMSSD change score were not predictors. A previous study suggested that blunted parasympathetic reactivation response hints at depression symptoms developing within the next 5 years (Phillips et al., 2011). While depression symptomology was not studied in the current study, it could be examined in the future to determine if the blunted response could be attributed to depression. Depression has

been noted to have a higher incidence in women with the *FMR1* premutation (Lachiewicz et al., 2010). A future study could look at the association of severity of depression with the various cardiac indices noted in this study. Additionally previously, it was found that participants with lower variability in resting heart rate cannot produce appropriate responses to cope with stressors as effectively which elucidates the fact that the ability to cope to stressors may be a precursor to anxiety, however it is not always a direct link with psychological disorders (Thayer et al., 2011).

An unexpected result observed in our study was that the severity of anxiety symptoms increased as the parasympathetic reactivation increased in the initial startle. This was unexpected as we were expecting that as the severity of anxiety symptoms increased, the parasympathetic reactivation would decrease. Passive coping occurs when the participant is unknown to the fact about how readily the startle is delivered and at what frequency (Chen et al., 2014). Active coping occurs when the participant is aware that a startle will be coming up shortly, so they ready their body for the startle (Chen et al., 2014). In our study, passive coping would occur during the first few startles, namely the initial startle that was delivered to observe an association with the severity of anxiety symptoms. Passive coping is characterized by the deceleration of heart rate, while active coping is denoted by the acceleration of heart rate. We have hypothesized that the premutation group was not able to get to that active coping stage, which is influenced by a controlled cognitive process, due to the inability to increase the acceleration of their heart rate; however, a future study would need to be done to confirm this hypothesis.

In this study we also investigated habituation responses. We discovered that neither the *FMR1* premutation nor the control groups produced a habituation response to the reoccurring startles. In a previous study, Jovanovic et al. (2009) evaluated whether the PTSD patients had an impaired habituation to subsequent startles and they also found that no habituation response was present to the startles. They concluded that there were no group differences found in the electrocardiogram (ECG), electromyography (EMG) or skin conductance test. Interestingly, they found PTSD patients initially showed a decreased startle magnitude, that rose in later trials, which was atypical as the general trend is initially increased startle magnitude that progressively decreases (Jovanovic et al., 2019). In another study, Walker et al. (2019) examined resilience, which was defined as positive adjustments to adverse stimuli, as a factor that could play a role in the habituation response in skin conductance levels, ECG, and EMG. They found that while heart rate did not habituate to reoccurring startles in their study, skin conductance levels did. Skin conductance level reflects sympathetic activity, whereas heart activity measures are influenced by both the parasympathetic and sympathetic systems, and therefore may not be as sensitive to sympathetically driven responses. This could hint at a possible limitation in our study, since we only examined heart activity indices as a measure for habituation, but future research could focus on additional physiological measures.

We also examined the RMSSD change score, following the methods of Chen et al. (2014). We did not find differences of group, trial, or their interaction when using this method. This method should show the coupled effects of both parasympathetic inhibition and parasympathetic reactivation. Chen et al. (2014), however, found that

RMSSD change score habituated in participants, although they did not use this model to compare group differences. Despite using the same parasympathetic-mediated measures as this particular study, we did not replicate the same findings in our sample.

Lastly, we looked at parasympathetic inhibition as a parasympathetic-mediated measure of heart rate. However, we found that this cardiac index was not a significant model for this study. Parasympathetic inhibition reflects the defensive reflex after a startle has been delivered, which is illustrated by the decrease in IBI, as noted in our study (Graham and Clifton, 1966). The parasympathetic inhibition is expected to be much more controlled when the participant is aware and hears more startles (Chen et al., 2014). We found however, that there was no difference between the control and the premutation group.

A possible future study would be to replicate our current study but also look at SCL and EMG to see if habituation could be noted with those two measures. It seems as previous studies had success with finding dysregulation of habituation with those measures instead. Additionally, we could further analyze the first startle for each participant to see if an overshoot occurred. An overshoot occurs in the parasympathetic reactivation when the first IBI post startle measures to be higher than the baseline IBI. This would help us further analyze the concept of habituation and if it is inconsistent in the premutation group.

In this study, we investigated whether there was a difference physiologically with how the premutation groups reacted to startles as compared to a control. It was discovered that during parasympathetic reactivation, the premutation group produced a blunted response to the reoccurring startles, hinting at autonomic dysregulation in the

premutation group. Additionally, parasympathetic reactivation, in the premutation group, was associated with the severity of anxiety symptoms in the initial startle. This study will contribute more information on autonomic regulation in the *FMR1* premutation regarding atypical physiological reactivity and its relationship to anxiety symptoms in this group.

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