University of South Carolina
Scholar Commons

Theses and Dissertations

Summer 2022

A Novel Cognitive Stress Paradigm to Assess Subtle Cognitive Differences in Women With the FMR1 Premutation

Jillian Margaret Gierman

Follow this and additional works at: https://scholarcommons.sc.edu/etd

 Part of the Speech Pathology and Audiology Commons

Recommended Citation

Gierman, J. M.(2022). *A Novel Cognitive Stress Paradigm to Assess Subtle Cognitive Differences in Women With the FMR1 Premutation.* (Master's thesis). Retrieved from https://scholarcommons.sc.edu/etd/6892

This Open Access Thesis is brought to you by Scholar Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact digres@mailbox.sc.edu.

A Novel Cognitive Stress Paradigm To Assess Subtle Cognitive Differences In Women With The FMR1 Premutation

By

Jillian Margaret Gierman

Bachelor of Sciences
University of North Carolina at Chapel Hill, 2018

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Sciences in

Speech-Language Pathology

Arnold School of Public Health

University of South Carolina

2022

Accepted by:

Jessica Klusek, Director of Thesis

Jane Roberts, Reader

Jean Neils-Strunjas, Reader

Roozbeh Behroozmand, Reader

Tracey L. Weldon, Vice Provost and Dean of the Graduate School

© Copyright by Jillian Margaret Gierman, 2022
All Rights Reserved.

DEDICATION

This thesis work is dedicated to my loving parents, Todd and Lisbeth Gierman, who have been a constant source of support and encouragement during the challenges of graduate school and life. Thank you for teaching me to always challenge myself and never stop growing.

And to my mentor, Jessie Klusek, who has been a role model to me academically and professionally. Thank you for always believing in me and inspiring me to write this thesis.

ABSTRACT

Fragile X premutation (FXPM) is a genetic mutation of the *FMR1* gene characterized by having between 55-200 CGG repetitions. FXPM women are at risk for a variety of reproductive, cognitive, and neuropsychiatric deficits, including fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is a late-onset neurodegenerative disorder characterized by tremor, gait ataxia, cognitive decline, brain atrophy, and deficits in executive functions. With the evidence supporting premature aging, prevalence of cognitive deficits, and risk of developing FXTAS and dementia, it is imperative to find a reliable measure that identifies at-risk FXPM women and their subtle cognitive phenotype. The LASSI-L is a novel cognitive stress paradigm that identifies cognitively impaired elderly adults from cognitively normal elderly adults. In the present study, we investigated the performance of FXPM women compared to non-carrier women to determine the sensitivity of the LASSI-L with regards to the subtle cognitive impairments associated with the FXPM. We hypothesized that FXPM women would have more vulnerability to proactive semantic interference, thus decreasing their ability to recover from proactive semantic interference. Moreover, we predicted that FXPM women would have higher percent intrusion errors (PIE) for both B1 Cued Recall and B2 Cued Recall. Lastly, we hypothesized that there would be a curvilinear relationship between the failure to recover from proactive semantic interference and CGG repeat length with the lowest scores being associated with the mid-range CGG repeat length (approximately 80-110). Results indicated increased vulnerability

to proactive semantic interference and increased failure to recover from proactive semantic interference in FXPM women relative to controls. Findings also showed that FXPM women had more semantic intrusion errors during recall. Additionally, FXPM performance on B1 and B2 Cued Recall were associated with CGG repeat length and educational attainment. FXPM women with CGGs in the mid-range repeat length (approximately 80-110) who had less than a bachelor's degree recalled fewer target words in B1 and B2 Cued Recall. These findings supported the hypotheses. The current study underscores the need for further research investigating MCI and AD prevalence in FXPM women.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Approximately 1 in 148 women in the U.S. have the fragile X premutation (FXPM), a genetic mutation of the *FMR1* gene characterized by having between 55-200 CGG repetitions (Maenner et al., 2013). Over the last couple of decades, research has found supportive evidence that FXPM women are at risk to a variety of clinical consequences including the most well-known risk of passing the genetic mutation to their children causing fragile X syndrome (FXS). FXS is the primary inherited form of intellectual disability and autism. FXPM women can pass a genetic mutation on the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene on the X chromosome that results in an expansion of over 200 CGG nucleotide repetitions (full mutation). This expansion mutation reduces the production of *FMR1* protein, which is necessary for cognitive functioning (Oostra & Willemsen, 2003). In the past decade, it has become more evident that FXPM women are at risk for a variety of reproductive, cognitive, and neuropsychiatric deficits, including fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS) (Hagerman & Hagerman, 2013; Movaghar et al., 2019; Wheeler et al., 2014).

FXTAS is a late-onset neurodegenerative disorder characterized by intention tremor, gait ataxia, brain atrophy, cognitive decline in memory, and difficulties in information processing, working memory, and inhibition (Hessl et al. 2005; Hagerman, Greco, & Hagerman, 2003). FXTAS commonly co-occurs with dementia, with rates as

high as 42% in older men diagnosed with FXTAS (Hoyos & Thakur, 2017; Seritan et al., 2013). FXTAS prevalence in FXPM men is approximately 40% and is between 8-16.5% in FXPM women (Jacquemont et al., 2004; Coffey et al., 2008; Rodriguez-Revenga et al., 2009). Additionally, a growing body of evidence indicates that FXTAS prevalence may be higher than previously thought, with more FXPM women being identified with FXTAS and dementia (Tassone et al., 2012; Al-Hinti et al., 2007; Karmon & Gadoth, 2007). In a 2012 study (Tassone et al.), eight FXPM women presented with intranuclear inclusions, and many of them had neurological changes consistent with Alzheimer's disease (AD) pathologies. Furthermore, FXPM women presented with similar intranuclear inclusions in cortical and hippocampal neurons, though reduced levels, when compared to FXPM men as described in studies conducted by Greco et al. in 2006 and in 2002 (Tassone et al., 2012). This suggests that although FXPM men display more obvious symptoms, both FXPM men and women have comparable neurophysiological deterioration. There is a need to further understand the subtle cognitive phenotype of FXPM women.

These cognitive subtleties result from female carriers possessing two X chromosomes; however, a growing body of research suggests that female carriers have a cognitive phenotype resulting from the premutation allele (Goodrich-Hunsaker et al., 2011). While the prevalence of FXTAS in women is reportedly lower than in men, female carriers are still at an increased risk of neurological and cognitive dysfunction. Female carriers with fathers diagnosed with FXTAS are at a significantly increased risk of neurological problems, including tremor and memory problems, compared to non-carrier women (Conchaiya et al., 2010). There have been few studies on FXPM women

due to the less apparent neuropsychological symptoms and deficits than FXPM men. Though subtle, this cognitive phenotype includes deficits in working memory, attention, and executive functioning (Loesch et al., 2003). Additionally, cognitive deficits in FXPM women have been shown to relate to age and CGG repeat length (Goodrich-Hunsaker et al., 2011; Klusek et al., 2020).

Previous studies have investigated the CGG repeat length within the FXPM women population. In 2020, Klusek et al. found that FXPM women with CGG repeats in the mid-range (approximately 80-100) had increased inhibition deficits as well as FXPM women with CGG repeat lengths in the higher range (approximately 130-140). In addition to executive functioning deficits, FXPM women with CGG repeat lengths in the mid-range and high-range have been shown to be at an increased risk for developing FXPOI and FXTAS. Studies found that mid-range FXPM women are at an increased risk for developing FXPOI (Allen et al., 2007; Allen et al., 2021; Lekovich et al., 2017). During an investigation of CGG repeat length and development of FXTAS, findings suggested that FXPM carriers with CGG lengths of greater than 70 repeats had increased likelihood of devleopign FXTAS (Jacquemont et al., 2006). Research suggests that CGG repeat length may have a significant effect on cognitive dysfunction and adverse health outcomes within the FXPM population.

Furthermore, the argument that FXPM carriers undergo premature aging has been supported in genetic research over the past decade, specifically through telomere length. Telomere length is a biomarker of aging, with length decreasing as age increases and accelerated attrition being a hallmark of age-related diseases, including dementia and AD. A study investigated telomere length among older FXPM men diagnosed with and

without FXTAS and dementia. Findings showed that male carriers had overall reduced telomere length regardless of diagnosis (Jenkins et al., 2008). In 2012, a similar study was conducted to analyze telomere length in younger FXPM men, which also found reduced telomere length in FXPM men ranging in ages 9-56 compared to age-matched noncarriers (Jenkins et al., 2012). A recent study assessed telomere length in FXPM women compared to non-carriers and found reduced telomere length in FXPM carriers, suggesting the cohort is 'biologically older' than the control group. Furthermore, findings indicated that FXPM women had less decline in telomere length with age compared to the non-carrier cohort (Albizua et al., 2017).

Due to the increasing evidential support of cognitive deficits associated with FXPM women and potential risks of developing FXTAS and dementia, it is imperative to find a reliable measure that identifies at-risk FXPM women and their subtle cognitive phenotypic differences. There are currently numerous neuropsychological assessments that screen for dementia, such as the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). While these are the most widely used psychogeriatric clinical assessments, findings show lower sensitivity when assessing older adults for pre-mild cognitive impairment (PreMCI) and mild cognitive impairment (MCI) (Brenton, Casey & Arnaoutoglou, 2018). The International Working Group on AD suggested using the Free and Cued Selective Recall Test (FCSRT) to assess AD due to its high sensitivity and specificity in distinguishing those with AD from controls and other dementia. In 2015, researchers looked at the FCSRT to diagnose MCI and findings supported the validity of the measure (Lemos, Santiago & Santana, 2014). The FCSRT has also been recognized as the most accurate diagnostic tool for prodromal AD;

however, recently, a study found the Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L) to be more accurate than the FCSRT in diagnosing prodromal AD, suggesting that the LASSI-L be used when assessing for pre-clinical signs of MCI and AD (Matias-Guiu et al., 2017).

The LASSI-L is a novel cognitive stress paradigm that identifies cognitively impaired elderly adults from cognitively normal elderly adults with 90% classification accuracy (Crocco et al., 2014). LASSI-L has become an increasingly prevalent assessment for detecting PreMCI, MCI, and Alzheimer's disease (AD) due to its sensitivity to subtle cognitive impairments otherwise undetected by other neuropsychological tests (Loewenstein et al., 2016). LASSI-L requires learning 15 words in 3 semantic categories and presents a competing semantically related list of words. It uses controlled learning and cued recall to measure proactive semantic interference, retroactive semantic interference, and, uniquely, the failure to recover from proactive semantic interference (Loewenstein et al., 2016). The failure to recover from proactive semantic interference is suggestive of cognitive impairment and associated with amyloid load in the brain, a biomarker of AD (Loewenstein et al., 2016). Furthermore, a study examining PreMCI detection and biomarkers of AD found associations between failure to recover from proactive semantic interference and reduced volume of the medial temporal lobe and other AD prone areas (Crocco et al., 2017). The unique failure to recover from proactive semantic interference measure has supporting evidence that indicates it to be a marker of pre-clinical neurodegenerative disease and early cognitive deficits (Crocco et al., 2018).

Additionally, the LASSI-L measures semantic intrusion errors during the free and cued recalls. For decades, there has been supporting evidence that elevated semantic intrusion errors are strongly linked to MCI and AD due to decreased inhibition for guessing and incomplete semantic processing (Lowenstein et al., 1995; Loewenstein et al., 2004). In 2004, Lowenstein et al. investigated semantic intrusions and interference using objects from two separate bags. For the first bag, less than 10% of cognitively normal participants had semantic intrusion errors for the first bag of objects in comparison to 25% of participants with MCI and 33% of participants with AD. The second bag caused 40% of participants in the MCI and AD cohorts to make semantic intrusion errors whereas the cognitively normal cohort was 12.2% (Lowenstein et al., 2004). More recently, Kitaigorodsky et al. (2021) investigated semantic intrusion errors in individuals who were cognitively normal and individuals diagnosed with MCI amyloid positive, as well as MCI amyloid negative. The findings showed that semantic intrusion errors for proactive semantic interference (Cued B1) and failure to recover from proactive semantic interference (B2 Cued Recall) for cognitively normal and MCI amyloid negative individuals were below the established LASSI-L threshold for impairment on Cued B1 and Cued B2, which are 5 or more and 4 or more, respectively (Kitaigorodsky et al., 2021).

Furthermore, Crocco et al. (2020) focused on percent intrusion errors (PIE) due to the rationale that semantic intrusion error number may not highlight the subtleties within subgroups of MCI, such as distinguishing amyloid negative and amyloid positive MCI. Their findings supported that PIE indices correlated with the severity of amyloid load in the brain, suggesting PIE as a way to identify at-risk individuals (Crocco et al., 2020).

This supports the understanding that elevated semantic intrusion errors and PIE are indicative of AD pathology. Using measures of semantic intrusion errors and PIE have implications for distinguishing cognitively normal individuals from those with AD pathologies.

Due to the subtle cognitive deficits that comprise the FXPM phenotype in women, the LASSI-L has potential to help identify and distinguish FXPM women from non-carriers due to its high classification accuracy and sensitivity to subtle cognitive impairments. In the present study we investigated the performance of women with FXPM compared to non-carrier women in order to determine the sensitivity of the LASSI-L with regards to the subtle cognitive impairments associated with the FXPM. We hypothesized that FXPM women would have more vulnerability to proactive semantic interference, thus decreasing their ability to recover from proactive semantic interference. Moreover, we predicted that FXPM women would have higher percent intrusion errors (PIE) for both B1 Cued Recall and B2 Cued Recall. Lastly, we hypothesized that there will be a curvilinear relationship between the failure to recover from proactive semantic interference and CGG repeat length with the lowest scores being associated with the mid-range CGG repeat length (approximately 80-110). Studies have evidence supporting female FXPM with CGG repeat length in the mid-range are clinically more at risk for cognitive deficits (Goodrich-Hunsaker et al., 2011; Klusek et al., 2020).

CHAPTER 2

METHODS

2.1 PARTICIPANTS

Seventy-four FXPM women and 68 control women, aged 30-55 years (*M*=44.54, *SD*=6.24), participated. Participants were involved in a larger study related to the language profile of FXPM women. Inclusionary criteria for the larger study required that participants were native speakers of English and had normal or corrected-to-normal visual and hearing acuity. FXPM status was confirmed through genetic testing which is defined by an allele ranging from 55 to 200 CGG repeats on the *FMR1* gene. Self-reported information on clinical diagnoses of FXTAS were gathered to describe the sample; no FXPM participants reported a clinical diagnosis of FXTAS. 78% of FXPM women had children with FXS, 7% had a child with the FXPM, 7% had no children, and 8% had biological children without FXS/FXPM.

Women with the FXPM were recruited nationally and in Canada through advertisements on social media, parent support networks, word-of-mouth from friends and family, national disability organizations, and the Research Participant Registry Core of the Carolina Institute for Developmental Disabilities at the University of North Carolina at Chapel Hill. Control women were recruited locally through advertisements on social media, word-of-mouth, flyers placed at the University of South Carolina and pediatrician offices, and email registries. Group characteristics are presented in Table 1.1.

Table 1.1. Group Characteristics

Variable		Group		Test of group differences (*p*-value)
		FXPM *n* = 74	Control *n* = 68	
Age (in years)				
	M (*SD*)	45.28 (6.60)	43.73 (5.73)	.140
	Range	30.29-55.59	33.15-54.13	
Race (%)				
	White	89%	91%	.032*
	Black	3%	9%	
	Asian	3%	0%	
	Other	5%	0%	
Educational Attainment (%)				
Less than Bachelor's Degree		28%	16%	.096
Bachelor's Degree		33%	28%	
Graduate Degree		39%	56%	

*p <.050

2.2 PROCEDURES

Assessments were administered within the context of a larger research protocol that lasted approximately 3.5 hours. The LASSI-L was administered about an hour into the protocol, proceeded by a language sample and cognitive testing. Questionnaires were sent via a REDCap survey queue two weeks prior to the scheduled assessment date. Assessments were conducted either in-person at a university laboratory setting, or via a

telehealth research battery administered via on a secure virtual platform. Telehealth assessments made up about 66% of the datapoints, with a similar proportion of women from each group participating via telehealth ($\chi^2 = 2.00$, p=.157). Individuals who participated in telehealth assessments were mailed packets which contained items necessary to complete the larger research protocol, including headphones with attached microphone that they were instructed to wear during the entire assessment to ensure adequate hearing and speaking volume. Telehealth participants completed the assessment in an area within the home free from distractions and during a time when there would be no interruptions. Buccal swabs were collected at the completion of the larger research protocol. Participants were compensated for their time at the conclusion of the larger study. Informed consent was obtained, and all procedures were approved by the Institutional Review Board of the University of South Carolina.

2.3 LASSI-L TASK

The LASSI-L was administered as an index of semantic interference within the scope of the battery for the larger study. For telehealth assessments, the LASSI-L was adapted for remote administration following the exact formatting, words, and order of the in-person administration via Microsoft PowerPoint in order to maintain consistency across assessment styles. The LASSI-L was adapted into a brief computerized assessment (LASSI-BC) during the course of the present study and demonstrated high test-retest reliability (Curiel Cid et al., 2021). Our virtual adaptation of the LASSI-L was created prior to the LASSI-BC due to the need to offer virtual assessments during COVID-19 pandemic.

In both in-person and telehealth administrations of the LASSI-L, participants were presented with 15 common words (List A) one word at a time, every 4 seconds. These words belonged to one of three categories (5 words per category): fruits, musical instruments, or articles of clothing. The words were presented in black 60-point Georgia font on a white background. The word order was pre-determined per standardized instructions of the LASSI-L task. Each time a participant was shown a word, she read it aloud as it appeared in front of her. After the participant had read each target word in List A aloud (15 words), she was asked to freely recall all the words (A1 Free Recall) in a maximum of 60 seconds. Then, she was asked to recall the words that belonged to each category (e.g., fruit) in a cued recall (A1 Cued Recall) with a maximum of 20 seconds per category.

After the cued recall, the participant was presented with List A for a second learning trial. Once she finished reading each word aloud, the participant was presented with each category and asked to recall the words that belonged to that category in a cued recall (A2 Cued Recall) with a maximum of 20 seconds per category. Then, the participant was shown 15 new words (List B) that are semantically related to List A, which belonged to the same three categories used for List A (i.e., fruits, musical instruments, articles of clothing). List B was presented in the same manner and style as List A. After the participant finished reading the 15 new words aloud, she was asked to freely recall all of the new words (B1 Free Recall) with a maximum response time of 60 seconds. This assesses proactive semantic interference effects. Then, the participant was presented with each category and asked to recall the words that belonged to the category in a cued recall (B1 Cued Recall), allotted a maximum of 20 seconds per category.

Following the same procedure as List A, List B was presented again, followed by a category-cued recall (B2 Cued Recall), which targets failure to recover from proactive semantic interference.

Lastly, to measure retroactive semantic interference, the participant was asked to think back to the words from List A and freely recall all the words in List A (A3 Free Recall), given a maximum of 60 seconds. Then, the participant was presented each category and asked to recall the words that belonged to each of the categories in a cued recall (A3 Cued Recall). Throughout each recall, the examiners made note of each intrusion recalled within the allotted time. Intrusions were categorized by words that were not a correct target word for the specified recall.

2.4 EVALUATION OF FMR1 CGG REPEAT LENGTH

All participants provided buccal swabs for *FMR1* CGG genotypic analysis. This analysis was used to confirm FXPM carrier status for the FXPM women and non-carrier status for the control women. The buccal swabs were analyzed using the Asuragen AmplideX® Kit (Chen et al., 2010; Grasso et al., 2014). The buccal swabs were sent to Rush University Medical Center and analyzed in the laboratory of Dr. Elizabeth Berry-Kravis.

2.5 PARENTING STRESS

The Parenting Stress Inventory-4 Short Form (PSI-4-SF) (Abidin, 2013) was collected as a potential covariate to probe for the potential influence of parenting-related stress on the outcome variables. The PSI-4-SF is a self-report questionnaire measuring parenting stress in three subscales: Parental Distress, Child Dysfunctional Interaction, and Difficult Child. These three subscales combine to create the Total Stress scale. The

purpose of this measure was to evaluate the magnitude of stress within the parent-child system. Stress can affect individuals physically and mentally, including decreased attention and memory. Additionally, chronic stress has been linked to accelerated diagnostic changes from MCI to dementia (Peavy et al., 2009; Peavy et al., 2012). Previous studies have investigated parenting stress within the context of FXPM women and found that FXPM women report higher levels of depression, anxiety, and overall stress as well as lower quality of life (Bourgeois et al., 2010; Bullard et al., 2021; Wheeler et al., 2008). The Total Stress Percentile, which provides an index of overall parent stress related to the parent-child relationship, was used in analyses.

2.6 DATA ANALYSIS

Analyses were conducted using 9.4 (SAS Institute, 2013). Descriptive statistics were computed and a correlation matrix was completed to inform model selection (Table 2.1). Pearson's correlations were also examined between parenting stress and the LASSI-L dependent variables within the subgroup of FXPM women who were mothers; no significant associations emerged (all p's >.178). Next, variables were examined for distribution. B1 and B2 intrusions showed significant right skew with overdispersion and therefore these variables were tested with negative binomial regression models that are designed for skewed count data. Group differences in LASSI-L B1 and B2 cued recall were tested with two general linear models testing group as a predictor of each outcome. Age and educational attainment, categorized as a three-level categorical variable (highest attainment of less than bachelor's, bachelor's degree, graduate degree) were covaried in the models. Assessment mode (in-person or telehealth) was also included as a covariate. Partial eta squared (η^2_p) effect sizes were computed models, with effects at 0.01, 0.06,

and 0.14 generally indicative of “small”, “medium”, and “large”, respectively (Cohen, 1988). Group differences for the B1 and B2 intrusions were tested using negative binomial regression models. Negative binomial models are appropriate for modeling data with significant positive skew and include an additional parameter, alpha, that accounts for overdispersion (White & Bennetts, 1996). The total number of Cued B1/B2 responses (total intrusion errors + total correct responses) were included as exposure variables in the models. The exposure variable modifies observations from a count into a rate to adjust for variation in opportunity for the event to occur, and thus, the inclusion of this exposure variable statistically adjusted for variation in the total number of responses on the occurrence of intrusions. Prior studies have adjusted for the total number of responses through creation of a percent of intrusion errors (PIE) variable consisting of the total intrusion errors divided by the total number of correct and incorrect responses on Cued B1 or Cued B2 recalls (Curiel Cid et al., 2020). It was not necessary to create a proportion variable in the present study given our use of the exposure variable in the negative binomial model to statistically control for the total number of responses. Covariates in the negative binomial models included age, education level, and assessment type. Cohen’s *d* effect sizes were calculated for all group contrasts, with *d’*s of .20, .50, and .80 reflecting small, medium, and large effects, respectively (Cohen, 1988).

To test the second research question regarding the association between CGG repeat length and LASSI-L performance within the FXPM group, general linear models tested CGG repeat length as a predictor of the B1 and B2 outcomes. Covariates included age, education level, and assessment type. Quadratic and cubic terms for CGG repeat length were probed in each model to test for potential curvilinear relationships.

Interactions between education level and the CGG terms were also probed to test for potential differential effects of CGG repeat length at different levels of educational attainment. Education interactions and higher-order polynomial terms were retained if they accounted for significant variance and their inclusion resulted in improved model fit. For all CGG models, regression diagnostics identified a case with 145 CGG repeats that had an unduly large influence on the regression coefficients, as indicated by a Cook's Distance value that was considerably larger than the Distance value of all other cases and far exceeded the suggested cut-off criteria of $D_i > 4/n\text{-}k\text{-}1$ (Cook, 1977). The CGG repeat of this case was much higher than the next highest CGG length in the dataset (112). This case was omitted from CGG repeat analyses; this decision is viewed as a conservative analytical approach to avoid drawing conclusions beyond the limits of the data given the sparse representation of CGG repeats above 112.

Table 2.1. Correlation Matrix

Measure	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**
1. B1 Cued Recall	1.00					
2. B2 Cued Recall	.69**	1.00				
3. B2 Cued Recall Transformation	.69**	.98**	1.00			
4. B1 Intrusions	-.38**	-.39**	-.38**	1.00		
5. B2 Intrusions	-.32**	-.48**	-.50**	.54**	1.00	
6. Age	.05	-.07	-.08	.15	.07	1.00

*$p < .050$; **$p < .001$

CHAPTER 3

RESULTS

3.1 DESCRIPTIVE STATISTICS

Descriptive statistics are presented in Table 3.1. The mean CGG repeat length in the FXPM group was 87 (*SD*=15), with a range of 55-145.

Table 3.1. Descriptive Statistics

Variable	Group	
M (SD)	**FXPM**	**Control**
B1 Cued Recall	9.03 (2.77)	10.40 (2.46)
B2 Cued Recall	12.59 (2.21)	13.70 (1.56)
B1 Intrusions	1.54 (1.73)	1.00 (1.27)
B2 Intrusions	1.07 (1.29)	0.62 (0.88)

Note. B1 Cued Recall measures proactive semantic interference. B2 Cued Recall measures recovery from proactive semantic interference.

3.2 GROUP DIFFERENCES IN LASSI-L PERFORMANCE

Proactive Semantic Interference (B1 Cued Recall)

Group was a significant predictor of B1 Cued Recall, with a medium effect size (p = .003, η^2_p = .06; Figure 3.1); control women recalled more items from the original target list than FXPM women. The covariates for age and assessment type did not account for significant variance in the outcome but educational attainment had a significant effect (p = .042, η^2_p = .05) such that those with less than a bachelor's degree recalled fewer items

than those who had attained a bachelor's degree (p =.012) but did not differ from those with graduate degrees (p =.165). See Table 3.2 for model results.

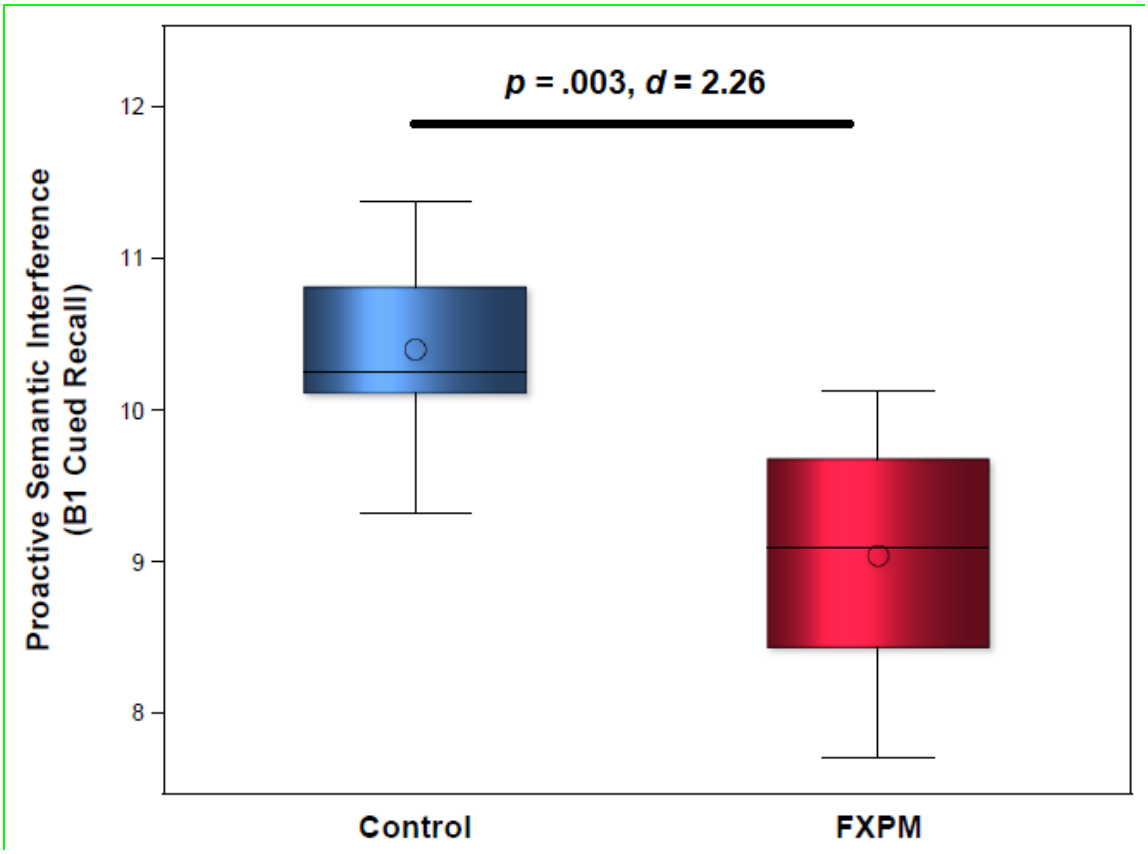

Figure 3.1. Group Differences in B1 Cued Recall

Recovery from Proactive Semantic Interference (B2 Cued Recall)

Group accounted for significant variance in B2 Cued Recall, with a medium effect size, $p = .002$, $\eta^2_p = .07$. On average, FXPM women recalled fewer target items than control women. Age and assessment mode did not account for significant variance in B2 Cued Recall ($ps > .401$) but educational attainment had a significant effect ($p = .001$, $\eta^2_p = .10$) such that those with attainment of less than a bachelor's degree recalled fewer items than those with a bachelor's degree ($p < .001$) and there was a trend for recall of fewer items relative to those with graduate degress ($p = .093$).

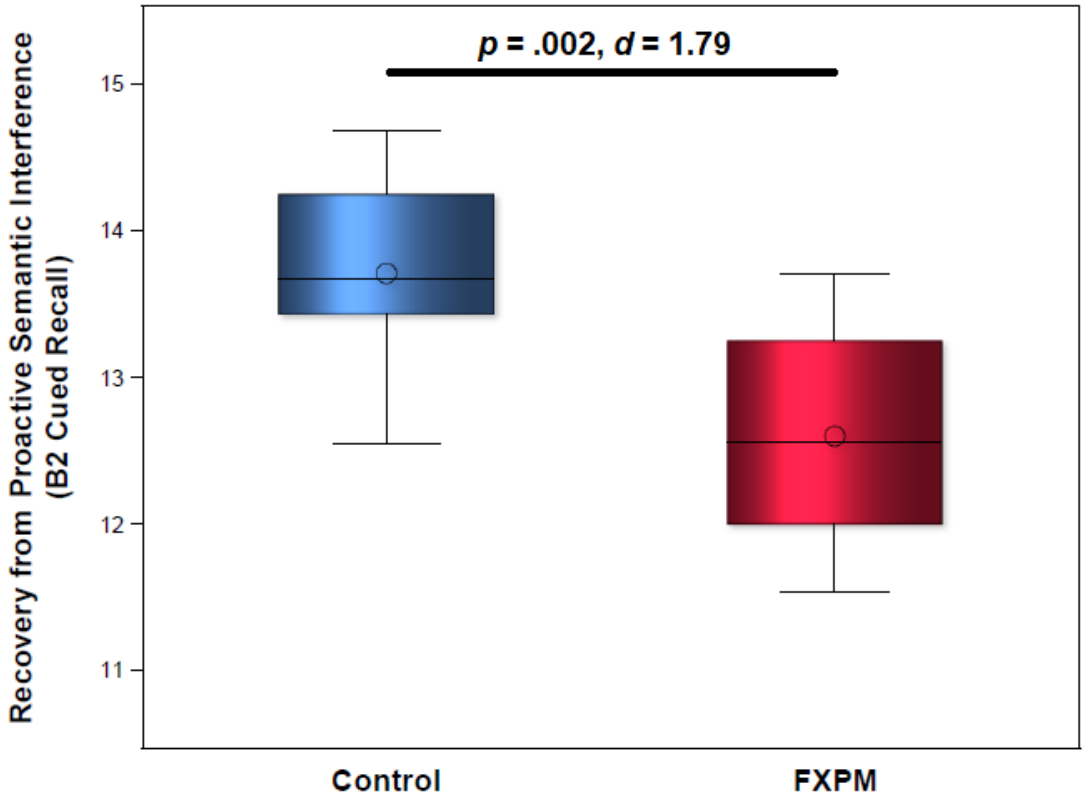

Figure 3.2. Group Differences in B2 Cued Recall

Table 3.2. Model Results: Group Comparisons on B1 and B2 Cued Recall

	Outcome Variable					
	B1 Cued Recall			**B2 Cued Recall**		
Predictor	F	*p*	η^2_p	F	*p*	η^2_p
Group	9.10	.003*	.06	10.20	.002*	.07
Age	0.90	.344	.01	0.22	.636	.00
Education	3.25	.042*	.05	7.16	.001*	.10
Assessment Type	0.01	.905	.00	0.71	.401	.01

*$p < .050$

Intrusion Errors

Model results are provided in Table 3.3. Group accounted for significant variance in the frequency of B1 and B2 Intrusion Errors, with increased errors in the FXPM groups; see Figure 3.3. The covariates for age, educational attainment, and assessment mode did not account for significant variance in either model.

Table 3.3. Model Results: Group Comparisons B1 and B2 Intrusions

	Outcome Variable			
	B1 Intrusions		B2 Intrusions	
Predictor	χ^2	*p*	χ^2	*p*
Group	4.44	.035*	5.65	.018*
Age	2.05	.152	0.26	.613
Education	1.83	.400	0.91	.635
Assessment Type	0.04	.843	2.48	.115

*$p < .050$

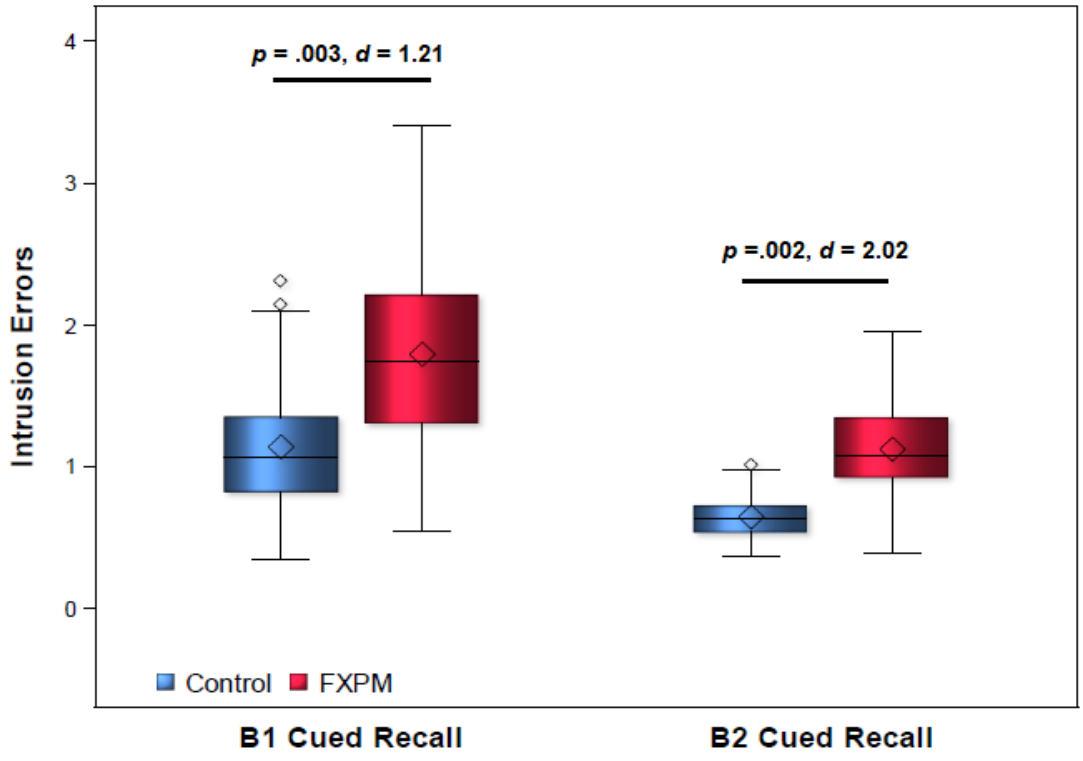

Figure 3.3. Group Differences in Intrusion Errors

3.3 ASSOCIATIONS WITH FMR1 CGG REPEAT LENGTH

The overall model testing CGG repeat length as a predictor of B1 Cued Recall was significant with the quadratic CGG model demonstrating the best fit, F (10, 60) = 3.40, p = .001, R^2 = .36. Significant interactions between educational attainment and linear (p =.039, η^2_p =0.10) and quadratic (p =.029, η^2_p =0.11) terms for CGG length were detected, indicating that the curvilinear association between CGG repeat length and B1 Cued Recall varied by level of educational attainment. In women with less than a bachelor's degree, a curvilinear effect was observed where B1 Cued Recall performance was decreased at mid-range CGG repeat sizes of about 80-100 and increased at lower CGG repeat lengths of about 55-80 and higher CGG repeat lengths of about 100-120. In contrast, mid-range CGG repeat lengths were associated with better B1 Cued Recall in those with bachelor's and graduate degrees. At higher CGG repeats of ~100-120, performance decreased in those with graduate degrees but remained similar to the performance at mid-range repeat sizes in those with bachelor's degrees.

The B2 Cued Recall model showed a similar pattern. The quadratic CGG model demonstrated the best fit (F [10, 60] = 3.21, p = .002, R^2 = .35) and significant interactions were detected between educational attainment and the linear (p =.026, η^2_p =0.11) and quadratic (p =.023, η^2_p =0.12) CGG terms. The curvilinear association between CGG repeat length and B2 Cued Recall performance varied by level of educational attainment, where mid-range CGG repeats were associated with poorer performance in those with less than a bachelor's degree and better performance in those with bachelor's and graduate degrees. B2 Cued Recall performance increased as CGGs approached lower (~55-80) and higher (~100-120) repeat lengths in those with less than a

bachelor's degree. In those with bachelor's and graduate degrees, performance decreased at higher and lower ends of the premutation range. See Figures 3.4 and 3.5 for graphical depiction, and Table 3.4 for model results. No significant CGG associations were observed with the B1 or B2 Intrusion variables.

Table 3.4 Model Results: CGG Associations with B1 and B2 Cued Recall

	Outcome Variable					
	B1 Cued Recall			**B2 Cued Recall**		
Predictor	F	*p*	η^2_p	F	*p*	η^2_p
Age	0.04	.850	.00	1.25	.268	.02
Education	3.04	.055	.09	3.52	.036*	.11
Assessment Type	0.24	.629	.00	0.03	.863	.00
Linear CGG	1.16	.286	.02	0.17	.678	.00
Quadratic CGG	1.17	.284	.02	0.38	.538	.01
Linear CGG x Education	3.44	.039*	.10	3.88	.026*	.11
Quadratic CGG x Education	3.78	.029*	.11	4.04	.023*	.12

*$p < .050$

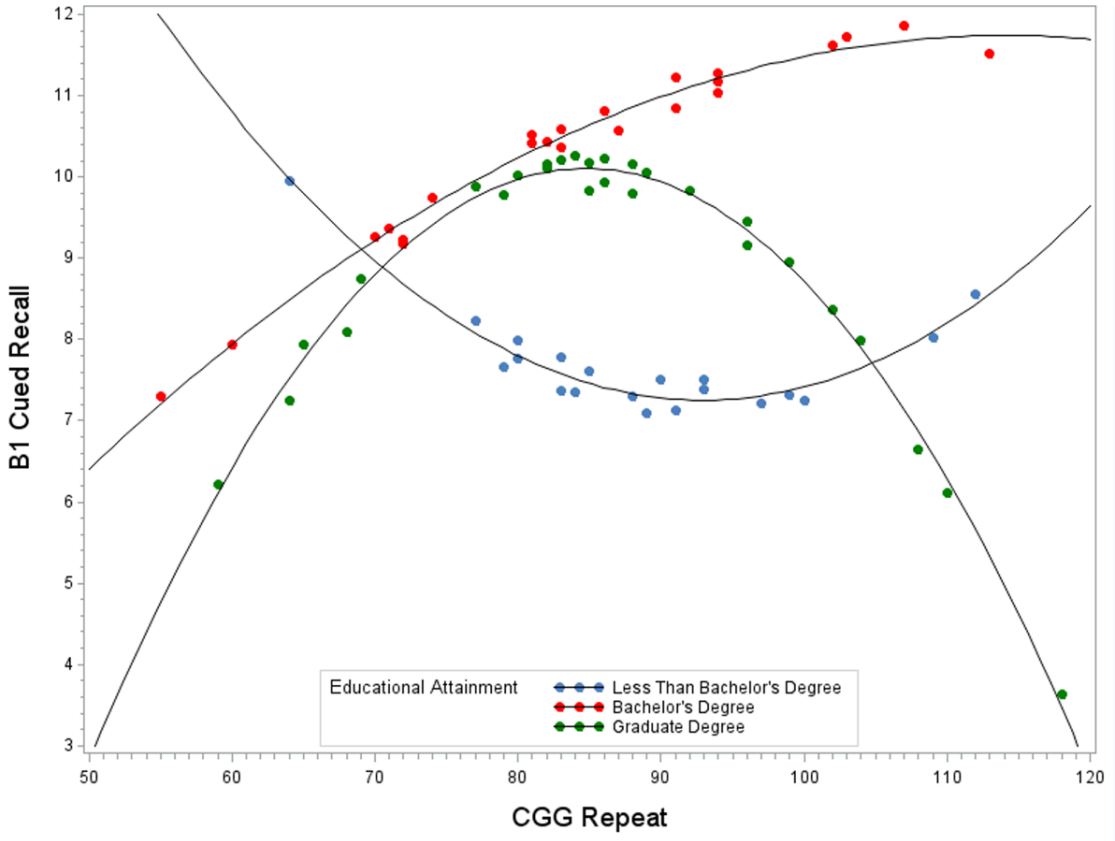

Figure 3.4. Association between CGG Repeat and Proactive Semantic Interference in FXPM Women

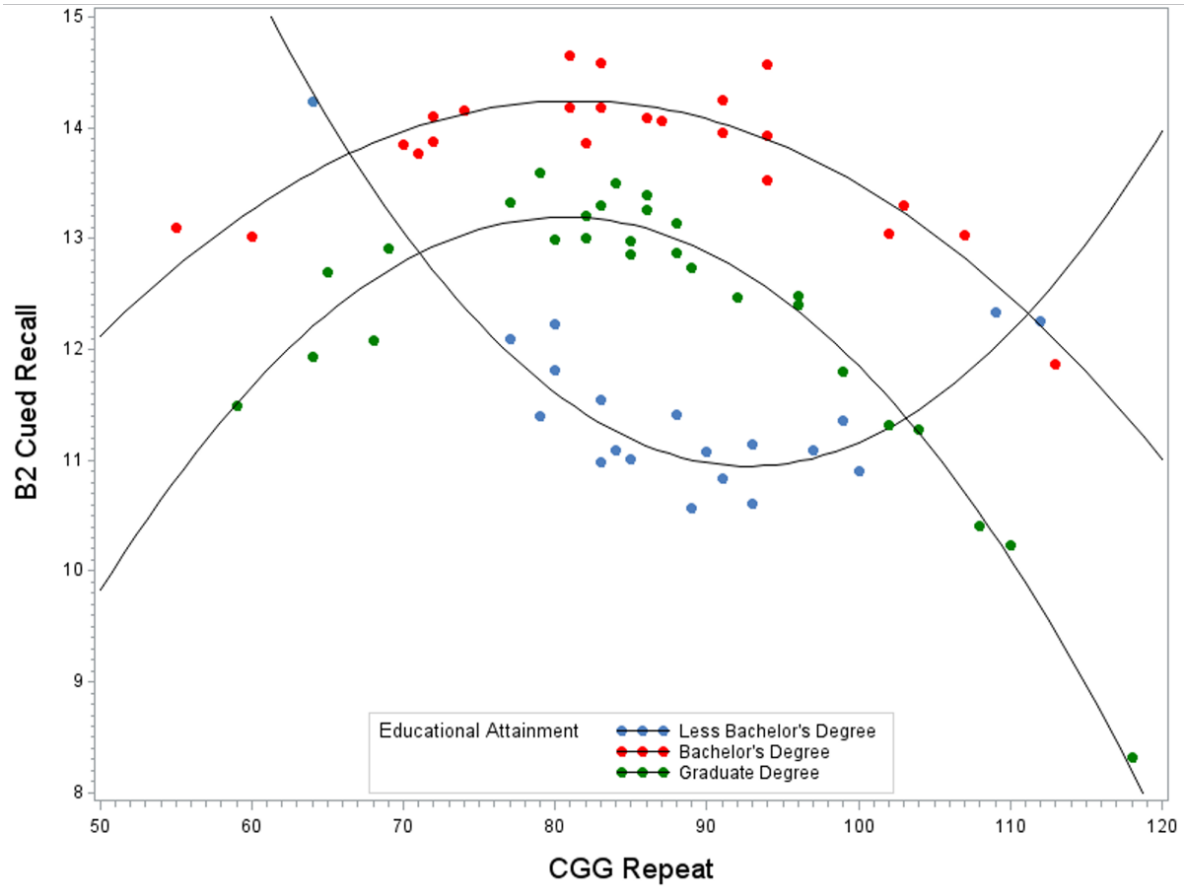

Figure 3.5. Association between CGG Repeat and Recovery from Proactive Semantic Interference in FXPM Women

CHAPTER 4

DISCUSSION

Over the years, research has identified FXPM women as being more vulnerable to cognitive dysfunction and a variety of other clinical disorders. Although subtle, these cognitive differences may have significant negative physical, mental, emotional, and social effects on FXPM women. This study aims to build upon those findings to better understand the subtle cognitive features of FXPM women. The current study represents the first investigation of cognitive differences in female FXPM using the LASSI-L measure. Results indicated increased vulnerability to proactive semantic interference and increased failure to recover from proactive semantic interference in FXPM women relative to controls. Findings also showed that FXPM women had more semantic intrusion errors during recall. Additionally, FXPM performance on B1 and B2 Cued Recall were associated with CGG repeat length and educational attainment. This study highlights the subtle cognitive phenotype of FXPM women that otherwise go undetected. Further understanding these cognitive differences may aid in clinical management for FXPM women. Future studies may explore neural connections and structural differences in FXPM women in connection to the LASSI-L to better understand the implications and findings of this unique measure.

FXPM women performed more poorly than controls in all measures analyzed in this study, which included B1 Cued Recall, B2 Cued Recall, B1 Intrusions, and B2 Intrusions. FXPM had increased susceptibility to proactive semantic interference (B1

Cued Recall) and failure to recover from proactive semantic interference (B2 Cued Recall), recalling fewer target words for both B1 Cued Recall and B2 Cued Recall than the control group. FXPM women demonstrated more accentuated difficulties to recover from proactive semantic interference than the control group. Failure to recover from proactive semantic interference has been associated with enlarged inferior lateral ventricles, cortical thinning, and increased amyloid load within the brain (Lowenstein et al., 2019; Lowenstein et al., 2017), which are strong indicators of MCI and AD. More specifically, failure to recover from proactive semantic interference is associated with volumetric reduction in brain regions associated with AD, including the superior parietal lobules, precuneus, entorhinal cortex, and hippocampus (Lowenstein et al., 2018; Curiel Cid et al., 2019; Lowenstein et al., 2017), which support attention and memory functions. FXPM women had difficulty recovering from proactive semantic interference, which has been associated with cognitive dysfunction, cortical atrophy, and/or presence of amyloid plaques within regions of the brain in prior research.

The current study also analyzed semantic intrusion errors within the B1 and B2 Cued Recall. FXPM women had higher intrusion errors in both B1 and B2 measures than non-carriers. Increased PIE for both B1 and B2 is associated with smaller hippocampal structure and the presence of amyloid plaques (Curiel Cid et al., 2020), which are key neurological features of AD. Elevated semantic intrusion errors may also be a cognitive marker of amyloid-positive MCI, which has similar underlying AD pathology (Kitaigorodsky et al., 2021). Additionally, numerous studies have investigated inhibition of FXPM women, suggesting that FXPM women have poor inhibitory control. Semantic intrusion errors have been linked to MCI and AD as a result of decreased inhibition and

incomplete semantic processing. Increased B1 and B2 intrusions provide further evidence of decreased inhibition and suggest incomplete semantic processing for women with FXPM, which could be indicative of neurodegeneration and AD pathologies. Future studies should look to understand the relationship of LASSI-L performance and neural structural differences of FXPM women to better understand the utilization of the LASSI-L as a potential assessment tool for identifying at-risk FXPM women.

Direct associations between CGG repeat length and LASSI-L performance were detected, with a gene-environment interaction reflected by education level. Among FXPM women with educational attainment of less than a bachelor's degree, mid-range CGG repeats were associated with poorer B1 and B2 Cued Recall performance, whereas FXPM women with higher educational attainment and mid-range CGGs did not show reduced performance. This is consistent with a body of literature demonstrating that lower educational attainment is strongly associated with increased health risks, such as AD, and increased exposure to negative life events (Beydoun et al., 2014; Lawrence, 2017; Raghupathi & Raghupathi, 2020; Verbeek et al., 2019). Prior studies of FXPM women have detected gene-environment interactions, with women carrying mid-range CGG repeats showing increased sensitivity to environmental stressors. In a study investigating mid-range CGG expansion and negative life events, mid-range FXPM women had stronger associations between life events and physiological and psychological outcomes when compared to women with smaller or larger CGG repeats. Mid-range FXPM women who were exposed to more negative life events had increased depressive symptoms, anxiety, and cortisol awakening response than mid-range women not exposed to negative life events (Seltzer et al., 2012). This indicates that mid-range

FXPM women are more susceptible to environmental stressors, which could explain the decreased B1 and B2 Cued Recall performance in mid-range FXPM women with lower educational attainment. Mid-range FXPM women with lower educational attainment may be at an increased risk for AD and other negative health outcomes. Future studies should investigate the relationship between lower educational attainment and risk of AD among mid-range FXPM women.

The current study underscores the need for further research investigating MCI and AD prevalence in FXPM women. Previous studies have suggested that FXPM women may be genetically predisposed to the biomarkers of such neurodegenerative diseases due to dysregulation of the amyloid-beta protein precursor (APP) (Westmark, 2018; McLane et al., 2019). Over the years, FXS mice studies have found that the *FMR1* protein binds to the APP mRNA, causing an overproduction of amyloid-beta in the brain (Westmark, 2018). A study investigating peripheral levels of amyloidogenic protein found that children with FXS had similar APP metabolization as seen in AD (McLane et al., 2019). Due to their genetic composition, FXPM women are genetically predisposed to developing neurodegenerative diseases. Future studies should look to better understand APP dysregulation in FXPM women.

4.1 LIMITATIONS

There are some limitations to the study design and its sample. The current study utilized an adapted virtual LASSI-L created to match the in-person assessment design. While the assessment type did not have significant effects on the results, it was not a standardized adaptation. Future studies should look to use the LASSI-BC when conducting the assessment virtually due to its high test-retest reliability and standardization. Other limitations related to the sample include lack of racial diversity,

which may limit the generalization of the results within the larger FXPM population. Furthermore, a larger portion of the sample had higher educational attainment compared to less than a bachelor's degree. Future studies should aim to further investigate the relationship between lower educational attainment and decreased LASSI-L performance within the female FXPM population.

CHAPTER 5

CONCLUSION

FXPM women are at an increased risk for premature aging and neurophysiological deterioration, and the findings of the current study provide more evidential support. FXPM women performed significantly worse in B1 and B2 Cued Recall and had elevated numbers of semantic intrusions, underscoring the effectiveness of the LASSI-L as a measure for identifying the subtle cognitive dysfunction occurring within this population. Overall findings suggest that FXPM women are at risk for MCI and AD. FXPM women with lower educational attainment who have CGG expansions that fall within the mid-range (approximately 80-100) may be at an increased risk for cognitive dysfunction, MCI, and AD. Future studies should aim to investigate the presence of AD biomarkers in FXPM women.

REFERENCES

Abdin, R. (2013). *Parenting Stress Index, Fourth Edition Short Form (PSI-4-SF)*: *Technical Manual.* PAR.

Albizua, I., Rambo-Martin, B. L., Allen, E. G., He, W., Amin, A. S., & Sherman, S. L. (2017). Women who carry a fragile X premutation are biologically older than noncarriers as measured by telomere length. *American Journal of Medical Genetics Part A*, *173*(11), 2985–2994. https://doi.org/10.1002/ajmg.a.38476

Allen, E. G., Sullivan, A. K., Marcus, M., Small, C., Dominguez, C., Epstein, M. P., et al. (2007). Examination of reproductive aging milestones among women who carry the FMR1 premutation. *Hum. Reprod.* 22, 2142–2152. doi: 10.1093/humrep/dem148

Allen, E. G., Charen, K., Hipp, H. S., Shubeck, L., Amin, A., He, W., Nolin, S. L., Glicksman, A., Tortora, N., McKinnon, B., Shelly, K. E., & Sherman, S. L. (2021). Refining the risk for fragile X–associated primary ovarian insufficiency (FXPOI) by FMR1 CGG repeat size. *Genetics in Medicine*, *23*(9), 1648–1655. https://doi.org/10.1038/s41436-021-01177-y

Al-Hinti, J. T., Nagan, N., & Harik, S. I. (2007). Fragile X premutation in a woman with cognitive impairment, tremor, and history of premature ovarian failure. *Alzheimer Disease & Associated Disorders*, *21*(3), 262–264. https://doi.org/10.1097/wad.0b013e31811ec130

Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., & Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis. *BMC Public Health*, *14*(1). https://doi.org/10.1186/1471-2458-14-643

Breton, A., Casey, D., & Arnaoutoglou, N. A. (2018). Cognitive tests for the detection of mild cognitive impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies. *International Journal of Geriatric Psychiatry*, *34*(2), 233–242. https://doi.org/10.1002/gps.5016

Bourgeois, J. A., Seritan, A. L., Casillas, E. M., Hessl, D., Schneider, A., Yang, Y., Kaur, I., Cogswell, J. B., Nguyen, D. V., & Hagerman, R. J. (2010). Lifetime prevalence of mood and anxiety disorders in Fragile X premutation carriers. *The Journal of Clinical Psychiatry*, *72*(02), 175–182. https://doi.org/10.4088/jcp.09m05407blu

Box, G. E., & Cox, D. R. (1964). An analysis of transformations. *Journal of the Royal Statistical Society: Series B (Methodological)*, *26*(2), 211–243. https://doi.org/10.1111/j.2517-6161.1964.tb00553.x

Bullard, L., Harvey, D., & Abbeduto, L. (2021). Maternal Mental Health and parenting stress and their relationships to characteristics of the child with Fragile X Syndrome. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.716585

Chen, L., Hadd, A., Sah, S., Filipovic-Sadic, S., Krosting, J., Sekinger, E., Pan, R., Hagerman, P. J., Stenzel, T. T., Tassone, F., & Latham, G. J. (2010). An information-rich CGG repeat primed PCR that detects the full range of fragile X expanded alleles and minimizes the need for Southern blot analysis. *The Journal of*

Molecular Diagnostics, *12*(5), 589–600. https://doi.org/10.2353/jmoldx.2010.090227

Chonchaiya, W., Nguyen, D. V., Au, J., Campos, L., Berry-Kravis, E. M., Lohse, K., Mu, Y., Utari, A., Hervey, C., Wang, L., Sorensen, P., Cook, K., Gane, L., Tassone, F., & Hagerman, R. J. (2010). Clinical involvement in daughters of men with Fragile X-associated tremor ataxia syndrome. *Clinical Genetics*, *78*(1), 38–46. https://doi.org/10.1111/j.1399-0004.2010.01448.x

Coffey, S. M., Cook, K., Tartaglia, N., Tassone, F., Nguyen, D. V., Pan, R., Bronsky, H. E., Yuhas, J., Borodyanskaya, M., Grigsby, J., Doerflinger, M., Hagerman, P. J., & Hagerman, R. J. (2008). Expanded clinical phenotype of women with the fmr1 premutation. *American Journal of Medical Genetics Part A*, *146A*(8), 1009–1016. https://doi.org/10.1002/ajmg.a.32060

Cohen, J. (1988). *Statistical Power Analysis for the behavioral sciences*. L. Erlbaum Associates.

Cook, R. D. (1977). Detection of influential observation in linear regression. *Technometrics*, *19*(1), 15. https://doi.org/10.2307/1268249

Crocco, E. A., Loewenstein, D. A., Curiel, R. E., Alperin, N., Czaja, S. J., Harvey, P. D., Sun, X., Lenchus, J., Raffo, A., Peñate, A., Melo, J., Sang, L., Valdivia, R., & Cardenas, K. (2018). A novel cognitive assessment paradigm to detect pre-mild cognitive impairment (premci) and the relationship to biological markers of Alzheimer's disease. *Journal of Psychiatric Research*, *96*, 33–38. https://doi.org/10.1016/j.jpsychires.2017.08.015

Curiel Cid, R. E., Crocco, E. A., Duara, R., Garcia, J. M., Rosselli, M., DeKosky, S. T., Smith, G., Bauer, R., Chirinos, C. L., Adjouadi, M., Barker, W., & Loewenstein, D. A. (2020). A novel method of evaluating semantic intrusion errors to distinguish between amyloid positive and negative groups on the Alzheimer's Disease Continuum. *Journal of Psychiatric Research*, *124*, 131–136. https://doi.org/10.1016/j.jpsychires.2020.02.008

Curiel Cid, R. E., Crocco, E. A., Kitaigorodsky, M., Beaufils, L., Peña, P. A., Grau, G., Visser, U., & Loewenstein, D. A. (2021). A novel computerized cognitive stress test to detect mild cognitive impairment. *The Journal of Prevention of Alzheimer's Disease*, 1–7. https://doi.org/10.14283/jpad.2021.1

Curiel Cid, R. E., Loewenstein, D. A., Rosselli, M., Matias-Guiu, J. A., Piña, D., Adjouadi, M., Cabrerizo, M., Bauer, R. M., Chan, A., DeKosky, S. T., Golde, T., Greig-Custo, M. T., Lizarraga, G., Peñate, A., & Duara, R. (2019). A cognitive stress test for prodromal alzheimer's disease: Multiethnic generalizability. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *11*(1), 550–559. https://doi.org/10.1016/j.dadm.2019.05.003

Goodrich-Hunsaker, N. J., Wong, L. M., McLennan, Y., Tassone, F., Harvey, D., Rivera, S. M., & Simon, T. J. (2011). Adult female fragile X premutation carriers exhibit age- and CGG repeat length-related impairments on an attentionally based enumeration task. *Frontiers in Human Neuroscience*, *5*. https://doi.org/10.3389/fnhum.2011.00063

Grasso, M., Boon, E. M. J., Filipovic-Sadic, S., van Bunderen, P. A., Gennaro, E., Cao, R., Latham, G. J., Hadd, A. G., & Coviello, D. A. (2014). A novel methylation PCR

that offers standardized determination of FMR1 methylation and CGG repeat length without Southern blot analysis. *The Journal of Molecular Diagnostics*, *16*(1), 23–31. https://doi.org/10.1016/j.jmoldx.2013.09.004

Greco, C. M., Berman, R. F., Martin, R. M., Tassone, F., Schwartz, P. H., Chang, A., Trapp, B. D., Iwahashi, C., Brunberg, J., Grigsby, J., Hessl, D., Becker, E. J., Papazian, J., Leehey, M. A., Hagerman, R. J., & Hagerman, P. J. (2005). Neuropathology of Fragile X-associated tremor/ataxia syndrome (FXTAS). *Brain*, *129*(1), 243–255. https://doi.org/10.1093/brain/awh683

Greco, C. M., Hagerman, R. J., Tassone, F., Chudley, A. E., Del Bigio, M. R., Jacquemont, S., Leehey, M., & Hagerman, P. J. (2002). Neuronal intranuclear inclusions in a new cerebellar tremor/ataxia syndrome among fragile X carriers. *Brain*, *125*(8), 1760–1771. https://doi.org/10.1093/brain/awf184

Hagerman, P. J., Greco, C. M., & Hagerman, R. J. (2003). A cerebellar tremor/ataxia syndrome among fragile X premutation carriers. *Cytogenetic and Genome Research*, *100*(1-4), 206–212. https://doi.org/10.1159/000072856

Hagerman, R., & Hagerman, P. (2013). Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome. *The Lancet Neurology*, *12*(8), 786–798. https://doi.org/10.1016/s1474-4422(13)70125-x

Hessl, D., Tassone, F., Loesch, D. Z., Berry-Kravis, E., Leehey, M. A., Gane, L. W., Barbato, I., Rice, C., Gould, E., Hall, D. A., Grigsby, J., Wegelin, J. A., Harris, S., Lewin, F., Weinberg, D., Hagerman, P. J., & Hagerman, R. J. (2005). Abnormal elevation OFFMR1 mrna is associated with psychological symptoms in individuals with the fragile X premutation. *American Journal of Medical Genetics Part B:*

Neuropsychiatric Genetics, *139B*(1), 115–121. https://doi.org/10.1002/ajmg.b.30241

Hoyos, L. R., & Thakur, M. (2016). Fragile X premutation in women: Recognizing the health challenges beyond primary ovarian insufficiency. *Journal of Assisted Reproduction and Genetics*, *34*(3), 315–323. https://doi.org/10.1007/s10815-016-0854-6

Jacquemont, S., Hagerman, R.J., Leehey, M.A., Hall, D.A., Levine, R.A., Brunberg, J.A., Zhang, L., Jardini, T., Gane, L.W., Harris, S.W., Herman, K., Grigsby, J., Greco, C.M., Berry-Kravis, E., Tassone, F. & Hagerman, P.J. (2004). Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. *JAMA* 291**,** 460-469.

Jacquemont, S., Leehey, M. A., Hagerman, R. J., Beckett, L. A., & Hagerman, P. J. (2006). Size bias of fragile X premutation alleles in late-onset movement disorders. *Journal of Medical Genetics*, *43*(10), 804–809. https://doi.org/10.1136/jmg.2006.042374

Jenkins, E. C., Tassone, F., Ye, L., Gu, H., Xi, M., Velinov, M., Brown, W. T., Hagerman, R. J., & Hagerman, P. J. (2008). Reduced telomere length in older men with premutation alleles of the fragile X mental retardation 1 gene. *American Journal of Medical Genetics Part A*, *146A*(12), 1543–1546. https://doi.org/10.1002/ajmg.a.32342

Jenkins, E. C., Tassone, F., Ye, L., Hoogeveen, A. T., Brown, W. T., Hagerman, R. J., & Hagerman, P. J. (2012). Reduced telomere length in individuals with FMR1

premutations and full mutations. *American Journal of Medical Genetics Part A*, 158a(5), 1060– 1065.

Karmon, Y., & Gadoth, N. (2007). Fragile X associated tremor/ataxia syndrome (FXTAS) with dementia in a female harbouring fmr1 premutation. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(6), 738–739. https://doi.org/10.1136/jnnp.2007.139642

Kitaigorodsky, M., Crocco, E., Curiel-Cid, R. E., Leal, G., Zheng, D., Eustache, M. K., Greig-Custo, M. T., Barker, W., Duara, R., & Loewenstein, D. A. (2021). The relationship of semantic intrusions to different etiological subtypes of MCI and Cognitively Healthy Older Adults. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *13*(1). https://doi.org/10.1002/dad2.12192

Klusek, J., Hong, J., Sterling, A., Berry-Kravis, E., & Mailick, M. R. (2020). Inhibition deficits are modulated by age and CGG repeat length in carriers of the FMR1 premutation allele who are mothers of children with Fragile X Syndrome. *Brain and Cognition*, *139*, 105511. https://doi.org/10.1016/j.bandc.2019.105511

Lawrence, E. M. (2017). Why do college graduates behave more healthfully than those who are less educated? *Journal of Health and Social Behavior*, *58*(3), 291–306. https://doi.org/10.1177/0022146517715671

Lekovich, J., Man, L., Xu, K., Canon, C., Lilienthal, D., Stewart, J. D., et al. (2017). CGG repeat length and AGG interruptions as indicators of fragile X-associated diminished ovarian reserve. *Genet. Med.* doi: 10.1038/gim.2017.220

Lemos, R., Simões, M. R., Santiago, B., & Santana, I. (2014). The free and cued selective reminding test: Validation for mild cognitive impairment and Alzheimer's disease. *Journal of Neuropsychology*, *9*(2), 242–257. https://doi.org/10.1111/jnp.12048

Loesch, D. Z., Bui, Q. M., Grigsby, J., Butler, E., Epstein, J., Huggins, R. M., Taylor, A. K., & Hagerman, R. J. (2003). Effect of the fragile X status categories and the fragile X mental retardation protein levels on executive functioning in males and females with fragile X. *Neuropsychology*, *17*(4), 646–657. https://doi.org/10.1037/0894-4105.17.4.646

Loewenstein, D. A., Acevedo, A., Luis, C., Crum, T., Barker, W. W., & Duara, R. (2004). Semantic interference deficits and the detection of mild alzheimer's disease and mild cognitive impairment without dementia. *Journal of the International Neuropsychological Society*, *10*(01). https://doi.org/10.1017/s1355617704101112

Loewenstein, D. A., Curiel, R. E., Duara, R., & Buschke, H. (2017). Novel cognitive paradigms for the detection of memory impairment in preclinical Alzheimer's disease. *Assessment*, *25*(3), 348–359. https://doi.org/10.1177/1073191117691608

Loewenstein, D. A., Curiel, R. E., Greig, M. T., Bauer, R. M., Rosado, M., Bowers, D., Wicklund, M., Crocco, E., Pontecorvo, M., Joshi, A. D., Rodriguez, R., Barker, W. W., Hidalgo, J., & Duara, R. (2016). A novel cognitive stress test for the detection of preclinical Alzheimer disease: Discriminative properties and relation to amyloid load. *The American Journal of Geriatric Psychiatry*, *24*(10), 804–813. https://doi.org/10.1016/j.jagp.2016.02.056

Loewenstein, D. A., Curiel, R. E., Wright, C., Sun, X., Alperin, N., Crocco, E., Czaja, S. J., Raffo, A., Penate, A., Melo, J., Capp, K., Gamez, M., & Duara, R. (2017).

Recovery from proactive semantic interference in mild cognitive impairment and normal aging: Relationship to atrophy in brain regions vulnerable to Alzheimer's disease. *Journal of Alzheimer's Disease*, *56*(3), 1119–1126. https://doi.org/10.3233/jad-160881

Maenner, M. J., Baker, M. W., Broman, K. W., Tian, J., Barnes, J. K., Atkins, A., McPherson, E., Hong, J., Brilliant, M. H., & Mailick, M. R. (2013). FMR1CGG expansions: Prevalence and sex ratios. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *162*(5), 466–473. https://doi.org/10.1002/ajmg.b.32176

Matias-Guiu, J. A., Cabrera-Martín, M. N., Curiel, R. E., Valles-Salgado, M., Rognoni, T., Moreno-Ramos, T., Carreras, J. L., Loewenstein, D. A., & Matías-Guiu, J. (2017). Comparison between FCSRT and Lassi-L to detect early stage alzheimer's disease. *Journal of Alzheimer's Disease*, *61*(1), 103–111. https://doi.org/10.3233/jad-170604

McLane, R. D., Schmitt, L. M., Pedapati, E. V., Shaffer, R. C., Dominick, K. C., Horn, P. S., Gross, C., & Erickson, C. A. (2019). Peripheral amyloid precursor protein derivative expression in fragile X syndrome. *Frontiers in Integrative Neuroscience*, *13*. https://doi.org/10.3389/fnint.2019.00049

Mothersead, P. K., Conrad, K., Hagerman, R. J., Greco, C. M., Hessl, D., & Tassone, F. (2005). Grand rounds: An atypical progressive dementia in a male carrier of the fragile X premutation: An example of fragile X-associated tremor/ataxia syndrome. *Applied Neuropsychology*, *12*(3), 169–178. https://doi.org/10.1207/s15324826an1203_7

Movaghar, A., Page, D., Brilliant, M., Baker, M. W., Greenberg, J., Hong, J., DaWalt, L. S., Saha, K., Kuusisto, F., Stewart, R., Berry-Kravis, E., & Mailick, M. R. (2019). Data-driven phenotype discovery of FMR1 premutation carriers in a population-based sample. *Science Advances*, *5*(8). https://doi.org/10.1126/sciadv.aaw7195

Oostra, B. A., & Willemsen, R. (2003). A fragile balance: FMR1 expression levels. *Human Molecular Genetics*, *12*(suppl 2). https://doi.org/10.1093/hmg/ddg298

Peavy, G. M., Jacobson, M. W., Salmon, D. P., Gamst, A. C., Patterson, T. L., Goldman, S., Mills, P. J., Khandrika, S., & Galasko, D. (2012). The influence of chronic stress on dementia-related diagnostic change in older adults. *Alzheimer Disease & Associated Disorders*, *26*(3), 260–266. https://doi.org/10.1097/wad.0b013e3182389a9c

Peavy, G. M., Salmon, D. P., Jacobson, M. W., Hervey, A., Gamst, A. C., Wolfson, T., Patterson, T. L., Goldman, S., Mills, P. J., Khandrika, S., & Galasko, D. (2009). Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *American Journal of Psychiatry*, *166*(12), 1384–1391. https://doi.org/10.1176/appi.ajp.2009.09040461

Raghupathi, V., & Raghupathi, W. (2020). The influence of education on health: An empirical assessment of OECD countries for the period 1995–2015. *Archives of Public Health*, *78*(1). https://doi.org/10.1186/s13690-020-00402-5

Rodriguez-Revenga, L., Madrigal, I., Badenas, C., Xunclà, M., Jiménez, L., & Milà, M. (2009). Premature ovarian failure and Fragile X Female Premutation carriers. *Menopause*, *16*(5), 944–949. https://doi.org/10.1097/gme.0b013e3181a06a37

Seltzer, M. M., Barker, E. T., Greenberg, J. S., Hong, J., Coe, C., & Almeida, D. (2012). Differential sensitivity to life stress in FMR1 premutation carrier mothers of children with Fragile X Syndrome. *Health Psychology, 31*(5), 612–622. https://doi.org/10.1037/a0026528

Seritan, A. L., Nguyen, D. V., Farias, S. T., Hinton, L., Grigsby, J., Bourgeois, J. A., & Hagerman, R. J. (2008). Dementia in fragile X-associated tremor/ataxia syndrome (FXTAS): Comparison with alzheimer's disease. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*(7), 1138–1144. https://doi.org/10.1002/ajmg.b.30732

Seritan, A., Cogswell, J., & Grigsby, J. (2013). Cognitive dysfunction in FMR1 premutation carriers. *Current Psychiatry Reviews*, *9*(1), 78–84. https://doi.org/10.2174/1573400511309010012

Tassone, F., Greco, C. M., Hunsaker, M. R., Seritan, A. L., Berman, R. F., Gane, L. W., Jacquemont, S., Basuta, K., Jin, L.-W., Hagerman, P. J., & Hagerman, R. J. (2012). Neuropathological, clinical and molecular pathology in female fragile X premutation carriers with and without FXTAS. *Genes, Brain and Behavior*, *11*(5), 577–585. https://doi.org/10.1111/j.1601-183x.2012.00779.x

Verbeek, T., Bockting, C. L. H., Beijers, C., Meijer, J. L., van Pampus, M. G., & Burger, H. (2019). Low socioeconomic status increases effects of negative life events on antenatal anxiety and depression. *Women and Birth*, *32*(1). https://doi.org/10.1016/j.wombi.2018.05.005

Westmark, C. J. (2018). Fragile X and app: A Decade in Review, a vision for the future. *Molecular Neurobiology*, *56*(6), 3904–3921. https://doi.org/10.1007/s12035-018-1344-x

Wheeler, A. C., Bailey Jr, D. B., Berry-Kravis, E., Greenberg, J., Losh, M., Mailick, M., Milà, M., Olichney, J. M., Rodriguez-Revenga, L., Sherman, S., Smith, L., Summers, S., Yang, J.-C., & Hagerman, R. (2014). Associated features in females with an FMR1 premutation. *Journal of Neurodevelopmental Disorders*, *6*(1). https://doi.org/10.1186/1866-1955-6-30

Wheeler, A. C., Skinner, D. G., & Bailey, D. B. (2008). Perceived quality of life in mothers of children with Fragile X Syndrome. *American Journal on Mental Retardation*, *113*(3), 159. https://doi.org/10.1352/0895-8017(2008)113[159:pqolim]2.0.co;2

White, G. C., & Bennetts, R. E. (1996). Analysis of frequency count data using the negative binomial distribution. *Ecology*, *77*(8), 2549–2557. https://doi.org/10.2307/2265753

Yoder, P. & Symons, F. (2010). *Observational Measurement of Behavior.* Springer Publishing Company, New York, NY.