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Verbal Inhibition Declines Among Older Women With High *FMR1* Premutation Expansions: A Prospective Study

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Abstract

The *FMR1* premutation has been associated with difficulties in executive functioning, including verbal inhibition. However, little is known about the longitudinal profiles of verbal inhibition among *FMR1* premutation carriers, particularly in women, and how individual factors such as aging and CGG repeat length may contribute to changes in verbal inhibition over time. The present study examined verbal inhibition performance (i.e., inhibition errors) on the Hayling Sentence Completion Task in a cohort of 92 women with the *FMR1* premutation across two timepoints approximately three years apart. We examined the effects of age, CGG repeat length, and their interactions on verbal inhibition over time. We also evaluated whether response latency affected verbal inhibition errors. We found no significant change in verbal inhibition in the full cohort during the three-year study period. However, a subset of *FMR1* premutation carriers, namely older participants with higher CGG repeats, evidenced greater declines in verbal inhibition over time. Longer response latencies did not compensate for verbal inhibition errors. The findings suggest that a subset of women with the *FMR1* premutation may be at earlier, increased risk for changes in executive functioning, which if confirmed, should be considered as part of the clinical profile associated with the premutation.

Keywords: *FMR1*, verbal inhibition, aging, CGG repeats, executive function, fragile X premutation carrier

1. Introduction

The *FMR1* gene is essential for neural development and synaptic functioning (Darnell et al., 2011). Located on the X chromosome, expansions of *FMR1* CGG trinucleotides at the 5' untranslated region can have phenotypic consequences, including fragile X syndrome (>200 CGG repeats) and the *FMR1* premutation (55-200 CGGs). The *FMR1* premutation (PM) is quite common, as approximately 1 in 150 females and 1 in 470 males in the U.S. are carriers of the variant (Seltzer, Baker, et al., 2012; Tassone et al., 2012). Risks associated with the PM include fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS), as well as elevated rates of mood and anxiety disorders and executive dysfunction in some individuals with the PM (Hagerman & Hagerman, 2002; Sullivan et al., 2005; Wheeler et al., 2017). Incomplete penetrance of these phenotypes, however, creates significant variability among PM carriers, and particularly for females given the presence of two X chromosomes (Hagerman & Hagerman, 2021; Hall et al., 2016). Moreover, penetrance of FXTAS and FXPOI are associated with age, thus the identification of age-related phenotypic changes among PM carriers has garnered substantive attention (Jacquemont et al., 2004). However, few studies have characterized PM phenotypes longitudinally among women with the PM, which can provide insight into the clinical risk profiles that may be present within this heterogenous group. One promising phenotype that may evidence change over time is verbal disinhibition, an aspect of executive dysfunction that has been previously linked to both age and *FMR1* CGG repeats (Cornish et al., 2011; Hunter et al., 2012; Klusek et al., 2020; Kraan, Hocking, Georgiou-Karistianis, et al., 2014). The present study explores longitudinal performance in verbal inhibition among female *FMR1* PM carriers in an effort to better understand age-related changes associated with clinical risk associated with the PM.

1.1 Executive Function in the PM

Among the phenotypes documented in the PM, executive functioning has been one of the most extensively studied. Executive functioning is an umbrella term for the higher-order cognitive functions associated with goal-directed behavior, such as working memory, inhibition, and attentional control (Diamond, 2013). Executive functions are notable in the PM due to FXTAS, an age-related neurodegenerative disorder characterized in part by executive dysfunction (Berry-Kravis & Hall, 2011). In addition to cognitive changes, individuals with FXTAS evidence reduced total brain and cerebellar volume, increased white matter disease (including those observed in the middle cerebellar peduncles), and intranuclear ubiquitin inclusions (Hagerman & Hagerman, 2021). However, many PM carriers experience executive difficulties regardless of whether or not they go on to receive a FXTAS diagnosis. Prior work has identified executive differences among women with the PM compared to controls on a range of tasks related to behavioral dyscontrol, attention shifting, verbal inhibition, and working memory (Klusek et al., 2019; Klusek et al., 2018; Kraan, Hocking, Georgiou-Karistianis, et al., 2014; Maltman et al., 2021; Shelton et al., 2014; Shelton et al., 2015; Shelton et al., 2016). Moreover, deficits in these areas may be linked to differences in neural function. For example, one study found associations between performance on an executive task and reduced ventrolateral prefrontal cortex activation among women with the PM (Shelton, Cornish, Clough, et al., 2017). Thus, it is possible that delineation of the executive phenotype among PM carriers can yield insight into underlying neurological associations (Berry-Kravis & Hall, 2011).

1.1.1 ***Verbal Inhibition.*** One domain of executive function, inhibitory control (also known as inhibition), has received substantial attention among PM carriers and has been consistently found to differ from controls. Inhibition involves controlling one's attention, behavior, or response to

override an impulse (Diamond, 2013). Deficits in inhibition have been observed across a number of domains among PM females, including spatial tasks, oculomotor tasks, and in language-based tasks among both PM men and women (Cornish et al., 2008; Kraan, Hocking, Bradshaw, et al., 2014; Kraan, Hocking, Georgiou-Karistianis, et al., 2014; Moser et al., 2021; Shelton et al., 2014). Given the consistency of these deficits across domains, it is possible that inhibition may reflect a key phenotype from which we can characterize clinical risk profiles among individuals with the PM.

Verbal inhibition has garnered substantial attention in recent work as a possible marker of clinical risk, as PM carriers evidence age- and CGG-related associations with performance. Studies of verbal inhibition among PM carriers to date have used the Hayling Sentence Completion Task, a measure in which participants complete sentences with a logical conclusion, but are then instructed to verbally inhibit the logical response to complete the sentence in an unrelated fashion (e.g., "London is a very busy tomato"). This task includes measures of verbal response inhibition errors as well as response latency. Prior work among a cross-sectional sample of men with the PM showed that older men exhibited more verbal inhibition errors relative to a control group (Hunter et al., 2012). Ample research on this measure among healthy controls has shown that older adults produce more errors in verbal inhibition than younger adults (Andrés & Van der Linden, 2000; Bielak et al., 2006), particularly after age 70 (Gibson et al., 2019), and that older adults evidence longer response latencies (Cervera-Crespo & González-Alvarez, 2017). Among women with the PM, there is some evidence to suggest age-related associations with increased verbal inhibition errors (Klusek et al., 2020; Kraan, Hocking, Georgiou-Karistianis, et al., 2014; Shelton et al., 2016). In particular, Klusek et al. (2020) demonstrated associations between verbal inhibition errors and latency with age in a large sample of PM

females. Other studies have demonstrated mixed results as to the effect of age, using both the Hayling and other metrics of verbal inhibition (e.g., the Stroop task). Differences in results may be due in part to smaller samples, the inclusion of younger cohorts (mean age <50), and the use of diverse measures of verbal inhibition, which may have obscured significant relationships with age (Kraan, Hocking, Georgiou-Karistianis, et al., 2014; Shelton et al., 2016). Thus, age-related associations among women with the PM may not be evident until later in life, and these relationships may require larger samples and consistent measures of verbal inhibition given the heterogeneity associated with the PM.

An important consideration among studies of the PM are the potential additive or interactive effects of *FMR1* CGG repeat length and aging. Among men with the PM, linear associations of increasing verbal inhibition errors and CGG repeats have been observed (Hunter et al., 2012), whereas among women, prior work suggests both linear and curvilinear associations of CGG repeat length and inhibition errors (Klusek et al., 2018; Shelton et al., 2014). However, these studies did not consider possible effects of aging. In a study of men with the PM that considered both age and CGG effects, Cornish et al. (2011) found that men with higher CGG repeats (>100 CGGs) evidenced age-related associations with verbal inhibition errors, whereas the same pattern was not observed in men with lower CGG repeats (<100). At least one prior study has examined potential age and CGG interaction effects on verbal inhibition among women with the PM (Klusek et al., 2020). In this study, they found effects of age and CGG repeat length, such that older age and the mid-range of CGG repeats (i.e., 80-100 repeats) independently predicted longer response latency on the Hayling, but they did not find similar patterns with verbal inhibition errors, nor did they find interactions between age and CGGs. However, these studies were not longitudinal, limiting conclusions about age-related changes to

verbal inhibition. Further, this work did not examine the effects of both response latency and inhibition errors in the same analyses. Without this component, it is unclear whether response latency may have a compensatory impact on verbal inhibition errors. That is, it is possible that longer latency on the task could reduce the number of inhibition errors made.

1.2 Research Questions

Building on prior work that examined cross-sectional associations of age, *FMR1* CGG repeat length, and verbal inhibition, this study investigated three research questions in the context of a longitudinal study: i) Does verbal inhibition performance worsen over time among women with the PM? ii) Do declines in verbal inhibition vary as a function of age and/or CGG repeat length? iii) To what extent are errors in verbal inhibition affected by the latency of the response? We predicted that errors in verbal inhibition would increase over time. Based on prior cross-sectional work among women with the PM (Klusek et al., 2020), we predicted that older age and mid-range CGG repeats would interact to predict increased verbal inhibition errors over time. We further predicted that errors in verbal inhibition would be exacerbated by shorter response latency.

2. Methods

2.1 Participants and Procedures

Participants included 93 women with the *FMR1* PM who were biological mothers of children with fragile X syndrome, and who did not have a diagnosis of FXTAS. They were part of a longitudinal study, *Family Adaptation to Fragile X Syndrome* (Mailick et al., 2018; Seltzer, Barker, et al., 2012), that included five measurement timepoints over the course of approximately 10 years. Inclusion in the present study was based on participation at time 4 (T4; 2016-2018) and time 5 (T5; 2019-2020), when verbal inhibition was measured. At T4, mothers' ages ranged from 44-76 (M=58.19, SD=7.03). The average interval between T4 and T5 was 37.5

months, and ranged from 35 to 43 months. Hayling data from T4 has been analyzed in prior research (Klusek et al., 2020); the present study builds on that work by including the subsequent T5 data in a subset of participants (93 of 134 participants), thus yielding longitudinal data.

Participants were recruited from advertisements in fragile X clinics and support groups, university-based research registries, and national organizations. All participants provided informed consent in accordance with the Declaration of Helsinki and all procedures were approved by the University of Wisconsin-Madison and Marshfield Clinic Institutional Review Boards. At each timepoint, participants completed an audio-recorded telephone interview and self-report questionnaires, including demographic information, as part of the broader study.

2.1.1 ***Hayling Sentence Completion Test.*** The Hayling (Burgess & Shallice, 1997) is a direct-assessment measure of verbal inhibition. The measure is comprised of two parts; in part one, participants complete 15 sentences with the last word missing, and the word must complete the sentence logically (e.g., "The rich child attended a private school"). In part two, participants are instructed to complete 15 sentences with a word that does *not* complete the sentence or relate to the sentence in any way (e.g., "The rich child attended a private purple"). Latency is coded for both the first and second parts of the Hayling; however, for the purpose of this study we will refer to only to response latency in the second part of the Hayling (which measures verbal inhibition) and do not include latency scores from part one. Errors are scored in part two only. Errors in verbal inhibition are coded if the participant completes the sentence logically (category A errors) or uses a semantically-related or comical word to complete the sentence (category B errors, e.g., "The rich child attended a private bathroom"). Category A errors are weighted more heavily than category B errors (A=3 points, B=1 point). The summed, weighted score is computed for the converted error score. Converted error scores can range from 0-78, with higher

scores indicative of greater difficulties in verbal inhibition. This score was selected as the primary variable of interest, as previous work suggests that converted error scores differentiate women with the PM from controls (Kraan, Hocking, Bradshaw, et al., 2014; Kraan, Hocking, Georgiou-Karistianis, et al., 2014), and that individuals with frontal lobe damage make more errors than individuals without such lesions (Robinson et al., 2015).

In this study, the Hayling was administered over the phone, as described in prior work (Klusek et al., 2020). Response latency was first scored during task administration by a trained examiner. Secondary timing of response latency was independently completed by a trained coder (first author) via audio recording. Converted error coding for T4 was completed as described previously (Klusek et al., 2020). T5 converted error coding was completed by the first author, and reliability coding was completed by a trained examiner on 20% of the files. Two-way random intra-class coefficients were used to evaluate reliability. Average inter-rater reliability was "excellent" (ICC (2,2) = .998) (Koo & Li, 2016). Hayling data were missing for one participant at T4, yielding a total of 92 participants in the present study.

2.2 Evaluation of *FMR1* CGG Repeat Length

FMR1 CGG repeat length was derived from buccal swabs at T4. Samples were processed at Rush University Medical Center in the laboratory of Dr. Elizabeth Berry-Kravis. The longer *FMR1* allele was used in all analyses (see Maltman et al., under review for further details).

2.3 Analysis Plan

Analyses were conducted in IBM SPSS Statistics, version 26 (IBM Corp., 2019). All variables were examined for normal distributions at each timepoint. Due to right skew, Hayling converted error scores at T4 and T5, as well as response latency, were square root transformed, consistent with prior work (Cornish et al., 2015; Shelton et al., 2016). For research question 1,

we conducted repeated measures analyses of covariance, controlling for education, to evaluate whether verbal inhibition errors increased over time. Education was ordinally coded on the following scale: 1 (less than high school), 2 (high school degree), 3 (college degree or equivalent), 4 (master's degree or above), and was treated as a categorical variable in all analyses. Response latency was also evaluated for change over time.

For research question 2, we conducted multiple regressions to investigate the extent to which age, CGG repeat length, and their interaction predicted change in verbal inhibition over time (i.e., T5 converted error score, T5 latency). Age and CGG repeat length were mean centered in all regression models for interpretability. The first model included education, the T4 converted error score, age, and CGG repeat length (long allele) as predictors. Subsequently, the age x CGG interaction term was included in the model. To evaluate research question 3, we used multiple regressions to examine whether response latency at T5 predicted verbal inhibition errors at T5. The model included age, education, and T5 response latency. Of note, we also investigated whether controlling for the short CGG allele influenced the findings and found no significant effects (*p*s> .254). Thus, we did not retain this variable in any of the final models. Regression diagnostics were completed using Cook's *D* based on the criteria $D>4=(1\text{-}k\text{-}n)$ and no outliers were observed.

3. Results

3.1 Descriptive Findings

Participant descriptives are presented in Table 1. The participant sample was highly educated, as 89.2% of individuals had obtained a college degree or higher. The average CGG repeat length on the long allele was 95, with a range of 67-138. At T4, 25% of the sample had scaled error scores in the "Impaired", "Abnormal" or "Poor" range based on norms outlined in

the Hayling test manual, and which correspond to at or below the 5th percentile (Burgess & Shallice, 1997). At T5, 19.4% of the sample had scaled error scores in the same range, which was not a significant change from T4 (p=.747).

[INSERT TABLE 1 HERE]

For research question 1, repeated measures ANCOVAs evaluated the extent to which verbal inhibition errors changed over time. After controlling for education, no significant changes were observed in the sample from T4 to T5 in the converted error score (F(1,90) = 2.92, p=.091, η_p^2 =.031) or in response latency (F(1,90) = 2.45, p=.121, η_p^2 = .027).

3.2 Age and CGG Effects

For research question 2 (shown in Table 2), we investigated the extent to which age and CGG repeat length predicted change in converted error scores from T4 to T5. The overall model using age as a predictor of the converted error score over time was significant F(3,88) =8.26, p<.001, R^2=.22. In model 1, we found a significant effect of age (b = .057, p=.008), suggesting that older age predicts greater change in the converted error score over time. The overall model including CGG repeat length as a predictor of the converted error score over time was significant F(4,87) = 6.45, p<.001, R^2 = .23. However, we found no linear effects of the CGG term on change in converted errors (b =.009, p =.319). This indicates that CGG repeat length does not independently predict change in converted error score.

[INSERT TABLE 2 HERE]

We also investigated the interaction between age and CGG repeats, which was the key focus of research question 2. The overall model was significant F(5,86) = 6.22, p<.001, R^2 = .27. As shown in table 2 (model 2) and in Figure 1, the age by CGG interaction term significantly predicted verbal inhibition errors (b = .003, p=.040), such that older participants (>58 based on

median split) who had greater CGG repeats (>100) exhibited greater increases (i.e., poorer performance) in the converted error score from T4 to T5 (y=.1+.3x). The covariates of education and T4 converted error score were significant predictors of T5 converted error score across all models for research question 2 (p-values <.041, .002, respectively). We also evaluated quadratic and cubic CGG effects, neither of which were significant predictors of change in the converted error score (p =.358, p =.412, respectively).

In addition to the converted AB error score, we evaluated influences of age and CGG repeat length on latency. No age (ps >.100), CGG (ps >.511), or interaction effects (p = .753) were observed on change in latency score from T4 to T5. Higher education significantly predicted faster latency at T5 (p = .008).

[INSERT FIGURE 1 HERE]

Figure 1. Older age and higher CGG repeats interact to influence change in verbal inhibition errors over time.
Note: Age is depicted by a median split (58 years), but was a continuous variable in all analyses.

3.3 Effects of Response Latency on Errors

For research question 3, we investigated the extent to which the converted error score at T5 might be predicted by response latency. The overall model was significant $F(5,86) = 6.79$, $p<.001$, $R^2 = .28$. As shown in Table 3, we found a significant effect of response latency (b=.187, p=.013), such that longer latency at T5 significantly predicted a greater converted error score at T5. Thus, longer latency was not compensatory, but rather reflected greater difficulty with this task. Education was not a significant predictor of converted errors at T5 in this model.

[INSERT TABLE 3 HERE]

4. Discussion

The present study examined verbal inhibition in a longitudinal sample of women with the *FMR1* PM across two time points approximately three years apart. To the best of our knowledge, this is the first investigation of verbal inhibition changes over time among women with the *FMR1* PM. We were interested in the extent to which age, CGG repeat length, and their interactions may have influenced verbal inhibition over time. In the full sample, no significant changes in verbal inhibition were observed between the two timepoints. Age independently predicted change in verbal inhibition over time, as has been shown in the general population (Andrés & Van der Linden, 2000; Bielak et al., 2006). CGG repeat length did not independently predict change in verbal inhibition over time. However, an interaction effect was observed between age and CGG repeat length. Follow-up analyses suggested that verbal inhibition worsened more among the subset of PM carriers who were older (>58 based on median split) and had higher CGG repeats (>100 CGGs). Finally, longer latency predicted *greater* error scores. In other words, longer latency did not appear to be a compensatory strategy in reducing inhibition errors. This study advances literature in the *FMR1* PM by highlighting the importance of longitudinal investigations of executive function, and specifically of verbal inhibition, as a promising marker related to clinical risk profiles.

Our first research question evaluated the extent to which verbal inhibition changed over time. In contrast with our prediction, after controlling for education, no changes in verbal inhibition were observed in the full sample. Prior work on adult PM carriers has identified differences in verbal inhibition compared to controls (Kraan, Hocking, Georgiou-Karistianis, et al., 2014; Shelton et al., 2016), but no studies have documented *changes* in verbal inhibition over time in this population. Our findings suggest that declines in verbal inhibition are not universal among women with the PM, particularly in the relatively short time period (three years)

evaluated here. As a group, PM carriers may decline in verbal inhibition over time, as prior work suggests declines in verbal inhibition after age 70 among the typical aging population (Gibson et al., 2019). However, a subset of PM carriers in the present study were observed to decline in verbal inhibition approximately 10 years earlier, with more verbal inhibition errors evident by age 58 for those with high CGGs. More work is needed to determine the time course for changes in verbal inhibition among both men and women with the PM who do and do not have children with fragile X syndrome, as well as to evaluate the extent to which changes are aligned with patterns observed in typical aging. These findings will have implications for aging research in the PM, as verbal inhibition declines may be associated with specific brain regions. For instance, Kogan and Cornish (2011) posited that errors in response inhibition may be related to brain regions susceptible to *FMR1*-mediated toxicity among men with the PM (Cornish et al., 2008). As such, a possible next step in this work could be to explore neural associations with verbal inhibition and other measures of *FMR1*-related expression (e.g., mRNA) among women.

Our second research question examined the manner in which age and CGG repeat length affected verbal inhibition over time. Contrary to our prediction that women with CGG repeats in the mid-range would demonstrate the greatest changes in verbal inhibition, we did not observe independent CGG effects. Although we predicted interactions between age and CGG repeat length in the mid-range, interactions occurred between age and CGG repeats at the higher end of the PM range (>100 repeats). This finding is consistent with some prior work among men with the PM, which suggested linear effects of age and CGG repeats on executive function (Hunter et al., 2012), and greater errors in verbal inhibition for men with >100 CGG repeats (Cornish et al., 2011). Among women with the PM, Klusek et al. (2020) found independent effects of age and mid-range CGG repeat length in a cross-sectional sample, which overlaps in part with

participants from this study. However, that study was primarily focused on latency, whereas this study considers verbal inhibition errors as the central variable in the analyses. We did, however, evaluate potential interactions between age and CGG repeats on latency, and did not find significant effects. Together, these findings suggest that verbal inhibition errors, rather than latency, may be more sensitive to *changes* in verbal inhibition among women with the PM, and thus may be a valuable metric for use in clinical contexts.

Our third research question evaluated the extent to which latency might affect verbal inhibition errors. In contrast with our prediction that longer latency would reduce verbal inhibition errors, we found that longer latency was associated with more errors. This suggests that latency is not necessarily compensatory. That is, if errors were explained by shorter latencies, this would indicate that errors were sacrificed in exchange for short latencies; however, given that we found the opposite pattern, this indicates that increased latency does not reduce the number of errors produced. We also examined whether latency was affected by age and CGG repeats. However, latency was not predicted by age, CGG repeat length, or their interactions, suggesting that the links between latency and errors were not specific to a particular subgroup of PM carriers, but rather were characteristic of the full sample.

Shelton et al. (2016) hypothesized that temporal restrictions influence performance on executive function tasks, including the Hayling. As such, reduced integrity of underlying neural mechanisms that influence efficient executive functioning could adversely affect both timing and access to correct responses. In other populations (e.g., individuals with mild cognitive impairment; Alzheimer's), verbal inhibition errors are posited to reflect difficulties in lexical-semantic access (Belleville et al., 2006). Alternatively, it may be that verbal errors are indicative of domain-general declines (i.e., across cognitive domains) (Belanger & Belleville, 2009;

Belleville et al., 2006), as links to working memory, intelligence, reasoning, and semantic fluency (Gibson et al., 2019) have been identified in other populations (e.g., healthy aging, Alzheimer's). In consideration of the temporal restrictions, verbal, and executive demands required in the Hayling, further exploration regarding the specificity of these findings is warranted.

Current findings are suggestive of a risk profile among a subset of women with the PM who have not been diagnosed with FXTAS (i.e., older age and high CGGs within the premutation range). Therefore, it will be critical to examine possible underlying mechanisms, as specific neural areas have been implicated in FXTAS (i.e., the cerebellum) but may also be relevant more generally to those who have higher CGGs in the premutation range. Findings from diffusion tensor- and magnetic resonance imaging studies suggest that the integrity of white matter connecting the cerebellum with prefrontal areas is essential for optimal executive functioning (Madden et al., 2009; Shelton, Cornish, Godler, et al., 2017). Reduced white matter integrity has been observed among men with the PM asymptomatic for FXTAS (Battistella et al., 2013), along with associations of verbal retrieval performance (Hippolyte et al., 2014). Thus, it may be that behavioral markers, such as verbal inhibition, could reflect earlier changes in neural functioning that may be related to later symptoms of FXTAS. More longitudinal work will be needed to explore this hypothesis among individuals who do and do not go on to develop FXTAS symptoms.

4.1 Limitations and Future Directions

This study was strengthened by a substantial number of women with the PM who participated in a decade-long study, which enabled the longitudinal examination of verbal inhibition described here. However, we were limited in that we only had two timepoints from

which Hayling data were available, which restricted our ability to determine how verbal inhibition patterns changed over a longer period of time. We were also limited in our sample characteristics, as the majority of the sample was highly educated. As we observed associations between education, errors, and latency, future research should include participants from more diverse socioeconomic backgrounds, which is likely to reveal a broader range of responses. The study is also limited in that it included only mothers of children with fragile X syndrome. Future research should consider the inclusion of both men and women with the PM who do and do not have children with fragile X to better understand the relative impact of parenthood and CGG repeat length on the verbal inhibition patterns observed here. Finally, future research should consider the inclusion of other markers of *FMR1*-related functioning, including activation ratio and mRNA, which could aid in explicating potential mechanisms underlying verbal inhibition decline in the subset of PM carriers who may have unique clinical risk profiles.

4.2 Conclusions

This study examined verbal inhibition among a cohort of mothers of children with fragile X syndrome studied longitudinally. We observed that a subset of this group, those with higher CGGs (>100 repeats) and older age (>58), exhibited declines in verbal inhibition within a three-year period. This work contributes to literature suggestive of subgroups of PM carriers who may be at increased clinical risk (Allen et al., 2020; Klusek et al., 2020; Maltman et al., 2021). Continued work in this area, particularly as it relates to underlying mechanisms, will help to elucidate which PM carriers may be at increased risk for FXTAS and other conditions common to the *FMR1* PM.

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Table 1. Participant Descriptives

	T4 (*n*=92)	T5 (*n*=92)
	M (SD), Range)	*M*, (SD), Range)
Education (College degree or higher)	89.2%	--
Age	58.19 (7.03), 44-76	60.83 (7.06), 47-79
CGG Repeat Length	95.00 (16.81), 67-138	--
Latency (seconds)	50.53 (32.06), 1-184	52.97 (36.39), 15-230
Converted Error Score	10.17 (12.08), 0-47	8.49 (9.86), 0-52
Transformed Converted Error Score [a]	2.67 (1.75), 0-6.86	2.51 (1.48), 0-7.21
Transformed Latency (seconds)	6.77 (2.17), 1.00-13.56	6.99 (2.08), 3.87 – 15.17

Note: T4: timepoint 4, T5: timepoint 5.
[a] Reflects square root transformation.

Table 2. Age and CGG Repeat Length Predict T5 Converted Error Score

		b	S.E.	*p*	R^2
Model 1	(Constant)	-.724	1.695	.670	.229
	Age	.057	.021	**.008**	
	Education	-.507	.223	**.025**	
	Converted Error Score (T4) [a]	.285	.080	**.001**	
	CGG Repeat Length	.009	.009	.319	
Model 2	(Constant)	-1.577	1.713	.360	.266
	Age	.061	.020	**.004**	
	Education	-.460	.220	**.040**	
	Converted Error Score (T4) [a]	.297	.079	**.000**	
	CGG Repeat Length	.014	.009	.118	
	Age x CGG	.003	.001	**.040**	

Note: Significant values in **bold**, marginal values in *italics*.
[a] Reflects square root transformation.

Table 3. Latency Predicts T5 Converted Error Score

	b	S.E.	*p*	R^2
(Constant)	-.353	1.284	.784	.275
Age (T4)	.036	.021	.092	
Education	-.340	.229	.142	
Converted Error Score (T4) [a]	.248	.080	**.003**	
Latency (T5) [a]	.176	.073	**.018**	

Note: Significant values in **bold**, marginal values in *italics.*
[a] Reflects square root transformation.

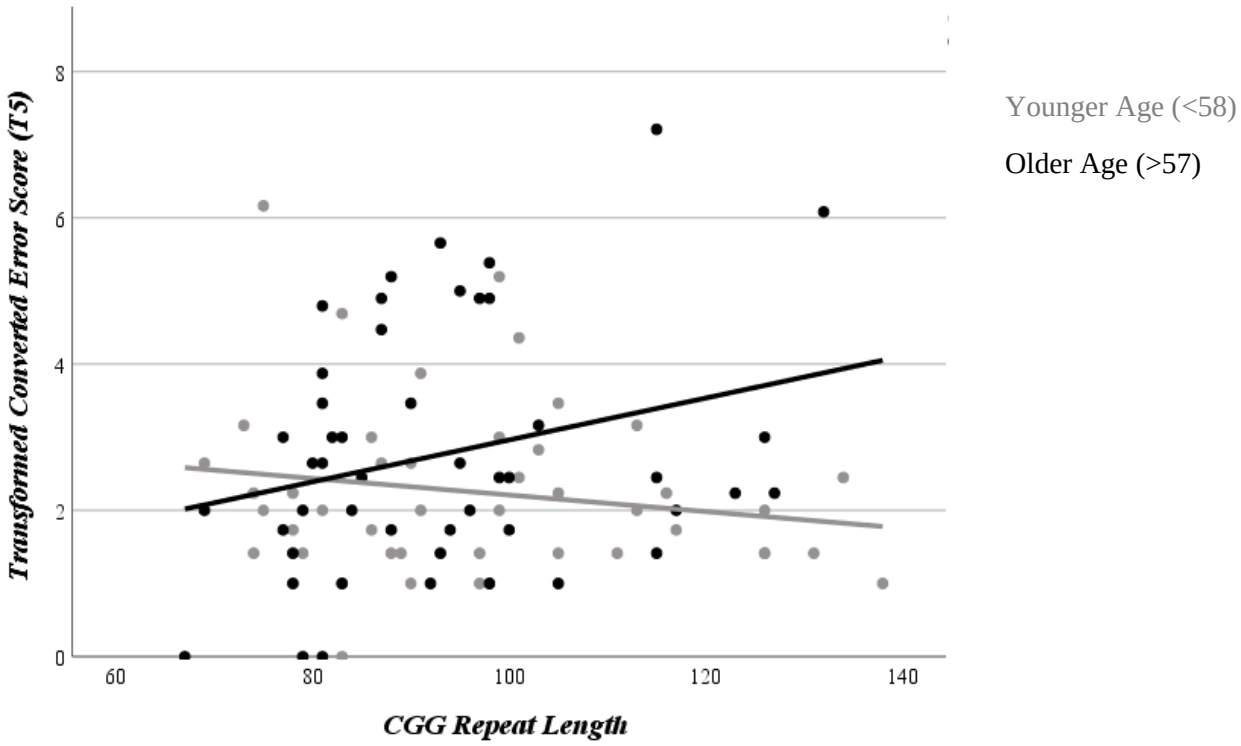

Figure 1. Older age and higher CGG repeats interact to influence change in verbal inhibition errors over time.
Note: Age is depicted by a median split (58 years), but was a continuous variable in all analyses.