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Antisaccade Performance as a Measure of Executive Dysfunction in Women With the *FMR1* Premutation

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ANTISACCADE PERFORMANCE AS A MEASURE OF EXECUTIVE DYSFUNCTION IN WOMEN WITH THE *FMR1* PREMUTATION

by

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Abstract

Women with the *FMR1* premutation appear to be at increased risk for executive dysfunction. Findings in this regard have been mixed, leading to controversy surrounding the executive phenotype. Inhibitory deficits have been a more consistently documented component of this cognitive profile (Klusek et al., 2020; Shelton et al., 2014). This study aimed to clarify the executive phenotype through use of the antisaccade task, a well referenced eye-tracking paradigm that targets oculomotor inhibition and motor control and imposes time constraints that may increase sensitivity to executive deficits in women with the *FMR1* premutation. The effects of aging were examined in both groups on performance in this paradigm, as emerging research has referenced cognitive decline with age in the *FMR1* premutation. Participants included 35 women with the *FMR1* premutation and 27 control women. Decreased abilities in both the motor and inhibitory command portion of this task were exhibited by women with the *FMR1* premutation. Longer latency was also associated with older age in the *FMR1* premutation group, suggesting premature aging in this population. These findings may elucidate the underpinnings of this phenotype, inform age-related decline in this population, and provide information to successfully target these deficits in order to improve quality of life

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Chapter 1

Introduction

There are estimated to be one million women in the United States who carry a genetic mutation known as the *FMR1* premutation (Maenner et al., 2013). The *FMR1* premutation is defined as an expansion of 55-200 CGG repeats on the *FMR1* gene found on the X chromosome. Women with the *FMR1* premutation are sometimes referred to as "fragile X carriers" because premutation repeat lengths are unstable upon intragenerational transmission, and may be translated into the full mutation when passed down from mother to child (Willemsen et al., 2011; Yu et al, 1991; Oberle et al., 1991; Nolin et al., 2003). The full mutation, which causes fragile X syndrome, is the result of an expansion of >200 CGG repeats on the *FMR1* gene. This population of individuals continues to be described in the literature, as fragile X syndrome is associated with serious neurodevelopmental consequences such as intellectual disability and autism spectrum disorder. The *FMR1* premutation also represents a clinical population of interest as recent evidence suggests that individuals with the *FMR1* premutation are at risk for a range of symptoms and disorders associated with their genetic status. However, the phenotype of the *FMR1* premutation continues to remain largely undefined in research, particularly in women who are believed to show a more subtle symptom profile due to the protective effects of the second X chromosome. There is a need for additional research aimed at defining the *FMR1* premutation phenotype, considering that the

premutation expansion affects 1 in 151 females and 1 in 486 males in the United States (Seltzer et al., 2012). Both males and females with the *FMR1* premutation may experience neurodevelopmental and neurodegenerative differences not seen in the general population (Shelton et al., 2014; Jacquemont et al., 2007). Some common medical and psychiatric challenges observed are immune mediated disorders, migraines and/or headaches, vestibular issues and mood disorders including depression and anxiety (Winarni et al., 2012; Au et al., 2013; Smith et al., 2012; Seltzer et al., 2012; Johnston et al., 2001; Lachiewicz et al., 2006; Seltzer et al., 2012). Two specific conditions, however, are solely associated with the *FMR1* premutation. This includes risk for developing a late-onset neurodegenerative condition known as fragile X tremor/ataxia syndrome (FXTAS), which typically first manifests over the age of 50 (Rodriguez-Revenga et al., 2009). Women with the premutation may also develop fragile X primary ovarian insufficiency (FXPOI), characterized by premature menopause, in about 20% of premutation carriers as compared to 1% of the general population (Shelton et al., 2014; Rodriguez-Revenga et al., 2009; Sherman, 2000). As both FXTAS and FXPOI are age-related disorders, researchers have begun to conceptualize the *FMR1* premutation as a condition of premature biological aging. This aligns with emerging evidence that other aspects of the *FMR1* premutation phenotype, such as executive dysfunction, also show age-related decline. For example, verbal inhibition deficits in women with the *FMR1* premutation are correlated with older age (Klusek et al., 2020).

Although cognitive deficits, particularly executive dysfunction, have been documented in prior research, the executive profile remains an area of controversy in women with the *FMR1* premutation (Loesch et al., 2003; Grigsby et al, 2008; Cornish et

al., 2008; Lachiewicz et al., 2006). Some studies have found evidence of executive deficits in the domains including verbal fluency, response inhibition, mental flexibility, and working memory (Shelton et al., 2014; Kogan et al., 2010). However, not all studies have found evidence of executive deficits (e.g., Hunter et al., 2008). Age of the sample is thought to be one source of inconsistency, given evidence that premutation symptoms may become more pronounced with age. Measurement effects may represent another source of inconsistency. For example, many studies employing self-report and broad neuropsychological test batteries have failed to detect executive differences between women with the *FMR1* premutation and controls (Hunter et al., 2008). In contrast, tasks that impose time constraints in the measurement of executive dysfunction have been more successful at differentiating women with the *FMR1* premutation from controls (Kraan et al., 2014; Shelton et al., 2016; Klusek et al., 2020).

In the present study, we employed the antisaccade task as a measure of response inhibition that may impose time constraints and therefore may have increased sensitivity to executive deficits in the *FMR1* premutation. In this paradigm, the participant is directed to look at or away from a target as it appears on a computer screen, as quickly as possible. The recorded eye movements are called 'prosaccades' (looking at the target) or 'antisaccades' (looking away from the object). Response time in the prosaccade condition, where the individual looks at the target, directly indexes sensory motor control (Peltsch et al., 2014). In contrast, the antisaccade trials require the participant to voluntarily inhibit an automatic response towards the visual stimulus by looking in the opposite direction, showing ability to suppress a prepotent response (Munoz & Everling, 2004). This condition provides an index of response suppression and voluntary motor

command. Variables commonly extracted from the prosaccade and antisaccade condition include peak velocity and latency which reflect activation and inhibition, subdomains of executive functioning, as well as motor control (Mirsky et al., 2011). Saccade latency can be described as the amount of time elapsed between the presentation of the stimuli and the initiation of a saccade (Carpenter, 1988). Peak velocity is a measure of how quickly the eyes move from an area of fixation to the target stimuli, after the eye movement is initiated. Finally, error rate for the antisaccade condition is measured when an individual directs their gaze towards the target when told to avert their gaze. Antisaccade error rates increase with decreased inhibition abilities (Antoniades et al., 2013; Hallett, 1978).

Although the antisaccade task appears relatively simple in nature, it measures various underlying cognitive processes that are otherwise difficult to assess. The ability to extract information on both the accuracy and the latency (timing) of responses is also advantageous as it may facilitate the detection of subtle deficits. Therefore, it has been suggested that performance on this paradigm may be useful in tracking the progression of neurodegenerative disease including Parkinson's, Alzheimer's, and spinocerebellar ataxia (Deubel & Schneider, 2003; Anderson & MacAskill, 2013; MacAskill & Anderson, 2016). For example, in individuals with Parkinson's, saccades are often hypometric and show prolonged latencies. Even early on in this disorder, increased errors are found in the antisaccade portion of the task (Gorges et al., 2015; Antoniades et al., 2015; MacAskill & Anderson, 2016). Individuals with the *FMR1* premutation are also at risk for neurodegenerative disease (FXTAS). Therefore, there is potential utility in applying the antisaccade task to the *FMR1* premutation because this measure may be more

sensitive to the earliest signs of neurodegeneration (Hagerman et al., 2004; Antoniades et al., 2015).

Preliminary evidence supports the promise of the antisaccade task as a measure of inhibition in individuals with the *FMR1* premutation. One study in 21 males with the *FMR1* premutation who were asymptomatic of FXTAS has been performed. Findings supported inhibitory deficits, marked by increased latency in the antisaccade condition, but no noticeable differences in oculomotor control were detected as indicated by performance on the prosaccade condition (Wong et al., 2014). However, this study solely examined males with the *FMR1* premutation therefore, it remains unclear whether these results generalize to women with the *FMR1* premutation who experience subtler symptoms due to the protective effects of the second X chromosome. A preliminary report by Shelton et al. (2014) found increases in antisaccade errors in a small sample size of 14 women with the *FMR1* premutation as compared to the control group. No other significant differences were found between these women with the *FMR1* premutation and controls in the latency of responses.

This study extends these preliminary findings to test oculomotor inhibition skills in a larger sample of women with the FMR1 premutation, and to test the presence of age effects. Our research questions are:

1. Do women with the *FMR1* premutation exhibit differences in performance on the antisaccade task (on both prosaccades & antisaccades) compared to neurotypical control women? *We hypothesize that women with the FMR1 premutation will show deficits in particular areas of this task including*

longer latency, slower peak velocity, as well as increased errors on the antisaccade portion of this task.

2. What is the effect of age on performance in the prosaccade and antisaccade condition of women with the *FMR1* premutation and does this differ from controls? *We hypothesize that as women with the FMR1 premutation age, they will exhibit increased errors as well as decreased latency on the antisaccade task.*

Chapter 2

Methods

Participants

Participants included 35 women with the *FMR1* premutation (55-200 CGG repeats; experimental group) and 27 mothers of typically developing children (control group). The control group comprised of mothers of typically developing children in order to reduce the possibility of a family history of fragile X syndrome, in turn, reducing the probability that the control participants carried the *FMR1* premutation themselves. There were several additional individuals (4 women with the *FMR1* premutation and 3 control women) who were recruited for this study but didn't participate in the eye tracking component due to inability to calibrate eye tracker (e.g., participant wore blue-light blocking glasses).

In facilitating recruitment, women with the *FMR1* premutation were recruited through social media and word of mouth as well as through their children who were participating in developmental studies of fragile X syndrome with nation-wide recruitment. Control women were recruited locally through social media, word of mouth, and flyers posted on the University of South Carolina campus as well as in local pediatricians' offices. Inclusionary criteria for the study were as follows: All participants were fluent speakers of English. Presence of the *FMR1* premutation was confirmed via

genetic testing or by medical record review. Children of the women in the control group were considered typically developing as determined by no parent reported history of developmental delay as well as parental screening for autism symptoms through the use of Social Communication Questionnaire (SCQ; Rutter et al., 2014). All control women scored above 80 on the Kaufman Brief Intelligence Test, 2nd edition (KBIT-2; Kaufman et al., 2013).

Procedures

The antisaccade task was integrated into a three-hour research protocol in which family outcomes as well as language and cognitive abilities were examined. This particular task took place an hour into the protocol, after executive functioning measures and language sample, and took about 20 minutes. Informed consent was obtained from all participants and procedures were approved by the Institutional Review Board of the University of South Carolina.

Measures

Apparatus/Instrumentation

Eye movement was measured using the Eyelink 1000 Plus eyetracker (SR Research Ltd, Ontario, Canada). Stimuli were presented on a Ben-Q 2420T monitor (530 mm x 300 mm x 768 pixels, 60 Hz). A chin rest, centered at a distance of 750 mm from the display screen, was used to facilitate correct positioning of the participant's head during recording, although recordings were conducted in remote mode. An initial nine-point calibration and validation were performed at the start of the procedure. Recalibration was performed as needed. Calibrations were accepted if the average error was less than <.5° and the maximum error <1.00°.

Stimuli/Paradigm

Design of the antisaccade task was modeled after the standardized protocol described by Antoniades et al., (2013). The paradigm consisted of ten prosaccade practice trials with feedback, a block of 60 prosaccade trials, five antisaccade practice trials with feedback, three blocks of 40 antisaccade trials each, and a final block of 60 prosaccade trials. Participants were offered breaks between each block, and the entire task lasted about 20 minutes. Prior to the prosaccade trials, participants were provided the following instructions: "Look at the central X; as soon as a new dot appears on the left or right, look at it as fast as you can." The instructions preceding the antisaccade trials were as follows: "Look at the central X; as soon as a new dot appears on the left or right, look the same distance in the opposite direction, as fast as you can." Directions were presented verbally by the examiner as well as visually on the screen.

Each block began with a drift check consisting of a 1° diameter black circle presented on the center of a grey screen. The drift check was followed by a fixation screen with a black "X" (1° x 1.5°) presented in the center of a grey screen. The central fixation "X" was surrounded by black flanking square markers (0.5° x 0.5°) presented 8° to the left and right, marking the potential target location. The fixation screen was displayed for an average of 1.5 seconds, and then followed by a blank grey screen that was displayed for an average of 150 ms (range from 100 ms to 200 ms). Then, the target screen was displayed consisting of a black box (1° x 1°) which appeared to the left or the right, 8° from the center of the screen. Target location was counterbalanced within each block so that the target would be presented equally across both locations. The target

screen was shown for 1 second and then was immediately followed by the fixation screen for the next trial, except for every tenth trial in which a drift correct was presented.

Data Cleaning and Extraction

First, the data were cleaned to exclude invalid trials. Trials were discarded if the latency of the saccade was shorter than 80 ms or longer than 600 ms, consistent with previous research (Shelton et al., 2014). The latency and peak velocity for both the prosaccade and antisaccade were analyzed as variables of interest. Only data from accurate saccades were included for these variables. Accuracy was also examined in the antisaccade condition, calculated as the percent of total trials correct. All participants contributed usable data for >80% of trials.

Data Analysis

Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Data were examined for normality and left skewing of the data was detected for percent correct for the antisaccade condition. The data for this left skewing was transformed by lambda of 2.5 using BoxCox procedure (Box & Cox, 1964) to find the optimal power transformation. However, use of the transformed variable analysis had no effect on model inferences; thus, analyses on the non-transformed data are reported to facilitate interpretation. In order to examine group differences on performance in each condition, a series of linear mixed models were performed, testing the effect of group, block number, and the interaction between groups and block number. Block number was added as a predictor to account for order effects. To address the second research question regarding the effect of age, a series of linear mixed models were performed testing the effect of group, block number, age, and the interaction between group and age. Given that the

primary models did not support the presence of significant group-by-block interaction effects for any of the outcomes, this interaction term was not included in the models testing age effects. The outcomes included latency and peak velocity for the antisaccade and prosaccade conditions, and the antisaccade error rates.

Chapter 3

Results

Group Comparisons on Prosaccade Indices of Voluntary Oculomotor Initiation

The mixed effects linear model showed a significant main effect for group (F [1, 60] = 9.01, p = .004; Figure 1), where the *FMR1* premutation group displayed longer latencies. Block number (F [1, 60] = 2.02, p = .161) and the interaction between group and block number (F [1, 60] = .11, p = .740) did not account for significant variance in the model. The mixed model testing group differences in prosaccade peak velocity showed no significant effects for group (F [1, 60] = .02, p = .901), block number (F [1, 60] = 1.55, p = .218), or group-by-block number interaction (F [1, 60] = .11, p = .744)

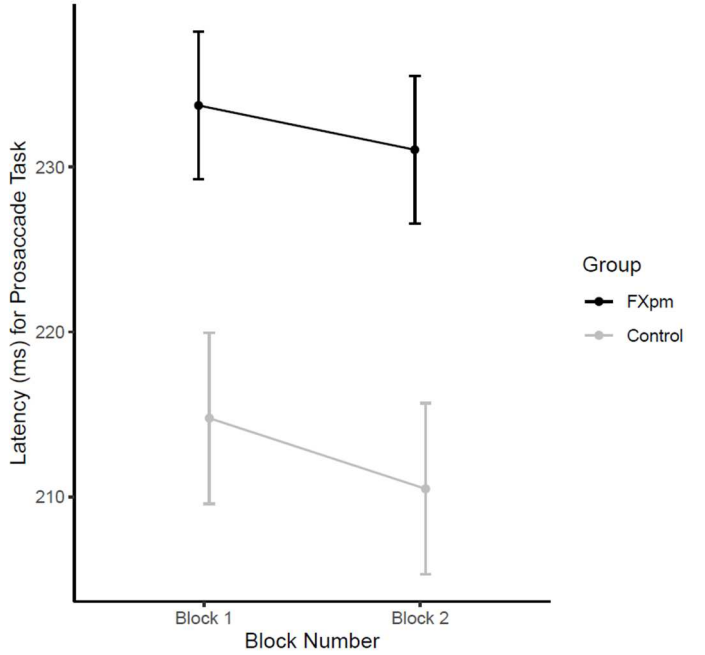
Group Comparisons on Antisaccade Indices of Oculomotor Inhibition

The mixed effects linear model showed a significant main effect for group on response latency (F [1, 60] = 13.03, p = .001; Figure 2), such that those with the *FMR1* premutation took longer to respond than the control group. There was no significant effect of block number (F [2, 60] = .68, p = .512) or the interaction between group and block number (F [2, 60] = 2.65, p = .079) on response latency. No group (F [1, 60] = .14, p = .706), block (F [2, 60] = 2.48, p = .092), or group-by-block (F [2, 60] = .26, p = .771) effects were observed for peak velocity. Finally, the mixed effect model testing the percentage of correct responses showed a significant main effect for group (F [1, 60] = 4.43, p = .040; Figure 3), with those with the *FMR1* premutation exhibiting a lower percentage of correct responses. Block number also had a significant effect on percent

correct (F [2, 60] = 4.22, p = .019), where accuracy decreased across blocks. There was not a significant interaction between group and block number, indicating that the order effect associated with block number was similar across the groups (F [2, 60] = .08, p = .926).

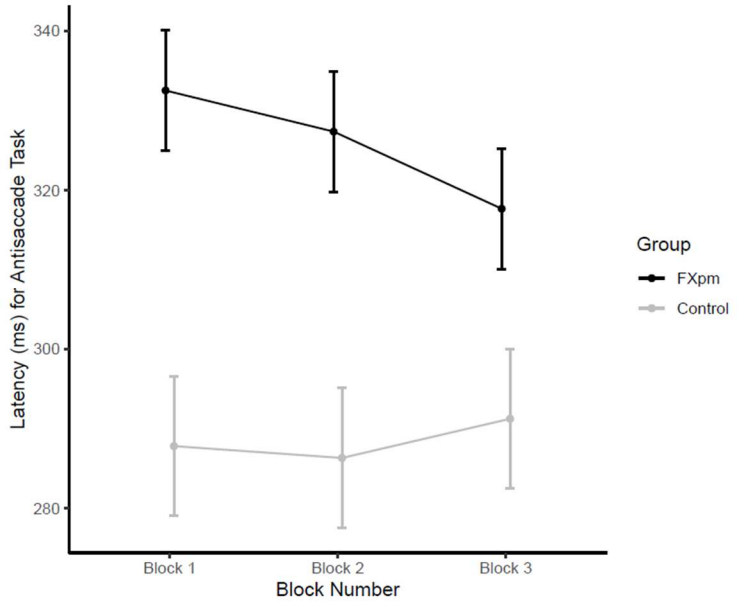
Age Effects on Prosaccade and Antisaccade Performances

Age effects were detected for both prosaccade and antisaccade latency variables. For the prosaccade model, a significant main effect for age was detected, where longer prosaccade latency (averaging across blocks) was associated with older age (F [1, 58] = 6.67, p = .012). See Figure 4. The interaction between group and age was not significant (F [1, 58] = 1.20, p = .278), indicating that the association between age and prosaccade latency was similar across the groups. Block did not account for significant variance in the model (F [1, 58] = 1.92, p = .171). For the antisaccade latency outcome, the main effect of age was not significant (F [1, 58] = 2.75, p = .103) but a significant group-by-age interaction was detected where older age was associated with longer latency (examining averages across blocks) in the *FMR1* premutation group but not in controls (F [1, 58] = 6.43, p = .014), see Figure 5. The effect of block was not significant (F [2, 58]= 0.98 p = .383). No main effects or interaction effects for age were observed for any of the other prosaccade or antisaccade outcomes (ps> .101).



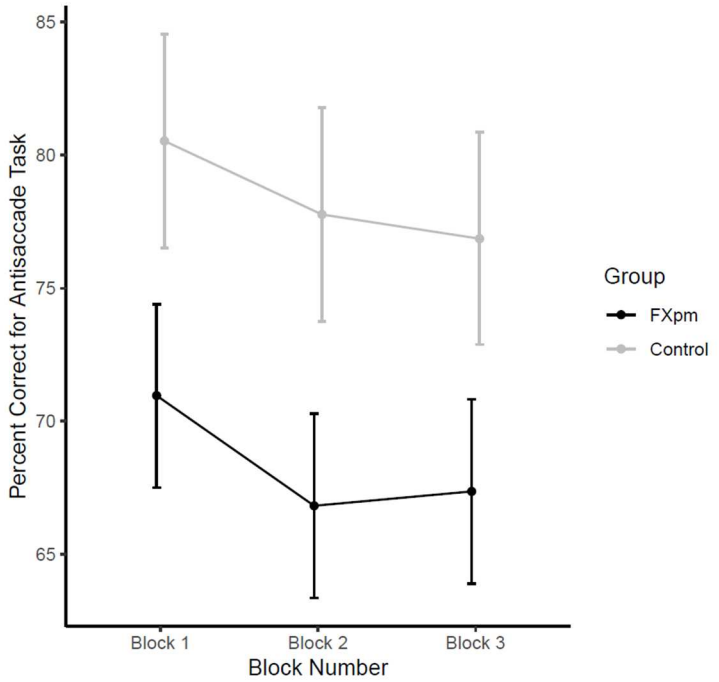
Note. FXpm = *FMR1* Premutation

Figure 3.1 Prosaccade latency across blocks and groups



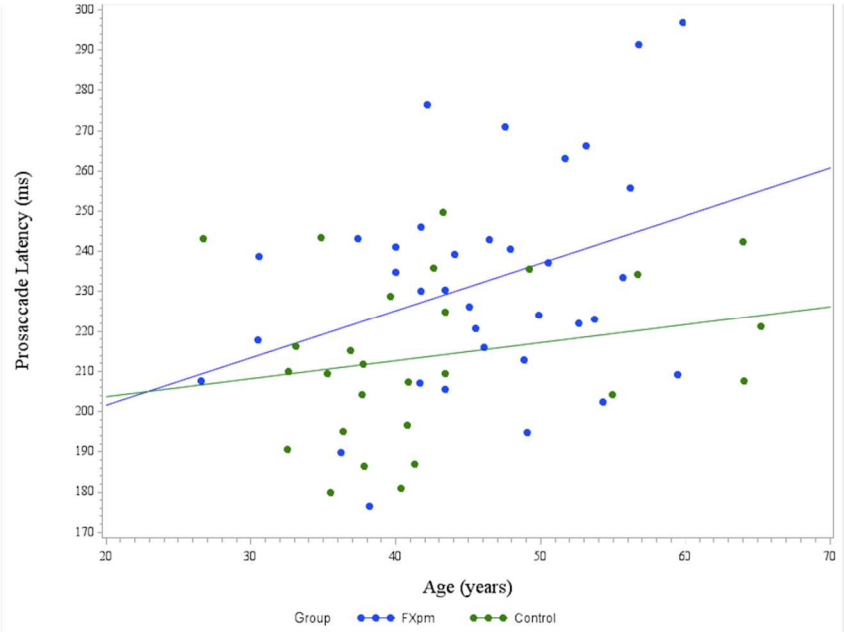
Note. FXpm = *FMR1* Premutation

Figure 3.2 Antisaccade latency across blocks and groups



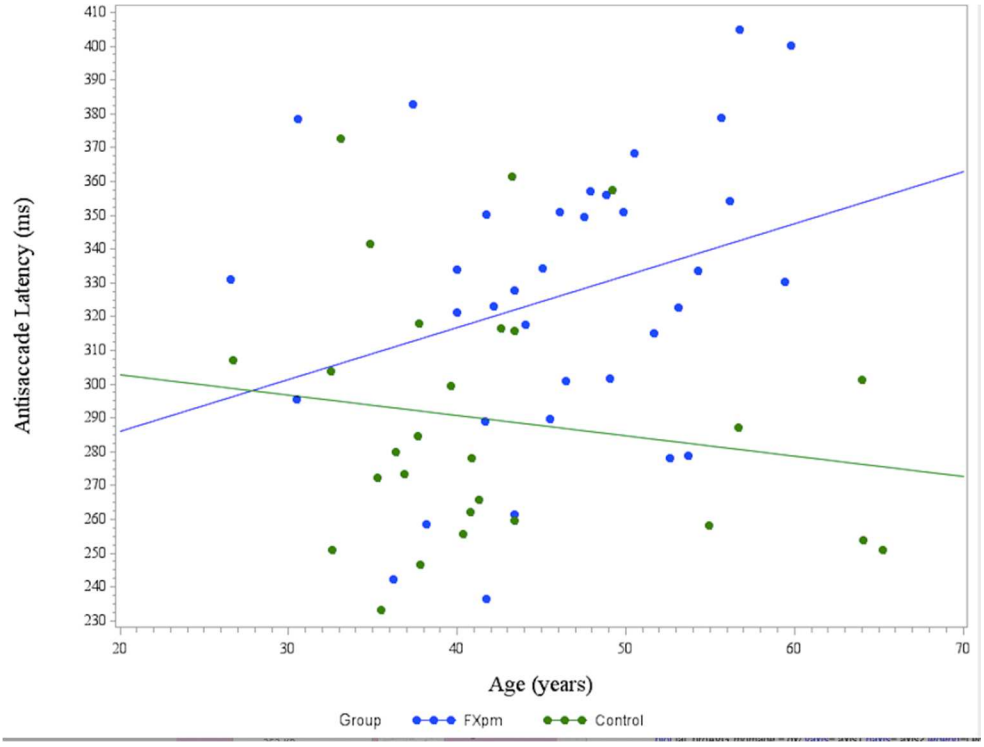
Note. FXpm = *FMR1* Premutation

Figure 3.3 Antisaccade percent correct across blocks and groups



Note. FXpm = *FMR1* Premutation

Figure 3.4 Association between age and prosaccade latency (average across blocks)



Note. FXpm = *FMR1* Premutation

Figure 3.5 Association between age and antisaccade latency (average across blocks) across the groups

Chapter 4

Discussion

The primary aim of this study was to further examine executive functioning deficits in women with the *FMR1* premutation. We used the antisaccade task, a measure sensitive to the timing of executive responses, which therefore may have increased sensitivity to subtle executive problems. We found that women with the *FMR1* premutation had significantly increased response latency and increased errors in the antisaccade condition suggesting inhibition deficits. Increased latency in the prosaccade condition was also detected, implying deficits in oculomotor abilities, specifically in motor initiation. Our secondary aim was to examine effects of aging within the *FMR1* premutation. Longer antisaccade latency was associated with older age in the *FMR1* premutation group, suggesting premature age-related decline in oculomotor inhibition in this population. These findings contribute to previous research supporting executive functioning deficits within this population as well as provide information with regards to identification of the age-related profile of this population that may inform prevention effort.

Group Differences on Antisaccade Latency & Percent Correct

Our findings suggest oculomotor inhibition difficulties in women with the *FMR1* premutation, as evidenced by poorer timing and accuracy on the antisaccade task relative to controls. Our findings notably support evidence of a previous study conducted by Shelton et al. (2014) that also detected increased antisaccade errors in women with the

FMR1 premutation. Inhibitory control deficits have also been observed in women with the *FMR1* premutation using other behavioral measures, such as the Hayling Sentence Completion test which requires verbal inhibition of a prepotent response (Kraan et al., 2014; Shelton et al., 2014). Thus our findings build on a growing body of evidence that supports inhibition deficits as an aspect of the *FMR1* premutation phenotype.

Age Effects Suggest Premature Age-Related Decline in the *FMR1* Premutation

We observed an association between older age and slower antisaccade latencies that was specific to the *FMR1* premutation group. This finding corroborates the results of our other recent report demonstrating age-related decline in verbal inhibition skills in women with the *FMR1* premutation (Klusek et al., 2020). In this study including a large sample of over 100 women with the *FMR1* premutation, we detected an association between older age and prolonged latency to inhibit an automatic verbal response during the Hayling Sentence Completion test. The current study builds on our prior findings through the inclusion of a control sample that allows us to confirm the specificity of the age effects to the *FMR1* premutation group. Curiously, age effects were specific to the latency variable and were not observed in error rate on the antisaccade task as well. This finding supports the idea that measures that require rapid, time responses may be a more sensitive measure to executive deficits in the *FMR1* premutation (Shelton et al., 2014). Overall, the results of this study suggest that executive functioning deficits in women with the *FMR1* premutation become more pronounced across middle adulthood, which may be important for the timing or prevention efforts and the development of interventions to support this group as they age.

Prosaccade Findings

In the prosaccade portion of this task, we found similar results to the antisaccade, with prolonged latencies for women with the *FMR1* premutation. Prosaccade performance reflects voluntary motor control and cognitive control (Yang et al., 2011; Munoz et al., 1998). With increased time to initiate this motor movement, this result infers that processing time is delayed in women with the *FMR1* premutation. Age effects were also observed for prosaccade latency, where older age was associated with longer latency. However, unlike the antisaccade age effects which were specific to the *FMR1* premutation group, both controls and women with the *FMR1* premutation showed longer prosaccade latency with age, suggesting that this is a normal pattern in healthy aging. These results suggest that inhibition skills may be more accurate than motor initiation in predicting the future progression of the disorder. This is somewhat surprising given that FXTAS, the neurodegenerative disease associated with the *FMR1* premutation, has a large motor component.

Strengths and Future Aims

Strengths of the present study include adding to prior studies with a larger sample size of participants of both women with the *FMR1* premutation as well as the control group. Previous studies are limited, with only one examining women with the *FMR1* premutation in which a sample size of 14 was included (Shelton et al., 2014). Of particular importance, the antisaccade task is backed by a significant amount of research to quantify cognitive deficits within various populations, especially those with neurodegenerative disorders. Protocol for this task was standardized based on Antoniades et al. (2013) for accurate comparison in future studies.

A future direction would be to examine performance on this task between women with the *FMR1* premutation without FXTAS and those women with FXTAS to determine any subtle differences. Similarly, longitudinal studies may be important to determine the onset and progression of FXTAS. Due to a paucity of evidence in women with the *FMR1* premutation, it is unknown whether oculomotor abnormalities are prevalent in FXTAS, or whether they precede the onset of other FXTAS motor signs. It is possible that eye movements can provide valuable markers of disease progression and severity in neurodegenerative disorders (Anderson & MacAskill, 2013).

Conclusions

Compared to controls, women with the *FMR1* premutation exhibited prolonged latencies in the antisaccade task with and without age factors included, illustrating the subtle inhibition deficits within this population. Similarly, women with the *FMR1* premutation had fewer successful trials on the antisaccade portion of the task again showing inhibition deficits. Finally, women with the *FMR1* premutation displayed prolonged latencies on the prosaccade portion of this task, implying a possible motor component to this disorder. Thus, this is a benchmark study in examining executive dysfunction within women with the *FMR1* premutation. These deficits may contribute to a decreased quality of life in women with the *FMR1* premutation and may necessitate clinical intervention in the future to aid in prevention of the progressive nature of this disorder.

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