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Response Inhibition Deficits in Women with the *FMR1* Premutation are Associated with Age and Fall Risk

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Abstract

One in 113-178 females worldwide carry a premutation allele on the *FMR1* gene. The *FMR1* premutation is linked to neurocognitive and neuromotor impairments, although the phenotype is not fully understood, particularly with respect to age effects. This study sought to define oculomotor response inhibition skills in women with the *FMR1* premutation and their association with age and fall risk. We employed an antisaccade eye-tracking paradigm to index oculomotor inhibition skills in 35 women with the *FMR1* premutation and 28 control women. The *FMR1* premutation group exhibited longer antisaccade latency and reduced accuracy relative to controls, indicating deficient response inhibition skills. Longer response latency was associated with older age in the *FMR1* premutation and was also predictive of fall risk. Findings highlight the utility of the antisaccade paradigm for detecting early signs of age-related executive decline in the *FMR1* premutation, which is related to fall risk. Findings support the need for clinical prevention efforts to decrease and delay the trajectory of age-related executive decline in women with the *FMR1* premutation during midlife.

Keywords: fragile X premutation; aging; antisaccade; executive function; FXTAS; falls

1. Introduction

Approximately 1 in 113-178 females are carriers of the *FMR1* premutation, which results from an expansion of 55-200 CGG repeats on the *Fragile X Mental Retardation-1* (*FMR1*) gene found on the X chromosome (Hantash et al., 2011; Seltzer et al., 2012; Toledano-Alhadef et al., 2001). Women with the *FMR1* premutation can pass an expanded CGG mutation of >200 repeats to their children, causing fragile X syndrome, a neurodevelopmental disorder characterized by intellectual disability (Schneider et al., 2009). Historically, the *FMR1* premutation was not considered to have its own clinical consequences. However, it is now clear that the *FMR1* premutation confers risk for a variety of medical, psychiatric, and cognitive challenges, which include neurodegenerative disease, infertility, migraines, hypertension, thyroid disease, anxiety, depression, social-communication difficulties, and mild autism-related traits (Hagerman & Hagerman, 2013; Klusek et al., 2019; Movaghar et al., 2019; Roberts et al., 2009; Wheeler et al., 2014, 2017). Cognitive-executive deficits have also been documented in women with the *FMR1* premutation, although this aspect of the phenotype has remained controversial due to inconsistent findings across reports.

A number of studies have failed to detect executive differences between women with the *FMR1* premutation and control women using standardized assessments of various executive skills, including mental flexibility, verbal fluency, and verbal and visual memory (Bennetto et al., 2001; Franke et al., 1999; Hunter et al., 2008; Reiss et al., 1993; Thompson et al., 1994). In contrast, the executive skill of response inhibition has been more consistently documented as an area of impairment in women with the *FMR1* premutation (Kraan et al., 2014a, 2014b; Shelton et al., 2014), although not without some divergent findings (i.e., Hunter et al., 2008), which highlights the need for further research focused specifically on response inhibition skills in women with the *FMR1* premutation. Response inhibition is a cognitive process that allows the suppression of a prepotent response (Miyake et al., 2000). The ability to inhibit a prepotent response is necessary to adapt to changes in the environment, and deficits in this area are related to a range of adverse outcomes, including suicidal ideation, self-injury, psychopathology, and antisocial behavior (Meza et al., 2016; Tremblay, 1994; Wright et al., 2014). Given the negative

consequences of inhibition deficits, elucidating the nature of response inhibition deficits in women with the *FMR1* premutation is critical to the development of effective clinical prevention and treatment efforts for this group.

Age effects have been proposed as a source of inconsistency in the extant literature on inhibition deficits in women with the *FMR1* premutation (Hunter et al., 2008), particularly given that progressive age-related deterioration in inhibitory control has been documented in men with the *FMR1* premutation (Cornish et al., 2008). Consistent with this suggestion, a recent study by Klusek et al. (2020) documented significant age-dependent changes in the response inhibition skills of women with the *FMR1* premutation. In this study of 134 women with the *FMR1* premutation (aged 39-88 years), older age was associated with slower inhibition of prepotent verbal responses, with age accounting for approximately 10% of the variation in inhibition skills. The expression of inhibition deficits was also associated with the length of the *FMR1* CGG repeat expansion, suggesting that both older age and genetic factors contribute to vulnerability for response inhibition deficits in women with the *FMR1* premutation (Klusek et al., 2020).

The study of age-related response inhibition deficits in women with the *FMR1* premutation is relevant to converging lines of research that highlight the *FMR1* premutation as an age-related condition that is associated with risk for neurodegenerative disease. About 16% of women with the *FMR1* premutation will develop fragile X-associated tremor/ataxia syndrome (FXTAS), a late-onset neurodegenerative disorder that is characterized by gait ataxia, action tremor, and executive dysfunction, including response inhibition deficits (Bourgeois et al., 2007; Grigsby et al., 2008; Hagerman, 2013). The identification of risk markers for the later development of FXTAS has been a topic of interest in the field, as the ability to identify at-risk individuals prior to the onset of symptoms will substantially improve the targeting and implementation of preventative measures (e.g., Allen et al., 2016; O'Keefe et al., 2015; Shelton et al., 2018). It remains unclear whether the inhibition difficulties experienced by women with the *FMR1* premutation during midlife represent a prodromal marker for FXTAS, or alternatively, a more generalized neurodevelopmental effect of the *FMR1* premutation (Berry-Kravis & Hall, 2011). Clarification of the relationship between inhibition deficits and FXTAS-associated motor deficits, such as

gait impairments and fall risk, would inform earlier FXTAS detection models and contribute to the understanding of the interaction between executive and neuromotor features linked to FXTAS. While verbal inhibition skills have been the focus of most prior research (Hunter et al., 2012; Klusek et al., 2018, 2020; Kraan et al., 2014a), a specific focus on oculomotor inhibition skills may be particularly useful in characterizing interrelated executive and neuromotor phenotypes. Eye movements and gait impairments often co-occur and share common neural substrates (Srivastava et al., 2018; Walton et al., 2015).

Neuroimaging evidence indicates that fronto-striatal-parietal brain regions and the cerebellum are activated during oculomotor inhibition performance (Jamadar et al., 2013, 2015) and posture-gait control (Srivastava et al., 2018; Takakusaki, 2017). Abnormalities of the cerebellum, including decreased cerebellar volume and white matter hyperintensities in the middle cerebellar peduncle, are common in FXTAS (Adams et al., 2007; Cohen et al., 2006; Hashimoto et al., 2011) and are implicated in FXTAS-associated gait and executive deficits (Birch et al., 2015; Filley et al., 2015). Cerebellar alterations, such as decreased cerebellar gray matter volume and structural alterations along the cerebellar-cortico pathways, are also present in individuals with the *FMR1* premutation who are asymptomatic for FXTAS (Battistella et al., 2013; Kraan et al., 2013a) and are thought to disrupt the integration and efficiency of brain networks that subserve dual motor and cognitive-executive performance in this group (Kraan et al., 2013b). Therefore, the study of oculomotor deficits in women with the *FMR1* premutation, and their relationship with gait disturbances, can lend insight into the neural circuits that are vulnerable to the effects of the *FMR1* premutation.

Oculomotor inhibition skills can be reliably indexed via a well-validated eye-tracking paradigm, the antisaccade task. This task has been used across a range of neurodegenerative disorders and is sensitive to subtle deficits exhibited during the early stages of disease onset in conditions such as Alzheimer's disease (Kahana Levy et al., 2018; MacAskill & Anderson, 2016). In the antisaccade task, participants are asked to inhibit an automatic visual response directed towards the target and instead look in the opposite direction. Both timing and accuracy indices are extracted to measure inhibitory control,

which is advantageous relative to inhibition measures that provide information on accuracy alone. Another advantage of the antisaccade task is that it imposes time constraints (participants are asked to respond as quickly as they can), which is thought to increase sensitivity to premutation-associated executive difficulties (e.g., Shelton et al., 2016). Moreover, the measurement of eye movements can provide a more direct measure of attentional engagement relative to inhibitory tasks that rely on verbal behavioral responses, which assume attentional engagement (Wong et al., 2014). While not a primary focus of this study, the antisaccade paradigm typically also includes a prosaccade condition in which participants simply look towards the visual target, providing a measure of visual orienting speed as reflected by the latency of responses (Ethridge et al., 2009; Hallett & Adams, 1980). Prosaccade responses were also examined in this study, as they may contribute to the literature on visual processing deficits in those with the *FMR1* premutation (Gallego et al., 2014; Kéri & Benedek, 2009, 2010).

Two prior preliminary studies employed the antisaccade task in the study of the *FMR1* premutation. One study, focusing on males with the *FMR1* premutation who were asymptomatic for FXTAS (n=21), found increased antisaccade response latency compared to a control group, supporting the presence of inhibition deficits (Wong et al., 2014). Another report by Shelton et al. (2014) used the antisaccade task in a small sample of 14 women with the *FMR1* premutation. Compared to control women, women with the *FMR1* premutation exhibited decreased antisaccade accuracy, although there were no differences in the latency of responses. These preliminary studies support the potential utility of the antisaccade task in capturing oculomotor inhibition deficits in the *FMR1* premutation that could represent the earliest signs of neurodegeneration.

In the present study, we aimed to clarify mixed findings in the extant literature regarding the executive phenotype of women with the *FMR1* premutation by contrasting the oculomotor inhibition skills of women with the *FMR1* premutation to those of control women. We hypothesized that women with the *FMR1* premutation would exhibit poorer performance on the antisaccade task relative to healthy controls, as indicated by longer response latency and decreased accuracy. Considering prior reports of visual processing deficits associated with the *FMR1* premutation (Kéri & Benedek, 2009, 2010), we also

hypothesized that women with the *FMR1* premutation would exhibit delayed visual orienting speed as marked by longer prosaccade latencies. Next, we tested age effects with the expectation that older age would be associated with poorer oculomotor inhibition in the women with the *FMR1* premutation group but not in control women. Finally, to shed light on the interface between inhibition deficits and neuromotor involvement that could be linked to FXTAS, we examined antisaccade performance in women with the *FMR1* premutation as a predictor of fall risk— a functional marker of gait impairment (Axer et al., 2010). Given the high prevalence of the *FMR1* premutation and emerging understanding of its neurocognitive effects, clarifying the age-related executive phenotype associated with this genotype has implications for the refinement of clinical prevention efforts to decrease and delay the trajectory of age-related executive decline in women with the *FMR1* premutation as they age.

2. Methods

2.1 Participants

Participants included 35 women with the *FMR1* premutation and 28 control women, aged 24-64 years. Participants were drawn from a larger study focused on social communication in women with the *FMR1* premutation (Klusek et al., 2019). Inclusionary criteria included: fluent speakers of English and a Brief IQ score of 80 or higher as measured by the Kaufman Brief Intelligence Test-II (Kaufman & Kaufman, 2004). The presence of the *FMR1* premutation (55-200 CGG repeats on *FMR1*) was confirmed via genetic testing or medical record review as part of the larger study. Although it was not an exclusionary criterion for the study, no participants with the *FMR1* premutation had a clinical diagnosis of FXTAS, per their self-report. Thirty-three of the 35 women with the *FMR1* premutation (94%) had a child diagnosed with fragile X syndrome. To reduce the likelihood of undiagnosed fragile X-related conditions occurring within controls, the control group was comprised of women who were biological mothers to children aged three years or older who had not been diagnosed or treated for any developmental delay or disorder.

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. There were several additional individuals (four women with the *FMR1* premutation and three control women) who were recruited for the larger study but were not able to participate in the eye-tracking component due to the inability to calibrate the eye tracker (e.g., participant wore blue-light blocking glasses which prevented proper illumination of the cornea). Group characteristics are presented in Table 1.

2.2 Procedures

The antisaccade task was integrated into a three-hour research protocol in which language and cognitive abilities were examined. This particular task took place about an hour into the protocol, following a language sample and other standardized assessments. Informed consent was obtained from all participants, and procedures were approved by the Institutional Review Board of the University of South Carolina.

2.3 Antisaccade Task

Apparatus/Instrumentation

Eye movements were measured using the Eyelink 1000 Plus eye tracker (SR Research Ltd, Ontario, Canada). The experiment was run using Experiment Builder (SR Research Ltd, Ontario, Canada) and displayed on a Ben-Q 2420T monitor (531.4 mm x 298.9 mm at a resolution of 1920 x 1080 pixels, 144 Hz). A chin rest ensured that the eye to screen distance was 950 mm; however, recordings were conducted in remote mode, which allows for the free movement of the head. Eye movements were sampled at 500 Hz and were parsed online using default saccade detection thresholds. An initial five-point calibration and validation were performed at the start of the recording. Recalibration was performed as needed. Calibrations were accepted if the average error was less than <.50°, and the maximum error <1.00°.

Stimuli/Paradigm

The 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. 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." Figure 1a displays the prosaccade sequence. 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." Figure 1b displays the antisaccade sequence. Directions were presented verbally by the examiner as well as visually on the screen.

Each block began with a drift check consisting of a 0.26° diameter black circle with a white bullseye center presented in the center of a white screen. The drift check was repeated every tenth trial, which allowed for recalibration as needed. The drift check was followed by a fixation screen with a black "X" (0.27° x 0.55°) presented in the center of a white screen. The central fixation "X" was surrounded by black flanking square markers (0.13° x 0.13°), shown 9° to the left and right of central fixation. These served to mark the potential target locations. The fixation screen was displayed for an average of 1.5 seconds (1 second minimum and 3.5 seconds maximum). Finally, the target screen was displayed, which consisted of a bold black box (0.27° x 0.27°, stroke width of 0.08°) which appeared 9° to the left *or* the right of central fixation. The target location was counterbalanced within each block so that the target would be presented equally across both locations. The target screen was shown for one second and then was immediately followed by the fixation screen for the next trial. Participants were offered breaks between each block, and the entire task lasted approximately 20 minutes.

Data Cleaning and Extraction

All saccade characteristics were calculated online. The variables of interest included the latency and accuracy of the first saccade greater than 1°, which occurred after the target square appeared. Trials were considered invalid and discarded if the latency of the saccade was shorter than 80 ms or longer than

600 ms (Ansari & Derakshan, 2010; Fischer et al., 1993). Latency was calculated as the time that elapsed between the onset of the target screen and the start time of the above described triggering saccade. Only data from correct/accurately directed saccades were included in the latency analysis. Accuracy was examined in the antisaccade condition and was calculated as the percent of total trials in which the saccade was initially directed to the non-target (correct) side of the screen. Accuracy of prosaccades is not reported as nearly everyone looked towards the target on almost all trials; thus, there was limited variance across the sample. All participants contributed valid data for >80% of the trials within each block.

2.4 Presence of Falls

Information relating to falls was obtained from an in-house questionnaire that inquired about family history of FXTAS and probed for several broad motor symptoms that could be indicative of FXTAS, such as tremor and Parkinsonian symptoms. In this report, we focused on the "falls" item given the connection between oculomotor function, gait impairment, and falls (Srivastava et al., 2018). Participants were asked, "Do you ever fall down?" with the response options of "Yes" or "No." Due to refinements in the assessment battery, eight participants were not administered this questionnaire during their in-person assessment and instead completed the questionnaire at a follow-up that occurred within a year of their in-person assessment. The proportion of those with concurrent data who endorsed falls (13%) did not significantly differ from the proportion of those whose data were sampled within the year (12.5%), $p = .662$.

2.5 Data Analysis

Analyses were conducted using SAS 9.4 (SAS Institute, 2013). Descriptive statistics were computed. Significant left skew was detected in the distribution of the percent correct for the antisaccade condition, and visual analysis of the residual plots for each model containing this variable confirmed the non-normal distribution of residuals. To correct for skew, the antisaccade accuracy variable was transformed by $\lambda = 2.5$ following the BoxCox procedure (Box & Cox, 1964) to find the optimal power

transformation[1]. The first research question regarded group differences in antisaccade performance, as indicated by prosaccade latency, antisaccade latency, and antisaccade accuracy. A series of linear mixed models were fit using restricted information maximum likelihood estimation with an unstructured covariance matrix to test group effects on each of the outcomes. Block number and its interaction with group were included in the models to account for potential order effects and attentional fatigue that might vary across the groups, considering evidence that individuals with the *FMR1* premutation may show faster rates of attentional fatigue (Hunter et al., 2012). Block number was specified as a random effect and nested within the individual. Fixed effects included group and a group-by-block number interaction. To address the second research question regarding the effect of age on each of the outcome variables of interest, a series of linear mixed models were performed using maximum likelihood estimation with an unstructured covariance matrix, testing the effect of group, block number, age, and the interaction between group and age. Overall model fit statistics for all models associated with the first research question did not support the presence of a group-by-block interaction effect for any of the outcomes, and thus this interaction term was not included in the age models to preserve degrees of freedom. Block number was specified as a random effect nested within the individual. Age was centered at the grand mean. Because age was found to significantly influence performance, we controlled for age in subsequent models. To address the final research question regarding the relationship with falls, three separate logistic regressions were performed to test prosaccade latency, antisaccade latency, and antisaccade accuracy as predictors of fall endorsement. Only one control participant endorsed falls, so we were unable to examine associations with antisaccade performance between groups, given the limited variance. Therefore, the logistic regression models testing the association between antisaccade task performance and fall endorsement were only conducted in the sample of women with the *FMR1* premutation. Group mean-centered age was included as a covariate. Performance on the antisaccade task was averaged across blocks

[1]Repeating analyses using un-transformed data yielded largely similar inferences.

to create a single variable representing the mean prosaccade latency, antisaccade latency, and antisaccade accuracy across blocks.

3. Results

3.1 Descriptive Statistics

Descriptive statistics presenting antisaccade performance across groups is presented in Table 2. Four women with the *FMR1* premutation endorsed falls (see Table 3 for descriptive statistics among the women with the *FMR1* premutation grouped by falls endorsement). The women who endorsed falls were aged 30, 41, 50, and 56 years. Scores on the Tremor Disability Questionnaire (Louis et al., 2000) were examined descriptively among the subset of women who endorsed falls to shed light on the presence of other motor symptoms potentially linked to FXTAS. This self-report measure asks about the impact of tremors on the completion of 30 different functional activities (e.g., threading a needle, signing your name). Scores range from 0 to 60, with higher scores indicating reduced efficiency or a need to modify the way the task is performed. The four participants who endorsed falls scored between 0 and 1 (M=0.50, SD=0.58) on the Tremor Disability Questionnaire, whereas the participants with the *FMR1* premutation who did not endorse falls scored between 0 and 5 (M=0.57, SD=1.17), suggesting that functional tremor symptoms were low overall and were not elevated among those who endorsed falls relative to the larger group of women with the *FMR1* premutation.

3.2 Group Comparisons on Prosaccade Latency

The linear mixed effects model showed a significant main effect for group on response latency (F [1, 61] = 9.55, p = .003; Figure 2), where the *FMR1* premutation group displayed longer prosaccade latencies compared to controls. Block number (F [1, 61] = 1.97, p = .165) and the interaction between group and block number (F [1, 61] = 0.10, p = .754) did not account for significant variance in the model.

3.3 Group Comparisons on Antisaccade Indices of Oculomotor Inhibition

The linear mixed effects model showed a significant main effect for group on response latency (F [1, 61] = 13.45, p < .001; Figure 3), 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, 61] = .68, p = .512) or the

interaction between group and block number (F [2, 61] = 2.66, p = .078) on antisaccade latency. The mixed effects model testing antisaccade accuracy showed a significant main effect for group (F [1, 61] = 4.56, p = .037; Figure 4), where those with the *FMR1* premutation exhibited lower accuracy. Block number also had a significant main effect on accuracy (F [2, 61] = 5.65, p = .006). Accuracy was significantly higher during the first block relative to the second block (t [61]=3.36, p=.001) and the third block (t [61]=2.17, p=.034). The interaction between group and block was not significant, indicating that the order effect was similar across the groups (F [2, 61] = 0.06, p = .939).

3.4 Age Effects on Prosaccade and Antisaccade Performance

Age effects were detected for both the prosaccade and antisaccade latency variables. For the prosaccade model, a significant main effect for age was detected, where longer prosaccade latency was associated with older age (F [1, 59] = 6.97, p = .011). Group accounted for additional significant variance in the model (F [1, 59] = 7.21, p = .009). The interaction between group and age was not significant (F [1, 59] = 1.27, p = .264), 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, 59] = 1.94, p = .169). For the antisaccade latency outcome, a significant main effect of group was detected (F [1, 61] = 15.23, p <.001), whereas the main effect of age was not significant (F [1, 61] = 2.52, p = .117). Additionally, the effect of block was not significant (F [2, 61] = 1.13, p = .329). A significant group-by-age interaction was detected (F [1, 61] = 7.27, p = .009), see Figure 5. Follow-up interaction contrasts showed that older age was associated with longer latency in the *FMR1* premutation group (F [1, 61], = 8.02, p = .006) but not in the control group (F [1, 61], = 0.72, p = .400). No main effects or interaction effects for age were observed for the antisaccade accuracy outcome (p's > .719).

3.5 Association Between Antisaccade Performance and the Presence of Falls

Results of the logistic regression model indicated that antisaccade latency was a significant predictor of fall endorsement in women with the *FMR1* premutation ($\chi 2$ [1] = 4.01, p = .045, OR = 1.12; Figure 6), such that for every 25 ms increase in antisaccade latency, the odds of reporting falls increased

17 times. Neither antisaccade accuracy nor prosaccade latency was a significant predictor of fall endorsement in women with the *FMR1* premutation (*p's* > .104).

4. Discussion

This study contributes to growing evidence that deficits in response inhibition are evident among women with the *FMR1* premutation and appear to be characterized by premature and progressive age-related deterioration across midlife. The expression of oculomotor inhibition deficits in women with the *FMR1* premutation was predictive of increased fall risk, which suggests a connection between certain executive phenotypes and gait impairment that could relate to FXTAS risk. An additional finding was that women with the *FMR1* premutation exhibited prolonged prosaccade latency, which builds on prior evidence of visual processing deficits associated with the *FMR1* premutation genotype. This study builds on the current understanding of neurodegenerative phenotypes associated with the *FMR1* premutation and supports the potential utility of preventative clinical interventions to decrease and delay the trajectory of cognitive-executive difficulties in women with the *FMR1* premutation across midlife.

4.1 Impaired Oculomotor Response Inhibition in the *FMR1* Premutation

Women with the *FMR1* premutation exhibited increased latency and reduced accuracy on the antisaccade task, supporting the presence of oculomotor inhibition deficits across multiple indices. These results contribute to burgeoning evidence that, as a group, middle-aged women with the *FMR1* premutation without clinical diagnoses of FXTAS experience impaired response inhibition skills (Klusek et al., 2018, 2020; Kraan et al., 2014a, 2014b; Shelton et al., 2014). This accumulation of evidence, which now draws from several different independent samples and incorporates a range of different inhibition measurement techniques, is notable because the field has previously lacked consensus as to whether executive deficits were present in women with the *FMR1* premutation (Hunter et al., 2008; Wheeler et al., 2014).

Unlike most prior studies that have employed a verbal inhibition task to evaluate response inhibition skills in women with the *FMR1* premutation, the present study employed the antisaccade task as a specific index of oculomotor inhibition skills. The task is thought to be advantageous as it has been

used across a range of other neurodegenerative diseases as a sensitive index of cognitive-executive dysfunction detectable early in disease progression (Kahana Levy et al., 2018; MacAskill & Anderson, 2016). Building on earlier preliminary reports by Shelton et al. (2014) and Wong et al. (2014), our findings support the antisaccade task as a measure that is sensitive to oculomotor response inhibition difficulties in individuals with the *FMR1* premutation who do not have clinical diagnoses of FXTAS. Unlike Shelton et al. (2014), who detected evidence of reduced antisaccade accuracy but not latency in women with the *FMR1* premutation, the present study supports reduced performance across both accuracy and latency measures. The discrepant finding is likely due to increased statistical power in the present study, as our sample is over twice the size of that of the Shelton report.

4.2 Premature Age-Related Decline in Response Latency

Longer antisaccade latency was associated with older age within women with the *FMR1* premutation but not in controls, which builds on emerging evidence that women with the *FMR1* premutation are vulnerable to premature age-related decline in inhibition skills during midlife (Klusek et al., 2020; Sterling et al., 2013). By incorporating comparison to healthy controls, we were able to build on prior findings to confirm the specificity of the age effects to the *FMR1* premutation group. It is notable that the detected age effects were specific to the antisaccade latency variable and were not observed for the accuracy variable as well. This pattern mirrors that of Klusek et al. (2020), who detected age-related decline in the latency, but not accuracy, of the responses of women with the *FMR1* premutation during a verbal inhibition task. Thus, a consistent pattern is emerging, such that indices that tap into response efficiency (i.e., the time it takes to suppress a response) are more sensitive to age-related deterioration than measures that rely on response accuracy alone. The incorporation of response-efficiency measures in future research may optimize sensitivity and enable detection of the earliest manifestations of age-related neurodegeneration in the study of the *FMR1* premutation.

4.3 Response Latency Predicts Fall Risk

Prolonged antisaccade latency was associated with heightened risk for falls in women with the *FMR1* premutation. The association between response latency and fall risk was striking, with each 25 ms

increase in antisaccade latency associated with a 17-fold increase in the odds of experiencing falls. Although falls are typically perceived as an indicator of motor dysfunction, a large body of literature demonstrates that cognitive-executive deficits exacerbate, and may even cause, gait impairment and contribute to fall risk in older adults in the general population (Herman et al., 2010; Segev-Jacubovski et al., 2011). Emerging evidence also suggests a connection between executive dysfunction and balance and gait impairments in individuals with FXTAS (O'Keefe et al., 2018). Here, we documented similar relationships, which is notable given our sample comprised of middle-aged women with the *FMR1* premutation (mean age=45.93 years) who did not have clinical diagnoses of FXTAS, and therefore, would not be expected to exhibit gross motor impairments. Given the effect of cognitive control on motor abilities in the general population and in those with the *FMR1* premutation (Herman et al., 2010; Kraan et al., 2013b), it is plausible that early executive deficits may lead to a decline in motor skills and increase risk of falls in individuals with the *FMR1* premutation, similar to the patterns that are observed in aging in the general population (Herman et al., 2010). Further understanding of the interface between executive deficits and motor-related impairments can inform the tailoring of therapeutics relevant for FXTAS or the *FMR1* premutation, more generally, to better account for interacting cognitive and motor profiles.

Neuroimaging evidence indicates that the cerebellum plays a role in both antisaccade performance (Jamadar et al., 2013, 2015) and posture-gait control (Takakusaki, 2017), suggesting that inhibitory control and falls may share neural substrates. Additionally, carriers with the *FMR1* premutation who are asymptomatic for FXTAS show cerebellar alterations (Battistella et al., 2013; Kraan et al., 2013a), which may be implicated in the patterns observed here. Studies on those with the *FMR1* premutation have investigated the influence of the cerebellum on postural control, a feature thought to be associated with later gait impairment in those with FXTAS, but few studies to date have examined cognitive and motor symptoms together. Given our findings and evidence highlighting the role of the cerebellum in both motor and cognitive function in the general population and those with FXTAS (Birch et al., 2015; Filley et al., 2015; Jamadar et al., 2013; Stoodley & Schmahmann, 2009; Takakusaki, 2017), future neuroimaging studies focused on the cerebellum may further understanding of the neural basis of

co-occurring cognitive-executive and motor symptoms in women with the *FMR1* premutation. By detailing the interface between cognitive-executive and motor symptoms in women with the *FMR1* premutation, this study informs patterns of symptom expression that may be traced to cerebellar dysfunction and could inform the search for reliable prodromal markers for FXTAS.

4.4 Evidence of Delayed Visual Orienting Speed in the *FMR1* Premutation

Prolonged prosaccade latency was detected in the women with the *FMR1* premutation relative to controls, suggesting slower visual orienting speed. These results differ from those of Wong et al. (2014) and Shelton et al. (2014), who did not detect impaired prosaccade performance in men and women with the *FMR1* premutation. Our ability to detect prosaccade impairments is likely related to improved statistical power relative to these previous reports, both due to the inclusion of a larger sample size as well as the use of a linear mixed effects model, which allows for multiple observations per case. The finding of impaired visual orienting speed is consistent with prior reports of visual information processing deficits in the *FMR1* premutation, which suggest impaired function of magnocellular visual pathways that are responsible for providing input to neural areas related to motion perception and location information (Kéri & Benedek, 2009, 2010). In some respects, the finding that women with the *FMR1* premutation exhibited prolonged prosaccade latencies is surprising. In the study of other neurodegenerative disorders, such as Alzheimer's disease, impaired prosaccade performance is considered a gross marker of impairment that does not typically come on-line until late in disease progression (Kahana Levy et al., 2018), although evidence of visual alterations early on has been reported in those with mild cognitive impairment, a precursor to Alzheimer's disease (Alichniewicz et al., 2013). Considering that the prosaccade deficits detected here were evidenced in our sample of middle-aged women who did not have clinical diagnoses of FXTAS and were not associated with premutation-specific age effects or fall risk, it is possible that delayed visual orienting speed in this group reflects a neurodevelopmental, rather than a neurodegenerative, process. Future studies may further delineate visual processing deficits in the *FMR1* premutation, which represent an understudied feature of the *FMR1* premutation that could have implications for learning and development (Dias, 2011; Kim et al., 2006; Revheim et al., 2006).

4.5 Strengths and Limitations

The use of the antisaccade task to quantify inhibition skills is a strength, as this is a well-validated task that has been studied extensively in clinical groups, especially in those with neurodegenerative disorders. The antisaccade paradigm used in this study followed Antoniades et al. (2013)'s recommendations for standardization, which facilitates replication and comparison across protocols. The reliance on self-reported fall endorsement as a marker of motor-related impairment may be viewed as a weakness, given that this is a blunt measure of motor involvement. Future studies may incorporate more precise indicators of measures of fall risk (e.g., gait speed; Kyrdalen et al., 2019) or direct measurement of other related motor skills, such as postural stability or gait ataxia. Likewise, our reliance on self-reported clinical diagnoses of FXTAS is a limitation. It is possible that some participants may have met criteria for FXTAS but had not yet been clinically identified (although the age of our sample and the late onset of FXTAS makes this relatively unlikely). Another limitation is the lack of racial diversity in the sample, which does not reflect the diversity of the broader *FMR1* premutation population and limits generalizability; future study on this topic in diverse samples is recommended. Finally, 94% of the participating women with the *FMR1* premutation were mothers to a child with fragile X syndrome. As sustained caregiver stress has been implicated in cognitive decline (e.g., Vitaliano et al., 2005), the influence of stressors associated with having a child with fragile X syndrome on our findings is not known and may limit generalization to the larger population of women with the *FMR1* premutation. Future studies should delineate the characterization of the executive phenotype in women with and without children with fragile X syndrome. Finally, it will be important in future work to follow participants longitudinally to identify the early symptoms that predict later conversion to FXTAS. The study of eye movements may be particularly useful in this regard because they have been used as sensitive markers of disease progression and severity in other neurodegenerative disorders (MacAskill & Anderson, 2016).

4.6 Conclusions

The present study adds to an expanding evidence base that supports response inhibition deficits as an aspect of the female *FMR1* premutation phenotype. Oculomotor inhibition deficits were associated with heightened fall risk and showed patterns of premature age-related decline across middle age. Deficits in prosaccade performance, reflecting impaired visual orienting speed, were also detected and did not appear to be linked with neurodegenerative processes. Overall, this study supports the presence of response inhibition deficits in women with the *FMR1* premutation that are evident in midlife and appear to worsen with age. These features may contribute to decreased quality of life as women age, and therefore, clinical prevention efforts to promote healthy cognitive aging may be warranted in this group.

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The authors report no disclosures or conflicts of interest.

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Table 1
Group characteristics

Variable	Group		
	Women with the *FMR1* Premutation	Control Women	Test of group differences (*p*-value)
Age (years)			
M (*SD*)	45.93 (8.13)	41.84 (10.54)	.087
Range	26.55-59.80	24.97-65.23	
Brief IQ[a]			
M (*SD*)	105.33 (12.86)	103.62 (11.66)	.623
Range	81.00-130.00	83.00-135.00	
CGG Repeat Length			
M (*SD*)	95.41 (17.37)		N/A
Range	64.00-147.00		
Maternal Education %			
Some high school	3%	0%	
High school graduate	15%	4%	
Some college/Associate's degree	35%	32%	.215
Bachelor's degree	21%	16%	
Some graduate work/Master's degree	26%	36%	
Professional/advanced degree	0%	12%	
Family Income %			
$0-$50,000	18%	21%	
$50,001-$100,000	38%	46%	.461
$100,001-$150,000	29%	25%	
>$150,001	15%	8%	
Race %			
Black/African American	3%	18%	
Asian	0%	4%	.061
White	97%	74%	
Other	0%	4%	

[a]Measured with the Kaufman Brief Intelligence Test-II (Kaufman & Kaufman, 2004).

Table 2

Descriptive Statistics

	Women with the *FMR1* Premutation		Control Women		Test of group differences (p-value)
	M (*SD*)	Range	*M* (*SD*)	Range	
Prosaccade Variables					
Latency (ms)	232.39 (29.32)	170.24-312.24	213.66 (21.64)	173.38-257.06	<.001
Accuracy (%)	97.67 (3.16)	87.50-100.00	98.31 (2.98)	86.00-100.00	.246
Antisaccade Variables					
Latency (ms)	325.86 (46.83)	228.15-433.43	289.11 (40.33)	220.38-450.14	<.001
Accuracy (%, untransformed)	68.38 (22.96)	11.54-100.00	78.60 (15.72)	31.58-100.00	<.001
Accuracy (transformed)	7088.22 (4026.86)	131.04-14372.33	8854.42 (3220.47)	1126.56-14372.33	.001

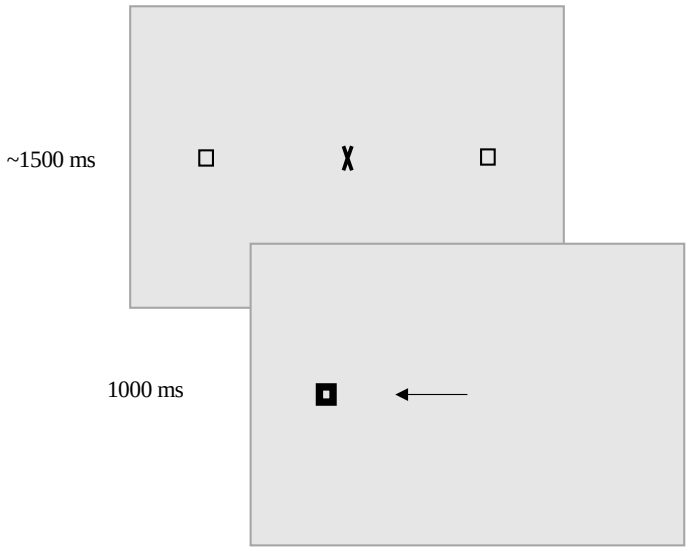
Table 3

Descriptive Statistics on the Presence of Falls in Women with the FMR1 Premutation

Presence of Falls	Frequency (%)	Prosaccade Latency (*M*(*SD*))	Antisaccade Latency (*M*(*SD*))	Antisaccade Accuracy (untransformed) (*M*(*SD*))	Antisaccade Accuracy (transformed) (*M*(*SD*))
Present	4 (12.90%)	253.27 (25.64)	375.43 (22.94)	63.18 (14.58)	5459.56 (2398.25)
Absent	27 (87.10%)	231.01 (26.64)	320.23 (34.03)	70.34 (21.33)	7347.21 (3870.88)

Figure 1a

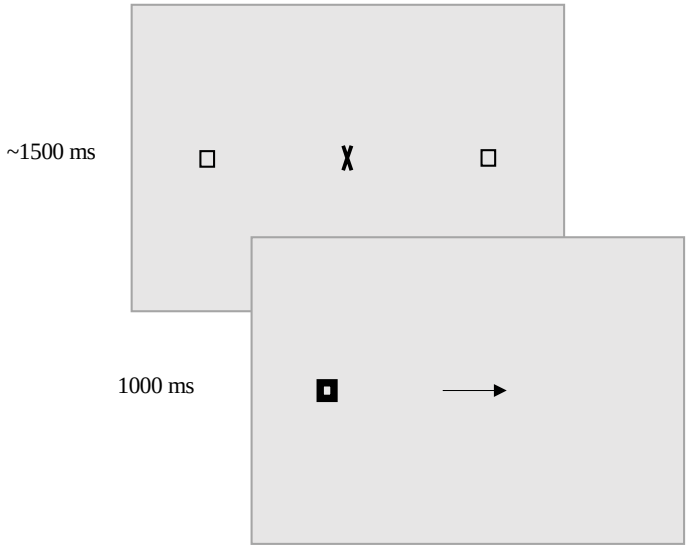
Prosaccade Trial



Note. The arrow represents the direction of eye gaze.

Figure 1b

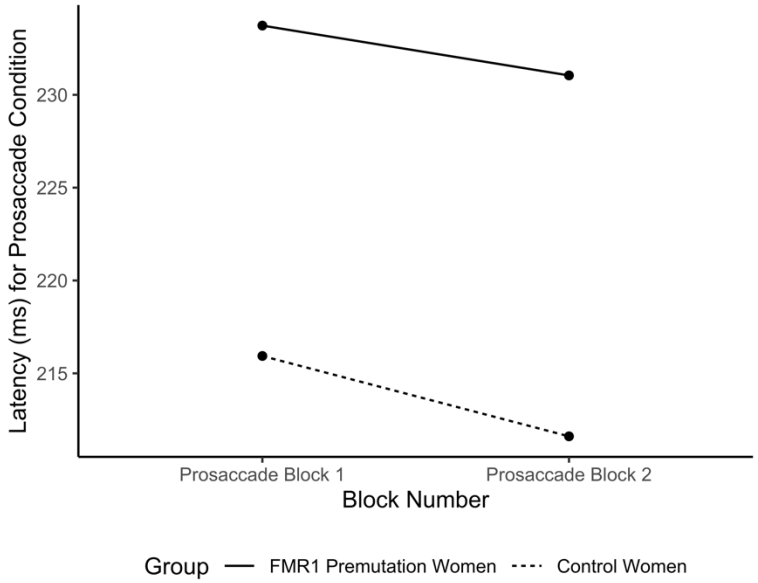
Antisaccade Trial



Note. The arrow represents the direction of eye gaze.

Figure 2

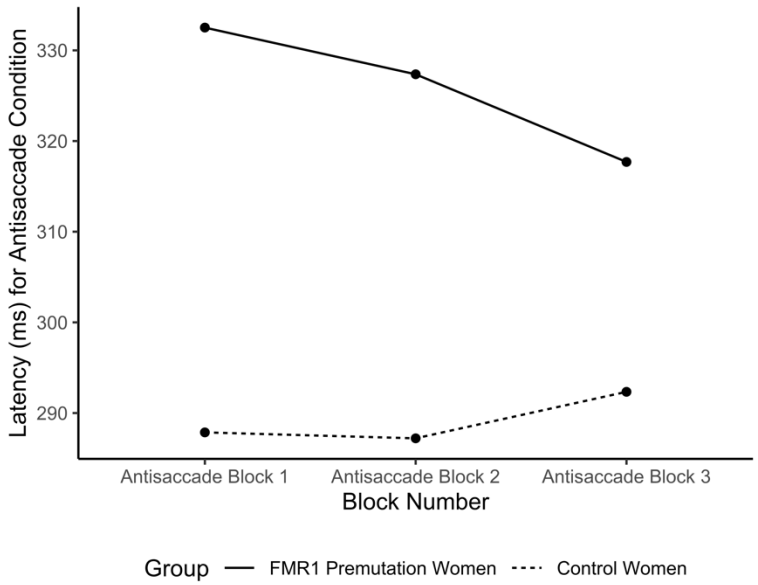
Prosaccade latency across blocks and groups



Note. Raw values for group means are presented in the figure.

Figure 3

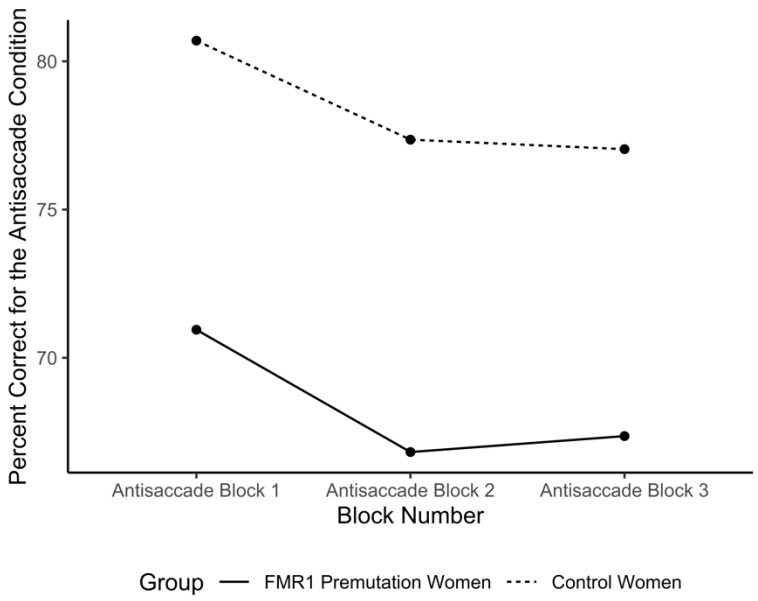
Antisaccade latency across blocks and groups



Note. Raw values for group means are presented in the figure.

Figure 4

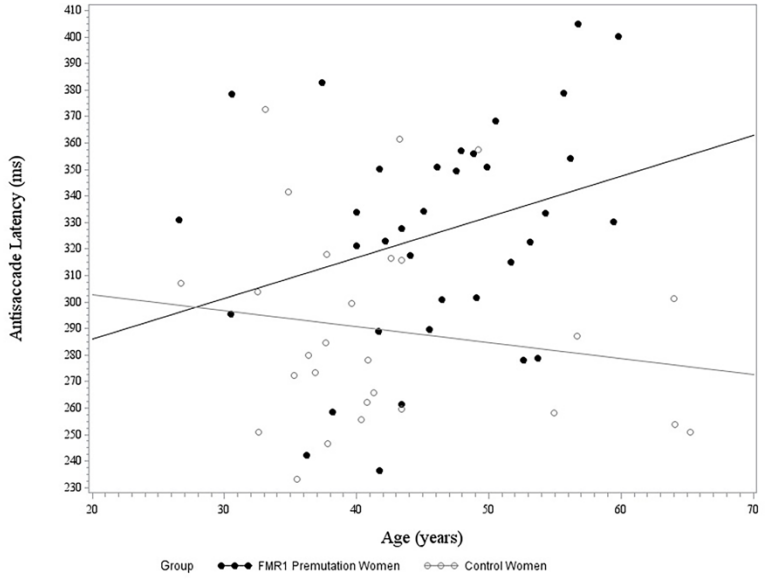
Antisaccade percent correct across blocks and groups



Note. Raw values for group means are presented in the figure. Untransformed values are presented for interpretability.

Figure 5

Associations between age and antisaccade latency across the groups



Note. Raw values are presented in the figure. Values for each individual are averaged across blocks.

Figure 6

Predicted Probabilities for Presence of Falls