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

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Introduction: Women with the *FMR1* premutation are at risk for passing on an expanded mutation of the gene to their children, causing fragile X syndrome, a disorder characterized by intellectual disability (Schneider et al., 2009). The *FMR1* premutation also confers risk for its own range of challenges, including mental health disorders, infertility, and neurodegenerative disease (Wheeler et al., 2014). Cognitive-executive difficulties have also been documented in those with the *FMR1* premutation, although due to inconsistent findings across reports, it remains a controversial aspect of the phenotype. Deficits in response inhibition have been more consistently documented, and therefore, sensitive measures of response inhibition are needed to clarify the nature of response inhibition deficits in women with the *FMR1* premutation. Additionally, research highlights the *FMR1* premutation as an age-related condition associated with neurodegenerative disease (FXTAS), and age-related deterioration in response inhibition skills has now been documented in women with the *FMR1* premutation (Klusek et al., 2020). The investigation of age effects, as well as the interface between inhibition difficulties and FXTAS-associated motor deficits, may be useful in the pursuit to understand whether inhibition difficulties are a prodromal marker for FXTAS or a more general neurodevelopmental effect of the *FMR1* phenotype. The present study aimed to clarify mixed findings related to cognitive-executive difficulties by employing an eye tracking paradigm, the antisaccade task, that measures response inhibition and is sensitive to early signs of neurodegeneration. We also examined age effects and the association between response inhibition antisaccade performance and fall risk, a functional marker of gait impairment.

Method: Participants included 35 women with the *FMR1* premutation and 28 control women. The antisaccade task, an eye tracking paradigm, directly measured oculomotor inhibition. The paradigm was modeled after a standardized protocol described by Antoniades et al. (2013). The task consists of "antisaccade" trials where participants are asked to inhibit an automatic visual response directed towards a target and instead look in the opposite direction, directly measuring response inhibition, and "prosaccade" trials where participants would simply look towards a visual target, providing a measure of visual orienting speed. The paradigm consisted of one prosaccade block, three antisaccade blocks, and a final prosaccade block. Latency for both antisaccade and prosaccade trials and accuracy for the antisaccade trials were used in the analyses. Information regarding presence of falls was obtained from an in-house questionnaire. Participants were asked, "Do you ever fall down?" with the response options of "Yes" or "No."

Results: A series of linear mixed effect models were conducted examining the effect of group on prosaccade latency and antisaccade latency and accuracy. The prosaccade latency model showed a significant main effect for group, where the *FMR1* premutation group displayed longer prosaccade latencies compared to controls (p=.003). The antisaccade latency model showed a significant main effect for group, where the *FMR1* premutation group displayed longer antisaccade latencies compared to controls (p<.001), and the antisaccade accuracy model was significant as well, with the *FMR1* premutation group demonstrating less accuracy (p=.037). Next, a series of linear mixed effect models examined group, age, and their interaction on prosaccade and antisaccade variables of interest. A significant main effect of age was detected, where longer prosaccade latency was associated with older age (p=.001). For the antisaccade latency outcome variable, a significant group-by-age interaction was detected (p=.009). Follow up contrasts showed that older age was associated with longer latency in the premutation group (p=.005) but not the control group (p=.435). A logistic regression was performed to test antisaccade and prosaccade variables as predictors of fall endorsement for the premutation group. Antisaccade latency was a significant predictor of fall endorsement (p=.045). For every 25 ms increase of antisaccade latency, the odds of endorsing falls increased 17 times.

Discussion: Our findings contribute to growing evidence of deficits in response inhibition among women with the *FMR1* premutation. These deficits appear to be characterized by premature and progressive age-related deterioration across midlife. Our findings related to fall endorsement and inhibition deficits in women with the *FMR1* premutation suggests a connection between cognitive-executive difficulties and gait impairment that could relate to FXTAS risk. The study increases understanding

of neurodegenerative phenotypes associated with the *FMR1* premutation and supports the utility of preventative interventions to decrease and delay the trajectory of executive difficulties in women with the *FMR1* premutation.

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