Title: Genetic and Environmental Influences on Self-Reported Cognitive Functioning: Associations of Diverse Measures of Stress Across the FMR1 CGG Repeat Range

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Introduction: Difficulties in executive function have been repeatedly documented among females who carry the premutation of the FMR1 gene (PM carriers; 55-200 FMR1 CGG repeats; see Wheeler et al., 2017 for a review). Prior evidence suggests that older FMR1 PM carriers may be at increased risk for neurodegenerative decline, characterized in part by executive dysfunction (Hagerman & Hagerman, 2016). Variability in the FMR1 gene (e.g., CGG repeat length) may contribute to a range of phenotypic outcomes including difficulties in executive function (e.g., Klusek et al., 2018), poor health, and differential sensitivity to stress (Mailick et al., 2018; Seltzer et al., 2012). Relatedly, heightened levels of stress may be associated with executive dysfunction across multiple populations, including older adults (Korten et al., 2016; Shields, Sazma, & Yonelinas, 2016). This suggests that executive dysfunction may be influenced by stressors common to maternal carriers of the FMR1 PM (i.e., parenting a child with FXS) as well as by age and variability in the FMR1 gene. However, it is possible that parenting a child with any disability may be a stressor that adversely influences executive function, even in individuals whose FMR1 CGG repeats are within the normal range. This study employed a cross-population comparison of maternal FMR1 PM carriers and mothers of children with and without other disabilities (including those with CGG repeats up to the PM range; see Table 1) to investigate the links between executive function, stress, age, and FMR1 CGG repeat variability.

Method: Participants included 974 mothers: 153 maternal FMR1 PM carriers, 144 maternal carriers of an intermediate CGG repeat expansion (gray zone mother group; 45-54 CGG repeats), 188 mothers with normal-range CGGs who had children with disabilities, and 489 mothers with normal-range CGGs who had typically developing children (see Table 1). Participants completed self-report measures of executive function (Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A; Roth, Isquith, & Gioia, 2005) and stress (Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). FMR1 CGG repeat length was determined from buccal and blood samples. Women diagnosed with the premutation who were mosaic for the full mutation were excluded from analyses. All participants were ≥40 years of age. Maternal age and education were controlled in all statistical analyses given associations with outcome measures. We predicted that stress, age, and FMR1 CGG repeat length would each uniquely influence executive function.

Results: Groups significantly differed in their overall executive functioning level ($F(4,1165) = 11.26, \ p = .00$). Specifically, mothers of children with disabilities (i.e., maternal PM carriers and maternal CGG repeat controls whose children have disabilities) had greater executive function difficulty than mothers who had only typically developing children (i.e., mothers with normal CGGs and mothers with gray zone CGGs; $p$-values <.05). Groups significantly differed in their perceived stress ($F(4,1071)=19.07, p=.00$), with the highest stress evident in maternal PM carriers and maternal CGG repeat controls whose children have disabilities.

Two separate hierarchical linear regression analyses were run to assess the prediction that stress, age, and CGG repeats would each uniquely contribute to executive function difficulty. The first analysis combined all participants into a single analytic sample (i.e., these models combined maternal PM carriers, gray zone mothers, and controls with and without children with disabilities). The second set of analyses evaluated separate regressions for each group. In the first analysis (with all groups combined), the
cumulative influence of age, maternal education, and perceived stress predicted 37.3% of the variance in global executive function (PSS b=.90, p=.00); 37.7% of the variance was predicted after including FMR1 CGG repeat length in the model (b=.03, p=.02). In the second set of analyses (each group analyzed separately), perceived stress significantly predicted 38.8% of variance in global executive function for maternal PM carriers (b=.95, p=.00) and 30.0% of variance for gray zone mothers (b=.90, p=.00). Inclusion of FMR1 CGG repeat length in the models marginally predicted 40.3% of variance for maternal PM carriers (b=.08, p=.07) and 33.6% of variance was predicted for gray zone mothers (b=.87, p=.01). Within the maternal control groups, similar effects were observed for perceived stress (b-values >.75, p-values <.01), but no significant effect of CGG repeat length was observed in control groups with or without children with disabilities (p-values >.41). Age was a significant predictor of executive function for all groups without PM expansions (b-values > .18, ps <.01).

Discussion: Consistent with prior work, PM carriers demonstrated greater executive function difficulty compared to the control group of mothers of typically developing children; however, this pattern of executive dysfunction was also observed for mothers of children with other disabilities suggesting that, regardless of genetic status, parenting a child with a disability may adversely influence executive function. Results further indicated that associations between age and executive function may not be evident in the PM, with the possibility that age-related executive decline may be obscured (or hastened) for maternal PM carriers. Perceived stress (PSS) was associated with executive dysfunction, regardless of group status. Intriguingly, FMR1 CGG repeat length expansions (45 and greater CGGs) appeared to influence executive function above and beyond levels of stress, suggesting that FMR1-related variability may play a distinct role in executive challenges separate from stressful parenting effects.

References:


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