Symposium Title: Stress, Risk, and Resiliency for Women with a FMR1 Premutation

Chair: Anne C. Wheeler¹ and Jessica Klusek²

Discussant: Marsha Mailick³

Overview: Accumulating evidence suggest that FMR1 premutation carriers are at heightened risk for stress-related illnesses¹-² as the result of the disruption of FMR1 protein development and subsequent differences in HPA axis regulation. As a result, mothers of children with fragile X syndrome (FXS) who have an FMR1 premutation may be especially vulnerable to negative outcomes in response to their children’s behavior problems³. This dual vulnerability of known genetic risk coupled with the chronic elevated stress related to raising a child with significant behavioral and developmental challenges can negatively impact well-being for both parent and child, and may increase risks for later-onset fragile-X associated conditions. However, consistent with the differential susceptibility hypothesis⁴, these same women may also be especially responsive to interventions that promote coping strategies to manage stress, such as Mindfulness Based Interventions (MBI). Multiple studies now show that MBIs may impact neural mechanisms⁵-⁷, such as amygdala functioning, and stabilize HPA axis dysregulation⁸ indicating a promising direction for intervention development.

The four presentations in this symposium are proposed by a multi-institution, multi-disciplinary panel of researchers focused on addressing the biological and environmental risks and protective factors for mothers of children with FXS. The first presentation will describe cardiac markers of autonomic function as a biomarker for psychological risk in women with a premutation and set the stage for discussion of downstream problems related to chronic stressors. The second presentation will describe results from a national survey exploring perceived global stress and daily hassles for mothers of children with FXS, as well as coping strategies most commonly used for managing stress in this population. The third and fourth presentations will delve into the use of MBI's as a potential strategy for reducing stress in these women. The third presentation will describe mindful parenting and acceptance as potential protective variables for women with a premutation. Finally, the fourth presentation will describe findings from a feasibility trial of a MBI using a smartphone app to help women with a premutation integrate mindfulness into their daily lives. Implications for future research will be discussed.

References:

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Paper Title: Autonomic Dysfunction in Mothers with the FMR1 Premutation: Depression, Anxiety, and Genetic Correlates

Authors: Jessica Klusek¹, Giuseppe LaFauci², Tatyana Adayev², W. Ted Brown², Flora Tassone³, and Jane Roberts⁴

Introduction: Autonomic dysfunction is implicated in a range of psychological conditions, including depression and anxiety. Mothers of children with fragile X syndrome, who are carriers of the FMR1 premutation, are at elevated risk for depression and anxiety. This study examined cardiac markers of autonomic function in mothers with the FMR1 premutation as potential biomarkers for psychological risk that may be linked to FMR1.

Methods: Baseline inter-beat interval and respiratory sinus arrhythmia (a measure of parasympathetic vagal tone) were measured in 35 mothers with the FMR1 premutation and 28 control mothers of typically developing children who were matched on age and IQ. The mothers completed the Beck Anxiety Inventory and the Beck Depression Inventory-II, as indices of continuous anxiety and depression symptoms. FMR1 genetic indices (i.e., CGG repeat, quantitative FMRP, FMR1 mRNA, activation ratio) were obtained for the mothers with the FMR1 premutation.

Results: Respiratory sinus arrhythmia was reduced in the mothers with the FMR1 premutation group relative to controls, even after controlling for age, medication use, and parenting stress level ($F [1, 51] = 4.17, p = 0.046; d = 0.54$). The groups did not differ on inter-beat interval, an index of general physiological arousal level ($F [1, 51] = 2.54, p = 0.051; d = 0.05$). General linear models tested associations between the physiological markers and depression and anxiety symptoms across groups, controlling for age, medication use, and parenting stress level. A significant group-by-respiratory sinus arrhythmia interaction was detected, where reduced respiratory sinus arrhythmia was associated with depression among control mothers but not among the mothers with the FMR1 premutation ($F [1, 48] = 7.83, p = 0.007, \eta^2_p = 0.14$). Higher FMR1 mRNA level predicted higher respiratory sinus arrhythmia in the mothers with the FMR1 premutation, with a strong effect size that was present even after controlling for potential confounds related to parenting stress, age, and medication use ($F [1, 18] = 4.88, p = 0.040; \eta^2_p = 0.21$).

Discussion: Mothers with the FMR1 premutation demonstrated autonomic dysregulation characterized by reduced vagal tone. Unlike patterns observed in the general population and in study controls, vagal activity and depression symptoms were decoupled in women with the FMR1 premutation, suggesting independence between autonomic regulation and psychopathological symptoms that is atypical and potentially specific to the FMR1 premutation. The association between vagal tone and FMR1 mRNA suggests that the FMR1 gene plays a role in autonomic regulation.
Paper Title: Stress, Daily Hassles, and Coping in Mothers of Children with Fragile X Syndrome

Authors: Wheeler, A.C.1, Miller, S1, Edwards, A1, Wylie, A1, Okoniewski, C1, & Moultrie, R1.

Introduction: Children with FXS are known to be at high risk for severe behavior problems, including aggression, hyperactivity, anxiety, inattention, and autism symptoms. These behaviors often result in high levels of stress for caregivers, an association that has been well established for mothers of children with FXS2–5. However, no studies have explored the impact of daily hassles and challenges as a factor in maternal well-being in this population. Further, how one naturally copes with both daily and chronic stressors can play a major role in the impact of stress on individual mental and physical well-being. This study explored different aspects of perceived stress and coping in premutation mothers of children with FXS.

Methods: Biological mothers of children with FXS participated in a national survey on stress, coping, and mindfulness in premutation carriers. 158 women completed the survey items focused on global perceived stress (Perceived Stress Scale), the frequency and intensity of common daily hassles (Parenting Daily Hassles Scale), and coping styles (Brief COPE).

Results: Women in this study reported elevated perceived stress levels relative to women in the US and comparable to other mothers of children with disabilities. Daily hassles were frequently reported, with the most challenges related to finding baby-sitters, managing kids in public, and having to change plans to meet their kids’ needs. Overall stress was highly correlated with the frequency (.48, p < .001) and intensity (.41, p < .001) of daily hassles. Use of problem-solving coping was associated with less overall stress, whereas those who reported more use of active avoidance were more likely to have high levels of anxiety (.53), depression (.57), stress (.54), and physical health symptoms (.37). Coping styles were not associated with maternal age, child age, or child behavior.

Discussion: Results from this study suggest that there are specific daily stressors that may cause and/or contribute to global perceived stress in mothers of children with FXS, providing some additional specific targets for intervention. Further, methods of coping appear to be protective and provide a direction for future intervention development targeting the development of more adaptive coping strategies for women with a premutation.

References/Citations:


1RTI International
**Paper 3 of 4**

**Paper Title:** Mindfulness and Acceptance in Mothers with a *FMR1* Premutation

**Authors:** Wheeler, A.¹, Miller, S.¹, Edwards, A.¹, Wylie, A¹.

**Introduction:** Women with an *FMR1* premutation may be at increased genetic risk for stress vulnerability. This increased vulnerability, when combined with stressful parenting that can result from raising children with fragile X syndrome (FXS), may result in negative physical and emotional outcomes. Mindfulness and acceptance have been found to be protective factors for parents of children with autism spectrum disorders¹, but these traits have not previously been explored among women with a premutation. This study explored the associations of child behavior severity with maternal stress, anxiety, depression, and physical health symptoms in premutation mothers of children with FXS.

**Methods:** 158 biological mothers of children with FXS participated in a survey focused on stress, coping and mindfulness. Standardized measures of stress, anxiety, depression, physical health symptoms, general mindfulness, mindful parenting, and acceptance of negative life events were administered along with parent report of the severity of their child’s behavior and co-occurring conditions.

**Results:** General mindfulness, mindfulness in the parenting role, and general acceptance were explored as potential mediators between child severity and maternal outcomes. Controlling for demographic variables, more child behavior severity was a significant predictor of higher stress (β = 0.79, p = .01, R² = .04), anxiety (β = 1.08, p < .001, R² = .08), depression (β = 0.69, p = .007, R² = .10), and physical health symptoms (β = 0.83, p < .001, R² = .13) in mothers. General mindfulness did not have an impact on any of these outcomes. However, mindful parenting and acceptance fully mediated the effects of child behavior severity on stress and depression and partially mediated the effects of child behavior severity on maternal anxiety and physical health symptoms.

**Discussion:** As expected, child behavior severity was a strong predictor of maternal well-being in all domains measured. However, parents who reported greater mindfulness in the parenting role and acceptance of negative life events were less likely to experience negative outcomes as a result of having a child with greater severity. These findings suggest that mindfulness-based approaches, especially those focused on improving mindful parenting and acceptance may promote health and well-being for mothers of children with FXS. These findings also have important health implications for all individuals with an *FMR1* premutation.

**References/Citations:**

¹RTI International
Paper Title: Social Outcomes and the Feasibility of an App-Based Mindfulness Intervention among Women with an FMR1 Premutation Experiencing Maternal Stress

Authors: Jessica Ezzell Hunter1, Charisma Jenkins1, Valerie Grim1, Sue Leung1, Krista Charen2, Debra Hamilton2, Emily Allen2, Stephanie Sherman2

Introduction: Women with an FMR1 premutation allele (PM) who have a child with fragile X syndrome (FXS) report elevated rates of maternal stress. In addition, our prior studies indicate that a subset of women with a PM are at risk of social anxiety, which could impact the establishment of social support networks, an important component of stress management. In-person mindfulness training sessions have been shown to be effective in alleviating maternal stress-related outcomes among mothers of children with intellectual and developmental disabilities. However, social anxiety could create a barrier to participating in in-person mindfulness sessions. Thus, the main goals of this pilot study were to assess the feasibility and adherence of an app-based mindfulness training program among mothers of children with FXS and to explore stress, social outcomes, and potential barriers to social support.

Methods: We recruited 18 women with a PM who are mothers of a child with FXS. Participants were asked to download the mindfulness smart phone app and complete a short mindfulness training program (10, 10-minute mindfulness sessions to be completed in 10 consecutive days). Participants were also asked to complete a set of questionnaires to assess maternal stress and social outcomes as well as a semi-structured interview to obtain their feedback on the app and further query stress and social outcomes.

Results: Of the 18 participants, self-reported adherence and access data provided by the maker of the mindfulness app indicated that 13 completed the mindfulness program. Of those who completed the mindfulness program, most (77%) found it helpful and indicated they planned to continue to use the app. Of those who found the app helpful, 60% met criteria for social anxiety based on the Social Phobia and Anxiety Inventory (SPAI). Among all participants, 67% indicated that they felt they had enough social support. Of the 14 women who indicated difficulties in reaching out for help when needed, 50% met criteria for social anxiety based on the SPAI.

Discussion: The results of this study indicate that an app-based mindfulness program is feasible among mothers of children with FXS, though not all are adherent. The app may be most effective among women struggling with social anxiety and are experiencing barriers to social support. This study provides guidance for interventions to alleviate distress associated with elevated maternal stress in women with a PM that could either address or accommodate impairments in social functioning. Addressing stress management and stress-related outcomes in women with a PM who are caring for a child with FXS has the potential to improve both their well-being and their families.

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