Title: Developmental Trajectories of Sex Differences in Negative Affect in Infants with FXS

Authors: Carla Wall & Jane Roberts

Introduction: Neurodevelopmental disorders, including autism spectrum disorder and fragile x syndrome (FXS), historically have been studied predominantly in males due to sex differences in their prevalence and the increased phenotypic variability in females. Particularly in FXS work, females have largely been excluded from much of the extant research; as a result, current assessments, biomarkers, and treatment recommendations are only potentially valuable for the male phenotype. Given the clear impact of early detection and intervention, it is important that characterizations of the early phenotype of FXS include sex differences. Because temperament is relatively stable and can be accurately measured in infancy, it is a useful approach to understanding early developmental trajectories. Temperament is known as individual differences in reactivity and regulation that are present early in development (M. K. Rothbart & Bates, 2006). Current measures utilize a three-factor model of temperament comprised of surgency, negative affect, and effortful control. This structure seems to hold in populations with FXS (Roberts et al., 2014). In the typically developing (TD) population, scholars have noted sex differences in temperament with girls rated higher on effortful control, boys higher on surgency, and no gender differences in negative affect (Else-Quest, Hyde, & Goldsmith, 2006). No studies have examined sex differences in temperament in infants with FXS and their relations to later outcomes. This work is particularly important to understanding the female phenotype in FXS, including comorbidities like anxiety and autism that have been associated with specific temperament profiles in males. Early negative affect has been shown to predict anxiety in preschool boys with FXS (Roberts, Tonnsen, Robinson, McQuillin, & Hatton, 2014), whereas negative affect in idiopathic ASD is predictive of ASD symptomology. In general, females have higher rates of anxiety; this is true for females with autism and less clear in females with FXS. Also, girls with high levels of autism symptoms are less likely to receive an ASD diagnosis than their equally symptomatic male peers (Dworzynski, Ronald, Bolton, & Happé, 2012). Because FXS is an X-chromosome linked, single-gene disorder associated with autism, it offers unique insight into the neurobiological sex differences in both disorders.

Method: Participants included a total of 46 infants assessed at both 12 and 24 months-of-age: 19 TD males, 13 males with FXS, seven TD females and seven females with FXS. Parents completed the Infant Behavior Questionnaire at 12 months (IBQ; Rothbart, 1978) and the Early Childhood Behavior Questionnaire at 24 months (ECBQ; Putnam, Gartstein, & Rothbart, 2006). An additional 20 participants will be added in the next 4 months, as well as outcome data on ASD and anxiety symptoms.

Results: Repeated measures analysis of variance (RM-ANOVA) was performed to assess differences in parent-reported negative affect by gender and diagnosis at 12 and 24 months of age. Results found a significant group x age interaction ($F(1.42) = 6.81, p = .013$, partial $\eta^2 = .14$), such that the TD group experienced a much steeper decrease in negative affect between 18-24 months. No effect of gender was evident. These preliminary findings will be confirmed with the larger dataset.

Discussion: This study found no sex differences in parent-reported temperament in TD children and those with FXS. This work is consistent with earlier reports of temperamental sex differences in TD infants and furthers our understanding of these patterns in those with FXS. In addition, TD males and females were reported to have less negative affect than their peers with FXS at 24 months, but not at 12 months. If future analyses with a larger dataset confirm these findings, it implies that treatment efforts directed at young children with FXS may not need to be adapted by gender which is critical information to guide these efforts. Future work should explore other measures of negative affect, such as physiological arousal and direct observations of behavior to the early patterns of behavior in females with developmental disorders to determine whether and when these differences may occur. This understanding can further the generation of assessments and detection of biomarkers that are sensitive to the female phenotype.
References