**Title**: Elevated Fear Responses Predict Later Social Anxiety Symptoms in Preschoolers with Fragile X Syndrome

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**Introduction**: Fragile X syndrome (FXS) is a rare genetic disorder strongly associated with intellectual impairment and a range of co-occurring conditions, including anxiety disorders. Anxiety is one of the most prevalent and impairing co-occurring conditions in FXS, with 77-86% of individuals meeting criteria for an anxiety disorder (e.g., social anxiety; Cordeiro et al., 2011). FXS is also the most common single-gene cause of autism spectrum disorder (ASD), accounting for 2-6% of ASD cases (Cohen et al., 2005; Crawford et al., 2002; Hagerman, 2008). Given the significant impact of anxiety on individuals with FXS, increasing attention has been directed toward its early detection to optimize intervention timing and improve outcomes. Behavioral inhibition (BI), a temperament trait marked by heightened reactivity to novelty (Fox et al., 2001), increases risk for anxiety symptoms in childhood (Clauss & Blackford, 2012). Prior studies have demonstrated that observed BI in the presence of a stranger predicts later social anxiety in children with FXS (Tonnsen et al., 2017). However, little is known about how different components of BI (e.g., bodily fear, facial fear, escape behaviors) individually predict later social anxiety in children with FXS. Moreover, the impact of ASD symptom severity on the relationship between BI and social anxiety remains underexplored. This study aims to investigate differences in BI and explore the relationship between early (36 months) BI in toddlers with FXS and later (60 months) social anxiety in preschoolers contrasted against NT children.

**Method**: Participants included 64 children with FXS (69% male) and 49 NT children (82% male). At 36 months (*M(SD)FXS* = 37.17(1.61); *M(SD)NT* = 36.88(1.50)) the Stranger Task (Goldsmith & Rothbart, 1999) was administered. Bodily fear, facial fear, and escape behavior were coded from video. Social anxiety symptoms were measured at 60 months (*M(SD)FXS* = 59.45(3.09); *M(SD)NT* = 59.21(2.70)), using the social anxiety subscale raw score from the Preschool Anxiety Scale-Revised (PAS-R, Spence et al., 2001). Autism symptom severity was measured using the calibrated severity scores (CSS; Gotham et al., 2009) from the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012). Path analysis was conducted to investigate if group differences were evident among aspects of BI at 36 months. Additionally, the analysis explored how ASD symptom severity, fear responses, group membership, and their interaction were associated with social anxiety symptoms at 60 months. Analyses were conducted in R (R Core Team, 2023) using the lavaan package (Rosseel, 2012).

**Results**: ASD symptom severity significantly predicted escape behaviors for children regardless of diagnosis group (*b* = 0.07, *p* = .024, Figure 1): As ASD severity score increased, escape behaviors increased. There were no other group differences between FXS and NT children for any of the behavioral fear composites (*p*s > .483). Facial fear at 36 months and ASD symptom severity scores both significantly predicted social anxiety at 60 months, such that as facial fear scores (*b* = 23.26, *p* = .004; Figure 2) or ASD symptom severity scores (*b* = 3.66, *p* = .001) increased, so did social anxiety symptoms. There were several significant fear-by-group interactions. The positive relationship between bodily fear and social anxiety (*b* = 38.31, *p* = .032, Figure 2), as well as between escape behaviors and social anxiety (*b* = 10.24, *p* = .007; Figure 2), was greater for FXS children relative to NT children. Additionally, the negative relationship between facial fear and social anxiety (*b* = -4.29, *p* = .030) as well as between escape behaviors and social anxiety (*b* = -2.71, *p* = .002), was greater for children with elevated ASD severity scores.

**Discussion:** While no group differences were found for aspects of BI after controlling for ASD severity, both facial fear and ASD severity at 36 months emerged as strong predictors of social anxiety at 60 months. Notably, interactions revealed that the positive relationships between bodily fear and social anxiety, as well as between escape behaviors and social anxiety, were significantly stronger for children with FXS compared to NT children. Conversely, the negative relationships between facial fear and social anxiety, as well as escape behaviors and social anxiety, were more pronounced in children with elevated ASD severity scores, such that as fear behaviors increased, social anxiety decreased, particularly so for those with more ASD symptoms. This could indicate that children with elevated ASD symptoms may express anxiety differently; more overt aspects of BI, such as escape and facial fear, might be less connected to internalized social anxiety and more connected to specific challenges in emotional regulation and social communication associated with ASD. Overall, these findings emphasize the complexity of anxiety development in children with FXS and underscore the necessity for identification of early indicators of anxiety, particularly those associated with aspects of BI like escape and bodily fear. Understanding the moderating effect of ASD severity can guide more tailored interventions aimed at mitigating anxiety symptoms in this vulnerable population.

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