2021 Gatlinburg Conference Poster Submission

Title: Longitudinal trajectories of respiratory sinus arrythmia suppression predict social anxiety symptoms in fragile X syndrome

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Introduction: Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by a mutation on the X chromosome. FXS presents with more severe symptoms in males due to the X-linked nature (Bagni et al., 2012). Notably, social anxiety is highly prevalent in both males and females with FXS, affecting approximately 13-60% of individuals (Cordeiro et al., 2011; Ezell et al., 2019), and parents report that anxiety is the most impairing symptom cluster in FXS (Bailey et al., 2008). However, little is understood about the prodromal (e.g. features present before formal diagnosis) features of social anxiety in infants and young children with FXS. Increased understanding of the early features of anxiety in FXS would enable earlier identification and intervention which, in turn, has the potential to improve long-term outcomes. Respiratory sinus arrythmia (RSA), a cardiac marker of parasympathetic nervous system activity, is associated with restoration and recovery of the emotional regulation system (Beauchaine & Thayer, 2015). Additionally, RSA has been demonstrated as a prodromal feature of social anxiety symptoms in typical development (TD) both during a baseline task and in response to a novel social situation (Beauchaine & Thayer, 2015; Brooker et al., 2013). In FXS, research has demonstrated that attenuated RSA suppression at 12 months of age is related to concurrent prodromal features of social anxiety (Black et al., under review). However, the development of RSA suppression across the first years of life , and how it relates to early emerging social anxiety symptoms, remains unknown. Hence, the objective of the current study is to characterize the trajectories of RSA suppression in response to a novel social situation in 12,24,36-month-old males and females with FXS in comparison to a typically developing (TD) control sample. Additionally, this study looks to examine the individual differences in RSA trajectories and its relationship to social anxiety symptoms at age 5.

Method: Participants were drawn from larger longitudinal studies of anxiety and autism spectrum disorder (ASD) in FXS. The current study included 27 (Female: *n*=13) infants and young children with FXS and 33 (Female: *n*=10) TD controls. Participants were tested across at least two timepoints between the ages of 12 and 36 months, resulting in a total of 121 observations (FXS: *n*=55; TD: *n*=66). Additionally, participants were assessed at 5 years old to measure symptoms of social anxiety. Heart activity was measured during a baseline period and in response to a novel social situation using either an Alive Wireless Heart Monitor (Alive Technologies, Copyright 2005-2009) or an Activwave Cardio Monitor (CamNtech Ltd., Cambridge, UK). RSA was extracted using CardioBatch software (Brain-Body Center, University of Illinois at Chicago). The Laboratory Temperament Assessment Battery (LabTAB) Stranger Approach paradigm was utilized to create a novel social situation (Goldsmith & Rothbart, 1996). RSA suppression was calculated as Baseline RSA-Stranger RSA. Social anxiety symptoms were measured via the social avoidance subscale of the Anxiety Depression and Mood Scale (ADAMS; Esbensen et al., 2003) at 5 years old as an outcome measure.

Results: To predict RSA suppression, we used a linear mixed effect model with the predictors group, age (grand mean centered at 23.76 months), and sex along with their interactions. The three-way interaction of Age*Group*Sex was significant, $F(1,57)=5.71$, $p=.020$, demonstrating differences in development across FXS males, FXS females, TD males, and TD females (See Figure 1). To predict social anxiety symptoms at outcome, RSA development (i.e., slope of change), group, and the group*slope interaction were entered as predictors in a linear regression. The main effects of slope ($t(32)=2.13$, $p=.041$, $\beta=0.37$) and group $t(32)=-2.17$, $p=.037$, $\beta=0.34$) significantly predicted social anxiety symptoms, and were not qualified by an interaction ($t(32)=-0.33$, $p=.745$, $\beta=-0.057$). Thus, a FXS diagnosis predicted higher levels of social anxiety symptoms. Moreover, an increase in RSA suppression over time was indicative of lower symptoms of social anxiety.

Discussion: Findings demonstrate that RSA suppression changes across time are different based on group and sex. Specifically, males and females with FXS displayed more suppression aross age than the TD males and females. However, TD males, TD females, FXS males and FXS females all differed in their rate of change overtime. Importantly, an increase in RSA suppression over time predicted lower social anxiety symptoms suggesting an important role of physiological regulation in response to a social challenge as an early indicator or predictor social anxiety. These findings have important implications demonstrating the

utility of a potential prodromal marker that could facilitate earlier identification of social anxiety, leading to intervention services at a younger age.

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