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Early Behavioral and Physiological Markers of Social Anxiety in Fragile X Syndrome

Conner J. Black

EARLY BEHAVIORAL AND PHYSIOLOGICAL MARKERS OF SOCIAL ANXIETY IN FRAGILE X SYNDROME

by

Conner J. Black

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Jane E. Roberts, Director of Thesis

Abigail L. Hogan , Reader

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

ABSTRACT

Background: Social Anxiety is diagnosed in approximately 10% of neurotypical children. If left untreated, negative outcomes are highly prevalent later in life. Thus, understanding the earliest features of social anxiety can help to mitigate detrimental outcomes. Fragile X Syndrome, which has a high prevalence of social anxiety, is a genetic syndrome which creates a unique opportunity to study the earliest predictors of social anxiety before formal diagnosis. Fragile X Syndrome presents with intellectual disability and an increased prevalence of maladaptive behaviors. The current study utilized a bio-behavioral approach to study the earliest marker of social anxiety in 12-month-old infants with fragile X syndrome.

Method: Participants included 32 infants with FXS (M (SD): 12.41 (1.49)) and 41 low risk controls ((M (SD): 12.41 (0.60)). Parent reported social behavioral inhibition was recorded from the Infant Behavior Questionnaire (IBQ-R), which reflects infants' responses in a social context. Observed social behavioral inhibition and physiology was measured during the Stranger Task of the Laboratory Temperament Assessment Battery (Lab-TAB). This task is designed to elicit social behavioral inhibition in infants and young children. Group differences were assessed using independent sample t-tests. Differences in physiological response was tested using a repeated measure mixed effect linear model with condition, group, Mullen ELC, and group by condition interaction included as predictors.

Results: . Parent-reported social behavioral inhibition was not significantly different between groups. Infants with FXS demonstrated less social behavioral inhibition but increased gaze vigilance towards the stranger in comparison to LRCs. Physiological response was blunted in infants with FXS, but not LRC peers.

Conclusions: Findings suggest that infants with FXS are showing both physiological and attentional markers of social anxiety at 12 months old. However, no differences were observed in either parent-reported or observed social behavioral inhibition. Results highlight the importance of a multi-method approach to understanding the complex phenotype of social anxiety in FXS. Future studies should examine longitudinal trajectories of infants with FXS to include social anxiety diagnosis outcome data.

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CHAPTER 1

INTRODUCTION

Anxiety is the most common childhood psychiatric disorder, with 8-20% of neurotypical (NT) children (i.e., children without a neurodevelopmental disability) diagnosed before adolescence (Costello, Egger, & Angold, 2005; EGGER et al., 2006; Franz et al., 2013). If left untreated, childhood anxiety can lead to serious issues later in life such as depression, suicidality, substance abuse, and personality disorders (Bijl & Ravelli, 2000). However, low-cost intervention early in childhood (e.g., in preschool) has been shown to produce long-term positive outcomes (Kennedy, Rapee, & Edwards, 2009; Rapee, 2013). Social anxiety is one of the most frequent and early emerging anxiety disorders that affects nearly 10% of children in preschool (Franz et al., 2013). Thus, understanding the early predictors of social anxiety in infants and very young children can improve early identification, facilitate early intervention, and optimize long-term outcomes. In NT preschool-aged children, a number of prodromal indicators of social anxiety have been identified to facilitate early and accurate identification of those at highest risk for an eventual diagnosis of social anxiety.

Behavioral inhibition , a temperament characteristic that includes features of fear, shyness, and withdrawal in response to novelty is one of the most robust predictors of both elevated social anxiety symptoms and diagnoses (J. A. Clauss, Avery, & Blackford,

2015; Jacqueline A. Clauss & Blackford, 2012; Mian, Wainwright, Briggs-Gowan, & Carter, 2011). Preschool children who demonstrate elevated behavioral inhibition across age areup to four times more likely to be later diagnosed with social anxiety diagnosis than NT controls without elevated behavioral inhibition (Jacqueline A. Clauss & Blackford, 2012). In particular, the presence of high behavioral inhibition within the first two years of life is a particularly salient risk marker for social anxiety later in life (Brooker Rebecca J. et al., 2013).

In addition to behavioral inhibition, several other factors have been identified that predict social anxiety including attentional and physiological dysregulation. Attentional dysregulation has long been shown to contribute to the development and maintenance of anxiety symptoms (Mogg & Bradley, 1998) For example, research on social anxiety in children has identified attention bias towards threatening images or vigilance (e.g. fearful or angry faces) as a feature of generalized anxiety (A. M. Waters, Bradley, & Mogg, 2014; WATERS, MOGG, BRADLEY, & PINE, 2008; Allison M. Waters, Henry, Mogg, Bradley, & Pine, 2010). Contrary to this, some studies suggest that attention bias away from threatening images is present in fear-based disorders such as social anxiety.

These attention biases appear to be rooted, in part, in atypical physiological regulation. Evidence to support the neurophysiological basis of attention bias suggests that increased neural recruitment has been associated with elevated gaze avoidance and social anxiety in children with elevated behavioral inhibition (Thai, Taber-Thomas, & Pérez-Edgar, 2016). Likewise, suppressed baseline respiratory sinus arrhythmia (RSA) has also been linked to elevated symptoms of anxiety (Greaves-Lord et al., 2010) as has

reduced RSA suppression in response to a novel social task (Brooker, Kiel, & Buss, 2016; Buss et al., 2013; Viana et al., 2017).

Collectively, this work demonstrates that signs of social anxiety are present and detectable very early in life. Given the high prevalence and impairment associated with social anxiety, studies that refine our understanding of the early signs are critical to advance our ability for early detection and treatment. One productive way to approach this work is to target homogenous populations who are at high risk for social anxiety. Fragile X syndrome (FXS) is a genetic disorder where individuals show increased rates of social anxiety (Cordeiro, Ballinger, Hagerman, & Hessl, 2011; Ezell et al., 2019).

FXS is a neurodevelopmental disorder that affects approximately 1 in 3700 males and 1 in 6000 females (Crawford, Acuña, & Sherman, 2001). It is caused by a CGG trinucleotide repeat expansion mutation of more than 200 repeats on the Fragile X Mental Retardation-1 (*FMR1)* gene on the X chromosome. Individuals with FXS often present with intellectual disability, maladaptive behaviors, and attention deficit hyperactivity disorder (AD/HD) symptoms (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013; Wheeler et al., 2014). Moreover, individuals with FXS are at increased risk for anxiety problems with up to 86% of males meting criteria for at least one anxiety disorder (Cordeiro et al., 2011). Social anxiety is one of the most highly prevalent disorders with 60.3% of males and 55.3% of females with FXS meeting for social anxiety (Cordeiro et al., 2011; Ezell et al., 2019).

While research has clearly documented the high prevalence of social anxiety in FXS, little is understood about early signs of social anxiety symptoms in young children

and infants with FXS. Research suggests that children with FXS display increased distress, gaze aversion, and avoidance during a social challenge task (Hessl, Glaser, Dyer-Friedman, & Reiss, 2006). And, emerging evidence suggests that elevated BI, as expressed through negative affect, in preschool-aged children with FXS is associated with social anxiety symptoms later in age (B. Tonnsen, Scherr, Reisinger, & Roberts, 2017; Wall et al., 2019). Of note, this work has shown that elevated negative affect is selective in predicting anxiety and not features of autism spectrum disorder in these young children with is important given that anxiety and autism spectrum disorder share features and are both commonly diagnosed in FXS (B. Tonnsen et al., 2017; Wall et al., 2019).

The role of attention and physiological arousal in relation to social anxiety in FXS has not been well-studied. To date, there is evidence that preschoolers with FXS demonstrate reduced gaze towards novel people (Scherr, Hogan, Hatton, & Roberts, 2017) and that school-age children demonstrate a greater bias towards angry over happy stimuli (Burris et al., 2017). Research has also documented reduced baseline and blunted modulation of RSA in the context of cognitive (Roberts, Boccia, Bailey, Hatton, & Skinner, 2001) and social challenges (B. L. Tonnsen, Shinkareva, Deal, Hatton, & Roberts, 2013). These papers demonstrate that atypical behavioral inhibition and physiological dysregulation is present in children with FXS. However, these studies primarily focused on preschool and older-aged children, and little is known in infancy.

The current study used a bio-behavioral approach to investigate the over-arching aim of detecting elevated behavioral inhibition and physiological dysregulation in 12-month-old infants with FXS. We include a comparison group of age-matched low risk

controls (LRC) to account for normal variation of social fear that is common in this age group. Multiple measures reflecting parent reported behavioral inhibition, direct observations of behavioral inhibition and putative physiological mechanisms of behavioral inhibition are used given the complexity and challenge of detecting early markers of social fear in infancy. We hypothesized that infants with FXS would display higher levels of social behavioral inhibition across both parent-reported and observed measures in addition to reduced RSA and blunted modulation of RSA that distinguished them from LRC. We also hypothesized that direct observations of behavioral inhibition would be related to RSA.

CHAPTER 2

METHOD

Participants

This study included 73 12-month-old infants distributed across two groups. The FXS group was comprised of 32 infants, and the low risk control (LRC) group included 41 infants (See Table 2.1). A FXS diagnosis was confirmed through molecular genetic report revealing >200 CGG repeats (i.e., full mutation FXS). LRCs were included based on absence of a family history of ASD or related disorder (i.e., tuberous sclerosis, FXS) and confirmation of typical development through study assessment (detailed below). Exclusion criteria for both groups included gestation of <37 weeks, presence of vision or hearing impairment, and English as the primary language spoken in the residence. Participants were recruited through a national registry for research and advertising through community resources as part of two larger longitudinal studies examining the emergence of ASD symptoms and anxiety in FXS, high risk controls, and low risk controls (1R01MH107573-01A1 & 2RO1MH090194-06).

Measures

We utilized a multi-method biobehavioral approach to characterize social behavioral inhibition. This included a parent report, two direct observation measures (composite and visual attention), and two measures of physiological regulation (RSA baseline, RSA stranger). Additionally, an RSA reactivity score was calculated to look at

differences between baseline and stranger. We also included a measure of early cognition and development given that infants with FXS have documented developmental delays.

Parent Reported Social Behavioral Inhibition

The Infant Behavior Questionnaire- Revised (IBQ-R;32) was used to assess parent reported social behavioral inhibition. The IBQ-R is a 191-item temperament questionnaire that asks parents to rate how often their child responds to a variety of situations on a Likert scale from 1 to 7 (higher scores indicate higher frequency). Specifically, we computed a social behavioral inhibition score that reflects fear to unfamiliar adults that has been done in previous work (Brooker Rebecca J. et al., 2013). The composite consisted of an average of eleven items and included questions such as "When introduced to an unfamiliar adult, how often did the baby cling to parent?".

Direct Observation of Social Behavioral Inhibition: Social Behavioral Inhibition Composite and Social Visual Attention

The Stranger Approach paradigm from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith & Rothbart, 1996) was used to assess observed social behavioral inhibition and visual attention in response to the approach of an unfamiliar adult. The task consists of three parts, approach of stranger towards the infant (10 seconds), stranger kneeling in front of the infant with a neutral expression (2 minutes), and withdrawal phase (30 seconds). Infants are seated on their mother's lap throughout the paradigm, and the stranger is an unfamiliar research associate dressed in a black skirt, hooded sweatshirt, baseball cap, and sunglasses. In this paper, only the kneel portion of

the paradigm was analyzed because of our focus on the most intense expression of fear and only the kneel phase has the requisite time to calculate RSA as described below.

Videotaped recordings of the Stranger Approach task were coded for escape behaviors, distress vocalizations, bodily fear, and visual attention using *Noldus The Observer XT* (version 10.0 software, Noldus Information Technology, Leesburg, VA, USA). Reliability was checked on 20% of videos, with Cohen's kappa ranging from 0.81 to 0.90. Escape behavior, distress vocalizations, and bodily fear were coded for both intensity and duration. More detail about the behavioral coding scheme can be found in Scherr et al. (2017). Composite scores were computed for escape behaviors, distress vocalizations, and bodily fear by multiplying the proportion of time spent at each intensity level with the intensity score, calculating a z-score then averaging the z scores (Song, Lin, Ward, & Fine, 2013). Visual attention was coded by measuring the proportion of time spent looking at Stranger.

Physiological Regulation: Baseline RSA, Stranger RSA, and RSA Reactivity

Heart activity was collected using a telemetry system that utilized two electrodes placed on the infant's chest to collect the ECG signal at a sampling rate of $\geq$ 300 Hz (Alive Technologies; CamNtech Ltd., Cambridge, UK). Trained research assistants edited and visually inspected the electrocardiogram signal to find arrhythmias, false heart periods, and artifacts using CardioEdit software (Brain-Body Center, University of Illinois at Chicago). If >10% of data was edited, the participant was excluded from further analyses. Respiratory sinus arrhythmia (RSA) was extracted via CardioBatch software (Brain-Body Center, University of Illinois at Chicago). CardioBatch samples

sequential heart periods in 250ms epochs and then utilizes a 21-point moving polynomial algorithm to de-trend the data. The data are filtered to remove variance associated with breathing parameters (.3-1.3 Hz) and RSA is then estimated by changing the variance to its natural logarithm. RSA was calculated using 30 second epochs. The baseline RSA was calculated by taking 30 second epochs of a three-minute baseline period where the infant would watch an engaging video short. Stranger RSA was calculated by taking the four 30-second epochs during the kneel phase and computing an average. RSA reactivity was calculated by taking the baseline RSA and subtracting the stranger RSA to create a measure of reactivity.

Cognitive Measure

The Mullen Scales of Early Learning (Mullen, 1995) is a developmental measure used to assess cognitive abilities in 0-68 month-year-old children. The Mullen measures development across five specific domain areas: Gross Motor, Fine Motor, Receptive Language, Expressive Language, and Visual Reception. The composition of four of the five sections, excluding Gross Motor, creates an early learning composite (ELC) with a mean of 100 and standard deviation of 15.

Procedure

Assessments typically took place at the research laboratory at the University of South Carolina with breaks allowed per the infant's behavior and parental input. All assessments were completed by a team of two or three trained research specialists. Ethics approval was obtained for this study through the University of South Carolina

Institutional Review Board. A brief developmental summary and monetary compensation was provided to the family upon completion of the assessment.

Statistical Analysis Plan

Pearson correlations were used to examine the relationship of the social behavioral inhibition scores to sex and cognitive scores as potential covariates. To assess differences across groups in parent-reported behavioral inhibition, the observed composite, and visual attention, independent samples *t*-tests were utilized. To determine within and across group differences in baseline RSA, RSA during the stranger, a repeated measure mixed effects linear model via PROC MIXED in SAS 9.4. Condition (baseline or stranger) was specified as repeated effect, nested within participant. Group, condition, Mullen ELC, and the group by condition interaction were included as predictors, and a random intercept was included to account for intra-individual differences in RSA. To describe the relationship between parent reported and observed social behavioral inhibition to RSA, correlations were run in both groups.

Table 2.1. Participant Characteristics

	FXS (n=32)	LRC (41)	P-Value
Age, M(SD)	12.41 (1.49)	12.41 (.60)	.995
Sex, F	10	9	.369
Mullen ELC, M(SD)	76.55 (21.52)	98.44 (12.83)	<.001

CHAPTER 3

RESULTS

Preliminary analyses indicated that the groups did not differ on chronological age or sex (Table 2.1). As expected, the group with FXS did evidence lower cognitive developmental scores that was associated with sex (see Table 3.1). Due to this observed difference the cognitive score was included in the main model of the paper.

Analyses indicate that the FXS and LRC groups did not differ on the parent reported social behavioral inhibition, (t (57) =.53, p = .600, d = .14) with marginal group differences emerging on the directly observed social behavioral inhibition composite, (t (63) = 1.820, p = .074, d = .45), and the visual attention, (t (62) = -1.95, p = .056, d = .47). Given the small sample sizes and the effect of small samples on p-levels, we emphasize the effect size estimates that both approach a medium effect of .50 (cite) indicating greater scores for the LRC on the composite and more visual attention towards the stranger for the FXS group.

Results from the repeated measures mixed effects linear model indicated no significant main effects of group, F (1,40) = .68, p=.414 or condition (baseline and stranger), F (1,40)=3.19, p=.082, but a significant condition by group interaction, F (1,40)=4.14, p=.049. Due to the significant interaction, we probed within group RSA reactivity between baseline and stranger. The LRCs displayed a significant decrease from baseline to stranger, t (40)=-3.10, p=.004 (Mean Change = 0.68) whereas the FXS group

did not, t (40)=.16, p=.997 (Mean Change = 0.04). Correlations between observed social behavioral inhibition and visual attention are displayed below in table 3.2. No significant correlations emerged between parent-reported social behavioral inhibition and social behavioral inhibition composite (see table 3.2). In the LRC group, a significant negative correlation emerged between RSA reactivity and proportion of time looking at stranger, demonstrating that a larger change in RSA was associated with less time looking at the novel person.

Table 3.1. Means and Standard Deviations of key variables

	FXS	LRC
Parent-Reported social behavioral inhibition	2.78 (1.06)	2.92 (1.01)
Social ehavioral Inhibition Composite	-0.19 (0.66)	0.062 (0.54)
Proportion of Time Looking at Stranger	0.49 (.25)	0.40 (.13)
Baseline RSA	4.21 (1.55)	4.53 (0.97)
Stranger RSA	4.17 (1.25)	3.86 (0.81)
RSA Reactivity	0.04 (1.33)	.68 (1.04)

Table 3.2. Correlations between Parent-reported fear, observed fear, and RSA in FXS and LRCs

FXS		1	2	3	4	5	6
1.	Parent-reported behavioral inhibition	1					
2.	Behavioral Inhibition Composite	-.222	1				
3.	Proportion of Time Looking at Stranger	-.081	-.352	1			
4.	RSA Reactivity	.001	-.112	.311	1		
5.	Mullen ELC	.188	-.066	.308	.408	1	
6.	Sex	.322	-.017	.048	-.015	-.509**	1
LRC							
1.	Parent-reported behavioral inhibition	1					
2.	Behavioral Inhibition Composite	-.187	1				
3.	Proportion of Time Looking at Stranger	.010	-.497**	1			
4.	RSA Reactivity	.199	.310	-.424*	1		
5.	Mullen ELC	-.203	-.069	.011	.011	1	
6.	Sex	-.041	.118	-.130	-.130	.046	1

*<.05 **<.01

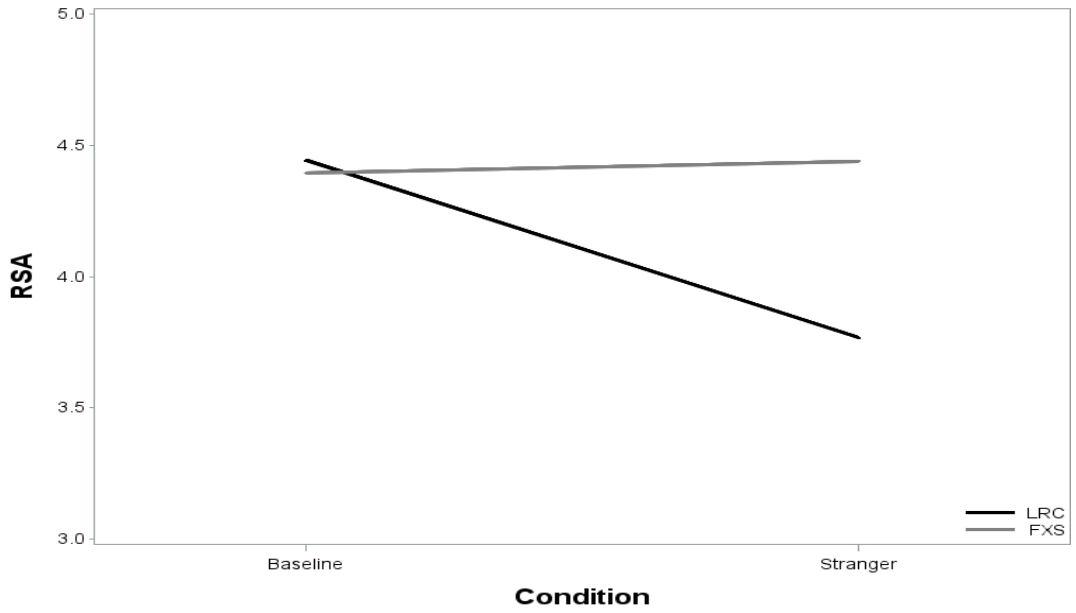

Figure 3.1. RSA by Group Across Condition

CHAPTER 4

DISCUSSION

Social anxiety is a highly prevalent and impairing condition that can be detected early in life. Understanding early prodromal features of social anxiety will facilitate early intervention leading to mitigation of the negative long-term outcomes. The present study is the first to examine social anxiety risk markers across multiple indices in infants with FXS, an etiologically distinct genetic group at high risk for social anxiety. Findings suggest that infants with FXS are displaying both early physiological and attentional markers of social anxiety that are detectable as early as 12-months-of-age.

Results from this study highlight the importance of a multi-method bio-behavioral approach to addressing complex questions as we have asked in this study. For example, we found differences across sources of data with parent reports indicating that the groups were similar while direct observations and physiological markers identified group differences. Likewise, the parent reports were not correlated with the direct observations or physiological markers whereas specific aspects of the direct observations were correlated with physiological markers in an informative and group-distinct manner.

The reduced sensitivity of the parent report to detect group differences likely reflects either a lack of parental awareness of early signs of social anxiety or a "normalization" of their child's behavior reflecting a focus on individual differences of the child as opposed to a comparison of the child to others. In other words, these parents

may have assimilated their child's behavior into a framework where they view their child's responses as typical because it is how the child typically responds. The perception of the parents of infants with FXS may also be skewed in regard to their own expectations of how a child with FXS "should act" with ratings potentially reflecting their own biases of how their infant is more like or less like other infants with FXS that they are aware of. In this study, the fact that parents of infants with FXS did not rate their infants as displaying elevated social anxiety in the face of evidence that direct observations support this, suggests that these parents may be either unaware or denying the presence of these behaviors. This conclusion is partially supported by multiple parents reporting that they did not perceive signs of anxiety in their child when the child was an infant but that they could see signs of anxiety during infancy in retrospect when their child was older (J. Roberts, personal communication, September 1st, 2011). Also, evidence exists that parents of children with FXS do not report increased levels of social anxiety despite an increase in social difficulty (Lesniak-Karpiak, Mazzocco, & Ross, 2003).

With regard to the direct observations, interesting group differences emerged that likely reflect the vulnerability of the FXS infant group. The LRC infant group reacted to the presentation of a novel and unresponsive social partner by evoking a more complex behavioral response through increased vocal distress, elevated bodily movement and engaging in escape behavior with reduced visual attention to the social target. In addition, there was a coupling of the behavioral responses to the physiological responses in the LRC group (e.g., RSA suppression) that was not observed in the FXS group. In contrast, the infants with FXS engaged in elevated visual attention towards the unresponsive

stranger and displayed virtually no physiological regulation in response to this social threat. Of note, neither the behavioral nor physiological responses were related to overall developmental ability in either group; thus, these maladaptive responses cannot be attributed to cognitive or developmental impairment.

Our findings have important implications. First, we report attention bias towards a social threat in the infants with FXS with nearly 50% of their time spent looking toward the stranger. Given that increased attentional vigilance is related to "distress" disorders (Allison M. Waters et al., 2010); our findings may suggest elevated risk for a more pervasive or generalized anxiety disorder rather than social anxiety disorder specifically. Second, our finding that RSA suppression is reduced in the infants with FXS and not coupled with their behavioral response suggests that this may be a useful biomarker to detect risk for anxiety in this group. These findings are consistent with our previous work demonstrating that early physiological dysregulation could precede and/or contribute to atypical behavioral responses. (Roberts, Tonnsen, Robinson, & Shinkareva, 2012). Both of these hypotheses need to be empirically validated through longitudinal studies.

Overall these findings support our hypothesis that infants with FXS display elevated prodromal features of anxiety through both direct behavioral and physiological markers. Strengths of the study include a bio-behavioral approach that includes both behavioral and physiological markers along with multiple measures within each domain (e.g., two direct observation measures). This approach is critical given the young age of our sample and the corresponding limited range of behaviors that can be sampled in infancy, particularly as the detection of early signs of anxiety as is our focus and signs of

anxiety are subtle and often absent in the first years of life. These issues are exacerbated by the complexity of the phenotype of FXS which includes developmental delays and social-communication deficits (Rogers, Wehner, & Hagerman, 2001). Finally, we included a well-matched LRC group to allow consideration of normative levels of social fear which are common at this age.

Despite these strengths, this study is limited by the use of only two groups which makes it hard to derive implications that may be unique FXS. Future studies should aim to explore these questions using another comparison group with of genetic etiology with developmental delay (i.e. Down syndrome). Another limitation is that we do not have outcome data. This is particularly important given evidence that high behavioral inhibition and atypical physiological responses across the first three years of life are very robust predictors of anxiety outcome in NT children (Brooker Rebecca J. et al., 2013). Longitudinal studies should be conducted to examine the relationship of these early indicators of anxiety to outcomes including both anxiety and autism spectrum disorder given their overlapping features and frequent co-occurrence in FXS.

In conclusion, the present study is the first to use a bio-behavioral approach to detect prodromal features of social anxiety in infants with FXS. Finding suggest that both behavioral and physiological signs are evident at 12-months-of-age in this high-risk sample which supports the influence of endogenous genetic factors. These findings aid in better understanding the FXS phenotype in infancy as well as deliver promise for the application of intervention that has worked in young typically developing children.

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