

## Children With Fragile X Syndrome Display Threat-Specific Biases Toward Emotion

Jessica L. Burris, Ryan A. Barry-Anwar, Riley N. Sims, Randi J. Hagerman, Flora Tassone, and Susan M. Rivera

### ABSTRACT

**BACKGROUND:** Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. FXS is caused by a silencing of the *FMR1* gene that results in a loss or absence of the gene's protein product, fragile X mental retardation protein. The phenotype of FXS is consistently associated with heightened anxiety, although no previous study has investigated attentional bias toward threat, a hallmark of anxiety disorders, in individuals with FXS.

**METHODS:** The current study employed a passive-viewing eye-tracking version of the dot probe task to investigate attentional biases toward emotional faces in young children with FXS ( $n = 47$ ) and without FXS ( $n = 94$ ).

**RESULTS:** We found that the FXS group showed a significantly greater bias toward threatening emotions than toward positive emotions. This threat specificity was not seen in either a mental age-matched group or a chronological age-matched group of typically developing children. Unlike the typically developing groups, the FXS group showed no bias toward positive emotion.

**CONCLUSIONS:** The current study shows that children with FXS have a significant bias toward threatening information, an attentional profile that has been linked with anxiety. It also supports the use of eye-tracking methodology to index neural and attentional responses in young children with FXS.

**Keywords:** Anxiety, Attention, Emotion, Eye tracking, Fragile X syndrome, Threat processing

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Fragile X syndrome (FXS) is an X-linked disorder caused by a trinucleotide repeat expansion on the *FMR1* gene on the X chromosome. The full mutation of the disorder occurs when this CGG repeat expansion number is greater than 200, which causes a loss of function of the gene via methylation (1). When fully methylated, the gene is silenced and no longer produces its protein product fragile X mental retardation protein (FMRP), which is crucial for proper synaptic functioning (2,3). The full mutation, FXS, occurs in approximately 1 in 2500 to 4000 male individuals and 1 in 7000 to 8000 female individuals (4).

The phenotype of FXS includes intellectual disability, attention problems, and anxiety (5). Cordeiro *et al.* reported that upward of 82.5% of individuals with FXS aged 5 to 35 years had clinical levels of anxiety. Social phobia and specific phobia were the most common, with 58% of the sample qualifying for multiple anxiety disorder diagnoses (6). Social phobia and posttraumatic stress disorder are more common in adults than in children with FXS (6). Talisa *et al.* showed that young children with FXS who present without anxiety disorders show less attention problems, hyperactivity, and aggression than those with heightened anxiety or those with heightened anxiety and autism spectrum disorder (ASD) (7). Rogers *et al.* also theorized that social anxiety presenting early in development of individuals with FXS may lead to shyness and problems with social interactions (8).

Olmos-Serrano and Corbin provided a review of the importance of the amygdala and frontal dysfunction in FXS that focused on adults but stressed the need for developmental work (9). This amygdala-prefrontal circuit is crucial in non-syndromic anxiety and in FXS (10). Individuals with anxiety atypically deploy attention to threatening stimuli more than control individuals and interpret ambiguous information as threatening. These findings have been documented in children with anxiety as early as school age (11). Holsen *et al.* also linked impairments in hippocampal activity during emotional face processing as a precursor to social anxiety, specifically for individuals with FXS (12).

Kim *et al.* showed that the amygdala is functionally atypical in adolescents on the FX spectrum (13). Their functional magnetic resonance imaging study showed that amygdala activation failed to increase more to fearful faces than to happy faces, as was observed in the control participants. Importantly, the individuals who presented the greatest anxiety levels were those whose neural signature to threat was the most atypical. This study supports a threat-specific processing profile in FXS that is linked to anxiety and related to, or potentially caused by, atypical functioning of the amygdala. Further exploration of these processes and their developmental origins in younger populations of children with FXS is unfeasible given the behavioral and attentional requirements of the magnetic

resonance imaging environment. The current study presents an alternative methodology that is appropriate for use in young and intellectually disabled populations that can describe the cognitive phenotype of affective processing in young children with FXS.

One promising avenue of exploration is attentional bias patterns to affect in young children with FXS. Owing to methodological and measurement limitations, we cannot directly measure anxiety in infants with FXS, but we can use attentional patterns toward affect, specifically threat, to investigate the phenotype of FXS, which can help to elucidate the underlying cognitive mechanisms related to heightened anxiety in FXS.

Bar-Haim *et al.* reported that nonanxious, typically developing adults did not show attentional biases toward threat and that a significant threat bias exists in individuals with nonsyndromic clinical and subclinical anxiety (14). Anxious children and adults showed similar patterns, although effect sizes are often smaller and variability is often greater in younger populations. Mogg *et al.* showed that bias patterns may differ based on the age of the individuals and on the timing parameters being used (15). It has also been reported that adolescents with anxiety show attentional biases specifically to threat regardless of the specific diagnosis (16). These findings provide support for the theory that there may be a basic error in information processing in anxiety, and they provide a framework for understanding anxiety and its mechanisms in young children with FXS by implicating attentional behavior toward threatening information in the environment as an important marker of this information processing error.

Attentional bias toward threat has typically been measured using the dot probe task (DPT). The classic version of the DPT consists of a brief presentation of two faces, usually paired by emotion: neutral–neutral, happy–neutral, and angry–neutral (17). These faces are followed by a probe that appears on the same side of one of the faces before it. On trials that are congruent, the probe appears on the same side of the screen as the emotional face. On incongruent trials the probe follows on the same side as the presentation of the neutral face. Individuals are tasked to indicate (usually with a button press) the side of the screen on which the probe appears. The theory behind the task is that people will be able to respond faster to a stimulus that appears in an attended region of their visual field than to a stimulus that appears in an unattended region (18). Attentional biases are calculated using the reaction time to the probe on incongruent versus congruent trials. If individuals are faster at detecting probes that appear in the same spatial location as the emotional faces, it indicates that their attentional system was biased toward that stimulus.

Children as young as 5 years have been administered the classic DPT (19), but the cognitive impairments that are present during early childhood in FXS make it challenging to administer the task. Likewise, infants lack the motor control and cognitive abilities to follow instructions and provide a motor response on the traditional DPT. Thus, the modification of the DPT to a completely passive-viewing eye-tracking paradigm, as we have done in the current study, allows for reliable measurement of attention to affect, a variable highly related to anxiety, in infants and in all individuals with FXS regardless of age. This use of eye tracking to index attentional biases toward threat is a prime example of how eye tracking

can be used to understand early cognitive and underlying neural processes in this atypically developing population.

FXS is an excellent candidate disorder for investigating the underlying cognitive mechanisms behind anxiety, and these cognitive mechanisms are an ideal target for investigation early in development. We currently do not have reliable and empirically validated measures of anxiety for very young individuals, and attentional biases toward threat in FXS, as measured by the DPT, have never been investigated. Given the correlation between anxiety and attentional biases toward threat, and the high percentage of anxiety symptoms in FXS, these biases may constitute a biomarker for anxiety in FXS and can aid in exploring the clinical phenotype of FXS.

We aimed to explore attentional bias patterns toward affect in young children with FXS. This could be the first step in developing an effective, sensitive, and empirically objective metric of anxiety risk in young individuals with FXS. We investigated attentional biases to emotion in young children with FXS using a modified, passive-viewing eye-tracking version of the DPT using angry and happy faces. To control for cognitive level and overall development, we collected data on a mental age–matched sample (MA group) and a chronological age–matched sample (CA group) of typically developing (TD) children. The current study initially investigated any preliminary relations between attentional bias patterns and sex given the large phenotypic differences seen between male and female individuals with FXS. It then explored any relation with ASD symptomatology, given the high comorbidity of ASD in FXS. Then we aimed to validate use of this modified version of the DPT in FXS. Given previous research on atypical neural processing (specifically of negative affect) in FXS, we predicted that the FXS group would show a significant attentional bias on trials that included threatening faces and not on trials that included happy faces.

## METHODS AND MATERIALS

### Participants

A total of 47 children with FXS (8 girls) were evaluated at the Medical Investigation of Neurodevelopmental Disorders Institute at the University of California, Davis. The children's chronological ages ranged from 7 months 29 days to 68 months 2 days (mean = 39 months 28 days, SD = 17 months 23 days). Cognitive level was assessed in the FXS group using the Mullen Scales of Early Learning (20), a standardized developmental assessment used for children aged 3 to 60 months. It consists of five subscales: gross motor, fine motor, receptive language, expressive language, and visual reception. The mental age of each participant in the FXS group was calculated by averaging the age equivalencies across four domains (excluding gross motor) and converting that to months and days. We excluded gross motor from this calculation because the scores are less valid in children over the age of 33 months (20). The FXS sample's mental ages ranged from 5 months 15 days to 51 months 21 days (mean = 21 months 29 days, SD = 11 months 3 days).

Autism symptomatology was measured in a subset of the children with FXS (28 of 47) who were administered an Autism Diagnostic Observation Schedule, either Module 1 or Module 2 (depending on their cognitive ability), by a trained clinician (21).

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Of the 28 children with FXS who completed an Autism Diagnostic Observation Schedule, 18 met the criterion for ASD (64%).

While all FXS participants had a clinically confirmed diagnosis in their medical record, FXS allele status was confirmed by *FMR1* DNA testing for a subset of the participants who consented to a blood draw during their research visit (35 of 47). This subset sample consisted of 20 individuals with the full mutation (5 girls), 8 with methylation mosaicism (1 girl), and 7 male individuals with size mosaicism. No individuals with the pre-mutation of the disorder were included. All statistical analyses reported below were completed with and without the 12 individuals who did not have confirmatory DNA testing, and no differences were seen; therefore, results for the entire FXS sample are reported here.

Two discrete TD comparison samples were recruited through letters to families in surrounding areas around Davis, California, and these individuals were given a certificate and a book for participating. The first sample was matched to the mental age of each individual in the FXS sample, and the two groups' mental ages were not statistically different ( $t_{47} = 0.013, p = .99$ ). The MA group had 47 participants (8 girls) with chronological ages (which in a TD sample should reflect the mental ages of the children) ranging from 5 months 14 days to 51 months 11 days (mean = 21 months 28 days, SD = 10 months 29 days). The second sample of TD children was matched to the chronological age of each individual in the FXS sample, and the two groups' chronological ages were not statistically different from one another ( $t_{92} = 0.10, p = .92$ ). The CA group had 47 participants (8 girls) with chronological ages ranging from 8 months 9 days to 67 months 22 days (mean = 40 months 9 days, SD = 18 months 1 day). None of the control participants was tested for developmental disabilities. A breakdown of ages across the three groups can be seen in Table 1. The Institutional Review Board of the University of California, Davis, approved the experimental protocol, and informed consent was obtained from a parent or caregiver of each participant.

**Stimuli**

The task was presented in two blocks, each consisting of 40 trials (see Figure 1 for task details). The task began with a 1000-ms central fixation cross, followed by a 500-ms face pairing that was then followed immediately by a 1500-ms asterisk probe that appeared in the same spatial location as one of the previous faces (see Figure 1). There were three categories of face pairings: 31 angry paired with neutral, 32 happy paired with neutral, and 17 neutral paired with neutral. Expressions were modeled by 28 different actors from the NimStim stimulus set (22). The angry, happy, and neutral closed-mouth images of 14 male and 14 female Caucasian, African American, and Asian faces were used. Images were trimmed so that all hair was removed from the images. Identity, sex and race of the face, emotion, probe side, and trial congruency all were randomized.

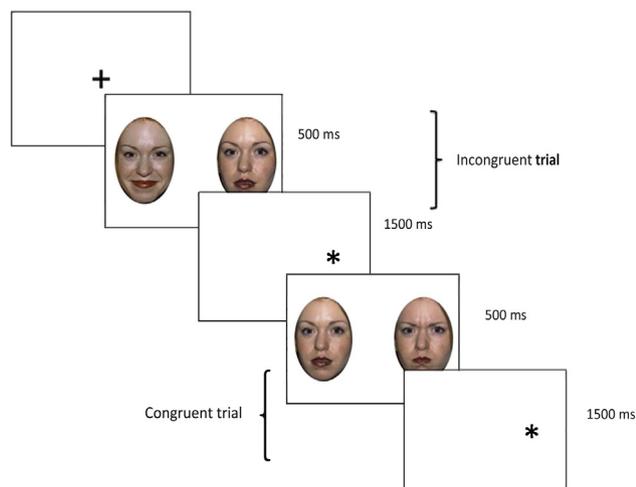
**Apparatus**

Stimuli were presented on a 17-inch Tobii 1750 LCD binocular eye tracker (1280 × 1024 pixels resolution) (Tobii, Stockholm,

**Table 1. Number of Trials and Performance to Emotion by Group**

	Chronological Age		Mental Age		Number of Trials		Angry Bias		Happy Bias	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
FXS Group	39.28 (17.23)	7.29 to 68.02	21.29 (11.03)	5.15 to 51.21	62.21 (14.91)	23 to 78	81.62 (129.23)	-201.73 to 428.68	9.50 (120.59)	-286.33 to 237.28
MA TD Group	21.28 (10.29)	5.14 to 51.11			70.68 (7.90)	45 to 80	43.17 (118.09)	-213.82 to 260.72	46.52 (89.48)	-155.92 to 267.48
CA TD Group	39.27 (17.28)	8.09 to 67.22			71.38 (7.47)	40 to 80	40.53 (122.23)	-210.81 to 306.68	48.92 (102.18)	-131.04 to 285.66

Age is presented in months.days. Number of trials is out of a total of 80 trials. Bias scores represent average latency to incongruent trials minus average latency to congruent trials. Chronological age values act as mental age values for both TD groups.  
CA, chronological age; FXS, fragile X syndrome; MA, mental age; TD, typically developing.



**Figure 1.** Trial sequence of the dot probe task.

Sweden) to record fixations during the task. Each child was seated on average 60 cm away from the eye tracker on a parent's lap. Eye-tracking data were collected at a sample rate of 50 Hz. The average accuracy of the recorded eye coordinates was about  $0.5^\circ$ , which is approximately 0.5 cm at a viewing distance of 60 cm. The average accuracy in timing is 25 to 35 ms. Drifts were compensated with an average error of  $0.5^\circ$ . When one eye could not be measured, data from the other eye were used to determine the gaze coordinates. The recovery time to full tracking ability after an offset was about 100 ms. Fixations were defined using the Tobii fixation filter, such that maximum angle between fixations was  $0.5^\circ$  and fixations needed to be longer than 60 ms. To control the presentation timing of the task, video stimuli of all trials were created using iMovie and were displayed using Tobii Studio. A standard five-point Tobii calibration was administered for all participants. Recalibration occurred if any single point was missed. Our goal was to only begin the task once all five points had a successful calibration; however, the minimum requirement to proceed with the task was a successful calibration of the center point for each eye.

### Data Analysis

A trial was included if the participant fixated the area of interest around the probe during the 1500-ms probe presentation time. The area of interest was defined as a circle around the probe with a 0.5-inch diameter. A bias score was calculated for each participant by subtracting the average latency to fixate the asterisk probe on congruent trials from incongruent trials. A positive value represented a vigilance for or a bias toward the emotional face, a score around zero indicated no bias, and a negative score indicated an avoidance of the emotional face.

First, given the genetic and phenotypic differences between sexes in FXS, exploratory analyses investigated any possible sex effects across the three groups on bias scores, and given the high comorbidity of ASD in FXS, we also probed any impact that autism symptom severity had on the key variables in the study. We then investigated the feasibility of

administering the task in the FXS population by statistically comparing the overall latency and number of trials for each group. We then compared the magnitude of attentional biases on both angry and happy trials within group using a repeated-measures analysis of variance to investigate whether the attentional bias patterns in the FXS group differed from those in the two TD groups and to compare each group's bias scores with chance levels in both emotional conditions to investigate the magnitude of affective bias scores within group.

### RESULTS

One-way analyses of variance for each emotion by sex revealed that happy bias and angry bias values did not significantly differ by sex in any of the three groups (all  $F_s < 1$ ,  $p_s > .05$ ). Autism severity, as measured by the Autism Diagnostic Observation Schedule in a subset of children with FXS, did not correlate with number of trials completed ( $r = .26$ ,  $p = .18$ ), overall latency ( $r = .07$ ,  $p = .72$ ), or either happy bias scores ( $r = -.31$ ,  $p = .11$ ) or angry bias scores ( $r = -.01$ ,  $p = .96$ ).

To measure feasibility of administration of the task, we compared numbers of trials on which children provided latencies to the probe across groups. Children with FXS provided latencies to the probe on an average of 62.21 trials out of 80, or 78% of the task. Children in the MA and CA groups provided latencies to the probe on an average of 70.68 trials (88%) and 71.38 trials (89%), respectively. These values were significantly different from one another,  $F_{2,138} = 10.73$ ,  $p < .001$ , with FXS being significantly lower than both the MA group ( $t_{92} = 3.48$ ,  $p < .001$ ) and the CA group ( $t_{92} = 3.73$ ,  $p < .001$ ) and the two TD groups not being significantly different from one another ( $t_{92} = 0.433$ ,  $p = .66$ ). The details related to these measures are presented in Table 1.

The latency values of individuals with FXS were on average slower than those of individuals in the CA group,  $t_{92} = 3.03$ ,  $p < .01$ ,  $d = 0.63$ , but were not significantly different from the MA group's overall latencies,  $t_{92} = 0.75$ ,  $p = .46$ ,  $d = 0.15$ . Overall latency, regardless of trial type, was not significantly correlated with chronological age,  $r_{45} = -.08$ ,  $p = .60$ , or mental age,  $r_{45} = -.02$ ,  $p = .87$ , in the FXS group, but it was negatively correlated in both the MA group,  $r_{45} = -.49$ ,  $p < .00$ , and the CA group,  $r_{45} = -.56$ ,  $p < .00$ , indicating that only the TD children were showing reduced latency with age. Overall latency was also not correlated with mental age in the FXS group ( $r = -.02$ ,  $p = .89$ ).

Once measures of task efficacy were evaluated, the primary hypothesis of the study—to investigate the magnitude and emotional specificity of attentional biases toward affect across these three groups—was examined. Average bias scores (presented in Table 1) were entered into a repeated-measures analysis of variance with one within-subjects factor, emotion (angry or happy), and one between-subjects factor, group (FXS, CA, or MA). The analysis showed no significant main effect of emotion,  $F_{1,138} = 1.96$ ,  $p = .16$ ,  $\eta_p^2 = .014$ , or group,  $F_{1,138} = .002$ ,  $p = .98$ ,  $\eta_p^2 < .00$ , but did show a significant group by emotion interaction,  $F_{2,138} = 3.29$ ,  $p = .04$ ,  $\eta_p^2 = .04$ . To explore this interaction, simple effects were investigated by performing a separate paired-samples  $t$  test on the bias score between emotions within each group. These tests revealed a

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significantly greater bias on angry trials than on happy trials in the FXS group,  $t_{46} = 2.57, p = .01, d = 0.54$ , but not in the CA group,  $t_{46} = 0.33, p = .74, d = 0.07$ , or the MA group,  $t_{46} = 0.16, p = .88, d = 0.03$ , indicating that children with FXS, but not children in the CA or MA group, were significantly more biased toward emotion on angry trials than on happy trials. Simple effects were also investigated by performing a separate paired-samples  $t$  test on the bias scores for each emotion between groups. While the angry bias scores in the FXS group were twice those in the TD groups, they were not significantly greater than those in either the MA group ( $t_{92} = 1.51, p = .14, d = 0.31$ ) or the CA group ( $t_{46} = 1.58, p = .12, d = 0.33$ ). Similarly, while the FXS group's bias scores to happy were closer to zero, they were not significantly less than those of either the MA group ( $t_{46} = 1.69, p = .09, d = 0.35$ ) or the CA group ( $t_{46} = 1.71, p = .09, d = 0.35$ ).

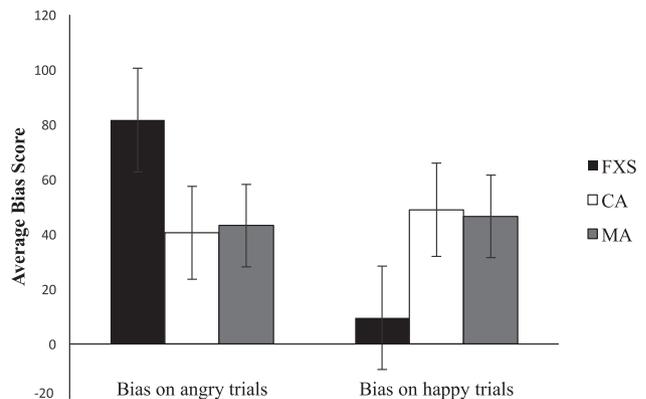
For angry bias scores, one-sample  $t$  tests indicated that scores were significantly greater than a chance bias score of zero (with zero indicating no difference in latency between the congruent and incongruent trials) for children in the FXS group (mean = 81.62, SD = 129.23;  $t_{46} = 4.33, p < .001, d = 0.54$ ), the CA group (mean = 40.53, SD = 122.23;  $t_{46} = 2.27, p = .02, d = 0.33$ ), and the MA group (mean = 43.17, SD = 118.09;  $t_{46} = 2.51, p = .02, d = 0.36$ ). For happy bias scores, one-sample  $t$  tests indicated that scores were significantly greater than a chance level of zero for children in the CA group (mean = 48.92, SD = 102.18;  $t_{46} = 3.28, p = .002, d = 0.44$ ) and the MA group (mean = 46.52, SD = 89.48;  $t_{46} = 3.56, p = .001, d = 0.47$ ), but not for children in the FXS group (mean = 9.50, SD = 129.23;  $t_{46} = 0.540, p = .59, d = 0.07$ ). Bias scores for each group can be seen in Figure 2.

## DISCUSSION

The current study investigated attentional biases toward affect in young children with FXS. We employed eye-tracking methodology to modify the DPT for use in both clinical and pediatric populations to better understand and explore the cognitive phenotype and attentional behavior of young children with FXS.

Children in the FXS group completed fewer trials than children in either TD group. This indicates a lessening in attentional behavior that is most likely related to syndrome-specific attentional deficits (1). However, children in the FXS sample still completed a significant portion of the task trials (78%), indicating that although their attentional impairments do affect their performance, these children can reliably complete this modified version of the DPT.

The FXS group showed a slower visual reaction time than the CA group. This could be related to cognitive and attentional deficits seen in the FXS group. The overall latency of the FXS group was not significantly different from that of the MA group, providing support for the idea that cognition ability, rather than physical maturation, is related to changes in latency. The findings related to latency provide support for analyzing the task in the traditional way (i.e., using a difference score between the incongruent and congruent trials). These difference scores allow examination of the task without being influenced by a group-level difference in overall latency. Thus, another strength of the task is that it allows for standardization



**Figure 2.** Average bias scores by group. Error bars represent standard error. CA, chronological age-matched group; FXS, fragile X syndrome group; MA, mental age-matched group.

of the clinical group's data to allow comparable analysis on the same measure with the TD groups.

In the FXS group, we see a significantly larger bias toward angry stimuli paired with neutral stimuli than toward happy stimuli paired with neutral stimuli. This result is supported by the previous literature demonstrating atypical processing, at the behavioral and neural levels, of affect by individuals with FXS (11). By contrast, no differences were seen in bias scores between angry and happy conditions in either of the TD groups.

Angry biases were greater than chance level in all three groups, suggesting that having some attentional bias toward threatening information is normative in young children. The average angry bias score in the FXS group was double that in the TD groups, although the difference was not significant. Happy bias scores in both TD groups were also significantly greater than chance, although the FXS group's average bias score on happy trials was not. While the FXS group's happy bias scores were closer to zero, they were not significantly less than either of the TD groups' scores. These findings indicate that individuals with FXS are not showing the typical bias toward positive affect but instead are showing a threat-specific bias pattern. The fact that the between-group comparisons did not reach significance is most likely due to the high amount of variability in the scores, but this highlights the importance of within-group differences between affective conditions. It is not simply the magnitude of the affective biases in FXS that differentiates this group from the typical comparison groups; it is also the threat specificity that is shown in their bias score patterns. These findings fit with those of Crawford *et al.*, who showed that, on an eye-tracking task, individuals with FXS preferentially allocated attention to negative emotion (disgust) more than they did to a positive emotion (23).

These findings could inform future treatment efforts. Bar-Haim reviewed attention bias modification, in which individuals with attentional biases toward threat are systematically attentionally trained toward positive stimuli (24). Waters *et al.* showed that attention bias modification can positively affect anxiety levels of pediatric populations with non-syndromic anxiety (25). Given that attention bias modification

can be similarly modified into a passive-viewing task as the current study modified the DPT, this could be an ideal treatment approach in FXS.

Future studies should recruit more female individuals with FXS to have greater statistical power to explore whether sex plays a role. It also would have been preferable to have autism symptomology and genetic variables in the entire sample (rather than the subset we had in the current study), although the data on the subsets of the FXS group showed no trend of either playing a role in the observed attentional bias. Future studies with older individuals with FXS should measure anxiety concurrently with attentional biases to directly link attentional biases toward affect to the heightened anxiety seen in the population.

The current study adds to the literature suggesting that there is a lack of typical bias toward positive affect and a threat specificity in the processing of affective information in young individuals with FXS. Aberrant processing of affective information in FXS could be directly related to the heightened levels of anxiety that are seen in FXS, and both could be related to the previously reported aberrant functioning of the amygdala in individuals with FXS. Given that the amygdala and its related neural structures are initially activated by the emotional faces in the DPT, our eye-tracking task can be used as an index of neural difference between individuals with FXS and age-matched TD control individuals. The constraints associated with typical functional neuroimaging techniques severely limit their use with young populations with developmental disorders. Thus, carefully designed eye-tracking tasks like the modified DPT presented here may allow researchers to index brain responses without requiring young children to undergo a more challenging neuroimaging procedure.

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## ARTICLE INFORMATION

From the Center for Mind and Brain (JLB, SMR), Department of Psychology (JLB, RNS, SMR), Medical Investigation of Neurodevelopmental Disorders Institute (RJH, FT, SMR), and Department of Biochemistry and Molecular Medicine (FT), University of California, Davis, and Department of Pediatrics (RJH), University of California, Davis, School of Medicine, Davis, California; and Department of Psychology (RAB-A), University of Florida, Gainesville, Florida.

Address correspondence to Susan M. Rivera, Ph.D., Department of Psychology, 202 Cousteau Place, Davis, CA 95618; E-mail: [srivera@ucdavis.edu](mailto:srivera@ucdavis.edu).

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