American Journal on Intellectual and Developmental Disabilities

Examining Phenotypic Differences in Gaze Avoidance Between Autism and Fragile X Syndrome

--Manuscript Draft--

Manuscript Number:	AJIDD-D-21-00011R2
Article Type:	Research Report
Keywords:	eye contact avoidance; developmental disability; Autism Spectrum Disorder; fragile x syndrome
Corresponding Author:	Scott S Hall Stanford University Stanford, California UNITED STATES
First Author:	Ellen H. Wilkinson
Order of Authors:	Ellen H. Wilkinson
	Tobias C. Britton
	Scott S Hall
Manuscript Region of Origin:	UNITED STATES
Abstract:	We examined potential phenotypic differences in eye gaze avoidance exhibited by boys with autism spectrum disorder (ASD) and boys with fragile X syndrome (FXS). In Study 1, the Eye Contact Avoidance Scale (ECAS) was administered to caregivers of boys aged 7-18 years with FXS (n =148), ASD (n =168), and mixed developmental disabilities (MDD; n =128). In Study 2, subsets of boys with FXS (n =31) and boys with ASD (n =25) received a brief behavioral treatment probe to improve eye contact. Results showed that boys with FXS obtained significantly higher scores on the ECAS compared to boys with ASD and MDD. Exposure to the brief behavioral treatment probe resulted in significant decreases in scores for boys with FXS, but not for boys with ASD

Examining Phenotypic Differences in Gaze Avoidance Between Autism Spectrum Disorder and Fragile X Syndrome

Abstract

We examined potential phenotypic differences in eye gaze avoidance exhibited by boys with autism spectrum disorder (ASD) and boys with fragile X syndrome (FXS). In Study 1, the Eye Contact Avoidance Scale (ECAS) was administered to caregivers of boys aged 7-18 years with FXS (*n*=148), ASD (*n*=168), and mixed developmental disabilities (MDD; *n*=128). In Study 2, subsets of boys with FXS (*n*=31) and boys with ASD (*n*=25) received a brief behavioral treatment probe to improve eye contact. Results showed that boys with FXS obtained significantly higher scores on the ECAS compared to boys with ASD and MDD. Exposure to the brief behavioral treatment probe resulted in significant decreases in scores for boys with FXS, but not for boys with ASD.

Keywords: eye gaze avoidance, developmental disability, autism spectrum disorder, fragile X syndrome

Examining Phenotypic Differences in Gaze Avoidance Between Autism Spectrum Disorder and Fragile X Syndrome

Autism spectrum disorder (ASD) is a behaviorally defined condition characterized by persistent deficits in social interaction and communication skills as well as the presence of restricted, repetitive patterns of behavior, interests or activities (American Psychiatric Association, 2013). Prevalence studies suggest that as many as 1 in 34 males and 1 in 144 females receive a diagnosis of ASD by age eight years (Maenner et al., 2020). Although several candidate genes have been identified in some samples of individuals with ASD (Satterstrom et al., 2020), the extent to which genes and/or environmental factors are involved in this disorder is largely unknown. ASD thus remains a uniquely challenging disorder from a research perspective because of the significant heterogeneity in presentation of symptoms between individuals.

Over the past few decades, an increasing number of studies have examined the phenotypic similarities and differences between individuals diagnosed with ASD and individuals diagnosed with fragile X syndrome (FXS), the most common known inherited cause of intellectual disability (Abbeduto et al., 2014; Hall et al. 2010; Hazlett et al., 2009; Niu et al., 2017). FXS is caused by a trinucleotide repeat expansion of >200 CGG repeats in the promoter region of the *FMR1* gene at locus 27.3 on the long arm of the X chromosome affecting 1 in 1/4000 to 1/5000 in males and ~1/6000 to 1/8000 in females (Crawford, Acuña, Sherman 2001; Coffee, Keith, Albizua, et al. 2009). Characteristic phenotypic features of the syndrome include impairments in intellectual functioning, social avoidance, communication impairments, and repetitive behaviors (Hall et al., 2010; Roberts et al., 2007; Smith et al., 2012). Given the overlap in symptoms between individuals with FXS and individuals with ASD, FXS has been described as the leading genetic cause of ASD (Kaufmann et al., 2017) with current estimates indicating

that approximately 50% of boys and 20% of girls with FXS typically receive a diagnosis of ASD (Bailey et al., 2008; Clifford et al., 2007; Hall et al., 2008).

Although the symptoms of individuals with ASD appear to overlap to those with FXS, more fine-grained analyses have revealed that the differences often outweigh the similarities (Crawford et al., 2017; Hall et al., 2010; Hazlett et al., 2009; Wolff et al., 2012). For example, Hall and colleagues (2010) compared boys and girls with FXS aged 5 to 25 years to the normative data available on items of the Social Communication Questionnaire (SCQ; Rutter et al. 2003) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2012): two instruments commonly employed to measure autism symptomatology. These authors reported that boys and girls with FXS were significantly less likely to exhibit impairments on the majority of the items related to communication and social functioning on the SCQ and ADOS compared to the normative samples of children with idiopathic ASD. Interestingly, in boys with FXS, the prevalence of unusual social gaze and repetitive behaviors, was found to be similar in the two groups, suggesting overlap in those specific domains.

Social gaze avoidance is often described as a hallmark behavioral feature of individuals diagnosed with FXS (Hall et al., 2009; Roberts et al, 2019) and is also listed among the behavioral criteria in the diagnosis of ASD. Examining the similarities and differences in social gaze avoidance in children with FXS compared to children with ASD could help to discriminate between the different mechanisms underlying social behavior in these disorders. Research has shown that increased levels of eye gaze avoidance can interfere in the development of social relationships but also impact adaptive behavior more generally (Freeth et al. 2013; Phillips et al. 1992). Increased levels of eye gaze avoidance have also been shown to inhibit learning and other downstream behaviors such as joint attention and imitation (Bruinsma et al. 2004; Elsabbagh et

al. 2012; Falck-Ytter et al. 2015; Senju & Johnson 2009b). Eye gaze is therefore important in the development of social relationships starting from birth and is increasingly important as relationships become more complex in adolescence when children begin making new friends (Freeth et al., 2013; Kleinke, 1986). Because of its influence on social development, eye gaze is often targeted for early interventions in children with ASD (Bauminger 2002; Chang et al. 2016; Steiner et al. 2013; Vismara & Rogers 2008).

Several theories have been advanced concerning potential mechanisms involved in eye gaze avoidance. These theories focus on dysfunction of arousal systems in the presence of social stimuli and the inability to interpret the intent and emotions of others (Senju and Johnson, 2009a). One prominent hypothesis – the "Eye Avoidance" hypothesis (Tanaka & Sung 2016) asserts that the avoidance of eye gaze may be adaptive because many individuals perceive this region of the face as socially threatening. Individuals therefore avert social gaze in order to protect themselves from discomfort and threat, resulting in a cascading "downward spiral", which further interferes with social processing. Support for this hypothesis comes from studies showing that children with ASD and children with FXS exhibit increased physiological arousal when required to look at faces as well as studies showing that children with ASD actively avoid the eye region of the face altogether (Dalton et al. 2005; Hall et al., 2009; Hutt & Ounsted 1966; Joseph et al. 2008; Roberts et al., 2019).

Alternatively, other researchers have suggested that hypoactivation of social processing systems in the brain in autistic infants may be responsible for the increased levels of gaze avoidance in ASD (Dawson et al., 2005; Grelotti et al., 2002). Dawson and colleagues argue that low reactivity inhibits learning of eye gaze behavior due to decreased levels of social reinforcement. Several researchers have suggested that eye gaze avoidance in children with ASD

may therefore result from deficits in attentional or associative mechanisms that ultimately manifests as gaze *indifference* (Dawson et al., 2005; Grelotti et al., 2002; Senju & Johnson, 2009b). Conversely, eye gaze avoidance in children with FXS may result from high levels of anxiety or hyperarousal that ultimately manifests as social gaze *aversion* (Cohen et al., 1989; Cohen, 1995; Hall et al., 2015).

These opposing mechanisms have been framed broadly as the *gaze indifference* and *gaze aversion* hypotheses respectively, each resulting in specific predictions for interventions (Moriuchi et al., 2017). For example, individuals who exhibit significant gaze *indifference* may benefit from interventions designed to increase the reinforcing value of social interaction, whereas individuals who exhibit significant gaze *aversion* may benefit from interventions designed to increase exposure to eye gaze (Dawson et al., 2005; Moriuchi et al., 2017; Senju & Johnson, 2009a). In a recent proof of concept study, Gannon and colleagues (2018) showed that boys with FXS could be successfully taught to exhibit increased levels of eye gaze following brief exposure to a behavioral skills training procedure designed to improve eye contact duration. Specifically, the intervention involved shaping longer durations of eye gaze in discrete trials according to a percentile reinforcement schedule. Importantly, the authors showed that the training did not necessarily result in increased symptoms of anxiety.

Additional support for the indifference versus aversion hypotheses in ASD and FXS comes from studies investigating gaze avoidance patterns during interactions with familiar versus unfamiliar people. In one of the first studies to investigate this phenomenon, Cohen and colleagues (1988) directly observed the gaze avoidance exhibited by prepubescent boys with FXS and those with ASD during interactions with a caregiver versus during interactions with a stranger. These authors reported that boys with ASD exhibited similar levels of gaze avoidance

in both conditions, suggesting that boys with ASD failed to discriminate between the parent and stranger, whereas boys with FXS exhibited higher levels of gaze avoidance during the interaction with the stranger. These findings have been supported by a recent longitudinal cohort study on the development and persistence of social avoidance in children with FXS (Roberts et al., 2019) in which individuals with FXS appeared to demonstrate a "warm up" effect as the person they were interacting with became more familiar (see Hall et al., 2009). These authors also reported that social gaze avoidance in FXS appeared to emerge during infancy and increased in severity during childhood before reaching relative stability during adolescence and young adulthood.

Researchers have also employed sophisticated eye-tracking paradigms to conduct more fine-grained analyses of the quality and quantity of eye gaze avoidance in individuals with ASD and those with FXS (Dalton et al., 2008; Klusek et al., 2020; Hong et al., 2019). For example, Hall and colleagues (2015) showed that individuals with FXS exhibited significantly shorter bouts of eye contact during a live face-to-face interaction with an unfamiliar examiner compared to age- and symptom-matched controls. Hong and colleagues (Hong et al., 2019) recently compared groups of individuals with FXS, ASD, and typically developing controls in the completion of emotional face and social preference eye-tracking tasks. These authors found that individuals with FXS exhibited increased gaze aversion but evidenced similar social preference to typically developing controls whereas individuals in the ASD group showed less social preference overall.

Although direct observations and eye–tracking metrics used in these studies can provide objective measures of social gaze behavior in vivo, these measures are expensive and time-consuming to implement on large numbers of participants. Given these issues, informant-based questionnaires and rating scales offer an alternative complementary approach (Aman & Singh,

1985; Sansone et al., 2012; Ozonoff et al., 2005). While informant-based questionnaires or rating scales can suffer from potential bias and recall effects, they allow researchers the opportunity to sample information from a range of social situations, as well as increase the potential for use of eye contact measures in large-scale multi-site studies (Nordahl-Hansen et al., 2014; Rosenberg et al., 2011).

One such informant-based measure recently employed to quantify difficulties in social behavior in this population is the Sociability Questionnaire for people with Intellectual Disabilities (SQID; Moss et al., 2016) which measures approach and avoidance behaviors across a range of social situations depending upon whether the person is interacting with a familiar or unfamiliar person. These authors administered the SQID to groups of individuals diagnosed with genetic syndromes associated with IDD (including FXS) as well as those with ASD. When individuals with FXS (n=142) and ASD (n=107) aged 4 to 49 years were compared on the SQID, individuals with FXS exhibited the highest levels of social avoidance during interactions with unfamiliar people whereas individuals with ASD did so during interactions with caregivers. There were no effects of age on the rates of avoidance behaviors reported in either group. These data suggest that questionnaires such as the SQID may be useful for measuring differences in social behavior between these disorders. It should be noted that the SQID does not include questions about eye gaze or eye contact specifically.

Given the dearth of assessment tools available to specifically measure eye gaze avoidance in children with IDD, Hall and Venema (2017) developed the Eye Contact Avoidance Scale (ECAS), a 15-item informant-based questionnaire designed to measure the severity of eye contact avoidance in children with FXS. Items in the scale are grouped into five domains and the caregiver provides quantitative ratings of eye contact during interactions with the caregiver,

friends & family, and unfamiliar people. These authors administered the ECAS to caregivers of 148 boys with FXS aged 8-16 years and found that boys with FXS exhibited a profile that appeared to be indicative of eye gaze aversion rather than indifference. Specifically, caregivers reported that their child often became anxious or upset when required to make eye contact with others, particularly when interacting with unfamiliar people. Ratings of eye contact avoidance were also significantly higher for children who had lower levels of communication ability and those who had a comorbid diagnosis of ASD. Given that a comparison group of boys with ASD was not included in the Hall & Venema (2017) study, however, the extent to which these characteristics are specific to FXS or whether similar profiles of eye contact avoidance may also be present in boys with ASD is unknown.

The profile of scores obtained on the ECAS may reveal patterns of eye gaze that are characteristic of either gaze aversion or gaze indifference. For example, if an individual exhibits high levels of anxiety when required to make eye contact, and eye gaze avoidance occurs at higher levels during interactions with an unfamiliar person compared to interactions with a caregiver, this profile may be indicative of gaze aversion. Conversely, if levels of eye gaze avoidance are similar regardless of whether the individual is interacting with a caregiver or an unfamiliar person, this profile may be indicative of gaze indifference.

The aims of the present study were therefore two-fold. The first aim was to validate the ECAS by comparing the profiles of scores obtained on the ECAS in three different groups of individuals with IDD: boys with FXS (n=148); boys with ASD (n=168); and comparison boys with mixed developmental disability (MDD; n=128). We hypothesized that boys with FXS would obtain significantly higher scores during interactions with unfamiliar people and exhibit higher levels of anxiety when required to make eye contact in comparison to boys with ASD or

boys with MDD. The second aim was to directly test the gaze aversion versus indifference hypothesis by administering the brief behavioral treatment probe described by Gannon et al. (2018) to a subsample of boys with ASD and boys with FXS. We hypothesized that administration of the brief treatment probe would result in decreased levels of gaze avoidance in boys with FXS, but not necessarily in boys with ASD given that the treatment procedures described by Gannon et al. (2018) are derived from an anxiety perspective rather than a social reinforcement perspective.

Study 1: Profiles of Eye Contact Avoidance in ASD and FXS

Participants

Participants were recruited as part of a larger study investigating the effects of brief social skills training for boys with FXS and other developmental disabilities. Advertisements were posted on relevant social media groups and at community behavioral health providers inviting caregivers to complete an online screening survey about their child. The introduction to the survey stated that the study was designed to evaluate and teach eye contact skills to boys with FXS and other developmental disabilities ages 7 to 18 years and that participants would need to complete the brief survey to determine if their son was eligible for the study. Informed consent was obtained from caregivers prior to completing the survey.

Completed survey responses were received for 168 boys with ASD, 128 boys with mixed developmental disability (MDD), and 148 boys with FXS, ages 7 to 18 years. All participants in the FXS group were reported by their caregivers to have a diagnosis of FXS and had participated in the study by Hall & Venema (2017). Caregivers reported that 81 (54.7%) boys with FXS indicated that their son had a comorbid diagnosis of ASD. All participants in the ASD group

were reported by their caregivers to have a diagnosis of ASD (but not FXS). In the MDD group, four were diagnosed with cerebral palsy, seven were diagnosed with Down syndrome, two were diagnosed with epilepsy, two were diagnosed with hydrocephalus, and 20 were reported to have a variety of other conditions. For the remainder of the sample, information concerning additional diagnoses was not provided by the caregiver. However, none reported a diagnosis of FXS or ASD. Table 1 summarizes the characteristics of the groups in terms of the child's age, communication ability, and eye gaze avoidance.

[Table 1]

There were no significant differences between the groups in terms of age ($F(2, 441) = .474$, $p = .62$). However, differences emerged between the groups in terms of communication ability ($\chi^2(4) = 32.39$, $p < .001$), with boys with FXS having lower levels of communication ability. Communication ability was therefore included as a covariate in the analyses.

Measures

Eye Contact Avoidance Scale (ECAS; Hall & Venema, 2017). The ECAS was administered to the child's primary caregiver via an online survey. In the first section of the ECAS, caregivers completed basic demographic information concerning their child's sex, age, diagnosis (e.g., FXS, ASD, developmental disability, Down syndrome, cerebral palsy) and communication ability (i.e. "Does your child use full sentences to communicate things he wants or needs?"; 0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = always). The second part of the ECAS contains 15 items specifically designed to measure eye gaze avoidance. Items on the ECAS are rated on a 0- to 4-point Likert scale (0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = always) in the following five domains of social functioning: 1) *Avoidance when speaking* (3 items); 2) *Avoidance when listening* (3 items); 3) *Inability to maintain* (3 items); 4) *Difficulty*

maintaining (3 items); and 5) *Gets anxious or upset* (3 items). Items within each domain are designed to elicit ratings from the perspective of (a) the *Caregiver* (e.g., does your child avoid eye contact when he talks to you?), (b) *Friends and family* (e.g., does your child avoid eye contact when he talks to friends & family"?), and (c) *Unfamiliar people* (e.g., does your child avoid eye contact when he talks to unfamiliar people?). Total domain scores (i.e. *Avoidance when speaking*, *Avoidance when listening*, *Inability to maintain*, *Difficulty maintaining,* and *Gets anxious or upset*) can be obtained by summing the scores across items in each domain (maximum possible score for each domain = 12). [Note that items on the *Inability to maintain* subscale are reverse scored so that higher scores in each domain reflect higher levels of eye contact avoidance]. Total subscale scores (i.e., *Caregiver*, *Friends & family,* and *Unfamiliar people*) can be obtained by summing the scores for the five items relating to the caregiver, friends & family, and unfamiliar people questions respectively (maximum possible score for each subscale = 20). Finally, a total score can be obtained by summing the scores across all 15 items (maximum possible total score = 60).

To examine the test-retest reliability of the ECAS, a subsample of 156 caregivers were asked if they would be willing to complete the survey again after a 4-week interval. Of those caregivers, 107 (68.6%) completed the survey a second time with the average time between surveys being 3.70 weeks (*SD* = 0.44) with a range of 3.5 to 5.3 weeks. There were no differences between the responders and nonresponders on any of the measured variables.

Data Analyses

Statistical analyses were conducted in SPSS Version 26. We first examined the internal consistency of the ECAS by computing item-total correlations and Cronbach's alpha coefficients for the domains, subscales, and total score for each group. We then examined test-retest

reliability by computing intraclass correlation coefficients (ICCs) for the domains, subscales, and total score for those respondents who had completed the ECAS a second time after a 4-week interval. To compare the scores between the three groups (i.e., FXS, ASD and MDD), we conducted analyses of covariance (ANCOVA) with group and age-band as the independent factors and communication ability included as the covariate in each analysis. To examine the profile of scores by level of familiarity on each domain, we ran a series of two-way repeated-measures analyses of covariance (RM-ANCOVA) with group as the between-subjects factor and level of familiarity as the within-subjects factor. Communication ability was included as the covariate in each analysis. Post-hoc tests were conducted using the Bonferroni adjustment for multiple comparisons with the alpha level set at 0.05. Eta squared was computed as a measure of effect size in each model. Finally, we conducted a subgroup analysis of the data to compare boys with FXS who had a comorbid diagnosis of ASD (n=81) to the group of boys with ASD (n= 168) on each domain and subscale of the ECAS.

Results

Internal Consistency and Test-Retest Reliability

Table 2 shows the internal consistency and test-retest reliability coefficients computed for each domain, subscale, and total score of the ECAS. For the total sample, Cronbach's alpha coefficients ranged from .87 to .93 for the domain scores, .86 to .88 for the subscale scores, and was .95 for the total score indicating excellent internal consistency. Corrected item-total correlations for the ECAS ranged from .61 to .82. ICCs ranged from .74 to .82 for the domain scores, .80 to .84 for the subscale scores and .83 for the total score, which indicates acceptable to good test-retest reliability.

[Table 2]

Group comparisons

The scores obtained on the domains, subscales and total scale of the ECAS are shown in Table 1. The highest mean total ECAS scores were obtained by boys with FXS (M = 41.2, SD = 8.9) followed by boys with ASD (M = 33.8, SD = 9.4) and boys with MDD (M = 29.7, SD = 13.1). In each group, the highest mean scores were obtained on the *Unfamiliar people* subscale followed by the *Friends & family* subscale and the *Caregiver* subscale.

ANCOVA analyses revealed a significant main effect of group on the total score ($F(2,432) = 30.04$, $p < .001$, $\eta^2 = .122$) but no main effect of age-band ($F(2,432) = 1.09$, $p > .05$, $\eta^2 = .005$) or group × age-band interaction ($F(4,432) = 0.66$, $p > .05$, $\eta^2 = .006$). There was also a significant effect of communication ability ($F(1,432) = 20.52$, $p < .001$, $\eta^2 = .045$) on the total score indicating that boys with lower levels of communication ability obtained higher total scores on the ECAS. Post-hoc tests revealed that boys with FXS obtained significantly higher total scores than boys with ASD who in turn obtained significantly higher total scores than boys with MDD (p-values < .001).

On the subscales of the ECAS, there were significant main effects of group on the *Caregiver* subscale score ($F(2,432) = 11.09$, $p < .001$, $\eta^2 = .049$), the *Friends & family* subscale score ($F(2,432) = 24.82$, $p < .001$, $\eta^2 = .103$), and the *Unfamiliar people* subscale score ($F(2,432) = 41.93$, $p < .001$, $\eta^2 = .163$). On the *Caregiver* subscale score, post-hoc tests revealed that boys with FXS and ASD obtained significantly higher scores than boys with MDD (p-values < .001). However, scores were similar between boys with FXS and boys with ASD on the *Caregiver* subscale (p-values > .05). On the *Friends & family* and *Unfamiliar people* subscales, boys with FXS obtained significantly higher scores than boys with ASD who in turn obtained significantly

higher scores than boys with MDD (all *p*-values < .001). As expected, there were also significant effects of communication ability on the subscales of the ECAS (*p*'s < .05), however, there were no significant effects of age-band (all *p*-values > .05).

Score Profiles

Figure 1 shows the profile of scores obtained on the ECAS by level of familiarity for each group.

[Figure 1]

Two-way repeated measures analyses of covariance (RM-ANCOVA) were conducted with group as the between-subjects factor and familiarity level as the within-subjects factor with communication ability included as the covariate. These analyses revealed two patterns. There was a significant group × familiarity interaction for scores obtained on the *Avoidance while speaking* domain ($F(4,876) = 4.74$, $p = .001$, $\eta^2 = .021$), *Avoidance while listening* domain ($F(4,876) = 3.76$, $p = .005$, $\eta^2 = .017$), and *Difficulty maintaining* domain ($F(4,876) = 2.97$, $p = .019$, $\eta^2 = .013$). Post-hoc tests revealed that levels of eye contact avoidance were similar between boys with FXS and ASD during interactions with caregivers on these domains (*p*'s > .05) but that boys with FXS exhibited significantly higher levels of eye contact avoidance during interactions with unfamiliar people compared to the other groups (*p*'s < .001).

The second pattern revealed significant group × familiarity interactions for scores obtained on the *Inability to maintain* ($F(4,876) = 24.12$, $p < .001$, $\eta^2 = .099$) and *Gets anxious or upset* domains ($F(4,876) = 11.68$, $p < .001$, $\eta^2 = .051$). On these domains, post-hoc tests revealed that boys with FXS exhibited significantly higher levels of eye contact avoidance compared to boys with ASD or MDD during interactions with caregivers (all *p*-values < .001). The differences between the groups became significantly more pronounced for boys with FXS during

interactions with *Friends & family* and *Unfamiliar people* (*p*-values < .001). By contrast, there were no differences between boys with ASD and boys with MDD on these domains at each level of familiarity (*p*-values > .05). Taken together, the data reveal significant differences in the profiles of eye contact avoidance between boys with FXS and boys with ASD on the ECAS.

Table 3 shows the results of the secondary analysis comparing boys with FXS who also had a comorbid diagnosis of ASD (*n*=81) to the group of boys with ASD (*n*=168). As expected, the data show that the subgroup of boys with FXS and comorbid ASD obtained significantly higher scores on all domains and subscales of the ECAS (all *p*-values < .001). The largest difference between the groups occurred on the *unfamiliar people* subscale of the ECAS ($F(1, 245) = 63.50$, $p < .001$, $\eta^2 = .206$) indicating that the difference in eye contact avoidance between the groups was particularly striking during interactions with unfamiliar people.

[Table 3]

Study 2: Response to Treatment

Participants

Participants who were screened in Study 1 were eligible for inclusion in Study 2 if they were male, aged 7 to 18 years, had a diagnosis of ASD or a diagnosis of FXS, and had obtained a total score of 30 points or greater on the ECAS. Participants who had other neurological or sensory impairments (e.g., head trauma and blindness), if they engaged in frequent and/or severe problem behaviors, or if they had any other known medical, psychiatric, or behavioral conditions that would preclude participation in the brief treatment probe were excluded. For participants with ASD, the diagnosis of ASD was confirmed by administration of the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; Lord et al., 2012). For participants with FXS,

evidence of aberrant methylation on the *FMR1* gene (> 200 CGG repeats) was confirmed by genetic report.

Sixty participants (33 boys with FXS and 27 boys with ASD) met the inclusion criteria for Study 2 and travelled to XXX University for the treatment probe evaluation with their primary caregiver. Four boys (2 FXS, 2 ASD) were unable to tolerate the intervention procedures and were subsequently withdrawn from the study. The demographic characteristics of the remaining 56 participants (31 FXS, 25 ASD) are shown in Table 4.

[Table 4]

Measures

All participants received baseline measures of social development and functioning upon enrollment in the study. These measures included the Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II; Sparrow et al., 2006), the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2012), and the Eye Contact Avoidance Scale (ECAS; Hall & Venema, 2017).

Procedures

Following baseline assessments (T1), participants in each group were randomized to receive the behavioral treatment probe at one of two levels: high dose or low dose. Participants randomized to the high dose group received a total of 400 treatment probe trials conducted in eight 1-hour blocks (50 trials per block) over 2 days. Participants randomized to the low dose group received 100-200 treatment probe trials conducted in four 1-hour blocks (50 trials per block) alternated with 1-hour blocks of unstructured play over 2 days. All intervention procedures were administered according to those described by Gannon et al. (2018). Briefly, the treatment probe involved reinforcing successively longer durations of eye contact with an

examiner in discrete trials according to a percentile reinforcement schedule. Prior to beginning each session, the therapist introduced a variety of relaxation exercises using deep breathing and progressive muscle relaxation techniques described in Gannon et al. (2018) to minimize the potential for anxiety. To evaluate effects of the treatment probe on subsequent levels of eye contact avoidance, the ECAS was administered to caregivers four weeks after completion of the treatment probe (T2).

Data Analyses

We first conducted independent t-tests to compare boys with FXS to boys with ASD on the measures. We then examined the effects of the treatment probe in each group by estimating changes in scores from T1 to T2 on the ECAS using standard linear mixed-effects modeling. In line with the intention to treat (ITT) principle, we included all individuals in the analyses as long as their data were available from the first assessment. Specifically, we estimated linear change over time, allowing for random intercepts and slopes. Effect sizes (Cohen's d) were calculated based on the observed standard deviation pooled across groups.

Results

At baseline, there were no differences between the groups in terms of age ($t(54) = .27$, $p > .05$) or levels of adaptive behavior ($t(54) = .27$, $p > .05$) (see Table 3). In the FXS group, 18 (58.1%) boys were fully verbal and received Module 3 of the ADOS-2, 12 (38.7%) boys used phrase speech and received Module 2, and 1 (3.2%) boy used single words and received Module 1. In the ASD group, 21 (84.0%) boys with ASD were fully verbal and received Module 3, 3 (12.0%) boys used phrase speech and received Module 2, and 1 (4.0%) boy used single words and received Module 1. Comparison of the groups indicated that there was a trend toward boys

with FXS having lower levels of verbal ability than boys with ASD, however this just failed to reach statistical significance ($\chi^2(2) = 5.37$, $p = .068$). On the ADOS-2, the comparison severity score (CSS) was 6.71 (*SD* = 2.27) for boys with FXS and 7.58 (*SD* = 1.44) for boys with ASD, a non-significant difference between the groups ($t(54) = -1.64$, p >.05). A significantly greater number of boys with FXS (72.7%) were taking psychoactive medications including stimulants, antidepressants, and antipsychotics compared to boys with ASD (34.4%), suggesting a potential bias toward medication use in children with FXS ($\chi^2(1) = 6.99$, $p = .008$). In terms of scores on the ECAS, levels of eye contact avoidance were similar between the groups on the domains of the ECAS and on the total score. However, boys with FXS obtained significantly lower scores compared to boys with ASD on the *Caregiver* subscale of the ECAS ($t(54) = 2.64$, $p = .011$).

Table 5 shows the changes in ECAS scores following administration of the behavioral treatment probe for each group. These data show that significant decreases in scores from T1 to T2 were obtained on all domains and subscales of the ECAS for boys with FXS (p-values < .05) with the exception of the *Avoidance while speaking* domain. By contrast, for boys with ASD, scores decreased significantly only on the *Difficulty maintaining* domain ($p = .036$) and scores increased significantly on the *Avoidance while listening* domain ($p = .004$). Comparison of the groups indicated that boys with FXS showed significantly greater decreases on the total score of the ECAS ($p = .023$, d = .62) compared to the ASD group. For boys with FXS, the mean decrease in the total ECAS score following treatment was 5.7 points ($p = .001$) whereas the mean decrease in total score for boys with ASD group was 1.04 points ($p > .05$).

[Table 5]

Discussion

Although some investigators have highlighted significant overlap in the behavioral

phenotypes of boys with ASD and boys with FXS, increasing evidence suggests important differences exist between the two disorders, particularly in critical social behaviors routinely considered part of the autism spectrum. We examined potential similarities and differences in eye contact avoidance exhibited by boys with FXS and boys with ASD using the Eye Contact Avoidance Scale (ECAS), a 15-item screening tool designed to quantify gaze avoidance under different scenarios and with different people (Hall & Venema, 2017). In Study 1, we compared the scores obtained on the ECAS between boys with FXS and boys with ASD as well as age-matched controls with MDD. We restricted the ages of the groups to 7 to 18 years because this age range is a critical developmental period when significant social relationships and friendships are formed.

We found that boys with FXS displayed significantly higher levels of eye gaze avoidance compared to boys with ASD who in turn exhibited higher levels of eye gaze avoidance compared to boys with MDD. Specific phenotypic differences between the groups emerged in terms of the ability to maintain eye contact with others and the extent to which the child exhibited anxiety when required to maintain eye contact with others. Specifically, boys with FXS were significantly more likely to become anxious or upset during interactions with others, and these effects became more pronounced for boys with FXS when interacting with less familiar people. By contrast, levels of anxiety when maintaining eye contact were significantly lower in boys with ASD during social interactions with unfamiliar people, and boys with ASD exhibited similar levels of eye contact avoidance to boys with mixed developmental disability. These data broadly support the studies conducted by Cohen et al. (1988) and Moss et al. (2016) suggesting that boys with ASD may be less able to discriminate between familiar and unfamiliar people compared to children with FXS. Taken together, these results suggest that boys with FXS

exhibited a profile that was consistent with eye gaze aversion, whereas boys with ASD and MDD exhibited profiles that were consistent with eye gaze indifference.

Results also support the construct validity of the ECAS, as it aligns with previous research in several facets. First, boys with FXS obtained significantly higher scores than boys with ASD on almost all domains and subscales of the ECAS. In turn, boys with ASD obtained significantly higher scores than boys with MDD on most domains and subscales. As eye gaze avoidance is not a common phenotypic feature for most children with developmental disabilities outside of ASD and FXS, this further supports the construct validity of the ECAS. Across all groups, boys with lower levels of verbal ability exhibited higher levels of eye gaze avoidance. This supports the results of several previous studies showing that difficulties in eye gaze behavior may be inversely related to communication ability (Cohen et al. 1991; Venter et al. 1992; Wetherby et al. 2007).

Interestingly, there has been no consensus on the effect of age on eye gaze avoidance in children with ASD and FXS. Several previous studies and reviews have reported that eye gaze avoidance may increase with age (Cohen et al., 1991; Roberts et al., 2019), while others have found that eye gaze avoidance may decrease (Chawarska & Shic, 2009; Phillips et al., 1992). In the present sample, we restricted the age range to 7 to 18 years and found no differences in the developmental trajectory of eye gaze avoidance across this critical developmental period. These data suggest that eye gaze avoidance was already well established in these groups. Longitudinal studies will be needed to fully examine the effect of maturational factors on eye gaze avoidance in these groups.

Although the psychometric properties of the ECAS described in Hall & Venema (2017) were promising for children with FXS, it was unclear whether this tool could be used to quantify

phenotypic differences in eye gaze avoidance in children with developmental disabilities in general. Over the past few decades, a consensus has emerged concerning the need for reliable and valid measures of social behavior that can be utilized in clinical trials for individuals with developmental disabilities (McConachie et al., 2015). These measures should aim to sample a range of social settings and situations, exhibit minimal floor effects, have well-established psychometric properties, and account for different levels of developmental functioning (Darling-Churchill & Lippman 2016; Snow & Van Hemel 2008). Unfortunately, many existing measures of social behavior have failed to meet these requirements (Anagnostou et al. 2015; Brugha et al. 2015; Rubio-Codina et al. 2016; Scahill et al. 2015). For example, in a recent review of outcome measures employed in intervention and observational studies of children with ASD, McConachie et al. (2015) identified several measures of social behavior employed for children up to 6 years of age, however, for many of the tools identified, limited information was available concerning reliability and validity, thereby limiting their potential use in clinical trials. Similarly, in a recent review of outcome measures for individuals with FXS, Budimirovic et al. (2017) identified few measures of social behavior with sufficient support for use in clinical trials. These authors noted that limited metrics were available to measure social behaviors such as social anxiety and social withdrawal (Kreiser & White 2014). Indeed, the measurement of these behaviors may be particularly challenging in individuals with developmental disabilities since, by definition, the behavioral repertoires of these individuals can be significantly restricted and many individuals may be unable to reliably report emotional states (Finlay & Lyons 2002; White & Roberson-Nay 2009).

The results of the reliability analysis in Study 1 showed that the internal consistency and test-retest reliability of the ECAS were found to be acceptable to good. Given the current

findings, which suggest that the ECAS extends outside of FXS to more phenotypically heterogeneous groups, the ECAS may be a viable option as a primary outcome measure in many facets of research. This includes intervention research and clinical work requiring the measurement of eye gaze avoidance, as well as in developmental research, in which there exists a need to gauge the level of specific behaviors such as eye gaze avoidance. Further studies could strengthen the psychometric properties of the scale, including an examination of its sensitivity and specificity using cut-off points.

In Study 2, we examined the extent to which eye gaze avoidance in each group was impacted by exposing boys with ASD and boys with FXS to a brief behavioral skills training probe. Our data show that short-term administration of the standardized behavioral treatment probe designed to increase the maintenance of eye contact resulted in significant decreases in eye gaze avoidance on the ECAS for boys with FXS but not in boys with ASD. This finding is important because many clinicians have argued that eye contact training may not be effective for boys with FXS. Indeed, the treatment probe appeared to be more effective in boys with FXS compared to boys with ASD on the majority of the domains and subscales of the ECAS. These data support the hypothesis that boys with FXS may benefit from interventions specifically designed to increase exposure to eye contact. We acknowledge however, that these data were collected on only one sample of boys with FXS who were able to travel to our research center. Future studies will be needed to examine whether the benefits of eye contact training are specific to particular children with FXS who are less likely to become distressed by intensive social interactions or whether this intervention can be applied to the whole spectrum of children with FXS.

The fact that boys with ASD did not appear to benefit from this intervention (at least in the time frame of the study) suggests that this type of intervention may not be optimal for children with ASD given that the intervention was not designed to increase the reinforcing value of social interaction. Several recent studies, however, have shown that eye contact can be shaped in children with ASD using basic reinforcement and generalization principles (e.g., Fonger & Malott, 2019; Cook et al., 2017). To our knowledge, this is the first study to examine the differential effects of behavioral treatment for eye gaze avoidance in these two groups. It should be noted that caregivers of the children in each group were not given specific instructions or training to implement eye contact training with their child either during or following implementation of the treatment probe. Any treatment effects that continued following exposure to the treatment probe could therefore be considered to be independent.

The study has several strengths. First, we were able to include a relatively large sample of boys with FXS and boys with ASD in Study 1. Additionally, the ECAS provides a scale for the measurement of eye gaze avoidance during interactions with the caregiver, friends/family, and unfamiliar people in five different domains. This allowed for a more fine-grained analysis of eye gaze behavior compared to other methods currently used. Importantly, the ECAS was not designed to replace direct observation but rather to provide a quick, accessible, cost-effective method for measuring eye gaze avoidance. Given that direct observations can be extremely time-consuming, require significant expertise to implement, and would be unable to sample a range of situations and people, it is unclear at this time whether direct observations would have been more informative.

This study also has several limitations that could be addressed in future research. First, we included only boys in this initial study given that eye gaze avoidance is commonly reported

in boys with FXS as well as in boys with ASD (Hall et al., 2009). However, the extent to which eye gaze avoidance occurs in females with FXS relative to females with ASD is unknown. Second, because responses were gathered using an online survey in Study 1 and the sample size was relatively large, it was not possible to confirm each participant's diagnosis in Study 1. Caregivers were, however, asked to list all diagnoses their child had received (genetic, developmental, medical, etc.) and we were therefore able to rule out FXS in the ASD group and both FXS and ASD in the MDD group. Furthermore, because the eligibility criteria for participation in Study 2 required individuals to obtain an ECAS score of 30 or above, the samples contained boys who exhibited more severe levels of eye contact avoidance, and therefore does not reflect the respective populations as a whole. Finally, we did not include a comparative sample of typically developing individuals. This would be useful in creating a normative dataset, allowing the measure to be used outside the developmental disability population, such as those with social anxiety disorder. Additionally, future studies should examine how sensitive the scale is to change following more intensive or longer duration of treatment.

Given that groups of children with FXS contain individuals with and without a diagnosis of ASD, investigators have increasingly begun to identify children with FXS who meet behavioral criteria for ASD (i.e., "FXS+ASD") and compare them to children with idiopathic ASD (Demark et al., 2003; Hernandez et al., 2009; Lee et al., 2016; McDuffie et al., 2012; Moss et al., 2013). In a secondary analysis, we therefore conducted these comparisons on the domains and subscales of the ECAS. We found that the differences between the groups were even more striking i.e., boys with FXS who had a comorbid diagnosis of ASD exhibited significantly higher levels of eye contact avoidance than boys with ASD. The effect was particularly large on the

unfamiliar people subscale. Indeed, the mean difference on the total score of the ECAS between the two groups was 10 points. In retrospect, we were not surprised by these findings for the following reasons. First, creating a subcategory of children with FXS+ASD serves to select children with higher levels of ASD symptomatology from the larger group of children with FXS. Thus, the subgroup of boys would, by definition, be more likely to exhibit behaviors that are consistent with ASD (i.e., lower levels of communication and social skills as well as higher levels of repetitive behaviors). Indeed, studies have shown that children with FXS+ASD tend to be more severely impaired on a variety of metrics such as nonverbal IQ, language, social interest, nonverbal communication and repetitive behaviors than those without comorbid ASD. When we compared the communication ability of boys with FXS who had a comorbid diagnosis (FXS+ASD) to those who didn't (i.e., "FXS-only") in the present study, boys who had the comorbid diagnosis had significantly lower levels of communication skills. This is because children in the "FXS+ASD" subgroup were, in a sense, selected from the larger group for those very characteristics. One way to overcome this issue would be to create a subgroup of children with ASD who are matched to the subgroup of children with FXS on those characteristics. However, the subgroup of children with ASD would then no longer be representative of the population of children with ASD. The utility of the subgroup approach should therefore be questioned. Another related issue is that by combining children with FXS and ASD into a subcategory, investigators may be unwittingly committing a category error (see Hall et al., 2010). This is because genetic disorders such as FXS, and behavioral disorders such as ASD, are defined at different categorical levels – FXS is defined at a biological level and ASD is defined at a behavioral level.

We therefore refrained from adopting a categorical approach and employed a more dimensional approach in Study 2. First, we recruited boys in each group who exhibited high levels of eye contact avoidance and then administered measures of autism symptomatology and adaptive behavior to check if the groups were similar. Fortunately, both groups in Study 2 were similar in terms of chronological age, adaptive behavior and severity of autistic symptomatology. This allowed us to examine the effect of the behavioral treatment probe on ECAS scores without these confounds. It should be noted however that we did not include a measure of IQ in Study 2. As has been pointed out by Abbeduto and colleagues (2014), comparison of children with FXS to IQ-matched samples of children with ASD would significantly restrict the sample of children with ASD, limiting the generalizability of the results. This is because almost all boys with FXS are diagnosed with an intellectual disability whereas less than half of boys with ASD typically fall into this category. Although the groups in Study 2 were matched on chronological age, adaptive behavior, and autistic symptomatology, it is possible that the groups were not matched on IQ.

In summary, the data from the present study indicates that syndrome-specific differences are evident in both the quality and quantity of eye gaze behavior between boys with FXS and boys with ASD. Given that boys with FXS exhibited more pronounced levels of eye gaze avoidance, particularly with unfamiliar people, and that boys with FXS were more likely to respond more positively to treatment following brief exposure to eye contact training than boys with ASD, these data support the hypothesis that different underlying mechanisms may be involved in this critical social behavior. These data further underscore the heterogeneity of eye gaze avoidance in these two disorders and highlight the need for investigators to design interventions according to a precision medicine approach.

References

Abbeduto, L., McDuffie, A., & Thurman, A. J. (2014). The fragile X syndrome-autism comorbidity: What do we really know? *Frontiers in Genetics*, *5*.

Aman, M. G., Singh, N. N., Stewart, A. W., & Field, C. J. (1985). The aberrant behavior checklist: A behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency, 89*(5), 485–491.

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th ed.). American Psychiatric Association: Washington DC.

Anagnostou, E., Jones, N., Huerta, M., Halladay, A. K., Wang, P., Scahill, L., … Dawson, G. (2015). Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder. *Autism*, *19*(5), 622–636.

Bailey D. B., Raspa M., Olmsted M. & Holiday D. B. (2008). Co-occurring conditions associated with FMR1gene variations: findings from a national parent survey. *American Journal of Medical Genetics.* Part A 146A, 2060–9.

Bauminger, N. (2002). The facilitation of social-emotional understanding and social interaction in high-functioning children with autism: Intervention outcomes. *Journal of Autism and Developmental Disorders*, *32*(4), 283–298.

Brugha, T. S., Doos, L., Tempier, A., Einfeld, S., & Howlin, P. (2015). Outcome measures in intervention trials for adults with autism spectrum disorders; a systematic review of assessments of core autism features and associated emotional and behavioural problems. *International Journal of Methods in Psychiatric Research*, *24*(2), 99–115.

Bruinsma, Y., Koegel, R. L., & Koegel, L. K. (2004). Joint attention and children with autism: A review of the literature. *Mental Retardation and Developmental Disabilities Research*

Reviews, *10*(3), 169–175.

Budimirovic, D. B., Berry-Kravis, E., Erickson, C. A., Hall, S. S., Hessl, D., Reiss, A. L., King, M. K., Abbeduto, L., & Kaufmann, W. E. (2017). Updated report on tools to measure outcomes of clinical trials in fragile X syndrome. *Journal of Neurodevelopmental Disorders*, *9*(1), 14.

Chang, Y. C., Shire, S. Y., Shih, W., Gelfand, C., & Kasari, C. (2016). Preschool deployment of evidence-based social communication intervention: JASPER in the classroom. *Journal of Autism and Developmental Disorders*, *46*(6), 2211–2223.

Chawarska, K., & Shic, F. (2009). Looking but not seeing: Atypical visual scanning and recognition of faces in 2 and 4-Year-old children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *39*(12), 1663–1672.

Clifford S., Dissanayake C., Bui Q. M., Huggins R., Taylor A. K. & Loesch D. Z. (2007). Autism spectrum phenotype in males and females with fragile X full mutation and premutation. *Journal of Autism and Developmental Disorders, 37*, 738–47.

Coffee, B., Keith, K., Albizua, I., Malone, T., Mowrey, J., Sherman, S. L., & Warren, S. T. (2009). Incidence of Fragile X Syndrome by Newborn Screening for Methylated FMR1 DNA. *The American Journal of Human Genetics*, *85*(4), 503–514.

Cohen, I. L., Vietze, P. M., Sudhalter, V., Jenkins, E. C., & Brown, W. T. (1991). Effects of age and communication level on eye contact in fragile X males and non-fragile X autistic males. *American Journal of Medical Genetics*, *38*(2–3), 498–502.

Cohen, I. L. (1995). A theoretical analysis of the role of hyperarousal in the learning and behavior of fragile X males. *Mental Retardation and Developmental Disabilities Research Reviews*, *1*(4), 286–291.

Cohen, I. L., Vietze, P. M., Sudhalter, V., Jenkins, E. C., & Brown, W. T. (1989). Parent-child dyadic gaze patterns in fragile X males and in non-fragile X males with autistic disorder. *Journal of Child Psychology and Psychiatry*, *30*(6), 845–856.

Constantino, J. N., & Gruber, C. (2005). *The Social Responsiveness Scale*. Western Psychological Services.

Cook, J. L., Rapp, J. T., Mann, K. R., McHugh, C., Burji, C., & Nuta, R. (2017). A practitioner model for increasing eye contact in children with autism. *Behavior Modification*, *41*(3), 382–404.

Crawford, D. C., Acuña, J. M., & Sherman, S. L. (2001). FMR1 and the fragile X syndrome: Human genome epidemiology review. *Genetics in Medicine*, *3*(5), 359–371.

Crawford, H., Moss, J., Oliver, C., & Riby, D. (2017). Differential effects of anxiety and autism on social scene scanning in males with fragile X syndrome. *Journal of Neurodevelopmental Disorders*, *9*(1), 9.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., … Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, *8*(4), 519–526.

Dalton, K. M., Holsen, L., Abbeduto, L., & Davidson, R. J. (2008). Brain function and gaze fixation during facial-emotion processing in fragile X and autism. *Autism Research*, *1*(4), 231–239.

Darling-Churchill, K. E., & Lippman, L. (2016). Early childhood social and emotional development: Advancing the field of measurement. *Journal of Applied Developmental Psychology*, *45*, 1–7.

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the nature of face processing

impairment in autism: Insights from behavioral and electrophysiological studies. *Developmental Neuropsychology*, *27*(3), 403–424.

Demark, J. L., Feldman, M. A., & Holden, J. J. (2003). Behavioral relationship between autism and fragile X syndrome. *American Journal on Mental Retardation*, *108*(5), 314.

Elsabbagh, M., Mercure, E., Hudry, K., Chandler, S., Pasco, G., Charman, T., … Johnson, M. H. (2012). Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Current Biology*, *22*(4), 338–342.

Esbensen, A. J., Rojahn, J., Aman, M. G., & Ruedrich, S. (2003). Reliability and validity of an assessment instrument for anxiety, depression, and mood among individuals with mental retardation. *Journal of Autism and Developmental Disorders*, *33*(6), 617–629.

Falck-Ytter, T., Carlström, C., & Johansson, M. (2015). Eye contact modulates cognitive processing differently in children with autism. *Child Development*, *86*(1), 37–47.

Finlay, W. M. L., & Lyons, E. (2002). Acquiescence in interviews with people who have mental retardation. *Mental Retardation*, *40*(1), 14–29.

Fonger, A. M., & Malott, R. W. (2019). Using shaping to teach eye contact to children with autism spectrum disorder. *Behavior Analysis in Practice*, *12*(1), 216–221.

Freeth, M., Foulsham, T., & Kingstone, A. (2013). What affects social attention? Social presence, eye contact and autistic traits. *PLoS ONE*, *8*(1).

Gannon, C. E., Britton, T. C., Wilkinson, E. H., & Hall, S. S. (2018). Improving social gaze behavior in fragile X syndrome using a behavioral skills training approach: A proof of concept study. *Journal of Neurodevelopmental Disorders*, *10*(1), 25.

Grelotti, D. J., Gauthier, I., & Schultz, R. T. (2002). Social interest and the development of cortical face specialization: What autism teaches us about face processing. *Developmental Psychobiology*, *40*(3), 213–225.

Hall S. S., Lightbody A. A. & Reiss A. L. (2008). Compulsive, self-injurious, and autistic behavior in children andadolescents with fragile X syndrome. *American Journal of Mental Retardation 113*, 44–53.

Hall, S. S. (2009). Treatments for fragile X syndrome: A closer look at the data. *Developmental Disabilities Research Reviews*, *15*(4), 353–360.

Hall, S. S., Frank, M. C., Pusiol, G. T., Farzin, F., Lightbody, A. A., & Reiss, A. L. (2015). Quantifying naturalistic social gaze in fragile X syndrome using a novel eye tracking paradigm. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *168*(7), 564–572.

Hall, S. S., Lightbody, A. A., Hirt, M., Rezvani, A., & Reiss, A. L. (2010). Autism in fragile X syndrome: A category mistake? *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(9), 921–933.

Hall, S. S. & Venema, K. M. (2017). A screening tool to measure eye contact avoidance in boys with fragile X syndrome. *Journal of Autism and Developmental Disorders*, 47, 2254-2264.

Hazlett, H. C., Poe, M. D., Lightbody, A. A., Gerig, G., MacFall, J. R., Ross, A. K., Provenzale, J., Martin, A., Reiss, A. L., & Piven, J. (2009). Teasing apart the heterogeneity of autism: Same behavior, different brains in toddlers with fragile X syndrome and autism. *Journal of Neurodevelopmental Disorders*, *1*(1), 81–90.

Hernandez, R. N., Feinberg, R. L., Vaurio, R., Passanante, N. M., Thompson, R. E., & Kaufmann, W. E. (2009). Autism spectrum disorder in fragile X syndrome: A longitudinal evaluation. *American Journal of Medical Genetics Part A*, *149A*(6), 1125–1137.

Hong, M. P., Eckert, E. M., Pedapati, E. V., Shaffer, R. C., Dominick, K. C., Wink, L. K., Sweeney, J. A., & Erickson, C. A. (2019). Differentiating social preference and social anxiety phenotypes in fragile X syndrome using an eye gaze analysis: A pilot study. *Journal of Neurodevelopmental Disorders*, *11*(1), 1.

Hunter, J., Rivero-Arias, O., Angelov, A., Kim, E., Fotheringham, I., & Leal, J. (2014). Epidemiology of fragile X syndrome: A systematic review and meta-analysis. *American Journal of Medical Genetics Part A*, *164*(7), 1648–1658.

Hutt, C., & Ounsted, C. (1966). The biological significance of gaze aversion with particular reference to the syndrome of infantile autism. *Behavioral Science*, *11*(5), 346–356.

Joseph, R. M., Ehrman, K., McNally, R., & Keehn, B. (2008). Affective response to eye contact and face recognition ability in children with ASD. *Journal of the International Neuropsychological Society*, *14*(6), 947–955.

Kaufmann, W. E., Kidd, S. A., Andrews, H. F., Budimirovic, D. B., Esler, A., Haas-Givler, B., Stackhouse, T., Riley, C., Peacock, G., Sherman, S. L., Brown, W. T., & Berry-Kravis, E. (2017). Autism Spectrum Disorder in fragile X syndrome: Cooccurring conditions and current treatment. *Pediatrics*, *139*(Supplement 3), S194–S206.

Kleinke, C. L. (1986). Gaze and eye contact: A research review. *Psychological Bulletin*, *100*(1), 78–100.

Klusek, J., Moser, C., Schmidt, J., Abbeduto, L., & Roberts, J. E. (2020). A novel eye-tracking paradigm for indexing social avoidance-related behavior in fragile X syndrome. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *183*(1), 5–16.

Kreiser, N. L., & White, S. W. (2014). Assessment of social anxiety in children and adolescents with autism spectrum disorder. *Clinical Psychology: Science and Practice*, *21*(1), 18–31.

Lee, M., Martin, G. E., Berry-Kravis, E., & Losh, M. (2016). A developmental, longitudinal investigation of autism phenotypic profiles in fragile X syndrome. *Journal of Neurodevelopmental Disorders*, *8*(1), 47.

Lord, C., Rutter, M., DiLavore, Pamela. C., Risi, S., Gotham, K., Bishop, S. L., Luyster, R. J., & Guthrie. (2012). *Autism diagnostic observation schedule: ADOS-2*. Western Psychological Services.

Maenner, M. J., Shaw, K. A., Baio, J., EdS1, Washington, A., Patrick, M., DiRienzo, M., Christensen, D. L., Wiggins, L. D., Pettygrove, S., Andrews, J. G., Lopez, M., Hudson, A., Baroud, T., Schwenk, Y., White, T., Rosenberg, C. R., Lee, L.-C., Harrington, R. A., … Dietz, P. M. (2020). Prevalence of Autism Spectrum Disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *MMWR. Surveillance Summaries*, *69*(4), 1–12.

McConachie, H., Parr, J. R., Glod, M., Hanratty, J., Livingstone, N., Oono, I. P., Robalino, S., Baird, G., Beresford, B., Charman, T., Garland, D., Green, J., Gringras, P., Jones, G., Law, J., Le Couteur, A. S., Macdonald, G., McColl, E. M., Morris, C., … Williams, K. (2015). Systematic review of tools to measure outcomes for young children with autism spectrum disorder. *Health Technology Assessment*, *19*(41), 1–506.

McDuffie, A., Kover, S., Abbeduto, L., Lewis, P., & Brown, T. (2012). Profiles of receptive and

expressive language abilities in boys with comorbid fragile X syndrome and autism. *American Journal on Intellectual and Developmental Disabilities*, *117*(1), 18–32.

Moriuchi, J. M., Klin, A., & Jones, W. (2017). Mechanisms of diminished attention to eyes in Autism. *American Journal of Psychiatry*, *174*(1), 26–35.

Moss, J., Richards, C., Nelson, L., Oliver, C. & Hall, S.S. (2013). Delineating the profile of autism spectrum disorder characteristics in Cornelia de Lange and fragile X syndromes. *American Journal on Intellectual and Developmental Disabilities,* 118, 55-73.

Moss, J., Nelson, L., Powis, L., Waite, J., Richards, C., & Oliver, C. (2016). A comparative study of sociability in Angelman, Cornelia de Lange, Fragile X, Down and Rubinstein Taybi syndromes and autism spectrum disorder. *American Journal on Intellectual and Developmental Disabilities*, *121*(6), 465–486.

Niu, M., Han, Y., Dy, A. B. C., Du, J., Jin, H., Qin, J., Zhang, J., Li, Q., & Hagerman, R. J. (2017). Autism symptoms in fragile X syndrome. *Journal of Child Neurology*, *32*(10), 903–909.

Nordahl-Hansen, A., Kaale, A., & Ulvund, S. E. (2014). Language assessment in children with autism spectrum disorder: Concurrent validity between report-based assessments and direct tests. *Research in Autism Spectrum Disorders*, *8*(9), 1100–1106.

Ozonoff, S., Goodlin-Jones, B. L., & Solomon, M. (2005). Evidence-based assessment of autism spectrum disorders in children and adolescents. *Journal of Clinical Child & Adolescent Psychology*, *34*(3), 523–540.

Phillips, W., Rutter, M., & Baron Cohen, S. (1992). The role of eye contact in goal detection: Evidence from normal infants and children with autism or mental handicap. *Development and Psychopathology*, *4*(3), 375–383.

Roberts, J., Crawford, H., Hogan, A. L., Fairchild, A., Tonnsen, B., Brewe, A., O'Connor, S., Roberts, D. A., & Abbeduto, L. (2019). Social avoidance emerges in infancy and persists into adulthood in fragile X syndrome. *Journal of Autism and Developmental Disorders*, *49*(9), 3753–3766.

Roberts, J. E., Weisenfeld, L. A. H., Hatton, D. D., Heath, M., & Kaufmann, W. E. (2007). Social approach and autistic behavior in children with fragile X syndrome. *Journal of Autism and Developmental Disorders*, *37*(9), 1748–1760.

Rogers, S. J., Wehner, E. A., & Hagerman, R. (2001). The behavioral phenotype in fragile X: Symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders: *Journal of Developmental & Behavioral Pediatrics*, *22*(6), 409–417.

Rosenberg, R. E., Kaufmann, W. E., Law, J. K., & Law, P. A. (2011). Parent report of community psychiatric comorbid diagnoses in autism spectrum disorders. *Autism Research and Treatment*, *2011*, 1–10.

Rubio-Codina, M., Araujo, M. C., Attanasio, O., Muñoz, P., & Grantham-McGregor, S. (2016). Concurrent validity and feasibility of short tests currently used to measure early childhood development in large scale studies. *PLoS ONE*, *11*(8), 1–18.

Rutter, M., Bailey, A., Lord, C., & Berument, S. (2003). *Social Communication Questionnaire*. Western Psychological Services.

Sansone, S. M., Widaman, K. F., Hall, S. S., Reiss, A. L., Lightbody, A., Kaufmann, W. E., Berry-Kravis, E., Lachiewicz, A., Brown, E. C., & Hessl, D. (2012). Psychometric study of the Aberrant Behavior Checklist in fragile X syndrome and implications for targeted treatment. *Journal of Autism and Developmental Disorders*, *42*(7), 1377–1392.

Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J.-Y., Peng, M., Collins, R., Grove, J., Klei, L., Stevens, C., Reichert, J., Mulhern, M. S., Artomov, M., Gerges, S., Sheppard, B., Xu, X., Bhaduri, A., Norman, U., … Walters, R. K. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell*, *180*(3), 568-584.e23.

Scahill, L., Aman, M. G., Lecavalier, L., Halladay, A. K., Bishop, S. L., Bodfish, J. W., … Dawson, G. (2015). Measuring repetitive behaviors as a treatment endpoint in youth with autism spectrum disorder. *Autism*, *19*(1), 38–52.

Senju, A., & Johnson, M. H. (2009a). Atypical eye contact in autism: Models, mechanisms and development. *Neuroscience and Biobehavioral Reviews*, *33*(8), 1204–1214.

Senju, A., & Johnson, M. H. (2009b). The eye contact effect: mechanisms and development. *Trends in Cognitive Sciences*, *13*(3), 127–134.

Smith, L. E., Barker, E. T., Seltzer, M. M., Abbeduto, L., & Greenberg, J. S. (2012). Behavioral phenotype of fragile X syndrome in adolescence and adulthood. *American Journal on Intellectual and Developmental Disabilities*, *117*(1), 1–17.

Snow, C. E., & Van Hemel, S. B. (2008). Early Childhood Assessment: Why, What, and How. *Board on Children, Youth, and Families, Board on Testing and Assessment, Division of Behavioral and Social Sciences and Education.* The National Academies Press.

Sparrow, S. S., Cicchetti, D. V., & Saulnier, C. A. (2016). *Vineland Adaptive Behavior Scales, Third Edition (Vineland-3)*. Psychological Corporation.

Steiner, A. M., Gengoux, G. W., Klin, A., & Chawarska, K. (2013). Pivotal response treatment for infants at-risk for autism spectrum disorders: A pilot study. *Journal of Autism and Developmental Disorders*, *43*(1), 91–102.

Tanaka, J. W., & Sung, A. (2016). The “eye avoidance” hypothesis of autism face processing. *Journal of Autism and Developmental Disorders*, *46*(5), 1538–1552.

Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *Journal of Child Psychology and Psychiatry*, *33*(3), 489–597.

Verkerk, A. J. M. H., Pieretti, M., Sutcliffe, J. S., Fu, Y.-H., Kuhl, D. P. A., Pizzuti, A., Reiner, O., Richards, S., Victoria, M. F., Zhang, F., Eussen, B. E., van Ommen, G.-J. B., Blonden, L. A. J., Riggins, G. J., Chastain, J. L., Kunst, C. B., Galjaard, H., Thomas Caskey, C., Nelson, D. L., … Warren, S. T. (1991). Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*, *65*(5), 905–914.

Vismara, L. A., & Rogers, S. J. (2008). The Early Start Denver Model: A case study of an innovative practice. *Journal of Early Intervention*, *31*(1), 91–108.

Wetherby, A. M., Watt, N., Morgan, L., & Shumway, S. (2007). Social communication profiles of children with autism spectrum disorders late in the second year of life. *Journal of Autism and Developmental Disorders*, *37*(5), 960–975.

White, S. W., & Roberson-Nay, R. (2009). Anxiety, social deficits, and loneliness in youth with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(7), 1006–1013.

Wolff, J. J., Bodfish, J. W., Hazlett, H. C., Lightbody, A. A., Reiss, A. L., & Piven, J. (2012). Evidence of a distinct behavioral phenotype in young boys with fragile X syndrome and autism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(12), 1324–1332.

Figure Caption

Figure 1. Scores obtained within each domain of the ECAS plotted by familiarity level for each group. Error bars are 95% confidence intervals.

Figure1

Click here to access/download;Figure;Picture1.jpg

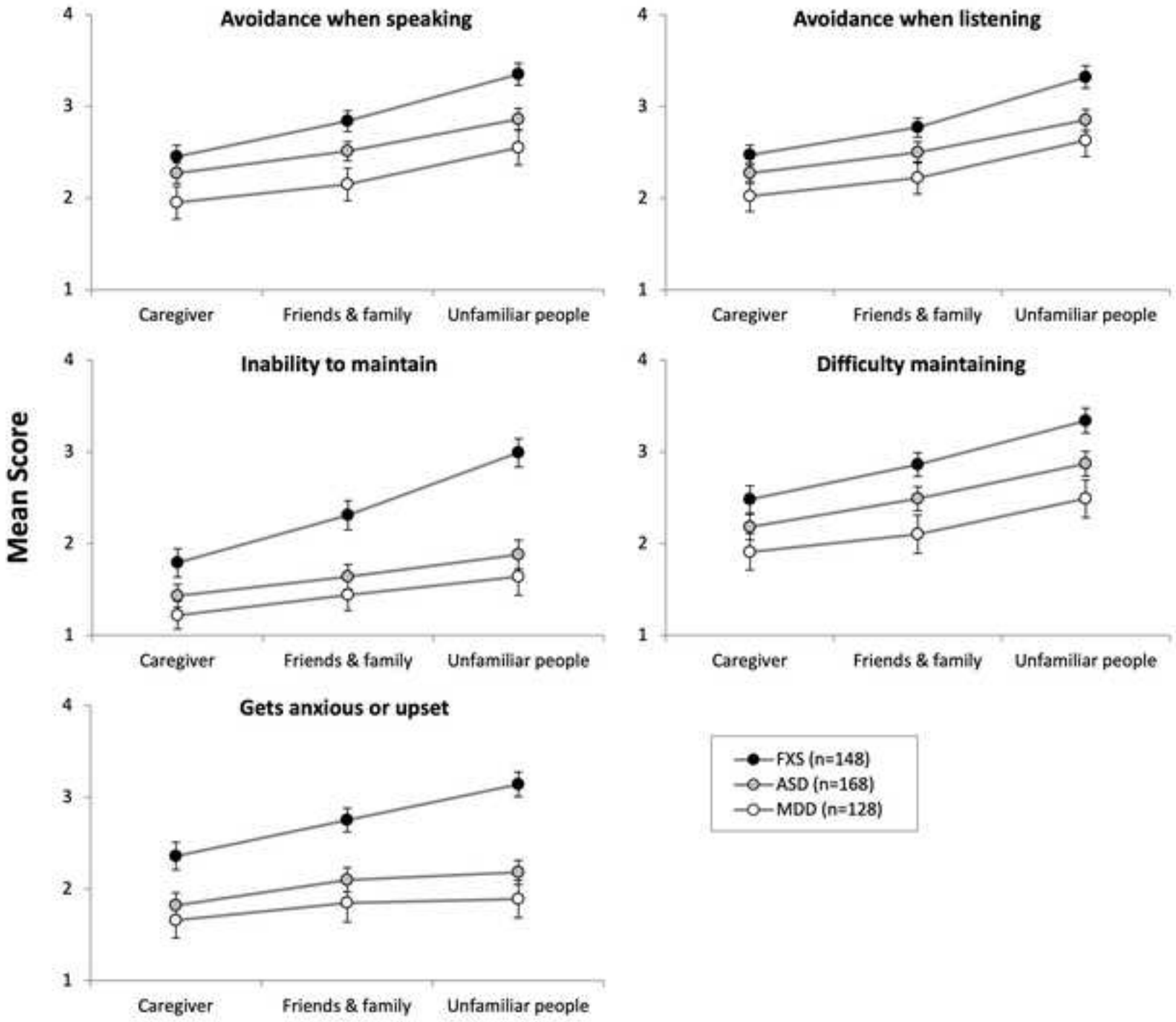

Table 1. Characteristics of participants in Study 1.

	Group		
	FXS *n*=148	ASD *n*=168	MDD *n*=128
Age in years (*M*, *SD*)	11.6 (2.60)	11.8 (3.07)	11.9 (3.03)
Age band (*n*, %)			
7 -10 years	70 (47.3%)	57 (33.9%)	45 (35.2%)
11-14 years	60 (40.5%)	77 (45.8%)	54 (42.2%)
15-18 years	18 (12.2%)	34 (20.2%)	29 (22.7%)
Communication ability (*n*, %) [a]			
Minimally verbal	48 (32.4%)	26 (15.5%)	17 (13.3%)
Partially verbal	70 (47.3%)	65 (38.7%)	68 (53.1%)
Fully verbal	30 (20.3%)	77 (45.8%)	43 (33.6%)
Eye contact avoidance [b] (*M*, *SD*)			
Domain			
Avoidance while speaking	8.6 (1.9)	7.6 (1.9)	6.6 (2.9)
Avoidance while listening	8.6 (1.7)	7.6 (2.0)	6.9 (2.7)
Inability to maintain	7.1 (2.5)	5.0 (2.5)	4.3 (2.8)
Difficulty maintaining	8.7 (2.2)	7.5 (2.4)	6.5 (3.3)
Gets anxious or upset	8.3 (2.8)	6.1 (3.1)	5.4 (3.7)
Subscale			
Caregiver	11.5 (3.5)	10.0 (3.4)	8.8 (4.3)
Friends & family	13.5 (3.2)	11.2 (3.3)	9.8 (4.6)
Unfamiliar people	16.1 (3.5)	12.6 (3.4)	11.2 (4.9)
Total score	41.2 (8.9)	33.8 (9.4)	29.7 (13.1)

[a] Minimally verbal: Never or rarely uses full sentences; Partially verbal: Sometimes or often uses full sentences; Fully verbal: Always uses full sentences

[b] Eye Contact Avoidance Scale (Hall & Venema, 2017)

Table 2. Internal consistency and test-retest reliability of the domains, subscales, and total score of the ECAS.

	Internal consistency			
ECAS	FXS (*n*=148)	ASD (*n*=168)	MDD (*n*=128)	Test-retest stability (*n*=107)
Domain				
Avoidance while speaking	.79	.82	.91	.82
Avoidance while listening	.79	.88	.89	.75
Inability to maintain	.86	.86	.89	.78
Difficulty maintaining	.82	.90	.94	.74
Gets anxious or upset	.89	.93	.95	.82
Subscale				
Caregiver	.83	.84	.88	.80
Friends & family	.82	.82	.89	.81
Unfamiliar people	.87	.78	.89	.84
Total Score	.92	.93	.96	.83

Table 3. Secondary analysis comparing children with FXS and comorbid ASD to those with ASD.

	FXS with comorbid ASD (*n*=81)	ASD (*n*=168)	*F*	*p*	η^2
ECAS score (*M*, *SD*)					
Domain					
Avoidance while speaking	9.0 (1.8)	7.6 (1.9)	16.01	<.001	.061
Avoidance while listening	8.9 (1.7)	7.6 (2.0)	14.68	<.001	.056
Inability to maintain	7.4 (2.6)	5.0 (2.5)	34.49	<.001	.123
Difficulty maintaining	9.2 (2.3)	7.5 (2.4)	15.70	<.001	.060
Gets anxious or upset	8.5 (2.6)	6.1 (3.1)	30.48	<.001	.111
Subscale					
Caregiver	12.2 (3.7)	10.0 (3.4)	12.38	<.001	.048
Friends & family	14.1 (3.0)	11.2 (3.3)	26.23	<.001	.097
Unfamiliar people	16.8 (3.2)	12.6 (3.4)	63.50	<.001	.206
Total score	43.1 (8.5)	33.8 (9.4)	37.08	<.001	.131

Table 4. Characteristics of Participants in Study 2

	FXS (*n*=31)	ASD (*n*=25)	*t*	*p*
Age in years (*M*, *SD*)	13.05 (2.77)	12.83 (3.83)	.27	NS
Adaptive Behavior[a] (*M*, *SD*)				
Communication skills	68.0 (10.4)	71.8 (11.0)	-1.33	NS
Daily living skills	74.8 (15.0)	73.2 (12.4)	.42	NS
Socialization skills	71.4 (12.9)	66.8 (8.8)	1.49	NS
Adaptive Behavior Composite	69.8 (11.7)	69.0 (9.1)	.27	NS
Autism severity (*M*, *SD*)[b]	6.71 (2.27)	7.58 (1.44)	-1.64	NS
Eye gaze avoidance (*M*, *SD*)[c]				
Domain				
Avoidance while speaking	7.74 (1.98)	8.64 (2.16)	-1.62	NS
Avoidance while listening	6.87 (2.26)	6.92 (2.29)	-.08	NS
Inability to maintain	5.71 (2.90)	6.52 (2.18)	-1.16	NS
Difficulty maintaining	7.55 (2.62)	8.60 (2.18)	-1.61	NS
Gets anxious or upset	7.39 (2.63)	6.96 (3.00)	.57	NS
Subscale				
Caregiver	9.52 (3.16)	11.84 (3.40)	-2.64	.011*
Friends & Family	10.84 (4.01)	11.24 (3.19)	-.41	NS
Unfamiliar people	14.90 (3.26)	14.56 (3.58)	.38	NS
Total score	35.26 (9.33)	37.64 (9.25)	-.95	NS

[a] Vineland Adaptive Behavior Scales, 2nd Edition (Sparrow et al. 2006) standard score
[b] Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; Lord et al., 2012) comparison severity score (CSS)
[c] Eye Contact Avoidance Scale (Hall & Venema, 2017)
*$p < .05$
NS: non-significant

Table 5. Estimated intention to treat effects on changes in ECAS scores from baseline to 4 weeks following implementation of a brief behavioral treatment probe in each group.

	Baseline to follow-up		
	FXS (*n*=31)	ASD (*n*=25)	Group Difference
Domain			
Avoidance while speaking	-1.11 (p < .001)**	-.54 (p = .108)	-.57 (p = .185, d = .37)
Avoidance while listening	-.25 (p =.512)	1.42 (p = .004)**	-1.67 (p = .006, d = .75)**
Inability to maintain	-1.18 (p = .009)**	-.75 (p =.116)	-.43 (p = .495, d = .19)
Difficulty maintaining	-1.32 (p = .020)*	-.63 (p = .036)*	-.70 (p = .277, d = .30)
Gets anxious or upset	-1.82 (p = .001)**	-.54 (p = .225)	-1.28 (p =.066, d = .51)
Subscale			
Caregiver	-2.21(p = .000)**	-.92 (p = .069)	-1.29 (p = .082, d = .48)
Friends & family	-1.43 (p = .023)*	.708 (p = .141)	-2.14 (p = .008, d = .72)**
Unfamiliar people	-2.04 (p = .002)**	-.83 (p = .137)	-1.20 (p = .144, d = .41)
Total score	-5.68 (p = .001)**	-1.04 (p = .412)	-4.64(p = .023, d = .62)*

*$p < .05$; **$p < .01$