# Abstract
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Abstract

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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
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 indifferenee (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.
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, η² = .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 \textit{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.

\textbf{Table 4]

\textbf{Measures}

All participants received baseline measures of social development and functioning upon enrollment in the study. These measures included the Vineland Adaptive Behavior Scales, 2\textsuperscript{nd} 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).

\textbf{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; Seahill 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.
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expressive language abilities in boys with comorbid fragile X syndrome and autism.


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.
Table 1. Characteristics of participants in Study 1.

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

\(^a\) 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.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Internal consistency</th>
<th>Test-retest stability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Internal consistency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FXS (n=148)</td>
<td>ASD (n=168)</td>
</tr>
<tr>
<td>Avoidance while speaking</td>
<td>.79</td>
<td>.82</td>
</tr>
<tr>
<td>Avoidance while listening</td>
<td>.79</td>
<td>.88</td>
</tr>
<tr>
<td>Inability to maintain</td>
<td>.86</td>
<td>.86</td>
</tr>
<tr>
<td>Difficulty maintaining</td>
<td>.82</td>
<td>.90</td>
</tr>
<tr>
<td>Gets anxious or upset</td>
<td>.89</td>
<td>.93</td>
</tr>
<tr>
<td>Subscale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver</td>
<td>.83</td>
<td>.84</td>
</tr>
<tr>
<td>Friends &amp; family</td>
<td>.82</td>
<td>.82</td>
</tr>
<tr>
<td>Unfamiliar people</td>
<td>.87</td>
<td>.78</td>
</tr>
<tr>
<td>Total Score</td>
<td>.92</td>
<td>.93</td>
</tr>
</tbody>
</table>
Table 3. Secondary analysis comparing children with FXS and comorbid ASD to those with ASD.

<table>
<thead>
<tr>
<th>Domain</th>
<th>FXS with comorbid ASD (n=81)</th>
<th>ASD (n=168)</th>
<th>F</th>
<th>p</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance while speaking</td>
<td>9.0 (1.8)</td>
<td>7.6 (1.9)</td>
<td>16.01</td>
<td>&lt;.001</td>
<td>.061</td>
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<tr>
<td>Avoidance while listening</td>
<td>8.9 (1.7)</td>
<td>7.6 (2.0)</td>
<td>14.68</td>
<td>&lt;.001</td>
<td>.056</td>
</tr>
<tr>
<td>Inability to maintain</td>
<td>7.4 (2.6)</td>
<td>5.0 (2.5)</td>
<td>34.49</td>
<td>&lt;.001</td>
<td>.123</td>
</tr>
<tr>
<td>Difficulty maintaining</td>
<td>9.2 (2.3)</td>
<td>7.5 (2.4)</td>
<td>15.70</td>
<td>&lt;.001</td>
<td>.060</td>
</tr>
<tr>
<td>Gets anxious or upset</td>
<td>8.5 (2.6)</td>
<td>6.1 (3.1)</td>
<td>30.48</td>
<td>&lt;.001</td>
<td>.111</td>
</tr>
<tr>
<td>Caregiver</td>
<td>12.2 (3.7)</td>
<td>10.0 (3.4)</td>
<td>12.38</td>
<td>&lt;.001</td>
<td>.048</td>
</tr>
<tr>
<td>Friends &amp; family</td>
<td>14.1 (3.0)</td>
<td>11.2 (3.3)</td>
<td>26.23</td>
<td>&lt;.001</td>
<td>.097</td>
</tr>
<tr>
<td>Unfamiliar people</td>
<td>16.8 (3.2)</td>
<td>12.6 (3.4)</td>
<td>63.50</td>
<td>&lt;.001</td>
<td>.206</td>
</tr>
<tr>
<td>Total score</td>
<td>43.1 (8.5)</td>
<td>33.8 (9.4)</td>
<td>37.08</td>
<td>&lt;.001</td>
<td>.131</td>
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</table>
Table 4. Characteristics of Participants in Study 2

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

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.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline to follow-up</th>
<th>FXS (n=31)</th>
<th>ASD (n=25)</th>
<th>Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance while speaking</td>
<td>-1.11 (p &lt; .001)**</td>
<td>-0.54 (p = .108)</td>
<td>-0.57 (p = .185, d = .37)</td>
<td></td>
</tr>
<tr>
<td>Avoidance while listening</td>
<td>-0.25 (p = .512)</td>
<td>1.42 (p = .004)**</td>
<td>-1.67 (p = .006, d = .75)**</td>
<td></td>
</tr>
<tr>
<td>Inability to maintain</td>
<td>-1.18 (p = .009)**</td>
<td>-0.75 (p = .116)</td>
<td>-0.43 (p = .495, d = .19)</td>
<td></td>
</tr>
<tr>
<td>Difficulty maintaining</td>
<td>-1.32 (p = .020)*</td>
<td>-0.63 (p = .036)*</td>
<td>-0.70 (p = .277, d = .30)</td>
<td></td>
</tr>
<tr>
<td>Gets anxious or upset</td>
<td>-1.82 (p = .001)**</td>
<td>-0.54 (p = .225)</td>
<td>-1.28 (p = .066, d = .51)</td>
<td></td>
</tr>
<tr>
<td>Subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver</td>
<td>-2.21(p = .000)**</td>
<td>-0.92 (p = .069)</td>
<td>-1.29 (p = .082, d = .48)</td>
<td></td>
</tr>
<tr>
<td>Friends &amp; family</td>
<td>-1.43 (p = .023)*</td>
<td>.708 (p = .141)</td>
<td>-2.14 (p = .008, d = .72)**</td>
<td></td>
</tr>
<tr>
<td>Unfamiliar people</td>
<td>-2.04 (p = .002)**</td>
<td>-0.83 (p = .137)</td>
<td>-1.20 (p = .144, d = .41)</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>-5.68 (p = .001)**</td>
<td>-1.04 (p = .412)</td>
<td>-4.64(p = .023, d = .62)**</td>
<td></td>
</tr>
</tbody>
</table>

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