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Implicit Discrimination of Basic Facial Expressions of Positive/Negative Emotion in Fragile X Syndrome and Autism Spectrum Disorder

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Abstract

Fragile X syndrome (FXS) and autism spectrum disorders (ASD) are characterized by impaired social functioning. We examined the spontaneous discrimination of happy and disgusted facial expressions, from neutral faces, in individuals with FXS (n = 13, M_{age} = 19.70) and ASD (n = 15, M_{age} = 11.00) matched on adaptive behavior and verbal abilities measured by the Vineland Adaptive Behavior Scale. Eye gaze to the eyes and mouth of neutral faces was also measured. Results suggest individuals with FXS and ASD distinguish facial expressions spontaneously in the same way. Individuals with FXS looked significantly less at the eye region of neutral faces than individuals with ASD. These results provide insight into similarities and differences in face processing in two neurodevelopmental disorders noted for their similarities in social behavior.

Key Words: *Fragile X syndrome; autism spectrum disorder; eye tracking; emotion discrimination; eye gaze*

The ability to discern emotional expressions is crucial for successful social interaction, as it allows us to better predict the behaviors and intentions of other people and to alter our own behavior accordingly. Performing the required processes that make social interaction successful is relatively effortless for most typically developing (TD) individuals, and the skill of emotion discrimination emerges as young as seven months of age in typical development (Caron, Caron, & Myers, 1982; Nelson & Dolgin, 1985). Impairments in understanding emotional expressions have been proposed to underlie the social difficulties in those with a variety of developmental and psychiatric disorders, and are thought to be particularly important in understanding the impairments and behaviors that are characteristic of individuals with autism spectrum disorder (ASD), social phobia, conduct disorder, and schizophrenia (Baron-Cohen, 1997, 2002; Brüne, 2005; Derntl et al., 2012; Happé & Frith, 1996; Rapee & Heimberg, 1997; Simonian, Beidel, Turner, Berkes, & Long, 2001). It is critically important, however, to understand the mechanisms and pathways by which impairments or atypicalities in face processing might impact upon social functioning, as well as how these mechanisms might be similar or different across different disorders.

Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability (Crawford, Acuña, & Sherman, 2001), affecting approximately 1 in 4,000 males and 1 in 8,000 females (Turner, Webb, Wake, & Robinson, 1996). FXS is caused by abnormalities in the Fragile X Mental Retardation 1 (FMR1) gene located on the Xq27.3 site. The FMR1 gene carries a trinucleotide cytosine-guanine-guanine (CGG) repeat. Individuals with the full FXS mutation have in excess of 200 CGG repeats compared to 6–45 repeats in TD individuals. The excessive repeats in individuals with the full mutation causes the FMR1 gene to become methylated, which results in reduced production of the protein FMRP (Tassone et al., 1999). Reduced levels of FMRP has consequences for brain structure and function by affecting synaptic

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plasticity (Willemsen, Oostra, Bassell, & Dictenberg, 2004) and causing long-term depression of the hippocampus and cerebellum (Bear, Huber, & Warren, 2004). Because FXS is an X-linked disorder, males with the full mutation are more severely affected than their female counterparts. The phenotype associated with FXS encompasses mild to profound intellectual disability alongside physical, cognitive, and behavioral manifestations (Cornish, Turk, & Hagerman, 2008).

ASD is characterized by impairments in social communication and interaction, as well as restricted or repetitive behaviors, interests, or activities (American Psychiatric Association, 2013). The DSM-V (American Psychiatric Association, 2013) diagnostic criteria for ASD include items relating to impairments in emotion processing and responding to facial expressions. Although not a diagnostic feature of ASD, it has been estimated that approximately 29% of individuals on the autism spectrum have mild to moderate intellectual disability, with approximately 38.5% presenting with severe to profound intellectual disability (Fombonne, 2005).

Impairments in social functioning, particularly reduced eye contact and pervasive shyness, are core characteristics of FXS (Cornish et al., 2008; Moss, Oliver, Nelson, Richards, & Hall, 2013). In addition, although the severity of these characteristics is considered to be milder and the profile of impairments somewhat atypical relative to individuals with idiopathic ASD (Bailey Jr. et al., 1998; Demark, Feldman, & Holden, 2003; Moss et al., 2013), the reported prevalence of ASD in individuals with FXS ranges from 50% to 75% (Clifford et al., 2007; García-Nonell et al., 2008; Hall, Lightbody, & Reiss, 2008). Indeed, the social impairments that are characteristic of individuals with FXS may appear strikingly similar to those observed in ASD with social withdrawal, limited eye contact, and reduced social reciprocity commonly observed in individuals with ASD and those with FXS (for a review, see Cornish, Turk, & Levitas, 2007).

Despite the apparent overlap in the behavioral phenotypes of those with FXS and those with ASD, the underlying mechanisms, and some particulars of the defining features, may differ somewhat between the two conditions. For example, boys with FXS show the tendency to warm up and display increasing levels of eye contact over time, whereas those with ASD do not (Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007). Cornish et al. (2007) have also suggested that although individuals with ASD and FXS both exhibit atypical eye gaze in social situations, different underlying mechanisms may be responsible for this behavior in the two disorders.

The subtle differences between ASD and FXS highlight the importance of directly comparing the two populations using careful and detailed assessments. To date, however, very few studies have directly examined whether the coarse-scale phenotypic similarities and differences in ASD phenomenology observed in individuals with FXS are also evident in the underlying social cognitive abilities of this group. Therefore, we directly compared participants with ASD with participants with FXS in the present study.

Emotion Recognition in FXS and ASD

Two primary studies are often referred to for demonstrating spared emotion recognition abilities in males with FXS (Simon & Finucane, 1996; Turk & Cornish, 1998). Turk and Cornish (1998) used three tasks to assess emotion perception in boys with FXS. The experimental tasks required participants to point to a response card that matched one of four emotions (happiness, sadness, fear, or anger) presented in previous visual or auditory stimuli. The results of this study replicated the previous findings of Simon and Finucane (1996). Together, these results suggest that both adult males and boys with FXS exhibit the same explicit facial emotion discrimination abilities as TD individuals. Despite this, more recent research has provided evidence for deficits in the recognition of specific emotional facial expressions, such as neutral and angry, in individuals with FXS (Hagan, Hoeft, Mackey, Mobbs, & Reiss, 2008; Shaw & Porter, 2013).

Until recently, individuals with ASD have commonly been reported to perform poorly on explicit tasks of emotion recognition. However, in a review of the emotion recognition research in ASD, Harms, Martin, and Wallace (2010) argue that, when confounding variables are controlled for, research findings indicate intact facial emotion recognition abilities in ASD. For example, Harms et al. (2010) review and discuss a large number of studies that failed to uncover any differences between individuals with ASD and TD individuals on measures of explicit emotion discrimination. In these studies, performance was best accounted for by level of verbal ability (Prior, Dahlstrom, &

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Squires, 1990), adaptive behavior (Fein, Lueci, Braverman, & Waterhouse, 1992), age (Fein et al., 1992), or intellectual ability (Loveland et al., 1997), as opposed to a diagnosis of ASD. The studies of emotion recognition in FXS and ASD to date have relied heavily on explicit measures. However, the results of recent studies indicate that performance on explicit measures of social processing and perception alone may not fully reflect the nature of these skills or abilities in this population. For example, Senju, Southgate, White, and Frith (2009) have reported that the eye-movements of individuals with Asperger's Syndrome (AS) during a passive theory of mind task previously employed with infant participants indicated that, unlike TD comparison adults, adult participants with AS did not spontaneously attribute mental states to others. This, despite the same group of AS individuals exhibiting intact performance on several other explicit false belief tasks. Using implicit measures, including those involving eye-tracking, therefore, has the capacity to provide novel insight into the mechanisms underlying social-cognitive functioning and behavior. In the context of the current experiment, the use of an implicit eye-tracking measure of emotional face processing allows us to study individuals with significant intellectual disability.

Looking to the Eyes in FXS and ASD

Eye tracking measures may also provide indicators as to which processes are required for emotion recognition, and whether or not a given population utilizes particular processes. The eye region has been proposed to be perhaps the most important region of the face for discerning emotional expressions (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001 but see also; Blais, Roy, Fiset, Arguin, & Gosselin, 2012; Dailey & Cottrell, 1999). For example, a genuine smile can be distinguished from a forced smile by studying the area around the eyes alone, with contraction of the orbicularis oculi muscle causing skin to gather around the eye during a genuine smile but not during a forced smile (Ekman, Davidson, & Friesen, 1990). Furthermore, dilation of the pupils of the eyes is believed to provide valuable information about an individual's level of emotional arousal (Bradley, Miccoli, Escrig, & Lang, 2008).

The literature on looking at the eye region has produced highly consistent findings for those with FXS, demonstrating that they look less at the eyes of the face. For example, Dalton and colleagues (Dalton, Holsen, Abbeduto, & Davidson, 2008) reported that, when passively viewing emotional and neutral faces, individuals with FXS displayed a lower average percentage of fixations to the eye region compared with TD individuals. These findings are in line with other studies reporting reduced looking to the eyes in FXS compared to TD individuals (Farzin, Scaggs, Hervey, Berry-Kravis, & Hessl, 2011; Holsen, Dalton, Johnstone, & Davidson, 2008). In addition, Farzin, Rivera, and Hessl (2009) used eye tracking to explore the manner via which individuals with FXS processed passively viewed photographs of human faces displaying calm, happy, and fearful expressions. The results of this study showed that the individuals with FXS spent less time fixating on the eye region, made fewer fixations to the eye region, and made more fixations to the nose region compared to sex and age matched TD controls. Interestingly, none of the findings in this study were correlated with severity of autistic symptomatology, suggesting the possibility that the underlying mechanisms of atypical gaze behavior in FXS were not related to ASD characteristics but, instead, to a mechanism of FXS itself. However, direct comparisons of gaze behavior between individuals with FXS and individuals with ASD are needed in order to confirm this. In contrast with these seemingly consistent findings, Shaw and Porter (2013) recently reported reduced attention to the eyes in FXS in comparison to a chronological age (CA) matched control group, but not a mental age (MA) matched control group, thus suggesting developmentally typical looking to the eye region. It is important to note, however, that the studies described above, with the exception of Farzin et al. (2009) and Farzin et al. (2011), included between 55% and 75 % females in the participant samples. Due to documented differences in the social phenotype between males and females with FXS (Roberts et al., 2007), it is important to consider gender effects separately in order to qualify these results in males versus females with FXS. The literature regarding whether individuals with ASD show typical looking patterns to the eye region is mixed with some studies reporting similar looking time to the eyes for ASD and TD individuals (Kirchner, Hatri, Heekeren, & Dziobek, 2011), and others reporting less looking

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to the eye region in ASD (Dalton et al., 2005; Hernandez et al., 2009).

In the current study, we investigate implicit emotion discrimination in individuals with FXS relative to individuals with ASD. Participants' spontaneous facial emotion discrimination was measured using an oddball paradigm in conjunction with a preferential looking measure, whereby emotional face stimuli were presented infrequently and irregularly within a series of neutrally expressive face stimulus presentations. Critically, this novel procedure does not require a verbal response, enabling us to examine implicit discrimination of basic emotional facial expressions in individuals with limited verbal and nonverbal abilities. Happiness and disgust were the expressions used in the present study due to their contrast in valence. Disgust was chosen as the negative expression because many other negative emotional expressions, such as sadness, fear, and anger, can often be experienced cognitively with no distinctive facial expression. For example, one may not always display a frown when experiencing sadness. Patterns of eye gaze across the eye, mouth, and other regions of the face were also measured during "standard" trials, which presented pairs of faces posed in neutral expressions, in order to examine and compare gaze to the eye region across participant groups.

To summarize, the current study was designed to examine whether individuals with FXS and individuals with ASD spontaneously discriminate between happy and neutral, and disgust and neutral, facial expressions in the same way, as well as whether individuals with FXS and individuals with ASD spend similar amounts of time looking to the eyes and mouth of neutrally expressive faces. By directly comparing looking patterns between individuals with ASD and individuals with FXS and comparatively less ASD symptomatology, it will be possible to elucidate whether any differences in emotion perception or attentional allocation to the eye region of a face in individuals with FXS are driven by FXS-specific mechanisms or ASD symptomatology.

Method

Participants

Thirteen individuals with fragile X syndrome (FXS; one female, M_{age} = 19.70, SD = 9.00) and 15 individuals with autism spectrum disorder (ASD; three female, M_{age} = 11.00, SD = 3.48) were included in the analyses. Data from 16 TD children (eight female, M_{age} = 7.13, SD = 1.61), and 12 TD adults (12 female, M_{age} = 21.92, SD = 2.97) are presented to provide emotion discrimination baseline information for the current paradigm. All participants had normal or corrected to normal vision. Table 1 presents the characteristics of participants with ASD and FXS. Due to the wide range of chronological ages and ability levels in our participants, the Vineland Adaptive Behavior Scale (VABS; Sparrow, Cicchetti, & Balla, 2005) was used in place of an intellectual quotient (IQ) measure. Raw scores derived from the sum of domains of the VABS (Sparrow et al., 2005) were used as a measure of adaptive behavior ability. This score, which reflects overall ability (but does not take into consideration CA), did not differ between those with ASD and those with FXS. Furthermore, the raw score for the communication subscale of the VABS (Sparrow et al., 2005) was used as a measure of verbal ability. This subscale includes items relating to the participant's receptive and expressive language, such as use of irregular verbs, as well as reading and writing abilities, and serves as a proxy for verbal IQ in the current samples. An additional two FXS participants, two ASD participants, and two TD children were tested, but did not provide viable data due to calibration difficulties, strabismus, nystagmus, an inability to sit still for the duration of the experiment, or providing valid data on less than 40% of trials in any one condition. An invalid trial was considered as such if the participant did not look at either face during the trial.

Participants with FXS and ASD were recruited through the Cerebra Centre for Neurodevelopmental Disorders participant database, and through a community outreach recruitment campaign. All participants had a confirmed diagnosis from a professional (pediatrician, general practitioner, psychiatrist, clinical psychologist, or educational psychologist for ASD; and pediatrician, general practitioner, or clinical geneticist for FXS). Participants in the ASD group had the following diagnoses: *Autistic Disorder* (n = 8), *Asperger Syndrome* (n = 2), and *Pervasive Developmental Disorder – Not Otherwise Specified* (n = 5). These ASD diagnoses were further verified through the administration of the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2002) by a trained administrator in the laboratory. Autism symptomatology in the

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Table 1
Participant Characteristics and Alpha Level for Comparison Between ASD and FXS Participants on: Chronological Age, Gender, Verbal Ability, Mobility, Adaptive Behavior Sum of Domains and Subscale Raw Scores as Measured by the Vineland Adaptive Behavior Scale – Survey Form, and Mean Score on the Social Communication Questionnaire (SCQ Alongside the Percentage of Participants in Each Group Meeting the Cut-Off Score for ASD on the SCQ and ADOS)

Characteristic	FXS (n = 13)	ASD (n = 15)	P
Age in years			
Mean (SD)	19.70 (9.00)	11.00 (3.48)	.005
Range	6.60–34.19	6.71–18.76	
Gender (% male)	92.31	80.00	.372
Speech (% verbal[a])	84.62	80.00	.761
Mobility (% mobile[b])	100.00	100.00	1.00
Adaptive Behavior Raw Score[c]			
Sum of domains (SD)	357.92 (95.64)	310.67 (124.38)	.276
Communication (SD)	119.00 (34.33)	124.07 (50.82)	.764
Daily Living Skills (SD)	120.92 (39.13)	95.47 (39.08)	.098
Socialization (SD)	119.69 (30.74)	91.13 (41.71)	.052
Mean SCQ[d] score (SD)	17.32 (4.24)	19.00 (6.71)	.047
Participants meeting SCQ cut-off for ASD (%)[e]	8 (66.66)	12 (85.71)	
Participants meeting ADOS cut-off for ASD (%)	N/A	15 (100.00)	N/A

Note. FXS = fragile X syndrome; ASD = autism spectrum disorder; ADOS = Autism Diagnostic Observed Scheduled. [a]Verbal defined as ability to speak/sign more than 30 words. [b]Mobile defined as ability to walk unaided. [c]Raw scores reflect raw performance, and can be considered a proxy to overall ability regardless of their relation to chronological age (i.e., developmental ability levels). [d]Social Communication Questionnaire (SCQ) data not returned from 1 participant with FXS and 1 participant with ASD. [e]A score of 15 or above is suggested by the authors of the SCQ to indicate the presence of an ASD.

FXS group was assessed using the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003).

TD children were recruited through the Infant and Child Laboratory participant database, while TD adults were recruited through the School of Psychology research participant pool, both at the University of Birmingham. This study was reviewed and approved by the School of Psychology Ethics Committee at the University of Birmingham. All participants aged 16 years and over provided informed consent, and parents of children less than 16 years of age provided written consent before taking part in the study.

Apparatus

The stimuli were generated by the Experiment Builder program (SR Research, Ontario, Canada) and presented on a 19-in CRT Screen at a screen resolution of 1024 X 768. Participants placed their head on a chin rest.6 m from the screen, in a dimly lit room with windows blacked out to avoid luminance changes. Chin rest and desk heights were adjusted so that eye gaze was central to the display screen. Eye-movements were recorded using an EyeLink 1000 Tower Mount system, which runs with a spatial accuracy of .5-1 visual angle (°), a spatial resolution of .01°, and a temporal resolution of two milliseconds (500Hz). A 5-point calibration was performed prior to each experimental block, as well as mid-block if necessary. A single-point drift correction to the calibration was made prior to every fifth trial. The eye-tracking camera was linked to a separate host PC to the one displaying the search stimuli. EyeLink software (SR research, Ontario, Canada) was used to control the camera and collect data, and was synchronized via an Ethernet cable with the display PC.

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Stimuli

During the eye-tracking task, an animated dolphin measuring .96 x 1.43 degrees of visual angle was used for calibration, as well as for drift correction and fixation 'cross' prior to each trial. The 38 static color photographs of male and female adult human faces were taken from the MacBrain Face Stimulus Set (Tottenham et al., 2009). During each trial, two faces were presented side by side. On the majority of trials, both faces displayed a neutral facial expression. For the remainder of trials, one of the two faces displayed a happy or disgusted expression. The faces displayed a straight-ahead gaze and an open mouth. Only the face, hair, and neck were visible. Faces subtended an average of 14.30 X 18.59 degrees of visual angle were displayed on a white background. They were positioned side by side, separated by a gap of 7.179 degrees of visual angle.

Measures

The following questionnaires were completed by the participant's primary caregiver.

Demographic questionnaire. The demographic questionnaire provides the following information about the participants: gender, date of birth, verbal ability (more than 30 signs/words), mobility (able to walk unaided), and information about the participant's diagnosis including the specific diagnosis given, who gave the diagnosis, and when.

Social Communication Questionnaire (Rutter et al., 2003). The SCQ is a 40-item informant questionnaire designed to assess behaviors associated with ASD such as social functioning and communication skills. All items on the SCQ yield a yes or no response. There are three subscales: Repetitive Behavior, Communication, and Social Interaction. The total score, which ranges from 0 to 40, indicates whether individuals score in the range suggested by Rutter et al. (2003) to indicate autism spectrum disorders or autism. Internal consistence and concurrent validity with the Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore & Risi, 2002) are good (Howlin & Karpf, 2004).

Vineland Adaptive Behavior Scale – Second Edition, Survey Interview Form (Sparrow et al., 2005). This semi-structured interview is administered to parents using open-ended questions which are designed to assess adaptive behavior which they consider is usually performed by the person they care for. Communication Skills, Daily Living Skills, and Socialization Skills make up the three subscales. There are two optional subscales, Motor Skills and Maladaptive Behavior, which were not administered for the present study as the Motor Skills domain is not appropriate for the age of our sample and the Maladaptive Behavior domain was not deemed necessary for the present study. The interview yields an Adaptive Behavior Composite (ABC) from the three domains. Standard scores, which are based on a sample of 3,000 children, can be calculated for each domain and the ABC. Content, criterion, and construct validity are all robust. Inter-rater and test-retest reliability are also robust. Due to the differences in CA between the ASD and FXS group, the VABS sum of domain raw score is used for developmental matching in the present study, because this is the measure's most direct indication of raw performance and abilities. The VABS sum of domain raw score served as a measure of adaptive behavior abilities, whereas the raw score for the communication subscale served as a measure of verbal abilities.

Procedure

Instruments. Participants completed the eye-tracking task, and parents of participants with FXS and ASD completed the SCQ (Rutter et al., 2003), and the VABS (Sparrow et al., 2005). The eye-tracking task was completed first. Parents completed the SCQ either while their child performed the eye-tracking task, or at home and returned it to the researchers. The VABS was either administered over the telephone following the testing session or face to face following the eye-tracking task. Participants in the ASD group returned for a follow-up session during which the ADOS (Lord et al., 2002) was administered. TD participants were only tested on the eye-tracking task.

Eye-tracking task. All participants were instructed to remain still during testing. Prior to each task block, the eye-tracker was calibrated using a 5-point calibration. During calibration, each participant followed the location of an animated blue dolphin positioned at the edges of the display area. The calibration procedure was repeated until successful. All participants achieved a full 5-point calibration. Between each trial the dolphin reappeared at the center of the screen to act as a point of fixation. Every five trials, the individually presented dolphin served as a 1-point drift correct to adjust calibration of the eye-tracker. If necessary, recalibration was undertaken.

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Participants were presented with 80 trials, during which two faces were presented simultaneously for 1,500 ms. The inter trial interval was displayed for 1,000 ms, except for trials when a drift correct was performed. Participants were instructed to look wherever they wished while the faces were presented on the screen, but to look at the dolphin that appeared between trials. Participants completed one of two experimental blocks, each with trials in a different pseudo-random trial presentation order. As a result of randomization, in one experimental block, 10 of 80 trials were "emotion trials" in which one emotionally expressive face was presented alongside one neutrally expressive face; in the other experimental block, 11 of 80 trials were emotion trials. The experimental block assigned to participants was counterbalanced within and across participant groups. The remaining trials were "standard" trials, in which two neutrally expressive faces were presented in order to habituate participants to the category of neutral facial expressions. During emotion trials, the emotionally expressive face displayed either happiness or disgust and was equally likely to appear on the left or right side of the screen. Happy faces were presented during approximately half of the emotion trials in both experimental blocks. Disgust was presented during the remainder of the emotion trials. The beginning of the testing block commenced with at least seven "standard" trials prior to the presentation of any emotion trials. Throughout the remainder of the experiment, emotion trials were separated by a minimum of four "standard" trials. The eye-tracking task lasted for a total of approximately 10 minutes.

Results

Fixations were assessed as occurring when eye movement did not exceed a velocity threshold of 30°/sec, an acceleration threshold of 8,000°/sec^2, or a motion threshold of .1°, and the pupil was not missing for three or more samples in a sequence. A fixation was assigned to a particular area of the face when the fixation coordinates were within a rectangular area (termed the "interest area" or IA) assigned to the area in question. Face IAs had been positioned automatically to cover the entire face presented on the left and right side of the screen, while bespoke predetermined left eye, right eye, and mouth IAs for each individual face were identified manually (see Figure 1). Trials were deemed "invalid" if the participant did not look at either face for the duration of the trial. Furthermore, if any condition consisted of more than 40% invalid trials, the participant's data were excluded from analyses.

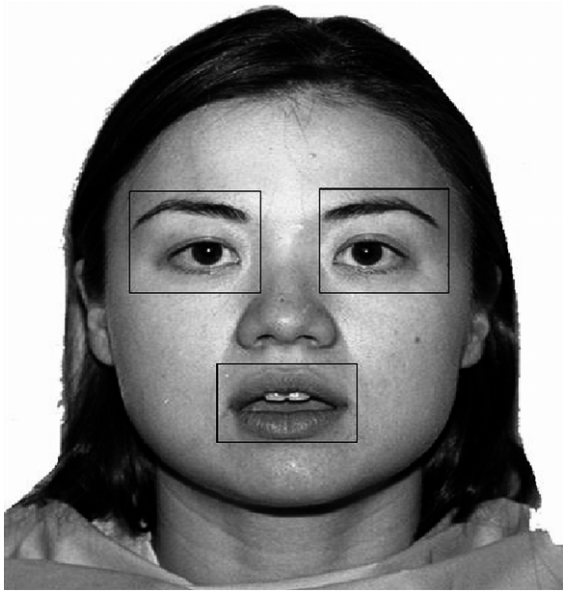

Figure 1. Example of left and right eyes and mouth interest areas (IAs). Fixation coordinates within the rectangular areas were assigned to eyes and mouth IAs, respectively.

Spontaneous emotion discrimination data are presented as proportion of trial spent looking, in seconds, at faces posed in happy, disgust, and neutral facial expressions. Eyes and mouth looking data were only analyzed during standard trials, on which both faces presented neutral expressions. These data are presented as a ratio of time spent looking at the sum of the left and right eyes, and the mouth region of neutral faces to the mean amount of time spent looking at neutral faces. The time taken to fixate to the eye and mouth regions of neutral faces is presented in milliseconds. All data were subjected to the Shapiro-Wilk test for normality. Where results from non-parametric tests, used when data were not normally distributed, did not differ from results from the equivalent parametric tests, the results from the parametric tests are reported. Except where mentioned, the alpha level for significance was .05.

Spontaneous Emotion Discrimination

To ensure that participants did not demonstrate a left/right looking bias regardless of the expression displayed, the total proportion of trial time spent

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looking at each face (dwell time percentage) during the standard trials, where both faces displayed a neutral expression, was calculated. These data were subjected to paired samples t-tests, which revealed no significant difference between dwell time percentage on the faces presented on the left of the screen and those presented on the right of the screen in any participant groups (FXS: $t(12) = -.865$, $p = .404$; ASD: $t(14) = -1.574$, $p = .138$). As there was no left/right looking bias, the remaining analyses concern only the expression trials, where one face displayed either a happy or a disgusted expression while the other face displayed a neutral expression.

The proportion of the trial spent looking at faces displaying a happy expression was calculated for happy faces and neutral faces presented side-by-side with happy faces. This process was repeated for dwell time percentage on faces displaying a disgusted expression and for neutral faces presented alongside disgusted faces. Paired samples t-tests were conducted to investigate whether participants spent a significantly higher proportion of the trial looking at happy relative to neutral faces during happy-neutral trials and disgust relative to neutral faces during disgust-neutral trials. These t-tests revealed that both participants with FXS and participants with ASD spent a higher proportion of the trial looking at disgust compared to neutral faces (FXS: $t(12) = 6.202$, $p < .001$; ASD: $t(14) = 8.847$, $p < .001$), but not happy compared to neutral faces (FXS: $t(12) = 1.573$, $p = .142$; ASD: $t(14) = 1.059$, $p = .307$). These analyses revealed the same results for TD participants (disgust vs. neutral: TD adult: $t(11) = 5.775$, $p < .001$; TD child: $t(15) = 4.059$, $p = .001$; happy vs. neutral: TD adult: $t(11) = 2.027$, $p = .068$; TD child: $t(15) = -1.599$, $p = .131$).

A looking preference for happy faces was calculated by subtracting the proportion of the trial spent looking at neutral faces during happy-neutral trials from the proportion of the trial spent looking at happy faces. This was repeated to calculate the disgust preference. Happy and disgust preferences were compared between participants with ASD and participants with FXS using independent samples t-tests. These tests indicated no between-groups difference of happy preference ($t(26) = -.413$, $p = .683$), or disgust preference ($t(26) = -.533$, $p = .598$). Figure 2 depicts the proportion of extra time spent looking at happy and disgust faces compared to neutral faces during oddball trials. In summary, participants with FXS and participants with ASD spent a higher proportion of time looking at disgust

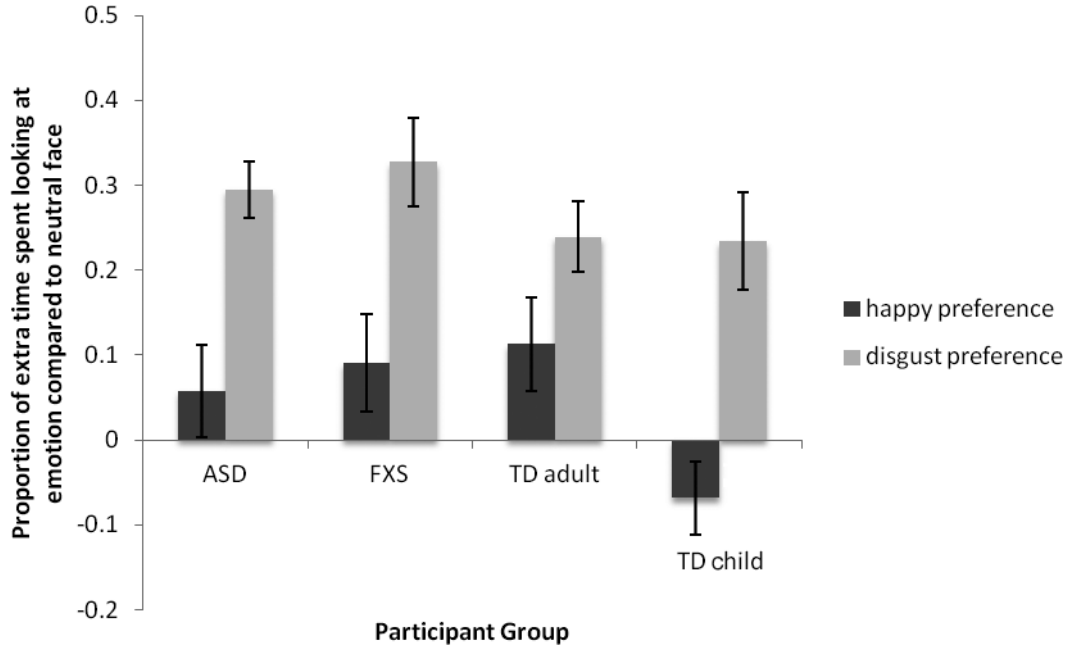

Figure 2. Proportion of extra time each group spent looking at happy versus neutral faces and disgust versus neutral faces during happy-neutral trials and disgust-neutral trials, respectively. Error bars represent standard error of the mean.

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versus neutral faces but not happy versus neutral faces. Due to participant differences in CA, an analysis of covariance (ANCOVA), with CA as the covariate, revealed that happy preference and disgust preference remained nonsignificant between groups (happy preference: $F(1, 25) = .766$, $p = .390$; disgust preference: $F(1, 25) = .056$, $p = .815$), indicating no effect of CA on happy or disgust preference.

Eyes/Mouth Looking Time

The duration of all fixations made within the left and right eye IAs, and the mouth IA, of both neutral faces during standard (neutral face pairs) trials were summed to reflect the amount of time in milliseconds that was spent looking at each eye and the mouth. In order to account for different looking time on faces, the average time each participant spent looking at the eyes and mouth of the neutral faces presented during standard trials was divided by the average amount of time that participant spent looking at both neutral faces. Therefore, the amount of time spent looking at the eyes and mouth is presented as a ratio to the amount of time spent looking at neutral faces overall. Emotional face (i.e., oddball) trials were not included in these analyses due to the low percentages of trials that they represented, as well as the fact that participant looking time was split between neutral and emotional faces on these trials.

To ensure that participants did not demonstrate a left or right eye looking bias, paired samples *t*-tests were conducted to compare looking time to the left and right eyes relative to the amount of time spent looking at the face These tests revealed no significant differences in ratio of looking time to left or right eyes in any participant group (ASD: $t(14) = -1.042$, $p = .315$; FXS: $t(12) = .094$, $p = .927$). Therefore, the ratio of time spent looking to the left and right eye, relative to the amount of time spent looking at faces, was summed for further analyses in order to investigate overall looking patterns to the eyes. Figure 3 depicts the ratio of time each group spent looking at the eye region of faces relative to time spent looking at faces.

In order to compare the ratio of time looking to the eye region of the faces between the participant groups, an independent samples t-test was conducted. The analysis revealed a significant between-groups difference in the ratio of time

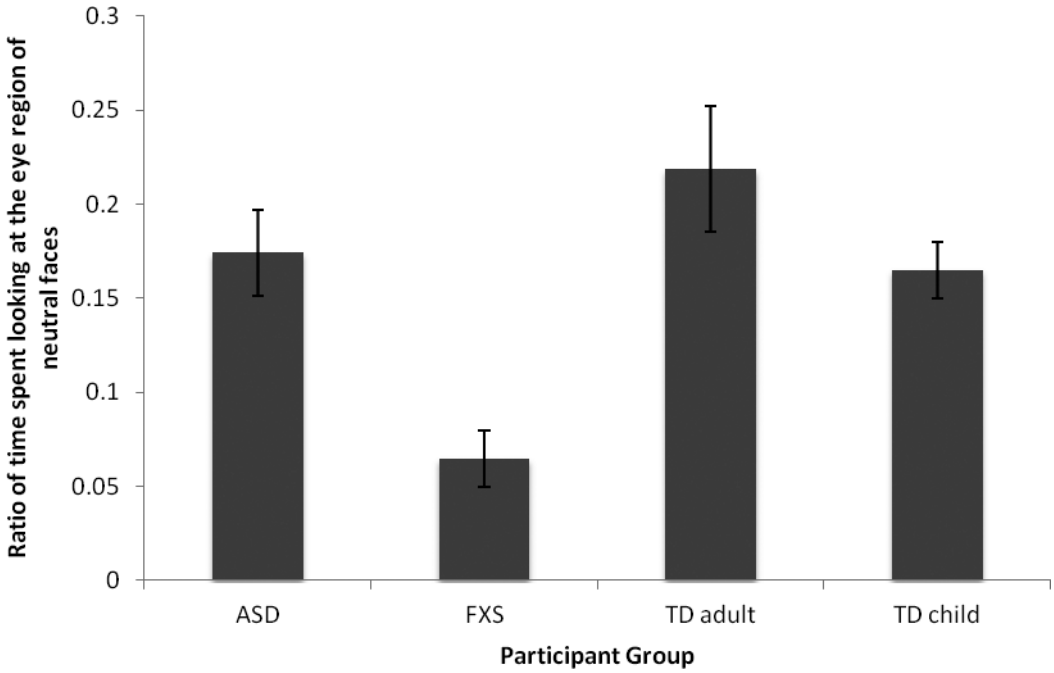

Figure 3. The ratio of time each group spent looking at the eye region (sum of left and right eye interest areas, IAs) of neutral faces relative to the amount of time spent looking at neutral faces. Error bars represent standard error of the mean. *Note*. FXS = fragile X syndrome; ASD = autism spectrum disorder; TD = typically developing individuals.

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spent looking at the eyes relative to the time spent looking at faces ($t(26) = 3.884$, $p = .001$). Mean figures (ASD mean: .174, SD: .088; FXS mean: .065, SD: .054) indicated that this significant difference was due to participants with FXS looking significantly less at the eyes than participants with ASD.

An ANCOVA, with CA as a covariate, remained significant ($F(1,25) = 16.480$, $p < .001$) indicating no effect of CA on the ratio of time spent looking at the eye region of faces. Furthermore, correlations between VABS raw score, VABS communication raw score, and SCQ total score, and ratio of time spent looking at the eye region in the FXS and ASD groups were not significant (sum of domains raw score: $r_p = -.290$, $p = .134$; communication raw score: $r_p = -.206$, $p = .293$; SCQ total score: $r_p = .123$, $p = .549$), further indicating that the observed effect was not related to global adaptive behavior ability, verbal ability or autism symptomatology in the two participant groups.

In order to compare the ratio of looking time to the mouth region of the faces relative to the rest of the face, an independent samples *t*-test was conducted. The analysis revealed no significant between-groups difference in the ratio of time spent looking at the mouth ($t(26) = -.690$, $p = .496$). Figure 4 depicts the ratio of time each group spent looking at the mouth relative to the rest of the face. Figure 5 presents looking time heat maps for each participant group.

To compare the time taken to fixate to the eye and mouth region in participants with FXS and participants with ASD, independent-samples t-tests were conducted. These revealed no difference between those with FXS and those with ASD in the time taken, in milliseconds, to fixate to the eye region of neutrally expressive faces ($t(26) = -1.207$, $p = .238$), or the mouth region of neutrally expressive faces ($t(26) = 1.226$, $p = .231$). An ANCOVA with CA as the covariate remained nonsignificant ($F(1, 25) = .422$, $p = .522$). Furthermore, correlations between VABS raw score, VABS communication raw score, SCQ total score, and the time taken to fixate to the eye region in the FXS and ASD groups were not significant (VABS raw score: $r_p = .091$, $p = .647$; VABS communication raw score: $r_p = -.025$, $p = .900$; SCQ total score: $r_p = .325$, $p = .106$).

To investigate whether gender effects influenced the results, all statistical analyses conducted in this study were reconducted excluding the one female with FXS and three females with

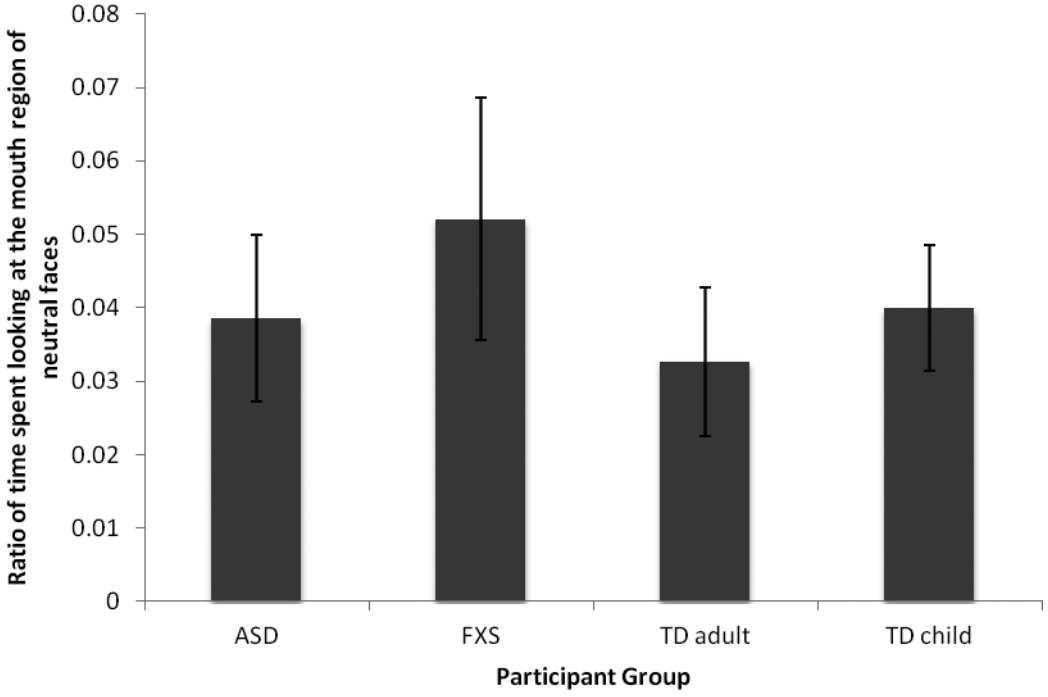

Figure 4. The ratio of time each group spent looking at the mouth region relative to the rest of the face during neutral face ("standard") trials. Error bars represent standard error of the mean. *Note.* FXS = fragile X syndrome; ASD = autism spectrum disorder; TD = typically developing individuals.

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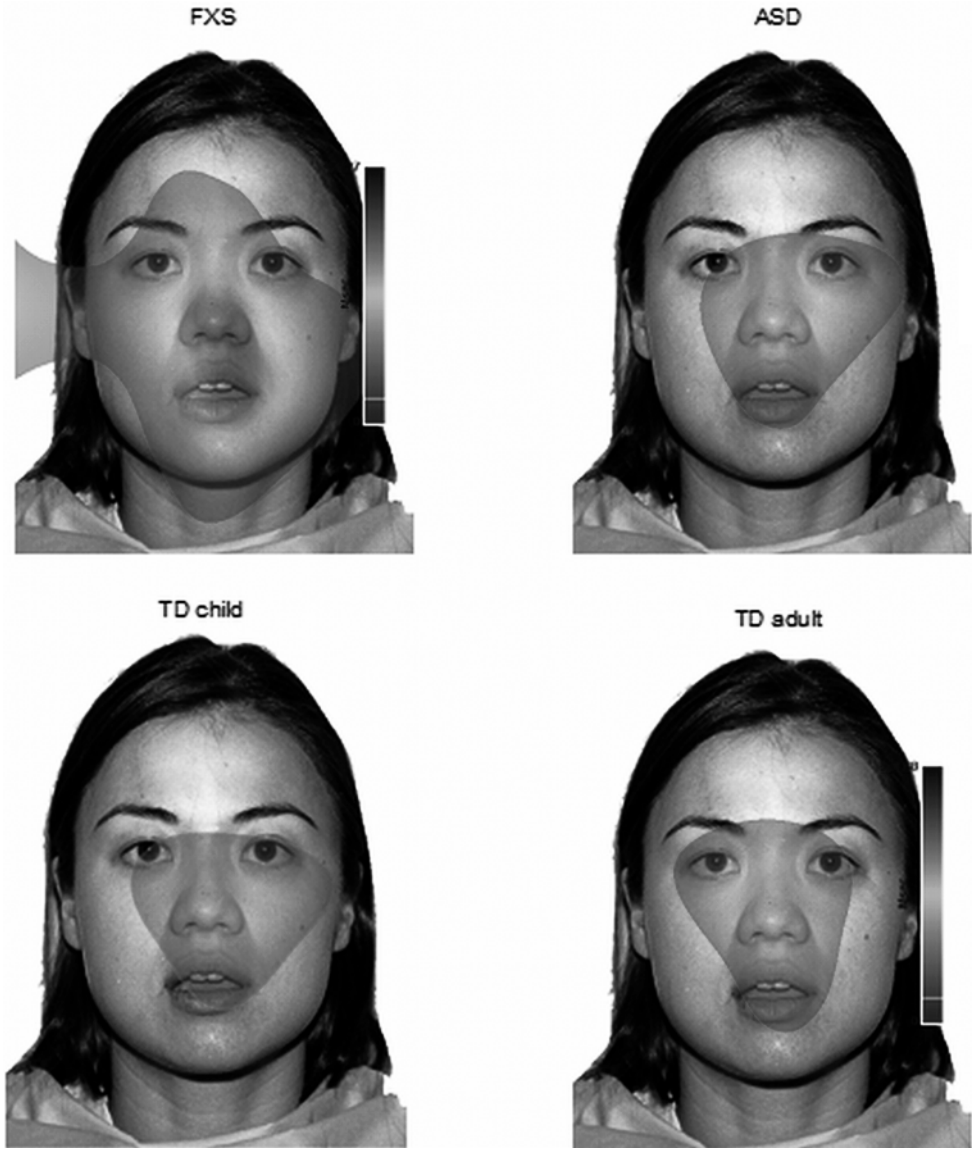

Figure 5. The heat maps showing the group average distribution of looking time in fragile X syndrome (FXS, top left), autism spectrum disorder (ASD, top right), typically developing child (TD child, bottom left) and typically developing adult (TD adult, bottom right).

ASD. All statistical results remained consistent with the findings reported above for these analyses including only the 12 male participants with FXS and 12 male participants with ASD.

Discussion

In the present study, we examined and compared the spontaneous discrimination of basic facial expressions of negative and positive emotion, as well as looking patterns to the eyes and mouth, in individuals with FXS versus individuals with ASD. Specifically, we examined and compared neutral and disgusted expression discrimination, as well as neutral and happy expression discrimination, in these individuals, along with time spent looking at the eye and mouth regions of neutral faces, relative to the rest of the face. The results demonstrated that implicit emotion discrimination did not differ between individuals with FXS and individuals with ASD. However, individuals with FXS exhibited consistently decreased looking to the eye region in relation to the rest of the face compared to the individuals with ASD. On the

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other hand, these two groups did not differ in the amount of time taken to fixate to the eye or mouth regions of faces. Together, these findings suggest that participants with FXS allocate the same degree of attentional priority for looking at the eye region as those with ASD, but the fact that participants with FXS looked less at the eye region overall suggests that they remove their fixation point from this region to a greater extent than those with ASD following this initial fixation.

Spontaneous discrimination of basic negative and positive facial emotions was assessed using a novel oddball paradigm in conjunction with a preferential looking measure. Specifically, participants were presented with pairs of neutral faces (standard trials), with neutral-disgust (negative) and neutral-happy (positive) pairs (oddball trials) presented infrequently. Participants in all groups looked significantly longer at faces posed in disgusted expressions compared with neutral faces during the target trials, whereas no participant group looked longer at the faces posed in happy expressions compared to neutral faces. Critically, no statistically significant group differences were found in terms of relative looking time to emotional faces in this study, which suggests that individuals with FXS perform similarly to individuals with ASD with regard to spontaneous discrimination of these two basic facial emotions.

As described previously, participants in both the FXS and ASD groups exhibited strong and significant preferential looking to disgust relative to neutral expressions, but no preference for looking to happy relative to neutral expressions. Furthermore, the TD children and adults exhibited the same pattern of emotion discrimination when examined using the same exact methods and procedures. We propose two potential explanations for these results. The first interpretation concerns the advantage that disgusted faces may have over happy faces with regard to capturing attention. Novel stimuli have been found to generate stronger neural signals in the visual cortex relative to familiar stimuli, therefore giving novel stimuli an *attentional* advantage (see Desimone & Duncan, 1995 for a review). Because disgusted faces are not as commonly seen in everyday life, as are happy faces, the novelty of the disgusted faces may have captured the attention of all participants to a greater extent than the happy faces. An alternative, yet complementary, interpretation of these results concerns the negativity bias, which is a phenomenon whereby individuals attend more to negative information than to positive information due to the increased *informational* value of negative information (Peeters & Czapinski, 1990). The negativity bias has been observed in a number of areas of psychological functioning. For example, toward the end of the first year of life, infants demonstrate a negativity bias, looking longer at fearful faces relative to happy faces (Ludemann & Nelson, 1988). Furthermore, individuals have been observed to differentially weight negative and positive information during impression formation, with negative information being more influential (Fiske & Taylor, 1991). Finally, it has been suggested that humans have evolved mechanisms to quickly detect threatening stimuli, and cues to environmental threats that increases their likelihood of survival (Öhman & Mineka, 2001). Therefore, disgusted expressions may be perceived as a cue to threat, thus capturing an individual's attention. Interestingly, children with and without ASD have both previously been found to exhibit a negativity bias in emotional face processing, demonstrated in faster reaction times to detect an angry face than a happy face in a visual search paradigm (Rosset et al., 2011). Although the present research concerns faces displaying a disgusted expression rather than an angry expression, similarities can be drawn regarding the negativity, novelty, and physical features between disgusted and angry faces.

Spontaneous looking patterns were assessed by examining and comparing the proportion of time participants with FXS and participants with ASD spent looking at the eye and mouth regions relative to the rest of the face during the standard trials (neutral face pairs). The results of this analysis indicate that participants with FXS looked significantly less at the eye region of the faces relative to the rest of the face in comparison to participants with ASD. Follow-up analyses further indicate that these findings were not driven by differences in chronological age, adaptive behavior, or verbal abilities of the participants. These findings provide further, direct evidence to support a growing body of literature that consistently suggests that reduced eye looking in individuals with FXS is not a product of autistic symptomatology (Dalton et al., 2008; Farzin et al., 2009; Farzin et al., 2011; Holsen et al., 2008). Overall, the current results provide compelling support for the hypothesis that there are subtle but important differences in the mechanisms that

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underlie impaired social functioning in those with idiopathic ASD and those with FXS (Bailey Jr. et al., 1998; Demark et al., 2003; Moss et al., 2013).

Previous studies have indicated increased looking time to the nose region in FXS (Farzin et al., 2009). Although this finding is interesting, looking time to the nose region was not investigated in the present study due to a focus on differences in looking to the eye region, which is associated with social communication, between those with FXS and those with ASD, two groups described as having similar social communication deficits. Furthermore, pupillary reactivity to emotional faces has been investigated in previous studies with interesting results (Farzin et al., 2009). Pupil dilation data were not analyzed in the present study due to the nature of the stimuli presented and associated participant looking behavior. Specifically, because the participants were allowed to view the face stimuli freely, the eye that was being tracked in participants was moving almost continuously throughout the experiment, and it is desirable for the tracked eye to remain still in order for pupil dilation data analysis to be performed due to the effects of luminance changes on pupil dilation during movement of gaze across the stimuli.

Whether or not individuals with ASD exhibited "typical" eye looking is beyond the scope of this study. However, the majority of previous literature suggests that those with ASD exhibit normal looking time to the eye region of faces that are presented in static photographs (Kirchner et al., 2011; Speer, Cook, McMahon, & Clark, 2007). Alternatively, previous studies that have convincingly reported decreased looking to the eyes in ASD have used moving/dynamic stimuli. For example, Klin and colleagues found that individuals with ASD looked at the eye region two times less than typical controls when the stimuli consist of dynamic videos of naturalistic social situations (Klin, Jones, Schultz, Volkmar, & Cohen, 2002). One possible explanation for the distinction in eye looking between dynamic and static eye looking is that participants with ASD look more towards the mouth when it is moving (see also Klin, Lin, Gorrindo, Ramsay, & Jones, 2009; McCleery, Allman, Carver, & Dobkins, 2007). Expanding on this, reports of a patient with amygdala damage and consequent impairments in spontaneously fixating to the eye region of both static and dynamic faces highlight the role of the amygdala in guiding fixations to the eye region. Whilst increased looking to the mouth was associated with dynamic stimuli, increased looking to the center of the face was associated with static stimuli (see Kennedy & Adolphs, 2010, for a review). This, as well as reports of amygdala dysfunction in individuals with the FXS premutation (Hessl et al., 2007), highlights the importance of studying social perception using static facial stimuli as well as dynamic stimuli.

There are some limitations to the present study, which are primarily related to differences in the participant samples. First, though obtaining ASD diagnostics for participants with FXS using the ADOS would be interesting, the results of the present study, in particular those indicating that participants with FXS look less at the eye than participants with ASD, are unlikely to be driven by ASD symptomatology in FXS. This is due to the lack of relationship between SCQ score and eye looking in the FXS sample, and due to participants with idiopathic ASD in the current study exhibiting increased looking to the eye region compared to participants with FXS. Future research should investigate the relationship between eye looking and autism symptomatology in individuals with FXS with and without an additional diagnosis of autism. Second, whereas there is a significant difference in CA between the groups in the current study, we were able to account for these differences in our statistical analyses, the results of which strongly suggested that the observed effects were not driven by these differences. Finally, although IQ measures were not administered for the present study, the VABS raw sum of domain score and communication raw score provide standard and reliable measures of adaptive behavior abilities and verbal abilities, respectively, that are comparable across the ASD and FXS groups.

There are also a number of strengths to the current study, including the direct comparisons between individuals with FXS and those with ASD. Furthermore, the FXS participant group in the current study primarily consisted of males, whereas the majority of previous studies on this topic with this population included a much higher proportion of females. In addition, the data from the current study were reanalyzed using male participants only and the findings remained the same. As noted earlier, it is important to qualify the results from previous studies regarding less eye-looking in FXS using a predominantly male sample, which the current study has achieved.

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In conclusion, participants with FXS and participants with ASD exhibited similar implicit discrimination of basic facial expressions of emotion, and mirrored the patterns of results from TD children and adults who were studied using the same paradigm and procedures. Specifically, participants in all groups spontaneously exhibited increased looking to disgusted faces relative to neutral faces, but not to happy faces relative to neutral faces, after being habituated to neutral faces. The finding that all groups exhibited increased looking time to disgust but not happy expressions suggests an ability for all groups to spontaneously identify and attend to a negative facial expression, perhaps due to the increased attentional or informational value of negative over neutral (and positive) expressions. However, participants with FXS spent relatively less time looking at the eye region of faces posed in neutral expressions relative to the rest of the face than did individuals with ASD. The current results, therefore, provide evidence that even though there are a number of clear similarities between FXS and ASD at the behavioral level, the mechanisms underlying these behaviors may differ. Cornish and colleagues (Cornish et al., 2007; Cornish et al., 2008) previously highlighted this suggestion, and proposed that social anxiety causes the atypical eye gaze in FXS whereas social indifference causes the same behavior in ASD. Our results are consistent with this hypothesis, and suggest particular similarities and differences in face processing mechanisms in FXS and ASD. Overall, the current findings indicate that divergent pathways likely subserve the similarities in behavioral functioning in FXS and ASD, and that the profile of ASD in FXS differs in subtle but potentially very important ways from that of idiopathic ASD.

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