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Visual attention patterns during a gaze following task in neurogenetic syndromes associated with unique profiles of autistic traits: Fragile X and Cornelia de Lange syndromes

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ABSTRACT

Background: Gaze following difficulties are considered an early marker of autism, thought likely to cumulatively impact the development of social cognition, language and social skills. Subtle differences in gaze following abilities may contribute to the diverse range social and communicative autistic characteristics observed across people with genetic syndromes, such as Cornelia de Lange (CdLS) and fragile X (FXS) syndromes.

Aims: To compare profiles of 1) visual attention to the eye region at critical points of the attention direction process, 2) whether children follow the gaze cue to the object, and 3) participant looking time to the target object following the gaze cue between groups and conditions.

Materials and methods: Children with CdLS ($N = 11$) and FXS ($N = 8$) and autistic ($N = 22$) and neurotypical ($N = 15$) children took part in a passive viewing paradigm adapted from Senju and Csibra (2008), in which videos of a central cue (ball/cartoon face/human face) directed attention towards one of two objects. Visual attention patterns were recorded via eye tracking technology.

Results: Neurotypical children were used as a reference group against which the autistic, CdLS and FXS groups were compared. Although autistic children looked at the eye region for significantly less time, they looked at the target object as frequently and for a similar duration as neurotypical children. Children with FXS looked at the target as frequently as neurotypical children but looked at it for comparatively less time. Both neurotypical children and children with CdLS frequently looked at the eye region, but children with CdLS were less likely to look at the target than neurotypical children.

Conclusions: Findings provide preliminary evidence of unique patterns of visual attention and gaze following strategies in children with CdLS, children with FXS and autistic

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children. These unique gaze following patterns may underpin the distinct profiles of social and communication autistic traits observed between these groups.

1.   Introduction

Visual attention patterns influence what and how individuals learn from the world around them, with far-reaching consequences across social development. A key early attentional mechanism that develops over the first year of life is the ability to follow an agent's shift in directed attention, or 'gaze following' (Brooks & Meltzoff, 2005). Gaze following is a precursor for a range of social and communication skills in neurotypical children, due to its role in referential learning (Gliga, Elsabbagh, Hudry, Charman, & Johnson, 2012). A reduction in gaze following is considered an early marker of autism (Bedford et al., 2012; Camero, Martínez, & Gallego, 2021), thought likely to cumulatively impact the development of social cognition, language (Gliga et al., 2012) and social skills such as gestures (Brooks & Meltzoff, 2005). It is therefore considered to be a critical mechanism that contributes to the social and communicative differences observed in autistic people.

Subtle differences in gaze following abilities may contribute to the diverse range of social and communicative autistic characteristics observed across people with genetic syndromes. Many genetic syndromes, such as Cornelia de Lange (CdLS) and fragile X syndrome (FXS), have a greater likelihood of reaching clinical cut-off scores on measures of autistic characteristics compared to the general population (Richards, Jones, Groves, Moss, & Oliver, 2015), yet these groups evidence distinct and diverse profiles of autistic characteristics that differ, in subtle ways, from those of autistic people who do not have a genetic syndrome (Bozhilova et al., 2023). People with FXS show broadly typical profiles of autistic traits but these characteristics are less pronounced compared to autistic people without a genetic syndrome (Rajaratnam et al., 2020). In addition, people with FXS show unique advantages in social smiling compared to autistic people without a genetic syndrome (McDuffie, Thurman, Hagerman, & Abbeduto, 2015; Wolff et al., 2012). In contrast, people with CdLS are characterised by high levels of autistic communication characteristics (Moss, Oliver, Nelson, Richards, & Hall, 2013), defined by reduced speech and selective mutism (Nelson, Crawford, Reid, Moss, & Oliver, 2017), but greater use of gestures compared to autistic people and people with Down syndrome (Moss, Howlin, Magiati & Oliver, 2012; Pearson et al., 2021).

People with these syndromes also show contrasting and atypical visual attention profiles. Children with CdLS and FXS are less likely to respond to other's gaze cues (Ellis, Moss, Stefanidou, Oliver, & Apperly, 2021) which may result from over- or under-attending towards another person's eyes respectively. People with FXS characteristically show extreme gaze avoidance (Wall, Shic, Varanasi & Roberts., 2022; Wolff, Gardner, Paccia, & Lappen, 1989). In contrast, those with CdLS show prolonged eye contact relative to people with FXS and Rubinstein-Taybi syndrome (Ellis, Oliver, Stefanidou, Apperly, & Moss, 2020). Over-attending to the eye region

may be linked to difficulties in shifting visual attention from the eye region to a referential object, i.e., following another's gaze. For example, people with William syndrome who over-attend towards the eyes and face are less likely to follow gaze cues towards an object compared to neurotypical participants (Riby, Hancock, Jones, & Hanley, 2013).

Such under- or over-attending to the eye region suggests there may be differences in processing the eye region as a critical 'cue' between individuals with CdLS and FXS. Gaze following consists of three key stages: 1) looking at the social partner's 'cue' (i.e., eyes), 2) following the directional cue when the person orients towards an object of interest, and 3) attending to the cued object (Bedford et al., 2012). The eye region is key during this process as social partners use their eyes to indicate communicative intent and direct attention towards the object (Senju & Csibra, 2008). As neurotypical infants develop, they increasingly look towards others' eye regions to gain information about the cue and, from ten months old, turn more often towards a target that an adult is turning towards when the adult's eyes are open compared to when they are closed. These findings indicate that understanding of other people's perceptual states is a very early developing skill (Brooks & Meltzoff, 2005).

However, under- and over-attending to the eye region (as observed in CdLS and FXS) may indicate divergence from this developmental trajectory that results in specific difficulties in detecting or interpreting gaze cues respectively. Under-attending to the eye region may create a *detection* issue, as it provides fewer opportunities to notice and interpret another person's communicative cue. In comparison, over-attending to the face but not shifting gaze, may indicate a difficulty with *interpreting* that the cue signals a partner's communicative intention (Babinet, Cublier, Demily, & Michael, 2022). These subtle differences in visual attention may differentially influence children's social-communication abilities and therefore underpin the differences in these abilities that emerge between these groups.

However, whilst using information from the eye region is a key strategy for neurotypical children (Senju & Csibra, 2008), successful gaze following may also result from alternative strategies, such as interpreting other perceptual information (e.g., detection of head motion) independently from social information (e.g., direct gaze or social attention) (Astor et al., 2020; Böckler, van der Well & Welsh, 2014). Comparing gaze following performance between situations which do or do not include social information (i.e., eyes) may help determine the degree to which the eye region is used and/or is critical for gaze following success in individuals with CdLS and FXS.

Whilst responding to social communicative cues, such as the eyes, is a key stage of gaze following (Senju & Csibra, 2008), difficulties interpreting these cues may also emerge during two other key stages of gaze following (i.e., following the directional cue and attending to the object). Previous work on

gaze following abilities in autistic children indicates mixed findings surrounding whether autistic children and their infant siblings do (e.g., Bedford et al., 2012) or do not (e.g., Congiu, Fadda, Doneddu, & Striano, 2016) follow the initial cue to the object relative to neurotypical children. However, converging findings indicate that autistic children (Congiu et al., 2016; Thorup, Kleberg & Falck-Ytter, 2016) and their infant siblings (Bedford et al., 2012) attend to a cued object for less time than neurotypical participants. This reduced length of duration has been shown to predict later likelihood of an infant receiving an autism diagnosis and later developing social and communicative difficulties in infant siblings of autistic children (Bedford et al., 2012). We may assume then, that autistic children who orient towards the target are showing a more automatic behaviour (Shepherd & Cappuccio, 2011), rather than interpreting the communicative intentional relevance of the cue, signalling that the target object warrants sustained attention (Behne, Carpenter, & Tomasello, 2005). It is therefore important to look at visual attention patterns across all stages of the gaze following process and consider how these may contribute to the diverse profiles of social and communication characteristics observed across autistic people, and people with other neurodevelopmental conditions associated with autism including people with FXS and those with CdLS.

Gaze following may be influenced by other central social attention processes, such as visual preferences towards social or non-social stimuli. Whereas autistic people without a genetic syndrome show generally lower levels of social attention (Hong et al., 2019), those with FXS and CdLS show unique profiles of social attention and avoidance that are dependent on context. People with CdLS and FXS show a similar looking time towards social compared to non-social scenes, but those with CdLS take longer than those with FXS only to look at social scenes in which a person moves towards them, as opposed to moving past them (Crawford et al., 2016). Adolescents and adults with FXS show reduced eye gaze when looking at emotional faces compared to neurotypical participants but show comparable levels of social preference as neurotypical participants, whereas autistic participants show less (Hong et al., 2019). These nuanced visual attention preferences may influence the strategies and the social and non-social processes each group may or may not use during gaze following. Investigating visual attention patterns between social stimuli (e.g., a person) compared to stimuli that vary in their 'social prominence' (e.g., a cartoon face and a 'non-social' object) may help identify whether there are subtle variations in profiles of social attention avoidance compared to one another and autistic people without a genetic syndrome. In addition, they provide further insight into whether challenges in gaze following are specific to social cues per se or reflect the consequences of broader attentional difficulties reported in these groups.

1.1.   Aims

To our knowledge, we will present the first cross-syndrome study to utilise eye tracking methods to characterise the detailed profiles of spontaneous gaze patterns in children with FXS and CdLS during a passive viewing gaze following task.

Gaze patterns of participants with FXS and CdLS, and comparison groups of autistic and neurotypical children were recorded during a passive viewing paradigm adapted from Senju and Csibra (2008), in which videos of a central cue (human face/cartoon face/ball) directed attention towards one of two objects. These genetically defined conditions offer an opportunity to understand mechanistic pathways from genes to behaviour across development that may contribute to the diversity of social and communication autistic characteristics observed in neurodevelopmental conditions associated with autistic characteristics. We will compare profiles of 1) visual attention to the eye region at critical points of the attention direction process, 2) whether children follow the gaze cue to the object, and 3) participant looking time to the target object following the gaze cue between groups and conditions.

We hypothesise that

1) Children with FXS and autistic children will spend less time looking to the eye region compared to neurotypical children, whereas children with CdLS will either spend the same amount or more time more looking at this region compared to neurotypical children.
2) Children with FXS and CdLS will be less likely to follow the gaze cue. We do not make any hypotheses for the autistic group due to the mixed literature.
3) Children with FXS and CdLS, and autistic children, will look at the cued target object for less time than neurotypical children.
4) Children with FXS and CdLS will show atypical visual attention patterns across conditions that vary in their 'socialness' relative to neurotypical and autistic children.

2.   Materials and methods

2.1.   Recruitment

Neurotypical children were recruited through local schools and word of mouth. Autistic children were recruited via local National Autistic Society branches, whereas children with CdLS or FXS were recruited from a participant research database held by the Cerebra Network for Neurodevelopmental Disorders and via syndrome support groups. A minimum age of four years was chosen for all groups as autism is rarely diagnosed before the age of three (van't Hof et al., 2020) and the ability to take part in the tasks was likely to be limited before the age of four. Neurotypical children were included if they were aged four to eight years and their parent reported they were reading at approximately the level of a 7-year-old or below (via book bands used widely in the UK). This ability level was chosen to ensure neurotypical children were comparable on level of ability with the syndrome groups, as it reflected the upper mental age of a group of individuals with CdLS and FXS from our previous studies with these populations (Ellis et al., 2020, 2021). Neurotypical children were excluded if they had a neurodevelopmental condition or a first-degree autistic relative. Autistic children were included if they were between four to ten years old, whereas children with CdLS and FXS were included if they were between four to seventeen years old. Other inclusion criteria required children to be mobile, to

be reported by parents to speak at least five words spontaneously and communicatively on a daily basis, and to have received a clinical diagnosis of ASD (autistic children) or a genetic syndrome (children with CdLS and FXS) by an appropriate professional (e.g., paediatrician, Psychiatrist, Clinical Geneticist). In addition, autistic children were included if they had a history of language delay and excluded if they had a genetic syndrome diagnosis. Only males with FXS were included due to reported sex differences in the behavioural phenotype associated with the condition (e.g., Martin, Bush, Klusek, Patel, & Losh, 2018).

2.2. Participants

Thirty-two neurotypical children, 22 autistic children, 8 children with FXS and 11 children with CdLS participated. Parents and legal guardians provided written and verbal informed consent on behalf of their child. Children who had capacity also gave written and/or verbal consent. The study was granted ethical approval by the University College London Research Ethics Committee (Project ID number: 12763/001) and at the Research Integrity and Governance Office at the University of Surrey (EGA ref: FHMS 19-20 013).

Our initial target sample size was 20 participants in each group, based on previous studies which report significant group effects with these sample sizes in genetic syndrome research (e.g., Crawford et al., 2020). However, due to the national COVID-19 lockdown occurring halfway through the project, we were unable to meet this target for children with CdLS and FXS. However, considering the rarity of the groups and evidence that small samples often have sufficient power to find key differences in rare syndromes (e.g., Guy, Ng-Cordell, Doherty, Duta, & Scerif, 2020), there is a sufficient rationale and data for preliminary investigation of gaze following profiles in these groups.

Prior to data analyses, we systematically excluded 17 neurotypical children so that all groups were comparable on BPVS raw score, and the neurotypical, autism and CdLS groups were comparable on sex. Neurotypical children with the highest BPVS raw scores were removed one-by-one, unless the removal of an individual led to significant differences ($p < .05$) in distribution of sex between the groups mentioned above, until there were no significant differences between groups and the effect size was small ($r < .30$). Table 1 reports the demographic information of the final sample. Importantly, the autistic [$t(35) = −.32$, $p = .753$, $r = .05$], FXS [$t(21) = .67$, $p = .513$, $r = .14$] and CdLS [$t(12.53) = 1.08$, $p = .300$,

$r = .29$] groups were all comparable to the neurotypical group on BPVS raw score. As many autistic children ($U = 71.50$, $p = .003$, $r = −.48$) and children with CdLS ($U = 40.00$, $p = .027$, $r = −.43$) and FXS ($U = 8.00$, $p < .001$, $r = −.70$) had a learning disability and thus showed delay in language ability relative to their chronological age, these groups were significantly older than the neurotypical group. We prioritized ensuring groups were comparable on a proxy of cognitive ability (BPVS raw score) over chronological age because cognitive ability, but not chronological age has been shown to be associated with early developing social cognitive abilities in autistic children, and children with CdLS and FXS (Ellis et al., 2020, 2021). This is supported by data in Supplementary materials table 1; BPVS raw score but not chronological age was associated with some gaze following outcomes predominantly in autistic children. Whilst autistic children ($X^2 = 3.56$, $p = .059$) and children with CdLS ($X^2 = .08$, $p = .781$) were comparable on distribution of sex with neurotypical children, children with FXS were not as we only included males with FXS ($X^2 = 7.89$, $p = .007$) (see recruitment section above). Importantly, the distribution of sex in autistic children corresponds to recent reports of sex ratios of autism diagnoses (Loomes, Hull, & Mandy, 2017). Whilst there were no between groups differences for mean SRS total T scores, the proportion of children with CdLS ($X^2 = 17.77$, $p < .001$) and FXS ($X^2 = 16.50$, $p < .001$) with a community autism diagnosis was significantly lower than that reported for autistic children. This profile reflects previous work that has demonstrated that whilst many individuals with CdLS and FXS show clinically significant levels of autism characteristics (Richards et al., 2015), identification of autism is significantly reduced and delayed in these populations in clinical practice (Reilly, Senior, & Murtagh, 2015).

2.3. Measures

The British Picture Vocabulary Scale, Third Edition (BPVS-3; Dunn, Dunn & Styles., 2009), suitable from 3 years to 16 years 11 months was used to assess participant's receptive vocabulary ability to provide a proxy of cognitive ability. Children were presented with test items consisting of four pictures and asked to indicate (by pointing or naming the corresponding number next to the picture) which picture illustrated the meaning of a word spoken by the examiner. The measure is suitable for individuals with intellectual disability as it is quick to administer and does not require the participant to read nor provide verbal responses. Raw BPVS scores were used as many participants had an intellectual disability and did not

Table 1 − Participant demographics.

	NT (N = 15)	AUT (N = 22)	FXS (N = 8)	CdLS (N = 11)	Group differences
Mean Chronological age in years (SD)[a]	5.44 (.81)	7.35 (2.44)	9.24 (2.62)	9.45 (2.74)	NT < AUT, FXS, CdLS
Mean BPVS raw score (SD)	81.67 (13.08)	84.27 (35.00)	76.88 (21.67)	70.73 (31.60)	
N female (%)	9 (60%)	6 (28.57%)	0 (0%)	6 (54.54%)	FXS < NT, AUT, CdLS
Mean SRS Total T scores	NA	91.21 (27.45)[a]	80.00 (8.16)[b]	76.75 (13.79)[a]	
N with community autism diagnoses (%)	0 (0%)	22 (100%)	3 (37.5%)[c]	4 (36.4%)	AUT < FXS < CdLS < NT

[a] Missing data from three participants.
[b] Missing data from one participant.
[c] Includes two children reported as having social communication disorder.

score high enough to be able to derive a standard score (only available for standard scores 70 and above).

Parents completed a range of questionnaires about their child, including a demographic questionnaire and the Social Responsiveness Scale, Second Edition (SRS-2; Constantino, 2012). The SRS-2 is a caregiver report that assesses social behaviours associated with autism. We used the school-age form, suitable for children aged between four to eighteen years. The SRS-2 provided an indication of the degree of autism characteristics shown by the autistic children, and the children with CdLS and FXS.

2.4.   Apparatus and stimuli

A remote screen-based Tobii Pro X3-120 (120 Hz sampling rate) eye tracker was used to record children's eye movement data. Stimuli were videos presented on a 15.6-inch Dell laptop Precision 5520 laptop using Tobii Studio software version 3.4.8 and connected to the eye tracker. Children took part in a five-point calibration prior to the main experiment. The experimental videos were approximately 5 min long in total. Animated parts of the stimuli were generated using Adobe Illustrator and videos were edited using Adobe Premiere Pro. Videos can be accessed using the following link: https://osf.io/sjnbh/

The passive viewing paradigm from Senju and Csibra (2008) was adapted, in which children watched videos of a central cue that turned towards one of two pairs of objects placed to the left and right of the cue (see Fig. 1). There were three conditions, which differed in the type of cue presented: a person condition, a cartoon condition and a ball condition (see Fig. 1). A cartoon condition was included as previous evidence indicates that autistic participants show greater approach and typical processing of cartoon relative to social stimuli (Silva, Da Fonseca, Esteves, & Deruelle, 2015). Each condition included eight trials (four looking left and four looking right to each of 4 object pairs), which were approximately ten seconds long. All children watched the trials in the same randomly selected order. The videos did not include sound.

During the person condition, the video began with a female model with a neutral facial expression looking down for two seconds in phase 1. The model then looked up at the camera for two seconds during a direct gaze phase 2, raised her eyebrows for one second during a communicative cue phase 3, and then turned towards one of the objects during the cue following phase 4. Eye contact and raised eyebrows indicated the model's communicative intent (Senju & Csibra, 2008). The cartoon condition consisted of an animated face, whereas the ball condition consisted of a ball of four colours, with a convergence point in the middle. Both the animated face and ball were designed to match the dimensions of the human agent's face. The point in the middle of the ball acted as a substitute for eye line and moved in the same way as the head in the social and animated conditions, with the exception that the ball 'bounced or 'moved up' at the point as the raised eyebrows in the social and animated conditions (Fig. 1).

2.5.   Procedure

Children were assessed either at the University or at their home over one or two research visits. Usually, children participated in the BPVS-3 first, followed by two five-minute eye-tracking tasks (including the data presented in the current study) and a short imitation task. Some autistic children, children with CdLS and FXS syndrome also took part in the Autism Diagnostic Observation Schedule Second Edition (ADOS-2; Lord et al., 2012). Due to the national COVID-19 lockdown occurring halfway through the project, we were not able to complete the ADOS-2 for a large proportion of participants. Therefore, these data are not presented in the current study. Parents completed questionnaires either during the research visit or in their own time before returning them to the research team via post.

2.6.   Data analysis

Fig. 2 shows the areas of interest (AOIs) defined for the target object, non-target object and eye region. Eye movement data (duration) was extracted from within all three AOIs during the first three seconds of the gaze following phase 4 and within the eye region during the communicative cue phase 3. Time to First Fixation data for the target object during the gaze following phase 4 was also extracted. Trials were excluded if participants didn't look at any of the three AOIs during the gaze following phase 4. A broader approach to including trials was used compared to previous studies (which only included trials where children looked at the eye region prior to following the cue) to account for the possibility that the current participants may use atypical strategies to look to the target object.

For each trial, we recorded whether participants' first fixation during the gaze following phase 4 was towards the target object (scored as 1) or not (scored as 0). These scores were averaged for each condition for each participant to derive a First Fixation Accuracy Score. In addition, we recorded whether participants looked at the target at any point during the gaze following phase 4 (scored as 1 if they did and 0 if they did not) and averaged these scores to generate a Look to Target Score for each participant. Respectively, these two metrics provide insight into 1) whether participants were immediately following the cue and 2) whether participants followed the cue, even if after a delay.

Direct eye gaze by an agent acts as a communicative-referential cue that elicits greater gaze following in neurotypical infants (Senju & Csibra, 2008). Therefore, we also investigated whether attention to the eye region improved cue following performance by calculating a First Fixation Accuracy Score and a Look to Target Score for each participant based only on trials in which participants also looked at the eye region during the gaze following phase 4. These two analysis approaches allowed us to achieve a balance in obtaining preliminary insight into the role of the eye region without stipulating stringent strategies for gaze following. When evaluating the use of the eye region, we again took a broader approach relative to other studies. Typically, studies have only included trials in which participants showed a specific neurotypical pattern of first looking at the eye region and then to the target object. However, this approach excludes individuals who may employ alternative strategies to achieve the same goal. We therefore took a more inclusive approach and included participants who looked at the eye region *at any point* during the gazing phase of the stimuli.
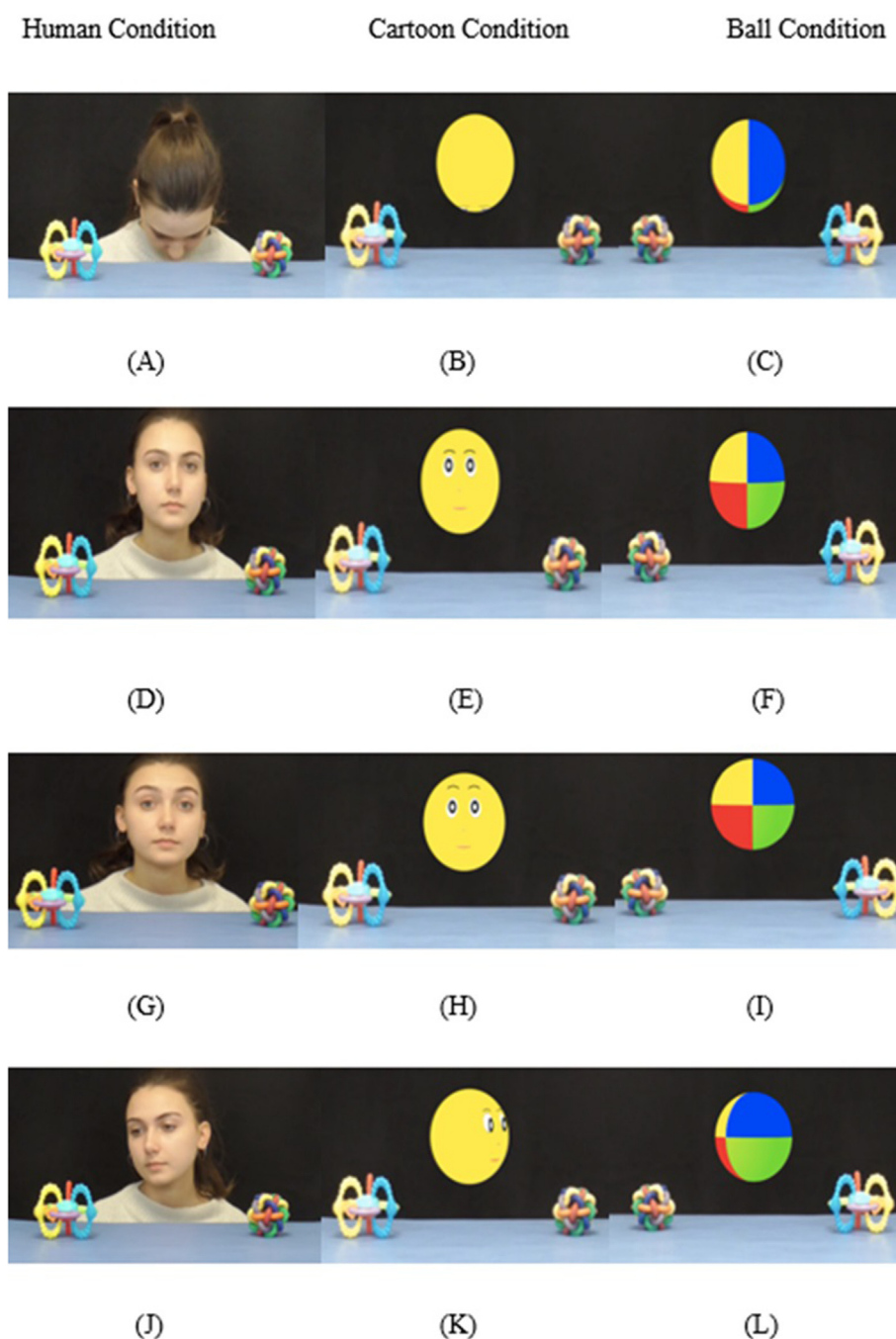
Fig. 1 – Stimuli timeline. Each video started with the central cue pointing down phase 1 (A–C), followed by a direct gaze phase 2 (D–F), followed by a communicative cue phase 3 (eyebrow raise) (G–I), and then a gaze following phase 4 (model/ animated face/ball looked/turned to one of the objects) (J–L).

Data were analysed using IBM SPSS statistics software. Due to the rarity of the syndrome groups and the disruption to data collection due to the Covid-19 pandemic, the CdLS and FXS group samples sizes are small. Whilst previous work indicates that these small samples often have sufficient power to find key differences in rare syndromes (e.g., Guy et al., 2020), comparisons across all four groups run the risk of masking meaningful differences between groups (a type II error). Our analysis strategy was therefore to use the neurotypical group as a reference group against which the autistic, CdLS and FXS groups could be compared using two-way mixed ANOVAs. This strategy balanced the ability to detect meaningful between group differences and patterns, whilst limiting the number of direct group comparisons (i.e., between the autistic, CdLS and FXS groups). However, to account for multiple tests, we interpreted only main effects and interactions with p values <.05 and large effect sizes ($n^2 \geq .14$) as statistically significant.

Fig. 2 — Visual display of AOIs at the end of the communicative cue phase 3 and the end of the gaze following phase 4.

Whilst a small proportion of data were non-normally distributed, we conducted two-way ANOVAs as the F statistic has been shown as robust to type 1 errors under a variety of conditions including non-normally distributed data, and small and uneven sample sizes (Blanca, Alarcón, Arnau, Bendayan, & Bono, 2017). Nevertheless, we checked any significant pairwise comparisons with non-parametric equivalents.

3. Results

3.1. Aim 1: Looking time to the eye region

The first aim of the study was to compare the profiles of visual attention to the eye region at critical points of the attention direction process between groups. Fig. 3 summarises the mean looking time (in seconds) to the eye region during the communicative cue phase 3 and the gaze following phase 4 across all conditions for autistic children, children with CdLS and children with FXS compared to the reference group of neurotypical children. To investigate these profiles for each neurodivergent group, 2 (group; neurotypical vs autism/CdLS/FXS) × 3 (condition; person vs cartoon vs ball) mixed ANOVAs were run on the mean duration of looking time to the eye

region during the communicative cue phase 3 and during the gaze following phase 4 across all trials.

3.1.1. Autistic children versus neurotypical children
For mean looking time to the eye region during the communicative cue phase 3 between autistic and neurotypical children, there were no main effects of condition or group, or any interactions. However, there was a main effect of group with a large effect size [$F(1, 35) = 5.51$, $p = .025$, $n^2 = .14$] in which autistic children looked at the eye region during the gaze following phase 4 for less time than the neurotypical children. There was no main effect of condition or an interaction on looking time to the eye region during gaze following phase 4.

3.1.2. FXS versus neurotypical children
For mean looking time to the eye region during the communicative cue phase 3 between children with FXS and neurotypical children, there was a main effect of condition with a large effect size [$F(2, 42) = 4.59$, $p = .016$, $n^2 = .18$]. Post-hoc follow up tests indicated that participants looked at the eye region for more time during the person condition compared to the cartoon condition [$t(22) = 2.84$, $p = .010$, $r = .52$]. In addition, there was no main effect of group on looking time to the eye region during the communicative cue phase 3, or an interaction. There were also no main effects or an interaction for mean looking time to the eye region during the gaze following phase 4.

3.1.3. CdLS versus neurotypical children
For mean looking time to the eye region during the communicative cue phase 3 between children with CdLS and neurotypical children, there were no main effects of condition or group, or any interaction. However, for mean looking time to the eye region during the gaze following phase 4, there was a main effect of condition with a large effect size [$F(2, 48) = 4.02$, $p = .024$, $n^2 = .14$]. Post-hoc follow up tests indicated that participants spent more time looking at the eye region during
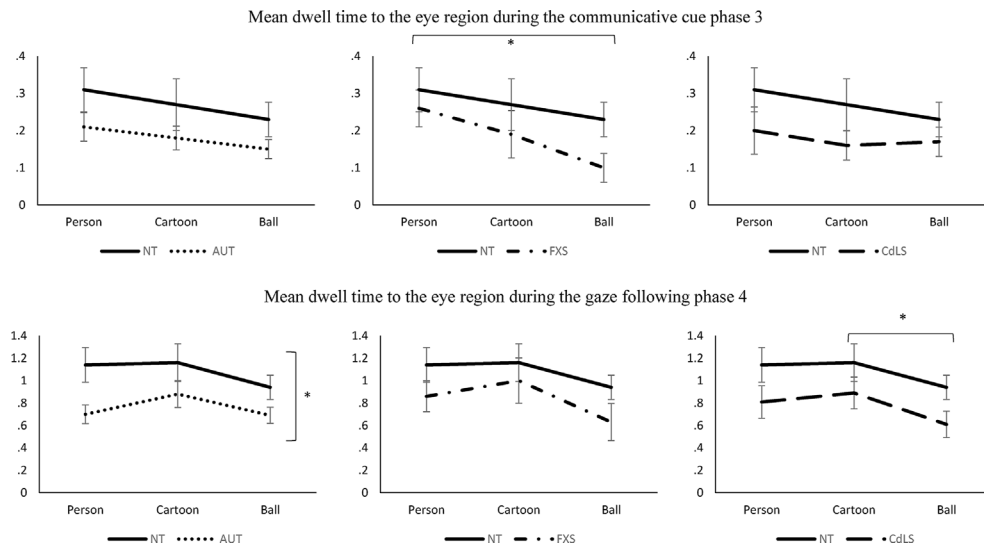

Fig. 3 — Mean looking time (in seconds) to the eye region during the communicative cue phase 3 and gaze following phase 4 by autistic children, children with CdLS and children with FXS compared to a baseline of neurotypical children across all the person, cartoon and ball conditions.
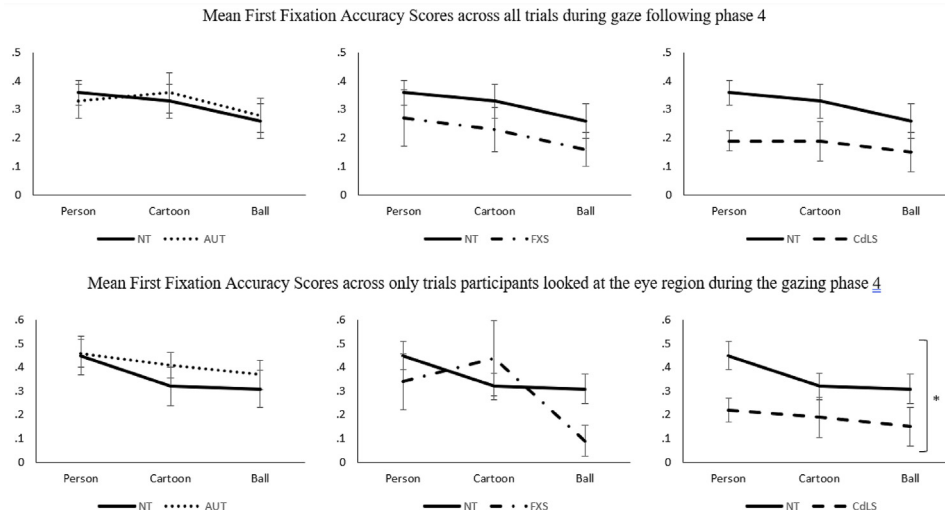
Mean First Fixation Accuracy Scores across all trials during gaze following phase 4

Mean First Fixation Accuracy Scores across only trials participants looked at the eye region during the gazing phase 4

Fig. 4 — Mean First Fixation Accuracy Score across all trials and during trials when participants looked at the eye region during the gaze following phase 4 for autistic children, children with CdLS and children with FXS compared to a baseline of neurotypical children across all the person, cartoon and ball conditions.

the ball condition compared to the cartoon condition [$t(25) = -3.05$, $p = .005$, $r = .27$]. There were no other significant differences between conditions. In addition, there was no main effect of group on looking time to the eye region during the communicative cue, nor an interaction.

3.2. Aim 2: Target fixation after the communicative cue

The second aim was to investigate whether gaze following performance differed between groups. Figs. 4 and 5 summarize the group mean First Fixation Accuracy Scores and Look to Target Scores reported firstly across all trials and secondly only in trials where participants also looked at the eye region during the gaze following phase 4. To investigate these profiles, again for each neurodivergent group, a 2 (group) × 3 (condition) mixed ANOVA was conducted on participants'

mean First Fixation Accuracy Scores and mean Look to Target Scores for all trials. Mixed ANOVAs were also run on First Fixation Accuracy Scores and mean Look to Target scores only for trials in which participants looked at the eye region during the gaze following phase 4. All neurotypical children looked at the eye region in each condition during the gaze following phase 4, in comparison to 19 out of 22 autistic children, six out of eight children with FXS and ten out of 11 participants with CdLS. There were no significant changes in demographic comparisons when removing those who did not look at the eye region (see Supplementary table 2).

3.2.1. Autistic versus neurotypical children
For mean First Fixation Accuracy Scores across all trials between autistic and neurotypical children, there were no main effects of condition or group, nor an interaction for First
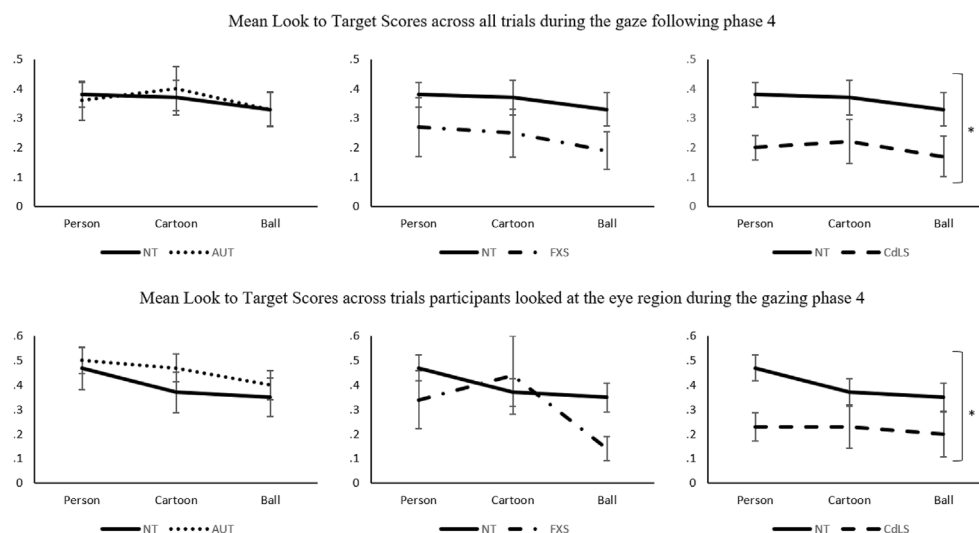
Mean Look to Target Scores across all trials during the gaze following phase 4

Mean Look to Target Scores across trials participants looked at the eye region during the gazing phase 4

Fig. 5 — Mean Look to Target Score across all trials and during trials when participants looked at the eye region during the gaze following phase 4 for autistic children, children with CdLS and children with FXS compared to a baseline of neurotypical children across all the person, cartoon and ball conditions.

Fixation Accuracy Scores across all trials nor for participants' First Fixation Accuracy Scores only for trials when they looked at the eye region during the gaze following phase 4. Similarly, there were no main effects or an interaction found for participants mean Look to Target Scores across all trials and across only trials where they looked at the eye region during the gaze following phase.

3.2.2. FXS versus neurotypical children

For mean First Fixation Accuracy Scores across all trials between children with FXS and neurotypical children, there were no main effects nor interactions. However, First Fixation Accuracy Score only for trials when participants looked at the eye region during the gaze following phase 4 revealed a large main effect of condition [$F_{(2, 38)} = 4.51$, $p = .018$, $n^2 = .19$]. Whilst post-hoc follow up tests revealed no differences between conditions, visual inspection of Fig. 1 indicates First Fixation Accuracy Scores were lower in the ball condition compared to the person and cartoon conditions. For Look to Target Scores, there were no main effects or interactions either when looking at all trials, or only at trials when participants looked at the eye region during the gaze following phase 4.

3.2.3. CdLS versus neurotypical children

For mean First Fixation Accuracy Scores across all trials between children with CdLS and neurotypical children, there were no main effects or interactions. However, for mean First Fixation Accuracy Scores for only trials where participants looked at the eye region there was a main effect of group with a large effect size [$F_{(1, 23)} = 57.92$ $p = .022$, $n^2 = .21$], in which children with CdLS were less likely to fixate first on the target compared to neurotypical children. There was no main effect

of condition or a significant interaction. Similarly to above, for mean Look to Target Scores, there was a large main effect of group for all trials [$F_{(1, 24)} = 5.42$, $p = .029$, $n^2 = .18$] and in just those trials where participants looked at the eye region $F_{(1, 23)} = 6.30$, $p = .020$, $n^2 = .22$). In both cases, the CdLS group were less likely to look at the target during the gaze following phrase 4 than the neurotypical group. Again, no main effect of condition or any interactions were found.

3.3. Aim 3: Looking time on the target object

The third aim was to investigate the mean looking time to the target object following the gaze cue across the groups. For each group, a 2 (group) × 3 (condition) mixed ANOVA was run on the mean looking time to the target during the gaze following phase 4. Fig. 6 summarises the mean duration of time spent looking at the target during the gaze following phase 4 across all conditions for autistic children, children with CdLS and children with FXS compared against the baseline group of neurotypical children.

When comparing the mean time spent looking at the target object during the gaze following phase 4 between autistic and neurotypical children, and between children with CdLS and neurotypical children, there were no main effects of condition or group, or any interactions. When comparing children with FXS and neurotypical children's mean time spent looking at the target object during the gaze following phase 4, there was a main effect of group with a large effect size [$F_{(1, 21)} = 5.27$, $p = .032$, $n^2 = .20$], in which the children with FXS looked at the target for less time compared to the neurotypical group (Fig. 6). There was no main effect of condition or an interaction.

Overall, findings highlight unique visual attention patterns during the gaze following task in autistic children, children
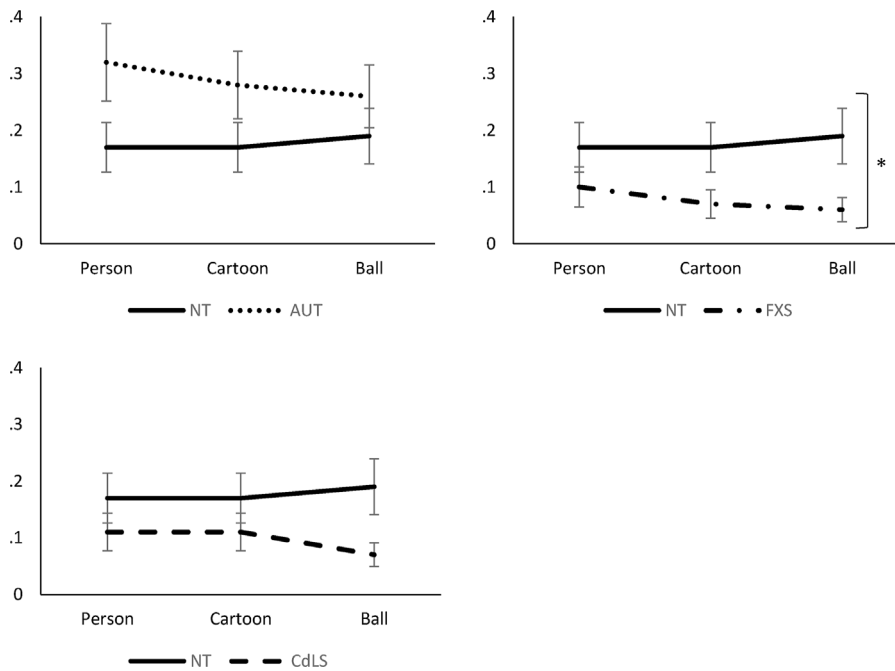

Fig. 6 − Mean time (in seconds) spent looking at the target during the gaze following phase 4 by autistic children, children with CdLS and children with FXS compared to a baseline of neurotypical children across all the person, cartoon and ball conditions.

with CdLS and children with FXS relative to neurotypical children. Figs. 7—9 provide a visual representation of these visual attention patterns for each group respectively.

4. Discussion

We present the first cross-syndrome study of gaze following performance in two groups of genetic syndromes associated with unique profiles of autistic traits (CdLS and FXS) alongside
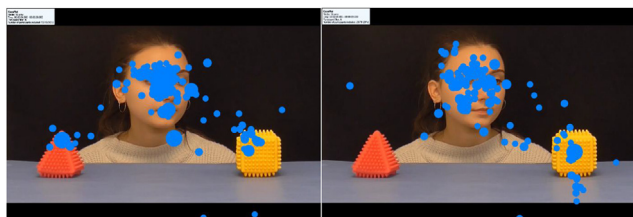

Fig. 7 — A visual representation fixation patterns in 15 neurotypical children (left) and 22 autistic children (right). Each dot represents a point where a child has fixated during the gaze following phase 4. Bigger dots indicate longer fixation time. Autistic children fixate for less time on the eye region but follow the cue as frequently and look at the target for as long as neurotypical children.
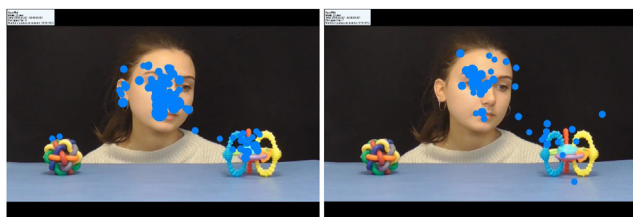

Fig. 8 — A visual representation of fixation patterns in 15 neurotypical children (left) and eight children with FXS (right). Each dot represents a point where a child has fixated during the gaze following phase 4. Bigger dots indicate longer fixation time. Neurotypical children fixate longer on the target than children with FXS.
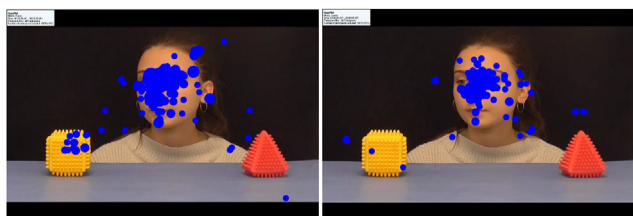

Fig. 9 — A visual representation of fixation patterns in 22 neurotypical children (left) and eleven children with CdLS (right). Each dot represents a point where a child has fixated. Bigger dots indicate longer fixation time. Both neurotypical children and children with CdLS frequently look at the eye region. However, whereas NT children look towards the target object, very few children with CdLS fixate on this location.

autistic children without a genetic syndrome, in comparison to a reference group of neurotypical children. Our findings provide preliminary evidence of unique patterns of visual attention and gaze following strategies in children with CdLS, children with FXS and autistic children. We showed that although autistic children looked at the eye region for significantly less time during gaze following phase 4, they nevertheless followed the target just as frequently, and looked at the target for a similar duration to neurotypical children (see Fig. 7). In contrast, children with FXS did not show any significant differences in time spent looking at the eye region, or the frequency with which they looked at the target, but the time spent looking at the target object was significantly lower than in neurotypical children (Fig. 8). Finally, whereas children with CdLS did not show any significant differences in time looking at the eye region nor the time spent looking at the target, they were less likely to follow the gaze cue to the target object relative to neurotypical children (Fig. 9).

The first aim was to compare profiles of visual attention to the eye region at critical points of the gaze following process between groups and conditions, as agents use their eyes to indicate communicative intent and direct others attention towards objects of interest (Senju & Csibra, 2008). Corresponding to previous eye tracking findings (Riby et al., 2013; Wang et al., 2020) and our first hypothesis, autistic children looked at the eye region during the gaze following phase 4 for significantly less time than neurotypical children. However, contrary to our hypothesis and previous findings (Wall et al., 2023), children with FXS did not look at the eye region for significantly less time than neurotypical children during either the communicative cue phase 3 or the gaze following phase 4. One possibility is that the analysis was underpowered to detect differences. However, even within group, the looking time across social and non-social conditions can be seen to be very similar in children with FXS, as in neurotypical children, indicating that both children with FXS and neurotypical children were as likely to look at the eyes of the person as they were to look at the colour convergence point of the ball. Hence, children with FXS were not specifically avoidant of eyes. As the current study used a multi-trial paradigm with a single agent, the lack of a difference between the neurotypical children and children with FXS may therefore have been due to 'warm-up' effects. Whilst people with FXS show significantly reduced eye contact upon first meeting an unfamiliar person (Wall et al., 2023), their eye contact increases across the duration of a social interaction (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009).

However, descriptive data (see Supplementary table 3) of participants looking time at the eye region during the first and second half of the paradigm indicates that gaze duration did not increase over time in children with FXS. Instead, findings may reflect that underlying reduced eye gaze between autistic children and children with FXS may be driven by different mechanisms. Whereas in autistic children, reduced eye gaze is considered to be the result of an attentional indifference (Senju & Johnson, 2009), reduced eye gaze in those with FXS is driven by social anxiety and hyper arousal (Cornish, Turk, & Hagerman, 2008). Previous work identifying gaze avoidance in people with FXS has been evaluated during live social interactions, known to be anxiety-provoking in those with FXS

(e.g., Wall et al., 2023) or have used eye-tracking paradigms that include unusual and decontextualized or emotional faces shown independently of any other stimuli (e.g., Farzin, Rivera, & Hessl, 2009) that people with FXS may find strange or aversive. In contrast, our paradigm was designed to evaluate responses to gaze following cues and was not designed to be anxiety provoking and did not include a live social interaction. Furthermore, the cues and facial expressions of the actor and cartoon stimuli were neutral and placed in the context of a broader scene. Future work should further investigate the role of anxiety and eye contact duration as well as its influence upon gaze following success in children with FXS.

The second aim was to compare profiles of cue following to the target object between groups and conditions during the gaze following phase 4. Figs. 4 and 5 indicate that First Fixation Scores and Look to Target Scores did not differ greatly, suggesting that if children looked at all, they were likely to do so on their first fixation.

Confirming our second hypothesis, children with CdLS showed a broad pattern of reduced looking towards the target during the gaze following phase 4. Specifically, children with CdLS were less likely than neurotypical children to look at the target object even in trials where they looked at the eye region. In addition, First Fixation Accuracy Scores were lower in children with CdLS compared to neurotypical children across trials in which they looked at the eye region. Despite looking at the eye region, children with CdLS may not understand the communicative nature of the eyes, indicating an interpretation rather than a detection issue of the communicative intention behind the eye signal (Babinet et al., 2022). However, low levels of gaze following in children with CdLS occurred across conditions, suggesting that difficulties may not be specific to social stimuli but may reflect atypical non-social perceptual processes. Therefore, lower gaze following may be indicative of difficulties of a simple reflexive reorienting behaviour towards what someone is attending, identified as the most basic level of cognitive processing used during cued attention (Shepherd & Cappuccio, 2011). A neural mechanism for future investigation in those with CdLS is the intraparietal sulcus, which shows strong activation when neurotypical people follow both social and non-social cues and is considered important for spatial encoding and mediating shifts of spatial attention (Materna, Dicke, & Thier, 2008). These difficulties were not observed in the autistic children nor the children with FXS, suggesting it is a unique area of difficulty in individuals with CdLS.

Whilst autistic children spent less time looking at the eye region, they were as successful at following the cue to the object as neurotypical children. Findings suggest they may use alternative gaze following strategies without spending as much time looking at the eye region. Diminished gaze following in infant siblings of autistic children has been found to be specific to responding to gaze direction, as it was not seen when gaze was combined with a head turn (Thorup, Nystrom, Gredeback, Bolte & Falck-Ytter, 2016). Likewise, studies in which autistic children did successfully gaze follow have involved an agent turning their head as well as shifting their gaze (e.g., Bedford et al., 2012), similar to the current study, whereas studies in which autistic children didn't gaze follow have consisted of an agent moving their eyes but not

their head (e.g., Congiu et al., 2016). Therefore, previous mixed findings of gaze following to target objects in autistic children and their infant siblings (Bedford et al., 2012; Congiu et al., 2016) may be due to some gaze paradigms focussing solely on the role of the eye region rather than allowing for alternative strategies, leading to an underestimation of abilities.

Our final aim was to compare profiles of participants' looking time at the target object following the gaze cue between groups and conditions. Children with FXS spent significantly less time looking at the target object compared to neurotypical children, despite not showing a difficulty in following the agent's turn to look at the object. Findings may indicate that whilst children with FXS may automatically orient in response to a directional gaze shift (Shepherd & Cappuccio, 2011), they may not understand the intention underlying the cue that the gazed upon target object has relevance. Therefore, results may be reflective of difficulty in a core social cognitive skill, i.e., shared intentionality, indicating difficulties in sharing joint mental states and attention with others (Ellis et al., 2021).

Alternatively, reduced looking time at the target may reflect a difficulty in sustained attention to non-social static stimuli (e.g., the target object in the current study). Young children with FXS do not show the 'gap effect', in which neurotypical children are slower to look at objects within peripheral vision when there is a central cue compared to when that central cue is removed before the peripheral stimulus appears (Chernenok, Burris, Owen, & Rivera, 2019). These findings may reflect an overall attentional engagement driven by atypical parietal networking functioning, a brain area important for inhibiting reflexive saccades, meaning that children did not have to disengage from one object in order to look at another. Findings also suggest that children with FXS spend less time processing static stimuli (Chernenok et al., 2019). Our data show a similar pattern — children with FXS easily shift towards the static target but do not attend to the target object for very long, whereas such differences are not observed in dynamic stimuli (i.e., the moving eye region/head). Such fleeting fixations may be due to specific non-social attentional difficulties as opposed to a social cognitive difficulty per say.

Contrary to previous findings (e.g., Bedford et al., 2012) autistic children did not spend significantly less time looking at the cued target object compared to neurotypical children. Again, contrasting findings may be due to differences in our data analysis procedure. Whilst mean looking time on the cued object was measured during the gaze following phase 4 in the current study, other studies only compared looking time during trials in which children's first fixation was towards the target object (Bedford et al., 2012) or trials in which children first looked at the eye region before looking at the target (Congiu et al., 2016). Our broader data inclusion strategy accounted for potential atypical visual patterns to follow the model's cue to the target object, and we propose that the first fixation may not be the only or most important opportunity to follow the gaze and extract relevant information from the target object during the cue and head turn.

As part of all three aims, we hypothesized that visual gaze patterns may vary across conditions between syndrome groups. There was variation across all analyses in patterns of main effects of conditions between the neurodivergent

groups. For example, children with FXS showed a similar decline between the person and ball conditions as neurotypical children in mean duration spent looking at the eye region during the communicative cue phase 3, except that the decline was non-significantly steeper in children with FXS (see Fig. 3). This resulted in a main effect of condition in which overall both neurotypical children and children with FXS showed a longer looking time at the eye region during the person conditions compared to the ball condition, whilst this effect was not observed when the other neurodivergent groups were compared to neurotypical children. This may indicate that social cues hold the attention of children with FXS, whom characteristically show broad attentional difficulties to non-social visual stimuli relative to mental-aged matched neurotypical controls (Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012) but high levels of social attention that are comparable to neurotypical individuals (Hong et al., 2019). These differing patterns of main effects of condition across the different groups may indicate potential interaction effects that were not detected in our analyses due to an underpowered sample. Future work should replicate our study with larger samples of children with CdLS and FXS to explore these subtler interactions.

There were several limitations to the study to consider when interpreting the data. Due to disruption to face to face testing during the COVID-19 pandemic, the sample of children with CdLS and FXS was limited in the current study. Regardless of the pandemic, limited sample sizes are a frequent issue in genetic syndrome research due to practical challenges in recruitment and assessment. Studies require recruiting families from across the country and therefore many families live far from the research base. Portable eye tracking technology, such as Tobii systems, reduce these barriers, as researchers can travel to participants' homes rather than requiring families, who often already experience high levels of day-to-day burden, to travel to the university. However, these systems are expensive, and projects become travel and time-intensive for the research team. In response to the COVID-19 pandemic, we explored whether we could continue the study using remote webcam-based technology. However, data collected from neurotypical children who participated remotely were not comparable to data from those who took part in face-to-face paradigms. Therefore, we were only able to report data collected prior to the pandemic in this study. Thus, our data analysis strategy was to detect meaningful differences and patterns in visual attention profiles, whilst limiting the number of group comparisons. Whilst these groups are rare individually, collectively they are common (Dodge et al., 2011) and have some of the highest level of clinical need due to their complex clinical presentations (Jenner, Richards, Howard, & Moss, 2023). These issues highlight that national and international collaboration is vital to pool resources and expand the reach of participants to increase sample sizes within these under-represented groups.

Due to the national COVID-19 lockdown occurring halfway through the project, we were not able to complete the ADOS-2. Whilst we used the SRS-2 to gain an approximation of level of autistic traits in each group, the ADOS-2 is considered to be a gold standard observational assessment for autism and is one of few autism assessments that has good diagnostic reliability

and validity across a range of abilities (Moss, Howlin & Oliver, 2012). Whilst both people with CdLS and FXS both have a heightened likelihood of showing high levels of autism characteristics, there is variability in the level of autism characteristics seen within each syndrome group (Richards et al., 2015).

It is therefore important to accurately report the level of autistic characteristics within studies as this may influence findings. For example, in those with FXS, those with and without co-occurring autism are distinguished by communication, and restricted interests and repetitive behaviours, but not in reciprocal social interaction autism characteristics when controlling for IQ (McDuffie et al., 2015). Larger samples would enable the exploration of whether individual differences are also observed in children with CdLS and FXS at the cognitive level (i.e., gaze following profiles), and whether and how they are associated with variability at the behavioural level (i.e., autism characteristics). Additional investigation into whether children with CdLS or FXS with co-occurring autism show convergence or divergence in gaze following profiles as autistic children without a genetic syndrome would provide insight into whether the same cognitive mechanisms may contribute to the emergence of autism in those with and without a genetic syndrome. However, a challenge with this approach is accurately defining who with CdLS or FXS does and does not have co-occurring autism, which is underdiagnosed in clinical practice despite groups showing high levels of these characteristics (Reilly et al., 2015). In addition, the cut-off scores for commonly used standardized diagnostic assessments of autism have not been validated within populations of people with genetic syndromes. Whilst some of these assessments have been adapted to improve their sensitivity and specificity for certain syndrome groups such as FXS, these are few and far between and often lead to only modest improvements (e.g., Kidd et al., 2020). Nevertheless, as discussed above the genetic syndrome field is often restricted by small sample sizes that restrict the ability to investigate any form of within-syndrome differences. Future collaboration across research sites will enable better opportunities to investigate whether these gaze following patterns are similar or different between children with CdLS and FXS with and without co-occurring autism.

Our analysis approach was broad to ensure we did not underestimate the abilities of children who used alternative but ultimately successful approaches to following a communicative cue towards a target object. Whilst we did find meaningful differences, it is possible that this approach did not capture important subtle differences in the different strategies. However, our approach ensured that we did not place neurotypical expectations of strategies on the neurodivergent groups.

5. Conclusions

In this study, visual attention patterns during a passive viewing gaze following paradigm were investigated in two genetic syndromes associated with unique profiles of social and communicative autistic characteristics. Findings indicate that children with CdLS show significant difficulties in gaze

following that may be underpinned by an atypical basic reorienting mechanism rather than being due to 'missing' or not detecting the communicative cue. In comparison, children with FXS didn't show any significant difficulties with gaze following, but did spend significantly less time looking at the target compared to neurotypical children. Our findings indicate that those with FXS may be able to orient towards an object but may not understand the communicative intention behind the cue or may simply have fleeting attention to non-social objects. Finally, autistic children showed atypical strategies to following the cue that rely on more general perceptual information (i.e., the head turn) rather than specific social information (i.e., looking at the eye region). Overall, our findings provide preliminary evidence of diverse visual attention patterns and strategies during a gaze following task between groups who all show high levels of autistic characteristics, and highlights the importance of not evaluating gaze following performance in neurodivergent populations based on neurotypical expectations.

Funding

Data statement

The conditions of our ethics approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact senior author Jo Moss. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of clinical data, including completion of a formal data sharing agreement and approval of the local ethics committee.

Pre-registration statement

No part of the study procedures or analysis plans was pre-registered prior to the research being conducted.

Analytic methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/criteria were established prior to data analysis, all manipulations, and all measures in the study.

Open practices

The study in this article has earned Open Material Badge for transparent practices. The material used in this study is available at: https://osf.io/sjnbh.

CRediT authorship contribution statement

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2024.02.012.

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