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Novel Paradigm for Eye Tracking and Vision Screening in Autism

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Abstract

Eye-tracking patterns in 41 pediatric subjects on the Autism Spectrum Disorder (ASD) were studied and compared to their siblings (N=30) and to age/gender matched controls (N=84). The five paradigms used were: 1-Horizontal and vertical motion video; 2-Face image; 3-Mute video of a talking face; 4-Animate/inanimate object; 5-The inverted scene. The ASD group had shorter fixation duration and less fixation count than controls. Percentage of fixation was decreased in the vertical motion video (p<0.001). Time to first fixation was significantly longer in the ASD group for the first horizontal motion video but not for the second vertical video. The ASD group, when presented with the face image, fixated faster on the mouth than controls (p=0.042), but with lower fixation duration and count. For the mute talking face video, first fixation on the eyes was slower than controls (p=0.006) with no observed effect of dynamic movement of the mouth compared to the static face image. Both ASD subjects and controls showed faster and longer fixation on the animate object image (p=0.001). The ASD group showed a decreased fixation count (p=0.014) with the inverted scene. Siblings were similar to the control group in most paradigms tested. Using the Plusoptix photo screener, all participants were screened for ocular disorders. Five % had astigmatism and 5% had exotropia in the ASD group. Seven % of the siblings had astigmatism. Twenty seven % of the control group had refractive errors. When correcting for SE by a regression model, no difference was found in eye tracking results with no association between eye-tracking parameters and refractive errors. In conlusion, children in the ASD group exhibited preferential mouth fixation, decreased general attention to all paradigms, and preferential fixation on animate versus inanimate targets.

Keywords: Autism Spectrum Disorder; Eye-Tracking; Vision Screening

Introduction

Autism Spectrum Disorders (ASDs) are a group of neurodevelopmental disorders characterized by impairment of socialization, communication, language, and behavior. According to DSM-IV criteria rare disorders, such as Rett syndrome, fragile X and childhood disintegrative disorder were included, but are considered as separate entities in the newer DSM-V classification. The Center for Disease Control and Prevention reported that 1 in 68 children had ASDs in 2010. This figure was placed at 1 in 59 in the United States of America in 2012 [1]. In Lebanon, the prevalence was reported as 1:68 in 2018 [2].

Children on the autism spectrum have a high rate of ocular disorders with reports stating that 40% of patients with ASD have ophthalmologic pathologies [3]. Of these patients, 29% had significant refractive errors, 21% had strabismus, and 10% had amblyopia. Other pathologic findings included nystagmus, ptosis, nasolacrimal duct obstruction, retinopathy of prematurity, cataracts, trochlear nerve palsy, uveal coloboma, euryblepharon, and optic nerve cupping [3]. Another study established that 52% of patients had ocular abnormalities, of which 41% were strabismus, 27% refractive errors, 7% anisometropia, and 11% amblyopia [4]. Due to the high prevalence of vision-threatening conditions, and, because children on the spectrum often are uncooperative, it was crucial to set recommendations for children with ASD to undergo comprehensive examinations by pediatric ophthalmologists. New photo-screeners require less cooperation and communication from the child as compared to the standard ophthalmological exam and may be better suited for screening for ocular disorders in children with ASD [5,6]. The plusoptiX photoscreener (Plusoptix GmbH, Atlanta, GA) is a handheld vision screener that can measure refractive errors, pupil diameter, and inter-pupillary distance [7]. Most amblyopia risk factors in children with ASD were detected on screening with this device [5,6]. The newer generation plusoptiX S12 employs faster and more informative technology and has not been studied in the ASD population [8].

Eye tracking technology allows a better understanding of eye movements in toddlers and children. It helps researchers measure how participants distribute their observations and assess psycho-behavioral patterns in different patient populations [9]. Recently, several eye-tracking studies of young children on the spectrum have been published, illustrating an emerging consensus that detailed characterization of young children with autism can be achieved at the level of eye movements. Due to the non-invasive and non-obstructive nature of the experiment, researchers have focused on corneal reflection eye tracking to qualify and quantify visual fixation of children with ASD in an attempt to interpret them in light of their altered socio-communicative skills. Group differences in eye-tracking parameters in infants between 6 and 10 months of age were detected in those who later developed ASD [9,10]. Another study showed that infants who spent less time looking at a presented scene ultimately developed ASD [11]. In a review on visual tracking studies in autism, Falck-Yitter et al. differentiate between different types of stimuli used to engage children with ASD: semi-naturalistic contexts such as complex scenes including those with static and dynamic faces, paired visual preference paradigms with a focus on preferential and cumulative looking time at different areas of interest, event-related designs and assessment of moving stimuli, distractions, and gaze shifts [9]. Studies of both static and dynamic faces generally uncovered consistent findings. Individuals with ASD fixated more on the mouth than on the eyes, and used the mouth more commonly for their assessment of emotions, recognition, and general apraisal [12,13].

Looking at eyes, (and not at the mouth) was linked with activation of the fusiform gyrus and amygdala in individuals with ASD on concomittant eye-tracking and functional MRI studies, suggesting that eye fixation generated a strong emotional response in these individuals leading to avoidance. Van der Geest et al. conducted two studies on gaze behavior involving human faces [13,14]. In the first study, stimuli were composed of faces with emotional expressions. In the second, faces with neutral expressions were in different orientations. Interestingly, the first study showed that both neuro-typically developing children and children with ASD exhibited the same fixation duration for upright faces with or without emotional expression. The second study established that while neuro-typically developing children diminished fixation duration toward faces projected upside down, children with ASD demonstrated similar fixation duration for both upside 'up' and upside 'down' faces, with less sensitivity to the orientation of faces [13,14]. In neuro-typically developing children, face perception is generally approached in an integrated fashion rather than by analyzing the different features of the face [13]. By using an inverted face as a stimulus, Pelphrey et al. argued that individuals undergoing the experiment had to revert to the perception strategies employed with non-face stimuli, or elemental analysis [15]. Most studies using inverted faces detected the 'face inversion effect' in the ASD group, albeit this was less pronounced than in the neuro-typically developing group, implying that children with ASD use a holistic face scanning approach when looking at upright faces. This is lost when looking at inverted faces [16]. By using both inverted and upright Mooney face stimuli, which necessarily require a holistic pereceptual approach, Naumann et al. found that participants with ASD had findings relatively comparable to those of controls and deduced that both groups employed a holistic approach in this experiment [17]. The holistic processing was less efficient in ASD. This may be explained by implicating less developed neural systems in the ASD group [17].

Clearly, an increasing number of studies have focused on eye-tracking patterns in children with ASD. A clear pattern of deficit in attentional engagement is identified among individuals with ASD, and it is implied that this is dependent on context and hard to generalize [18]. Other studies have tried to correlate these differences with outcomes like social skills, diagnosis, and severity of ASD. M. Murias et. al have demonstrated that certain eye-tracking patterns, such as attention on the actor's face/mouth, correlate with five different validated measurements of social communication [19]. Another study demonstrated that eye-tracking measurements may accurately provide a qualitative diagnosis of ASD and a quantitative assessment of its severity [20]. None of these studies included concurrent vision screening to detect ocular disorders affecting eye gaze behavior. Goals of this study are detection of differential eye tracking patterns in subjects with ASD using novel testing paradigms, while simultaneously screening for concomitant vision disorders, and to compare them to siblings who are at high risk for ASD and control children.

Methods

Population

This was a study of 41 previously diagnosed children with ASD between 2 years and 17 years, as well as 30 of their siblings considered at high risk for ASD. In parallel, 84 healthy age-matched children were the control group. The latter included children presenting to the pediatric ophthalmology service for routine visits with hyperopic or myopic spherical equivalent refraction up to 2 diopters. This study was approved by the Institutional Review Board at the American University of Beirut. Written informed consent was obtained from parents or legal guardians and assent forms were provided. Participants with a gestational age below 36 weeks, hearing loss or visual impairment determined at birth, non-febrile seizures, medical conditions associated with autistic features such as fragile X Syndrome, tuberous sclerosis, Rett syndrome or any other identified genetic disorder were excluded from the study. Also, those unable to cooperate for accurate calibration on the eye tracker were excluded. Two such children were excluded out of 43 recruited in the ASD group. Information pertaining to severity of ASD and eye contact was obtained from the subjects' neurologic assesssment, DSM-5 criteria, and performance on standardised ASD screening tools including the Childhood Autism Rating Scale (CARS) and the Autism Diagnostic Observation Schedule (ADOS).

Vision screening and eye examination

The plusoptiX S12 vision screener (Plusoptix GmbH, Atlanta, GA) was used for vision screening. The camera was set off by pulling the trigger. The sound attracted attention and both eyes were captured on screen in a white rectangle with an automatically registered measurement. Screening results displayed on the screen and data on spherical equivalent refraction in diopters (D) of each eye were recorded (Figures 1a and 1b). To confirm the results of the vision screen, a comprehensive pediatric eye examination was performed. This entailed visual acuity testing including age-dependant "fix and follow" testing for infants, "central steady & maintained" testing for older preverbal children and vision charts such as Allen pictures and ETDRS charts for verbal children. Also, structure of the anterior segment elements encompassing pupil, iris and lens were analysed. Motility examination for eye misalignment and cycloplegic manual retinoscopy to detect refractive errors (30 minutes after pupillary dilation with Mydriacyl 1% and Cyclopentolate 1%, applied twice 10 minutes apart) and posterior segment examination using indirect ophthalmoloscopy were carried out.

Figure 1a: PlusoptiX S12 vision screener.

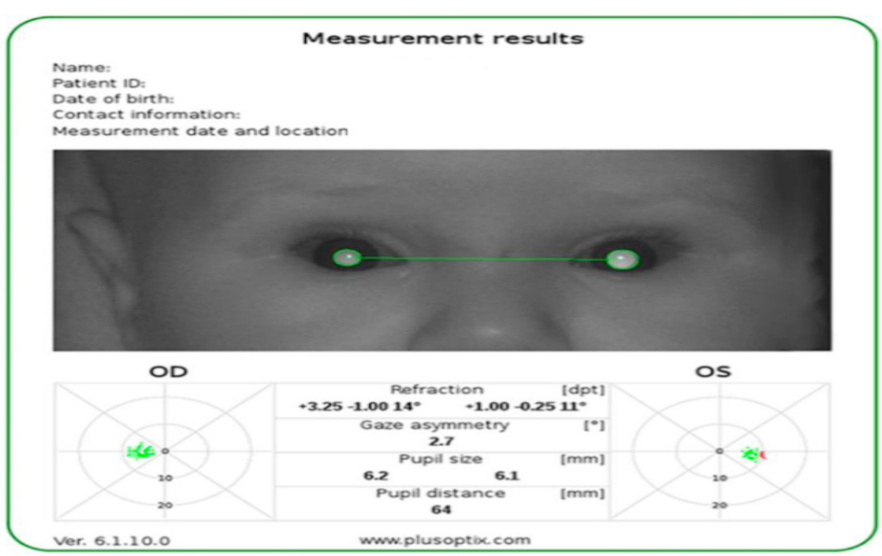

Figure 1b: Screening results displayed on the screen of the machine.

Eye tracking

Tobii 1750 Eye Tracker (Danderyd, Sweden) was used to perform the eye tracking examination. The recordings were integrated on a 17-inch monitor, while the infant was seated on a parent's lap or older subjects sitting by themselves approximately 65 cm from the monitor. Cameras with a frequency of 50 Hz and placed under the monitor recorded reflections from an infrared light. The eye tracker compensates for head motion and movements faster than 10 cm/s. ClearView software was used to display stimuli from static and dynamic images with a five-point calibration prior to the assessment. The formal ClearView filter for both eyes was used. Fixations were defined as gaze within a 30 pixel radius for at least 100 ms. Successful calibration was a prerequisite for proceeding with the full testing paradigm. When patients calibrated well, the trial was conducted. If poor fixation occurred then the experiment was repeated with the help of parents and other examiners. Two patients from the ASD group were excluded from the analysis due to calibration issues and a low proportion of valid data points. Of a total of 43 patients recruited, 41 were included in the final analysis.

Five paradigms were studied:

1. Horizontal and vertical motion paradigms evaluated subject tracking of a moving element, a cartoon of a dog, in both horizontal and vertical directions (Figure 2a). This is an example of event-related design, where latency and duration of fixations on an object of interest, orientation of gazes, and oculomotor functioning provide information about attentional and visual functioning [9]. The hypothesis was that participants with ASD would follow the target appropriately, but with shorter fixation durations on the moving target and disengaging their gaze earlier as reported in prior studies [21,22]. Another hypothesis was that differences in fixation patterns would emerge from studying gazes at horizontally and vertically moving targets.
2. Still image of a smiling face paradigm contained two areas of interest, the eyes and the mouth of a smiling girl. This assesses the preferential gaze of the three groups on one of the two areas while looking at a still face image (Figure 2b). The hypothesis was that this paradigm would replicate the commonly encountered preferential mouth fixation observed in ASD.
3. Video of a talking face without sound contained the same areas of interest as in the still image paradigm. This explores the effect of mouth movement on the different parameters analyzed. It has been suggested that audiovisual synchrony was the source of the preferential staring at the mouth in videos of talking faces [23,24], this paradigm was employed here to establish reproducibility of mouth preference without the presence of sound.
4. The image containing an animate and inanimate object, included two areas of interest: the animate monkey and the inanimate element laptop. The goal here was uncovering the existence of a preferential tracking pattern on one of the elements (Figure 2c). This is an example of a paired visual preference paradigm, traditionally used to demonstrate that neuro-typically developing children prefer looking at biological motion and socially loaded scenes compared to children with ASD [9]. Given the evidence that children with ASD pay more attention to the inanimate aspects of their surrounding than to animate features, it was hypothesized that children with ASD will prefer the laptop to the monkey.
5. Image of an inverted scene consisted of the inverted image of a man in a room. Distraction was evaluated in the three groups due to the inversion. (Figure 2d). The 'inverted face effect' is described in eye-tracking experiments where both the recognition and perceptual approach differed from looking at upright faces [25,26]. Studies do not consistently demonstrate that this effect exists for non-face objects. This paradigm combines a living human being in a semi-naturalistic setting and inverts the image. Goals were to identify differences in the fixation and gazes in children with ASD compared to siblings and typically developing children.

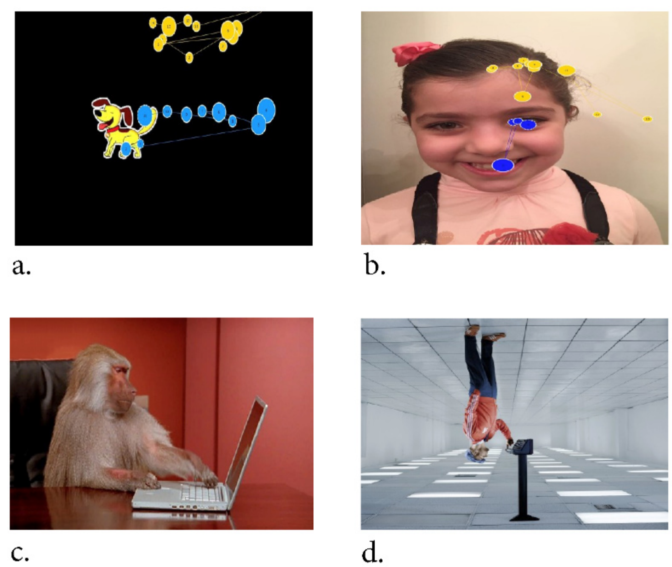

Figure 2a-2d: a. Horizontal and vertical motion paradigm, showing the subjects' fixation points on eye tracking testing. Blue: control, Yellow: subject with autism spectrum disorder **b.** Still face image paradigm, showing subject fixation points on eye tracking testing. Blue: control; Yellow: subject with autism spectrum disorder **c.** Animate/inanimate image paradigm **d.** Inverted scene paradigm

The total duration of the experiment was 47 seconds as shown in (Figure 3), which represents the model used along with the duration of each paradigm. Six parameters were analyzed in every paradigm.

1. Time to first fixation in seconds, which represents the time from the start of the stimulus display until the participant fixates on an area of interest (AOI) for the first time.
2. First fixation duration in seconds or duration of the first fixation on an AOI.
3. Total fixation duration in seconds or duration of all fixations within an AOI.
4. Fixation count or the number of times the participant fixated on an AOI.
5. Percentage of fixation or number of times participants fixated at least once within an AOI divided by the total number of fixation recordings in the test.
6. Average fixation duration, obtained by dividing the total fixation duration by fixation counts.

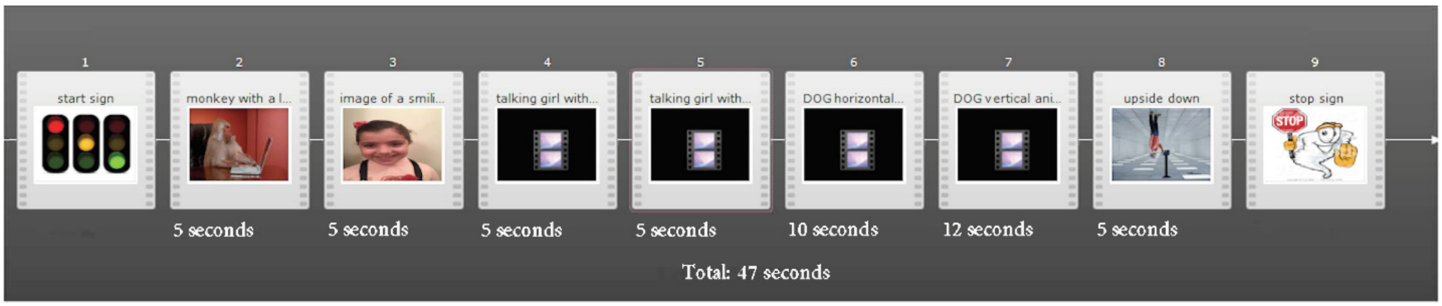

Figure 3: Overview of the model of the experiment showing all testing paradigms and the duration of each.

Statistical analysis

A preliminary statistical power analysis was executed to detect the appropriate sample size for this study. To obtain a power of 80% and based on previous studies with similar duration of testing paradigms, between 30 and 90 subjects needed to be recruited in each arm. All data variables were entered into SPSS V22 software. Vision screening results and demographic variables were analyzed and compared between the three groups using the ANOVA single factor test. *Chi square* test was used to compare frequencies among categorical variables such as gender. Eye tracking parameters were recorded and analyzed comparing the children with ASD, their siblings, and neurotypically developing children using One-Way Anova test when the data of eye tracking related scores fit the normal frequency distribution, and its non-parametic counterpart (Kruskal Wallis) if the data did not fit the normal distribution. When the difference across the 3 groups was statistically significant, Post-Hoc tests determined which specific groups were statistically significantly different from each other. A Bonferroni correction, Tukey's HSD test, and Tamhane's T2 test were also applied to account for multiple testing. Comparison between two areas of interest (e.g. total fixation duration on laptop vs. monkey) in the same paradigm was achieved with the paired t-test. Additional unadjusted and adjusted linear regression analyses were performed to further explore the relationship between fixation duration and autism status controlling for other covariates, including age and fixation count. Log transformation was used for fixation duration to make the skewed data approximately normally distributed in order to conduct the regression analysis. Correlation with neurologic data of autism severity scale and eye contact was performed. Statistical significance was set at p-value <0.05.

Results

One hundred fifty-five subjects were enrolled in this study: forty one diagnosed with ASD and 30 of their siblings considered at high risk from a total of 40 families, as well as 84 controls. Demographic data pertaining to mean age and gender differed at a borderline statistical significance across the three groups. Subgrouping of age and visual acuity did not significantly differ among the three groups and the means of spherical equivalent for both right and left eyes were similar between ASD, sibling and control groups (Table 1). In the ASD group, 2 participants out of 41 (5%) had refractive anomalies (astigmatism) and were prescribed eye glasses. Two had exotropia (5%). Their siblings included 2 cases of astigmatism out of 30 (7%) but had no motility defects. In the control group, 23 out of 84 (27%) had refractive errors and were wearing glasses with no motility abnormalities present. These errors did not interfere with the tracking process.

ASD severity (Table 1):

The severity of ASD was assessed using several criteria or screening tools, including DSM-V criteria, CARS-2 and ADOS-2 screening tools. Seventeen patients (41%) were considered mild cases, 12 (29%) fell in the moderate cases category, 10 (24%) were severe, and no data was available on 3 or 1%. The neurologic assessment of participants with ASD using DSM-V criteria or CARS, 8 (19%) had good eye contact, 23 (55%) had inconsistent eye contact, 7 (17%) presented poor eye contact, and there was no available information on 3 (7%). A negative correlation between severity of ASD and eye contact was noted. Severe cases had significantly poorer eye contact, while those on the milder ASD spectrum had better eye contact (p≤0.001).

	ASD (n=41)	**Siblings (n=30)**	**Controls (n=84)**	**p-value**
Gender n(%)				
Male	25 (61)	19 (63.3)	36 (42.9)	0.06[a]
Female	16 (39)	11 (36.7)	48 (57.1)	
Ratio (F/M)	0.68	0.58	1.33	
Mean Age (years)	9 ± 4.5	7.4 ± 3.8	7.3 ± 3.9	0.06[b]
Age group n (%)				
≤3 years	8 (19.5)	4 (13.3)	16 (19)	
3 years to 12 years	23 (56.1)	23 (76.7)	58 (69)	<0.27[a]
> 12 years	10 (24.4)	3 (10)	10 (11.9)	
Mean Vision (LogMAR)				
Right eye	0.04± 0.2	0.07 ± 0.1	0.08 ± 0.1	0.52[b]
Left eye	0.03 ± 0.2	0.06 ± 0.2	0.09 ± 0.1	0.59[b]
Mean Spherical Equivalent (diopters)				
Right eye	0.3 ± 0.1	0.3 ± 0.8	0.01 ± 1.7	0.3[b]
Left eye	0.3 ± 0.3	0.3 ± 0.7	0.1 ± 1.9	0.5[b]
Autism severity n (%)				
Mild	17 (41.5)			
Moderate	12 (29.3)			
Severe	10 (24.4)			
No data	2 (4.8)			

[a] Pearson Chi-Square test
[b] Anova test

Table 1: Demographics of study subjects.

Horizontal and vertical motion paradigms: (Table 2, Figure 2a):

Significant tracking differences were noted between groups on horizontal gaze, notably the time to fixation (P=0.009), total fixation duration (P<0.001), and fixation count (P<0.001). Further pairwise comparisons established that ASD subjects took longer to fixate for the first time compared to either sibling or control groups. Furthermore, the total fixation duration for the ASD group was shorter than that of both sibling and control groups, although average fixation duration was longer, and this was statistically significant. Fixation count was also lower in the ASD group compared to the control group. This meant that children in the ASD group took a longer time to start following the moving dog, and tracked the dog for shorter durations than children in the other two groups.

In comparison, vertical gaze showed significant differences between groups for the following parameters: total fixation duration (P=0.001), fixation count (P=0.002) and percentage of fixation (P<0.001). The pairwise comparisons further demonstrated quite similar results to the horizontal motion paradigm. The total fixation duration for the ASD group was lower than for the control group. The fixation counts in the ASD group were lower than the counts in both the sibling and control groups. Additionally, the percentage of fixation was lower for the ASD group when compared to both sibling and control groups. This meant that in the vertical gaze experiment, children in the ASD group also followed the moving dog for shorter periods of time without there being a significant delay in the time to first fixation of the area of interest that was present in the horizontal motion.

In conclusion, in both horizontal and vertical gazes, the ASD group demonstrated decreased total fixation duration and fixation count, with a delay in time to first fixation only noticed in horizontal gaze.

	ASD (n=41)	Siblings (n=30)	**Controls (n=84)**	P value	Pairwise tests of significance
Horizontal Motion					
Time to first fixation (seconds)	4.31± 2.39	3.75 ± 1.50	3.70 ± 1.02	**0.009**	ASD>S; ASD>C
First fixation duration (seconds)	0.41 ± 0.20	0.28 ± 0.08	0.44 ± 0.16	0.107	
Total fixation duration (seconds)	2.68 ± 4.15	3.91 ± 2.79	4.08 ± 2.67	**<0.001**	ASD<S; ASD<C
Fixation count	6.56 ± 17.70	10.50 ± 14.26	9.65 ± 15.97	**<0.001**	ASD<S; ASD<C
Average fixation duration (seconds)	0.50 ± 0.87	0.37 ± 0.14	0.44 ± 0.18	**0.008**	ASD>C
Percentage of fixation	98 ± 2	97 ± 3	95 ± 5	0.808	
Vertical Motion					
Time to first fixation (seconds)	2.49 ± 2.49	2.56 ± 1.36	2.55 ± 1.89	0.643	
First fixation duration (seconds)	0.37 ± 0.19	0.27 ± 0.07	0.35 ± 0.14	0.517	
Total fixation duration (seconds)	4.07 ± 8.62	5.45 ± 7.37	5.92 ± 4.99	**0.001**	ASD<C
Fixation count	8.17 ± 32.95	11.97 ± 20.17	11.19 ± 23.70	**0.002**	ASD<S; ASD<C
Average fixation duration (seconds)	0.52 ± 0.23	0.46 ± 0.21	0.60 ± 0.38	0.233	
Percentage of fixation	85 ± 13	100 ± 0	100 ± 0	**<0.001**	ASD<S; ASD<C

Table 2: Eye tracking parameters for horizontal and vertical motion paradigms (mean ±SD).

Still image of a smiling face (Table 3, Figure 2b)**:**

When looking at the eyes of the girl in the image, significant differences between groups were noted in total fixation duration (P=0.004) and fixation count (P=0.049). The pairwise comparisions revealed that the ASD group had a shorter total fixation duration on the eyes when compared to sibling and control groups. They also had less fixation count, as compared to controls. When looking at the mouth, significant differences between groups were noted on all of the fixation parameters. The pairwise comparisons showed that the ASD group had a shorter time to first fixation on the mouth compared to the control group, as well as a shorter first fixation duration, total fixation duration, and percentage of fixation on the mouth compared to both sibling and control groups. When comparing fixation on eye vs mouth in the image, all subjects showed preferential visual tracking patterns to the eyes. Only siblings and controls demonstrated significantly faster first fixation on eyes vs. mouth with longer duration and higher fixation counts. This meant that children in the ASD group looked at the mouth faster than children in the other two groups. They also stared at the eyes for shorter durations than siblings and controls.

	ASD (n=41)	**Siblings (n=30)**	**Controls (n=84)**	*P value	Pairwise tests of significance
Time to first fixation (seconds) Eyes Mouth	 0.59 ± 0.74 0.95 ± 1.75 **p-value=0.10	 0.28 ± 0.16 1.32 ± 1.66 p-value=**0.001**	 0.34 ± 0.27 1.24 ± 1.35 p-value=**0.001**	0.443 **0.042**	ASD<C
First fixation duration (seconds) Eyes Mouth	0.22 ± 0.03 0.17 ± 0.04 p-value=0.16	0.22 ± 0.01 0.28 ± 0.06 p-value=0.23	0.33 ± 0.31 0.27 ± 0.08 p-value=0.41	0.330 **0.038**	ASD<S; ASD<C
Total fixation duration (seconds) Eyes Mouth	1.47 ± 1.10 0.42 ± 0.32 p-value=**0.001**	2.05± 1.05 0.65 ± 0.25 p-value=**0.001**	2.15 ± 0.99 0.64 ± 0.28 p-value=**0.001**	**0.004** **0.007**	ASD<C ASD<S; ASD<C
Fixation count Eyes Mouth	5.54 ± 17.35 1.29 ± 2.91 p-value=**0.001**	7.13 ± 14.12 2.23 ± 2.81 p-value=**0.001**	7.19± 10.79 2.04 ± 2.01 p-value=**0.001**	**0.049** **0.018**	ASD<C ASD<S; ASD<C
Average Fixation Duration (seconds) Eyes Mouth	0.27 ± 0.12 0.35 ± 0.14 **p-value=0.013**	0.28 ± 0.13 0.32 ± 0.19 **p-value=0.29**	0.31 ± 0.14 0.32 ± 0.24 p-value=0.63	0.371 0.421	
Percentage of fixation Eyes Mouth	93 ± 7 50 ± 26 p-value=**0.001**	97 ± 3 87 ± 12 p-value=0.18	99 ± 1 87 ± 12 p-value=**0.001**	0.193 **<0.001**	ASD<S; ASD<C

ASD: Autism Spectrum Disorder; C: Controls; S: Siblings

*P value: signifies differences among the 3 groups: ASD, siblings and controls

**p-vlaue: signifies differences between eyes and mouth

Table 3: Eye tracking parameters for the face image paradigm (mean ± SD).

Video of a talking face without sound (Table 4)**:**

In the mute video, when looking at the eyes, significant differences between groups were noted for time to first fixation (P=0.006), total fixation duration (P=0.028), and percentage of fixation (P=0.02). The pairwise comparisons revealed that the time to first fixation was longer while the total fixation duration was shorter in the ASD group compared to controls. Also, the ASD group had lower percentage of fixation on the eyes compared to sibling and control groups. When looking at the mouth, statistically significant differences between groups were present for first fixation duration (P=0.003), total fixation duration (P<0.001), fixation count (P=0.031), and percentage of fixation (P=0.020). Specifically, the pairwise comparisons revealed shorter first fixation duration, total fixation duration, and average fixation duration in the ASD group compared to both sibling and control groups, as well as lower fixation counts and percentages of fixation in the ASD group compared to controls.

Interestingly, all of the participants, including those in the ASD group, had a longer total duration of fixation on the eyes than on the mouth. First fixation duration however was shorter on the eyes in the ASD group. This meant that the findings were similar between the dynamic depiction of a talking face and the static image of the face. Participants in the ASD group still showed avoidance of gaze at eyes in the face image/video with longer time to first fixation and shorter durations compared to siblings and controls.

	ASD (n=41)	Siblings (n=30)	Controls (n=84)	*P value	Pairwise tests of significance
Time to first fixation (seconds) Eyes Mouth	0.32 ± 0.42 0.86 ± 1.36 **p-value=**0.01**	0.17 ± 0.26 1.01 ± 1.18 p-value=**0.001**	0.10 ± 0.07 0.63 ± 0.37 p-value=**0.001**	**0.006** 0.523	ASD<C
First fixation duration (seconds) Eyes Mouth	0.40 ± 0.78 0.40 ± 0.48 p-value=0.47	0.22 ± 0.03 0.95 ± 1.09 p- value=**0.001**	0.37 ± 0.61 0.91 ± 0.91 p- value=**0.001**	0.977 **0.003**	ASD<S; ASD<C
Total fixation duration (seconds) Eyes Mouth	2.75 ± 2.71 0.75 ± 1.06 p-value=**0.001**	3.62 ± 1.11 1.61 ± 1.63 p-value=**0.001**	3.63 ± 1.39 1.74 ± 1.76 p-value=**0.001**	**0.028** **<0.001**	ASD<C ASD<S; ASD<C
Fixation count Eyes Mouth	6.51 ± 17.96 1.29 ± 1.96 p-value=**0.001**	7.90 ± 7.68 2.13 ± 4.67 p-value=**0.001**	7.16 ± 8.50 2.06 ± 2.25 p-value=**0.001**	0.216 **0.031**	ASD<C
Average Fixation Duration (seconds) Eyes Mouth	0.54 ± 0.44 0.70 ± 0.79 p-value=**0.217**	0.55 ± 0.28 1.03 ±0.85 p-value<**0.001**	0.59 ±0.45 0.96 ± 0.67 p-value<**0.001**	0.190 **0.026**	ASD<C
Percentage of fixation Eyes Mouth	87 ± 11 59 ± 25 p-value=**0.001**	100 ± 0 80 ± 17 p-value=**0.01**	98 ± 2 81 ± 16 p-value=**0.001**	**0.020** **0.020**	ASD<S; ASD<C ASD<C

ASD: Autism Spectrum Disorder; C: Controls; S: Siblings
*P value: signifies differences among the 3 groups: ASD, siblings and controls
**p-vlaue: signifies differences between eyes and mouth

Table 4: Eye tracking parameters for the video without sound paradigm (mean ± SD).

Image of an inanimate and animate object (monkey/ laptop paradigm), (Table 5), (Figure 2 c):

When looking at an inanimate subject such as the laptop, significant differences were established only in relation to percentage of fixation (P=0.038). This was lower in the ASD group than in controls based on pair wise comparisons. On the other hand, when looking at an animate subject (monkey), the differences between the 3 groups were statistically significant in all fixation parameters, except time to first fixation. The ASD group had shorter first fixation durations and total fixation durations, lower fixation counts, and lower percentage fixation. Differences between focusing on the monkey vs. laptop were present mainly in the control group and to a lower extent, in the ASD group, where subjects looked more, faster and longer at the animate element or monkey compared to siblings and controls. In all three groups however, there was preferential visual fixation at the animate element in the image or the monkey (when comparing fixation directly on the laptop versus monkey).

	ASD (n=41)	Siblings (n=30)	Controls (n=84)	*P value	Pairwise tests of significance
Time to first fixation (seconds) Laptop Monkey	1.05 ± 1.65 0.55 ± 0.68 **p-value=**0.03**	1.17 ± 1.09 0.86 ± 1.13 p-value=0.13	1.10 ± 0.93 0.40 ± 0.19 p-value=0.001	0.547 0.253	
First fixation duration (seconds) Laptop Monkey	0.22 ± 0.04 0.30 ± 0.15 p-value=0.08	0.26 ± 0.04 0.34 ± 0.08 p-value=0.12	0.28 ± 0.05 0.37 ± 0.09 p-value=**0.01**	0.300 **0.034**	ASD<C
Total fixation duration (seconds) Laptop Monkey	0.72 ± 0.38 1.32 ± 1.35 p-value=**0.001**	1.06 ± 0.65 1.44 ± 0.94 p-value=0.07	0.91 ± 0.39 1.87 ± 0.97 p-value=**0.001**	0.099 **0.012**	ASD<C
Fixation count Laptop Monkey	2.49 ±4.86 3.26 ± 6.55 p-value=0.06	3.77 ± 9.15 3.80 ± 5.13 p-value=0.48	3.26 ± 5.62 4.52 ± 4.47 p-value=**0.001**	0.086 **0.014**	ASD<C
Average Fixation Duration (seconds) Laptop Monkey	0.29 ± 0.11 0.47 ± 0.37 P=value 0.018	0.28 ± 0.15 0.40 ± 0.21 p-value=0.005	0.30 ± 0.16 0.44 ± 0.23 p-value=0.001	0.625 0.484	
Percentage of fixation Laptop Monkey	73 ± 20 80 ± 16 p-value=0.19	87 ± 12 97 ± 3 p-value=0.09	90 ± 9 95 ± 5 p-value=0.08	**0.038** **0.011**	ASD<C ASD<S; ASD<C

ASD: Autism Spectrum Disorder; C: Controls; S: Siblings
*P value: signifies differences among the 3 groups: ASD, siblings and controls
**p-vlaue: signifies differences between eyes and mouth

Table 5: Eye tracking parameters for the inanimate/animate paradigm (mean ± SD).

Inverted scene paradigm (Table 6, Figure 2 d):

Fixation count was different across the 3 groups and this was statistically significant. Specifically, participants with ASD had significantly lower fixation count when compared to controls based on pair-wise comparisons.

	ASD (n=41)	**Siblings (n=30)**	**Controls (n=84)**	P value	Pairwise tests of significance
Time to first fixation (seconds)	0.43 ± 1.02	0.15 ± 0.13	0.11 ± 0.05	0.757	
First fixation duration (seconds)	0.20 ± 0.04	0.15 ± 0.01	0.21 ± 0.29	0.766	
Total fixation duration (seconds)	2.71 ± 1.99	3.05 ± 1.52	3.25 ± 1.40	0.084	ASD<C
Fixation count	9.32 ± 22.47	11.33 ± 23.06	11.83 ± 18.16	**0.014**	
Average Fixation Duration (seconds)	0.30 ± 0.12	0.28 ± 0.09	0.33 ± 0.53	0.341	
Percentage of fixation	93 ± 7	93 ± 6	96 ± 03	0.620	
ASD: Autism Spectrum Disorder; C: Controls					

Table 6: Eye tracking parameters for the inverted scene paradigm (mean ± SD).

Relationship between log total fixation duration & ASD status, controlling for fixation count, age, gender, and refractive errors:

The linear regression analysis showed that in the horizontal motion paradigm, adjusting for fixation count in addition to age, gender, and refractive errors, the log total fixation duration decreased by 0.46 seconds in the ASD group (P<0.05) and by 0.19 seconds in the sibling group when compared to controls (p-value not signficant). Similarly, in the vertical gaze paradigm, the adjusted log total fixation duration decreased by 0.15 seconds in the ASD group and by 0.19 seconds in the sibling group when compared to controls, without the difference being statistically significant.

When looking at the eyes in the smiling girl paradigm, the log total fixation duration decreased by 0.27 seconds in the ASD group compared to control (P<0.05), after adjusting for other covariates. Similarly, for the mute video paradigm, the log total duration decreased by 0.51 seconds in the ASD compared to the control group (P<0.05). For the remaining paradigms adjusting for fixation count, age, gender and refractive errors did not show major changes in the log fixation duration in ASD vs. control or sibling vs. control groups. On further evaluation of the regression model, the changes obtained in all parameters occurred when adjusting to fixation count specifically and not age, gender, or refractive errors. This meant that adjustment for fixation count was necessary when comparing the ASD and control groups, and further increased the statistically significant differences noted in the motion paradigm and the face image/ video paradigms. When computing the eye-tracking parameters seperately for males and females, the males in the ASD group were found to have the same statistically significant differences compared to the male siblings and control group as was reported for the total group for the vertical and horizontal motion paradigm. Only the total fixation duration and the percentage fixation were significantly different in the female ASD group compared to female siblings and controls for the same paradigm (P=0.038 and P<0.001 respectively). In all the other paradigms females and males had relatively similar results, mirroring those of the whole group.

Correlation between vision screeening and eye examination:

Only a small percentage of the ASD group (5%) had refractive errors and were already wearing corrective lenses at the time of vision screening. Vision screening could be successfully performed in 76% of children with ASD, 93% of siblings and 96% of controls. The Plusoptix S12 underestimated hyperopia in the ASD and sibling groups by 0.9 and in controls by 0.2 Diopters. The intraclass correlation coefficient (ICC) for spherical equivalents indicated excellent agreement between the Pluoptix S12 and manual cycloplegic retinoscopy upon comprehensive eye examintaion in the control group (ICC= 0.9) and moderate agreement in the high risk group of siblings (ICC =0.6) and ASD group (ICC=0.5). When correcting for SE by a regression model, no difference was determined in eye tracking results indicating that there was no association between eye-tracking parameters and refractive errors in our cohort.

Discussion

Participants with ASD exhibited shorter total fixation duration and less fixation counts than their siblings and neurotypically developing children across most eye tracking paradigms indicating a generally reduced attention in the ASD group. Vision screening results validated and confimred by complete eye examinations did not demonstrate a high rate of ocular disorders in this group as only 5% had refractive errors. Mean visual acuity and spherical equivalent values were similar in the ASD group compared to controls and siblings. Five % of ASD subjects had refractive errors and 5% motility problems, compared to 7% refractive errors in siblings and 27% in controls with no motility problems in the latter two groups. The control group was recruited from the ophthalmogy clinic while presenting for check-up or for follow-up for refractive errors; the rates of refractive errors detected in them do not represent that of the general population. The high rate of refractive errors in this group did not affect their performance on the eye tracker and served to demonstrate the absence of significant correlation between refractive errors and eye-tracking findings. In this study, five testing paradigms were used:

1. The horizontal/vertical motion paradigm showed that subjects with ASD took more time to begin fixating on horizontal motion, and had less fixation counts than siblings and controls. This indicated delayed and reduced visual attention to the horizontally moving dog in the ASD group. This delay in fixation was not observed in the vertical motion video that followed the horizontal motion video, which pointed towards either a possible 'learned behavior' upon exposure to a second similar paradigm, or to less interest in horizontally moving targets. Percentage fixation was, however, decreased in the vertical video.

2. The face of a girl in the still image paradigm showed that the ASD group fixated later and for shorter periods of time on the eyes than did the other groups. All participants had longer fixation durations on the eyes compared to the mouth.

3. When presented with a mute video of a talking girl, fixation on eyes was more prominent than on the mouth in all groups, but the ASD group needed a longer time to first fixate on the eyes compared to controls, again showing avoidance of eyes on initial gaze. Similar to many previous studies that reported preferential gazing at the mouth in children with ASD, results indicated that even after adjusting for total fixation time, children in the ASD group focused less on either mouth or eyes than did children in the other two groups, with preferential gaze behaviour towards the mouth. Hosozawa et al. report a general inattention to faces along with non-preferential fixation on eyes or mouth in their ASD cohort [27]. Children with specific language impairment, however, concentrated more on the mouth than both typically developing and ASD children. This was stipulated to be due to compensation for specific language deficits in the latter group [27]. The findings were similar in this study when looking at a still image or a dynamic mute video of a girl talking. The video was muted in order to exclude the confounding preference to audiovisual synchrony that has been reported in the literature.

4. The animate/inanimate object paradigm uncovered preferential fixation on the animate element or monkey rather than on the inanimate element or laptop in all groups. At the outset, the expectation was that children in the ASD group would show preferential attention to the inanimate element, especially that it was a computer with a keyboard. With the ubiquitous presence of computers, ipads, and televisions in households, numerous researchers reported that children with ASD were absorbed by and spent a lot of time using electronic screen media [28,29]. Taking advantage of that fact, computer-based learning has been incorporated in many educational programs for children with ASD [30]. In the present cohort, preferential attention to the animate object for most parameters emerged with longer fixation duration on the monkey compared to the laptop.

5. The inverted scene showed similar eye tracking patterns to above paradigms, with decreased fixation counts in the ASD group. Other parameters did not reach statistical significance. This only supported the general inattention of the ASD group, which did not differ when a semi-naturalistic scene was inverted.

Siblings showed no significant differences in any of the paradigms studied when compared to neurotypically developing children.

A number of previous studies examined eye movement recordings in patients with ASD, demonstrating that eye contact alteration in these patients might be controversial [10,31,32]. Some studies negated gaze aversion in ASD as concluded in the study by Adrien et al [31]. In another study, utilizing pictures and video paradigms, 26 two-year old toddlers with ASD did not have significant defiant eye contact compared to 38 age and gender-matched controls, but were rather indifferent to eye gaze [33]. Similar to findings in this study regarding fixation on eye vs. mouth in a face paradigm, a meta-analysis summarizing 14 studies concluded that ASD subjects fixated less on eyes than controls, with no significant differences in mouth gaze, and this was attributed to a heterogeneity in mouth fixation studies [10].

Others found no alteration in patients with ASD with age ranges from infancy to adulthood, as they did not pay less attention to the face, and did not concentrate solely on the mouth [18]. In another study with results supporting findings in this present study, the percentage of fixation in 11 subjects with ASD aged between 4 and 20 years was decreased compared to 17 controls and 14 girls with Rett disease, on 3 paradigms including human faces [34]. On the other hand, other studies showed preferential gaze towards the mouth in a human face, where the severity of social disability in these patients correlated with the gravity of the altered eye contact [23]. Attention difficulties were expressed in patients with ASD when performing tasks, and this persisted into adulthood. In one study using an interactive paradigm, ASD adults manifested deficient joint attention, and diffuclt communication when they were confronted with tasks requiring eye gaze, in comparison to neurotypically developing adults [32]. In the present study older subjects were included (2 years to 17 years) more than in most previous studies on toddlers, fixation on eyes was significantly reduced in ASD subjects whether presented with a still face image or a mute talking face. In fact, preferrential attention to the mouth with a significant shorter time to first fixation vs. controls was documented more so in the still image than in the talking video, pointing to a frank preference of fixation on the mouth in a still face that is not explained by confounding mouth movements or sounds during speech.

In contrast to previous literature which assessed mainly pictures and videos of human faces and focused mostly on eye contact and preferential looking to mouth vs eyes, this study explored several other testing paradigms. In the vertical/horizontal motion video, a significant delay was observed in first fixation in horizontally moving targets and decreased percentage of fixation in vertically moving targets in the ASD group. These challenges may be a helpful guide to physical/behavioural therapy in subjects with ASD, where patients are presented with moving objects/toys or required to pay attention to videos.

While it has been noted in clinical and every day settings that autistic children are invariably attracted to keyboards, screens, computers and mobiles, it was not demonstrated that a definite preference for the laptop vs. the monkey was present in our study. Percentage of fixation was lower in the ASD group both on the monkey and laptop elements. One explanation could be that in this particular image, the monkey was in face view while the keyboard was partially obstructed (Figure 2, bottom left). When gazing at the money, fixation duration and fixation counts were decreased compared to controls, and this was not observed when the laptop was the object of interest.

When observing an inverted scene, similar trends in eye movements were confirmed in the ASD group with lower fixation count indicating reduced general attention. According to previous published reports, when presented with upright and upside-down faces, ASD subjects fixated more and longer on the eyes in the upside down orientation, and more and longer on the mouth in the upright position referred to as “the inverted face effect” [14]. While this effect was observed when the stimuli were faces, it was not observed with a semi-naturalistic inverted scene where only general attention was affected akin to other paradigms presented. This is to be kept in mind when presenting patients with ASD with different stimuli during behavioural therapy.

Limitations to this work included the limited sample size, although it was higher than that in most cited studies. This precluded solid subgrouping by age and/or severity of ASD, which would give more valuable information and may be confounding variables in eye movement recordings. Some families resisted enrollment of siblings, probably due to the fear of uncovering early diagnoses of ASD, hence the lower number of siblings than ASD subjects. The control group was selected from children presenting to the pediatric eye clinic at the American University of Beirut and not from a community setting, which presented a bias as a higher rate of refractive error was present inherently in this group. This, however, did not interfere with their ability to perform eye tracking with excellent calibration. Additionally, groups were not IQ-matched which could be another confounder and the control group did not receive formal testing/ screening for ASD.

In conclusion, children with ASD demonstrated differential eye tracking patterns using novel testing paradigms. A universal trend to lower fixation duration and fixation counts was observed across most studied paradigms in keeping with the general decrease in attention in this group, and this persisted, after correction for fixation count. When contemplating a face, attention to the mouth element was faster in the ASD group than in controls. This was demonstrated to a larger extent with a still image compared to a mute video and, therefore, could not be attributed to mouth movement or audiovisual synchrony in real life. Participants with ASD fixated less on both eyes and mouth than did children from the other two groups, with shorter documented durations and counts. Different challenges were noted on gaze at moving objects with a delay in fixation at horizontally moving targets and a decreased percentage of fixation at vertically moving ones. Interestingly, when presented with a similar video of a moving target for a second time but in a different direction, children with ASD fixated at the target faster than in the first experiment, comparagble to the other two groups. Definite preferential looking at an inanimate object vs. a living being could not be demonstrated. These observations were independent of subject age and were not confounded by any ocular abnormalities. These findings are valuable to incorporate in therapy and have implications for autism intervention programs, focusing not only on face gaze/ processing but on other elements important for social fluency including motion processing, interpretation of inverted everyday scenes, and gaze at interactive living things vs non-living objects. Last but not least, sex differences in autism are just beginning to be addressed and all future studies should keep this in mind.

Compliance with Ethical Standards

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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