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Eye gaze and pupillary response in Angelman syndrome

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ABSTRACT

Background: Angelman syndrome (AS) is a rare neurological disorder characterized by severe developmental disability, communication impairment, elevated seizure risk, and motor system abnormalities.

Aims: The aims of this study were to determine the feasibility of social scene eye tracking and pupillometry measures in individuals with AS and to compare the performance of AS participants to individuals with idiopathic Autism Spectrum Disorder (ASD) and typically developing controls (TDC).

Methods and procedures: Individuals with AS and age- and gender- matched controls completed a social eye tracking paradigm. Neurobehavioral characterization of AS participants was completed via a battery of psychological testing and caregiver behavioral evaluations.

Outcomes and results: Eight of seventeen recruited AS participants completed the eye tracking paradigm. Compared to TDC, AS subjects demonstrated significantly less preference for social scenes than geometric shapes. Additionally, AS subjects showed less pupil dilation, compared to TDC, when viewing social scenes versus geometric shapes. There was no statistically significant difference found between AS and ASD subjects in either social eye tracking or pupillometry.

Conclusions and implications: The use of eye tracking and pupillometry may represent an innovative measure for quantifying AS-associated impairments in social salience.

What this paper adds

The remarkably abnormal social gaze preference and pupillometry findings of individuals with AS in this study provide important information about the impact of this neurodevelopmental disorder on functional social attention, interest, and subsequent arousal. The use of eye tracking and pupillometry may represent an innovative measure for quantifying AS-associated impairments in social salience and pathophysiology.

1. Introduction

Angelman syndrome (AS) is a rare neurological disorder characterized by severe developmental disability affecting between 1 in 10,000–20,000 individuals (Buckley, Dinno, & Weber, 1998; Clayton-Smith & Laan, 2003; Wink et al., 2015). AS is caused by

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disruption of the maternally-inherited E3 ubiquitin protein ligase gene (UBE3A) located in chromosome region 15 (15q11-q13) (Clayton-Smith & Laan, 2003; Kishino, Lalande, & Wagstaff, 1997; Tan, Bacino, Skinner, Anselm, & Glaze, 2011). Individuals with AS suffer from functionally severe developmental delay, movement and seizure disorders, communication impairment, and a distinctive behavioral profile, which includes a happy demeanor, frequent laughter, excitability, and love of water. These symptoms are often accompanied by microcephaly, limited attention span, and stereotypical movements (Clayton-Smith & Laan, 2003; Dagli, Buiting, & Williams, 2011; Tan et al., 2011). Historically, there has been debate as to whether AS can be deemed an autism related disorder with several reports concluding that a subset of individuals with AS suffer from concurring Autism Spectrum Disorder (ASD) (Peters, Beaudet, Madduri, & Bacino, 2004; Peters, Horowitz, Barbieri-Welge, Taylor, & Hundley, 2012) and others concluding that this diagnostic trend is the result of severe cognitive delay and stereotypic behaviors (Grafodatskaya, Chung, Szatmari, & Weksberg, 2010; Moss & Howlin, 2009; Williams, 2010). Individuals with AS often receive treatment for medical and behavioral comorbidities, but there are no treatments that address the core features of the disorder. The development of quantitative biological and neurophysiological markers, which more clearly describe core phenotypic features of AS, may help define subgroups of persons with AS, inform outcome measure development, and contribute to development of the personalized medicine approach.

Eye tracking measures, such as the evaluation of gaze points and pupil size, provide promising strategies to quantify the severity of symptoms and resolve subgroup heterogeneity across developmental disabilities (Boraston & Blakemore, 2007; Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004). Klin et al. (2002) demonstrated that social scene eye tracking paradigms function as valid replications of social scene viewing in an experimental setting. Through these methods, social impairment in individuals with ASD has been correlated with gaze fixations away from eye regions and toward objects. Pelphrey et al. (2002) demonstrated that adult males with ASD struggle to recognize emotions when viewing faces, suggesting potential abnormal processing of core facial features related to emotion expression. Recently, several studies have reported that preference for geometric patterns over social scenes, as measured by eye tracking paradigms, can predict diagnosis of ASD in infants, toddlers, and adolescents (Gaietto et al., 2014; Pierce, Conant, Hazin, Stoner, & Desmond, 2011; Shi et al., 2015).

Pupillary response is a method of measuring cognitive load and arousal through autonomic response (Hess & Polt, 1960; Janisse, 1977). Bradley et al. (2008) found a positive correlation between skin conductance and pupillary dilation supporting pupillometry as a measure of sympathetic nervous system activity, which modulates emotional processing. Recently, pupillary response has been utilized to assess autonomic nervous system arousal in response to social stimuli in developmentally disabled populations. For example, individuals with ASD demonstrated decreased pupillary dilation to emotional faces, which some have theorized may be due to decreased intrinsic reward or responsiveness from social situations and cues (Anderson, Colombo, & Jill Shaddy, 2006; Sepeta et al., 2012).

Despite the extensive work in ASD and other developmental disorders, no eye tracking research has been published in AS to date. Eye tracking measures have the potential to non-invasively provide objective behavioral data in subjects with grossly impaired communication and, therefore, may be ideal in use of individuals with significant developmental delay such as AS. Eye tracking may also provide independent neurophysiological indices to complement the traditional caregiver report measures and psychological testing currently relied upon in AS research and clinical assessment, potentially helping to clarify diagnostic dilemmas in AS.

In this study, our primary aim was to evaluate the feasibility of utilizing social eye tracking and pupillometry measures in subjects with AS. We hypothesized that some individuals with AS would be able to complete the eye tracking paradigms and provide evaluable eye tracking data, but we also expected that some individuals would not be able to complete study procedures due to cognitive, physical, and communication limitations. Furthermore, impaired cognition and attention have been shown to have an impact on social awareness and functioning in AS, other developmental disabilities, and some psychiatric disorders (Liddle, 2000; Smith & Matson, 2010; Williams, 2010). Consequently, despite the happy demeanor and social disposition of many individuals with Angelman Syndrome, we hypothesized that, compared to healthy controls, AS individuals would show less preference for and have abnormal autonomic response to social stimuli as shown by gaze and pupillary response measures. We additionally wished to explore how performance in individuals with AS compared to prior eye tracking studies of social deficits in ASD.

2. Materials and methods

2.1. Subjects

Seventeen individuals with a confirmed genetic diagnosis of AS were recruited at Indiana School of Medicine and Cincinnati Children's Hospital by the same investigators (CAE, EVP, LKW) between 2012 and 2015 as part of an ongoing effort to evaluate the neurobehavioral and molecular phenotype of AS (Erickson et al., 2016; Wink et al., 2015). AS subjects were characterized as UBE3A deletion or non-deletion genotype according to clinical diagnostic sequencing of the UBE3A gene. Age- and gender-matched typically developing individuals and age- and gender-matched individuals with ASD were retrospectively selected from two other studies (by the same investigators) to serve as controls. All participants or their guardians (as indicated) provided written informed consent for study participation according to protocols approved by the local Institutional Review Boards.

2.2. Measures

Neurobehavioral characterization of individuals with AS was completed via a battery of psychological testing and caregiver behavioral evaluations. The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) was used as a measure of cognitive functioning (Bayley & Reuner, 2006). The caregiver rated Aberrant Behavior Checklist (ABC) was used to assess

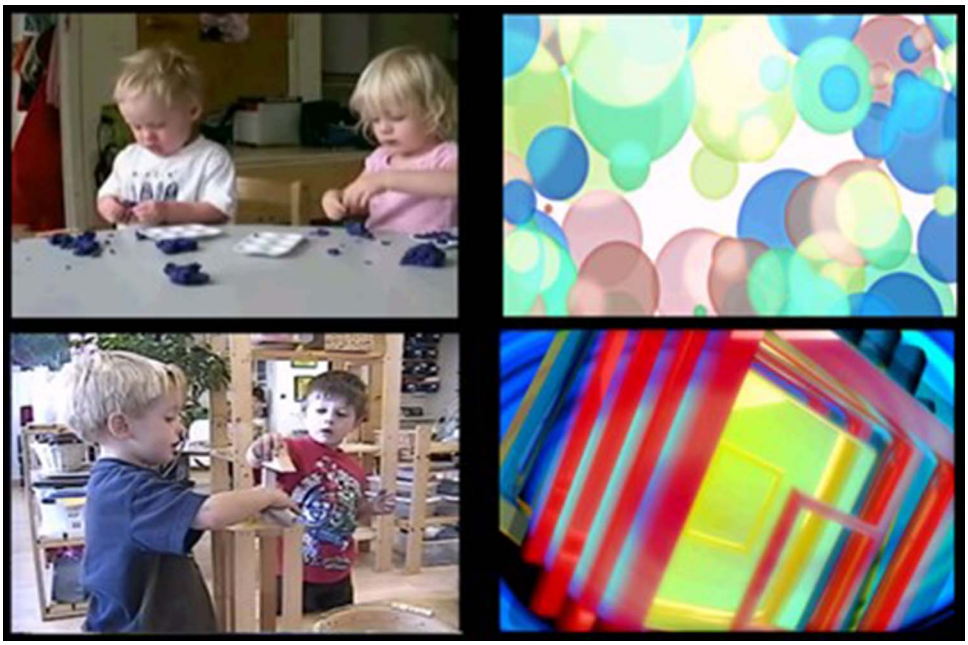

Fig. 1. Still images of two of the video pairs used in the social scenes and geometric patterns eye tracking task. Videos were presented in pairs with the social scenes randomly assigned to either the left or right side.

maladaptive behaviors including irritability, social withdrawal, stereotypy, hyperactivity, and inappropriate speech (Aman, Singh, Stewart, & Field, 1985; Constantino & Gruber, 2007). The ABC inappropriate speech subscale was not reported due to the severe speech impairment associated with AS. The Social Responsiveness Scale (SRS) was used to measure the severity of social impairment across awareness, cognition, communication, motivation, and autistic mannerisms subscales (Constantino & Gruber, 2007). Adaptive functioning was evaluated via the Vineland Adaptive Behavior Scales Interview Edition, 2nd Edition (VABS-II) (Sparrow, Balla, Cicchetti, Harrison, & Doll, 1984).

2.3. Apparatus, procedure, and stimuli

Eye tracking data was acquired using a Tobii T120 infrared binocular eye tracker with an integrated 17-inch flat-panel monitor running Tobii Studio (Version 3.0, Tobii Technology, Sweden). The eye tracker samples gaze point and pupil diameter at a rate of 120 Hz. Eye tracking measures, such as gaze and saccades, were analyzed using Tobii Studio (Tobii Pro, Stockholm, Sweden). All pupil data was exported to Microsoft Excel and analyzed in SPSS version 23.0 (IBM Corp., Armonk, New York). Successful calibration using the Tobii Studio "5-point infant calibration" routine was required prior to starting the paradigm.

Eye tracking was conducted in a single session in a quiet room. Following calibration, participants were verbally instructed to view the paradigm which consisted of side-by-side silent video clips of social interaction scenes (SS) and animated geometric scenes (GS) (Fig. 1). The 60 s paradigm consisted of three different 20 s video clips of paired SS and GS. The side of the presentation of the SS clips was counterbalanced such that 50% of participants saw SS on the left side to control for potential lateral bias. SS videos consisted of motion clips portraying toddlers playing cooperatively obtained from child development trainings (Videatives, Amherst, Massachusetts, USA). Similar to previous methods, geometric shape stimuli were adapted from animated screen savers (Video Blocks, Reston, Virginia, USA; Pierce et al., 2011).

2.4. Analyses

Rectangular Areas of Interest (AOI) were defined around both the SS and the GS portions of the stimulus. Measures included *total viewing time* (TV), *saccade rate* (SR) and *social scene preference ratio* (SSPR). Total Viewing time: TV was determined by the total amount of the 60 s task spent viewing the screen. Saccade Rate: SR was calculated by dividing the total number of fixations (each gaze to a new location) over TV. Social Scene Preference Ratio: SSPR was calculated by dividing SS viewing time by the combined amount of SS and GS viewing time. Consistent with prior studies (Pierce et al., 2011), *a priori* cut-offs of TV less than 20 s or less than 1 s viewing either SS or GS were used to exclude subjects from analyses.

$$SSPR = \frac{SS\ \ viewing\ \ time}{SS\ viewing\ \ time\ +\ GS\ viewing\ \ time}$$

For pupil data, only time points where pupil diameters were recorded were included. *Total Pupil time* (TP) was determined by the

total amount of the 60 s task that pupil diameter was recorded. SS and GS pupil diameters were determined by computing the mean pupil diameter for each eye within the specific AOIs. The first 250 ms following a gaze shift to an AOI was removed to account for pupillary adjustment to stimulus. The mean pupil diameters for the left and right eyes were then averaged to produce the SS and GS pupil diameters. To evaluate the pupillary response while viewing the SS compared to GS, *Social Pupil Difference* (SPD) was computed by subtracting the average GS pupil diameter from the average SS pupil diameter. A secondary measure of baseline pupil diameter was determined from the average of the first 250 ms of recorded pupil data at the beginning of the paradigm, as seen in previous pupillometry studies (Farzin, Scaggs, Hervey, Berry-Kravis, & Hessl, 2011; Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010; Sepeta et al., 2012)

$$SPD = Social\ Pupil - Geometric\ Pupil$$

2.5. Statistics

To explore any potential neurobehavioral differences in AS subjects who completed versus those unable to complete the eye tracking paradigm, we employed independent samples *t*-tests to compare phenotypic measures (Table I). Next, a chi-square test of independence was calculated to evaluate potential relationships between UBE3A genotype and eye tracking completion. To compare completed AS eye tracking data to our ASD and TDC groups, differences in TV, SR, and SSPR between AS, ASD, and TDC groups were analyzed using a one-way multivariate analysis of covariance (MANCOVA) with age as a covariate. For statistically significant results, main effects of each dependent variable were examined with univariate ANOVAs followed by post-hoc comparisons using Bonferroni's method to adjust for multiple comparisons. To measure group differences in pupillometry measures, a separate MANCOVA was conducted for TP and SPD with age as well as baseline pupil diameter as covariates. Similar to the previous MANCOVA, for statistically significant results, univariate ANOVAs and post-hoc comparisons were run to determine specific group differences. Pearson product-moment correlation coefficients were computed to assess the relationship of behavioral measures with SSPR and SPD in AS subjects. A two-tailed $p < 0.05$ was used as a threshold for statistical significance within this study.

3. Results

3.1. Sample

Seventeen individuals with AS participated in the study, consisting of eleven males and six females, aged from 1 to 26 years. All subjects were diagnosed with severe intellectual disability based on BSID-III scores. Demographic, psychometric, and clinical measures are summarized in Table 1. For various reasons, two AS subjects did not complete BSID-III and one did not complete ABC-C and SRS.

3.2. Feasibility

Of the seventeen AS subjects, eight subjects (47%) completed the eye tracking paradigm. The most common reasons for

Table 1
AS Subject Phenotyping.

	Successful Eye tracking	Unsuccessful Eye Tracking	Total AS Subject Group
n	8 (47.1%)	9	17
Age	12.4 ± 10.7	11.9 ± 5.4	12.2 ± 8.1
Gender (%male)	50.0	77.8	64.7
UBE3A Deletion (%deletion)	37.5	44.4	41.2
BSID Cognitive Subscale	19.5 ± 5.0	17.1 ± 6.0	18.1 ± 5.5
VABS-II Communication Subscale	42.1 ± 18.6	43.0 ± 10.3	42.6 ± 14.3
VABS-II Daily Living Skills Subscale	46.3 ± 20.7	43.7 ± 14.3	44.9 ± 17.1
VABS-II Socialization Subscale	52.3 ± 22.8	52.7 ± 13.1	52.5 ± 17.7
VABS-II Motor Skills Subscale	60.8 ± 6.1	58.7 ± 9.3	60.0 ± 6.8
VABS-II Adaptive Behavior Composite	44.8 ± 20.7	44.9 ± 12.9	44.8 ± 16.5
ABC Irritability Subscale	10.9 ± 13.1	20.2 ± 9.6	16.1 ± 11.9
ABC Lethargy Subscale	3.0 ± 2.6	10.6 ± 11.3	7.3 ± 9.3
ABC Stereotypy Subscale	4.1 ± 3.6	9.1 ± 6.3	6.9 ± 5.8
ABC Hyperactivity Subscale*	14.3 ± 11.0	27.7 ± 11.1	21.8 ± 12.7
SRS Social Awareness Subscale	63.7 ± 7.4	70.6 ± 9.6	67.6 ± 9.1
SRS Social Cognition Subscale	75.1 ± 8.2	76.3 ± 6.9	75.8 ± 7.3
SRS Social Communication Subscale	72.3 ± 9.4	79.9 ± 12.5	76.6 ± 11.5
SRS Social Motivation Subscale*	54.0 ± 9.5	69.6 ± 14.2	62.8 ± 14.4
SRS Autistic Mannerisms Subscale	81.3 ± 19.4	85.9 ± 18.0	83.9 ± 18.1
SRS Total Score	73.1 ± 8.1	81.3 ± 12.1	77.8 ± 11.1

* $p < 0.05$ by independent samples *t*-test (ADOS: Autism Diagnostic Observation Schedule, VABS II: Vineland Adaptive Behavior Scale II, ABC—C: Aberrant Behavior Checklist — Community, SRS: Social Responsiveness Scale).

Table 2
Eye Tracking Measures.

	AS	ASD	TDC
TV (seconds)	41.0 ± 7.6	46.6 ± 13.9	48.3 ± 14.2
SR (sac/sec)	2.03 ± 0.86	2.64 ± 2.80	1.81 ± 0.31
SSPR	0.49 ± 0.23[a]	0.62 ± 0.25[a]	0.89 ± 0.08[b,c]
TP (seconds)	42.1 ± 10.4	41.4 ± 14.4	43.6 ± 17.6
SPD (mm)	−0.01 ± 0.14[a]	0.15 ± 0.22	0.37 ± 0.12[b]

Descriptive statistics reported as means ± standard deviation.
(AS: Angelman Syndrome, ASD: Autism Spectrum Disorder, TDC: Typically Developing Control, TV: Total Viewing Time, SR: Saccade Rate, SSPR: Social Scene Preference Ratio, TP: Total Pupil Time, SPD: Social Pupil Difference, mm: millimeters, sac/sec: saccades per second)
[a] Statistically different from TDC (MANCOVA followed by ANOVA and Bonferroni post hoc testing).
[b] Statistically different from AS (MANCOVA followed ANOVA and by Bonferroni post hoc testing).
[c] Statistically different from ASD (MANCOVA followed by ANOVA and Bonferroni post hoc testing).

incompletion were failed calibration and physical limitations, including posture and excessive movement. We identified an association between lower ABC hyperactivity [t = 2.40, p = 0.031] and higher SRS social motivation scores [t = 2.49, p = 0.026] with ability to provide evaluable eye tracking data in the AS subject group. However, we observed no association between UBE3A deletion and non-deletion genotypes in ability to provide useful data. AS subjects who were able to provide evaluable eye tracking data were then compared to ASD and TDC groups in eye tracking and pupillometry measures (Table 2).

3.3. Social eye tracking

A statistically significant main effect for group (AS, ASD, or TDC) on our social eye tracking measures was observed [based on Wilk's λ, F(6, 36) = 2.95, p = 0.019, observed power = 0.840]. The main effect for group was accounted for by the difference in preference for social scenes as shown by Social Scene Preference Ratio (SSPR) [F(2, 24) = 8.20, p = 0.0025]. Age was not found to have a main effect on social eye tracking measures [based on Wilk's λ, F(3, 36) = 0.841, p = 0.49, observed power = 0.196]. Both AS (p = 0.0020) and ASD (p = 0.042) subjects showed less preference for SS than TDC (Fig. 2). Furthermore, 87.5% of AS subjects and 75% of ASD subjects performed lower on SSPR than the lowest TDC. AS and ASD subjects did not statistically differ from one another in social scene preference (p = 0.66). We also identified an inverse relationship between SSPR and SRS social motivation scores [r = −0.772, p = 0.042], indicating AS subjects who showed less preference for SS were more impaired in social motivation. Of note, no statistically significant differences in Total Viewing time (TV) [F(2, 24) = 0.764, p = 0.48] nor Saccade Rate (SR) [F(2, 24) = 0.524, p = 0.60] were identified between AS, ASD, and TDC subjects.

3.4. Pupillometry

There was a statistically significant main effect for group (AS, ASD, or TDC) on pupillometry measures [based on Wilk's λ, F(4, 36) = 3.22, p = 0.024, observed power = 0.774]. The main effect for group was accounted for by the difference in pupil changes between social scenes and geometric stimuli as measured by Social Pupil Difference (SPD) [F(2,24) = 6.22, p = 0.0084]. Age was not found to have a main effect on pupillometry measures [based on Wilk's λ, F(2, 36) = 0.106, p = 0.90, observed power = 0.064]. Compared to TDC, individuals with AS showed no pupil change when viewing social scenes versus geometric patterns (p = 0.0080). ASD subjects did not statistically differ in SPD from AS (p = 0.078) or TDC groups (p = 0.54). Additionally, there was no statistically

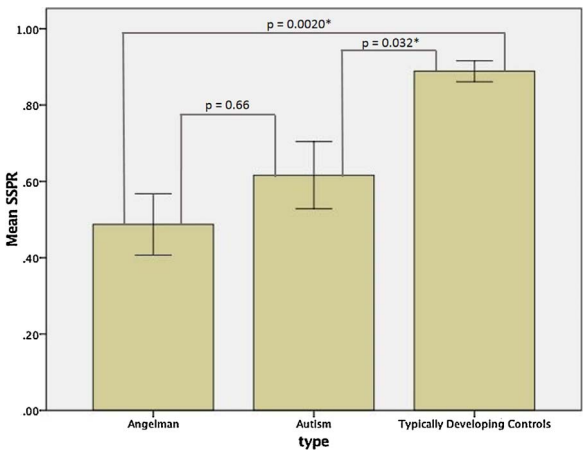

Fig. 2. SSPR (Mean ± SEM) of AS, ASD, and TDC groups (*p < 0.05 by Bonferroni post-hoc comparisons).

significant difference observed in Total Pupil time (TP) between AS, ASD, and TDC [F(2, 24) = 0.592, p = 0.56].

4. Discussion

This novel study is the first to demonstrate the feasibility of completing eye tracking paradigms in individuals with AS. Just under half of individuals with AS in this cohort successfully completed the social scenes and geometric patterns side-by-side eye tracking paradigm. This rate falls somewhat below rates seen in studies of moderately severe ASD and other developmental disabilities (Dalton et al., 2005; Djukic, McDermott, Mavrommatis, & Martins, 2012). However, the notable trend toward increased success in individuals with less interfering behavior suggests that with thoughtful paradigm design and behavioral support, we may be able to improve upon these results. Future studies in AS may consider screening potential participants with the ABC-C and SRS to determine eligibility. Using behavioral intervention techniques such as social stories (Reynhout & Carter, 2006), practicing sitting at the eye tracker, and providing rewards for participation may be beneficial (Summers & Szatmari, 2009). Additionally, participation was impacted for some participants due to an inability to sit upright or excessive head movement. Thus, future studies should consider enhanced seating design for posture support and head stability.

Consistent with our hypothesis, individuals with AS in this study demonstrated a lower preference for social stimuli than TDC as measured by SSPR, though the AS and ASD groups did not statistically differ from each other on this measure. Furthermore, analysis of social pupil differences (SPD) revealed that individuals with AS did not show the increased pupil dilation in response to social scenarios that was seen in TDC. Again, no statistically significant difference in SPD was seen between the AS and ASD groups, though the ASD group also did not statistically differ from TDC on this measure. Of note, the ASD group exhibited extensive variability in SPD, a common phenomenon observed across autism symptoms and phenotypes (Lombroso, Ogren, Jones, & Klin, 2009), which may explain the lack of ASD-TDC and ASD-AS differences in this sample.

The abnormal social gaze preference and pupillometry findings of individuals with AS in this study provide important information about the impact of this neurodevelopmental disorder on functional social attention, interest, and subsequent arousal. However, the mechanisms underlying these abnormalities remain unclear. The striking similarity to the ASD control group raises questions regarding impaired social interest in individuals with AS, especially considering the inverse relationship noted between the SSPR and SRS social motivation scores in this study. In ASD, reduced interest in social gaze and impaired pupillary response, indicating lack of arousal, is believed to reflect a decreased interest and intrinsic reward to visual social stimuli (Klin, Jones, Schultz, & Volkmar, 2003; Sepeta et al., 2012). However, individuals with AS are known to have prominent interest in social interaction (Pelc, Cheron, & Dan, 2008), causing us to hesitate suggesting a similar mechanism in this population. One possible explanation for the social processing deficit seen in our AS group is Cortical Visual Impairment (CVI), a common phenomenon seen in individuals with intellectual disabilities or neurological problems (Sheldon, 2014). CVI is impairment in visual processing that is not the result of ophthalmologic impairment and is distinct from the mechanical features of the eye (Roman et al., 2010). Considering the negative impact of CVI on a wide range of visual processes including but not limited to poor visual attention (Jan, Groenveld, Sykanda, & Hoyt, 1987), difficulties interpreting complex visual scenes (Dutton, McKillop, & Saidkasimova, 2006; Roman-Lantzy, 2007), and variability in contrast (Good, 2001), it must be considered as a potential method for explaining the social processing deficit seen in our AS group. Additionally, it is possible that the level of sensory input from the GS videos in regard to low-level features such as contrast, luminance, and motion could impact preferences for individuals with AS. Future studies should explore the effects of these potential mechanisms on social processing in AS.

There are several limitations to the present study that must be considered. First, a future study would do well to match stimuli based on contrast, luminance, and motion to avoid these low-level features influencing the interpretation of results. Second, while we did not include an eye exam or test for visual acuity in the present study, it would be beneficial to do so in the future. Although most studies have indicated only mild, non-pathological ophthalmological impairments, such factors may influence the present results, especially considering the common occurrence of strabismus in this population (Dickinson, Fielder, Young, & Duckett, 1990; Mah, Wallace, & Powell, 2000; Michieletto, Bonanni, & Pensiero, 2011). Third, high level of disability in the AS group could result in a floor effect for both eye tracking and behavioral measures. Future studies are needed to evaluate if these measures can accurately phenotype the most severely affected AS individuals and whether additional training or special preparation can increase protocol completion rates. A mental-age match control group may expand upon the impact of intellectual disability on these measures. Finally, while our age group was large in range and we found no effect of age on social eye tracking and pupillometry measures, our small sample size limits the ability to assess the effect of development on these measures. Due to this and the novelty of using eye tracking measures in AS, it is necessary to replicate our findings within larger AS cohorts, including test-retest analysis.

In conclusion, our social preference and pupillometry measures may hold promise as quantitative markers of AS pathophysiology but additional studies are needed. Future work using a larger sample size of individuals with AS could be useful to standardize these eye tracking measures and elucidate differences among individuals with AS. Additionally, combining social eye tracking paradigms with High Density EEG could further explore the underlying biological mechanisms at work in this population and holds potential to develop personalized treatment.

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References

Aman, M. G., Singh, N. N., Stewart, A. W., & Field, C. J. (1985). Psychometric characteristics of the aberrant behavior checklist. *American Journal of Mental Deficiency*.

Anderson, C. J., Colombo, J., & Jill Shaddy, D. (2006). Visual scanning and pupillary responses in young children with autism spectrum disorder. *Journal of Clinical and Experimental Neuropsychology*, *28*(7), 1238–1256.

Bayley, N., & Reuner, G. (2006). *Bayley scales of infant and toddler development: Bayley-III, Vol. 7*. San Antonio, Tex, USA: Harcourt Assessment, Psych. Corporation.

Boraston, Z., & Blakemore, S. J. (2007). The application of eye-tracking technology in the study of autism. *The Journal of Physiology*, *581*(3), 893–898.

Bradley, M. M., Miccoli, L., Escrig, M. A., & Lang, P. J. (2008). The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology*, *45*(4), 602–607.

Buckley, R. H., Dinno, N., & Weber, P. (1998). Angelman syndrome: Are the estimates too low? *American Journal of Medical Genetics*, *80*(4), 385–390.

Clayton-Smith, J., & Laan, L. (2003). Angelman syndrome: A review of the clinical and genetic aspects. *Journal of Medical Genetics*, *40*(2), 87–95.

Constantino, J. N., & Gruber, C. P. (2007). *Social responsiveness scale (SRS)*. Los Angeles, CA: Western Psychological Services.

Dagli, A., Buiting, K., & Williams, C. (2011). Molecular and clinical aspects of Angelman syndrome. *Molecular Syndromology*, *2*(3–5), 100–112.

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

Dickinson, A. J., Fielder, A. R., Young, I. D., & Duckett, D. P. (1990). Ocular findings in Angelman's (happy puppet) syndrome. *Ophthalmic Paediatrics and Genetics*, *11*(1), 1–6.

Djukic, A., McDermott, M. V., Mavrommatis, K., & Martins, C. L. (2012). Rett syndrome: Basic features of visual processing—a pilot study of eye-tracking. *Pediatric Neurology*, *47*(1), 25–29.

Dutton, G., McKillop, E., & Saidkasimova, S. (2006). *Visual problems as a result of brain damage in children*. BMJ Publishing Group Ltd.

Erickson, C. A., Wink, L. K., Baindu, B., Ray, B., Schaefer, T. L., Pedapati, E. V., & Lahiri, D. K. (2016). Analysis of peripheral amyloid precursor protein in Angelman Syndrome. *American Journal of Medical Genetics Part A*, *170*(9), 2334–2337.

Farzin, F., Scaggs, F., Hervey, C., Berry-Kravis, E., & Hessl, D. (2011). Reliability of eye tracking and pupillometry measures in individuals with fragile X syndrome. *Journal of Autism and Developmental Disorders*, *41*(11), 1515–1522.

Gaietto, K., Shaffer, R., Warner, K., Mathieu-Frasier, L., Wink, L. K., & Erickson, C. (2014). Eye tracking utilizing age matched social scenes and geometric shapes. *International meeting for autism research (IMFAR)*.

Good, W. V. (2001). Development of a quantitative method to measure vision in children with chronic cortical visual impairment. *Transactions of the American Ophthalmological Society*, *99*, 253.

Grafodatskaya, D., Chung, B., Szatmari, P., & Weksberg, R. (2010). Autism spectrum disorders and epigenetics. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(8), 794–809.

Hess, E. H., & Polt, J. M. (1960). Pupil size as related to interest value of visual stimuli. *Science*, *132*(3423), 349–350.

Jan, J., Groenveld, M., Sykanda, A., & Hoyt, C. (1987). Behavioural characteristics of children with permanent cortical visual impairment. *Developmental Medicine & Child Neurology*, *29*(5), 571–576.

Janisse, M. P. (1977). *Pupillometry: The psychology of the pupillary response*. Halsted Press.

Kishino, T., Lalande, M., & Wagstaff, J. (1997). UBE3A/E6-AP mutations cause Angelman syndrome. *Nature Genetics*, *15*(1), 70–73.

Kliemann, D., Dziobek, I., Hatri, A., Steimke, R., & Heekeren, H. R. (2010). Atypical reflexive gaze patterns on emotional faces in autism spectrum disorders. *The Journal of Neuroscience*, *30*(37), 12281–12287.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism? *Archives of General Psychiatry*, *59*(9), 809–816.

Klin, A., Jones, W., Schultz, R., & Volkmar, F. (2003). The enactive mind, or from actions to cognition: Lessons from autism. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *358*(1430), 345–360.

Liddle, P. (2000). Cognitive impairment in schizophrenia: Its impact on social functioning. *Acta Psychiatrica Scandinavica*, *101*(400), 11–16.

Lombroso, P. J., Ogren, M. P., Jones, W., & Klin, A. (2009). Heterogeneity and homogeneity across the autism spectrum: The role of development. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(5), 471–473.

Mah, M. L., Wallace, D. K., & Powell, C. M. (2000). Ophthalmic manifestations of Angelman syndrome? *Journal of American Association for Pediatric Ophthalmology and Strabismus*, *4*(4), 248–249.

Michieletto, P., Bonanni, P., & Pensiero, S. (2011). Ophthalmic findings in Angelman syndrome. *Journal of American Association for Pediatric Ophthalmology and Strabismus*, *15*(2), 158–161.

Moss, J., & Howlin, P. (2009). Autism spectrum disorders in genetic syndromes: Implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. *Journal of Intellectual Disability Research*, *53*(10), 852–873.

Pelc, K., Cheron, G., & Dan, B. (2008). Behavior and neuropsychiatric manifestations in Angelman syndrome. *Neuropsychiatric Disease and Treatment*, *4*(3), 577.

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual scanning of faces in autism? *Journal of Autism and Developmental Disorders*, *32*(4), 249–261.

Peters, S. U., Beaudet, A. L., Madduri, N., & Bacino, C. A. (2004). Autism in Angelman syndrome: Implications for autism research. *Clinical Genetics*, *66*(6), 530–536 CGE362 [pii].

Peters, S. U., Horowitz, L., Barbieri-Welge, R., Taylor, J. L., & Hundley, R. J. (2012). Longitudinal follow-up of autism spectrum features and sensory behaviors in Angelman syndrome by deletion class. *J Child Psychol Psychiatry*, *53*(2), 152–159. http://dx.doi.org/10.1111/j.1469-7610.2011.02455.x.

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism? *Archives of General Psychiatry*, *68*(1), 101–109.

Reynhout, G., & Carter, M. (2006). Social Stories™ for children with disabilities. *Journal of Autism and Developmental Disorders*, *36*(4), 445–469.

Roman, C., Baker-Nobles, L., Dutton, G. N., Luiselli, T. E., Flener, B. S., Jan, J. E., ... Newcomb, S. (2010). Statement on cortical visual impairment. *Journal of Visual Impairment & Blindness*, *104*(2), 69–72.

Roman-Lantzy, C. (2007). *Cortical visual impairment: An approach to assessment and intervention*. American Foundation for the Blind.

Sepeta, L., Tsuchiya, N., Davies, M. S., Sigman, M., Bookheimer, S. Y., & Dapretto, M. (2012). Abnormal social reward processing in autism as indexed by pupillary responses to happy faces. *Journal of Neurodevelopmental Disorders*, *4*(1), 1.

Sheldon, E. (2014). *Education children with angelman syndrome: Moving beyond social inclusion*.

Shi, L., Zhou, Y., Ou, J., Gong, J., Wang, S., Cui, X., ... Luo, X. (2015). Different visual preference patterns in response to simple and complex dynamic social stimuli in preschool-aged children with autism spectrum disorders. *PloS One*, *10*(3), e0122280.

Smith, K. R., & Matson, J. L. (2010). Social skills: Differences among adults with intellectual disabilities, co-morbid autism spectrum disorders and epilepsy. *Research in Developmental Disabilities*, *31*(6), 1366–1372.

Sparrow, S. S., Balla, D. A., Cicchetti, D. V., Harrison, P. L., & Doll, E. A. (1984). *Vineland adaptive behavior scales*.

Summers, J., & Szatmari, P. (2009). Using discrete trial instruction to teach children with Angelman syndrome. *Focus on Autism and Other Developmental Disabilities*, *24*(4), 216–226.

Sweeney, J. A., Takarae, Y., Macmillan, C., Luna, B., & Minshew, N. J. (2004). Eye movements in neurodevelopmental disorders? *Current Opinion in Neurology*, *17*(1), 37–42.

Tan, W. H., Bacino, C. A., Skinner, S. A., Anselm, I., Barbieri-Welge, R., Bauer-Carlin, A., & Glaze, D. G. (2011). Angelman syndrome: Mutations influence features in early childhood. *American Journal of Medical Genetics Part A*, *155*(1), 81–90.

Williams, C. A. (2010). The behavioral phenotype of the Angelman syndrome. *Paper presented at the american journal of medical genetics part C: Seminars in medical genetics*.

Wink, L. K., Fitzpatrick, S., Shaffer, R., Melnyk, S., Begtrup, A. H., Fox, E., & Lahiri, D. (2015). The neurobehavioral and molecular phenotype of Angelman Syndrome. *American Journal of Medical Genetics Part A*, *167*(11), 2623–2628.