Research in Developmental Disabilities 68 (2017) 88–94

Contents lists available at ScienceDirect

Research in Developmental Disabilities

journal homepage: www.elsevier.com/locate/redevdis

Eye gaze and pupillary response in Angelman syndrome

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ARTICLE INFO

Keywords:
Angelman syndrome
Pupillometry
Eye tracking
Developmental disabilities

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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http://dx.doi.org/10.1016/j.ridd.2017.06.011
Received 29 September 2016; Received in revised form 9 March 2017; Accepted 23 June 2017

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