Review Article
Less fixation on the eyes is associated with severe social disability in individuals with autism spectrum disorder

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Abstract: Objective: Previous studies’ findings regarding fixation on the eyes or mouth and level of social disability in people with autism spectrum disorder (ASD) are controversial. This meta-analysis aimed to assess the association between eye gaze patterns and social impairments. Methods: We searched the PubMed, Embase, and PsycINFO databases for studies that reported the Pearson’s correlation coefficient (r) between time fixated on the eyes or mouth and level of social disability in people with ASD. Subgroup analyses were conducted according to stimuli type. Results: Twelve cross-sectional studies comprising 15 study groups with 317 participants were included. The amount of time fixated on the eyes was linked to the level of social disability (r = -0.300, 95% CI -0.397 to -0.197). The result was more pronounced when the patients viewed image stimuli (r = -0.414, 95% CI -0.565 to -0.236, I² = 0%). Furthermore, we found a significant relationship between mouth fixation and social disability when patients viewed images (r = 0.319, 95% CI -0.080 to 0.530, I² = 0%), but not when they viewed videos (r = -0.197, 95% CI -0.178 to 0.523, I² = 80.4%). Conclusions: This study showed that less eye fixation was associated with greater social impairment in individuals with ASD, providing further evidence that reduced eye fixation is a strong hallmark of the early detection, diagnosis and prediction of social deficits in ASD. Future studies should further investigate the relationship between mouth fixation and social impairment.

Keywords: Autism spectrum disorder, social disability, eye tracking, fixation

Introduction
Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by impaired social interaction and restricted and repetitive behaviour [1, 2]. It was initially described by Kanner in 1943. Atypical social behaviours are a core diagnostic feature of ASD. As the current diagnostic tools for autism, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) [1], Autism Diagnostic Observation Schedule (ADOS) [3], Childhood Autism Rating Scale (CARS) [4] and Autism Diagnostic Interview-Revised (ADI-R) [5], are primarily based on direct or indirect observations of behaviour, which can be influenced by subjective assessment and varying symptoms, objective physiological response indicators must be collected.

In recent decades, eye-tracking technology has been widely used to research social attention and behaviours. Studies have research eye gaze duration and the specific eye gaze fixation on the eyes and/or the mouth in people with ASD compared to controls [6-8]. However, findings in the past decades have been contradictory. Recently, Papagiannopoulou et al. [9] published a systematic review and meta-analysis of eye-tracking studies and reported that children with ASD have significantly reduced gaze fixation on the eye region of the face than controls. However, no significant difference was found in terms of fixation on the mouth region. Chita-Tegmark’s systematic review and meta-analysis [10] showed that individuals with autism spend less time than typically developing controls attending to social stimuli. Another study characterized 700 complex natural scene
images using model-based eye tracking and found that, faces and locations had less salience for people with ASD than for matched controls, as indicated by their social gaze [11].

However, the association between the absence of preferential looking towards the eyes or mouth and an individual’s level of social disability remains a topic of debate. Jones and Klin [12] uncovered a highly significant negative correlation between the time spent looking at the eyes and social competence, where less fixation on the eyes predicted greater social disability. Another study with a larger sample was consistent with this finding [13]. However, Birmingham et al. [14] indicated that participants with ASD who displayed more impaired communication spent more time looking at the eyes. Other studies failed to find any significant association between these variables [15, 16]. Correlational analyses of fixation patterns to the mouth area and social functioning are also ambiguous.

Given that previous studies found inconsistent results, a meta-analysis might help to clarify these relationships. Therefore, the present study aims to assess the relationship between eyes or mouth fixation and social functioning in adults with ASD.

Methods

Search strategy and selection criteria


We included studies that met the following criteria: (1) the patient group had a diagnosis of high- or low-functioning autism disorder, Asperger’s syndrome or pervasive developmental disorder; (2) an eye-tracking experiment was performed to measure facial processing and response to social and non-social stimuli; (3) social functioning was measured by social functioning scales (if the study reported several results of different scales, we preferentially selected the results of the Autism Diagnostic Observation Schedule (ADOS) or Autism Diagnostic Interview-Revised (ADI-R)); and (4) the number (n) of patients and the Pearson’s correlation coefficient (r) between the percentage...
## Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample (women)</th>
<th>Age (y), average (range or SD)</th>
<th>Stimuli type</th>
<th>Fixation time</th>
<th>Diagnostic criteria</th>
<th>Developmental level</th>
<th>Social function measures</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujio 2016</td>
<td>21 (0)</td>
<td>27.6 (7.7)</td>
<td>Images/video</td>
<td>Percentage of time fixation to the eyes and mouth</td>
<td>DSM-IV-TR and DISCO</td>
<td>High function, IQ &gt; 85</td>
<td>SRS</td>
<td>No</td>
</tr>
<tr>
<td>Amestoy 2015</td>
<td>27 (4)</td>
<td>17.3 (U)</td>
<td>Images</td>
<td>Total time fixation to the eyes and mouth</td>
<td>DSM-IV-TR, ADI-R, ADOS</td>
<td>High function, IQ &gt; 85</td>
<td>ADOS</td>
<td>No</td>
</tr>
<tr>
<td>Hansley 2015</td>
<td>11 (4)</td>
<td>26 (8.1)</td>
<td>Video</td>
<td>Percentage of time fixation to the eyes and mouth</td>
<td>DSM-IV-TR</td>
<td>High function, IQ &gt; 110</td>
<td>SRS</td>
<td>NA</td>
</tr>
<tr>
<td>Gillespie-Smith 2014</td>
<td>21 (1)</td>
<td>13.6 (2.4)</td>
<td>Images</td>
<td>Percentage of time fixation to the eyes</td>
<td>CARS</td>
<td>Low, mild and high function</td>
<td>SCQ</td>
<td>NA</td>
</tr>
<tr>
<td>Jones 2013</td>
<td>11 (0)</td>
<td>1.1 (2-24 m)</td>
<td>Video</td>
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<td>ADOS</td>
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<td>ADOS</td>
<td>NA</td>
</tr>
<tr>
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<td>109 (26)</td>
<td>10.1 (NA)</td>
<td>Video</td>
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<td>DSM-IV-TR, ADOS, ADI-R</td>
<td>High function, IQ &gt; 85</td>
<td>ADOS</td>
<td>No</td>
</tr>
<tr>
<td>Kirschner 2011</td>
<td>20 (5)</td>
<td>31.9 (7.6)</td>
<td>Images</td>
<td>Percentage of time fixation to the eyes and mouth</td>
<td>DSM-IV-TR, ADI-R</td>
<td>IQ &gt; 100</td>
<td>ADI-R</td>
<td>NA</td>
</tr>
<tr>
<td>Falck-Ytter 2010a</td>
<td>15 (3)</td>
<td>5.2 (0.9)</td>
<td>Video</td>
<td>Total time fixation to the eyes and mouth</td>
<td>DSM-IV-TR</td>
<td>NA</td>
<td>ADI-R</td>
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</tr>
<tr>
<td>Falck-Ytter 2010b</td>
<td>12 (1)</td>
<td>6.6 (0.7)</td>
<td>Video</td>
<td>Total time fixation to the eyes and mouth</td>
<td>DSM-IV-TR</td>
<td>High function</td>
<td>SCQ</td>
<td>NA</td>
</tr>
<tr>
<td>Norbury 2009</td>
<td>28 (1)</td>
<td>14.9 (U)</td>
<td>Video</td>
<td>Percentage of time fixation to the eyes</td>
<td>DSM-IV-TR, ADI-R, ADOS</td>
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<td>No</td>
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<tr>
<td>Jones 2008</td>
<td>15 (4)</td>
<td>2.3 (0.6)</td>
<td>Video</td>
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<td>ADI-R, ADOS</td>
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<td>NA</td>
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<td>13.6 (2.7)</td>
<td>Video</td>
<td>Total time fixation to the eyes and mouth</td>
<td>ADI-R, ADOS</td>
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<td>ADOS</td>
<td>NA</td>
</tr>
<tr>
<td>Klin 2002</td>
<td>15 (0)</td>
<td>15.4 (7.2)</td>
<td>Video</td>
<td>Total time fixation to the eyes and mouth</td>
<td>DSM-IV-TR, ADI-R, ADOS</td>
<td>IQ &gt; 100</td>
<td>ADOS</td>
<td>NA</td>
</tr>
</tbody>
</table>

SRS: Social Responsiveness Scale; SCQ: Social Communication Questionnaire; ADOS: Autism Diagnostic Observation Schedule; CARS: Childhood Autism Rating Scale; ADI-R: Autism Diagnostic Interview-Revised; U: Not Available; DISCO: Diagnostic Interview for Social and Communication Disorders; DSM: Diagnostic and Statistical Manual of Mental Disorders.
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The quality assessment of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Total</th>
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<td>U</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>U</td>
<td>6</td>
</tr>
<tr>
<td>Amestoy 2015</td>
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<td>Y</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>U</td>
<td></td>
<td>4</td>
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<td>Hanley 2015</td>
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<td>Y</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Gillespie-Smith 2014</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>U</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>U</td>
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</tr>
<tr>
<td>Jones 2013</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
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<td>Rice 2012</td>
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<td>N</td>
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<td>N</td>
<td>U</td>
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<td>N</td>
<td>N</td>
<td>U</td>
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<tr>
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<td>Y</td>
<td>N</td>
<td>U</td>
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<td>U</td>
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<tr>
<td>Speer 2007</td>
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<td>Y</td>
<td>Y</td>
<td>U</td>
<td>U</td>
<td>Y</td>
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<td>N</td>
<td>N</td>
<td>U</td>
<td>5</td>
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<tr>
<td>Klin 2002</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>U</td>
<td>6</td>
</tr>
</tbody>
</table>

[19]. First, each effect size $r$ was transformed into a Fisher's $z$-value using the following formula:

$$Fisher's \ z = 0.5 \times \ln((1 + r)/(1 - r))$$

Formula 1

Then, we calculated the standard errors (SEs) as follows:

$$SE = SQRT(1/(n - 3))$$

Formula 2

Third, data (Fisher's $z$ and 95% CI) from the various studies were combined using random- or fixed-effects meta-analysis. Finally, the summary Fisher's $z$-value was back-transformed into the summary Pearson's $r$ value using the following formula:

$$Summary \ r = (\exp(2Z) - 1)/(\exp(2Z) + 1), \ where \ Z = the \ summary \ Fisher's \ z-value$$

Formula 3

The $F$ statistic was used to test the heterogeneity ($P < 0.10$ or $I^2 > 50\%$ was regarded as significant). The results of studies were pooled using a fixed-effects model if the heterogeneity was non-significant. Otherwise, a random-effects model was used. To explain the heterogeneity in the meta-analysis, we conducted subgroup analyses using stimuli materials.

A sensitivity analysis was performed by computing the summary Pearson's $r$ values when one study was removed from the meta-analysis, and publication bias was assessed by inspecting the funnel plots. We used Stata version 12.0 (Stata Corp LP, College Station, TX) to perform all the analyses. The $p$-values were 2-tailed, and the statistical significance level was set at 0.05.

Results

Selected studies and characteristics

The search initially yielded 767 potential references, and 49 of them qualified for full review. Ultimately, 12 articles [8, 12, 13, 15, 16, 20-26] with 15 study groups met all the criteria and were analysed (Figure 1).

Table 1 provides a detailed description of the 15 study groups from the 12 papers. These papers included a total of 317 ASD patients who ranged in age from 2 months to 55 years and met the diagnostic criteria of the DSM-IV-
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TR, ADOS, ADI-R or CARS. Most participants were high-functioning, with a mean IQ > 85. Their social function was measured by the SRS, ADOS, SRS, SCQ or ADI-R. The quality assessment of the included studies is presented in Table 2. One study group was low-quality [26], one study group was high-quality [12], and the others were moderate in quality.

Overall correlation between eyes or mouth fixation and social ability

The correlation coefficient ($r$) between eye fixation and social ability was reported for all the study groups, whereas the correlation coefficient ($r$) between mouth fixation and social disability was reported for only ten study groups that included 258 individuals [13, 15, 16, 20-22, 25, 26]. The data were pooled and calculated using the fixed-effects model in the eyes groups, as the heterogeneity ($I^2 = 44.2\%$) was non-significant. Figure 2 shows the negative correlation between the percentage of time fixated on the eyes and the level of social disability ($r = -0.300$, 95% CI -0.397 to -0.197), which was transformed from the Fisher’s $z$-value. As shown in Figure 3, the correlation between the degree of mouth fixation and the level of social impairment was insignificant ($r = 0.226$, 95% CI -0.050 to 0.470); however, the heterogeneity ($I^2 = 75.0\%$) was significant. Furthermore, no evidence of publication bias was detected by the visual inspection of the funnel plot (Supplementary Figures 1, 2).

Subgroup analyses and sensitivity analyses

We performed a subgroup analysis on stimuli materials, as different stimuli may influence the results. As shown in Figure 4, a more pronounced significant relationship was observed between the time spent looking at the eyes and social impairment when the patients viewed image stimuli ($r = -0.414$, 95% CI -0.565 to -0.236, $I^2 = 0\%$). A significant result was also found when video stimuli were used ($r = -0.327$, 95% CI -0.523 to -0.100), but the heterogeneity rose to 57.9%. On the other hand, we found a
Figure 3. Forest plot of the association between the time spent looking at the mouth and social impairment in individuals with ASD. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher’s z-value is shown on the last row of the graph. CI: confidence interval.
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Figure 4. Forest plot of subgroup analyses according to stimuli material, outcome: fixation on the eyes. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher’s z-value is shown on the last row of the graph. CI: confidence interval.

Figure 5. Forest plot of subgroup analyses according to stimuli material, outcome: fixation on the mouth. The square box in the graph portrays the weight of each study contributed to the analysis. The overall summary Fisher’s z-value is shown on the last row of the graph. CI: confidence interval.

significant relationship between mouth fixation and social disability in the image ($r = 0.319$, 95% CI -0.080 to 0.530, $I^2 = 0\%$), but not in the video ($r = -0.197$, 95% CI -0.178 to 0.523, $I^2 = 80.4\%$) trial (Figure 5).

Several methods were used to test the sensitivity and confirmed that the outcomes were not influenced by the use of a fixed- or random-effects model.

Discussion

In this study, we found a significant negative correlation between the percentage of time fixated on eyes and the level of social disability in individuals with ASD, indicating that reduced eye fixation is linked to poor social awareness. However, the degree of mouth fixation was not related to social disability. These findings are consistent with the results of an aforementioned meta-analysis [9] that indicated that ASD patients have significant impairments in gaze fixation on the eyes but no significant difference in terms of fixation on the mouth region. Consequently, we can infer that eye fixation plays a more important role as a biomarker of early detection and diagnosis and even a predictor of social deficit in ASD than mouth fixation. To the best of our knowledge, this is the first meta-analysis to evaluate the association between eye gaze pattern and social impairments.

The underlying mechanisms of atypical eye gaze in people with ASD are poorly understood. According to previous studies, dysfunctions in several brain regions can lead to atypical eye
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gaze. The fusiform face area (FFA) has been specifically highlighted in the last two decades [27, 28]. Scholars speculated that significantly diminished activity in the FFA in response to facial stimuli correlated with facial processing deficits in individuals with ASD [29, 30]. Another brain region that has received considerable research attention is the amygdala, which has been closely tied to ASD and to abnormal eye gaze in a number of studies [31, 32]. Evidence from magnetic resonance imaging (MRI) studies has shown that individuals with ASD display abnormal amygdala activation when they fixate on the eyes of faces [33]. Amygdala damage also impairs social judgements about people’s faces within complex scenes [14]. Differences in other regions such as the superior temporal sulcus, cerebellum, and temporal lobe have also been reported between ASD subjects and controls during facial expression tasks [34, 35]. These differences have also been associated with the level of social impairment.

Another debatable topic is the relationship between mouth fixation and social disability. Chawarska et al. [36] found decreased attention to the mouth in children with ASD compared to typically developing children. However, Papagiannopoulou et al. [9] revealed that no significant effect was found for the patterns of eye movements that involved looking at the mouth between people with ASD and healthy controls. These results are not surprising, given that a positive correlation was found between the amount of mouth fixation and verbal development in toddlers [36] and adolescents [16] with ASD and in infants at risk of autism [37]. Additionally, Norbury et al. [16] demonstrated that increased fixations on the mouth were associated with variation in language acquisition and greater communicative competence in children with ASD. The participants in Papagiannopoulou's meta-analysis were mostly those with high-functioning autism who had a higher IQ and language skills compared to people with low- and mild-functioning autism, which yielded a nonsignificant result between people with ASD and healthy controls [1, 9]. Our study included mostly high-functioning people with autism. We discovered that the degree of mouth fixation was not related to social disability either. However, it should be noted that the lack of a finding of a significant difference relating to mouth fixation might be influenced by high heterogeneity. After performing a sub-group analysis for stimulus type in our study, we discovered a positive significant relationship between mouth fixation and social disability in the image group, meaning that greater fixation on the mouth predicted greater social disability in people with ASD when they looked at pictures. This may be due to their compensating for reduced eye fixation and, thus, their taking more time to look at the mouth and other regions of the face to collect information [38, 39]. However, the contradictory results should be further clarified in the future.

How to choose a stimulus type for an eye-tracking study is also commonly debated. The results vary in terms of how sensitive they are to the deficits of people with ASD. Both static images and dynamic stimuli were used widely in previous decades; however, dynamic stimuli have become increasingly more popular recently. Data from Speer et al. [8] showed that individuals with autism fixated less on the eyes when they viewed social-dynamic stimuli but not isolated-static stimuli. Data from a more recent study with a larger sample size revealed that the interactive task has significant classification power between ASD and control groups [40]. They argued that slowing down the facial dynamics’ presentation tended to enhance facial exploration of the mouth and/or eyes in toddlers with ASD [41]. Static stimuli neither consistently produced group differences nor were as effective as dynamic stimuli at eliciting individual differences in social attention. However, our study uncovered different results. A more pronounced significant relationship was found between the time spent looking at the eyes/mouth and social impairment when the patients viewed static image stimuli but not social-dynamic stimuli. Additionally, the heterogeneity in the dynamic stimuli study was significant. In our opinion, although dynamic stimuli might produce a more complicated and realistic social environment [15, 42], they should be used with caution, as they also increase the heterogeneity among studies. Digitized colour video clips, including a story with a social interaction, emotional responses [16] and complicated backgrounds, are all confounding factors that lead to inconsistent results. In short, eye-tracking stimulus materials vary across studies, as there was no standard paradigm. The unstructured, natural test paradigm with con-
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trol variables should be developed for further research.

Although this study yielded promising results, it suffers from several limitations. First, the number of participants who were enrolled is limited, although it is large compared to ASD studies to some extent because it is difficult to include people with ASD in research. The association between mouth fixation and social disability was not significant, which might be due to the limited number of included studies and participants. Therefore, this finding should be interpreted with caution. Second, the findings are largely based on high-functioning people with autism, whereas low-functioning people with autism might experience greater benefits from early detection and diagnosis. Clinically and technologically, children with lower functioning generally have moderate to severe ASD and often present with one or several comorbid disorders (attention disorders, motor disorders, language disorders, emotional disorders, etc.) [43]. Therefore, they generally cannot participate in eye-tracking studies. Future research is needed to determine whether the results can be extended to individuals with autism who demonstrate lower cognitive functioning. Third, in most of the studies, the association between eyes/mouth fixation and social impairment was measured at a single time point. Data from Jones and Klin [24] revealed that the results might change as they grow. Rutherford and Towns [44] also demonstrated that social skills training can impact the facial processing strategy and tests performed. Thus, follow-up research is necessary to examine the stability of the results.

Conclusion

In conclusion, this study showed that less eye fixation was associated with greater social impairment in individuals with ASD. Our findings provide additional evidence that reduced eye fixation is a strong hallmark of the early detection, diagnosis and prediction of social deficits in individuals with ASD. Therefore, intervention and treatment aimed at improving social responsiveness can be conducted at an early stage of the disorder. The relationship between mouth fixation and social impairments should be further investigated in future research.

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Disclosure of conflict of interest

None.

Authors’ contribution

S.X and X.X were responsible for the initial plan, study design, conducting the study, data interpretation, and manuscript drafting. X.X and S.X was responsible for statistical analysis. T.L and H.R were responsible for data collection, and data extraction. Y.T, S.X, and Y.H were responsible for data interpretation and manuscript drafting.

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al connectivity in autism spectrum disorders during face processing. Brain 2008; 131: 1000-1012.


Supplementary Table 1. Literature search strategy for Pubmed

#2 (((“Autistic Disorder”) OR “Autism Spectrum Disorder”) OR Autism) OR Asperger) OR ASD
#3 #1 OR #2
#5 (((“Eye movement”) OR “Eye tracking”) OR “Eye gaze”) OR Fixation) OR “Visual Scanning”
#6 #4 OR #5
#7 “Social Behavior Disorders” [Mesh]
#8 (((“Communicative competence”) OR “Social competence”) OR “Social attention”) OR “Social interaction”) OR “Social engagement”) OR “Social deficits”
#9 #7 OR #8
#10 #3 AND #6 AND #9
#11 Humans [MeSH]
#12 #10 AND #11

Supplementary Table 2. AHRQ quality assessment criteria for Cross-Sectional

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Define the source of information (survey, record review)</td>
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<tr>
<td>2) List inclusion and exclusion criteria for exposed and unexposed</td>
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<tr>
<td>subjects (cases and controls) or refer to previous publications</td>
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<td>3) Indicate time period used for identifying patients</td>
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<td>4) Indicate whether or not subjects were consecutive if not</td>
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<td>population-based</td>
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<td>5) Indicate if evaluators of subjective components of study were</td>
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<td>masked to other aspects of the status of the participants</td>
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<td>6) Describe any assessments undertaken for quality assurance</td>
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<td>purposes (e.g., test/retest of primary outcome measurements)</td>
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<td>7) Explain any patient exclusions from analysis</td>
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<td>8) Describe how confounding was assessed and/or controlled.</td>
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<td>9) If applicable, explain how missing data were handled in the</td>
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<tr>
<td>analysis</td>
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<tr>
<td>10) Summarize patient response rates and completeness of data</td>
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<td>collection</td>
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<td>11) Clarify what follow-up, if any, was expected and the</td>
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<td>percentage of patients for which incomplete data or follow-up was</td>
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<td>obtained</td>
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</table>
Fixation on eyes and social disability

**Supplementary Figure 1.** Funnel plot, outcome: fixation on eyes.

**Supplementary Figure 2.** Funnel plot, outcome: fixation on mouth.