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# PREPRINT

RUNNING TITLE: PARSING HETEREOGENEITY IN AUTISM

Parsing Heterogeneity in Autism Spectrum Disorders: Visual Scanning of Dynamic Social Scenes in School-Aged Children

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### Abstract

**Objective:** To examine patterns of variability in social visual engagement and their relationship to standardized measures of social disability in a highly heterogeneous sample of school-age children with autism spectrum disorders (ASD). Method: Eye-tracking measures of visual fixation during free-viewing of dynamic social scenes were obtained for 109 children with ASD (mean age= $10.2 \pm 3.2$  years), 37 of whom were matched to 26 typically developing (TD) children (mean age= $9.5 \pm 2.2$  years) on gender, age and IQ. The smaller subset allowed for between-group comparisons whereas the larger group was used for within-group examinations of ASD heterogeneity. Results: Between-group comparisons revealed significantly attenuated orientation to socially salient aspects of the scenes, with the largest effect size (Cohen's d=1.5) obtained for reduced fixation on faces. Within-group analyses revealed a robust association between higher fixation on the inanimate environment and greater social disability. However, the associations between fixation on the eyes and mouth and social adaptation varied greatly, even reversing, when comparing different cognitive profile subgroups. **Conclusions:** While patterns of social visual engagement with naturalistic social stimuli are profoundly altered in children with ASD, the social adaptivity of these behaviors varies for different groups of children. This variation likely represents different patterns of adaptation and maladaptation that should be traced longitudinally to the first years of life, before complex interactions between early predispositions and compensatory learning take place. We propose that variability in

these early mechanisms of socialization may serve as proximal behavioral

manifestations of genetic vulnerabilities.

[244 words]

Given the vast phenotypic heterogeneity in autism spectrum disorders (ASD)<sup>1</sup>, the prospect of successfully mapping identified etiologies upon behavioral markers is likely to require mediating phenotypes, or 'endophenotypes' – more elementary heritable traits – capable of yielding more homogeneous samples<sup>2</sup>. This need is particularly pressing given that the mapping of autistic symptomatology directly onto genetic markers utilizing components (e.g., symptom clusters) or aspects of the phenotype (e.g., language dysfunction) has yielded only modest results to date<sup>3</sup>. Genotypic heterogeneity has proved equally baffling, with unique identified mutations accounting for only a small number of cases <sup>4-5</sup>. It is in this context that developmental cognitive science may provide the necessary bridge between molecular pathobiology and clinical behavior <sup>6-7</sup>.

A candidate approach has been to study the altered ways in which individuals with ASD look at social stimuli relative to controls <sup>8</sup>. Several eye-tracking studies, primarily using static human faces, have focused entirely on the percent of viewing time associated with the eyes region relative to the mouth region of human faces <sup>9</sup>. Typically, results indicated less fixation time on the eyes region of the face <sup>10-13</sup>, with more variation in fixation on the mouth region; some studies found increased fixation on the mouth region of the face <sup>12</sup> whereas others found no differences in this regard <sup>10,11</sup>. In contrast to studies using static faces, studies using dynamic social scenes have consistently identified atypical viewing patterns in individuals with ASD <sup>9</sup>. In general, however, this literature is consistent with Langdell's <sup>14</sup> original hypothesis: individuals with autism show attenuated reliance on information from the eyes region of the face

and, at least in some situations, over-reliance on information from the mouth region of the face when performing structured viewing tasks (e.g., recognition of face identity or emotional expressions).

Our past work has used eye-tracking measures to focus on mapping and quantifying social visual engagement in individuals with ASD <sup>15-18</sup>, targeting a defining symptom of the condition within an experimental setup that approximates their everyday social experiences, and in which their social adaptive deficits are most pronounced <sup>19</sup>. Previously, we studied very homogeneous groups: prototypically high-functioning. highly-verbal adults with autism <sup>18</sup> and toddlers with autism <sup>17</sup>. In both cases, we found altered patterns of looking at social scenes. Adults with autism focused two times less on the eyes region of faces while focusing two times more on the mouth relative to controls. Reduced eyes fixation was the strongest diagnostic discriminator. However, attenuated eyes fixation was not correlated with level of social disability. Instead, increased fixation on the mouth region was a strong predictor of lower levels of social disability and higher levels of social ability. In a similar study with toddlers with ASD, measures of visual fixation again yielded robust between-group differences in the amount of fixation on eyes and mouth regions. Unlike in the adult sample, for these 2year-olds, increased fixation to eyes was correlated with higher levels of social ability. In both studies, with adults and with toddlers, individuals with ASD displayed increased fixation on background objects compared to controls.

In summary, these results, obtained from both proximal and distal points in development, indicate an alternative path of neural and behavioral specialization <sup>19-22</sup>,

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one guided by diminished experience in social action and interaction in the presence of increased pursuit of physical, not social, connections in their surrounding world. In our studies to date, however, the data from adults represent the cumulative effects of long-term atypical experiences, while the data from toddlers represent a time in which symptomatology profiles are still emerging. In the present study we intended to close this age gap by focusing on patterns of visual fixation in school-age children, examining a time when clinical profiles are more stable than in toddlerhood and yet closer to the emergence of the syndrome than in adulthood.

In addition to this primary aim, we wanted to explore a secondary hypothesis that cognitive profile would moderate the relationship between visual fixation patterns and social disability in a broad, heterogeneous sample. Past studies of school-age children with ASD have highlighted profiles of cognitive functioning as useful in parsing heterogeneity in the disorder. One of the most valuable predictors is overall level of intellectual functioning, or full scale IQ (FSIQ). Though intellectual disability is commonly comorbid in ASD, higher FSIQ is associated with better outcomes for both social and adaptive behavior<sup>23</sup>. Similarly, an uneven cognitive profile, with a significant discrepancy between verbal and nonverbal IQ (VIQ and NVIQ), or an IQ split, is common in ASD, present in over 40% of affected individuals <sup>24</sup>. Discrepancies in either direction, with higher VIQ or NVIQ, have been associated with poorer social outcomes <sup>25</sup>. Other cites: 26-29

As we measure these individuals' attempts to make sense of complex social scenes, we hope to shed light on their real-life difficulties in social interaction. Having

studied endpoints of development during toddlerhood and adulthood <sup>17,18</sup>, we focused in the present study on school-age children; and given our interest in parsing the heterogeneity of ASD, we widened considerably the spectrum of participants involved. We began by comparing patterns of visual fixation to dynamic social stimuli in children with ASD relative to a well-matched sample of control children. We then enlarged the sample of children with ASD in order to expand the heterogeneity of the group with a view to examine more closely the possible mediating roles of cognitive profiles on patterns of visual fixation.

## **Participants & Methods**

### Participants

One hundred and thirty-five children participated, all with the written informed consent of their parents and/or legal guardians. Children were recruited through a federally-funded research project based in the Autism Program of the Yale Child Study Center, New Haven, CT. The research protocol was approved by the Human Investigations Committee of the Yale University School of Medicine, and families were free to withdraw from the study at any time. All children had normal or corrected-tonormal vision and no history of auditory impairment.

# PLEASE INSERT TABLE 1 ABOUT HERE

All N=135 children completed the experimental procedures and together comprised N=109 children with ASD and N=26 TD children (**Table 1**). A subset (N=37) of the entire ASD sample was matched to the TD group on gender ratio, chronological age, FSIQ, VIQ, and NVIQ. The subset ASD sample contributed data to between-group

analyses in comparison to TD controls, while the entire sample of ASD children (N=109) contributed data to within-group analyses of the relationship between eye-tracking measures, levels of social disability and cognitive profiles. IQ measures were derived from the *Differential Abilities Scale*<sup>30</sup>. Measures of social disability or autistic symptomatology were derived from the Autism Diagnostic Observation Schedule (ADOS) <sup>31</sup>. Given the wide range of ADOS modules used in this large sample (Modules 2, 3, and 4), we used the ADOS Calibrated Severity Score <sup>32</sup> (higher scores denote more severe autistic symptomatology), a measure standardized across modules. For inclusion in the ASD group, children had to meet all three of the following conditions: (1) meet criteria for either autism or an autism spectrum disorder on the ADOS, (2) meet criteria for autism on the Autism Diagnostic Interview – Revised (ADI-R)<sup>33</sup>, and (3) be independently assigned, by two experienced clinicians upon review of all available data. including standardized testing and videotaped material of diagnostic examination, a diagnosis of Autistic Disorder (Aut), Asperger's Disorder (Asp), or Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS). In the entire ASD sample, 37.6%, 12.8%, and 49.5% were assigned an Aut, Asp and PDD-NOS diagnosis, respectively. In the ASD subset matched to TD children, 32.4%, 29.7%, and 37.8% were assigned an Aut, Asp and PDD-NOS diagnosis, respectively. None of the children meeting ADOS and ADI-R criteria for inclusion in the study failed to meet clinician-assigned, best estimate diagnoses within the autism spectrum. In the rare case of disagreement between ADOS and ADI-R criteria, as a widely accepted gold standard, the clinician-assigned, best estimate diagnosis took priority. 34-35 TD children were included only if there was neither history nor current presentation of intellectual disabilities (defined as  $FSIQ \ge 70$ ) or social disabilities (a negative screen on the *Autism Screening Questionnaire*<sup>36</sup>), and no first- or second-degree relatives with ASD or related disorders.

**Table 1** provides participant characterization data and statistical comparisons. We matched the ASD subset (N=37) to the TD group (N=26) by removing 72 children with ASD. The 72 children removed were comparable to the 37 used in the matched comparison in regards to gender ratio (Male/Female, 53/19 and 30/7, respectively) and chronological age (years, 10.02 (2.33) and 10.22 (3.53), mean (sd)). Using the ADOSderived severity score to assess autistic symptomatology, the two groups also had comparable levels of social disability (6.75 (2.48) and 7.45 (2.49), respectively). However, the distribution of clinician-assigned diagnoses was significantly different (Aut/Asp/PDD-NOS, 29/3/40 and 12/11/14, respectively, p<.001). In regards to IQ scores, Full Scale IQ (FSIQ) was significantly lower for the N=72 excluded ASD children relative to the ASD subset (88.71 (19.85) and 112.03 (15.23), respectively, p < .001), as was Verbal IQ (VIQ) (88.54 (19.69) and 111.35 (16.30), respectively, p<.001), and Nonverbal IQ (NVIQ) (92.31 (19.44) and 111.35 (14.51), respectively, p<.001). From a data analysis standpoint, therefore, as we moved from our well-matched ASD vs. TD comparisons to the within-group ASD analyses we broadened the ASD group by adding N=72 children who were somewhat lower functioning in VIQ (and FSIQ) but comparable in age, gender and social disability. The full sample of N=109 ASD school-age children covered a relatively wide age range ( $\pm$  1SD, ~7 to 13 years), IQ distribution ( $\pm$  1SD,

FSIQ of ~ 75 to 118), and severity of autism  $^{32}$  (± 1SD, ADOS Severity Score of ~ 4.5 to 9.5). While there was a wide range in FSIQ (42-149), the overall level of cognitive functioning of the full ASD sample was still relatively high. However, this sample of N=109 is, to the best of our knowledge, the largest eye-tracking sample of ASD individuals that has been presented in the literature.

#### Stimuli

Children's visual scanning and fixations were measured with eye-tracking while they viewed 2 films of self-contained, 5 to 7 minute social scenarios presenting schoolage children interacting in naturalistic contexts. These were intended to reflect everyday experiences of this age group (**Figure 1a** shows the beginning of one clip, Supplemental Materials 1 contains example video stimulus). The first clip offered a narrative of a girl trying to fit in and make friends at school. In the second film clip, a group of boys play baseball on a summer day. The scenes presented nuanced social interaction in a visually complex environment.

# PLEASE INSERT FIGURE 1 ABOUT HERE

The scenes were shown as full-screen audiovisual stimuli on a 20-inch (50.8cm) computer monitor (refresh rate of 60 Hz noninterlaced). Video frames were 8-bit color images, 640x480 pixels in resolution. Video frame rate of presentation was 30 frames per second. The audio track was a single (mono) channel sampled at 44.1 kHz.

Prior to presentation of experimental stimuli, we included a test of each child's ability to shift and stabilize gaze, as a minimal control against obvious symptoms of eye

movement disorders. Children were shown a series of video clips and animations and the elicited behaviors—saccading to a target and maintaining fixation—were measured. All children passed by saccading to a target within 500 milliseconds and maintaining stable foveation with less than  $5^{\circ}$ /sec of drift for at least 1 second  $^{37}$ .

### Experimental Procedure

Eye-tracking was accomplished using a dark pupil-corneal reflection videooculography technique with hardware and software created by ISCAN, Inc. (Woburn, MA). The system was mounted unobstrusively on the bill of a baseball cap and utilized a target-tracking method that enables highly accurate eye-tracking without having to restrain the participant's head (accuracy within  $\pm 0.3^{\circ}$  over a  $\pm 20^{\circ}$  horizontal and vertical range). Participants sat in a comfortable armchair, 25" from a 20" computer screen mounted flush within a black wooden panel. Data were collected at a rate of 60 samples/second and recorded to video at the standard rate of 30 frames/second.

#### Data Processing

Analysis of eye movements and coding of fixation data were performed with inhouse software. The first phase of analysis was an automated identification of nonfixation data, comprising blinks, saccades, and fixations directed away from the stimuli presentation screen. Saccades were identified by eye velocity using a threshold of 30°/second <sup>37</sup>. Blinks were identified by eyelid closure as indexed by the speed of change in pupil size (as the closing eyelid covers the pupil and causes more rapid change than what typically occurs during dilation and constriction) as well as by change in the y-coordinate of center-of-pupil data. The blink detection algorithm was previously verified in a set of younger participants in our eye-tracking studies both through visual analysis of video images and through simultaneous eye-tracking and EMG recording.<sup>17</sup> Off-screen fixations, when a participant looked away from the video screen, were identified by fixation coordinates beyond the screen bounds. From within the 488.4 seconds of total viewing data (14,652 video frames), total non-fixation data were not significantly different between the three groups of children (N=72 ASD children included in the ASD Full Sample, N=37 ASD subset included in the matched comparison to the TD group, and N=26 TD sample). Data are provided in seconds: for saccades, 81.28 (34.99), 82.48 (37.98), 88.46 (21.81), respectively,  $F_{2,132}$ =.437, *p*=.647; for blinks, 26.06 (23.77), 48.24 (38.36), 38.54 (27.01), respectively,  $F_{2,132}$ =7.44, *p*<.001; and for off-screen fixations, 45.47 (40.17), 19.24 (24.97), 8.44 (13.74), respectively,  $F_{2,132}$ =15.56, *p*<.001; and for all non-fixation data (saccades + blinks + off-screen), 152.80 (67.49), 149.97 (59.94), 135.44 (40.41), respectively,  $F_{2,132}$ =.781, *p*=.460.

Eye movements identified as fixations were coded relative to four regions-ofinterest (ROIs) that were defined within all video stimuli: eyes, mouth, body (neck, shoulders, and contours around eyes and mouth such as hair), and object (surrounding inanimate stimuli) (**Figure 1b**). The regions-of-interest were defined by hand-tracing for all frames of video (14,652), and were then stored as binary bitmaps (via software written in MATLAB). Automated coding of fixation time to each region-of-interest then consisted of a numerical comparison of each child's coordinate fixation data with the bitmapped ROIs. All aspects of the experimental protocol were performed by personnel blind to diagnostic status of child. Most aspects of data acquisition and all aspects of coding, processing, and data summary were automated to ensure separation between the diagnostic characterization protocol and the experimental protocol.

#### Results

Matched ASD (N=37) and TD (N=26) samples: Visual Fixation Time on Regionsof-Interest (ROI)

# PLEASE INSERT FIGURE 2 ABOUT HERE

The ASD group and TD group, matched on age and IQ, had significantly different visual fixation times on all ROIs (eyes, mouth, body and object) (**Figure 2**). The ASD group focused less on eyes [30.9% (13.1) vs. 41.1% (14.3), respectively,  $t_{61}$ = -2.94, p=.005] and mouth [17.5% (8.4) vs. 24.6% (13.8), respectively,  $t_{61}$ = -2.518, p=.014] than controls, and more on the body [27.6% (7.3) vs. 19.0% (4.4), respectively,  $t_{61}$ = 5.37, p<.001] and object regions [24.0% (12.4) vs. 15.3% (5.1), respectively,  $t_{61}$ =3.39, p=.001]. The most significant comparison was in regards to the face region (eyes and mouth together): the ASD group spent only 48.4% (13.4) of their viewing time focused on faces relative to the TD group's 65.7% (8.0) ( $t_{61}$ = -5.87, p<.001; Cohen's d =1.5). These results replicated our previous findings of altered visual engagement with dynamic social scenes in toddlers <sup>17</sup> and in adults <sup>18</sup> with ASD. However, in contrast to those previous studies, percent fixation on the mouth region in the ASD group was significantly lower than that of the TD sample. This is not unexpected: the past studies used mostly close-ups on faces, whereas the current stimuli portrayed whole

individuals. Thus a direct comparison of absolute percent fixation time on ROIs would ignore the fact that in this study, characters' faces occupied much less screen area and were involved in scenes that contained a great deal of movement and actions on objects. That, despite the nature of the stimuli, the TD group spent 2/3 of their viewing time focused on faces provides the pertinent benchmark comparison.

# Full Sample of School-Age Children with ASD (N=109): Visual Fixation Time on Regions-of-Interest (ROIs)

As noted, we added N=72 school-age children with ASD to the ASD subset (N=37) used in the matched comparison to the TD group (N=26), thus creating a heterogeneous group of N=109 school-age children with ASD. The 72 children had, on average, FSIQs and VIQs about fifteen points lower than the matched ASD subset. And yet, percent visual fixation times on ROIs were virtually identical in the two groups, differing by no more than a few percentage points (in the N=72 added group: eyes: 30.8% (13.4); mouth: 16.0% (9.2); body: 30.0 % (10.3); and object: 23.3% (8.4)).

# Full Sample of School-age Children with ASD (N=109): Patterns of Visual Fixation Time as Predictors of Social Disability

In this larger and more heterogeneous sample of ASD school-age children, the association between higher object fixation and higher social disability was significant (r=.245; p=.014), although the effect size was small. The relationships between eyes and mouth fixations and level of social disability were numerically even weaker (r=-.183,

p<.1; and r=-.135, p=.179, respectively). These negligible correlations were in contrast to the significant relationship between visual attention and ADOS scores in our past homogeneous adult and toddler samples.

# PLEASE INSERT TABLE 2 ABOUT HERE

Full Sample of School-age Children with ASD (N=109): Do Visual Fixation Patterns Predict Levels of Social Disability Differently in Individuals with Different Cognitive Profiles?

To explore our secondary hypothesis—whether different cognitive profiles modulate the relationship between visual attention and social disability—we assessed the effect of a discrepancy between VIQ and NVIQ as well as the effect of differences in FSIQ. We first examined children in our sample with a clinically significant VIQ advantage <sup>38</sup>(VIQ Split group, VIQ-NVIQ  $\ge$  12 points) (**Table 2**). Within this group, there was a significant relationship between visual fixation and ADOS severity scores (*r*=-.65, *p*=.013)—higher mouth looking predicted lower social disability, explaining over 40% of the variance in ADOS scores (**Figure 3**). The correlation between object-looking and ADOS severity scores failed to reach significance (r=.32, p=.27), but this may have been due to the small sample size of this subgroup. However, eyes-looking was not predictive of disability (r=.10, p=.73).

We also isolated the children with a split in the opposite direction, with a NVIQ advantage of at least 12 points (NVIQ Split group, NVIQ-VIQ  $\ge$  12 points). While this group did not significantly differ from the VIQ Split group on FSIQ or on the percentage

of fixation time spent on the eyes, mouth or objects, none of the correlations between visual fixation and social disability were significant (all *r*<.17).

We next examined the role of FSIQ in children with an even IQ profile, those without a significant discrepancy between VIQ and NVIQ, Within this group, both eyelooking and object-looking significantly correlated with social disability (r=-.29, *p*<.05 and r=.27, *p*<.05, respectively), but the relationship between mouth-looking and social disability was almost zero (r=.09). Since FSIQ ranged from 42 to 149 in our heterogeneous sample, we explored FSIQ as a potential moderator of the relationship between mouth-looking and ADOS severity scores. Using hierarchical multiple linear regression to assess a moderational effect <sup>39</sup>, we mean-centered our FSIQ and mouth fixation variables and tested for main and interaction effects. The resulting model accounted for 17.8% of the variance in ADOS severity scores (R<sup>2</sup>=17.8, F<sub>3.54</sub>=3.90, p=.014). While there was a main effect of FSIQ on ADOS scores (β=-.03, p=.03), the interaction term FSIQ × Mouth Looking was also significant (β=.51, *p*=.008).

To further probe the moderating effect of FSIQ and reveal what level of FSIQ was necessary for mouth-looking to significantly correlate with ADOS severity score, we used the Johnson-Neyman technique. Rather than conventional tests of simple slopes, this method reveals which regions, or values, of the moderator yield a significant relationship between the predictor and outcome variables <sup>40,41</sup>. We found that the correlation between mouth-looking and social disability only became significant at a FSIQ of 98 or higher. Based on this value, we divided the group of children with an even IQ profile into a group of lower FSIQ individuals (Lower Even FSIQ group, FSIQ < 98)

and higher IQ individuals (Higher Even FSIQ group, FSIQ  $\ge$  98), and then re-examined the correlation between mouth-looking and ADOS severity score within each group. Indeed, for the Lower Even FSIQ group, there was no significant relationship (r=-.083, p=.67), whereas for the Higher Even FSIQ group, higher mouth-looking was significantly associated with greater social disability (r=.473, p<.01) (**Figure 3**). These two correlations significantly differed from each other (z=-2.15, p=.031). Similarly, the relationships between social disability and both eyes-looking and object-looking were stronger in the Higher Even FSIQ group than in the Lower Even FSIQ group (eyes: r=-.412, p=.03 vs. r=-.221, p=.25; object: r=.448, p=.015 vs. r=.171, p=.38), but the correlations did not significantly differ between groups.

Having identified four distinct subgroups based on cognitive profile within our broad sample of children with ASD, we next compared the VIQ Split group to the Higher Even FSIQ group. These two groups were matched on both VIQ ( $t_{47}$ =1.25, p=.22) and level of social disability ( $t_{47}$ =-.527, p=.57). However, for the VIQ Split group, higher mouth looking predicted *less* social disability (*r*=-.65, *p*=.013), whereas in the Higher Even FSIQ group, higher levels of mouth-looking predicted *more* social disability (*r*=.473, p<.01). These two correlations were significantly different from each other (z=-3.56, p<.001).

#### PLEASE INSERT FIGURE 3 ABOUT HERE

# Discussion

In this study, we used eye-tracking measures of spontaneous viewing of scenes involving complex social interactions to quantify strategies of social visual monitoring in school-age children and to parse the heterogeneity present in ASD. We began by examining results for a group of N=37 children with ASD and N=26 TD children, wellmatched on gender ratio, chronological age, FSIQ, VIQ and NVIQ. We then performed more in-depth within-group analyses for a larger and more heterogeneous sample of N=109 ASD children, comprising the original ASD group and N=72 additional children with ASD. All participants demonstrated normative eye-movement function. Our dependent variables were percent fixation time (from total viewing) on eyes, mouth, body and object ROIs; our independent measures were ADOS Severity scores (indicating levels of autistic symptomatology) and IQ scores.

Comparing matched ASD and TD groups, the ASD group significantly differed from the TD group on all ROI comparisons. Children with ASD focused less on eyes and mouth regions and more on body and object regions. The strongest predictor of group membership was fixation on the face area (eyes and mouth regions together). These results replicate our previous work with toddlers <sup>17</sup> and adults <sup>18</sup> with ASD demonstrating altered visual engagement with dynamic social scenes. Unlike in those studies, however, in this sample of school-age children with ASD, percent mouth fixation did not exceed that of the TD sample. This was not unexpected given the nature of stimuli used in this study. The result underscores the fact that visual fixation patterns relative to faces or social scenes are paradigm-specific. When comparing different eyetracking studies, conclusions based only on absolute percent fixation times on ROIs may be misleading. Typical controls completing the same paradigm provided the normative benchmark: higher percent fixation on faces in the TD group relative to the ASD group reached an effect size of Cohen's d=1.5.

Examining the larger and more heterogeneous sample of children with ASD highlighted the presence of variability in the interplay between social visual engagement and social disability. Underneath similar summary fixation results lay different patterns of social adaptation and maladaptation. One pattern was robust: higher object fixation predicted higher social disability. However, neither lower eyes nor lower mouth percent fixation was significantly associated with higher levels of social disability in the full ASD group, in contrast to findings with past samples.

Given the importance of IQ as a predictor of outcome <sup>23</sup> as well as this sample's wide range of FSIQ (FSIQ varied ± 1SD from 75 to 118) and cognitive discrepancies (VIQ-NVIQ varied ± 1SD from -18 to +13), we explored how cognitive profile affects the social adaptation and maladaptation of visual attention patterns. In children with an even IQ profile, FSIQ moderated the relationship between mouth-looking and social disability. Higher mouth fixation and lower social disability were significantly more strongly correlated for children with Higher Even FSIQ. This Higher Even FSIQ group also had stronger relationships between eyes-looking and social disability compared to children with Lower Even FSIQ, though these differences were not significant.

The moderating effect of FSIQ suggests that individuals with lower FSIQ may be engaging with the video stimuli in a qualitatively different way from higher functioning individuals. Although overall looking times for all ROIs did not differ based on FSIQ, the Lower Even FSIQ group spent a great amount time looking off-screen (42.10 seconds (32.8) vs. 27.04 (37.7),  $t_{59}$ =1.66, *p*=. 1), perhaps reflecting a different pattern of social engagement with the video stimuli. As a result, our summary measures of visual fixation on particular regions of the face, for example, likely yield less insight into their social adaptation. More detailed measures of visual attention, which our lab is currently developing<sup>42</sup>, may be more sensitive to determine the predictive value of visual engagement patterns.

Most interesting, however, were the different profiles obtained for two subgroups matched on VIQ: one with higher FSIQ (but even VIQ and NVIQ) and one with a discrepantly high VIQ. While in both cases higher object fixation predicted higher levels of social disability, patterns of mouth fixation indicated a different result: despite comparable levels of percent fixation on the mouth regions overall, higher mouth fixation predicted *higher* social disability in the children with higher FSIQ and an even IQ profile and *lower* social disability in the children with the VIQ split. In other words: in Higher Even FSIQ children mouth looking was associated with a *detriment* in social adaptation; in VIQ split children mouth looking was associated with an *enhancement* in social adaptation.

We hypothesize that this pattern is likely due to that fact that, for these disproportionately verbal individuals, fixation on linguistic cues may be the main route to social success. This reliance means that children who are more glued to the mouth, the source of language, are picking up more social information than their highly verbal peers who are looking elsewhere in the scene. However, children without this VIQ split may have other avenues into social understanding, perhaps from other facial cues. For children with high, even FSIQ, being too glued to the mouth is a maladaptive strategy. The discrepancy highlights the significance of stimuli characteristics during eye-tracking studies. Without dynamic stimuli and the accompanying audio, the mouth-language pairing present in naturalistic social interaction is otherwise absent.

There are several limitations to the current study. While our N=109 sample was very large for studies of this type, the individual subgroups were of a limited size, so our sample had limited power to detect interactions between continuous variables in the context of multiple linear regression. Of note, while we did compute multiple correlations for each subgroup, our evaluation of the difference between these coefficients was based on sample size and strength of association, values which are independent of our significance threshold. Still, due to the low power of the subgroup design in concert with the relatively high overall IQ of the full ASD sample, we do not intend for the particular IQ subgroupings from this study to be used as definitive classifications. Additionally, it is possible that other individual variables also moderate the relationship between visual fixation and social adaptation. For example, an important future direction would be to assess whether linguistic functioning (beyond VIQ) also serves as a moderator. <sup>43</sup>

Additionally, while we focused on IQ profiles as possible moderators of patterns of social visual engagement, it is important to note that, from a developmental standpoint, this association does not necessarily imply directionality. In a recent study <sup>38</sup>, we showed that, for toddlers with ASD, measures of social visual engagement taken at the age of 2 years were stronger predictors of cognitive function 15 months later than the same measures of cognitive function taken at the age of 2. For children with ASD, disruptions of social development may significantly determine the subsequent course of cognitive development. This is hardly surprising given that so much learning is accomplished through shared experiences with others and that communication is by definition a social adaptive function <sup>19</sup>. In the context of the present study, therefore, it might not be farfetched to hypothesize that longstanding atypical experiences in social development might have contributed to cognitive profiles measured later in life, a possibility that is taking hold conceptually <sup>44</sup>, in longitudinal work involving young children with ASD <sup>42</sup> and in early intervention research <sup>45</sup>.

Future challenges will also include an attempt to capitalize on these methods in order to optimize teaching strategies for individual children. One lesson from the present study is that, for some children at least, an attempt to normalize their social behavior may not contribute to increased social adaptation. For them, one might reinforce a strategy that, while atypical and suboptimal, makes them more able to cope with the demands of everyday social life. Our results indicate the importance of considering not a just a child's autism diagnosis, but other individual characteristics that shape his or her interaction with the world.

Finally, our attempt to parse heterogeneity in ASD by measuring visual scanning of dynamic social scenes in school-age children also carries a lesson for efforts to identify mediating phenotypes for genetics research. When we move from more proximal observations of genetically-determined behaviors in infancy and toddlerhood years to measurements of symptoms and of learning styles later in life, we are likely to wrestle with results that originate from complex and iterative interactions between early predispositions (abilities and disabilities) and the individual's life experiences and treatment effects <sup>19</sup>. The search for successful endophenotypic constructs is more likely to succeed through studies of infants and a focus on evolutionarily highly conserved and developmentally early emerging social adaptive skills <sup>20</sup>. To use an analogy, were one to have a shortened leg, there would be no limp in one's gait if the person lived in outer space in the absence of gravity. A limp would be the result of having to acquire biped locomotion over terrain that is gravity-bound. A search for the causes of the limp should focus on why the leg was short, not on the infinitely complex resultants of lifetime attempts to negotiate different kinds of terrain with variable levels of help and prosthetic artifacts.

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**Table 1:** Participants in Matched, Between-Group Comparisons (N=37 ASD v. N=26 TD), and in Combined ASD Sample for Within-ASD-Group Analyses (N=37 + N=72 Additional ASD participants, N=109 Total ASD participants)

	Additional ASD Group (N=72)	Matched ASD Group (N=37)	Matched TD Group (n=26)	Pairwise Comparison: Matched TD vs. ASD
Sex, M/F	53/19	30/7	18/8	X <sup>2</sup> =2.439
Age, years	<b>10.2</b> (3.5)	<b>10.0</b> (2.3)	<b>9.5</b> (2.2)	T <sub>73</sub> =-0.907
FSIQ	<b>88.7</b> (19.8)	<b>112.0</b> (15.2)	<b>110.4</b> (15.9)	T <sub>73</sub> =-0.424
VIQ	<b>88.5</b> (19.7)	<b>111.4</b> (16.3)	<b>110.7</b> (15.8)	T <sub>73</sub> =-0.160
NVIQ	<b>92.3</b> (19.4)	<b>111.4</b> (14.5)	<b>107.1</b> (15.5)	T <sub>73</sub> =1.111
ADOS Severity Score	<b>6.8</b> (2.5)	<b>7.5</b> (2.5)		
Dx, Aut/Asp/PDD-NOS	29/3/40	12/11/14		

# Mean (SD)

Abbreviations: FSIQ, Full-Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Performance Intelligence Quotient; ADOS, *Autism Diagnostic Observation Schedule*; Dx, Diagnosis: Aut, Autistic Disorder; Asp, Asperger's Disorders; PDD-NOS, Pervasive Developmental Disorder, Not Otherwise Specified.

Note: Higher ADOS Severity Scores denote higher levels of social disability.

	VIQ Split (n=18)	NVIQ Split (n=30)	Lower Even FSIQ (n=30)	Higher Even FSIQ (n=31)	F <sub>3,104</sub> Values		
FSIQ	<b>97.4</b> (20.5)	<b>92.4</b> (18.2)	<b>79.4</b> (13.9)	<b>116.9</b> (12.9)	28.491***		
VIQ	<b>109.9</b> (19.0)	<b>82.8</b> (17.3)	<b>82.1</b> (14.0)	<b>115.2</b> (10.8)	37.811***		
NVIQ	<b>88.1</b> (18.7)	<b>103.9</b> (16.6)	<b>82.8</b> (14.3)	<b>115.5</b> (11.8)	27.906***		
ADOS Severity Score	<b>6.7</b> (2.6)	<b>7.4</b> (2.4)	<b>7.4</b> (2.5)	<b>6.2</b> (2.5)	1.514		
Dx, Aut/AS/PDD- NOS	4/5/9	16/2/12	12/2/16	9/5/17	X <sup>2</sup> <sub>6</sub> =9.74		
VISUAL FIXATION TIME							
Eyes, %	<b>29.3</b> (10.2)	<b>27.7</b> (13.4)	<b>34.0</b> (13.2)	<b>31.7</b> (14.5)	1.256		
Mouth, %	<b>19.1</b> (12.2)	<b>16.3</b> (7.6)	<b>14.4</b> (8.4)	<b>17.2</b> (8.2)	1.139		
Body, %	<b>26.3</b> (8.1)	<b>32.9</b> (11.8)	<b>27.8</b> (7.7)	<b>28.7</b> (8.2)	2.583		
Object, %	<b>25.3</b> (13.4)	<b>23.1</b> (5.7)	<b>24.1</b> (12.7)	<b>22.5</b> (7.7)	0.342		

**Table 2**: Comparisons of IQ and Visual Fixation Patterns across four distinct cognitive profile groups of children with ASD.

Mean (SD)

\*\*\*p<0.001

Abbreviations: FSIQ, Full-Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Performance Intelligence Quotient; ADOS, *Autism Diagnostic Observation* 

*Schedule;* Dx, Diagnosis: Aut, Autistic Disorder; Asp, Asperger's Disorders; PDD-NOS, Pervasive Developmental Disorder, Not Otherwise Specified.

# **Figure Captions**

**Figure 1**: Stimuli (A) and Region-of-Interest Coding (B). Eye-tracking data were collected while school-age children viewed video clips of children and adults engaged in social interaction within naturalistic visual settings. Eye movements identified as fixations were coded into four regions-of-interest, identified within all videos: eyes = red, mouth = green, body (neck, shoulders and contours around eyes and mouth, such as hair) = blue, and object (all other surrounding inanimate stimuli) = yellow.

**Figure 2**: Percent fixation time on regions-of-interest in the matched ASD and TD samples. *Error bars represent SEM.* \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001

**Figure 3**: Correlations between visual fixation patterns and levels of social disability across cognitive profile subgroups of children with ASD. Abbreviations: FSIQ, Full-Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; NVIQ, Performance Intelligence Quotient; ADOS, *Autism Diagnostic Observation Schedule*. Note: Higher ADOS Severity Scores denote higher levels of social disability.