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Distinguishing Gaze Aversion and Gaze Indifference in Two-Year-Olds with Autism

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Distinguishing Gaze Aversion and Gaze Indifference in Two-Year-Olds with Autism

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Abstract

Distinguishing Gaze Aversion and Gaze Indifference in Two-Year-Olds with Autism
By Jennifer M. Moriuchi

Because atypical eye contact is one of the most prominent symptoms of autism spectrum disorders (ASD), identifying the underlying social-cognitive mechanism that accounts for atypical eye contact is key for understanding the neural etiology of ASD. Two hypotheses, each associated with a specific neural model, have been proposed: the gaze aversion account suggests that children with ASD actively avoid the eyes, whereas the gaze indifference account suggests that children with ASD are insensitive to the social cues conveyed by the eyes. To differentiate between these accounts, eye-tracking measures of visual attention were obtained from two-year-olds with autism and typically-developing peers during free-viewing of videos of approaching caregivers. Gaze patterns were examined in response to both physical priming and social cuing for eyes fixation. Across all analyses, results failed to provide evidence of gaze aversion and instead supported the gaze indifference account. These findings indicate that toddlers with ASD passively omit eye contact due to a broader insensitivity to social salience and provide guidance for future neural modeling of the disorder.

Keywords: autism, eye-tracking, gaze aversion, hyperarousal, amygdala

Distinguishing gaze aversion and gaze indifference in two-year-olds with autism

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Abstract

Identifying the social-cognitive mechanisms underlying atypical eye contact in autism spectrum disorders (ASD), one of the most prominent symptoms of the disorder, is key for understanding underlying neuropathology. Two hypotheses, each associated with a specific neural model, have been proposed: the gaze aversion account suggests that children with ASD actively avoid the eyes, whereas the gaze indifference account alternately suggests that children with ASD are insensitive to the social cues conveyed by the eyes. To differentiate between these accounts, eye-tracking measures of visual attention were obtained from two-year-olds with autism and typically-developing peers during free-viewing of videos of approaching caregivers. Gaze patterns were examined in response to both physical priming and social cuing for eyes fixation. Across all analyses, results failed to provide evidence of gaze aversion and instead supported the gaze indifference account. These findings indicate that toddlers with autism passively omit eye contact due to a broader insensitivity to social salience and provide guidance for future neural modeling of the disorder.

Keywords: autism, eye-tracking, gaze aversion, hyperarousal, amygdala

Distinguishing gaze aversion and gaze indifference in two-year-olds with autism

Atypical eye contact is among the most striking and early-emerging diagnostic symptoms of autism. Convergent evidence from clinical observation, behavioral experiments, and eye-tracking paradigms has shown that children with autism spectrum disorders (ASD) look less at others' eyes compared to typically-developing (TD) children[1–3]. However, the underlying cause of reduced visual attention to the eyes in ASD remains controversial. Given that atypical gaze is a core feature contributing to deficits in initiating and modulating reciprocal social interactions observed in ASD[4–6], the question is nonetheless critical in clarifying the etiology and underlying neuropathology of the disorder.

Two possible explanations for atypical gaze in ASD have emerged from past research: one hypothesis is that children with ASD purposefully look away from the eyes due to *gaze aversion*, specifically avoiding eye contact because the eyes have negative emotional saliency. Alternately, the atypical gaze of children with ASD may be due to *gaze indifference*, a broader insensitivity to the significant social cues conveyed by the eyes. In other words, one hypothesis indicates an active avoidance with implicit understanding of the social significance of eye contact, whereas the other indicates general insensitivity to the underlying social signal. These mutually exclusive hypotheses suggest different impairments within the social brain network involved in social interaction and processing gaze.

Based on the gaze aversion account, eye contact leads to heightened affective arousal, an autonomic system response mediated by heightened activation in subcortical structures involved in emotional regulation, particularly the amygdala[7,8]. The hyperaroused response appears to be specific to direct eye contact and sensitive to perceived social approach, as studies of affective response to gaze have reported greater autonomic arousal, as measured by skin-conductance

response, to both still images and live viewing of an actress directing her gaze toward the viewer rather than away from the viewer[9,10]. Through the repeated co-occurrence of eye contact and heightened physiological arousal, an unwanted state, it is proposed that eye contact gains negative reward value for children with ASD[11,12]. Not looking at another's eyes represents an adaptive, motivated response to withdraw and prevent aversive hyperarousal in response to eye contact[13–16]. Supporting this view, studies in adolescents and adults with ASD have found a positive correlation between the amount of time spent looking at the eyes of static face images and the degree of amygdala activation[17] as well as level of self-reported social anxiety[18,19]. Correspondingly, adults with ASD are more likely than TD peers to reorient attention away from the eyes[20,21], a response also associated with increased amygdala activation[22]. Within the gaze aversion model, amygdala hyperactivation is, therefore, the cause rather than a consequence of the atypical eye contact in ASD.

Based on the gaze indifference account, children with ASD do not view eye contact as informative, socially salient stimuli in the same way as TD children and, consequently, are not motivated to specifically orient to eye contact. Due to diminished preference for social stimuli that continues from early development, children with ASD develop broad, underlying impairments in social cognition and perception[1,23]. Not looking at another person's eyes is, therefore, a passive omission and the result of insensitivity to the underlying social signal from another person rather than a specifically motivated response to eye contact[24–26]. Rather than hyperactivation, the gaze indifference account suggests hypoactivation throughout the social brain system in response to eye contact. Insensitivity to the social salience of the eyes implicates dysfunction of the right posterior superior temporal sulcus (STS), which is attuned to the inferred communicative intentionality of eye gaze[27,28] and has been shown to be hyporesponsive to gaze

cues in ASD[29,30]. Reduced STS activation would then influence reduced downstream activation in the rest of the social brain network, including the amygdala.

Although results of past studies finding amygdala hyperactivation and autonomic hyperarousal associated with attention to the eyes in ASD would seem to contraindicate the gaze indifference account, it remains unclear whether the atypical amygdala activation contributes to the atypical gaze behavior in ASD. Recent neural and physiological evidence has suggested that the observed hyperactivation and hyperarousal to the eyes of others in adults with ASD may not be negatively valenced[25,26], which argues against an aversive response. As an alternate explanation, atypical amygdala activation may be a developmental consequence of indifference to eye contact. The extant studies addressing the gaze aversion and indifference accounts have included only older adolescent and adult participants. To help clarify the current neural findings, the current study will assess active gaze avoidance in ASD much earlier in development, before potential compensatory mechanisms might emerge.

In addition, the current study will use more detailed, temporally-sensitive measures of eyes fixation in order to define specific gaze behavior profiles associated with the gaze aversion and indifference accounts. Most of the current evidence defines atypical eyes fixation as simply looking less at another's eyes[17]. A few recent studies have included more temporally-sensitive measures[20,21], such as reflexive saccades, but these were assessed in response to complex or degraded, non-naturalistic stimuli. Identifying the mechanism underlying atypical gaze behavior, particularly in assessing the passive omission of eye contact suggested by the gaze indifference hypothesis, will require examining response to eye contact in a more naturalistic, dynamic context with increased external validity. We hypothesized that if the gaze aversion account were correct, the visual attention of children with ASD would be sensitive to social, not physical cues

for eyes fixation. If the gaze indifference account were correct, children with ASD would be sensitive to physical cues and insensitive to social cues for eyes fixation.

Results

Overall distribution of visual fixations

Eye-tracking data was collected from 26 toddlers with ASD and 38 typically-developing peers matched on chronological age and nonverbal cognitive function (Table 1) as they viewed 9 video clips of actresses portraying caregivers gazing directly at the viewer and engaging in naturalistic, age-appropriate interactions (Fig. 1a). Visual fixation time on the eyes and mouth significantly differed between the ASD and TD groups (Fig. 2). Children with ASD looked significantly less at the eyes ($t_{1,62}$ = 5.06, $P < 0.001$) and more at the mouth ($t_{1,62}$ = -3.42, P = 0.001) relative to TD controls. Fixation time on body and object regions did not differ across groups (body: $t_{1,62}$ = -0.90, P = 0.37; object: $t_{1,62}$ = -1.13, P = 0.26). These results replicated previous findings of atypical visual attention to dynamic social scenes in toddlers with ASD and indicated that our ASD group exhibited atypical visual attention to the eyes, the basic behavioral criterion for either gaze aversion or gaze indifference.

Response to physical priming for eyes fixation

To explore the gaze aversion and indifference hypotheses, we investigated response to a physical cue priming for eyes fixation. Our physical cue was a centering stimulus that was presented between video clips to ensure that all viewers began by fixating the same location (Fig. 1a). Participant data was excluded if a child's point of regard significantly deviated from the location of the centering stimulus. Because the position of the actress within the frame slightly differed across clips, participants' initial fixation was primed for a different location on the actress' face in each clip (Fig. 1b). As measured in degrees along an axis of distance from the

midline of the actress' face, the relative primed location was sometimes near the eyes to provide more eyes priming and sometimes below the eyes to give less eyes priming (Fig. 1c).

Using the varying degrees of eyes priming, we first examined if reaction time, measured as the latency to first saccade, was associated with the degree of physical priming for eyes fixation. The gaze aversion account predicted a significant correlation between reaction time and degree of eyes priming; children with ASD would be reflexively faster in saccading away specifically when physically primed to look more at the eyes (Fig. 3a). The gaze indifference account predicted no relationship; latency to first saccade would not differ based on the degree of eyes priming. We found no significant correlation between latency to first saccade and degree of physical priming for eyes fixation in either the TD (Fig. 3b; $r = -0.40$, $P = 0.28$) or the ASD group ($r = -0.39$, $P = 0.30$).

We next examined if the level of eyes fixation at a given moment was influenced by the degree of physical priming for eyes fixation. No sustained relationship would indicate gaze aversion; even when primed for eyes fixation, children would avoid looking at the eyes (Fig. 4a). On the other hand, if eyes priming were associated with eyes fixation, it would indicate gaze indifference. We calculated the correlation between the degree of eyes priming and the mean level of eyes fixation at each frame over the first 3.0 s of the video clips. At 0 s, the first frame of the video clips, degree of eyes priming was significantly associated with level of eyes fixation in both the TD (Fig. 4b; $r = 0.88$, $P = 0.002$) and ASD groups ($r = 0.85$, $P = 0.004$), indicating that participants were appropriately attending to the physical priming stimulus. By 0.5 s into the clips, there was no association with degree of eyes priming in the TD group ($r = 0.55$, $P = 0.18$), but the association remained significant in the ASD group ($r = 0.93$, $P < 0.001$). Only at 1.0 s into the clips was the degree of eyes priming no longer significantly associated with the level of

eyes fixation in both the TD ($r = 0.25$, $P = 0.52$) and ASD groups ($r = 0.57$, $P = 0.11$). The strength of the relationship continued to decrease at 2.0 s into the clips in both groups (TD: $r = -0.21$, $P = 0.58$; ASD: $r = 0.27$, $P = 0.48$).

Examining the correlation calculated continuously on a moment-by-moment basis, we specified the duration of the physical priming effect in each group, or the consecutive time from the start of the clip over which the correlation was significant at an α level of 0.05. In the TD group, the duration of the physical priming effect was 0.30 s, and in the ASD group was 0.83 s, nearly three times as long (Fig. 4c). To test the null hypothesis that the group difference in duration of physical priming effect was due to particular characteristics of our sample, we calculated a bootstrapped mean and 95% confidence interval for the duration of the physical priming effect across 5000 resamplings with replacement for both the TD and ASD groups. The confidence intervals (Fig. 4d; TD: 0 to 0.37 s; ASD: 0.57 to 1.0 s) were non-overlapping, which provided evidence against the null hypothesis and supported the conclusion that the effect of physical priming lasted significantly longer in children with ASD. When primed for eyes fixation, children with ASD did look at the eyes more and did so for a significantly longer time relative to TD children, a result supporting the gaze indifference account.

Because the effect of physical priming endured for nearly three times as long in the ASD group relative to the TD group, we further assessed whether our result could be due to a basic attentional or oculomotor issue. Past studies have suggested that children with ASD have a general difficulty disengaging attention[31,32]. However, there was no between-group difference in the time until first disengagement, measured as the latency to first saccade (Fig. 3c; $t = 1.47$, $P = 0.14$). In addition, as noted previously, the latency to first saccade was not associated with the degree of physical priming for eyes fixation in either the TD or ASD group. Together, the results

indicated that the duration of the physical priming effect in the ASD group was not simply due to ASD participants' 'sticky' fixation.

Response to implicit social cuing for eyes fixation

After the influence of physical priming faded, we examined response to implicit social cues from the actress that were promoting attention to the eyes through the remainder of the video clips. Leveraging the assumption that TD children were engaged with and sensitive to the nonverbal, affective social signal from the actress[33,34], we indexed the degree of implicit social cuing for eyes fixation based on quartiles of the TD group's moment-by-moment likelihood of eyes fixation. We calculated each individual's percentage of eyes fixation within the temporal windows corresponding to each quartile to examine whether children's attention to the eyes was temporally sensitive to implicit social cuing.

Based on the gaze aversion account, children with ASD would avoid the eyes specifically at times with the strongest social cues for eyes fixation (Fig. 5a). In contrast, based on the gaze indifference account, children with ASD would show no change in their likelihood of eyes fixation based on the degree of social cuing for eyes fixation. Because we were primarily interested in within-group effects, we conducted separate repeated measures ANOVAs using group mean likelihood of eyes fixation averaged across clips in each quartile. We found a significant main effect of the level of social cuing in the TD group (Fig. 5b; $F_{1.1,9.0} = 30.09$, $P < 0.001$), which was expected given the construction of the social cuing measure. We also found a significant main effect of the quartile of eyes salience in the ASD group (Fig. 5c; $F_{1.3,10.3} = 4.92$, $P = 0.04$), indicating that ASD children's likelihood of eyes fixation did differ based on the degree of social cuing for eyes fixation. Contrasting our predictions based on the gaze aversion and indifference accounts, children with ASD were actually more likely to look at another's eyes

at the same times as when TD children were most likely to look at the eyes. However, the pertinent result is that children with ASD were certainly not less likely to look the eyes in response to the strongest social cuing for eyes fixation, providing evidence against specific, socially-sensitive gaze avoidance in the ASD group and against the gaze aversion hypothesis.

To further clarify whether visual attention was sensitive to the degree of eyes salience, we examined group fixation density, calculated using kernel density analysis, within each quartile of eyes salience. Based on the gaze aversion account, we hypothesized that children with ASD, reflexively reorienting to avoid eye contact, would show decreased fixation density at times with the strongest social cues for eyes fixation (Fig. 6a). Alternately, based on the gaze indifference account, we hypothesized that the fixation density of children with ASD would not differ based on the degree of social cuing for eyes fixation. We calculated within-group repeated measures ANOVAs using group mean fixation density within each quartile. In the TD group, we found a significant main effect of the degree of social cuing for eyes fixation (Fig. 6b; $F_{1.8,14.5} = 4.14$, $P = 0.04$). Fixation density spiked in the highest quartile of degree of social cuing, likely reflecting specific temporal convergence on the eyes in the TD group. In contrast, in the ASD group, there was no difference in fixation density based on the degree of social cuing (Fig. 6c; $F_{1.4,11.6} = 0.19$, $P = 0.76$), providing evidence against aversive reorienting specifically in response to increased social salience of the eyes and suggesting a lack of sensitivity to the underlying social signal.

Discussion

The current study used temporally-sensitive measures of visual attention to assess whether the atypical eye contact of two-year-olds with ASD is better explained as gaze aversion or gaze indifference. Summary measures of visual fixation patterns throughout the clips

replicated past findings of reduced attention to the eyes in toddlers with ASD relative to TD peers[2]. All analyses failed to provide evidence for the gaze aversion account that children with ASD look less at the eyes because they are averse to, hyperaroused by, and consequently avoidant of eye contact. Instead, results suggested that children with ASD look less at the eyes because they are insensitive to the social significance of eye contact and are therefore not compelled to look specifically at the eyes.

Supporting our hypotheses based on the gaze indifference account, at the start of the video clips, the gaze patterns of children with ASD were highly sensitive to physical priming. The level of eyes fixation was not only strongly associated with the degree of physical priming for eyes fixation in the ASD group, but the association endured for a significantly longer time in the ASD group than in the TD group. The results are consistent with past studies indicating greater sensitivity to physical cues in ASD[35,36]. In addition, children with ASD were neither faster nor more likely to saccade away from the eyes compared to TD participants, contraindicating a simple disengagement difference[31] and suggesting that children with ASD did not attempt to actively flee or avoid looking at the eyes. Because there was no between-group difference in general latency to first saccade, whereas TD children may have reoriented to attend to the underlying social signal from the actress, children with ASD seem to have remained sensitive to the physical priming and may have simply shifted their gaze within the region primed, arguing against a specific aversive response to the eyes.

These findings seem to contradict past results indicating that adults with ASD were both faster and more likely to reflexively saccade away from the eyes when physically primed for eyes fixation[20]. However, it is important to note the differences between studies both in participant age (adults rather than toddlers) and stimuli type (still faces rather than dynamic

videos). Developmentally, that toddlers do not exhibit the same avoidance behaviors as adults in response to the eyes within a more externally valid context suggests that gaze aversion and consequent avoidance may be a learned, compensatory mechanism mediated by action-outcome learning in some individuals rather a causative factor in ASD.

After the effects of physical priming faded, children with ASD did not specifically redirect their attention away from the eyes with sensitivity to implicit social cuing promoting eyes fixation, again supporting the gaze indifference account. Unexpectedly, children with ASD actually looked at the eyes more in response to increased social cuing for eyes fixation. We hypothesize that this may be due to coincidental co-occurrence of social and physical cues during the clips; ongoing analyses are attempting to resolve this question. Nevertheless, the pertinent finding is that children with ASD did not look at the eyes less as social cuing for eyes fixation increased. Though past work in adults has suggested that individuals with ASD were more likely to look away from the eyes of partially obscured still faces specifically when the eyes conveyed the most social information[21], the developmental focus and greater external validity of the naturalistic stimuli used in the current study help to provide evidence that the atypical eye contact observed in children with ASD is not caused by gaze aversion.

Taken together, our results strongly supported the gaze indifference account of atypical eye contact rather than the gaze aversion account. However, there are limitations to the current study. First, because our results were generally based on group measures or group means, it is possible that an unrecognized subgroup of children with ASD in our sample did express gaze aversion. As we sought to identify the mechanisms underlying the core diagnostic feature of atypical eye contact, we assumed that any disruption would be consistent across the spectrum, but this may not be true in some instances, such as non-idiopathic autism. Second, though we

designed our analyses to have higher external validity and greater temporal and spatial sensitivity than similar extant measures of gaze aversion, our findings were based on novel behavioral measures not previously validated. Important future directions will be to assess these measures in populations with more clinically-defined, empirically-supported profiles of gaze aversion, such as children with Fragile X syndrome[37], as well as in participants with co-registered neurological and physiological measures.

Nonetheless, the results of the current behavioral study do provide guidance toward understanding the neuropathology of ASD. The lack of support for the gaze aversion account indicates that specific amygdala dysfunction is not the underlying cause of atypical eye contact in ASD. Because reduced attention to the eyes appears to be due instead to a passive indifference to the social signal from another, observed amygdala dysfunction is likely secondary to deficits in the STS system subserving attunement to social intentionality. These findings are corroborated by recent evidence from studies indicating differential deficits in gaze behavior between adults with ASD and individuals with amygdala lesions[38,39]. Thus, rather than focusing on amygdala-specific impairments[40,41], we suggest that future studies focus on impairments earlier in the social brain network, beginning with the STS, in order to understand the neural mechanisms of gaze indifference and associated broader social cognitive impairments in ASD.

Methods

Participants

Sixty-four children participated and completed the experimental protocol, which has been previously described elsewhere[2], with the written informed consent of their parents or legal guardians. Children were recruited through a federally-funded research project based in the Autism Program at 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. All children had normal or corrected-to-normal vision and no history of auditory impairment.

The 64 participants included 26 toddlers with an autism spectrum disorder (ASD) diagnosis and 38 typically-developing (TD) toddlers (Table 1). Groups were matched on sex ratio, chronological age, and nonverbal cognitive ability, measured by mental age equivalents obtained from the Visual Reception subtest of the Mullen Scales of Early Learning[42] (Mullen). The groups differed on verbal functioning, measured by the average of mental age equivalents obtained through the Receptive and Expressive Language subtests of the Mullen.

To qualify for inclusion in the ASD group, children met the following three conditions: (1) met criteria for Autistic Disorder or ASD on the *Autism Diagnostic Observation Schedule*[43], Module 1, a measure of social disability or autistic symptomatology; (2) met criteria for Autistic Disorder or ASD on the *Autism Diagnostic Interview – Revised*[44], a parent report measure of early social development and autistic symptomatology; (3) received a diagnosis of Autistic Disorder (21 of 28 children) or Pervasive Developmental Disorder-Not Otherwise Specified (7 of 28 children) by two experienced clinicians upon independent review of all available data, including standardized testing and video of the diagnostic examination.

To quality for inclusion in the TD group, it was required that children exhibited no developmental delays, had no known genetic syndrome, and had no family history of ASD.

All aspects of the clinical characterization protocol were performed by personnel blinded to the existing diagnostic status of the child.

Stimuli

Children were shown 9 video clips, each presenting an actress looking directly into the camera and portraying the role of a caregiver speaking to the viewer in toddler-directed speech

(Fig. 1a). Caregivers were filmed in front of a background that approximated a child's room, including colorful pictures and shelves of toys and stuffed animals.

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

Before presentation of experimental stimuli, we tested 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 animations to elicit and measure the specific gaze behaviors of saccading to a target and maintaining fixation. All children passed by saccading to a target within 500 ms and maintaining stable foveation with less than 5° per second of drift for at least 1 second.

Experimental Procedure

Children were accompanied at all times by a parent or primary caretaker. Buckled into a car seat on a pneumatic lift, children were positioned so that viewing height and distance from the screen (76.2 cm) were standardized. Lights in the room were dimmed so that only images on the screen could be seen easily. Audio was played through speakers concealed in the wall panel. The experimenter was hidden from the child's view by a curtain, but was able to monitor the child at all times using a live video feed.

Eye-tracking was accomplished using a dark pupil/corneal reflection video-oculography technique with hardware and software created by ISCAN (Woburn, MA). The system was mounted on a wall, concealed from the child's view by an infrared filter in the wall panel, to allow for remote data collection. The equipment is accurate to within ±0.3° across a ±20°

horizontal and vertical field of view. Data were collected at a rate of 60 samples per second and recorded to video at the standard rate of 30 frames per second.

Children were individually calibrated using a 5-point system prior to presentation of experimental videos. To ensure accurate eye-tracking data, the calibration was regularly checked between videos through the duration of testing. If the recorded point of regard had shifted more than 3°, data collection was paused and the 5-point calibration procedure repeated.

Data Processing

Most aspects of data acquisition and all aspects of coding and data processing were automated to ensure separation between diagnostic characterization and the experimental protocol. Analysis of eye movements and coding of fixation data were performed with in-house software. Non-fixation data, comprising saccades, blinks, and off-screen fixations, were automatically identified in the first phase of analysis. Saccades were flagged based on eye velocity, using a threshold of 30° per second. Blinks were flagged by eyelid closure, as indexed by the speed of change in pupil size as well as by change in the y-coordinate of center-of-pupil data. The blink detection algorithm was previously verified in toddlers using a similar experimental procedure with eye-tracking and simultaneous EMG recording[45]. Off-screen fixations (i.e., when a child looked away from the video screen) were flagged by fixation coordinates beyond the possible screen bounds. Across the 148.5 s of total viewing data (4456 frames), all measures of non-fixation data were not significantly different between the TD and ASD groups. Data are provided in percentages: for saccades, M_{TD} (mean) = 14.4, s.d.$_{TD}$ = 4.7, M_{ASD} = 16.1, s.d.$_{ASD}$ = 6.1, $t_{1,62}$ = -1.19, P = 0.24; for blinks, M_{TD} = 4.9, s.d.$_{TD}$ = 7.2, M_{ASD} = 3.6, s.d.$_{ASD}$ = 2.4, $t_{1,62}$ = 0.88, P = 0.38; and for off-screen fixations, M_{TD} = 14.7, s.d.$_{TD}$ = 9.8, M_{ASD} = 17.2, s.d.$_{ASD}$ = 12.9, $t_{1,62}$ = 0.83, P = 0.41.

Eye movements identified as fixations were coded relative to four regions-of-interest (ROIs) that were defined within all video stimuli: eyes, mouth, body (neck, shoulders, and contours around the eyes and mouth, including hair), and object (background setting and inanimate objects). ROIs were hand-traced for all video frames (4456 frames) and were then stored as binary bitmaps (via software written in MATLAB). Automated coding of fixation time to each ROI consisted of a numerical comparison of each child's coordinate fixation data against the bitmapped ROIs. Percentage of fixation time on each ROI was calculated relative to an individual's total fixation time.

Physical priming for eyes fixation

An animated centering stimulus played prior to each video clip to orient viewers' gaze towards the screen and to draw attention to a common fixation point. The centering stimulus was presented in the center of an otherwise blank screen and was 1.5^{o} in visual angle with alternating blue and white sections that rotated counter-clockwise in time to a chiming sound. Presentation of stimuli video clips began directly following offset of the centering stimulus. To ensure that children were fixating the center of the screen, if a child's initial point of fixation was flagged as a significant outlier from the group distribution using the Tukey method, that viewing of the clip was excluded from analyses. In total, 16 individual clip viewings were excluded in the TD group, and 14 were excluded in the ASD group.

Serendipitously, we found that because the position of the actresses slightly differed in each clip, the location of the centering stimulus (i.e., the center of the screen), corresponded to a slightly different place on the actress' face in each clip such that viewers' gaze was sometimes primed for fixation closer to the eyes and sometimes farther below the eyes and nose and closer to the mouth. Degree of eyes priming was quantified for each clip based on the vertical distance,

measured in degrees of visual angle, from the center of the nose, used as a proxy for the center of the face, to the primed location of the centering stimulus (Range: -1.1^{o} to 2.7^{o}). Degree of eyes priming did not vary systematically with order of clip presentation ($r_s = 0.17$, $P = 0.67$).

Latency to first saccade

Latency to first saccade was calculated in seconds for each clip viewed by a participant. Analyses focused on saccades occurring within the first 2.0 s of clips in an attempt to ensure that included saccades were in response to the stimulus at onset rather than later content in the videos. Group means in each clip were used to calculate a Pearson correlation coefficient for the potential association between latency to first saccade and the degree of physical priming for eyes fixation. Group means across all clips were compared using a *t* test to assess any broader group differences in disengagement.

Moment-by-moment level of eyes fixation

To assess the effect of physical priming for eyes fixation, we quantified each individual's level of eyes fixation on a moment-by-moment basis at the beginning of clips. Similar to our summary measure of the percentage of eyes fixation across all clips, our time-sensitive measure of eyes fixation was calculated as the number of frames fixating the eyes relative to the total number of frames coded as fixation within a centered moving window of 433 ms, the mean fixation duration across all participants. Using group means of this more time-sensitive measure of eyes fixation, we then calculated the Pearson correlation between level of eyes fixation and the degree of priming for eyes fixation at each frame through the first 3.0 s of the clips. After filtering the *p*-value of the correlation at each moment using a moving window of 433 ms, we determined the duration of the effect of physical priming in both groups based on the time from the start of the clip over which the correlation was significant at an α level of 0.05. Although this

method required many comparisons, we did not explicitly lower our threshold for significance because correlations were analyzed dependently rather than independently.

To further assess group difference in the duration of the physical priming effect, we used permutation testing to calculate bootstrapped group means and 95% confidence intervals. In each of 5000 TD and ASD groups randomly resampled with replacement from the original samples, we calculated the duration of the physical priming effect as previously described. We proceeded to construct 95% confidence intervals for each group based on the 2.5^{th} and 97.5^{th} percentiles of the duration of the physical priming effect across the 5000 resampled groupings. Examining the degree of overlap in the TD and ASD confidence intervals allowed us to determine whether differences observed in the duration of the physical priming effect were due to chance group patterns.

Social cuing for eyes fixation

After the influence of physical priming faded, implicit social cuing for eyes fixation was quantified and indexed based on quartiles of the TD group's likelihood of eyes fixation. We used the TD group's moment-by-moment likelihood of eyes fixation, or the percentage of TD participants attending to the eyes relative to the total number of TD participants fixating the stimuli in each frame, as a metric based on the assumption that TD children were engaged with and responsive to the underlying social signal from the actress[33,34]. Though the eyes often convey the greatest social relevance, TD viewers' likelihood of eyes fixation at a given moment naturally varied between 0 and 100% across the clips. Separating moments within each clip based on quartiles of the TD group's likelihood of eyes fixation yielded temporal windows with varying degrees of social cuing for eyes fixation. We then calculated each individual's percentage of eyes fixation in the temporal windows corresponding to each quartile and

conducted within-group repeated measures ANOVAs to examine whether children's attention to the eyes was temporally sensitive to the degree of implicit social cuing.

Fixation density

Fixation density was calculated using an adaptation of a novel computational method developed in the lab. Using the coordinate fixation data from TD participants, the visual salience of all areas of the onscreen image was calculated by kernel density analysis[46] in each frame through the duration of videos to generate a temporally- and spatially-sensitive measure of visual salience. Deviation from the median salience value was calculated for each TD and ASD participant on a moment-by-moment basis. These values were averaged across frames associated with each quartile of degree of social cuing for each participant then within each group to yield a measure of group fixation density. We conducted within-group repeated measures ANOVAs to determine whether groups' fixation density was sensitive to the degree of implicit social cuing for eyes fixation.

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Table 1. Participant characteristics

	ASD Group (N = 26)	TD Group (N = 38)	Test statistic	*P* value
Sex, male/female	**21/5**	**26/12**	$X^2 = 1.21$	0.27
Age, months	**27.1** (6.5)	**24.1** (8.0)	$t_{1,62} = -1.61$	0.11
Nonverbal function, months	**21.6** (9.0)	**24.8** (9.8)	$t_{1,62} = 1.33$	0.19
Verbal function, months	**16.3** (12.4)	**24.8** (9.2)	$t_{1,62} = 3.15$	0.003**
ADOS social score	**9.9** (3.5)			
Dx, Aut/PDD-NOS	**19/7**			

Clinical characterization information is provided as mean (s.d.) for children with autism spectrum disorders (ASD) and typically-developing (TD) peers. Nonverbal function, age-equivalence score in months on the Visual Reception subtest of the Mullen Scales of Early Learning[42]; Verbal function, age-equivalence scores in months on the Receptive and Expressive Language subtests of the Mullen Scales of Early Learning[42]; ADOS Social Score, total score on the social algorithm of the Autism Diagnostic Observation Schedule[43] (higher scores denote higher levels of social disability); Dx, diagnosis; Aut, Autistic Disorder; PDD-NOS, Pervasive Developmental Disorder-Not Otherwise Specified. ** $P < 0.005$.

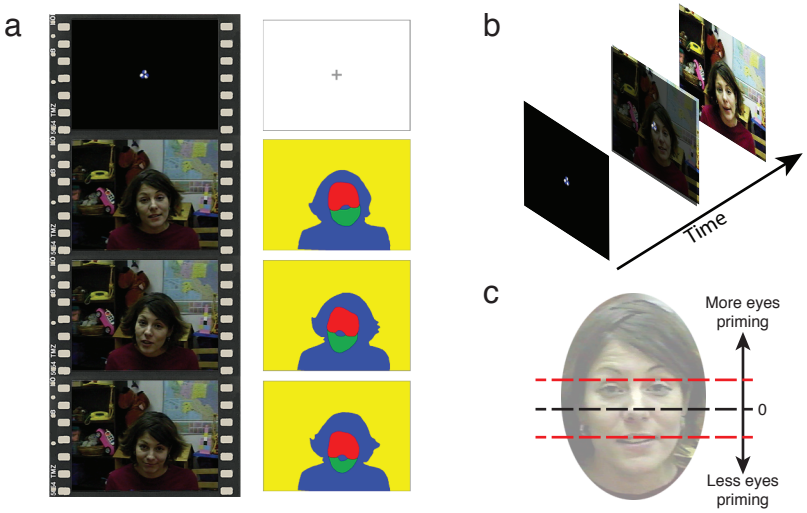

Figure 1. Experimental stimuli and physical priming for eyes fixation. (a) Example still images from 1 of 9 videos used in the study. Following a centering stimulus, all videos showed actresses portraying caregivers, looking directly into the camera. Regions-of-interest coding was completed in each frame for all videos (eyes = red, mouth = green, body [neck, shoulders, contours around eyes and mouth, such as hair] = blue, object [and surrounding inanimate stimuli] = yellow). (b, c) Based on the location of the centering stimulus relative to the midline of the actress' face, attention was sometimes physically primed for more eyes fixation and sometimes for less eyes fixation.

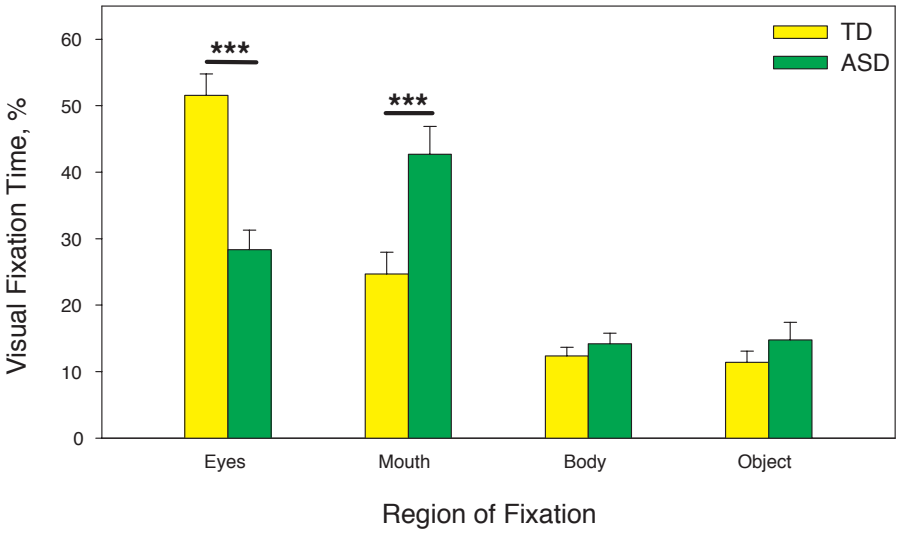

Figure 2. Percent fixation time (mean + s.e.m.) on eyes, mouth, body, and object regions. Two-year-olds with autism spectrum disorders (ASD) show reduced attention to the eyes relative to typically-developing (TD) peers.

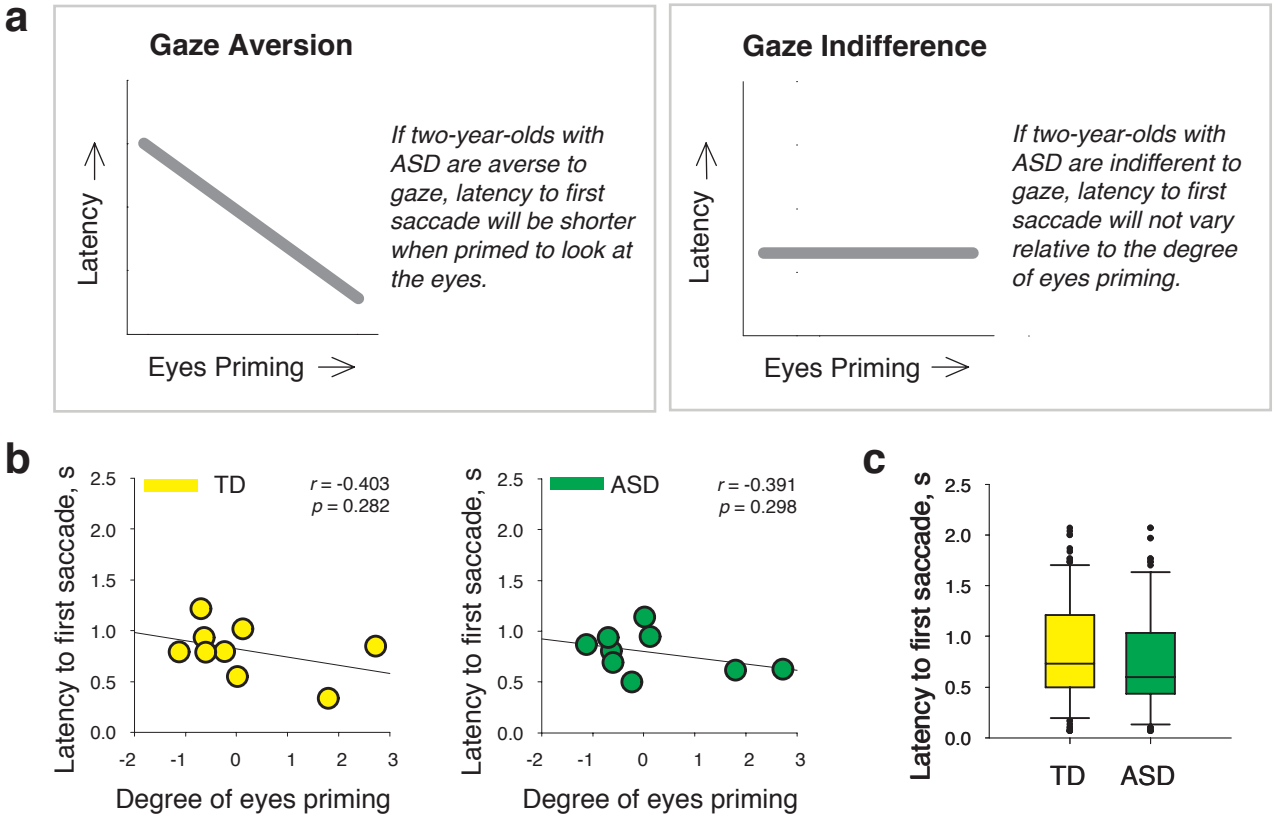

Figure 3. Latency to first saccade following physical priming for eyes fixation. (a) Hypothesized results supporting gaze aversion or gaze indifference in two-year-olds with autism spectrum disorders (ASD). (b) Correlation between the degree of physical priming for eyes fixation (vertical distance between the center of the face and the primed location, measured in degrees of visual angle) and the latency to first saccade in children with ASD and typically-developing (TD) peers. (c) Boxplots comparing the latency to first saccade in TD and ASD children. Note: The lower and upper boundaries of the standard boxplots are at the 25th and 75th percentiles, and the vertical lines extend to the 10th and 90th percentiles. The horizontal line across the box marks the median of the distribution.

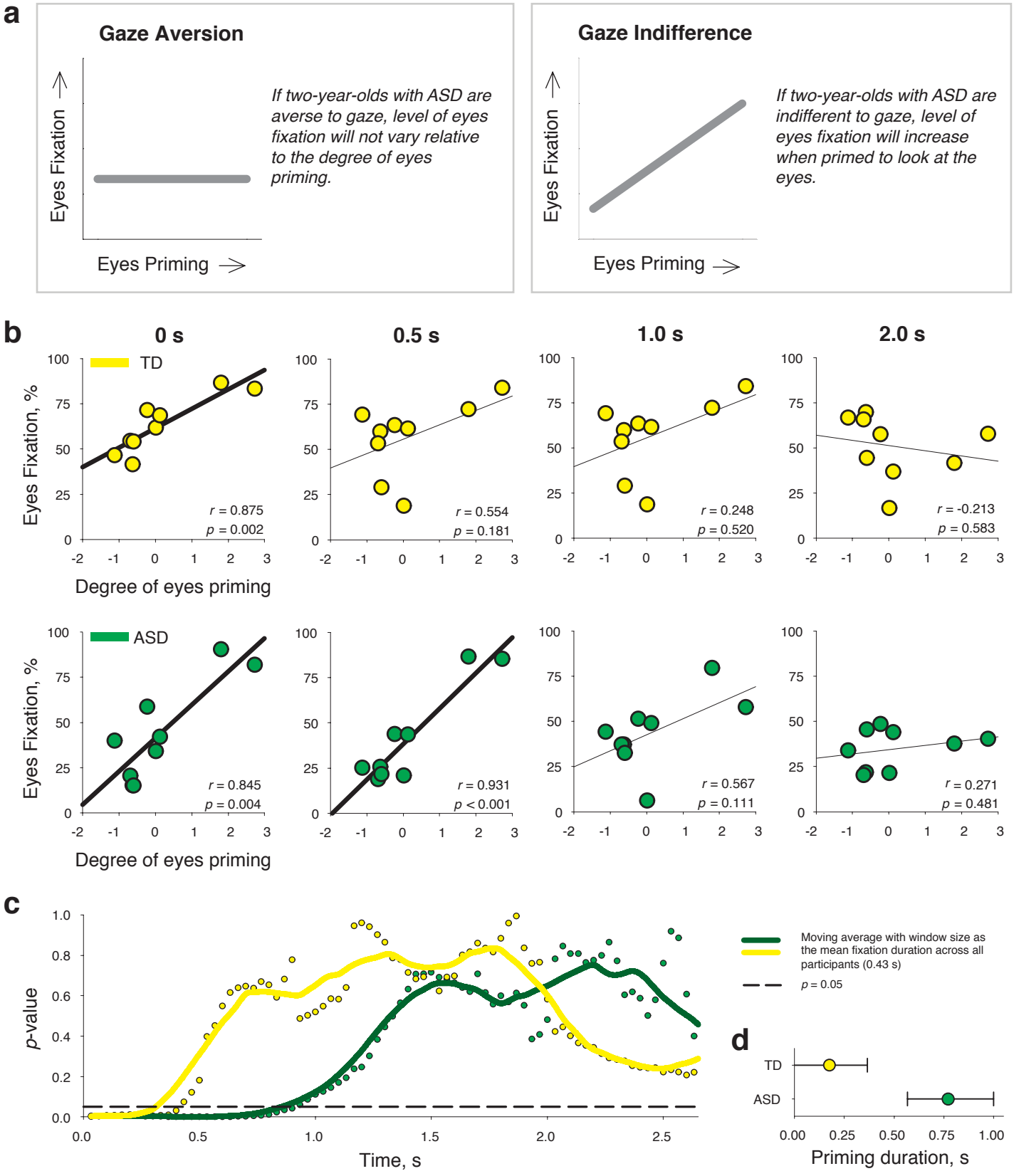

Figure 4. Level of eyes fixation in response to physical priming. (a) Hypothesized results supporting gaze aversion or gaze indifference in two-year-olds with autism spectrum disorders (ASD). (b) Correlations between the degree of physical priming for eyes fixation and moment-by-moment percentage of eyes fixation (calculated within a moving window the size of the mean fixaiton duration across all participants [0.43 s]) in children with ASD and typically-developing (TD) peers. (c) The *p*-value of the correlation plotted across time. (d) Bootstrapped mean and 95% confidence interval of the physical priming effect duration on eyes fixation based on 5000 resamplings. The degree of physical priming and the level of eyes fixation were significantly correlated ($P < 0.05$) for a longer duration at the start of the clips in the ASD group than in the TD group.

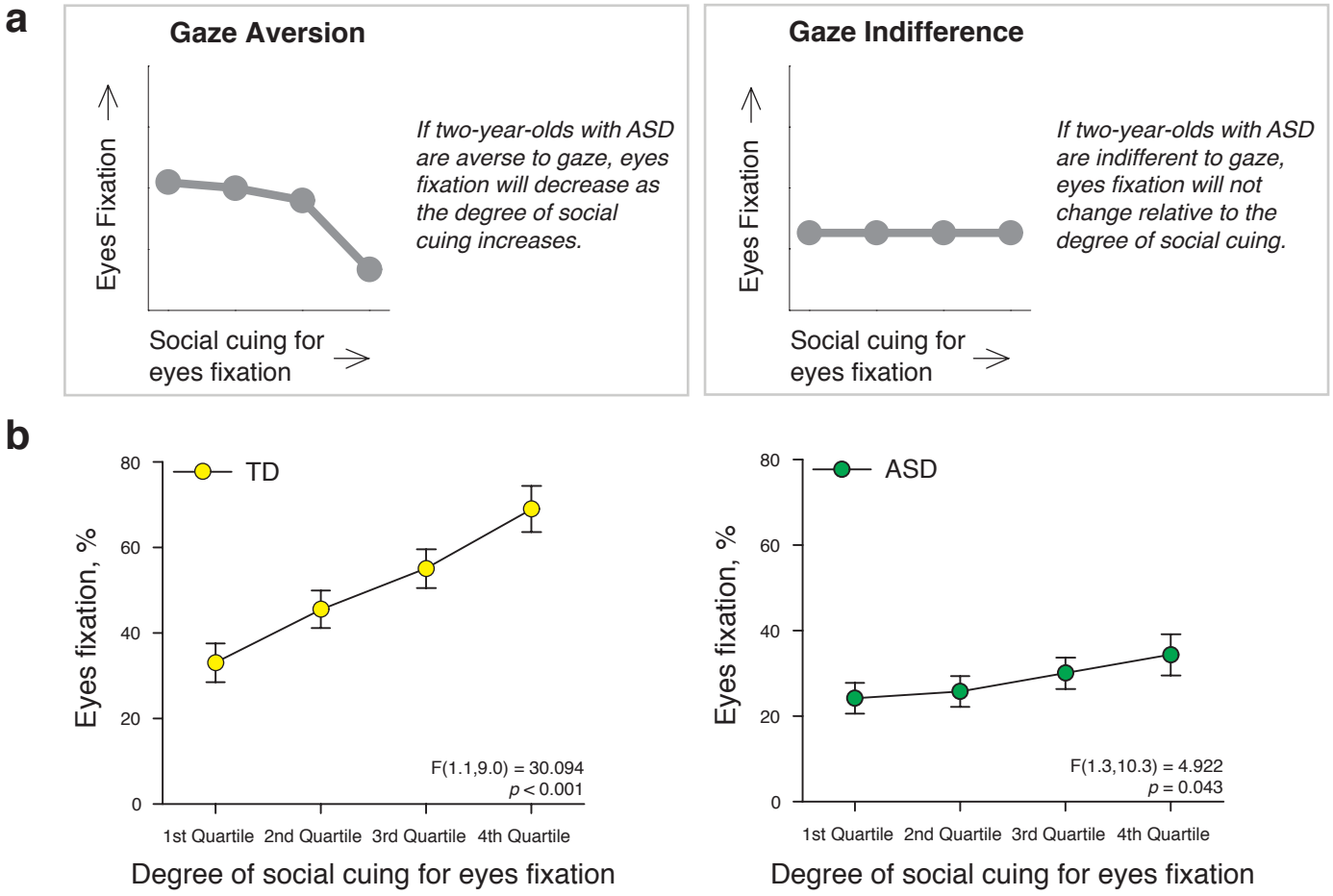

Figure 5. Level of eyes fixation in response to social cuing. After physical priming effects faded, implicit social cuing promoting eyes fixation was indexed based on the likelihood of eyes fixation in each clip in the group of typically-developing (TD) toddlers. (a) Hypothesized results supporting gaze aversion or gaze indifference in two-year-olds with autism (ASD). (b) Mean (± s.e.m.) likelihood of eyes fixation during periods of increasing social cuing, calculated by quartile, for TD and ASD toddlers. Both the TD and ASD groups show a significant difference in the likelihood of eyes fixation across quartiles.

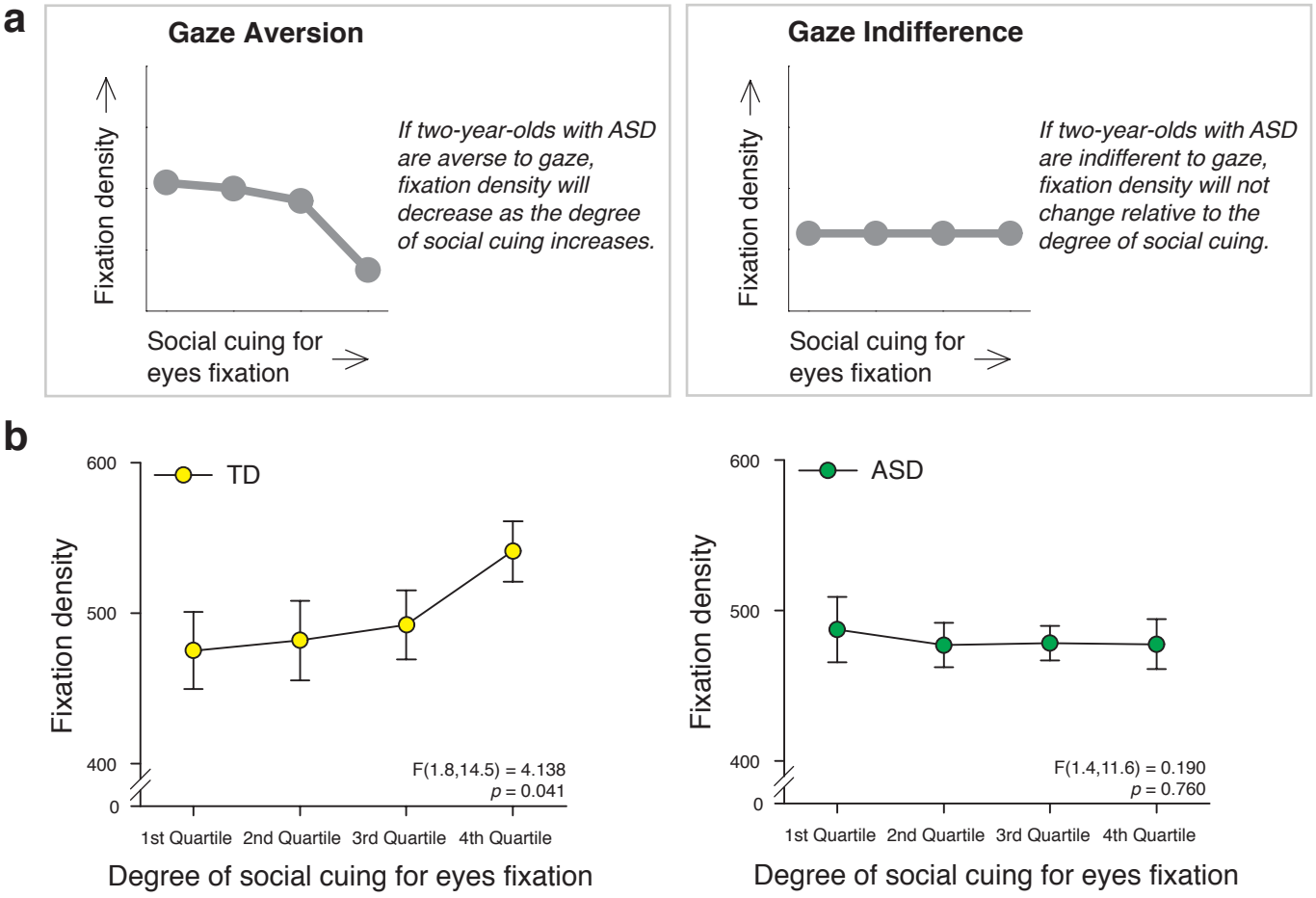

Figure 6. Fixation density in response to social cuing. Implicit social cuing promoting eyes fixation was indexed based on the likelihood of eyes fixation in each clip in the group of typically-developing (TD) toddlers. (a) Hypothesized results supporting gaze aversion or gaze indifference in two-year-olds with autism (ASD). (b) Mean (± s.e.m.) group fixation density during periods of increasing social cuing, calculated by quartile, for TD and ASD toddlers. The TD group shows a significant difference across quartiles; the ASD group shows no difference in fixation density relative to the degree of social cuing.