

Absence of Preferential Looking to the Eyes of Approaching Adults Predicts Level of Social Disability in 2-Year-Old Toddlers With Autism Spectrum Disorder

Warren Jones, BA; Katelin Carr, BA; Ami Klin, PhD

Context: Within the first week of life, typical human newborns give preferential attention to the eyes of others. Similar findings in other species suggest that attention to the eyes is a highly conserved phylogenetic mechanism of social development. For children with autism, however, diminished and aberrant eye contact is a lifelong hallmark of disability.

Objective: To quantify preferential attention to the eyes of others at what is presently the earliest point of diagnosis in autism.

Design: We presented the children with 10 videos. Each video showed an actress looking directly into the camera, playing the role of caregiver, and engaging the viewer (playing pat-a-cake, peek-a-boo, etc). Children's visual fixation patterns were measured by eye tracking.

Participants: Fifteen 2-year-old children with autism were compared with 36 typically developing children and with 15 developmentally delayed but nonautistic children.

Main Outcome Measure: Preferential attention was measured as percentage of visual fixation time to 4 re-

gions of interest: eyes, mouth, body, and object. Level of social disability was assessed by the Autism Diagnostic Observation Schedule.

Results: Looking at the eyes of others was significantly decreased in 2-year-old children with autism ($P < .001$), while looking at mouths was increased ($P < .01$) in comparison with both control groups. The 2 control groups were not distinguishable on the basis of fixation patterns. In addition, fixation on eyes by the children with autism correlated with their level of social disability; less fixation on eyes predicted greater social disability ($r = -0.669$, $P < .01$).

Conclusions: Looking at the eyes of others is important in early social development and in social adaptation throughout one's life span. Our results indicate that in 2-year-old children with autism, this behavior is already derailed, suggesting critical consequences for development but also offering a potential biomarker for quantifying syndrome manifestation at this early age.

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Author Affiliations: Interdepartmental Neuroscience Program, Yale University School of Medicine (Mr Jones), and Yale Child Study Center (Mr Jones, Ms Carr, and Dr Klin), New Haven, Connecticut. Ms Carr is now with the Department of Psychology, University of Connecticut, Storrs.

FROM THE FIRST HOURS OF LIFE, typically developing human newborns give preferential attention to people. They prefer the sound of a human voice to that of silence and prefer their own mother's voice to that of an unknown woman.¹ Four-day-old newborns distinguish between a face looking toward them and a face looking away,² and by 3 months, infants look more at a person's eyes than at other parts of the face (and more at a person's face than elsewhere on the body).³ Infants are capable of imitating facial gestures of a person,⁴ while they do not mimic similar movements made by a mechanical device.⁵ Taken together, this evidence shows many instances in which typically developing infants engage preferentially with what is social in the world around them. In these cases,

the social dimension is behaviorally salient and appears to command the greatest portion of the typically developing child's attention.

For toddlers with autism, the available evidence suggests otherwise.⁶ Autism is a disorder defined by altered engagement with the social world; the core diagnostic features are deficits in social interaction and communication and the presence of repetitive behaviors and restricted interests lacking in social exchange value.⁷⁻⁹ The most robust markers for early diagnosis of autism in children focus specifically on disruptions of typical engagement with other people: reduced interaction with and looking at others; failure to respond to the calling of one's name; diminished eye contact; and inability to join in imitative games and reciprocal vocalizations.¹⁰⁻¹²

Recent work within our laboratory with a well-characterized 15-month-old child with autism¹³ finds similar indications.¹⁴ In comparison with a typically developing 15-month-old child (matched on nonverbal functioning) and a typically developing 9-month-old infant (matched on verbal functioning), the 15-month-old child with autism showed markedly different patterns of looking. While viewing video scenes of actresses playing the role of a caregiver, the child with autism looked at her eyes less than half as much as either control. The child with autism also spent an increased percentage of time fixating on the actresses' mouths.

Preferential attention to the eyes of others is an important facilitator of socialization and social adaptation not only in early childhood^{15,16} but also throughout later life.^{17,18} Research in older individuals with autism indicates that altered patterns of looking at the social world are also present in adolescence and adulthood. In natural viewing tasks (free viewing of video scenes of complex social interaction), visual fixation patterns reveal significant between-group differences: high-functioning adolescents with autism focus 2 times less on the eye region of faces while focusing 2 times more on the mouth, body, and object regions relative to age- and verbal IQ-matched controls.^{19,20} Reduced fixation on the eyes was the strongest predictor of having autism (Cohen $d=3.19$). In structured viewing tasks, such as looking at still images of faces showing exemplar emotions, adults with autism exhibit increased fixation to atypical or nonfeature areas of the face (eg, looking at the cheeks, chin, or hairline rather than at the eyes).²¹ In face-recognition tasks²² as well as when making judgments about facial emotions,^{23,24} children with autism show an over-reliance on information from the mouth region and an increased fixation on the mouth area.²⁵

These findings suggest that altered looking patterns—less looking at the eyes and increased looking at mouth, body, and object areas—indicate reliable quantifiers of social disability and altered engagement with the social world in autism. Along with these studies of visual scanning, studies of eye movements in autism—ie, studies of the movements of the eyes themselves rather than of the content of what the eyes are directed toward—have confirmed normal oculomotor function in children with autism in maintaining steady fixation as well as in velocity, duration, latency, and accuracy of saccades.²⁶ Other studies have found no difference in rates of intrusive saccades,²⁷ in vestibular-ocular reflex,²⁸ or in foveopetal ocular drift.²⁷ To date, these studies suggest that the mechanics of oculomotor function appear to be generally intact in individuals with autism and that differences in looking behavior may arise more from “disturbances in the maturation and integration of complex neocortical systems”²⁹ rather than from disturbances of basic eye movement. (When experimental tasks that place greater demands on a participant's deployment of attention and recruitment of prefrontal cortex are used,^{26,30} researchers have found differences in a prosaccade task [though some results have been conflicting³¹]. Another area in which differences have been found is in smooth pursuit eye movements, in which there have been conflicting reports of deficits³² and no deficits.³³)

Our questions here are directed at the content of what 2-year-old toddlers focus on when watching video scenes of others. Observations of mutual gaze and of preferential attention to the eyes, even in other species,³⁴⁻³⁷ underscore the importance of the eyes in social interaction and development, suggesting that attention to others' eyes is a fundamental and highly conserved phylogenetic mechanism. In this study, we sought to address 2 questions: Is looking at the eyes of approaching adults altered in children with autism by the age of 2 years? and Do any such alterations relate to the child's level of social disability?

METHODS

PARTICIPANTS

Sixty-six children participated, all with the written informed consent of their parents and/or legal guardians. 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-to-normal vision.

The 66 participants comprised 3 groups: 15 toddlers with autism spectrum disorders (ASDs), 36 typically developing children, and 15 toddlers with developmental delays but without autism (**Table 1**). The typically developing children were matched to those with autism by chronological age and nonverbal mental age, while the developmentally delayed, nonautistic children were matched to the children with autism by verbal mental age and chronological age. The developmentally delayed, nonautistic children were included as controls to test the specificity of any findings, ie, to test the degree to which any departure from normative results could be attributed to autism rather than to the effects of generalized, nonautistic developmental delays. Overall, mean chronological age of the 66 children was 2.1 years (SD, 0.65 years). All 66 children completed the experimental procedures. Thirteen additional children were enrolled in the study but did not complete the experimental protocol (4 children with ASD, 5 typically developing children, and 4 developmentally delayed, nonautistic children). Reasons for failure to complete the procedure were not systematic with respect to group but were typical of 2-year-old children. Some children were unwilling to sit in the car seat while others fell asleep or could not remain sufficiently still for reliable calibration (tested as described below).

Children were recruited through a federally funded Studies to Advance Autism Research and Treatment Center based in the Autism Program of the Yale Child Study Center, New Haven, Connecticut. All toddlers were medically screened for visual and auditory function as part of a comprehensive pediatric and genetics protocol that included general physical and neurological examination. Developmental measures of nonverbal and verbal mental function were obtained with the Mullen Scales of Early Learning.³⁸ For inclusion in the autism group, children had to fulfill all 3 of the following conditions: (1) meet criteria for either autism or ASD on the Autism Diagnostic Observation Schedule (ADOS)¹⁵ (90% met criteria for autism), (2) meet criteria for autism on the Autism Diagnostic Interview-Revised (ADI-R),³⁹ and (3) be assigned—independently by 2 experienced clinicians on review of all available data, including standardized testing and videotaped material of diagnostic examination—a diagnosis of either autism (80% of the group) or ASD (20% of the group). Developmentally delayed, nonautistic children were included in the project only if the clinicians' diagnostic impressions ruled out the presence of ASD.

Table 1. Clinical Characterization of Participants

Characteristic	Mean (SD)			$F_{2,63}$	P Value ^a	Pairwise P Value		
	ASD Group (n=15)	TD Group (n=36)	DD Group (n=15)			ASD vs TD	ASD vs DD	TD vs DD
Sex, M/F, No.	11/4	24/12	11/4					
Age, y	2.28 (0.58)	2.03 (0.68)	2.06 (0.66)	0.801	.45	.65	> .99	> .99
Nonverbal function, y ^b	1.77 (0.47)	2.10 (0.82)	1.77 (0.75)	1.634	.20	.45	> .99	.46
Verbal function, y ^c	1.17 (0.66)	2.09 (0.77)	1.25 (0.86)	10.501	.001	.001	> .99	.002
ADOS score ^d	10.07 (3.51)		6.00 (3.93)		.008			
Vineland Socialization score, y ^e	1.01 (0.40)	1.87 (.60)	1.28 (0.59)	14.249	< .001	.001	.60	.004

Abbreviations: ADOS, Autism Diagnostic Observation Schedule¹⁵; ASD, autism spectrum disorder; DD, developmentally delayed, nonautistic (verbal mental age controls); TD, typically developing (nonverbal mental age controls).

^aAnalysis of variance results (t test for ADOS, $t_{26}=2.89$).

^bAge-equivalence scores on the Visual Reception subtest of the Mullen Scales of Early Learning.³⁸

^cCorresponds to the age-equivalence scores on the Receptive and Expressive Language subtests of the Mullen Scales of Early Learning.³⁸

^dSocial algorithm total score.

^eVineland Adaptive Behavior Scales,⁴⁰ age-equivalence scores from Vineland Socialization Domain.



Figure 1. Experimental stimuli and regions of interest. A, Example still images from 1 of 10 videos used in the study. All videos showed actresses playing the role of a caregiver, looking directly into the camera, and entreating the viewing child by engaging in childhood games (with both video and audio). B, Example regions of interest (as coded for all frames of all video stimuli) corresponding to each still image in A and color coded as follows: red=eyes; green=mouth; blue=body; and yellow=object. Video stimuli were presented and analyzed at 30 frames/s.

Typically developing children were included only if they had neither a history nor current presentation of developmental delay or social disabilities. None of the children included in the control groups had a positive family history of ASD.

Table 1 provides participant characterization data and statistical comparisons. The 3 groups were well matched for chronological age. The ASD group was well matched on nonverbal mental age to the typically developing group and on verbal mental age to the developmentally delayed, nonautistic group. As expected, the ASD group had significantly higher autistic social symptomatology than the developmentally delayed, nonautistic group. Levels of social adaptive behavior, as measured with the Vineland Adaptive Behavior Scales, Expanded Form,⁴⁰ were significantly lower in the ASD group relative to the typically developing group but not statistically different from levels obtained in the developmentally delayed, nonautistic group.

STIMULI

The children were shown 10 video clips, each presenting an actress looking directly into the camera and playing the role of a caregiver, entreating the viewing toddler by engaging in childhood games (eg, playing pat-a-cake) (**Figure 1A**). The actresses were filmed against backgrounds that emulated a child's room, with pictures, shelves of toys, and stuffed animals (**Figure 1A** and **Figure 2**).

The scenes were shown as full-screen audiovisual stimuli on a 50.8-cm (20-in) computer monitor (refresh rate of 60 Hz noninterlaced). Video frames were 8-bit color images and 640 × 480 pixels in resolution. Rate of presentation was 30 frames/s. The audio track was a single (mono) channel sampled at 44.1 kHz. The duration of each video clip varied with the content of the social scene, with a mean duration of 22 seconds and a range from 10 to 38 seconds.

Before presentation of experimental stimuli, we included a test of each child's ability to shift and stabilize gaze. We included this procedure as a minimal control against obvious symptoms of eye movement disorders that would be expected to compromise a child's ability to fixate on movies of social content. Children were shown a series of video clips and animations and the elicited behaviors—saccading to a target and maintaining fixation—were measured as a minimal check of eye movement function. All children passed the test by saccading to a target within 500 milliseconds and maintaining stable foveation with less than 5° of drift per second for at least 1 second.⁴¹



Figure 2. Example visual scanpaths and fixation time summaries for 3 toddlers watching the same video of an actress playing the role of a caregiver. Each frame shows 2 seconds of eye-tracking data overlaid on a single still image (the still image on which data are plotted is the midpoint of the 2-second window of plotted data). Saccades are plotted as thin white lines with white dots, while fixation data are plotted as larger white dots. A, Data from a toddler with autism. B, Data from a typically developing toddler. C, Data from a developmentally delayed but nonautistic toddler. Bar graphs show percentages of fixation time to each region of interest (eyes, mouth, body, and object). Bar graphs are for individual children for a single movie (and thus include no error bars). Eye-tracking data were recorded at 60 Hz.

EXPERIMENTAL PROCEDURE AND SETTING

Toddlers were accompanied at all times by a parent or primary caregiver. To begin the experimental session, a 2-year-old participant and caregiver entered the laboratory room while a familiar children's video (eg, *Baby Mozart* or *Elmo*) played on the computer monitor. The child was buckled into a car seat mounted on a small pneumatic lift so that viewing height (line of sight) was standardized for all children. Viewers' eyes were 76.2 cm from the computer monitor, which subtended an approximately $23^\circ \times 30^\circ$ portion of each viewer's visual field. Lights in the room were dimmed so that only images displayed on the computer monitor could be seen easily. The computer monitor was mounted flush within a wall panel, and audio was played through a set of concealed speakers. During testing, the experimenter was concealed from the child's view but able to monitor the child at all times by means of an eye-tracking camera and by a second video camera that filmed a full-body image of the child.

Visual fixation patterns were measured with eye-tracking equipment, described in more detail in the "Data Acquisition and Analysis" section. To begin the process of data collection, after the child was comfortably watching a familiar children's video, calibration targets were flashed onscreen by the experimenter. This was done via software that paused the playing video and presented a calibration target on the otherwise blank screen. A 5-point calibration scheme was used, employing a variety of small cartoon animations as well as spinning and/or flashing points of light, ranging in size from 0.5° to 1.5° of visual angle, all with accompanying sounds. The calibration routine was then followed by a verification of calibration in which more animations were presented at 9 on-screen points.

Throughout the remainder of the testing session, animated targets (as used in the calibration process) were interspersed between experimental videos to measure drift in data. In this way, accuracy of the eye-tracking data was verified before beginning the experimental trials and was then repeatedly checked between video segments as the testing continued. In the case of drift exceeding 3° , data collection was stopped and the calibration procedure was repeated before additional videos were presented. Recalibrating in this manner was performed after a large change in the child's head or body posture.

DATA ACQUISITION AND ANALYSIS

Visual fixation patterns were measured with eye-tracking equipment using hardware and software created by ISCAN Inc (Woburn, Massachusetts). The eye-tracking technology was video-based and used a dark pupil/corneal reflection technique with eye movement data collected at a rate of 60 Hz. This is double the frequency of stimuli presentation and of sufficient resolution to identify onset and offset of saccades at a threshold rotational velocity of $30^\circ/\text{s}$. The eye-tracking camera was remotely mounted, concealed from the child's view behind an infrared filter in the wall panel. The camera was mounted on a motorized gimbal programmed to pan and tilt in response to movements by the child. This arrangement was used in place of a magnetic or infrared head tracker, which are also commonly used to compensate for movement. Tracking for the equipment is accurate to within $\pm 0.25^\circ$ across a $\pm 20^\circ$ horizontal and vertical field of view, but given the size of calibration targets and the age of participants, $\pm 0.5^\circ$ over the same field of view is a more conservative estimate of accuracy.

Analysis of eye movements and coding of fixation data were performed with in-house software. The first phase of analysis was an automated identification of nonfixation data, compris-

ing blinks, saccades, and fixations directed away from the stimuli presentation screen. Saccades were identified by eye velocity using a velocity threshold of $30^\circ/\text{s}$.⁴¹ 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 verified in separate participants in 2 ways, by visually comparing numerical data with video images and by simultaneous eye-tracking and electromyography recording. Latency measures between our algorithm and the electromyography measures were less than 10 milliseconds different (less than the sampling detection threshold of the eye tracker). The algorithm accurately detected all blinks recorded in the electromyography signal. Off-screen fixations (when a participant looked away from the video) were identified by fixation coordinates beyond the screen. From within the total viewing data (231.9 seconds or 6957 video frames), nonfixation data were not significantly different between the 3 groups: for saccades, ASD group = 21.5% (6.2%), typically developing group = 18.1% (4.7%), and developmentally delayed, nonautistic group = 19.8% (9.5%), $F_{2,63} = 1.6$, $P = .21$; for blinks, ASD group = 8.7% (8.1%), typically developing group = 7.8% (5.8%), and developmentally delayed, nonautistic children group = 8.1% (5.4%), $F_{2,63} = 0.1$, $P = .91$; for off-screen fixations, ASD group = 11.7% (10.8%), typically developing group = 10.1% (7.4%), and developmentally delayed, nonautistic group = 11.9% (5.6%), $F_{2,63} = 0.38$, $P = .68$; and for all nonfixation data (saccades + blinks + off-screen fixation), ASD group = 41.8% (15.4%), typically developing group = 35.9% (10.2%), and developmentally delayed, nonautistic children group = 39.8% (14.9%), $F_{2,63} = 1.31$, $P = .28$.

Eye movements identified as fixations were coded into 4 regions of interest 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 hand traced for all frames of the video (6957 frames) and were then stored as binary bitmaps (via software written in MATLAB; MathWorks Inc, Natick, Massachusetts). 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 regions of interest.

All aspects of the experimental protocol were performed by personnel blind to the diagnostic status of the child. Most aspects of data acquisition and all aspects of coding, processing, and data summary are automated to ensure separation between the diagnostic characterization protocol and the experimental protocol.

STATISTICAL ANALYSIS

To compare fixation patterns across groups relative to regions of interest, we performed a repeated measures analysis of variance (diagnostic group [3 levels] \times percentage of fixation time [4 levels]). Percentages of fixation time were defined as percentages of visual fixation time to each region of interest: eyes, mouth, body, and object. We used Bonferroni corrections with significance level set at $P < .0125$ for all post hoc comparisons.

We performed correlations between percentage of fixation time to each region of interest in relation to the primary outcome measure of social disability, which was the algorithm score on the social cluster of the ADOS. We also performed correlations between percentage of fixation time to each region of interest in relation to measures of verbal and nonverbal functioning and chronological age for each of the 3 groups.

Table 2. Percentage of Visual Fixation Time on Eyes, Mouth, Body, and Object Regions in 2-Year-Old Toddlers

Region	Visual Fixation Time, Mean (SD), %			$F_{2,63}$	P Value	Pairwise P Value		
	ASD Group	TD Group	DD Group			ASD vs TD	ASD vs DD	TD vs DD
Eyes	30.0 (15.5)	54.2 (15.1)	54.7 (19.5)	12.867	<.001	<.001	<.001	>.99
Mouth	39.1 (20.3)	23.6 (12.7)	24.7 (15.6)	5.599	.006	.005	.04	>.99
Body	17.9 (7.5)	13.0 (9.4)	13.6 (5.3)	1.849	.17	.19	.49	>.99
Object	13.0 (8.8)	9.1 (5.3)	6.9 (5.5)	3.609	.03	.14	.03	.82

Abbreviations: ASD, autism spectrum disorder; DD, developmentally delayed, nonautistic (verbal mental age controls); TD, typically developing (nonverbal mental age controls).

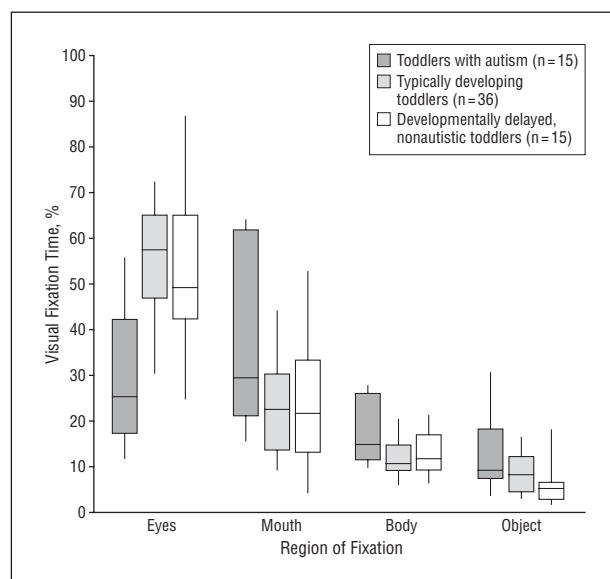


Figure 3. Visual fixation by 2-year-old toddlers watching scenes of a caregiver. Box plots show percentage of total fixation time during 10 videos to each of 4 regions of interest: eyes, mouth, body, and object. Typically developing toddlers and developmentally delayed, nonautistic toddlers exhibit no significant differences in fixation to eyes, mouth, body, and object regions, whereas 2-year-old children with autism have reduced fixation to eyes and increased fixation to mouths. Plots show the median, 10th, 25th, 75th, and 90th percentiles.

RESULTS

We observed marked differences in percentages of visual fixation time on the eye and mouth regions between the toddlers with ASD and toddlers in both of the 2 control groups (**Table 2**). Example individual data for a single movie are plotted in Figure 2. The group of toddlers with autism fixated significantly less on the eye region relative to the typically developing group and the developmentally delayed, nonautistic group (**Figure 3**). The autism group also fixated significantly more on the mouth region relative to the typical group and the developmentally delayed, nonautistic group. In contrast, the 2 control groups did not differ significantly from one another in fixation to any 1 of the 4 regions of interest. Percentage fixation on the body was comparable across the 3 groups. Percent fixation on the object region was comparable for the autism and typically developing groups but differed significantly between the autism and developmentally delayed, nonau-

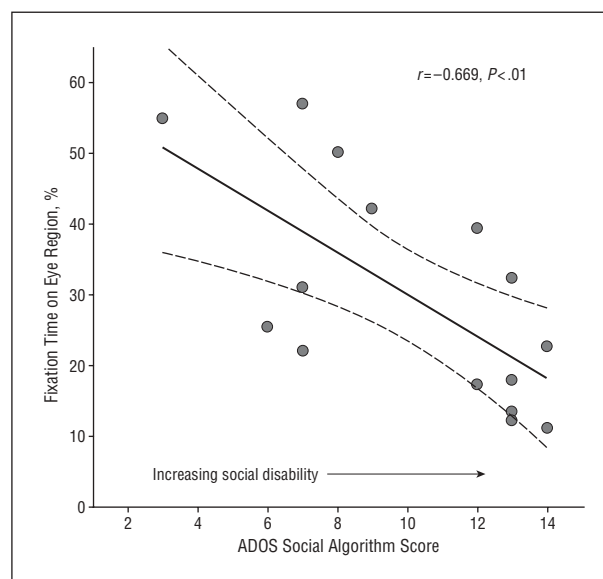


Figure 4. Correlation of fixation time on eyes and level of social disability in 2-year-old toddlers with autism ($n=15$). Less fixation on eyes predicts greater social disability. ADOS indicates Autism Diagnostic Observation Schedule.¹⁵

tistic groups (but only at the $P < .05$ level, thus above the threshold of $P < .0125$ set for corrections based on multiple comparisons). This trend indicated that the autism group showed greater percentage of fixation on objects. Analyses based on sex, across and within each of the diagnostic groups, revealed no significant effects.

The most powerful predictor of group membership was fixation on the eye region (Cohen $d=1.56$ and $d=1.40$, respectively) for comparisons of autism vs typical developing and autism vs developmentally delayed, nonautistic groups. The relationship between fixation on the eye region and level of social competence is evidenced in the correlation between levels of eye fixation and levels of social disability ($r=-0.669$, $P < .01$) (**Figure 4**). Less fixation on eyes predicted greater levels of social disability. None of the other correlations was statistically significant.

COMMENT

Unlike typically developing and developmentally matched controls, toddlers with ASD failed to exhibit preferen-

tial fixation to the eyes of approaching adults and preferred instead to look at the mouth region. For the toddlers with autism, lower levels of eye fixation were associated with greater social impairment in everyday life.

The present results show that by 2 years of age, a time of relatively early clinical diagnosis, children with autism already exhibit markedly different patterns of looking at the world. In addition, the relationship between fixation on eyes and level of social disability suggests that this measure may be useful for quantifying the social phenotype in autism early in development.

SIGNIFICANCE FOR SOCIAL DEVELOPMENT

The visual fixation data for these 2-year-old children with autism directly contrast the sensitivities and visual preferences evident in typical development from the first days of life.^{1,2,4} In addition, both the typically developing children and the children with nonautistic developmental delays show a striking similarity in visual fixation to the eye and mouth regions (Figure 3). This similarity is evidence of the fundamental nature of looking at the eyes of others: this behavior did not vary in relation to non-verbal or verbal functioning but instead appears to be more directly related to a child's social functioning. That children with significant, yet nonautistic, developmental delays displayed normative social visual behavior further emphasizes that preferential fixation to the eyes of others is a robust and early-emerging phenomenon not confounded by cognitive impairment.

The specificity of this impairment to the ASD group suggests that the social-affective deficits in children with autism may in part reflect a lack of preferential attention to the eyes of others early in life. Failure to look at the eyes of others during critical windows of development and looking at other parts of the world instead suggest an altered path for learning about the world. This is consistent with theories of how a developing infant actively contributes to his or her own brain specialization by attending differentially to the surrounding environment.^{42,43} In the case of these 2-year-old children with ASD, this early altered course of experience is likely to have a profound impact on later social development. Because the eye region of the face is critical for extraction of expression information,^{44,45} if a child has less experience observing and reacting to the eyes of others, that child is very likely to develop less expertise about social cues conveyed by the eyes, with cascading effects on further socialization. Likewise, shared or mutual gaze is important both for early social development^{15,16,46-48} and for social adaptation throughout one's life span.^{17,18,49-52} Over the course of development in a child with autism, lacking that experience and interaction would intensify the effects of atypical neural specialization, altering the formation of the social mind and brain.⁵³

It is worth noting, of course, that this altered set of experiences in and of itself does not cause autism. We need only take the example of congenitally blind⁵⁴ or deaf children⁵⁵ to recognize that different paths of interaction and learning do not, by themselves, lead to the specific and lifelong impairments in social interaction and communication that are hallmarks of ASD.⁶⁻⁹ And yet, dep-

rivation of a fundamental avenue of interaction with the social world, as in congenital blindness, can lead to autistic-like behaviors^{54,55} and social cognitive deficits.^{56,57} As a rule, however, learning about the social world is a multimodal (or "supramodal"⁵⁸) process, and a variety of sensory mechanisms may, even by themselves, provide sufficient inroads into social learning.

In the case of toddlers with ASD, altered patterns of looking serve as an index of both altered interaction with the normative social world and of an altered predisposition. Rather than spending more time looking at peoples' eyes, these children with autism are instead increasing their visual interaction with less socially relevant aspects of their environment. The circumstances for active learning in this case are critically different from those of a congenitally blind child. Rather than seeking social interaction via alternate channels (auditory or tactile, as a blind or deaf child might), the child with autism is using ostensibly intact sensory systems⁵⁹⁻⁶¹ to actively seek out alternate experiences.

INCREASED VISUAL FIXATION ON THE MOUTH REGION

In toddlers learning to speak, some fixation on the mouth region is to be expected given the role of bimodal perception (auditory and visual) in the process of speech acquisition.⁶² This, however, is unlikely to explain the increased visual fixation on the mouth region in the ASD group since they were well-matched to the developmentally delayed, nonautistic group on verbal functioning. Also, visual fixation patterns for the developmentally delayed, nonautistic group were very similar to those obtained for the typically developing group despite the significant discrepancy in stage of language acquisition between the 2 groups (Table 1). Finally, looking at the mouth did not correlate with level of verbal function or with chronological age for any of the 3 groups. Therefore, language acquisition does not seem to account for the increased visual fixation on the mouth region in the ASD group.

In work with older and highly verbal individuals with autism (with normative verbal IQ), increased looking at the mouth rather than the eyes has also been observed.²⁰ While the present results with 2-year-old children show similar patterns of looking, it seems unlikely that an underlying mechanism would be the same at these 2 very different developmental points. In older and highly verbal individuals with autism, correlation between mouth fixation and social competence suggested that looking at the mouth served as a compensatory strategy. Increased fixation on mouths correlated with increased levels of social ability and decreased levels of autistic symptomatology. As these individuals had good language skills alongside hallmark deficits in processing of nonverbal communication (such as processing of prosody, facial expressions, body language, and gestures), we hypothesized that they were attempting to rely on language as an inroad to understanding naturalistic social situations, focusing on the mouth as the source of that language.

The toddlers in our study, however, present a different case. From previous work with a 15-month-old child with autism,¹⁴ we hypothesize that looking at another per-

son's mouth may be driven by attention to audiovisual synchrony. Children with autism may focus on the mouth initially because of its physically contingent properties, seeing the world in terms of its physical features rather than its social-affective context. This theoretical speculation suggests an alternative learning path for language acquisition: learning about language by parsing the physical relationship between motion and sound, rather than learning speech sounds as signifiers within a social context. This hypothesis would fit with both language delays and with persistent suprasegmental and pragmatic difficulties in individuals with autism (difficulties, for instance, in understanding sarcasm and nonliteral speech, where competence depends more on language within a social context than on language as a direct mapping of sound to single meaning).

SIGNIFICANCE FOR UNDERSTANDING OF ONTOGENETIC MECHANISMS IN AUTISM

Our results offer evidence that toddlers with autism lack an early-emerging bias for preferential attention to the eyes of approaching adults. This in turn suggests disruption of the normative process of socialization, a process predicated on spontaneous searching for the eyes of others and increasing responsiveness to the gaze signals contained therein. Mutual gaze, gaze following, and even language acquisition⁶³ are parts of a progressively more complex social interaction that has its beginnings in eye contact with others. Divergence from this process is likely to result in atypical formation and specialization of the social mind and brain.^{42,64}

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Correspondence: Ami Klin, PhD, Yale Child Study Center, Yale University School of Medicine, 230 S Frontage Rd, New Haven, CT 06520 (ami.klin@yale.edu).

Author Contributions: Both Mr Jones and Dr Klin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Jones and Klin. *Acquisition of data:* Jones, Carr, and Klin. *Analysis and interpretation of data:* Jones and Klin. *Drafting of the manuscript:* Jones and Klin. *Critical revision of the manuscript for important intellectual content:* Jones, Carr, and Klin. *Statistical analysis:* Jones and Klin. *Obtained funding:* Jones and Klin. *Administrative, technical, and material support:* Jones, Carr, and Klin. *Study supervision:* Jones and Klin. *Technological expertise:* Jones.

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REFERENCES

- DeCasper AJ, Fifer WP. Of human bonding: newborns prefer their mothers' voices. *Science*. 1980;208(4448):1174-1176.
- Farroni T, Csibra G, Simion F, Johnson MH. Eye contact detection in humans from birth. *Proc Natl Acad Sci U S A*. 2002;99(14):9602-9605.
- Haith MM, Bergman T, Moore MJ. Eye contact and face scanning in early infancy. *Science*. 1977;198(4319):853-855.
- Meltzoff AN, Moore MK. Imitation of facial and manual gestures by human neonates. *Science*. 1977;198(4312):75-78.
- Meltzoff AN. Understanding the intentions of others: re-enactment of intended acts by 18-month-old children. *Dev Psychol*. 1995;31(5):838-850.
- Carter AS, Davis NO, Klin A, Volkmar FR. Social development in autism. In: Volkmar FR, Paul R, Klin A, Cohen D, eds. *Handbook of Autism and Pervasive Developmental Disorders*. 3rd ed. New York, NY: John Wiley & Sons; 2005:312-334.
- Lord C, Rutter M, DiLavore PC, et al. *Autism Diagnostic Observation Schedule: WPS (ADOS-WPS)*. Los Angeles, CA: Western Psychological Services; 1999.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. ed 4. Washington, DC:1994.
- Volkmar FR, Lord C, Bailey A, Schultz RT, Klin A. Autism and pervasive developmental disorders. *J Child Psychol Psychiatry*. 2004;45(1):135-170.
- Osterling JA, Dawson G, Munson J. Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. *Dev Psychopathol*. 2002;14(2):239-251.
- Chawarska K, Paul R, Klin A, Hannigen S, Dichtel LE, Volkmar F. Parental recognition of developmental problems in toddlers with autism spectrum disorders. *J Autism Dev Disord*. 2007;37(1):62-72.
- Landa RJ, Holman KC, Garrett-Mayer E. Social and communication development in toddlers with early and later diagnosis of autism spectrum disorders. *Arch Gen Psychiatry*. 2007;64(7):853-864.
- Klin A, Chawarska K, Paul R, Rubin E, Morgan T, Wiesner L, Volkmar F. Autism in a 15-month-old child. *Am J Psychiatry*. 2004;161(11):1981-1988.
- Klin A, Jones W. Altered face scanning and impaired recognition of biological action in a 15-month-old infant with autism. *Dev Sci*. 2008;11(1):40-46.
- Brooks R, Meltzoff AN. The importance of eyes: how infants interpret adult looking behavior. *Dev Psychol*. 2002;38(6):958-966.
- Trevarthen C, Aitken KJ. Infant intersubjectivity: research, theory, and clinical application. *J Child Psychol Psychiatry*. 2001;42(1):3-48.
- Emery NJ. The eyes have it: the neuroethology, function and evolution of social gaze. *Neurosci Biobehav Rev*. 2000;24(6):581-604.
- Kampe KKW, Frith CD, Dolan RJ, Frith U. Reward value of attractiveness and gaze [erratum published in *Nature*. 2002;416(6881):602]. *Nature*. 2001;413(6856):589-590.
- Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Defining and quantifying the social phenotype in autism. *Am J Psychiatry*. 2002;159(6):895-908.
- Klin A, Jones W, Schultz RT, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry*. 2002;59(9):809-816.
- Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J. Visual scanning of faces in autism. *J Autism Dev Disord*. 2002;32(4):249-261.
- Joseph RM, Tanaka J. Holistic and part-based face recognition in children with autism. *J Child Psychol Psychiatry*. 2003;44(4):529-542.
- Spezio ML, Adolphs R, Hurley RS. Abnormal use of facial information in high-functioning autism. *J Autism Dev Disord*. 2007;37(5):929-939.
- Spezio ML, Adolphs R, Hurley RS, Piven J. Analysis of face gaze in autism using "Bubbles." *Neuropsychologia*. 2007;45(1):144-151.
- Langdell T. Recognition of faces: an approach to the study of autism. *J Child Psychol Psychiatry*. 1978;19(3):255-268.
- Minshew NJ, Luna B, Sweeney JA. Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. *Neurology*. 1999;52(5):917-922.
- Nowinski CV, Minshew NJ, Luna B, Takarae Y, Sweeney JA. Oculomotor studies of cerebellar function in autism. *Psychiatry Res*. 2005;137(1-2):11-19.
- Goldberg MC, Landa R, Lasker A, Cooper L, Zee DS. Evidence of normal cerebellar control of the vestibulo-ocular reflex (VOR) in children with high-functioning autism. *J Autism Dev Disord*. 2000;30(6):519-524.
- Sweeney JA, Takarae Y, Macmillan C, Luna B, Minshew NJ. Eye movements in neurodevelopmental disorders. *Curr Opin Neurol*. 2004;17(1):37-42.
- Kemner C, Verbaten MN, Cuperus JM, Camfferman G, van Engeland H. Abnor-

- mal saccadic eye movements in autistic children. *J Autism Dev Disord*. 1998; 28(1):61-67.
31. van der Geest JN, Kemner C, Camfferman G, Verbaten MN, van Engeland H. Eye movements, visual attention, and autism: a saccadic reaction time study using the gap and overlap paradigm. *Biol Psychiatry*. 2001;50(8):614-619.
 32. Takarae Y, Minshew NJ, Luna B, Krisky CM, Sweeney JA. Pursuit eye movement deficits in autism. *Brain*. 2004;127(pt 12):2584-2594.
 33. Kemner C, van der Geest JN, Verbaten MN, van Engeland H. In search of neurophysiological markers of pervasive developmental disorders: smooth pursuit eye movements? *J Neural Transm*. 2004;111(12):1617-1626.
 34. Myowa-Yamakoshi M, Tomonaga M, Tanaka M, Matsuzawa T. Preference for human direct gaze in infant chimpanzees (Pan troglodytes). *Cognition*. 2003; 89(2):B53-B64.
 35. Bard KA, Costall A, Myowa-Yamakoshi M, Tanaka M, Costall A, Matsuzawa T. Group differences in the mutual gaze of chimpanzees (Pan troglodytes). *Dev Psychol*. 2005;41(4):616-624.
 36. van Lawick-Goodall J. The behaviour of free-living chimpanzees of the Gombe Stream Nature Reserve. *Anim Behav Monographs*. 1968;1:161-311.
 37. de Waal FB. Darwin's legacy and the study of primate visual communication. *Ann N Y Acad Sci*. 2003;1000:7-31.
 38. Mullen EM. *Mullen Scales of Early Learning: AGS Edition*. Circle Pines, MN: AGS; 1995.
 39. Rutter M, LeCouteur A, Lord C. *The Autism Diagnostic Interview, Revised*. Los Angeles, CA: Western Psychological Services; 2003.
 40. Sparrow SS, Balla DA, Cicchetti DV. *Vineland Adaptive Behavior Scales, Expanded Form*. Circle Pines, MN: American Guidance Service; 1984.
 41. Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 3rd ed. Oxford, England: Oxford University Press; 1999:94.
 42. Klin A, Jones W, Schultz R, Volkmar F. The enactive mind, or from actions to cognition: lessons from autism. *Philos Trans R Soc Lond B Biol Sci*. 2003; 358(1430):345-360.
 43. Varela FJ, Thompson E, Rosch E. *The Embodied Mind: Cognitive Science and Human Experience*. Cambridge, MA: The MIT Press; 1991.
 44. Whalen PJ, Kagan J, Cook RG, Davis FC, Kim H, Polis S, McLaren DG, Somerville LH, McLean AA, Maxwell JS, Johnstone T. Human amygdala responsivity to masked fearful eye white. *Science*. 2004;306(5704):2061.
 45. Whalen PJ. Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. *Curr Dir Psychol Sci*. 1998;7(6):177-188.
 46. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *Int J Dev Neurosci*. 2005; 23(2-3):143-152.
 47. Farroni T, Mansfield EM, Lai C, Johnson MH. Infants perceiving and acting on the eyes: tests of an evolutionary hypothesis. *J Exp Child Psychol*. 2003;85 (3):199-212.
 48. Farroni T, Johnson MH, Csibra G. Mechanisms of eye gaze perception during infancy. *J Cogn Neurosci*. 2004;16(8):1320-1326.
 49. Tomasello M, Carpenter M, Call J, Behne T, Moll H. Understanding and sharing intentions: the origins of cultural cognition. *Behav Brain Sci*. 2005;28(5):675-735.
 50. Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR. A mechanism for impaired fear recognition after amygdala damage. *Nature*. 2005;433 (7021):68-72.
 51. Adams RB, Gordon HL, Baird AA, Ambady N, Kleck RE. Effects of gaze on amygdala sensitivity to anger and fear faces. *Science*. 2003;300(5625):1536.
 52. Kawashima R, Sugiura M, Kato T, Nakamura A, Hatano K, Ito K, Fukuda H, Kojima S, Nakamura K. The human amygdala plays an important role in gaze monitoring: a PET study. *Brain*. 1999;122(pt 4):779-783.
 53. Grelotti DJ, Klin A, Gauthier I, Skudlarski P, Cohen DJ, Gore JC, Volkmar FR, Schultz RT. fMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism. *Neuropsychologia*. 2005;43(3): 373-385.
 54. Perez-Pereira M, Conti-Ramsden G. *Social Interaction and Language Development in Blind Children: Essays in Developmental Psychology*. East Sussex, England: Psychology Press; 1999.
 55. Marschark M. *Psychological Development of Deaf Children*. Oxford, England: Oxford University Press; 1997.
 56. McAlpine LM, Moore CL. The development of social understanding in children with visual impairments. *J Vis Impair Blind*. 1995;89(4):349-358.
 57. Hobson RP, Bishop M. The pathogenesis of autism: insights from congenital blindness. *Philos Trans R Soc Lond B Biol Sci*. 2003;358(1430):335-344.
 58. Bidet-Caulet A, Voisin J, Bertrand O, Foloupt P. Listening to a walking human activates the temporal biological motion area. *Neuroimage*. 2005;28(1):132-139.
 59. Hadjikhani N, Chabris CF, Joseph RM, Clark J, McGrath L, Aharon I, Feczko E, Tager-Flusberg H, Harris GJ. Early visual cortex organization in autism: an fMRI study. *Neuroreport*. 2004;15(2):267-270.
 60. Ceponiene R, Lepistö T, Shestakova A, Vanhala R, Alku P, Nääätänen R, Yaguchi K. Speech-sound-selective auditory impairment in children with autism: they can perceive but do not attend. *Proc Natl Acad Sci U S A*. 2003;100(9):5567-5572.
 61. Tharpe AM, Bess FH, Sladen DP, Schissel H, Couch S, Schery T. Auditory characteristics of children with autism. *Ear Hear*. 2006;27(4):430-441.
 62. Kuhl PK, Meltzoff AN. The bimodal perception of speech in infancy. *Science*. 1982; 218(4577):1138-1141.
 63. Brooks R, Meltzoff AN. The development of gaze following and its relation to language. *Dev Sci*. 2005;8(6):535-543.
 64. Johnson MH. Functional brain development in humans. *Nat Rev Neurosci*. 2001; 2(7):475-483.