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Repetitive behavior with objects in infants developing ASD predicts diagnosis and later social behavior as early as 9 months

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Abstract

We evaluated repetitive behavior with objects in infants at risk for autism spectrum disorder (ASD) from 9–36 months of age, and associations between early repetitive behavior and social engagement. Infant siblings of children with ASD (high-risk) or typical development (low-risk) were administered a task eliciting repetitive object use at 9, 12, 15, 18, 24, and 36 months of age. Infants (n=147) were classified into one of 3 outcome groups at 36 months: Low-Risk Non-ASD (n=58), High-Risk Non-ASD (n=72), and ASD (n=17). Behavior was coded from video for frequencies of unusual visual inspection, spinning, and rotating behaviors. Differences in unusual visual inspection were most prominent, consistent, and present earliest: At 9 months, the ASD group engaged in this behavior more frequently than both other groups, persisting through 36 months. Differences in frequencies of spinning and rotating were later-appearing, more time-limited, and/or related to familial ASD risk rather than ultimate diagnosis. Sensitivity and specificity estimates for the presence of unusual visual inspection at 9 months of age were in the moderate range (0.60 and 0.68, respectively) for ASD vs. Low-Risk Non-ASD comparisons, generally increasing over time. Unusual visual inspection at 9 months predicted 12-month social behavior controlling for 9-month social behavior, but not vice versa, with no evidence of moderation by ASD diagnosis. In summary, unusual visual inspection of objects is present and stable by 9 months of age in infants developing ASD and predicts reduced social engagement 3-months later. Close monitoring of this behavior may aid early detection.

General Scientific Summary

This study found that infants who developed autism exhibited more frequent unusual visual inspection of objects—a particular type of repetitive behavior involving prolonged visual inspection, examination of the object from odd angles or from peripheral vision, or squinting or blinking repeatedly while examining the object—by 9 months of age compared to those who

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did not develop autism. Unusual visual inspection at 9 months predicted 12-month social behavior controlling for 9-month social behavior, but not vice versa, consistent with major theories of autism suggesting that an increased focus on objects early in life has detrimental cascading effects on social behavior. Taken together, these results suggest that close monitoring of unusual visual inspection of objects by 9 months of age may be an important aspect of early detection and may be valuable to integrate into early screening and diagnostic tools.

Keywords

Autism spectrum disorder; repetitive behavior; siblings; high-risk

Prior studies examining the earliest manifestations of autism spectrum disorder (ASD) have largely focused on the development of social-communication behaviors. However, it is becoming increasingly recognized that aspects of repetitive behavior—a core component of the diagnostic criteria for ASD (American Psychiatric Association, 2013)—may also emerge early in life (Elison et al., 2014; Ozonoff et al., 2008; Wolff et al., 2014). What has been less well established is whether such behaviors are evident prior to the first birthday, how these behaviors develop throughout infancy and early childhood, and how patterns of early repetitive behavior relate to social development.

Much of the initial work focused on the onset of repetitive behaviors in ASD used retrospective or cross-sectional designs focused on children already diagnosed with the disorder. For example, Osterling and colleagues reviewed home videos of first birthday parties and found a higher frequency of repetitive motor actions among infants later diagnosed with ASD relative to typically developing (TD) infants (Osterling, Dawson, & Munson, 2002). Werner et al. interviewed parents of 3–4 year-olds with ASD about their child's development between birth and 2 years of age, finding that parents of children with ASD retrospectively reported higher levels of repetitive behaviors between 10–12 months of age relative to TD children, and between 16–18 months of age relative to children with other developmental delays (Werner, Dawson, Munson, & Osterling, 2005). Similarly, Watson and colleagues retrospectively administered the First Year Inventory (Baranek et al., 2003), assessing social communication and sensory-regulatory behaviors among 12-month-olds, to parents of preschoolers and found higher levels of parent-reported repetitive play and behavior among children with ASD relative to TD children, but not relative to children with other developmental delays (Watson et al., 2007).

Because of the reliance on retrospective methods, this initial work could not directly assess or probe for behaviors of interest before the onset of ASD, making it difficult to determine when in development these core symptoms emerge. To remedy methodological issues related to retrospective and cross-sectional designs, more recent studies have focused on infants at heightened risk for developing ASD (i.e., infant siblings of children with ASD; Ozonoff et al., 2011), recruiting infants shortly after birth who are followed prospectively to an age at which ASD diagnosis can be determined, typically around 3 years of age. This design provides an opportunity to prospectively track the emergence of core symptoms.

The first study to systematically evaluate early repetitive behaviors with objects within a prospective infant sibling design examined object exploration behavior via an experimental task administered to 12-month-olds. In this study, Ozonoff and colleagues (Ozonoff et al., 2008) coded developmentally typical behaviors (i.e., shaking/waving, banging/tapping, mouthing, throwing/pushing objects) as well as behaviors hypothesized to be developmentally atypical (i.e., spinning, rolling, rotating, unusually visually inspecting objects), finding that the high-risk infants who developed ASD showed significantly more spinning, rotating, and unusual visual inspection of objects at 12 months of age relative to infants with TD outcomes or with other, non-ASD developmental concerns. The findings related to unusual visual inspection—defined as looking out of the corners of the eyes, holding an object up very close to the face, looking at something with one eye closed, or staring at an object uninterrupted for ≥10 seconds—were especially striking, with average scores in the ASD group more than four standard deviations above the mean of the TD group (Ozonoff et al., 2008).

More recently, Elison and colleagues (Elison et al., 2014) examined stereotyped motor mannerisms and repetitive use of objects in 12-month-old infant siblings of children with or without ASD via observational coding of behavior (the Repetitive and Stereotyped Movement Scales during the Communication and Symbolic Behavior; Morgan, Wetherby, & Barber, 2008; Wetherby, Allen, Cleary, Kublin, & Goldstein, 2002). They found that the high-risk infants who developed ASD by 24 months of age showed higher levels of stereotyped motor mannerisms at 12 months relative to the low-risk and high-risk infants who did not develop ASD. The high-risk ASD group and the high-risk non-ASD group also displayed higher levels of repetitive object manipulation than the low-risk group, but did not differ themselves (Elison et al., 2014). Similarly, Damiano and colleagues (Damiano, Nahmias, Hogan-Brown, & Stone, 2013) found that high-risk infant siblings displayed higher rates of repetitive and stereotyped movements involving object and body use relative to low-risk infants at 15 months of age, but the high-risk infants who developed ASD did not differ from the high-risk infants who did not, suggesting that the presence of these behaviors may be related to ASD risk, but not specific to ASD.

Most studies focused on the early emergence of repetitive behaviors in infant sibling samples have evaluated such behaviors at only a single time point, with a few exceptions. For example, Loh and colleagues (Loh et al., 2007) found that infants later diagnosed with ASD displayed certain stereotypic movements or postures more frequently at 12 and 18 months relative to the TD group (although, notably, those with ASD did not differ from the high-risk non-ASD group in several of these behaviors). Another study used parent report (Repetitive Behavior Scale–Revised; Bodfish, Symons, Parker, & Lewis, 2000) at 12 and 24 months of age to evaluate longitudinal patterns of repetitive behavior in infant siblings, finding that infants who were diagnosed with ASD at 24 months of age showed higher parent-reported scores on this measure at 12- and 24-months, with increasing scores between these two time points (Wolff et al., 2014). However, this study did not include direct assessment of repetitive behaviors and made diagnostic determinations before all children with ASD had likely been identified (i.e., by 36 months of age; Ozonoff et al., 2015). Additionally, no studies, to our knowledge, have evaluated these behaviors at more than two time points, beginning in the first year of life, within an infant sibling sample.

Combined, these studies of prospectively evaluated infants at risk for ASD suggest that repetitive behaviors in ASD emerge earlier than originally thought—present by 12 months of age in multiple studies—and that assessment of these behaviors during infancy may be an important component of early detection efforts. However, a primary gap in this literature is that little is known about the longitudinal course of these behaviors early in life, especially prior to 12 months of age, using direct assessment methods. Additionally, virtually nothing is known about the predictive associations between patterns of early emerging repetitive behaviors with objects and social behaviors. This latter point is especially salient because better understanding relationships between object- versus socially-oriented behaviors early in life could have important theoretical implications for the conceptualization of processes underlying ASD emergence. Understanding whether reduced social interest early in life leads to increased focus on objects, or whether increased focus on objects early on results in reduced social interest over time, is therefore critical. This study addresses these points by directly and repeatedly assessing infant object-directed behaviors during a task designed to provide opportunities for a range of repetitive object uses (Ozonoff et al., 2008), and by examining predictive associations between these behaviors and examiner-rated social engagement.

Method

Overview of Procedure

The present investigation utilizes data from a prospective longitudinal study of infants at risk for ASD and was conducted under the approval of the University's Institutional Review Board. Informed consent was obtained from parents prior to conducting assessments. Infants were assessed by expert clinical examiners unaware of group membership, with ongoing administration and scoring fidelity procedures in place. Infants were evaluated at 9, 12, 15, 18, 24, and 36 months of age. At the 36-month assessment, participants were classified into one of three outcome groups: ASD (all high-risk), High-Risk Non-ASD, and Low-Risk Non-ASD. Participants were classified with ASD if they received a comparison score ≥4 on the Autism Diagnostic Observation Schedule (ADOS) and met *DSM-IV-TR* criteria for Autistic Disorder or PDD-NOS.

Participants

Participants were infant siblings of children with ASD (high-risk group) or typical development (low-risk group). The primary inclusion criterion for the high-risk group was status as a younger sibling of a child with ASD. Diagnosis of the affected older sibling was confirmed by meeting ASD criteria on both the ADOS (Lord et al., 2000) and the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003); exclusion criteria included birth before 32 weeks' gestation and a known genetic disorder (e.g., fragile × syndrome) in the older affected sibling. The primary inclusion criterion for the low-risk group was status as a younger sibling of a child with typical development, confirmed by an intake screening questionnaire and scores below the ASD range on the SCQ. Exclusion criteria for the low-risk group were birth before 36 weeks' gestation; developmental, learning, or medical conditions in any older sibling; and ASD in any first-, second-, or third-degree relative.

Of 185 eligible enrolled infants, *n*=22 dropped out of the study before the 18-month visit. Of the remaining 163 infants, *n*=156 (95.7%) completed a final outcome visit at 36 months of age. Of these 156, *n*=8 were excluded due to having fewer than 3 visits with valid object exploration task data and *n*=1 low-risk participant with an ASD outcome was excluded, resulting in a final analyzed sample of *n*=147 (*n*=89 high-risk; *n*=58 low-risk). The final analyzed sample did not differ from the non-retained sample in demographic characteristics, with the exception of household income (see Supplemental Table S1).

Participants were enrolled by 9 months of age; 71% of the sample had their first assessment at 6 months. Among the proband-infant pairs, 91.4% of the high-risk group and 80.9% of the low-risk group were full biological siblings. At the 36-month visit, 17 infants were classified as having ASD (all high-risk), 72 were classified as High-Risk Non-ASD, and 58 were classified as Low-Risk Non-ASD. Table 1 displays sample characteristics by outcome group. All participants had object exploration data available for at least 3 visits (*n*=22 had all 6 visits, *n*=52 had 5, *n*=43 had 4, and *n*=30 had 3). Missingness was 51.7% at 24 months and otherwise ranged from 13.6% (9 months) to 27.9% (18 months). Missingness was not systematically associated with outcome group or key sociodemographic variables at any visit (see Supplemental Table S2 for details); the only difference found was for gestational age at 24 months: those missing 24-month task data had lower gestational ages by approximately 1.5 weeks on average. Reasons for missingness by outcome group at each age are shown in Supplemental Table S3 and generally were related to video recording problems/missing video, missed visits, incomplete/invalid administrations, or child difficulties completing the task. At 24 and 36 months, the object exploration task was not originally administered due to concerns that the toy set would not be of interest. However, it became clear that children of this age did have interest in the toy set and the task was therefore re-introduced. This impacted all familial risk/outcome groups and resulted in *n*=43 missing at 24 months (56.6% of all missing 24-month data), and *n*=2 missing at 36 months (5.7% of all missing 36-month data).

Measures

Object exploration task.—This task was administered at 9, 12, 15, 18, 24, and 36 months of age (see Table S4 for mean age at each visit by outcome group). Virtually identical to the task described in Ozonoff et al. (2008), this 2.5-minute task involved the presentation of four different objects (rattle, round plastic ring, round metal lid, set of 5 toy cars) to participants, one at a time, for 30 seconds each. After each object had been administered individually, all objects were presented together for an additional 30 seconds. Behavior was later coded from video by highly-trained raters unaware of group membership using Noldus: The Observer 5.0. The focus in this manuscript is on unusual visual inspection, rotating behavior, and spinning behavior based on prior work in an independent sample (Ozonoff et al., 2008; note that not all behaviors coded in the original study were coded in the present sample). *Unusual visual inspection* was defined as prolonged visual inspection (>10 seconds), examination of the object from odd angles or from the infant's peripheral vision, or squinting or blinking repeatedly while examining the object. *Rotate* was defined as turning, flipping, or rotating the object at least twice. *Spin* was defined as dropping, tossing, or manipulating an object in order to make it spin or

wobble. Both unusual visual inspection and rotating behavior were coded for frequencies and durations, while object spinning was coded as frequency only since the duration of object spinning was not controlled by the child. Therefore, for consistency across behaviors, we focus on frequencies of each behavior in the present study.

A total of 8 coders were trained and required to achieve initial intraclass correlation coefficients (ICCs) of ≥80% with a master coder. An additional 20% of files were double-coded for ongoing reliability purposes. Mean *(SD)* ICCs for double-coded files were good-to-excellent for frequencies of the behaviors examined: unusual visual inspection=0.88 *(0.08)*; spin=0.95 *(0.04)*; rotate=0.75 *(0.22)*.

Examiner-rated social engagement.—At the end of each assessment session, examiners unaware of risk status rated 3 social behaviors using a 5-point scale (1=Very Frequent, 2=Frequent, 3=Occasional, 4=Rare, 5=None): Frequency of eye contact, frequency of shared affect, and overall social responsiveness. The scores were reverse scored so that higher scores equated to better social engagement and then summed to create a social engagement score ranging from 3 to 15. This measure was selected because it is independent of the object exploration task and was completed at every age. In previous studies, it distinguished infants with typical versus atypical development by 12 months of age (Ozonoff et al., 2010, 2014) and has been shown to be strongly positively associated with objectively-coded gaze-to-face and social smile behaviors (Ozonoff et al., 2010). Due to the addition of the third item on this scale partway through data collection, this item was missing in 37 of the 882 total observations. This issue was addressed analytically by using multiple imputation.

Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000).—This is a semi-structured standardized interaction and observation that measures symptoms of ASD. It has empirically-derived cutoffs for ASD and Autistic Disorder. Psychometric studies report high inter-rater reliability and agreement in diagnostic classification (autism vs. non-spectrum). The ADOS was used for diagnostic classification purposes in both the older sibling (to verify inclusion criteria) and the participant (to determine outcome).

Mullen Scales of Early Learning (MSEL; Mullen, 1995).—This standardized developmental test for children birth to 68 months was used to evaluate cognitive functioning. Four subscales were administered: Fine Motor, Visual Reception, Expressive Language, and Receptive Language. Raw scores can be converted to *T*-scores and an overall score of all four subscales, the Early Learning Composite, can be obtained using published normative data. MSEL subscales have excellent internal consistency (median 0.91) and test-retest reliability (median 0.84).

Data Analytic Plan

Repetitive behavior.—Repetitive behavior data were right-skewed and clustered at zero, with a high percentage of children not exhibiting these behaviors (ranging from 50% at 12 months to 56% at 36 months for unusual visual inspection, from 34% at 12 months to 65% at 36 months for rotate, and from 58% at 15 months to 75% at 6 months for spin).

Thus, generalized linear mixed-effects models (GLMM) for count data (McCulloch, Searle, & Neuhaus, 2008) with a negative binomial distribution (to account for overdispersion) and a log link were used to model repetitive behavior trajectories and to evaluate group differences between 9 and 36 months of age. This approach explicitly accounts for multiple measurements per child, allows for unequally spaced and missing observations, and produces valid inference under the assumption that data are missing at random (MAR). In models for count data using the negative binomial distribution, log of the mean (rather than the mean) is modeled as a linear combination of predictors. To account for slight variations in task duration, the duration of the task (in minutes) was log-transformed and entered into the model as an offset. This resulted in a rate parameterization, in which the outcome of interest was the number of repetitive behaviors per minute and the regression coefficients represented the linear effect of the predictor variables on the log of the rate of repetitive behavior. Empirical (sandwich) variance estimators were used to make the analysis robust against misspecification of the covariance structure and to adjust for small-sample bias.

Preliminary analyses suggested nonlinear trends over time. Thus, for each behavior we first fitted a model that included a main effect for outcome (ASD, High-Risk Non-ASD, Low-Risk Non-ASD), linear, quadratic, and cubic effects of age at visit (measured in years, centered at 9 months) and interactions between the age effects and outcome. Due to centering, the intercept in the model provides an estimate of the mean level in the reference group (Low-Risk Non-ASD) at the age of first visit (9 months). In addition, the model provides estimates for the average difference at 9 months between the ASD and Non-ASD groups, as well as the linear and quadratic effect of age in the reference group (Low-Risk Non-ASD). The interaction terms between outcome and the linear, quadratic, and cubic effects of age allowed for differences between groups in the linear, quadratic and cubic trajectory, respectively. Higher order age effects and their interaction with outcome were tested and removed from the final model if they did not contribute significantly to the model. To account for within-child correlations, the models included random effects for child-specific intercepts and linear slopes. Linear contrasts were constructed to estimate trajectories (e.g., ASD, High-Risk Non-ASD) and differences in trajectories (e.g., ASD vs. High-Risk Non-ASD) not directly provided by the models, as well as outcome group differences at each visit age. All models were validated both graphically and analytically.

Sensitivity/specificity.—Based on the GLMM results, we selected the repetitive behavior that most consistently distinguished the ASD group from the other two groups at the earliest ages and calculated sensitivity and specificity of the presence of this repetitive behavior in identifying ASD at each age. We operationalized repetitive behavior as a binary variable (presence versus absence), first calculating estimates for having ≥1 instance of the behavior between the ASD versus Non-ASD groups (collapsing low-risk and high-risk groups) at each individual age, and then comparing the ASD and Low-Risk Non-ASD groups. Since sample size varied by visit, we used multiple imputation to fill in missing data and ensure in-range values, so that estimates would be based on the same sample across visits. Since missing object exploration task data ranged from 13.6% to 51.7% across visits, we followed conservative recommendations and used 100 imputations (Graham, Olchowski, & Gilreath, 2007). Sensitivity/specificity analyses were conducted on each of the 100 complete data sets

and results were combined according to Rubin's rules (Rubin, 1987). We also conducted secondary analyses using the complete case data available at each visit.

Associations between repetitive behavior and social engagement.—We next examined associations between examiner-rated social engagement and the repetitive behavior that best distinguished the groups at the earliest ages (i.e., 9 and 12 months). Because our primary goal was to test the initial developmental cascade linking the earliest detectable repetitive behavior and social behavior, we specifically examined associations between 9 and 12 months of age. Using a series of nested models, we evaluated predictive associations between rates of 9-month repetitive behavior and 12-month examiner ratings of social engagement, controlling for 9-month examiner ratings, and examined whether diagnostic status (ASD vs. Non-ASD) moderated these associations. We first fitted a model for 12-month examiner ratings of social engagement using only 9-month repetitive behavior as a predictor. To this model, we added 9-month examiner social engagement ratings to assess whether the association between 9-month repetitive behavior and 12-month examiner social engagement ratings persisted when controlling for 9-month examiner social engagement ratings. Finally, we added terms for diagnostic status (ASD vs. Non-ASD) and the interaction between 9-month repetitive behavior and diagnostic status to evaluate whether the association was moderated by diagnostic status. We applied the same analytic strategy to test whether 9-month examiner ratings predicted 12-month repetitive behavior, after controlling for 9-month repetitive behavior.

Both repetitive behavior and social engagement were analyzed as counts using generalized linear models with either negative binomial (repetitive behavior) or Poisson (social engagement) distributions and a log link. Examiner-rated social engagement was rescaled by subtracting the score from the maximum (15) to better fit distributional assumptions. The models for repetitive behavior accounted for the differences in duration by using log-transformed task duration as an offset. Since some children were missing repetitive behavior and/or social engagement data at either 9 or 12 months, multiple imputation was employed. We generated 100 complete datasets, performed analyses on each complete dataset, and combined the results according to Rubin's rules (Rubin, 1987).

All analyses were implemented in SAS Version 9.4 (SAS Institute, Cary, North Carolina). All tests were two-sided, and p-values <0.05 were considered statistically significant.

Results

Coded Repetitive Behavior with Objects

Table 2 summarizes the results (on the log scale) of the GLMM for the 3 repetitive behavior codes from 9 to 36 months of age. To facilitate interpretation, we calculated estimates and 95% confidence intervals (CI) on the original scale (see Figures 1 and 2) and assessed differences among outcome groups at each visit (see Table S5).

Unusual visual inspection.—As illustrated in Figure 1, the ASD group differed significantly from both other groups as early as 9 months of age, engaging in 139% (estimated difference [est.]=2.39, 95% CI=1.13–5.05) more unusual visual inspection of

objects compared to the Low-Risk Non-ASD group, and 115% (est.=2.15, 95% CI=1.09–4.25) more unusual visual inspection compared to the High-Risk Non-ASD group. In terms of change over time, the Low-Risk Non-ASD group demonstrated a significant decrease in unusual visual inspection between 9 and 36 months. The ASD group had significantly different linear and curvilinear trajectories than the Low-Risk Non-ASD group, while the High-Risk Non-ASD group demonstrated relatively similar patterns of change over time compared to the Low-Risk Non-ASD group. This pattern resulted in the ASD group maintaining significantly higher levels of unusual visual inspection from both other groups across all visits, while the two Non-ASD groups did not differ at any age (see Table S5).

Rotate.—The frequency of rotating behavior was similar among the outcome groups at 9 months of age (Figure 2a). Interactions between age and outcome group were present (see Table 2) resulting in different patterns of change among the 3 groups from 9 to 36 months. The Low-Risk Non-ASD group exhibited a gradual decrease in rotating behavior until 24 months, levelling off through 36 months. The ASD group had significantly different linear and curvilinear trajectories than the Low-Risk Non-ASD group, while the High-Risk Non-ASD group demonstrated significant quadratic age effects compared to the Low-Risk Non-ASD group. Combined, this resulted in similar levels of rotating behavior at 36 months (see Table S5). Significant group differences between the ASD and Low-Risk Non-ASD groups were observed between 15 and 24 months. Compared to the Low-Risk Non-ASD group, the ASD group engaged in 66% (est.=1.66, 95% CI=1.02–2.71) more rotating behavior at 15 months, 97% (est.=1.97, 95% CI=1.15–3.38) more at 18 months, and 116% (est.=2.16, 95% CI=1.12–4.15) more at 24 months. The ASD and High-Risk Non-ASD groups did not differ at any age.

Spin.—As illustrated in Figure 2b and Table 2, the ASD group differed significantly from both non-ASD groups at 9 months of age, engaging in 86% (est.=0.14, 95% CI=0.03–0.76) less frequent object spinning behavior compared to the Low-Risk Non-ASD group, and 82% (est.=0.18, 95% CI=0.04–0.93) less frequent object spinning compared to the High-Risk Non-ASD group. Higher order interactions between curvilinear age effects and group were present. The ASD group exhibited an increase in this behavior until 18 months, followed by a decrease through 36 months. The Low-Risk Non-ASD group demonstrated modest increases in object spinning from 9 to 36 months, while the High-Risk Non-ASD group exhibited a similar pattern of gradual increases until 24 months of age, at which point there was a sharp decrease. These patterns resulted in similar levels of object spinning among the groups at 36 months (see Table S5). The remaining significant group differences were observed between the ASD and High-Risk Non-ASD groups at 18 and 24 months, and between the ASD and Low-Risk Non-ASD groups at 18 months.

Sensitivity/Specificity

Since unusual visual inspection best distinguished the groups at the earliest ages and most persistently over time (i.e., at each age), we selected this behavior for sensitivity/specificity calculations. Sensitivity and specificity of the presence of unusual visual inspection in predicting ASD classification were evaluated at each age, first differentiating ASD from all Non-ASD participants (i.e., collapsing across the High-Risk Non-ASD and Low-Risk

Non-ASD groups) and then from the Low-Risk Non-ASD group only (see Table 3). Acceptable levels of both sensitivity and specificity for a screening measure in predicting ASD outcome (i.e., above 0.70; Sandler et al., 2001) vs. All Non-ASD (Low-Risk and High-Risk) were not achieved until 15 months of age (0.73 and 0.72) though, notably, sensitivity decreased at 18 months (0.69) and then returned to >0.70 at 24 months (i.e., 0.76) (see Table 3). Although not reaching traditionally acceptable sensitivity/specificity values for developmental screening, estimates for unusual visual inspection at 9 months of age were in the moderate range (0.60 and 0.68, respectively) for the ASD vs. Low-Risk Non-ASD comparisons. Results of the secondary analysis using complete data generally paralleled those obtained using multiple imputation, with the largest difference at 24 months with estimates biased downward and confidence intervals wider than those from the primary analysis, which is expected given the larger percent of missing data (Supplementary Table S6).

Associations Between Repetitive and Social Behaviors

Similar to sensitivity/specificity analyses, because unusual visual inspection best distinguished the groups at the earliest ages, we selected this behavior for analyses focused on associations between repetitive and social behaviors. Table 4 shows results from count regression models. Controlling for outcome group and 9-month social engagement ratings, unusual visual inspection at 9 months of age predicted social engagement at 12 months, B=0.21 SE=0.08, p=0.01, 95% CI=0.05, 0.38, with higher levels of unusual visual inspection predicting lower levels of social engagement (on the original scale). Diagnostic status did not moderate the association between 9-month unusual visual inspection and 12-month social engagement.

The reversed model, examining the association between 9-month social engagement ratings and 12-month unusual visual inspection, controlling for 9-month unusual visual inspection, was non-significant; 9-month social engagement did not significantly predict 12-month unusual visual inspection over and above 9-month unusual visual inspection, B=−0.07, SE=0.09, p=0.41, 95% CI=−0.24, 0.10, nor did diagnostic status moderate this association, B=−0.06, SE=0.19, p=0.75, 95% CI=−0.44, 0.31.

Discussion

Our findings indicate that repetitive behaviors with objects are evident early in development and, in particular, that unusual visual inspection of objects is present and stable as early as 9 months of age in infants developing ASD. Compared to differences in unusual visual inspection, differences in frequencies of spinning and rotating behavior were generally somewhat later-appearing, time-limited, and/or suggestive of differences based on risk for ASD rather than differences specific to outcome. In the current study, the presence of unusual visual inspection showed moderate sensitivity/specificity in predicting ASD outcomes across ages. We also found that unusual visual inspection at 9 months predicted 12-month levels of examiner-rated social engagement over and above baseline social engagement ratings across the entire sample, but not vice versa. Such associations were not

moderated by diagnostic status, although our ability to detect such effects may be reduced as a result of the relatively small sample size.

It is important to note that aspects of repetitive behavior are normative in development during the first year of life (Thelen, 1979). Indeed, in the present sample, the Low-Risk Non-ASD and High-Risk Non-ASD groups engaged in the repetitive behaviors examined to some degree. Still, the magnitude of the difference in levels of unusual visual inspection between groups in our sample was striking, with rates significantly higher among infants who developed ASD by 9 months and persisting through 36 months of age. This replicates and extends an earlier finding in 12-month-olds which suggested that this behavior may be a particularly distinctive feature of the early autism phenotype (Ozonoff et al., 2008), and is one of the earliest behavioral predictors of ASD yet documented. This finding is also consistent with research describing frequent atypical visual exploration of objects—and in particular, an increased frequency of lateral glances—among young children with ASD compared to typically developing children (Mottron et al., 2007). Such behaviors have been theorized to relate to perceptual differences commonly seen in individuals with ASD (Mottron et al., 2007). In this context, our finding of increased frequencies of unusual visual inspection of objects may be evidence of very early and persistent efforts to regulate visual information as a result of possible perceptual atypicalities among infants developing ASD.

Patterns of differences over time were somewhat similar between rotating and spinning behavior. Higher frequencies of rotating emerged at 15 months in the ASD group compared to the Low-Risk Non-ASD group (but not the High-Risk Non-ASD group), persisting through 24 months of age, whereas the ASD group began to exhibit higher frequencies of spinning behavior from both Non-ASD groups at 18 months; by 24 months of age this difference was restricted to the ASD vs High-Risk Non-ASD contrast. The lack of a significant difference in frequencies of rotating behavior between the ASD and High-Risk Non-ASD group may suggest that increased rotating behavior is more related to familial risk for ASD rather than specific to an ASD outcome.

The current pattern of findings is similar to previous work, with slight variations around timing of differences. Specifically, Ozonoff et al. (2008) found higher levels of all three repetitive behaviors among 12-month-olds who later developed ASD. In the present study, group differences in unusual visual inspection were significant by 9 months and continued at 12 months and beyond, replicating the previous finding of group differences in this behavior in 12-month-olds. However, differences in the other two behaviors did not appear until 15–18 months, resulting in similar patterns but at slightly later ages than in the earlier report. Ultimately, the most striking difference from the 2008 study related to unusual visual inspection was replicated.

Given that the earliest and most prominent differences we found were in the frequency of unusual visual inspection, and with an eye toward early screening, we were interested in evaluating how well the presence versus absence of a single instance of this behavior distinguished the group of infants who developed ASD from those who did not. At 9 months of age, 63% of the infants who developed ASD engaged in this behavior at least once versus only 37% of the infants who did not develop ASD (whether high- or

low-risk). By 18 months, more than two thirds of the group who developed ASD engaged in unusual visual inspection at least once versus less than a quarter of the Non-ASD group. Although sensitivity/specificity estimates were generally not within the acceptable range for developmental screening measures, they do suggest the potential value of monitoring for this particular behavior early in life.

Another goal was to better understand the ways in which early repetitive use of objects and social behavior influence each other. Because the earliest difference in repetitive behavior was found for unusual visual inspection, we focused our efforts on relations between this specific behavior and social engagement. Across the entire sample and not accounting for the influence of diagnostic status, unusual visual inspection at 9 months significantly predicted examiner-rated social engagement at 12 months over and above 9-month examiner-rated social engagement. In contrast, the reverse associations were not significant (i.e., 9-month examiner-rated social engagement did not predict 12-month unusual visual inspection after controlling for 9-month unusual visual inspection). Moderation analyses did not suggest moderation of these associations by diagnostic status. Prior studies have examined object-directed looking among infants developing ASD, finding no differences in the duration of object looking (Ozonoff et al., 2010). However, such studies did not (a) examine object looking in contexts designed to elicit repetitive object use, nor (b) specifically examine unusual visual inspection of objects, which is qualitatively distinct from simple object looking. Our findings—focused on behavior characterized by peering at objects from different angles, close-up inspection of objects, or prolonged object looking—are consistent with theories suggesting that an increased focus on objects early in life has detrimental cascading effects on social development (see Dawson, 2008; Landry & Bryson, 2004; Zwaigenbaum et al., 2005) and may contribute to emerging deficits in social behavior in infants who are developing ASD. These findings may also imply that early, intense object focus is one factor that drives later deficits in social behavior, but that early deficits in social behavior do not appear to drive a later tendency to be more object focused.

The present study is, to our knowledge, the first to prospectively evaluate repetitive behaviors with objects beginning at 9 months of age using direct assessment methods in a sample of infants at risk of ASD, but it is not without limitations. This includes limiting our evaluation of repetitive behavior to three individual behaviors and one specific context (play with objects). Other types of repetitive behaviors are relevant, such as stereotyped motor behaviors, and worth investigating in future studies. We used two powerful tools—multiple imputation and generalized mixed-effects models—to handle missing data. These approaches yield valid results in the presence of data missing at random. However, our results may be biased if missingness depends not only on the variables we used to impute missing values, but also on the missing values themselves. While there is no way to test whether the assumption that our missing data is missing at random (MAR) (except by obtaining follow-up data from non-responders), our careful examination of missingness and reasons for missingness suggests MAR is plausible in our data (e.g., over half of the missingness at the most problematic visit age was due to data not intended to be collected in the first place; most of the missingness is intermittent). Moreover, Collins, Shafer, & Kam (2001) have shown that in many realistic situations, departures from MAR assumptions may only have a minor impact on estimates and standard errors. Finally, our sample of infants

with ASD outcomes is small in terms of moderation analyses and in terms of obtaining robust sensitivity/specificity estimates; it will be important to replicate our findings in larger samples. Nevertheless, our findings provide an initial sense of the potential utility of unusual visual inspection as an early indicator of ASD based on direct observation.

This study was strengthened by a longitudinal design, with all participants completing the object exploration task at a minimum of 3 of the 6 study visits. Future studies should evaluate the correspondence between objectively coded early repetitive behaviors and prospectively-collected parent report of these behaviors. If parent report and objective coding of repetitive behaviors are strongly correlated, this would suggest that parental report may be sufficient for early screening. This would be much more clinically applicable than our second-by-second behavioral coding system, although our task is short in duration and could potentially be modified to be live-coded for behavior frequencies.

Overall, we found that unusual visual inspection of objects is present in ASD earlier than previously thought and is, to our knowledge, one of the earliest behavioral predictors of ASD outcome yet documented. Differences in frequencies of the other behaviors examined (rotate, spin) were somewhat less striking, in that they tended to be later-appearing, more time-limited (e.g., differing at only one or two timepoints), and/or suggestive of differences based on risk for ASD rather than specific to eventual diagnosis (e.g., similar frequencies of rotating behavior between ASD and High-Risk Non-ASD groups). Unusual visual inspection of objects appears to be predictive of social behavior three months later, but not vice versa when accounting for baseline behavior. Perhaps because social-communication impairments are often thought to be apparent in ASD before the development of repetitive behaviors (see Szatmari et al., 2016 for a discussion of this point), most early screening tools primarily focus on assessing social-communication behavior and typically do not incorporate specific items about visual inspection of objects. Instead, they tend to include items about repetitive behaviors more broadly or not at all. Our findings suggest that close monitoring of unusual visual inspection of objects by 9 months of age may be an important aspect of early detection efforts and may be valuable to integrate into early screening and diagnostic tools.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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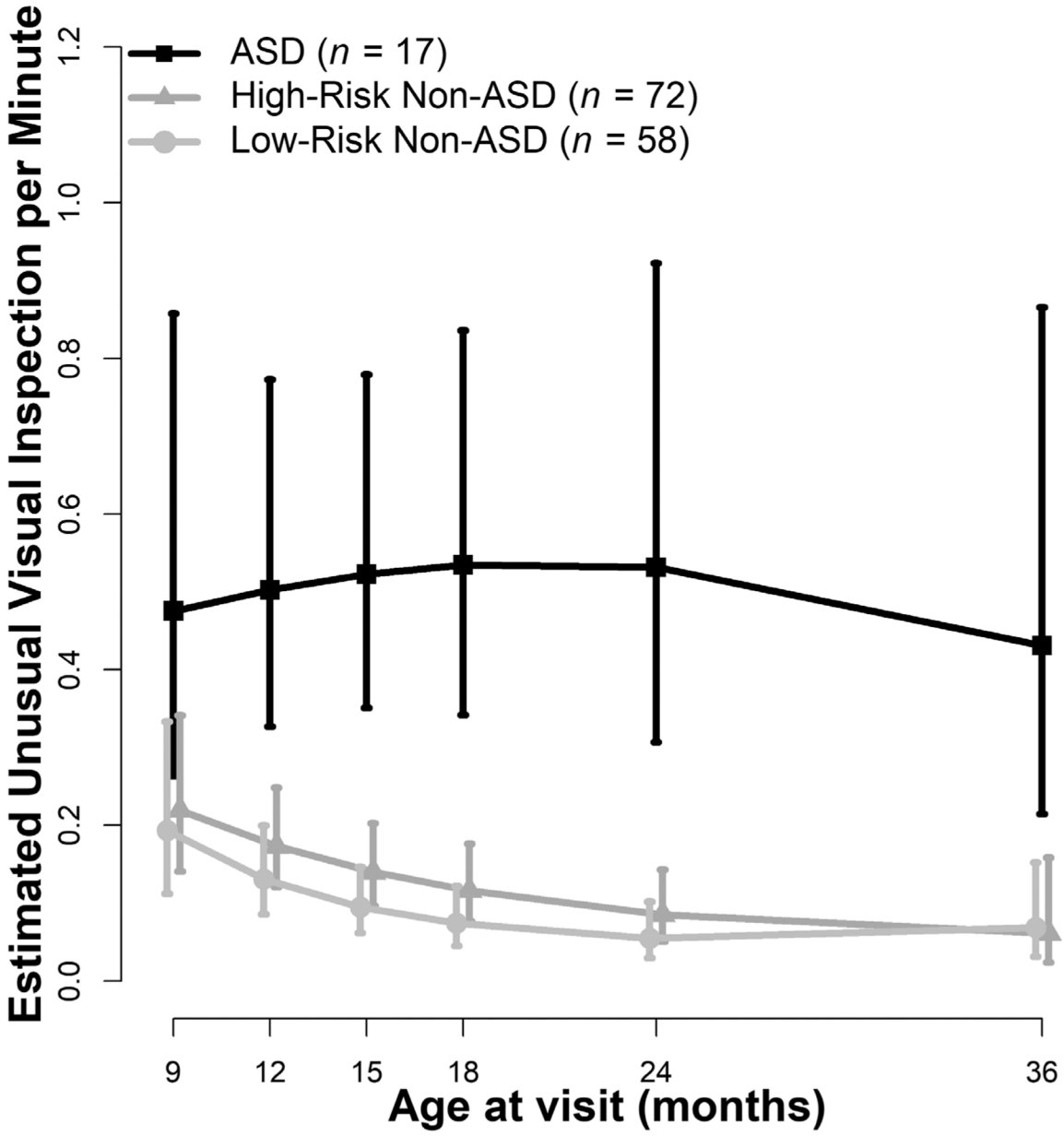

Figure 1.
Estimated marginal means (and 95% confidence intervals) for frequencies of unusual visual inspection of objects from 9 to 36 months of age.

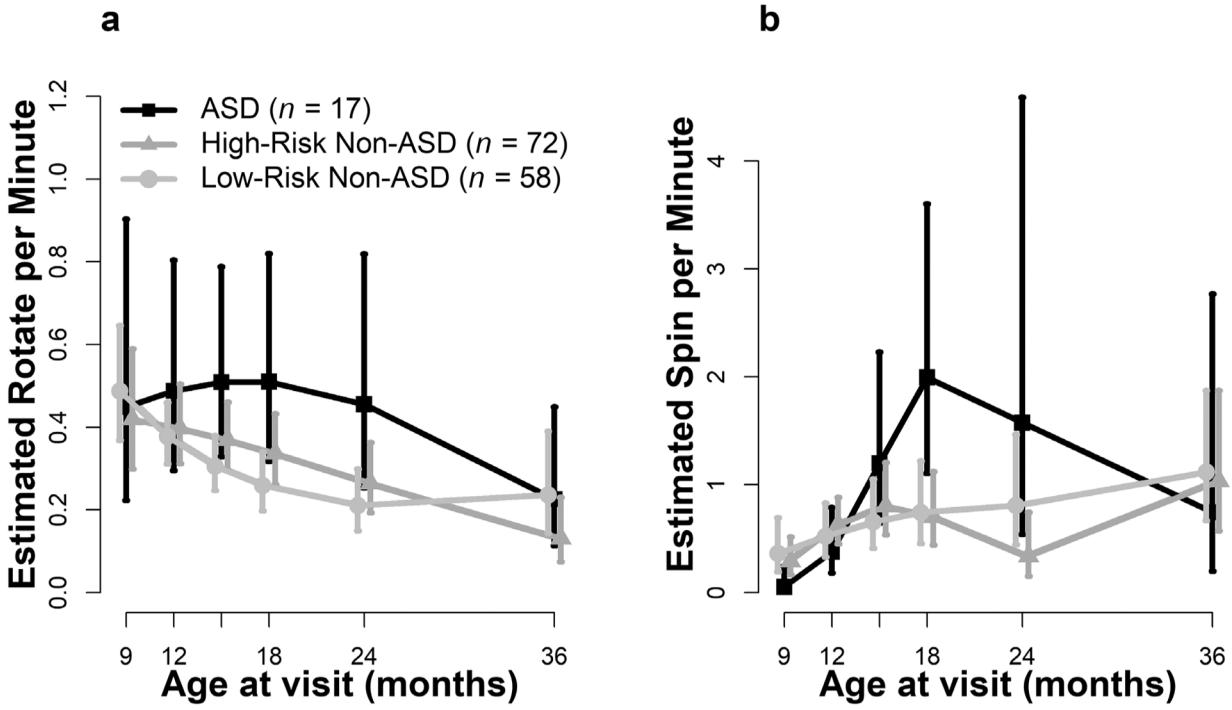

Figure 2.

Estimated marginal means (and 95% confidence intervals) for frequencies of (a) object rotating and (b) object spinning behavior from 9 to 36 months of age.

Table 1.

Participant characteristics.

	ASD (*n*=17)	High-Risk Non-ASD (*n*=72)	Low-Risk Non-ASD (*n*=58)	*p*-value
Male Sex, *n* (%)	14 (82.4%)	41 (56.9%)	35 (60.3%)	0.15
Race[a], *n (%)*				0.41
White	11 (68.9%)	44 (64.7%)	41 (75.9%)	
Non-White	5 (31.3%)	24 (35.3%)	13 (24.1%)	
Hispanic Ethnicity[b], *n (%)*	5 (31.3%)	12 (17.4%)	11 (19.3%)	0.45
Income[c], *n* (%)				0.07
Under $50k	2 (14.3%)	4 (6.2%)	6 (11.8%)	
$50k–$80k	5 (35.7%)	9 (13.9%)	10 (19.6%)	
$80k–$100k	2 (14.3%)	7 (10.8%)	8 (15.7%)	
$100k–$125k	0 (0%)	11 (16.9%)	7 (13.7%)	
$125k–$150k	2 (14.3%)	11 (16.9%)	7 (13.7%)	
$150k or higher	3 (21.4%)	23 (35.4%)	13 (25.5%)	
Maternal Education[d], *n* (%)				0.19
Less than College	8 (47.1%)	24 (34.3%)	14 (24.6%)	
College or Higher	9 (52.9%)	46 (65.7%)	43 (75.4%)	
Gestational Age (weeks), *mean*	39.8 (1.7)	38.7 (1.8)	39.4 (1.1)	0.003
Mullen Scales of Early Learning, 36 months [e]				
ELC, *mean (SD)*	85.5 (18.5)	103.3 (19.0)	109.3 (13.8)	<0.001
Autism Diagnostic Observation Scale, 36 months				
Comparison score, *mean (SD)*	6.6 (1.6)	1.8 (1.0)	1.3 (0.5)	<0.001

Note. ASD, Autism Spectrum Disorder; ELC, Early Learning Composite. Due to rounding, percentages may not sum to 100. Overall group differences were assessed using χ^2 tests for all categorical variables except income (for which Cochran-Mantel-Haenszel test for ordinal data was used) and Wilcoxon two-sample nonparametric tests for continuous variables.

Missing for:

[a] 1 participant in ASD group, 4 in High-Risk Non-ASD, 4 in Low-Risk Non-ASD;

[b] 1 participant in ASD group, 3 in High-Risk Non-ASD, 1 in Low-Risk Non-ASD;

[c] 3 participants in ASD group, 7 in High-Risk Non-ASD, 7 in Low-Risk Non-ASD;

[d] 2 participants in High-Risk Non-ASD group, 1 in Low-Risk Non-ASD;

[e] 3 participants in ASD group, 2 in High-Risk Non-ASD.

Table 2.

Parameter estimates (*SE*) for the mixed-effects negative binomial regression models predicting unusual visual inspection, rotate, and spin.

	Unusual visual inspection		Rotate		Spin	
	Estimate (*SE*)	***p*-value**	**Estimate**	***p*-value**	**Estimate (*SE*)**	***p*-value**
Estimated trajectory for Low-Risk Non-ASD group						
Baseline (9 months)	−1.64 (0.28)	<0.001	−0.72 (0.14)	<0.001	−1.01 (0.33)	0.002
Linear change with age (years)	−1.69 (0.61)	0.006	−1.10 (0.39)	0.005	1.74 (1.13)	0.12
Quadratic change with age (years)	0.55 (0.24)	0.02	0.35 (0.16)	0.03	−1.30 (1.21)	0.28
Cubic change with age (years)	—	—	—	—	0.33 (0.34)	0.33
Estimated trajectory for ASD group						
Baseline (9 months)	−0.74 (0.30)	0.01	−0.80 (0.36)	0.02	−2.94 (0.78)	<0.001
Linear change with age (years)	0.26 (0.61)	0.67	0.41 (0.68)	0.55	9.73 (3.10)	0.002
Quadratic change with age (years)	−0.13 (0.24)	0.57	−0.32 (0.25)	0.21	−7.88 (3.51)	0.03
Cubic change with age (years)	—	—	—	—	1.81 (1.04)	0.08
Estimated trajectory for High-Risk Non-ASD group						
Baseline (9 months)	−1.52 (0.22)	<0.001	−0.87 (0.17)	<0.001	−1.23 (0.29)	<0.001
Linear change with age (years)	−0.99 (0.48)	0.04	−0.18 (0.38)	0.63	4.37 (1.43)	0.002
Quadratic change with age (years)	0.19 (0.22)	0.38	−0.15 (0.16)	0.35	−5.54 (1.77)	0.002
Cubic change with age (years)	—	—	—	—	1.71 (0.54)	0.002
Estimated difference between ASD and Low-Risk Non-ASD groups						
Baseline (9 months)	0.90 (0.40)	0.03	−0.08 (0.39)	0.83	−1.93 (0.84)	0.02
Linear change with age (years)	1.95 (0.85)	0.02	1.51 (0.77)	0.05	7.99 (3.30)	0.02
Quadratic change with age (years)	−0.68 (0.33)	0.04	−0.66 (0.30)	0.03	−6.57 (3.71)	0.08
Cubic change with age (years)	—	—	—	—	1.48 (1.10)	0.18
Estimated difference between High-Risk Non-ASD and Low-Risk Non-ASD groups						
Baseline (9 months)	0.13 (0.33)	0.70	−0.15 (0.22)	0.50	−0.22 (0.43)	0.60
Linear change with age (years)	0.70 (0.75)	0.35	0.92 (0.54)	0.09	2.62 (1.82)	0.15
Quadratic change with age (years)	−0.36 (0.31)	0.25	−0.50 (0.23)	0.03	−4.24 (2.14)	0.048
Cubic change with age (years)	—	—	—	—	1.38 (0.63)	0.03
Estimated difference between ASD and High-Risk Non-ASD groups						
Baseline (9 months)	0.77 (0.37)	0.04	0.07 (0.40)	0.86	−1.71 (0.83)	0.04

	Unusual visual inspection		Rotate		Spin	
	Estimate (*SE*)	***p*-value**	**Estimate**	***p*-value**	**Estimate (*SE*)**	***p*-value**
Linear change with age (years)	1.25 (0.77)	0.11	0.59 (0.76)	0.44	5.37 (3.42)	0.12
Quadratic change with age (years)	−0.32 (0.31)	0.31	−0.17 (0.29)	0.57	−2.33 (3.94)	0.55
Cubic change with age (years)	—	—	—	—	0.10 (1.17)	0.93

Note. ASD, autism spectrum disorder; SE, standard error. Negative binomial mixed-effects regression models included the fixed effects reflected above, random effects for child-specific intercept and linear slope and an offset for log transformed task duration (in minutes).

Table 3.

Sensitivity and specificity for presence of unusual visual inspection at each age using multiple imputation to handle missing data.

Age	ASD		Non-ASD		Low-Risk Non-ASD		ASD vs. All Non-ASD		ASD vs. Low-Risk Non-ASD	
	True Positive	False Negative	False Positive	True Negative	False Positive	True Negative	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
9mos	10.3	6.7	48.3	81.7	18.6	39.4	60.4 (36.6–84.1)	62.9 (53.9–71.9)	60.4 (36.6–84.1)	67.9 (55.2–80.7)
12mos	10.6	6.4	47.5	82.5	19.0	39.0	62.5 (37.5–87.6)	63.4 (54.2–72.7)	62.5 (37.5–87.6)	67.2 (53.6–80.8)
15mos	12.4	4.6	37.1	92.9	15.5	42.6	72.8 (50.5–95.2)	71.5 (63.0–80.0)	72.8 (50.5–95.2)	73.4 (60.6–86.1)
18mos	11.7	5.3	25.4	104.6	11.4	46.6	68.8 (43.0–94.5)	80.4 (72.6–88.3)	68.8 (43.0–94.5)	80.3 (67.7–92.9)
24mos	12.9	4.1	20.0	110.0	11.4	46.6	75.8 (52.3–99.2)	84.6 (76.5–92.7)	75.8 (52.3–99.2)	80.3 (67.6–93.0)
36mos	12.0	5.0	23.1	106.9	13.6	44.4	70.5 (48.8–92.2)	82.2 (74.6–89.9)	70.5 (48.8–92.2)	76.6 (64.2–89.0)

Note. ASD, autism spectrum disorder; CI, confidence interval. Two separate analyses were conducted for each visit, one comparing the ASD vs. combined Non-ASD groups (i.e., Low-Risk and High-Risk Non-ASD) and one comparing the ASD vs. Low-Risk Non-ASD groups. To account for differences in sample size at each visit, sensitivity, specificity, and CI were calculated after generating 100 complete data sets using multiple imputation, analyzing each data set, and pooling the results. True positive, false negative, false positive, and true negative frequencies at each visit from 100 complete data sets were averaged and therefore may not be integers. Sensitivity is the percentage of those diagnosed at 36 months who engaged in any unusual visual inspection at the specified visit, calculated as True Positives/(True Positives+False Negatives) × 100. Specificity is the percentage of those without a diagnosis at 36 months who did not engage in unusual visual inspection at the specified visit, calculated as True Negatives/(True Negatives+False Positives) × 100.

Table 4.

Associations between unusual visual inspection, social engagement, and diagnostic status from 9 to 12 months of age.

Predictor	Model 1		Model 2		Model 3	
	Estimate (*SE*)	*p*-value	Estimate (*SE*)	*p*-value	Estimate (*SE*)	*p*-value
Models predicting 12-month social engagement						
Unusual visual inspection (9mos)	0.36 (0.07)	<0.001	0.21 (0.08)	0.01	0.16 (0.10)	0.10
Social engagement (9mos)	–	–	−0.12 (0.03)	<0.001	−0.12 (0.03)	<0.001
Diagnostic status	–	–	–	–	0.26 (0.18)	0.14
Unusual visual inspection (9mos)*Diagnostic status	–	–	–	–	0.02 (0.17)	0.92
Models predicting 12-month unusual visual inspection						
Social engagement (9mos)	−0.16 (0.07)	0.04	−0.07 (0.09)	0.41	−0.04 (0.09)	0.64
Unusual visual inspection	–	–	0.54 (0.25)	0.03	0.47 (0.24)	0.05
Diagnostic status	–	–	–	–	1.28 (2.10)	0.54
Social engagement (9mos)*Diagnostic status	–	–	–	–	−0.06 (0.19)	0.75

Note. SE, standard error.

Associations with 12-month examiner social engagement ratings were assessed using Poisson regression models with log link function. For this analysis, 12-month examiner social engagement ratings were rescaled so smaller values correspond to better social engagement. Associations with 12-month unusual visual inspection were assessed using negative binomial regression models with log link function and log scaled 12-month task duration (in minutes) as offset. To account for differences in sample size available at each visit, we generated 100 complete data sets using multiple imputation, analyzed each data set, and pooled the results. Diagnostic status was a binary variable (ASD vs. Non-ASD), with Non-ASD as reference.