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Response to Distress in Infants at Risk for Autism: A Prospective Longitudinal Study

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Abstract

Background—Infants and preschoolers with ASD show impairment in their responses to other people's distress relative to children with other developmental delays and typically developing children. This deficit is expected to disrupt social interactions, social learning, and the formation of close relationships. Response to distress has not been evaluated previously in infants with ASD earlier than 18 months of age.

Methods—Participants were 103 infant siblings of children with autism and 55 low-risk controls. All children were screened for ASD at 36 months and 14 were diagnosed with ASD. Infants' responsiveness to distress was evaluated at 12, 18, 24, and 36 months. An examiner pretended to hit her finger with a toy mallet and infants' responses were video-recorded. Attention to the examiner and congruent changes in affect were coded on four-point Likert scales.

Results—Cross-sectional and longitudinal analyses confirm that the ASD group paid less attention and demonstrated less change in affect in response to the examiner's distress relative to the high-risk and low-risk participants who were not subsequently diagnosed with ASD. Group differences remained when verbal skills and general social responsiveness were included in the analytic models.

Conclusions—Diagnostic groups differ on distress response from 12 to 36 months of age. Distress-response measures are predictive of later ASD diagnosis above and beyond verbal impairments. Distress response is a worthwhile target for early intervention programs.

Keywords

autism; early identification; siblings; empathy; infancy

Introduction

Research on infants' behavioral responses to another person's distress suggests that empathic concern typically emerges between the first and second birthdays. Infants demonstrate pro-

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social responses to another person's distress as early as 12 months (Zahn-Waxler & Radke-Yarrow, 1982). These behaviors and expressions of empathic concern occur with increasing frequency across the second year, whether the infant caused or merely witnessed the distress (Zahn-Waxler, Radke-Yarrow, Wagner & Chapman, 1992). Within the same developmental time frame, toddlers with autism were observed to be less responsive to distress than typically developing children and children with other developmental delays (Charman et al., 1997). Differential responsiveness in 20-month-olds with ASD suggests that atypical patterns of development may be detectable even earlier in life. The current study sought to determine whether infants later diagnosed with autism can be distinguished from those not on the autism spectrum as early as 12 months of age on the basis of their response to another person's distress. Identifying signs of autism at 12 months would support efforts to screen for autism and thereby begin treatment earlier in development than has previously been possible.

This study evaluated distress-response behavior in infants at risk for autism and low-risk controls from 12 to 36 months of age. Having a biological sibling with autism is the strongest indicator of risk for autism in infants (Bailey et al., 1995; Steffenburg et al., 1989). Prospective longitudinal studies of infant siblings of children with autism have generated promising results regarding early warning signs as well as features of autism in non-autistic siblings. Several of these studies have administered variations of the still-face paradigm (SFP; Cohn & Tronick, 1983) at 4 and 6 months of age and found no differences on most measures of social engagement between siblings of children with autism and low-risk infants (Ibanez, Messinger, Newell, Lambert & Sheskin, 2008; Yirmiya et al., 2006). In one study, high-risk infants looked less to the eyes and more to the mouth during the SFP (Merin, Young, Roger & Ozonoff, 2007), but these differences were not related to diagnostic measures at 24 months (Young, Merin, Rogers & Ozonoff, 2009). Our group (Rozga et al., 2010) found no differences in infants' behavior during the SFP at 6 months between infants with ASD, high-risk non-ASD infants, and low-risk controls. These studies are generally consistent in reporting that responses to mothers' withdrawal from social engagement do not distinguish infants with ASD or the entire group infant siblings of children with autism from low-risk controls at 6 months.

Infants' attenuated response to the sound of their own names between 9 and 12 months was a feature that distinguished those with ASD from typically developing infants in retrospective studies using home videos from first birthday parties (Baranek, 1999; Osterling & Dawson, 1994). One prospective study found that high-risk infants were *more* responsive to their names than low-risk infants at 4 months (Yirmiya et al., 2006). Others reported no difference between groups at 6 months, but high-risk infants were *less* responsive to their names at 12 months than low-risk infants (Nadig et al., 2007; Zwaigenbaum et al., 2005).

The suggestion that differences in social engagement emerge after 6 months, but before 12 months is supported by the finding of decreases in gaze to faces, social smiles, and directed vocalizations during this period among infants later diagnosed with autism (Ozonoff et al., 2010). Deficits in infants' response to attention-directing behavior at 12 months have been associated with diagnostic outcomes at 33 months (Yoder, Stone, Walden & Malesa, 2009) and 36 months (Rozga et al., 2010). Cumulatively, these studies indicate an onset of behavioral symptoms of autism between 6 and 12 months. In particular, they suggest a general decline in infants' attention to social cues.

This study sought to determine whether the lack of response to another person's distress is explained by a decline in social attention generally or whether responding to affective information poses distinct challenges for infants with autism. Administering the distress-response measure to infants at high- and low-risk for autism at 12, 18, 24, and 36 months

allowed comparison between groups both longitudinally and at each time point. In addition to comparing developmental trajectories between high-risk infants who subsequently met criteria for ASD with those who were not on the autism spectrum, we were able to determine whether distress response differentiates non-autistic siblings of children with autism from typically developing controls.

This study was organized by four hypotheses. (1) We expected that children with ASD would be less likely to demonstrate high levels of attention and affective response to distress than high- and low-risk infants not diagnosed with ASD. We expected to see these differences as early as 12 months of age and across the second and third years. (2) The siblings of children with autism who were not diagnosed with autism at 36 months would be less responsive to distress across time points than the low-risk controls. (3) Among infants genetically at risk for autism, distress-response measures would help predict which infants would be diagnosed with ASD and which infants would develop typically. (4) Finally, we expected that distress response and general social responsiveness would account for unique portions of the variance in ASD diagnostic outcome.

This study makes three contributions to the literature on social-emotional development in autism: it explores the response to another person's distress earlier in life than has been documented previously; it evaluates response to distress in children who subsequently develop autism as well as non-autistic siblings of children with autism; and it tracks distress response prospectively and longitudinally, from the end of the first year to the end of the third year of life.

Method

175 infants entered the study at 6, 12, or 18 months of age and response to another person's distress was assessed at as many of the following ages as was possible given the child's age at enrollment: 12, 18, and 24, and 36 months of age. 111 participants were considered to be at elevated risk for autism because they had at least one older sibling with autism. These participants were recruited through the UCLA Autism Evaluation Clinic, other autism-related studies at UCLA, and organizations offering support for children with autism. 64 low-risk controls, with no family history of autism, were recruited by means of a mass mailing to families based on birth records indicating that they had an infant in the target age range. The UCLA Human Subjects Protection Committee approved the research protocol and parents provided informed consent for all participating probands and infants. Characteristics of the sample are summarized in Table 1. Details concerning age at enrollment and attrition are presented in an electronic appendix, Table E-1.

Infant participants were screened for autistic symptomatology at 18, 24, and 36 months using the Autism Diagnostic Observation Schedule - Generic (ADOS; Lord et al., 2000). On the basis of data collected at the 36-month assessment, 14 children who met diagnostic criteria for ASD – autistic disorder, Asperger's syndrome, or pervasive developmental disorder-not otherwise specified (PDD-NOS) – were assigned to the ASD outcome group. Thirteen of the children who met criteria for ASD at 36 months had an older sibling with autism. One child in the ASD group had been considered at low risk for autism because no immediate family member had autism. Distress-response data from four time points (12, 18, 24, and 36 months) were compared among three groups: the ASD group, high-risk participants who did not meet criteria for ASD, and low-risk participants who did not meet criteria for ASD. Four fraternal twin pairs contributed data to this study: 2 pairs in the ASD group and 1 pair in each of the other two groups.

Diagnostic Classification

Autism diagnoses of affected older siblings in high-risk families were confirmed by assessment at the UCLA Autism Evaluation Clinic using the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), the Autism Diagnostic Observation Schedule (ADOS-G; Lord et al., 2000), and criteria detailed in the *Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM-IV; 2000). The low-risk control group was screened for history of autism or developmental problems in the extended family.

For infant participants, diagnostic classifications were made following the 36-month assessment using the ADI-R, the ADOS-G, and DSM-IV criteria. The ADOS-G (Lord et al., 2000) is a structured observational measure comprised of play-based activities that elicit behaviors relevant to a diagnosis of autism spectrum disorders. Diagnostic classification on the ADOS is generated by means of an empirically derived algorithm, using score thresholds in social reciprocity, communication, and a combination of these two domains.

The Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter & Couteur, 1994) was administered following the 36-month assessment session to parents of participants who met criteria on the ADOS at any time point. The ADI-R is a ninety-three-item interview administered to parents or other caregivers to elicit information about children's skills and behaviors in the three domains of diagnostic significance in accordance with the DMS-IV (American Psychiatric Association, 2000). Examiners were trained and confirmed reliable to administer and score the ADOS and the ADI according to their authors' specifications. A clinician reviewed the case files of all participants who demonstrated features of ASD at any time point. The clinician determined whether the child met DSM criteria for a diagnosis of autistic disorder, Asperger's syndrome, or PDD-NOS. Children who met criteria for any of these three disorders at 36 months were included in the ASD group.

Language Skills

The Mullen Scales of Early Learning (MSEL; Mullen, 1995), a standardized measure of cognitive function for infants and preschool-age children, was administered at 12, 18, 24, and 36 months. The MSEL provides age equivalents for four developmental domains: Visual Reception, Fine Motor, Expressive Language, and Receptive Language. Age equivalents from the two language domain scores were averaged to generate verbal mental age (in months). Since the ASD group is expected to have inferior language skills relative to the low- and high-risk non-ASD groups, verbal mental age was evaluated as a covariate in comparisons of distress-response behaviors.

Response to Name

One item from the ADOS evaluates the amount and the intensity of auditory stimulus needed to elicit a child's response to the sound of his/her own name. Scores from the administration of this item at the 18-month visit were used as a measure of general social responsiveness. While the child is engaged with a toy, the examiner stands 3-5 feet from the child at an angle that would require the child to turn to look at the examiner. The examiner calls the child's name once or twice. If the child does not respond, the press is repeated up to 4 times. Scores were dichotomized as no impairment (child orients to the sound of her/his name on the first or second clear press, item score = 0) vs. any impairment (child orients after the second clear press or the child does not orient to the sound of her/his name, item scores > 0).

Response to Another Person's Distress

Variants of the distress-response measure used in this study have been used in previous studies exploring empathic response in children with autism (Bacon, Fein, Morris,

Waterhouse, et al., 1998; Charman et al., 1997; Dawson et al., 2004; Sigman, Kasari, Kwon & Yirmiya, 1992). Prior to administration, the examiner briefed the accompanying caregiver about the task and asked the caregiver to position him/herself out of the child's immediate view. The examiner and the child took turns playing a toy xylophone to ensure that the child's attention was engaged. The examiner pretended to hit her finger with the toy mallet and withdrew from play. She neither made eye contact nor spoke to the child. The examiner gasped or said "ouch" and held her hand still at chest level for a period of 15 seconds after which the examiner assured the child that s/he was not hurt. Seven examiners administered the task to both high- and low-risk participants.

Video recordings of children's behavior and facial expression were coded for amount of attention and for congruent affective response to the examiner's distress on separate 4-point Likert scales. The scales are based on those used in previous studies of empathic response in children with autism from our lab (Sigman et al., 1992; Yirmiya, Sigman, Kasari & Mundy, 1992). The current scales are most similar to those used in a study reporting that children with autism were not differentially aroused by other people's emotional displays (Corona, Dissanayake, Arbelle, Wellington & Sigman, 1998). The attention score was based on the amount of time the child spent looking at the examiner or referencing a parent. The scale is conceptually derived to reflect levels of attention to the distressed examiner, i.e. no interest/attention (<1s looking to examiner or parent, score of 0); brief attention (1-4s looking time, score of 1); clear attention (5-8s looking time, score of 2); and sustained attention/clear interest (>8s looking time, score of 3).

The four-point *affect* scale captures the extent to which the participant's affective state changes relative to baseline in a manner suggestive of concern or distress during the 15s display of distress. Behaviors that trigger higher scores on the affect scale include referencing the parent in a manner that indicates worry or distress; seeking a parent for comfort; and verbalizing concern or the desire to help. Children who were upset or sought a parent for comfort received a code of 3, as did children who made more direct displays of concern for the examiner's well-being, such as going toward the examiner or asking the examiner if s/he was all right. Distinctions among scores of 1, 2, and 3 reflected the number, intensity, and duration of behaviors that signified concern or distress. Children who appeared to be amused by the examiner's display received a score of 0, as did those who ignored the examiner and those who attended, but displayed no affective response.

Reliability

Six research assistants, blind to diagnostic outcomes, achieved reliability on the coding scales. Forty-four videotapes of the distress task (25% of participants and all four time points) were coded for reliability. Coders' ratings on both scales were analyzed using a two-way mixed model intra-class correlation based on absolute agreement between coders. This method of analysis is used for cases in which each item is rated by multiple judges who are the only judges of interest. The judges are considered a fixed effect, while the target ratings are a random effect. The Single Measure Reliability for 6 research assistants and the third author was .92 for the attention scale and .81 for the affect scale.

Analytic Approach

To test our first hypothesis concerning group differences in distress-response behavior across the second and third years of life, longitudinal data were evaluated using ordinal logistic random effects models (SAS PROC GLIMMIX). This analytic approach was employed because the underlying Likert scales, although ordered, may not represent equal differences in distress response between successive values and are therefore more appropriately treated as categorical. Ordinal logistic regression evaluates the cumulative

probability of the ordered levels of the outcome variables, one at a time, as a function of the covariates. The corresponding regression equations are assumed to be parallel on the logit scale and are estimated simultaneously. Thus, a common coefficient is assumed for each covariate across all the equations although the intercepts are allowed to differ.

Attention and affective response were evaluated as separate outcomes. Our primary models included main effects for diagnostic group and age, a group-by-age interaction, and a random intercept to account for the correlation of measurements within subjects over time. Secondary models were run including gender, verbal mental age, household income, and maternal education as covariates. This step was taken to address the possibility that observed differences in distress-response behaviors were driven by factors other than diagnostic status.

Three regression equations are required to compare the probability of all possible contrast options for each construct. The contrasts are (a) score of 0 vs. scores of 1, 2, or 3; (b) scores of 0 or 1 vs. scores of 2 or 3; and (c) scores of 0, 1, or 2 vs. a score of 3. Cumulative logistic regression modeling allowed us to analyze all three contrasts simultaneously. The signs and magnitudes of the covariate coefficients indicate the direction and extent of the impact of the covariates on the probability of higher levels of attention or affect. A positive coefficient for chronological age means that the probability of achieving a higher score on the attention or affect scales increases over time. Where the primary models indicated significant group differences, we performed post-hoc cumulative logistic regressions for each time point in order to specify the age(s) at which attention or affective response differed and between which groups, in accordance with our second hypothesis.

Our third hypothesis concerned the prediction of diagnostic outcome based on early clinical measurements. We wished to determine what combination of factors best discriminated infants who would later be diagnosed with ASD from those who appeared to be developing typically, and in particular whether an individual's distress-response scores were predictive of progression to ASD over and above the risk associated with heritability. To test this we used stepwise logistic regression models with 36-month ASD diagnostic status as the outcome, and verbal mental age, attention and affective response as predictors, restricting the analyses to the high-risk participants. Initial models used only 12- and 18-month measurements in order to determine the earliest age at which these behaviors improved the prediction of diagnostic outcome. Next, we added later time points to determine the extent to which using only early measurement caused a loss of predictive accuracy. Cross-validated error rates and standard information fit criteria were considered in the evaluation of models. The methods used to identify the best predictors of diagnosis were also employed to determine whether the relationship between distress response and diagnosis was robust to the inclusion of a measure of infants' responsiveness to the sound of their own name in the models.

Results

Attention and affective response scores were compared among 3 groups, across 4 time points. The low-risk control group (LRC; $n = 55$) was made up of infants with no family history of autism and who did not meet criteria for ASD at 36 months. The high-risk non-ASD group was made up of autism siblings who did not meet criteria for ASD at 36 months ($n=88$). Children in the ASD group met criteria for autistic disorder, Asperger's syndrome, or PDD-NOS at 36 months ($n=14$). Mean ADOS scores for the three comparison groups are presented in electronic appendix Table E-2.

484 administrations of the response-to-distress measure were coded. Details regarding attrition and disqualified administrations of the distress task for each comparison group are presented in electronic appendix Table E-1. Forty-one administrations could not be coded because the child's face was occluded on the video recording or the caregiver spoke during task administration. Participants who provided data at all four time points did not differ from participants who missed visits or those who withdrew from the study in terms of group classification, ADOS scores, verbal, or non-verbal mental age.

Raw scores for attention and affective response to distress for the three groups at all four time points are represented in Figures 1 and 2. In general, infants later diagnosed with ASD had low scores on both scales of responsiveness at the 12-month time point and the scores increased little over the period studied. Children who did not meet criteria for ASD had variable scores at 12 months and high scores on both scales at the 24 and 36 months visits.

Group comparisons across time points

Our first hypothesis was that infants diagnosed with ASD at 36 months were less likely to achieve high levels of attention and affective response to another person's distress. We began by testing all four time points simultaneously, using three cumulative logistic regression models to predict higher levels of attention and affective response to distress from 12 to 36 months of age. Predictors in Model 1 were chronological age (CA), diagnostic group, and an age-by-group interaction term. Model 2 included CA and diagnostic group, but no interaction term. Model 3 included CA, diagnostic group, concurrent verbal mental age (VMA), household income, and mother's educational attainment. The small ASD sample limits statistical power to test moderating effects. Each of the three models was run twice, once with attention to distress as outcome and a second time with affective response as outcome.

Results of the longitudinal analyses are summarized in Table 2. In support of our first hypothesis, group was a significant predictor of attention and affect in all three models. CA and VMA were highly correlated in all three groups. CA was not significantly related to affective response when VMA was included in the model. Gender was not related to either distress response variable. Group was a significant predictor of both distress-response variables, even when VMA, household income, and mothers' educational attainment were included in the models. Model 3 indicates that measures of socio-economic status were significantly related to affective response, but not to attention.

Group effects were attributable to differences between the ASD group and both groups of children not diagnosed with ASD. The high-risk non-ASD group and the LRC group did not differ on either variable at any time point, with one exception: the high-risk non-ASD group demonstrated more affective response than the LRC group at 12 months. This difference appears to explain the significant age-by-group interaction in the prediction of affective response to distress across the four time points. In an effort to interpret the interaction, we tested the model without data from the 12-month time point and once again with the 12-month data but combining the two non-ASD groups, analyzing them as a single group. The interaction effect was not evident in either of these test cases. CA was a significant predictor of the attainment of high levels of attention and affect and had a positive slope in the models that did not include VMA. The loss of a group-by-CA interaction indicates that, after 12 months, the relationship between CA and affective response did not differ between groups. Significant relationships between CA, group, and the two distress-response response variable justified testing group differences at each time point.

Group comparisons at each time point

Results of the analyses for each time point are summarized in Table 3. Details of comparisons among the three groups, including odds ratios, are presented in electronic appendix Table E-3. In further support of hypothesis number 1, the ASD group demonstrated the lowest levels of attention and affective response to another person's distress by 12 months and at all subsequent time points. At all time points except for 12 months, the high- and low-risk groups that did not meet criteria for ASD did not differ from each other. At 12 months, the ASD group showed the least affective response and the high-risk non-ASD group showed the highest level of response. Contrary to our second hypothesis, we did not find evidence that non-autistic siblings of children with autism are less responsive to another person's distress than low-risk controls.

We attempted to rule out several possible mediators of the effects reported above. Gender was not related to attention or affective response at any time point. Relationships between classification group and distress-response variables were robust to the inclusion of VMA, household income, and maternal education in the regression models. Finally, we re-ran the cross-sectional analyses excluding the participants who enrolled in the study at 18 months. This step was taken because autism-related impairment is evident by 18 months of age and we sought to determine whether late-enrollers showed more symptoms of autism than early-enrollers and therefore had a disproportionate influence on observed group differences. All effects reported above held when we limited the sample to infants enrolled in the study by 12 months.

Ranking of predictors

Cumulative logistic regression models indicate differences between groups on both distress scales, even after adjusting for verbal skills and SES. To test our third hypothesis about the usefulness of the distress-response measure to ascertain risk for autism over and above that associated with heritability, we ran a sequence of stepwise logistic regression analyses with diagnostic status at 36 months as the response to determine which variables, especially at early time points, best predicted diagnostic outcome. Because language and distress-response variables were strongly related to outcome at all time points (all p -values $< .01$), we sought to compare the variables' relative usefulness in predicting ASD outcomes.

In initial multivariable models using only 12 and 18-month data, 12-month VMA and the two distress scales at 18 months were the best predictors of diagnostic outcomes. The best of these models was identified using a backward stepwise procedure, which selected affective response at 18 months and VMA at 12 months (see electronic appendix Table E-4). In this sample, 14.1% of high-risk participants were diagnosed with ASD. Thus the optimal predictive error rate obtainable without using the language and distress measures is 14.1%, and all of the error is attributable to misclassifying affected infants. The subsequent logistic regression models incorporating language and distress provided predicted probabilities of an eventual ASD diagnosis. The error rates for these models depend on the threshold used to predict whether a child will be diagnosed with ASD. For rare but important outcomes, this threshold is usually set between the sample percentage of the rare event (to achieve the right ratio of outcomes) and 50% (where a subject is more likely than not to have the specified outcome). Here we selected a 30-40% probability threshold for ASD diagnosis to balance the competing goals of minimizing the error rate and maximizing the number of ASD subjects correctly identified. The best-fitting model (12-month VMA and 18-month affect) yields a cross-validated error rate of 8.5-9.9%. Most importantly, the number of false negatives is on average only 2 out of 14. Classification accuracy for the ASD group can be improved further by selecting a lower probability threshold. We fit additional stepwise models incorporating the 24- and 36-month data. The overall prediction error rates were not

significantly better than those using the 12-18 month data, suggesting that key information about diagnostic outcome is available early in development. However these results must be interpreted with some caution since the number of subjects with available data at all time points for these latter models was substantially diminished.

Relations with overall social responsiveness

Given evidence that infants with ASD are less responsive to another person's distress than high- and low-risk infants not on the autism spectrum, we sought to determine whether distress response was merely a marker of attenuated social responsiveness that is well-documented in 12-month-old infants with autism (Ozonoff et al., 2010; Rozga et al., 2010; Yoder, Stone, Walden & Malesa, 2009). Infants who oriented to the sound of their own name on at least one of the first two clear presses by the examiner ($n = 96$) were compared to those who showed any impairment in responding (non-zero scores; $n = 84$). We ran a logistic regression with response to name and each distress-response variable at 18 months as predictors and with diagnostic group as outcome. The relationship between diagnosis and each distress-response variable is robust to the inclusion of response to name in models (attention: $p = 0.0016$; affective response: $p = 0.0145$). Response to name added marginally to the prediction of diagnostic outcome when analyzed with attention to distress ($p = 0.0642$), and significantly when analyzed with affective response ($p = 0.0341$).

We ran stepwise logistic regression analyses to determine the relative value of predictors as described in the preceding subsection. Response to name was not significantly related to diagnostic outcome in any of the models that also included VMA. Response to name did not improve the prediction of outcome above the best-fitting model described above (affective response to distress at 18 months and VMA at 12 months). While response to name may account for a distinct portion of the variance in diagnostic outcome from the individual distress-response measures, its contribution can be completely accounted for by mental age. Supporting our fourth hypothesis, the atypical distress response that characterizes the ASD group is not mediated by general social responsiveness.

Discussion

This study sought to determine whether response to another person's distress differentiates infants subsequently diagnosed with autism from high- and low-risk infants who were not on the autism spectrum at 36 months of age. Infants subsequently diagnosed with ASD paid less attention and showed less affective response to another person's distress at every time point from 12 to 36 months and across time points. Low levels of responsiveness to another person's distress at 12 and 18 months are indicative of elevated risk for ASD diagnosis at 36 months. Verbal abilities were concurrently related to infants' and toddlers' responses to distress and to diagnostic outcome, but groups differed in their response to distress at all time points even after controlling for verbal skills.

Normatively, negative emotions are salient almost from birth. As early as the first day after birth, infants cry when they hear another infant crying (Martin & Clark, 1982). From three months, infants are negatively aroused by a caregiver's simulation of depressive behavior, operationalized as withdrawal from social interaction accompanied by a flattening of affect (Cohn & Tronick, 1983). At ten months, infants consistently orient toward another person's distress (Zahn-Waxler & Radke-Yarrow, 1982) and, at 12 months, they are more responsive to maternal displays of negative emotional expression than to pleasant or ambiguous displays of emotion (Carver & Vaccaro, 2007; Hornik, Risenhoover & Gunnar, 1987).

Our observation that infants subsequently diagnosed with ASD pay less attention and demonstrate lower levels of affective response to other people's negative emotions suggests

an aspect of social interaction that is disrupted by autism at a critical developmental stage. Inability to decipher emotional messages or indifference to them is likely to interfere with social learning, social interaction, and the formation of close relationships. We observed that distress response was related to language skills at all time points. These possible consequences of atypical response to negative emotion are all core features of autism (American Psychiatric Association, 2000).

Among the measures examined at 12 and 18 months, we found that language age at 12 months and affective response at 18 months were the best predictors of diagnostic outcome among infant siblings of children with autism. Distress response significantly improves the identification of infants at highest risk of being diagnosed with ASD, over and above language skill, general social responsiveness, and the risk associated with heritability.

Attenuated responsiveness to distress in infants with autism suggests difficulty identifying with others. This is consistent with the claim that dysfunction of the mirror neuron system (MNS) is implicated in autism (Dapretto et al., 2006; Oberman, et al., 2005). Normatively, activation of the MNS is similar between model and observer in emotionally expressive behavior as well as in goal-directed motor activity (Carr, Iacoboni, Dubeau, Mazziota & Lenzi, 2003), suggesting that observed behaviors are encoded as if experienced directly. Several studies with children and adults have implicated the MNS in empathic processes (Carr et al., 2003; Decety, Michalska, & Akitsuki, 2008; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008). The MNS helps engender interpersonal understanding and has been associated with imitation (Iacoboni, 2005) and language (Arbib, 2009). These findings and theories are consistent with our observation of shared variance between language skills and empathic processes. Taken together, they suggest that early intervention targeting attentiveness to other people's emotional signals may improve interpersonal understanding as well as the development of language skills.

We expected to see atypical distress response in high-risk participants who did not meet criteria for ASD at 36 months (Bailey et al., 1998). Overall, the high-risk non-ASD group did not differ significantly from low-risk controls in terms of their attention and affective response to distress. The one difference we observed between these two groups was not in the expected direction: the high-risk non-ASD group had higher affective response scores at 12 months than the low-risk controls, though this difference disappeared after 12 months. This finding may result from combining infants' concerned and distressed responses to the examiner's distress in a single affective-response category. The stronger affective response among high-risk 12-month-olds may indicate the contagion of the examiner's distress rather than concern for the examiner's well-being (Hatfield, Cacciopo & Rapson, 1994). Accordingly, a stronger affective response in the high-risk group may not reflect further developmental progress, especially at 12 months of age. Our observation of minimal affective response of any kind in the ASD group suggests that the single affective-response variable is an effective discriminator with respect to later ASD diagnosis. Future research addressing distinctive patterns of empathic development in infants who are not subsequently diagnosed with ASD may do well to consider concern and distress separately.

Limitations of this study include a small group of infants with ASD and a substantial amount of attrition in the high- and low-risk non-ASD groups between 24 and 36 months. If parents withdrew their toddlers from the study because they were no longer concerned about the risk of autism or developmental delays, we would expect to observe a weakening of differences between groups. Fortunately, no such effect was observed. We compared children who provided data at four time points to those who missed visits and those who withdrew from the study. We found no differences in diagnostic outcome, verbal skills, non-verbal skills, or autism symptoms between these groups.

Future research should track infants who are under-responsive to another person's distress and who are not diagnosed with ASD at 36 months. These children may be at risk for diagnosis with atypical autism after 36 months or for other clinical conditions associated with low levels of empathy, such as conduct disorder and psychopathy (*e.g.*, Keltner & Kring, 1998). Infants' responses to positive changes in another person's emotional state and variability in infants' emotional expressiveness should also be explored. Treatment studies should explore the extent to which responsiveness to the distress of others can be improved and whether such improvement has a secondary impact on the quality of social interactions, peer relationships, and social learning for children on the autism spectrum.

Key Points

- Response to distress is impaired in infants, preschoolers, and adolescents with autism spectrum disorders.
- Responsiveness to other people's distress is implicated in the quality of interactions, relationships, and social learning.
- Distress response has not been studied in infants at risk for autism prior to 18 months of age.
- This prospective longitudinal study provides evidence that infants subsequently diagnosed with autism spectrum disorder are less attentive and emotionally responsive to other people's distress as early as 12 months and the impairment is continuous across the second and third years.
- Distress response is a useful early warning sign of autism spectrum disorder and a worthwhile target of early intervention for infants at risk for autism.

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References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: 2000.
- Arbib MA. Evolving the language-ready brain and the social mechanisms that support language. *J Commun Disord.* 2009; 42(4):263–71. [PubMed: 19409574]
- Bacon AL, Fein D, Morris R, Waterhouse L, Allen D. The responses of autistic children to the distress of others. *J Autism Dev Disord.* 1998; 28(2):129–142. [PubMed: 9586775]
- Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychol Med.* 1995; 25(1):63. [PubMed: 7792363]
- Bailey A, Palferman S, Heavey L, Le Couteur A. Autism: The phenotype in relatives. *J Autism Dev Disord.* 1998; 28(5):369–392. [PubMed: 9813774]
- Baranek GT. Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. *J Autism Dev Disord.* 1999; 29(3):213–24. [PubMed: 10425584]

- Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences*. 2003; 100(9):5497–5502.
- Carver LJ, Vaccaro BG. 12-month-old infants allocate increased neural resources to stimuli associated with negative adult emotion. *Developmental Psychology*. 2007; 43(1):54–69. [PubMed: 17201508]
- Charman T, Swettenham J, Baron-Cohen S, Cox A, Baird G, Drew A. Infants with autism: An investigation of empathy, pretend play, joint attention, and imitation. *Dev Psychol*. 1997; 33:781–789. [PubMed: 9300211]
- Cohn JF, Tronick EZ. Three-Month-Old infants' reaction to simulated maternal depression. *Child Development*. 1983; 54(1):185–193. [PubMed: 6831986]
- Corona R, Dissanayke C, Arbelle S, Wellington P, Sigman M. Is affect aversive to young children with autism? Behavioral and cardiac responses to experimenter distress. *Child Development*. 1998; 60(6):1494–1502. [PubMed: 9914635]
- Dapretto M, Davies MS, Pfeifer JH, Scott AA, Sigman M, Bookheimer SY, et al. Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci*. 2005; 9(1):28–30. [PubMed: 16327784]
- Dawson G, Toth K, Abbott R, Osterling J, Munson J, Estes A, et al. Early social attention impairments in autism: Social orienting, joint attention, and attention to distress. *Dev Psychol*. 2004; 40(2): 271–282. [PubMed: 14979766]
- Decety J, Michalska KJ, Akitsuki Y. Who caused the pain? An fmri investigation of empathy and intentionality in children. *Neuropsychologia*. 2008; 46(11):2607–2614. [PubMed: 18573266]
- Hatfield, E.; Cacioppo, JT.; Rapson, RL. Emotional contagion. New York: Cambridge University Press; 1994.
- Hoppes K, Harris SL. Perceptions of child attachment and maternal gratification in mothers of children with autism and down syndrome. *Journal of Clinical Child Psychology*. 1990; 19(4):365–370.
- Hornik R, Risenhoover N, Gunnar M. The effects of maternal positive, neutral, and negative affective communications on infant responses to new toys. *Child Dev*. 1987:937–944.
- Iacoboni M. Neural mechanisms of imitation. *Curr Opin Neurobiol*. 2005; 15(6):632–7. [PubMed: 16271461]
- Ibanez LV, Messinger DS, Newell L, Lambert B, Sheskin M. Visual disengagement in the infant siblings of children with an autism spectrum disorder (ASD). *Autism*. 2008; 12(5):473–85. [PubMed: 18805943]
- Keltner D, Kring AM. Emotion, social function, and psychopathology. *Review of General Psychology*. 1998; 2:320–342.
- Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord*. 2000; 30(3):205–223. [PubMed: 11055457]
- Lord C, Rutter M, Couteur A. Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994; 24(5):659–685. [PubMed: 7814313]
- Martin GB, Clark RD. Distress crying in neonates: Species and peer specificity. *Dev Psychol*. 1982; 18(1):3–9.
- Merin N, Young GS, Ozonoff S, Rogers SJ. Visual fixation patterns during reciprocal social interaction distinguish a subgroup of 6-month-old infants at-risk for autism from comparison infants. *J Autism Dev Disord*. 2007; 37(1):108–21. [PubMed: 17191096]
- Mullen, EM. Mullen scales of early learning manual. Circle Pines, MN: American Guidance Service; 1995.
- Nadig AS, Ozonoff S, Young GS, Rozga A, Sigman M, Rogers SJ. A prospective study of response to name in infants at risk for autism. *Arch Pediatr Adolesc Med*. 2007; 161(4):378–83. [PubMed: 17404135]
- Oberman LM, Hubbard EM, McCleery JP, Altschuler EL, Ramachandran VS, Pineda JA. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Brain Res Cogn Brain Res*. 2005; 24(2):190–8. [PubMed: 15993757]

- Osterling J, Dawson G. Early recognition of children with autism: A study of first birthday home videotapes. *J Autism Dev Disord.* 1994; 24(3):247–57. [PubMed: 8050980]
- Ozonoff S, Iosif AM, Baguio F, Cook IC, Hill MM, Hutman T, et al. A Prospective Study of the Emergence of Early Behavioral Signs of Autism. *J Am Academy of Child and Adolescent Psychiatry.* 2010; 49(3):256–266.
- Pfeifer JH, Iacoboni M, Mazziotta JC, Dapretto M. Mirroring others' emotions relates to empathy and interpersonal competence in children. *Neuroimage.* 2008; 39(4):2076–2085. [PubMed: 18082427]
- Rozga A, Young GS, Hutman T, Rogers SJ, Ozonoff S, Sigman M. Identifying Autism and the Broader Autism Phenotype in the First Year of Life: Contribution of Measures of Mother-Infant Interaction and Nonverbal Communication. 2010 Article submitted for publication.
- Sigman M, Kasari C, Kwon JH, Yirmiya N. Responses to the negative emotions of others by autistic, mentally retarded, and normal children. *Child Dev.* 1992:796–807. [PubMed: 1505241]
- Steffenburg S, Gillberg C, Hellgren L, Andersson L, Gillberg IC, Jakobsson G, et al. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry.* 1989; 30(3):405–16. [PubMed: 2745591]
- Yirmiya N, Gamliel I, Pilowsky T, Feldman R, Baron-Cohen S, Sigman M. The development of siblings of children with autism at 4 and 14 months: Social engagement, communication, and cognition. *J Child Psychol Psychiatry.* 2006; 47(5):511–23. [PubMed: 16671934]
- Yirmiya N, Sigman M, Kasari C, Mundy P. Empathy and cognition in high-functioning children with autism. *Child Dev.* 1992; 63(1):150–160. [PubMed: 1551323]
- Young GS, Merin N, Rogers SJ, Ozonoff S. Gaze behavior and affect at 6 months: Predicting clinical outcomes and language development in typically developing infants and infants at risk for autism. *Dev Sci.* 2009; 12(5):798–814. [PubMed: 19702771]
- Zahn-Waxler, C.; Radke-Yarrow, M. The development of altruism: Alternative research strategies. In: Eisenberg, N., editor. *The Development of Prosocial Behavior.* New York: Academic Press; 1982. p. 109-137.
- Zahn-Waxler C, Radke-Yarrow M, Wagner E, Chapman M. Development of concern for others. *Dev Psychol.* 1992; 28(1):126–136.
- 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):143–52. [PubMed: 15749241]

Abbreviations

ADI-R	Autism Diagnostic Interview – Revised
ADOS-G	Autism Diagnostic Observation Schedule - Generic
ASD	autism spectrum disorder
LRC	low-risk controls
MNS	mirror neuron system
MSEL	Mullen Scales of Early Learning
PDD-NOS	pervasive developmental disorder – not otherwise specified
VMA	verbal mental age

Figure 1.
Proportion of attention scores by group and time point

Figure 2.
Proportion of affective response scores by group and time point

Table 1
Sample Characteristics

	ASD	High-Risk Non-ASD	Control Group	Groups Differ
Gender (% Male)	64%	50%	56%	
Race (% Caucasian)	50%	56%	53%	
Maternal Education				+
High school/some college	33%	19%	10%	
College degree	67%	38%	35%	
Graduate school	0%	41%	55%	
Family Income				+
Less than \$50K	33%	16%	13%	
\$50K to \$100K	25%	29%	18%	
More than \$100K	42%	51%	69%	
12-month time point	n = 12	n = 74	n = 52	
Chronological age	12.2 (.4)	12.2 (.5)	12.2 (.3)	
Verbal mental age	9.3 (1.1)	12.2 (1.8)	11.7 (1.9)	*
Non-verbal mental age	13.6 (1.3)	14.8 (1.4)	14.7 (1.5)	✦
18-month time point	n = 14	n = 86	n = 47	
Chronological age	18.2 (.4)	18.2 (.5)	18.6 (2.5)	
Verbal mental age	13.1 (3.7)	18.5 (3.7)	18.4 (3.6)	*
Non-verbal mental age	17.6 (2.0)	19.8 (2.7)	19.7 (2.7)	✦
24-month time point	n = 14	n = 72	n = 52	
Chronological age	24.5 (.7)	24.3 (.8)	24.4 (.5)	
Verbal mental age	19.6 (6.6)	26.3 (5.0)	26.3 (4.5)	*
Non-verbal mental age	23.2 (2.2)	25.8 (3.2)	25.8 (3.4)	✦
36-month time point	n = 14	n = 60	n = 35	
Chronological age	36.0 (.3)	36.4 (1.0)	36.13 (.6)	
Verbal mental age	30.4 (9.5)	38.5 (5.6)	38.5 (5.1)	*
Non-verbal mental age	33.7 (8.0)	41.3 (5.2)	40.8 (4.7)	*

Note: Assessment-related data are presented as Mean (Standard Deviation). Chronological and mental-age data are reported in months. Mental-age data were obtained using the MSEL. Chi-squared analyses and t-tests indicate that the ASD group differs from both other groups as represented by the following symbols: ✦ $p < 0.05$, + $p < 0.01$, * $p < 0.001$.

Table 2
Longitudinal Models Predicting Attention and Affect

Model	Predictors in Model	Attention <i>p</i>	Affect <i>p</i>
1	Chronological Age	0.0221	<0.0001
	Group ^a	0.0012	0.0011
	CA*Group	0.6528	0.0246
2	Chronological Age	0.0002	<0.0001
	Group ^a (no interaction)	<0.0001	<0.0001
3	Chronological Age	0.0126	0.9822
	Group ^a	<0.0001	<0.0001
	Verbal Mental Age	<0.0001	0.0045
	Household Income	0.5873	0.0267
	Mother's Education	0.5972	0.0218
	Gender	0.9724	0.7288

^aGroup 1 was less likely to achieve higher levels of attention and affect than groups 2 and 3. Groups 2 and 3 did not differ.

Table 3
Cross-Sectional Models Predicting Attention and Affective Response

Time Point	Response Variable	Model 1	Model 2*			
		Group alone	Group	Verbal Mental Age	Income	Mother's Education
12 months	Attention	0.0012	.0617	.0220	.6211	.7711
	Affect	0.0004	.0337	.0040	.0983	.1892
18 months	Attention	<0.0001	.0005	.2220	.0690	.1433
	Affect	0.0015	.0057	.7414	.0036	.0224
24 months	Attention	<0.0001	.0002	.0127	.1792	.0357
	Affect	<0.0001	.0035	.0503	.4819	.7267
36 months	Attention	<0.0001	.0207	.0002	.0598	.0157
	Affect	0.0004	.0249	.5622	.8607	.0669

Results of between-group comparisons are listed in Table E-2, in an electronic appendix to this article. The high-risk and low-risk non-ASD groups did not differ on either variable at any time point, except that the high-risk group had higher affect scores at 12 months. Otherwise, group effects are driven by differences between the ASD group and both non-ASD groups.

* Gender was included as a covariate as well as verbal mental age, income, and mother's education, but was not significant in any of the analyses and has been left out of the table.