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Recommended Citation

Marrus, Natasha; Grant, Julia D; Harris-Olenak, Brooke; Albright, Jordan; Bolster, Drew; Haber, Jon Randolph; Jacob, Theodore; Zhang, Yi; Heath, Andrew C; Agrawal, Arpana; Constantino, John N; Elison, Jed T; and Glowinski, Anne L, "Genetic architecture of reciprocal social behavior in toddlers: Implications for heterogeneity in the early origins of autism spectrum disorder." Development and Psychopathology. 32, 4. 1190 - 1205. (2020).
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Development and Psychopathology (2020), **32**, 1190–1205
doi:10.1017/S0954579420000723

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Special Issue Article

Genetic architecture of reciprocal social behavior in toddlers: Implications for heterogeneity in the early origins of autism spectrum disorder

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Abstract

Impairment in reciprocal social behavior (RSB), an essential component of early social competence, clinically defines autism spectrum disorder (ASD). However, the behavioral and genetic architecture of RSB in toddlerhood, when ASD first emerges, has not been fully characterized. We analyzed data from a quantitative video-referenced rating of RSB (vrRSB) in two toddler samples: a community-based volunteer research registry ($n = 1{,}563$) and an ethnically diverse, longitudinal twin sample ascertained from two state birth registries ($n = 714$). Variation in RSB was continuously distributed, temporally stable, significantly associated with ASD risk at age 18 months, and only modestly explained by sociodemographic and medical factors ($r^2 = 9.4\%$). Five latent RSB factors were identified and corresponded to aspects of social communication or restricted repetitive behaviors, the two core ASD symptom domains. Quantitative genetic analyses indicated substantial heritability for all factors at age 24 months ($h^2 \geq .61$). Genetic influences strongly overlapped across all factors, with a social motivation factor showing evidence of newly-emerging genetic influences between the ages of 18 and 24 months. RSB constitutes a heritable, trait-like competency whose factorial and genetic structure is generalized across diverse populations, demonstrating its role as an early, enduring dimension of inherited variation in human social behavior. Substantially overlapping RSB domains, measurable when core ASD features arise and consolidate, may serve as markers of specific pathways to autism and anchors to inform determinants of autism's heterogeneity.

Keywords: quantitative autistic traits, reciprocal social behavior, toddlers, twins, vrRSB

(Received 2 December 2019; revised 15 April 2020; accepted 19 April 2020)

Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental syndrome whose core symptoms of social communication deficits and restricted, repetitive interests and behaviors (American Psychiatric Association, 2013) arise during toddlerhood and generally persist throughout the lifespan. The long-term benefit of early intervention has prompted strong interest in early identification and characterization of the nature and timing of developmental differences associated with ASD. Prospective studies of infants at elevated familial risk for ASD have shown that the autistic syndrome, which is clinically ascertainable around age 24 months, is preceded by a heterogeneous constellation of delays, including not only forerunners of core symptoms, but also gross and fine motor dysfunction, for example, which appear nonspecific for ASD (Estes et al., 2015; Landa, Gross, Stuart, & Bauman, 2012; Zwaigenbaum et al., 2005). An important question for disentangling the origins of ASD is to ultimately determine how ASD-specific features interact with nonspecific behavioral liabilities to consolidate as the autistic syndrome during toddlerhood.

Dimensional measurement of core autistic features in toddlers, by quantifying variation across the typical–atypical continuum, can identify domains whose developmental deviation confers increased liability for ASD (Cicchetti, 1993, 1984). Reciprocal social behavior (RSB), which entails social awareness, the drive to engage with others, and the ability to appropriately interpret and respond to interpersonal cues, describes an aspect of social competency that in part defines ASD. Variation in RSB has been measured from preschool age onward using the Social Responsiveness Scale (SRS), a well-validated instrument that indexes quantitative autistic traits in terms of deficiencies of RSB. Population-based studies using the SRS have shown that

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Cite this article: Marrus N *et al* (2020). Genetic architecture of reciprocal social behavior in toddlers: Implications for heterogeneity in the early origins of autism spectrum disorder. *Development and Psychopathology* **32**, 1190–1205. https://doi.org/10.1017/S0954579420000723

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variation in RSB (i.e., quantitative autistic traits) is continuously distributed throughout the population; corresponds to ASD diagnosis and severity; is highly heritable, sharing genetic factors with ASD; and exhibits trait-like stability from school age into adulthood (Constantino, Hudziak, & Todd, 2003; Constantino & Todd, 2003; Skuse et al., 2009; Wagner et al., 2019). Characterizing the behavioral and genetic architecture of RSB in toddlerhood could thus elucidate diverse developmental pathways preceding the emergence and stabilization of core autistic symptoms.

A common methodology to evaluate the behavioral architecture of ASD has been factor analysis, often based on ASD symptom measures (e.g., the Autism Diagnostic Interview, Revised) in affected populations (Boomsma et al., 2008; Frazier, Youngstrom, Kubu, Sinclair, & Rezai, 2008) (for a review, see Shuster, Perry, Bebko, & Toplak, 2014). Because ASD develops in the context of both ASD-specific and nonspecific features, rather than originating as its own "natural kind," such characterizations are most relevant to its symptom architecture. By comparison, quantitative measures of early RSB appropriate for the general population are more likely to inform ASD's developmental architecture. One study using the SRS in 4-year-olds supported a unitary-factor structure (Duku et al., 2013), consistent with research in older children and adults (Cen et al., 2017; Constantino et al., 2004; Kamio et al., 2013). Two-factor structures matching core ASD symptom domains of social communication and restricted, repetitive interests and behaviors have also been observed (Frazier et al., 2014; Takei et al., 2014); overall, these findings illustrate that these core diagnostic features aggregate throughout the typical–atypical continuum after the age of reliable ASD diagnosis. In contrast, one population-based study in toddlers, pooling binarized responses for ASD-related items from several developmental screeners, found a three-factor structure consisting of social interaction, communication, and stereotyped and rigid patterns (Beuker et al., 2013). This result suggests that multiple domains may contribute to the emergence of ASD, although the use of categorical scoring likely constrained the ability to resolve unique dimensions.

Recently, our team has developed and validated the video-referenced rating scale of RSB (vrRSB), a downward extension of the SRS for toddlers, which similarly measures quantitative autistic traits across the typical–atypical continuum, as indexed by levels of deficiency in RSB. To address the inherent challenges of acquiring valid and reliable ratings of emerging RSB in toddlers, the vrRSB embeds a video-based scoring anchor, which provides a frame of reference for caregivers rating their child (Marrus et al., 2015, 2018). This measure has shown favorable psychometric properties, including continuously distributed scores in the general population (Marrus et al., 2015, 2018), criterion validity based on correlations with the competency scale on the Infant–Toddler Social and Emotional Assessment (ITSEA) (Lasch, Wolff, & Elison, 2019), and the ability to differentiate toddlers with and without ASD (Marrus et al., 2015; 2018). RSB quantified by the vrRSB also appears heritable (Marrus et al., 2015) and independent from other aspects of psychopathology (Hawks, Marrus, Glowinski, & Constantino, 2019). In preschoolers, we demonstrated that several heritable, nonspecific ASD features such as motor and attentional dysfunction (Pohl et al., 2019) independently explained the variance in RSB; this suggests that the early structure of RSB could affect how both ASD-specific and nonspecific behavioral domains contribute to the emergence of autism. However, the vrRSB's innovative design has not yet been used to delineate RSB's phenotypic and genetic architecture in toddlerhood, the earliest stage at which core autistic features become consolidated.

In this study, we obtained parent-report ratings on the vrRSB in two large toddler samples: a singleton community-based sample recruited through a volunteer research registry ($n = 1{,}563$) and an ethnically diverse, longitudinal twin cohort ascertained through state birth records and assessed at ages of 18 and 24 months ($n = 714$). To evaluate the behavioral structure of toddler RSB, we conducted an exploratory factor analysis (EFA) in the larger sample, followed by a confirmatory factor analysis (CFA) in the twin sample. Through quantitative genetic analyses of twin data, we estimated genetic and environmental influences on subdimensions of RSB in toddlers and the extent of overlap in these influences across factors and across age. Based on existing evidence of multiple factors underlying early ASD-related behavioral variation, as well as the emergence of ASD in the context of diverse developmental delays, we hypothesized the identification of at least two heritable, inter-correlated RSB factors, which would in turn have implications for mechanisms of heterogenous origins of ASD.

Methods

Participants

University of Minnesota Institute of Child Development (ICD) sample. As previously reported (Sifre et al., 2018), between May 2015 and July 2016, parents of toddlers aged 17–26 months were recruited from the University of Minnesota ICD research participant registry. Parents were initially identified from Minnesota birth records and invited to join the registry voluntarily. All parents with children of the appropriate age range were invited to participate during the study period, unless their toddler was already participating in an ongoing ICD study or had participated in the prior six months. There were no exclusion criteria. The data for the present analyses entailed online questionnaires collected at an initial study time point. Following best practices for survey administration (Singer & Ye, 2013), parents were sent an introductory email describing the research 3 days before receiving an online consent form and questionnaires. Of the 4,268 families invited, 2,112 (49.5%) participated and completed at least one questionnaire. Participants were excluded for providing responses suggesting invalid data (e.g., unrealistically fast survey completion), and the source sample for these analyses contained 1,866 children aged 17.0–26.9 months. To more closely match the age of this cohort with both the initial 18-month assessment in the Early Reciprocal Social Behavior Study (ERSB, see below) and the age of the video-scoring anchor used in the vrRSB, data from children aged 17.0–21.9 months were retained for analyses, resulting in a final total of 1,563 participants, comprising 1,549 singletons and seven twin pairs (six pairs of non-Hispanic ethnicity and six pairs of Caucasian race). Participants reflected the racial/ethnic composition of Minneapolis but showed less socioeconomic diversity (Sifre et al., 2018). Study procedures were approved by the University of Minnesota Human Research Protection Program and Institutional Review Board and parents provided informed consent and permission for their child's participation.

ERSB twin sample. Population-based cohorts including families with toddler-aged twins from Missouri and California sites were recruited for a longitudinal study of the development of

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ERSB. Caregiver data were collected through structured telephone interviews and mailed paper questionnaires when the twins were 18, 24, 36, and 48 months of age. To be eligible, the consenting family member had to be over the age of 18 years, the twins' legal guardian and primary caregiver, and fluent in English. Parents provided informed consent and permission for their twins' participation. Study procedures were approved by the Stanford University Institutional Review Board, the State of California's Committee for the Protection of Human Subjects, the Washington University School of Medicine Human Research Protection Office (IRB) and the State of Missouri Department of Health and Senior Services Institutional Review Board.

Recruitment and enrollment for the Missouri site have been described previously (Hawks et al., 2019; Marrus et al., 2015). Briefly, twins were epidemiologically ascertained through the Missouri Family Register, a database of birth records providing a source population of 619 twin pairs born during the calendar years 2011–2013. In total, 330 of these families were contacted by phone to discuss enrollment; of these, 180 enrolled and 156 provided complete vrRSB data at age 18 months and were included in these analyses. As per the birth records, there were no appreciable differences between those enrolled and not enrolled, except for a higher proportion of parents with college and graduate degrees (Hawks et al., 2019).

At the California site, Hispanic families residing in California with living twins born between January 1, 2012 and December 31, 2012 were identified from state birth records ($n = 2{,}873$). Of these, 455 responded to the initial contact by phone requesting a screening interview and 313 were enrolled. Of the enrolled families, 201 families provided vrRSB data at age 18 months and were included in analyses. Compared with the families who did not enroll, the participants showed higher parental education, a lower proportion of government program usage, higher acculturation (given a higher proportion of mothers born in the USA), older parental age and a higher proportion of multi-racial fathers (see supplementary Table S1).

Measures

Demographics. Demographic information was collected at family level (e.g., household income), child level (e.g., sex, race/ethnicity, age), and parent level (e.g., education). Parents in the ICD sample provided this information via an online questionnaire; in the ERSB sample, these variables were collected by telephone interview or from birth records.

RSB measures: vrRSB and Social Responsiveness Scale 2 (SRS-2). The vrRSB is a caregiver/clinician-report rating scale of RSB (Marrus et al., 2015, 2018). It represents a downward extension of the SRS-2 (Constantino & Gruber, 2012), which is a well-validated measure that screens for ASD by indexing levels of quantitative autistic traits as deficits in RSB, assessed through items probing behaviors relevant to core ASD symptom domains. The vrRSB addresses the challenge of valid, reliable quantification of early developmental manifestations of RSB through a video montage providing a "frame of reference" (Bing, Whanger, Davison, & VanHook, 2004; Lievens, De Corte, & Schollaert, 2008). For the first 13 items, caregivers watch a 3-minute video of a typically-developing, 19-month-old child engaging in an interactive play session with an adult and then rate their own child in comparison with the videotaped child. For the remaining 31 standard questionnaire items, parents rate their overall impression of their child's RSB in the past month across settings. The vrRSB was completed online in the ICD cohort or via a paper questionnaire in the ERSB cohort, whose parents accessed the video via a mailed DVD, jump drive copy, or online via a password-protected link. To assess later RSB, the preschool version of the SRS-2 was collected at 36 months of age in the ERSB sample.

Modified Checklist for Autism in Toddlers (M-CHAT) (ERSB twins only). This parent-report measure screens for early signs of ASD in children aged 16–30 months. The M-CHAT includes 23 Yes/No items that measure the attainment of developmental milestones (e.g., interest in other children, pointing, and pretend play). Missing two or more critical items resulted in a failing score, which has been shown to correspond to higher risk of ASD (Robins, Fein, Barton, & Green, 2001).

Perinatal interview (ERSB twins only). Selected perinatal variables were collected via telephone interview using the perinatal module from the parent version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA, Bucholz et al., 1994), which was based on the Diagnostic Interview for Children and Adolescents (DICA), an instrument with good validity and reliability data (Reich, 2000). The DICA includes questions regarding complications during pregnancy, as well as whether the mother smoked, drank alcohol, or took illicit or other addictive drugs while pregnant. The module also covers the period from birth through 18 months and asks about the child's medical history, physical disabilities, and early sleeping and eating patterns. Selected perinatal variables were used to examine maternal–infant risk factors associated with RSB, as well as a composite score of child medical problems.

Goldsmith Child Zygosity Questionnaire (ERSB twins only). Zygosity was assigned using the Goldsmith Child Zygosity Questionnaire (Price et al., 2000), a 27-item parent-report measure querying physical similarity between the twins, including the frequency with which one twin is mistaken for the other by parents, relatives, and strangers. A modified stepped algorithm first reviewed whether item responses suggested differences consistent with dizygosity, followed by evaluating responses consistent with monozygosity. This method corresponds to DNA marker/blood type determinations in 94.8% of cases (Price et al., 2000). In a random subset of families ($n = 24$), agreement between this measure and DNA-based genotypic assignment, using DNA collected by buccal swab, was 100%.

Analyses

Psychometrics. Student *t* tests compared group differences in total score on the vrRSB (RSB total score) based on sex and passing versus failing the M-CHAT. Internal consistency was calculated using Cronbach's α. In the ERSB sample, intraclass correlation coefficients (ICCs) evaluated the test–retest reliability of the vrRSB. To analyze relationships between RSB (the dependent variable) and sociodemographic, prenatal, and child medical risk factors (independent variables), a regression analysis using a generalized linear model was performed (IBM SPSS Statistics for Windows, version 26, IBM Corp., Armonk, NY, USA), which clustered twins by family and adjusted standard errors through a robust sandwich variance estimator, thereby accounting for the non-independence of twins' data. Categorical variables, coded as zero and one, respectively, included sex (male/female), maternal education (no/yes college degree), ethnicity (non-Hispanic/Hispanic), and maternal alcohol and tobacco use

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in pregnancy (no/yes). Income was coded in terciles (low, medium, and high) determined for each site. Maternal and paternal age, both associated with higher offspring ASD risk (e.g., Sandin et al., 2016), were continuous variables. To account for the correlations between maternal and paternal age ($r = .74$, $p < .001$ in the ERSB sample), we analyzed standardized residuals for maternal age regressed on paternal age and paternal age regressed on maternal age.

Exploratory factor analysis (EFA) (ICD sample). An EFA of vrRSB data from the ICD sample was performed in MPlus Version 7.4 (Muthén & Muthén, 2012) using a weighted least-squares mean-variance adjusted (WLSMV) estimator, which allowed analysis of tetrachoric correlations from ordinal vrRSB item-level data. Items were rated on a scale between zero and three. For video-referenced items, these values corresponded to the options "not at all," "somewhat but less than the child in the video," "about the same as the child in the video," and "more than the child in the video", respectively. For non-video-referenced items, the options were "not true," "sometimes true," "often true," and "almost always true." Because the vrRSB indexes deficiency in RSB, in forward-scored items, higher values indicated greater RSB deficits. All 44 items were included, of which 21 were reverse-coded. The ICD sample was used for the EFA given its larger size, which enhanced the power to resolve latent factors, as well as some concern for biased estimation of factors in the ERSB sample due to non-independence of twin data and an increased likelihood of developmental delays in twins (Sutcliffe & Derom, 2006). An oblique (quartimin) rotation was used as it favors more parsimonious factor structures (Jennrich & Sampson, 1966) while permitting correlated factors, which have previously been observed for quantitative autistic traits (Frazier et al., 2014). Solutions with 1–12 factors were estimated. Preliminary EFAs displayed several common factors in males and females (i.e., factors that exhibited face validity for the same latent constructs and shared the majority of items across sexes). So, to improve the power to detect stable factors, both sexes were analyzed together. Candidate factor solutions were first evaluated based on examining inflection(s) in the scree plot, which indicate when additional factors make increasingly minimal contributions to explained variance. Potential solutions were then compared in terms of fit indices, including the comparative fit index (CFI), the Tucker–Lewis index (TLI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Following common guidelines, thresholds for a good fit were CFI and TLI $\geq .95$, RMSEA $\leq .05$ and SRMR $\leq .08$ (Hu & Bentler, 1999). We next evaluated item loadings on each factor, using a cut-off of 0.3 as a marker of substantive contributions to a given factor's variance. Factors were then reviewed for interpretability and, for completeness, we explored all solutions whose factors had eigenvalues ≥ 1, as per the Kaiser criterion of factor retention. In choosing a final hypothesized factor solution, we prioritized parsimony when considering similarly interpretable solutions.

Confirmatory factor analysis (CFA) (ERSB twin sample). We performed separate CFAs for 18- and 24-month vrRSB scores on all twin data in MPlus using the WLSMV estimator. At age 18 months, scores of two or three on item 20 ("seems odd or weird")—indicative of impairment in this aspect of RSB—occurred relatively infrequently ($n = 3$ out of 636 participants), consistent with a primarily typically-developing profile in the context of a general population sample. To ensure model convergence, reduce undue influence of outlier values, and generate stable model estimates while retaining participant data, item 20 scores for these three cases were "winsorized" to a high score of one. Model fit indices included the CFI, TLI, and RMSEA.

Quantitative genetic analyses (ERSB twin sample). Quantitative genetic analyses (Neale & Maes, 2004) estimated relative contributions of genetic and environmental influences to each of the derived factors for RSB and their covariance. These twin models (i.e., *ACE* models) quantify the extent to which variance in and covariance between phenotypes of interest are attributable to additive genetic factors (*A*), shared environmental factors (*C*, environmental influences that make twins more similar to each other), and nonshared environmental factors (*E*, environmental influences not shared by twins, as well as error variance) (Neale & Maes, 2004). In cases where correlations within dizygotic (DZ) twin pairs (who share 50% of their segregating loci identical by descent) were less than half of the corresponding correlations for monozygotic (MZ) twin pairs (who share, on average, 100% of their segregating loci), nonadditive genetic factors (*D*) were modeled in place of *C*, as classical twin models are under-identified for the joint estimation of *C* and *D*.

Quintavariate Cholesky (lower triangular) decompositions were used to assess the degree of genetic and environmental influence on each factor, as well as the overlap across the five factors, separately, at ages 18 and 24 months. A full Cholesky model allows for influences on the first variable to also load onto all subsequent variables, and for novel influences on each subsequent variable to load onto all remaining variables. Genetic and environmental correlations from such models are expected to be invariant to the relative ordering of the variables. The significance of individual genetic and environmental contributions was tested by constraining the relevant parameter to zero, or equating it to another parameter, depending on the goal of the analysis, and comparing the fit of the consequent more parsimonious submodel to the preceding model and calculating the difference in −2 times the log-likelihood of the two models, which is distributed as a χ^2 test for the given degrees of freedom. Due to the computational complexity of combining the five-factor solutions across both time points in a single model for the given sample size, we examined the genetic and environmental overlap across ages 18 and 24 months individually for each of the five factors through separate bivariate Cholesky models. Thus, a Cholesky model, for instance of factor 1 at ages 18 and 24 months, revealed stable versus developmentally salient genetic and environmental influences on that factor across the two time points. Models were fitted using the statistical package Mx (Neale, 2000) and using full-information maximum-likelihood estimation with raw data. All models included the site (Missouri or California) and premature birth (<32 weeks and 33–35 weeks gestation) as covariates in the means model. Given limited power to detect sex differences in the relative contribution of genetic and environmental influences (due to the small sample size), the proportions of variance attributable to each component were equated for boys and girl in all models, with mean scores for males and females estimated separately.

Results

Psychometrics of vrRSB

Regarding the participants' sociodemographic characteristics (Table 1), the ICD sample, in comparison with the ERSB sample, showed a slightly older toddler age of assessment ($t(2,278) = 22.20$,

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Table 1. Participant characteristics of the ICD and ERSB samples

	ICD (n = 1,563)	ERSB (n = 714)		
		Missouri site	California site	Combined
Initial assessment age (months)*[a]	19.3 (1.1)	17.9 (0.7)	18.7 (1.0)	18.2 (0.9)
Mean gestational age (weeks)*	39.4 (2.0)	35.4 (2.4)	35.4 (2.6)	35.4 (2.5)
Sex				
Male	821 (52.5%)	154 (49.4%)	189 (48.4%)	343 (48.0%)
Female	742 (47.5%)	158 (50.6%)	213 (51.6%)	371 (52.0%)
Zygosity				
Monozygous male pairs	n/a	60 (19.2%)	68 (16.9%)	128 (17.9%)
Monozygous female pairs	n/a	62 (19.9%)	78 (19.4%)	140 (19.6%)
Dizygous male pairs	n/a	52 (16.7%)	50 (12.4%)	102 (14.3%)
Dizygous female pairs	n/a	56 (17.9%)	56 (13.9%)	140 (19.6%)
Opposite sex pairs	n/a	72 (23.1%)	124 (30.8%)	196 (27.5%)
Undetermined	n/a	10 (3.2%)	26 (6.5%)	36 (5.0%)
Income terciles**				
Low	354 (24.6%)	128 (41.0%)	176 (43.8%)	304 (42.6%)
Middle	838 (53.6%)	76 (24.3%)	128 (31.8%)	204 (28.6%)
High	371 (23.7%)	102 (32.7%)	92 (22.9%)	194 (27.2%)
Unknown	n/a	6 (1.9%)	6 (1.5%)	12 (3.8%)
Race*[a]				
Caucasian	1358 (86.9%)	246 (86.4%)	310 (77.1%)	556 (77.9%)
Black/African-American	16 (1.0%)	26 (8.3%)	0 (0%)	26 (3.6%)
Other	199 (12.1%)	38 (12.2%)	80 (19.9%)	118 (14.6%)
Unknown	n/a	2 (0.6%)	12 (3.0%)	14 (2.0%)
Ethnicity*[a]				
Non-Hispanic	1013 (64.8%)	286 (91.7%)	0 (0%)	286 (40.1%)
Hispanic	64 (4.1%)	22 (7.1%)	402 (100%)	424 (59.4%)
Unknown	486 (31.1%)	4 (1.3%)	0%	4 (0.3%)
18-month RSB total score*[a]	21.3 (7.6)	21.8 (9.8)	23.5 (10.7)	22.8 (10.3)
M-CHAT (n, % failures)	n/a	15 (4.8%)	21 (5.2%)	36 (5.0%)
Maternal education*[a] (n, % college degree or higher)	632 (90%)	220 (70.5%)	174 (43.3%)	394 (55.2%)
Maternal age (years)	n/a	30.6 (5.1)	30.5 (5.8)	30.6 (5.5)
Paternal age (years)	n/a	32.4 (5.9)	32.8 (7.1)	32.6 (6.6)
Gestational age (weeks)*		35.5 (2.4)	35.4 (2.6)	35.4 (2.5)
Maternal tobacco in pregnancy[a] (n, % yes)	n/a	44 (14.1%)	14 (3.5%)	58 (8.1%)
Maternal alcohol in pregnancy (n, % yes)	n/a	46 (14.7%)	65 (16.2%)	111 (15.5%)
Child medical problem score[a]	n/a	0.61 (0.91)	0.23 (0.56)	0.40 (0.74)

Notes: [a] Significant difference for California (CA) and Missouri (MO) samples. *Significant difference ($p < .05$) for Institute of Child Development (ICD) and Early Reciprocal Social Behavior (ERSB). **See supplementary material for values. M-CHAT = Modified Checklist for Autism in Toddlers.

$p < .001$), slightly lower mean RSB total scores ($t(2,275) = -11.30$, $p < .001$), a marginally higher percentage of males ($\chi^2(1, n = 2,277) = 3.77$, $p = .053$), older mean gestational age, as anticipated for a singleton versus twin sample ($t(2,186) = 40.07$, $p < .001$), a lower percentage of Hispanic ethnicity ($\chi^2(1, n = 1,787) = 623.37$, $p < .001$) and African-American race ($\chi^2(1, n = 1,956) = 21.23$, $p < .001$), and a higher proportion of mothers with college degrees ($\chi^2(1, n = 1,416) = 215.38$, $p < .001$). (See supplementary

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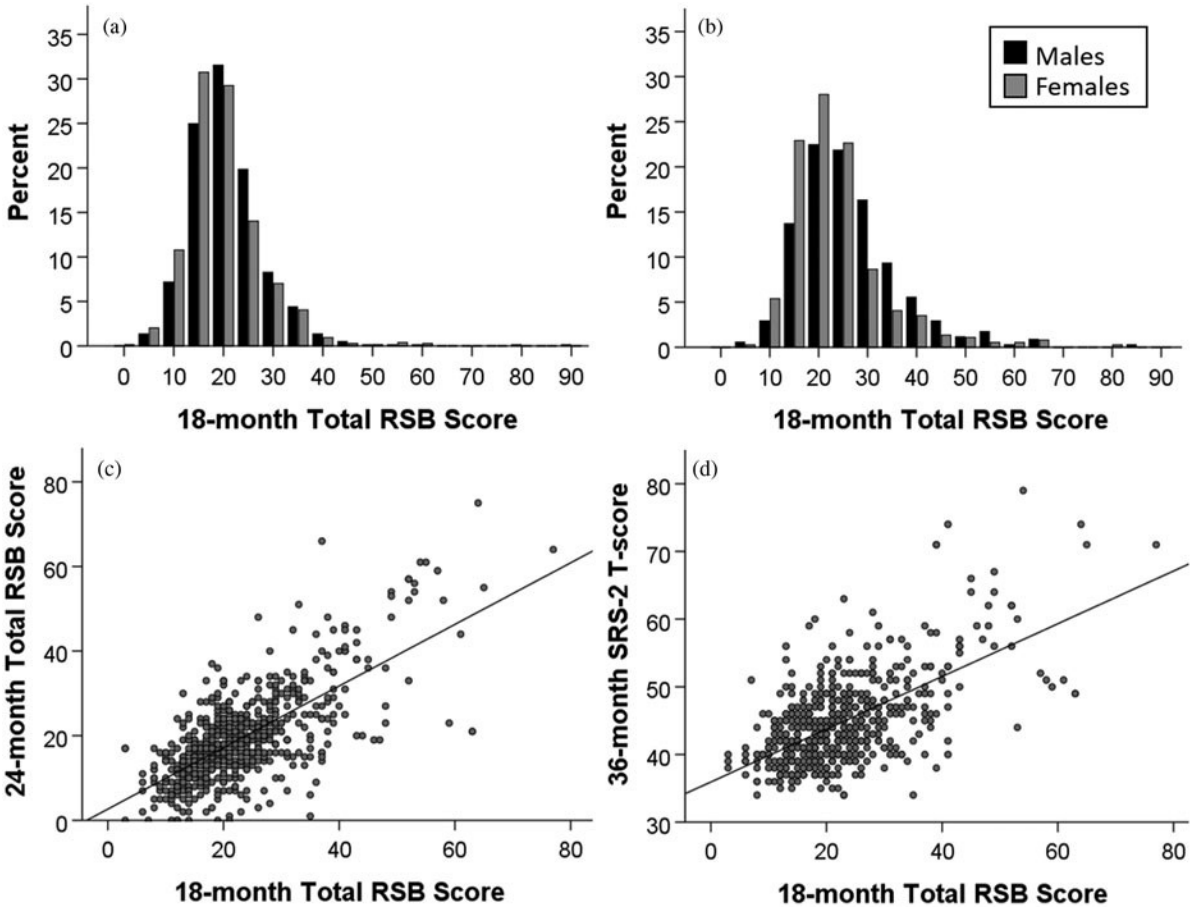

Figure 1. a, b: RSB total score distributions by sex for the samples from the Institute of Child Development (ICD) and the Early Reciprocal Social Behavior (ERSB) study, respectively. Higher scores indicate increased deficiency in reciprocal social behavior (RSB); lower scores indicate greater competence. In both groups, black bars (males) are generally larger than gray bars (females) for values in the upper half of the score range, consistent with males showing slightly lower RSB than females. c: Strong cross-age correlations of 18-month and 24-month RSB scores (intraclass correlation coefficient (ICC) = .70, $p < .05$) indicate good test–retest reliability. d: Strong correlations of 18-month RSB total score with 36-month total SRS score (ICC = .56, $p < .05$), which quantifies autistic traits in terms of RSB deficits, supports the vrRSB's ability to quantify trait-like variation in RSB.

material for statistics comparing the Missouri and California sites in the ERSB sample.)

Total scores on the vrRSB, plotted for males and females, were unimodal and continuously distributed in both the ICD sample, a singleton cohort, and the ERSB sample, a twin cohort comprised of over 50% Hispanic toddlers (Figure 1). Because vrRSB scores are based on deficits in RSB relevant to ASD, higher scores denote lower social competency and greater quantitative autistic traits. Both distributions displayed similarly positive skews (skew ICD sample = 1.80; skew ERSB sample = 1.63), which has also been observed for measures of RSB using the SRS in older children (e.g., Constantino & Todd, 2003), and is consistent with high scores corresponding to atypical RSB. Significant sex differences were observed in both samples (ICD: $t = 2.82$, $df = 124$, $p < .006$, Cohen's $d = 0.19$; ERSB: $t = 3.35$, $df = 124$, $p < .001$, Cohen's $d = 0.33$), whereby females showed lower RSB total scores and greater RSB, in agreement with prior findings using the vrRSB (Marrus et al., 2015) and the SRS (Constantino & Gruber, 2012). Strong internal consistency of items was uniformly observed ($\alpha_{ICD} = .83$, $\alpha_{ERSB} = .89$; both $p < .001$), along with strong test–retest reliability in the ERSB sample at ages 18 and 24 months (ICC = .70, $p < .001$), as previously reported in a subset of this population (Marrus et al., 2015). Contemporaneous 18-month data on the M-CHAT showed that children who failed the M-CHAT had significantly higher RSB total scores (i.e., greater deficiency in RSB; $t(36) = -7.32$, $p < .001$, Cohen's $d = 1.53$). Total 18-month RSB scores also showed strong associations with quantitative autistic traits measured on the SRS at age 36 months (ICC = .56, $p < .001$).

In the ERSB sample, which contained data on both sociodemographic and medical history, relationships were first tested between RSB and sociodemographic variables (age, sex, maternal education, ethnicity, and income) using a generalized linear model (see supplementary Table S2). Only sex ($\beta = -3.35$, $p < .001$), maternal education ($\beta = -2.94$, $p < .001$), and income (specifically high vs. other terciles; $\beta = -2.46$, $p < .001$) showed significant negative relationships to the RSB scores. These variables were retained in a follow-up model that also included selected prenatal and child medical factors (Table 2). Here, female sex, as expected, and higher maternal education were significantly associated with lower RSB scores, signifying greater RSB. Income was no longer statistically significant. Among the prenatal and medical risk factors, gestational age—previously shown to be negatively related to vrRSB score (Sifre et al., 2018) —was significant in the expected direction, as lower gestational age was associated with higher RSB scores and worse RSB. Child medical problems also showed a significant association, whereby more medical problems

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Table 2. Evaluation of sociodemographic and medical contributors to reciprocal social behavior (RSB)

	Unstandardized coefficients				
	B	Standard error	95% Confidence interval	Wald $\chi^2(1)$	Significance
Intercept	36.35	5.95	(24.70, 48.01)	37.35	<.001
Gender	−3.02	0.72	(−4.44, −1.61)	17.53	<.001
Maternal education	−4.01	0.86	(−5.70, −2.33)	21.75	<.001
High income	−1.29	0.85	(−2.95, .38)	2.29	.13
Maternal age	0.77	0.65	(−0.51, 2.05)	1.40	.24
Paternal age	−0.70	0.53	(−1.74, .33)	1.78	.18
Smoking in pregnancy	1.99	1.45	(−0.84, 4.83)	1.90	.17
Alcohol in pregnancy	1.67	1.07	(−0.43, 3.78)	2.43	.12
Gestational age (weeks)	−0.43	0.16	(−0.74, −0.12)	7.29	.007
Child medical problems	1.59	0.73	(0.52, 2.64)	4.68	.031
Scale	94.10				

Note: Parameters, including *B* (beta) coefficients and scale parameter, and results of significance testing are shown for generalized linear model. The variable "High income" variable referenced the high-income tercile (code = 1) to low-and middle-income terciles (code = 0). Codes of 0 and 1 were assigned to male/female, non-Hispanic/Hispanic, and no college degree/college degree, respectively.

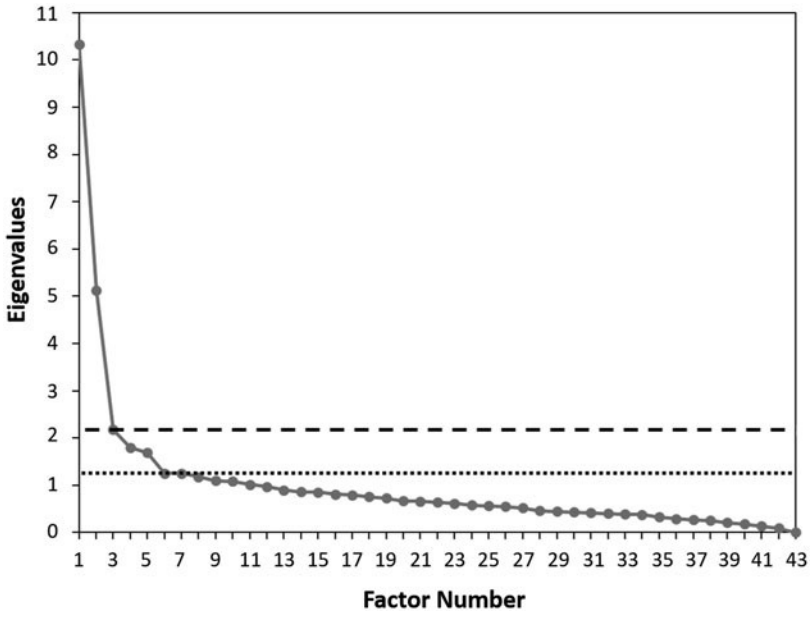

Figure 2. Scree plot for exploratory factor analysis of RSB total scores in Institute of Child Development (ICD) sample consisting of 1,563 toddlers aged 17–21.99 months. Each dot marks additional factors for higher-order solutions. Dashed lines mark inflection points, which indicate the number of factors for hypothetical solutions based on a relative decline in incremental variance explained by additional factors. The line with large dashes marks the first inflection point denoting a two-factor solution. The line with small dashes marks the second inflection point denoting a five-factor solution.

corresponded with higher RSB scores. A linear regression model retaining only significant variables (see supplementary Table S1) was significant ($F(4, 699) = 12.22$, $p < .001$) and explained 9.4% of the variance in 18-month-old RSB.

Latent factors of toddler RSB

An EFA was performed on the larger ICD sample to identify latent factors of RSB in toddlers. The scree plot revealed two inflection points (Figure 2), suggesting either a two-factor or five-factor solution. The eigenvalue for the second factor (5.13) was notably larger than that for the fifth factor (1.25), and the five-factor solution accounted for a robustly larger proportion of variance (38.0% vs. 30.0%, Table 3). For the two-factor solution, only the RMSEA fit index (RMSEA = .038) fell within thresholds indicating good fit (Table 3), and therefore we proceeded with the five-factor solution, which was further supported by multiple strong fit indices (CFI = .95, TLI = .94, RMSEA = .024, SRMR = .048) and good interpretability, as each of the five factors constituted distinct, self-contained characteristics that emerge in early childhood and are pertinent to the fifth edition of *Diagnostic and statistical manual of mental disorders* (DSM-5) core ASD symptoms (Table 4). Four factors corresponded to dimensions of interpersonal behavior relevant to the development of social communication: social motivation (F1-SM), functional communication (F2-FC), social avoidance (F4-SA), and social

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Table 3. Parameters for candidate factor solutions from exploratory factor analysis (EFA)

Solution	Eigenvalue	Variance	RMSEA	SRMR	TFI	CLI	Interpretability
One-factor	10.33	23.4%	.061	.13	.62	.60	F1-RSB
Two-factor*	5.13	30.0%	.038	.069	.86	.84	F1-social communication; F2-behavioral atypicality
Three-factor	2.18	33.0%	.031	.059	.91	.89	F1, F2 as above; F3-social orienting
Four-factor	1.80	35.6%	.026	.053	.94	.93	F1-social motivation; F2-functional communication; F3-behavioral atypicality; F4-social orienting
Five-factor*	1.69	38.0%	.024	.048	.95	.94	F1, F2 as above; F3-RRB; F4-social avoidance; F5-social orienting
Six-factor	1.25	39.9%	.021	.045	.96	.95	F1-social motivation; F2-directive communication (2-item); F3-social avoidance; F4-responsive communication; F5-RRB; F6-social orienting
Seven-factor	1.25	41.8%	.020	.042	.97	.96	F1, F2 as above; F3-RRB; F4-social awkwardness; F5-responsive communication; F6-social avoidance; F7-discoordination and emotional restriction
Eight-factor	1.18	43.6%	.019	.038	.98	.96	F1, F2 as above; F3-social awkwardness; F4-responsive communication (2-item); F5-RRB; F6-imagination and emotional closeness; F7-social avoidance; F8-social orienting
Nine-factor	1.10	45.3%	.018	.036	.98	.97	F1, F2 as above; F3-responsive communication; F4-social awkwardness; F5-RRB; F6-social avoidance; F7-emotional closeness; F8-social attention; F9-interactiveness
10-factor	1.09	47.1%	.017	.034	.98	.97	F1-F4 as above; F5-emotional restriction; F6-social avoidance; F7-RRB; F8-social attention; F9-interactiveness; F10-perseveration (2-item)
11-factor	1.02	48.7%	.016	.032	.99	.97	F1-F4 as above; F5-social avoidance; F6-RRB; F7-flexibility; F8-social attention; F9-reactivity (2-item); F10-interactiveness; F11-aloofness (1-item)

Note: * Factors immediately to the left of an inflection point on the scree plot. Variance represents a cumulative percentage of variance in total reciprocal social behavior (RSB) explained by a given factor solution. Factors are named according to face validity for an overarching behavioral construct, or constructs, when a singular domain could not be identified. RRB = restricted, repetitive interests and behavior. F = factor.

orienting (F5-SO), while the remaining factor corresponded to restricted, repetitive interests and behavior (F3-RRB)—the second core ASD symptom domain. vrRSB items uniformly demonstrated primary loadings above preset selection criteria (≥0.3), except for "seems uncoordinated," whose primary loading, which was on the F3-RRB factor, was .27. Given known associations between motor atypicalities and restricted, repetitive interests and behavior in ASD, this item showed appropriate face

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Table 4. Five-factor structure for RSB

	Factor				
Item	F1-SM	F2-FC	F3-RRB	F4-SA	F5-SO
Happy to include you when playing	0.78				
Interested in whether you pay attention	0.65				
Looks at you when you are playing together	0.60				
On the same wavelength with you	0.43 (0.38 F2)				
Has a sense of humor	0.44				
Able to express feelings by a change in facial expression	0.40				
Responds positively to adults who try to hold his/her attention	0.39 (−0.37 F4)				
Tries to involve others in play	0.38				
Able to let you know what he/she doesn't want		0.78			
Able to let you know what he/she does want		0.74			
Understands simple verbal requests		0.60			
Cooperates with adults' requests for help		0.49			
Able to pretend		0.39			
When seeing a spinning object, stares for over 5 minutes			0.82		
Has a strange way of playing with toys			0.70		
Repetitive, odd behavior such as hand flapping or rocking			0.67		
Obsessed with sensory interests			0.65		
Concentrates too much on parts of toy			0.58		
Narrow range of things that he/she is interested in			0.51		
Seems to interact with people as if objects			0.51		
Withdraws/isolates when you attempt to play with him/her			0.49 (0.42 F2)		
Behaves in ways which seems strange or bizarre			0.43 (0.32 F4)		
Is content to play with same toys for hours			0.38		
Wanders aimlessly from one activity to another			0.38		
Seems to prefer to be by self			0.37		
Stares or gazes off into space			0.36		
Emotionally distant, doesn't show feelings			0.35 (−0.34 F1)		
Seems overly sensitive to sounds, textures, smell			0.33 (0.31 F4)		
Seems uncoordinated for his/her age			0.27		
Avoids people who try to be emotionally close				0.69	
Seems odd or weird				0.60	
Avoids starting social interactions with peers or adults				0.56	
Has overly serious facial expressions				0.37	
Avoids eye contact or unusual eye contact				0.33	
Difficulty with changes in routine				0.30	
Unusual response to being held, cuddled				0.30	
Interested in what people are doing					0.69
Capable of expressing joy by smiling, facial gestures					0.62
Responds to his/her name being called					0.58
Focuses attention on things others look at/listen to					0.57
When offered stuffed animal, will interact/pretend					0.56

(*Continued*)

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Table 4. (*Continued.*)

Item	Factor				
	F1-SM	F2-FC	F3-RRB	F4-SA	F5-SO
Able to imitate others' actions					0.54
Reacts to changes in others' tone of voice and facial expression					0.53
Indicates by point wants or interests					0.50

Factor names correspond to behaviors represented in aggregate by each series of items. F1-SM = factor 1, social motivation; F2-FC = factor 2, functional communication; F3-RRB = factor 3, restricted, repetitive interests and behavior; F4-SA = factor 4, social avoidance; F5-SO = factor 5, social orienting. Significant loadings ≥ 0.3 ($p < .05$) are shown, with one exception ("seems uncoordinated") in which the largest significant loading is shown. Social motivation entails the disposition to enjoy and seek social interactions and connections with others (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Over, 2016). Functional communication includes expressive, receptive, or symbolic skills promoting information exchange. Restricted, repetitive interests and behaviors involve tendencies towards repetitive actions, fixations, limited interests, or atypical responses to sensory stimuli. Social avoidance reflects behaviors inhibiting opportunities for interpersonal interaction. Social orienting refers to the ability to direct attention to social stimuli and respond contingently.

Table 5. Inter-factor correlations for exploratory factor analysis (EFA) and confirmatory factor analysis (CFA)

	EFA					CFA				
	F1-SM	F2-FC	F3-RRB	F4-SA	F5-SO	F1-SM	F2-FC	F3-RRB	F4-SA	F5-SO
Social motivation (F1-SM)	–	.38*	.12*	.17*	.40*	–	.85*	.41*	.43*	.67*
Functional communication (F2-FC)		–	.07	.07	.27*	.93*	–	.40*	.33*	.66*
Restricted, repetitive interests and behavior (F3-RRB)			–	.43*	.31*	.41*	.34*	–	.96*	.61*
Social avoidance (F4-SA)				–	.27*	.50*	.32*	.95*	–	.49*
Social orienting (F5-SO)					–	.62*	.63*	.58*	.56*	–

Notes: For the CFA (based on Early Reciprocal Social Behavior study data), correlations above the diagonal apply to twins at age 18 months and correlations below the diagonal apply to twins at age 24 months. Stronger factor intercorrelations were found for the CFA, for which, in contrast to the EFA (based on Institute of Child Development data), each item variable was modeled to load onto only one factor. Note that positive correlations across all factors reflect all items being scored to indicate lower levels of RSB and increased quantitative autistic traits.
*$p < .05$.

validity for this factor. As anticipated for the oblique rotation, each of the five RSB factors significantly correlated with other factors in the solution, with correlations in the small to moderate range, consistent with partially independent factors (significant r values of .12–.43, $p < .05$; Table 5).

Examination of higher-order solutions entailing eigenvalues ≥1 showed small, incremental improvements in variance and fit indices (Table 3). However, these solutions displayed several challenges to interpretability: (a) factors containing two items, comprising a limited behavioral range; (b) more frequent low-factor loadings (i.e., <0.3) and cross-loadings, (c) factors with few items, each describing distinct capacities (e.g., motor coordination and emotion in the seven-factor solution), and (d) internally contradictory primary loadings for typical and atypical behaviors on a single factor.

A CFA of the five-factor structure in the twins tested its generalizability as a simple factor structure, in which each variable was loaded onto a single factor. Within the twin data at age 18 months, the CFA showed acceptable fit (CFI = .90, TFI = .90, RMSEA = .037); this was slightly less than observed for the EFA, in keeping with the imposition of a hypothesized factor structure on a distinct sample. Inter-factor correlations (all $p < .001$) were moderate to high ($r = .32$–.96; Table 5), and factors demonstrated good internal consistency (Cronbach $\alpha = .69$–.81). The strongest inter-factor correlations were observed for (a) F3-RRB and F4-SA and (b) F1-SM and F2-FC. F1-SM and F2-FC exhibited higher correlations with F5-SO, another factor promoting social competency, than correlations with either F3-RRB or F4-SA (the factors corresponding to less social engagement). Similar fit indices (CFI = .92, TFI = .81, RMSEA = .037), inter-factor correlations (Table 5), and internal consistency of the factors ($\alpha = .63$–.88) were observed based on a CFA of 24-month-old vrRSB data. To test the developmental stability of these factors, we assessed correlations between (a) factor scores at 18 and 24 months and (b) 18-month factor scores and SRS scores at age 36 months. All factors showed significant ($p < .001$) within-factor, cross-age correlations from 18 to 24 months (F1-SM: $r = .54$, F2-FC: $r = .52$, F3-RRB: $r = .68$, F4-SA: $r = .63$, F5-SO: $r = .65$) and significant ($p < .001$) correlations with SRS score from 18 to 36 months (F1-SM: $r = .33$, F2-FC: $r = .31$, F3-RRB: $r = .59$, F4-SA: $r = .55$, F5-SO: $r = .50$), indicating trait-like properties for these subdomains of RSB.

Genetic structure of RSB factors at age 18 months

To characterize the relative contributions of genetic and environmental influences on RSB, we first obtained MZ and DZ twin concordances for each of the five factors (Table 6). For all five factors at age 18 months, correlations were significant, with MZ twins showing greater concordances than DZ twins (MZ: .68–.89; DZ: .40–.53). DZ twin concordances were over half the value of MZ twin concordances, justifying subsequent

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Table 6. Monozygotic (MZ) and dizygotic (DZ) twin concordances and parameter estimates from quintavariate twin models for five RSB factors at ages 18 and 24 months

	rMZ	rDZ	Additive genetic (*A*)	Shared environment (*C*)	Nonshared environment (*E*)
18 months: $n = 126$ MZ pairs, $n = 191$ DZ pairs					
Social motivation (F1-SM)	0.83 (0.76, 0.87)	0.40 (0.27, 0.51)	0.72 (0.64, 0.79)	0.08 (0.04, 0.14)	0.19 (0.15, 0.25)
Functional communication (F2-FC)	0.89 (0.84, 0.92)	0.48 (0.36, 0.58)	0.73 (0.63, 0.80)	0.14 (0.07, 0.22)	0.14 (0.11, 0.18)
Restricted, repetitive interests and behavior (F3-RRB)	0.72 (0.62, 0.79)	0.52 (0.41, 0.62)	0.39 (0.29, 0.49)	0.33 (0.25, 0.40)	0.29 (0.23, 0.36)
Social avoidance (F4-SA)	0.68 (0.57, 0.76)	0.53 (0.42, 0.63)	0.40 (0.30, 0.50)	0.31 (0.23, 0.40)	0.29 (0.23, 0.36)
Social orienting (F5-SO)	0.86 (0.81, 0.90)	0.49 (0.37, 0.59)	0.47 (0.38, 0.55)	0.33 (0.28, 0.39)	0.20 (0.15, 0.26)
24-months: $n = 116$ MZ pairs, $n = 177$ DZ pairs					
Social motivation (F1-SM)	0.81 (0.74, 0.87)	0.43 (0.30, 0.54)	0.70 (0.57, 0.79)	0.13 (0.04, 0.22)	0.18 (0.13, 0.24)
Functional communication (F2-FC)	0.80 (0.72, 0.86)	0.49 (0.36, 0.59)	0.61 (0.47, 0.73)	0.18 (0.08, 0.29)	0.21 (0.16, 0.28)
Restricted, repetitive interests and behavior (F3-RRB)	0.81 (0.73, 0.86)	0.47 (0.34, 0.58)	0.65 (0.52, 0.77)	0.16 (0.06, 0.27)	0.19 (0.14, 0.26)
Social avoidance (F4-SA)	0.78 (0.69, 0.84)	0.42 (0.29, 0.53)	0.67 (0.54, 0.78)	0.13 (0.04, 0.23)	0.20 (0.15, 0.27)
Social orienting (F5-SO)	0.84 (0.77, 0.88)	0.46 (0.34, 0.57)	0.82 (0.77, 0.87)	—	0.18 (0.13, 0.23)

Note: 95% confidence intervals in parentheses. All MZ and DZ twin concordances (rMZ and rDZ, respectively) and variance components for *A* (additive genetic factors), *C* (shared environmental factors), and *E* (nonshared environmental factors) were significant at $p < .05$. No shared environmental influences were found for social orienting at age 24 months.

quantitative genetic analyses (i.e., *ACE* models) of additive genetic factors (*A*), shared environmental factors (*C*) (vs. nonadditive genetic effects (*D*)), and nonshared environmental factors (*E*).

Results for the best fitting five-factor model at age 18 months indicated additive genetic influences on all factors (*A*, Table 6). Among the five RSB factors, the strongest genetic contributions were observed for F1-SM and F2-FC, with $A \geq .72$. These heritability estimates were significantly greater than those for the remaining three factors ($A = .39$–$.47$), as confidence intervals were nonoverlapping. Conversely, shared environmental contributions ($C = .31$–$.33$) were significantly greater for F3-RRB, F4-SA, and F5-SO, although the contributions of *C* did not exceed *A* for any of these three factors. Nonshared environmental contributions (*E*) were similar for all factors, with F2-FC exhibiting the lowest influence of *E* (.14).

Cross-factor genetic and environmental correlations (Table 7) also showed a high degree of overlapping genetic influences ($r_A = 0.88$–1.00). F3-RRB demonstrated nearly complete genetic overlap ($r_A \geq .96$) with all four other factors. F1-SM, F4-SA, and F5-SO showed similarly high genetic correlations with all other factors, except F2-FC. Among the factors, F2-FC exhibited the most unique genetic influences at age 18 months, although even for the lowest genetic correlation ($r_A = .88$), this corresponded to only 16% of the total phenotypic variance being attributable to factor-specific genetic influences. Unlike genetic influences, inter-factor correlations for environmental influences were not uniformly high but, importantly, two pairs of factors showed nearly complete overlap of *C*: F1-SM and F2-FC and F3-RRB and F4-SA ($r_C = .97$ for both), and one pair did so for *E*: F3-RRB and F4-SA ($r_E = .94$).

Genetic structure of RSB factors at age 24 months

For RSB at age 24 months, MZ and DZ pair concordances also suggested predominantly genetic influences on variance in RSB factors, with F3-RRB and F4-SA showing higher values for MZ concordances at age 24 versus 18 months. In the quintavariate *ACE* model, all factors showed significant additive genetic influences ($A = .61$ to $.82$, Table 6). Larger genetic influences were observed for F3-RRB, F4-SA, and F5-SO at 24 months in comparison with age 18 months. These factors also showed lower point estimates of shared and nonshared environmental influences

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Table 7. Genetic, shared environmental, and nonshared environmental correlations between RSB factors at age 18 months

	F1-SM	F2-FC	F3-RRB	F4-SA	F5-SO
Genetic correlations (above diagonal) and shared environmental correlations (below diagonal)					
Social motivation (F1-SM)	—	0.88* (0.84, 0.91)	0.97* (0.89, 1.00)	0.97* (0.92, 0.98)	1.00*
Functional communication (F2-FC)	0.97* (0.92, 0.997)	—	0.97* (0.87, 1.00)	0.89* (0.75, 0.97)	0.88* (0.84, 0.91)
Restricted, repetitive interests and behavior (F3-RRB)	−0.97* (−0.96, −0.98)	-0.89* (-0.78, -0.96)	—	0.96* (0.94, 0.97)	0.97* (0.89, 1.00)
Social avoidance (F4-SA)	−1.00*	−0.97* (−0.92, −0.997)	0.97* (0.96, 0.98)	—	0.97* (0.92, 0.98)
Social orienting (F5-SO)	0	0.24* (0.08, 0.40)	0.23* (0.18, 0.30)	0	—
Nonshared environmental correlations					
Social motivation (F1-SM)	—				
Functional communication (F2-FC)	0.66* (0.55, 0.74)	—			
Restricted, repetitive interests and behavior (F3-RRB)	0.24* (0.09, 0.39)	0.28* (0.13, 0.43)	—		
Social avoidance (F4-SA)	0.32* (0.18, 0.46)	0.23* (0.07, 0.38)	0.94* (0.92, 0.95)	—	
Social orienting (F5-SO)	0.48* (0.36, 0.60)	0.51* (0.38, 0.62)	0.46* (0.34, 0.57)	0.31* (0.18, 0.44)	—

Notes: Correlations are based upon the best-fitting model. For the upper rows, genetic correlations are above the diagonal. Shared environmental correlations are below the diagonal. Nonshared environmental correlations are below the diagonal in the lower part of the table. 95% confidence intervals in parentheses. *$p < .05$. RSB = reciprocal social behavior.

than at age 18 months ($C = 0–.18$, $E = .18–.21$), although given some overlap in confidence intervals, these numerical differences were not statistically significant.

In contrast to the findings at age 18 months, the 24-month cross-factor *ACE* correlations showed only two instances of nearly fully overlapping genetic influences (Table 8). These included F1-SM and F2-FC, which demonstrated a higher genetic correlation (r_A) at 24 months ($r_{A24} = .95$ vs. $r_{A18} = .88$), and F3-RRB and F4-SA ($r_A = .96$ at both ages). Unlike at age 18 months, F3-RRB did not show near-complete overlap of *A* with the other factors ($r_A = .67–.74$), and F5-SO also showed lower genetic correlations with F1-SM and F4-SA ($r_{A18} > .97$, $r_{A24} = .68–.75$). For 24-month shared environmental influences, the best-fitting model demonstrated a common *C* component for factors one through four and no *C* for F5-SO. Nonshared environmental correlations (r_E) were generally moderate; at the extremes, F1-SM and F2-FC plus F3-RRB and F4-SA showed strong overlap ($r_E = .82–.89$), while r_E for F2-FC and F4-SA was not significant.

Bivariate within-factor genetic and environmental correlations for ages 18 and 24 months

ACE models for ages 18 and 24 months indicated some age-specific differences in the contributions of *A*, *C*, and *E* to variance in RSB during toddlerhood. In a final series of bivariate models, we therefore calculated r_A, r_C, and r_E within each of the five RSB factors between ages 18 and 24 months to test whether novel genetic and environmental influences could be detected across age. Proportions of variance attributable to *A*, *C*, and *E* resembled prior quintavariate models, except that no statistical support for *C* was observed for F3-RRB, F4-SA, and F5-SO at age 24 months (see supplementary Table S3). For each of the five factors, cross-age correlations related primarily to overlapping genetic influences (Table 9; $r_A = .75–1.00$), with F3-RRB, F4-SA, and F5-SO showing no evidence for developmentally-specific genetic influences at age 24 months. For F1-SM and F2-FC, a high value of r_A was also observed, although the confidence intervals did not support complete overlap, consistent with some degree of novel additive genetic influences at age 24 months. This evidence was most substantive for F1-SM ($r_A = .75$, 31% phenotypic variance due to unique 24-month genetic influences at 24 months), and more modest for F2 ($r_A = .81$, 21% phenotypic variance due to unique 24-month genetic influences). Attribution of within-factor cross-age covariance to *C* was underpowered. There was considerable support for novel nonshared environmental influences (or age-specific measurement error) for all factors, with F5-SO showing no correlation of *E* on 18- and 24-month assessments.

Discussion

In this paper, through use of a recently developed video-referenced parent-report questionnaire, we described the early behavioral and genetic architecture of RSB—a competency whose clinical-level impairment defines ASD. To our knowledge, this work entails the largest epidemiologic, genetically informative sample in which a validated quantitative measure of variation in social competency has been explored in toddlers. The vrRSB quantified five heritable, inter-correlated, trait-like RSB subdimensions in toddlers with substantially overlapping genetic influences at ages of 18 and 24 months. Among these five subdimensions, both genetic and environmental influences

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Table 8. Genetic and nonshared environmental correlations between RSB factors at age 24 months

	F1-SM	F2-FC	F3-RRB	F4-SA	F5-SO
Social motivation (F1-SM)	—	0.95* (0.92, 0.97)	0.74* (0.60, 0.89)	0.82* (0.70, 0.95)	0.75* (0.67, 0.83)
Functional communication (F2-FC)	0.82* (0.75, 0.87)	—	0.74* (0.56, 0.93)	0.74* (0.56, 0.95)	0.78* (0.69, 0.88)
Restricted, repetitive interests and behavior (F3-RRB)	0.31* (0.14, 0.47)	0.23* (0.05,0.39)	—	0.96* (0.96, 0.97)	0.67* (0.58, 0.77)
Social avoidance (F4-SA)	0.43* (0.27, 0.57)	0.08 (-0.11, 0.26)	0.89* (0.84, 0.92)	—	0.68* (0.58, 0.77)
Social orienting (F5-SO)	0.41* (0.25, 0.55)	0.49* (0.35, 0.61)	0.45* (0.29, 0.58)	0.33* (0.17, 0.48)	—

Notes: Genetic correlations are above the diagonal; nonshared environmental correlations are below the diagonal. Shared environmental influences on factors F1, F2, F3, and F4 could be specified as being on a single factor, and there were no shared environmental influences on factor F5 at 24-months. 95% confidence intervals in parentheses. *$p < .05$. RSB = reciprocal social behavior.

Table 9. Genetic, shared environmental, and nonshared environmental correlations between 18-month and 24-month factor scores

	Additive genetic (r_A)	Shared environment (r_C)	Nonshared environment (r_E)
Social motivation (F1-SM)	0.75* (0.63, 0.87)	−1.00 (−1.00, 0.06)	0.42* (0.25, 0.56)
Functional communication (F2-FC)	0.81* (0.65, 0.96)	−1.00 (−1.00, 0.28)	0.22* (0.04, 0.38)
Restricted, repetitive interests and behavior (F3-RRB)	1.00*	N/A	0.27* (0.12, 0.41)
Social avoidance (F4-SA)	1.00*	N/A	0.27* (0.12, 0.41)
Social orienting (F5-SO)	1.00*	N/A	−0.04 (−0.19, 0.12)

Notes: Within-factor correlations for bivariate models across ages 18 and 24 months. No shared environmental contributions were observed for factors F3–F5. 95% confidence intervals in parentheses. *$p < 0.05$.

differed in their proportional contributions, their inter-factor overlap at each age, and their cross-age overlap, demonstrating distinct levels at which toddler social development reflects dynamic influences of genes and environment. The observed phenotypic homology between toddler RSB factors and core autistic symptom domains highlights developmental continuity in RSB's population structure and the opportunity for early quantitative measurement of RSB to index origins of ASD's heterogeneity.

RSB in toddlers is measurable in ethnically diverse populations

An important aspect of this study involved deployment of the vrRSB within an ethnically diverse sample. Across the two study samples, comparable score distributions, internal consistency, and factor structure confirmed the vrRSB's generalizability, consistent with prior studies showing cross-cultural validity of quantitative autistic traits (Cen et al., 2017; Cheon et al., 2016; Kamio et al., 2013). No significant relationship between RSB and ethnicity was observed; rather, socioenvironmental factors broadly implicated in risk for developmental delays (including lower maternal education, income, and gestational age, as well as a higher burden of medical problems (Evans & English, 2002; Hediger, Overpeck, Ruan, & Troendle, 2002; Hernandez, 1997; McLoyd, 1998; Sifre et al., 2018)) accounted for a small proportion of RSB's variance, as expected for a heritable trait. Strong correlations of 18-month vrRSB and 36-month SRS scores substantiated the vrRSB's ability to quantify trait-like variation in enduring aspects of RSB (Wagner et al., 2019), further corroborating the stable psychometric properties of this instrument.

Multiple subdimensions underlie RSB in toddlerhood

Five inter-correlated RSB factors were identified using both EFA and CFA in population-based samples of toddlers. These subdimensions mapped to core ASD symptom domains by describing capacities influencing social communication (i.e., social motivation, functional communication, social avoidance, and social orienting), as well as restricted, repetitive interests and behavior, and displayed moderate to high intercorrelations at ages 18 and 24 months based on the CFA (Table 5). High inter-factor correlations for (a) restricted repetitive interests and behavior and social avoidance and (b) social motivation and functional communication could suggest a more parsimonious factor structure for the twin data, although some inflation in inter-factor correlations was expected due to enriched genetic similarity, and a factor structure derived from this smaller sample would pose challenges to generalizability. The present interpretation is supported by the superior fit of the five-factor structure versus lower-order solutions in the larger ICD sample, moderate inter-factor correlations in the EFA, similarly high correlations in a prior two-factor structure of RSB (Frazier et al., 2014), and face validity of each factor. Overall, variation across these five RSB subdimensions, encompassing characteristics both promoting (i.e., social motivation, functional communication, and social orienting) and discouraging (i.e., social avoidance and restricted, repetitive interests and behavior) interpersonal engagement, jointly underlie the typical development of RSB and, conversely, quantitative autistic traits in toddlers. The existence of partially independent, heritable RSB subdimensions, their correlation with later autistic traits at age 36 months, and the potential for different profiles of ability

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across subdimensions may explain heterogeneity in developmental pathways culminating in ASD. Use of the vrRSB to quantify these RSB dimensions, in conjunction with measures of other heritable, nonspecific domains implicated in ASD (Marrus et al., 2018; Pohl et al., 2019) could thus advance individualized screening and treatment strategies.

Like previously published factor structures using the SRS, the toddler RSB structure separates socially-anchored factors from restricted, repetitive interests and behavior, conforming to the latter's formulation as a distinct core ASD symptom domain and demonstrating homology in RSB's architecture over development. Although the observed five-factor structure contrasts with the unitary- and two-factor structures generally reported for the SRS, we note that the prior studies involved older children and that, in the current EFA, the poor fit and low variance explained by a one- or two-factor solution strongly supported additional factors. Interestingly, one especially well-powered factor analysis of the SRS ($n > 9000$; Frazier et al., 2014) provides some support for five RSB subfactors, including a social avoidance domain, which were parsed within an overarching two-factor structure of social communication and autistic mannerisms involving restricted, repetitive interests and behavior. The identification of five separable RSB factors in a substantially smaller toddler population could imply that RSB subdomains are more differentiated in early life and become progressively interrelated, thereby promoting long-term stability of RSB (Wagner et al., 2019) and, relatedly, the clinical autistic syndrome.

Variation in RSB factors is largely attributable to genetic influences

Quantitative *ACE* models confirmed a major role for genetic influences in the development of RSB, especially by age 24 months, consistent with the high heritability for ASD and autistic traits in older children ($h^2 = 60–90\%$, c.f. Bai et al., 2019). Additive genetic influences (*A*) overlapped across factors, suggesting that common genetic influences underlie partially independent dimensions whose developmental deviation results in ASD. Shared environmental influences (*C*) also displayed instances of high cross-factor overlap, including a single *C* factor for F1-SM, F2-FC, F3-RRB, and F4-SA at age 24 months. Thus, during toddlerhood, convergent effects from genetic and shared environmental influences may enhance relatedness among RSB factors, either promoting accelerated social growth or the consolidation of ASD symptoms. Nonshared environmental influences (*E*), which also include potential measurement error, generally contributed comparable variance to *C*, but displayed more modest cross-factor overlap, making *E* more likely to produce divergence across factors, a possible source of heterogeneity, as has been observed for RSB in identical twins with ASD (Castelbaum, Sylvester, Zhang, Qiongry, & Constantino, 2019).

Dynamic genetic and environmental influences act on RSB during toddlerhood

Cross-sectional profiles of genetic and environmental influences revealed differential heritability for several RSB factors at ages 18 and 24 months—a relatively brief interval marked by rapidly advancing social skills. High heritability of RSB (i.e., $h^2 > .6$), apparent for all factors at age 24 months, was observed only for F1-SM and F2-FC at age 18 months. In contrast, F3-RRB, F4-SA, and F5-SO showed a relatively high impact from shared environment factors at 18 months but not at 24 months, suggesting differential sensitivity to genetic and environmental effects among RSB factors during toddlerhood. Levels of cross-factor overlap for these influences also varied at ages 18 to 24 months, with less evidence for inter-factor genetic covariance at 24 months, implying that relationships between factors themselves may change over the course of development.

Bivariate models directly testing for novel genetic and environmental influences found that, between the ages of 18 and 24 months, F1-SM and F2-FC showed evidence for novel genetic influences, and all factors showed evidence for novel nonshared environmental influences (which could also include differences in measurement error). Thus, genetic and environmental liabilities that contribute to the development of ASD, may come "online" at different critical times in early development (Constantino, 2019), and impact the presentation of ASD through the initial age of diagnosis. This temporal specificity highlights that the timing and targets of interventions may both be crucial for optimizing outcomes in ASD.

Limitations

The analyses identified a single factor for restricted, repetitive interests and behavior. However, we note that more comprehensive measures of this domain have identified several factors (Lam & Aman, 2007; Lam, Bodfish, & Piven, 2008; Wolff, Boyd, & Elison, 2016), which could have been discernible with a greater number of relevant items and a larger sample. While our qualitative evaluation of sex-specific exploratory factor structures did not reveal conceptual differences, nuanced factorial variance that we did not test for is possible. Our sample size also precluded testing for sex differences in our twin models, although we did adjust for the effects of sex as a covariate. Given evidence for sex-based modulation of ASD risk, future analyses in larger samples should explore the impact of sex on the factorial and genetic architecture of RSB, as well as longitudinal variability of these measures (c.f. Sifre, Berry, Wolff, & Elison, under review). In addition, our approach to examining developmental effects was specifically targeted at the variable impact of genetic and environmental influences on single factors at ages 18 and 24 months. Comparisons of the estimated genetic covariance between factors at these ages are thus informal, as we were underpowered to model all five factors simultaneously across both time points. Lastly, although the present twin sample was ethnically diverse, inclusion criteria specifying caregivers fluent in English may have under-represented less acculturated Hispanics. Continued studies of RSB in racially diverse, under-represented minorities are warranted to evaluate the generalizability of the findings.

In conclusion, we have shown that video-referenced ratings of RSB in toddlers can feasibly be implemented across diverse populations, can quantify heritable subdimensions of RSB, and may inform mechanisms of heterogeneity in ASD. At the same time, substantial inter-correlations among RSB subdimensions reflect the long-term association between core symptom clusters (social communication and restricted, repetitive interests and behavior) that define ASD population-wide and through adulthood. While variation in the early overlap and timing of genetic and environmental influences across these subdimensions underscores the complex ontogeny of ASD, it also draws attention to the opportunity for multiple targets for intervention. Future research on the origins, clinical course, and early treatment of ASD would benefit

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from specifying the trajectories of RSB subdimensions relative to specific genetic and environmental susceptibility factors, as well as tracking their response to early preventive and therapeutic interventions.

Supplementary Material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579420000723

Acknowledgements. Project support included grants R01 MH104324 (PI Elison), R25 MH112473 (co-PI Glowinski), K02 DA032573 (PI Agrawal), R01 HD068479 (PI Constantino), U54 HD087011 (Intellectual and Developmental Disabilities Research Center at Washington University, National Institute of Child Health and Human Development, co-PI JNC), and K08 MH112891 (PI Marrus). We thank all the participating families for their generous time and effort. We also wish to acknowledge the scientific contribution of deceased co-author and colleague Theodore Jacob, whose expertise and dedication to understanding genetic and environmental influences on psychiatric disorders helped make this work possible.

Conflicts of Interest. Author J.N.C. receives royalties from Western Psychological Services for the commercial distribution of the Social Responsiveness Scale. The remaining authors have no conflicts of interest to declare.

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