Deficits in reciprocal social behavior are a characterizing feature of autism spectrum disorder (ASD). Autism-related variation in reciprocal social behavior (AVR) in the general population is continuously distributed and highly heritable—a function of additive genetic influences that overlap substantially with those which engender clinical autistic syndromes. This is the first long-term prospective study of the stability of AVR from childhood through early adulthood, conducted via serial ratings using the Social Responsiveness Scale, in a cohort-sequence study involving children with ASD, other psychiatric conditions, and their siblings ($N = 602, \text{ages} = 2.5–29$). AVR exhibits marked stability throughout childhood in individuals with and without ASD.

Given that deficits in this endophenotype modify the severity of an array of other forms of psychopathology, tracking the course of AVR across its entire range of variation over the course of early childhood to young adulthood is of critical importance. Therefore, we conducted a novel examination of the longitudinal course of AVR in both affected and unaffected individuals. To quantify AVR in clinical and general population samples, we utilized the SRS, a research standard for the characterization of inherited traits that comprise ASD. Because (a) the genetic causes of ASD substantially overlap with those underlying subclinical autistic traits; (b) confirmatory factor analyses of SRS ratings exhibit measurement invariance across ages (Frazier et al., 2014); and (c) the very high monozygotic twin correlation for SRS scores in unaffected individuals ($\sim 0.80$, Constantino & Todd, 2003) establishes relatively narrow constraints on the possible influence
of error on an individual measurement, we hypothesized that AVR would exhibit stability not only in clinically affected individuals, but also across its entire range of variation. If the longitudinal trajectories of AVR are stable, it is conceivable that measurements of AVR in early childhood could make strong predictions over the course of an individual’s life, particularly with respect to social interaction and adaptation in the context of any neuropsychiatric condition of childhood.

Method

Study Design

The study utilized a longitudinal cohort-sequential design (Nesselroade & Baltes, 1979; Appendix S1). Subjects were enrolled on a rolling basis over the course of the study (Appendix S2).

Sample

This report is a continuation of a previously published study (Constantino et al., 2009), an ongoing longitudinal evaluation of AVR. The subject group comprised 602 socio-economically diverse, predominantly Caucasian individuals, aged 2.5-29 years. Appendix S3 provides details on the recruitment process. To be eligible for the study, the subject needed to be either (a) an individual with an ASD diagnosis (henceforth referred to as “ASD subject”), (b) the sibling of an ASD subject, (c) an individual with a non-ASD psychiatric diagnosis (“psych subject”), (d) or the sibling of a psych subject. Subjects were excluded from the study if any ambiguity existed regarding a singular primary ASD diagnosis. Appendix S4 provides details on the diagnostic process and sample characteristics.

Measures

The SRS

The SRS is a 65-item measure of AVR, which capitalizes on observations of children in naturalistic social contexts, by parent and/or teacher report. Its internal consistency is very high ($\alpha = 0.95$), and it distinguishes ASD-affected individuals from controls with a Cohen’s $d$ effect size of $2.7$ and from individuals with other psychiatric conditions with an effect size of $1$ (Constantino & Gruber, 2007; Constantino, Przybeck, Friesen, & Todd, 2000). It characterizes variation in the two Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V) domains of ASD: social communication and interaction and restricted interests and repetitive behaviors. Prior studies of the SRS in clinical and epidemiological populations have established that these two subdomains encompass a unitary factor structure (Constantino et al., 2004), with the exception of one analysis of 14,744 subjects, which suggested a minimally better fit for a two-factor structure (Frazier et al., 2012, the two factors being highly intercorrelated). Given this factor structure and that restriction of the number of SRS items erodes its ability to distinguish between clinical groups (Constantino & Todd, 2003), we elected to use the empirically supported total score as the metric of analysis; however, subdomain analyses are provided in Appendices S7, S9, and S10.

Autism Diagnostic Observation Schedule, 2nd ed. and Autism Diagnostic Interview–Revised

To provide an independent measurement of autistic traits, we conducted Autism Diagnostic Observation Schedule, 2nd ed. and Autism Diagnostic Interview–Revised assessments on a subset of ASD-affected subjects ($N = 68$; Appendix S5).

Procedures

We mailed SRSs to all parents, and to teachers of school-age subjects. Teacher reports were a secondary measure, with different teachers reporting on a given subject in successive years. The teacher who completed the SRS had known the child for a minimum of 2 months and was selected by the parent as most knowledgeable of the child. SRSs were requested annually.

We enrolled a total of 1,026 subjects, of which 268 did not continue (overall attrition rate = 26.1%). Of the remaining 758 subjects, 156 had SRS reports completed exclusively by fathers or unspecified informants; in order to ensure informant homogeneity, we restricted this analysis to subjects with maternal and/or teacher ratings (which are most extensively validated), resulting in our final subject total of 602. This sample included 530 subjects who had more than one SRS; the 72 subjects who had only one SRS were included in the dataset for the purposes of baseline analyses. For the 602 subjects included in the analysis, 1,997 maternal SRSs were performed for 592 subjects, and 1,586 teacher measures were performed for 515 subjects, with 10 subjects having only teacher measures and 87 subjects having only maternal measures.
Tables 1 and 2 provide descriptive statistics of maternal and teacher assessments, respectively, including selected sample characteristics as a function of specific groupings of subjects. Some of the planned annual follow-up assessments were not returned by informants (missing); the mean duration of follow-up for each group compared to the mean number of SRSs reflects the average number of annual assessments missing. Appendix S2 provides further depictions of the sample.

**Data Analysis**

In order to analyze the agreement between maternal and teacher ratings and between successive ratings by mothers and teachers, we used non-parametric LOESS (locally weighted regression) curve fitting and regression analysis. We employed fixed effects and mixed models to analyze the longitudinal course of serial maternal ratings as a function of group, age, and age squared; and used Bayesian information criterion (BIC) as the model selection tool. The primary contrasts are between the three ASD groups, the psychiatric comparison group, and unaffected controls (with group subsuming gender). Because we found only modest differences in SRS scores between the unaffected siblings of both ASD subjects and psych subjects, we pooled these control groups. See Appendix S6 for analyses of predictors of dropout and missing data. All analyses were conducted using SAS 9.4, with the exception of the graphs in the Appendices S1 and S2, which were conducted in R (RStudio, 2018).

**Results**

**Interrater Agreement**

Very substantial agreement existed between maternal-report and teacher-report SRS scores, as demonstrated by the homology in mean scores. For all available pairings of maternal and teacher-report data ($N = 1,401$ pairs), the correlation between maternal and teacher ratings was $0.71$ ($p < 0.01$), depicted by the linear relationship in Figure 1 (which overwhelmingly reflects independent observations because serial ratings of any given subject in successive years were completed by different teachers). Appendix S7 provides further detail on the interrater agreement analysis. Given the strong maternal-teacher interrater reliability and higher consistency of maternal raters over time, all primary analyses were conducted on maternal data.

### Table 1

**Maternal SRS Measures**

| Subject type                          | Number of subjects | $M_{age}$ (SD) baseline | Age range: baseline | $M_{age}$ (SD) latest: follow-up | Age range: latest follow-up | Total number SRS | Mean baseline SRS (SD) | Mean duration of follow-up | Mean number of SRS (SD) | Range of follow-up years |
|---------------------------------------|--------------------|-------------------------|--------------------|----------------------------------|-----------------------------|---------------------|------------------------|-----------------------------|--------------------------|---------------------------|
| Male ASD simplex family               | 170                | 8.0 (3.9)               | 2.6–18.0           | 12.4 (4.9)                       | 16.1–23.8                   | 646                 | 101.8 (29.0)          | 4.4                         | 3.80 (2.09)               | 0–14.0                    |
| Male ASD multiplex family             | 89                 | 6.1 (2.8)               | 3.0–15.7           | 11.2 (4.0)                       | 16.1–23.8                   | 378                 | 94.0 (32.6)           | 5.1                         | 4.25 (1.94)               | 0–12.6                    |
| Female ASD simplex/multiplex family  | 40                 | 8.3 (3.7)               | 3.1–16.2           | 12.2 (5.2)                       | 10.6–17.0                   | 133                 | 101.5 (29.1)          | 3.9                         | 3.32 (1.66)               | 0–12.0                    |
| Male unaffected siblings              | 149                | 8.1 (4.2)               | 2.6–22.2           | 12.0 (5.2)                       | 17.9–23.1                   | 412                 | 25.6 (19.9)           | 4.0                         | 2.77 (1.28)               | 0–11.7                    |
| Female unaffected siblings            | 64                 | 9.8 (4.7)               | 2.9–21.7           | 12.3 (5.0)                       | 12–21.4                     | 116                 | 21.0 (24.9)           | 2.5                         | 1.81 (0.77)               | 0–10.3                    |
| Male psych condition                 | 43                 | 11.4 (3.5)              | 4.3–21.5           | 17.0 (4.2)                       | 9.6–12.7                    | 196                 | 51.4 (34.1)           | 5.7                         | 4.56 (1.82)               | 0.1–15.1                  |
| Male unaffected siblings, psych-     | 37                 | 10.6 (5.0)              | 3.0–28.7           | 15.5 (5.5)                       | 15.3–24.1                   | 116                 | 19.1 (20.0)           | 4.9                         | 3.14 (1.29)               | 0–9.4                     |
| affected family                      |                    |                        |                    |                                  |                             |                     |                        |                             |                          |                           |
| Total                                 | 592                | 8.4 (4.2)               | 2.6–28.7           | 12.6 (5.1)                       | 9.5–22.7                    | 1,997               | 63.9 (45.6)           | 4.3                         | 3.37 (1.85)               | 0–15.1                    |

*Note. SRS = Social Responsiveness Scale; ASD = autism spectrum disorder.*
AVR at Baseline

Consistent with numerous previously published studies, the mean baseline maternal SRS score for each of the ASD-affected groups differed by approximately three standard deviations from that of unaffected children and by approximately two standard deviations from psychiatric controls. The maternal baseline SRS scores of individuals who met DSM–IV diagnostic criteria for Autistic Disorder averaged an additional 12.7 points (SD = 3.6; p < .01) above the scores of individuals who met criteria for DSM–IV Asperger Disorder or Pervasive Developmental Disorder Not Otherwise Specified.

No significant differences existed in baseline scores between male ASD subjects from simplex families and multiplex families, or between male and female ASD subjects, regardless of familial category (p-values between .57 and .92). Baseline scores of male and female unaffected siblings, as well as nonaffected psychiatric condition siblings, exhibited no significant differences (p > .75). Figure 2 depicts maternal SRS scores as a function of group.

Table 3 summarizes relative influences of selected subject characteristics on baseline maternal SRS scores. As expected, possessing a psychiatric diagnosis other than ASD elevated maternal SRS scores significantly (p < .01). In keeping with prior observations in multiplex family samples, unaffected siblings of individuals with ASD demonstrated mild aggregations of quantitative autistic traits, exhibiting a mean SRS score difference of 6.5 points higher than siblings of psychiatric controls; however, multiplex families comprised only a fraction of our total sample, in which this difference did not reach statistical significance. Age of child influenced maternal baseline SRS score (p = .02). Whether or not the child was capable of phrase speech also affected baseline SRS; specifically, nonverbal individuals (N = 24) were characterized by lower SRS scores.

Stability of AVR Over Time

When considering the entire sample, there was pronounced preservation of interindividual variation in AVR over time. Table 4 summarizes test–retest correlations of successive maternal and teacher total SRS scores of all subjects from baseline through the final follow-up measurement (Appendix S9 provides test–retest correlations of SRS subdomains). Test–retest correlations were extremely high for successive maternal ratings (~.90) and strong (~.70) for successive teacher ratings (which almost always involved different teachers for any given subject; Table 4). None of the
individuals with an ASD diagnosis experienced a magnitude of reduction in maternal SRS scores over the longitudinal period that would have been consummate with loss of diagnosis.

The scatter plot in Figure 3 depicts 527 randomly selected pairs of successive maternal total SRS scores, one pair per subject, with linear regression (blue) and nonparametric loess (black) superimposed (Appendix S9 provides rationale for random selection and scatter plots by SRS subdomain). The linear and nonparametric curves are at an extremely high level of agreement, and the correlation between ratings is .91. A linear regression with SRS at first assessment and time between measurements achieves $R^2 = .85$, indicating that baseline SRS is an extraordinarily strong predictor of all future measurements. A comparison between ASD and non-ASD subjects for coefficients of 2-year stability from baseline revealed no significant difference. In this subset, average age at first measurement is 9.4 years ($SD = 4.8$, range = 1.6–28.7), and the average time between measurements is 2.0 years ($SD = 1.27$, range = 0.04–10.2). There is a slight suggestion that at the higher values, maternal ratings underestimate those of teachers.

**AVR Over the Life Course**

A spaghetti plot depicting the individual childhood trajectories of maternal-report total SRS scores for study subjects with more than one maternal SRS ($N = 527$) is depicted as a function of ASD diagnostic status in Figure 4, revealing a marked distinction between affected and unaffected individuals throughout the course of childhood and adolescence. (Appendix S10 provides SRS subdomain spaghetti plots.)
To explore possible differences in longitudinal course for the seven groups, we developed growth curve models, specifying each group’s trajectory of maternal SRS rating as a function of age, utilizing loess smoothing with approximate 95% CI (Figure 5). There was no effect of control group origin, $F(2, 247) = 0.53, p = .59$, and only a mild suggestion of a trend for decreasing SRS scores with age, $F(1, 396) = 2.86, p = .09$; and no evidence of an age by control group interaction, $F(2, 396) = 1.23, p = .29$.

The growth curves reveal strong preservation of interindividual differences, by relatively consistent CIs over the full range of ages, except for later ages, in which sample size eroded statistical power to specify the precise trajectory. The data indicate a relative absence of differences among subgroups within the respective ASD-affected and ASD-unaffected populations. ASD-affected females exhibited trends

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**Table 3**  
**Influences on Baseline Maternal SRS Scores**

| Variable                             | Estimate | N   | T     | p-Value |
|--------------------------------------|----------|-----|-------|---------|
| Teacher score                        | 0.22     | 505 | 11.9  | <.01*   |
| ASD                                  | 63.50    | 592 | 15.2  | <.01*   |
| Other psych diagnosis                | 28.30    | 592 | 6.1   | <.01*   |
| Unaffected sibling: simplex and multiplex families$^a$ | 2.90     | 592 | 0.7   | .48     |
| Age                                  | −0.36    | 592 | −2.3  | .02*    |
| Gender                               | 1.38     | 592 | 0.5   | .59     |
| Verbal$^b$                           | −11.50   | 592 | −2.3  | .02*    |
| IQ$^c$                               | −0.21    | 228 | −2.8  | .06     |

*Note. Relative influences of selected subject characteristics on baseline maternal SRS scores for all subjects. SRS = Social Responsiveness Scale; ASD = autism spectrum disorder.  
$a$Elevated in comparison to psychiatric sibling controls and population norms. $b$Capable of phrase speech. $c$Appendix S8 provides IQ tests utilized. *Statistically significant.

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**Table 4**  
**Mother and Teacher Test–Retest Correlations**

| Interval | Mothers | Teachers |
|----------|---------|----------|
|          | Avg. time lag | Test-retest correlation | Avg. time lag | Test-retest correlation |
| 1        | 527     | 1.95     | .90       | 508     | 1.78     | .74       |
| 2        | 347     | 1.64     | .91       | 312     | 1.54     | .69       |
| 3        | 239     | 1.73     | .93       | 112     | 1.92     | .74       |
| 4        | 137     | 1.86     | .92       | 71      | 1.97     | .71       |
| 5        | 86      | 1.80     | .93       | 49      | 1.71     | .63       |
| 6        | 55      | 1.61     | .95       | 15      | 1.35     | .56       |
| 7        | 16      | 1.45     | .95       | 5       | 1.34     | .60       |

*Note. Correlations between successive measurements showing the stability of both maternal and teacher total Social Responsiveness Scale scores.
for improvement. IQ scores failed to predict the longitudinal course of SRS scores within any group.

We fitted fixed effects models as well as random effects models (intercept, slopes) to the data, with group, age, age-squared, and interaction terms between group and age and age squared (Table 5). The model with random intercepts but fixed slopes (Model 2) fit the data the best, based on BIC (Table 6). There is strong evidence of a group effect, $F(4, 587) = 48.91, p < .01$, age, $F(1, 1,402) = 11.05, p < .01$, and curvilinearity, $F(1, 1,402) = 26.75, p < .01$, as well as evidence that the time courses vary by group (interaction with age, $F(1, 1,402) = 2.90, p < .02$; interaction with age squared, $F(1, 1,402) = 4.7, p < .01$. The group effect is driven primarily by the differences between typically developing children (TDC) and the three ASD groups (all $p < .01$), and that the difference between TDC and psychiatric controls is less pronounced (an increase of ~31 SRS points, $p = .05$). We also find that the age by group interaction is primarily driven by differences in slopes in the female ASD group, which is the only group presenting with a distinct decrease and substantial curvilinearity, $t(1,402) = 3.28, p < .01$ and $t(1,402) = 4.08, p < .01$, respectively.

**Discussion**

This cohort-sequential study demonstrated that AVR exhibits trait-like stability from preschool to young adulthood across the entire range of variation in which it manifests in childhood. Interindividual variation in SRS scores was highly preserved, and growth curve modeling confirmed a

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**Figure 3.** Stability of randomly selected pairs of successive maternal Social Responsiveness Scale measurements ($N = 527$ pairs). The shaded light blue around the darker blue regression line is the 95% CI. The dotted line is the 45° line.

**Figure 4.** Individual childhood trajectories of maternal-report total Social Responsiveness Scale scores as a function of autism spectrum disorder (ASD) diagnostic status ($N = 527$).
marked degree of measurement reliability over time. Furthermore, the course of individuals’ scores from early childhood to young adulthood reflected distinct separations in symptom burden for deficiency in AVR, overwhelmingly differentiating controls from ASD-affected individuals. As hypothesized on the basis of stability of ASD diagnoses, these results demonstrate that throughout the entire distribution observed in nature, AVR exhibits stability from childhood to early adulthood. In this sense, subclinical variations in AVR are as stable as autism itself.

With stability of .91, AVR exceeds that of IQ (~.63; Plomin & Deary, 2015), a core construct in psychology of individual differences, behavioral genetics, and human development; and other psychopathological syndromes measured from adolescence to early adulthood, such as conduct disorder (~.50; Murray & Farrington, 2010) and borderline personality disorder (~.52; Bornvalova, Hicks, Iacono, & McGue, 2009; Chanen et al., 2004).

These data are in keeping with other prior studies that have identified marked stability of clinical autistic syndromes over the life course (Gotham, Pickles, & Lord, 2012). One found that the number and severity of repetitive sensorimotor behaviors either persisted or somewhat improved (Richler, Huerta, Bishop, & Lord, 2010). A recent 10-year prospective study demonstrated two trajectories in the Vineland Adaptive Behavior Scale: one with modest gains and another with stable impairments (Baghdadi et al., 2011). Other work has described six developmental trajectories for core autism symptom domains, with most showing a stable to slight improvement in functioning, such that a high-functioning individual generally remained as such longitudinally. Most

Table 5

| Model Fitting of Longitudinal Data | df | Model 1 | Model 2 | Model 3 |
|-----------------------------------|----|---------|---------|---------|
| AIC                               | 9  | 17,915.9| 17,813.9| 17,937.6|
| BIC                               | 9  | 17,924.7| 17,885.6| 17,846.8|
| Group                             | 9  | 4,587   | 22.18   | 48.91   |
| p < 0.01                          |    | p < 0.01| p < 0.01| p < 0.01|
| Age                               | 9  | 1,1402  | 2.27    | 11.05   |
| p = 0.09                          |    | p < 0.01| p < 0.01| p < 0.01|
| Age squared                       | 9  | 1,1402  | 6.73    | 26.75   |
| p < 0.01                          |    | p < 0.01| p < 0.01| p < 0.01|
| Age x Group                       | 9  | 4,1402  | 1.19    | 2.90    |
| p = 0.31                          |    | p = 0.02| p < 0.01| p < 0.01|
| Age Squared x Group               | 9  | 4,1402  | 1.57    | 4.70    |
| p = 0.18                          |    | p < 0.01| p < 0.01| p < 0.01|

Note. Model 1: fixed effects only; Model 2: random intercept, fixed slope; Model 3: random intercept and slope. All models assume a spatial exponential residual correlation structure and include group, age, age squared, and interaction between group and age and age squared. AIC = Akaike’s information criterion; BIC = Bayesian information criterion. 

*For the corresponding Type III test of fixed effect.

Table 6

| Model 2: Fixed Effects Estimates | Estimate | SE | t | p-Value |
|---------------------------------|----------|----|---|---------|
| Intercept                       | 25.76    | 3.85| 6.68| < .01   |
| Male ASD (simplex)              | 69.84    | 6.16| 11.33| < .01   |
| Male ASD (multiplex)            | 62.94    | 7.08| 8.88| < .01   |
| Female ASD                      | 47.51    | 1.78| 4.03| < .01   |
| Male psych                      | 31.94    | 6.25| 1.97| .05     |
| Age                             | 0.04     | 0.04| 0.94| < .01   |
| Age x Male ASD (Simplex)        | 1.81     | 1.23| 1.46| .14     |
| Age x Male ASD (Multiplex)      | 1.06     | 0.99| 1.07| .29     |
| Age x Female ASD                | 5.95     | 1.82| 3.28| < .01   |
| Age x Male Psych                | 0.27     | 0.21| 1.27| .21     |
| Age x Male ASD (Simplex)        | 0.94     | 0.04| 0.04| < .01   |
| Age x Age x Male ASD (Simplex)  | 0.02     | 0.02| 0.02| < .01   |
| Age x Age x Male ASD (Multiplex)| 0.02     | 0.02| 0.02| < .01   |
| Age x Age x Female ASD          | 0.02     | 0.02| 0.02| < .01   |
| Age x Age x Male Psych          | 0.02     | 0.02| 0.02| < .01   |

Note. Model 2: random intercept, fixed slope. This model, which fit the data best, assumes a spatial exponential residual correlation structure and includes group, age, age squared, and interaction between group and age and age squared. ASD = autism spectrum disorder.
low-functioning individuals also maintained stable levels of functioning, with the exception of a group of “bloomers” who throughout time achieved levels of functioning similar to higher functioning individuals (Fountain, Winter, & Bearman, 2012). Yet critically, no studies have examined the course of AVR across the entire range of variation, a knowledge gap this study sought to address.

There are several limitations of this study. First, the SRS does not capture the entirety of the complex construct of reciprocal social behavior; however, the field of social development is still grappling with how to define the construct, assign its parameters, and fully quantify it. Second, due to the cohort-sequential design, no individual was studied from early childhood to adulthood. Third, the affected subjects were receiving a variety of forms of therapy, and although their trajectories could have been influenced by the interventions, their SRS scores still remained stable (see also Marrus, Underwood-Riodan, Randall, Zhang, & Constantino, 2014). Finally, this prospective longitudinal study lacked statistical power to fully define specific trajectories of subgroups of subjects. The study was, however, adequately powered to detect very modest time-rated changes in standardized scores of AVR—on the order of less than one-half of a standard deviation over a decade—for major groupings of affected and unaffected subjects. Supporting our current results of longitudinal stability in typically developing individuals, the means and standard deviations of SRS scores of our unaffected sibling sample match epidemiological, cross-sectional SRS data acquired from cross-cultural studies in Europe (Bölte, Pousta, & Constantino, 2008) and Asia (Kamio et al., 2013). Thus, this study offers the first-ever population-wide appraisal of the stability of AVR using normed quantitative measurements over the entire course of childhood.

Beginning early in infancy, children become socially specialized (Johnson, 2001). The essential role of sociality in human development highlights the significance of inherited determinants of social variation, one of which has potential to be indexed by measurements of AVR as deployed in this longitudinal study. It will require a next generation of studies to determine the nature of AVR’s interactions with other genetic and environmental influences to confer susceptibility or resilience to maladaptive social and emotional outcomes. Characterization of AVR stands to enhance the precision of future biomarker research exploring neural and psychophysiological signatures of social and emotional development, the promise of which is to advance understanding of the mechanisms by which genes influence behavior and to elucidate specific targets for preventive intervention of inherited syndromes of social and neurodevelopmental impairment.

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**Supporting Information**

Additional supporting information may be found in the online version of this article at the publisher’s website:

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Appendix S2. Sampling Frame and Study Design
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Appendix S9. Stability of Social Communication and Interaction and Restricted Interests and Repetitive Behaviors
Appendix S10. Subdomains of Autism-Related Variation in Reciprocal Social Behavior Over the Life Course