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A Psychometrically Robust Screening Tool To Rapidly Identify Socially Impaired Monkeys In The General Population

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Abstract

Naturally low-social rhesus macaques exhibit social impairments with direct relevance to autism spectrum disorder (ASD). To more efficiently identify low-social individuals in a large colony, we exploited, refined, and psychometrically assessed the macaque Social Responsiveness Scale (mSRS), an instrument previously derived from the human ASD screening tool. We performed quantitative social behavior assessments and mSRS ratings on a total of $N = 349$ rhesus macaques (*Macaca mulatta*) housed in large, outdoor corrals. In one cohort ($N = 116$), we conducted inter-rater and test-retest reliabilities, and in a second cohort ($N = 233$), we evaluated the convergent construct and predictive validity of the mSRS-Revised (mSRS-R). Only 17 of the original 36 items demonstrated inter-rater and test–retest reliability, resulting in the 17-item mSRS-R. The mSRS-R showed strong validity: mSRS-R scores robustly predicted monkeys' social behavior frequencies in home corrals. Monkeys that scored 1.5 standard deviations from the mean on nonsocial behavior likewise exhibited significantly more autistic-like traits, and mSRS-R scores predicted individuals' social classification (low-social vs. high-social) with 96% accuracy (likelihood ratio chi-square = 25.07; $P < 0.0001$). These findings indicate that the mSRS-R is a reliable, valid, and sensitive measure of social functioning, and like the human SRS, can be used as a high-throughput screening tool to identify socially impaired individuals in the general population.

Lay Summary:

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Author Contributions

K.J.P., J.P.C., J.P.G., and C.F.T. designed the study. CFT wrote the first draft of the manuscript, collected behavioral data, analyzed the data, and created the tables. A.C.M. collected behavioral data. J.P.G., J.P.C., and K.J.P. supervised statistical analysis of the data. J.P.G. created the figures. K.J.P., J.P.C., and B.M. procured project funding and site access. All authors reviewed and meaningfully contributed to editing the manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Variation in autistic traits can be measured in humans using the Social Responsiveness Scale (SRS). Here, we revised this scale for rhesus macaques (i.e., the mSRS-R), and showed that macaques exhibit individual differences in mSRS-R scores, and at the behavioral extremes, low-social vs. high-social monkeys exhibit more autistic-like traits. These results suggest that the mSRS-R can be used as a screening tool to rapidly and accurately identify low-social monkeys in the general population.

Keywords

autism spectrum disorder (ASD); Social Responsiveness Scale; social behavior; rhesus macaque; social deficits; psychometrics; animal model

Introduction

Autism spectrum disorder (ASD) is a prevalent (1 in 54 U.S. children), male-biased (4:1, M:F), and poorly understood neurodevelopmental condition characterized by core social interaction impairments and the presence of restricted, repetitive behaviors [American Psychiatric Association, 2013; Maenner et al., 2020]. Progress in detecting and treating ASD has been impeded by the difficulty of studying disease biology directly in human patients and reliance on model organisms in which control animals lack the sophisticated social skills and cognitive abilities critical for modeling behavioral symptoms relevant to human ASD. These constraints underscore the tremendous value in advancing animal models with more behavioral homology to the human disease, and in developing the tools needed to identify and phenotype them easily, quickly, and accurately.

Naturally low-social rhesus macaques have recently emerged as a promising ASD model. Rhesus monkeys exhibit stable and pronounced individual differences in complex social functioning [Phillips et al., 2014], and at the social behavioral extremes of the population, low-social monkeys initiate fewer affiliative interactions, spend less time in physical contact and grooming, and display more inappropriate social behavior compared to high-social monkeys [Capitanio, 1999; Sclafani et al., 2016]. Rhesus monkeys later classified as low-social in adulthood also exhibit deficits in their ability to discriminate familiar and novel faces and accurately interpret and respond to social cues as infants [Sclafani et al., 2016], abilities often impaired in individuals with ASD. Moreover, because autistic traits are common and continuously distributed across the general human population [Baron-Cohen, Wheel-wright, Skinner, Martin, & Clubley, 2001; Constantino & Todd, 2003, 2005; Ronald et al., 2006], and can be present subclinically in relatives of autistic probands [Constantino et al., 2006; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997], the naturally occurring variation in rhesus monkey social behavior makes them a potentially powerful model of the polygenic risk factors that contribute to ASD [Gaugler et al., 2014].

However, because social impairments associated with ASD reflect the extreme end of a continuous distribution of social traits, researchers need a tool that can rapidly and accurately identify naturally low-social rhesus monkeys in the general population. Such a tool exists for this purpose in humans: the Social Responsiveness Scale (SRS). The SRS is a 65-item survey-based instrument that quantitatively assesses the presence and severity of autistic traits in children and adults in the general human population [Chan, Smith, Hong, Greenberg, & Mailick, 2017; Constantino & Gruber, 2012]. The SRS was developed for use in the United States, but has since been shown to accurately measure autistic traits in multiple and diverse human societies [Bölte, Poustka, & Constantino, 2008; Jussila et al., 2015; Stickley et al., 2017]. Importantly, SRS scores of ASD-diagnosed vs. unaffected siblings differ robustly at 1.5 standard deviations above the general population mean [Constantino, 2011; Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Virkud, Todd, Abbacchi, Zhang, & Constantino, 2009]. SRS scores are also strongly correlated with research diagnostic assessment scores on the instruments (i.e., the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview-Revised) used to confirm a clinical diagnosis of ASD [Connolly, Glessner, & Hakonarson, 2013; Constantino et al., 2003].

The SRS was first “reverse translated” for use in nonhuman primates by removing items related to language or items that were difficult to interpret across species. The resulting 36-item chimpanzee SRS was given to care staff to complete on an initial sample of primarily adult chimpanzees ($N = 29$) [Marrus et al., 2011]. More recently, Feczko, Bliss-Moreau, Walum, Pruett, and Parr [2016] adapted the chimp SRS for use in rhesus macaques (i.e., the macaque SRS, or mSRS). The mSRS instrument was administered by research and care staff on $N = 105$ randomly selected adult rhesus macaques. However, 87% of these macaques were adult females and no young animals were studied. Although item-level inter-rater reliabilities were conducted, these analyses were based on a very small sample ($N = 16$) and test–retest reliability was not assessed. Importantly, the mSRS was not evaluated in conjunction with social behavior observations, and no socially impaired monkeys were studied. Thus, whether this instrument could accurately identify socially impaired animals was unknown.

Indeed, careful psychometric evaluation of measurement scales is rare in preclinical research [Constantino, 2002; Fonio, Golani, & Benjamini, 2012; Nestler & Hyman, 2010]. Such work is, however, essential for evaluating the validity of animal models to facilitate streamlined translation to patients. The present study, therefore, was designed to exploit the use of the existing mSRS, but to refine it, and interrogate its psychometric properties. We did so in the largest sample of rhesus monkeys studied to date, spanning development into adulthood, including young male animals in keeping with the early onset and male-biased nature of ASD. Our specific aims were threefold. We first refined the existing mSRS to increase the internal validity of the instrument. We then assessed inter-rater reliability and test–retest reliability of each mSRS item and established internal consistency reliability of the resulting 17-item mSRS-Revised (mSRS-R). Finally, we evaluated the convergent construct validity and predictive validity of our revised instrument. We did so by evaluating the relationship between mSRS-R scores and social behavior frequencies obtained by observing animals in their outdoor field corrals, and by testing the accuracy of mSRS scores to differentiate low-social and high-social animals at the behavioral extremes of our sample. We hypothesized that mSRS-R scores would predict quantitative social behavior frequencies as well as social classification (low-social vs. high-social). We found the mSRS-R to be a reliable and valid instrument that sensitively measures autistic-like traits in rhesus monkeys. These collective findings suggest that the mSRS-R, like the human SRS, can be used as a high-throughput screening tool to rapidly identify socially impaired individuals in the general population.

Methods

Subjects and Housing

Subjects included a total of *N* = 349 rhesus macaques (*Macaca mulatta*) born at the California National Primate Research Center (CNPRC). All subjects lived in mixed age and sex groups of up to 150 individuals in large, outdoor, half-acre (0.19 ha) field corrals (30.5 m wide × 61 m deep × 9 m high). Soon after birth, monkeys were tattooed and dye-marked prior to behavioral observation to facilitate easy identification. Monkeys had *ad libitum* access to Lixit-dispensed water. Primate laboratory chow was provided twice daily and fruit and vegetable supplements were provided weekly. Outdoor field corrals, enhanced with various toys, swinging perches, and other enrichment, provided a stimulating environment for the subjects.

Our study included two cohorts. We conducted reliability analyses on a sample of *N* = 116 rhesus macaques (31 males, 85 females) with a mean (*SD*) age of 7.05 (5.94) years with a range of 1.66–23.46 years. Individuals in this reliability cohort lived in two field corrals. Corral 1 consisted of *N* = 127 rhesus macaques (*N* = 33 males, *N* = 94 females). Within Corral 1, we studied *N* = 69 animals (*N* = 9 males, *N* = 60 females) ranging from 3.44 to 23.46 years old at the time of rating (*M* = 10.30, *SD* = 5.75). Corral 2 consisted of *N* = 154 rhesus macaques (*N* = 56 males, *N* = 98 females). Within Corral 2, we studied *N* = 47 animals (*N* = 22 males, *N* = 25 females) ranging from 1.66 to 2.89 years old at the time of rating (*M* = 2.28, *SD* = 0.53). We conducted validity analyses on a separate sample of *N* = 233 male rhesus macaques. Individuals in this cohort were housed among 16 field corrals. Mean (*SD*) age was 3.62 (1.12) years with a range of 1.25–6.27 years at the time of the study. All procedures were ethically reviewed and approved by the Institutional Animal Care and Use Committee of the University of California, Davis and Stanford University. All procedures complied with the Guide for the Care and Use of Laboratory Animals and National Institutes of Health policies on the care and use of animals.

Refining the Original mSRS to Enhance Internal Validity

Prior to data collection, we optimized the mSRS in three distinct ways. First, unlike the original study [Feczko et al., 2016], which used a four-point scale (1 = not true, 2 = sometimes true, 3 = often true, and 4 = almost always true), we chose to implement a seven-point Likert scale. The psychological literature has shown that seven-point Likert scales provide the optimal number of intervals for rating traits of personality [Cox, 1980; Symonds, 1924]. Additionally, this scale enabled greater granularity in social behavior evaluation and better accommodated a neutral response (i.e., a score of 4), an important feature that facilitates accurate responding by raters [Symonds, 1924]. Using the seven-point Likert scale, responses were quantified such that 1 = displays either total absence or negligible amounts of the trait, 2 = displays small amounts of the trait on infrequent occasions, 3 = displays somewhat less than average amounts of the trait, 4 = displays about average amounts of the trait, 5 = displays somewhat greater than average amounts of the trait, 6 = displays considerable amounts of the trait on frequent occasions, or 7 = displays extremely large amounts of the trait.

Second, we removed unclear terminology. To quantify rhesus macaque behavior more objectively and increase internal validity, we modified two questions (18 and 29) that used the term, “emotionally.” Emotionality is not well-defined in the nonhuman primate literature [Bliss-Moreau, 2017], whereas prosocial behavior is a more clearly defined construct [Jaeggi, Burkart, & Van Schaik, 2010]. Prosocial behaviors may include the initiation of play, grooming, or any interactions that are cooperative in nature such as sharing toys, food, or space. Thus, we changed question 18, “Avoids other monkeys that may want to be emotionally close to him/her,” to state, “Avoids others that behave prosocially towards the subject.” Likewise, we changed question 29, “Is emotionally distant, does not show his/her feelings” to “Is indifferent to others’ initiation of social interactions; lacks facial expressions.”

Finally, we created an enhanced ethogram to provide examples of species-specific behaviors. Question 25, for instance, “Has repetitive, odd behaviors such as hand flapping, rocking/swaying, tumbling or spinning,” was clearly derived from the human SRS. Therefore, we expanded the definition of this question to target macaque-specific behaviors including the display of (motor or self-directed) stereotypical behaviors such as digit sucking, self-clasping, self-hitting, and self-biting. These changes made the mSRS more ecologically relevant to the test species, thereby increasing the internal validity of the instrument.

To prevent biases, questions were worded in both the frequent and infrequent direction. Twenty-six questions were asked in the frequent direction, for example, “Would rather be alone than with others,” in which a higher score indicated greater social impairment. Ten questions were worded in the infrequent direction, for example, “Plays appropriately with peers,” in which a lower score indicated greater social impairment. Responses to the latter were reverse-scored prior to the final summary, such that higher scores were related to greater social impairment [Feczko et al., 2016]. Therefore, using the seven-point Likert scale, the final summed mSRS scores could range between 36 and 252. See Appendix S1 for the refined and expanded 36-item macaque Social Responsiveness Scale (mSRS).

Collecting mSRS Ratings for Reliability Analyses in the First Cohort

We evaluated two types of rater reliability: inter-rater reliability and test–retest reliability. For inter-rater reliability, each monkey was scored by different raters within a 1-week period. For test–retest reliability, each monkey was scored by the same raters on two different occasions, with 2 weeks intervening between a given rater’s evaluations of a given monkey. A total of six raters completed mSRS ratings on two different field corrals (i.e., three raters per corral), at two different time points. In all cases, raters were told not to discuss their ratings with other observers, effectively blinding them to other raters’ scores. Although the raters’ experience working with monkeys and observing animals in these particular field corrals varied, all raters had at least 6 months (and up to 2 years) of experience observing monkeys in their respective corral, and at least 1.5 years (and up to 5 years) of experience working with rhesus macaques more generally.

Collecting Behavioral Observations and mSRS Ratings for Validity Analyses in the Second Cohort

Behavioral observations were performed over a 2-year period. Prior to conducting behavioral observations, observers became reliable on data collection with ≥90% agreement on all behavioral categories. Subjects were observed unobtrusively in their home field corrals. Each observer conducted 10-min focal samples on subjects during two observation periods per day (0830–1030 and 1045–1300), 4 days per week, for 2 weeks. Each observer watched a maximum of nine subjects, residing in one to three corrals, during the 2-week period. We used instantaneous sampling [Altmann, 1974] in which we recorded, at 15-sec intervals, whether the subject was engaged in any of the following behaviors: alone (subject is not within an arm's reach of any other animal and is not engaged in play), proximity (subject is within an arm's reach of another animal), contact (subject is touching another animal in a nonaggressive manner), groom (subject is engaged in a dyadic interaction with one animal inspecting the fur of another animal using its hands and/or mouth), or play (subject is involved in chasing, wrestling, slapping, shoving, grabbing, or biting accompanied by a play face [wide eyes and open mouth, without bared teeth] and/or a loose, exaggerated posture and gait; the behavior must have been deemed unaggressive to be scored) [Parker et al., 2018]. Within 24 hr of the completion of each 2-week behavioral observation period and after returning to their desks, observers rated each subject on the mSRS.

Determining Social Classification within the Second Cohort

Monkeys were rank-ordered on their total frequency of nonsocial behavior ($M = 400.19$, SD = 75.98) summarized across the 16 focal behavior samples collected per subject [Parker et al., 2018]. Animals were classified based on whether their scores were 1.5 SD above the mean ($N = 14$, low-social) or 1.5 SD below the mean ($N = 14$, high-social). We chose to use 1.5 SD from the mean of the general population based on the fact that when parents and classroom teachers rate the severity of ASD-diagnosed vs. undiagnosed populations, the point of greatest differentiation of the respective distributions occurs at a point that is approximately 1.5 SD away from the general population mean [Constantino, 2011; Constantino et al., 2010; Virkud et al., 2009].

Data Analysis

Data were analyzed using SPSS statistical package version 25 (SPSS Inc., Chicago, IL) or JMP Pro 14 (SAS Institute Inc., Cary, NC). Using the refined mSRS (see Appendix S1), we evaluated item-level reliabilities using intra-class correlations (ICC) [McGraw & Wong, 1996; Shrout & Fleiss, 1979] in our first study cohort. Because this population contained monkeys housed in two field corrals with three raters per corral, for inter-rater reliability and test–retest reliability, we calculated ICC coefficients for each item for each corral separately. To assess the inter-rater reliability of each item (i.e., different raters score the same animal consistently), ICC (2A, C) [McGraw & Wong, 1996] estimates were calculated. We employed a random-effects model because it is appropriate for evaluating rater-based clinical assessments designed for routine use and because we plan to generalize the results of the reliability analysis to any raters who possess similar experience with subjects.

Because we were concerned with whether raters' scores of the group of subjects were correlated in an additive manner for inter-rater reliability, we employed the consistency (rather than absolute agreement) type of ICCs. To assess the test–retest reliability of each item (i.e., the same rater scores a given animal consistently at multiple time points), ICC (3A, A) [McGraw & Wong, 1996] estimates were calculated. For test–retest reliability, absolute agreement (rather than consistency) was chosen because measurements would have little meaning if there were no agreement between repeated measurements within the same individual rater. In addition, we used a mixed-effect model because in test–retest reliability the results only represent the reliability of the specific raters involved [Koo & Li, 2016]. Item-level reliability estimates from these analyses were then used to generate the 17-item mSRS-R. We used Cronbach's alpha to evaluate the internal consistency reliability of the resulting 17-item mSRS-R in both study cohorts.

Convergent construct validity of our instrument was next evaluated using multiple regression to assess the relationships between the mSRS-R and quantitative social behavior frequencies (alone, proximity, contact, groom, and play) obtained from the observations conducted on the second study cohort. Predictive validity of the mSRS-R was evaluated in this second cohort by testing whether mSRS-R scores predicted the behavioral extremes of the sample (i.e., low-social vs. high-social) using logistic regression. Finally, we tested whether low-social and high-social monkeys differed in their mSRS-R scores using a General Linear Model. All validity analyses were repeated including age and rank [Linden, McCowan, Capitanio, & Isbell, 2019] as covariates; the study findings were unchanged.

Results

Evaluating Inter-Rater and Test–Retest Reliability of the Original 36-Item mSRS

Using the refined mSRS (Appendix S1), we calculated item-level reliabilities on a sample of male and female monkeys ($N = 116$). Because this cohort contained animals housed in two different field corrals with three unique raters associated with each corral, we calculated ICC coefficients for each item for each corral separately. As expected, some items showed stronger inter-rater or test–retest reliability than others. Tables 1 and 2 display reliability estimates for individual mSRS items in each of the two corrals. The decision to retain an item in our revised scale was based upon demonstration of (a) an ICC that was significantly different from zero for inter-rater reliability in both corrals, and (b) an ICC that was significantly different from zero for test–retest reliability in both corrals. Additionally, if an item failed to generate score variability (i.e., a given rater scored all subjects the same for a particular item), the item was omitted. A total of 17 items met all three criteria, resulting in the mSRS-R (see Appendix S2). Next, we evaluated the internal consistency reliability of the mSRS-R. We found the mSRS-R to have acceptable internal consistency (Cronbach's alpha = 0.750). Final summed total scores on the mSRS-R could range between 17 and 119. Observed mSRS-R total scores in this sample ranged from 45 to 80. The distribution of mSRS-R total scores for this sample is plotted in Figure 1.

Evaluating Convergent Construct Validity: The Relationship Between mSRS-R Scores and Quantitative Social Behavior Frequencies

Due to the male-biased prevalence of ASD, we focused the remaining analyses on a second sample of young male monkeys ($N = 233$). We first evaluated the internal consistency reliability of the mSRS-R in this more homogeneous second sample and found the mSRS-R to have high internal consistency (Cronbach's alpha = 0.924). Observed mSRS-R total scores in this sample ranged from 23 to 101. The distribution of mSRS-R total scores in this sample is plotted in Figure 2. Because the mSRS-R measures raters' impressions of social traits (and not the frequency of specific social behaviors), we next evaluated whether mSRS-R scores were predictive of variation in quantitative social behavior frequencies obtained by focal observations of monkeys in their outdoor field corrals. We know that age and rank may impact social behavior in nonhuman primates [Vessey, 1984]; therefore, we first evaluated whether there was any effect of age and/or rank on mSRS-R scores. We found that neither age ($r = 0.098$, $N = 233$; $P = 0.135$) nor rank ($r = 0.027$, $N = 233$; $P = 0.683$) significantly correlated with mSRS-R scores. Nevertheless, because recent studies have sometimes found effects of age and/or rank on social responsiveness in nonhuman primates [Faughn et al., 2015; Feczko et al., 2016; Marrus et al., 2011], we included these variables as covariates in the linear regression models that we used to test whether the mSRS-R was predictive of social behavior frequencies. We found that higher mSRS-R scores (indicating greater social impairment) predicted the frequency of time spent alone (Table 3). Moreover, mSRS-R scores significantly and negatively predicted all other social behavior frequencies including proximity, contact, groom, and play such that higher mSRS-R scores were predictive of lower social behavior frequencies (Table 3). These findings demonstrate convergent validity such that mSRS-R scores are in fact related to observable social behaviors (as they theoretically should be) and construct validity such that the instrument measures what it claims to measure, social behavior (or lack thereof) [Garner, Gaskill, Weber, Ahloy-Dallaire, & Pritchett-Corning, 2017].

Evaluating Predictive Validity: The Relationship between mSRS-R Score and Social Classification

To evaluate predictive validity, we again used our sample of $N = 233$ young males. Subjects were classified as low-social ($N = 14$) or high-social ($N = 14$) based on the frequency of time spent alone, differentiated by greater than 1.5 SD above or below the sample mean, respectively. Next, we tested whether mSRS-R scores were predictive of social classification using logistic regression. As predicted, an individual's score on the mSRS-R predicted social classification with 96% accuracy (likelihood ratio chi-square = 25.07; $P < 0.0001$; Figure 3), demonstrating predictive validity. As would be expected, the converse was also true: Low-social monkeys exhibited greater social impairments, scoring significantly higher (LSM ± SE: 66.86 ± 2.81) on the mSRS-R compared to high-social monkeys (LSM ± SE: 41.93 ± 2.81) (GLM: $F_{1,26} = 39.48$, $P < 0.0001$; Figure 3).

Discussion

Here, we refined the original 36-item mSRS [Feczko et al., 2016] by enhancing the internal validity of the instrument and subsequently identifying reliable items to yield a 17-item revised scale, the mSRS-R. The mSRS-R generated a broad distribution of scores across the largest sample of rhesus monkeys studied to date and proved sensitive in identifying the presence of, and individual differences in, autistic-like traits using a similar instrument to detect them as that used in the human population. Collectively, these findings indicate that, like the human SRS, the mSRS-R is a psychometrically robust instrument that can be used as a high-throughput screening tool to rapidly identify socially impaired individuals in the general population.

Several similarities to cross-species SRSs support the translational applicability of the mSRS-R. Similar to the human SRS [Constantino, 2013], the mSRS-R demonstrated high internal consistency. Consistent with the human [Constantino, 2011] and chimpanzee [Marrus et al., 2011] SRS, across the entire population of rhesus macaques, the mSRS-R displays a continuous distribution. Furthermore, age did not correlate with mSRS-R scores, similar to what is observed in humans [Constantino, Przybeck, Friesen, & Todd, 2000] and chimpanzees [Faughn et al., 2015; Marrus et al., 2011]. The ability of the mSRS-R to detect a continuous range of social responsiveness and show similar relationships to intrinsic factors (e.g., age) as the human condition provides support for the construct validity of this instrument.

In the present study, we found that mSRS-R scores positively predicted the frequency of time spent alone. In contrast, higher mSRS-R scores were negatively predictive of prosocial behavior, including the frequency in which subjects were observed in proximity, contact, grooming, and playing with other monkeys. This is the first study to demonstrate that SRS scores in a nonhuman primate species are strongly related to quantitative social behavior measures. Moreover, these quantitative behavior measures confirmed that the mSRS-R measures what it was designed to measure: variation in social behavior. These results support the convergent construct validity of the instrument.

The human SRS is able to identify individuals with ASD and differentiate them from socially competent individuals [Constantino et al., 2003, 2007]. Therefore, unlike in previous nonhuman primate studies, we evaluated whether mSRS-R scores were able to differentiate socially impaired monkeys from their socially competent peers. This was indeed the case, as mSRS-R scores differentiated low-social and high-social animals with 96% accuracy, demonstrating the robust predictive validity of the instrument.

Previous research from our group has used the frequency observed in a nonsocial state (i.e., alone) as a means by which to classify rhesus monkeys at the behavioral extremes of a study population as low-social or high-social animals. We have also documented that low-social compared to high-social monkeys exhibit lower concentrations of the “social” neuropeptide arginine vasopressin in cerebrospinal fluid [Parker et al., 2018]. Importantly, we have forward translated this biomarker finding to three cohorts of ASD patients [Oztan et al., 2018; Oztan et al., 2020; Parker et al., 2018]. Here, we reverse translated the SRS to our macaque model and showed that low-social vs. high-social monkeys exhibit greater social impairments on an instrument used in humans to screen for ASD. The ability to bidirectionally translate ASD-associated bio-markers and screening tools to identify autistic traits underscores the importance of this primate model. Indeed, given the high homology between rhesus monkeys and humans, low-social rhesus monkeys could provide a powerful platform for testing the safety and efficacy of novel compounds, thereby accelerating the development of medications to improve social functioning in people with ASD in a way previously unachievable with existing animal models.

Previous research has found that higher SRS scores were associated with lower rank in chimpanzees [Faughn et al., 2015] and macaques [Feczko et al., 2016]. It is therefore somewhat surprising that we found no relationship between mSRS-R scores and rank, especially considering our sample is the largest nonhuman primate sample in which social responsiveness has thus far been evaluated. We first note that the social dominance hierarchy in rhesus macaque society is linear and significantly different from that of chimpanzees and humans. Rhesus macaques form dominance hierarchies based on matrilineal kinship as females remain in their natal groups while males emigrate shortly after puberty. Rank, therefore, is typically quantified separately for males and females. The previous study in rhesus macaques sampled 105 monkeys, 91 of which were females, whereas we specifically focused our rank analyses on 233 males due to the male-biased prevalence of ASD. Therefore, it is possible that rank interacts with social responsiveness differently in male and female rhesus macaques, a possibility that warrants investigation. Second, rank was classified categorically (low, middle, and high) in these previous studies, whereas here we used a more ecologically relevant, continuous variable indicative of the proportion of individuals the subject outranked in their respective corral [Linden et al., 2019], which was based on observational data rather than raters' impressions of subjects' rank. Thus, while it is certainly possible that higher mSRS-R scores may be associated with lower rank in nonhuman primates, given the discrepancies outlined above and our current results, we caution against concluding a causal relationship between the two.

This study had several limitations that warrant discussion. First, our sample was male-biased, and our validity analyses were conducted only in males, in keeping with ASD's prevalence (4:1, M:F) [Maenner et al., 2020]. However, growing evidence indicates that female children with ASD need to display higher levels of autistic traits to garner medical attention, and tend to be diagnosed at later ages than males on the spectrum [Loomes, Hull, & Polmear Locke Mandy, 2017], suggesting that ASD may be under-detected in female children. Since studies focused exclusively on males impede identification of sex-specific disease mechanisms, work is now needed to systematically evaluate social responsiveness in female rhesus macaques. Second, the youngest animals assessed in the present study were 1 year of age, which corresponds to roughly 3 years of age in humans [Kiluany, Moss, Rosene, & Herndon, 2000; Tigges, Gordon, McClure, Hall, & Peters, 1988]. As with humans [Volkmar, Chawarska, & Klin, 2005], social impairments emerge early in macaque development. By 3–4 months of age, infant monkeys already show social information processing abnormalities that put them at risk for poor social developmental outcomes [Sclafani et al., 2016]. The mSRS-R now needs to be deployed as a prospective screening tool to identify when social impairments first emerge in infant macaques. Finally, we did not examine the relationship between mSRS-R scores and cognitive ability, so it is possible that the observed social cognition impairments were driven by more global deficits in cognition. However, SRS and IQ scores have been shown to be unrelated in humans [Constantino et al., 2003; Constantino et al., 2000], suggesting that the social impairments we observed on the mSRS-R are likely to be primarily social in nature.

In conclusion, our findings suggest that the mSRS-R reliably measures autistic-like traits in rhesus monkeys, which are continuously distributed across the general population. This study likewise provides substantial validation for the mSRS-R as a powerful screening tool to rapidly identify naturally occurring low-sociality in this species. Finally, this instrument stands to have broad applicability: for use in other macaque species, as a tool to assess the presence of autistic-like traits in transgenic macaques, and as a translational primary outcome measure to facilitate the rapid advancement of promising therapeutic agents to clinical trials in patients with ASD.

Supplementary Material

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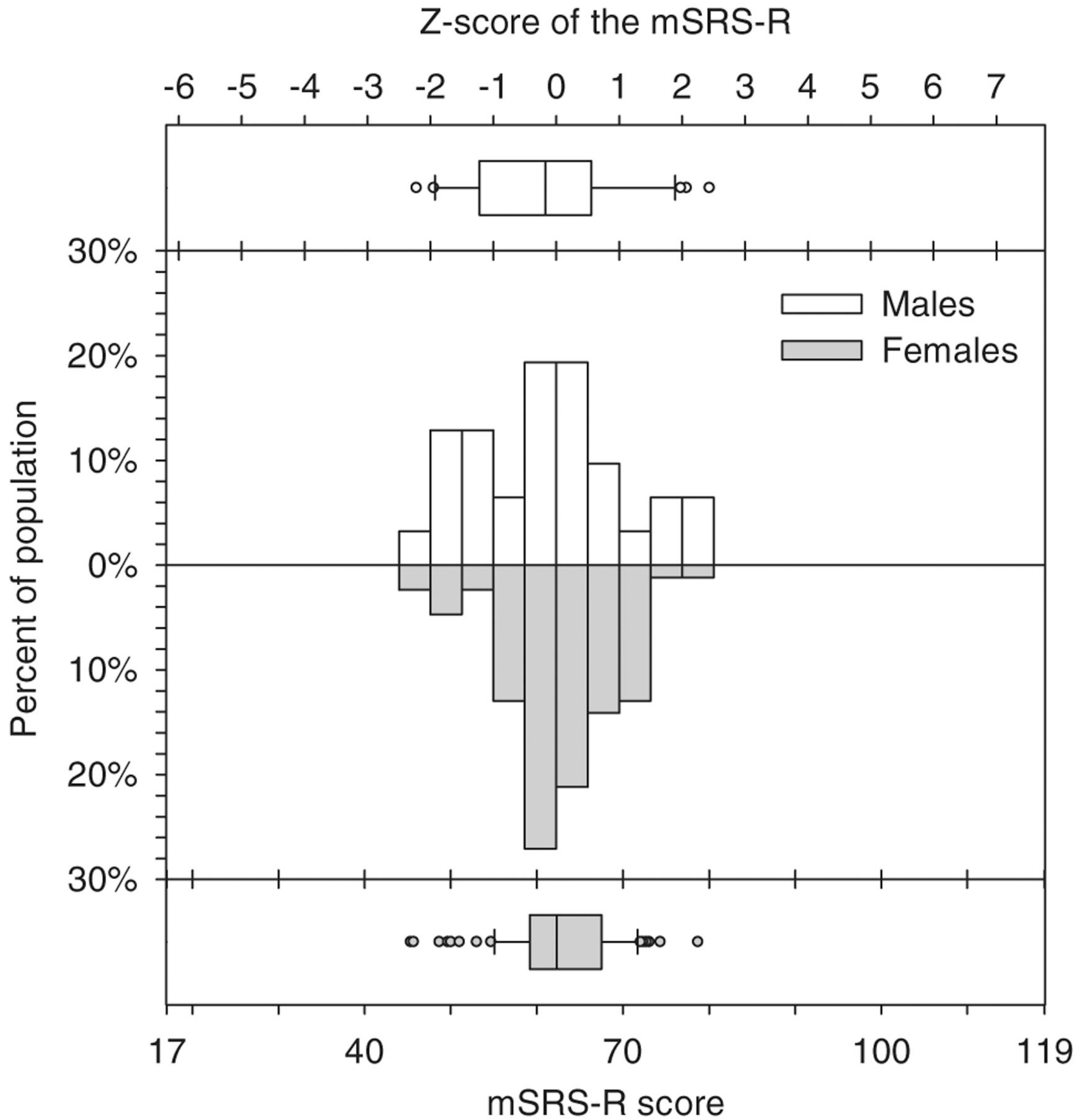

Figure 1.

Distribution of macaque Social Responsiveness Scale-Revised (mSRS-R) scores in a sample of male and female rhesus monkeys. Box plot indicates the 25th–75th interquartile range with the whiskers representing the 10th and 90th percentiles, and the centerline the median score (N = 31 males; N = 85 females).

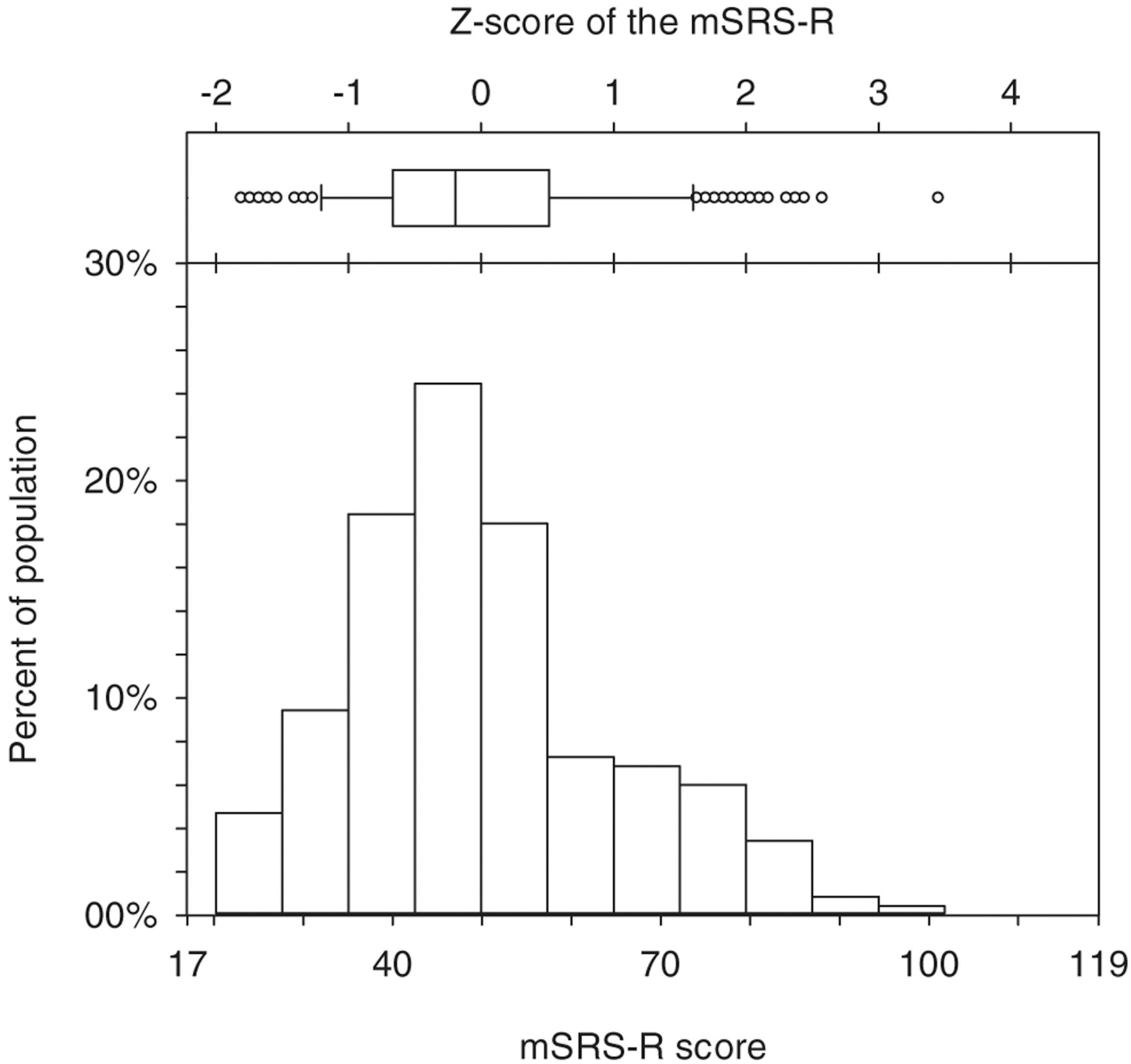

Figure 2.

Distribution of macaque Social Responsiveness Scale-Revised (mSRS-R) scores in a large sample of male rhesus monkeys. Box plot indicates 25th–75th interquartile range with the whiskers representing the 10th and 90th percentiles, and the centerline the median score (*N* = 233 males).

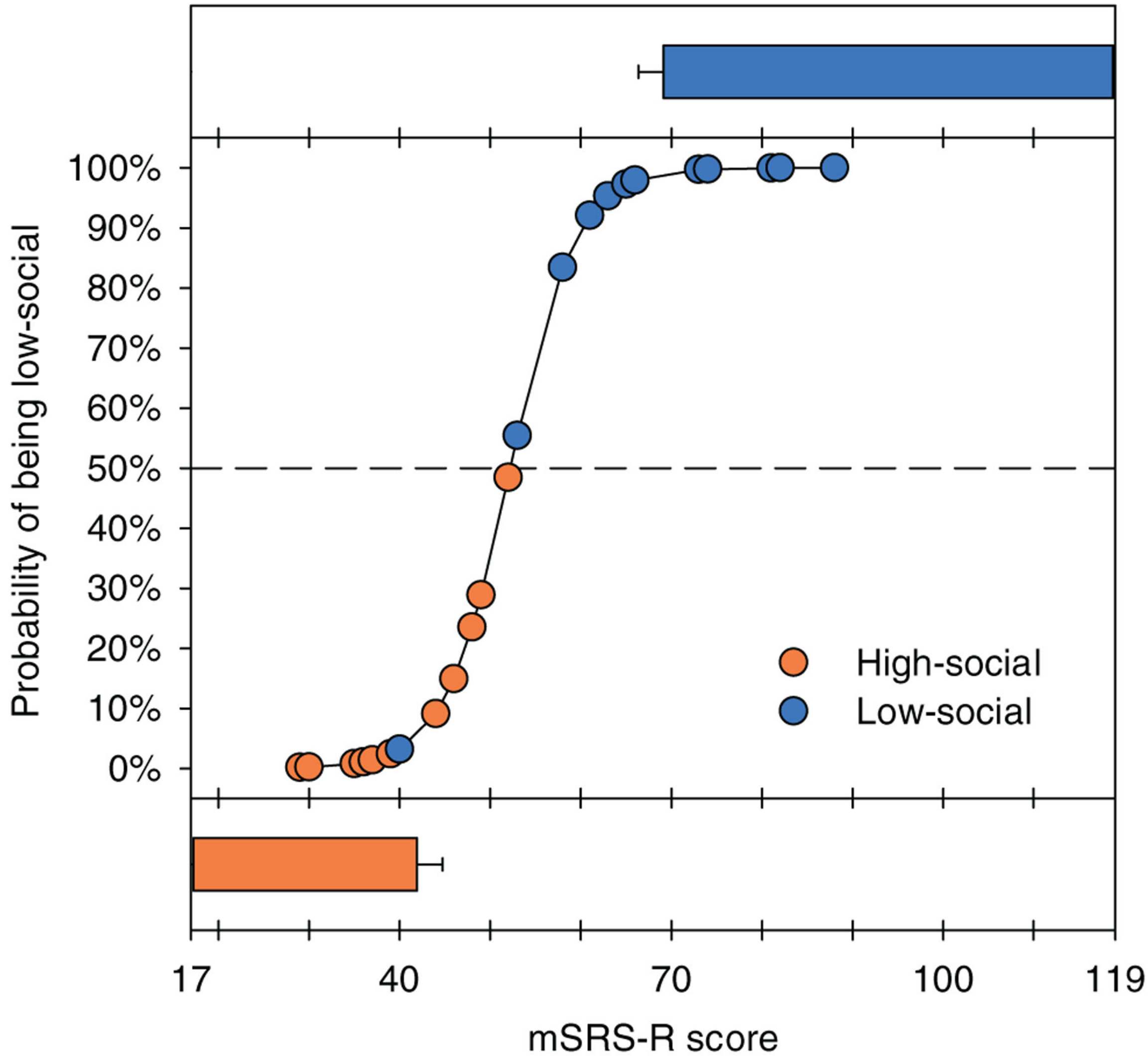

Figure 3.

The probability of being low-social is predicted by the macaque Social Responsiveness Scale-Revised (mSRS-R) score. The logistic regression model correctly classified 27 of 28 monkeys (96%). Low-social monkeys (blue circles) plotted above, and high-social monkeys (orange circles) plotted beneath, the dashed lines (which represent 50% probability) are correctly classified. The corresponding general linear model analysis yields the least squares mean ± standard error bars plotted above and below the logistic regression panel.

Table 1.

Inter-rater reliabilities for each item on the 36-item macaque Social Responsiveness Scale (mSRS)

	Inter-rater reliability estimates			
	Corral 1 (*N* = 69)		Corral 2 (*N* = 47)	
Item descriptor (#)	**ICC**	***P***	**ICC**	***P***
Alone (3)[a]	0.692	<0.001***	0.684	<0.001***
Attentive (22)	−0.128	0.707	−0.049	0.563
Avoidant (15)[a]	0.723	<0.001***	0.525	0.001***
Awkward (17)[a]	0.556	<0.001***	0.385	0.025*
Bizarre (4)[a]	0.634	<0.001***	0.384	0.025*
Change (13)	0.513	<0.001***	0.328	0.053
Comforting (14)[a]	0.714	<0.001***	0.637	<0.001***
Communicative (6)	0.401	0.006**	−0.122	0.662
Coordinated (7)	0.469	0.001***	−0.100	0.633
Disruptive (28)[a]	0.848	<0.001***	0.608	<0.001***
Distant (29)	0.582	<0.001***	0.367	0.032*
Eye contact (9)	0.239	0.090	0.003	0.485
Fidgety (1)[a]	0.521	<0.001***	0.757	<0.001***
Grooms (34)	0.675	<0.001***	0.440	0.009**
Imitative (11)	−0.308	0.891	0.392	0.022*
Interactive (10)[a]	0.716	<0.001***	0.436	0.010**
Invasive (27)	0.148	0.214	−0.067	0.588
Investigative (36)	0.676	<0.001***	0.238	0.135
Likable (35)[a]	0.524	<0.001***	0.656	<0.001***
Noisy (26)	0.390	0.008**	0.611	<0.001***
Playful (12)[a]	0.767	<0.001***	0.671	<0.001***
Prosocial (18)	0.577	<0.001***	0.346	0.043*
Responsive (8)	0.526	<0.001***	0.264	0.107
Restrictive (19)	0.237	0.092	−0.054	0.569
Repetitive (25)[a]	0.836	<0.001***	0.573	<0.001***
Self-confident (5)[a]	0.634	<0.001***	0.848	<0.001***
Sensitive (21)	0.505	<0.001***	0.218	0.159
Serious (23)[a]	0.558	<0.001***	0.364	0.033*
Silly (24)[a]	0.619	<0.001***	0.441	0.009**
Socially confident (2)[a]	0.875	<0.001***	0.840	<0.001***
Stares (32)[a]	0.428	0.003**	0.417	0.014*
Tense (31)[a]	0.648	<0.001***	0.409	0.017*

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	Inter-rater reliability estimates			
	Corral 1 (*N* = 69)		Corral 2 (*N* = 47)	
Item descriptor (#)	**ICC**	***P***	**ICC**	***P***
Touch (30)	0.249	0.080	0.300	0.074
Species-typical (33)	−0.723	0.993	−0.750	0.981
Upset (16)	0.227	0.104	0.389	0.023*
Wanders (20)	0.271	0.061	−0.023	0.523

Inter-rater reliability values are shown separately for each of the two corrals studied. Each item is listed with its corresponding mSRS item number in parentheses. Each item's reliability estimate is reported as an ICC (2A, C) with a corresponding *P* value (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$), indicating if it significantly differed from zero.

[a]Indicates the variable was retained in the mSRS-Revised.

Table 2.

Test–retest reliabilities for each item on the 36-item macaque Social Responsiveness Scale (mSRS)

	Test-retest reliability estimates											
	Corral 1						Corral 2					
	Rater 1		Rater 2		Rater 3		Rater 1		Rater 2		Rater 3	
Item descriptor (#)	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***
Alone (3)[a]	0.535	<0.001***	0.863	<0.001***	0.881	<0.001***	0.796	<0.001***	0.693	<0.001***	0.795	<0.001***
Attentive (22)	0.276	0.046*	0.721	<0.001***	0.769	<0.001***	0.433	0.027*	0.814	<0.001***	0.504	0.010**
Avoidant (15)[a]	0.706	<0.001***	0.864	<0.001***	0.908	<0.001***	0.875	<0.001***	0.804	<0.001***	0.653	<0.001***
Awkward (17)[a]	0.531	0.001***	0.533	0.001***	0.740	<0.001***	0.858	<0.001***	0.803	<0.001***	0.666	<0.001***
Bizarre (4)[a]	0.565	<0.001***	0.857	<0.001***	0.850	<0.001***	0.896	<0.001***	0.827	<0.001***	0.588	0.001***
Change (13)	0.509	0.001***	0.588	<0.001***	0.740	<0.001***	0.399	0.019*	0.843	<0.001***	−0.081	0.603
Comforting (14)[a]	0.539	<0.001***	0.847	<0.001***	0.855	<0.001***	0.308	0.014*	0.841	<0.001***	0.809	<0.001***
Communicative (6)	0.187	0.164	0.871	<0.001***	0.667	<0.001***	0.407	0.041*	0.475	0.016*	0.648	<0.001***
Coordinated (7)	0.134	0.248	0.866	<0.001***	0.702	<0.001***	0.941	<0.001***	N/A	N/A	0.874	<0.001***
Disruptive (28)[a]	0.549	<0.001***	0.924	<0.001***	0.839	<0.001***	0.805	<0.001***	0.872	<0.001***	0.986	<0.001***
Distant (29)	0.699	<0.001***	0.777	<0.001***	0.785	<0.001***	0.347	0.080	0.828	<0.001***	0.683	<0.001***
Eye contact(9)	0.400	<0.001***	0.609	<0.001***	0.521	0.001***	0.728	<0.001***	0.621	0.001***	0.786	<0.001***
Fidgety (l)[a]	0.634	<0.001***	0.679	<0.001***	0.643	<0.001***	0.935	<0.001***	0.786	<0.001***	0.698	<0.001***
Grooms (34)	0.740	<0.001***	0.879	<0.001***	0.904	<0.001***	0.639	<0.001***	0.712	<0.001***	0.198	0.231
Imitative (11)	0.636	<0.001***	N/A	N/A	N/A	N/A	0.106	0.281	0.788	<0.001***	0.749	<0.001***
Interactive (10)[a]	0.707	<0.001***	0.839	<0.001***	0.899	<0.001***	0.868	<0.001***	0.773	<0.001***	0.738	<0.001***
Invasive (27)	0.025	0.448	0.663	<0.001***	N/A	N/A	0.599	0.001***	0.651	<0.001***	0.303	0.115
Investigative (36)	0.793	<0.001***	0.801	<0.001***	0.845	<0.001***	0.410	0.036*	0.928	<0.001***	0.626	0.001***
Likable (35)[a]	0.356	0.018*	0.654	<0.001***	0.719	<0.001***	0.821	<0.001***	0.842	<0.001***	0.717	<0.001***
Noisy (26)	N/A	N/A	0.832	<0.001***	0.743	<0.001***	0.933	<0.001***	0.873	<0.001***	0.802	<0.001***
Playful (12)[a]	0.933	<0.001***	0.992	<0.001***	0.932	<0.001***	0.758	<0.001***	0.705	<0.001***	0.659	<0.001***
Prosocial (18)	0.565	<0.001***	0.745	<0.001***	0.771	<0.001***	0.859	<0.001***	0.233	0.183	0.679	<0.001***

	Test-retest reliability estimates											
	Corral 1						Corral 2					
	Rater 1		Rater 2		Rater 3		Rater 1		Rater 2		Rater 3	
Item descriptor (#)	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***	**ICC**	***P***
Responsive (8)	0.304	0.053	0.600	<0.001***	0.327	0.054	0.670	<0.001***	0.647	<0.001***	0.511	0.008**
Restrictive (19)	0.511	<0.001***	0.636	<0.001***	0.786	<0.001***	−0.003	0.504	0.851	<0.001***	−0.358	0.845
Repetitive (25)[a]	0.986	<0.001***	0.978	<0.001***	0.653	<0.001***	0.351	0.003**	0.821	<0.001***	0.679	<0.001***
Self-confident (5)[a]	0.565	<0.001***	0.857	<0.001***	0.850	<0.001***	0.931	<0.001***	0.909	<0.001***	0.847	<0.001***
Sensitive (21)	0.589	<0.001***	0.716	<0.001***	0.025	0.458	0.603	0.001***	0.659	<0.001***	0.252	0.161
Serious (23)[a]	0.726	<0.001***	0.610	<0.001***	0.714	<0.001***	0.819	<0.001***	0.873	<0.001***	0.701	<0.001***
Silly (24)[a]	0.992	<0.001***	0.942	<0.001***	0.960	<0.001***	0.853	<0.001***	0.918	<0.001***	0.894	<0.001***
Socially confident (2)[a]	0.765	<0.001***	0.923	<0.001***	0.964	<0.001***	0.917	<0.001***	0.889	<0.001***	0.881	<0.001***
Stares (32)[a]	0.848	<0.001***	0.624	<0.001***	0.579	<0.001***	0.551	0.003**	0.868	<0.001***	0.512	0.008**
Tense (31)[a]	0.513	<0.001***	0.570	<0.001***	0.907	<0.001***	0.922	<0.001***	0.841	<0.001***	0.691	<0.001***
Touch (30)	0.812	<0.001***	N/A	N/A	0.194	0.075	0.885	<0.001***	0.820	<0.001***	<0.001	0.500
Species-typical (33)	0.142	0.219	0.502	0.001***	−0.041	0.565	0.432	0.031*	0.354	0.070	0.504	0.006**
Upset(16)	0.574	<0.001***	0.652	<0.001***	0.647	<0.001***	0.624	<0.001***	−0.190	0.772	0.336	0.084
Wanders (20)	0.162	0.131	0.754	<0.001***	0.464	0.006**	0.345	0.070	−0.166	0.697	0.539	0.003**

Test–retest reliability values are shown separately for each of the two corrals studied. Each item is listed with its corresponding mSRS item number in parentheses. Each item's reliability estimate is reported as an ICC (3A, A) with a corresponding P value (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$), indicating if it significantly differed from zero. Any item that failed to generate score variability for a given rater (i.e., a given rater scored all subjects the same for a particular item) is denoted by "N/A".

[a] Indicates the variable was retained in the mSRS-Revised.

Table 3.

Relationships between macaque Social Responsiveness Scale-Revised (mSRS-R) scores and quantitative social behavior frequencies in a large sample of male rhesus monkeys

Behavior	*b*	SE *b*	*β*	*P*
Alone				
Constant	296.57	20.65		
Age	11.13	5.45	0.16	0.042
Rank	−68.39	19.97	−0.27	0.001
mSRS-R	1.98	0.31	0.39	<0.001
Proximity				
Constant	115.47	11.40		
Age	−1.91	3.01	−0.06	0.525
Rank	23.19	11.03	0.18	0.037
mSRS-R	−0.62	0.17	−0.24	<0.001
Contact				
Constant	109.59	13.29		
Age	−7.53	3.51	−0.18	0.033
Rank	41.78	12.86	0.28	0.001
mSRS-R	−0.64	0.20	−0.21	0.001
Groom				
Constant	35.78	10.98		
Age	10.20	2.90	0.29	0.001
Rank	8.77	10.62	0.07	0.410
mSRS-R	−0.37	0.16	−0.14	0.024
Play				
Constant	82.59	5.12		
Age	−11.89	1.35	−0.58	<0.001
Rank	−5.35	4.95	−0.07	0.281
mSRS-R	−0.35	0.08	−0.22	<0.001

Summary of multiple regression analyses for predictors of behavioral frequencies ($N = 233$ males). Reported values include unstandardized regression coefficients (*b*) and associated standard error (SE *b*), standardized regression coefficients (*β*), and corresponding *P* values for variables as predictors of behaviors (alone, proximity, contact, groom, and play).