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Brief Report: Autism Symptoms in Infants with Fragile X Syndrome

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Abstract

Fragile X syndrome (FXS) is the most common known genetic cause of autism spectrum disorder (ASD). Although 50–75 % of children with FXS meet ASD criteria, no studies have compared ASD symptoms in infants with FXS versus other high risk groups, such as siblings of children with ASD (ASIBs). Using the Autism Observation Scale for Infants, our findings indicate that 53 % of 12-month infants with FXS fall in the "at risk" category compared to 17 and 6 % for age-matched ASIBs and controls, respectively. Elevated atypical motor behaviors were associated with elevated risk for FXS. Cross-syndrome comparisons are essential to understanding the heterogeneity of ASD and identifying candidate markers that will facilitate differential diagnosis of ASD in genetic disorders such as FXS.

Keywords

Autism; Fragile X; Infants; Autism Observation Scale for Infants

Introduction

Autistic spectrum disorder (ASD) is a severe neurodevelopmental disorder with onset early in development. The average age of diagnosis remains at 3 years of age and older (Valicenti-McDermott et al. 2012), despite evidence that ASD symptoms emerge during the first 2 years of life (for a review, see Zwaigenbaum et al. 2013). Early identification of ASD is the focus of much research given evidence that early diagnosis and implementation of ASD-specific treatment are effective (Dawson et al. 2010; Zwaigenbaum et al. 2013). This work is challenged, however, by the subtlety or absence of symptoms in the first years of life, variable onset, heterogeneity of the disorder and symptom overlap with other disorders.

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Fragile X syndrome (FXS) is a single gene disorder with a prevalence of 1 in 3600. Although rare, FXS is the most common known single gene cause of ASD, accounting for approximately 1–2 % of ASD cases (Devlin and Scherer 2012). The association of ASD in FXS is clearly established, as 50–75 % of males meet diagnostic criteria for ASD (Kaufmann et al. 2004; Hall et al. 2008; Harris et al. 2008). Thus, FXS represents an identified single gene disorder at high risk for ASD that affords prospective monitoring for the emergence and stability of ASD features given that FXS can be definitively diagnosed prenatally or at birth (McCary and Roberts 2013). While a positive diagnosis of FXS can be made prenatally, the average age of diagnosis of FXS is 38 months of age in the absence of a family history (Bailey et al. 2009), evidencing a significant gap in time to intervention for these children.

Indeed, initial studies of early emerging signs of ASD are underway, and findings from our group indicate that broad development and adaptive behavior of infants with FXS reflect etiologically distinct profiles that distinguish infants with FXS from infant siblings of children with autism (ASIBs; Roberts et al. 2016). Specifically, developmental skills are significantly delayed across all major domains in infants with FXS as early as 6 months of age compared to ASIBs, with the deficit between these groups widening through the second year of life. In research focused on behavioral and heart-defined phases of attention in male infants with FXS contrasted to typical controls and ASIBs 6–12 months of age, we identified distinct behavioral and heart-defined attention in ASIBs versus FXS, with both high-risk groups exhibiting abnormalities compared to typical controls (Tonnsen et al. 2015). These findings provide novel evidence of distinct cross-group differences, as well as within-group predictors of clinical ASD risk, across ASIB and FXS groups. These differences highlight the heterogeneity of developmental processes related to ASD risk and the potential presence of similar behavioral profiles with distinct biological signatures across etiologically distinct groups.

Cross-syndrome research contrasting infants at high risk for ASD has great potential to contribute to parsing the heterogeneity of ASD, as well as to refine efforts to identify candidate markers that will facilitate diagnosis of ASD from associated disorders with non-specific or identified etiologies such as FXS. However, no studies have been published examining core ASD symptoms in infants with FXS contrasted to ASIBs, and we aim to address this gap in the literature. This gap may be due in part to the limited ability of clinical measures to identify ASD risk in early infancy, and the uncertain stability of these early symptoms as predictors of ASD diagnostic outcomes in toddlerhood (Estes et al. 2015; Gammer et al. 2015). In this preliminary study, we contrast the profile of ASD symptoms in 12-month-old infants with FXS to ASIBs and infants who are typically developing (TD). We are interested in identifying “risk factors” for ASD in infants with FXS, as well as the concordance of risk factors in FXS versus ASIBs, to document potential etiologically distinct ASD risk profiles across these two high risk groups.

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Methods

Participants

Participants included 15 male infants with FXS, 23 ASIBs, and 17 TD chronological-age matched controls assessed at 12 months of age. Demographic information is outlined in Table 1. Participants were recruited from an ongoing longitudinal study examining the early emergence of autism in high risk populations (PI: Roberts). FXS was documented by genetic report and ASIB status was determined by a diagnosis of ASD in an older full sibling through community clinical ASD diagnoses. Syndromic ASD was ruled out in all older siblings of the ASIB group. Typical development was defined as the absence of known or suspected delays and no history or indicators of ASD. Participants with neurological conditions or gestation <37 weeks were excluded, and the TD group was restricted to those with developmental composite scores within 1 standard deviation of the mean.

Measures

Autism Indicators—The Autism Observation Scale for Infants (AOSI; Bryson et al. 2008) is a semi-structured 20 min play observation designed to identify putative signs of autism in infants aged 6–18 months. The AOSI includes 19 items rated on a scale from “normal function” (score 0), “inconsistent, partial, or questionable behavior” (score of 1) to “deviates from normal development” (score of 2 or 3). The AOSI provides a Total Score that ranges from 0 to 50, which is calculated by summing the first 16 items. A sum of markers is also calculated representing a binary determination of the same 16 items, which are shown to be most discriminating of a later diagnosis of ASD. The presence of seven or more markers is considered a risk indicator for later autism in high risk populations (Bryson et al. 2008; Zwaigenbaum et al. 2005). Inter-rater reliability for total (.93) and marker scores (.92) is excellent and test–retest reliability (.61) is strong (Bryson et al. 2008). The sensitivity and specificity of the AOSI is 84 and 98 % respectively for 12-month-old ASIBs later diagnosed with ASD (Zwaigenbaum et al. 2005).

Developmental Age—The Mullen Scales of Early Learning (MSEL; Mullen 1995), a standardized measure of development for children birth to 69 months of age, was administered to all participants. Due to infants with FXS exhibiting standard scores at the floor of the MSEL (Roberts et al. 2009), we used a global developmental age score by averaging the age equivalents across four MSEL domains (visual reception, fine motor, receptive language, and expressive language) as done in previous studies (Roberts et al. 2009; Humphrey et al. 2004).

Autism Diagnostic Outcomes—The Autism Diagnostic Observation Schedule (ADOS-2; Luyster et al. 2009) is a semi-structured play based measure designed to elicit social interaction. A calibrated severity score can be obtained from a child's total score, with higher scores indicating greater autism symptom severity. The ADOS-2 toddler module was administered to a subset of participants (n = 39; 10 FXS, 16 ASIB, 13 TD) who had reached 24-months of age in our ongoing longitudinal study. ADOS-2 outcome data were not available for 7 ASIBs, 5 infants with FXS, and 4 TD controls as they had not yet reached 24-months of age at the time of these analyses.

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Procedures

Parents provided informed written consent. Participants were assessed in the laboratory at the University of South Carolina as part of an ongoing longitudinal study examining early indicators of autism in high-risk populations. Research staff was trained to research reliability standards on the AOSI and ADOS-2. Administrations were coded via video, and 20 % of administrations were verified by a reliable coder. Inter-rater reliability was 89 % at the item level for the AOSI.

Analyses and Results

Analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). First, we examined whether groups (TD, FXS, ASIB) differed in (1) continuous AOSI Total Scores, (2) the proportion of participants who exceeded the AOSI autism risk threshold, and (3) AOSI item-level performance. In participants with available ADOS scores ($n = 39$), we also examined the association between AOSI and ADOS-2 scores, as well as whether significant group differences between high- and low-risk groups were maintained with the subset of high-risk infants who exceeded the ADOS-2 risk threshold.

Due to the small sample size and non-normal distribution of AOSI and ADOS-2 scores, nonparametric methods were used across analyses, consistent with previous studies in similar FXS samples (e.g. Tonnsen et al. 2015). Given the lower developmental ages in FXS (Wilcoxon $Z = 4.52$, one-tailed $p < .001$) and ASIB ($Z = 2.28$, $p = .01$), and evidence that elevated AOSI scores may be associated with developmental level in ASIBs in some studies (Georgiades et al. 2013), Spearman partial correlations were conducted to determine whether mental age should be covaried. Mental age did not correlate with either AOSI total score or number of markers in the overall sample (total score $\rho = -.19$, $p = .16$; markers $\rho = -.15$, $p = .27$). These results were maintained at the group level, although the ASIB group exhibited a trend of higher number of markers in infants with lower mental age ($\rho = -.39$, $p = .07$). Given these nonsignificant findings, mental age was not covaried in subsequent models.

Group Differences

To test our hypothesis that high-risk groups would exhibit higher AOSI total scores than TD controls, we compared groups using nonparametric one-way Kruskal Wallis analyses. Total scores are presented in Table 1. AOSI total score varied by group [$\chi^2 (2) = 9.87$, $p = .007$]. Post hoc Dunn's pairwise multiple comparison tests (Dunn 1964) were conducted using SAS macro *KW_MC* (Elliott and Hynan 2011) to determine group differences at a family wise error rate of 0.05. The FXS group exhibited higher AOSI total score than the TD group. The remaining group differences were not significant. Box plots of AOSI total scores by group are presented in Fig. 1.

Group differences in the proportion who exceeded the autism risk threshold (AOSI number of markers >7; Zwaigenbaum et al. 2005) were examined with Fisher's Exact Test, with post hoc pairwise comparisons conducted using adjusted Type I error rate of $\alpha = .05/3 = .016$. Groups significantly differed in the proportion of participants exceeding the autism risk

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threshold (p = .007): TD = 6 % (*n* = 1), ASIB = 17 % (*n* = 4), FXS = 53 % (*n* = 8). Pairwise comparisons indicated significant group differences in FXS versus TD (one-tailed p = .004) and FXS versus ASIB (p = .02). ASIB and TD groups did not significantly differ in risk rates (p = .28).

To examine group differences in AOSI item performance, we employed a series of Fisher's Exact Tests with an adjusted α = .05/19 = .003. Post hoc pairwise Fisher's Exact Tests were conducted to determine between-group differences. Each analysis examined group differences in the proportion of participants with elevated (≥1) versus non-elevated (0) scores. Table 2 displays frequency of item scores (0, 1, 2+) and results of statistical group comparisons. As summarized in this table, item analyses indicated significant group differences in the proportion of groups exhibiting risks on Motor Control and Atypical Motor Behavior Items, with planned pairwise analyses indicating higher proportions in the FXS versus TD and ASIB groups. A similar trend emerged with higher scores in the FXS group for Social Babbling (p = .04), Eye Contact (p = .03), Social Interest (p = .004), Atypical Sensory Behavior (p = .02), Engagement (p = .01) and Social Referencing (p = .08), although these group differences were not statistically significant using the adjusted p < .003. Figure 2 depicts the proportion of participants with elevated scores (i.e. ≥ 1) on each item, separated by group.

Autism symptom outcomes (ADOS severity scores) were available in a subset of participants (*n* = 39; 10 FXS, 16 ASIB, 13 TD) and are described in Table 1. To test our hypothesis that higher AOSI scores would be associated with higher ADOS scores, we examined both Spearman correlations between the two variables, as well as whether categorical classification on the AOSI [denoted AOSI(+) versus AOSI(−) based on >7 makers endorsed] predicted categorical classification on the ADOS [denoted ADOS(+) versus ADOS(−) based on algorithm scores]. Across groups, AOSI total scores positively correlated with ADOS severity scores (ρ= .43, p = .007). Participants with ADOS(+) scores were more likely to have previously received AOSI(+) scores (Fisher's one-tailed p = .03) and exhibited higher AOSI total scores (Wilcoxon Z = 2.28, one-tailed p = .01). Table 3 presents the correspondence between AOSI and ADOS categorical classifications by group. The AOSI incorrectly classified 30 % of infants with FXS and 38 % of ASIBs. Of the 29 infants with AOSI(−) scores, 21 % (*n* = 6) received ADOS(+) scores (0 of 3 FXS; 6 of 14 ASIBs; 0 of 12 TD). Of the 10 infants with AOSI(+) scores, 60 % (*n* = 6) received ADOS(+) scores (4 of 7 FXS; 2 of 2 ASIBs, 0 of 1 TD). Notably, 50 % of infants with FXS (*n* = 3) who received AOSI(+) scores later received ADOS(−) scores, and 43 % of ASIBs (*n* = 6) who scored AOSI(−) later received ADOS(+) scores. Thus, the specificity and sensitivity of the AOSI to ADOS varied across groups, with higher “false positives” in FXS and higher “false negatives” in ASIBs. Additionally, mean AOSI total scores varied across groups, with higher means in the FXS group, regardless of ADOS cutoff scores. AOSI total scores by risk group and ADOS cutoff scores are depicted in Table 4.

Discussion

We present initial findings from our longitudinal study of the emergence of ASD in two etiologically distinct groups of 12-month-old infants at ASD-high risk, FXS and ASIBs. We

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examined prevalence rates of infants designated as “at risk” on the AOSI followed by an item level analysis to identify if specific behaviors differentiated the groups. While our focus was on infants at high risk for ASD independent of later autism diagnostic categorization, we include 24-month outcome data on a subset of participants. These steps are important given limited cross-syndrome studies and findings that ASIBs display a continuum of ASD features and impairment, potentially indicative of the “broader autism phenotype” (Brian et al. 2008; Georgiades et al. 2013; Szatmari et al. 2000). To our knowledge, this is the first published study aimed at early detection of autism in FXS using the AOSI and one of a handful describing infant development in FXS (Farzin et al. 2011; Roberts et al. 2009, 2012).

Our results indicate that infants with FXS displayed a higher total AOSI score than both ASIBs and typical controls, which did not differ from each other. Consistent with this finding, a higher proportion of infants with FXS were designated as “at risk” for ASD based on AOSI scores, with 53 % meeting criteria in the FXS group contrasted to 17 % of ASIBs and 6 % of typical controls. These rates are consistent with existing data indicating that infants with FXS are approximately three times more likely to meet diagnostic criteria for ASD than ASIBS (50–75 % versus 20 % respectively). Also, given the nearly universal presence of an intellectual disability in males with FXS and the overlapping features of intellectual disabilities and ASD with low IQ noted as a risk factor for ASD, it is not surprising that over half the infants with FXS were in the “at risk” group. Thus, while infants with FXS and ASIBs are both at risk for ASD and for a developmental delays, the prevalence for these conditions is appreciably greater in FXS, with more variability present in nonsyndromic ASD (Landa et al. 2013; Roberts et al. 2009; Thurman et al. 2015).

The relationship between AOSI and ADOS-2 severity scores was moderate across groups (r = .43), which is consistent with reports from other ASIB studies (r = .30; Gammer et al. 2015). These findings indicate a fair degree of continuity of autistic-like behavioral atypicality from 12 to 24 months of age. Of note, the mean AOSI score for the ASIBs who met criteria for ASD was similar to the FXS who did *not* meet for ASD (9.00 versus 9.67 respectively), with higher scores among those with FXS who met criteria (16.00). These data suggest that 12-month-old infants with FXS present with more severe behavioral disruption, regardless of later ASD diagnostic test performance. Also, our data indicate that a higher proportion of infants with FXS display “autistic like” behaviors at 12 months that do not translate into an ASD diagnosis at 24 months (e.g., false positives), with 3 of 7 infants with FXS who exceeded the AOSI cutoff *not* exceeding the ADOS cutoff. In comparison, both ASIBs who exceeded the AOSI threshold also exceeded the ADOS cutoff. Although these findings must be replicated in larger samples, data suggest that consistent with ASIBs, infants and toddlers with FXS display a range of autism features independent of diagnostic classification, supporting the presence of an early broader autism phenotype in FXS that parallels that of ASIBs (Gammer et al. 2015; Georgiades et al. 2013).

At a discrete behavioral level, we found that relative to ASIBs and TD controls, infants with FXS were characterized by increased atypical motor behaviors, atypical sensory behaviors, and insistence on sameness, as well as reduced social babbling, eye contact, social referencing, motor control, and social referencing. However, only atypical motor behavior

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and motor control were retained when controlling for multiple comparisons. It is striking to note that 60 % of the infants with FXS displayed a definite and clear display of atypical motor behaviors, compared to no ASIBs and one TD control. Qualitatively, these behaviors included hand flapping, body rocking, finger posturing and whole body posturing. In terms of motor control, 80 % of the infants with FXS displayed poor motor control contrasted to 14 % in ASIBs and 12 % in typical controls in our study. Atypical motor control, in particular, appears to represent a distinct risk marker for later ASD diagnoses in multiple high risk groups (Landa et al. 2013; Bhat et al. 2012), and previous ASIB studies suggested it was the only AOSI item to distinguish ASIBs who later were diagnosed with autism from those who did not receive an ASD diagnosis (Brian et al. 2008, 2013). Similarly, it has been reported that atypical motor control was the only AOSI item to load onto one of the two discriminant functions found to differentiate ASIBs later diagnosed with autism from those who did not and from typical controls (Brian et al. 2008). Evidence for a distinct role of motor function to the prediction of ASD outcomes is supported in FXS with fine motor delays strongly associated with increased severity of autistic behavior in young children with FXS (Roberts et al. 2009; Zingerevich et al. 2009), and by fine motor deficits representing the strongest discriminant factor differentiating infants with FXS to typical controls and ASIBs (Roberts et al. 2016). In contrast, elevated restricted and repetitive behaviors have been shown to be universal across children with FXS with and without co-morbid ASD diagnoses (Thurman et al. 2015) suggesting that atypical motor movement may be a non-specific marker in FXS. Likewise, the salience of motor atypicalities for ASD diagnoses is not a universal finding, with evidence supporting social interactive items including orientation to name and social referencing, not motor items, as distinguishing items for ASIBs (Gammer et al. 2015). Thus, while motor abnormalities have been proposed as a putative endophenotype for ASD (Esposito and Paşca 2013), motor dysfunction may be a common ASD risk factor across both ASIBs and FXS or may represent a second-order effect representing developmental delays more globally.

Although we report novel findings in a low-incidence sample of infants with FXS, a population that is difficult to recruit and therefore underrepresented in the literature, the small sample size of this study is inherently limiting. Further work is needed to determine whether findings generalize to the broader population of infants with FXS, particularly females who often exhibit more subtle symptomatology. Given cross-group differences in item ratings and high false positive rate of categorical AOSI cutoffs in FXS, our data also suggest that further research is needed to determine the utility of the AOSI as a clinical screening tool for autism in FXS. For example, it may be possible that nearly universal atypicalities in motor domains among infants with FXS may inflate scores in this group, resulting in higher rates of false positives. Notably, this possibility does not negate the use of the AOSI in non-ASIB samples, as the measure did produce variability in scores among infants with FXS, which may be useful in characterizing the broader phenotype of autism symptoms in this population. Thus, replicating our findings and examining the psychometric properties of the AOSI with a larger study is critical given our limited sample and lack of comprehensive longitudinal data.

In summary, our initial results indicate that infants with FXS may be distinguished from ASIBS and typical controls based on both categorical risk status and specific behavioral

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markers of ASD by 12 months of age. The profile of ASD risk markers in infants with FXS appear similar, yet not identical, to risk markers in ASIBs. Relative to ASIBs, infants with FXS display more pervasive and severe behavioral manifestations of autistic features independent of ASD diagnostic categorization.

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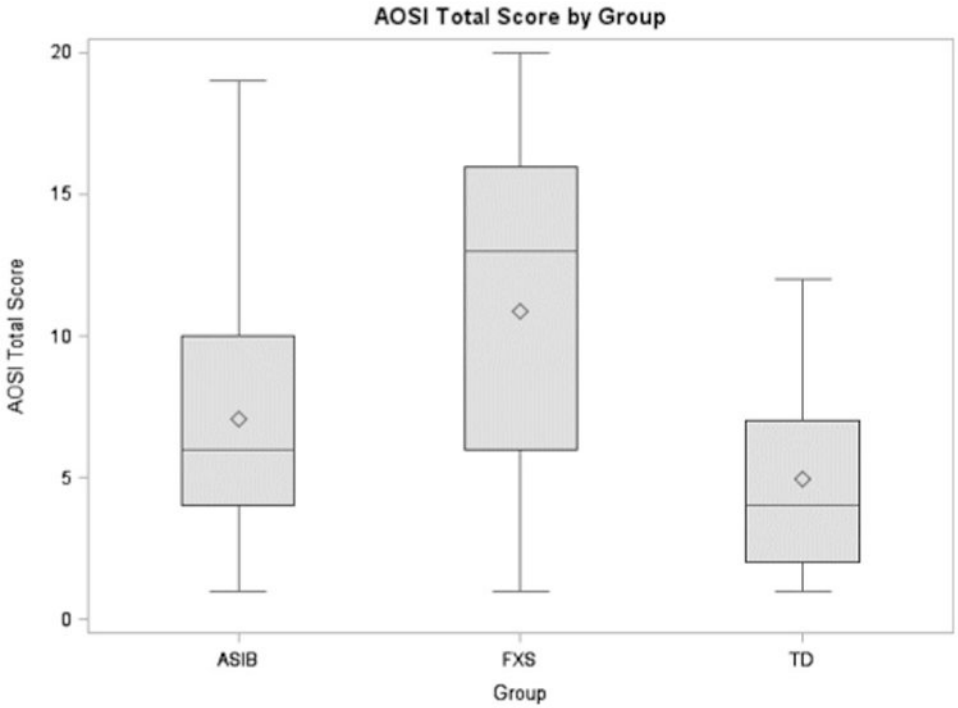

Fig. 1. AOSI total score by group

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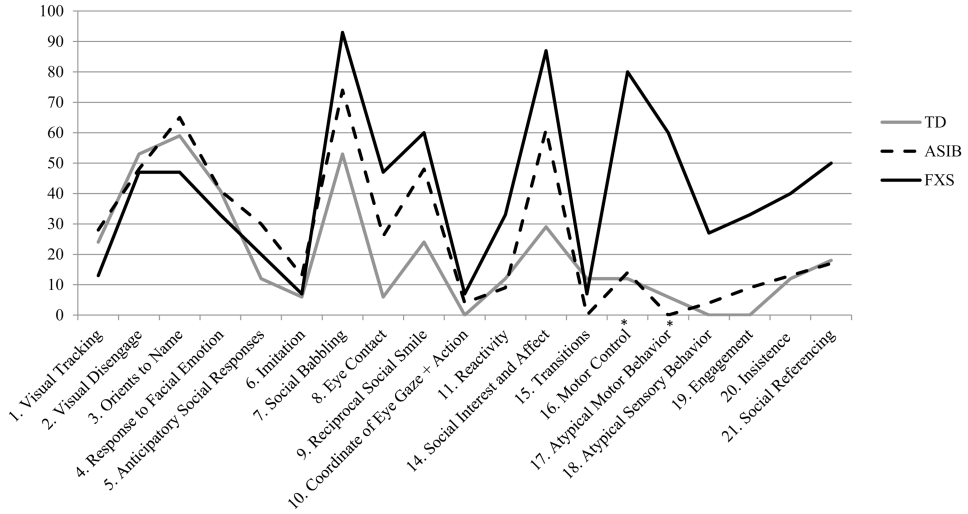

Fig. 2.

Elevated AOSI items by group. *Indicates group differences significant at $\alpha < .003$

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Table 1

Sample characteristics

	FXS					ASIB					TD				
	N	*Mean*	*SD*	*Min*	*Max*	*N*	*Mean*	*SD*	*Min*	*Max*	*N*	*Mean*	*SD*	*Min*	*Max*
Chronological age	15	12.33	1.27	9.37	14.35	23	12.38	0.75	10.42	13.94	17	12.24	0.49	11.01	13.12
Age equivalent	15	8.62	2.30	5.25	11.50	23	11.88	2.04	6.25	16.00	17	13.50	2.40	10.50	21.75
Early learning SS	15	69.80	13.77	50	97	23	94.96	14.52	60	118	17	106.24	7.35	89	119
AOSI total score	15	10.87	5.69	1	20	23	7.09	4.59	1	19	17	4.94	3.61	1	12
AOSI N markers	15	6.4	2.87	1	9	23	4.61	2.46	1	10	17	3.35	2.26	1	8
ADOS total score	10	11.80	8.15	2	26	16	8.88	6.41	1	23	13	2.77	2.05	0	7
ADOS severity	10	4.60	3.03	1	10	16	3.75	2.57	1	10	13	1.31	0.63	1	3

Age equivalent and early learning composite standard score (SS) were measured using the Mullen Scales of Early Learning (Mullen 1995)

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Table 2

Frequency of item scores (0, 1, 2+) on the AOSI and results of group comparisons

	FXS (n = 15)			ASIB (n = 23)			TD (n = 17)			Fisher's p value			
	% 0	% 1	% 2+	% 0	% 1	% 2+	% 0	% 1	% 2+	Three group	FXS versus ASIB	FXS versus TD	ASIB versus TD
1. Visual tracking	87	0	13	72	18	9	76	18	6	.65	–	–	–
2. Visual disengage	53	0	47	52	9	39	47	0	53	1.0	–	–	–
3. Orients to name	53	13	33	35	48	17	41	35	24	.58	–	–	–
4. Response to facial emotion	67	27	7	59	27	14	59	29	12	.88	–	–	–
5. Anticipatory social responses	80	7	13	70	26	4	88	6	6	.42	–	–	–
6. Imitation	93	0	7	87	9	4	94	0	6	.85	–	–	–
7. Social babbling	7	20	73	26	26	48	47	41	12	.04	–	–	–
8. Eye contact	53	–	47	74	–	26	94	0	6	.03	–	–	–
9. Reciprocal social smile	40	33	27	52	22	26	76	18	6	.12	–	–	–
10. Coordination of eye gaze + action	93	7	0	96	4	0	100	0	0	.74	–	–	–
11. Reactivity	67	20	13	91	9	0	88	12	0	.16	–	–	–
12. Social interest and affect	13	60	27	39	48	13	71	24	6	.004	–	–	–
13. Transitions	93	7	0	100	0	0	88	12	0	.26	–	–	–
14. Motor control	20	67	13	86	14	0	88	12	0	<.001	<.001	<.001	.63
15. Atypical motor behavior	40	0	60	100	0	0	94	0	6	<.001	<.001	.001	.43
16. Atypical sensory behavior	73	0	27	96	0	4	100	0	0	.02	–	–	–
17. Engagement	67	33	0	91	4	4	100	0	0	.01	–	–	–
18. Insistence	60	33	7	87	13	0	88	6	6	.10	–	–	–
19. Social referencing	50	36	14	83	13	4	82	18	0	.08	–	–	–

Results are compared to adjusted α = .003 to account for multiple comparisons. Pairwise p values reflect one-tailed analyses

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Table 3

Correspondence between AOSI and ADOS categorical classifications by group

	n ADOS(−)				*n* ADOS(+)				Total
	FXS	ASIB	TD	Total	FXS	ASIB	TD	Total	
AOSI(−)	3	8	12	23	0	6	0	6	29
AOSI(+)	3	0	1	4	4	2	0	6	10
Total	6	8	13	27	4	8	0	12	39

ADOS(+) indicates severity score >4; AOSI(+) indicates Number of Markers >7

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Table 4

AOSI total scores for low risk TD and high-risk ASIB and FXS groups by 24-month outcome

	TD (*n* = 13)	ASIB (*n* = 16)		FXS (*n* = 10)	
		ADOS−(*n* = 8)	ADOS+ (*n* = 8)	ADOS− (*n* = 6)	ADOS+ (*n* = 4)
AOSI Total Score	5.46 (3.80)	5.00 (1.69)	9.00 (3.89)	9.67 (5.65)	16.00 (3.16)

Excludes infants who did not participate in ADOS-2. ADOS+ indicates above cutoff, ADOS- indicates below cutoff