Journal of Autism and Developmental Disorders (2021) 51:839–848
https://doi.org/10.1007/s10803-020-04371-0

ORIGINAL PAPER

Screening for Behavioral Signs of Autism Spectrum Disorder in 9-Month-Old Infant Siblings

Lori-Ann R. Sacrey[1,2] · Lonnie Zwaigenbaum[1,2] · Susan Bryson[3] · Jessica Brian[4,5] · Isabel M. Smith[3] · Wendy Roberts[6] · Peter Szatmari[5,7,8] · Tracy Vaillancourt[9] · Caroline Roncadin[5,10] · Nancy Garon[11]

Published online: 14 January 2020

Abstract
Despite considerable progress in characterizing the early signs of autism spectrum disorder (ASD), more remains to be learned about how symptoms emerge in the first year of life. Parents with a new baby who already had at least one biological child diagnosed with ASD (high-risk) or no family history of ASD (low-risk) completed two measures when their baby was 9 months of age, the Autism Parent Screen for Infants (APSI) questionnaire and the interview-based Parent Concerns Form. Children underwent a blinded independent diagnostic assessment for ASD at age 3 years. Total scores on the APSI and the Parent Concerns Form were both able to independently differentiate high-risk children who were later diagnosed with ASD from other high-risk and low-risk children who were not. Using logistic regression, we found that the total score on the APSI predicted ASD outcomes at age 3 with 70% accuracy, but the Parent Concerns Form did not contribute any unique variance when the APSI was already in the model. The results suggest that the APSI identifies early features predictive of ASD in high-risk infants and can be used to flag them for targeted follow-up and screening.

Keywords Autism spectrum disorder · Parent report · High-risk siblings · Prospective · Screening · Early detection

Screening for Behavioral Signs of Autism Spectrum Disorder in 9-Month-Old Infant Siblings

Although parents often report concerns about development in the first two years of their children's lives (Chakrabarti and Fombonne 2005; Sacrey et al. 2015), many children with autism spectrum disorder (ASD) remain undiagnosed until age 4 or later (Daniels and Mandell 2014; Public Health Agency of Canada 2018). There is ample evidence that intervening before age 2 improves outcomes for individuals on the autism spectrum (Brian et al. 2016; Rogers et al. 2014; Schreibman et al. 2015; Zwaigenbaum et al. 2015). Due to the benefits of early intervention, the need grows for early detection measures that target the under 2 age range. Although biological markers of atypical patterns of early brain growth, connectivity, and function have shown potential for detecting children as young as 6 months who are at risk of an ASD diagnosis (Bosl et al. 2018; Elsabbagh et al. 2012; Hazlett et al. 2017; Emerson et al. 2017; Lewis

✉ Lori-Ann R. Sacrey
sacrey@ualberta.ca

1 Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

2 Department of Pediatrics, Autism Research Centre – E209, Glenrose Rehabilitation Hospital, 10230-111 Avenue, Edmonton, AB T5G 0B7, Canada

3 Dalhousie University/IWK Health Centre, Halifax, NS, Canada

4 Bloorview Research Institute, Toronto, ON, Canada

5 University of Toronto, Toronto, ON, Canada

6 ISAND, Toronto, ON, Canada

7 The Hospital for Sick Children, Toronto, ON, Canada

8 Centre for Addiction and Mental Health, Toronto, ON, Canada

9 University of Ottawa, Ottawa, ON, Canada

10 McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada

11 Mount Allison University, Sackville, NB, Canada

et al. 2017), such methods are costly and present technical barriers to implementation as primary screens, particularly in non-urban areas. Hence, behaviorally based measures remain worthy of consideration in support of the goal of early detection of emerging symptoms.

Currently available ASD screening measures focus almost exclusively on toddlers 12 months of age or older. One exception, the Infant–Toddler Checklist, is reported to differentiate infants later diagnosed with ASD from those with other communication delays as early as 9 months (Wetherby et al. 2008). However, in subsequent research this tool has been used mainly to screen after 12 months (Pierce et al. 2011). Other commonly utilized ASD screens are designed for older toddlers; for example, the Modified Checklist for Autism in Toddlers is administered at 16–30 months (Robins et al. 2014). A recent report on a novel screen for behavioral signs of ASD, the Autism Parent Screen for Infants (APSI; Sacrey et al. 2018a) compared children with an older sibling diagnosed with ASD ('high-risk' siblings) to children without a family history of ASD ('low-risk' comparison) and found that the total score on the questionnaire could differentiate children later diagnosed with ASD from other high-risk and low-risk children as early as when the siblings were 6 months old. The paper reported item-level analyses comparing high-risk siblings who were diagnosed with ASD at age 3 to those who were not at both ages 6 (only two items were discriminatory) and 12 (13 items) months. However, this paper provided no item-level details of the questionnaire's performance at 9 months. The period between 6 and 12 months of age encompasses many important developmental changes; therefore, in-depth analyses were warranted.

In this study, we evaluated two measures of early behavioral features of ASD in 9-month-old infants who were at heightened risk of ASD by virtue of having at least one older sibling diagnosed with ASD (HR sibling), and in a comparison group of LR infants, with no family history of ASD. The Autism Parent Screen for Infants (APSI; Bryson et al. 2006; Sacrey et al. 2018a, b) is a 26-item parent-report questionnaire that can be completed in 5–10 min. To determine if parent reports on general development were also informative for later ASD diagnoses or provided additive information on top of 'autism-specific' behaviors queried by the APSI, parents also were interviewed using the Parent Concerns Form, a structured 5–10-min interview, developed to examine parent-reported concerns in ten broad domains: sleep, diet, sensory interests, gross/fine motor development, repetitive movements, communication, communication regression, social skills, play, and behavioral problems. It was previously shown to have predictive utility in an HR sample beginning at 6–9 months (Sacrey et al. 2015). The APSI and Parent Concerns Form were completed when children were 9 months old, and all children underwent diagnostic evaluation for ASD at 36 months of age by examiners who were blind to risk status and prior assessments. Our main objective was to examine if scores on the 9-month assessments distinguished HR infants who were diagnosed with ASD at 36 months from HR and LR infants who were not diagnosed with ASD at 36 months.

Methods

Participants

Two groups of children were recruited for the study: HR [infants with an older sibling with ASD and LR (no first- or second-degree relatives with ASD). For the HR group, diagnosis of ASD in the older sibling (i.e., proband) was confirmed by a clinical assessment or a review of diagnostic records, using DSM-IV-TR criteria. Neither the HR infant siblings nor the probands had identifiable neurological or genetic conditions, or diagnosed sensory (i.e., hearing or visual] or neuromotor disorders. The LR controls, recruited from local communities, were included on the basis of having no first- or second-degree relatives with an ASD diagnosis. All participants were born at 36–42 weeks gestation, with birth weights greater than 2500 g, and no reports of birth complications or NICU stays. Infant siblings of children with ASD were recruited from families attending one of four multidisciplinary ASD diagnostic centers [locations blinded], or from surrounding community clinical practices. The research ethics board at each institution approved this study and all families gave written informed consent prior to enrollment.

Children from our larger study [reference blinded] were included if they had (1) a completed APSI questionnaire at 9 months, (2) a completed Parent Concerns Form at 9 months, and (3) undergone a 3-year diagnostic assessment. A total of 82 HR infant siblings and 54 LR controls were included in the analyses. Although there were LR children in the larger study who were diagnosed with ASD, none had both a completed APSI and Parent Concerns Form at 9 months, thus none of the LR children included here was diagnosed with ASD. Table 1 presents detailed participant characteristics.

Measures

Caregivers completed the APSI and were interviewed using the Parent Concerns Form when their children were aged 9 months. Children were assessed at age 3 using the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview- Revised during their diagnostic assessment. ***The Autism Parent Screen for Infants*** (APSI; Bryson et al. 2006) is a 26-item forced-choice (yes, sometimes, no) parent-report questionnaire with content similar to the Autism

Table 1 Participant characteristics

Characteristic	HR-ASD	HR-N	LR		X^2	*p*
N	31	51	54		–	–
Sex (% boy)	71.0%	45.1%	51.9%		5.31	.07
Age	M(SD)	M(SD)	M(SD)		X^2	*p*
9-month visit	9.24 (0.32)	9.21 (0.38)	9.21 (0.32)		2.49	.29
36-month visit	39.25 (4.06)	38.94 (3.04)	39.35 (4.01)		0.005	.99
Respondent	%	%	%		X^2	*p*
Mother	89.5	82.3	94.1		11.29	.08
Father	2.6	1.0	4.4		–	–
Other	7.9	16.7	1.5		–	–
ADOS	M (SD)	M (SD)	M (SD)	Median	X^2	*p*
SA severity	6.00 (1.82)[ab]	2.48 (1.64)	2.08 (1.52)	2.00	55.05	<.001*
RRB severity	7.43 (1.72)[ab]	4.94 (2.42)[a]	3.33 (2.30)	5.00	57.33	<.001*
Total severity	6.23 (1.57)[ab]	2.34 (1.53)	1.76 (1.34)	2.00	65.68	<.001*
ADI-R	M (SD)	M (SD)	M (SD)	Median	X^2	*p*
Total score	21.50 (9.99)[ab]	6.67 (4.12)	3.71 (3.07)	6.00	67.19	<.001*

HR-ASD high-risk sibling with autism spectrum disorder; *HR-N* high-risk sibling without autism spectrum disorder; *LR* low-risk control; *M(SD)* mean and standard deviation; *ADOS* autism diagnostic observation schedule; *SA* social affect; *RRB* restricted interests and repetitive behavior; *ADI-R* autism diagnostic interview-revised

Significant post hoc: a = different from LR, b = different from HR-N; *follow-up corrected alpha levels all < .045

Observation Scale for Infants (Bryson et al. 2008). It thus covers a wide range of behavioral symptoms, including impairments in eye contact, visual tracking, responding to name, imitation, language, social development, joint attention, gestures, play, visual examination of objects, and emotion regulation. For example, to the question, "Does your child use gestures, such as waving good-bye, nodding his/her head, or blowing a kiss?", response choices are "definitely," "possibly," or "no", which are scored '0', '1' and '2', respectively. The APSI was designed to monitor putative signs of ASD in infants aged 6–24 months, and takes approximately 5–10 min to complete. More items with scores indicating the presence of ASD-like behavior result in a higher score. The APSI has fair to excellent internal consistency (range: .77 at 6 months to .92 at 24 months) in a sample of HR children who received an ASD diagnosis at 36 months (reference blinded).

The Parent Concerns Form (Sacrey et al. 2015) is designed to collect information via interview about parent concerns during the first two years of life in children at LR and HR of ASD. It thus covers a wide range of behavioral symptoms, including general concerns (sleep, diet, sensory, motor), behavioral concerns (social, play, behavioral problems, repetitive behaviors/restricted interests), and communication concerns (verbal/nonverbal, regression). The Parent Concerns Form was designed to monitor infants aged 6–24 months and takes approximately 10–15 min to complete. Responses were digitally transcribed into a master file using Microsoft Excel (Microsoft Excel for Mac 2011, Version 14.4.1). A coder blind to group membership (first author) coded the data file using a binary system of "0" and "1", with "0" representing the absence of a concern and "1" the presence of a concern. If a domain was left blank or if parents indicated "None" or "N/A", this was coded as "0." More domains with a score of '1' indicating the presence of a concern resulted in a higher score. A second coder, also blind to group status, coded 30% of all of the Parent Concern Forms. Analysis of inter-rater reliability (i.e., coding for presence or absence of a concern within a domain) was completed using Cohen's kappa, with an overall reliability of 0.71. Reliability was analyzed for each domain using Fleiss's (1981) criteria, and ranged from 0.60 (good) to 1.0 (excellent) at sleep: 0.91; diet: 0.94; sensory: 0.60; gross/fine motor: 0.69; repetitive motor: 0.69; communication: 0.60; communication regression: 1.0; social: 0.64; play: 0.76; behavioral problems: 0.64).

Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2000) includes standardized activities and 'presses', which are used to elicit communication, social interaction, imaginative use of play materials, and repetitive behavior (Lord et al. 1989). Inter-rater reliability for the ADOS is excellent (Lord et al. 2000). The scoring algorithm was revised to optimize discrimination of ASD from other developmental disabilities and is organized into two domains, Social Affect (including Communication and Social items), and Restricted Repetitive Behaviors (Gotham et al. 2007). The original version of the ADOS was used in this study by a clinician or research staff member who had achieved

research reliability. The ADOS consists of four modules, each of which is appropriate for individuals of differing language levels. To optimize comparability across modules (and thus, across language levels), we used the 36-month ADOS severity metric (Gotham et al. 2009).

Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994) is an investigator-directed interview that elicits information regarding social development, verbal and non-verbal communication skills, and the presence of repetitive, stereotyped interests and behavior required to make an ICD-10 or DSM-IV-TR diagnosis of ASD. The questions are designed to distinguish qualitative impairments from developmental delays. The ADI-R discriminates well between ASD and other forms of developmental disability, and inter-rater reliability is excellent (Lord et al. 1994). The ADI-R was administered when children were 36 months of age by a clinician that had achieved research reliability.

Diagnostic Procedure

At 36 months of age, each participant underwent an independent diagnostic evaluation, conducted by an expert clinician blind to results from previous study visits. ASD diagnoses were assigned using DSM-IV-TR criteria, based on the best judgment of the clinician (developmental pediatrician, child psychiatrist, or clinical psychologist, all with at least 10 years of diagnostic experience). Based on this assessment, participants were classified as HR infants diagnosed with ASD (HR-ASD), HR infants not diagnosed with ASD (HR-N), and LR infant not diagnosed with ASD (LR).

Statistical Analysis Plan

Scores on diagnostic measures were compared using the Kruskal–Wallis test with group (HR-ASD, HR-N, LR) as the independent variable and scores on the assessments as the dependent variables for descriptive purposes in SPSS version 25 for iOS. Next, total scores/counts on the APSI and Parent Concern Form at 9 months were compared using the Kruskal–Wallis Test with group as the independent measure, total scores on the two assessments as dependent variables, and sex as a covariate. Finally, the predictive utility of the 9-month measures was examined using logistic regression, with diagnostic outcome (ASD vs non-ASD) as the dependent variable and total scores/counts on the 9-month measures as predictors.

To take multiple comparisons into account, we used Benjamini and Hochberg (1995) corrections. In this method, the p-values are ordered smallest to largest. The alpha level for each test is then set at $\frac{k*a}{m}$ with k corresponding to the p-value's rank (lowest p value = 1) and m corresponding to the number of comparisons, which in this case was 3 (for group comparisons on total scores), 21 (for item level comparisons on APSI), or 12 (for item domain level comparisons on the Parent Concern Form). This method decreases the chance of false positives; comparisons stop once one of the t tests is rejected. For items associated with group differences, post hoc analyses were used to distinguish items for which HR-ASD and HR-N groups did not differ but scored higher than the LR group from those for which HR-ASD scored higher than both non-ASD groups, suggesting a specific association with ASD (this method uses a 'q' to denote the critical alpha level rather than a 'p'). Effect sizes were calculated for group differences on the Total score between the three groups using Cohen's d, with 0.2–0.49 = small effect, 0.5–0.79 = medium effect, and 0.8 + = large effect (Cohen 1988).

To provide a preliminary assessment of the predictive utility of the APSI, we used receiver operator characteristics (ROC) analyses to assess the sensitivity and specificity of the APSI at each age with respect to ASD diagnosis at age 3. Analyses were limited to the HR cohort, to examine specifically the potential properties of the APSI specifically within that context. To determine the optimal cut-point for the total score, Youden's index was used, which is defined as the maximum vertical distance between the ROC curve and the diagonal or chance line [Youden's index (J) = sensitivity + specificity − 1 (Akobeng 2007)]. Other determinants of screening accuracy included: (1) sensitivity, defined as the proportion of HR siblings with ASD correctly classified by total score/count on the APSI or Parent Concern Form; (2) specificity, defined as the proportion of HR siblings not diagnosed with ASD correctly classified by total score/count on the APSI or Parent Concern Form; (3) positive predictive validity (PPV), the proportion of HR siblings with ASD who are correctly identified as HR siblings with ASD [(true positive/(true positive + false positive)]; (4) negative predictive validity (NPV), the proportion of HR siblings without ASD who are correctly identified as HR siblings without ASD [(true negative/(true negative + false negative)] and; (5) false positives, the proportion of HR siblings who did not have ASD yet screened positive on the APSI or Parent Concern Form (Fischer et al. 2003).

Results

Participant Characteristics and Outcome

Chi Square analyses on Outcome Group (HR-ASD, HR-N, LR) and APSI and Parent Concern Form respondent (mother, father, other) were not significant ($X^2 = 11.29$, $p = .08$), with mothers completing the majority of questionnaires or interviews across the three outcome groups (the same individual completed both the questionnaire and the interview). A Chi Square analyses on Sex (boy, girl) by

Outcome Group did not result in a significant effect of infant sex ($X^2 = 5.31$, $p = .07$), nor did the comparison for Outcome Group and actual ages of the children at assessment at '9-months' ($X^2 = 2.49$, $p = .29$) or '36-months' ($X^2 = .005$, $p = .99$) between groups.

As expected, the Kruskal–Wallis test run on Outcome Group resulted in significant group differences for scores on diagnostic measures at 36 months, as detailed in Table 1. Generally, children in the HR-ASD group had the highest scores on ASD symptom measures (ADOS and ADI-R) and children in the LR group had the lowest scores, with scores for the children in the HR-N group falling between the other two groups.

Group Performance on 9-Month Measures

A group effect was seen for APSI total score ($X^2 = 14.29$, $p < .001$), with post hoc testing (significance q value of .033) showing that the HR-ASD group differed significantly from both the HR-N and LR groups (ps $< .01$; ds $= .65$ and .91, respectively), who did not differ ($p = .21$, $d = .32$) from each other. A group effect was seen for Parent Concern Form total count ($X^2 = 12.84$, p = .002), with post hoc testing showing that the HR-ASD group differed significantly from both the HR-N and LR groups (ps $< .01$; ds $= .44$ and .82, respectively), who also did not differ ($p = .06$, $d = .48$) from each other.

Logistic Regression

Two separate models were examined for the HR group only, with the dependent variable in each being diagnostic outcome (HR-ASD = 1, HR-N = 0). Each model contained different blocks of independent variables. Because we were interested in the predictive utility of the measures, we ran two separate models. First, we entered the APSI total score as a solo predictor into the first block. The results from Model 1 indicate that children with higher total scores at 9 months were more likely to be diagnosed with ASD than children with lower scores [Wald(1) = 7.35, p = .007], correctly predicting outcome for 70.7% of children (overall model = X^2 (1) = 8.60, p = .003). Total number of concerns on the Parent Concerns Form was entered as a second variable (with APSI total score) in Model 2. This addition did not improve prediction (X^2 (1) = .032, p = .86) remaining at 70.7%. The APSI total score remained significant according to the Wald test (Wald(1) = 4.23, p = .04).

In the second model, we first entered total number of concerns on the Parent Concerns Form as a solo predictor into the first block. The results from Model 1 indicated that children for whom parents expressed a higher total number of concerns at 9 months were more likely to be diagnosed with ASD than children with fewer reported concerns (Wald(1) = 3.80, p = .05), correctly predicting outcome for 63.4% of children (overall model = X^2 (1) = 4.07, p = .04). Total score on the APSI was entered as a second variable (with total number of concerns on Parent Concerns Form) in Model 2. This addition improved prediction (X^2 (1) = 8.63, p = .01) to 70.7% (as seen in Model 1). According to the Wald test, total number of concerns on Parent Concerns Form was no longer significant (Wald(1) = .032, p = .86); only the APSI total score was significant in the full model (Wald(1) = 4.23, p = .04).

APSI Individual Questions

We explored item-level data to determine whether particular questions on the APSI distinguished children who later would be diagnosed with ASD at 36 months from other HR and LR children who were not diagnosed. Item-level data were assessed using Fisher's Exact Testing, with group as the independent variable and individual questions as the dependent variable. Significant group differences emerged for 7 of 26 APSI items (ps $< .05$). Follow-up tests were completed on these seven items and the alpha was corrected for multiple comparisons using the Benjamini and Hochberg (1995) correction, resulting in a significant q value of 0.03. Table 2 displays the percentage of children in each group who received a score of 1 (% 1) or a score of 2 (% 2) on each item. Post hoc tests showed that 19 items did not differentiate between groups, four items differentiated between the HR-ASD group and the two non-ASD groups (HR-N and LR), two items differentiated only between the HR-ASD and LR groups, and one item differentiated the LR group from the HR groups (who did not differ). The four items that distinguished the HR-ASD group from the other two groups were 'responding to name', 'imitation', 'back-and-forth vocalizations', and 'eye contact'.

Parent Concerns Form Domains

We explored domain-level responses to determine whether particular domains on the Parent Concerns Form distinguished children who would later be diagnosed with ASD at 36 months from other HR and LR children who were not diagnosed. Domain-level data were assessed using Fishers Exact Testing, with group as the independent variable and individual questions as the dependent variable.

Significant group differences were obtained for 4 of 10 domains (ps $< .05$). Follow-up tests were completed on these four domains and the alpha was corrected for multiple comparisons using the Benjamini and Hochberg (1995) correction, resulting in a significant q value of 0.02. As displayed in Table 3, post hoc tests showed that six domains did not differentiate between groups, no items differentiated between

Table 2 Group differences for individual APSI questions at 9 months of age

APSI AT 9 months	HR-ASD (n = 34)		HR-N (n = 82)		LR (n = 62)		HR-ASD vs HR-N	HR-ASD vs LR	HR-N vs LR
Item	% 1	% 2	% 1	% 2	% 1	% 2	p value	p value	p value
1. Visual tracking	3.2	6.5	1.9	–	–	3.7	.26	.41	.36
2. Visual fixation	25.8	19.4	25.5	9.8	27.8	20.4	.46	1.0	.26
3. Respond to name[$]	19.4	32.3	21.6	1.9	22.2	1.9	.001*	.001*	1.0
4. Response to facial emotion	58.1	19.4	52.1	18.8	50.9	5.6	.82	.05	.07
5. Anticipatory social response	25.8	0	11.8	0	7.5	0	.13	.02	.52
6. Imitation[$]	43.3	30.0	50.0	6.0	33.3	0	.01*	.001*	.02*
7. Vocalize with you[$]	54.8	12.9	27.5	3.9	11.1	0	.004*	.001*	.02*
8. Eye contact[$]	19.4	12.9	3.9	0	3.7	3.7	.001*	.009*	.56
9. Reciprocal social smile	9.7	0	7.8	2.0	1.9	0	1.0	.14	.12
10. Coordinate actions with gaze	19.4	9.7	13.7	3.9	18.5	7.4	.44	.93	.58
11. Reactivity[$]	29.0	19.4	15.7	5.9	11.1	1.9	.04	.001*	.45
12. Cuddle with you	25.8	6.5	21.6	3.9	18.5	1.9	.92	.30	.48
13. Difficult to soothe	22.6	3.2	15.7	5.9	3.7	3.7	.69	.01*	.11
14. Social interest and affect	16.1	9.7	10.0	2.0	7.4	0	.18	.02	.60
15. Difficulty with change	12.9	3.2	9.8	5.9	11.1	1.9	.90	1.0	.63
16. Hand use/holding objects[$]	25.8	6.5	20.0	0	9.3	1.9	.17	.04	.16
17. Repetitive motor behaviours[$]	16.1	16.1	11.8	1.9	0	3.7	.05	.001*	.01*
18. Another person's hand as tool	6.7	0	3.9	0	7.4	0	.62	1.0	.68
19. Unusual sensory behaviours	12.9	6.5	5.9	–	3.7	1.9	.07	.12	.83
20. Focusing attention on objects	32.3	6.5	20.4	2.0	20.4	1.9	.22	.19	1.0
21. Insistence on object	9.7	0	7.8	1.9	5.6	3.7	1.0	.48	.89
22. Resist play/fixed play	3.2	0	0	2.0	3.7	0	.62	1.0	.36
23. Share interests with others	35.5	16.1	27.5	11.8	16.7	7.4	.58	.03	.25
24. Distal point	13.3	80.0	4.1	91.8	14.8	79.6	.25	1.0	.14
25. Use gestures	12.9	71.0	20.0	56.0	22.2	40.7	.47	.02	.26
26. Loss of skill	3.2	3.2	3.9	0	3.7	0	.72	.72	1.0

APSI Autism Parent Screen for Infants; *HR-ASD* high-risk sibling with autism spectrum disorder; *HR-N* high-risk sibling without autism spectrum disorder; *LR* low-risk control

$ = items with a group-level difference at $p < .05$; * = significant post hoc following Benjamini & Hochberg correction with alphas < .03; % 1 or % 2 = percentage of children who scored a '1' or a '2' on each item

the HR-ASD group and the two non-ASD groups (HR-N and LR), two items differentiated only between the HR-ASD and LR groups, one item differentiated the LR group from the two HR groups (who did not differ), and one item differentiated the LR group from the HR_N groups.

Individual Classification of the APSI and Parent Concerns Form Within the HR Group

ROC curve analyses were completed to identify cut-off scores at each age that optimized the predictive utility of the APSI and Parent Concerns Form at 9 months with respect to subsequent ASD diagnosis at age 3. The area under the curve (AUC) for APSI total score was significant (i.e., the overall 'area under the curve' differed from 0.5, the value expected by chance) (AUC = .66, p = .016; CI (95%) = .53–.79), whereas the AUC for total number of parent concerns did not (AUC = .60; p = .13; CI (95%) = .47–.73). Sensitivity, specificity, PPV, and NPV for the total score on the APSI at 9 months were 0.42, 0.90, 0.72, and 0.72, respectively (cutoff = 14). Although the overall model was not significant, estimates for sensitivity, specificity, PPV, and NPV for the total score on the Parent Concern Form at 9 months were 0.39, 0.81, 0.54, and 0.68 respectively (cutoff = 3).

Discussion

This study compared the utility of two measures, the APSI and the Parent Concerns Form, in screening and predicting ASD in HR infants. These measures were completed when the children were 9 months old, either by parents (APSI)

Table 3 Group differences for percentage of concerns reported for domains at 9 months of age

Domani at 9 months	HR-ASD (n = 34)	HR-N (n = 82)	LR (n = 62)	HR-ASD vs HR-N	HR-ASD vs LR	HR-N vs LR
Domain	%	%	%	p value	p value	p value
Sleep	29	22	11	.60	.07	.19
Diet	16	22	13	.78	.75	.30
Sensory	35	16	15	.06	.03	1.0
Motor	48	27	24	.06	.03	.82
Repetitive motor[$]	26	14	0	.24	.001*	.005*
Language[$]	29	14	7	.15	.01*	.35
Language lost[$]	6	10	0	.71	.13	.02*
Social	16	8	4	.29	.09	.43
Play[$]	16	2	0	.03	.005*	.49
Behavior	19	14	9	.70	.20	.64

HR-ASD high-risk sibling with autism spectrum disorder; *HR-N* high-risk sibling without autism spectrum disorder; *LR* low-risk control
$ = group effect at $p < .05$; * = BH $q < .02$

or parents and an interviewer (Parent Concerns Form) and all children underwent a blinded diagnostic assessment for ASD at age 3. There were five main results. First, total score/count on the APSI and Parent Concerns Form differentiated the HR-ASD group from the HR-N and LR groups. Second, logistic regression analyses revealed that parent concerns gathered through interview did not account for significant additional variance in predicting ASD outcomes at 3 years once APSI total score was considered. Third, four APSI items distinguished between the HR-ASD group and the other two groups (who did not differ). Fourth, there were no differences between the two HR groups when the domain-level responses on the Parent Concerns Form were analyzed. Fifth, ROC analyses indicated that total score on the APSI, but not the Parent Concerns Form, could predict ASD outcomes at age 3. These results echo previous studies that suggest the APSI may be a viable option to support detection of emerging ASD symptoms in HR children as early as 9 months of age.

Total score on the APSI and total count on the Parent Concerns Form at 9 months differentiated children with and without ASD (both HR-N and LR, who did not differ). That total scores on both measures differentiated HR groups is consistent with previous research suggesting that parents may detect subtle behavioral differences that may not be readily apparent during a brief interaction with an unfamiliar adult, even though that person may have specialized knowledge of early signs of ASD (Stadnick et al. 2016; Schertz et al. 2016; Sacrey et al. 2018a, b). A recent report by Sacrey et al. (2018a, b) directly compared parent ratings on the APSI to clinical ratings on the Autism Observation Scale for Infants (AOSI; Bryson et al. 2008) for the 19 shared items (the APSI was developed from the items queried on the AOSI). At both 12 and 18 months, direct comparison using interclass correlations (ICC) showed poor agreement (ICC's < .03) for both HR groups, who were compared separately. A comparison of group differences on the individual items showed that parents of HR siblings who were later diagnosed with ASD endorsed more items at both 12 and 18 months (12 items at both time points) compared to parents who had an HR infant who did not receive a diagnosis of ASD. In contrast, clinician assessment of these same items resulted in endorsement of fewer items (three items at both 12 and 18 months).

The results of the regression and ROC analyses indicated that total score on the APSI, but not the Parent Concerns Form, at 9 months of age was able to predict ASD outcomes at age 3. The resultant sensitivity in this sample was lower than that reported by Sacrey et al. (2018a, b) for 9 months, but the specificity was comparable. The current study reported sensitivity and specificity at 0.42 and 0.90, respectively, whereas Sacrey et al. (2018a, b) reported 0.62 and 0.87, respectively. The lower specificity seen in this sample was not due to a different cut-off value resulting from Youden's index (both this analysis and that from Sacrey et al. (2018a, b) suggested 14), but may be due to the lower number of HR infants included in our sample (given the inclusion requirements of both the APSI and Parent Concerns Form completed at 9 months). Our study also provided preliminary positive and negative predictive values, both at 0.72, which are 'fair' for clinical usefulness (Cicchetti et al. 1995). Of the infants who fell within the other 28% of PPV, other clinical concerns were identified for three (anxiety, ADHD-related behaviour, compulsive behavior, and language impairment), and no clinical concerns were identified for two at age 3. Given that the psychometric values were obtained at 9 months, these results warrant further examination in a community sample.

The four items (responding to name, imitation, back-and-forth vocalizations, and eye contact) that distinguished between the HR siblings who would be diagnosed with ASD at age 3 from other HR and LR infants (who did not differ) map onto the domain of 'Social Communication and Interaction.' This is in contrast to items at 6 months, at which time only one of the two distinguishing items (back-and-forth vocalizations versus visual tracking) mapped onto the domain of 'Social Communication and Interaction domain (Sacrey et al. 2018a, b). Although total count on the Parent Concern Form also differentiated between the two HR groups, there were no domain-level differences between the two HR groups and total count did not contribute to prediction of 36-month outcomes, once variance in APSI scores was included in the regression model. Thus, of the two potential early screeners, the 26-item APSI better captured relevant information regarding ASD risk and allowed greater standardization and consistency of ascertainment than the parent interview. That parents of high-risk children can recognize such differences lends support to intensified efforts towards surveillance of early signs of ASD in HR infants, as recommended by the American Academy of Pediatrics over a decade ago (Johnson et al. 2007). Our findings are encouraging with respect to the potential viability of earlier ASD screening, at least in high-risk children. Previous behavioural measures have generally failed to identify ASD symptoms in children younger than 12 months in the general population (Zwaigenbaum and Penner 2018; Williams 2016), with notable exceptions: the Infant–Toddler Checklist has shown promise as a screener for ASD between 9 and 24 months of age in a community sample (Wetherby et al. 2008), and persistent failure to respond to name on the AOSI from 9 to 24 months indicated increased likelihood of ASD outcomes in an HR sample (Miller et al. 2017). However, it is important to consider the potential implications of shifting efforts to identify earlier risk indicators of ASD. Mounting evidence of neuroplasticity in infancy supports intervening with children to modify early experiences and potentially place these young children on a more adaptive developmental trajectory (Wan et al. 2018). Moreover, the usual long delay between the onset of parental concerns and confirmation of ASD diagnosis (Daniels and Mandell 2014) motivates efforts towards early detection and screening as corresponding earlier initiation of intervention pre-diagnosis. Yet, as the field gains traction toward ASD risk detection earlier in infancy (Klin and Jones 2018), we move further outside of the existing evidence base for intervention (Wan et al. 2018; Rogers et al. 2014; Steiner et al. 2013), and encounter increasing ambiguities about potentially efficacious approaches.

Evidence is growing that biological markers indexing atypical patterns of early brain growth, connectivity, and function may detect risk of subsequent ASD diagnoses with remarkable accuracy as young as 6 months. Resting electroencephalograms (EEG; Bosl et al. 2018), event related potentials (ERP; Elsabbagh et al. 2012), and in particular, magnetic resonance imaging (MRI) studies of cortical volume and surface area (Hazlett et al. 2017), cerebral spinal fluid (Shen and Piven 2017), and connectivity (Emerson et al. 2017; Lewis et al. 2017) are all now associated with published estimates of classification accuracy at 6 months of 80% or higher, relative to subsequent ASD diagnoses in HR samples. Such findings have informed a proposed conceptual model of ASD in which atypical neurodevelopmental processes lead to cascading changes consolidating into the ASD phenotype. In such a model, measurable differences in brain development occur prior to overt behavioral manifestations, and thus have potential for 'pre-symptomatic' detection (Piven et al. 2017). This 'pre-symptomatic' period (i.e., age 6–12 months) is hypothesized to be associated with non-specific 'domain-general' features such as atypical motor control, reported in other studies (Flanagan et al. 2012; LeBarton and Landa 2018). However, the current study suggests that subtle behavioral features (e.g., inconsistent responding to name, also reported at 9 months by Miller et al. (2017), imitation, back-and-forth vocalizations, and eye contact) more closely related to DSM-5 ASD symptom domains may be detectable by parents in their everyday experience with their infants. It is essential to operationalize and test the earliest behavioral manifestations of ASD as potential targets for interventions that could be implemented for infants at risk, including those identified on the basis of biomarker measurement. Although scientific and technological advances may lead to implementation of 'next generation' early detection methods such as eye tracking (Klin et al. 2015) and quantitative behavioral measurement (Manfredonia et al. 2018) in primary care, the current findings highlight that parent report remains an informative as well as a highly scalable strategy in the first year of life, particularly in lower-resource settings (Durkin et al. 2015).

The main limitation of the current study is its exclusive focus on infants with an older sibling with ASD. This feature characterizes much of the current literature on behavioral and biological manifestations of ASD during infancy due to the efficiency of the HR sibling design, but is potentially problematic with respect to generalizability to non-familial samples. Sensitization of parents to behavioral features of ASD based on prior experience with their diagnosed children may underlie the strong predictive performance of the present measures. As well, replication in independent high-risk cohorts (not only younger siblings, but also infants with other risk factors for ASD, such as prematurity and specific genetic diagnoses) will be needed to assess utility in those populations. That said, the current study contributes to the growing evidence that

ASD manifests behaviorally in the first year of life, which could inform ASD surveillance and screening efforts as well as novel treatment strategies.

Acknowledgement The authors would like to thank the research assistants at each site for their help with data collection and the parents and children who participated in our study. The study was funded by Canadian Institutes of Health Research (CIHR) and Kids Brain Health Network.

Author Contributions LRS made substantial contributions to conception and design, collected and analyzed the data and prepared the first draft of the paper, and approved the final draft. LZ, SB, JB, IMS, WR, PS, TV, CR, and NG contributed to the conception of the project, provided a critical review of the manuscript, and approved the final draft.

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