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ORIGINAL PAPER

The Effect of Gestational Age on Symptom Severity in Children with Autism Spectrum Disorder

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Abstract Between 2006 and 2010, two research-validated instruments, Social Communication Questionnaire (SCQ) and Social Responsiveness Scale (SRS) were filled out online by 4,188 mothers of Autism Spectrum Disorder (ASD) children, aged 4–21, as part of voluntary parental participation in a large web-based registry. Univariate and multivariate linear regression analysis (adjusted for child's sex, ability to verbalize, categorical IQ score, and fetal growth rate) demonstrated significantly higher SCQ and SRS scores for ASD children of both preterm (<37 weeks) and post-term (>42 weeks) gestational age (GA) compared to ASD children of normal GA, thus indicating that both preterm and post-term children manifest increased ASD symptomatology. Normal GA at birth appears to mitigate the severity of autistic social impairment in ASD children.

Keywords Autism Spectrum Disorder symptoms · Preterm · Post-term · Post-mature · SCQ · SRS

Introduction

Autism Spectrum Disorder (ASD), a behaviorally-defined neurodevelopmental disorder, is characterized by impaired communication and social interactions and by the presence of repetitive/stereotypical behaviors. Two research-validated ASD instruments: Social Communication Questionnaire (SCQ) and Social Responsiveness Scale (SRS) can be used to quantify the number and/or frequency of autistic traits (Charman et al. 2007; Constantino and Gruber 2009; Rutter et al. 2010). The higher the score on either instrument, the higher the likelihood that the child exhibits increased ASD symptomatology.

Undoubtedly, many factors contribute to the expression of the highly heterogeneous ASD disorder with its multiple behavioral and biological phenotypes. It is plausible that gestational age (GA) at birth may be one contributor to the risk of ASD and its severity. Evidence is emerging that the pathophysiology of ASD begins prenatally. Impaired intrauterine cerebellar development is suggested by combination of the lack of retrograde atrophy of the inferior olivary neurons and the decreased numbers of Purkinje cells found in ASD cerebellums (Bauman 1996; Bauman and Kemper 2005). More evidence of an intrauterine etiology is the increase of cortical minicolumns in ASD brains; the number of minicolumns is dependent upon number of founder cells that are generated during the first trimester (Casanova et al. 2010).

Several studies suggest a substantially increased risk of ASD in preterm babies (Hultman et al. 2002; Glasson et al. 2004; Limperopoulos et al. 2008; Johnson et al. 2010; Pinto-Martin et al. 2011). However, the association of GA with ASD severity has not been examined. We hypothesized that SCQ and SRS scores (i.e. markers for severity of autistic impairment) would be increased in ASD children of preterm GA but we aimed to examine the effect of GA in general (both preterm and post-term GA) on ASD severity.

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Methods

Setting

The data source of this study was the Interactive Autism Network (IAN), an online, voluntary, U.S.-based ASD research database that is constantly updated via ongoing recruitment of parents of ASD children who access the site by web search, advertisements and/or word of mouth. The IAN operates a Community Forum that is open to anyone interested in developing a better understanding of ASD. However, enrollment in the IAN research ASD database is limited to American children whose ASD diagnosis had been established by a professional. The child had to have received one of the following diagnoses: Autism or Autistic Disorder, Asperger Syndrome, Childhood Disintegrative Disorder, Pervasive Developmental Disorder-Not Otherwise Specified, Pervasive Developmental Disorder, or Autism Spectrum Disorder. Once a child is enrolled by a parent who had legal authority to have given consent, the other parent becomes eligible for participation as well. The parents participate by filling out secure online surveys regarding their child's ASD.

Instruments

IAN Questionnaires

Parents complete an initial online registration form including a profile for each ASD-affected child; parents report information about child's sex, race, categorical IQ score (<40, 41–55, 56–70, 71–85, 86–115, 116–130, >130), birth weight (BW), and other medical and social demographics. Regarding GA, the parent is asked "What was the length of the pregnancy?" and then given 4 possible response choices: (a) very premature or very early (fewer than 34 weeks), (b) premature or early (34 weeks through 36 weeks, (c) on or near due date (37 weeks through 41 weeks), or (d) more than 2 weeks late (42 or more). Parents complete two research-validated ASD screening instruments (SCQ and SRS Questionnaires). Registered participants receive biweekly email reminders to complete outstanding questionnaires.

Social Communication Questionnaire (SCQ)

The SCQ (Western Psychological Services, Los Angeles, California) is a dichotomous (yes/no) research-validated parent-completed ASD tool consisting of 40 items based on DSM-IV-TR criteria for ASD and the Autism Diagnostic Interview-Revised. A score of 15 or more is suggestive of ASD. It is applicable to subjects of any chronological age >4 years, provided that their mental age is >2 years (Rutter et al. 2010).

Social Responsiveness Scale (SRS)

The SRS (Western Psychological Services, Los Angeles, California) is a validated, 65 item, parent/teacher-completed ASD tool with a emphasis in detecting social deficits. A Likert scale response format (not true, sometimes true, often true, almost always true) is used to produce a scale that is reliable across a range of symptom severity. SRS raw scores undergo conversion (which adjusts for gender) into standardized SRS scores called SRS T-scores (Mean 50, SD 10). A difference in T-score of 5 points (1/2 of a standard deviation [SD]) is clinically significant. Clinical T-score screening categories of <55, 55–59, 60–75 and >75 suggest unaffected/borderline status, mild to moderate, or severe autistic features, respectively (Constantino and Gruber 2009).

There are separate SRS T-scores available for each of 5 different domains of ASD symptomatology (Constantino and Gruber 2009). Since each category is separately standardized (Mean 50, SD 10), the total SRS T-score has the same score range, mean and SD as the categories; thus the total SRS T-score is NOT equal to the sum of the individual categorical domain scores. The SRS domains are:

(1) Social Awareness: the ability to pick up on social cues
(2) Social Cognition: the ability to interpret social cues once they are picked upon
(3) Social Communication: expressive social communication
(4) Social Motivation: The extent to which a respondent is motivated to engage in social-interpersonal behavior; anxiety, inhibition and empathy are included in this category
(5) Autistic Mannerisms: includes stereotypical behaviors or highly restricted interests characteristic of autism.

Analysis

We performed statistical analyses on Total SCQ scores, Total SRS T- scores and on the categorical domains of the SRS T-scores using SAS statistical software, (SAS Institute Inc, Cary, NC), in relation to GA, categorized very preterm (<34 weeks), preterm (34–36 weeks) term (37–41 weeks) and post-term (≥42 weeks). Because of our study's focus on pregnancy factors, we limited our analyses to data from maternally-completed questionnaires. Between 2006 and 2010, SCQ and SRS Questionnaires were completed by 4,188 mothers of ASD children aged 4–21 years. For skipped or declined questions, data was recorded as missing. Our analyses are based on non-missing de-identified data provided to us by IAN.

Because SCQ has been shown to be a validated instrument in an ASD population regardless of the cognitive function (Rutter et al. 2010), we performed our statistical analyses for SCQ scores on the full ASD cohort. On the other hand, SRS Scores had been validated on a cohort with normal cognitive functioning (Constantino et al. 2000). Therefore, we performed our statistical analyses of SRS scores on a subcohort (IQ > 70) of our ASD population in addition to the full ASD cohort.

To avoid the biases in analyses that fail to consider the selection for impaired fetal growth that is characteristic of many premature infants (Paneth 2008), we incorporated into our analyses, a maturity parameter called the fetal growth ratio (FGR). We derived an approximate FGR by dividing the child's birth weight by the median dataset birth weight in the GA category. The higher the FGR, the greater is the fetal growth of an infant in relation to the median fetal growth of the cohort of the same GA category. The categorical nature of our GA data did not allow us to more exactly calculate FGR by week of GA.

Results

Source of Diagnosis of ASD

50% of the ASD cohort had received their diagnosis by a medical physician, 25% by team of health professionals, 18% by clinical psychologist, 7% other.

Demographics of the ASD Cohort

The ASD study cohort composition was 82.4% male, 92.1% White, and 7.8% Hispanic. Mean BW was 3,365 g (SD: 675 g). 94.8% were singletons and 52.6% were first-borns. See Table 1 for breakdown of demographics by GA.

SCQ and SRS Characteristics by Age Group (Table 2)

The mean SCQ score in our full cohort was 22.9 (SD 6.9) with 87.8% scoring above the suggested ASD screening cutoff of 15. The mean SRS T-Score was 86.3 (SD 14.9) with 77.2% scoring above 75, the cutoff for severe ASD symptomatology. Birth before or after 2000 was unrelated to the distribution of GA categories (<34 weeks, 34–36 weeks, 37–41 weeks, ≥42 weeks) or severity of autistic symptomatology. A score on the SRS > 75 was found in 79.6% of older children and 75.4% of younger children. However, there was a small, yet statistically significant (t test, $p < 0.05$, data not shown) difference in mean SCQ and SRS scores (2.7 point difference in SCQ score, 2 points difference in SRS score) between the older ASD subcohort and the younger ASD subcohort. A higher percentage of the older subcohort (10.7%) had Aspergers' Syndrome compared to the younger group (3.5%).

Table 1 Demographics and birth characteristics of autism spectrum disorder study cohort by gestational age

	GA < 34 weeks N = 164	GA 34–36 weeks N = 525	GA 37–41 weeks N = 3,264	GA ≥ 42 weeks N = 235
Gender				
Male	79.9% (131/164)	82.3% (432/525)	82.3% (2,688/3264)	85.1% (200/235)
Race				
White	90.9% (149/164)	93.9% (493/525)	91.9% (2998/3,264)	92.8% (218/235)
Black	4.9% (8/164)	6.7% (35/525)	3.7% (121/3,264)	3.0% (7/235)
Other	4.3% (7/164)	5.7% (3/525)	4.4% (145/3,264)	4.3% (10/235)
Ethnicity	7.3%	7.2%	7.9%	7.2%
Hispanic	(12/164)	(38/525)	(259/3,264)	(17/235)
Child age (years) during study participation	Mean 10.9 (SD 3.8)	Mean 10.4 (SD 3.6)	Mean 10.8 (SD 3.9)	Mean 11.9 (SD 3.8)
Mean birth weight	1599 g (SD: 743)	2817 g (SD: 584)	3509 g (SD: 496)	3782 g (SD: 474)
Birth type: singleton	66.5% (109/164)	80.8% (424/525)	98.2% (3,204/3,264)	100% (235/235)
Birth order: first	54.9% (90/164)	50.9% (267/525)	52.1% (1701/3,264)	62.5% (147/235)

Table 2 Comparison of older versus younger ASD sub-cohorts

	Full ASD cohort N = 4,188	Birth year <2000 N = 1,772	Birth year ≥2000 N = 2,416
Very preterm (<34 weeks)	3.9% (164/4,188)	4.6% (81/1,772)	3.4% (83/2,416)
Preterm (34–37 weeks)	12.5% (525/4,188)	11.3% (201/1,772)	13.4% (324/2,416)
Full term (37–42 weeks)	77.9% (3264/4,188)	76.4% (1354/1,772)	79.1% (1910/2,416)
Post term (>42 weeks)	5.6% (235/4,188)	7.7% (136/1,772)	4.1% (99/2,416)
Mean SCQ score	22.9 (SD 6.9)	24.3 (SD 7.3)	21.8 (SD 6.4)
SCQ score > 15 (ASD screen cutoff)	87.8% (3,675/4,188)	89.0% (1,577/1,772)	86.8% (2,097/2,416)
Mean SRS T-Score	86.3 (SD 14.9)	87.4 (SD 15.1)	85.4 (SD 14.8)
SRS T-score > 60 (≥mild symptoms)	95.8% (4,009/4,188)	95.9% (1,700/1,772)	95.6% (2,309/2,416)
SRS T-score > 75 (severe ASD symptoms)	77.2% (3,232/4,188)	79.6% (1,420/1,772)	75.4% (1,822/2,416)
Asperger's diagnosis	6.5% (274/4,188)	10.7% (189/1772)	3.5% (85/2416)

Characteristics of ASD Cohort by Gestational Age (Table 3)

ASD Children of normal GA (37–41 weeks) had lower mean SCQ and SRS T scores (22.6, 85.6 respectively) than ASD children of very preterm (24.6, 90.0), preterm (23.7, 88.1) or post-term (25.5, 88.4) GA. No significant difference was found in any GA category in proportion of children with reported motor delay (data not shown) but a significant difference was found for the mean age of first steps (*t* test, $p < .0001$) and mean age of first words (*t* test, $p < .001$) between GA < 37 weeks and GA ≥ 37 weeks. ASD children of GA < 37 weeks also were more likely to have reported IQ scores below 70 ($p < 0.05$) compared to GA ≥ 37 weeks. Self-injurious behavior was more common in both the preterm group ($p < .01$) and post-term group ($p < 0.05$) compared to children born at term. Mothers first noticed that something was wrong with her child on average of 20.2 months. This mean age of first concern for GA < 37 weeks was 1.7 months younger than for GA ≥ 37 weeks ($p < .01$).

Effect of GA on SCQ Scores (Table 4)

On univariate linear regression, the SCQ scores in the very preterm, preterm and post-term GA categories were significantly increased by a modest 1.1–2.1 points above the term GA SCQ score; on the other hand, for each increase in 100 g in BW, the SCQ score declined by 0.5 points. These GA and BW effects are consistent with one another; larger babies tend to be closer to term GA and thus would have lower SCQ scores than smaller, preterm babies. However, the FGR maturity parameter, which separates the effect of BW from GA had no significant effect on SCQ scores. Lack of verbal ability and IQ < 70 significantly increased SCQ scores by +3.5 points, +3.6 points respectively. Gender had no significant effect.

Multivariate linear regression analysis (with adjustment for sex, ability to verbalize, impaired cognitive function and FGR) demonstrated that both preterm and post-term GA caused a modest increase of +1.7 to +2.3 points on SCQ scores.

Effect of GA on SRS T-Scores (Table 5, Table 6)

On univariate analysis of the subcohort IQ > 70 (Table 5), SRS T-scores increased between 2.2 and 4.6 points depending upon GA category compared to term. The size of this effect was considerable. Infants born <34 weeks had SRS scores nearly ½ SD higher than births at term; less severely preterm births (34–37 weeks) scored nearly ¼ SD higher, and post-term infants 1/3 of an SD higher. Lack of verbal ability had a very large effect (+30 points; 3 SD's) on raising the SRS score. Male gender (−8.2 points) and

Table 3 Characteristics of autism spectrum disorder study cohort by gestational age

Total N = 4188	GA < 34 weeks N = 164 (3.9%)	GA 34–36 weeks N = 525 (12.5%)	GA 37–41 weeks N = 3,264 (77.9%)	GA ≥ 42 weeks N = 235 (5.6%)
Mean SCQ score	24.6	23.7	22.6	25.5
	(SD 6.5)	(SD 6.7)	(SD 7.0)	(SD 6.9)
Mean SRS T-score	90	88.1	85.6	88.4
	(SD 15.7)	(SD 15.6)	(SD 14.8)	(SD 14.3)
Reported motor delay	66.3%	55.0%	44.2%	51.7%
	(108/163)	(287/522)	(1426/3,228)	(120/232)
IQ Score < 70	26.2%	28.5%	22.6%	22.4%
	(16/61)	(65/228)	(320/1417)	(26/116)
Currently non-verbal	3.7%	4.8%	2.4%	1.4%
	(6/164)	(25/525)	(78/3264)	(3/235)
Currently non-walking	0.6%	0.6%	<0.1%	0.0%
	(1/164)	(3/525)	(2/3264)	(0/235)
Self-injurious behavior	61.6%	51.0%	47.7%	59.1%
	(101/164)	(268/525)	(1556/3,261)	(139/235)
First words (months)	Mean 17.2	Mean 14.7	Mean 16.3	Mean 18.0
	(SD 7.0)	(SD 4.8)	(SD 12.2)	(SD 15.4)
First steps (months)	Mean 19.4	Mean 17.8	Mean 13.5	Mean 13.1
	(SD 11.7)	(SD 12.6)	(SD 6.1)	(SD 4.3)
Age of first concern to mom (months)	Mean 16.9	Mean 19.4	Mean 20.5	Mean 20.4
	(SD 13.5)	(SD 16.9)	(SD 15.9)	(SD 16.6)

Table 4 Effect of gestational age on SCQ scores of full ASD cohort

	Univariate effect on SCQ score (in points) N = 4188	Univariate 95% CI (in points)	Multivariate effect on SCQ score (in points) N = 1818	Multivariate 95% CI (in points)
Referent: GA:37–41				
GA: < 34 weeks	+2.1***	(+1.1, +3.1)	+1.7	(−0.1, +3.6)
GA: 34–36 weeks	+1.1***	(+0.5, +1.7)	+2.3**	(+0.2, +3.2)
GA ≥ 42 weeks	+2.0***	(+1.1, +2.9)	+2.1**	(+1.8, +3.5)
Covariates				
Non-verbal	+3.5**	(+1.6, +4.2)	+0.7	(−3.6, +2.2)
Male	+0.4	(+0.0, +1.1)	+0.7	(−1.5, +1.1)
IQ < 70	+3.6***	(+2.9, +4.4)	+3.6***	(−2.8, −4.4)
Fetal growth ratio (FGR)	+0.4	(−0.9, +1.5)	−0.8	(−2.7, +1.2)
Birthweight (per 100 g)	−0.5*	(−0.6, −0.2)	(Not in multi-variate model due to collinearity with GA and FGR)	

* $p < .05$, ** $p < .01$, *** $p < .001$

FGR (−5.3 points) were strongly associated with lower SRS scores. Analysis on full ASD cohort demonstrated similar results to the subcohort IQ > 70 analysis (Table 6).

Multivariate linear regression analysis of subcohort IQ > 70 (Table 5), adjusted for sex, ability to verbalize, and FGR demonstrated similar increases of GA (+2.5 to +4.8 points), on SRS scores depending upon GA category, and similar effect sizes to the entire cohort (Table 6).

SRS ASD Skill Subdomains in the ASD SubCohort IQ > 70 (Table 7 and Fig. 1)

On multivariate analysis: for GA < 34 weeks, there were significant SRS score increases in the domains of Social Cognition and Social Communication. For GA 34–36 weeks, there were significant increases in the domains of Social Cognition, Social Awareness and Social

Table 5 Effect of gestational age (GA) on social responsiveness scale (SRS) T-scores in ASD sub-cohort IQ > 70

	Univariate effect on SRS T-score (in points) N = 1395	Univariate 95% CI (in points)	Multivariate effect on SRS T-score (in points) N = 1395	Multivariate 95% CI (in points)
Referent: GA:37–41				
GA: < 34 weeks	+4.6*	(+0.2, +9.0)	+4.8*	(+0.4, +9.1)
GA: 34–36 weeks	+2.2	(−1.8, +4.7)	+2.5*	(+0.1, +4.9)
GA ≥ 42 weeks	+3.3*	(+0.1, +6.4)	+4.1**	(+0.9, +7.2)
Covariates				
Non-verbal	+30.0*	(+1.0, +59.0)	+32.6*	(+4.3, +60.9)
Male	−8.2**	(−6.1, −10.3)	−7.5***	(−5.9, −10.1)
Fetal growth ratio	−5.3*	(−0.7, −9.9)	−1.6	(−2.4, +3.1)
Birthweight (per 100 g)	−0.13**	(−0.11, −0.15)	(Not in multi-variate model due to collinearity with GA and FGR)	

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 6 Effect of gestational age (GA) on SRS total T-scores on full ASD cohort

	Univariate effect on SRS T-score (in points) N = 4188	Univariate 95% CI (in points)	Multivariate effect on SRS T-score (in points) N = 1818	Multivariate 95% CI (in points)
Referent: GA:37–41				
GA: < 34 weeks	+4.4***	(+2.1, +6.8)	+5.1**	(+1.5, +8.8)
GA: 34–36 weeks	+2.4***	(+1.1, +3.9)	+2.7**	(+0.8, +4.8)
GA ≥ 42 weeks	+2.8**	(+0.8, +4.8)	+3.3**	(+0.9, +6.2)
Covariates				
Non-verbal	+9.5***	(+6.8, +12.4)	+6.9*	(+1.1, +12.7)
Male	−8.5***	(−7.4, −9.7)	−8.5***	(−6.8, −10.2)
IQ < 70	+7.9***	(+6.3, +9.4)	+6.7***	(+5.2, +8.3)
Fetal growth ratio	−4.6*	(−0.6, −8.6)	−2.6	(−6.5, 1.2)
Birthweight (per 100 g)	−0.21***	(−0.17, −0.23)	(Not in multi-variate model due to collinearity with GA and FGR)	

* $p < .05$, ** $p < .01$, *** $p < .001$

Motivation. For GA > 42 weeks, there were significant increases in the domains of Social Communication, Social Motivation and Autistic Mannerisms (Table 7). For GA < 34 weeks, there was the largest increase in symptoms in the domains of Social Cognition skills, Social Communication skills, and Autistic Mannerisms. For GA 34–37, ASD skills in all SRS domains appeared to be almost equally affected. For GA > 42 weeks, Social Motivation Skills and Autistic Mannerisms were most affected (Fig. 1).

Discussion

In a large volunteer sample, ASD Children born before 37 weeks (preterm) or after 42 weeks (post-term) have a modest increase in scores on two different validated ASD instruments, SCQ and SRS, indicating that these children exhibit at least some degree of increased ASD symptomatology compared to ASD children born at normal term. Because the SRS is designed to quantify autistic impairment along a standardized scale whereas the SCQ is intended as an ASD screening instrument, the SRS was the more sensitive of the two instruments in demonstrating the outcome of this study.

Prior studies have demonstrated a higher ASD prevalence in preterm children (Hultman et al. 2002; Glasson et al. 2004; Limperopoulos et al. 2008; Johnson et al. 2010; Pinto-Martin et al. 2011). We build on this by showing that the expression of autistic traits differs in preterm ASD children compared to ASD children of normal GA. There are significantly higher SCQ and SRS scores in preterm

Table 7 ASD Sub-cohort: IQ > 70 (N = 1395) effect of gestational age on SRS domain T-scores

Subcategories of SRS T-scores (referent: GA 37–41 weeks)	GA < 34 weeks univariate/multivariate (in points)	GA: 34–36 weeks univariate/multivariate (in points)	GA ≥ 42 weeks univariate/multivariate (in points)
Social cognition	**+5.6*/+5.7****	+2.0/**+2.3***	+1.9/+2.6
Social awareness	+1.7/+1.8	**+2.4*/+2.5***	+1.9/+2.4
Social communication	**+5.2*/+5.2***	+1.7/+2.0	**+3.2*/+2.6****
Social motivation	+1.4/+1.6	+2.3/**+2.5***	**+3.9*/+4.4****
Autistic mannerisms	+4.6/+4.7	+ 1.7/+2.1	+2.8/**+3.9 ***

The multivariate model adjusts for verbalization, fetal growth ratio and sex

Significant point values are shown in bold

* $p < .05$, ** $p < .01$

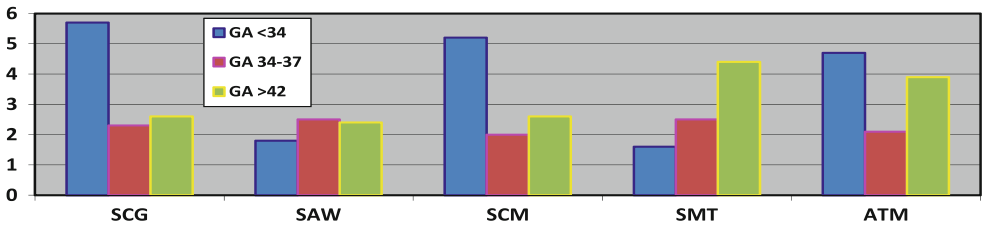

Fig. 1 Increase of SRS domain T-scores (in points) for each GA category (As compared to term GA) as predicted by multivariate Model* in the ASD sub cohort: IQ > 70 (N = 1395).

*multivariate model adjusted for: ability to verbalize, gender, fetal growth rate; *SCG* social cognition skills, *SAW* social awareness skills, *SCM* Social communication skills, *SMT* social motivation skills, *ATM* autistic mannerisms

ASD children. The greatest magnitude of score increases are seen in the very preterm (GA < 34) with their SRS T-score increase equal to almost 50% of one SRS SD; 50% of one SRS SD is considered to be a clinically significant rise in ASD symptom severity (Constantino and Gruber 2009). Furthermore some categories of autistic symptoms appear to be differentially affected in relation to degree of prematurity. For GA < 34 weeks, the largest increase in ASD impairment occurs within the domains of Social Cognition, Social Communication and Autistic Mannerisms. However, for GA 34–36 weeks, all five domains of symptom types appear to be relatively equally affected.

We observed other differences in the presentation of ASD in preterm children. Mothers of preterm children first noted autism symptomatology earlier than did the mothers of term children. This finding may reflect the extra attention paid by mothers to the development of preterm babies. Second, we observed a significant increase in self-injurious behavior in preterm compared to term ASD children.

How might prematurity affect the expression of symptoms in children with ASD? The extrauterine environment in which the preterm brain matures may possibly alter gene expression and result in impaired neurodevelopment. Twin studies that have shown that highly heritable autistic traits are modified by environmental factors (Whitaker et al. 1997; Rosenberg et al. 2009; Lichtenstein et al. 2010). Best-fit models have estimated that the shared environment component [58%, CI: 30% to 80%]of twins contributes more to the broad phenotype of ASD than the genetic heritability component [38%, CI: 14%-67%] (Hallmayer et al. 2011). Another possibility is that some ASD children are somehow pre-programmed to be born preterm. If this is the case, then perhaps the prematurity and ASD act as co-morbid conditions, with one potentially affecting the expression of the other.

Though we have found no prior studies examining ASD prevalence or symptomatology in post-term infants, we have shown that the expression of autistic traits appear to differ in post-term ASD children compared to ASD children of normal GA. Post-term GA may affect the expression of the ASD phenotype for several reasons: (1) increased fetal exposures during prolonged intrauterine development, (2) increased risk of malnutrition due to placental failure, and/or (3) increased risk of instrument assisted and Cesarean delivery (Olesen et al. 2003). Prolonged gestation has been shown to be associated with other neurologic disorders such as early epilepsy (Ehrenstein et al. 2007). Another possibility is that post-term infants are pre-programmed for prolonged gestation. If that is the case, then GA ≥ 42 weeks and ASD may act as co-morbid conditions with one possibly influencing the manifestation of the other.

For unknown reasons, the girls in our ASD cohort are more severely affected (i.e. higher SRS T-scores) than the boys. Perhaps the biological risk factors accounting for the difference in incidence of ASD between the sexes are not the same as the risk factors accounting for ASD symptom severity (Auyeung et al. 2009). It has been hypothesized that females with ASD need to inherit a greater genetic liability to manifest the disorder. One study in support of this has demonstrated that ASD males from families containing a female with ASD have higher repetitive behavior scores than ASD males from families containing only males with ASD (Szatmari et al. 2011).

The main limitation of this large ASD cohort study is the volunteer nature of the sample. The second limitation is that all the data is from maternal report. However, a study using the same IAN database has reported that over 90% of the children in this ASD database screen ASD positive by validated instruments, thus suggesting that the parent-reported ASD status is highly accurate. (Rosenberg et al. 2009). The mothers in our study had to recall GA of their children between 4 and 21 years after birth. Though maternal recall of offspring BW has been shown to be highly accurate even 17 years after birth, (Lucia et al. 2006), there is no study available specifically on maternal recall of GA. However, the accuracy of our maternally-reported variables is indicated by the consistent correlation between GA, BW and acquisition of developmental milestones. For example, as would be expected, the mean BW of the ASD cohort progressively increases and mean age of first steps progressively decreases with increasing GA. Furthermore, in our study, mothers were only asked to choose a GA, thus simplifying the response.

Our study includes a wide age span (4–21 years old) of participants. Undoubtedly, there have been changes in diagnostic criteria of ASD as well as advances in preterm care leading to more preterm survival over this time frame. However, a comparison of the characteristics of our ASD cohort born before and after the year 2000 indicate that the two groups were similar in GA category distribution and in proportion of severely impaired, and manifested only small differences in mean SCQ and SRS scores. The higher percentage of ASD children with Asperger in the older cohort is consistent with the older mean age of Asperger's diagnosis (Mean: 11 years) compared to other forms of ASD diagnosis (Mean: 3 years old) (Foster and King 2003; Mandell et al. 2005).

In summary, normal GA at birth appears to somewhat mitigate the severity of autistic social impairment in ASD children. Furthermore, the categories of ASD traits that are most affected by GA appear to differ for preterm and postterm children.

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