Language regression is associated with faster early motor development in children with autism spectrum disorder

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Language regression (LR) is a consistent and reproducible phenomenon that is reported by ~25% of parents who have children with autism spectrum disorder (ASD). However, there is controversy regarding the etiological and clinical significance of this phenomenon. Here, we examined data from a cohort of 218 children with ASD from the Negev Autism Center in Israel. We identified 36 children with ASD who were reported to exhibit clear LR by their parent on three independent occasions and compared them to 104 children whose parents did not report any concern of regression (NR). We compared a variety of key developmental characteristics across these two groups. We found that the age at which children with ASD in the LR group achieve key developmental milestones of crawling, walking, and use of first words is significantly younger than the age of children in the NR group, and comparable to the age of typically developing children. In contrast, no differences were observed in physical growth characteristics such as head circumference, weight, or height between the groups. Furthermore, almost all children with LR were born close to full term (>35 weeks) and none had a history of hypotonia. Notably, despite their apparently typical early development, children with LR were diagnosed with more severe symptoms of ASD than children with NR. These results strengthen the motivation to continue and study LR among children with ASD and suggest that early detection and intervention studies of ASD may benefit from stratifying children into LR and NR groups. ***Autism Res*** *2019, 00: 1–12.* © 2019 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: The presence of language regression (LR) among children with autism is still a matter of scientific debate. Here, we show that children with autism and reported LR start to crawl, talk, and walk at the same age as other typically developing children and significantly earlier than other children with autism. These findings, along with other medical differences between these groups, suggest that children who experienced LR comprise a distinct subgroup within the autism spectrum.

Keywords: autism spectrum disorder; language regression; early development; motor development

Introduction

A major goal of contemporary research of autism spectrum disorder (ASD) is to characterize the large behavioral, biological, and clinical heterogeneity apparent across children with ASD. This is critical for developing new early detection measures and therapies for specific subtypes of ASD (i.e., personalized medicine) [Loth et al., 2016; State et al., 2012]. One well-known developmental characteristic that may hold relevant potential is regression [Hansen et al., 2008]. Regression (i.e., loss of previously acquired skills) is reported by parents of approximately one-third of children with ASD [Barger, Campbell, & McDonough, 2013]. The clinical significance and utility of this phenomenon have been debated for many years [Pearson, Charman, Happé, Bolton, & McEwen, 2018] with some suggesting that regression may characterize unique subgroups of children with ASD with distinct etiologies [Stefanatos, 2008; Tuchman & Rapin, 1997] and others suggesting that regression, to one degree or another, is a common finding in most children with ASD [Ozonoff et al., 2010; Thurm, Powell, Neul, Wagner, & Zwaigenbaum, 2018].

An important aspect of the debate about regression is its precise definition. Some studies have defined regression broadly as the loss of any skill including motor and cognitive skills, while others have focused on the social communication and language skills that are specific to ASD [Barger et al., 2013; Hansen et al., 2008; Ozonoff

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et al., 2010; Stefanatos, 2008; Thurm et al., 2018; Tuchman & Rapin, 1997]. The precise definition is important, because the prevalence of regression differs from ~40% in studies where regression is broadly defined to less than 25% in studies where regression is defined by loss of language [Barger et al., 2013]. This has motivated most studies to focus on language regression (LR), which is often identified by asking the parents if their child used at least 3–5 words consistently for a period of at least 1–3 months and then stopped using these words for at least 1 month. Parental reports of such loss of language are strongly correlated with retrospective observer-coded home videos [Goldberg, Thorsen, Osann, & Spence, 2008], thereby demonstrating the reliability of LR reports in contrast to other types of regression [Goldberg et al., 2008; Ozonoff et al., 2010, 2011]. The average age of LR in ASD is 21 months [Barger et al., 2013] and children with LR tend to be diagnosed with ASD earlier than children with no regression (NR) [Kalb, Law, Landa, & Law, 2010], presumably because loss of language abilities motivates the parents to seek immediate clinical care.

While children with ASD and LR exhibit timely language onset [Lord, Shulman, & DiLavore, 2004] in contrast to children with ASD and NR [Baird et al., 2008; Jones & Campbell, 2010; Kalb et al., 2010; Landa & Garrett-Mayer, 2006; Lord et al., 2004], both groups of these children exhibit similar language difficulties later in life (after regression) [Howlin, Savage, Moss, Tempier, & Rutter, 2014; Pickles et al., 2009]. This suggests that the initial use of language in children with LR does not benefit the development of later language abilities [Rogers, 2004]. Some studies have reported that children with ASD and LR exhibit relatively lower cognitive scores [Goin-Kochel, Esler, Kanne, & Hus, 2014; Rogers & DiLalla, 1990; Tuchman & Rapin, 1997; Zachor & Ben-Itzchak, 2016] and higher autism severity scores [Goin-Kochel et al., 2014; Kalb et al., 2010; Richler et al., 2006; Werner, Dawson, Munson, & Osterling, 2005] than children with ASD and NR, but others have not found differences across groups [Hansen et al., 2008; Lord et al., 2004; Ozonoff et al., 2011; Shumway et al., 2011]. Most studies have reported no differences in demographic characteristics such as gender ratio [Jones & Campbell, 2010; Stefanatos, 2008] and parental age [Christopher, Sears, Williams, Oliver, & Hersh, 2004]. The mixed reports regarding phenotypic differences across LR and NR groups have generated an ongoing debate regarding the potential benefit of studying children with LR as a distinct subtype of autism [Pearson et al., 2018; Thurm et al., 2018]. Prospective studies of high-risk infants have reported that most infants who develop ASD exhibit many subtle forms of regression in a variety of social behaviors. This suggests that regression may be better defined as a dimension, whereby different children with ASD exhibit different types of skill loss at various developmental time-points [Thurm et al., 2018].

The relationship between language and motor development has rarely been examined in the context of LR. Several lines of evidence suggest that motor milestones such as initial age of crawling and walking are significantly delayed in children with ASD, in general, as compared with typically developing (TD) children [Davidovitch, Stein, Koren, & Friedman, 2018; Lloyd, MacDonald, & Lord, 2013; Ozonoff et al., 2008]. While some have suggested that motor impairments are an early prodrome that is evident already during the first few months of life [Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998], others have reported that significant differences in fine and gross motor abilities appear only at the age of 12–14 months [Brian et al., 2008; Landa & Garrett-Mayer, 2006]. Delayed motor development may also be related to reports of low muscle tone (i.e., hypotonia) in infants who later develop ASD [Serdarevic et al., 2017]. Interestingly, the rates of motor development and language development seem to be correlated in TD children [Iverson, 2010] and in those with ASD [Bedford, Pickles, & Lord, 2016; Lebarton & Iverson, 2013]. Since children with ASD and LR develop language in a timely manner, we hypothesized that they would also exhibit timely initiation of crawling and walking abilities in contrast to children with ASD and NR. Two previous studies have suggested that this is indeed the case [Kalb et al., 2010; Ozonoff et al., 2008].

When considering differences in the rates of initial language and motor development in children with ASD, it is important to examine potentially associated physiological development measures such as weight, height, and head circumference (HC). Abnormally fast HC growth during the first year of life has been proposed as an early biomarker of ASD [Courchesne et al., 2001; Dementieva et al., 2005; Hazlett et al., 2017; Webb et al., 2007], although large controversy exists regarding the validity and reliability of this measure [Dinstein, Haar, Atsmon, & Schtaerman, 2017; Gray, Taffe, Sweeney, Forster, & Tonge, 2012; Raznahan et al., 2013; Zwaigenbaum et al., 2014]. Some have suggested that such excessive HC growth in children with ASD is specific to children with regression [Nordahl et al., 2011], while others have suggested that excessive HC growth is common to children with and without regression [Webb et al., 2007]. Here, we examined these issues by analyzing data from a cohort of children with ASD at the Negev Autism Center, which reliably represents the ASD population in the southern district of Israel (the Negev) [Meiri et al., 2017].

Methods

Participants

We examined the records of 218 children from the Negev Autism Center (www.negevautism.org) regional ASD database [Meiri et al., 2017] who fulfilled DSM-5 and

ADOS criteria for ASD and whose parents completed an intake questionnaire. DSM-5 criteria were determined by both a physician (child psychiatrist or pediatric neurologist) and a developmental psychologist. In all cases, the diagnosis was confirmed using the Autism Diagnostic Observation Scale-2 [Lord et al., 2012], which was performed by an expert clinician. All children were recruited to the study between 2015 and 2018. Parents of participating children signed an informed consent form and the study was approved by the Soroka University Medical Center (SUMC) Helsinki committee.

Assessment of LR

Parents of all 218 children completed an intake questionnaire, which contained the following questions about regression: (a) Did your child experience loss of language skills? (b) Did he/she use three words or more fluently and then stop? (c) Did your child experience loss of nonverbal communication skills? (e.g., eye contact or hand gestures) (d) Did your child experience loss of motor skills? (e.g., ability to hold a spoon). Parents were asked to give examples for each positive answer and specify the age that the ability was lost. Parents of 123 children with ASD reported that their children did not exhibit any loss of language, communication, or motor skills, parents of 78 children reported loss of language skills and parents of 17 children reported loss of nonverbal communication skills (Fig. 1). To validate reports of regression, we examined the initial clinical record that was submitted by the clinician who first met the family. In 119 of cases with no reported regression, there was no mention of any skill loss in the child's clinical records. These cases formed the NR group. In 48 of the reported LR cases, the clinician described specific examples of language loss in the clinical report (e.g., "first words were on time, the child used to point at an object and say words accordingly, at 16 months a regression occurred…," "…said his first words at nine months, a few months later he stopped using the words"). Of these 48 cases, we were able to successfully recontact 46 families and perform a structured phone interview to verify the LR. In 37 of these cases, the parents verified that their child consistently used at least three words for a period of at least 1 month and then stopped (in 33 of these cases parents reported loss of five words or more). These cases formed the LR group. The group with nonverbal regression was very small and, therefore, excluded from further analyses.

Measures

The parent intake questionnaire also included questions regarding the age that the child achieved specific developmental milestones such as crawling, eating solid foods, walking, and using words. Additional information was extracted from the SUMC patient records. This included paternal and maternal age at birth, gestational age at birth, HC, weight, and height at birth, age at diagnosis, ADOS scores, and cognitive scores from either the Bayley Scales of Infant and Toddler Development—third edition

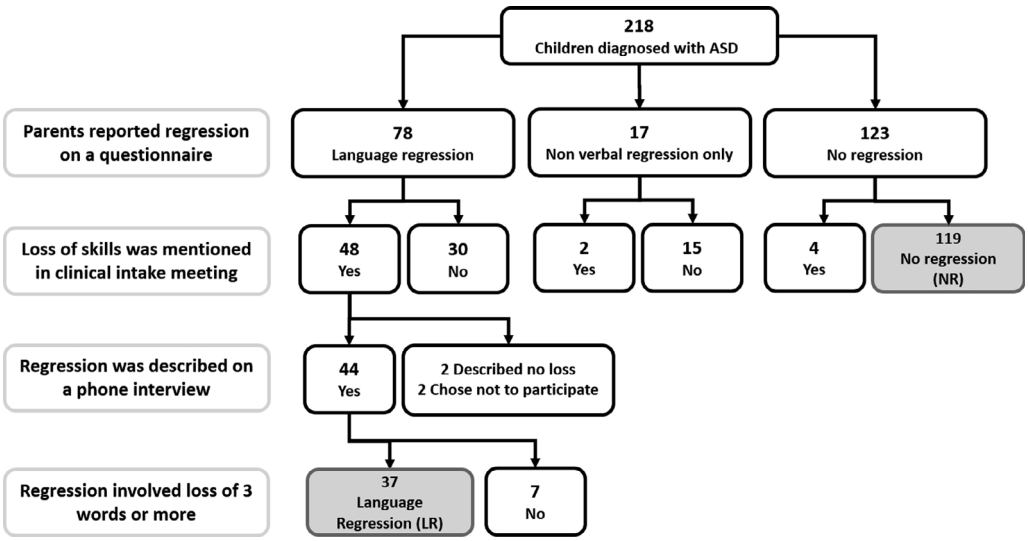

Figure 1. Assessment of language regression. Records of 218 children with a diagnosis of ASD were examined and classified into three subgroups: (a) cases where parents reported language regression; (b) cases where parents reported nonverbal regression (e.g., loss of eye contact); (c) cases where the parents did not report any concern of regression. These reports were scrutinized by examining the initial clinical intake report of all children and recontacting the parents of children in the regression group. The language regression (LR) group was limited to cases where regression involved loss of at least three words as verified by both clinical intake and a second interview of the parents. The no regression group (NR) was limited to cases where there was no mention of regression in both the parent reports and the clinical records.

(Bayley-III) [Albers & Grieve, 2007] or the Wechsler Preschool and Primary Scale of Intelligence—third edition (WPPSI-III) [Wechsler, 1991].

We obtained retrospective HC, weight, and height measurements from the national infant health clinics ("Tipat Halav"), which are administered by the Israeli Ministry of Health. All babies in Israel are invited to visit these clinics at the ages of 1, 2, 4, 6, 9, 12, and 18 months in order to measure their development and administer vaccinations. Mandatory HC, weight, and height measurements are performed by the nurses at these clinics to ensure healthy growth rates and identify developmental problems. We extracted these data for 18 children from the LR group, whose growth measures were available to us [Kerub, Haas, Meiri, Davidovitch, & Menashe, 2018], as well as to 18 children from the NR group, and 36 TD children from the same data set that were matched to the children in the LR group by gender and gestational age. Notably, TD children were selected if they had no concern regarding their development during their visits at the infant health clinics as described before [Kerub et al., 2018]. Finally, we used linear interpolation across measurement time-points to generate a growth curve for each measure in each of these children.

Statistical Analyses

Analyses were performed using R-studio (R-studio Inc., Boston, MA) and MATLAB (Mathworks Inc., Natick, MA). Differences of key demographic, behavioral, and developmental characteristics between the LR and NR groups were assessed using appropriate univariate statistics. Specifically, comparisons of continuous variables were performed with *t*-tests for normally distributed variables and with nonparametric Mann–Whitney tests for variables that violated the normality assumption. One-way ANOVA with Scheffe post hoc analysis was used for comparisons of the three groups. Ages (in months) of motor and language milestones were ln transformed to better represent their sample distribution and Pearson's R was used to assess the correlations between pairs of these ln transformed measures. Chi-square and Fisher-exact tests were used to compare the distribution of nominal variables between the groups. All statistical tests were two sided and statistical significance was set at a *P*-value of 0.05. Bonferroni correction for multiple testing was used when necessary.

Results

Sample Characteristics

The mean age of LR in our sample was 17.02 months (SD = 4.4). In 33 cases, LR involved loss of five words or more, and in the remaining four cases, it involved loss of 3–4 words. In addition to word loss, parents of 28 of the children with LR (75%) also reported loss of nonverbal social skills, and parents of five children with LR (13%) reported loss of motor skills. The time between LR onset and the time of ASD diagnosis, where parents first reported such skill loss in their child, was on average 15.1 months (SD = 7.3).

There were no significant differences between the NR and LR groups in gender, ethnicity, maternal and paternal ages, and gestational age (Table S1). However, premature births (<35 weeks) were more common in the NR group than the LR group (13% vs. 3%, respectively; Fig. 2). Since premature births are often associated with difficulties in motor development [Bos, Van Braeckel, Hitzert, Tanis, & Roze, 2013], we decided to exclude all children born at a gestational age <35 weeks. Consequently, one child with LR and 15 children with NR were excluded from further analyses. In addition, we created a tightly matched NR subgroup, consisting of 36 children who were matched by gender, ethnicity, and gestational age at birth (±7 days) to the LR group. All further analyses were performed with these refined subgroups.

Diagnosis Age and Severity of Symptoms

Children in the LR group were diagnosed significantly earlier than NR children (Table 1). In addition, there were significant differences in the ADOS modules used between the LR and NR groups. Specifically, children with ASD in the LR group were more often assessed with nonverbal ADOS modules in comparison to children in the NR group (Table 1). This demonstrates that the vast majority of children with ASD and LR were indeed nonverbal at the time of diagnosis as expected in a situation

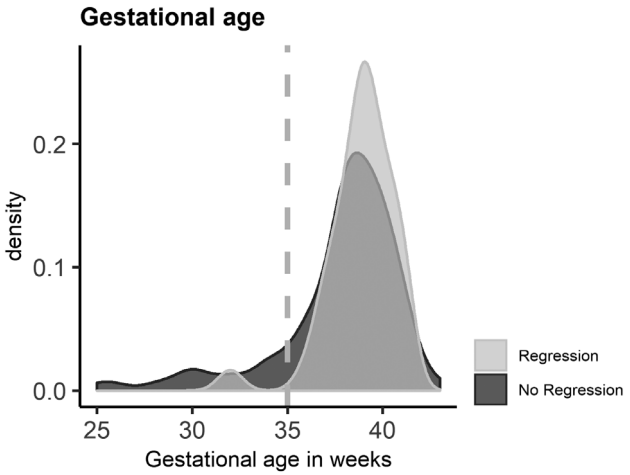

Figure 2. Density plot of gestational age, in weeks, for the LR (bright gray) and NR (dark Gray) groups. Note the heavy long tail of the NR distribution indicating premature births at <35 weeks (indicated by dashed vertical line).

Table 1. Diagnosis Age, Symptom Severity as Quantified by ADOS, Cognitive Tests, and DSM5 Clinical Assessment

Characteristics	Regression $N = 36$	Matched NR $N = 36$	All NR $N = 104$	Statistics	P-value
Diagnosis age[a] [Mean (SD)]	32.1 (9.1)	42.5 (14.7)	40.6 (15.6)	(a) $W = 938$	(a) 0.001**
				(b) $W = 2459$	(b) 0.005**
ADOS module					
Nonverbal modules (Toddler/1) [n (%)]	32 (89%)	21 (58%)	40 (39%)	(a) χ^2 (1, $N = 72$) = 7.1	(a) 0.007**
Verbal modules (2/3) [n (%)]	4 (11%)	15 (42%)	64 (61%)	(b) χ^2 (1, $N = 140$) = 8	(b) 0.004**
ADOS total score [Mean (SD)]	20.1 (4.44)	17.2 (5.52)	17.2 (5.92)	(a) $W = 450$	(a) 0.02*
				(b) $W = 1365$	(b) 0.01*
ADOS comparison score [Mean (SD)]	8 (1.37)	7.44 (1.7)	7.42(1.84)	(a) $W = 534$	(a) 0.18
				(b) $W = 1566$	(b) 0.1
Cognitive scores					
Below 70 [n (%)]	4 (18%)	6 (20%)	18 (26%)	(a) χ^2 (1, $N = 52$) = 3.2	(a) 0.1
70 and above [n (%)]	18 (82%)	24 (80%)	51 (74%)	(b) χ^2 (1, $N = 91$) = 21	(b) 0.6
DSM level of support A (social domain)					
Level 1 (requiring support) [n (%)]	1 (3%)	7 (22%)	16 (18%)	(a) χ^2 (2, $N = 65$) = 6.5	(a) 0.03*
Level 2 (requiring substantial support) [n (%)]	12 (36%)	13 (41%)	36 (40%)	(b) χ^2 (2, $N = 122$) = 5.8	(b) 0.05*
Level 3 (requiring very substantial support) [n (%)]	20 (61%)	12 (37%)	37 (42%)		
DSM level of support B (restricted-repetitive domain)					
Level 1 (requiring support) [n (%)]	0 (0%)	7 (22%)	17 (19%)	(a) χ^2 (2, $N = 65$) = 6.5	(a) 0.01*
Level 2 (requiring substantial support) [n (%)]	22 (67%)	17 (53%)	48 (54%)	(b) χ^2 (2, $N = 122$) = 7.3	(b) 0.02*
Level 3 (requiring very substantial support) [n (%)]	11 (33%)	8 (25%)	24 (27%)		

(a) Comparison between LR and matched NR groups.
(b) Comparison between LR and all NR groups.
*$P < 0.05$; **$P < 0.01$.
[a]Age in months.

where noticeable LR motivates the parents to seek immediate clinical care.

Children in the LR group had more severe ASD symptoms than children in the LR groups as indicated by their significantly higher ADOS total scores and their tendency to be assigned higher DSM-5 severity levels by the physicians (i.e., requiring higher levels of support) than children in the NR groups (Table 1). Similar trends were also apparent in the ADOS comparison scores and the cognitive scores, however, these differences were not statistically significant (Table 1). These suggest that clinical impression of the children with LR raised more concern for the existence of severe developmental symptoms.

Early Motor and Language Development

Analysis of parental reported developmental milestones (Fig. 3) revealed that there were no significant difference between the LR and NR groups in the age at which children started eating solid foods ($P > 0.7$). However, children in the LR group started crawling significantly earlier than children in the all NR group did (Mean = 7.41, SD = 2.06 vs. Mean = 8.9, SD = 3.24, $P = 0.02$). The same trend was observed in a comparison to the matched NR group (Mean = 8.28, SD = 2.95, $P = 0.2$). Similarly, children with ASD and LR started walking earlier (Mean = 12.7, SD = 1.95) than children in the matched NR (Mean = 15.7, SD = 4.72,

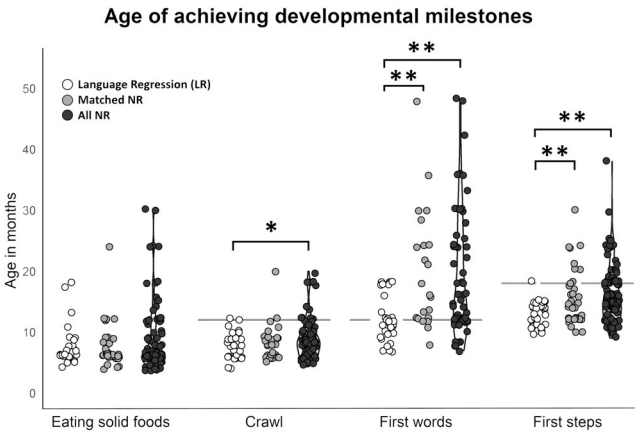

Figure 3. Age of developmental milestones in the LR (while color), matched NR (gray color), and All NR (black color) groups. Each point represents a single child. Gray horizontal lines depict the ages of the CDC milestone check list (concern if child does not crawl by 12 months, walk by 18 months, and use first words by 12 months). Note that eight nonverbal children from the matched NR group and 27 nonverbal children from the All NR group are excluded from the "First words" graph. Similarly, three children from the All NR group that did not walk at the time of the study are excluded from the "First steps" graph. Asterisks: groups with statistically significant difference. *<0.05, **<0.01.

$P = 0.004$) and all NR groups (Mean = 16.1, SD = 4.76, $P < 0.001$). These differences remained statistically significant ($P < 0.05$) even when excluding children with NR that did not walk at the time of intake. In addition, children with ASD and LR began using words earlier than children in the matched NR and all NR groups did, even after excluding nonverbal children from the NR groups (Mean = 12.4, SD = 3.67 vs. Mean = 20.1, SD = 9.8, and Mean = 19.9, SD = 11.4 respectively; $P < 0.001$ for both comparisons). In line with previous studies, we found significant positive correlations between the age of crawling and walking ($r = 0.63$, $P < 0.0001$), crawling and talking ($r = 0.28$, $P = 0.01$), and walking and talking ($r = 0.40$, $P < 0.0001$) (Fig. S1). This demonstrated the general relationship between motor and language development in our sample.

Furthermore, we examined the distribution of parent reports in relation to the relevant World Health Organization (WHO) norms and Center for Disease Control (CDC) milestones checklist. According to the WHO norms, 99.5% of TD children start crawling before the age of 11.4 months and start walking before the age of 17.5 months [De Onis, 2006]. According to the CDC norms, parents should be concerned if their children do not start crawling and using single words by the age of 12 months and walking by the age of 18 months (Fig. 3, gray horizontal lines). Using these thresholds imply that motor and speech delays were far more common in the NR groups than the LR group. Specifically, none of the children with LR started crawling after the age of 12 months compared to seven children in the All NR group (6.7%; $P = 0.1$), and one child in the matched NR group (2.8%; $P = 0.4$). Similarly, none of the children in the LR group started walking after the age of 18 months, compared to 24 children in the All NR group (23.1%; $P < 0.001$), and seven children in the matched NR group (19.4%; $P = 0.004$). Ten children in the LR group started talking after the age of 12 month (27.8%) compared to 63 children in the All NR group (60.6%; $P < 0.001$), and 23 children in the match LR group (63.9%; $P < 0.001$). Parental reports also revealed a striking difference in the number of children who were diagnosed with hypotonia before their ASD diagnosis. While none of the children with LR had such a diagnosis, 3 of the 36 (7%) children in the matched NR group and 7 of 104 (7%) children in the All NR group had a previous diagnosis of hypotonia.

General Physiological Development

Since motor and language development may depend on general physiological development, we extracted infant growth measures (i.e., HC, weight, and height) from the records of the Israeli national infant health clinics (see Methods). Records were extracted for a subset of 18 children with LR and 18 matched children with NR for whom there were at least five measurements between birth and the age of 18 months. Similar data for an additional group of 36 TD children matched by gender and gestational age were also extracted from the same infant health clinics. An analysis of variance with post hoc Scheffe criterion indicated that children in the NR group were born with significantly smaller HC (Mean = 33.4, SD = 1.2) compared to both children with LR (Mean = 34.5, SD = 0.96, $P = 0.023$) and TD children (Mean = 34.6, SD = 1.2, $P = 0.004$). No difference was found in HC at any of the subsequent time points as well as in weight or height in the first 18 months of life of these children ($P > 0.05$). These results demonstrate that by the age that crawling, walking, and speaking were expected to emerge, there were no significant physiological differences across the two ASD groups, who were not significantly different from a matched TD control sample.

Discussion

Our results reveal that children with ASD and LR exhibit relatively typical early motor development in comparison to children with ASD and NR. All children with ASD and LR started crawling and walking before the CDC published thresholds for developmental delay concerns (Fig. 3). Furthermore, none of the children with LR had a diagnosis of hypotonia as opposed to 7% of the children with NR. These differences in early motor development across groups were not due to gross differences in physical development as demonstrated by detailed weight, height, and HC measurements in the 18 months following birth, which were not significantly different across groups from 3 months after birth and on (Fig. 4). Finally, the age at which children started speaking their first words was significantly correlated with their initial crawling and walking ages (Fig. S1), suggesting that the speed of language and motor development are indeed related to each other in children with ASD as previously reported in typical development [Iverson, 2010] and ASD [Bedford et al., 2016; Lebarton & Iverson, 2013]. The significant differences across groups suggest that children with ASD and LR have distinct early developmental profiles, which may also be associated with different underlying physiology and different risk factors.

Indeed, we also found that premature birth (a potent risk factor for ASD and other developmental problems [Schieve et al., 2016]) was four times more common in the NR group than the LR group (Fig. 2). This suggests that previous reports regarding the ASD risk associated with premature birth may be more relevant to ASD with NR, further highlighting a potentially distinct developmental profile. Note that we excluded all cases of premature births from our analyses and also performed the main comparisons between LR and NR subgroups that

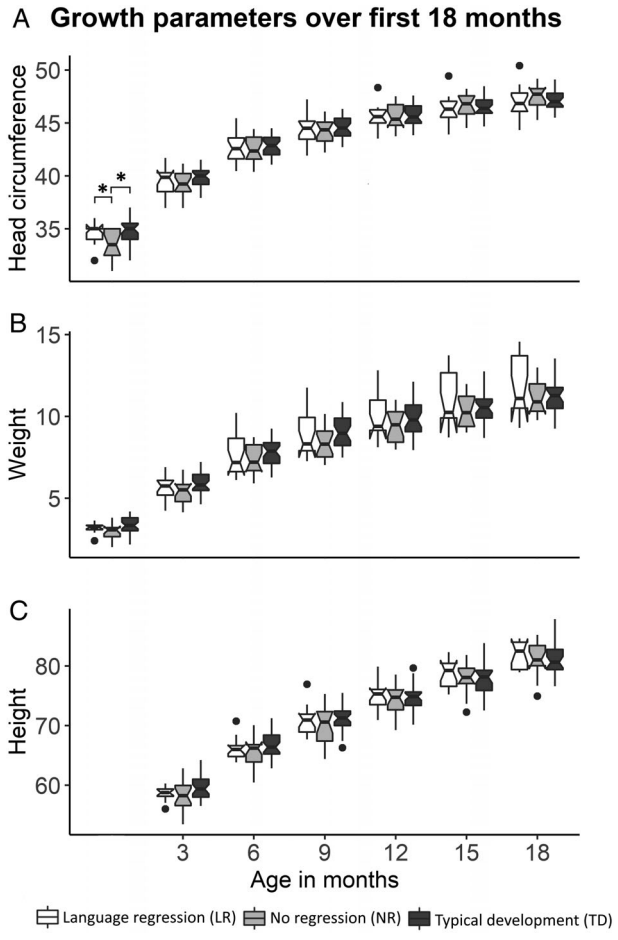

Figure 4. Physiological growth in a subsample of children with ASD and matched controls. Boxplot of physiological measures taken at 0, 3, 6, 9, 12, 15, and18 months for a subset of children with LR (white color), NR (gray color), and typical development (black color). Asterisks: significant differences between groups ($P < 0.05$). (**A**) Head circumference; (**B**) weight; and (**C**) height.

were matched with respect to birth week. This ensures that the reported differences in motor development between NR and LR groups were not due to pregnancy length.

Regression in ASD

LR seems to be a unique phenomenon of ASD [Pickles et al., 2009]. In retrospective studies that rely on parental reports, such as ours, the prevalence of regression varies according to its precise definition. Prevalence was highest in studies where regression was defined broadly as the loss of any skill including language, social, motor, and cognitive skills (~40%) and lowest in studies where regression was confined to loss of language (25%) [Barger et al., 2013]. Within LR studies, prevalence rates decreased as skill requirements increased (i.e., the number of words and the length of time that the child used them) [Pearson et al., 2018]. In our study, children with LR were identified as those who used at least three words for a period of at least 1 month and then stopped using them. We also applied a stringent verification protocol to ensure the validity of parent reports. This included cross-referencing the initial clinical interview with the initial parent intake questionnaire, and performing an additional verification using a follow-up phone interview. This resulted in a final LR prevalence rate of 17% (37 out of 218). Note that our goal was not to assess LR prevalence rates, but rather to identify valid LR cases with high confidence and compare them to NR cases.

LR is a dramatic change that happens relatively early in development (17 months in our sample and 21 months, on average, in other samples [Barger et al., 2013]). This change is likely to create anxiety in parents and motivate them to seek clinical care. It is, therefore, not surprising that ASD diagnosis age was significantly younger in LR cases in comparison to NR cases (Table 1), as was also reported in previous studies [Kalb et al., 2010]. Since LR is likely to be more dramatic and noticeable than other forms of regression, earlier age of diagnosis may be more strongly associated with this extreme form of regression.

Interestingly, prospective studies that have examined the development of infants at risk for ASD have suggested that subtle forms of regression in eye contact, joint attention, and other social communication skills were apparent in the vast majority (>80%) of children who eventually received an ASD diagnosis [Pearson et al., 2018]. These milder forms of regression often remained unnoticed by the parents who reported similar rates of regression in these studies (29%) to those commonly reported in retrospective studies [Ozonoff et al., 2018]. This suggests that parent report of LR indicates the most severe form of regression within a continuum of skill loss that is apparent to different extents in many cases of ASD.

Language Development in ASD

Children with ASD have heterogeneous language delays and difficulties [Tager-Flusberg, 2016], which were previously considered a criterion for diagnosis in the DSM IV. While some children with ASD exhibit delays in the emergence of language, which may resemble cases of specific language impairment [Lindgren, Folstein, Tomblin, & Tager-Flusberg, 2009], others start communicating with single words in a relatively timely manner and then lose this ability (i.e., LR) [Lord et al., 2004], yet others start communicating with single words and then plateau without regressing [Goin-Kochel et al., 2014]. Several studies have reported that children with ASD and LR start speaking, on average, earlier than children with ASD and NR [Barger et al., 2013], as was also found in our study (Fig. 3). Despite this early initiation of speech abilities in

children with ASD and LR, both groups of children with ASD seem to exhibit similar language difficulties later in life during adolescence and adulthood [Howlin et al., 2014; Pickles et al., 2009]. However, longitudinal studies that assess language capabilities in individuals with ASD over extended periods of time are extremely rare and include very small samples. It is, therefore, unclear whether children with ASD and LR eventually demonstrate better or worse language capabilities than children with ASD and NR.

Motor Development in ASD

A variety of studies have reported that, in general, children with ASD exhibit early motor delays and abnormalities during the first year of life [Arabameri & Sotoodeh, 2015; Brian et al., 2008; Davidovitch et al., 2018; Landa & Garrett-Mayer, 2006; Lloyd et al., 2013]. Prospective studies of infants at risk have shown that early concerns regarding motor development at 6 months of age were significantly higher in cases where infants were later diagnosed with ASD in contrast to those who were not [Sacrey et al., 2015]. Indeed, a prospective study of the Danish national registry revealed that children who later received an ASD diagnosis started sitting and walking at later ages than the TD population [Lemcke, Juul, Parner, Lauritsen, & Thorsen, 2013]. Furthermore, hypotonia, apraxia, and deficits in early postural control are considered risk factors for ASD (Teitelbaum et al., 1998; Tuchman & Rapin, 2002).

Our results reveal that these early motor problems are likely to be more common in children with ASD and NR than those with LR, who seem to develop early gross motor skills in a relatively typical manner. This was evident when examining age of initial crawling and initial walking (Fig. 3). Similar findings have also been reported in two previous retrospective studies. The first reported that children with ASD with broadly defined regression took their first steps earlier that children without regression [Kalb et al., 2010]. The second reported that children with ASD and LR started rolling, sitting, crawling, and walking earlier than children with ASD and NR, as reported both by parents and by retrospective coding of home videos [Ozonoff et al., 2008]. We also found that hypotonia was significantly more prevalent in children with ASD and NR in comparison to children with ASD and LR.

Taken together, accumulating evidence suggests that children with ASD and LR develop relatively typical motor abilities during the first year of life, as opposed to children with ASD and NR. Indeed, relatively typical early motor development would be expected in children who exhibit relatively typical early language development, since motor development and language development seem to be correlated in both typical development [Iverson, 2010] and in ASD [Bedford et al., 2016; Lebarton & Iverson, 2013].

LR and Symptom Severity

Previous studies have reported mixed findings regarding symptom severity differences across LR and NR groups. While some have reported that children with ASD and LR exhibit more severe ASD symptoms [Goin-Kochel et al., 2014; Kalb et al., 2010; Richler et al., 2006; Werner et al., 2005] and lower cognitive scores [Goin-Kochel et al., 2014; Rogers & DiLalla, 1990; Tuchman & Rapin, 1997; Zachor & Ben-Itzchak, 2016], other studies have not [Hansen et al., 2008; Catherine Lord et al., 2004; Ozonoff et al., 2011; Shumway et al., 2011]. In the current study, we found that children with ASD and LR were classified by physicians as requiring higher levels of support according to DSM 5 criteria and exhibited significantly higher ADOS scores (Table 1).

Note that this relatively high symptom severity in children with ASD and LR was apparent after diagnosis despite the relatively typical early motor and language development in this group. We assume that more extreme cases of regression motivate parents to seek immediate clinical care, as apparent in the significant earlier diagnosis age of the LR group. Such cases, where parents clearly describe regression in their clinical interview, are likely to involve larger transitions from relatively typical initial development to more severe ASD symptoms. Given our strict inclusion criteria, our sample is likely to have a relatively high proportion of severe regression cases, which may explain the difference in ASD severity.

LR as a Subtype of ASD

Should children with ASD and LR be considered a distinct subtype of ASD? The answer depends on the utility of LR as a reliable indicator of a distinct ASD etiology (or subgroup of etiologies) involving additional distinct behavioral and physiological features. With this in mind, a variety of studies have examined the association of specific genetic, physiological, and behavioral characteristics with LR.

While LR seems to exhibit weak familial concordance across siblings with ASD [Parr et al., 2011], several genetic syndromes associated with ASD exhibit a high incidence of regression. Rett Syndrome (girls with MECP2 deletions), by definition, involves extensive regression in social and motor capabilities [Charman et al., 2002]. Similarly, 70% of boys with MECP2 duplication syndrome also exhibit broadly defined regression [Peters et al., 2013]. In Phelan-McDermid Syndrome (SHANK3 mutations), 65% of children exhibit broadly defined regression [De Rubeis et al., 2018], as do 61% of children with mitochondrial disease [Shoffner et al., 2010]. Rare mutations in genes

encoding postsynaptic density proteins have also been associated with increased rates of LR in the Simons Simplex Collection [Goin-Kochel, Trinh, Barber, & Bernier, 2017]. While most children with ASD and regression do not have specific known genetic abnormalities, these results demonstrate that specific genetic abnormalities can create high rates of regression.

Physiological characteristics associated with LR include higher rates of epilepsy and/or epileptiform activity that have been reported in some studies [Hrdlicka et al., 2004; Tuchman & Rapin, 1997; Zhang, Xu, Liu, Li, & Xu, 2012], but not in others [Baird, Robinson, Boyd, & Charman, 2006; Canitano, Luchetti, & Zappella, 2005]. In some cases, epileptic seizures may be causally related to LR [Tuchman & Rapin, 2002], as reported in Landau–Kleffner [Deonna & Roulet-Perez, 2010], RETT [Charman et al., 2002], and Phelan-McDermid [De Rubeis et al., 2018] Syndromes. While the overall relationship between epilepsy and regression in ASD is significant, a recent meta-analysis has reported that is it relatively weak [Barger, Campbell, & Simmons, 2017]. This suggests that while many children with ASD and regression do not have epilepsy, some types of epilepsy are associated with high rates of regression [Tuchman & Rapin, 2002].

With these examples in mind, it seems that LR itself is not a reliable indicator of a specific etiology. However, combining parent report of LR with additional criteria, such as specific genetic or physiological profiles may narrow down the space of optional etiologies and yield informative subgrouping of more homogeneous ASD subtypes. Eventually, the benefit of such categorizations will be tested by their utility in determining prognosis, response to treatment, and availability of biomarkers for early diagnosis.

Conclusions

Regression continues to define a unique and disturbing developmental phenomenon in ASD. While regression does not represent a single distinct etiology of ASD, extreme cases of regression involving clear loss of language abilities may represent a specific "sub-space" of ASD etiologies that involve less premature births and hypotonia along with relatively typical initial motor development. Longitudinal follow-up of these cases will reveal whether they exhibit additional differences, in comparison to NR cases, that may indicate distinct outcomes or differences in response to specific treatments.

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Supporting Information

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

Supplementary Figure S1 Scatter plots demonstrating the relationships between pairs of motor and language milestones. Gold: children with ASD and language regression. Blue: children with ASD and without language regression. Each point represents a single child. Measures are presented on a natural logarithm (ln) scale. Pearson's correlation coefficients are noted in each panel along with their statistical significance.

Supplementary Table 1 Sample Characteristics.