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Early and persistent motor delay in infants at-risk of developing autism spectrum disorder: A prospective study

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Abstract

The aim was to build a profile of motor development in infant siblings of children diagnosed with autism. Infants at high familial risk of developing autism spectrum disorder and those at low-risk were tested longitudinally between 6 and 24 months. Data were analysed from the gross and fine motor scales of the Mullen Scales of Early Learning and the Vineland Adaptive Behavior Scales at three age points. Low-risk and at-risk infants differed significantly on motor scales at all three visits, with significantly lower motor scores in the at-risk group evident from the age of 6 months based on parental report. Poorer gross and fine motor skills in the at-risk group were only evident on the direct standardised assessment from 12 months. Only gross motor scores were highly correlated across the two measures. A combination of standardised assessments and parental reports may therefore provide the best method for early identification of motor atypicalities in the broader autism phenotype.

Autism spectrum disorders (ASD) are a group of pervasive neurodevelopmental disorders that affect 1 in 100 to 150 children (Baird et al., 2006), and are diagnosed on the basis of a triad of impairments, including the delayed or atypical development of social interaction and communication and markedly restricted activities and interests (American Psychiatric Association, 2000). Although the diagnostic criteria require symptoms to be present before the age of three, and despite parents often reporting the recognition of symptoms in infants younger than 18 months (Chawarska et al., 2007), diagnosis before a child is 2 years old is rare (Charman & Baird, 2002).

In recent years, however, a better understanding of the heritability and genetic underpinnings of ASD (Abrahams & Geschwind, 2008; Autism Genome Project, 2007; Bailey et al., 1995) has led to a focus on the family members of individuals already diagnosed with ASD, who may show a number of subclinical characteristics of ASD (termed the 'Broader Autism Phenotype': Bolton et al., 1994; Pickles et al., 2000). In particular, a number of studies of infants who have older siblings with a diagnosis, and are therefore at increased risk of developing ASD themselves, have begun to emerge (see Elsabbagh & Johnson, 2007, 2010, and Rogers, 2009, for recent reviews). These ongoing studies are finding subtle differences between at-risk and low-risk infants on a range of behavioural and neuroimaging methods early in childhood. While atypicalities or impairments have been found in the core diagnostic areas of social communication and language (Landa, Holman & Garrett-Mayer, 2007; Yirmiya, Gamliel, Shaked & Sigman, 2007; Zwaigenbaum et al., 2005) and repetitive

behaviours (Iverson & Wozniak, 2007), other areas of cognition and behaviour, such as visual attention (Zwaigenbaum et al. 2005; Elsabbagh et al., 2009), sensory-related behaviours (Zwaigenbaum et al. 2005) and motor development (Iverson & Wozniak, 2007; Landa & Garrett-Mayer, 2006; Toth, Dawson, Meltzoff, Greenson & Fein, 2007) which have previously been considered "secondary symptoms" (Rogers, 2009, p. 133), have also been highlighted as possible key features of early development in ASD. The current report will focus on the last of these possible risk markers, considering differences between at-risk and low-risk infants in developing motor skills between the ages of 6 and 24 months.

Studies of motor skills in school-age children with ASD have repeatedly reported motor dysfunction in their participants, including difficulties with manual dexterity, ball skills and balance (Green et al., 2009; Manjiviona & Prior, 1995). Research with younger children already diagnosed with ASD (Provost, Lopez & Heimerl, 2007) retrospective studies of motor behaviour in infancy through video analysis (Baranek, 1999; Ozonoff et al., 2008; Teitelbaum, Teitelbaum, Nye, Fryman, Maurer, 1998) and prospective studies of at-risk infants (Iverson & Wozniak, 2007; Landa & Garrett-Mayer, 2006; Toth et al., 2007), have documented further atypicalities, ranging from subtle discrepancies in early motor skills to more severe difficulties. Although there are not always significant differences in the mean age of achieving key motor milestones, such as independent sitting, crawling and walking (Iverson & Wozniak, 2007; Ozonoff et al., 2008) a higher proportion of children in at-risk groups are delayed in these skills (Iverson & Wozniak, 2007). Understanding these early motor symptoms is not only useful in improving later motor functioning, but may also prevent knock-on effects on other domains, including those associated with the core deficits in ASD (Rogers, 2009; Iverson, 2010). Indeed, there is increasing evidence for a link between motor development and the development of social interaction skills, including joint attention and social referencing (Campos et al., 2000). Early identification of motor symptoms in infancy could therefore have important implications for intervention and outcomes in individuals with ASD in later life.

The purpose of the current report was to follow trajectories of motor development in a prospective at-risk sample on broad motor measures, as assessed by the Gross and Fine Motor scales on the Mullen Scales of Early Learning (MSEL: Mullen, 1995) and the Vineland Adaptive Behavior Scales-II (VABS: Sparrow, Cicchetti & Balla, 2005). This will be the first prospective study to measure the correlation between standardised and parental report measures of motor development in infants at risk of developing ASD compared to low-risk infants, providing vital insights into the importance of the two types of assessment in effectively highlighting early motor delay. Strong correlation across the two tests would suggest that motor ability can be measured equally well by both parental report and direct observation, while poor correlation may suggest that both types of assessment are necessary for a good understanding of the motor profile of young infants. As both the MSEL and VABS have been standardised within typically-developing populations, it is expected that there will be good correlation between these two measures on motor scales within the low-risk group. It is not clear if the same effect will be found in the at-risk group, although a recent study suggested that scores correlated well in children with autism after the age of 12 months (Lloyd, MacDonald & Lord, 2011). Following at-risk and low-risk samples longitudinally from the age of 6 months also allows investigation of the changes over developmental time in addition to differences found between the groups at any of the three age points individually. Based on previous research with prospective samples (Landa & Garrett-Mayer, 2006; Toth et al., 2007), it is predicted that infants in the at-risk group will have significantly poorer motor skills than those in the low-risk group, and that any differences on the MSEL would be present after the age of 12 months (Landa & Garrett-Mayer, 2006). Lower motor scores on

the VABS in the at-risk group should be evident before the age of 24 months (Toth et al., 2007), although as this is the first study to compare groups on the VABS at earlier ages, it is not clear how early these differences may emerge.

Methods

Participants

Participants were families taking part in an ongoing longitudinal research program: The British Autism Study of Infant Siblings (BASIS; www.basisnetwork.org), a UK collaborative network facilitating research with infants at-risk for autism. Ethical approval was given by the NHS NRES London REC 08/H0718/76. One hundred and four at-risk and low-risk infants were recruited from a database of volunteers on the basis that they had an older sibling with a confirmed clinical diagnosis of ASD (at-risk: *N* = 54, males = 22) or an older sibling with no diagnosis of ASD or related conditions, and no family history of ASD (low-risk: *N* = 50, males = 20). Infants were assessed at 6-10 (hereafter "7 months"), 12-15 (hereafter "14 months") and 24 months of age and were matched for gender and chronological age. Participant information for the two groups is presented in Table 1. At the time of enrolment, none of the infants had been diagnosed with any medical or developmental condition. Infants at-risk all had an older sibling (hereafter, proband) with a community clinical diagnosis of ASD (or in 4 cases, a half-sibling). Proband diagnosis was confirmed by two expert clinicians using the Development and Wellbeing Assessment (DAWBA: Goodman et al., 2000) and the parent-report Social Communication Questionnaire (SCQ: Rutter, Bailey & Lord, 2003). Most probands met criteria for ASD on both the DAWBA and SCQ (n = 43). While a small number scored below threshold on the SCQ (n = 4) no exclusions were made, due to meeting threshold on the DAWBA and expert opinion. For three probands, data were only available for either the DAWBA or the SCQ, and for four additional probands, neither measure was available (aside from parent-confirmed local clinical ASD diagnosis at intake). Parent-reported family medical histories were examined for significant medical conditions in the proband or extended families members, with no exclusions made on this basis. Infants in the low-risk group were recruited from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development, London, UK. Inclusion criteria included full-term birth, normal birth weight, and lack of any ASD within first-degree family members (as confirmed through parent interview regarding family medical history). All low-risk infants had at least one older-sibling (in 5 cases, only half-sibling/s). Screening for possible ASD in these older siblings was undertaken using the SCQ, with no child scoring above instrument cut-off.

-----Table 1 about here ------

Materials

The MSEL (Mullen, 1995) is a standardised test of early cognitive and motor development between the ages of 0-68 months, consisting of measures of receptive and expressive language, visual reception and gross and fine motor skills, and was conducted at 7, 14 and 24 months. The motor domain of the MSEL is made up of the Gross Motor subdomain, including items such as the infant's ability to hold up his/her head, roll over,

stand and walk, and the Fine Motor subdomain, assessing abilities such as grasping small objects and moving them between different locations. Items are scored as 'present' or 'absent'. The Visual Reception scale measures visual perceptual ability using items such as visual tracking of different stimuli and the identification of an object, as demonstrated by correct use of that object when placed in front of the child (e.g., a spoon). The close connection of many of these items to general stages of cognitive development make this useful for assessing the role of any general developmental delay on the infant's motor abilities (Lloyd et al., 2011). In the current analysis we use the Visual Reception scale from the Mullen to account for general developmental differences. Raw scores are transformed into T-Scale scores, with a mean of 50 and a standard deviation of 10.

The VABS-II (Sparrow et al., 2005) was also completed for infants at all three visits. This instrument measures communication, daily living, socialisation and motor skills, as well as maladaptive behaviour. Only the motor skills domain from each test will be considered in this report and will be separated into Gross and Fine Motor subdomains. The Gross and Fine Motor scales of the VABS contain similar types of items to those making up the MSEL. Parents and caregivers reported whether they had seen a particular behaviour on a scale of "Never", "Sometimes" or "Usually". They could also respond "Don't Know" or "No opportunity" to any of the items. Raw scores may be transformed into v-Scale scores, with a mean of 15 and a standard deviation of 3. Both the v-scale scores from the VABS-II and the T-scale scores from the MSEL will be referred to as 'standardised scores' for the purposes of this paper.

Procedure

The two standardised assessments were conducted during testing visits consisting of a range of tasks, with the MSEL carried out during all three visits. Before testing began, the protocol was explained in detail to the parents and the infants were given time to adapt to their new surroundings and the researchers. The administration of the testing protocol was flexible and child-led, since not every child was able to complete all tasks at all age points due to fatigue or timing issues. In terms of the VABS-II, this questionnaire was most often completed at home by the parents prior to the lab visit, but time was taken by researchers to go through any unanswered or difficult questions with the parents during the testing session to ensure that enough data were collected at each age point. At 24 months, the interview version of the questionnaire was conducted by a researcher during the visit.

Results

As in Landa & Garret-Mayer (2006), inferential analyses were conducted on raw scores of both the MSEL and VABS for each visit (7 months, 14 months and 24 months), although standardised scores and age equivalents are also presented in Table 2 for the reader's information. As the motor scales on the MSEL and VABS were not always completed for every infant at all three visits, cross-sectional analyses were conducted initially on the whole data set, with differences between the groups on the four scales compared within each visit. Planned contrasts between groups on gross and fine motor scales were corrected for multiple comparisons, using a probability value of $p = .01$.

---Table 2 about here---

Cross-sectional analyses

At 7 months of age, at-risk infants had significantly lower raw gross and fine motor scores on the VABS, $t(100) = 2.72$, $p = .01$ (Gross Motor), $t(100) = 3.83$, $p < .001$ (Fine Motor) than the low-risk group. The groups did not differ significantly on these scales on the MSEL (ts < 2, ps = .03). As depicted in Figure 1, scores were still significantly lower in the at-risk group on the VABS at 14 months, $t(96) = 2.79$, $p = .01$ (Gross Motor), and $t(95) = 3.66$, $p < .001$ (Fine Motor). On the MSEL, fine motor raw scores now differed between groups, $t(98) = 3.45$, $p = .001$, but no significant differences were found for gross motor raw scores, $t(99) = 1.60$, $p = .11$. By 24 months, differences between low- and at-risk groups were only found in gross motor skills, and reached our criterion for significance on the MSEL, $t(72) = 6.00$, $p < .001$, but not on the VABS, $t(97) = 2.05$, $p = .04$. Fine motor skills did not differ significantly on either measure, $t(93) = 1.99$, $p = .05$ (MSEL), and $t(97) = .54$, $p = .59$ (VABS).

In order to clarify if differences in motor abilities between groups were simply signs of overall developmental delay, scores on the Visual Reception scale on the MSEL, which has been related to non-verbal problem solving[30], were also compared between at-risk and low-risk groups. When scores on this scale were compared between at-risk ($M = 10.53$; $SD = 2.33$) and low-risk ($M = 11.30$, $SD = 1.97$) groups, no significant differences were found at 6 months old, $t(101) = 1.81$, $p = .07$, suggesting that any between-group differences in motor abilities found by this age would not be the result of a more general delay in the at-risk group.

Longitudinal analyses

The pattern of differences between groups in the cross-sectional data was supported by preliminary analyses conducted on the longitudinal data from only those children who had completed each of the tasks at all three visits (MSEL: low-risk $N = 34$, at-risk $N = 37$; VABS: low-risk $N = 44$, at-risk $N = 49$). A 2(Motor domain) x 2(Group) x 3(Visit) mixed analysis of variance (ANOVA) on the MSEL data revealed that the low-risk group had significantly higher raw scores overall than the at-risk group, $F(1,69) = 16.55$, $p < .001$, $\eta_p^2 = .19$, and that performance on the task improved with age, $F(2,138) = 1479.46$, $p < .001$, $\eta_p^2 = .96$. Significant interactions between MSEL motor domain and visit, $F(2,138) = 12.99$, $p < .001$, $\eta_p^2 = .16$, and between all three factors, $F(2,138) = 6.40$, $p < .01$, $\eta_p^2 = .09$, reflect the pattern found in the whole dataset (see Figure 1), wherein there was a greater relative improvement in gross motor ability between 14 and 24 months than in fine motor ability in the low-risk group, while the two domains improved at a similar rate in the at-risk group, suggesting a different pattern of development in these two groups.

A further 2(Motor domain) x 2(Group) x 3(Visit) mixed ANOVA on the VABS data revealed similar effects, with the low-risk group generally performing better than the at-risk group, $F(1,91) = 12.59$, $p = .001$, $\eta_p^2 = .12$, and performance improving with age, $F(2,182) = 1730.62$, $p < .001$, $\eta_p^2 = .95$. However, the relatively greater improvement in gross motor skills compared to fine motor skills was evident for both groups, $F(2,182) = 473.62$, $p < .001$,

η_p^2 = .84. Finally, while overall improvement in motor ability was similar between visits in the low-risk group, the greatest increase in the at-risk group was between 14 and 24 months.

----- Figure 1 about here -----

Correlations between measures on gross and fine motor scales

Bivariate correlation analyses were finally conducted between the gross motor raw scores on the MSEL and VABS and the fine motor raw scores on the two measures at each visit. The full results of these analyses are presented in Table 3. Gross motor scores on the two measures were highly correlated in both low- and at-risk groups. Highly significant correlations between fine motor scores on the MSEL and VABS were present between the two measures at all three visits for the at-risk group, whereas scores in the low-risk group only correlated at 7 months.

----- Table 3 about here ----

Discussion

The current report aimed to measure motor development over infancy in those at-risk of developing ASD and those at low-risk, and was the first to directly compare a parental report (VABS) and a standardised assessment (MSEL) of gross and fine motor skills between the two groups at the age of 7 months. Within-group analyses revealed that scores on gross motor scales were highly correlated between the two measures in both groups, although correlations between fine motor scales were more dependent on the age of testing. In addition, the VABS revealed earlier differences between groups on both gross and fine motor skills, with lower scores in the at-risk group than the low-risk group as early as 7 months. Scores on the MSEL, on the other hand, only differed significantly from the age of 14 months, as in previous research (Landa & Garrett-Mayer, 2006).

The difference in the strength of correlations between gross and fine motor skills on the two measures is an interesting point that could begin to inform the early screening of ASD once diagnostic outcome is confirmed in our sample. In particular, the strong correlation between the two gross motor scales could be due to the easier detection of changes in these abilities compared to fine motor skills, with important developmental milestones such as sitting unsupported and crawling being easily observable by both parents and researchers over the study timescale. In addition, while previous prospective research has suggested that overt behavioural differences between low- and at-risk groups are not always reliably observed in the first year of life (Elsabbagh et al., 2010; Rogers, 2009), the current data suggest that motor delay can be identified as early as 7 months through the use of parental report. This supports previous evidence that differences in motor skills could be revealed on the VABS but not on the MSEL (Toth et al., 2007), although infants were tested at a much earlier age in the current study. This difference was revealed despite similar abilities in the domain of visual reception, which we used as a measure of general cognitive functioning, suggesting that the motor delay was not necessarily the consequence of a more

generalised deficit in cognition. As presented in Figure 1, the disparity between the groups on motor scores on the MSEL increases on both scales with age, suggesting that the assessment may be more reliable with older children and those that can complete more items of the test. A combination of the two measures would therefore seem to provide a clearer picture of developing motor skills in low- and at-risk groups in infancy. However, the changing pattern of differences between groups suggests that more fine-grained assessments of motor abilities should also be considered, as there may be specific skills within fine and gross motor domains that are particularly weak and cause lower scores on the overall scales. Identification of the contributions of various skills to general motor delay will be an important next step in understanding atypical motor development in infants at-risk of developing ASD.

While the current analyses are an important first step in understanding differences in motor skills between these groups, it would be useful in future studies to collect data from the VABS between the ages of 7 and 14 months in order to document rapid motor changes within this age band. This will provide greater scope for understanding individual differences in later motor abilities. Combining this measure with an examination of parent-child interaction during this more focused time period could also help to identify any more general differences in families of at-risk infants compared to the low-risk families that could contribute to the lower reported scores on the VABS by parents of at-risk siblings. Finally, a diagnosis of ASD at a later age is necessary in order to assess the effect of subgroup membership on motor outcomes, and follow-up testing with the current participants when they reach 36 months, and as they continue into childhood, will therefore be vital. We can then investigate how motor skills, in isolation and in relation to other cognitive abilities, differ between individuals who go on to develop ASD and those who do not, increasing our understanding of early motor delay as a risk factor for developing ASD.

Conclusion

The current study has replicated previous evidence of motor delay in at-risk infants (Iverson & Wozniak, 2006; Landa & Garrett-Mayer, 2006; Toth et al., 2007). It adds new knowledge by highlighting the importance of utilising both standardised and parental report measures to provide a clearer picture of developing motor abilities in both naturalistic and controlled situations. Due to the potential importance of early motor skills on the development of other cognitive domains (Iverson, 2010), it is vital that more research focuses on the motor profiles of infants, particularly those at-risk of developing ASD, as atypical motor development may contribute to differences seen in other areas that make up the diagnostic criteria for ASD. It is important to note that, even if infants in the at-risk group do not go on to develop ASD, poorer motor development as early as 7 months could have a negative impact on their language, social and cognitive development. Early intervention could therefore be important in ameliorating the effects of motor difficulties on development in all cases, and may be of particular significance for those at increased risk of developing ASD.

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Table 1

Participant characteristics for at-risk and low-risk infants at the three visits

Visit	Group	*N*	Age (months)	No. of males	MSEL: ELC*
7 months	*Low-risk*	50	7.4 (1.2)	20	101 (11)
	At-risk	54	7.3 (1.2)	22	94 (12)
14 months	*Low-risk*	48	13.9 (1.3)	19	106 (15)
	At-risk	54	13.7 (1.6)	22	97 (17)
24 months	*Low-risk*	49	23.9 (0.7)	19	116 (14)
	At-risk	52	23.9 (1.1)	21	102 (20)

**Early Learning Composite score on the MSEL, summed from the T-scores of fine motor, expressive and receptive language, and visual reception scales, with a mean of 100 and standard deviation of 15.*

Table 2

Mean raw scores, standardised scores (SS), age equivalence scores in months (AE) and standard deviations for gross and fine motor scales on MSEL and VABS for low-risk and at-risk groups at the three visits

	7 month visit			**14 month visit**			**24 month visit**		
Low-risk	*Raw*	*SS*	*AE*	*Raw*	*SS*	*AE*	*Raw*	*SS*	*AE*
MSEL Gross Motor	11.36 (1.72)	50.4 (9.1)	8.4 (1.7)	18.67 (3.80)	51.1 (16.1)	15.3 (3.7)	28.70 (2.30)	59.9 (8.1)	27.8 (3.5)
MSEL Fine Motor	11.60 (2.30)	58.0 (9.4)	9.6 (2.3)	19.26 (1.41)	61.2 (9.1)	17.4 (1.7)	25.79 (2.24)	54.3 (8.8)	25.5 (2.8)
VABS Gross Motor	11.61 (5.44)	14.7 (2.6)	7.1 (2.0)	33.66 (10.41)	15.3 (2.6)	14.3 (3.8)	54.17 (6.09)	15.4 (1.7)	25.5 (5.3)
VABS Fine Motor	10.65 (3.13)	15.5 (2.5)	8.5 (2.8)	18.46 (3.46)	17.2 (2.2)	18.1 (4.5)	26.74 (5.16)	16.3 (2.4)	27.3 (7.0)
At-risk									
MSEL Gross Motor	10.51 (2.27)	45.4 (10.0)	7.5 (2.2)	17.42 (4.02)	46.3 (16.6)	14.1 (3.8)	24.95 (3.04)	45.2 (11.2)	22.4 (4.3)
MSEL Fine Motor	10.58 (2.42)	52.5 (10.5)	8.6 (2.4)	17.74 (2.71)	54.9 (12.4)	15.9 (2.9)	24.85 (2.35)	49.9 (9.4)	24.3 (2.9)
VABS Gross Motor	8.57 (5.85)	12.7 (3.0)	5.5 (2.6)	27.94 (9.82)	14.0 (2.6)	12.2 (3.4)	51.50 (6.81)	14.7 (1.9)	23.4 (5.3)
VABS Fine Motor	8.21 (3.30)	13.8 (2.7)	6.7 (2.1)	15.78 (3.70)	15.2 (2.5)	14.5 (4.9)	26.23 (4.23)	16.1 (2.1)	27.4 (4.7)

Table 3

Correlations between raw scores on the gross motor scales of the MSEL and VABS tests, and between fine motor scales of the MSEL and VABS tests, for low-risk and at-risk groups at the three visits

Age (months)	Group			
	Low-risk		***At-risk***	
	Gross Motor	*Fine Motor*	*Gross Motor*	*Fine Motor*
7	.89**	.51**	.87**	.53**
14	.92**	-.03	.92**	.50**
24	.51*	.21	.43*	.41*

Note the number of participants in each group that completed both measures differs between ages.

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

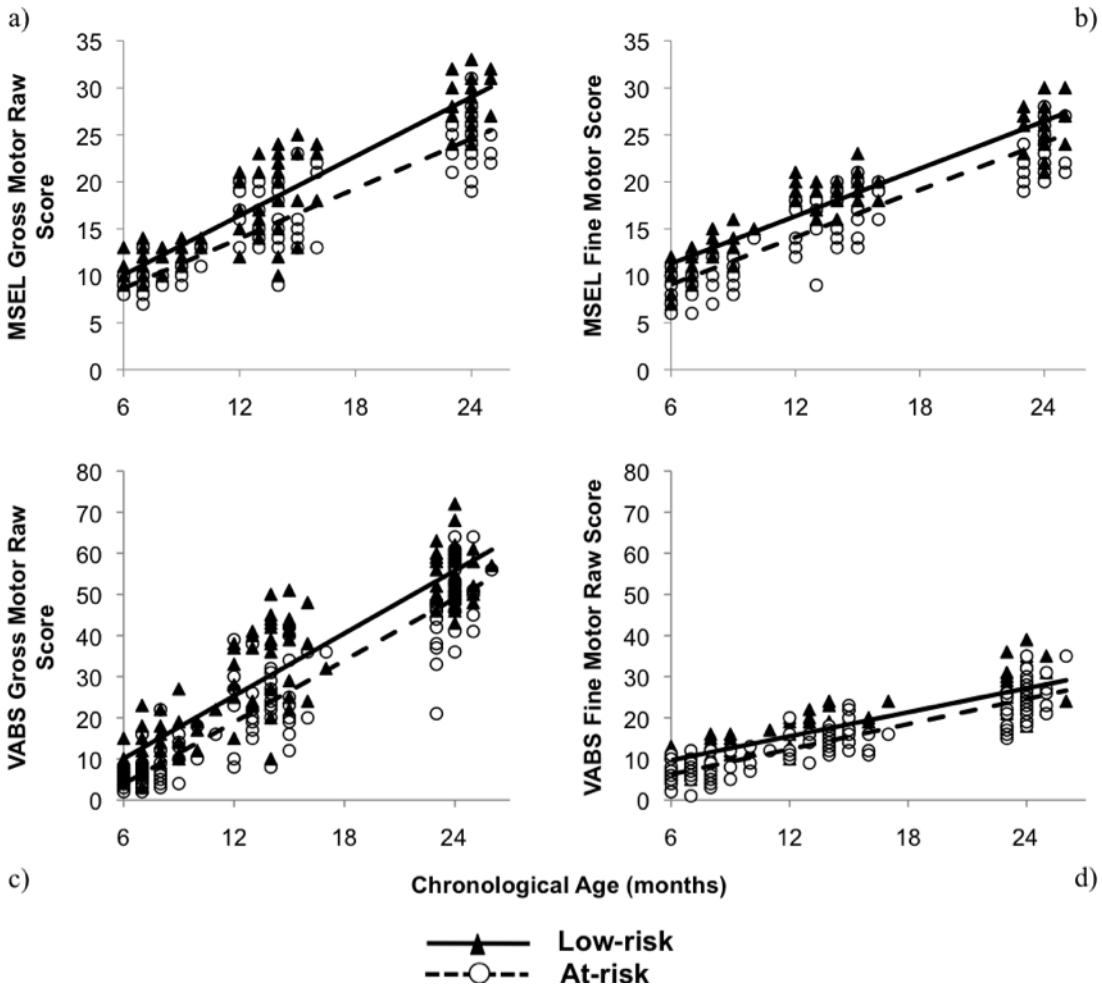

Fig. 1 Developmental trajectories for infants in low-risk and at-risk groups with scores at all three visits for gross and fine motor scales of the Mullens Scales of Early Learning (a and b) and the Vineland Adaptive Behavior Scales (c and d).