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Predictors of longer-term development of expressive language in two independent longitudinal cohorts of language-delayed preschoolers with Autism Spectrum Disorder

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Running Head: PREDICTORS OF LANGUAGE DELAY

Predictors of longer-term development of expressive language in two independent longitudinal cohorts of language-delayed preschoolers with Autism Spectrum Disorder

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Abstract

Background: Studies estimate that 30% of individuals with autism are minimally verbal. Understanding what factors predict longer-term expressive development in children with language delays is critical to inform identification and treatment of those at-risk for persistent language impairments. The present study examined predictors of expressive language development in language-delayed preschoolers followed through later school-age and young adulthood.

Methods: Children using single words or less on the Autism Diagnostic Observation Schedule (ADOS) at approximately 3 years old were drawn from the Early Diagnosis (EDX) and Pathways in ASD longitudinal cohorts. Age-3 predictors of Age-19 ADOS language level were identified using Classification and Regression Trees (CART) in the EDX sample. Linear mixed models examined the effects of CART-identified predictors on Vineland expressive communication (VExp) trajectories from Age-3 to Age-19. The same linear mixed models were examined in the Pathways sample, identifying predictors of VExp from ages 3 to 10.5 years.

Results: Significantly delayed fine motor skills (T-score < 20) was the strongest CART predictor of Age-19 language. In the linear mixed models, time, Age-3 fine motor skills and initiation of joint attention (IJA) predicted VExp trajectories in the EDX sample, even when controlling for Age-3 visual receptive abilities. In the Pathways sample, time and Age-3 fine motor skills were significant predictors of VExp trajectories; IJA and cognitive skills were not significant predictors.

Conclusions: Marked deficits in fine motor skills may be a salient proxy marker for identifying language-delayed children with ASD who are at risk for persistent language impairments. This finding adds to the literature demonstrating a relation between motor and language development in ASD. Investigating individual skill areas (e.g., fine motor and nonverbal problem-solving skills), rather than broader indices of developmental level (e.g., nonverbal IQ) may provide important cues to understanding longer-term language outcomes that can be targeted in early intervention.

Keywords: autism spectrum disorder, language, motor skills, longitudinal studies

Introduction

Preschool expressive communication, nonverbal cognition, joint attention and motor skills predict expressive language development in children with autism spectrum disorder (ASD). To date, the studies providing evidence for these predictors have included children with and without language delays[1] (e.g. Anderson et al., 2007; Bedford, Pickles, & Lord, 2016; Pickles, Anderson, & Lord, 2014; Sigman & McGovern, 2005; Siller & Sigman, 2008). Thus, much of what is known about predictors of expressive language development is influenced by variability in initial skill levels (i.e., children with and without spoken language). Studies report that as many as 50-74% of preschool children with ASD (mean ages 41-46 months) are minimally verbal (MV) (Thurm et al., 2014; Rose, Trembath, Keen, & Paynter, 2016). Even following intervention, estimates in later preschool-age samples (mean ages 59-66 months) suggest that 25-44% continue to be MV (Norrelgen et al., 2015; Rose et al., 2016, Smith, Mirenda, & Zaidman-Zait, 2007). Consistent with this, studies estimate that approximately 30% of young adults with ASD are MV (Pickles et al., 2014). Notably, definitions of MV used in these studies varied, ranging from nonverbal or very few words to occasional phrases. Although proportions may vary depending on the assessment method and definition used (Bal, Katz, Bishop & Krasileva, 2016; Rose et al., 2016), these studies highlight a clear need to explicitly explore which factors predict whether a child with significant language delays will remain MV beyond the preschool years. A focus on specific skill areas may point to critical treatment targets and promote development of more effective interventions. The current study examines predictors of expressive language development in two independent longitudinal cohorts of preschoolers with ASD and delayed

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1For conciseness, we use the terms “expressive language delay” and “language delay” interchangeably to refer to delays in spoken language. We acknowledge that language is a broader concept, including both expressive and receptive components that extend beyond speech and therefore want to clarify our intended meaning in this context.

language [defined as using single words or less during the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999), administered at approximately Age-3].

Previous studies have examined concurrent skills in children defined as language delayed by retrospective parent report. For example, Wodka, Mathy, and Kalb (2013) found that higher nonverbal cognition and lower levels of social impairment were associated with acquisition of phrase or fluent speech (as opposed to continuing to use single words or less) after 4 years of age. Children in this study were defined as language delayed based on parents' retrospectively reported acquisition of phrase speech at 4 years old or later on the Autism Diagnostic Interview – Revised (ADI-R; Rutter et al., 2003). Retrospective reports of language onset on the ADI-R are affected by 'telescoping' (i.e., reporting events as having occurred more recently than they actually occurred) and can result in misclassification of children as language delayed (Hus, Taylor, & Lord, 2011). Thus, it is important to examine predictors in longitudinal studies.

A few studies have examined short-term language outcomes in young children with ASD with varying degrees of language delay. For example, Stone and Yoder (2001) studied predictors of spoken language in a small sample (n = 35) of 23-35 month olds (Mean age = 30.9) with average expressive language estimates of 12.5 months (ranging from 3-28 months) from the Sequenced Inventory of Communication Development Revised (Hedrick et al., 1984). Results indicated that expressive language, motor imitation, joint attention, play and number of speech/language therapy hours measured at 2 years correlated significantly with expressive language at 4 years; controlling for age 2 expressive language, both motor imitation and number of speech/language therapy hours predicted language at age 4. Ellis-Weismer and Kover (2015) found that nonverbal cognition and autism symptom severity at 2.5 years predicted expressive language at 5.5 years; maternal education, adaptive social skills and response to joint attention did not make independent contributions. Of the 66 toddlers using fewer than 5 words on the ADOS at 2.5 years, 24% were MV at 5.5 years. Yoder and colleagues (2015) reported that, in a sample of 87 preschoolers with ASD (mean 2.89 +/- 0.6 years), 60% were MV (i.e., used ≤20 words per parent report and ≤5 words during a 15-minute language sample) 16 months later. Response to joint attention, number of intentional communicative acts, parental linguistic responses, and consonant inventory each independently predicted expressive language growth over the 16-month period. Motor imitation, non-imitative oral motor function, parental attention during child vocalization, object play and receptive vocabulary were not significant predictors, possibly due to strong correlations with other predictors (Yoder et al., 2015). In another sample of 47 preschoolers (3.56 +/- 0.85 years) who were using single words or less on the ADOS, Thurm and colleagues (2015) reported that 36% developed phrase speech by age 5. Nonverbal cognitive ability emerged as the strongest predictor of expressive language skills; change in ADOS social severity scores also predicted expressive language but was not significant when nonverbal cognitive ability was added to the model. In a slightly older sample of 35 children (3.79 +/- 0.82 years) who used fewer than 60 words at baseline, initial number of words, verbal imitation skills, use of objects to pretend, and number of gestures to initiate joint attention were associated with faster expressive vocabulary growth across a two-year period (Smith et al., 2007).

Taken together, these studies provide evidence for an array of factors that predict expressive development in young children with varying levels of language delay. Some factors are fairly consistent across studies (e.g., nonverbal cognition), whereas evidence for motor, imitation and social-communicative skills is more variable. Variation in predictors that emerged as statistically significant across studies could be attributed to differences in sample characteristics or reflective of differences in language measures or how language outcome was defined. Furthermore, small samples likely limited power to explore the importance of predictors that are highly correlated or may have cascading developmental effects. For example, Iverson (2010, 2018) has posited that acquisition of motor skills in the early developmental period provides opportunities to engage with the environment that are critical to language development. Fine and gross motor skills, as well as age of independent walking, have emerged as predictors of expressive language development in samples of mixed language levels (e.g., Bedford et al., 2016; Leonard et al., 2014). In both studies, motor skills remained significant predictors when covarying visual receptive abilities, each measured by the Mullen Scales of Early Learning (MSEL; Mullen, 1995). In addition to highlighting a role for motor skills in expressive language development, these findings demonstrate the importance of considering Fine Motor and Visual Reception skills separately. These MSEL subscales are often averaged to represent nonverbal cognition, which consistently emerges as a strong predictor of expressive language outcomes. Parsing broad constructs into individual subcomponents could highlight specific skill areas that are more easily translated into intervention targets.

A challenge to this area of research is the limited availability of large longitudinal cohorts with detailed clinical assessments in which to simultaneously examine multiple early predictors of longer-term language outcomes. The present study addresses this by using two independent longitudinal samples to explore predictors of language development in language-delayed preschoolers with ASD: The Early Diagnosis (EDX) study, and the Pathways in ASD study. EDX recruited 192 children referred to clinics in North Carolina (NC) and Chicago for possible ASD before 37 months (Lord et al., 2006). Children were assessed at approximately 2, 3, 9 and 19 years and many parents completed phone interviews at 14 years. Children in NC were also assessed at age 5. The Pathways in ASD study recruited 421 children diagnosed with ASD between 2 and 4 years of age at five regional centers across Canada. Children were assessed at approximately 3, 4, 4.5, 6.5, 8.5 and 10.5 years. Notably, child age at study entry varied for both EDX and Pathways studies; ages used to reference each assessment reflects the average age of children seen at that time point.

In contrast to previous studies, this study aimed to identify factors that predict longer-term expressive language development in language-delayed children, with the goal of identifying potential behavioral markers for risk of ongoing language impairment that would inform areas for more focused intervention development. To this end, we used the modestly sized EDX sample of 86 language-delayed children as a “discovery” cohort to implement Classification and Regression Tree (CART), an exploratory technique to identify which predictors from the aforementioned literature best predicted categorical language outcomes (verbal or MV during the ADOS). Although there is good correspondence between ADOS-based language categories and other measures of language (Bal et al., 2016), such broad categories may fail to capture additional, meaningful variability in language outcomes. Therefore, we then applied the CART-identified predictors to a linear model to examine whether they also predicted trajectories of a standardized, continuous measure of real-world expressive language use collected in the EDX sample. Finally, we sought to replicate findings from the EDX model in the larger (n = 181) Pathways sample,. In particular, our interest was in exploring the predictive value of narrower skill domains that are assessed in standard clinical practice and could be directly targeted in intervention (e.g., fine motor skills, initiation of joint attention), rather than broad constructs, such as ASD symptom severity.

Methods

Participants

Discovery cohort. The EDX cohort was limited to 86 children diagnosed with ASD who were classified as language-delayed on the ADOS (see below) and completed the MSEL at Age-3 and were seen again at either Ages-9 or -19 (mean = 18.99, SD = 1.08 years). The full EDX cohort (including participants with and without language delay, regardless of number of times seen) has been previously used to examine influences of diagnostic groupings (i.e., autism, PDD-NOS and non-spectrum; Anderson et al., 2007) and age of walking (Bedford et al., 2016) on language trajectories from ages 2 to 9.

Replication cohort. Pathways participants (n = 181) were selected from the larger sample to meet the following criteria: completed the Merrill-Palmer-Revised Scales of Development (M-P-R; Roid & Sampers, 2004) and exhibited delayed language at Age-3 on the ADOS, and assessed at approximately Age-10.5 years (mean = 10.75, SD = 0.25 years).

Participant characteristics and statistical comparisons within and across samples for the measures described below are provided in Table 1. At Age-3, the EDX sample was older (M_{diff} = 4.39 months; t(265) = 4.68, $p < .001$), had fewer children with “extremely delayed” nonverbal cognitive skills (i.e., 30% vs. 63%; $X^2(1) = 30.60$, $p < .001$) and fewer children classified as verbal at the last time point (48% vs. 70%; $X^2(1) = 11.98$, $p < .001$), relative to the Pathways sample. Research was approved by ethical review boards at all sites; parents provided informed consent for participation.

[Table 1 here]

Measures – Language abilities

Categorical Language Groups. Overall level of language from the ADOS (Lord et al., 2000) and PreLinguistic-ADOS (DiLavore et al., 1995) was used to classify children into language groups. Children administered a Module 1 at Age-3 (i.e., using single words or less) were classified as "language delayed"; participants administered a Module 1 at Age-10.5 (Pathways) or Age-19 (EDX) were classified as "minimally verbal." Children using at least phrase speech (i.e., administered a Module 2, 3 or 4) were classified as "Verbal."

In the EDX sample, ADOS language level was stable for 92% of 51 participants seen at both Age-9 and Age-19, therefore *most recent language* reflects Age-9 language level for the 29 participants not seen at Age-19. Previous studies have shown high correspondence (88%-100%) between language status based on the ADOS and parent-report measures (Bal et al., 2016).

Expressive Language. The Vineland Adaptive Behavior Scales (original or 2nd edition; Sparrow, Balla, Cicchetti, 1984; Sparrow, Cicchetti, Ball, 2005) Expressive age equivalent (VExp) was used as a continuous estimate of expressive language abilities because of floor effects with standard scores for many children and for simplicity of interpretation. In contrast to the categorical language estimate based on language observed during a brief, standard assessment, the Vineland yields a parent-reported estimate of "real-world" language use in different contexts.

Measures – Predictors of language abilities

Age of walking. Parent-reported age of independent walking (WALK) was taken from the ADI-R administered at Age-3 in both studies. Retrospective reports of this milestone have been shown to be stable (Hus et al., 2011).

Developmental level. EDX participants were assessed using the MSEL (Mullen, 1995) at Age-3. T-scores from four domains [Fine Motor, Visual Reception, Expressive and Receptive Language] were used; scores below the floor (T = 20) were entered as 19. Because the MSEL Gross Motor scale only yields T-scores to 33 months, age equivalents were used to estimate gross motor skills; scores above the ceiling were entered as 34. Pathways Age-3 developmental level was assessed using the M-P-R (Roid & Sampers, 2004). Standard scores from Fine Motor and Cognitive scales were used; scores below the floor (SS = 10) were entered as 9. Based on CART, categorical splits were made at 3 standard deviations below the mean; MSEL T-scores <20 and M-P-R SS <55 were considered "extremely delayed."

Early social skills. Response to joint attention (RJA), spontaneous initiation of joint attention (IJA), and imitation were items from the PL-ADOS and ADOS.

Correlations between predictors are provided in Table S1 in the Supplemental Materials.

Statistical Analyses

Predictors of categorical MV status at EDX Age-19. Classification and Regression Tree (CART; R library *rpart*) was used as an exploratory technique to investigate which previously identified predictors of language development predicted categorical language outcomes in the language-delayed EDX sample. CART is a non-parametric statistical approach used for exploring relationships between variables. In this study, the outcome of interest is categorical (i.e., most recent language: Verbal vs. MV), therefore models are classification trees. CART employs a recursive partitioning method that aims to reduce impurity in the grouping. In other words, this technique aims to identify the variable most strongly associated with the categorical outcome and splits observations on a cut-point that divides the sample into groups (referred to as "nodes") that are more homogeneous with respect to the categorical outcome. This continues until all nodes are "pure" (i.e., all participants have the same outcome) or until a criterion is met (here, a minimum of 10 participants was set in order for a node to be further split). In comparison to linear parametric methods, CART does not assume that the relationships between the predictors and the outcome are linear, nor does it require interactions to be pre-specified.

Thus, CART can be a useful method to inform variable selection and relationships between predictors for testing in other models (Strobl, Malley, & Tutz, 2009). Predictors examined included: Age-3 MSEL T-scores (Fine Motor [FM-T], Visual Reception, Expressive Language, Receptive Language), MSEL Gross Motor age equivalents, ADOS language level, WALK, Imitation, RJA and IJA. Although predictors were selected for previously demonstrated associations with language, sample size limited our ability to test all putative predictors and their interactions in the same model. Therefore, CART was implemented to identify the set of variables that best predicted directly observed language outcome for testing in the subsequent analyses described below.

Predictors of expressive language development. The availability of Vinelands provided an opportunity to assess whether the CART-identified predictors of categorical language outcomes based on direct observation would also predict parent-reported language use in real-world contexts. Linear mixed models (MIXED, SPSS 24, IBM Corp, 2016) were used to assess whether the Age-3 predictors identified in the CART analyses would predict parent-reported expressive language (VExp) trajectories to Age-19 in the EDX language-delayed cohort. Nonverbal problem solving (as a continuous T-score or standard score, unless otherwise noted), sex, race and maternal education were entered as covariates in all models. All categorical cut-offs were based upon cut-points in the CART. Model.1 was derived from CART in the language-delayed EDX sample (n = 86): Time, Age-3 Fine Motor T-score, IJA (2 vs 0-1), WALK, Time-by-Fine Motor, Time-by-IJA, Time-by-Fine Motor-by-IJA. Considering the prominence of nonverbal IQ as a predictor in previous studies (usually the average of MSEL Visual Reception and Fine Motor domains), a *secondary* analysis (Model.1b) was conducted to explore whether Fine Motor and IJA skills would remain significant when early nonverbal problem solving skills were considered. Thus, Model.1b added Age-3 Visual Reception T-Score (<20 vs ≥20) and a Time-by-Visual Reception interaction. Model.1 and Model.1b were then applied to the Pathways sample to replicate findings in an independent sample. Predictors were identical, except M-P-R Fine Motor and Cognitive scores (SS<55 vs ≥55) replaced MSEL Fine Motor and Visual Reception scores, respectively. While CART analysis of categorical language outcome in the EDX sample provided a useful tool for variable selection, application of linear models to predict VExp in the EDX sample provided an important reference to interpret subsequent Pathways analyses. Non-replication in the Pathways sample could not be attributed to differences in language outcome measures, and instead would warrant consideration of the clinical significance of predictors identified in the EDX sample.

For these analyses, multiple imputation using a Markov chain Monte Carlo method (Raghunathan et al, 2001; Reynolds, 2000) was used to compute VExp data that were missing at any time point (EDX: n = 156, Pathways: n = 151 data points). Imputation details are provided in the *Supplemental Materials*. Results reported below reflect pooled estimates and statistics across the 100 imputations. Estimated marginal means (EMM) were used to plot trajectories by language group. Significance level was set at $\alpha \leq .005$ to reduce Type I error (Benjamin et al., 2017); $\alpha \leq .05$ are reported as marginal.

Results

Predictors of categorical MV status at Age-19: EDX

CART was applied to the language-delayed sample (n = 86). In CART.1 (Figure 1), the first split shows that MSEL Fine Motor scores were the best predictor; only 9/40 children with extremely delayed scores (i.e., FM-T <20, right branch) developed phrase speech; the majority (31/40) remained MV. Of the remaining 46 children with FM-T ≥20 (left branch), all 13 who initiated joint attention (IJA = 0 or 1) developed phrase speech. Among the 33 children with less-delayed Fine Motor and impaired IJA (scores of 2 or 3), WALK predicted language status. Ten of 14 children (71%) who walked after 13 months were classified as verbal at Age-19, whereas only 9 of 19 (47%) who walked before 13 months went on to develop at least phrase speech. In other words, the 19 children who went on to become verbal were approximately evenly divided by those who walked before or after 13 months; 71% (10/14 children) of this subgroup who remained MV walked before 13 months.

[Figure 1 here]

Predictors of expressive language development: EDX

In the language-delayed sample (Model.1, Figure 2A, Tables S2 and S3), there was a marginal Time-by-Fine Motor interaction (p = .04) reflecting that the less-delayed FM group exhibited more gains in VExp than the extremely delayed FM group. Marginal time-by-IJA interactions (*p* = .04) reflected similar relationships; children who initiated joint attention (i.e., IJA = 0 or 1) tended to have higher VExp and showed more gains in VExp. WALK was not a significant predictor.

In the secondary analysis, when Visual Reception was added as a categorical predictor to explore whether early nonverbal problem solving better accounted for effects of Fine Motor and IJA (Model.1b), the time-by-Fine Motor interaction was significant (*p* < .001) and the time-by-IJA interaction remained marginal (*p* = .01; Tables S2 and S4; Figure S1A). The time-by-Visual Reception interaction was non-significant, demonstrating that children's VExp trajectories did not differ based on their levels of nonverbal problem-solving skills at Age-3, when other factors in the model were taken into account.

[Figure 2 here]

Predictors of expressive language development: Pathways

Consistent with EDX Model.1, as shown in Figure 2B and Tables S2 and S5, in the Pathways language-delayed sample, a significant time-by-Fine Motor interaction ($p < .001$) indicated that the less delayed FM group (i.e., T>20) exhibited greater gains in VExp from ages 4.5 to 10.5 than the extremely delayed FM group. IJA was not a significant predictor; VExp trajectories for children exhibiting IJA and those with impaired IJA did not differ.

When the Cognitive subscale score was explored as a categorical predictor in secondary Model.1b, the interaction was not significant, again reflecting that Age-3 nonverbal cognitive performance did not independently predict VExp trajectories when taking into account fine motor and IJA skills. However, the time-by-Fine Motor remained significant ($p < .001$; Tables S2 and S6; Figure S1B).

Discussion

We sought to identify predictors of expressive language development in preschoolers with ASD and delayed language. Results suggest that fine motor skills may be a key predictor of language outcomes for this subgroup of children who used single words or less during the ADOS at Age-3. Specifically, children with extremely delayed Fine Motor scores at Age-3 (i.e., MSEL T-score <20 and M-P-R standard score <55, reflecting performance more than three standard deviations below the mean) were more likely to remain MV and made fewer gains in parent-reported expressive language skills. The distinction of three standard deviations was data-driven (i.e., that was the cut-point identified by the CART). However, we caution against application of this number as a clinical cut-off. In consideration of measurement error, particularly at the extremes of a test scale, the clinically important point is that *marked deficits* in fine motor skills, and not simply fine motor delays, in the preschool years were associated with more severe later language impairments, reflected in both language used during a standard assessment (ADOS) and real-world language use in other contexts reported by parents (Vineland). This finding remained significant when controlling for early nonverbal problem-solving skills, and was replicated in an independent longitudinal cohort. Notably, this replication was conducted in a sample assessed at similar ages and defined as language-delayed using the same instrument criterion, but using different developmental tests (i.e., MSEL, M-P-R) that each yield standard estimates of key predictors (i.e., fine motor and cognitive abilities), suggesting a robust effect.

Motor skills and language are closely related in typical development (e.g., Siegel, 1981; Iverson, 2010; Leonard & Hill, 2014). Oral motor skills are critical to speaking and studies suggest a relationship between oral motor and fine motor skills in both typical development (e.g., Iverson & Thelen, 1999) and children with ASD (Gernsbacher et al., 2008). The association between fine motor skills and language may be particularly strong in children with ASD (e.g., Gernsbacher et al., 2008; Mody et al., 2017). At-risk infants (i.e., siblings of children with ASD) also show impaired language and fine motor skills, relative to children with typically developing siblings (Garrido et al., 2017), and a relation between infant fine motor skills and preschool language outcomes (Choi et al., 2018).

To our knowledge, this is the first study to demonstrate the association between fine motor skills and later language outcomes specifically in children with ASD and delayed language. Compared to infant sibling studies, which thus far have examined fine motor skills in infancy and toddlerhood, the present study identified a relation between fine motor skills assessed at approximately 3 years of age and language outcomes in later childhood or young adulthood. Although it is unknown whether earlier motor impairments contributed to the delayed development of language, these findings suggest that very impaired fine motor skills may be a harbinger of longer-term language problems in language-delayed preschoolers with ASD.

The association between fine motor and language skills has been hypothesized as a developmental cascade, in which delay of skills in one domain, such as fine motor, could limit the child’s interactions with the environment, thereby limiting the opportunities that may facilitate language learning (see Iverson et al., 2010, for review). For example, infants who can pick up toys are more likely to share toys with caregivers, who then respond by verbally labeling the objects. The present study may lend some support for a developmental cascade framework; in the language-delayed EDX sample, whether or not a child initiated joint attention emerged as a salient predictor of language outcomes, but only for children with better fine motor skills at Age-3 (Figure 1). This finding was not replicated in the Pathways cohort, which may simply reflect the complexity in how developmental delays in one domain influences development across other domains. Better understanding of these developmental cascades could inform intervention development. For example, researchers have demonstrated that early fine motor skills are amenable to intervention and may affect later skills that support learning (e.g., Libertus et al., 2016). However, this intervention was implemented with non-delayed 3-month-old infants. Therefore, it is an empirical question as to whether targeted treatment could remediate severe fine motor deficits in preschool children (i.e., scores as low as three standard deviations below the mean) in order to affect language development, or whether fine motor delays would need to be identified and targeted earlier. It is likely that a multidisciplinary team approach, including occupational and speech-language therapists, would be needed to design and implement such an intervention, which would then warrant careful evaluation of efficacy.

Some skills (e.g., imitation, response to joint attention) previously demonstrated to predict language in mixed-language samples did not emerge as significant predictors in the discovery analyses. It may be that the predictive value of these skills is stronger in children with more language skills; many children in the EDX sample had significant language delays that resulted in T-scores below the floor for their age. Regardless, this study should not be interpreted as evidence that these other skills are not important to language development in language-delayed children with ASD. Many predictors are moderately correlated (see Table S1) and their development is likely highly interdependent and complex.

Although fine motor skills emerged as a predictor of expressive language development in two independent cohorts using different measures of fine motor skills, it is possible that scores on fine motor subscales are a function of how developmental tests are organized, rather than specific fine motor skill deficits. For example, it may be easier to engage children with ASD to complete fine motor tasks, compared to items assessing nonverbal problem-solving skills. On both the MSEL and the M-P-R, fine motor tasks provide more opportunities to manipulate objects and have more concrete indicators of success (e.g., putting items in a container) compared to visual reception/cognitive subscale tasks (e.g., finding hidden objects, matching). It is also possible that engagement with the environment, motivation to interact with objects, or other unknown factors affect fine motor and language development and account for the observed association. Consideration of how engagement and motivation affect test performance, as well as broader opportunities for learning, will be important to consider in future research.

Age of walking was not a significant predictor of language trajectories after accounting for other factors; however, it is interesting that only 29% of the group who walked at 13 months or later were classified as MV at age-19, compared to 53% of earlier walkers (before 13 months;

Figure 1). It is also important to note that the “later” walkers were not necessarily delayed walkers; groups were split at 13 months based on the CART and not on conventionally defined delay (e.g., ≥16 months; Johnson et al., 1990). Nonetheless, this result is somewhat counterintuitive, as we might expect fewer MV adults to have been early walkers (considering that later walking is associated with broader developmental impairment). This may provide further evidence that expressive impairments in children with ASD are not always attributable to global developmental delay or intellectual disability (ID) (Bal et al., 2016). A previous study reported fewer children with ASD and ID were delayed walkers (compared to children with ID, but no ASD), suggesting that some children with ASD may “arrive at their ID via a different route” (p. 5; Bishop et al., 2016) than their non-ASD counterparts. Distinguishing pathways that may lead to language or intellectual impairment are complex — reminding us that milestones such as walking or speech are markers of these developmental processes, not simply delays within specific systems.

Our results suggest that more careful attention to patterns of development across skill areas (e.g., fine and gross motor, nonverbal problem solving) may provide important clues to understanding longer-term language outcomes. The tendency to use broad indices of developmental level or disorder (e.g., nonverbal IQ, autism symptom severity) may stem in part from small sample sizes that limit power to investigate multiple predictors. However, the mounting evidence for uneven patterns of development across skill domains, particularly in individuals who remain MV, warrants more powerful approaches. Understanding whether the link between fine motor and language skills reflects associations with other motor deficits affecting speech (Gernsbacher et al., 2008), developmental cascades, or unknown factors that affect development of both skill areas (e.g., engagement with the environment) will be particularly important to informing specific intervention targets. Such an approach may also provide a more direct path to investigating biological processes underlying specific skills that will contribute to understanding of pathophysiology and potentially, early biomarkers.

Limitations

While this study aimed to explore a list of empirically-driven factors that have been shown to predict language development and outcomes in mixed-language-level samples, several skills suggested as predictors of language in previous studies were not included (e.g., phonetic inventory, oral motor skills and play levels). In addition, while intervention is likely an important predictor of language development in some minimally verbal children (see Tager-Flusberg & Kasari, 2013), systematic investigation of timing and dosage of varying intervention types across samples was beyond the scope of this study. As it was, considering the small sample size of the language-delayed EDX cohort, we may have lacked power to investigate the relative contributions of the 10 included predictors of later language outcomes. Interpretation may also be limited by ascertainment bias (i.e., for EDX, referrals for ASD in the early-to-mid-1990s). CART provided a useful exploratory tool to identify the most salient predictors in this sample. One possible limitation of CART, however, is the potential for over-fitting and lack of generalization to other samples. The exploration of CART-identified predictors in the linear mixed models in the EDX cohort provides some validation. Moreover, replication in the independent Pathways sample, which was slightly younger and more cognitively impaired at the start of the study, and recruited nearly a decade after the EDX study, addresses concerns regarding generalization to other samples, as well as the sample size and power to investigate the number of predictors and interactions in the EDX analyses. Severe impairment in fine motor skills emerged as a significant predictor of language outcomes using two different developmental assessments, each controlling for another aspect of nonverbal cognition — suggesting robustness in this finding. However, we cannot rule out measurement confounds related to developmental assessment of fine motor skills.

Conclusions

This study adds to the literature suggesting a relation between motor and expressive language development. It also points to severe fine motor delays as a particularly salient marker for identifying language-delayed children with ASD who are at risk for persistent language impairments. The present findings also highlight that parsing broad constructs (e.g., nonverbal IQ) may yield a clearer picture of factors affecting expressive language development, and inform the development of interventions that can benefit affected children.

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Table 1.
Age-3 sample characteristics

		EDX language-delayed sample		Pathways language-delayed sample										
Age-3 language		≥ 5 words		1-4 words		no words		≥ 5 words		1-4 words			no words	
		M (SD)			M (SD)			M (SD)			M (SD)	M (SD)		M
N		16		36		34		44		66			71	
Age (months)		42.63 (4.26)			41.39 (5.84)			**40.68 (5.96)**			38.55 (5.26)	38.09 (8.44)		**34.8**
% Male		93.8		88.9		79.4		93.2		81.8			91.5	
% White		62.5		66.7		47.1		59.5		68.5			58.1	
% MatEd BA or higher		56.3		*62.5*		47.1		55.0		*36.5*			39.1	
% Verbal at last assessment^{1}		87.5		47.2		29.4		95.5		69.7			53.5	
% Extremely Delayed FM^{2}	12.5^{a}		47.2		61.8^{a}		27.3^{f}	53.0				67.6^{f}		
% Extremely Delayed VR/Cog^{2}	6.3^{d}		**27.8**		**44.1**^{d}		40.9^{g,h}	**71.2**^{g}				**77.5**^{h}		
% Extremely Delayed EL^{2}		81.3	91.7		97.1									
% Extremely Delayed RL^{2}		62.5	88.9		94.1		50.0^{a,b}		84.8^{a}			90.1^{b}		
VExp Age (month		15.69 (6.01)^{a,d,e}		*9.33 (4.26)*^{b,d}			7.53 (4.52)^{c,e}			20.66 (6.40)^{f,g}		*14.35 (6.67)*^{f,h}	9.89 (4.95)	

s)						
VRec Age (months)	18.38 (6.53)^{a,b}	12.83 (5.96)^{b}	11.35 (4.34)^{a}	18.66 (8.34)^{c}	14.10 (7.79)	12.32 (7.14
Age of Walking (months)	12.00 (2.22)	15.17 (7.44)	18.06 (8.33)	13.57 (3.14)	13.94 (3.87)	15.0

Note. **Bold** values indicate significant (♋< .005) subgroup differences across samples, $^{a\text{-}h}$ significant (♋< .005) within sample differen
lettered values; MatEd = Maternal Education; BA = Bachelor's degree; FM = Fine Motor; VR = Visual Reception; EL = Expressive La
Receptive Language; Extremely Delayed = Mullen T-score < 20 (EDX) and Merrill Palmer SS < 55 (Pathways); Cog = Cognitive; Vex
Behavior Scales, Expressive Communication subdomain; [1]last assessment = Age-19 for EDX and Age-10.5 for Pathways; [2]FM & VR T
Mullen Scales of Early Learning for EDX and FM & Cog SS from Merrill-Palmer-Revised Scales of Development for Pathways

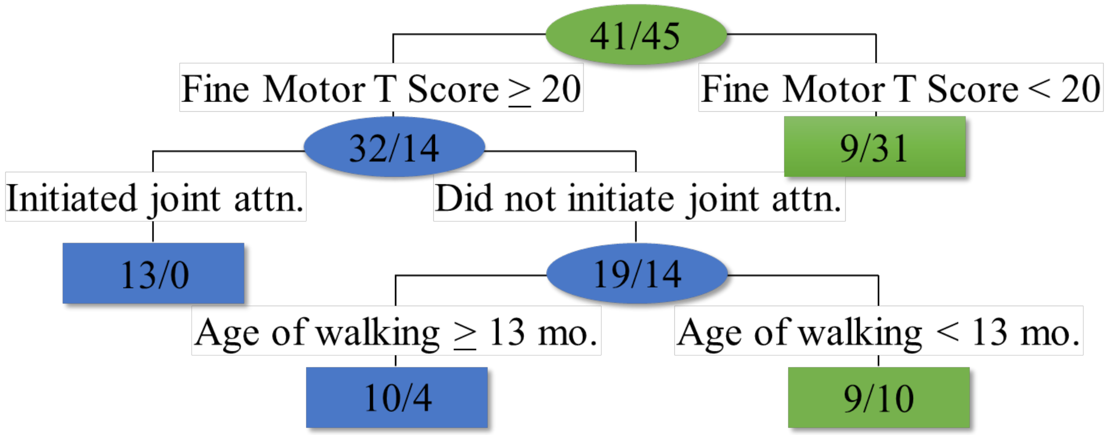


Figure 1. CART predicting categorical language outcomes in the language-delayed EDX sample (n=86). Numbers in boxes/ovals indicate most recent language (V/MV); i.e., 41/45=41 children were using at least phrases by Age-19; 45 were MV at Age-19. Joint Attention is taken from the ADOS (Initiated reflects a score of 0 or 1, Did not initiate indicates a score of 2).

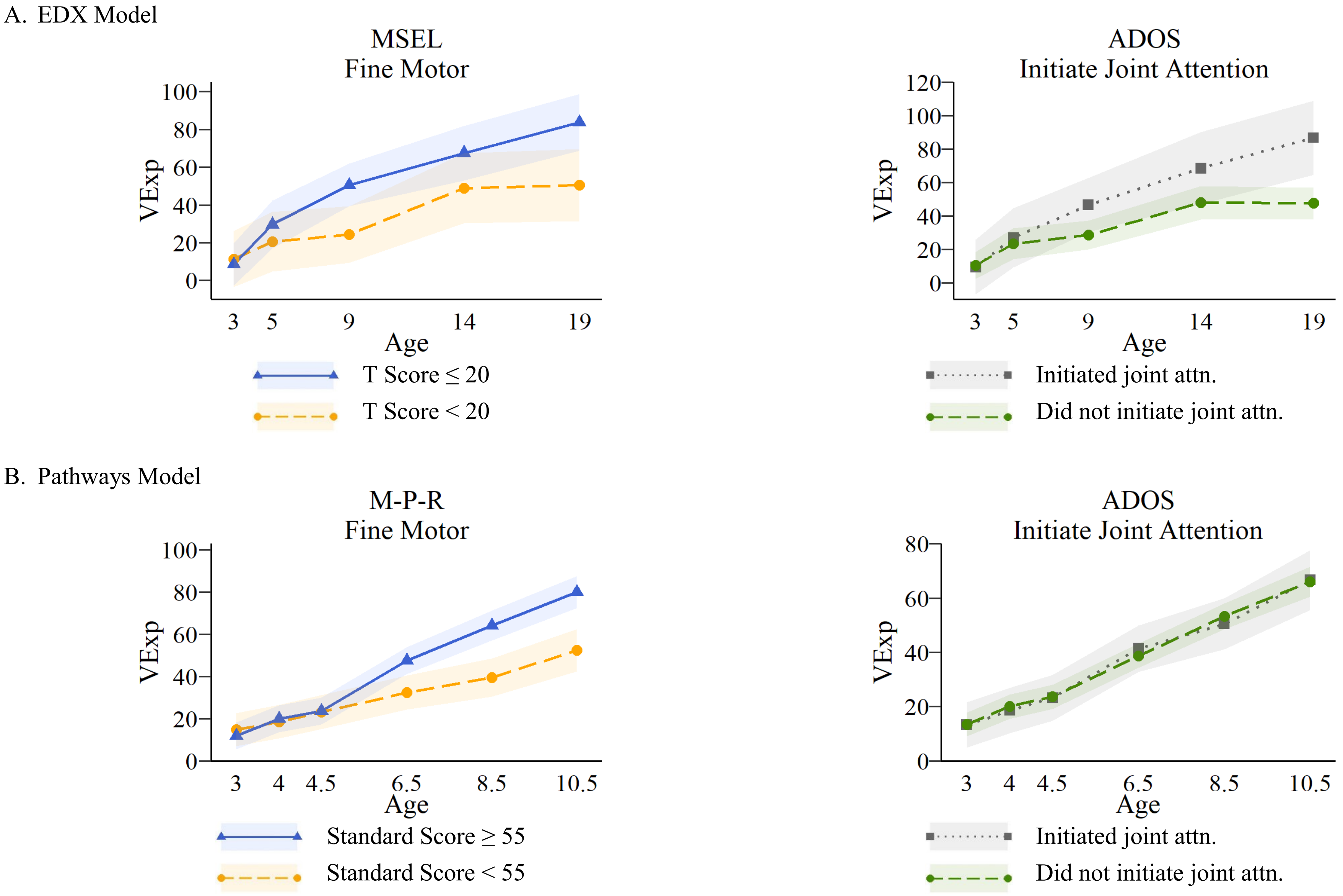


Figure 2. Parent-reported expressive language skills in language-delayed children by categorical predictors.

VExp=Vineland Expressive age equivalent (months); MSEL=Mullen Scales of Early Learning; ADOS=Autism Diagnostic Observation Schedule; M-P-R= Merrill Palmer-Revised Scales of Development.

Methods

Imputation

Multiple imputation using a Markov chain Monte Carlo method (Raghunathan et al, 2001; Reynolds, 2000) was used to compute VExp data that were missing at any time point (EDX: n = 156, Pathways: n = 151 data points). Using all Vineland data available (i.e., Ages-3, 5, 9, 14, 19 for EDX, Ages-3, 4, 4.5, 6.5, 8.5 and 10.5 for Pathways), Age-3 Fine Motor score (EDX: MSEL T-score; Pathways: M-P-R standard score), IJA score and nonverbal problem solving (EDX: MSEL Visual Reception T-score; Pathways: M-P-R Cognitive standard score), WALK, most recent language (EDX: Age-9/19, Pathways: Age 10.5 ADOS language level) and demographic factors (gender, race, maternal education), 100 imputed datasets using 50 iterations were generated. Children with and without imputed data did not differ on sex or Age-3 language level. Race and maternal education differences reflected ascertainment and attrition patterns, as previously reported (Bal et al., 2018). Language outcome groups did not differ on race or maternal education, therefore differences in missing vs. imputed cases are not anticipated to bias results. No race/ethnicity or education differences were seen in children with or without imputed data in the Pathways sample. Nonetheless, race and maternal education were used in the imputation and controlled for in all analyses.

Table S1
Correlations amongst Age-3 predictors

ADOS ite

	Fine Motor	Visual Reception	Receptive Language	Expressive Language	Age Walking (ADI-R)	Response to Joint Attention	Spo Init A
Fine Motor							
Visual Reception	**0.65**						
Receptive Language	0.24	**0.59**					
Expressive Language	**0.37**	**0.72**	**0.72**				
Age Walking	-0.20	-0.26	-0.06	-0.09			
Response to Joint Attention	-0.07	-0.22	**-0.46**	-0.26	0.00		
Spontaneous Init. Of Joint Attention	-0.26	-0.21	-0.22	-0.16	0.18	**0.50**	
Functional and Symbolic Imitation	-0.29	-0.30	-0.35	-0.34	0.13	0.27	

Bold indicates p<.001; *Age equivalents for Gross Motor; T-scores for all other domains

Table S2
F-tests from mixed models

	Language-Delayed EDX		Language-Delayed Pathways	
	Model.1	Model.1b	Model.1	Model.1b
Time[a]	**22.33 (4, 274.16)**	**19.50 (4, 275.99)**	**59.02 (5, 690.52)**	**61.80 (5, 694.**
Language	-	-	-	-
Fine Motor (FM)	*7.13 (1, 96.09)*	**15.17 (1, 94.36)**	*8.14 (1, 197.26)*	**21.00 (1, 193.**
Init of Joint Attention (IJA)	*8.05 (1, 94.91)*	**12.84 (1, 93.93)**	0.08 (1, 192.75)	0.11 (1, 193.
Age of Walking (WALK)	.33 (1, 101.16)	-	1.25 (1, 204.80)	-
Time x Language	-	-	-	-
Time x FM	*3.01 (4, 274.16)*	1.51 (4, 276.10)	**6.40 (5, 690.55)**	**5.63 (5, 693.**
Time x IJA	*3.30 (4, 274.16)*	*4.29 (4, 276.00)*	0.62 (5, 690.53)	0.71 (5, 693.
Time x WALK	-	-	-	-
Time x Language x FM	-	-	-	-
Time x FM x IJA	1.34 (5, 188.64)	-	0.49 (6, 462.55)	-
Age-3 assessment age	*8.82 (1, 101.10)*	2.11 (1, 99.82)	1.87 (1, 205.69)	2.21 (1, 206.
Degree	3.33 (1, 108.16)	1.56 (1, 106.94)	2.66 (1, 295.18)	3.20 (1, 298.
Male	0.32 (1, 101.05)	0.50 (1, 99.86)	1.55 (1, 205.06)	1.45 (1, 205.
Age-3 VR T-Score/Cog SS	**16.01 (1, 101.23)**	0.16 (1, 94.16)	*8.58 (1, 207.33)*	2.79 (1, 194.
White	*6.15 (1, 101.55)*	4.05 (1, 100.45)	1.73 (1, 489.38)	2.40 (1, 495.
Time x VRT	-	0.48 (4, 276.08)	-	0.33 (5, 693.

Bold indicates p<.001; *italics indicates p<.05*

Table S3
Model.1 – EDX (pooled estimates across 100 imputations)

	Estimate	SE	t	p
Intercept	-70.34	27.31	-2.58	0.010
Age-19	47.50	8.73	5.44	0.000
Age-14	47.14	8.68	5.43	0.000
Age-9	24.32	7.75	3.14	0.002
Age-5	17.03	7.33	2.33	0.020
Fine Motor T-score	-6.15	8.98	-0.68	0.493
Spontaneous Initiation of Joint Attention	-10.13	11.48	-0.88	0.378
Age-19 x FM	-20.87	12.23	-1.71	0.088
Age-14 x FM	-19.52	12.32	-1.58	0.113
Age-9 x FM	-12.74	10.90	-1.17	0.243
Age-5 x FM	-8.47	9.78	-0.87	0.387
Age-19 x IJA	55.56	18.00	3.09	0.002
Age-14 x IJA	23.77	17.59	1.35	0.177
Age-9 x IJA	35.53	14.26	2.49	0.013
Age-5 x IJA	8.34	13.25	0.63	0.529
Age-19 x FM x IJA	-12.40	24.56	-0.50	0.614
Age-14 x FM x IJA	14.10	23.52	0.60	0.549
Age-9 x FM x IJA	-14.68	19.25	-0.76	0.446
Age-5 x FM x IJA	10.89	20.88	0.52	0.602
Age-3 x FM x IJA	18.10	19.03	0.95	0.342
Walk	-1.89	5.18	-0.36	0.716
VR T-score	1.40	0.37	3.83	0.000
Chronological Age (at Age-3)	1.45	0.53	2.75	0.006
Male	2.53	7.17	0.35	0.724
White	-11.66	5.19	-2.25	0.025
Mat Ed BA+	-8.78	5.33	-1.65	0.099

Age-# indicates time relative to Age-3; FM = Fine Motor T-score < 20, relative to FM T-score ≥ 20; VR = Visual Reception; IJA = Spontaneous Initiation of Joint Attention < 2, relative to IJA = 2; Walk = Age of Walking < 13 months, relative to Walk ≥ 13; Mat Ed BA+ = Maternal Education of Bachelor’s degree or higher, relative to Mat Ed some college or less

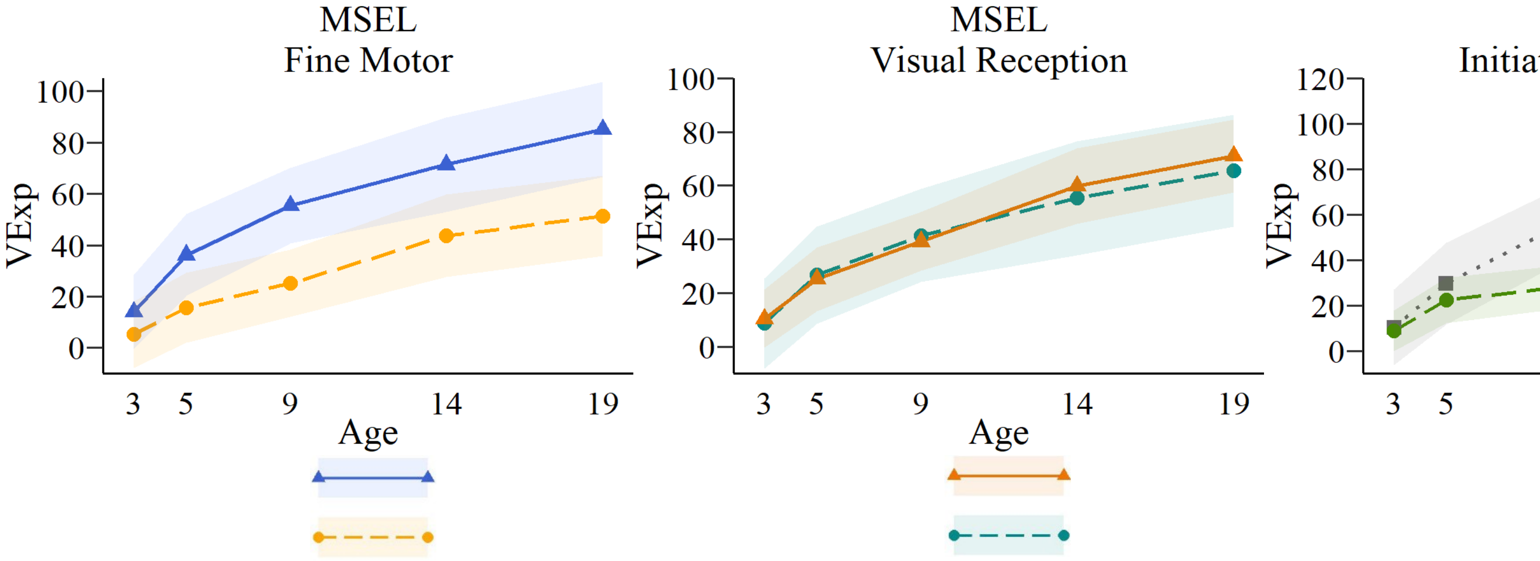
Table S4

Model.1b - EDX

	Estimate	SE	t	p
Intercept	-7.40	21.61	-0.34	0.732
Age-19	50.79	8.60	5.91	0.000
Age-14	47.72	8.51	5.61	0.000
Age-9	27.32	7.53	3.63	0.000
Age-5	17.54	6.98	2.51	0.012
Fine Motor T-Score <20	-8.83	9.64	-0.92	0.359
Spontaneous Initiation of Joint Attention < 2	1.38	9.21	0.15	0.881
Visual Reception T-Score <20	-1.71	10.39	-0.16	0.869
Age-19 x FM	-24.88	14.26	-1.74	0.081
Age-14 x FM	-18.78	14.52	-1.29	0.196
Age-9 x FM	-21.38	12.13	-1.76	0.078
Age-5 x FM	-11.68	10.69	-1.09	0.275
Age-19 x IJA	44.48	14.88	2.99	0.003
Age-14 x IJA	22.13	14.61	1.51	0.130
Age-9 x IJA	24.27	11.74	2.07	0.039
Age-5 x IJA	6.06	10.57	0.57	0.567
Age-19 x VR	-3.66	15.47	-0.24	0.813
Age-14 x VR	-2.78	16.05	-0.17	0.863
Age-9 x VR	4.00	13.30	0.30	0.764
Age-5 x VR	3.28	11.54	0.28	0.776
Chronological Age	0.65	0.48	1.35	0.176
Male	4.26	7.42	0.57	0.566
White	-9.98	5.45	-1.83	0.067
Mat Ed BA+	-5.93	5.39	-1.10	0.271

Age-# indicates time relative to Age-3; FM = Fine Motor T-score < 20, relative to FM T-score ≥ 20; VR = Visual Reception T-score < 20, relative to VR T-score ≥ 20; IJA = ADOS Spontaneous Initiation of Joint Attention < 2, relative to IJA = 2; Mat Ed BA+ = Maternal Education of Bachelor's degree or higher, relative to Mat Ed some college or less

A. EDX



B. Pathways

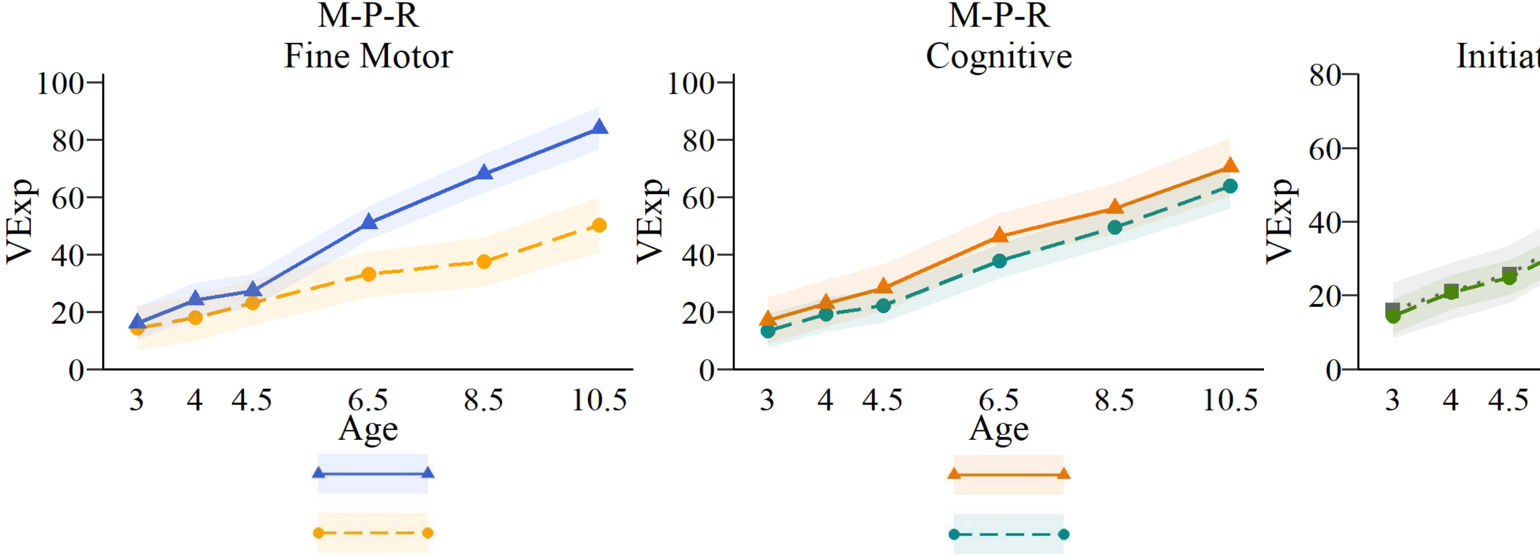


Figure S1. Model.1b: Parent-reported expressive language skills in language-delayed children by categorical predictors.

VExp=Vineland Expressive age equivalent (months); MSEL=Mullen Scales of Early Learning; ADOS=Autism Diagnostic Observation Schedule; M-P-R= Merrill-Palmer-Revised Scales of Development

Table S5

Model.1 - Pathways

	Estimate	SE	t	p
Intercept	-12.73	8.80	-1.45	0.148
Age-10.5	70.72	5.34	13.25	0.000
Age-8.5	56.33	5.01	11.24	0.000
Age-6.5	35.36	4.57	7.73	0.000
Age-4.5	12.40	4.24	2.92	0.003
Age-4.0	8.86	3.50	2.53	0.011
Fine Motor Standard Score < 55	4.09	5.24	0.78	0.435
Spontaneous Init of Joint Attention < 2	0.98	5.52	0.18	0.859

Age-10.5 x FM	-36.46	6.68	-5.46	0.000
Age-8.5 x FM	-33.11	6.36	-5.21	0.000
Age-6.5 x FM	-20.20	5.85	-3.45	0.001
Age-4.5 x FM	-4.54	5.41	-0.84	0.401
Age-4.0 x FM	-4.60	4.46	-1.03	0.303
Age-10.5 x IJA	-5.15	8.68	-0.59	0.553
Age-8.5 x IJA	-8.06	8.05	-1.00	0.316
Age-6.5 x IJA	0.62	7.26	0.09	0.932
Age-4.5 x IJA	-1.29	6.76	-0.19	0.849
Age-4.0 x IJA	-1.54	5.61	-0.27	0.784
Age-10.5 x FM x IJA	9.55	11.85	0.81	0.421
Age-8.5 x FM x IJA	8.64	11.13	0.78	0.438
Age-6.5 x FM x IJA	2.10	9.71	0.22	0.829
Age-4.5 x FM x IJA	-0.05	9.60	-0.01	0.996
Age-4.0 x FM x IJA	-1.77	9.54	-0.19	0.853
Age-3.0 x FM x IJA	-2.28	9.47	-0.24	0.810
Walk	-2.65	2.55	-1.04	0.299
Cognitive Standard Score	0.25	0.09	2.81	0.005
Chronological Age	0.21	0.16	1.29	0.198
Male	4.30	3.78	1.14	0.255
White	2.46	2.47	1.00	0.318
Mat Ed BA+	3.61	2.53	1.43	0.154

Age-# indicates time relative to Age-3; Fine Motor Standard Score is < 55, relative to FM SS ≥ 55; Walk = Age of Walking < 13 months; IJA = ADOS Spontaneous Initiation of Joint Attention < 2, relative to IJA = 2; Mat Ed BA+ = Maternal Education of Bachelor's degree or higher, relative to Mat Ed some college or less

Table S6

Model.1b - Pathways

	Estimate	SE	t	p
Intercept	1.28	7.84	0.16	0.870
Age-10.5	70.14	5.87	11.94	0.000
Age-8.5	55.80	5.41	10.31	0.000
Age-6.5	36.45	4.97	7.34	0.000
Age-4.5	12.98	4.60	2.82	0.005
Age-4.0	8.84	3.75	2.36	0.018
Fine Motor Standard Score < 55	-1.66	5.37	-0.31	0.757
Spontaneous Init of Joint Attention < 2	1.67	4.54	0.37	0.713
Cognitive Standard Score < 55	-3.68	5.60	-0.66	0.511
Age-10.5 x FM	-32.03	8.18	-3.92	0.000
Age-8.5 x FM	-28.99	7.69	-3.77	0.000
Age-6.5 x FM	-16.12	7.05	-2.29	0.022
Age-4.5 x FM	-2.43	6.52	-0.37	0.710
Age-4.0 x FM	-4.39	5.46	-0.80	0.421
Age-10.5 x IJA	-1.38	7.25	-0.19	0.849
Age-8.5 x IJA	-4.59	6.52	-0.70	0.482
Age-6.5 x IJA	1.72	6.00	0.29	0.775
Age-4.5 x IJA	-0.74	5.55	-0.13	0.894
Age-4.0 x IJA	-1.38	4.56	-0.30	0.762
Age-10.5 x Cog	-2.89	8.72	-0.33	0.740
Age-8.5 x Cog	-2.72	7.95	-0.34	0.732
Age-6.5 x Cog	-4.85	7.36	-0.66	0.510
Age-4.5 x Cog	-2.54	6.81	-0.37	0.710
Age-4.0 x Cog	-0.14	5.71	-0.02	0.980
Chronological Age	0.23	0.16	1.41	0.158
Male	4.19	3.82	1.10	0.272
White	3.01	2.48	1.21	0.226
Mat Ed BA+	4.04	2.56	1.58	0.115

Age-# indicates time relative to Age-3; Fine Motor Standard Score is < 55, relative to FM SS ≥ 55; Cognitive Standard Score is < 55, relative to Cog SS ≥ 55; IJA = Spontaneous Initiation of Joint Attention , relative to IJA = 2; Mat Ed BA+ = Maternal Education of Bachelor’s degree or higher, relative to Mat Ed some college or less