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RESEARCH ARTICLE

Severe communication delays are independent of seizure burden and persist despite contemporary treatments in *SCN1A*+ Dravet syndrome: Insights from the ENVISION natural history study

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Abstract

Objective: Dravet syndrome (DS) is a developmental and epileptic encephalopathy characterized by high seizure burden, treatment-resistant epilepsy, and developmental stagnation. Family members rate communication deficits among the most impactful disease manifestations. We evaluated seizure burden and language/communication development in children with DS.

Methods: ENVISION was a prospective, observational study evaluating children with DS associated with *SCN1A* pathogenic variants (*SCN1A*+ DS) enrolled at age ≤5 years. Seizure burden and antiseizure medications were assessed every 3 months and communication and language every 6 months with the Bayley Scales of Infant and Toddler Development 3rd edition and the parent-reported Vineland Adaptive Behavior Scales 3rd edition. We report data from the first year of observation, including analyses stratified by age at Baseline: 0:6–2:0 years:months (Y:M; youngest), 2:1–3:6 Y:M (middle), and 3:7–5:0 Y:M (oldest).

Results: Between December 2020 and March 2023, 58 children with DS enrolled at 16 sites internationally. Median follow-up was 17.5 months (range = .0–24.0), with 54 of 58 (93.1%) followed for at least 6 months and 51 of 58 (87.9%) for 12 months. Monthly countable seizure frequency (MCSF) increased with age

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(median [minimum–maximum] =1.0 in the youngest [1.0–70.0] and middle [1.0–242.0] age groups and 4.5 [.0–2647.0] in the oldest age group), and remained high, despite use of currently approved antiseizure medications. Language/communication delays were observed early, and developmental stagnation occurred after age 2 years with both instruments. In predictive modeling, chronologic age was the only significant covariate of seizure frequency (effect size = .52, $p = .024$). MCSF, number of antiseizure medications, age at first seizure, and convulsive status epilepticus were not predictors of language/communication raw scores.

Significance: In infants and young children with *SCN1A*+ DS, language/communication delay and stagnation were independent of seizure burden. Our findings emphasize that the optimal therapeutic window to prevent language/communication delay is before 3 years of age.

KEYWORDS

communication/language delays, developmental and epileptic encephalopathy, Dravet syndrome, ENVISION, natural history study

1 | INTRODUCTION

Dravet syndrome (DS) is a developmental and epileptic encephalopathy mostly caused by loss-of-function variants in the voltage-gated sodium channel alpha-1 subunit gene, *SCN1A*.[1,2] Individuals with DS have frequent, often prolonged, drug-resistant seizures, developmental and motor impairment, and behavioral and sleep problems.[3–13]

No approved disease-modifying therapies exist for DS. Although multiple antiseizure medications (ASMs) are utilized to reduce seizures, they do not address neurodevelopment[14] or the communication deficits that families find most concerning for individuals with DS.[9,15,16]

A clear understanding of the early development of DS manifestations and the potential therapeutic window for intervention with a disease-modifying therapy is lacking. Although onset of DS is typically around age 6 months,[17] there are no prospective, contemporary, long-term data describing the range of phenotypic features and their evolution in infants and young children with DS.[14] The ENVISION natural history study (NCT04537832) obtained longitudinal data in children ≤5 years old at enrollment to prospectively characterize early development and determine appropriate endpoints for future DS clinical trials. We report an analysis from ENVISION focused on seizure burden and language/communication development in participants followed for at least 1 year.

Key points

- Seizure burden increased with age and remained high despite the use of currently approved antiseizure medications.
- Seizure burden and *SCN1A* pathogenic variant type were not significant predictors of language/communication skills.
- Gains in language/communication skills slowed or halted after 2 years of age.
- To prevent language/communication development delays, disease-modifying therapeutic interventions should ideally be initiated before age 3 years.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This prospective, observational, multicenter study included children aged 6 months to 5 years at enrollment with a clinical diagnosis of DS and a pathogenic or likely pathogenic *SCN1A* variant (*SCN1A*+ DS). Pathogenicity was classified per American College of Medical Genetics and Genomics variant interpretation guidelines.[18] Children with a comorbid condition or additional pathogenic variant in another gene potentially confounding the DS phenotype and those with large intragenic deletions resulting

in haploinsufficiency of additional genes were excluded. For missense variants, priority was given to *de novo* variants. Missense variants without inheritance information were included if they met the following criteria: absent in the general population database gnomAD,[19] reported in another individual with DS,[20] in ClinVar,[21] or considered pathogenic based on (1) their missense tolerance ratio (MTR; MTR <5% = strong evidence of pathogenicity),[22] (2) variant localization in a pathogenic enriched region (PER) in silico,[23] (3) previous reports in another loss-of-function *SCN* gene disorder, and (4) a >70% probability of development of DS based on the *SCN1A*-epilepsy prediction model.[20] Inclusion and exclusion criteria are shown in Table S1.

ENVISION was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines, Declaration of Helsinki, and Clinical Investigation of Medicinal Products in the Pediatric Population. Study protocol was approved by institutional review boards or ethics committees of each institution. Signed informed consent was obtained from parents/legal guardians.

2.2 | Clinical assessments

Participants were evaluated quarterly for 1 year. Baseline data included gene variant type, epilepsy and developmental history, and presence of comorbidities (motor features, behavioral problems, or neurodevelopmental diagnoses, including attention-deficit/hyperactivity disorder [ADHD] or autism spectrum disorder [ASD]).

Seizure burden was assessed using an electronic diary completed for 28 days leading up to each post-Baseline visit. The seizure diary was developed by the study sponsor (Encoded Therapeutics) with input from the investigators, the Epilepsy Study Consortium (https://www.epilepsyconsortium.org/), and an independent panel of caregivers of individuals living with *SCN1A*+ DS. Month 3 visit was the first study visit with seizure data (i.e., seizure diary was not required before Baseline). The diary captured daily seizure counts and rescue medications used for calculation of monthly countable seizure frequency (MCSF), total seizure-free days (days free of both countable and noncountable seizures), number of prolonged seizures (lasting 5–30 min) and episodes of status epilepticus (seizure lasting >30 min),[24] and days of rescue medication use. MCSF was defined as the (scaled) sum of countable seizures over 28 days, comprising focal motor seizures with observable clinical signs (including hemiclonic seizures), and tonic, generalized tonic–clonic/clonic, and atonic seizures. Only diaries with 75% completion were included in the analysis.

Communication/language were assessed at Baseline, Month 6, and Month 12 using Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III), which assesses skills from birth to 42 months[25]; parent-reported Vineland Adaptive Behavior Scales 3rd edition (VABS-III), designed for all ages[26]; and Wechsler Preschool & Primary Scale of Intelligence 4th edition (WPPSI-IV), for ages 2.5–7.5 years[27] (not reported due to insufficient data to derive language composite scores for analysis). Although assessments were chosen based on age, the BSID-III was used for older participants if developmental status rendered the WPPSI-IV unfeasible. BSID-III and WPPSI-IV were administered in person by a trained clinician. Raw and normalized scores (with respect to a neurotypical population) were collected at the domain and subdomain levels. Age equivalent (AE; age at which the observed raw score is typically achieved in a neurotypical population) and developmental quotient (DQ; AE/chronologic age × 100) were calculated (Table S2).[28] Person ability scores (growth scale values [GSVs] and growth scale equivalents [GSEs]) accurately assessed change in skill attainment over time.[29]

2.3 | Statistical methods

Data were summarized descriptively by nominal visit (Baseline [−60 days to Day 1] and Months 3, 6, 9, and 12 [±14 days]) using age stratified at Baseline. The youngest group was 6 months to 2 years (0:6 to 2:0), the middle group was 2 years 1 month to 3 years 6 months (2:1 to 3:6), and the oldest age group was 3 years 7 months to 5 years (3:7 to 5:0) at Baseline. Where applicable, bivariate tests were used to compare sample statistics, confidence intervals (CIs) to quantify the associated variability, and regression, correlation, and Kaplan–Meier methods to explore trends between seizure and language/communication endpoints.

To quantify the (linear) impact of age on longitudinal BSID-III and VABS-III scores, a piecewise linear mixed-effects approach (MIXED procedure in SAS) utilizing a random subject term was used to model the continuous endpoints based on the fixed effects of age (at the endpoint evaluation), sex, pathogenic variant type, seizure onset age, Baseline MCSF category, and Baseline ASM usage. The Baseline MCSF categorization included three groups (seizures per 28 days): MCSF = 0, MCSF = 1–3, and MCSF > 3, and the piecewise approach was used to estimate a change in the linear trajectory (at a given age) by selecting the model with the highest log-likelihood across a nuisance age parameter with predefined cutoffs from 2:0 to 4:0.

We performed a principal component analysis (PCA) to distill the multidimensional clinical information into a simplified dimensional space. We restricted our analysis to clinical variables that were available for >40 individuals: Baseline VABS-III Adaptive Behavior Composite (ABC) standard, Month 6 MCSF, Month 6 days of rescue medication use, and Month 6 VABS-III ABC standard. The first two principal components accounted for 42.7% and 31.6% of the data variance, respectively.

Statistical analyses were performed using R version 4.2.1 (or higher) and/or SAS version 9.4 (or higher).

3 | RESULTS

3.1 | Baseline characteristics

Between December 2020 and March 2023, 70 children with DS were screened and 58 enrolled at 16 sites in the United States, the United Kingdom, Spain, and Australia (Figure S1). Median follow-up was 17.5 months (range = .0–24.0 months), with 54 of 58 (93.1%) followed for at least 6 months and 51 of 58 (87.9%) for 12 months. Baseline participant characteristics are shown in Table 1. The median age was 2.3 years

TABLE 1 Baseline participant characteristics, variant types, and antiseizure medications.

Characteristic	Age group, years:months			
	0:6 to 2:0, $n=27$	2:1 to 3:6, $n=18$	3:7 to 5:0+, $n=13$	Total, $N=58$
Age, years, mean (SD) (minimum, maximum)	1.3 (.4) (.5, 2.0)	2.8 (.4) (2.2, 3.5)	4.3 (.5) (3.6, 4.9)	2.4 (1.3) (.5, 4.9)
Sex, *n* (%)				
Male	14 (51.9%)	7 (38.9%)	7 (53.8%)	28 (48.3%)
Female	13 (48.1%)	11 (61.1%)	6 (46.2%)	30 (51.7%)
Hispanic or Latino, *n* (%)				
Yes	4 (14.8%)	2 (11.1%)	2 (15.4%)	8 (13.8%)
No	23 (85.2%)	16 (88.9%)	11 (84.6%)	50 (86.2%)
Race, *n* (%)				
White	23 (85.2%)	14 (77.8%)	8 (61.5%)	45 (77.6%)
American Indian or Alaska Native	0	0	1 (7.7%)	1 (1.7%)
Asian	2 (7.4%)	2 (11.1%)	1 (7.7%)	5 (8.6%)
Black or African American	2 (7.4%)	0	0	2 (3.4%)
Other	1 (3.7%)	2 (11.1%)	3 (23.1%)	6 (10.3%)
Variant type, *n* (%)				
Truncating	22 (81.5%)	14 (77.8%)	5 (38.5%)	41 (70.7%)
Missense	5 (14.8%)	4 (22.2%)	8 (53.8%)	17 (25.9%)
Antiseizure medications, *n* (%)				
Clobazam	13 (48.1%)	10 (55.6%)	10 (76.9%)	33 (56.9%)
Valproic acid	16 (59.3%)	10 (55.6%)	5 (38.5%)	31 (53.4%)
Cannabidiol	11 (40.7%)	6 (33.3%)	8 (61.5%)	25 (43.1%)
Levetiracetam	15 (55.6%)	3 (16.7%)	4 (30.8%)	22 (37.9%)
Fenfluramine	6 (22.2%)	8 (44.4%)	7 (53.8%)	21 (36.2%)
Stiripentol	8 (29.6%)	6 (33.3%)	1 (7.7%)	15 (25.9%)
Topiramate	3 (11.1%)	2 (11.1%)	4 (30.8%)	9 (15.5%)
Clonazepam	3 (11.1%)	1 (5.6%)	0	4 (6.9%)
Ethosuximide	1 (3.7%)	2 (11.1%)	1 (7.7%)	4 (6.9%)
Perampanel	0	0	2 (15.4%)	2 (3.4%)
Amantadine	0	1 (5.6%)	0	1 (1.7%)
Cannabis sativa, nonpharmaceutical grade	0	0	1 (7.7%)	1 (1.7%)
Phenobarbital	0	0	1 (7.7%)	1 (1.7%)

(range = .5–4.9 years) and 46.6% of participants were younger than 2 years at Baseline. Truncating variants were identified in 70.7% of participants and pathogenic missense variants in 25.9%.

3.2 | Seizure burden

Median age at first seizure was 5.0 months (range = 2.0–10.0). The cohort had a median of three seizure types (range = 1–7). The most common seizure types at baseline were tonic–clonic (84.3%) and hemiclonic (83.0%). Tonic–clonic/clonic and focal motor seizures with clearly observable clinical signs (including hemiclonic seizures) occurred in >75% participants by age 1 year (Figure 1A). Myoclonic seizures, focal seizures without motor signs, and absence seizures were present in 50% of participants by age 4 years (Figure 1A). Seven (13.7%) participants had atonic seizures, and four (7.8%) had tonic seizures.

Seizure burden increased with age from a median (range) MCSF of 1.0 in the youngest (1.0–70.0) and middle (1.0–242.0) age groups to 4.5 (.0–2647.0) in the oldest age group (Figure 1B, Table S3), noting that the Month 3 visit was the first study visit with seizure diary data. Participants with extremely high seizure burden (>14 seizures and/or use of rescue medication on >4 days within a 28-day period) increased over time from 8/49 (16.3%) at Month 3 to 10/46 (21.7%) at Month 6 and 12/42 (28.6%) at Month 12. Participants with atonic seizures had particularly high seizure burden and overlapped with the extremely high seizure burden subset. At Month 12, median MCSF was 14.0 (range = 0.0–2549.0, $n = 27$) for those with atonic/tonic seizures compared with 2.2 (range = 0.0–100.0, $n = 18$) for those without.

Potential predictors of seizure frequency were examined using a mixed model with log-transformed MCSF. Age at the time of assessment was the only significant covariate (effect size = .52, $p = .024$); age at first seizure, sex, pathogenic variant type, and the number of Baseline ASMs were not predictive of seizure burden.

3.3 | ASM use

At Baseline, participants were taking a median of 3 ASMs (range = 0–7), which increased with age (3 in the youngest vs. 4 in the oldest age group). Clobazam (56.9%), valproic acid (53.4%), cannabidiol (43.1%), levetiracetam (37.9%), and fenfluramine (36.2%) were the most frequently used ASMs (Table 1). In the youngest group, fenfluramine and stiripentol were used in 22.2% and 29.6%, respectively,

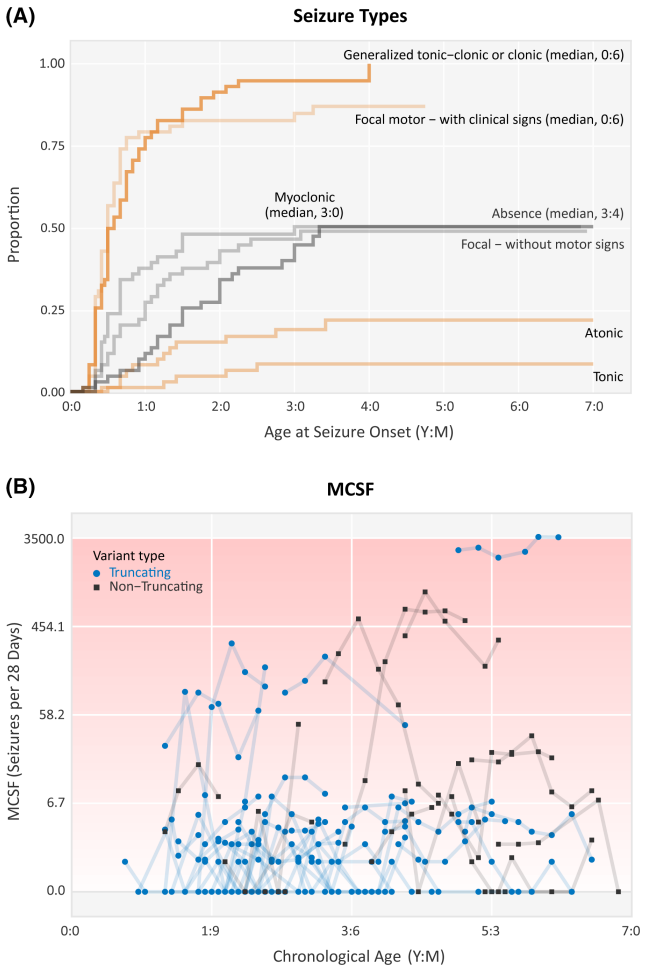


FIGURE 1 High seizure burden among young children with Dravet syndrome ($n = 58$). (A) Reversed Kaplan–Meier curves of seizure onset age by seizure type. Median age (years:months [Y:M]) of seizure onset (for each seizure type) is displayed when 50% of participants experience onset. (B) Monthly countable seizure frequency (MCSF), shown on a log scale. Longitudinal data from each individual participant are represented by a series of data points linked with connecting lines. Endpoints derived with <75% completeness (21/28 days) at each nominal visit are excluded. Ages are represented as Y:M.

often off-label. The most frequent combination (clobazam, stiripentol, and valproic acid) was used in 8 (13.8%) participants. Twelve participants (21%) were on the ketogenic diet at Baseline.

The mean number of days requiring rescue medication per 28 days was 1.4 (range = 0.0–15.0) at Month 3 and 1.5 (range = 0.0–11.0) at Month 12 (Table S5). Rescue medication days per 28 days was higher in the oldest (means ranged 1.9–2.8 across all visits) compared with the youngest (means ranged 0.9–1.3 across all visits) group. Seventy-four serious adverse events attributed to seizures were reported in 29 patients over the follow-up period.

3.4 | Language/communication outcomes

3.4.1 | BSID-III at Baseline

Using the BSID-III assessment, we observed language impairments at Baseline, particularly in children older than 2 years. Data for the oldest age group were limited due to BSID-III's intended administration age. Receptive and expressive language skills were similar, with raw scores of 16.1 (SD = 6.5) and 18.4 (SD = 8.3), respectively, and scaled scores of 5.4 (SD = 2.8) and 5.9 (SD = 3.4), compared with an expected normative score of 10.0 (range = 8.0–12.0; Table S6). The mean composite language score, which combines receptive and expressive, was 74.6 (SD = 16.6), against a normative mean score of 100 (SD = 15). Notably, a significant difference in mean composite language scores was seen between the youngest (79.0, SD = 15.9) and middle (62.0, SD = 11.9) age groups ($p = .003$); the middle age group scored >2 SD below the standard. Despite an average age of approximately 29 months at Baseline, the language skills in this cohort mirrored those of a neurotypical 13-month-old (mean language DQ = 58.5%, SD = 27.4).

3.4.2 | BSID-III longitudinal evolution in overall cohort

BSID-III language assessment showed limited acquisition of language skills over time. Whereas mean BSID-III receptive language raw scores increased by 2.1 points/year of chronologic age, the scaled scores decreased by .8 points/year (Figure 2A,B, Table S6). Likewise, mean BSID-III expressive language raw scores increased by 3.1 points/year of chronologic age ($p < .001$; Figure 2C), whereas scaled scores decreased by 1.1 points/year ($p = .012$; Figure 2D, Table S6). The modest increase in raw scores and decrease in scaled scores indicates slower language skill acquisition compared with neurotypical peers, meaning that participants with DS are falling further behind age-appropriate expectations. Person ability scores measured by GSEs revealed an average increase in receptive and expressive language of 13.2 and 24.1 points per year, respectively (Figure S3, Table S6). Language developmental age, as shown by AE scores, remained stagnant at around age 1 year, despite increasing chronologic age (Figure S2), which led to a drop in communication DQ from 58.5 (SD = 27.4) at Baseline to 50.5 (SD = 25.2) at Month 12.

3.4.3 | BSID-III longitudinal evolution by age groups

Examination by age revealed distinct patterns between participants ≤2 (youngest age group) and >2 years (middle age group) old at Baseline. In the youngest age group, mean raw scores for BSID-III expressive and receptive language both increased modestly over time (expressive language at Baseline [15.9, SD = 6.0] to Month 12 [19.3, SD = 7.2, mean delta = 3.5, 95% CI = 1.1–5.9]; receptive language at Baseline [17.8, SD = 8.8] to Month 12 [23.2, SD = 7.6, mean delta = 6.0, 95% CI = 3.1–8.8]). In the middle group, mean expressive language raw scores remained stagnant from Baseline (19.3, SD = 6.2) to Month 12 (17.5, SD = 6.2), but receptive language showed a nonsignificant decline in the middle age group from Baseline (17.1, SD = 8.2) to Month 12 (13.1, SD = 3.9). GSEs showed a significant increase in expressive (mean delta = 45.5 points, SD = 44.8, 95% CI = 26.1–64.9) and receptive language (mean delta = 24.7 points, SD = 49.4, 95% CI = 3.3–46.0) from Baseline to Month 12 in children <2 years old, but no significant change in those ≥2 years old (Table S6). These data indicate a lack of language skill acquisition, particularly after age 2 years. Mean DQ in the youngest group did not change significantly from Baseline (69.0%, SD = 25.2) to Month 12 (62.5%, SD = 20.8), whereas the middle age group showed severely impaired mean DQ at Baseline (39.3%, SD = 16.8) that worsened at Month 12 (24.7%, SD = 7.9). These findings indicate that, over a 1-year period, children <2 years old improved their language development by an AE of 6 months, whereas children ≥2 years old improved by only 1 month.

3.4.4 | VABS-III at Baseline

The VABS-III provides comprehensive understanding of communication abilities across the age range of study participants. At Baseline, mean raw score for the receptive communication subdomain (0 lowest to 78 total/best) was 34.9 (SD = 17.2) overall, with age-group means of 27.5 (SD = 16.4), 38.3 (SD = 16.1), and 46.3 (SD = 12.9) for the youngest, middle, and oldest age groups, respectively. Similarly, the mean raw score for the expressive communication subdomain (0 worst to 98 total/best) was 33.3 (SD = 18.3) overall, with age-group means of 23.7 (SD = 11.5), 37.8 (SD = 18.0), and 47.9 (SD = 19.4), respectively (Table S7). VABS-III communication raw scores showed no significant differences between the youngest, middle, and oldest groups (one-way analysis of variance, $p = .14$ for receptive and $p = .35$ for expressive communication), illustrating substantially slowed or halted skill acquisition. Composite communication scores showed

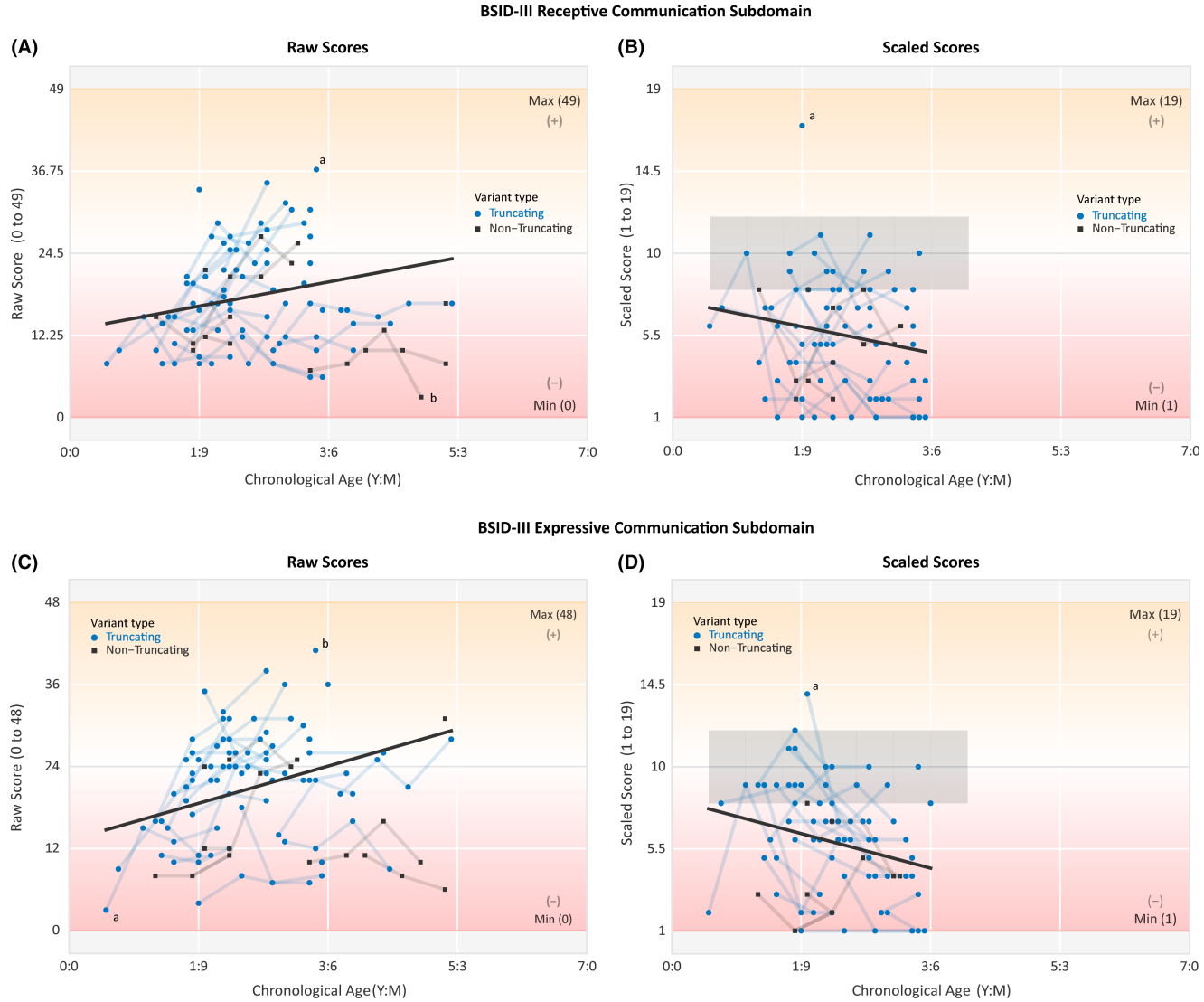


FIGURE 2 Bayley Scales of Infant and Toddler Development 3rd edition (BSID-III) language domain. (A) Receptive communication subdomain raw scores. A linear mixed model shows that scores increased by 2.1 points per year ($p = 0.006$). [a]The highest recorded score was 37 on a scale of 0 (minimum) to 49 (maximum) in a child at age 3:4 years:months (Y:M). [b]The lowest score was 3 in a child at age 4:9 Y:M. (B) Receptive communication subdomain scaled scores. A linear mixed model shows that scores decreased by .8 points per year ($p = .056$). [a]The highest recorded score was 17 on a scale of 1 (minimum) to 19 (maximum) in a child at age 1:9 Y:M. The gray shaded area denotes the normative range from 8 to 12 points. (C) Expressive communication subdomain raw scores. A linear mixed model shows that scores increased by 3.1 points per year ($p < .001$). [a]The lowest recorded score was 3 on a scale of 0 (minimum) to 48 (maximum) in a child at age 0:6 Y:M. [b]The highest score was 41 in a child at age 3:4 Y:M. (D) Expressive communication subdomain scaled scores. A linear mixed model shows that scores decreased by 1.1 points per year ($p = .012$). [a]The highest recorded score was 14 on a scale of 1 (minimum) to 19 (maximum) in a child at age 1:10 Y:M. The gray shaded area denotes the normative range from 8 to 12 points. Across all figures, higher scores (raw and scaled) are better (+) and lower scores are worse (−).

that prior to age 2 years, participants were comparable to neurotypical peers, but those ≥2 years old had substantial delays in communication. The mean composite communication score (normative mean = 100, SD = 15) for the entire cohort was 78.8 (SD = 16.0) and decreased with age: 89.1 (SD = 10.0), 71.8 (SD = 15.4), and 65.6 (SD = 13.0) for the youngest, middle, and oldest groups, respectively (Table S7). The difference between the middle and older cohorts was approximately 1 SD compared with neurotypical peers, indicating a growing disparity in their relative communication abilities over time.

3.4.5 | VABS-III longitudinal evolution in overall cohort

Mean raw scores for VABS-III receptive communication increased by 15.0 points/year before age 2 years then

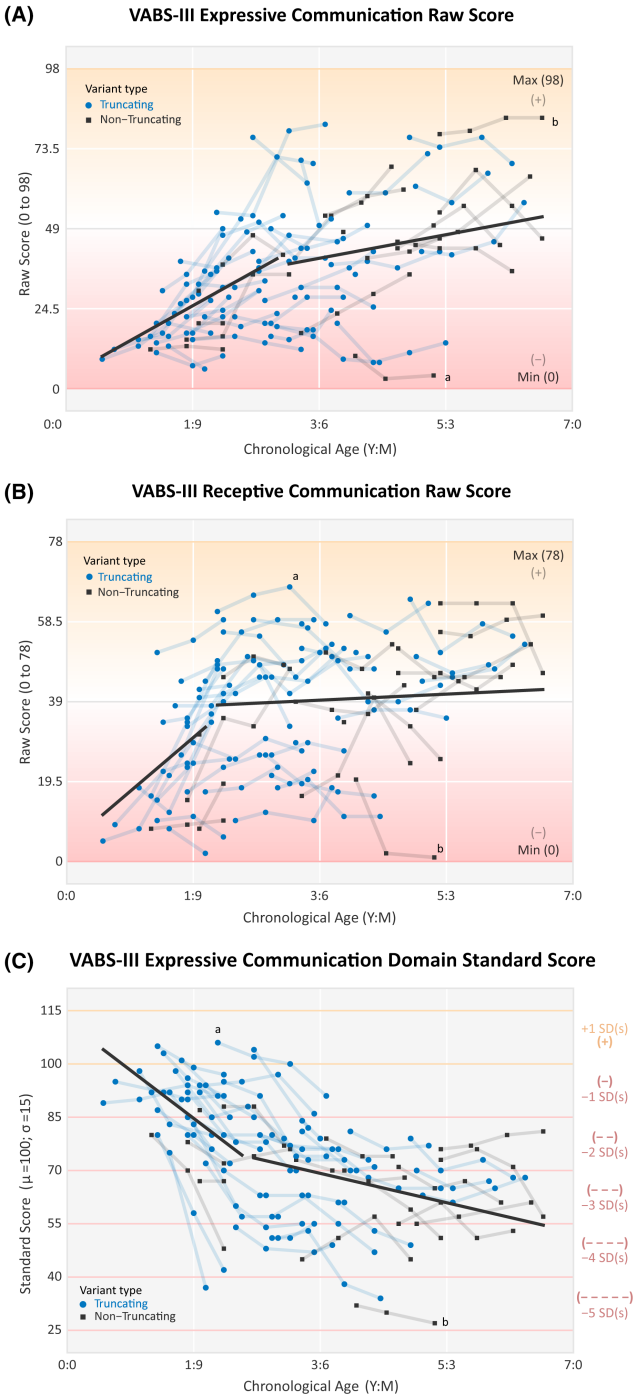


FIGURE 3 Vineland Adaptive Behavior Scales 3rd edition (VABS-III) communication domain. (A) VABS-III raw scores for expressive communication subdomain. A piecewise linear mixed model shows that scores increase by 12.4 points per year before age 3:0 years:months (Y:M; $p < .001$) and by 4.1 points per year afterward ($p = .001$). [a]The lowest recorded score was 3 on a scale of 0 (minimum) to 98 (maximum) in a child at age 4:5 Y:M. [b]The highest score was 83 in a child at age 6:1 Y:M. (B) VABS-III raw scores for the receptive communication subdomain. A piecewise linear mixed model shows that scores increase by 15.0 points per year before age 2:0 Y:M ($p < .001$) and by .8 points per year afterward ($p = .331$). [a]The highest recorded score was 67 on a scale of 0 (minimum) to 78 (maximum) in a child at age 3:1 Y:M. [b]The lowest score was 1 in a child at age 5:1 Y:M. (C) VABS-III communication domain standard score. A piecewise linear mixed model shows that scores decrease by 15.5 points per year before age 2:6 Y:M ($p < .001$) and by 4.7 points per year afterward ($p < .001$). [a]The highest recorded score was 106 in a child at age 2:1 Y:M. [b]The lowest score was 27 in a child at age 5:1 Y:M. Across all figures, higher scores (raw and standard) are better (+) and lower scores are worse (−).

slowed to .8 points/year (Figure 3A). Mean VABS-III expressive communication raw scores increased by 12.4 points/year before age 3 years and then decreased to 4.1 points/year (Figure 3B). Expressive and receptive language GSVs increased by an average of 4.7 (SD = 7.1, 95% CI = 2.7–6.8) and 4.0 points (SD = 12.5, 95% CI = .5–7.6) from Baseline to Month 12, respectively. However, 7.7% of participants showed a decline of >1 SD in receptive language GSVs, whereas 53.8% had no significant change (Table S7).

Mean standard scores in the communication domain (normative mean = 100, SD = 15) decreased from Baseline (78.8, SD = 16.0) to Month 12 (69.5, SD = 16.6, mean delta = −8.5, 95% CI = −11.3 to −5.7). Over 1 year, mean scores decreased by a full SD prior to age 3.5 years (15.5 points/year; Figure 3C), with all participants decreasing >1 SD below the normative mean (<85 points) after age 3.5 years. A distinct pattern of language development over time was observed in 5 participants with expressive communication normalized scores >1 SD higher than their receptive scores. Only 1 participant with this unique language development was noted to have neurodevelopmental problems (features of ADHD or ASD) at Baseline. There was no difference in the VABS-III communication mean standard score at any time point between participants receiving or not receiving fenfluramine (Table S4).

3.4.6 | VABS-III longitudinal evolution by age groups

VABS-III receptive and expressive communication raw scores showed limited gains that slowed progressively after age 2 years (Figure 3A,B). For the youngest group, the mean receptive communication raw score increased from 27.5 (SD = 16.4) at Baseline to 38.3 (SD = 16.1) at Month 12 (mean delta = 9.8, 95% CI = 5.7–13.9), and expressive scores increased from 23.7 (SD = 11.5) to 35.5 (SD = 17.0, mean delta = 11.8, 95% CI = 6.8–16.7). For the middle age group, mean receptive communication raw

scores decreased slightly from 38.3 (SD = 16.1) at Baseline to 35.1 (SD = 16.0) at Month 12. In the oldest, expressive communication raw scores remained relatively unchanged from Baseline (mean = 47.9, SD = 19.4) to Month 12 (mean = 50.8, SD = 25.2). GSV increases from Baseline to Month 12 were most prominent in the youngest for both receptive (mean delta = 10.4, SD = 9.9) and expressive (mean delta = 7.8, SD = 7.0) language (Table S7). Those younger than 2:6 showed an average increase of 13.5 points/year for receptive and 8.6 for expressive language, with skill acquisition plateauing afterward (Figure S3). When considering normalized standard scores, the communication gap with respect to neurotypical children widened over time. The youngest group's mean communication domain standard scores declined significantly from 89.1 (SD = 10.0) at Baseline to 77.5 (SD = 16.3) at Month 12 (mean delta = −13, 95% CI = −17.7 to −8.4). The middle age group's scores decreased from 71.8 (SD = 15.4) to 62.7 (SD = 11.9), and the oldest group's scores remained low from Baseline (65.6, SD = 13.0) to Month 12 (61.6, SD = 13.0; Table S7).

3.5 | Correlations and predictors

A strong positive correlation was observed between the receptive and expressive language/communication subdomain raw scores within each and across both BSID-III and VABS-III assessments (R^2 ranged from 77% to 84%; Figure 4A). The correlation between normalized scores on the VABS-III communication domain and BSID-III language domain was relatively high at 77%. Unsurprisingly,

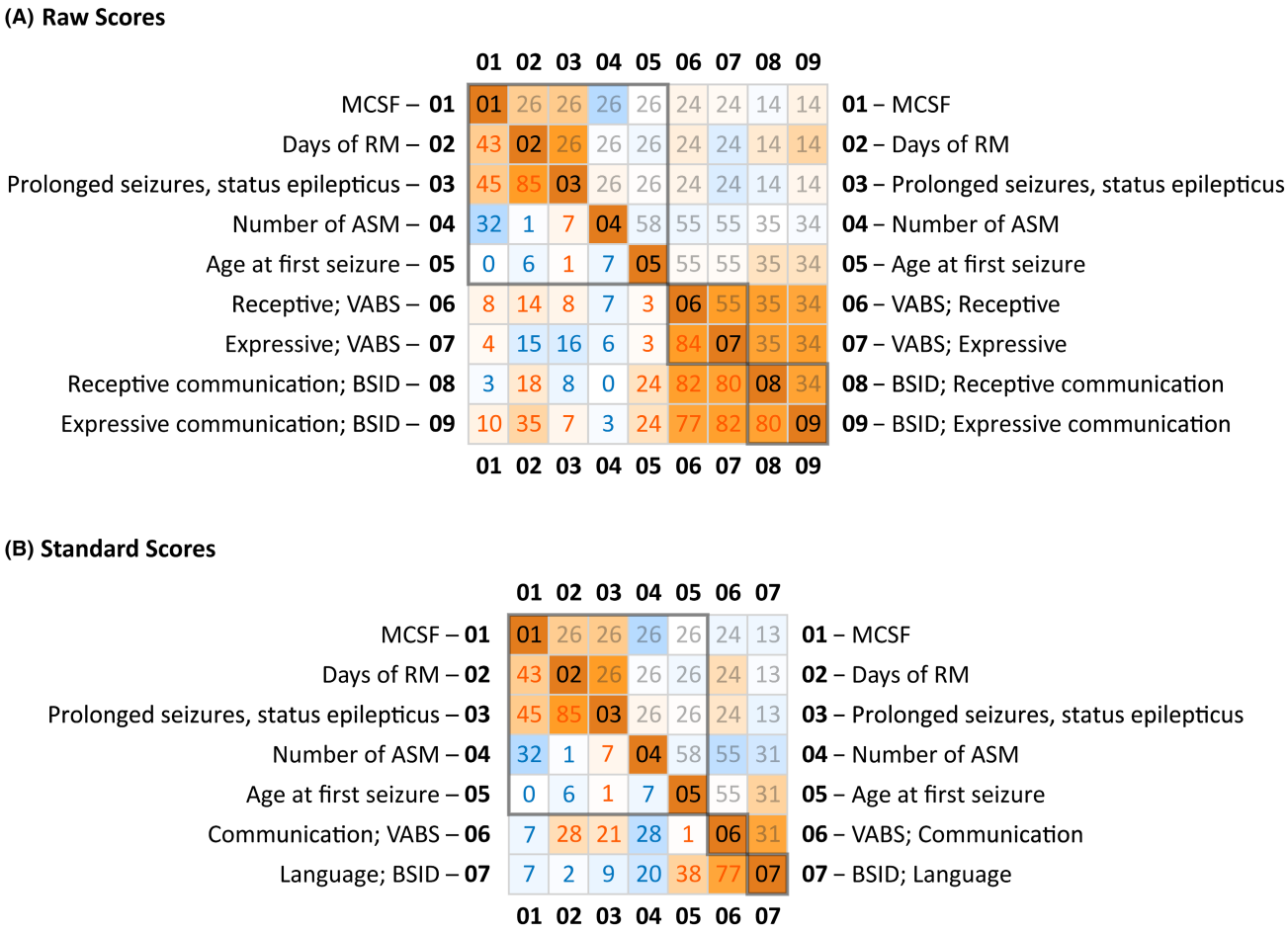


FIGURE 4 Pearson correlation analysis of language and communication assessments with seizure assessments. (A) Raw scores. (B) Standard scores. ASM, anti-seizure medications; BSID, Bayley Scales of Infant and Toddler Development; MCSF, monthly countable seizure frequency; RM, rescue medication; VABS, Vineland Adaptive Behavior Scales. Pairwise Pearson correlations observed between baseline characteristics and select assessment scores are visualized as colored boxes in a stacked matrix. Darker shades of orange and blue indicate correlations closer to 1 and −1, respectively. Correlation coefficients are superimposed on boxes in the lower half of the matrix; for example, an orange 54 implies a positive correlation of 54%; a blue 23 implies a negative correlation of 23%. Gray numbers on boxes in the upper half of the matrix indicate the number of data points going into each pairwise correlation calculation. The boxes on the diagonal of the matrix are marked by bold numbers corresponding to the assessment tool variable ID numbers, for ease of visualization.

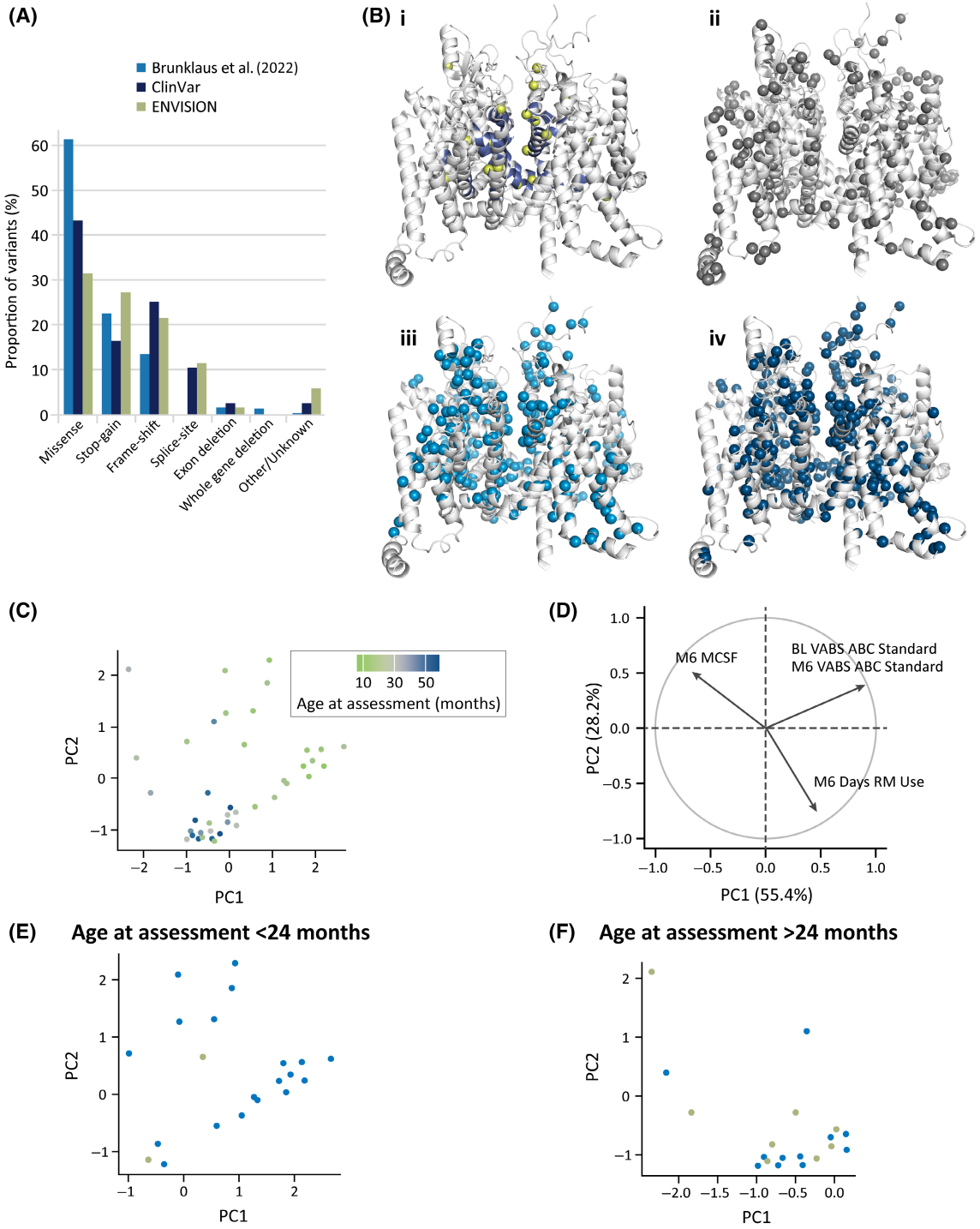
there was a strong correlation (R^2 =85%) between prolonged seizures/status epilepticus counts and days of rescue medication use. Weak positive correlations were observed between age at first seizure and BSID-III language composite scores (R^2 = 38%; Figure 4B) and BSID-III expressive language raw scores and days of rescue medication use (R^2 = 35%; Figure 4A). There were no other notable relationships between seizure activity (rescue medication days, MCSF, number of antiseizure medications, age at first seizure, prolonged seizure/status epilepticus) and language/communication raw scores (Figure 4A) or normalized scores (Figure 4B) from BSID-III or VABS-III.

Mixed-effects models were used to further quantify the impact of various seizure-related covariates on language sequelae. The only significant predictor for the VABS-III communication domain standard score was age (−17.1 [$p < .001$] points/year and −3.7 [$p = .002$] points/year before and after age 2.5 years, respectively). Age at seizure onset, sex, type of genetic variant, MCSF, and ASMs (clobazam, valproic acid, cannabidiol, and fenfluramine) were not significant predictors of norm-referenced scores on the VABS-III. When examining VABS-III expressive and receptive communication separately, similar results were observed. For expressive communication, age (increase by 11.6 points/year [$p < .001$] and 4.4 points/year [$p = .005$] before and after age 3 years, respectively) and use of clobazam (−13.9 points/year, $p = .03$) were the only significant variables. For receptive communication raw scores, only age showed a significant effect (increase by 9.9 points/year [$p < .001$] and 1.5 points/year [$p = .109$] before and after age 2 years, respectively).

We tested whether genetic variant type explained the heterogeneity in clinical phenotype seen among individuals with DS at the molecular level. The ENVISION cohort displayed a slightly lower proportion of missense variants (26%) in contrast to the previous largest DS genetic study[20] and the variants documented in the ClinVar database[27,30] (Figure 5A,B).

To identify differences in clinical presentation by variant type, we only analyzed participants with complete medical data. Due to the myriad of clinical assessments available for our cohort, we applied PCA to distill information. This approach reduced the correlated phenotypic evaluations in our cohort into two overarching scores: principal component 1 (PC1) and principal component 2 (PC2). Together, these scores accounted for 83.6% of the clinical presentation variance of DS determined by the selected assessments (see Materials and Methods). The conversion of many phenotypes into two representative variables (PC1 and PC2) enabled investigation of phenotypic similarity and differences among all patients on a two-dimensional scatterplot (Figure 5C). When exploring whether genetic variant type led to clear phenotypic divisions among participants, a separation became evident in the PC1 domain when comparing carriers of truncating versus missense variants (Figure 5C). PC1 also correlated with age at enrollment, and carriers of missense variants were older. After adjusting for age, the phenotypic difference between groups was not significant (Figure 5D). Likewise, mixed models showed that genetic variant types had no significant effect on communication/language outcomes.

FIGURE 5 Comparative analysis of genetic variant types in Dravet syndrome: distribution, phenotypic variation, and clinical significance. (A) Comparison of *SCN1A* variant distribution among multiple datasets: variant types among participants screened in ENVISION (70 individuals) compared with Brunklaus et al.[20] (1018 individuals) and the ClinVar database (likely) pathogenic variants (1421 variants).[21] All variants other than those labeled as Missense or Other/Unknown are considered truncating variants. (B) Visualization of *SCN1A* missense variants from multiple cohorts on the protein structure (7dtd): (i) ENVISION cohort (green) + essential three-dimensional sites (blue); (ii) population variants (gnomAD database); (iii) Brunklaus cohort[20]; (iv) ClinVar (likely) pathogenic variants. (C) Phenotypic spectrum correlated with age at assessment. The phenotypic spectrum was linked to the age at which children were assessed. Utilizing principal component analysis (PCA), phenotypic variability across individuals and clinical assessments was condensed into two principal components: PC1 and PC2. Participants with similar phenotypic attributes are grouped within these components. The PCA includes four consistent parameters observed across all 41 participants: Baseline (BL) Vineland Adaptive Behavior Scales (VABS) Adaptive Behavior Composite (ABC) standard, Month 6 (M6) monthly countable seizure frequency (MCSF), M6 days of rescue medication (RM) use, and M6 VABS ABC standard. The observed phenotypic differences can be attributed to variation in the age of assessment. Notably, PC1 exhibits a significant correlation with the age at onset (Pearson correlation −.46, $p = .002$). (D) Parameter impact on PCs. This segment visualizes the directional impact of specific clinical variables on PC1 and PC2. Both BL VABS ABC standard and M6 VABS ABC standard are highly correlated, with a primary effect on PC1 scores. An increase in PC1 values is indicative of higher ABC standard scores. Conversely, elevated M6 MCSF scores correspond to a reduction in PC1 values. The M6 days RM use parameter dominantly influences PC2 values. An increase in M6 days RM use is associated with a decline in PC2 values. (E, F) No phenotype differences between missense and protein truncating variants are observed when corrected for age at seizure and neurocognitive assessments. (E) Individuals with an age at assessment of <24 months; most individuals carry a truncating variant. (F) Individuals with an age at assessment of >24 months; individuals carry missense (green) and truncating variants (blue). No clear separation of individuals by variant type is observed in either of the two age at assessment cohorts.



4 | DISCUSSION

This analysis of the ENVISION study provides contemporary, prospective data that underscore the persistent seizure burden and progressively worsening language/communication impairment in young children with DS, despite treatment with the current standard of care.[31]

Data on DS outcomes are important for evaluating the ongoing health needs of these children, particularly in the context of recently approved ASMs for DS (i.e., fenfluramine, cannabidiol, and stiripentol). Our predictive modeling suggests that the current standard of care with ASMs approved for DS has little to no impact on language/communication outcomes. With potential disease-modifying therapies on the horizon, these data identify optimal therapeutic windows and relevant outcome measures for clinical trials, and provide valuable context to interpret the magnitude of potential treatment effects.

The ENVISION cohort comprises participants harboring *SCN1A* pathogenic variants and the prototypical DS

phenotype. Given the scarcity of contemporary and prospective data in infants and young children living with DS, the cohort was enriched for children aged <2 years at Baseline to improve understanding of features related to the onset and evolution of DS from early life.[14] Stratification across three age groups (0:6–2:0, 2:1–3:6, 3:7–5:0 years:months) revealed that developmental trajectory was already impacted by 2 years of age, and clear differences compared with neurotypical peers were observed after age 3 years.

While seizure burden was heterogenous in ENVISION, MCSF generally increased with age from infancy up to 7 years of age and remained high, despite the use of currently approved ASMs.[31] Moreover, children with DS who had atonic seizures also had an extremely high seizure burden. Atonic seizures are not frequently reported to be associated with DS, occurring in only 22% of individuals.[17] In ENVISION, children with and without atonic seizures did not show any significant difference in language/communication scores, suggesting atonic seizures are not a negative predictor for language development in DS.

Language/communication delays in DS grow with increasing age, negatively impact socialization and learning, and are a source of serious concern to families.[9,15,16] These delays were observed early in ENVISION, and developmental stagnation after age 2 years occurred consistently across assessment instruments. The pattern of stagnation was similar for both receptive and expressive language, highlighting the global nature of the delay. Interestingly, in some children, the VABS-III scores showed an aberrant pattern of language development, with expressive scores exceeding receptive language scores. This may be the result of caregiver bias in the interpretation of expressive language and should be studied further with clinician-administered instruments.

The predominant pathophysiologic theory for DS (interneuron hypothesis) posits that haploinsufficiency of $Na_V1.1$ results in selective deficits in inhibitory interneuron function due to relative reliance of these interneurons on $Na_V1.1$ for action potential generation.[32,33] Additional mechanistic theories include complex network dysfunction including hyperexcitable corticohippocampal circuits,[33] dorsal-stream vulnerability,[34] and a sensorimotor–cerebellar framework.[12] In ENVISION, the early onset of language/communication deficits supports the presence of complex network dysfunction. Future ENVISION analyses of other DS features will explore this further.

The ENVISION study highlights that developmental delay and functional impairment in DS are evident in most children by age 2 years. The ability to communicate not only impacts short- and long-term outcomes like socialization,[35,36] education, and safety for these children, but also has a persistent and growing impact on their ability to integrate into society and live independently. These data suggest that disease-modifying therapies aimed at preventing or limiting cumulative deficits in receptive and expressive language/communication should aim to treat children with DS earlier than age 3 years to optimize potential therapeutic benefit. Additionally, these data support early neurodevelopmental interventions, such as early intervention programs, to help manage developmental delays in DS.

Baseline characteristics, including gene variant type, were not predictive of seizure burden or language/communication outcomes. Moreover, children's language development fell further and further behind age expectations independently of seizure burden, in contrast to prior reports.[37] Both correlation and predictive modeling analyses suggested that seizure burden alone cannot determine neurodevelopmental outcomes in young children with DS. The absence of a correlation between seizure burden and language development contrasts with previous reports linking DS manifestations to the frequency of convulsive seizures.[38] This disparity may stem from the younger age of the ENVISION cohort and use of currently approved treatments that effectively reduce the frequency of convulsive seizures, prolonged seizures, and status epilepticus. Consequently, this limits potential secondary impacts on language development, unlike older studies and cohorts. Additionally, the prospective nature of the ENVISION data allows for more accurate seizure counts and highlights potential differences in the analysis of seizure burden across studies. Notably, this study focuses specifically on language development, rather than global or visuomotor development, which has been previously shown to correlate with persistent seizures.[39] These findings indicate that in children with DS, regardless of gene variant type, the underlying pathophysiologic mechanism(s) affects neurodevelopmental outcomes from an early age. Although early use of appropriate ASMs may improve the seizure phenotype in young children, they do not appear to meaningfully impact neurodevelopmental outcomes. Further work is necessary to determine the extent of potential associations or interdependencies between seizure frequency and neurodevelopmental outcomes in DS, particularly in the context of emerging disease-modifying therapeutic strategies for this channelopathy.[1]

Limitations of the ENVISION study include lack of race/ethnicity diversity, the relatively short time frame for measuring changes in language/communication development, and use of parent-reported versions of the VABS-III instrument (instead of the semistructured interview) and seizure diary, which rely on parent compliance and classification of seizure type. Nonetheless, ENVISION adds prospectively collected data—at four time points over the course of 1 year—to our knowledge about development

in children with DS from a relatively large patient cohort with >40% of participants aged <2 years at enrollment.

5 | CONCLUSIONS

Prospective data from the ENVISION natural history study of infants and young children with *SCN1A*+ DS demonstrate that language/communication development delay and stagnation occur independently of seizures. To ensure the best possible results for children and families with DS, it may be ideal to administer disease-modifying therapies before the child reaches 3 years old. This may help prevent or address language and communication delays at an early stage, maximizing the potential benefits of the treatment.

AUTHOR CONTRIBUTIONS

M. Scott Perry: Conceptualization (lead); writing–original draft (lead); data curation (equal); study design (lead). **Ingrid E. Scheffer:** Conceptualization (supporting); writing–original draft (supporting); study design (lead). **Joseph Sullivan:** Study design (supporting); writing–review and editing (equal). **Andreas Brunklaus:** Study design (lead); writing–review and editing (equal). **Susana Boronat:** Data curation (equal); writing–review and editing (equal). **James W. Wheless:** Data curation (equal); writing–review and editing (equal). **Linda Laux:** Study design (supporting); writing–review and editing (equal). **Anup D. Patel:** Data curation (equal); writing–review and editing (equal). **Colin M. Roberts:** Data curation (equal); writing–review and editing (equal). **Dennis Dlugos:** Study design (supporting); writing–review and editing (equal). **Deborah Holder:** Data curation (equal); writing–review and editing (equal). **Kelly G. Knupp:** Data curation (equal); writing–review and editing (equal). **Matt Lallas:** Data curation (equal); writing–review and editing (equal). **Steven Phillips:** Data curation (equal); writing–review and editing (equal). **Eric Segal:** Data curation (equal); writing–review and editing (equal). **Patricia Smeyers:** Data curation (equal); writing–review and editing (equal). **Dennis Lal:** Statistical analysis (supporting); writing–review and editing (equal). **Elaine Wirrell:** Study design (supporting); writing–review and editing (equal). **Sameer Zuberi:** Study design (supporting); writing–review and editing (equal). **Tobias Brünger:** Statistical analysis and visualization (supporting); writing–review and editing (equal). **Mary Wojnaroski:** Data curation (equal); writing–review and editing (equal). **Benit Maru:** Data curation (equal); writing–review and editing (equal). **Penrose O'Donnell:** Data curation (equal); writing–review and editing (equal). **Magda Morton:** Data curation (equal); writing–review and editing (equal). **Emma James:** Writing–original draft (supporting); data curation (equal); writing–review and editing (equal). **Maria Candida Vila:** Writing–original draft (lead); data curation (equal); writing–review and editing (equal). **Norman Huang:** Data curation (lead); statistical analysis and visualization (lead); writing–review and editing (equal). **Jacqueline S. Gofshteyn:** Conceptualization (lead); writing–original draft (lead); data curation (equal); supervision (lead); writing–review and editing (equal). **Salvador Rico:** Conceptualization (lead); data curation (lead); writing–original draft (lead); study design (lead).

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CONFLICT OF INTEREST STATEMENT

M.S.P. has received support for speaking engagements from Zogenix/UCB, NobelPharma, and Marinus; for consulting from Zogenix/UCB, Biocodex, Stoke Therapeutics, Marinus, Bright Minds, Eisai, Jazz Pharmaceuticals, and Neurelis; and for research (paid to institution) from Zogenix/UCB, Stoke Therapeutics, Encoded Therapeutics, Neurocrine, and Takeda Pharmaceutical Company. I.E.S. has received support for serving on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, RogCon, Takeda Pharmaceutical Company, UCB, Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, LivaNova, Nutricia, Zuellig Pharma, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, BioMarin, Encoded Therapeutics, and Eisai; has served as an investigator for Anavex Life Sciences, Cerecin, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder, Epygenyx, ES Therapeutics, GW Pharma, Marinus, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceutical Company, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and Zynerba; has consulted for Care Beyond Diagnosis, Epilepsy Consortium, Atheneum Partners, Ovid Therapeutics, UCB, Zynerba Pharmaceuticals, BioMarin, Encoded Therapeutics, and Biohaven Pharmaceuticals; and is a nonexecutive director of Bellberry and a director of the Australian Academy of Health and Medical Sciences and the Australian Council of Learned Academies. She may accrue future revenue on pending patent WO61/010176 (filed 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics and licensed to various diagnostic companies; and has a patent Molecular Diagnostic/Theranostic Target for Benign Familial Infantile Epilepsy (BFIE) [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012–009). J.S. has received support for contracted research from Zogenix, UCB, Stoke Therapeutics, Bio-Pharm Solutions, Encoded Therapeutics, Xenon Pharmaceuticals, Neurocrine Biosciences, and Takeda Pharmaceutical Company; for consulting from Epilepsy Study Consortium, Greenwich Biosciences, Epygenix Therapeutics, Marinus Pharmaceuticals, Bright Minds, Longboard, Praxis, CAMP4, Rapport, Locanabio, Ceribell, and Cerecin; and for participation on a data safety monitoring board for NeuroPace. He holds restricted stock units in Epygenix Therapeutics. He serves as a board member and Medical Advisory Board member for the Dravet Syndrome Foundation and as Chair of the Scientific Advisory Board for PCDH19 Alliance. A.B. has received honoraria for presenting at educational events, serving on advisory boards, and consultancy work for Biocodex, Jazz/GW Pharmaceuticals, Encoded Therapeutics, Stoke Therapeutics, Nutricia, and UCB/Zogenix. S.B. has received speaking honoraria from Jazz Pharmaceuticals and has served as a paid consultant on advisory boards for Biocodex and UCB. J.W.W. has received grant support from Shainberg Foundation, TSC Alliance, Neuro Event Labs, NIH, Envision, Xenon, Stoke Therapeutics, Neurelis, Marinus, Epiwatch, UCB, Longboard, SKLSI, and Biohaven; support for speaker's bureau from LivaNova, Eisai, Supernus, Jazz Pharmaceuticals, UCB, Neurelis, BioMarin, SKLSI, and Azurity; and consulting fees from Jazz Pharmaceuticals, Neurelis, Marinus, BioMarin Consultant, and Azurity. L.L. has served as a consultant for Biocodex and participated in research that includes the following: GW Pharma, Zogenix, Biocodex, Stoke Therapeutics, Encoded Therapeutics, Epygenix therapeutics, Xenon, Praxis, Neurocrine, and Ovid Therapeutics. A.D.P. has received institutional research support from Encoded, Stoke Therapeutics, NIH, and PCORI. D.D. has received salary support for research from the Epilepsy Study Consortium and the Pediatric Epilepsy Research Foundation and is an investigator on research grants awarded to his institution from Encoded Therapeutics. K.G.K. has received research funding from Zogenix, Encoded, Eisai, and West Pharmaceuticals; has participated on data and safety monitoring boards for GW Pharmaceuticals and Epygenix; and has received consulting fees from BioMarin, Zogenix, Encoded, Eisai, Stoke Therapeutics, and Biocodex. M.L. is a paid consultant for Jazz Pharmaceuticals. E.S. is a consultant for Neurelis, GW Pharmaceuticals, Encoded Pharmaceuticals, Aquestive, and UCB and a speaker for Neurelis, GW Pharmaceuticals, Lundbeck, Eisai, Aquestive, UCB, and Novartis. D.L. has received consulting fees from Encoded. E.W. has received support for serving on data and safety monitoring boards for Acadia, Amicus, Neurocrine, Longboard, and Encoded; she has also received funding to her institution as a site investigator for Stoke Therapeutics, Marinus, and Takeda Pharmaceutical Company. 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Pharmaceuticals, and Encoded Therapeutics. M.W. has served as a paid consultant for Autism Speaks. P.O. is a consultant for Encoded Therapeutics. B.M. is employed by SSI Strategy and has received consulting fees from Encoded Therapeutics. M.M., E.J., M.C.V., N.H., J.S.G., and S.R. are employees of Encoded Therapeutics. None of the other authors have any conflict of interest to disclose.

PATIENT CONSENT STATEMENT

Signed informed consent was obtained from the parents or legal guardians of all individual participants included in the study.

CLINICAL TRIAL REGISTRATION

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SUPPORTING INFORMATION

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

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