Cross-validation of the Vineland-3 with Independent Assessments of Cognition and Adaptive Skills in CLN3 Disease

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Background

CLN3 disease is an autosomal-recessively inherited, childhood-onset neurodegenerative lysosomal storage disorder, caused by mutations in the CLN3 gene on chromosome 16p12.

Symptoms begins between 4-6 years of age. Clinical features include early and profound vision loss, cognitive and motor impairments, dementia, seizures, and premature death in the second or third decade of life.

There are no approved disease modifying therapies as yet for CLN3 disease. The Unified Batten Disease Rating Scale (UBDRS) is a reliable, valid, NCL-specific tool for evaluating symptoms and function. However, there are few other few specific measures to characterize how affected patients "feel and function".

Aim

To determine associations among potential outcome assessments to evaluate function in CLN3 disease:

Clinician-Reported: UBDRS Capability scale
Observer-Reported: Vineland Adaptive Behavior Scales-Third edition (Vineland-3)
Performance Assessment: (NPT) Neuropsychological assessment battery

Methods

We identified individuals enrolled in our natural history study, who had each completed the UBDRS, Vineland-3, and NPT concurrently.

UBDRS Capability scores based on actual vision (range=0-14) and Physical function score (range=0-112) were calculated; higher scores indicate greater impairment or symptom severity.

Composite scores (defined in results section) for global cognitive and language function were constructed by calculating the average of the z scores (mean = 0, sd = 1) for selected NPT tasks.

Bivariate correlations among the variables were evaluated, and the multiple R was assessed to determine how well cognitive performance was predicted by the linear combination of clinician-based assessment (UBDRS) and parent report (Vineland-3).

Sample Characteristics

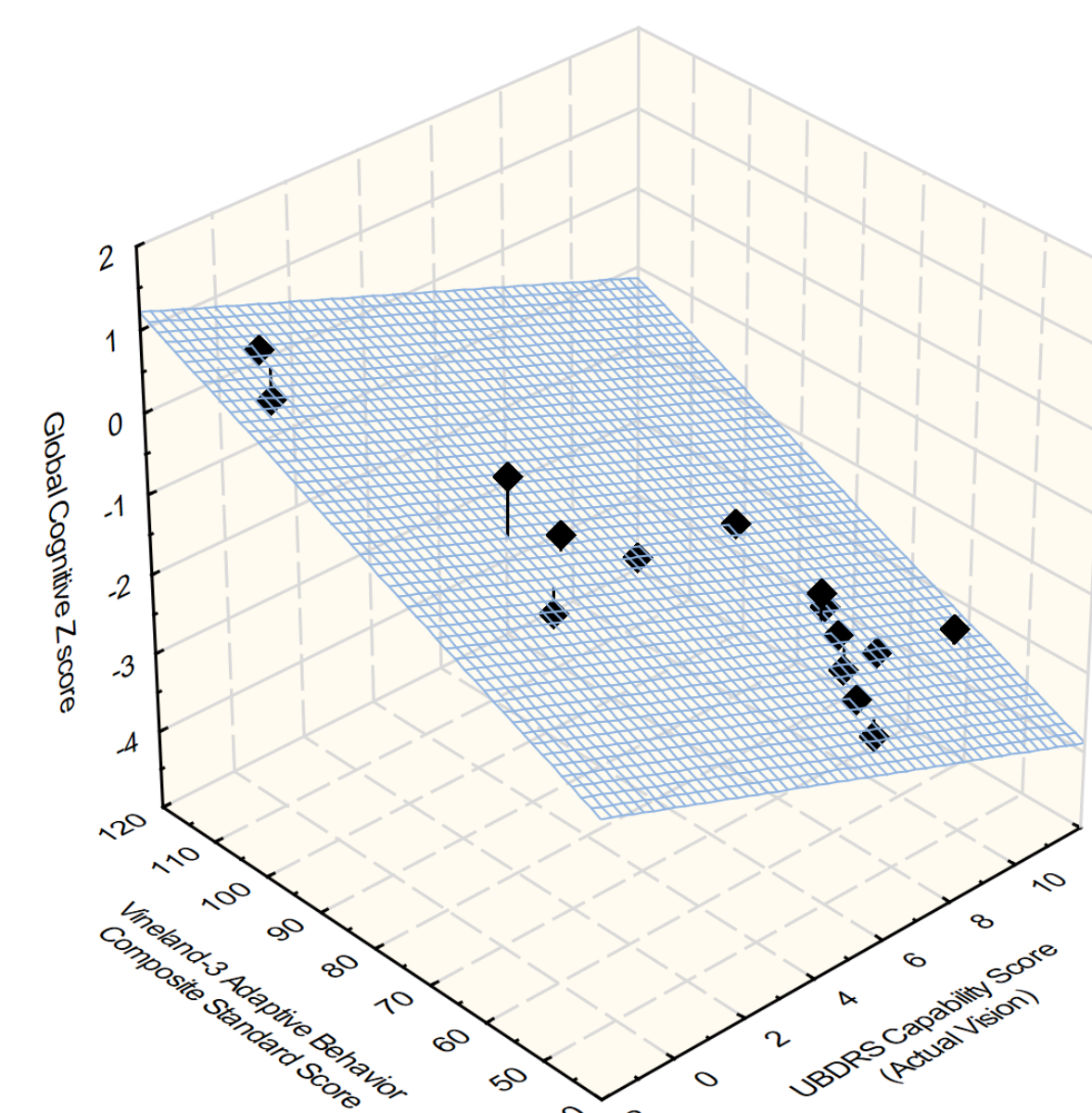N = 20 individuals with genetically confirmed CLN3 disease
- 9 males / 11 females
- N = 19 with vision loss (ranging from mild to severe [blind])
- N = 4 with repeat (two) Vineland-3 assessments

	UBDRS	Vineland-3	NPT
n=17	X	X	X
n= 3	X	X	

	Mean	SD	min	max
Age	13.46	5.15	3.00	25.00
Vineland-3 ABC Composite	66.55	21.70	20.00	112.00
UBDRS Capability	5.85	3.64	0.00	11.00
Global Cognitive Z score	-1.59	1.27	-3.00	0.67

Cognitive test performance, Parent-rated adaptive function, and Clinician-rated capability are highly inter-correlated (R^2 = .94)

Prediction of Cognitive Function by UBDRS Capability x Vineland-3
Capability-Actual:ABCSS:GlobalCogZ: Multiple R(z/xy) = 0.9693, p = 0.00000
GlobalCogZ = -3.2454-0.1681*x+0.0344*y

Bivariate correlations (Pearson r)

|	ABC	Cog
Cog	.93**	
Cap	-.81*	-.91**

*p <.01; **p <.001

Cog = Global Cognitive Z Score (Cog)
Cap = UBDRS Capability Score
ABC = Vineland-3 Adaptive Behavior Composite Score

Global Cognitive Z Score: Average of the z scores for selected Wechsler subtests: Vocabulary, Similarities, Information, Digit Span Forward, Digit Span Backward

Modest declines in adaptive function in affected individuals

Vineland-3 Adaptive Behavior Composite (ABC) and Domain Scores: First (t1) and Second (t2) Assessments
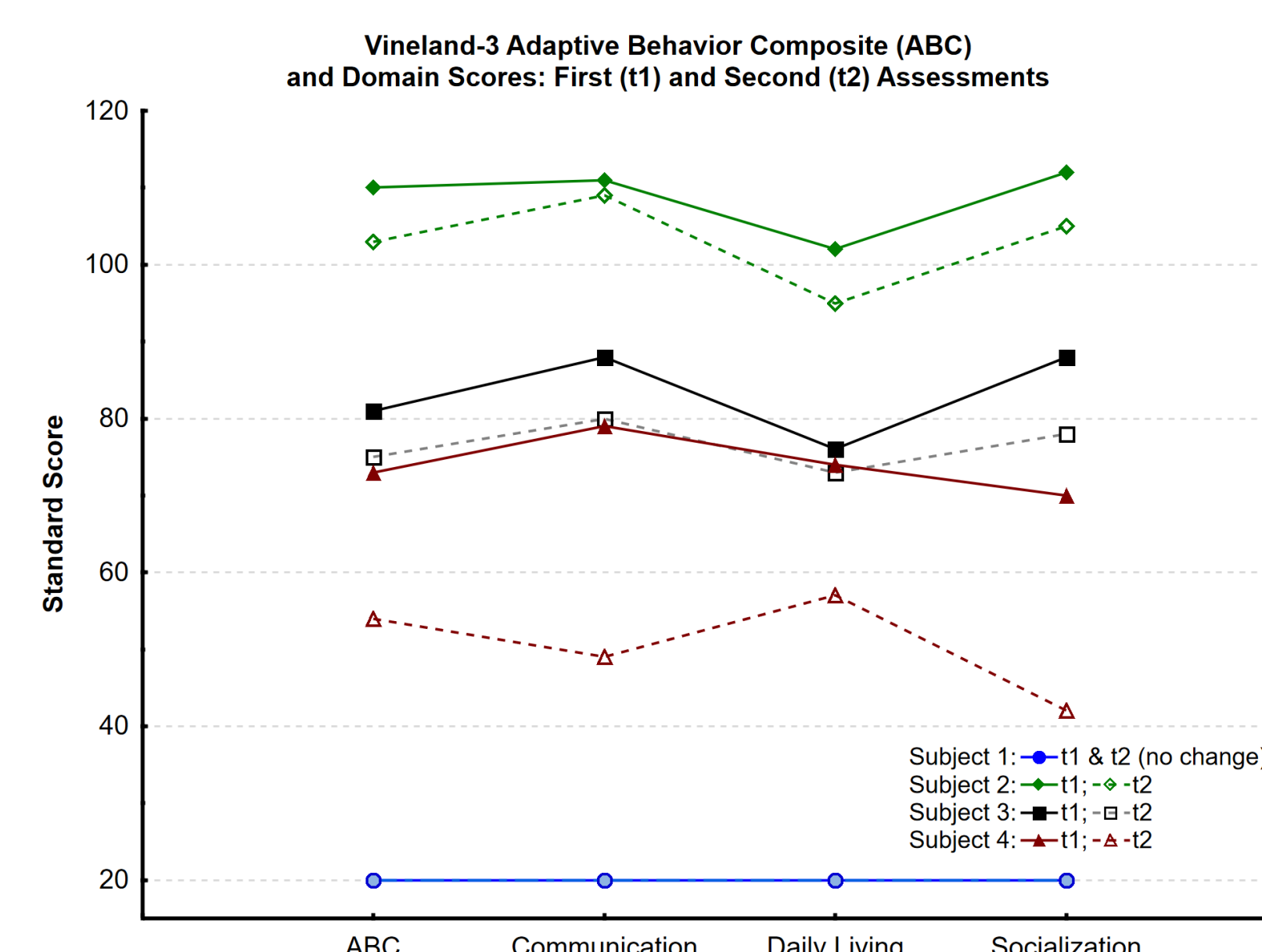
- First (t1) and second (t1) assessments for 4 subjects with repeat Vineland-3 forms
- Subject #1 is at floor of measure; no change x 10 mos.
- Subjects #2, #3, #4: change x 6 mos.
- Age-adjusted Standard Scores: mean=100, sd = 15

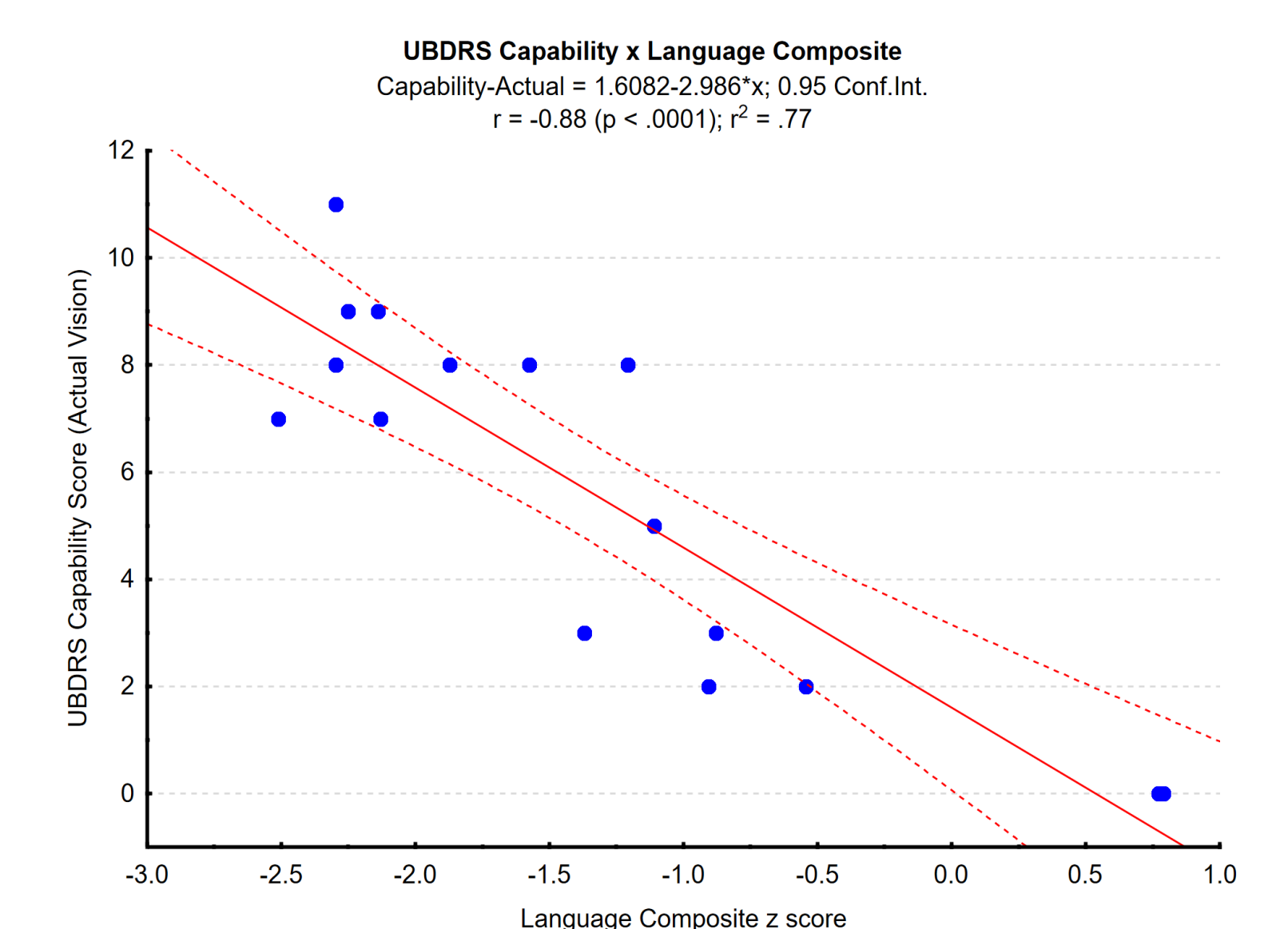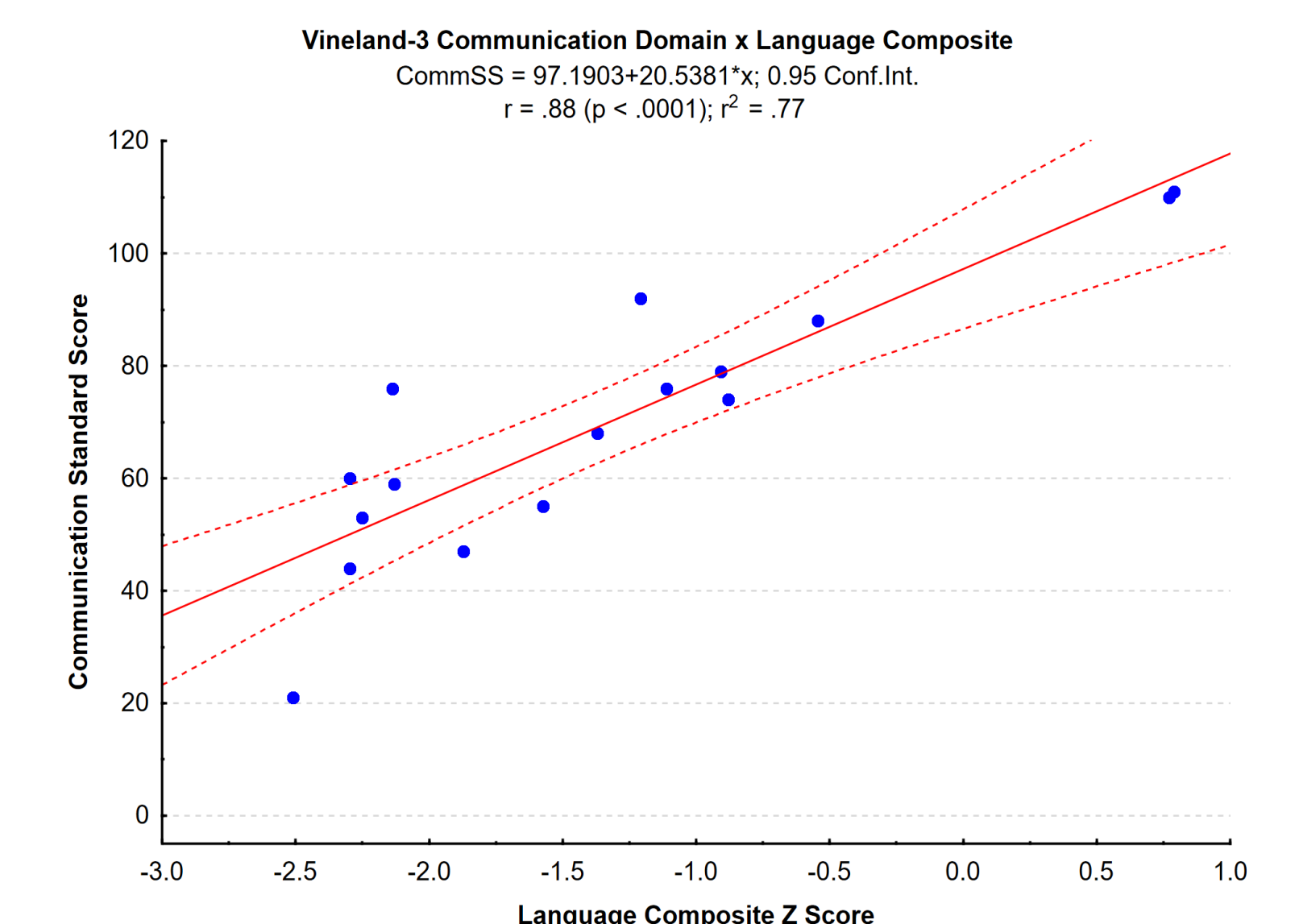| Subject Age (in years)	
	Time 1 – Time 2
Subject 1	25.2 – 26.0
Subject 2	11.6 – 12.1
Subject 3	14.8 – 15.2
Subject 4	11.5 – 12.0

- GSVs are used to track _within-subject_ changes over time in Vineland-3 Sub-domains.
- Growth Score Values (GSVs) are not norm-referenced but higher scores indicate greater capability. GSV Scores range from 10-197
- Changes in GSVs from 1st to 2nd assessment are significant at p<.05 (2tailed)

Vineland-3 Growth Score Value Change (over 6-10 months)

Significant changes, Time 1 to Time 2 (p < .05):
Subject 1: Play & Leisure
Subject 2: Receptive, Expressive, Interpersonal Relationships, Coping Skills
Subject 3: All subdomains _except_ Expressive
Subject 4: Expressive, Written, Domestic
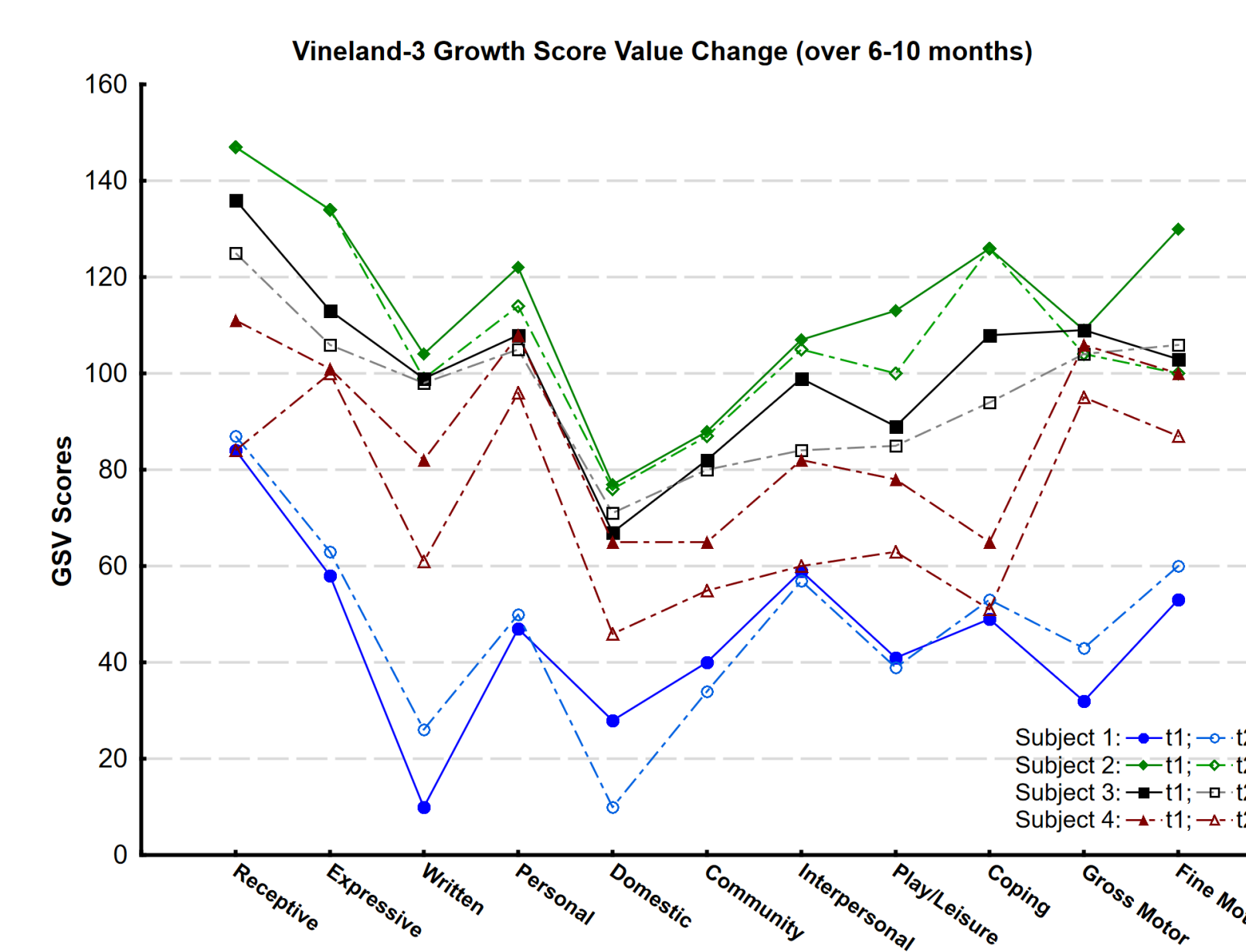
Composite Language score correlates well with independent ratings of communication skills (parent report) and overall capability (clinician rating)

Vineland-3 Communication Domain x Language Composite
CommSS = 97.1903+20.5381*x; 0.95 Conf.Int.
r = .88 (p < .0001); r² = .77

UBDRS Capability x Language Composite
Capability-Actual = 1.6082-2.986*x; 0.95 Conf.Int.
r = -.88 (p < .0001); r² = .77

Language composite score: Average of the z scores for WRAML-2 Sentence Recall, Verbal Fluency, and Wechsler subtests: Similarities, Vocabulary

Discussion

There is high concordance among three different assessments of function in CLN3 disease, distinguished by different methods and informants.

The UBDRS, a disease-specific assessment of symptoms and function for NCL disorders, correlates well with clinical gold-standard assessments of cognition, language, and adaptive function.

The Vineland-3 Adaptive Behavior Scales may be sensitive to broad (Domain) and specific (sub-Domain) changes in adaptive function over a relatively short period of time.