

Association Between NPC Severity Score Domains and Corresponding Items of the Performance-based Scale for the Assessment and Rating of Ataxia (SARA)

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Background

- Niemann-Pick disease type C (NPC), (estimated 1:100,000 live births), presents and progresses heterogeneously with motor function loss and impairments in coordination, swallowing, speech and cognition, causing serious morbidity and reduced life expectancy.
- The NPC Clinical Severity Scale (NPCCSS), a disease-specific, clinician-reported outcome measure quantifies disease progression. Initially 17 domains, a 5-Domain version (5DNPCCSS) was developed, focusing on core symptoms; Ambulation, Speech, Fine Motor Skills, Swallow and Cognition. This tool has been extensively validated.^{1,2}
- The 5DNPCCSS was the primary endpoint used to evaluate NPC progression in the arimoclomol NPC-002 trial (ClinicalTrials.gov: NCT02612129).³
- The SARA test (Scale for Assessment and Rating of Ataxia) was a secondary endpoint. This cerebellar ataxia-related impairment scale consists of 8 items⁴, 6 of which can be matched and compared with related 5DNPCCSS domains (see **Table 1**).

Purpose

- To investigate correlations between relevant 5DNPCCSS domains and corresponding SARA test items to potentially provide further supportive evidence for 5DNPCCSS validity as a tool for evaluating NPC progression.

Methods and Statistics

- 50 children, 2-18 (mean 11.1) years with ≥ one neurological symptom, recruited to NPC-002, were included. Neurological symptom onset: 1 patient (2%) classified pre-/perinatal, 8 (16%) early infantile, 17 (34%) juvenile.
- Applicable 5DNPCCSS domains and corresponding SARA test items are shown in **Table 1**.
- The association between pooled 5DNPCCSS and SARA scores, collected for arimoclomol and placebo at Months 0, 6 and 12, was assessed using Polychoric and Spearman correlations (**Table 2**).
- Correlation heat maps and kernel plots illustrate score correlations and distributions between the two scales.
- Correlation Heat Maps (Figure 1):** Absolute baseline scores for SARA items and corresponding 5DNPCCSS domains pooled across treatments (arimoclomol and placebo) are shown on the x- and y-axis, respectively.
 - The patient frequency (count) for each score pair is shown inside map tiles and visualized by tile color.

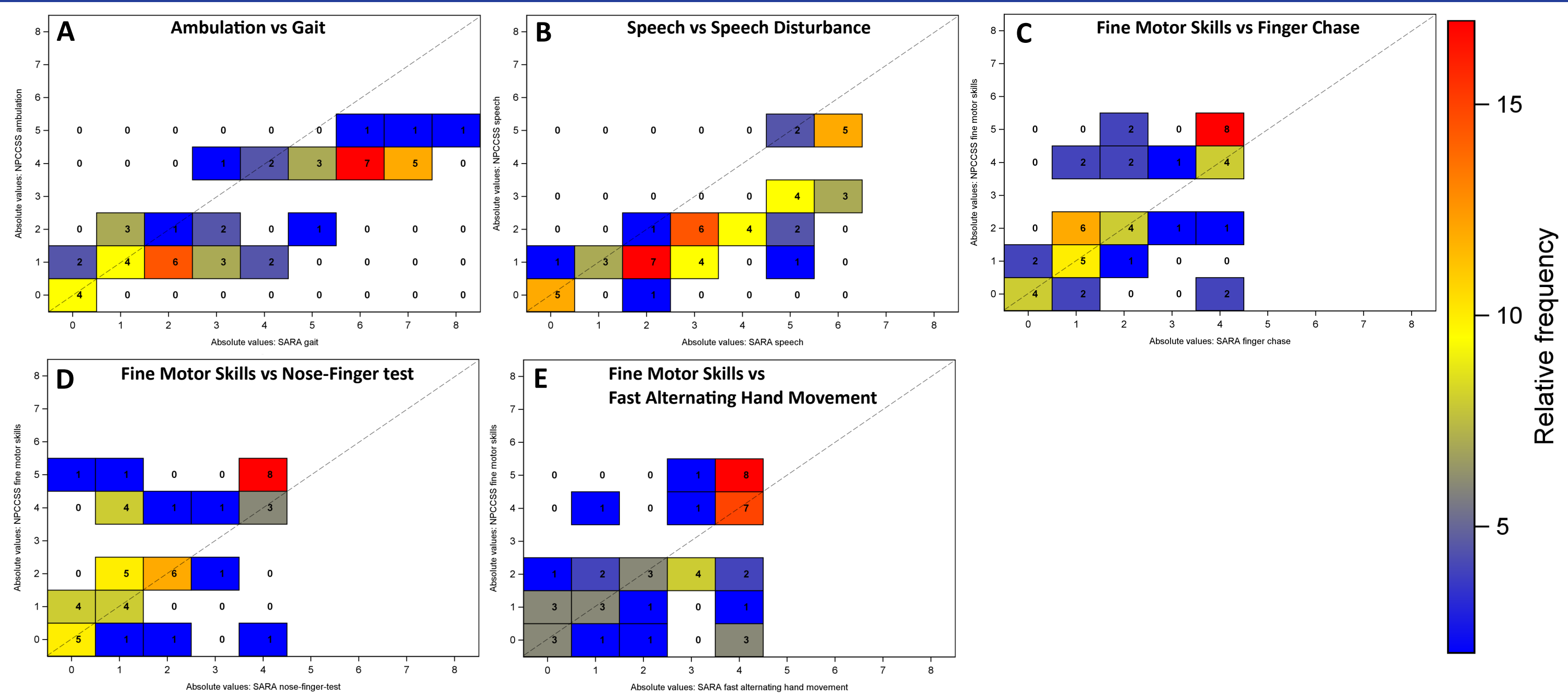
- Kernel Plots (Figure 2):** Pooled 5DNPCCSS and SARA scores for arimoclomol and placebo collected at Months 0, 6, and 12 were normalized by dividing each score with the maximum possible score per respective scale item/domain. The number of bins was set to 6 to match the discrete 0-5 point range of each 5DNPCCSS domain.

Table 1: Overview of Matched 5DNPCCSS Domains and SARA Test Items

5DNPCCSS Domain	SARA Test Item
Ambulation	Gait, Heel-Shin Slide
Speech	Speech Disturbance
Fine Motor Skills	Finger Chase, Nose-Finger Test, Fast Alternating Hand Movements

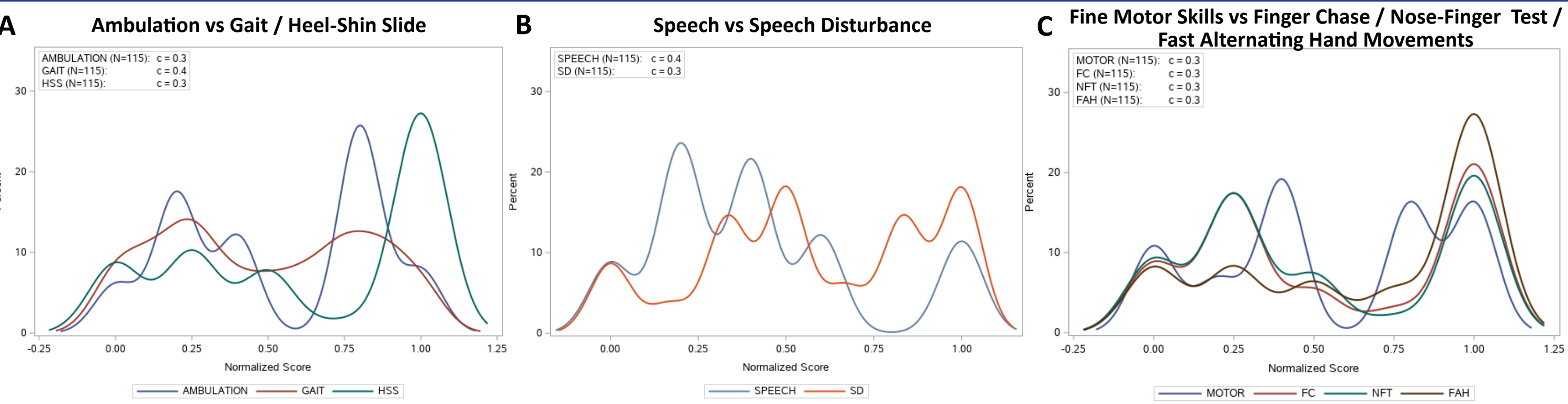
Results

Figure 1: Correlation Heat Maps of Absolute Baseline (Month 0) Scores for 5DNPCCSS Domains and Corresponding SARA Test Items



- The heat maps (**Figure 1A-E**) generally support the correlations found in Polychoric and Spearman correlation analyses (see **Table 2**): most high-frequency cells lie on the diagonal indicating good correlation between the two scales. Results for Months 6 and 12 were similar (not shown).
- Kernel Plots (**Figure 2A-C**) show comparable score distributions between 5DNPCCSS domains and corresponding SARA items providing further support for the moderate to strong correlations between the two scales (pooled scores across both treatments and Months 0, 6 and 12).
- Table 2** shows the results of Polychoric and Spearman correlations that demonstrate moderate to strong correlations between 5DNPCCSS domains and corresponding SARA test items.

Figure 2: Kernel Plots Comparing Distributions of Normalized Scores of Matched 5DNPCCSS Domains and SARA Test Items



HSS: Heel-Shin Slide; SD: Speech Disturbance; MOTOR: Fine Motor Skills; FC: Finger Chase; NFT: Nose-Finger Test; FAH: Fast Alternating Hand Movements. Includes data from combined treatments/visits.

Results (Cont.)

Table 2: Correlations Between 5DNPCCSS Domains and Corresponding SARA Test Items

5DNPCCSS Domain vs SARA Test Item	Month	n	Polychoric Correlation Coefficient	Spearman Correlation Coefficient
Ambulation vs Gait	0	49	0.91	0.85
	6	44	0.97	0.92
	12	41	0.94	0.90
Speech vs Speech Disturbance	0	49	0.94	0.89
	6	44	0.99	0.94
	12	41	0.97	0.92
Fine Motor Skills vs Finger Chase	0	47	0.74	0.66
	6	43	0.85	0.76
	12	40	0.93	0.85
Fine Motor Skills vs Nose-Finger Test	0	47	0.71	0.62
	6	43	0.85	0.76
	12	40	0.88	0.81
Fine Motor Skills vs Fast Alternating Hand Movements	0	46	0.67	0.58
	6	43	0.82	0.73
	12	40	0.82	0.76

Correlations are based on scheduled visits and include records obtained after onset of escape medication. n: number of patients contributing with data.

Conclusions

- Correlations performed between individual 5DNPCCSS domains and corresponding performance-based SARA test items showed strong associations and alignment between the two instruments for all analysis methods used.
- These results provide further support that the evaluated 5DNPCCSS domains are appropriately standardized to allow for reliable and reproducible scoring of disease severity in NPC patients.

References

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