Comparative Analysis of Validated Measures of Cognitive, Behavioral, and Motor Impairments in a Pediatric Population of Neurofibromatosis Type 1

Lindsey E. Aschbacher-Smith MS[1], David A. Huddleston MBA[1], Karlee Migneault BS[1], Kim M. Cecil PhD[1], James Leach MD[1], Mark DiFrancesco PhD[1], Nancy Ratner PhD[1], Brittany N. Simpson MD[1], Elizabeth K. Schorry, MD[1], Carlos E. Prada MD[2], Donald L. Gilbert MD MS[1] 1Cincinnati Childrens Hospital and University of Cincinnati College of Medicine, 2Lurie Children's Hospital, Chicago

PURPOSE

To establish brain-based, objective measures that reflect severity of cognitive, behavioral, and motor impairments in Neurofibromatosis Type 1 (NF1) as outcome measures for clinical trials.

BACKGROUND

In Neurofibromatosis Type 1 (NF1), a genetic disorder affecting 1 in 2,000 individuals, approximately 50% of children exhibit impaired executive function, learning, and/or motor function. Currently, assessing severity of these problems involves subjective rating scales. This impedes accurate measurement of responses to potential therapeutics. We hypothesized that objective brain-based techniques such as Transcranial Magnetic Stimulation (TMS) and MRI-based measures would correlate with clinical assessments.

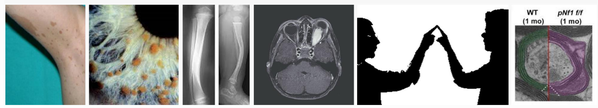

Figure 1: Manifestations: A) Café au Lait Macules; B) Lisch Nodules; C) Osseous Lesions; D) Optic Pathway Glioma and other tumors; E) Impaired coordination; F) Myelin Decompaction

MATERIALS AND METHODS

We assessed behavior, executive function, and motor development using standardized scales and tests. We measured inhibition and excitation in left motor cortex and biochemical (neurotransmitter/metabolite) concentrations in anterior cingulate cortex. We explored associations between clinical assessments and brain measures using Spearman Correlations.

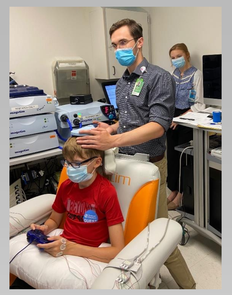

Figure 2: Transcranial Magnetic Stimulation (TMS)

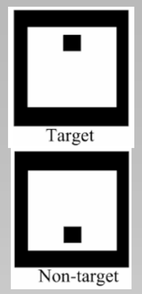

Figure 3: Test of Variables of Attention (TOVA)

RESULTS

Demographics (n=25)	
Age	8-16 range, 12.4 mean, 3.0 S.D.
Sex	12 Female
Race	23 Caucasian, 2 African American
Ethnicity	25 non-Hispanic

Correlations between Behavior Rating Inventory of Executive Function (BRIEF) Scores and Motor Thresholds

	Executive Function		Behavioral Regulation		Metacognition	
	r	p	r	p	r	p
TMS: Resting Motor Threshold	0.74	0.001	0.62	0.014	0.76	0.001

Poor executive function (ADHD, BRIEF scores, and Tests of Visual Attention (TOVA) scores) correlated with both impaired motor development (PANESS scores) and TMS measures of motor cortex excitability.

CONTACT

Donald.Gilbert@cchmc.org
Lindsey.Aschbacher-Smith@cchmc.org

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Motor Function and ADHD characteristics

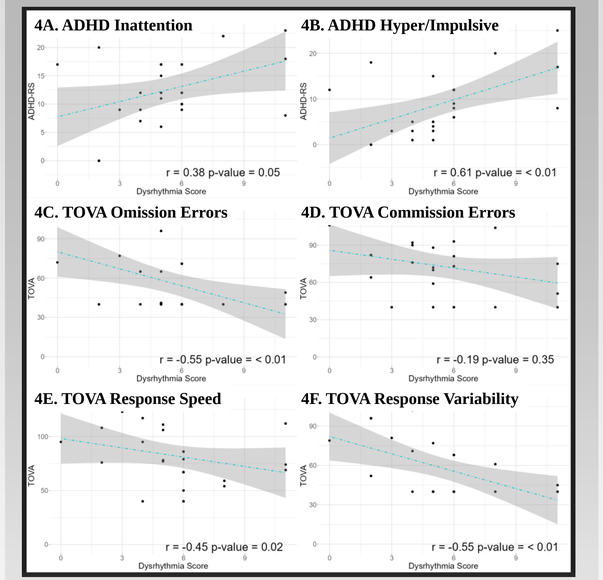

Figure 4: Finger movement dysrhythmia correlates with more severe ADHD symptoms (4A, 4B) and worse function on Test of Visual Attention (4C, 4E, 4F). All correlations nonparametric Spearman. P values exploratory, not corrected for multiple comparisons. Dysrhythmia a sub score component of the PANESS.

CONCLUSIONS

Quantitative, objective brain-based TMS, motor development assessments, and executive function scales can improve assessment of cognitive, behavioral, and motor impairments in children with NF1 and strengthen therapeutic trials.