A Longitudinal Study of Cognitive Function in Classical Homocystinuria (HCU) Demonstrates Distinct Deficits in Inhibitory Control

Benjamin Goodlett[1], Sagar A. Vaidya[2], Feriandas Greblikas[2], Ying Chen[2], Marcia Sellos-Moura[3], Mehul Shah[2], Lionel Pinto[2], Harvey Levy[1]

[1]Boston Children's Hospital, Boston, MA; [2]Travere Therapeutics, San Diego, CA; [3]Newbury Biopharma Group, West Newbury, MA

RESULTS

Table 1. Demographics and Baseline Characteristics

- Sixty-two patients with HCU were enrolled as of 15 JUL 2021 (52% male; age range 5-53 years; 94% white) and had a median of 5 visits over 3.3 years

	Pediatric (N=30)	Adult (N=32)	Total (N=62)
Age (years), mean (SD)	10.3 (3.5)	33.0 (9.9)	22.0 (13.7)
Age group, n (%)			
5 to 11 years	18 (60.0)	0	18 (29.0)
12 to 17 years	12 (40.0)	0	12 (19.4)
18 to 65 years	0	32 (100.0)	32 (51.6)
Gender, n (%)			
Male	15 (50.0)	17 (53.1)	32 (51.6)
Female	15 (50.0)	15 (46.9)	30 (48.4)
Race, n (%)			
White	29 (96.7)	29 (90.6)	58 (93.5)
Black or African American	1 (3.3)	2 (6.3)	3 (4.8)
Not Provided	0	1 (3.1)	1 (1.6)
Baseline homocysteine level (µM), mean (SD)*	89.1 (81.1)	129.4 (96.2)	109.6 (90.6)
Concomitant medications, n (%)			
Betaine	22 (73.3)	24 (75.0)	46 (74.2)
Vitamin B6	25 (83.3)	15 (46.9)	40 (64.5)
Metabolic formula	16 (53.3)	10 (31.3)	26 (41.9)

*Pediatric, N=27; Adult, N=28; Total, N=55.
SD, standard deviation.

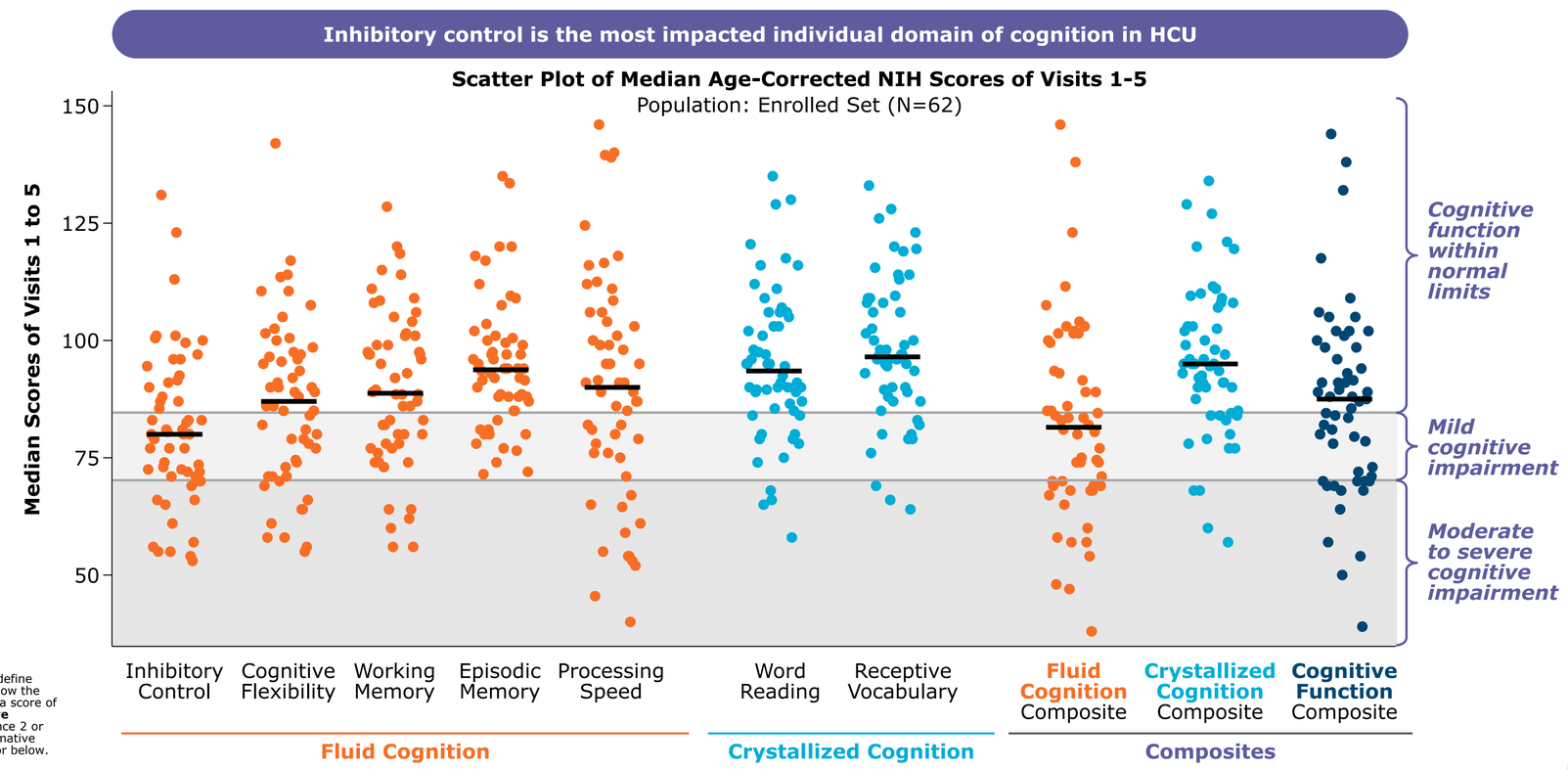
Table 2. Intra-class Correlation Coefficient (ICC) for NIHTB-Cognition Battery

- Intra-class correlation (ICC) scores indicated a high level of stability in cognition scores across the study period
- Higher ICC values mean greater stability in scores. The data below generally mean that the scores were very stable over time (5 visits).

Individual Domain Scores	ICC Value
Fluid Cognition	
Inhibitory Control	0.81
Cognitive Flexibility	0.71
Working Memory	0.74
Episodic Memory	0.60
Processing Speed	0.74
Crystallized Cognition	
Word Reading	0.83
Receptive Vocabulary	0.74
Composite Scores	**ICC Value**
Fluid Cognition Composite	0.82
Crystallized Cognition Composite	0.86
Cognitive Function Composite	0.90

Figure 2. Median NIHTB-Cognition Battery Individual Domain and Composite Scores of Visits 1-5

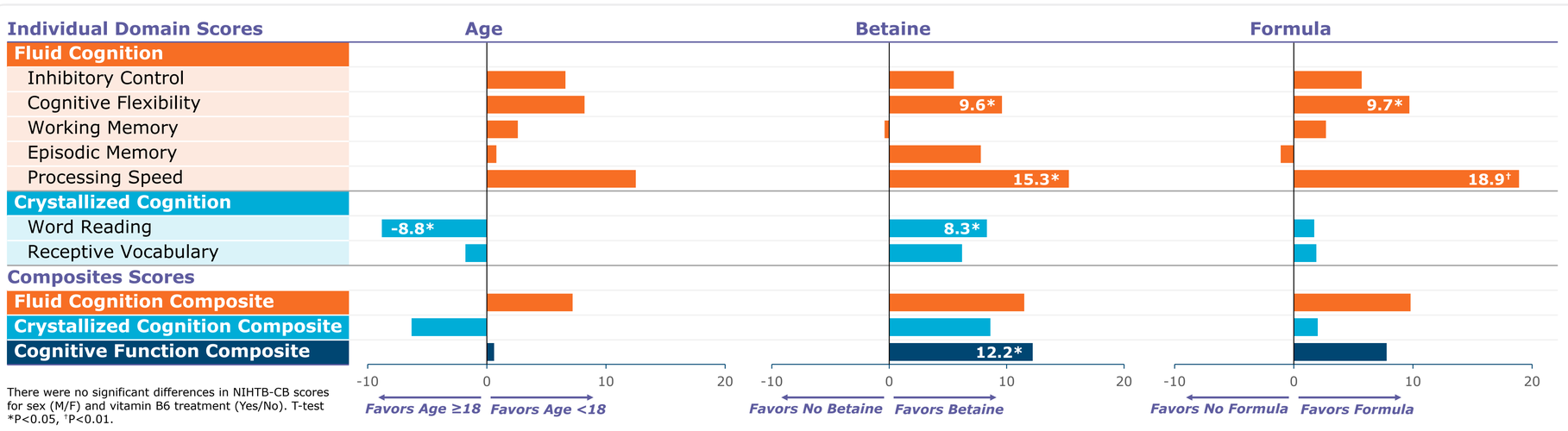
- Overall cognition was found to be impaired in HCU patients with a cognitive function composite mean score of 86.8 (SD=20.00)
- Large differences were observed in cognitive performance between subdomains, with the greatest deficit in inhibitory control (mean=81.0, SD=16.47), while receptive vocabulary was nearly normal (mean=98.0, SD=15.49)



Mild cognitive impairment is used to define performance 1-2 standard deviations below the normative sample which corresponds to a score of 85 to 71. **Moderate to severe cognitive impairment** is used to define performance 2 or more standard deviations below the normative sample, corresponding to a score of 70 or below.

Figure 3. Mean Difference in NIHTB-CB Scores for Cognitive Performance by Age and Treatment with Betaine or Formula

- Concomitant treatment with betaine or formula was associated with significantly higher cognition scores in several subdomains, as well as the mean cognitive function composite (no betaine versus betaine, 77.3 and 89.5, respectively, p=0.012)



There were no significant differences in NIHTB-CB scores for sex (M/F) and vitamin B6 treatment (Yes/No). T-test *P<0.05, †P<0.01.

CONCLUSIONS

- This is the first study to examine cognitive deficits in classical homocystinuria (HCU) patients longitudinally using the NIH Toolbox Cognition Battery (NIHTB-CB)
- This study confirms that HCU still leads to substantial cognitive deficits despite current standard-of-care treatment provided in key academic centers
- Intra-class correlation coefficient (ICC) analysis indicated that cognitive scores were stable over the period studied. The expectation from these results translates to stability in cognition over ~2 years.
- Subdomain analysis of the NIHTB-CB demonstrated the greatest deficit in inhibitory control
- Subgroup analyses showed that betaine and formula treatment were associated with higher cognitive scores (eg, cognitive flexibility), indicating that these domains may be more responsive to treatment
- These results suggest there are unique areas of cognition affected by HCU as measured by the NIHTB-CB and provide support for focused evaluation and treatment

DISCLOSURES

BG, MSM: Consultant, Travere Therapeutics. **SV, FG, YC, MS, LP:** Employees and stockholders, Travere Therapeutics. **HL:** Investigator and consultant, Travere Therapeutics, Inc.

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INTRODUCTION

- Classical homocystinuria (HCU) is a slowly progressive genetic disease due to mutations in the *cystathionine beta-synthase* (*CBS*) gene, which leads to elevated homocysteine in the body[1]
- HCU is characterized by developmental delay/ intellectual disability, ectopia lentis and/or severe myopia, skeletal abnormalities (excessive height and length of the limbs), and thromboembolism[1]
- Neuropsychiatric abnormalities are common in HCU; however, the presentation is variable[2]
- Although there exists a solid foundation of research in HCU establishing its impact on intellectual functioning, previous studies were cross-sectional and focused on overall summary scores
- Additional evaluation of the impact of HCU on cognitive function over time and on subdomains of cognition is important to further inform our understanding of how HCU affects the day-to-day lives of patients and how to design potential new treatment options

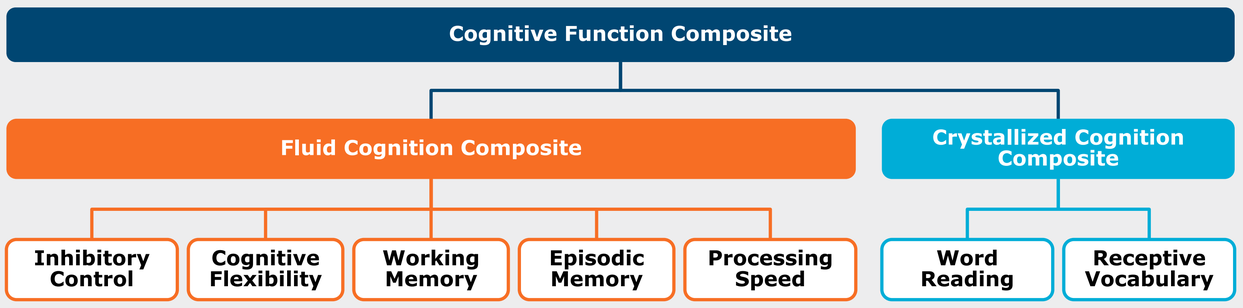
Objectives

- To understand if the impact of HCU on cognitive function is global or if there is a differential impact on individual domains of cognition
- To determine if there are meaningful changes in cognition longitudinally over a time frame that is relevant to potential clinical trials

METHODS

- This is a prospective, observational, longitudinal, multicenter, multinational, natural history study of HCU
  - Target enrollment for this study is 150 participants at 8 sites across the US, UK, and Ireland
  - Enrolled patients will have clinically documented diagnosed HCU based on the presence of elevated levels of total homocysteine and either enzymatic or genetic confirmation of HCU
- Cognitive function is evaluated with the Cognition Battery and Early Cognition Battery subsets of the NIH Toolbox (hereinafter referred to as NIHTB-CB), a multi-dimensional assessment tool used to measure cognitive functioning of patients at every visit over the course of the study (validated for the age groups included in this study) **(Figure 1)**
  - These assessments are performed on a tablet every 6 months over a period of 78-months (6.5-years) in person by qualified research staff
  - Each assessment includes 7 activities and takes approximately 40 minutes to complete
- For each individual or composite score, observed values and change from baseline of uncorrected standard score, age-corrected standard score, and fully corrected T-score were summarized by age group and study visit

Figure 1. The NIHTB-CB Is Comprised of Seven Individual Domains and Three Composites



LIMITATIONS

- Study population was primarily Caucasian and from study sites within US, UK, and Ireland only
- There was heterogeneity in HCU treatment across patients, and in both the level and duration of treatment that patients received
- The NIHTB-CB is focused on domains of cognition that are broadly relevant to clinical trials. Other domains of cognition may be vulnerable in HCU but were not included within this specific study.
- The observation period for the analysis was two years and evaluation of longer-term data is needed given the slow progressive nature of HCU

Contact information: Medinfo@Travere.com

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