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Utilization of NIH Toolbox Cognition Battery in a Rare Disease Conference Setting

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Congenital **C**entral **H**ypoventilation **S**yndrome (CCHS) Overview

- Approximately 1,200 cases worldwide
- Characterized by:
  - Hypoventilation asleep and in severe cases awake and asleep
  - Autonomic nervous system (the system that functions automatically to keep us alive) dysregulation
  - ↑ **risk for neurocognitive deficits**

Etiology of CCHS

- *PHOX2B* is the disease-defining gene for CCHS
- It is expressed early in the embryology of the ANS
- There are 2 types of CCHS-related *PHOX2B* mutations:
  - **Polylanine repeat expansion mutation (PARM)**: expansion of normal 20 alanine repeat region to 24-33 repeats on one allele (90-92% of CCHS cases); genotypes 20/24 to 20/33
  - **Non-polyalanine repeat mutation (NPARM)**: missense, nonsense, frameshift, & stop codon mutations

(8-10% of CCHS cases)

PHOX2B Genotype/CCHS Phenotype Association

- In general, patients with NPARMs and longer PARMs have a more severe CCHS phenotype
  - Need for 24 hour/day artificial ventilation
  - Hirschsprung disease
  - Risk of a tumor of neural crest origin

Endogenous Daily Exposures in CCHS

Repeated exposure to hypoxemia & hypercarbia

Impaired regional oxygenation in the brain

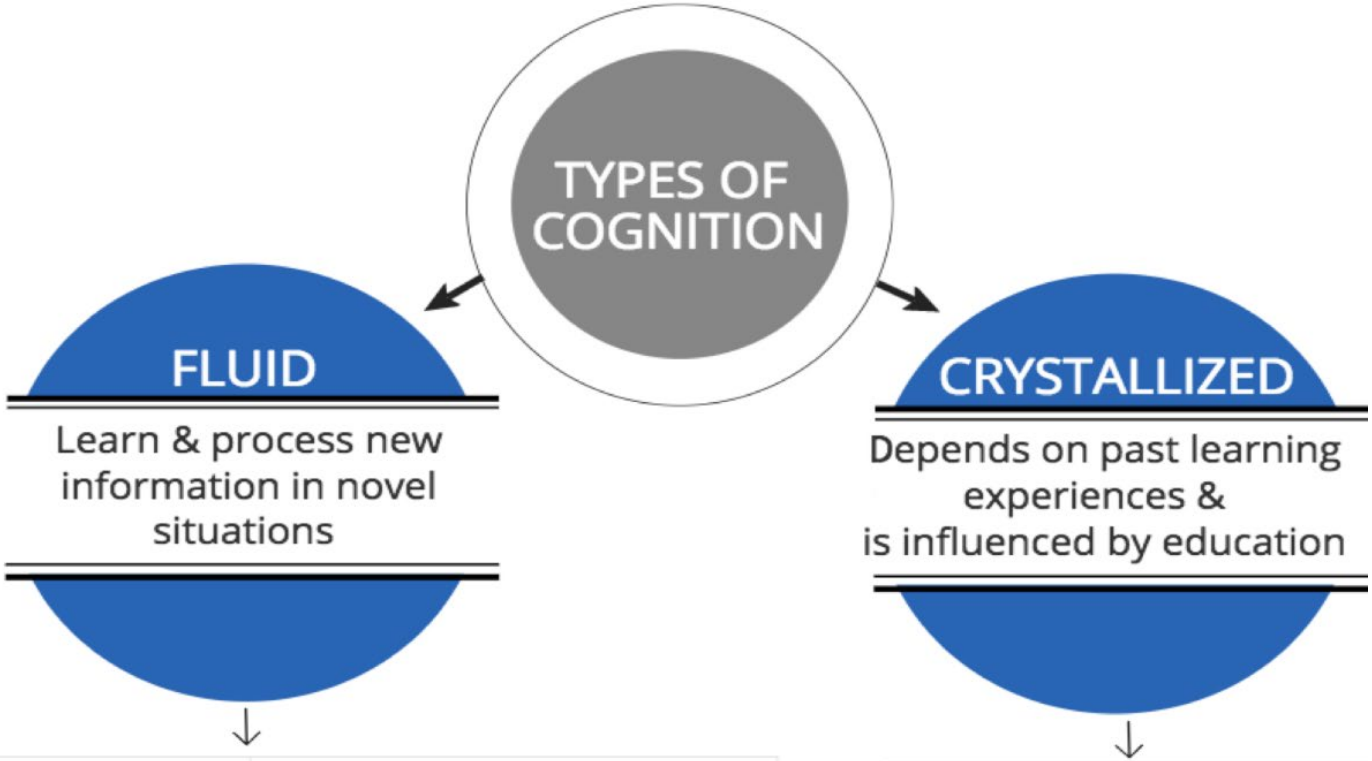
Negative effects on neurocognitive outcome?

Prior CCHS Neurocognitive Research

- School age CCHS patients have mean FSIQ values one SD below the norm, with a broad range of neurocognitive outcomes (Zelko et al., 2010)
- Preschool age CCHS patients with the *PHOX2B* 20/25 genotype have normal mean FSIQ, but longer PARMs have reduced FSIQ as in school age patients (Charnay et al., 2016)
- Need for larger cohorts to better understand factors that impact neurocognitive outcome
- Given the rarity of CCHS, large cohorts are challenging to evaluate in a narrow testing window

How did we evaluate cognition?

- NIH Toolbox Cognition Battery (NTCB)



COGNITIVE ABILITIES	NTCB TESTS
Working Memory	List Sorting Working Memory
Episodic Memory	Picture Sequence Memory
Processing Speed	Pattern Comparison Processing Speed Test
Executive Function & Attention	Flanker Inhibitory Control and Attention, Dimensional Change Cards Sort
Executive Function	Dimensional Change Cards Sort

COGNITIVE ABILITIES	NTCB TESTS
Language	Picture Vocabulary, Oral Reading Recognition

Prior Clinical Implementation of NTCB

- NIH Toolbox Cognition Battery (NTCB) has been administered in 38 CCHS patients over a 3 year period at Lurie Children's Hospital (n=35) and Seattle Children's Hospital (n=3)

- Previously administered in a traditional, clinical setting:
  - A controlled environment
  - Quiet
  - Limited distractions
  - Private testing room

2018 CCHS Family Network Meeting

- Offered an opportunity to collect a larger CCHS cohort in short time frame
- This cohort represented a diverse range of management and compliance with ATS recommendations for CCHS

2018 CCHS Family Network Meeting

- But…..a non-traditional testing environment
  - Network meeting conducted in hotel conference setting, with no access to private individual rooms for research

Research Objectives

1. Evaluate the ability to capture valid neurocognitive performance data using NTCB testing with a protocol modified to accommodate environmental limitations in non-traditional testing setting

2. Collect neurocognitive performance data from a large cohort of CCHS patients representing patients not followed by the largest and most comprehensive center for CCHS in the world (Lurie Children's)

Hypothesis

- We hypothesized that NTCB can be used to assess neurocognition in CCHS patients in a non-traditional setting (hotel conference center) and that performance results of this cohort will not be significantly different than the cohort collected in the more traditional, controlled clinical setting

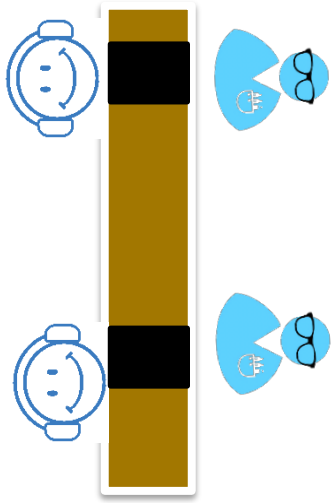
Methods
Recruitment & Consent Process

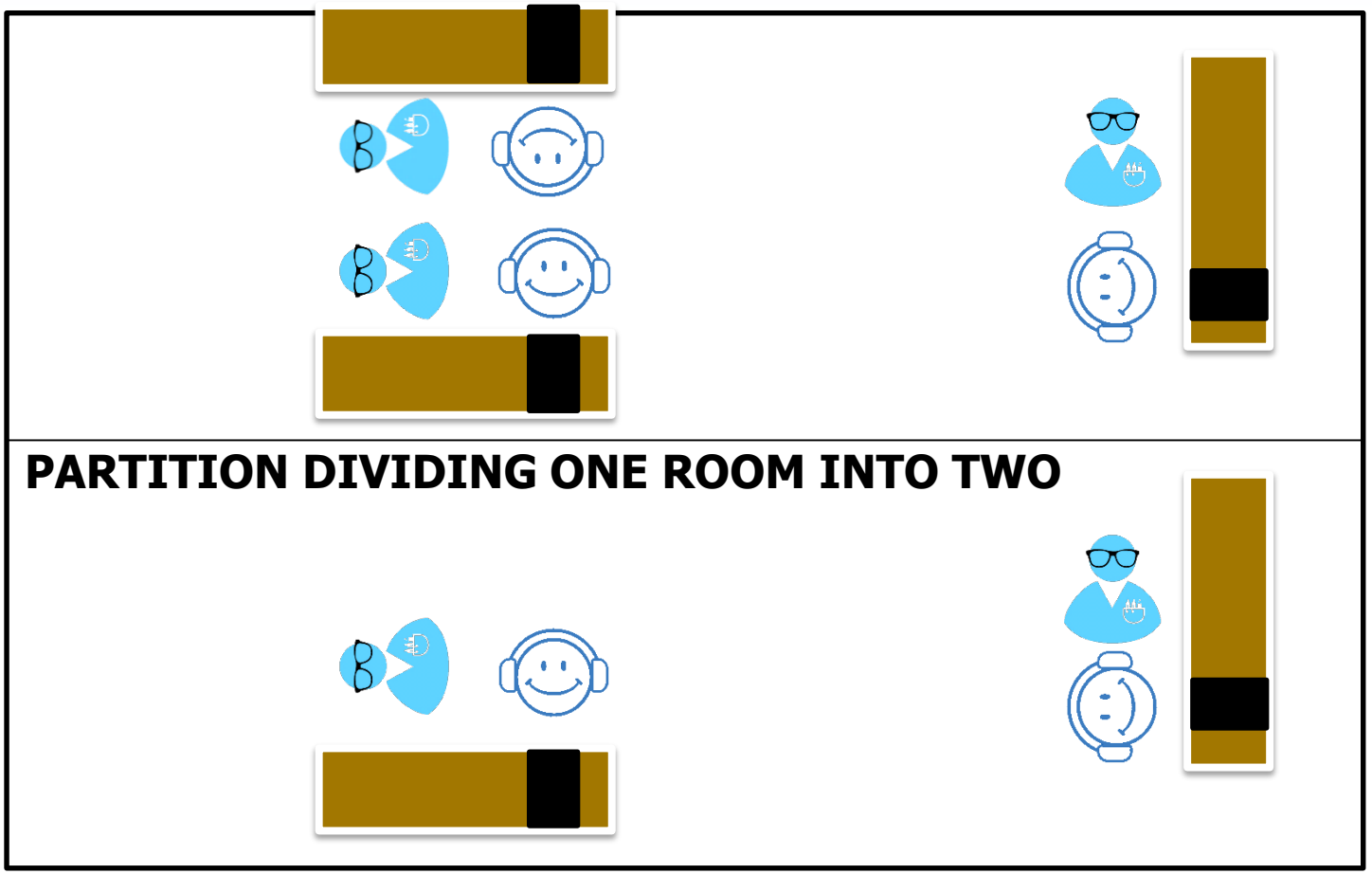
- **Research team members on site (n=7)**

- ***Eight-hour window for testing***
  - consented participants
  - administered NTCB assessments
  - Completed REDCap ANS dysregulation questionnaire specific to CCHS phenotype for each consented participant

Methods
Room Set-up

CONSENT & REDCap Questionnaire Station





Methods
Environmental Limitations & Adjustments

- A single room
- Noise and distractions from other participants and hallway
- Recruitment constraints by conference organizers

Methods
Statistical Analyses

- Age-corrected scores for clinic vs. conference groups tested with unpaired t-tests
- Fluid vs. crystallized composite scores tested with paired t-tests
- Age-corrected scores were tested against the population mean of 100 with Student's t-tests

Results
Comparison of Clinic & Conference Cohorts

NTCB Collection Site	Clinic	Conference
Age Range	5-35 years	5-37 years
Mean Age	15.5 years	18.3 years
Number of Participants	38	29
Duration of Data Collection	3 years	<1 day

Neurocognition was assessed in **29** unique patients in **EIGHT hours**!

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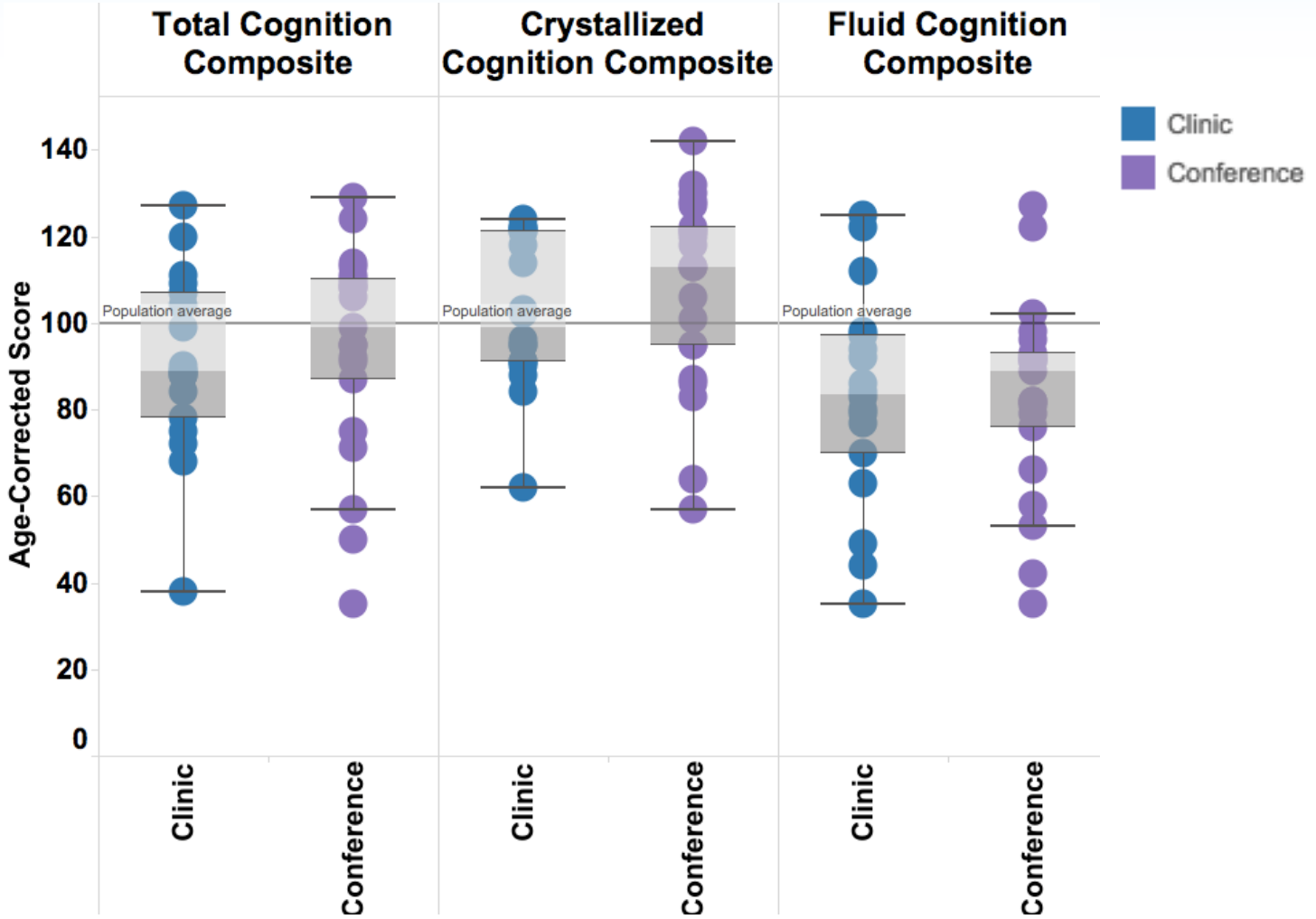
Results: Clinic vs. Conference Scores



CCHS NTCB age-corrected scores were not significantly different when stratified by testing environment (p>0.05 for all scores)

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Results
Summary of Conference CCHS Findings

- Normal composite
- Above average crystallized scores
- Below average fluid cognition scores
- ***All major findings replicate findings previously identified in our clinical cohort***

Conclusions

- Our results support the validity of using the NTCB to collect neurocognitive data using a modified protocol in a non-traditional setting
- The NTCB data replicate previous findings that crystallized cognition scores are higher than fluid scores in CCHS
- The NTCB is a robust tool because it allowed us to effectively nearly double our CCHS NTCB number of tested subjects in 8 hours at a bustling rare disease conference compared to the tightly regulated clinic cohort collected over three years
- The NTCB is easy to implement, yet a powerful tool to assess neurocognition, especially in a rare disease population

Future Directions

- Our results
  - support the use of a modified NTCB protocol in future studies to overcome environmental limitations of a non-traditional testing environment
  - support the power of NTCB for increasing study cohort sizes in rare diseases, with testing at rare disease conferences

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Thank you!

cchs NETWORK

CCHS FOUNDATION

Northwestern University NUCATS Clinical and Translational Sciences Institute

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CAMP Exceptional Student Summer Researcher Program

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