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Neurocognitive monitoring in congenital central hypoventilation syndrome with the *NIH Toolbox*®

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Abstract

Congenital central hypoventilation syndrome (CCHS) is a rare neurocristopathy, caused by mutations in the paired-like homeobox gene *PHOX2B*, which alters control of breathing and autonomic nervous system regulation, necessitating artificial ventilation as life-support. A broad range of neurocognitive performance has been reported in CCHS, including an array of cognitive deficits. We administered the *NIH Toolbox*® *Cognition Battery* (*NTCB*), a novel technology comprised of seven tasks presented via an interactive computer tablet application, to a CCHS cohort and studied its convergent and divergent validity relative to traditional clinical neurocognitive measures. The NTCB was administered to 51 CCHS participants, including a subcohort of 24 who also received traditional clinical neurocognitive testing (Wechsler Intelligence Scales). Age-corrected NTCB scores from the overall sample and subcohort were compared to population norms. Associations between NTCB indices and Wechsler Intelligence scores were studied to determine the convergent and divergent validity of the NTCB. NTCB test results indicated reduced Fluid Cognition, which measures new learning and speeded information processing ($p < 0.001$), but intact Crystallized Cognition, which measures past learning, in CCHS relative to population norms. Moderate to strong associations ($r > 0.60$) were found between age-corrected NTCB Fluid and Crystallized indices and comparable Wechsler indices, supporting the convergent and discriminant validity of the NTCB. Results reveal deficits of Fluid Cognition in individuals with CCHS and indicate that the NTCB is a valid and sensitive measure of cognitive outcomes in this population. Our findings suggest that the NTCB may play a useful role in tracking neurocognition in CCHS.

KEYWORDS
artificial ventilation, attention, autonomic (dys)regulation, cognition, control of breathing, executive functioning, intelligence, neuropsychology, *PHOX2B*, processing speed

1 | INTRODUCTION

Congenital central hypoventilation syndrome (CCHS), which is characterized by alveolar hypoventilation with insufficient or absent ventilatory response to hypoxia and hypercapnia, is a rare disorder of autonomic nervous system (ANS) regulation. Although it typically presents in the newborn period, a small subset of individuals with CCHS is not identified until later in life, described as having Later-Onset CCHS (LO-CCHS).[1] Throughout this report, the term CCHS is used to describe patients with disease onset both in the newborn period and thereafter.

CCHS arises from a pathogenic mutation of the paired-like homeobox gene *PHOX2B*, which is critical for the development of the ANS and neural structures necessary for control of breathing.[2] Artificial ventilation is necessary for survival throughout the individual's lifetime. Less severely affected patients are able to breathe spontaneously when awake, while those who are more severely affected require continuous (24-h/day) artificial ventilatory support. Even individuals who appear to breathe adequately while awake have attenuated or absent physiologic responses and behavioral perceptions of hypoxemia and hypercapnia.[3]

The potential for repeated hypoxemic and hypercarbic events from severe cyanotic breath-holding spells, exertional physiologic compromise, and suboptimal or noncompliant ventilatory support places individuals with CCHS at risk for adverse neurodevelopmental outcomes. Alterations of brain structure and function intrinsic to CCHS have been identified which may be exacerbated by hypoxic events, with changes to cortical and subcortical structures that may contribute to neurocognitive deficits.[4–7]

Overall intellectual functioning in CCHS varies broadly, ranging from below average to superior, and several areas of cognitive vulnerability have been identified.[8–15] Differences have been noted in cognitive subdomains such as fluid reasoning, visuoperceptual reasoning, clerical/processing speed, working memory, sequential processing, and verbal ability. Variables found to be related to cognitive outcomes have included *PHOX2B* genotype,[13,14] age at assessment (i.e., preschool vs. school-age),[10] introduction of positive pressure ventilation via tracheostomy in the first 3 months of life[15,16] and compliance with recommended ventilatory support and limitations on strenuous activities.[1] The broad spectrum of cognitive outcomes in CCHS underscores the need for longitudinal neurocognitive testing, with the aim to personalize management and optimize cognitive functioning.

Due to the extreme rarity of CCHS (~1/200,000 live births),[2] with an estimated 3000 patients identified since 1970,[17] and the spectrum of outcomes seen in this condition, it has been difficult to administer individual neurocognitive testing to a cohort large enough to allow detailed study of associations between disease factors, treatment factors, and cognitive outcomes. Furthermore, variation in the neurocognitive tools used in clinical care and research across institutions makes collaborative studies difficult. Considering these factors as well as the labor-intensity and cost of traditional clinical assessment techniques, we sought an alternate approach to neurocognitive assessment with the goal of facilitating both research and clinical monitoring in CCHS. We identified the *NIH Toolbox® Cognition Battery (NTCB)*, a novel transferable technology comprised of seven tasks administered via a computer tablet application.[18]

The NTCB tasks were designed to sample aspects of cognition sensitive to mental status changes associated with neurological and other medical conditions and their treatments.[19–21] The tasks fall into two clusters, one measuring Crystallized Cognition and one measuring Fluid Cognition. Crystallized Cognition depends upon past learning experiences and is relatively stable in the face of neurologically-based mental status changes. An example of Crystallized Cognition is performance on a picture vocabulary test. Fluid Cognition depends upon an individual's current capacity for new learning and speeded information processing, particularly in novel situations, which tends to be more sensitive to neurologic dysfunction. An example of Fluid Cognition is performance on a test of the ability to remember increasingly lengthy picture sequences. The NTCB requires 30–45 min to complete, is designed to be administered by individuals without professional training in psychological assessment, has been extensively normed,[19,22–24] and has been utilized as a research tool with several clinical populations[25–30] as well as individuals with intellectual disabilities.[31,32] A unique feature of the NTCB is that it is designed as a life-span measure which can be administered from 3 through 85 years of age, making it useful for longitudinal follow-up. However, preschool children are administered an abbreviated version of the test which does not produce indices of Fluid and Crystallized Cognition.

We studied the NTCB as a tool for measuring neurocognitive outcomes in individuals with CCHS. Our aims were to (1) use the NTCB to enhance our understanding of neurocognitive outcomes of individuals with CCHS by studying Crystallized and Fluid Cognition, and (2) validate the NTCB in CCHS by examining its associations with traditional clinical neurocognitive assessment results. We predicted that NTCB Fluid Cognition scores in CCHS subjects would be depressed compared to population norms but that NTCB Crystallized Cognition scores would not, and that the convergent and divergent validity of the NTCB Crystallized and Fluid Cognition indices would be supported by their associations with traditional clinical neurocognitive performance indices.

2 | MATERIALS AND METHODS

2.1 | Study design and population

Individuals aged 7 years and above with *PHOX2B* mutation-confirmed CCHS (including LO-CCHS) were recruited for participation between June 2018 and July 2021 from three sources: the Center for Autonomic Medicine in Pediatrics (CAMP) at Ann & Robert H. Lurie Children's Hospital of Chicago, Seattle Children's Hospital, and the 2018 CCHS Family Network Conference in Saint Louis. This study was approved by the Internal Review Boards of the Ann & Robert H. Lurie Children's Hospital of Chicago and Seattle

Children's Hospital. Consent for participation was obtained from subjects age 18 years and older, and from parents of individuals under 18 years of age. Assent for participation was also obtained from individuals between 12 and 17 years of age.

2.2 | Measures

The NTCB was administered to all participants.[18] The NTCB is an array of tasks measuring Crystallized Cognition (Picture Vocabulary, Oral Reading Recognition) and Fluid Cognition (Dimensional Change Card Sort, Flanker Inhibitory, List Sorting, Picture Sequence Memory, Pattern Comparison) which was developed for administration on iPad (Apple, Cupertino, CA) tablets. The NTCB Crystallized and Fluid Cognition indices are combined to form a summary Total Cognition Composite. The NTCB records temporal parameters of item responses at the millisecond level, allowing precise measurements of reaction time and processing speed. NTCB test results used in all analyses for the current study were adjusted for the examinee's age, and expressed with reference to a population mean of 100 and standard deviation (SD) of 15. Given the focus of the current investigation upon NTCB Fluid and Crystallized indices, only administrations of NTCB that produced those indices (i.e., to school-age and older individuals) were included. All NTCB testing was done by examiners trained in its administration using manuals and instructional video materials designed by the measure's developers and available online. At the CCHS Family Conference, participants were tested with the NTCB in a partitioned room with sound-canceling headphones and a one-on-one examiner in immediate proximity. All other participants were tested with the NTCB in a quiet, individual room with the individual examiner in immediate proximity to the subject.

2.2.1 | Traditional neurocognitive measures

The Wechsler Abbreviated Scale of Intelligence, 2nd Ed. (WASI-II) and the Working Memory and Processing Speed subtests of the Wechsler Adult/Children's Intelligence Scales were administered during clinical inpatient testing at CAMP to a subcohort.[33–35] These measures provided age-adjusted Wechsler indices of Verbal Comprehension, Perceptual Reasoning, Full Scale Intelligence, Working Memory, and Processing Speed, with a mean of 100 and SD of 15. All Wechsler testing was completed by psychometricians specially trained in the administration of these clinical measures. The psychometricians who administered clinical neurocognitive measures were different from the examiners who administered NTCB testing. All test administrators were blinded to the study outcomes.

2.3 | Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics for Windows, version 25. Shapiro–Wilk tests of the normality of NTCB variable distributions showed no significant differences at α level of 0.05, so parametric tests were used to compare the CCHS population to population norms for NTCB variables. For the entire cohort, age-corrected NTCB scores from 51 school-age administrations of the test battery were compared to the general population mean of 100 and SD of 15 using single-sample *t*-tests, with a two-sided α level of 0.05. Within the clinical subcohort of 24 participants, single-sample *t*-tests with a two-sided α level of 0.05 were used to compare NTCB scores and Wechsler scores to the general population mean of 100 and SD of 15. Pearson's correlations were then used within the same subcohort to study associations between NTCB scores and Wechsler scores, interpreted in accordance with Dancey and Reidy guidelines that a correlation of 0.1 is considered weak, 0.4 moderate, and 0.7 strong.[36] Effect sizes for *t*-tests were calculated using Cohen's *d*, interpreted in accordance with guidelines that an effect size of 0.2 is considered small, 0.5 medium, and 0.8 large.[37]

3 | RESULTS

3.1 | Sample characteristics

The NTCB was administered to 51 participants: 26 (51%) from Lurie Children's Hospital (CAMP), 24 (47%) from the 2018 CCHS Family Network, and 1 (2%) from Seattle Children's Hospital. Five of the 51 participants (10%) had LO-CCHS. Because Lurie Children's Hospital was also using the NTCB as a longitudinal research tool, 23 CAMP patients had received NTCB testing more than once, at different clinical visits. For those individuals, the results of their *first* NTCB examination (and the clinical neurocognitive examination conducted at the same visit) were used for analyses, to avoid confounding due to practice effects on NTCB test results.[20] Twenty-four CAMP participants who also received traditional clinical neurocognitive testing during their annual clinical follow-up evaluations comprised a subcohort used to study associations of those results with NTCB results. Four of the 24 participants comprising the clinical subcohort (17%) had LO-CCHS. Clinical and demographic characteristics of the study population are presented in Table 1 for the entire cohort of 51 participants.

3.2 | CCHS comparisons with general population norms

Comparisons of age-corrected NTCB scores against general population norms, with effect sizes, are presented in Table 2 for the overall cohort, and in Table 3 for the subcohort used to study associations of NTCB results with Wechsler clinical test results. These analyses show significantly depressed Fluid Cognition ($p < 0.001$) and Total Cognition Composite ($p \leq 0.01$) scores. In contrast, Crystallized Cognition scores did not differ significantly from population norms. As indicated by Cohen's *d*, the effect for Fluid Cognition is large, the effect for the Total Cognition Composite is small to medium, and the Crystallized

TABLE 1 Clinical and demographic information for full CCHS cohort

Variable	Value
Age at neurocognitive testing (years)	Range: 7.37–37.34
Mean ± standard deviation	17.03 ± 8.43
Sex, *n* (%)	
Female	30 (60)
Male	21 (40)
Race/ethnicity, *n* (%)	
White	42 (82)
White/Hispanic or Latinx	5 (10)
Black and/or African American	1 (2)
Native American or Alaska Native	1 (2)
Multiracial	2 (4)
Maternal education, *n* (%)	
Less than high school	2 (4)
High school graduate	3 (6)
Partial college, at least 1 year of specialized training	5 (10)
Associate's degree	6 (12)
Bachelor's degree	21 (41)
Graduate or professional training	11 (22)
Not provided	3 (6)
Diagnosis, *n* (%)	
CCHS	46 (90)
LO-CCHS	5 (10)
PHOX2B variant/genotype[a], *n* (%)	
PARMs	
20/25	16 (31)
20/26	11 (22)
20/27	15 (29)
20/31	1 (2)
20/32	1 (2)
20/33	3 (6)
NPARMs	4 (8)

Abbreviations: CCHS, congenital central hypoventilation syndrome; LO-CCHS, Later-Onset CCHS.

[a]*PHOX2B* variant/genotype indicates the number of alanines on each allele for the polyalanine repeat expansion mutations (PARMs) (normal genotype is 20/20; 20/25 indicates an extra 5 alanines on the affected allele; 20/26 indicates an extra 6 alanines on the affected allele; 20/27 indicates an extra 7 alanines on the affected allele, etc.). Non-PARMs (NPARMs) indicate variants that do not include a polyalanine expansion but have other disruptive *PHOX2B* mutations.

TABLE 2 Full CCHS cohort (*n* = 51): age-corrected NTCB scores

NTCB index	Mean (SD)	*t*	*p*	*N*	Cohen's *d*
Fluid Cognition	82.65 (20.12)	−6.16	<0.001	51	−0.86
Crystallized Cognition	102.59 (21.27)	0.87	0.39	51	0.12
Total Cognition Composite	92.78 (19.64)	−2.60	0.01	50	−0.37

Note: Normative population mean = 100, SD = 15. *t*-tests represent comparisons of cohort with the normative population mean.

Abbreviations: CCHS, congenital central hypoventilation syndrome (including Later-Onset CCHS); NTCB, NIH Toolbox® Cognition Battery (also known as NIH Toolbox).

Cognition index failed to meet criteria for a small effect.[37] Within the clinical subcohort, NTCB Cohen's *d* effect sizes are similar to those in the overall sample except that the Total Cognition Composite effect was large rather than medium.

As indicated in Table 4, no Wechsler indices in the clinical subcohort were significantly depressed relative to general population norms, and effect sizes for the comparisons were correspondingly small to negligible.

3.3 | Associations between age-corrected NTCB scores and Wechsler scores

Pearson's correlations, presented in Table 5, show that all three NTCB indices were significantly and positively associated with nearly all the Wechsler indices, with two exceptions being nonsignificant associations between the NTCB Crystallized Cognition index and the Wechsler Perceptual Reasoning and Processing Speed indices. Applying Dancey and Reidy interpretative guidelines,[36] the NTCB Fluid Cognition index shows strong positive correlations with the Wechsler indices of Perceptual Reasoning and Processing Speed, and moderate positive correlations with Wechsler Working Memory, Verbal Comprehension, and Full Scale IQ. In contrast, the NTCB Crystallized Cognition index shows moderate positive correlations with Wechsler Verbal Comprehension, Working Memory, and Full Scale IQ but weak positive correlations with Wechsler Perceptual Reasoning and Processing Speed.

4 | DISCUSSION

Our data indicate that the NTCB is a sensitive measure of neurocognitive outcomes in individuals with CCHS, a rare-disease population dependent upon technology-based physiological monitoring and artificial ventilation for survival. Our NTCB test results converge with previous findings on neurocognition in CCHS

TABLE 3 Clinical CCHS subcohort with concurrent formal neurocognitive testing ($n = 24$): age-corrected NTCB scores

NTCB Index	Mean (SD)	*t*	*p*	*N*	Cohen's *d*
Fluid Cognition	84.92 (17.64)	−4.19	<0.001	24	−0.86
Crystallized Cognition	97.91 (18.43)	−0.54	0.592	23	−0.11
Total Cognition Composite	92.52 (14.36)	−2.50	0.020	23	−0.52

Note: Normative population mean = 100, standard deviation (SD) = 15. *t*-tests represent comparisons of subcohort who received clinical neurocognitive assessment with the normative population mean.

Abbreviations: CCHS, congenital central hypoventilation syndrome (including Later-Onset CCHS); NTCB, NIH Toolbox® Cognition Battery (also known as NIH Toolbox).

TABLE 4 Clinical CCHS subcohort with concurrent formal neurocognitive testing ($n = 24$): Wechsler scores

Wechsler index	Mean (SD)	*t*	*p*	*N*	Cohen's *d*
Full Scale IQ[a]	94.71 (16.21)	−1.57	0.131	24	−0.32
Verbal Comprehension[a]	96.25 (16.32)	−1.10	0.282	24	−0.23
Perceptual Reasoning[a]	93.79 (17.81)	−1.67	0.108	24	−0.34
Working Memory[b]	95.50 (14.54)	−1.45	0.161	22	−0.31
Processing Speed[b]	98.09 (24.58)	−0.373	0.713	23	−0.08

Note: Corrected for age; Normative population mean = 100, SD = 15. *t*-tests represent comparisons of subcohort who received clinical neurocognitive assessment with the normative population mean.

Abbreviation: CCHS, congenital central hypoventilation syndrome (including Later-Onset CCHS).

[a]WASI-II = Wechsler Abbreviated Scale of Intelligence, 2nd Ed.

[b]Wechsler Intelligence Scale (child/adult version appropriate to age of subject).

school-age patients, indicating reduced Fluid Cognition but intact Crystallized Cognition. From these findings, individuals with CCHS resemble their peers in their ability to demonstrate knowledge and skills automatized from prior learning, as indicated by competencies such as vocabulary and reading decoding. Once automatized, such competencies are relatively impervious to neurologic insult in most clinical populations. In contrast, individuals with CCHS diverge from peers at novel learning and problem-solving activities, especially when those activities emphasize speed and efficiency and depend upon attention, Working Memory, and executive skills. Fluid Cognition is based upon processes such as attention, working memory, and executive skills which are presumably more vulnerable to disruption in CCHS by alterations of brain structure or function in early development and/or ongoing physiological perturbations such as oxygen desaturations and hypercarbia. When a patient's NTCB test results are found to be depressed, further inquiry is necessary to guide clinical care which may include comprehensive clinical neurocognitive or psychoeducational assessment, and collaborative data gathering from other information sources such as educators and family members. Our results suggest the possible use of the NTCB as a tool for clinic-based screening, though such screening would also need to include other sources of information about academic functioning, attention, executive skills, behavior, and emotional adjustment.

The current results add to existing evidence that patients with CCHS often experience adverse cognitive outcomes secondary to their medical condition. However, individual cognitive outcomes in CCHS vary widely from superior functioning to cognitive disability, and our understanding of the factors that contribute to this variability is limited. While previous studies have indicated deficits in CCHS on traditional clinical measures such as the Wechsler Intelligence Scales, ours is the first study to explore the validity of computer-based assessments of Crystallized and Fluid Cognition in individuals who are affected by this condition.

Furthermore, patterns of association between age-corrected NTCB scores and Wechsler scores support the convergent and discriminant validity of the Fluid and Crystallized indices of the NTCB in CCHS. Fluid Cognition scores were strongly associated with Wechsler Perceptual Reasoning and Processing Speed, but showed a weaker association with Verbal Comprehension and an intermediate association with Working Memory. In contrast, the Crystallized Cognition index showed weak associations with Perceptual Reasoning and Processing Speed but stronger associations with Verbal Comprehension and Working Memory. These associations indicate that the Fluid and Crystallized indices of the NTCB measure facets of cognition that differ in CCHS, and which are differentially related to intellectual subcomponents measured by the Wechsler Intelligence Scales. Finally, the effect sizes found in our clinical subcohort for the NTCB relative to the general population mean, particularly the large effect of the Fluid Cognition index (Cohen's $d = -0.86$), contrast sharply with much smaller effects found for Wechsler indices (Cohen's *d* ranging from −0.08 to −0.34), suggesting that the NTCB provides cognitive outcome measurements that are more sensitive to cognitive dysfunction in CCHS than traditional clinical methods.

Our findings are in harmony with existing literature supporting the validity of the NTCB as a measure in other clinical populations, including individuals with intellectual disability (ID). In prior studies the NTCB has shown good to excellent convergent validity with "gold standard" measures of intellectual ability such as the Wechsler and Stanford Binet scales.[19,23,24,29,31] Beyond its strong associations with clinical reference measures, the NTCB has demonstrated sensitivity to cognitive deficits in several clinical populations. Consistent with

TABLE 5 Clinical CCHS subcohort with concurrent formal neurocognitive testing ($n = 24$): Pearson's correlations between age-corrected NTCB and Wechsler indices

	Full Scale IQ[a]	Verbal Comprehension[a]	Perceptual Reasoning[a]	Working Memory[b]	Processing Speed[b]
Fluid Cognition[c]	0.690**	0.496*	0.733**	0.609**	0.737**
	N = 24	*N* = 24	*N* = 24	*N* = 22	*N* = 23
Crystallized Cognition[c]	0.581**	0.626**	0.378	0.483*	0.186
	N = 23	*N* = 23	*N* = 23	*N* = 21	*N* = 22
Cognitive Function Composite[c]	0.689**	0.595**	0.642**	0.547*	0.646**
	N = 23	*N* = 23	*N* = 23	*N* = 21	*N* = 22

Abbreviation: CCHS, congenital central hypoventilation syndrome (including Later-Onset CCHS); NTCB, NIH Toolbox® Cognition Battery (also known as NIH Toolbox).

[a]WASI-II = Wechsler Abbreviated Scale of Intelligence, 2nd Ed.

[b]Wechsler Intelligence Scale (child/adult version appropriate to age of subject).

[c]NTCB = NIH Toolbox Cognitive Battery (scores age-corrected).

*Significance at 0.05 level (2-tailed).

**Significance at 0.01 level (2-tailed).

our results demonstrating reduced Fluid Cognition in individuals with CCHS, NTCB Fluid Cognition deficits have been identified in individuals with Duchenne muscular dystrophy,[28] traumatic brain injury,[29,38] and a variety of other neurologic disorders.[39] Those studies have also found NTCB Crystallized Cognition indices to be relatively intact, similar to our findings in CCHS. The validity of the NTCB has also been supported in individuals with fragile X syndrome, Down syndrome, and ID, attesting to its broad range of applicability.[31,32] Together, these studies strongly support the validity and sensitivity of NTCB as a measure of cognitive outcomes in neurologically and developmentally vulnerable populations.

While our findings support the validity of the NTCB in our sample of individuals with CCHS who are 7 years of age or older, they do not address the validity of NTCB in younger children. The NTCB can be used to study neurocognitive functioning starting at age 3 years. However, the specific tasks administered in the preschool version of the NTCB differ from those in the version administered to school-age and older individuals, who were the focus of our investigation. The preschool version does not provide indices of Fluid and Crystallized ability, which were of particular interest based on our previous CCHS research. As a result, in this initial investigation we focused on school-aged and older NTCB administrations which provided Fluid and Crystallized ability indices. Preschool NTCB indices should be a focus of future research as they may be particularly relevant if they can inform our understanding of CCHS in early childhood, optimizing care in the critical early years of the disorder.

Despite these encouraging results, there are several limitations to our study. First, our sample is predominantly White and representative of patients reported in previous CCHS literature, but it is not representative of the diversity of the overall US population. Second, the socioeconomic status (SES) of our sample is above the general population norm, as illustrated by the fact that the majority of participants' mothers have a Bachelor's degree or higher.[40] Given known associations between SES and the NTCB Crystallized Cognition measure,[23] we acknowledge the possibility that findings could differ in CCHS individuals of lower SES. Previously, in a parent-control study we found that, despite having parents whose education level was above the US average, children with CCHS score significantly below parental controls on Shipley-2 indices of intelligence, vocabulary, and abstraction.[12] This issue clearly deserves further exploration in future research. Third, we did not have traditional clinical neurocognitive assessments (Wechsler scales) for all participants. Fourth, our sample size is relatively small. This limited our ability to study associations of cognitive outcomes with disease factors such as *PHOX2B* genotypes and the subgroup of individuals with LO-CCHS, as well as treatment factors such as methods of artificial ventilation. However, because CCHS is a rare disorder with fewer than 3000 patients identified since 1970 worldwide,[17] our sample is large compared to the number of CCHS cases worldwide and other cohorts reported in the literature.

While NTCB test results provide a sensitive assessment of neurocognitive functioning, we acknowledge that our understanding of the external validity of NTCB indices is emerging. For example, little information is available about how NTCB test results are related to outcomes in academic and other contexts relevant to everyday life. This lack of knowledge limits inferences about NTCB results and their clinical interpretation. As a result, the NTCB cannot be considered an equivalent replacement for a comprehensive clinical neurocognitive evaluation. Particularly given limitations of racial and socioeconomic diversity in our cohort, further studies will be needed, of more diverse samples, to investigate the external validity of the NTCB and understand how it can be utilized in clinical care.

Our findings supporting the validity of the NTCB as a measure of cognitive outcomes in individuals with CCHS have clear implications for both clinical care and research. Because adverse cognitive

outcomes are seen in many but not all individuals with CCHS, for optimal clinical care it is important to understand as early as possible if a patient is experiencing cognitive difficulties and, if so, the nature of those difficulties, to guide appropriate therapeutic and educational interventions. Thereafter, ongoing surveillance is recommended to detect changes that may occur over time due to both disease and treatment factors in CCHS. Barriers to such surveillance, such as lengthy waits for specially trained neurocognitive assessment specialists and having sufficient time to conduct assessments during clinical visits, are frequently encountered in CCHS and other chronic illnesses requiring neurocognitive monitoring.[28] The NTCB can overcome these barriers by offering a brief assessment that can be administered by virtually any practitioner or technician with minimal training. Its ease of administration combined with its validation through rigorous comparisons to "gold standard" metrics supports the use of NTCB as a component of neurocognitive follow-up in individuals with CCHS and in other rare disease, technology-dependent, and/or ID populations. Additionally, the low cost and time-efficiency of the NTCB make it a powerful tool for collaborative research.

5 | CONCLUSIONS

Our findings indicate that the NTCB is a valid and sensitive tool for monitoring neurocognitive outcomes in CCHS. Given its ease of administration, short duration, and low cost, it is well-suited for tracking neurocognitive development longitudinally in school-age children and adults with CCHS, and it may be more sensitive to disease-related cognitive dysfunction than traditional clinical neurocognitive assessment techniques. Although we do not recommend that the NTCB replace traditional comprehensive neurocognitive assessments, its accessibility and validity suggest that it may play a role in ongoing monitoring, and in screening for the need for further cognitive evaluation. Our findings also suggest that the NTCB holds great promise as a tool for longitudinal monitoring of neurocognition in other rare disease populations, especially those patients without access to medical centers with expertize in formal neurocognitive testing.

AUTHOR CONTRIBUTIONS

Remi Z. Welbel: Writing—original draft; writing—review and editing; formal analysis; investigation; conceptualization. **Casey M. Rand**: Conceptualization; methodology; investigation; supervision; project administration; writing—review and editing; funding acquisition. **Amy Zhou**: Formal analysis; writing—review and editing; conceptualization; methodology; investigation; funding acquisition. **Allaa Fadl-Alla**: Data curation; investigation; writing—review and editing. **Maida Lynn Chen**: Investigation; resources; writing—review and editing. **Debra E. Weese-Mayer**: Conceptualization; methodology; funding acquisition; writing—review and editing; formal analysis; writing—original draft; supervision. **Frank A. Zelko**: Conceptualization; methodology; investigation; writing—original draft; writing—review and editing; formal analysis; supervision.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *Am J Respir Crit Care Med*. 2010;181(6):626-644.
2. Weese-Mayer DE, Rand CM, Zhou A, Carroll MS, Hunt CE. Congenital central hypoventilation syndrome: a bedside-to-bench success story for advancing early diagnosis and treatment and improved survival and quality of life. *Pediatr Res*. 2017;81(1-2):192-201.
3. Di Lascio S, Benfante R, Cardani S, Fornasari D. Research advances on therapeutic approaches to congenital central hypoventilation syndrome (CCHS). *Front Neurosci*. 2020;14:615666.
4. Kumar R, Macey PM, Woo MA, Alger JR, Keens TG, Harper RM. Neuroanatomic deficits in congenital central hypoventilation syndrome. *J Comp Neurol*. 2005;487(4):361-371.
5. Macey PM, Richard CA, Kumar R, et al. Hippocampal volume reduction in congenital central hypoventilation syndrome. *PLoS One*. 2009;4(7):e6436.
6. Kumar R, Macey PM, Woo MA, Harper RM. Selectively diminished corpus callosum fibers in congenital central hypoventilation syndrome. *Neuroscience*. 2011;178:261-269.
7. Kumar R, Woo MS, Macey PM, Woo MA, Harper RM. Progressive gray matter changes in patients with congenital central hypoventilation syndrome. *Pediatr Res*. 2012;71(6):701-706.

8. Silvestri JM, Weese-Mayer DE, Nelson MN. Neuropsychologic abnormalities in children with congenital central hypoventilation syndrome. *J Pediatr*. 1992;120(3):388-393.
9. Shimokaze T, Sasaki A, Meguro T, et al. Genotype-phenotype relationship in Japanese patients with congenital central hypoventilation syndrome. *J Hum Genet*. 2015;60(9):473-477.
10. Charnay AJ, Antisdel-Lomaglio JE, Zelko FA, et al. Congenital central hypoventilation syndrome: neurocognition already reduced in preschool-aged children. *Chest*. 2016;149(3):809-815.
11. Zelko FA, Nelson MN, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE. Congenital central hypoventilation syndrome: neurocognitive functioning in school age children. *Pediatr Pulmonol*. 2010;45(1):92-98.
12. Zelko FA, Stewart TM, Brogadir CD, Rand CM, Weese-Mayer DE. Congenital central hypoventilation syndrome: broader cognitive deficits revealed by parent controls. *Pediatr Pulmonol*. 2018;53(4):492-497.
13. Macdonald KT, Mosquera RA, Yadav A, Caldas-Vasquez MC, Emanuel H, Rennie K. Neurocognitive functioning in individuals with congenital central hypoventilation syndrome. *BMC Pediatr*. 2020;20(1):194.
14. Trang H, Bourgeois P, Cheliout-Heraut F. Neurocognition in congenital central hypoventilation syndrome: influence of genotype and ventilation method. *Orphanet J Rare Dis*. 2020;15(1):322.
15. Ogata T, Muramatsu K, Miyana K, Ozawa H, Iwasaki M, Arakawa H. Neurodevelopmental outcome and respiratory management of congenital central hypoventilation syndrome: a retrospective study. *BMC Pediatr*. 2020;20(1):342.
16. Irahara K, Ogata T, Ozawa H, et al. [Relation between psychological development and respiratory management in patients with congenital central hypoventilation syndrome in Japan]. *No To Hattatsu*. 2015;47(5):343-347.
17. Weese-Mayer DE, Rand CM, Khaytin I, et al. Congenital Central Hypoventilation Syndrome. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews(R)*, 2021:1-28.
18. National Institutes of Health and Northwestern University. Toolbox_Scoring_and_Interpretation_Guide_for_iPad_v1.7 5.25.21. 2021. https://nihtoolbox.force.com/s/article/nih-toolbox-scoring-and-interpretation-guide
19. Scott EP, Sorrell A, Benitez A. Psychometric properties of the NIH Toolbox Cognition Battery in healthy older adults: reliability, validity, and agreement with standard neuropsychological tests. *J Int Neuropsychol Soc*. 2019;25(8):857-867.
20. Akshoomoff N, Beaumont JL, Bauer PJ, et al. VIII. NIH Toolbox Cognition Battery (CB): composite scores of crystallized, fluid, and overall cognition. *Monogr Soc Res Child Dev*. 2013;78(4):119-132.
21. Casaletto KB, Umlauf A, Beaumont J, et al. Demographically corrected normative standards for the english version of the NIH Toolbox Cognition Battery. *J Int Neuropsychol Soc*. 2015;21(5):378-391.
22. Distefano R, Fiat AE, Merrick JS, et al. NIH Toolbox executive function measures with developmental extensions: reliability and validity with preschoolers in emergency housing. *Child Neuropsychol*. 2021;27(6):709-717.
23. Akshoomoff N, Newman E, Thompson WK, et al. The NIH Toolbox Cognition Battery: results from a large normative developmental sample (PING). *Neuropsychology*. 2014;28(1):1-10.
24. Weintraub S, Dikmen SS, Heaton RK, et al. The cognition battery of the NIH toolbox for assessment of neurological and behavioral function: validation in an adult sample. *J Int Neuropsychol Soc*. 2014;20(6):567-578.
25. Calderon J, Bellinger DC, Hartigan C, et al. Improving neurodevelopmental outcomes in children with congenital heart disease: protocol for a randomised controlled trial of working memory training. *BMJ Open*. 2019;9(2):e023304.
26. Hood AM, King AA, Fields ME, et al. Higher executive abilities following a blood transfusion in children and young adults with sickle cell disease. *Pediatr Blood Cancer*. 2019;66(10):e27899.
27. Hwang G, Dabbs K, Conant L, et al. Cognitive slowing and its underlying neurobiology in temporal lobe epilepsy. *Cortex*. 2019;117:41-52.
28. Thangarajh M, Kaat AJ, Bibat G, et al. The NIH Toolbox for cognitive surveillance in Duchenne muscular dystrophy. *Ann Clin Transl Neurol*. 2019;6(9):1696-1706.
29. Tulsky DS, Carlozzi NE, Holdnack J, et al. Using the NIH Toolbox Cognition Battery (NIHTB-CB) in individuals with traumatic brain injury. *Rehabil Psychol*. 2017;62(4):413-424.
30. Carlozzi NE, Tulsky DS, Wolf TJ, et al. Construct validity of the NIH Toolbox Cognition Battery in individuals with stroke. *Rehabil Psychol*. 2017;62(4):443-454.
31. Shields RH, Kaat AJ, McKenzie FJ, et al. Validation of the NIH Toolbox Cognitive Battery in intellectual disability. *Neurology*. 2020;94(12):e1229-e1240.
32. Hessl D, Sansone SM, Berry-Kravis E, et al. The NIH Toolbox Cognitive Battery for intellectual disabilities: three preliminary studies and future directions. *J Neurodev Disord*. 2016;8(1):35.
33. Wechsler D. *Wechsler Adult Intelligence Scale*. 4th ed. NCS Pearson; 2008.
34. Wechsler D. *Wechsler Abbreviated Scale of Intelligence—Second Edition*. 2nd ed. NCS Pearson; 2011.
35. Wechsler D. *Wechsler Intelligence Scale for Children—Fifth Edition*. NCS Pearson; 2014.
36. Dancey CP, Reidy J. *Statistics without Maths for Psychology*. Pearson/Prentice Hall; 2007.
37. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. New York: Routledge; 1988.
38. Holdnack JA, Iverson GL, Silverberg ND, Tulsky DS, Heinemann AW. NIH toolbox cognition tests following traumatic brain injury: Frequency of low scores. *Rehabil Psychol*. 2017;62(4):474-484.
39. Carlozzi NE, Goodnight S, Casaletto KB, et al. Validation of the NIH Toolbox in individuals with neurologic disorders. *Arch Clin Neuropsychol*. 2017;32(5):555-573.
40. U.S. Census Bureau (2019). Table 1: Educational attainment of the population 18 years and over, by age, sex, race, and hispanic origin: 2019. Accessed September 27, 2021. https://www.census.gov/data/tables/2019/demo/educational-attainment/cps-detailed-tables.html

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