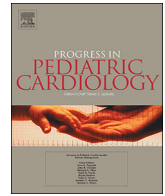




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Cognitive training in children with hypoplastic left heart syndrome: A pilot randomized trial

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ABSTRACT

Neurodevelopmental disabilities are common sequelae of congenital heart disease, particularly cognitive impairments that impede academic achievement. Cognitive training has been shown to be effective in improving working memory in other patient groups. Computerized cognitive training programs may hold potential for children and adolescents with congenital heart disease, but are untested in this population. In this single-center, single-blinded, randomized controlled trial, the feasibility and efficacy of Cogmed Working Memory Training (Cogmed) was compared with observation in children with hypoplastic left heart syndrome 8 to 16 years of age. Participants were randomized to either Cogmed at home for 5 weeks with coaching by a study team member or an observation control group. Baseline, 6–8 weeks later (post-intervention), and 6-month assessments of working memory were completed. Participants randomized to the Cogmed intervention (n = 10) demonstrated greater improvement than controls (n = 10) on measures of working memory, the Wechsler Intelligence Scale for Children-V Working Memory Index and the National Institutes of Health Toolbox Cognitive Battery post-training that were statistically significant (Cohen's $d = 0.76$, $p < .001$ and $d = 0.43$, $p < .01$) compared to controls over the same time period. Improvements were not maintained at 6-month follow-up. Three children withdrew from cognitive training, and one additional child did not complete at least 20 of 25 cognitive training sessions despite coaching. In conclusion, study findings show computerized cognitive training is feasible for most children with hypoplastic left heart syndrome, but shorter sessions may improve adherence. Training-related improvements in working memory occur, though continued reinforcement may be necessary for these gains to be maintained.

1. Introduction

As recent surgical advances have allowed 85% of the 40,000 children born annually with congenital heart disease in the United States [1] to survive into adulthood [2], there are now over 1 million adults with congenital heart disease in the United States and this number continues to grow [3–5]. One of the most pronounced areas of non-cardiac impairment in congenital heart disease is neurocognitive development and function [6]. Early in life, medical procedures carry the

risk of poor cerebral perfusion and thromboembolic complications such as stroke, as well as the risk of general anesthesia which may be particularly significant in the developing brain [7]. A meta-analysis found that children with hypoplastic left heart syndrome incur the largest cognitive deficits [8]. A more recent meta-analysis confirmed that children with hypoplastic left heart syndrome show decrements in overall cognitive function of nearly 1 standard deviation, a large effect size [9]. Correlates of neurocognitive deficits are far reaching, including difficulties in social and emotional functioning and educational

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Fig. 1. Study flow diagram.

The diagram shows how each study participant moved through the study via the baseline study visit (T1), randomization, intervention and two subsequent study visits (T2 and T3).

attainment [10,11]. One study found that by 9 years of age, one-third of the children with hypoplastic left heart syndrome had received remedial academic support [12]. Cognitive remediation programs may hold promise for these children. Cogmed is an adaptive training program that has been utilized in multiple pediatric populations to specifically target deficits in working memory, a key cognitive ability for learning and storing new information, the development of academic skills, and psychosocial adjustment in congenital heart disease patients [13,14]. In a pilot randomized control trial of cognitive remediation versus waitlist control in survivors of childhood brain tumor and leukemia, the intervention group demonstrated greater improvement immediately post-training than controls on measures of working memory (effect size [ES], 0.84) [15] with improvements maintained at 6-month follow up [16]. Several reviews have examined the efficacy of cognitive training programs in children and adults and suggest that cognitive training can be effective in improving specific cognitive skills closely related to the training (near-transfer) such as working memory, although generalization to other cognitive skills that seem unrelated to the cognitive training such as non-verbal abilities or mathematics (far-transfer) has received considerably less support [17–20]. Thus, computerized cognitive training programs may hold potential for children and adolescents with congenital heart disease but are untested in this population and require further research before dissemination to providers and families. A recent American Heart Association Scientific Statement on neurodevelopmental outcomes in children with congenital heart disease noted further efforts are needed to identify the best approaches to remediation.” [21] The goals of this study were to 1) test the feasibility and acceptability of cognitive training with an established cognitive training program (Cogmed) prior to embarking on a larger study; and 2) assess cognitive improvements (a) at baseline versus (vs.) immediate post-test comparison, and (b) at baseline vs. 6-month follow-up comparison of the longer-term effects of Cogmed in children with hypoplastic left heart syndrome who are post-Fontan, the third stage of hypoplastic left heart syndrome palliative cardiac surgeries [22], and 8–16 years of age. We hypothesized that the program would be feasible for children with hypoplastic left heart syndrome to complete, and those receiving the Cogmed intervention would show greater improvement in working memory compared to controls with hypoplastic left heart syndrome who did not receive Cogmed.

2. Materials and methods

Children and adolescents were sequentially recruited from the pediatric cardiology clinic at a single tertiary medical center. Participants were approached if they were ages 8–16 years, with hypoplastic left heart syndrome and the completion of Fontan surgery. Participants were excluded if: they were diagnosed with DiGeorge syndrome (chromosome 22q11 deletion), Down syndrome, or other suspected genetic syndromes, or prematurity (< 37 weeks gestation) as these may contribute to pre-existing cognitive deficits unrelated to congenital heart disease. Children with neurological impairment (i.e. autism or other significant intellectual disability) that might impact Cogmed utilization were also excluded. Further, children with epilepsy managed with a daily anticonvulsant were excluded because seizures requiring a daily anticonvulsant are known to worsen cognition [23,24],

particularly working memory.

All children had a baseline standardized neurological examination by a pediatric neurologist to confirm no major disabilities and were rated using the validated pediatric stroke outcome measure [25]. Scores are assigned for 5 domains: right sensorimotor, left sensorimotor, expressive and receptive language, cognitive/behavioral and are summed for a total pediatric stroke outcome measure score. In each domain, a score of 0 is normal, 0.5 is mild impairment, 1 is moderate and 2 is severe. When all domains are summed, 0 is normal and 10 is the maximum score.

After baseline cognitive and neurological assessment, children were randomized into the Cogmed intervention group and observational control group through block randomization [26]. Group randomization was performed at a 1:1 ratio. Block random assignment was performed by computer (R Project for Statistical Computing) by an unblinded member of our research team who was not involved in any other study procedures.”

Investigators who performed cognitive testing or analyzed testing data were blinded to the allocation. Cognitive function was assessed at three study visit timepoints: baseline (Timepoint 1, T1), immediately post-intervention (6–8 weeks; Timepoint 2, T2), and follow-up (6 months; Timepoint 3, T3) for Cogmed and control participants (Fig. 1). Children randomized to the observation group were offered access to Cogmed training at the end of the 6-month study period. The commercially available Cogmed software package (<http://www.cogmed.com>) was utilized. Cogmed has the strongest support for efficacy in clinical trials and is the only program with a version specifically designed for children and adolescents [27,28]. Cogmed is easy to use, requires pointing and clicking, and requires the same skill level as simple computer games. The Cogmed training program consists of repeated practice on a specific set of working memory, processing speed, and attention tasks that encompass aspects of executive function. Those randomized to Cogmed were asked to complete a standard “dose” of the program; i.e., program sessions lasting 50 min (typically 30–45 min of active training), 5 days per week over a 5-week period for a total of 25 sessions. Each session was recorded online. The frequency and duration of these sessions was tracked. To increase compliance, trained coaches provided supportive contact by phone, text message, and email one to two times per week.

For assessment of general intellectual functioning, participants were administered the Wechsler Intelligence Scale for Children–Fifth Edition (WISC-V) [25] at baseline to assess overall cognitive function. Working Memory was assessed with the subtests of the WISC-V measuring working memory index (WMI; digit span and picture span subtests) were assessed at baseline as a part of the full WISC-V and working memory subtests were administered 6–8 weeks later, after the 5 weeks of training for the Cogmed group, and at 6 months for both groups. Participants also completed the National Institutes of Health Toolbox Cognition Battery (NTCB), composed of five subtests measuring processing speed, working memory and attention, that yield a Fluid Cognition Composite. The NTCB is a standardized, computerized battery intended to serve as a brief (30 min), convenient assessment of neuropsychological function for children [29,30] that is designed to control for practice effects. Our primary outcomes included change in WISC-V WMI scores and the NTCB measure of working memory (List Sorting).

Table 1
Characteristics of randomized study participants with hypoplastic left heart syndrome.

	Randomized to Cogmed intervention (n = 10)	Randomized to observation (n = 10)
Age (^a M (SD))	11.6 (2.45)	10.8 (2.70)
Sex (n, (% male))	8 (80)	8 (80)
Race/ethnicity, White non-Hispanic	9 (90)	100 (100)
Hispanic	1 (10)	0 (0)
Age at first cardiac surgery (days) (M (SD))	6.3 (4.71)	3.9 (1.73)
Surgeries before age 5 years (M (SD))	3.5 (0.53)	3.3 (0.67)
Total number surgeries (M (SD))	3.7 (0.67)	4.3 (2.45)
Full scale IQ (M (SD))	82.2 (13.5)	88.7 (13.2)
Special education in school (n, % yes)	5 (50)	5 (50)
Attention deficit hyperactivity disorder on daily medication	0 (9)	1 (10)
Cognitive risk factors ^b , n (%)		
Premature birth	0 (0)	0 (0)
Genetic syndrome	0 (0)	0 (0)
History of ECMO	6 (60)	0 (0)
Cardiopulmonary resuscitation	4 (40)	0 (0)
Prolonged hospitalization (> 2 weeks)	5 (50)	4 (40)
Perioperative seizures	0 (0)	3 (30)
Known neuroimaging abnormality	0 (0)	2 (20)
Neurological function, (M (SD))		
Total PSOM ^c	0.5 (0.71)	0.35 (0.63)
Cognitive/behavioral PSOM	0.5 (0.71)	0.25 (0.63)

^a M = mean, SD = standard deviation.

^b Only six children had neuroimaging (4 had MRI, 2 had CT), abnormalities were minor.

^c PSOM = pediatric stroke outcome measure.

Statistical analyses were conducted with the Statistical Package for Social Sciences — version 25 (SPSS, 2010) and Mplus — version 8. Means and standard deviations were computed for demographics, cognitive risk factors, neurological function, and baseline FSIQ. The Cogmed versus (vs) control group effect was assessed for (a) the baseline vs. post-intervention difference and (b) for the baseline vs. follow-up difference, using the Mplus cross-group mean-constraint function and full information maximum likelihood estimation (to retain participants with partial data). Our a priori directional hypotheses for improvement in working memory with training justified setting one-tailed alpha = 0.05. A sample of 20 patients (10 per group) using one-tailed tests and an alpha of 0.05, provided power = 0.81 to detect a large effect (Cohen's $d = 0.80$). Previous studies of Cogmed in children have reported similar effects on working memory ($d = 0.75$ to 0.93) [15,31].

The study was approved by the Vanderbilt University Medical Center institutional review board. Parents or guardians provided written informed consent and children assented to participate.

3. Results

Participant demographics by group are summarized in Table 1 and showed that participants with hypoplastic left heart syndrome randomized to the Cogmed (N = 10) and control (N = 10) groups were well matched. The combined FSIQ at baseline was on average 85.45 (SD = 13.44).

In terms of feasibility and acceptability of our protocol, all 10 participants in the control group completed all three study visits. Among those in the cognitive intervention group: 7 completed all three study visits; 6 of 7 completed at least 20 of 25 Cogmed training sessions [15]. Overall, children randomized to Cogmed completed a median of 23.5 sessions, interquartile range (IQR) 15–25, prior to reassessment at T2. The median active training time for Cogmed sessions was 44 min, IQR 39–45 min. Among the 3 participants (age range 8–16 years, FSIQ range 76–89), withdrew from the study: 2 participants withdrew after T1 during the cognitive training period; 1 participant cited frustration with time commitment and concentration required for Cogmed sessions and the other participant moved out of state prior to T2 due to changes in family structure. The participant that withdrew prior to T3 also cited frustration with time commitment and concentration required for

Cogmed sessions. Of those randomized to Cogmed 7 completed a post-training feasibility and acceptability interview. All parents were somewhat or very satisfied with their child's participation in the study, but only 3 of 7 (42%) said their child sometimes, often or always enjoyed the Cogmed program. Concerns cited by parents included: felt their child was often or always frustrated by the program (2) or felt their child was often bored with the Cogmed training program (2). On the exit questionnaire, all parents suggested that 50-minute training sessions were quite long and that shorter training times would make the Cogmed training easier for children and families.

To assess for improvement related to Cogmed, we compared the groups in terms of mean WISC-WMI and the NTCB List Sorting test. We found significant improvement in both the WISC-WMI and the NTCB List Sorting task from baseline (T1) to post-intervention (T2) with cognitive training (Table 2). For WISC-WMI, the effect was large (Cohen's $d = 0.76$, using the pooled SD = 14.15, $p < .001$). For NTCB List Sorting scores, the difference approached a medium effect size ($d = 0.43$, $p < .01$). Over this same period, the control group did not show significant improvement on either variable; effect sizes were $d = 0.24$ and -0.24 , respectively, $p = NS$. For both variables, the change from T1 to T2 was significantly larger for Cogmed than control

Table 2
Working memory means and standard deviations at three timepoints.

Measure	Cogmed group		Control group	
	Mean	SD	Mean	SD
WISC-WMI				
Time 1	93.90	13.70	93.40	13.37
Time 2	104.67	14.61	97.20	17.59
Time 3	100.40	16.32	95.40	14.47
NTCB list sorting				
Time 1	93.30	12.82	97.20	15.27
Time 2	99.17	14.34	94.03	10.70
Time 3	97.53	10.85	99.80	15.79

Time 1 = baseline, Time 2 = 6–8 weeks post-intervention, Time 3 = 6 months. Wechsler Intelligence Scale for Children-V Working Memory Index (WISC-WMI).

National Institutes of Health Toolbox Cognition Battery (NTCB).

Table 3
Significance tests comparing working memory and list sorting at three time-points.

Effects	WISC-WMI ^a			NTCB list sort ^b		
	χ^2	df	p	χ^2	df	p
T1 ^c vs T2 for Control group	1.018	1	ns	1.907	1	ns
T1 vs T2 for Cogmed group	14.69	1	< 0.001	6.877	1	0.004
T1 vs T3 for Control group	0.324	1	ns	0.393	1	ns
T1 vs T3 for Cogmed group	2.574	1	0.054	0.650	1	ns
Group \times Time interaction (T1 vs T2)	2.712	1	0.049	8.174	1	0.002
Group \times Time interaction (T1 vs T3)	0.771	1	ns	0.063	1	ns
Full group \times Time interaction (T1 vs T2 vs T3)	2.712	2	ns	9.181	2	0.005

^a Wechsler Intelligence Scale for Children-V Working Memory Index (WISC-WMI).

^b National Institutes of Health Toolbox Cognition Battery (NTCB) list sort.

^c Time (T) 1 = baseline, T2 = 6–8 weeks post-intervention, T3 = 6 months.

(see Table 3, Group \times T1 vs T2 interaction for WISC-WMI, $p = .049$ and for NTCB, $p = .002$).

From T1 to T3, the change in WISC-WMI for the Cogmed group was smaller than it was for the T1 to T2 interval, and approached significance ($d = 0.43$, $p = .054$). For the control group, the change was not significant ($d = 0.14$, $p = \text{NS}$). Fig. 2 displays the changes in the WISC-WMI over time and delineates some practice effects with repeated testing, though control WMI improvements were non-significant. Among the Cogmed group, WISC-WMI increased from mean 93.9 (T1) to 104.6 (T2), however, significant improvements were not maintained at 6-month follow-up, mean 100.4 (T3). For NTCB List Sorting task the T1 to T3 change was not significant for either group (Cogmed: $d = 0.36$; Control: $d = 0.17$; $p = \text{NS}$). The Group \times T1 vs T3 interaction was nonsignificant for both variables (WMI: $d = 0.77$; NTCB: $d = 0.06$; $p = \text{NS}$).

4. Discussion

In this randomized sample of school-aged children with hypoplastic left heart syndrome, greater improvements were seen in working memory among the Cogmed intervention group than the control group at post-intervention, though both groups showed some improvement, presumably due to practice effects with repeated testing. Cogmed training improved working memory significantly when assessed soon after training, but this large effect was not sustained and only approached significance ($p = .054$) at the 6-month timepoint. A possible explanation is that improving working memory in the face of a challenge such as congenital heart disease requires longer sustained

practice and intervention than is used in the standard dose of the Cogmed program used here. Another factor is that 6 children in the intervention group had received extracorporeal membrane oxygenation (ECMO) compared to none in the control group, suggesting a more complex clinical course and thus potentially higher risk for cognitive difficulties, though FSIQ and WISC-WMI were not significantly different between the randomized and control groups.

The current study focused on near-transfer of the effects of the Cogmed program by utilizing measures of working memory that directly reflect the skills that are taught in the program as our primary dependent variable. Consistent with previous research, we found significant short-term effects favoring the group randomized to Cogmed. Cogmed has been shown to increase working memory capacity [20,32–37] in other patient populations and has also demonstrated some evidence of far-transfer effects, to cognitive skills that were not directly addressed through training, in reading comprehension [38] and attention deficit hyperactivity disorder symptoms [31–33,39]. Although studies have mostly focused on short-term effects, several studies have shown somewhat more durable effects of Cogmed training, including improvements in working memory at 3-month [32] and 6-month post-training [36].

We selected the study population, children and adolescents with hypoplastic left heart syndrome, due to known significant cognitive issues, with the idea that these children and families would be inclined to participate and would benefit from the training. However, despite approaching all children with hypoplastic left heart syndrome seen in pediatric cardiology clinics who met inclusion criteria, interest in this study was greatest in males. Adherence to the training protocol which required 5 training sessions per week for 5 weeks proved challenging for these families of school-aged children, despite at least weekly text and phone call reminders and coaching support. Many cited difficulties with busy schedules, felt parental supervision of cognitive training was necessary and challenging to provide, and despite the video game-based model, felt the program was taxing in addition to required schoolwork. Interestingly, all parents suggested that shorting Cogmed training sessions would be helpful. While our study utilized the standard training protocol of 50-minute sessions (with 30–45 min of active training) 5 days per week for 5 weeks, Cogmed does offer a training option for 25-minute sessions, 5 days per week for 8 weeks that might be more acceptable.

The small sample size was intended to assess feasibility of the study protocol for a planned larger study; thus, we were underpowered to detect all but large effects. However, the methods for a larger, single center study with a similar study protocol were recently published by another research team [40]; the inclusion criteria are less restrictive: children with congenital heart disease who underwent open-heart surgery prior to 12 months of age, and were 7 to 12 years of age at study entry. We look forward to the results of this work.

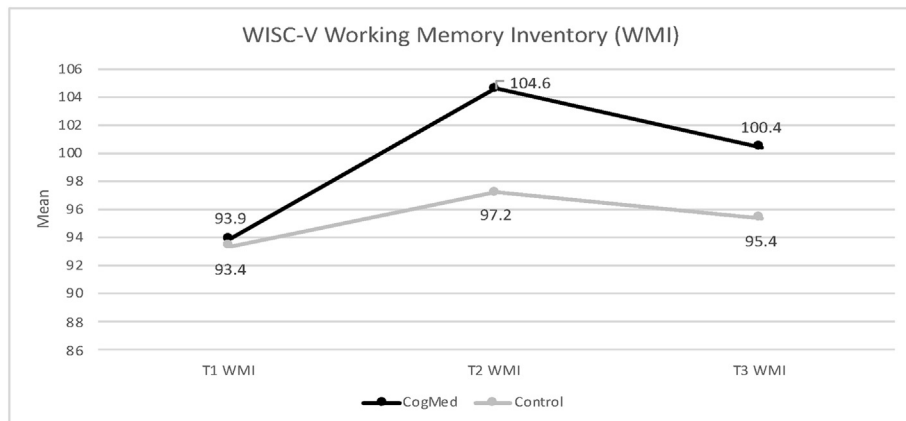


Fig. 2. Mean working memory index at three study timepoints in children with hypoplastic left heart syndrome: Cogmed intervention and control participants.

Working memory was assessed at baseline (T1), 6–8 weeks (after 5-week Cogmed intervention, T2), and 6 months after baseline testing (T3) in children with hypoplastic left heart syndrome randomized to Cogmed training ($n = 10$) or observation ($n = 10$).

Cognitive training in children and adolescents has been shown to be effective for specific cognitive skills but there is little evidence of generalizability to other areas of cognition where training was not received [41], which is a limitation. While it is likely that there are practice effects with measures of cognition, both groups of children (Cogmed and control groups) received testing at the same intervals, so practice effects should not have affected our ability to examine differences between the groups, if present. Another possibility is that with this small sample, we are not able to see smaller long-term effects. The small sample size did not allow adjustment for all covariates. Table 1 demonstrates that while it was not possible to match this small sample on all potential risk factors for cognitive impairment, baseline cognitive function did not vary, and neurological exam findings were similar in the intervention and control groups with mild issues detectable in both groups. Finally, we had a directional hypothesis that after cognitive training, working memory would improve or be unchanged. We did not believe working memory would, on average, worsen over a 6-month time-period. Hence, our sample size and power calculations were based on one-tailed analysis methods.

5. Conclusion

Cognitive training holds promise for children with congenital heart disease, though larger studies are needed. This study was labor intensive for both participants and study staff. Future directions could include simplifying the study protocol before consideration of a multi-site study, working with families to allow more independent cognitive training for children and adolescents, and expanding the study population for a larger, more diverse sample of children with congenital heart disease. The long-term goal is integrating feasible and efficacious cognitive training in a clinical setting to improve cognitive skills in these children.

Author statement

Concept/design: Jordan, Compas, and Markham.

Data collection: Gindville, Lee, Patel, Murphy, Prussien, and Siciliano.

Data analysis/interpretation: Jordan, Compas, Cole, Siciliano, Murphy, and Markham.

Writing/Drafting article: Siciliano and Jordan.

Critical revision of article: All authors.

Approval of article: All authors.

Formal Analysis/Statistics: Cole, Jordan, and Siciliano.

Project administration: Gindville, Lee, and Patel.

Funding secured by: Jordan and Compas.

Declaration of competing interest

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No authors report conflicts of interest.

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