Randomized Controlled Trial of Working Memory Intervention in Congenital Heart Disease

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Objectives To evaluate the efficacy of Cogmed Working Memory Training compared with the standard of care to improve executive function and social outcomes in adolescents with congenital heart disease (CHD) who underwent open-heart surgery in infancy and to identify factors associated with changes in outcomes following the intervention.

Study design In a single-center, randomized controlled trial, adolescents (13-16 years) with CHD were randomly assigned to either Cogmed (home-based 45-minutes sessions for 5-8 weeks) or to a control group. The primary outcome was working memory. Secondary outcomes included inhibitory control and cognitive flexibility as well as parent-reported executive function, symptoms of attention deficit hyperactivity disorder, and social outcomes. All measures were assessed at baseline, post-treatment (1-3 weeks post-training) and at 3-month follow-up. Data were analyzed using an intention-to-treat approach.

Results Sixty adolescents with CHD participated (28 assigned to Cogmed). No improvement at the post-treatment or 3-month follow-up assessments was found for the primary outcome measure of working memory. Compared with the control group, participants assigned to the intervention demonstrated benefits in inhibitory control and attention at the 3-month follow-up (P = .02) and in parent-reported cognitive regulatory skills at post-treatment and 3-month follow-up (P = .02 and P = .04, respectively). Preterm birth, biventricular CHD, and history of attention deficit hyperactivity disorder diagnosis were associated with improved response to the intervention.

Conclusions Cogmed intervention produced improvements in the self-regulatory control abilities of adolescents with CHD. The training did not enhance other areas of executive function or behavioral outcomes. Further studies are needed to evaluate the longer-term potential benefits to other domains. *(J Pediatr 2020;227:191-8)*.

Trial registration Clinicaltrials.gov: NCT02759263.

Pediatric survivors of complex congenital heart disease (CHD) present with a high prevalence of neurocognitive[1-5] and psychiatric disorders.[1,6] Executive function[7-9] and attention impairments[10-12] are among the areas of most frequent vulnerability. Executive functions are higher-order skills that have a protracted developmental trajectory with important changes occurring during adolescence.[13,14] Youth with CHD face particular challenges with reduced attention and working memory skills, poor inhibitory control (ie, control of attention and emotional regulation), and deficits in cognitive flexibility. These executive impairments have been associated with worse psychosocial health status and quality of life in patients with CHD,[15] posing a threat to their mental health, educational achievement, and future employability.

Cogmed Working Memory Training ("Cogmed") is an evidence-based, computerized program designed to improve core dimensions of executive function, attention, and daily life organizational skills. It has been used with various pediatric populations, including children with attention deficit hyperactivity disorder (ADHD)[16-19] and children[20] and adolescents[21] born extremely preterm. Benefits of this intervention in patients with CHD have not been investigated, and clinical trials are needed to demonstrate its feasibility and potential efficacy.

This trial sought to assess the efficacy of Cogmed in improving executive function and social outcomes in adolescents with CHD who underwent open-heart surgery in infancy. Our primary aim was to evaluate the effects of a Cogmed intervention on executive function and related neuropsychological outcomes at post-treatment and 3 months' follow-up, compared with a control group of adolescents with CHD receiving the standard of care (ie, regular cardiology follow-up without specific neurodevelopmental care including Cogmed). Our secondary aim was to explore cognitive, medical,

ADHD	Attention deficit hyperactivity disorder
BRIEF-2	Behavioral Rating Inventory of Executive Function, second edition
CHD	Congenital heart disease
NIH	National Institutes of Health

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and sociodemographic factors associated with changes in selected neurodevelopmental and behavioral scores for adolescents with CHD who received the intervention.

Methods

This study was a single-center, randomized controlled trial to test the efficacy of Cogmed Working Memory Intervention vs the standard of care in 13- to 16-year old adolescents with critical CHD. This study was registered in ClinicalTrials.gov (NCT02759263) and approved by the local institutional review board. Written consent from the primary caregiver or a legal guardian and written assent from the child were obtained for all participants. The trial was conducted and reported following CONSORT guidelines.

Eligibility criteria included (1) a diagnosis of CHD requiring open-heart surgery before age 1 year; (2) aged 13-16 years at the time of assessment; (3) ≥6 months postcardiac surgery; (4) English and/or Spanish speaker; and (5) a history of cardiology care at Boston Children's Hospital. Eligible participants also needed to have access to home Internet and to a computer on which the Cogmed Intervention could be installed. Exclusion criteria were as follows: (1) presence of any chromosomal anomaly and/or genetic syndromes; (2) severe physical and/or sensory impairments (hearing, visual, or psychomotor); (3) IQ scores <85 at baseline assessment; (4) confirmed diagnosis of an autism spectrum disorder or a severe developmental disorder that would prevent successful completion of the planned study assessments; (5) scheduled to undergo major cardiac surgery in the 6 months following enrollment; and (6) received, receiving, or scheduled to receive Cogmed or any other computerized behavioral training program targeting executive function or ADHD. Adolescents with a history of epilepsy or stroke or a concurrent diagnosis of ADHD (treated or untreated) were not excluded.

Participants completed a baseline neuropsychological assessment of general cognitive function, working memory, inhibitory control, cognitive flexibility, and processing speed.[22] Parental reports of everyday-life executive function (ie, behavioral, cognitive, and emotional regulation)[23] as well as ADHD symptomatology[24] and social functioning[25] also were collected. Participants who met all eligibility criteria, including Full-Scale IQ ≥85,[26] were randomized to either the intervention (Cogmed) or to a control group (standard of care). Randomization was based on permuted blocks of varying sizes with stratification by type of CHD (univentricular vs biventricular) and baseline level of executive function (a score <85 vs ≥85 on the Working Memory test from the National Institutes of Health [NIH] Toolbox Assessment of Neurological and Behavioral Function).[22] Cogmed intervention was done at home, and families in the control group were offered the intervention, at no cost, at the end of the study. Outcome measures were also collected 1-3 weeks and 3 months after completion of the intervention. Adolescents in the control group were evaluated at similar time intervals. Investigators and research assistants collecting neurodevelopmental data were blinded to subjects' treatment group assignment, medical and surgical history, as well as any interim event occurring between baseline and 3-month follow-up.

The standard RM version of Cogmed designed for children 7 years and older was used. The intervention consisted of 12 different adaptive tasks, ie, task complexity levels were automatically adjusted to match each child's working memory capacity. All tasks became more difficult as a function of performance on a session-by-session basis. The Cogmed standard program involved 25 training sessions over a 5- to 8-week period. Each training session took approximately 45-50 minutes to complete. A participant was considered compliant if he or she completed at least 20 training sessions. Important features of the Cogmed Working Memory Program included the intensive and structured practice of targeted skills (eg, working memory and control of attention) in a computerized environment at home, which typically facilitates compliance. Cogmed home intervention was closely monitored by a certified coach following Cogmed standard guidelines (ie, daily monitoring of performance and weekly follow-up calls with the participants and their parents). The certified coach tracked compliance to the intervention by monitoring each session completed. Training was actively encouraged by the coach at each weekly follow-up call. Adolescents assigned to the control group received standard of care recommended by their medical home physician or other caregivers.

Table I summarizes the outcome measures of this trial. The primary outcome measure was the List Sorting Working Memory Test from the NIH Toolbox Assessment of Neurological and Behavioral Function (mean = 100; SD = 15).[22] This measure has a test–retest reliability of 0.89. Secondary outcome measures included tests of attention and inhibitory control, cognitive flexibility, and processing speed (all with mean = 100; SD = 15), as well as parental reports of daily-life executive function, ADHD symptoms, and social and autism spectrum–related outcomes (ie, social awareness, social cognition, communication, social motivation, and restricted interests or repetitive behavior) (mean = 50; SD = 10 for all parental reports). Medical and surgical data were collected by a study nurse and research assistants using the child's medical records and parental reports.

The efficacy of Cogmed was evaluated by comparing within-subject differences (baseline to post-treatment and baseline to 3-month follow-up) between treatment groups using an intention-to-treat analysis. With a 2-sided type I error rate of 5% and assuming a within-subject correlation of 0.70, a sample of 60 participants (30 per group) provided 80% power to detect a difference of 0.5 SD or larger between treatment groups on the List Sorting Working Memory Test.[22] This corresponds to a difference of approximately 7.5 units given an expected SD of 15. We also had 80% power to detect a mean difference of 0.60 SD with 10% attrition (27 per group) and 0.64 SD with 20% attrition (24 per group).

Table I. Trial outcome measures

Domains	Measures	Informant	Description	Baseline	Post-treatment	3-month follow-up
Primary outcome						
Working memory	NIH Toolbox List Sorting Working Memory Test[22]	Child	Measure of the ability to process information across the visual and verbal modalities, to hold this information in a short-term buffer, and to actively manipulate it mentally	+	+	+
Secondary outcomes						
Inhibitory control	NIH Toolbox Flanker Inhibitory Control and Attention Test[22]	Child	Measure of the ability to control automatic response tendencies that may interfere with achieving a goal	+	+	+
Cognitive flexibility	NIH Toolbox Dimensional Change Card Sort Test[22]	Child	Measure of an individual's capacity to switch among multiple aspects of a task (ie, alternating dimensions such a colors and shapes)	+	+	+
Processing speed	NIH Toolbox Pattern Comparison Processing Speed Test[22]	Child	Test of the amount of time needed to process a set amount of visual information	+	+	+
Daily-life executive functions	BRIEF-2[23]	Parent	Standardized questionnaire measuring everyday life executive functioning, including behavioral, emotional, and cognitive regulation abilities	+	+	+
ADHD symptoms	Conners 3[24]	Parent	Standardized questionnaire evaluating ADHD symptoms	+	+	+
Social outcomes	SRS-2[25]	Parent	Standardized questionnaire focused on autism spectrum disorders and traits including ratings for social awareness, social cognition, communication, motivation, and restricted interests/repetitive behaviors	+	+	+
General cognitive ability	WISC-V Full-Scale IQ[26]	Child	Standardized measure of general intelligence	+		

SRS-2, Social Responsiveness Scales, 2nd Edition; *WISC-V*, Wechsler Intelligence Scale for Children, 5th Edition.
+ indicates that a test was performed at this time point. All NIH Toolbox Tests and the WISC-V Full-Scale IQ score have a mean of 100 with a SD of 15, with a greater score indicating better functioning. Parent reports (BRIEF-2, Conners 3, and SRS-2) have a mean score of 50 and SD of 10, with a greater score indicating worse outcomes. Post-treatment assessments were conducted 1-3 weeks after cessation of training for the intervention group or 6-8 weeks after baseline for the control group. The 3-month follow-up assessments were conducted approximately 3 months after cessation of training for the intervention group or 4-6 months after baseline for the control group.

Fisher exact tests, *t* tests, and Wilcoxon rank sum tests were used to compare the treatment groups at baseline. Two-sample *t* tests and linear regression were used to assess differences between the intervention and control groups for continuous outcomes (ie, differences of differences in means). Subjects who did not return for post-treatment or 3-month follow-up assessments were excluded from the analyses for which they were missing data. Group comparisons are presented as both unadjusted and adjusted for CHD type (univentricular vs biventricular) and history of ADHD diagnosis as potentially important confounders. Sensitivity analyses were conducted including participants who completed at least 20 Cogmed training sessions (ie, compliant participants). Finally, stepwise linear regression analyses were conducted to identify medical, neurodevelopmental and sociodemographic factors associated with improvements in selected outcome variables (ie, Working Memory, Inhibitory Control and Attention, Cognitive Flexibility, Daily-life parent-reported Executive Function and parent-reported social outcomes) among subjects in the intervention group. Significant improvement in the Akaike information criterion and multivariable $P < .05$ were required for entry into the final models.

Results

A total of 390 patients meeting eligibility criteria on medical records were contacted via postal mail and invited to participate in the trial. Of these, 17 adolescents met exclusion criteria not previously identified on medical records, 63 parents opted out, and 250 families were unable to be reached. Sixty eligible adolescents were enrolled between June 2016 and September 2018 and participated in the trial, meeting trial goals, with 28 assigned to the intervention group (**Figure**; available at www.jpeds.com). Nonparticipants (ie, those who opted out or were unreachable) were less likely to be of white race compared with participants (74% vs 90%, $P = .003$). Participants did not significantly differ from nonparticipants in sex, race, ethnicity, single-ventricle CHD, or age ($P > .05$ for each). Of the 60 participants, 6 adolescents were lost to follow-up after enrollment (due to lack of time to come back for an evaluation or unknown). Participants lost to follow-up did not significantly differ from those who fully participated in the trial.

Baseline medical and sociodemographic characteristics did not significantly differ between the intervention and the control groups for most variables (**Table II**). Parents of

Table II. Baseline patient characteristics

Variables	Intervention (n = 28)	Control (n = 32)
Sociodemographic characteristics		
Male	18 (64)	14 (44)
White race	24 (86)	30 (94)
Primary caregiver college education	22 (79)	29 (91)
Marital status of primary care giver		
Married/partnered	17 (61)	29 (91)
Single/separated/divorced*	11 (39)	3 (9)
Preoperative characteristics		
Birth weight, kg	3.2 ± 0.8	3.2 ± 0.8
Gestational age <37 wk	5 (18)	4 (12)
Univentricular CHD anatomy	8 (29)	8 (25)
NYHA classification		
Class I + II	25 (89)	30 (94)
Class III + IV	3 (11)	2 (6)
Operative characteristics		
Total number of open cardiac operations	2 [1-4]	1 [1-3]
Heart transplant	1 (4)	1 (3)
Hospital stay >2 wk for first operation	7 (29)	6 (24)
Cardiac catheterization (yes/no)	19 (68)	19 (59)
Total number of cardiac catheterizations	2 [1-7]	1 [1-14]
Any events or major complications	18 (64)	22 (69)
ECMO	2 (7)	1 (3)
Seizure	4 (14)	2 (6)
Stroke	1 (4)	0 (0)
Neurodevelopmental characteristics		
Formal diagnosis of ADHD/ADD (lifetime)	7 (25)	4 (12)
Any current ADD/ADHD medication	4 (14)	4 (12)
Use of prescribed medication for ADD/ADHD (lifetime)	7 (25)	4 (12)
Formal diagnosis of anxiety, depression, or other psychiatric disorders (lifetime)	7 (25)	5 (16)
Any current prescribed anxiety, depression, or other psychiatric disorder medications	2 (7)	2 (6)
Use of prescribed medication for anxiety, depression, or any other psychiatric disorders (lifetime)	2 (7)	3 (9)
Formal diagnosis of learning disability (lifetime)†	9 (32)	1 (3)
History of neurodevelopmental interventions		
Early intervention or psychological intervention	13 (46)	8 (25)
Occupational therapy	14 (50)	11 (34)
Physical therapy	13 (46)	13 (41)
Special education in a separate classroom with individualized support	4 (14)	1 (3)
Individualized education program in a regular classroom	12 (43)	7 (22)
Psychotherapy and/or counseling	15 (54)	12 (38)
Baseline List Sorting Working Memory ≤85	1 (4)	3 (9)
Global Cognitive Scales		
WISC-V Full-Scale IQ	101.7 ± 11.7	105.7 ± 10.6
WISC-V Verbal Comprehension Index	101.0 ± 11.7	104.4 ± 9.4
WISC-V Perceptual Reasoning Index	102.8 ± 10.8	108.9 ± 12.0
WISC-V Working Memory Index	101.4 ± 12.3	103.3 ± 12.9
WISC-V Processing Speed Index	102.1 ± 9.9	100.9 ± 15.5

ADD, attention deficit disorder; *ECMO*, extracorporeal membrane oxygenation; *NYHA*, New York Heart Association.
Values are n (%), mean ± SD, or median [range].
*$P < .01$.
†$P < .001$.

adolescents who were assigned to the intervention group were more likely to be single, separated, or divorced (39% vs 9% in the control group, $P = .01$). The proportion of adolescents with a history of learning disability was greater in the intervention group (32% vs 3% in the control group, $P < .001$).

Participants in the intervention group completed a median of 24.5 days of training (IQR, 3-25) and had a mean index improvement of 24.9 ± 14.2 (mean ± SD), ie, improvement on trained tasks. Nineteen adolescents (68%) in the intervention group completed at least 20 sessions and were considered compliant to the intervention. The median length of training for compliant participants was 25 days (IQR 20-25), and their mean index improvement was 26.4 ± 14.2.

Table III summarizes the comparisons between the intervention and control groups from baseline to post-treatment. Analyses showed no significant group difference from baseline to post-treatment in our primary outcome measure (List Sorting Working Memory). Compared with the control group, parents of adolescents who received Cogmed reported better outcomes on the Behavioral Rating Inventory of Executive Function, second edition (BRIEF-2) Cognitive Regulation Index (ie, approximately 3-point decrease in cognitive regulation problems, **Table IV** [available at www.jpeds.com]) and a trend toward better overall executive function on the BRIEF-2 Global Executive Composite ($P = .06$). No other significant differences were found on other neuropsychological or behavioral measures post-treatment. These results persisted after adjustments for type of CHD (univentricular vs biventricular) and ADHD diagnosis.

At the 3-month follow-up, adolescents who received Cogmed showed significantly improved inhibitory control and attention ($P = .02$), better cognitive regulation skills, as reported by their parents (BRIEF-2 Cognitive Regulation Index, $P = .03$), less restricted interests and repetitive behavior concerns ($P = .03$), and a trend toward faster processing speed ($P = .06$) (**Table V**). After adjustments, significant differences between the intervention and control groups persisted for inhibitory control (ie, about 5-point increase at the NIH Toolbox Flanker task) and attention and cognitive regulation skills (ie, about 3-point decrease in Executive function problems as reported by the parent BRIEF-2 Cognitive Regulation and Global Executive Composite). **Table VI** (available at www.jpeds.com) shows differences from baseline to 3-month follow-up. In sensitivity analyses restricted to the 19 compliant adolescents, there was better parent-reported cognitive regulation ($P = .03$) and better social awareness as well as a trend toward better social outcomes (Total Social Responsiveness Scale Score, $P = .06$) for the intervention group compared with the control group at post-treatment. These differences remained after adjustments (**Table VII**; available at www.jpeds.com). At 3-month follow-up, adolescents who were compliant to the intervention tended to have better scores on inhibitory control and attention

Table III. Treatment group differences between the intervention and control groups at post-treatment

	Intervention		Control				
	Baseline (n = 28)	Post-treatment (n = 23)	Baseline (n = 32)	Post-treatment (n = 32)	Unadjusted difference of differences, mean ± SE		
Measures	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		*P* value*	*P* value†
NIH Toolbox							
List Sorting Working Memory	101.1 ± 10.6	106.6 ± 13.2	103.9 ± 15.2	105.0 ± 12.5	3.1 ± 3.7	.40	.47
Flanker Inhibitory Control and Attention	78.8 ± 9.5	83.5 ± 8.9	83.2 ± 14.9	84.1 ± 13.0	3.9 ± 2.3	.09	.11
Dimensional Change Card Sort	93.0 ± 13.7	97.1 ± 16.7	94.3 ± 17.9	100.9 ± 17.4	−1.1 ± 3.5	.76	.84
Pattern Comparison Processing Speed	90.8 ± 19.4	103.1 ± 17.8	95.7 ± 19.7	106.3 ± 20.2	0.2 ± 4.3	.97	.97
BRIEF-2 Parent							
Global Executive Composite	60.5 ± 12.3	57.5 ± 12.3	54.5 ± 11.1	54.1 ± 11.9	−2.3 ± 1.2	.06	.06
Behavioral Regulation Index	54.2 ± 11.7	52.3 ± 10.5	51.2 ± 10.5	49.3 ± 10.3	0.5 ± 1.4	.70	.76
Emotion Regulation Index	58.2 ± 14.2	56.4 ± 13.6	54.3 ± 11.6	52.0 ± 11.3	1.0 ± 1.6	.54	.62
Cognitive Regulation Index	61.8 ± 12.3	58.3 ± 11.6	55.3 ± 12.2	56.1 ± 13.3	−4.1 ± 1.5	.01	.01
Conners 3-Parent							
ADHD Index	66.1 ± 17.1	61.3 ± 15.9	60.7 ± 17.2	58.9 ± 18.9	−3.4 ± 4.3	.43	.30
Hyperactivity and Impulsivity Index	58.9 ± 15.2	57.8 ± 14.6	54.1 ± 15.6	52.8 ± 14.2	−0.5 ± 2.5	.83	.82
SRS-2 Parent							
Total score	57.8 ± 12.2	55.3 ± 12.0	52.0 ± 11.3	51.1 ± 11.9	−1.6 ± 1.4	.26	.18
Awareness	55.1 ± 9.4	53.1 ± 10.8	51.3 ± 11.6	51.0 ± 11.1	−1.8 ± 2.0	.38	.37
Cognition	57.2 ± 10.9	55.2 ± 12.6	50.7 ± 10.2	49.0 ± 10.6	0.0 ± 1.9	.99	.84
Communication	56.7 ± 11.4	54.6 ± 11.1	50.8 ± 9.9	50.1 ± 10.8	−1.8 ± 1.3	.18	.09
Motivation	56.7 ± 15.2	54.0 ± 15.1	54.1 ± 13.2	53.9 ± 13.9	−2.1 ± 1.9	.26	.19
Restricted Interests and Repetitive Behavior	57.8 ± 12.5	56.4 ± 10.1	52.4 ± 11.1	51.7 ± 10.9	−1.2 ± 1.8	.50	.53

All NIH Toolbox scores are age-corrected standard scores. Greater scores on the BRIEF-2 Parent, Conners 3-Parent, and SRS-2 Parent reflect worse outcomes.
**P* values are for the difference of differences, calculated by a 2-sample *t*-test.
†*P* values are for the difference of differences, adjusting for CHD type and ADHD diagnosis.

and processing speed ($P = .07$ for both) and better total scores on the Social Responsiveness Scales, 2nd Edition, parent questionnaire ($P = .03$) as well as on the communication ($P = .05$) and restricted interests and repetitive behavior scales compared with the control group in unadjusted and adjusted models (**Table VIII**; available at www.jpeds.com).

Stepwise linear regression analyses in the intervention group showed that improvement in scores post-treatment on the List Sorting Working Memory test were associated with having biventricular CHD ($\beta = 11.06$, $P = .04$), a history of ADHD ($\beta = 15.03$, $P = .008$), and no history of a learning disability diagnosis ($\beta = -13.41$, $P = .01$). At post-treatment, greater primary caregiver education level was associated with a larger decrease in social cognition difficulties as rated by parents on the Social Responsiveness Scales, 2nd Edition ($\beta = 6.55$, $P = .02$).

Stepwise linear regression analyses in the intervention group conducted on the 3-month follow-up data showed that improvement in List Sorting Working Memory scores were associated with premature birth (<37 weeks' gestation) ($\beta = 15.7$, $P = .03$). No other factor was significantly associated with any of the other outcome variables (inhibitory control, cognitive flexibility, daily-life executive function, and social outcomes).

Discussion

Although a 5-week intense Cogmed training did not have a statistically significant effect on improving working memory, it resulted in improvement of particular secondary outcomes relevant to executive functions, both immediately after treatment and at 3-month follow-up. Changes postintervention can be interpreted as clinically moderate, with a 5-point increase in scores for inhibitory control and approximately 3- to 4-point decrease in parent-reported difficulties with executive function as recorded by the BRIEF-2.

The use of Cogmed to selectively enhance working memory skills and other executive components has been supported by several randomized controlled trials in a variety of clinical pediatric populations including children and adolescents with ADHD[16-19,27] and/or learning disabilities,[19,28] youth born preterm or very low birth weight,[20,21,29,30] and children who underwent neonatal extracorporeal membrane oxygenation and/or congenital diaphragmatic hernia.[31] Our findings contrast with these previous studies, as our group with CHD did not show any significant benefits following Cogmed training on neuropsychological measures of working memory, cognitive flexibility, or processing speed postintervention. However, they significantly improved their inhibitory control (ie, resistance to visual interference and suppression of automatic responses) and cognitive regulation skills, including better planning, organization, and task-monitoring. Similar to studies in cohorts with diagnosed inattentive or combined-ADHD,[31] parents of adolescents with CHD in our trial reported improvements in metacognitive aspects of executive functions.

One potential explanation for the absence of benefit on the skills targeted by the Cogmed program (ie, working memory) may stem from differences in baseline working memory

Table V. Treatment group differences between the intervention and control groups at 3-month follow-up

	Intervention		Control				
	Baseline (n = 28)	3-month follow-up (n = 22)	Baseline (n = 32)	3-month follow-up (n = 32)	Unadjusted difference of differences		
Measures	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	mean ± SE,	*P* value*	*P* value†
NIH Toolbox							
List Sorting Working Memory	101.1 ± 10.6	106.3 ± 12.0	103.9 ± 15.2	105.7 ± 13.8	1.9 ± 3.3	.56	.65
Flanker Inhibitory Control and Attention	78.8 ± 9.5	83.4 ± 9.1	83.2 ± 14.9	82.7 ± 11.2	5.7 ± 2.4	.02	.02
Dimensional Change Card Sort	93.0 ± 13.7	96.2 ± 14.0	94.3 ± 17.9	97.2 ± 13.6	2.3 ± 4.1	.58	.59
Pattern Comparison Processing Speed	90.8 ± 19.4	113.6 ± 22.6	95.7 ± 19.7	108.2 ± 19.8	9.0 ± 4.6	.06	.05
BRIEF-2 Parent							
Global Executive Composite	60.5 ± 12.3	57.0 ± 13.7	54.5 ± 11.1	53.3 ± 10.1	−1.9 ± 1.6	.23	.29
Behavioral Regulation Index	54.2 ± 11.7	52.7 ± 11.9	51.2 ± 10.5	49.1 ± 10.0	0.8 ± 2.0	.67	.59
Emotion Regulation Index	58.2 ± 14.2	55.4 ± 13.6	54.3 ± 11.6	50.5 ± 10.4	0.8 ± 1.9	.68	.59
Cognitive Regulation Index	61.8 ± 12.3	57.9 ± 13.0	55.3 ± 12.2	55.7 ± 11.6	−4.1 ± 1.5	.03	.04
Conners 3-Parent							
ADHD Index	66.1 ± 17.1	61.3 ± 15.9	60.7 ± 17.2	58.9 ± 18.9	0.5 ± 3.9	.90	.98
Hyperactivity and Impulsivity Index	58.9 ± 15.2	57.6 ± 15.2	54.1 ± 15.6	52.6 ± 12.3	−0.5 ± 2.4	.83	.95
SRS-2 Parent							
Total score	57.8 ± 12.2	55.3 ± 12.0	52.0 ± 11.3	51.1 ± 11.9	−2.5 ± 1.7	.14	.12
Awareness	55.1 ± 9.4	53.1 ± 9.7	51.3 ± 11.6	51.1 ± 10.1	−1.9 ± 1.9	.33	.20
Cognition	57.2 ± 10.9	56.6 ± 12.3	50.7 ± 10.2	49.6 ± 9.9	0.4 ± 2.1	.86	.97
Communication	56.7 ± 11.4	56.0 ± 11.3	50.8 ± 9.9	51.7 ± 10.5	−2.5 ± 1.5	.09	.09
Motivation	56.7 ± 15.2	55.6 ± 14.1	54.1 ± 13.2	55.1 ± 15.3	−2.4 ± 2.3	.30	.25
Restricted Interests and Repetitive Behavior	57.8 ± 12.5	54.9 ± 9.6	52.4 ± 11.1	52.4 ± 11.8	−4.1 ± 1.8	.03	.08

All NIH Toolbox scores are age-corrected standard scores. Greater scores on the BRIEF-2 Parent, Conners 3-Parent, and SRS-2 Parent reflect worse outcomes.
**P* values are for the difference of differences, calculated by a 2-sample *t*-test.
†*P* values are for the difference of differences, adjusting for CHD type and ADHD diagnosis.

levels. In contrast to our sample of adolescents with CHD, participants in most Cogmed studies have some degree of baseline working memory impairment, leaving more room for improvement. Indeed, at baseline our group with CHD displayed age-expected working memory, cognitive flexibility, and processing speed outcomes. However, baseline scores on the inhibitory control and attention test were 1 to 2 SD below the expected mean in both groups (intervention and control), suggesting an important vulnerability of inhibitory processes in this sample. In this context, it can be hypothesized that the intervention's benefits could be seen in the areas of greatest developmental need. We could not determine whether Cogmed has greater benefits for adolescents with working memory impairments because only 3 participants had working memory scores >1 SD below the mean.

Although it remains unclear why only some components of executive function responded to the intervention, the transfer of benefits from working memory training to inhibitory control and cognitive regulation abilities may be explained by underlying common neural substrates.[32] Working memory training is thought involve the activation of prefrontal and parietal networks and subcortical regions such as the basal ganglia.[33] These subcortical structures have been specifically associated with impulse control and behavioral regulation[32,33] and may have relatively independent pathways to higher-order brain networks. Thus, it may be hypothesized that individual differences in the baseline efficiency of core executive processes may modulate the neuroplasticity following a cognitive intervention. If this hypothesis is supported by future analyses, a detailed understanding of a patient's executive function phenotype will be necessary to target the best intervention strategy. Of note, our results in adolescents may differ from findings in younger children with CHD. Indeed, executive functions greatly change with age in terms of onset and speed of development.[13] Thus, the benefits of Cogmed or any other executive function–focused intervention may vary greatly depending on the age at administration. Evidence from meta-analyses of working memory training suggest that greater benefits are generally seen in children (<10-12 years)[34] but also can be seen in adolescents and adults with a certain degree of cognitive difficulties.[35]

Strengths of this trial are that we included blinded outcome assessments for all neuropsychological visits (NIH Toolbox and Wechsler Intelligence Scale for Children, 5th Edition), assessed short- and middle-term outcomes, and achieved a good retention rate (around 80% for the intervention group and 100% for the control group). We accounted for factors that could have influenced training outcomes (ie, type of CHD and presence of ADHD). Among limitations, our trial enrolled higher-functioning adolescents with CHD (ie, IQ >85 and no associated severe neurodevelopmental disorders), which may limit the generalizability of our findings to the broader population with CHD. The randomization procedures did not obtain balance between the intervention and control groups in primary caregiver's marital status and proportion of children with a learning disability. Parents' reports were not blinded and could have over- or under-represented behavioral changes after

intervention. In this pilot study, we did not evaluate other variables that could have impacted participants' responses to the intervention, such as parental support and supervision during the training, motivation, or home environment. In addition, compliance to the intervention was not possible for approximately 30% of adolescents assigned to Cogmed. The intensity of the intervention and lack of motivation may have been a barrier to complete the program for this age group. Finally, we do not know if any effect of the Cogmed intervention persists over time.

Future trials may consider incorporating additional components to the training that could improve compliance for adolescents (ie, dose-variations with shorter training sessions or better reward systems). As most computerized intervention programs, Cogmed requires licenses fees, technology (ie, appropriate internet connection and a computer/tablet), as well as neurodevelopmental follow-up. These requirements may pose a barrier to access for some families of children with CHD. Alternative interventions, such as mindfulness or a combination of physical and cognitive training, could be compared with the efficacy of Cogmed in larger multicenter studies. This approach could lead to a better understanding of intervention efficacy on multiple areas of vulnerability in CHD such as mental health, which will promote better cognitive and psychological outcomes throughout the lifespan. ■

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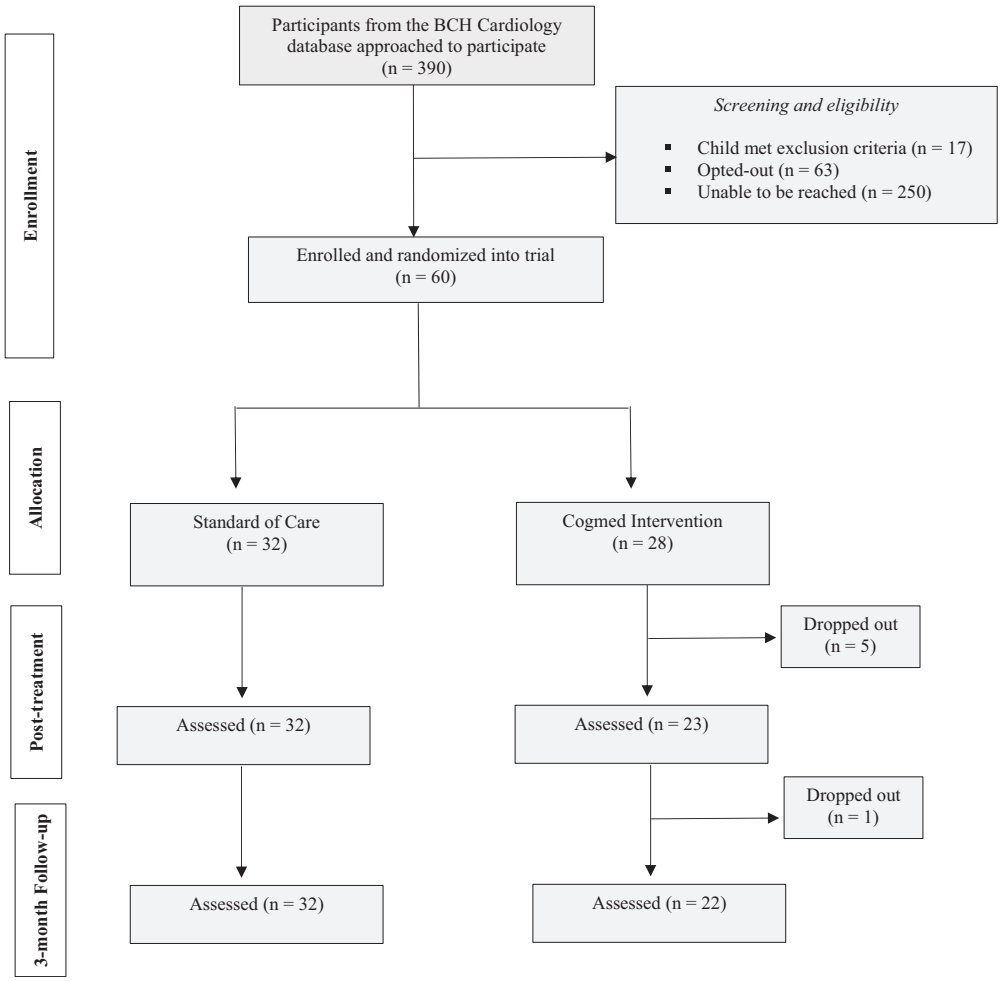

Figure. CONSORT diagram of participant flow. Among the 17 adolescents who met exclusion criteria not previously identified on medical records, 7 were not eligible on phone interview (2 had unexpected future surgery scheduled within the study time-frame, 1 had a visual impairment, 2 had used a similar program, and 2 had chromosomal anomalies), 1 child was not consented for clinical medical reasons, and 9 children had an IQ <85 at baseline and/or had severe clinical issues that would have disrupted the administration of the intervention. *BCH*, Boston Children's Hospital.

Table IV. Differences from baseline to post-treatment in the intervention and control groups

	Intervention		Control	
	Post-treatment-baseline		Post-treatment-baseline	
Measures	Mean ± SD	*P* value*	Mean ± SD	*P* value*
NIH Toolbox				
List Sorting Working Memory	4.2 ± 13.4	.15	1.1 ± 13.3	.65
Flanker Inhibitory Control and Attention	4.8 ± 7.7	.01	0.9 ± 8.9	.57
Dimensional Change Card Sort	5.6 ± 16.2	.11	6.7 ± 9.6	<.01
Pattern Comparison Processing Speed	10.8 ± 19.0	.01	10.6 ± 13.2	<.01
BRIEF-2 Parent				
Global Executive Composite	−2.7 ± 4.5	.01	−0.4 ± 4.5	.61
Behavioral Regulation Index	−1.3 ± 5.4	.24	−1.9 ± 4.8	.03
Emotion Regulation Index	−1.3 ± 5.1	.22	−2.3 ± 6.2	.04
Cognitive Regulation Index	−3.3 ± 6.4	.02	0.8 ± 4.5	.32
Conners 3-Parent				
ADHD Index	−5.2 ± 15.4	.12	−1.8 ± 15.9	.52
Hyperactivity and Impulsivity Index	−1.8 ± 10.3	.42	−1.2 ± 8.4	.41
SRS-2 Parent				
Total score	−2.5 ± 6.0	.05	−0.9 ± 4.5	.26
Awareness	−2.0 ± 8.3	.25	−0.2 ± 6.6	.83
Cognition	−1.7 ± 8.0	.33	−1.7 ± 6.1	.13
Communication	−2.6 ± 5.0	.02	−0.7 ± 4.9	.41
Motivation	−2.3 ± 7.4	.14	−0.2 ± 6.3	.85
Restricted Interests and Repetitive Behavior	−2.0 ± 8.4	.28	−0.7 ± 4.9	.42

SRS-2, Social Responsiveness Scales, 2nd Edition.
All NIH Toolbox scores are age-corrected standard scores. Greater scores on the BRIEF-2 Parent, Conners 3-Parent, and SRS-2 Parent reflect worse outcomes.
**P* values are for the difference, calculated by a paired *t*-test.

Table VI. Differences from baseline to 3-month follow-up in the intervention and control groups

	Intervention		Control	
	3 month-baseline		3 month-baseline	
Measures	Mean ± SD	*P* value*	Mean ± SD	*P* value*
NIH Toolbox				
List Sorting Working Memory	3.7 ± 12.1	.16	1.8 ± 12.1	.41
Flanker Inhibitory Control and Attention	5.1 ± 9.4	.02	−0.5 ± 8.2	.72
Dimensional Change Card Sort	5.2 ± 16.0	.14	3.0 ± 13.9	.24
Pattern Comparison Processing Speed	21.5 ± 18.6		12.6 ± 15.1	
BRIEF-2 Parent				
Global Executive Composite	−3.1 ± 5.9	.02	−1.2 ± 5.5	.21
Behavioral Regulation Index	−1.2 ± 7.9	.48	−2.1 ± 6.4	.08
Emotion Regulation Index	−3.0 ± 7.6	.07	−3.8 ± 6.5	
Cognitive Regulation Index	−3.1 ± 6.8	.04	0.4 ± 5.2	.66
Conners 3-Parent				
ADHD Index	−1.5 ± 10.6	.5	−2.1 ± 16.2	.48
Hyperactivity and Impulsivity Index	−2.0 ± 6.4	.16	−1.5 ± 10.1	.42
SRS-2 Parent				
Total score	−2.3 ± 6.0	.09	0.2 ± 5.9	.84
Awareness	−2.1 ± 7.2	.19	−0.2 ± 6.9	.88
Cognition	−0.7 ± 8.8	.7	−1.1 ± 6.7	.37
Communication	−1.6 ± 5.0	.15	0.9 ± 5.4	.34
Motivation	−1.4 ± 7.7	.4	1.0 ± 8.5	.52
Restricted Interests and Repetitive Behavior	−4.1 ± 7.2	.01	−0.0 ± 6.2	.98

All NIH Toolbox scores are age-corrected standard scores. Greater scores on the BRIEF-2 Parent, Conners 3-Parent, and SRS-2 Parent reflect worse outcomes.
**P* values are for the difference, calculated by a paired *t* test.

Table VII. Treatment group differences between adolescents compliant to the intervention (≥20 Cogmed sessions) and adolescents in the control group at post-treatment

	Intervention-compliant		Control				
	Baseline (n = 19)	Post-treatment (n = 19)	Baseline (n = 32)	Post-treatment (n = 32)	Unadjusted difference of differences,		
Measures	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	mean ± SE	*P* value*	*P* value†
NIH Toolbox							
List Sorting Working Memory	103.5 ± 10.9	106.2 ± 12.5	103.9 ± 15.2	105.0 ± 12.5	1.6 ± 3.9	.69	.72
Flanker Inhibitory Control and Attention	78.8 ± 10.6	83.5 ± 9.2	83.2 ± 14.9	84.1 ± 13.0	3.8 ± 2.5	.14	.15
Dimensional Change Card Sort	92.0 ± 13.7	97.2 ± 18.3	94.3 ± 17.9	100.9 ± 17.4	−1.4 ± 3.7	.70	.78
Pattern Comparison Processing Speed	92.2 ± 21.0	104.5 ± 19.0	95.7 ± 19.7	106.3 ± 20.2	1.7 ± 4.5	.70	.67
BRIEF-2 Parent							
Global Executive Composite	58.3 ± 11.9	56.1 ± 11.0	54.5 ± 11.1	54.1 ± 11.9	−1.9 ± 1.2	.13	.12
Behavioral Regulation Index	52.4 ± 11.7	51.4 ± 9.7	51.2 ± 10.5	49.3 ± 10.3	0.9 ± 1.5	.56	.61
Emotion Regulation Index	57.4 ± 13.7	55.2 ± 12.3	54.3 ± 11.6	52.0 ± 11.3	0.2 ± 1.7	.93	.96
Cognitive Regulation Index	59.2 ± 12.2	57.1 ± 11.1	55.3 ± 12.2	56.1 ± 13.3	−2.9 ± 1.3	.03	.03
Conners 3-Parent							
ADHD Index	67.2 ± 17.1	61.3 ± 16.8	60.7 ± 17.2	58.9 ± 18.9	−4.1 ± 4.7	.38	.29
Hyperactivity and Impulsivity Index	59.2 ± 16.0	57.0 ± 15.0	54.1 ± 15.6	52.8 ± 14.2	−1.0 ± 2.7	.73	.70
SRS-2 Parent							
Total score	58.8 ± 13.2	55.2 ± 11.8	52.0 ± 11.3	51.1 ± 11.9	−2.7 ± 1.4	.06	.05
Awareness	55.8 ± 10.2	51.6 ± 10.0	51.3 ± 11.6	51.0 ± 11.1	−3.9 ± 1.9	.05	.05
Cognition	58.0 ± 11.5	54.5 ± 11.6	50.7 ± 10.2	49.0 ± 10.6	−1.8 ± 1.7	.29	.29
Communication	57.6 ± 12.1	54.8 ± 10.7	50.8 ± 9.9	50.1 ± 10.8	−2.1 ± 1.4	.16	.11
Motivation	57.9 ± 16.9	54.6 ± 15.9	54.1 ± 13.2	53.9 ± 13.9	−3.0 ± 2.0	.13	.12
Restricted Interests and Repetitive Behavior	59.2 ± 13.3	56.2 ± 10.2	52.4 ± 11.1	51.7 ± 10.9	−2.3 ± 1.9	.24	.22

All NIH Toolbox scores are age-corrected standard scores. Greater scores on the BRIEF-2 Parent, Conners 3-Parent, and SRS-2 Parent reflect worse outcomes.
**P* values are for the difference of differences, calculated by a 2-sample *t*-test.
†*P* values are for the difference of differences, adjusting for CHD type and ADHD diagnosis.

Table VIII. Treatment group differences between adolescents compliant to the intervention (≥20 Cogmed sessions) and adolescents in the control group at the 3-month follow-up

	Intervention-compliant		Control				
	Baseline (n = 19)	3-month follow-up (n = 18)	Baseline (n = 32)	3-month follow-up (n = 32)	Unadjusted difference of differences,		
Measures	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	mean ± SE	*P* value*	*P* value†
NIH Toolbox							
List Sorting Working Memory	103.5 ± 10.9	106.2 ± 12.5	103.9 ± 15.2	105.7 ± 13.8	0.7 ± 3.6	.86	.91
Flanker Inhibitory Control and Attention	78.8 ± 10.6	82.5 ± 8.6	83.2 ± 14.9	82.7 ± 11.2	4.8 ± 2.6	.07	.06
Dimensional Change Card Sort	92.0 ± 13.7	96.4 ± 15.4	94.3 ± 17.9	97.2 ± 13.6	2.2 ± 4.4	.62	.60
Pattern Comparison Processing Speed	92.2 ± 21.0	113.7 ± 24.7	95.7 ± 19.7	108.2 ± 19.8	9.3 ± 5.0	.07	.06
BRIEF-2 Parent							
Global Executive Composite	58.3 ± 11.9	55.8 ± 13.1	54.5 ± 11.1	53.3 ± 10.1	−1.1 ± 1.6	.51	.56
Behavioral Regulation Index	52.4 ± 11.7	51.3 ± 12.1	51.2 ± 10.5	49.1 ± 10.0	0.7 ± 2.2	.76	.73
Emotion Regulation Index	57.4 ± 13.7	54.9 ± 12.6	54.3 ± 11.6	50.5 ± 10.4	0.6 ± 2.1	.79	.72
Cognitive Regulation Index	59.2 ± 12.2	56.7 ± 12.9	55.3 ± 12.2	55.7 ± 11.6	−2.9 ± 1.3	.20	.21
Conners 3-Parent							
ADHD Index	67.2 ± 17.1	65.7 ± 18.8	60.7 ± 17.2	58.9 ± 18.9	1.7 ± 4.3	.70	.75
Hyperactivity and Impulsivity Index	59.2 ± 16.0	57.5 ± 15.9	54.1 ± 15.6	52.6 ± 12.3	−0.3 ± 2.7	.92	.96
SRS-2 Parent							
Total score	58.8 ± 13.2	55.9 ± 11.8	52.0 ± 11.3	51.1 ± 11.9	−3.9 ± 1.7	.03	.03
Awareness	55.8 ± 10.2	52.2 ± 8.6	51.3 ± 11.6	51.1 ± 10.1	−3.5 ± 2.0	.08	.07
Cognition	58.0 ± 11.5	55.7 ± 10.4	50.7 ± 10.2	49.6 ± 9.9	−1.9 ± 1.9	.33	.35
Communication	57.6 ± 12.1	56.0 ± 11.8	50.8 ± 9.9	51.7 ± 10.5	−3.2 ± 1.6	.05	.06
Motivation	57.9 ± 16.9	56.2 ± 14.6	54.1 ± 13.2	55.1 ± 15.3	−3.7 ± 2.4	.13	.14
Restricted Interests and Repetitive Behavior	59.2 ± 13.3	54.8 ± 9.7	52.4 ± 11.1	52.4 ± 11.8	−5.1 ± 2.0	.01	.03

All NIH Toolbox scores are age-corrected standard scores. Greater scores on the BRIEF-2 Parent, Conners 3-Parent, and SRS-2 Parent reflect worse outcomes.
**P* values are for the difference of differences, calculated by a 2-sample *t* test.
†*P* values are for the difference of differences, adjusting for CHD type and ADHD diagnosis.