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Brain training – Can it reduce attention and working memory impairments in very preterm children?

Peter Anderson

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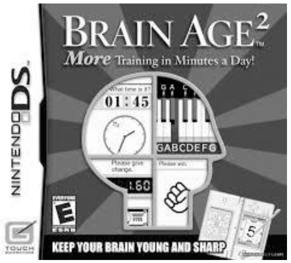
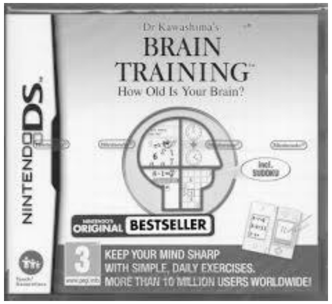
COGMED





Big Business

- Digital-brain-health market
  - 2005 - $210 mil
  - 2009 - $600 mil
  - 2013 - $1.3 bil   ($715m software)
  - 2020 - $6.15 bil ($3.38bil software)
- Lumosity
  - > 70 million members
- End users – only 20% are <18 years

Core principles of cognitive training

- Cognitive skills can be improved with training
- Activities practiced regularly and intensely
- Activities adapt to the individual's current level of performance
- Engaging and fun
  - Computer-games
- Improvement in trained activities will transfer to benefits in other domains and everyday functions

COGMED

Cogmed Program

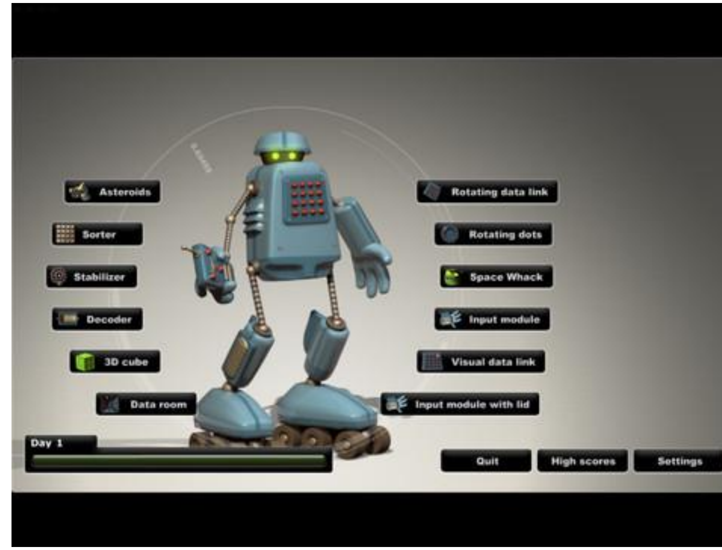
- Designed by Torkel Klingberg at Karolinska Institute
- Utilises cognitive training principles to improving attention and working memory
- Training is regular and intensive (30-40 mins, 5 days per week, for 5 weeks)
- Training commences at the child's baseline
- Demands/complexity constantly adapts to child's ability
- Activities designed to be engaging and fun
- Rewards system
- Training is based on implicit learning rather than explicit learning

Cogmed Process

- Administered by certified coaches
  - Health or educational professional
- Training aid (parent or teacher)
- Completed at home or school
- Monitoring of training – coach calls, training web

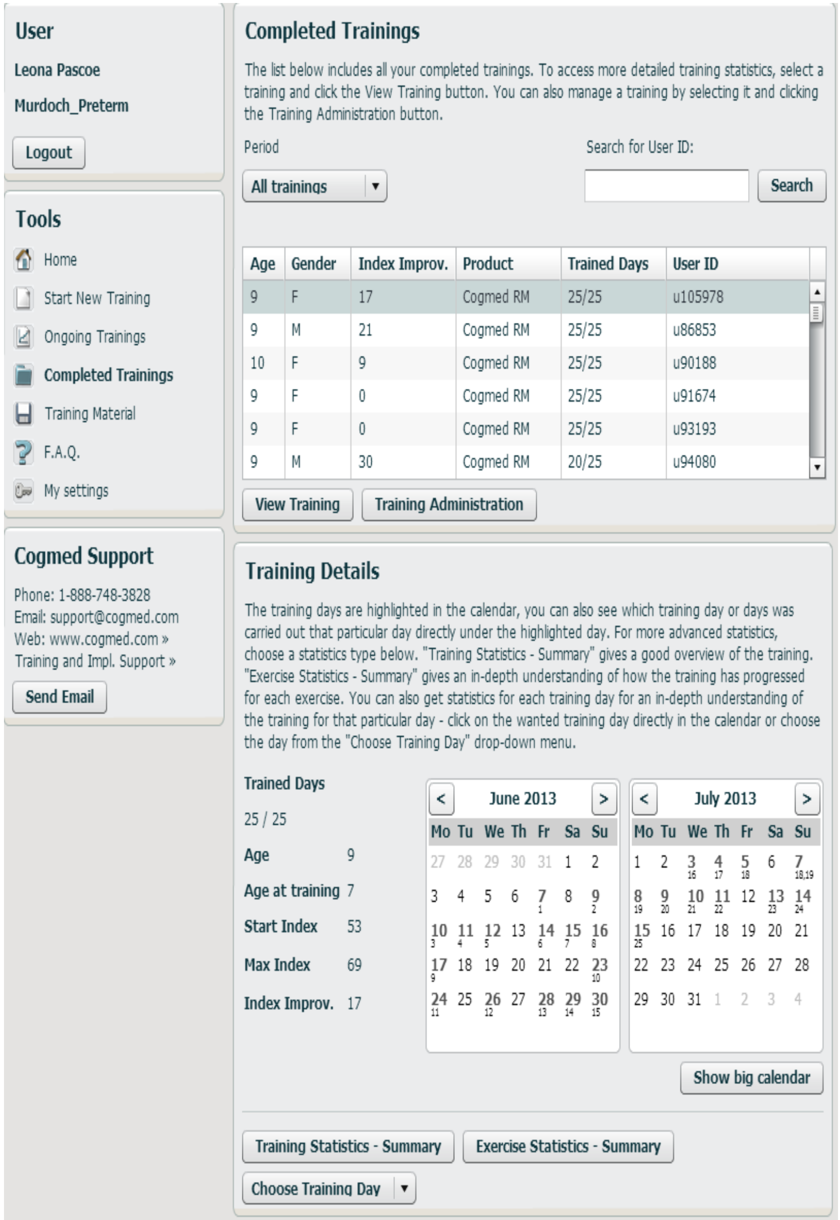
Cogmed JM (Preschool)

Cogmed RM (School age)



Cogmed QM (Adolescent & Adult)

Online Coach Training Web



Efficacy

- Performance gains
  - on trained (working memory) activities
- Near transfer effects
  - Gains on similar but different tasks to trained activities
- Far transfer effects
  - Gains in overall cognitive functioning (eg. IQ)
  - Gains in academic functioning
  - Improved behaviour & adaptive functioning

Level of Evidence

- What level of evidence is needed to support individual cognitive training programs?
  - ? Magnitude of effect
  - ? Duration of effect
  - ? Cost effectiveness

Published research (Pearson's website)

- ADHD (26 papers)
- Anxiety (1 paper)
- Typical / healthy samples (16 studies)
- Brain injury (7 papers)
- Cancer (4 papers)
- Downs syndrome (1 paper)
- Epilepsy (1 paper)
- Fragile X (1 paper)
- Hearing impaired (3 papers)
- Low IQ (2 papers)
- Low language (2 papers)
- Low WM / Academics / Classroom behaviour (8 papers)
- Mild cognitive impairment (2 papers)
- Preterm birth (3 papers)
- PTSD (1 paper)
- Stroke (1 paper)
- Substance abuse (1 paper)
- Typical (20 papers)

Research Summary

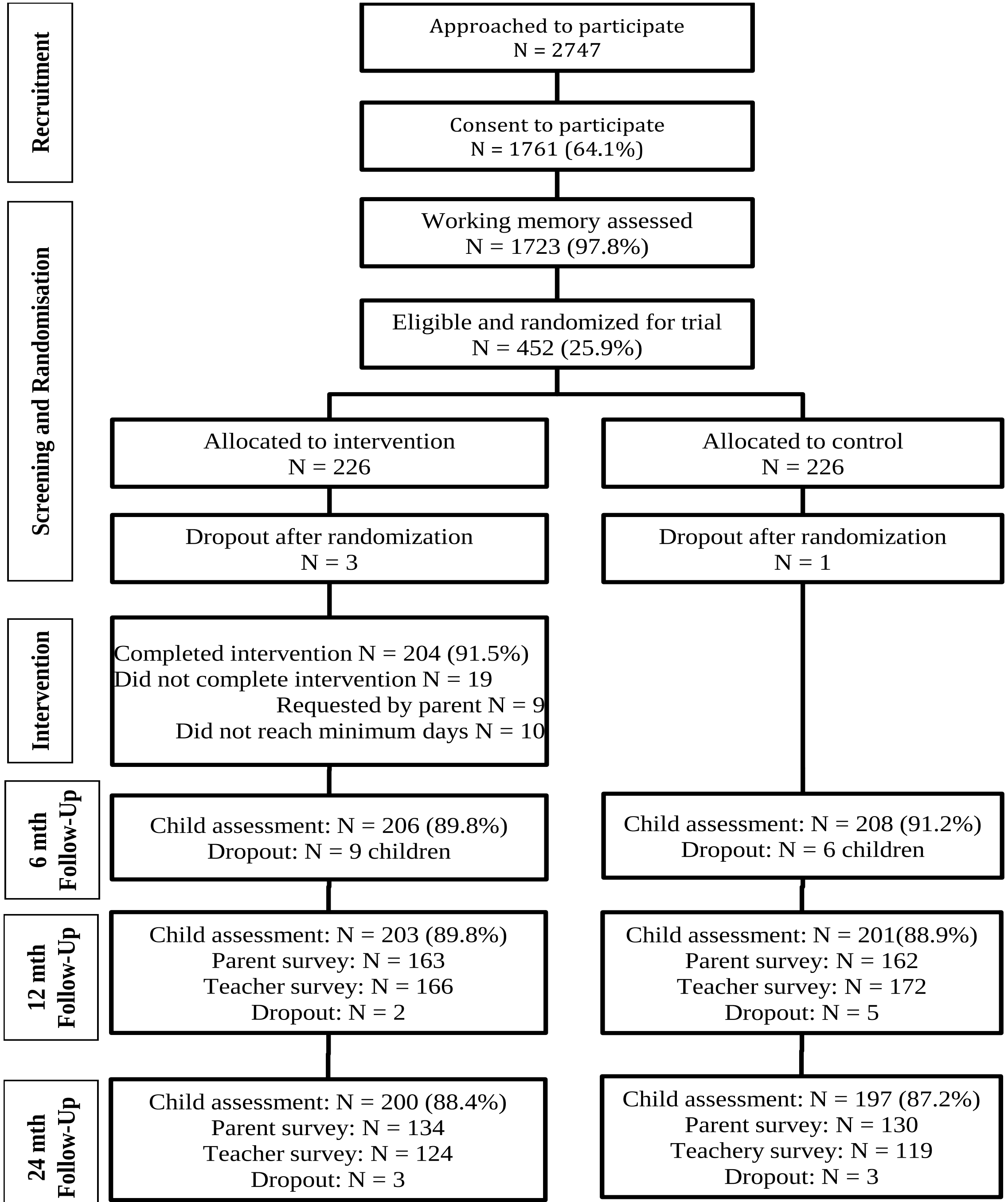
- Design Issues
  - Non RCT studies
  - Passive control groups
  - Limited long-term follow-up
  - Small samples
  - Various selection criteria
- Immediate near-transfer effects
  - Visuo-spatial WM
- Immediate far-transfer effects
  - Yes: daily inattention (parent report)
  - No: Inhibition, nonverbal reasoning
- Delayed effects
  - unknown

Original Investigation

Academic Outcomes 2 Years After Working Memory Training for Children With Low Working Memory
A Randomized Clinical Trial

Gehan Roberts, MPH, PhD; Jon Quach, PhD; Megan Spencer-Smith, PhD; Peter J. Anderson, PhD; Susan Gathercole, PhD; Lisa Gold, PhD; Kah-Ling Sia; Fiona Mensah, PhD; Field Rickards, PhD; John Ainley, PhD; Melissa Wake, MBChB, MD, FRACP

JAMA Pediatr. doi:10.1001/jamapediatrics.2015.4568
Published online March 7, 2016.


Recruitment
Screening and Randomisation
Intervention
6 mth Follow-Up
12 mth Follow-Up
24 mth Follow-Up
Approached to participate N = 2747
Consent to participate N = 1761 (64.1%)
Working memory assessed N = 1723 (97.8%)
Eligible and randomized for trial N = 452 (25.9%)
Allocated to intervention N = 226
Allocated to control N = 226
Dropout after randomization N = 3
Dropout after randomization N = 1
Completed intervention N = 204 (91.5%)
Did not complete intervention N = 19
Requested by parent N = 9
Did not reach minimum days N = 10
Child assessment: N = 206 (89.8%)
Dropout: N = 9 children
Child assessment: N = 208 (91.2%)
Dropout: N = 6 children
Child assessment: N = 203 (89.8%)
Parent survey: N = 163
Teacher survey: N = 166
Dropout: N = 2
Child assessment: N = 201(88.9%)
Parent survey: N = 162
Teacher survey: N = 172
Dropout: N = 5
Child assessment: N = 200 (88.4%)
Parent survey: N = 134
Teacher survey: N = 124
Dropout: N = 3
Child assessment: N = 197 (87.2%)
Parent survey: N = 130
Teachery survey: N = 119
Dropout: N = 3

Short term & working memory: 6 months

Outcome	Mean (SD)		Adjusted		
	Intervention (I)	Control (C)	I-C	95% CI	P
AWMA					
Digit Recall	103 (14)	102 (13)	0.2	-2.0 to 2.4	0.9
Dot Matrix	101 (15)	96 (15)	5.5	2.9 to 8.1	<0.001
Mister X	105 (16)	107 (16)	-2.3	-5.1 to 0.5	0.1
Backwards Digit	104 (17)	101 (13)	2.9	0.02 to 5.8	0.04

Short term & working memory: 12 months

Outcome	Mean (SD)		Adjusted		
	Intervention (I)	Control (C)	I-C	95% CI	P
AWMA					
Digit Recall	104 (15)	103 (13)	-0.4	-2.5 to 1.7	0.7
Dot Matrix	103 (16)	96 (15)	7.8	4.4 to 11.1	<0.001
Mister X	105 (16)	107 (16)	-1.0	-4.4 to 2.5	0.6
Backwards Digit	103 (14)	102 (14)	1.8	-0.9 to 4.5	0.2

Primary outcomes: 12 & 24 months

WRAT-4	Mean (SD)		Adjusted		
	Intervention (I)	Control (C)	I-C	95% CI	P
12 months					
Word reading	104 (15)	106 (13)	-1.8	-3.8 to 0.2	0.1
Comprehension	103 (16)	105 (16)	-2.0	-4.8 to 0.7	0.2
Spelling	103 (17)	105 (17)	-1.9	-4.4 to 0.6	0.1
Math	92 (14)	94 (16)	-2.6	-5.5 to 0.2	0.07

Primary outcomes: 12 & 24 months

WRAT-4	Mean (SD)		Adjusted		
	Intervention (I)	Control (C)	I-C	95% CI	P
12 months					
Word reading	104 (15)	106 (13)	-1.8	-3.8 to 0.2	0.1
Comprehension	103 (16)	105 (16)	-2.0	-4.8 to 0.7	0.2
Spelling	103 (17)	105 (17)	-1.9	-4.4 to 0.6	0.1
Math	92 (14)	94 (16)	-2.6	-5.5 to 0.2	0.07
24 months					
Word reading	101 (15)	103 (13)	-2.0	-4.3 to 0.3	0.1
Spelling	103 (17)	106 (16)	-2.4	-5.5 to 0.6	0.1
Math	94 (16)	97 (16)	-3.0	-5.4 to -0. 7	0.01

Will Cogmed work for very preterm children?

Attention & Working Memory Deficits

- Fundamental cognitive skills
  - Needed for more complex cognitive skills & new learning
- Considered core deficits in preterm children

 ORIGINAL ARTICLES

Computerized Working Memory Training Improves Function in Adolescents Born at Extremely Low Birth Weight

Gro C. C. Løhaugen, PhD, Ida Antonsen, MS, Asta Håberg, PhD, Arne Gramstad, PhD, Torstein Vik, MD, PhD, Ann-Mari Brubakk, MD, PhD, and Jon Skranes, MD, PhD

Objective To evaluate the effect of a computerized working memory training program on both trained and non-trained verbal aspects of working memory and executive and memory functions in extremely low birth weight (ELBW; <1000 g) infants.

Study design Sixteen ELBW infants and 19 term-born control subjects aged 14 to 15 years participated in the training program, and 11 adolescents were included as a non-intervention group. Extensive neuropsychological assessment was performed before and immediately after training and at a 6-month follow-up examination. Both training groups used the CogMed RM program at home 5 days a week for 5 weeks.

Results Both groups improved significantly on trained and non-trained working memory tasks and on other memory tests indicating a generalizing effect. Working memory capacity was improved, and effects were maintained at the 6-month follow-up examination. There was no significant improvement in the non-intervention group at the 6-week follow-up examination.

Conclusions The computerized training program Cogmed RM was an effective intervention tool for improving memory and reducing core learning deficits in adolescents born at ELBW. *(J Pediatr 2011;158:555-61)*.

Cogmed training – ELBW & Term adolescents (14-16 yrs)

Table II. Non-trained working memory tasks from the Wechsler Memory Scale, before, immediately after training and at 6-month follow-up: raw scores

		ELBW (n = 16)	
Function	Measure	Before training Mean (SD) n = 16	Immediately after training Mean (SD) n = 16
Verbal working memory	Digit span, total correct raw score	13.4 (2.4)	15.9 (2.8)†
	Digit span, forwards, number of items	5.7 (0.8)	6.3 (1.0)*
	Digit Span, backwards number of items	3.7 (0.7)	4.7 (0.9)†
	Letter-number sequencing, total score	7.4 (2.3)	10.2 (2.8)*
Visuo-spatial working memory	Spatial span, total correct raw score	15.1 (2.8)	20.6 (2.3)‡
	Spatial span, number of items forward	5.6 (0.7)	6.8 (0.8)†
	Spatial span number of items backwards	4.6 (1.0)	6.3 (0.2)‡

*$P \leq .05$ versus before training (baseline; Wilcoxon signed-rank test for two related samples).
†$P \leq .01$ versus before training (baseline; Wilcoxon signed-rank test for two related samples).
‡$P \leq .001$ versus before training (baseline; Wilcoxon signed-rank test for two related samples).

Lohaugen et al., 2011, J Pediatr, 158, 555-561.

Cogmed training – ELBW & Term adolescents (14-16 yrs)

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Function	Measure	ELBW (n = 16) Before training Mean (SD) n = 16	ELBW (n = 16) Immediately after training Mean (SD) n = 16	ELBW (n = 16) 6-month follow-up Mean (SD) n = 12
Verbal working memory	Digit span, total correct raw score	13.4 (2.4)	15.9 (2.8)†	16.0 (3.1)*
	Digit span, forwards, number of items	5.7 (0.8)	6.3 (1.0)*	6.3 (1.1)*
	Digit Span, backwards number of items	3.7 (0.7)	4.7 (0.9)†	4.4 (0.5)*
	Letter-number sequencing, total score	7.4 (2.3)	10.2 (2.8)*	8.8 (3.5)
Visuo-spatial working memory	Spatial span, total correct raw score	15.1 (2.8)	20.6 (2.3)‡	19.4 (2.7)†
	Spatial span, number of items forward	5.6 (0.7)	6.8 (0.8)†	6.3 (0.9)*
	Spatial span number of items backwards	4.6 (1.0)	6.3 (0.2)‡	5.8 (0.8)†

*$P \leq .05$ versus before training (baseline; Wilcoxon signed-rank test for two related samples).
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		ELBW (n = 16)			Control (n = 19)	
Function	Measure	Before training Mean (SD) n = 16	Immediately after training Mean (SD) n = 16	6-month follow-up Mean (SD) n = 12	Before training mean (SD) n = 19	Immediately after training Mean (SD) n = 19
Verbal working memory	Digit span, total correct raw score	13.4 (2.4)	15.9 (2.8)†	16.0 (3.1)*	14.8 (2.9)	17.9 (4.1)‡
	Digit span, forwards, number of items	5.7 (0.8)	6.3 (1.0)*	6.3 (1.1)*	6.0 (1.0)	6.7 (1.0)*
	Digit Span, backwards number of items	3.7 (0.7)	4.7 (0.9)†	4.4 (0.5)*	4.2 (0.9)	5.2 (1.2)*
	Letter-number sequencing, total score	7.4 (2.3)	10.2 (2.8)*	8.8 (3.5)	8.4 (1.7)	11.4 (2.4)‡
Visuo-spatial working memory	Spatial span, total correct raw score	15.1 (2.8)	20.6 (2.3)‡	19.4 (2.7)†	17.7 (2.1)	22.8 (2.6)‡
	Spatial span, number of items forward	5.6 (0.7)	6.8 (0.8)†	6.3 (0.9)*	5.8 (0.5)	7.3 (0.9)‡
	Spatial span number of items backwards	4.6 (1.0)	6.3 (0.2)‡	5.8 (0.8)†	5.6 (0.6)	6.7 (0.8)‡

*$P \leq .05$ versus before training (baseline; Wilcoxon signed-rank test for two related samples).
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Cogmed training – ELBW & Term adolescents (14-16 yrs)

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Function	Measure	ELBW (n = 16)			Control (n = 19)		
		Before training Mean (SD) n = 16	Immediately after training Mean (SD) n = 16	6-month follow-up Mean (SD) n = 12	Before training mean (SD) n = 19	Immediately after training Mean (SD) n = 19	6-month follow-up Mean (SD) n = 17
Verbal working memory	Digit span, total correct raw score	13.4 (2.4)	15.9 (2.8)†	16.0 (3.1)*	14.8 (2.9)	17.9 (4.1)‡	17.2 (4.1)*
	Digit span, forwards, number of items	5.7 (0.8)	6.3 (1.0)*	6.3 (1.1)*	6.0 (1.0)	6.7 (1.0)*	6.6 (0.9)
	Digit Span, backwards number of items	3.7 (0.7)	4.7 (0.9)†	4.4 (0.5)*	4.2 (0.9)	5.2 (1.2)*	4.8 (1.2)
	Letter-number sequencing, total score	7.4 (2.3)	10.2 (2.8)*	8.8 (3.5)	8.4 (1.7)	11.4 (2.4)‡	10.4 (3.3)*
Visuo-spatial working memory	Spatial span, total correct raw score	15.1 (2.8)	20.6 (2.3)‡	19.4 (2.7)†	17.7 (2.1)	22.8 (2.6)‡	22.2 (2.1)‡
	Spatial span, number of items forward	5.6 (0.7)	6.8 (0.8)†	6.3 (0.9)*	5.8 (0.5)	7.3 (0.9)‡	7.1 (0.7)†
	Spatial span number of items backwards	4.6 (1.0)	6.3 (0.2)‡	5.8 (0.8)†	5.6 (0.6)	6.7 (0.8)‡	6.5 (0.6)†

*$P \leq .05$ versus before training (baseline; Wilcoxon signed-rank test for two related samples).
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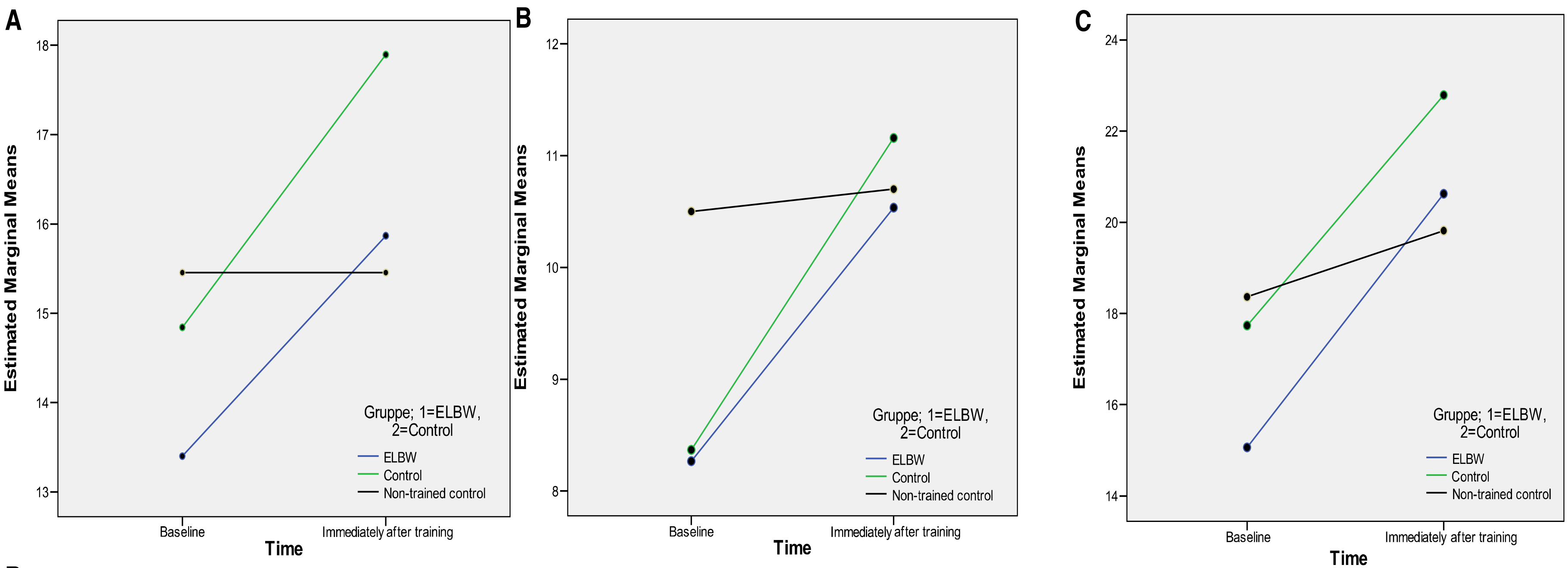
Lohaugen et al., 2011, J Pediatr, 158, 555-561.

Working memory tasks across 2 time-points:
(1) baseline and (2) immediately after training.



Cogmed training – VLBW preschoolers (5-6yrs)

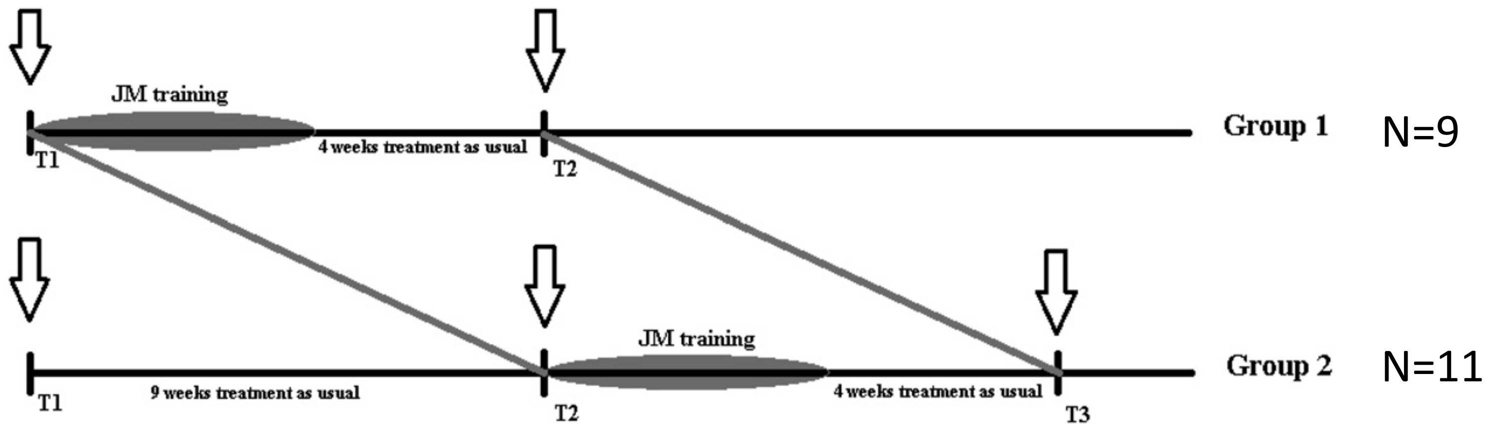


FIGURE 2

Stepped wedge design. The study population was divided into 2 groups. The figure illustrates the time points of testing (white arrows) and training in the 2 groups. The results from pre- and posttraining testing in both groups combined were compared to investigate any training effects in the whole sample.

Working Memory Training Improves Cognitive Function in VLBW Preschoolers
Kristine Hermansen Grunewaldt, Gro Christine Christiansen Løhaugen, Dordi Austeng, Ann-Mari Brubakk and Jon Skranes
Pediatrics 2013;131;e747; originally published online February 11, 2013;
DOI: 10.1542/peds.2012-1965

Cogmed training – VLBW preschoolers (5-6yrs)

TABLE 2 Training Effects on Nontrained Visual and Verbal Working Memory Tasks

	Pretraining Mean (SD) *n* = 20	Posttraining Mean (SD) *n* = 20	Effect Size, η^2	95% CI of the Difference	*P*	Children With Improvement, %
Spatial span						
Forward	4.2 (1.6)	4.7 (2.3)	0.05	(−1.7 to 0.6)	.27	55
Backward	2.3 (1.6)	3.6 (2.2)	0.34	(−2.2 to −0.4)	.01	70
Total	6.4 (3.0)	8.3 (4.2)	0.20	(−3.7 to −0.1)	.03	75
Digit span						
Forward	5.5 (1.5)	5.5 (1.5)	0.001	(−0.6 to 0.5)	.93	40
Backward	1.25 (1.4)	1.7 (1.1)	0.13	(−0.9 to 0.1)	.10	35

Wilcoxon signed rank test for 2 related samples.

Cogmed training – VLBW preschoolers (5-6yrs)

TABLE 3 Training Effects on Attention and Language Tasks from NEPSY

	Pretraining Mean (SD) n = 20	Posttraining Mean (SD) n = 20	Effect Size, η^2	95% CI	P	Children With Improvement, %
Visual attention total time	233.5 (41.0)	212.6 (44.3)	0.16	(−2.0 to 43.8)	.12	30
Auditory attention and response set	49.6 (28.8)	58.2 (30.4)	0.26	(−15.5 to −1.6)	.01	75
Phonological processing	9.3 (5.5)	12.6 (4.7)	0.42	(−5.2 to −1.4)	.00	80
Comprehension of instructions	17.3 (2.8)	18.4 (2.8)	0.12	(−2.4 to 0.3)	.11	60
Repetition of nonsense words	28.9 (8.1)	34.5 (10.7)	0.25	(−10.4 to −0.9)	.02	70
Memory for faces	20.0 (6.2)	24.9 (5.7)	0.49	(−7.4 to −2.5)	.00	80
Narrative memory	12.9 (5.0)	17.5 (5.9)	0.43	(−7.1 to −2.0)	.00	75
Sentence repetition	15.7 (4.3)	17.7 (4.1)	0.35	(−3.3 to −0.7)	.01	75

Wilcoxon signed rank test for 2 related samples.

Computerized working memory training has positive long-term effect in very low birthweight preschool children

KRISTINE HERMANSEN GRUNEWALDT[1,2] | JON SKRANES[1,3] | ANN-MARI BRUBAKK[1,2] | GRO C C LÄHAUGEN[1,3]

1 Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim; **2** Department of Pediatrics, St. Olav University Hospital, Trondheim; **3** Department of Pediatrics, Sørlandet Hospital, Arendal, Norway.

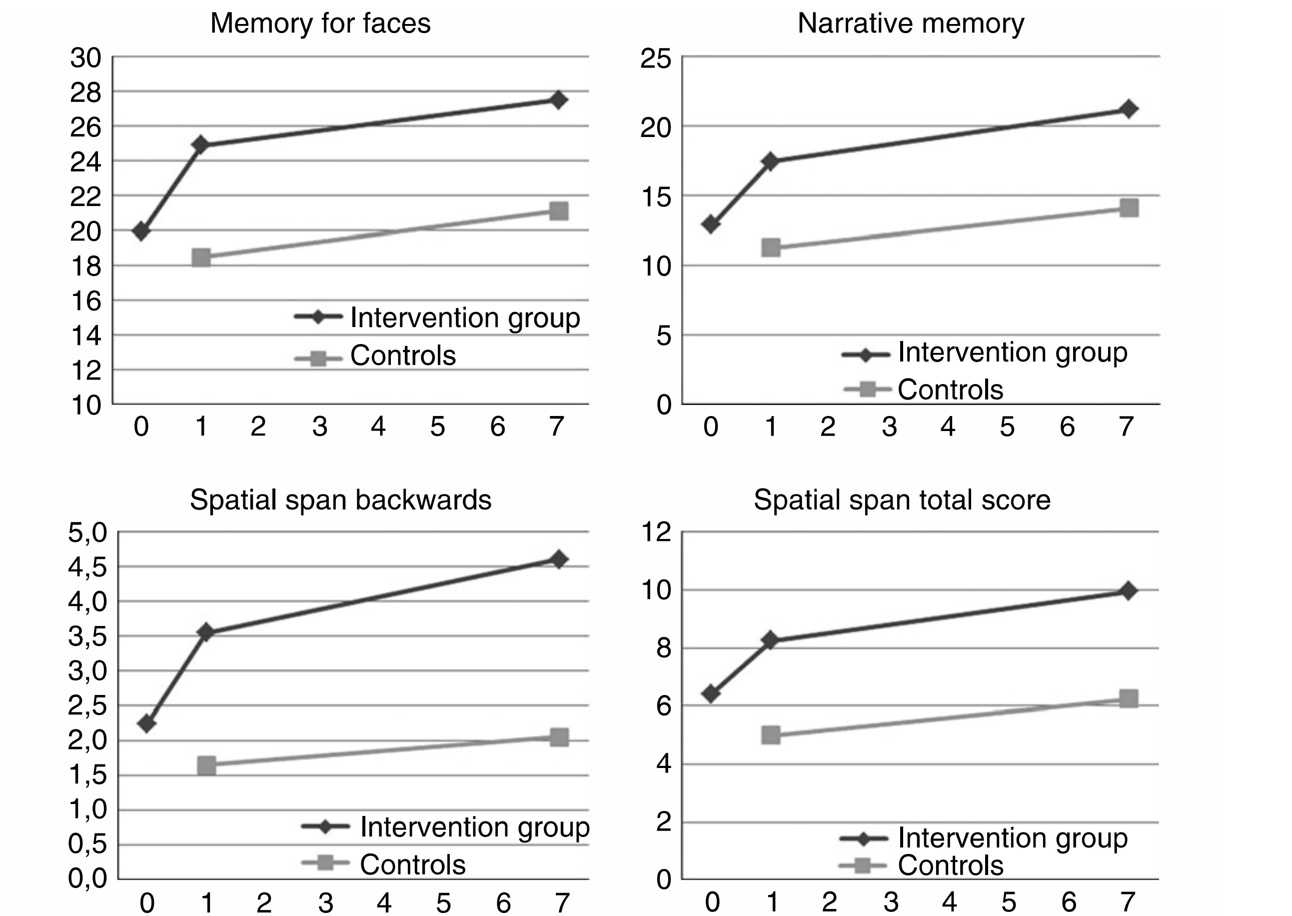


Figure 1: Neuropsychological tests with significantly better performance gains in the intervention group than the comparison group. The figures show raw scores at two time points in the comparison group, and at three time points in the intervention group. The intervention group had higher scores at follow-up and increased performance gain during follow-up than the comparison group.

Computerized working memory training has positive long-term effect in very low birthweight preschool children

KRISTINE HERMANSEN GRUNEWALDT[1,2] | JON SKRANES[1,3] | ANN-MARI BRUBAKK[1,2] | GRO C C LÄHAUGEN[1,3]

1 Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim; 2 Department of Pediatrics, St. Olav University Hospital, Trondheim; 3 Department of Pediatrics, Sørlandet Hospital, Arendal, Norway.

Table III: Changes in neuropsychological test scores and parental questionnaires during follow-up from baseline to 7mo follow-up in the two study groups

	Intervention group (*n*=20)			Comparison group (*n*=17)			
	Baseline Mean (SD)	Follow-up Mean (SD)	Wilcoxon signed-rank *p* value	Baseline Mean (SD)	Follow-up Mean (SD)	Wilcoxon signed- rank *p* value	GLMM, *p* value (PES)
Visual attention total time	212.6 (44.3)	207.3 (33.8)	0.573	250.4 (38.6)	231.9 (25.5)	0.059	0.077 (0.092)
Phonological processing	12.6 (4.7)	17.0 (5.4)	0.001	10.3 (1.9)	15.5 (4.0)	0.007	0.422 (0.019)
Auditory attention and response set	58.2 (30.4)	68.7 (28.2)	0.009	28.2 (30.4)	39.8 (23.7)	0.061	0.167 (0.055)
Comprehension of instructions	18.4 (2.8)	18.6 (2.5)	0.627	16.1 (2.9)	16.5 (2.6)	0.819	0.068 (0.095)
Memory for faces	24.9 (5.7)	27.5 (3.8)	0.006	18.5 (4.8)	21.1 (7.0)	0.088	0.012 (0.171)
Narrative memory	17.5 (5.9)	21.2 (3.8)	0.008	11.3 (5.3)	14.1 (6.3)	0.036	0.002 (0.240)
Statue	27.6 (2.6)	27.8 (3.0)	0.656	25.2 (3.0)	25.4 (6.7)	0.129	0.203 (0.047)
Repetition of nonsense words	34.5 (10.7)	37.8 (4.1)	0.210	31.9 (7.3)	35.5 (4.3)	0.010	0.972 (0.001)
Sentence repetition	17.7 (4.1)	18.6 (2.7)	0.177	17.8 (3.3)	18.9 (3.4)	0.043	0.186 (0.051)
Spatial span forwards	4.7 (2.3)	5.4 (1.0)	0.595	3.4 (1.3)	4.2 (1.3)	0.010	0.226 (0.043)
Spatial span backwards	3.5 (2.2)	4.6 (1.8)	0.073	1.7 (1.3)	2.1 (1.1)	0.191	0.003 (0.232)
Spatial span total score	8.3 (4.2)	10.0 (2.3)	0.151	5.0 (2.3)	6.2 (2.1)	0.015	0.025 (0.140)
Digit span forwards	5.5 (1.5)	6.3 (1.5)	0.009	4.7 (1.4)	5.1 (1.2)	0.266	0.052 (0.106)
Digit span backwards	1.7 (1.1)	2.5 (1.2)	0.007	1.1 (1.3)	1.6 (1.2)	0.145	0.471 (0.015)
ADHD rating scale							
Inattention	5.8 (4.5)	6.0 (5.8)	0.972	5.8 (5.3)	4.6 (6.7)	0.107	0.171 (0.054)
Hyperactivity	5.2 (4.2)	4.9 (4.9)	0.659	6.2 (5.3)	6.2 (7.3)	0.411	0.759 (0.003)
Total score	11.0 (7.7)	10.8 (9.8)	0.812	11.9 (10.0)	10.8 (13.7)	0.213	0.292 (0.033)
Vineland Adaptive Behavior Scales							
Communication	43.3 (3.6)	46.7 (6.1)	0.002	41.9 (3.9)	44.7 (5.3)	0.027	0.259 (0.036)
Daily living skills	47.4 (6.3)	47.5 (7.6)	0.968	45.2 (3.8)	45.8 (5.2)	0.736	0.293 (0.032)
Socialization	50.7 (5.9)	53.7 (5.9)	0.070	48.1 (4.6)	49.7 (6.1)	0.366	0.037 (0.119)
Problem behaviour	32.2 (5.0)	30.9 (4.5)	0.108	33.3 (4.6)	32.1 (4.1)	0.138	0.417 (0.019)

Computerized working memory training has positive long-term effect in very low birthweight preschool children

KRISTINE HERMANSEN GRUNEWALDT[1,2] | JON SKRANES[1,3] | ANN-MARI BRUBAKK[1,2] | GRO C C LÄHAUGEN[1,3]

1 Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim; **2** Department of Pediatrics, St. Olav University Hospital, Trondheim; **3** Department of Pediatrics, Sørlandet Hospital, Arendal, Norway.

Table III: Changes in neuropsychological test scores and parental questionnaires during follow-up from baseline to 7mo follow-up in the two study groups

	Intervention group (*n*=20)			Comparison group (*n*=17)			
	Baseline Mean (SD)	Follow-up Mean (SD)	Wilcoxon signed-rank *p* value	Baseline Mean (SD)	Follow-up Mean (SD)	Wilcoxon signed- rank *p* value	GLMM, *p* value (PES)
Visual attention total time	212.6 (44.3)	207.3 (33.8)	0.573	250.4 (38.6)	231.9 (25.5)	0.059	0.077 (0.092)
Phonological processing	12.6 (4.7)	17.0 (5.4)	0.001	10.3 (1.9)	15.5 (4.0)	0.007	0.422 (0.019)
Auditory attention and response set	58.2 (30.4)	68.7 (28.2)	0.009	28.2 (30.4)	39.8 (23.7)	0.061	0.167 (0.055)
Comprehension of instructions	18.4 (2.8)	18.6 (2.5)	0.627	16.1 (2.9)	16.5 (2.6)	0.819	0.068 (0.095)
Memory for faces	24.9 (5.7)	27.5 (3.8)	0.006	18.5 (4.8)	21.1 (7.0)	0.088	0.012 (0.171)
Narrative memory	17.5 (5.9)	21.2 (3.8)	0.008	11.3 (5.3)	14.1 (6.3)	0.036	0.002 (0.240)
Statue	27.6 (2.6)	27.8 (3.0)	0.656	25.2 (3.0)	25.4 (6.7)	0.129	0.203 (0.047)
Repetition of nonsense words	34.5 (10.7)	37.8 (4.1)	0.210	31.9 (7.3)	35.5 (4.3)	0.010	0.972 (0.001)
Sentence repetition	17.7 (4.1)	18.6 (2.7)	0.177	17.8 (3.3)	18.9 (3.4)	0.043	0.186 (0.051)
Spatial span forwards	4.7 (2.3)	5.4 (1.0)	0.595	3.4 (1.3)	4.2 (1.3)	0.010	0.226 (0.043)
Spatial span backwards	3.5 (2.2)	4.6 (1.8)	0.073	1.7 (1.3)	2.1 (1.1)	0.191	0.003 (0.232)
Spatial span total score	8.3 (4.2)	10.0 (2.3)	0.151	5.0 (2.3)	6.2 (2.1)	0.015	0.025 (0.140)
Digit span forwards	5.5 (1.5)	6.3 (1.5)	0.009	4.7 (1.4)	5.1 (1.2)	0.266	0.052 (0.106)
Digit span backwards	1.7 (1.1)	2.5 (1.2)	0.007	1.1 (1.3)	1.6 (1.2)	0.145	0.471 (0.015)
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Aims

- Evaluate the efficacy of Cogmed in EP/ELBW 7 yr-olds compared to a placebo program
  - Primary outcome: academic functioning at 24 mths post intervention
- Assess neural changes associated with Cogmed
  - MRI pre- and post-intervention
  - Structural, DTI, rs-MRI, fMRI
- Reporting only on short-term outcom

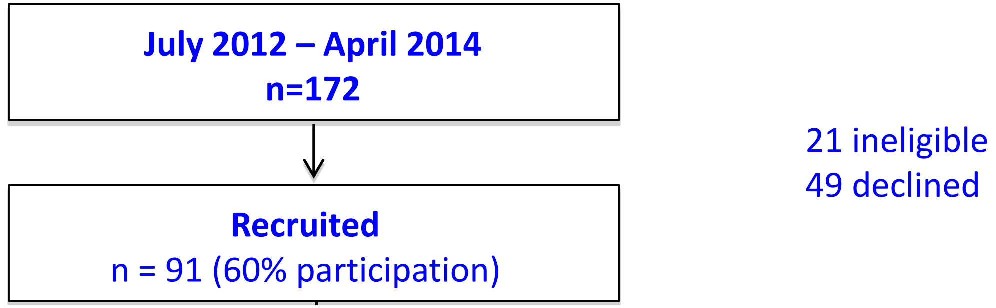
Design

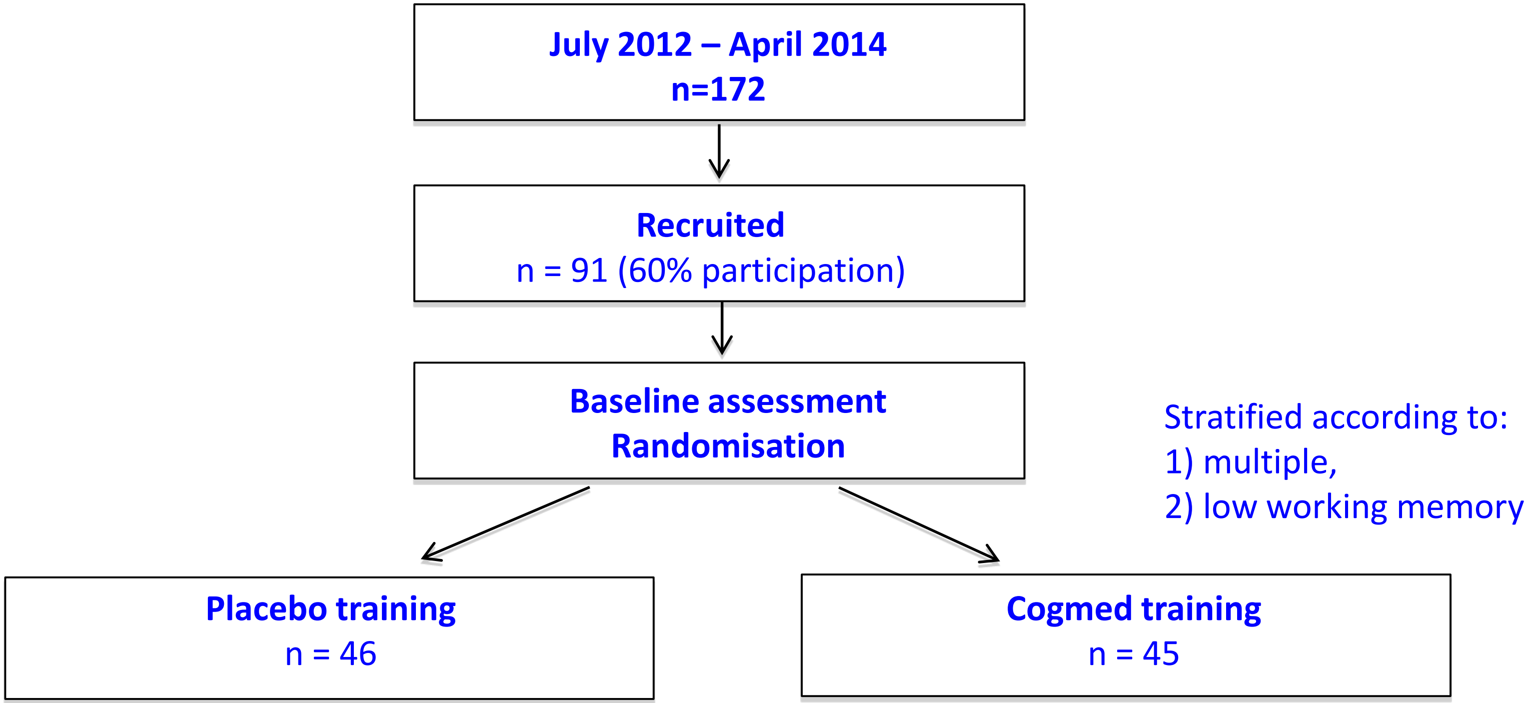
- Double-blinded, placebo-controlled RCT of EP/ELBW children aged 7 years
  - Cogmed
  - Placebo (identical program, but low complexity level)
- All EP and/or ELBW (<1000g) children born in Victoria in 2005 who survived to age 2
  - Exclusions:
    - Children with a severe intellectual/sensory/physical impairment
    - Families unable to support their child

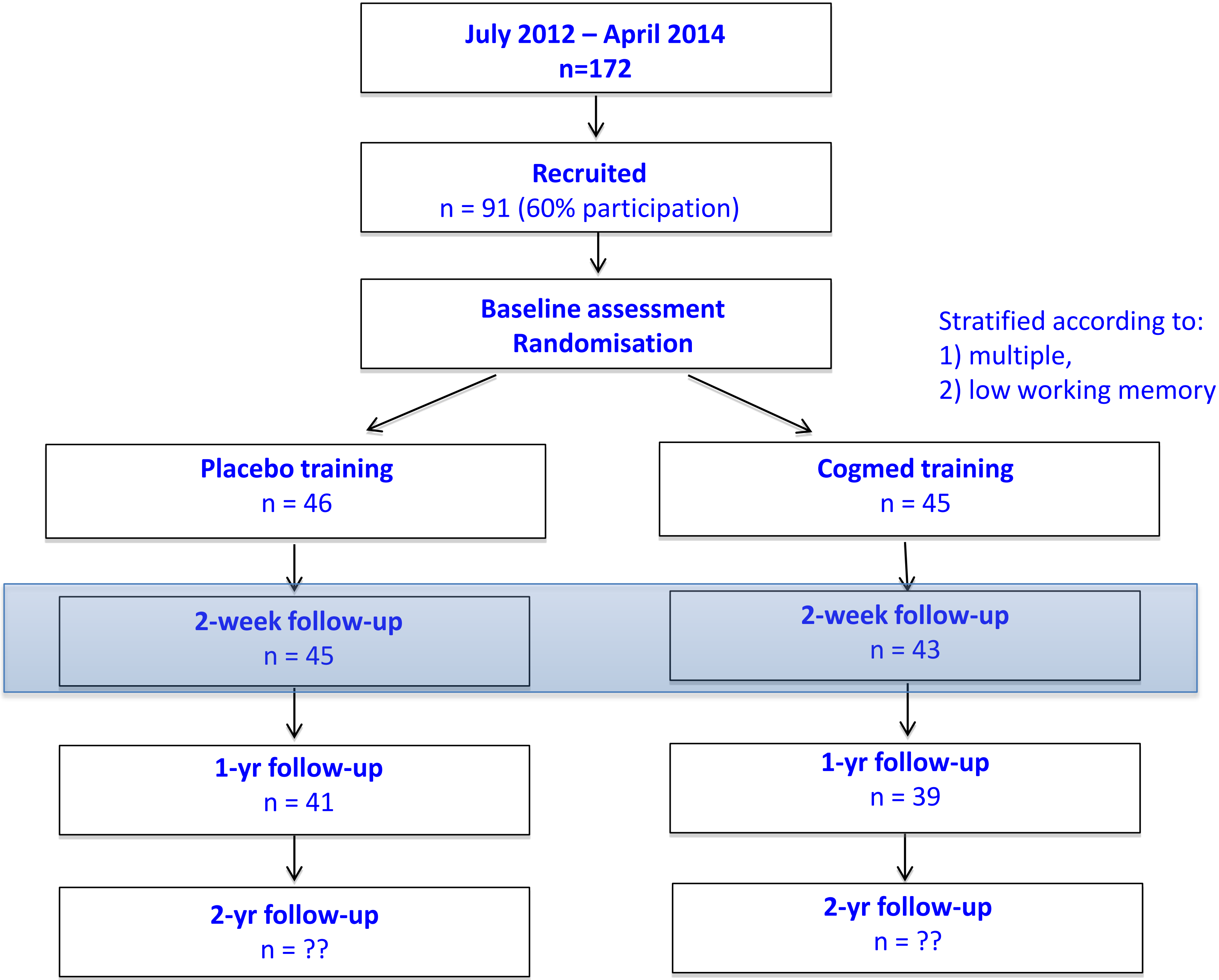
Cognitive Measures

Cognitive Domain	**Measure**
General Cognitive Ability:	DAS-II, General Conceptual Ability (GCA)
Selective Attention:	Sky Search
Sustained Attention:	Score!
Shifting Attention:	Creature Counting
Visual Immediate Memory:	Block recall
	Mazes recall
Verbal Immediate Memory:	Digit Recall
	Word List Recall
Visual Working Memory:	Mister X
Verbal Working Memory	Backward Digit Recall

July 2012 – April 2014
n=172


July 2012 – April 2014
n=172
21 ineligible
49 declined
Recruited
n = 91 (60% participation)


July 2012 – April 2014
n=172
Recruited
n = 91 (60% participation)
Baseline assessment
Randomisation
Stratified according to:
1) multiple,
2) low working memory
Placebo training
n = 46
Cogmed training
n = 45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1) multiple,
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Placebo training
n = 46
Cogmed training
n = 45
2-week follow-up
n = 45
2-week follow-up
n = 43
1-yr follow-up
n = 41
1-yr follow-up
n = 39
2-yr follow-up
n = ??
2-yr follow-up
n = ??

Clinical & Demographic Characteristics

Clinical & Demographic Variables	Cogmed (n=45)	Placebo (n=46)
Gestational age (weeks), M (SD)	27.3 (2.3)	26.9 (1.8)
Birth weight (grams) , M (SD)	841 (147)	891 (196)
Males, n (%)	22 (49)	17 (37)
Multiple birth, n (%)	11 (24)	13 (28)
Bronchopulmonary dysplasia (BPD), n (%)	23 (51)	20 (44)
Proven necrotising enterocolitis (NEC), n (%)	3 (7)	6 (13)
Grade III/IV intraventricular hemorrhage IVH, n (%)	3 (7)	2 (4)
Cystic periventricular leukomalacia (PVL), n (%)	1 (2)	1 (2)
Corrected age, M (SD)	7.6 (0.4)	7.6 (0.4)
Social risk, median (interquartile range)	2 (1-3)	2 (1-3)

Baseline Performance

Cognitive Domain	Measure	Cogmed (n=45)	Placebo (n=46)
General Cognitive Ability:	DAS-II, M (SD)	96.8 (11.4)	100.6 (13.4)
Selective Attention:	Sky Search, M (SD)	8.2 (3.2)	8.8 (3.5)
Sustained Attention:	Score!, M (SD)	6.5 (3.7)	7.5 (4.0)
Shifting Attention:	Creature Counting, M (SD)	9.6 (3.4)	7.6 (3.7)
Visual Immediate Memory:	Block recall, M (SD)	87.1 (18.7)	87.4 (15.4)
	Mazes recall, M (SD)	83.1 (9.6)	83.7 (11.3)
Verbal Immediate Memory:	Digit Recall, M (SD)	93.6 (16.7)	94.8 (16.8)
	Word List Recall, M (SD)	95.4 (13.7)	99.0 (16.1)
Visual Working Memory:	Mister X, M (SD)	103.5 (12.8)	106.4 (14.3)
Verbal Working Memory	Backward Digit Recall, M (SD)	86.2 (13.0)	88.3 (14.0)

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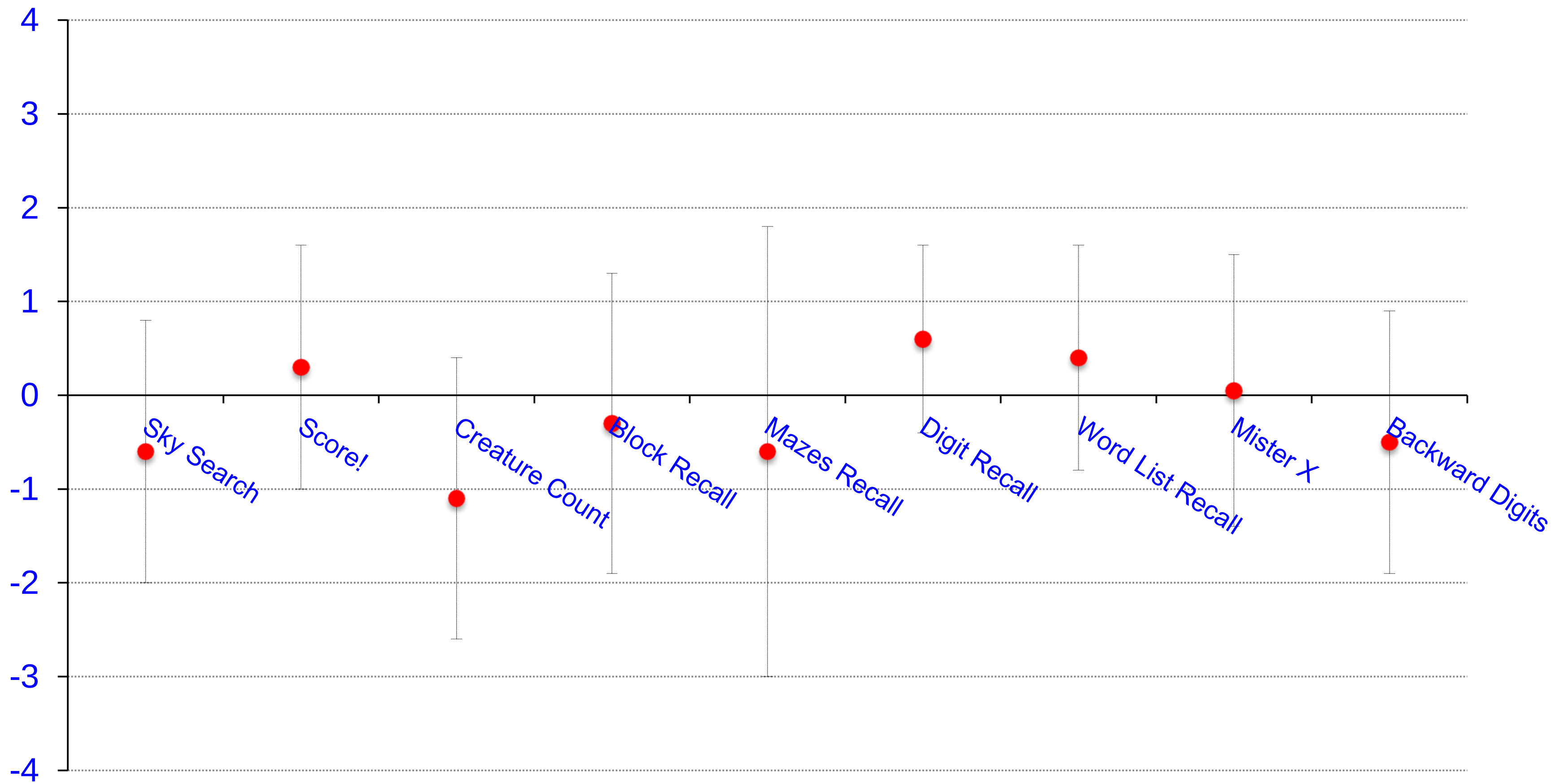
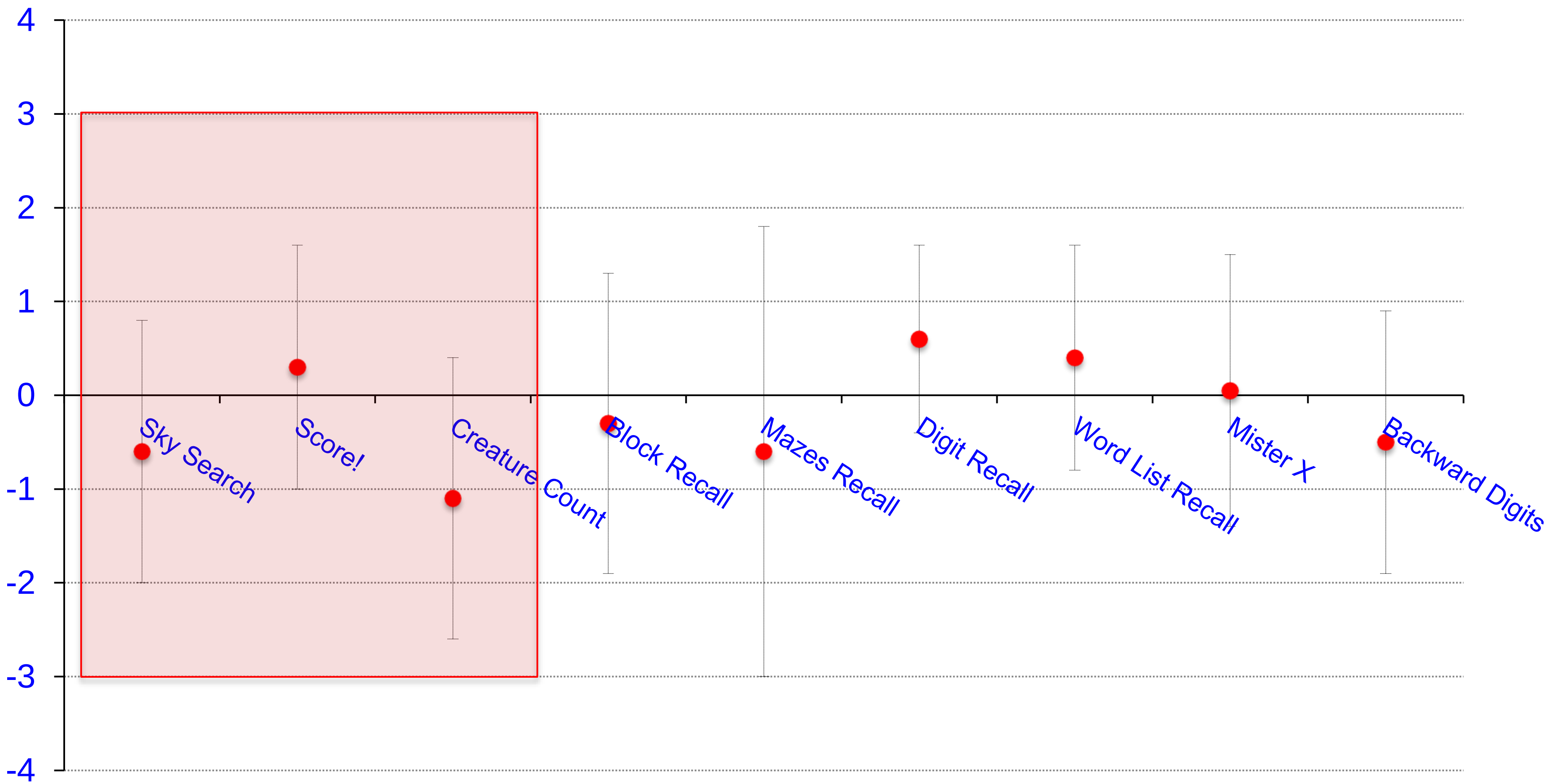
Adjusted between group differences on attention and working memory measures post-intervention



Regressions adjusted for baseline performance. Error bars represent 95% confidence interval of adjusted mean differences.

Adjusted between group differences on attention and working memory measures post-intervention



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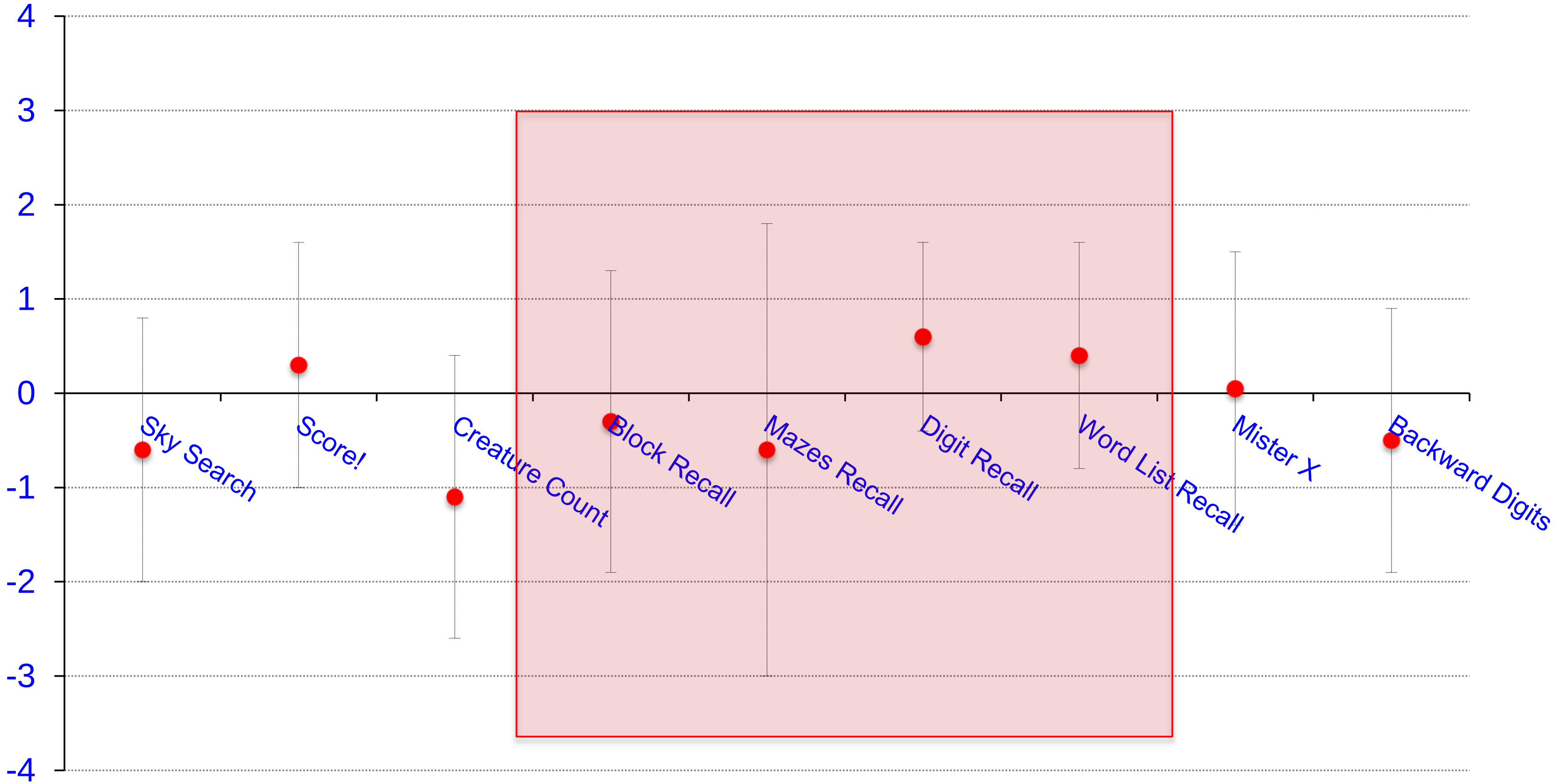

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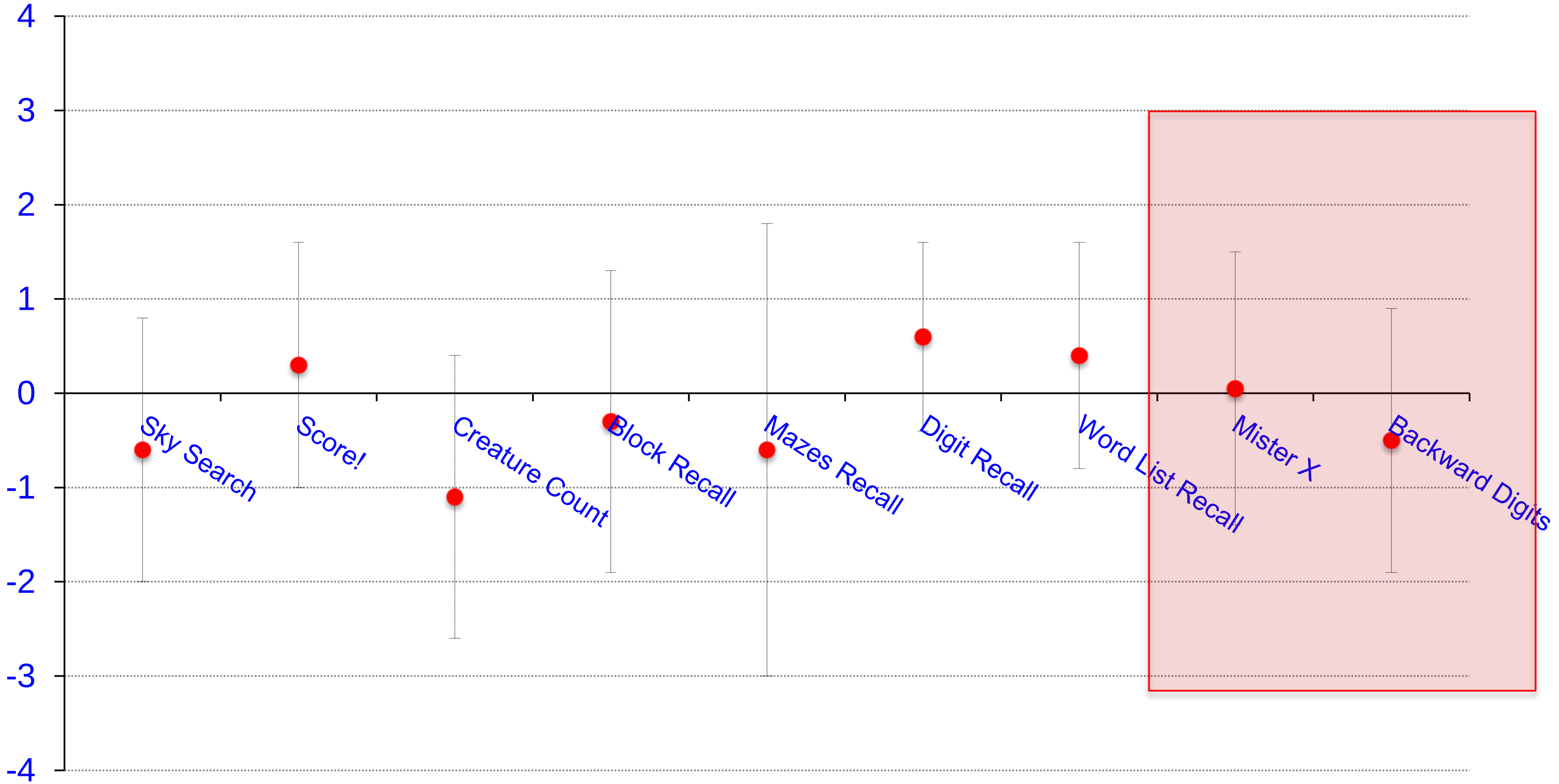

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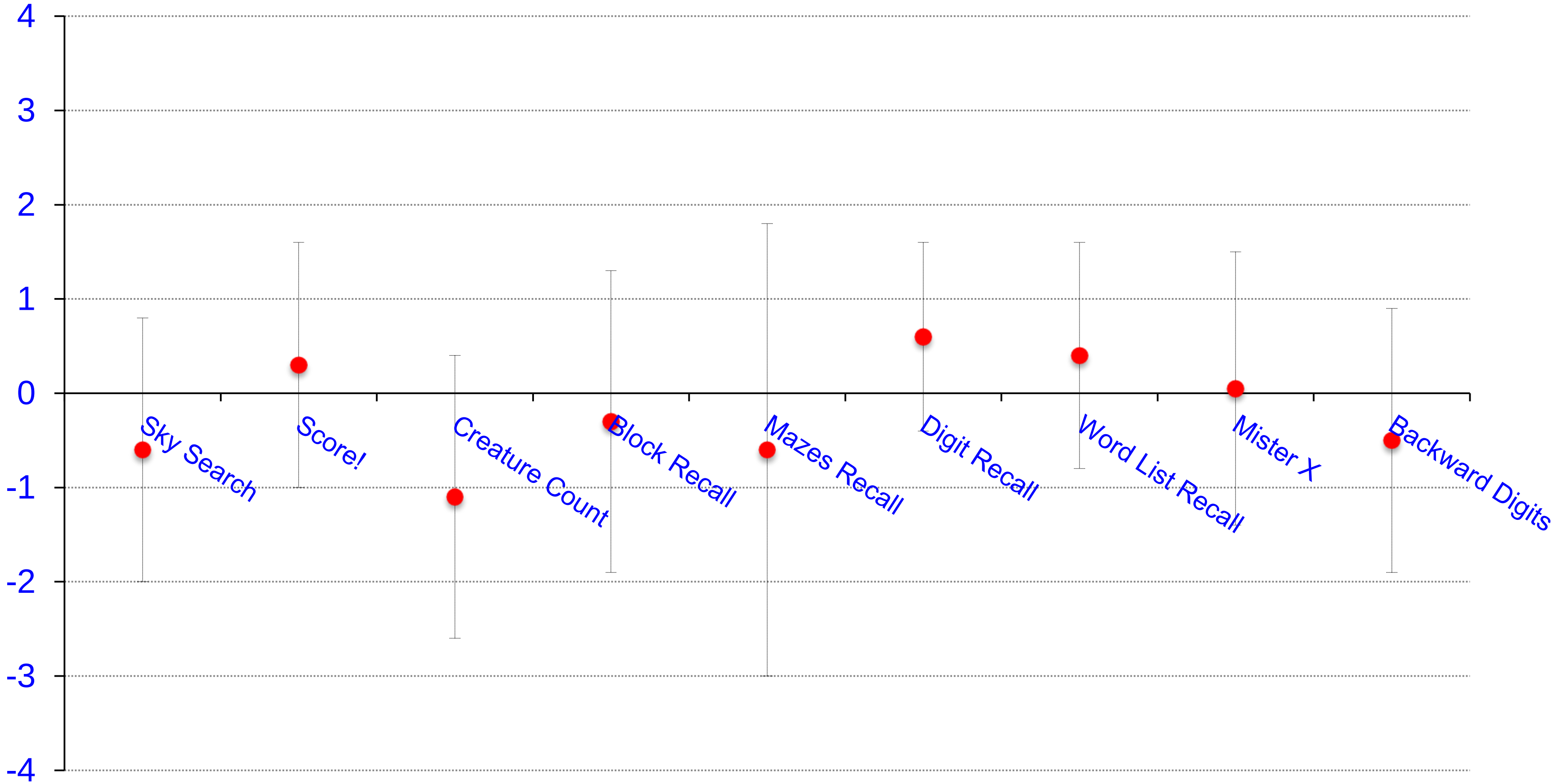
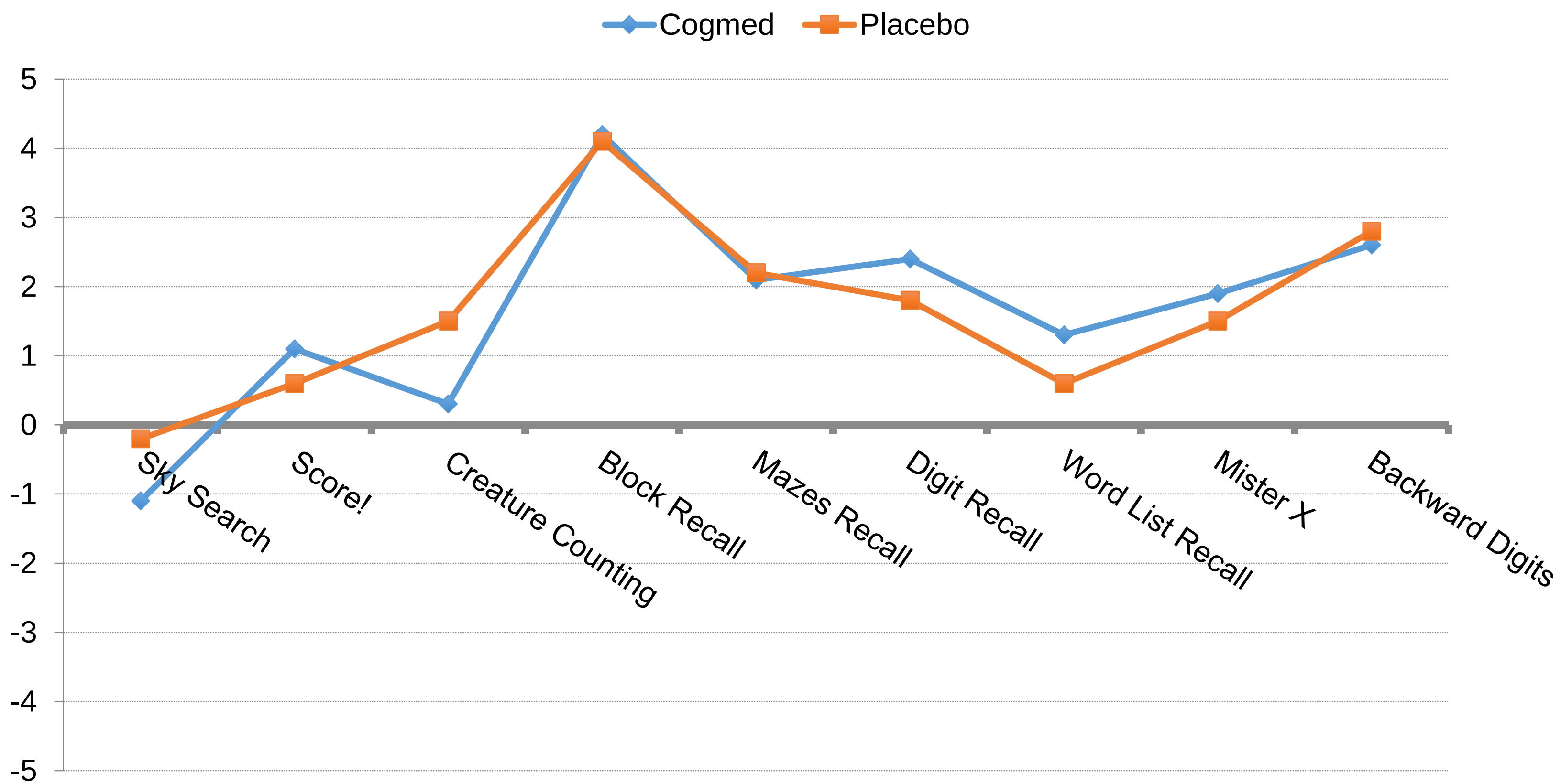
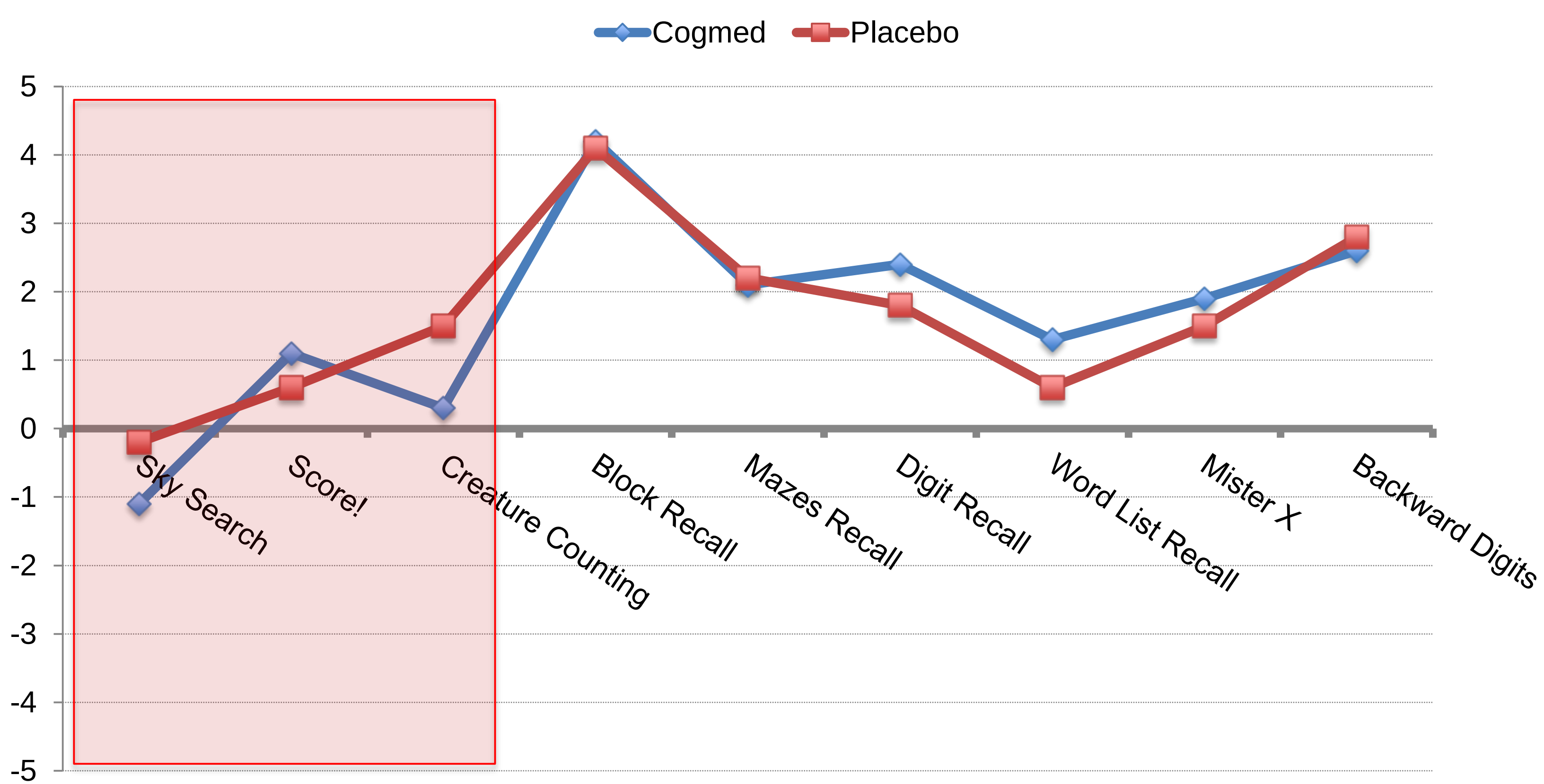


These findings persisted after adjustment for baseline performance, sex, multiples, low working memory status, and baseline IQ.

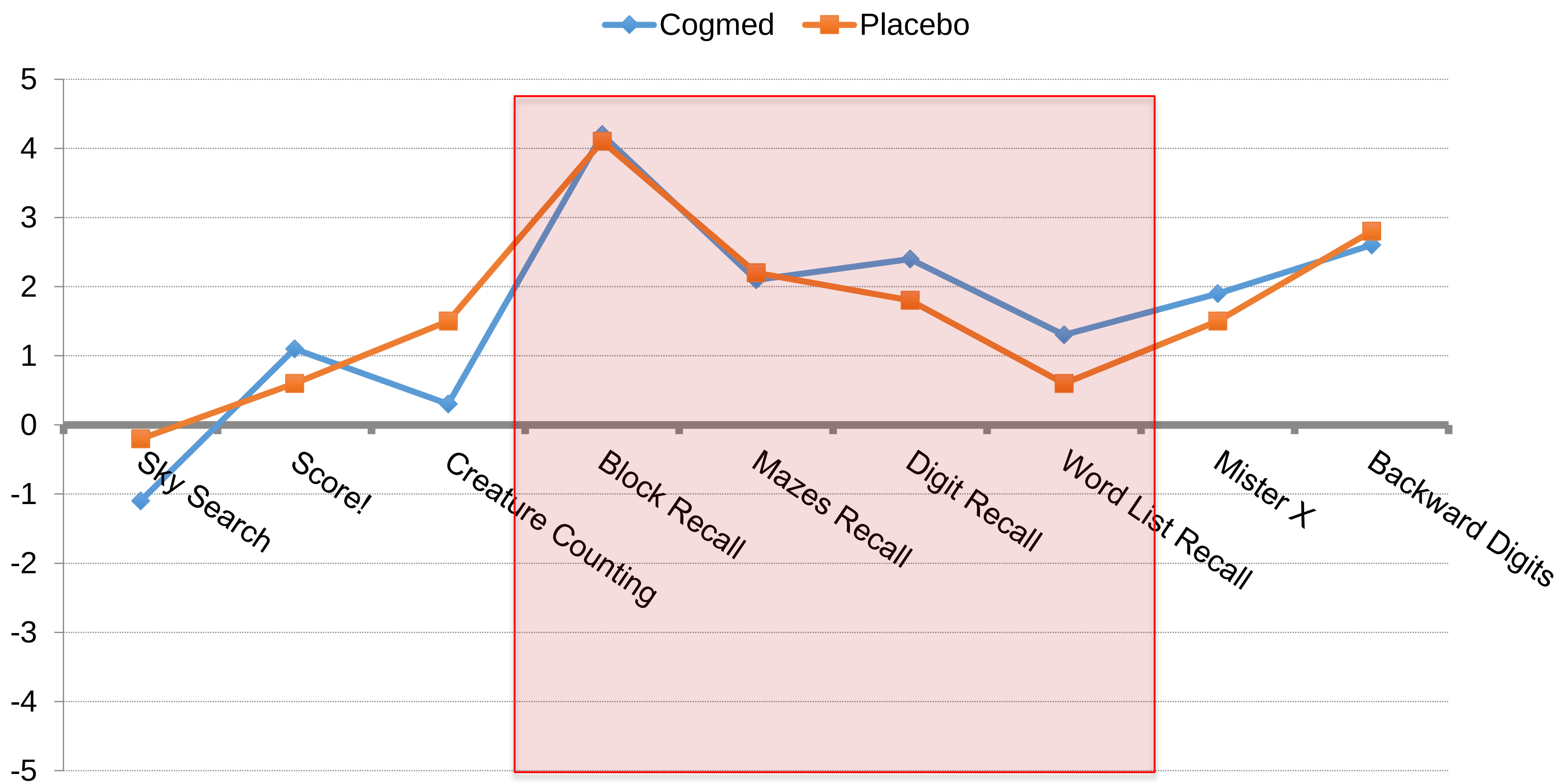
Change in attention and working memory measures from baseline to post-intervention



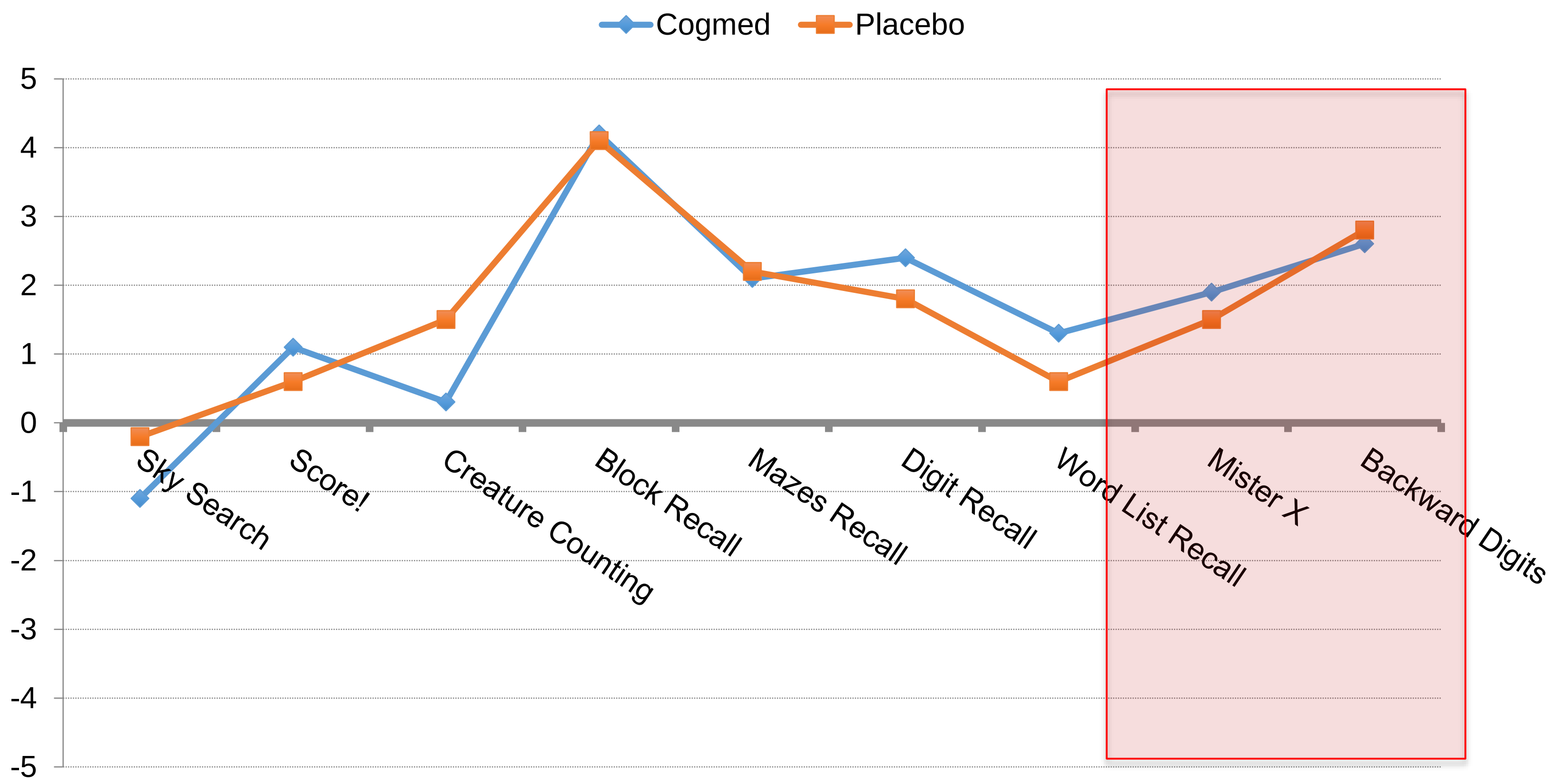
Change in attention and working memory measures from baseline to post-intervention

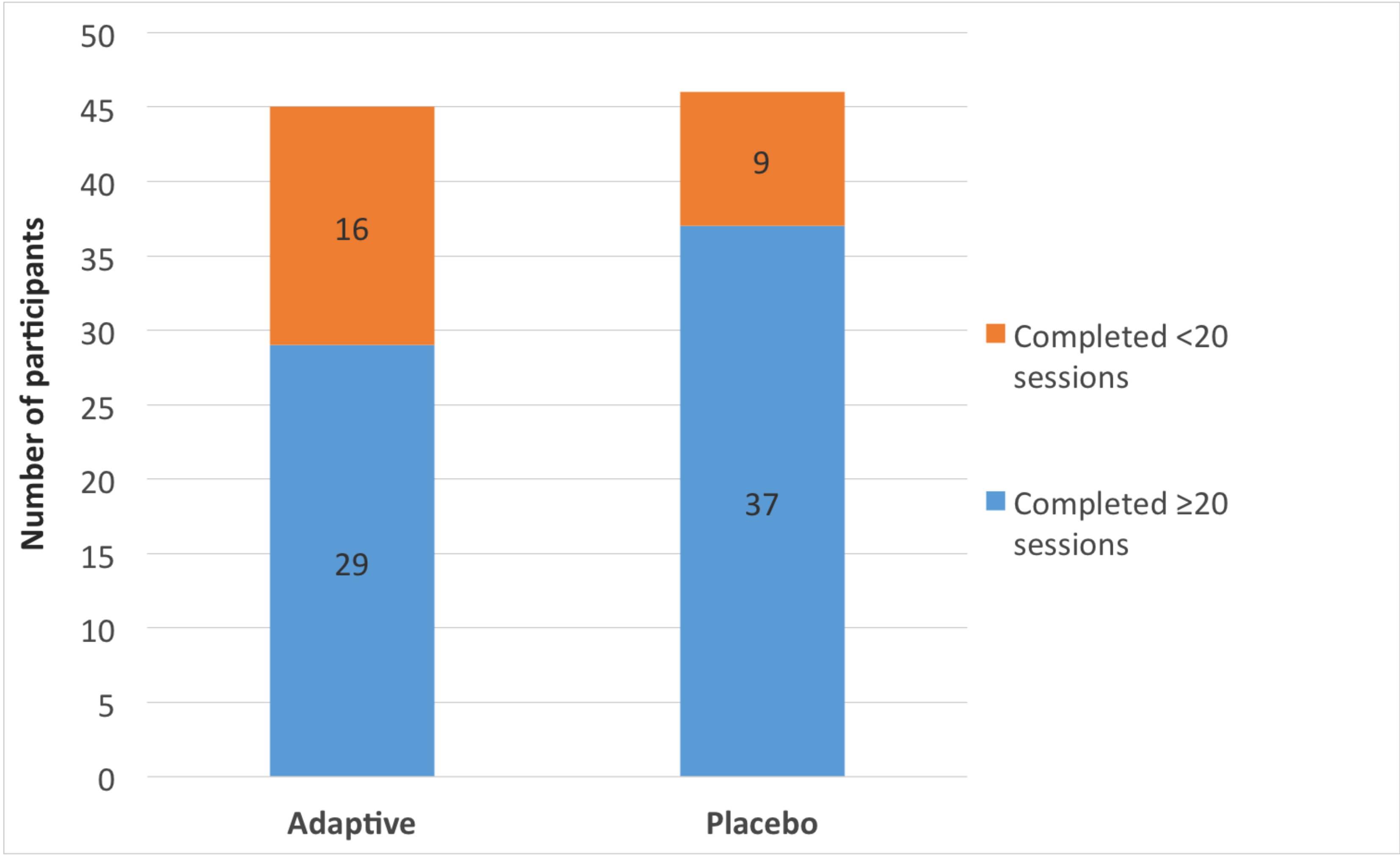


Change in attention and working memory measures from baseline to post-intervention



Change in attention and working memory measures from baseline to post-intervention




Number of participants
50
45
40
35
30
25
20
15
10
5
0
16
29
9
37
Adaptive
Placebo
Completed <20 sessions
Completed ≥20 sessions

Summary

- No differences between Cogmed and placebo groups post training in working memory or attention.
- Slight improvements in working memory (not attention) were observed in Cogmed and placebo groups.
- Need to determine which children benefited from program
- Compliance was not great
  - Program was too difficult
  - Too demanding: time & effort

Conclusions

- Cognitive training may help to enhance core deficits in very preterm children
- Research evidence with Cogmed is mixed
  - Cogmed & Placebo programs resulted in improved performance
- More research with Cogmed is needed
  - Which families are suited to Cogmed?
  - Which children will benefit?
  - Do benefits persist long-term?
  - Does improved working memory translate into better academic functioning and behaviour?

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IMPRINT team
Leona Pascoe
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Kate Lee
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Deanne Thompson
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Marc Seal
Jian Chen
Megan Spencer-Smith

Memory Maestros team
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Melissa Wake
Jon Quach
Lisa Gold
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Sue Gathercole
Megan Spencer-Smith
Field Rickards
Kah-Ling Sia

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Attention Impairment Rates

	EP / ELBW	Term Controls	OR
Selective Attention*	34%	17%	2.4
Sustained Attention*	30%	15%	2.4
Shifting Attention*	27%	9%	3.6
Divided Attention*	37%	16%	3.1

Anderson et al., (2011) Dev Neuropsychol, 36, 57-73

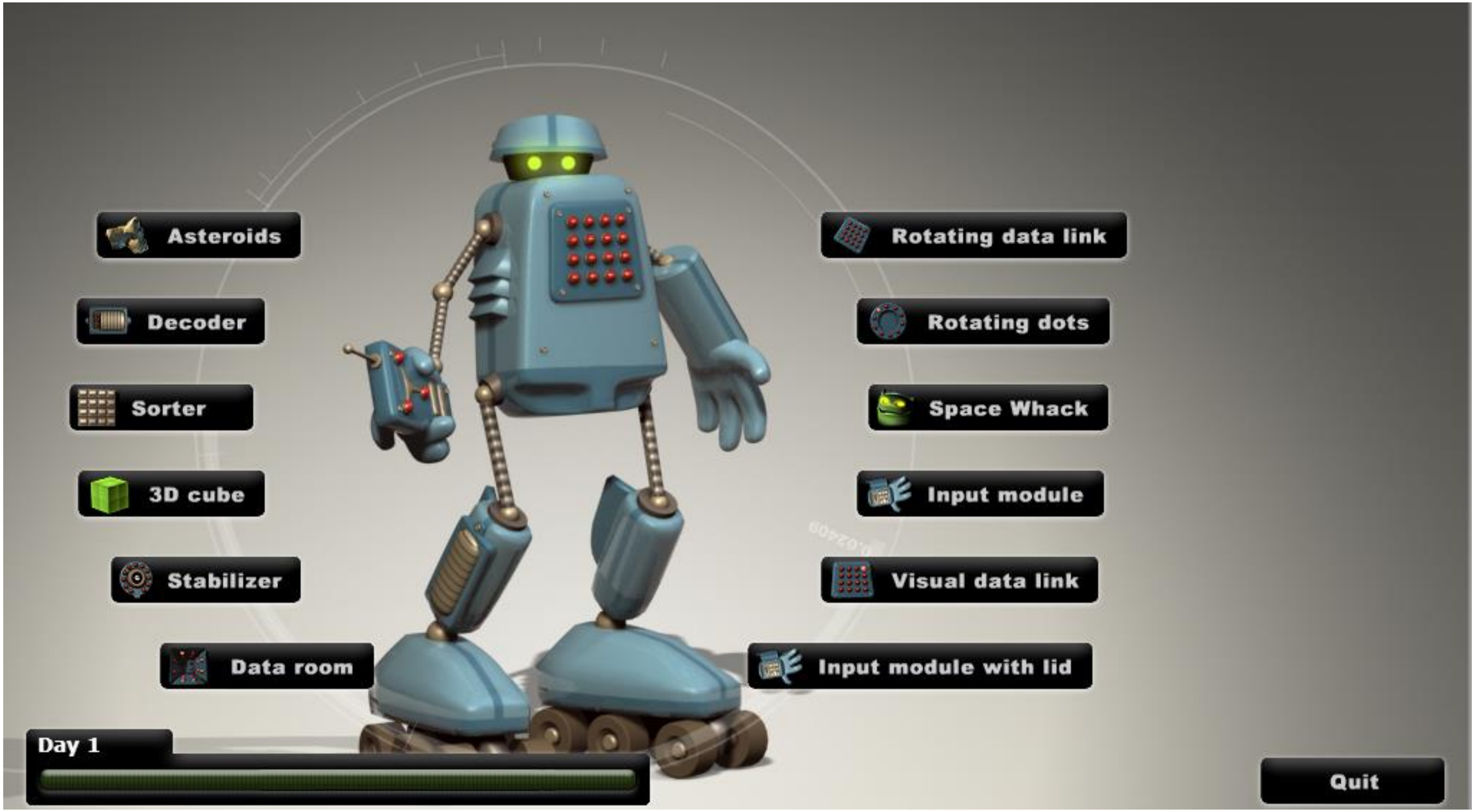
Working Memory Impairment Rates

Frequency of children who performed in the impaired range (>1.0 standard deviation below the term group mean) on memory and learning outcome measures

	VPT Sample (n = 198)%	*Term Sample (n = 70)%*	*Odds Ratio (95% CI)*	p
Immediate Memory				
Digits Forward	27.8	10.1	3.20 (1.39, 7.40)	< .01
Block Recall	39.3	18.4	2.91 (1.47, 5.76)	< .01
Working Memory				
Digits Backwards	36.2	16.2	2.97 (1.43, 6.16)	< .01
CVLT-C Trial 1	19.3	10.1	2.11 (0.88, 5.11)	.09

Omizzolo et al., (2014), Memory, 22, 605-15

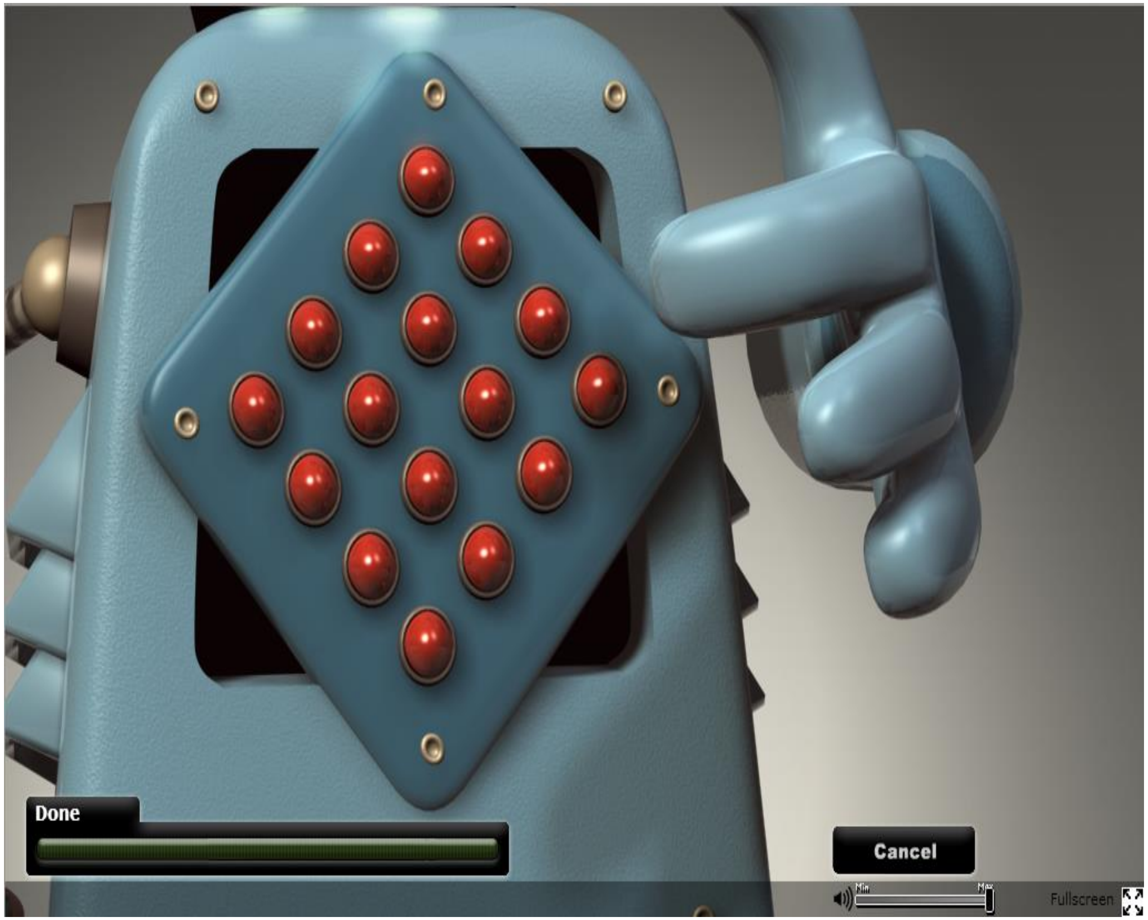
Cogmed RM


Asteroids
Decoder
Sorter
3D cube
Stabilizer
Data room
Rotating data link
Rotating dots
Space Whack
Input module
Visual data link
Input module with lid
Day 1
Quit

Asteroids

Level
5
4
3
2
1
Go!
Done
Cancel
Instructions
Min
Max
Fullscreen

Rotating Data Link



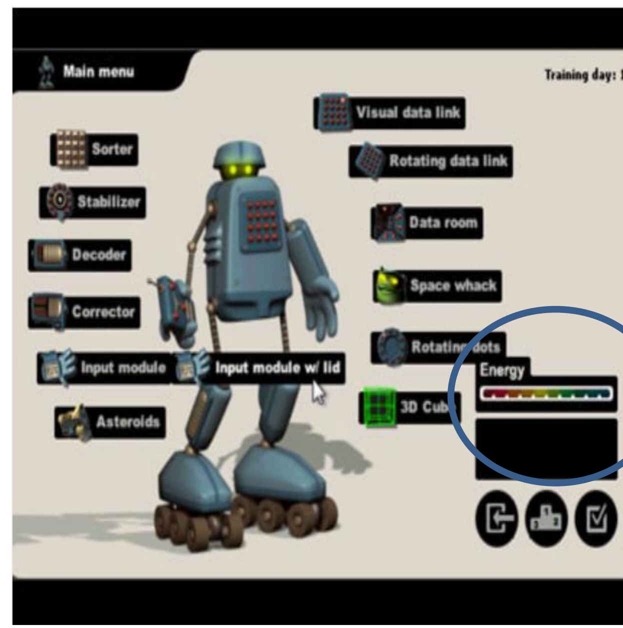
Rotating Dots

Input Module

Robo-racing

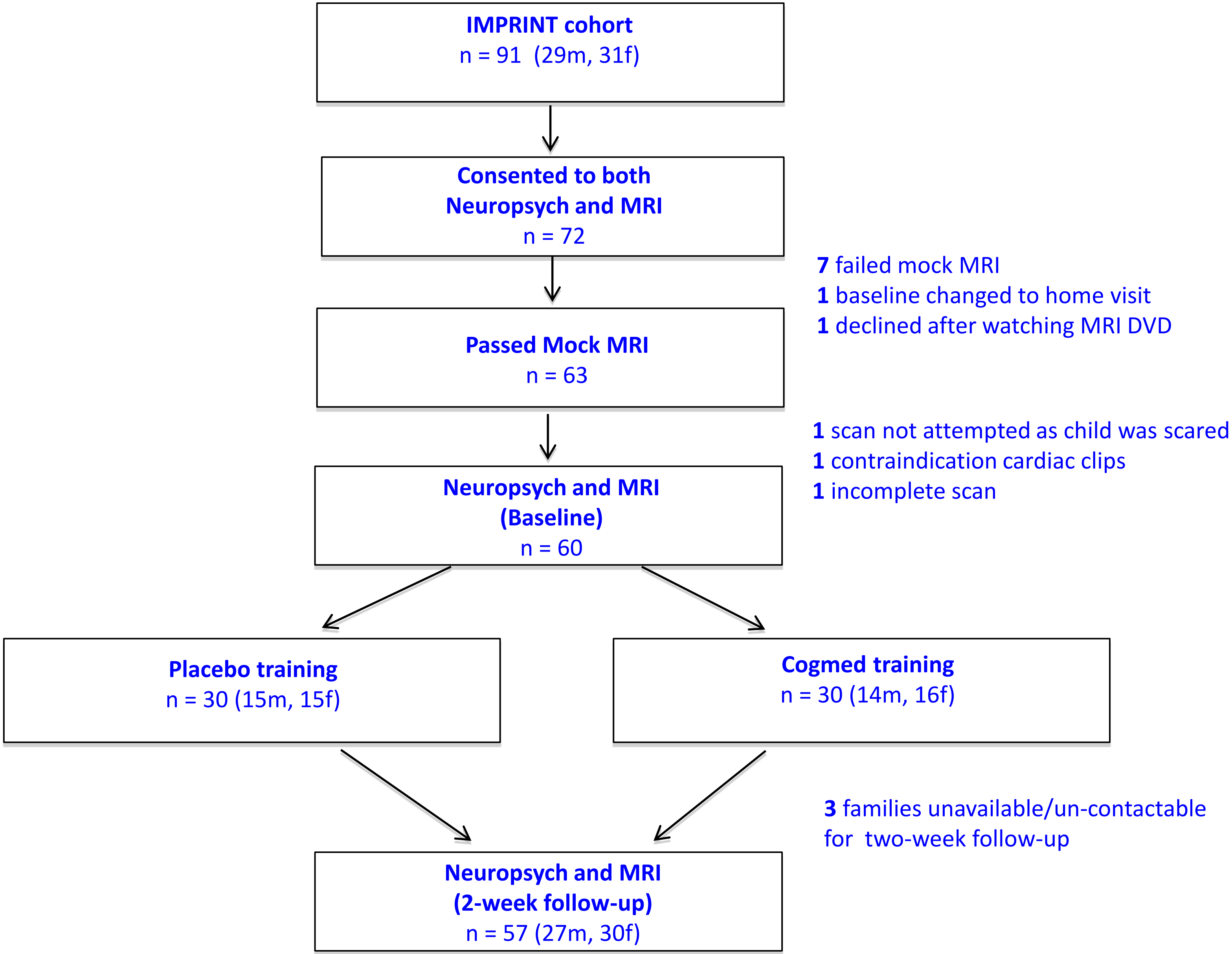

Energi
44.5


Input module
1 2 3
4 5 6
7 8 9
Energy
Points 0


Main menu
Training day: 1
Visual data link
Sorter
Rotating data link
Stabilizer
Data room
Decoder
Space whack
Corrector
Input module
Input module w/ lid
Energy
Asteroids

Training-based neuroplasticity

- Baseline and post-intervention assessments
- Performed using 3T Siemens Magnetom Trio, Tim system, 32 channel head coil
- T_1-weighted images
- T_2-weighted images
- Diffusion weight images
- Resting state MRI
- Task-based fMRI


IMPRINT cohort
n = 91 (29m, 31f)
Consented to both
Neuropsych and MRI
n = 72
7 failed mock MRI
1 baseline changed to home visit
1 declined after watching MRI DVD
Passed Mock MRI
n = 63
1 scan not attempted as child was scared
1 contraindication cardiac clips
1 incomplete scan
Neuropsych and MRI
(Baseline)
n = 60
Placebo training
n = 30 (15m, 15f)
Cogmed training
n = 30 (14m, 16f)
3 families unavailable/un-contactable
for two-week follow-up
Neuropsych and MRI
(2-week follow-up)
n = 57 (27m, 30f)

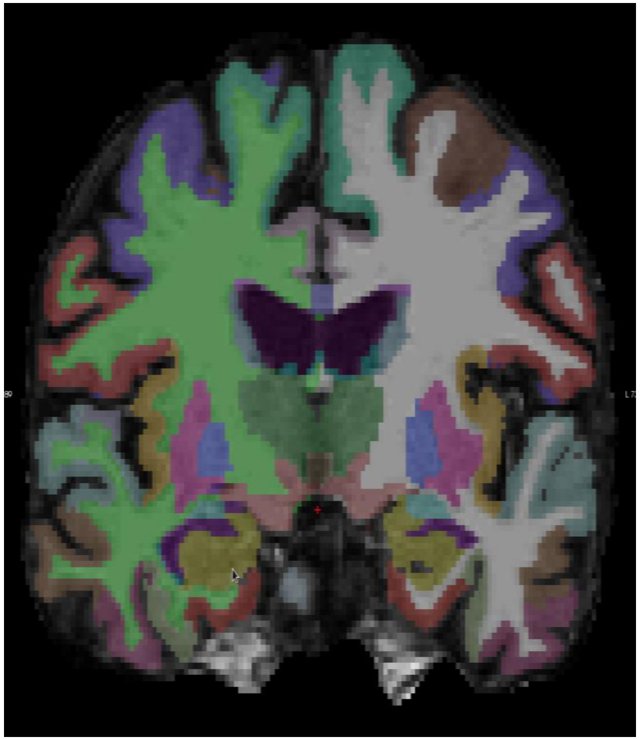
Structural brain changes

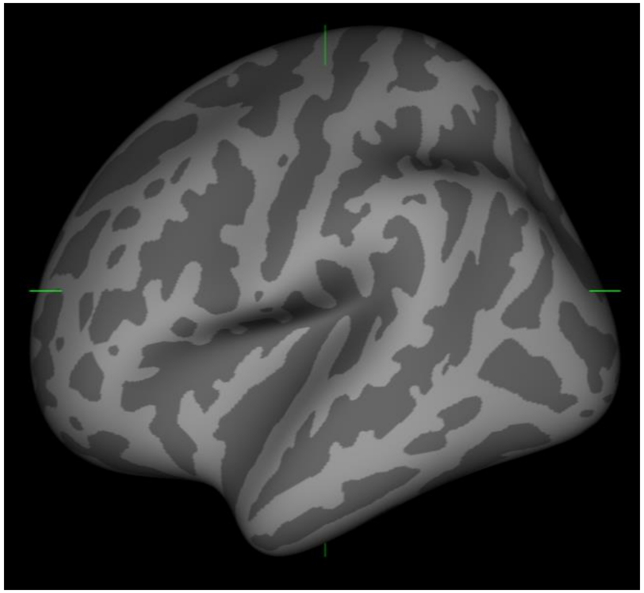
- Freesurfer image analysis suite (version 5.3.0)

– Vertex-wise statistical analysis of the data Qdec (Query, Design, Estimate, Contrast)
  - – cortical thickness,
  - – area,
  - – volume,
  - – curvature
  - – sulcal depth

- false discovery rate correction was applied

– 35 participants had usable pre- and post-training structural images
  - 18 in Cogmed group, 17 in placebo group





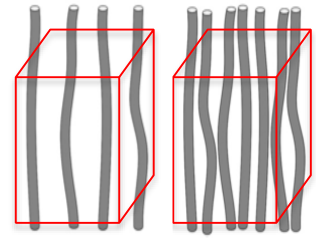
Freesurfer Results

1. Data were compared between the pre- and post-intervention scans for all participants
   - No statistically significant differences
2. Interactions between time point (pre- vs post-intervention) and group (Cogmed vs placebo) were investigated
   - No statistically significant Interactions

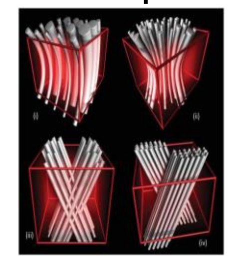
Diffusion-weighted MRI

1) Tract-Based Spatial Statistics (TBSS)

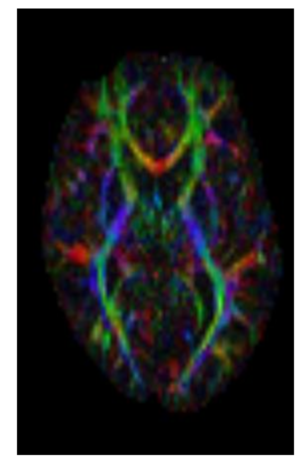
Axon density



Axon dispersion



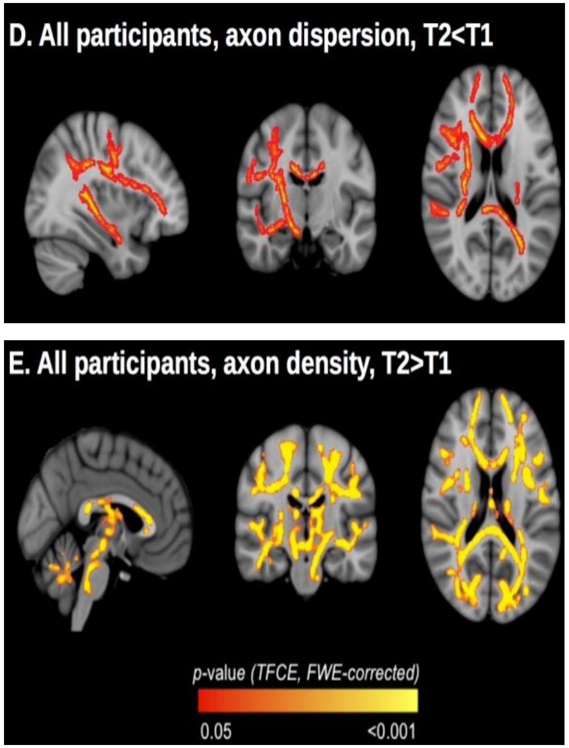
2) Probabilistic tractography with constrained spherical deconvolution using MRtrix software



TBSS Results

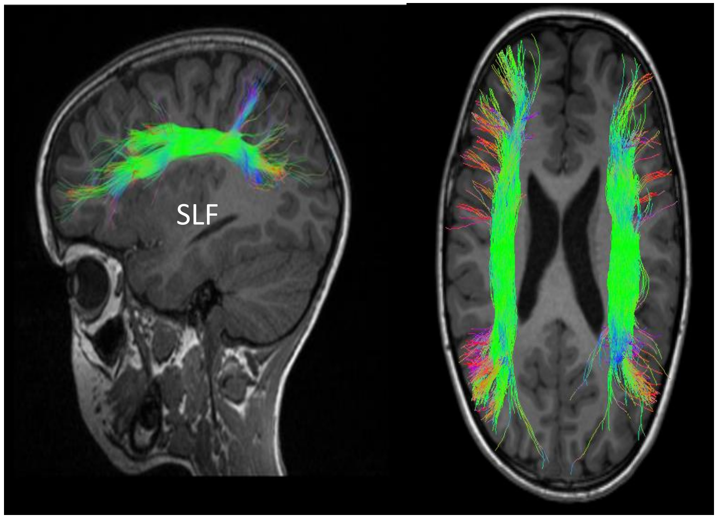
- Lower axon dispersion and higher axon density in the post-intervention scan compared with the pre-intervention scan

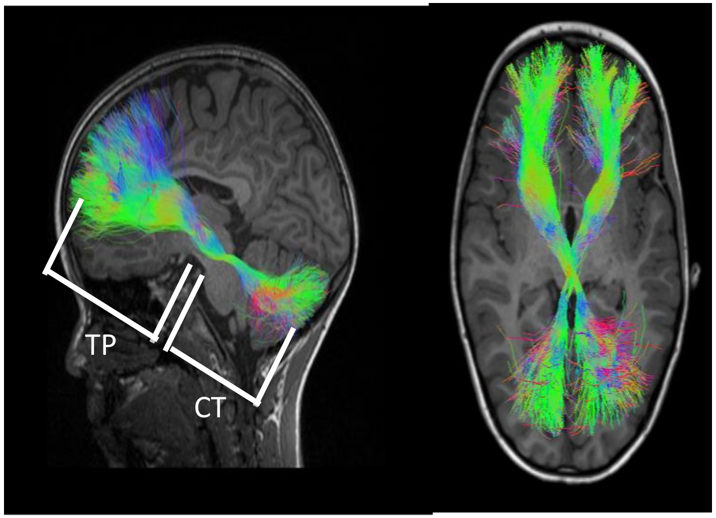
- No significant interactions between time point (pre- vs post-training) and group (Cogmed vs placebo)



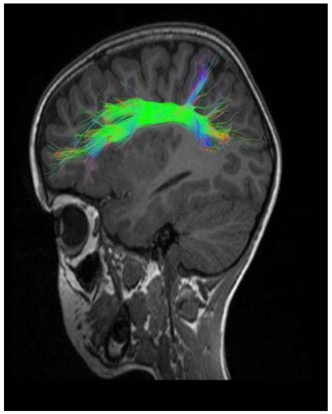
Tracts of interest

SLF: Superior longitudinal fasciculus
CT: Cerebellar-thalamic tract
TP: Thalamic-prefrontal tract



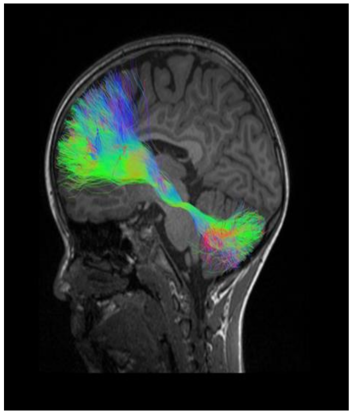


Training based neuroplasticity



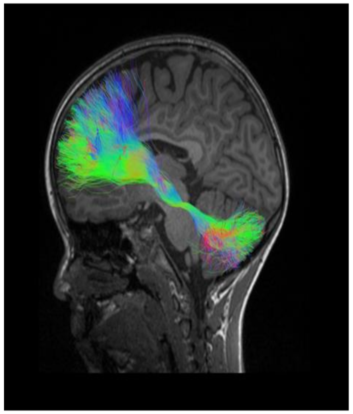
Superior longitudinal fasciculus (SLF)

No change over time
Cogmed = Placebo



Cerebello-thalamic tract (CT)

No change over time
Cogmed = Placebo



Thalamic-prefrontal tract (TP)

No change over time
Cogmed = Placebo

No change in microstructural maturity over time

Ongoing Trials

- 9 registered trials – ongoing
  - ADHD
  - Cerebral Palsy
  - Hearing Aids
  - Preterm
  - Typical (low WM)
  - MCI
  - MS
  - Substance Abuse

Klingberg et al (2005), J Am Acad Child Adolesc Psychiatry, 44, 177-186

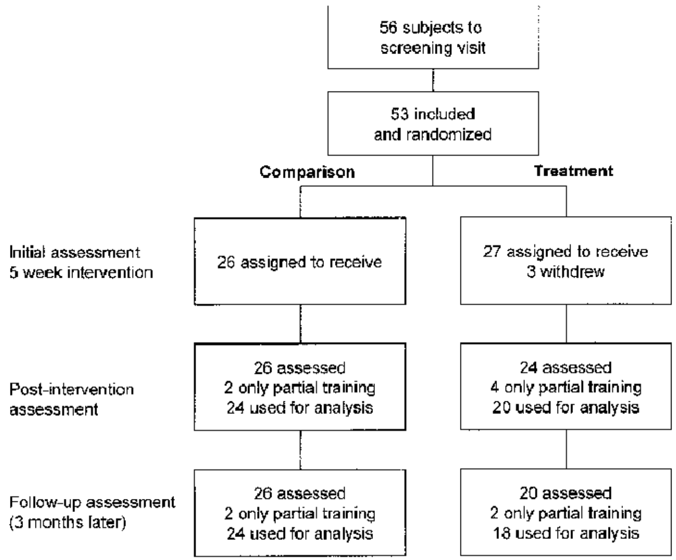
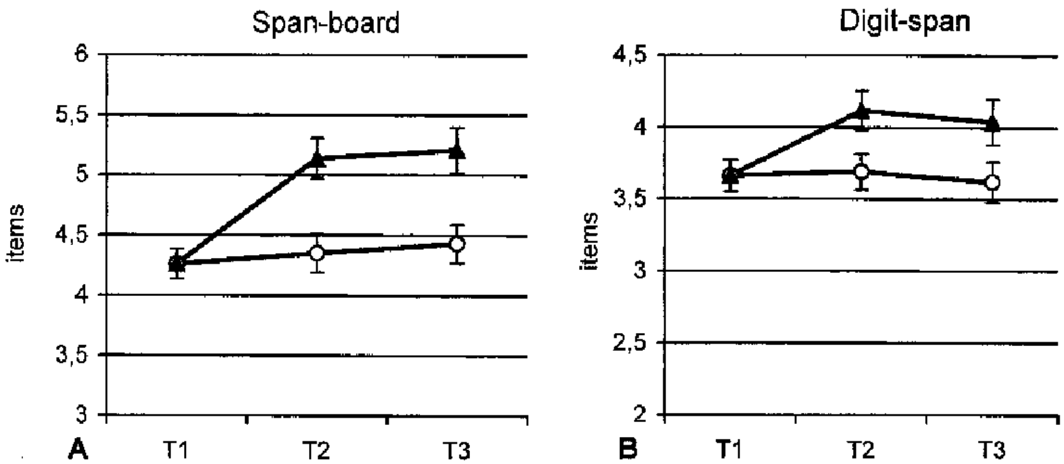


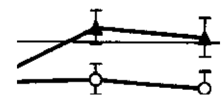
Fig. 1 Flow of participants through the trial.

Subject Characteristics[a]

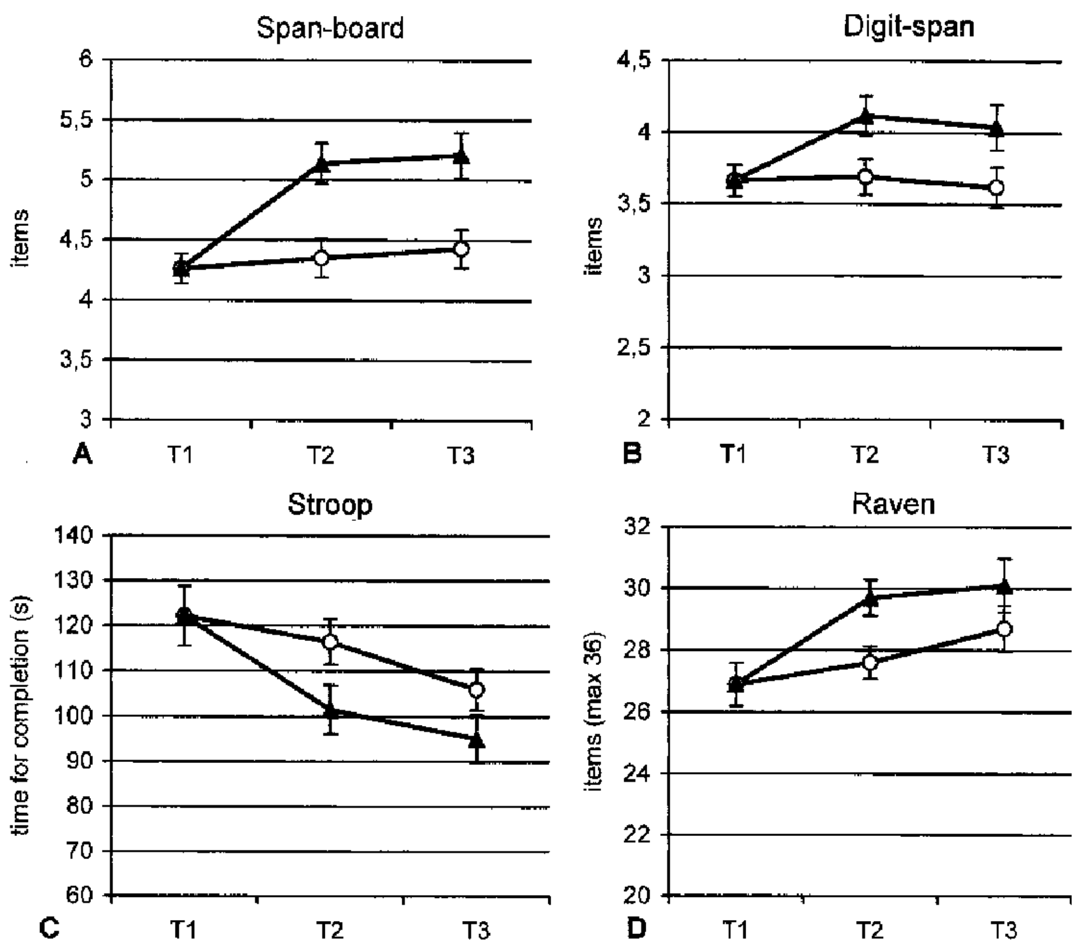
	Comparison	Treatment	Total
Boys	22/20	22/16	44/36
Girls	4/4	5/4	9/8
ADHD combined	16/15	22/15	38/30
ADHD inattentive	10/9	5/5	15/14
Age, yr, mean (SD)	9.8 (1.3)/9.7 (1.3)	9.9 (1.3)/9.8 (1.4)	9.8 (1.3)/9.8 (1.3)

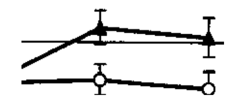
Klingberg et al (2005), J Am Acad Child Adolesc Psychiatry, 44, 177-186





Klingberg et al (2005), J Am Acad Child Adolesc Psychiatry, 44, 177-186





Melby-Lervag & Hulme (2013), Developmental Psychology, 49, 270-291

Immediate near-transfer – working memory

	No. of studies (k)	Effect size (d)	Heterogeneity I^2
Immediate Verbal WM	4	1.18	83%
Immediate Visuo-spatial WM	8	0.86	24%

Hulme & Melby-Lervag (2012), J Appl Res Mem Cogn, 1, 197-200

Immediate far-transfer – visual reasoning

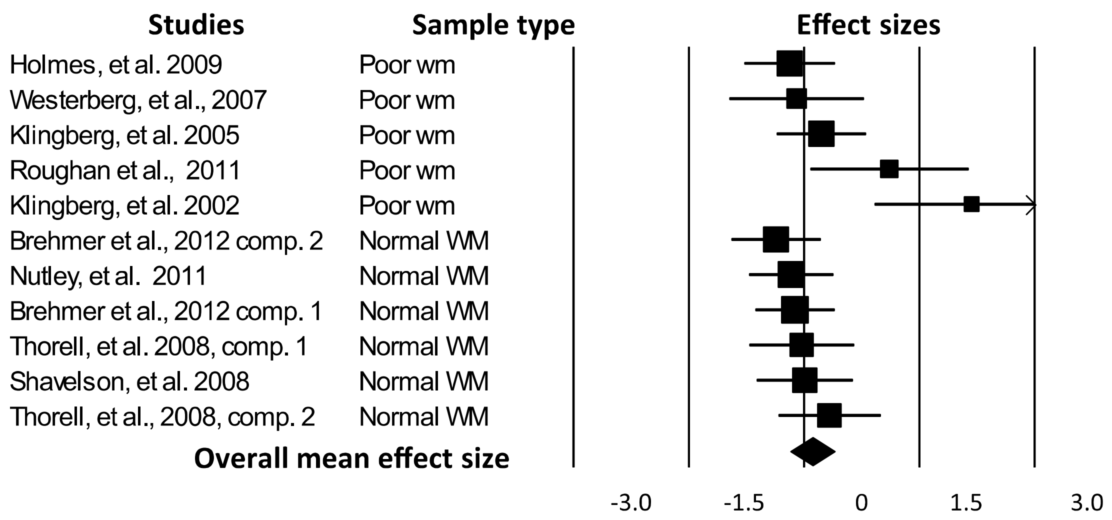


Fig. 1. Forest plot for immediate effects of CogMed training on nonverbal ability showing overall average effect size and confidence interval (Cohen's *d*, displayed by ♦) and individual effect sizes for each study (Cohen's *d*, displayed by ■ with confidence intervals represented by horizontal lines; horizontal lines with arrows indicate that the confidence interval exceeds ±3 Cohen's *d*).

Spencer-Smith & Klingberg (2015), PLOS One, 10(3)

Immediate far-transfer – reported attentive behaviour

Study or Subgroup	Cogmed Mean	Cogmed SD	Cogmed Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beck 2010	5.72	2.92	27	7.5	1.79	24	10.3%	−0.71 [−1.28, −0.15]
Brehmer 2012a	25.66	12.37	29	31.69	12.39	26	11.6%	−0.48 [−1.02, 0.06]
Brehmer 2012b	31.85	9.77	26	38.79	19.11	19	9.3%	−0.47 [−1.07, 0.13]
Chacko 2013	−16.51	5.84	38	−14.24	6.06	36	15.8%	−0.38 [−0.84, 0.08]
Egeland 2013	15	5.6	33	16.2	6.2	34	14.5%	−0.20 [−0.68, 0.28]
Green 2012	67	12.2	12	70.9	8.3	14	5.5%	−0.37 [−1.15, 0.41]
Gropper unpublished	48.75	17.72	39	55.65	15.11	23	12.3%	−0.41 [−0.93, 0.12]
Grunewaldt 2013	−6.9	5.3	9	−5.1	4.5	11	4.2%	−0.35 [−1.24, 0.54]
Hardy 2013	60.8	15.42	11	74	8.08	6	3.0%	−0.93 [−1.99, 0.12]
Klingberg 2005	13	6.5	17	15.5	7.2	19	7.7%	−0.36 [−1.02, 0.30]
Roughan 2011	12.57	11.12	7	28.88	11.69	8	2.5%	−1.34 [−2.50, −0.18]
Westerberg 2007	29.2	12.1	9	43	13.8	9	3.4%	−1.01 [−2.01, −0.02]
Total (95% CI)			**257**			**229**	**100.0%**	**−0.47 [−0.65, −0.29]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.44$, $df = 11$ ($P = 0.84$); $I^2 = 0\%$

Test for overall effect: $Z = 5.03$ ($P < 0.00001$)

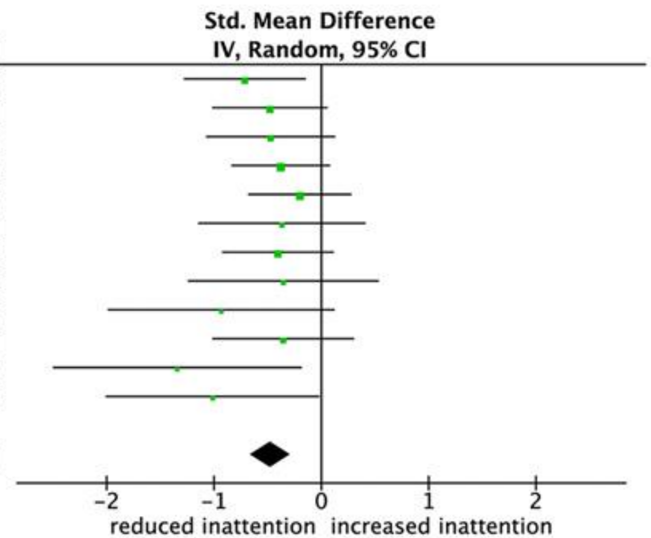


Fig 2. Forest plot for inattention in daily life after the training. The overall pooled effect size (standardised mean difference, displayed as a diamond) as well as individual study effect sizes (displayed as rectangles) and their 95% confidence intervals (represented by horizontal lines) are shown.

Hulme & Melby-Lervag (2012), J Appl Res Mem Cogn, 1, 197-200

Immediate far-transfer – Inhibitory control

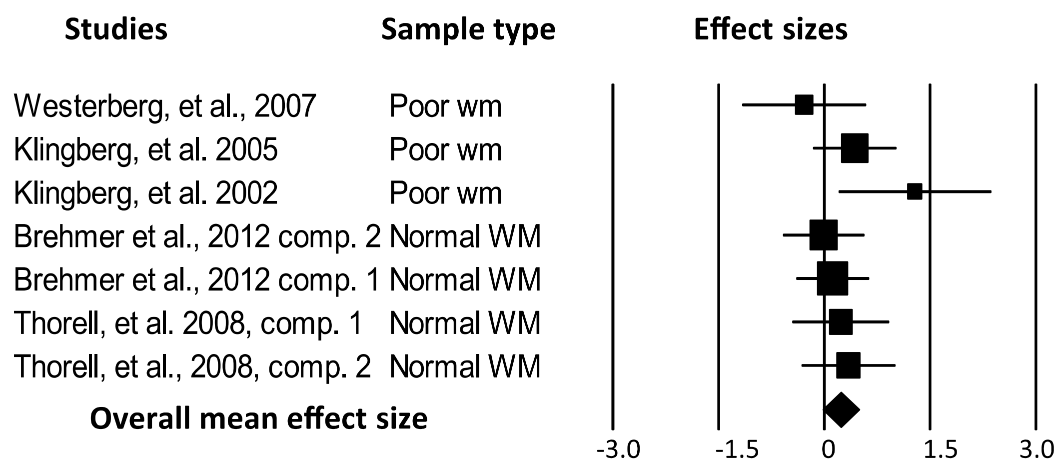


Fig. 2. Forest plot for immediate effects from CogMed training on Stroop task performance showing overall average effect size and confidence interval (Cohen's *d*, displayed by ♦) and individual effect sizes for each study (Cohen's *d*, displayed by ■ with confidence intervals represented by horizontal lines).

Spencer-Smith & Klingberg (2015), PLOS One, 10(3)

Delayed far-transfer – reported attentive behaviour

	Cogmed			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Brehmer 2012a	25.55	12.94	28	30.27	11.78	26	19.5%	−0.38 [−0.91, 0.16]
Brehmer 2012b	32.23	8.79	26	37.79	16.2	19	15.8%	−0.44 [−1.04, 0.16]
Egeland 2013	15.3	5.3	33	16.5	5.6	34	24.6%	−0.22 [−0.70, 0.26]
Gropper unpublished	46.17	23.69	24	53.52	18.35	21	16.3%	−0.34 [−0.93, 0.25]
Hardy 2013	57.8	13.59	11	68.3	8.35	6	5.2%	−0.82 [−1.87, 0.22]
Klingberg 2005	13.6	7.9	17	14.5	5.6	20	13.5%	−0.13 [−0.78, 0.52]
Roughan 2011	17.71	12	7	23.71	15.81	7	5.0%	−0.40 [−1.46, 0.66]
Total (95% CI)			**146**			**133**	**100.0%**	**−0.33 [−0.57, −0.09]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.61$, df = 6 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 2.73 (P = 0.006)

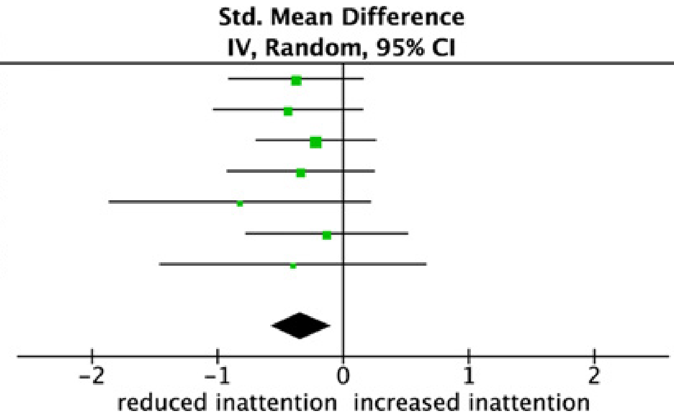


Fig 3. Forest plot for inattention in daily life following a delay after the training. The overall pooled effect size (standardised mean difference, displayed as a diamond) as well as individual study effect sizes (displayed as rectangles) and their 95% confidence intervals (represented by horizontal lines) are shown.