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Long-term academic functioning following Cogmed Working Memory Training® for children born extremely preterm: a randomized controlled trial

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Abbreviations

EP – extremely preterm

ELBW – extremely low birth weight

Abstract

Objective: To assess the effectiveness of Cogmed Working Memory Training® compared with a placebo program in improving academic functioning 24 months' post-training in extremely preterm/extremely low birth weight 7-year-olds.

Study Design: A multicenter double-blind, placebo-controlled randomized controlled trial was conducted across all tertiary neonatal hospitals in the state of Victoria, Australia. Participants were 91 extremely preterm/extremely low birth weight 7-year-olds born in Victoria in 2005. Children were randomly assigned to either the Cogmed or placebo arm and completed the Cogmed or placebo program (20-25 sessions of 35-40 minutes duration) at home over 5-7 weeks. Academic achievement (word reading, spelling, sentence comprehension and mathematics) was assessed at 24 months' post-training, as well as at 2 week's and 12 month's post-training, via standardized testing inclusive of working memory, attention and executive behavior assessments. Data were analyzed using an intention-to-treat approach with mixed effects modeling.

Results: There was little evidence of any benefits of Cogmed on academic functioning 24 months' post-training, as well as on working memory, attention or executive behavior at any age up to 24 months' post-training compared with the placebo program.

Conclusions: Given evidence from the trial, we currently do not recommend administration of Cogmed for early school-aged children born extremely preterm/extremely low birth weight to improve academic functioning.

Trial registration: Australian New Zealand Clinical Trials Registry, anzctr.org.au; ACTRN12612000124831

Attention and working memory are critical for higher-order learning and functioning and areas of concern for children born extremely preterm (EP; <28 weeks' gestational age).(1-5) Impairments in these domains are speculated to underpin problems in academic functioning.(6) As such, EP children may benefit from cognitive training interventions designed to enhance attention and working memory.(7) While the most effective age for cognitive training is not yet clear, meta-analyses suggest younger individuals may benefit more.(8, 9) Early school age may be an effective period to target, given that rapid cognitive development and the acquisition of literacy and numeracy concepts occur at this time.(10)

Cogmed Working Memory Training® is a widely-used commercial working memory training program, suggested to improve working memory, attention, executive functioning, and basic educational skills in the short-term.(11-13) Preterm research outcomes with Cogmed have generally been positive, though limited to three small, non-randomized studies with sample sizes ranging from 12 to 20.(14-17) All three studies (two in preschoolers and one in adolescents) reported training-related memory benefits persisting up to 7 months (14-17), as well as improvements in auditory attention and phonemic awareness.(14, 17) Training benefits to academics and everyday behavior have not been explored in EP children, and further research is needed to examine these outcomes, preferably with larger, double-blind, placebo-controlled randomized controlled trials(18). Training-induced improvement should not be assumed given recent evidence from a large population-based randomized controlled trial of Cogmed in children with low working memory reporting little long-term benefit for working memory or academic functioning compared with usual classroom teaching.(19)

This randomized controlled trial aimed to assess the effectiveness of Cogmed in EP/ extremely low birth weight (ELBW; birth weight <1000 g) 7-year-olds to improve academic functioning up to 24 months' post-training, compared with a placebo training program.

METHODS

This study was a double-blind, placebo-controlled, randomized trial of the Cogmed program with 7-year-old children born EP and/or ELBW called the Improving Memory in a Preterm Randomised Intervention Trial (IMPRINT).(20) IMPRINT is registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12612000124831) and approved by the relevant Human Research & Ethics Committees. The trial was conducted and reported in accordance to CONSORT guidelines (Figure 1; Supplement 1), and written consent was obtained from the primary caregiver of participating children.

Participants

Children in the 2005 Victorian Infant Collaborative Study (VICS) cohort (n=221) were invited to take part in the trial at their 7-year follow-up appointment from June 2012 to April 2014 (21) and 91 of these children were enrolled in IMPRINT (Figure 1 supplies further participant details). Initial sample size calculations based on 80% power and a type-1 error rate of 5%, determined that a sample of 63 participants in each treatment arm (126 in total) would detect a difference of 0.5 SD in our primary outcome (academic functioning) 24 months' post-training between the Cogmed and placebo groups.(20) We failed to achieve our proposed sample size due to unexpected challenges during recruitment and a lower than anticipated rate of eligibility (Figure 1).

Procedure

Participants completed a baseline assessment of general cognitive function, working memory, attention, behavior and academic functioning. Participants were subsequently randomized to either the Cogmed (intervention) or placebo groups in a 1:1 ratio, using block randomization with variable block sizes, stratified by singleton versus surviving multiple births

(twins/triplets) and 'low' versus 'age-typical' working memory capacity at the baseline assessment. Surviving twins and triplets were allocated to the same intervention group to reduce contamination, and low working memory capacity was defined as a score less than or equal to the 20th percentile on the Backward Digit Recall subtest from the Working Memory Test Battery for Children (WMTB-C).(22) Participants were allocated the next available sequential number in the required strata, which corresponded to an opaque envelope containing the treatment allocation managed by the project coordinator and trial's research assistant. A biostatistician who was independent of the study generated the randomization schedule. The Cogmed and placebo interventions were undertaken in the home over 5 to 7 weeks and participants and their families remained blinded to treatment allocation throughout the study. The primary outcome measure was collected 24 months following training, with two interim assessments at 2 weeks and 12 months post-training (refer to Table 1 for more information on the trial's secondary outcomes measures). Assessments were conducted at the Murdoch Children's Research Institute in Melbourne by blinded assessors.

Intervention

The trial employed the RM version of Cogmed designed for children aged 7 years and above. The training program comprises a recommended 20 to 25 training sessions completed over a 5 to 7 week period. Each training session takes 35 to 50 minutes and comprises 8 different interactive, computerized working memory activities (for further information see Pascoe et al., 2013). Some important features of Cogmed are that training is 1) adaptive, and matches the difficulty level of each activity based on the child's current performance on that activity on a trial-by-trial basis, 2) based on implicit learning, and 3) designed to be engaging and fun with built-in positive reinforcement. The placebo program was a non-adaptive version of Cogmed, designed for the purpose of trial evaluations. The placebo program is identical to

Cogmed except the activities are set to a low level of complexity throughout the training period to ensure the training does not tax working memory.

Measures

Table 1 summarizes the outcome measures of the trial. Our primary outcome measure of academic functioning was assessed across four domains of word reading, sentence comprehension, spelling and math computation (Table 1). Secondary outcomes measures included working memory, attention, behavior, and general intellectual functioning (Table 1). Perinatal data were collected from the child's medical record, and social risk was assessed using a social risk index (range 0-12).(23) Social risk scores were dichotomized with scores <2 classified as lower social risk, and those ≥2 classified as higher social risk.(24)

Statistical Analyses

Data were analyzed using Stata 14.0 and an intention-to-treat approach.(25) Treatment effects for academic, cognitive and behavioral outcomes at each time-point were assessed using a single mixed-effects regression model for each outcome applied to the baseline, 2-week, 12-month and 24-month time-points. Models included a random effect for participants to allow for the clustering of repeated observations within an individual, a separate intervention effect at each follow-up time-point, and a separate residual term at each of the 4 measurement time-points. This approach accounts for missing data by enabling all participants with baseline data, equivalent to all participants, to be included in the analysis. Results were adjusted for working memory performance at baseline (normal versus low) and surviving multiple versus singleton birth as used in the randomization. Secondary analyses were performed adjusted for sex, social risk and IQ as potentially important confounders. A sensitivity analysis was conducted restricted to participants who completed at least 20 training sessions in line with Cogmed recommendations.

RESULTS

Demographic and training characteristics

Demographic and clinical characteristics were similar between study participants and eligible non-participants (n = 60) except for gestational age, which was higher in participants than non-participants (27.1 weeks on average versus 26.4 weeks). Characteristics were also similar between treatment groups at baseline (Table 2). Participants in the Cogmed group completed 19 training sessions on average (SD 7.7, range 1-25) across the training period, compared with 21 sessions (SD 6.7, range 2-25) in the placebo group. 30 children (67%) in the Cogmed group completed ≥20 sessions, compared with 37 (80%) children in the placebo group. The average length of training was 6.2 weeks (SD 1.0) in the Cogmed group and 6.0 weeks (SD 1.2) in the placebo group.

Outcomes

Figure 2 summarizes the outcome comparisons between Cogmed and placebo groups. In terms of the primary outcome, there was little evidence of a group difference in academic achievement 2 weeks, 12 months or 24 months post-training. Similarly, there was little evidence of a treatment benefit for working memory, immediate memory, attention or behavioral outcomes at the three follow-up time-points (Table 3; online). In the secondary analyses, adjustment for sex, social risk and IQ had little effect on treatment group differences for all outcomes in the secondary analyses (Table 4; online). The sensitivity analyses (restricted to children who completed ≥20 training sessions) indicated weak evidence of greater spelling performance and immediate verbal memory (Digit Recall) in the Cogmed group compared with the placebo group at 2 weeks' post-training; however the evidence for these differences was not maintained at 12 or 24 months' post-training (Figure 3; Table 5; online)

DISCUSSION

In contrast to previous studies in preterm cohorts, we found little evidence of short or long-term benefits of Cogmed on academic functioning, working memory, attention or behavioral outcomes. These findings are of relevance because computerized cognitive training programs like Cogmed are popular tools for cognitive enhancement, with benefits reported across a range of domains. Our findings lead us to conclude that the use of Cogmed at early school age in EP/ELBW children is not effective in improving outcomes for these children.

Previous Cogmed studies with preterm preschoolers and adolescents, which reported benefits, were not randomized controlled trials and had small samples.(14-17) Benefits observed in training studies that adopt non-robust methodologies and small samples may be attributed to extraneous factors,(18) rather than cognitive training. The gold standard for determining intervention effectiveness is double-blind, placebo-controlled, randomized designs with an intention-to-treat analytic approach,(18) and our study is the first to meet this recommendation in EP/ELBW children.

In our trial, we wished to evaluate the adaptive feature of continuous adjustment of difficulty level according to performance of Cogmed training. Therefore, we used an active control condition in which the control group received the same intervention as the Cogmed group, except the working memory load was set to a low level. In contrast, previous studies of Cogmed in preterm children have employed passive control (usual care, no training),(17) waitlist control,(14) or term born control (completed Cogmed)(15, 16) conditions. This may have contributed to differences in the outcomes of the studies.

A further difference is that previous preterm studies have recruited younger or older preterm individuals rather than early school-age children as in the present study.(14, 17) Given that working memory capacity undergoes considerable growth and development

during the early to middle childhood years, the benefits of Cogmed may vary depending on the age at administration. Evidence from meta-analyses of working memory training is mixed, with a trend for stronger training benefits at younger ages in typically developing children (4-13 years),(8) but greater benefit reported at older ages (>10 years) in children and adolescents with learning difficulties.(26)

Working memory training has been reported to benefit academic functioning and behavior (far-transfer effects).(27-29) As parents are likely to enroll their children in programs like Cogmed to improve educational outcomes and behavior, the primary outcome of our trial was academic functioning. Several trials have reported no short-term(30, 31) or long-term(19, 32) improvements in literacy and numeracy performance following Cogmed, consistent with our findings. Thus, the weight of evidence from high-quality studies suggests that Cogmed does not improve academic functioning.

The evidence for benefits of Cogmed on behavior is mixed,(18, 33) and compromised by small, non-randomized controlled studies and unblinded raters. There is some evidence that Cogmed reduces inattentive or attention deficit hyperactivity disorder (ADHD) symptoms as reported by caregivers,(33) even in preterm samples.(14, 15) However, caregivers are often invested in the training, and bias may alter their perceptions and ratings of their child's inattentive behavior following training. There is little evidence that Cogmed benefits socio-emotional or executive behaviors,(18, 19) consistent with our findings. Similarly, we found little evidence that Cogmed benefited cognitive attention outcomes. Absence of gains in academic functioning, behavior and attention may be expected if no working memory gains are observed.

Strengths of our study are that we used blinded treatment allocation and outcome assessments, assessed short- and long-term outcomes, recruited a large sample, achieved an excellent retention rate (87-97%), analyzed the data on an intention-to-treat basis and

accounted for child factors known to influence training outcomes (baseline working memory and IQ). A limitation was the lower than anticipated levels of training compliance from participants. Analyses restricted to those who completed training generally revealed our primary results to be robust, although these sensitivity analyses found weak evidence that the Cogmed group performed better on tests of spelling and immediate verbal memory (Digit Recall) two weeks after training compared with the placebo group. Another limitation was a smaller than desired sample, but group differences were small and potentially not clinically meaningful. Finally, we did not assess the influence of factors such as the home environment, caregiver involvement and training motivation, which may contribute to training outcomes(34-36).

On the basis of the present findings, we cannot currently recommend Cogmed for cognitive enhancement in EP/ELBW early school-age children. However, we acknowledge that inter-individual variability in response to cognitive training is likely.(35, 37) Future studies should investigate individual differences on training outcomes, as subgroups of individuals may benefit more than others.(38-40) It may be that greater success with working memory training will come from integrating different intervention approaches that target various mechanisms and processes involved in learning.(41)

In conclusion, our randomized controlled trial provides little support that Cogmed is efficacious for improving academic functioning 24 months' post-training in EP/ELBW early school-aged children. Detailed investigations are now needed to evaluate if Cogmed is efficacious for specific subgroups of children.

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Figure Legends

Figure 1. CONSORT diagram of participant flow. Children in the 2005 Victorian Infant Collaborative Study (VICS) cohort comprised all children born EP or ELBW in the state of Victoria in 2005 and who did not have a congenital abnormality known to affect neurodevelopment. 172 (78%) children in the VICS cohort attended their 7-year VICS neuropsychological follow-up assessment during the recruitment window where they were informed of the trial. 21 children were excluded (16 had a severe intellectual, sensory or physical impairment that affected their capacity to complete or understand the training; 2 had families unable to assist them through the program; 2 relocated during the trial period; 1 had previous exposure to Cogmed) and out of 151 eligible children, 91 children enrolled and participated in the trial (60%).

Figure 2. Treatment group differences in A) academics, B) working memory, C) immediate verbal memory, D) immediate visual-spatial memory, E) attention and, F) behavior at 2 weeks', 12 months' and 24 months' post-training. Point estimates reflect regression coefficients from mixed effect models where a group difference >0 reflects a higher score in the Cogmed group, and a group difference <0 reflects a lower score in the Cogmed group. Vertical error bars represent 95% confidence intervals (CI).

Figure 3. Sensitivity analysis of treatment group differences in A) academics, B) working memory, C) immediate verbal memory, D) immediate visual-spatial memory, E) attention and, F) behavior at 2 weeks', 12 months' and 24 months' post-training in participants who completed ≥20 sessions of training (n=30 in Cogmed group and n=37 in placebo group). Point estimates reflect regression coefficients from mixed effect models where a group difference >0 reflects a higher score in the Cogmed group, and a group difference <0 reflects a lower score in the Cogmed group. Vertical error bars represent 95% confidence

intervals (CI).