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Investigating the brain structural connectome following working memory training in children born extremely preterm or extremely low birth weight

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ABSTRACT

Children born extremely preterm (EP, <28 weeks' gestation) or extremely low birth weight (ELBW, <1000 g) are a vulnerable population at high risk of working memory impairments. We aimed to examine changes in the brain structural connectivity networks thought to underlie working memory performance, after completion of a working memory training program (Cogmed) compared with a placebo program in EP/ELBW children. This was a double-blind, placebo-controlled randomised trial (the Improving Memory in a Preterm Randomised Intervention Trial (IMPRINT)). Children born EP/ELBW received either the Cogmed or placebo program at 7 years of age (n = 91). A subset of children had magnetic resonance imaging (MRI) of the brain immediately pre- and two weeks post-training (Cogmed n = 28; placebo n = 27). T_1-weighted and diffusion-weighted images were used to perform graph theoretical analysis of structural connectivity networks. Changes from pre- to post-training in structural connectivity metrics were mostly similar between randomised groups, except potentially for the density of connections, which increased more in the Cogmed group compared with the placebo group. There was little evidence that changes in structural connectivity metrics were related to changes in working memory performance from pre- to post-training. Overall, our results provide little evidence that the Cogmed working memory training program has training-specific effects on structural connectivity networks in EP/ELBW children.

SIGNIFICANCE STATEMENT

This double-blind, placebo-controlled, randomised trial investigated the effects of the Cogmed working memory training program on whole-brain structural connectivity networks in a cohort of children born extremely preterm or extremely low birth weight. We found little evidence that the Cogmed program influenced brain structural connectivity networks compared with a placebo program. There was also little evidence for relationships between brain structural connectivity networks and working memory performance. There is currently limited evidence that Cogmed can result in changes in brain structure in EP/ELBW children. Additional large randomised controlled trials are needed to validate this.

INTRODUCTION

Children born extremely preterm (EP, <28 weeks' gestational age) or extremely low birth weight (ELBW, <1000 g) have high rates of cognitive impairments (Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2004; Hutchinson et al., 2013; Kerr-Wilson, Mackay, Smith, & Pell, 2012), and may have a specific vulnerability for working memory deficits (Anderson, 2014). Some studies have found that cognitive training programs targeting working memory, such as Cogmed®, are associated with improved working memory in children born preterm, as well as children with low working memory, and typically developing children (Grunewaldt, Lohaugen, Austeng, Brubakk, & Skranes, 2013; Grunewaldt, Skranes, Brubakk, & Lahaugen, 2016; Lee, Pei, Andrew, K, & Rasmussen, 2017; Lohaugen et al., 2011; Roberts et al., 2016; Sala & Gobet, 2017). However, we performed a randomised controlled trial of the Cogmed program in 7-year-olds born EP/ELBW (the Improving Memory in a Preterm Randomised Intervention Trial (IMPRINT)), which demonstrated little benefit of Cogmed on short-term or long-term working memory performance compared with a placebo program (Anderson et al., 2018b). Despite the lack of cognitive benefits in our trial, it is important to investigate whether the working memory training led to neural changes in the brain.

On a regional, microstructural level, we have previously reported that the neurite density index in the white matter measured using diffusion magnetic resonance imaging (MRI) increased over the 5-7 weeks intervention period in EP/ELBW 7-year-olds participating in the Cogmed working memory training program (Kelly et al., 2020). However, this increase over time was similar for children who participated in the placebo program, suggesting the changes were not training-specific (Kelly et al., 2020). Working memory is thought to rely on numerous distributed brain regions operating within large-scale networks (Bressler & Menon, 2010; Constantinidis & Klingberg, 2016). Thus, working memory training may be more likely to influence brain integration, rather than individual brain regions.

Previously, we investigated the effect of the working memory training on functional connectivity networks in EP/ELBW children using resting-state functional MRI (Tseng et al., 2019). We found little evidence that changes in intra-network or inter-network resting-

state functional connectivity strength from pre-training to post-training differed between the Cogmed and placebo groups (Tseng et al., 2019). However, we found evidence that participating in the Cogmed program influenced brain-behaviour relationships. Increased functional connectivity in the precuneus network was associated with working memory improvements following participation in the Cogmed program, but not the placebo program (Tseng et al., 2019). This suggested that functional connectivity changes may facilitate working memory performance following Cogmed training in EP/ELBW children.

However, these functional connectivity findings may not necessarily correspond with changes to the structural connectome as measured using diffusion MRI. While several studies have suggested that functional connectivity is constrained by its underlying structural connectivity, differences in structural and functional network organisation have been reported (Lim, Radicchi, van den Heuvel, & Sporns, 2019). This may be expected given functional connectivity and structural connectivity are based on different underlying MRI signals, and utilise different methods for estimating connections between regions (Lim et al., 2019). While functional connectivity incorporates both direct and indirect relationships between brain regions, structural connectivity estimates a direct relationship between two brain regions (Lim et al., 2019). Given these differences, additional studies on structural connectivity networks would be beneficial. Graph theory is a powerful mathematical framework for understanding complex networks, which has proven useful in quantifying changes in the brain structural connectome during development and in association with preterm birth (Collin & van den Heuvel, 2013; Thompson et al., 2016).

Studies examining the effects of working memory training on structural connectivity networks in healthy adults are promising. One study found that Cogmed was associated with increased efficiency in communication between regions within frontoparietal attention networks compared with a placebo training program (Caeyenberghs, Metzler-Baddeley, Foley, & Jones, 2016). These findings may not be directly comparable with studies in children or vulnerable populations. To date, no study has examined the influence of Cogmed training on structural connectivity networks in children, including EP/ELBW children. It also remains to be determined whether structural connectivity changes are associated with working memory changes following Cogmed training in EP/ELBW children.

In the current study, we aimed to compare changes in the brain structural connectome from pre-training to two weeks post-training between EP/ELBW children who participated in the Cogmed and placebo program. We also aimed to investigate whether changes in structural connectivity were related to changes in working memory performance from pre-training to two weeks post-training in EP/ELBW children, and whether these relationships differed for children who participated in the Cogmed and placebo programs.

METHODS

Participants

Participants were part of a double-blind, placebo-controlled, randomised trial of Cogmed in 7-year-old children born EP/ELBW, referred to as the IMPRINT trial (Anderson et al., 2018a; Pascoe et al., 2013). A subset of participants underwent brain MRI pre-training (n = 60; 30 in the Cogmed group and 30 in the placebo group), of which the majority also underwent MRI post-training (n = 57; 28 in the Cogmed group and 29 in the placebo group) (Kelly et al., 2020). Exclusions relating to image quality resulted in the final sample size of n = 28 participants in the Cogmed group and n = 27 participants in the placebo group, who had usable MRI data from at least one timepoint (Figure 1). The study was approved by the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne. Written informed consent was obtained from primary caregivers.

Baseline perinatal and demographic measures

Perinatal data were obtained from medical records. Social risk was assessed using a social risk index based on family structure, education of the primary caregiver, occupation of the primary income earner, employment status of the primary income earner, language spoken at home, and maternal age at birth, as previously described (Anderson et al., 2018b; Roberts et al., 2008; Roberts, Lim, Doyle, & Anderson, 2011). The social risk index ranges from 0-12 and was dichotomised around the median such that scores <2 indicate lower social risk and scores ≥2 indicate higher social risk.

Cogmed and placebo training

The Cogmed working memory training program has been previously described in detail (Anderson et al., 2018a; Kelly et al., 2020; Pascoe et al., 2013). In brief, children completed Cogmed (RM version), which involves practicing a range of computerised working memory activities for 45 minutes, 5 days a week over a 5–7 week period. The minimum number of training sessions to be defined as compliant is 20. In the Cogmed program, the difficulty level of tasks increased adaptively on a trial-by-trial basis to match the child's current performance. The placebo version of the program involved the same activities, but the difficulty level was set to a consistent low level, to avoid taxing working memory.

MRI acquisition

MRI was performed prior to randomisation and two weeks post-training using a 3T Siemens Magnetom Trio, Tim system with a 32-channel head coil, at The Royal Children's Hospital, Melbourne, Australia. T_1-weighted images were acquired with an ultrafast magnetisation-prepared rapid gradient-echo (MPRAGE) sequence: repetition time (TR) = 1,900 ms; echo time (TE) = 2.27 ms; flip angle = 9°; field of view (FOV) = 210 × 210 mm; matrix size = 256 × 256; sagittal slices; slice thickness = 0.85 mm; in-plane resolution = 0.82 mm. Diffusion-weighted images were acquired with an echo planar imaging (EPI) sequence: *b*-values of 3,000 s/mm^2; 45 gradient directions; 5 *b*-value = 0 s/mm^2 images; TR = 8,500 ms; TE = 112 ms; FOV = 225 × 225 mm; matrix size = 98 × 98; 2.3 mm axial slices; in-plane resolution = 2.3 mm. Along with the diffusion images, a single pair of *b* = 0 s/mm^2 images were acquired with reversed phase encoding.

Image pre-processing

T_1-weighted images were pre-processed using the longitudinal stream of the FreeSurfer image analysis suite, version 6 (Fischl, 2012; Reuter, Schmansky, Rosas, & Fischl, 2012). Each participant's FreeSurfer output was visually checked and manually edited as required, and 12 images were excluded due to movement or other artefact, or enlarged ventricles which interfered with image processing (Figure 1). Intracranial volume (ICV) was calculated from the cross-sectional FreeSurfer data.

Diffusion-weighted images were pre-processed using the Functional MRI of the Brain Software Library (FSL), version 5.0.11. Images were corrected for susceptibility-induced

distortions based on the reversed phase-encoded images using the FSL 'topup' tool (J. L. Andersson, Skare, & Ashburner, 2003) and motion and eddy-current-induced distortions using the FSL 'eddy' tool, incorporating outlier replacement and *b*-vector reorientation (J. L. R. Andersson et al., 2017; J. L. R. Andersson, Graham, Zsoldos, & Sotiropoulos, 2016; J. L. R. Andersson & Sotiropoulos, 2016; Leemans & Jones, 2009). We visually examined corrected diffusion images, and obtained quantitative metrics relating to image quality using the FSL QUality Assessment for DMRI (QUAD) and Study-wise QUality Assessment for DMRI (SQUAD) tools (Bastiani et al., 2019), following which four images were excluded due to movement or other artefact (Figure 1). Images were brain extracted using the FSL Brain Extraction Tool (BET) (S. M. Smith, 2002).

For each participant, the brain extracted, first b = 0 s/mm^2 image was registered to the T_1-weighted image (skull-stripped using the Advanced Normalisation Tools (ANTs) software and intensity-inverted to better match the b = 0 s/mm^2 image) using linear registration with the FSL Linear Image Registration Tool (FLIRT) (Jenkinson, Bannister, Brady, & Smith, 2002) and non-linear registration with ANTs (Avants, Epstein, Grossman, & Gee, 2008). Cortical parcellations, including 74 regions per hemisphere (Destrieux, Fischl, Dale, & Halgren, 2010), and subcortical segmentations (7 regions per hemisphere (Fischl et al., 2002)) derived from FreeSurfer were brought into b = 0 s/mm^2 space by applying the inverse of the transformation matrix.

Whole brain tractography

Using MRtrix3Tissue (version 5.2.8, https://3Tissue.github.io), a fork of MRtrix3 (J. D. Tournier et al., 2019), response functions for single-fibre white matter, as well as grey matter and cerebrospinal fluid, were estimated from the data themselves based on an unsupervised method (Dhollander, Mito, Raffelt, & Connelly, 2019). Response functions (per tissue type) were averaged across participants. Single-Shell 3-Tissue constrained spherical deconvolution (SS3T-CSD) was performed to obtain white matter-like fibre orientation distributions as well as grey matter-like and cerebrospinal fluid-like compartments in all voxels (Dhollander & Connelly, 2016). Bias field correction and global intensity normalisation across participants were performed directly on the 3-tissue compartments (Raffelt et al., 2017).

Tractography was performed using a probabilistic Second-order Integration over Fiber Orientation Distributions (iFOD2) algorithm with MRtrix3 (J.D. Tournier, Calamante, & Connelly, 2010), based on the white matter fibre orientation distributions from SS3T-CSD. White matter masks from FreeSurfer were used as the seeds for tractography, the 162 cortical and subcortical regions were used as inclusion regions, and brainstem and cerebellum regions were used as exclusion regions. Spherical-deconvolution informed filtering of tractograms (SIFT2) was performed on the tractograms (R. E. Smith, Tournier, Calamante, & Connelly, 2015b).

Graph construction and metrics

Streamlines were mapped to the relevant nodes defined by the cortical and subcortical parcellations using the 'tck2connectome' tool from MRtrix3. A radial search was performed from each streamline endpoint to locate the nearest node (R. E. Smith, Tournier, Calamante, & Connelly, 2015a). In the resulting 162 x 162 connectome matrices, columns and rows represent nodes, and cells represent edges, with edges reflecting the sum of streamline weights. Each contribution to the connectome edge was scaled by the inverse of the two node volumes (Hagmann et al., 2008). Matrices were made symmetric, and the matrix diagonal was set to zero. We also set biologically implausible inter-hemispheric subcortical connections to zero. Connectome edges were multiplied by the SIFT proportionality coefficient. This step (along with the prior group average response function and global intensity normalisation) allows for quantitative comparison of connection density between participants (R.E. Smith, Raffelt, Tournier, & Connelly, 2020). The weighted, undirected connectivity matrices were thresholded to preserve the top 30% of the strongest weights, to produce graphs with the same number of edges, and ensure that any differences in the subsequently calculated measures were caused by changes in topology rather than density (Beare et al., 2017; Pascoe et al., 2018). Graph summary measures were computed using the networkX package (http://networkx.github.io). The structural connectivity measures of interest, which characterise several different properties of the whole-brain structural connectome, were raw density, global efficiency, local efficiency, small worldness, characteristic path length, average clustering coefficient, and modularity, as detailed in our previous publications (Beare et al., 2017; Pascoe et al., 2018;

Thompson et al., 2016). Raw density is the proportion of edges present relative to all edges within the graph. Global efficiency is a measure of integration within the brain, local efficiency is a measure of clustering or segregation of brain regions, and small-worldness is a measure of the balance between integration and segregation. Characteristic path length is the average shortest path length between all pairs of nodes in the network. The clustering coefficient measures how close a node neighbourhood is towards being a "clique"; average clustering coefficient is the ratio of the number of triangles of edges in the neighbourhood to the number of possible triangles of edges, averaged over all nodes in the graph. Modularity is the difference between the fraction of edges within communities and the expected fraction of edges between communities in the graph. We refer to our prior publications for further details on the structural connectivity measures (Beare et al., 2017; Pascoe et al., 2018; Thompson et al., 2016).

Working memory performance

Working memory was assessed as part of a large battery of tests prior to randomisation and two weeks post-training at the Murdoch Children's Research Institute, Melbourne. The assessments of interest for the current study included the Working Memory Test Battery for Children (WMTB-C) and the Automated Working Memory Assessment (AWMA), as detailed previously (Alloway, 2007; Anderson et al., 2018b; Pickering & Gathercole, 2001). Immediate verbal memory was assessed using the Digit Recall subtest (from the WMTB-C). Immediate visual-spatial memory was assessed using Block Recall (WMTB-C). Backward Digit Recall (WMTB-C) was administered to assess verbal working memory. Backward Block Recall (WMTB-C) and Mister X (AWMA) were administered to assess visual-spatial working memory (Anderson et al., 2018b). Given our interest in examining change over time, raw scores for all measures were used in line with previous studies (Anderson et al., 2018b).

Statistical analyses

Statistical analyses were performed using Stata version 16. To address aim one, linear mixed effects models were applied to the structural connectivity measures from the pre-training and post-training timepoints simultaneously. The mixed models included fixed effects for timepoint and group (Cogmed or placebo), and an interaction between

timepoint and group to assess whether the change over time varied by group. The models also included adjustment for potential confounders of age at pre-training MRI, sex and ICV (as a time-varying confounder). A random effect was included in all models to allow for clustering between repeated measures on individuals. For this aim, all participants with usable data from at least one timepoint were included in the analysis.

To address aim two, change variables for structural connectivity measures and working memory performance scores were calculated (value at timepoint 2 – value at timepoint 1). Then, the relationship between the change in structural connectivity measures and the change in working memory scores was assessed using linear regression. Models included a group-by-metric interaction to assess if the relationship between the change in structural connectivity measures and the change in working memory scores was different in the Cogmed and placebo groups. Analyses included adjustment for age at pre-training MRI, sex, change in ICV, and baseline score on the relevant working memory assessment. For this aim, participants with missing data at either timepoint were excluded from the analysis.

We repeated both the aim 1 and aim 2 analyses adjusting for baseline general cognitive ability, social risk and birth weight, to ensure these variables were not influencing the results. We also repeated the analyses excluding the participants who completed fewer than the recommended minimum of 20 training sessions, to investigate whether lack of compliance and therefore lower training duration or intensity influenced the results.

All results are presented as regression coefficients, along with their confidence intervals and *p*-values. The results were interpreted based on the overall pattern of results across all of the measures simultaneously rather than interpreting each regression coefficient or *p*-value in isolation.

RESULTS

Participant characteristics

Table 1 shows clinical and demographic characteristics of the included participants. These characteristics were generally similar for the Cogmed and placebo groups, however, the Cogmed group had a slightly lower birth weight and slightly lower general cognitive ability compared with the placebo group (Table 1). The number of completed training sessions was similar between the Cogmed and placebo groups, however a small number of participants in both groups completed fewer than the recommended minimum of 20 sessions (Table 1). The clinical and demographic characteristics of the included participants were generally representative of the larger trial (Supplementary Table 1).

Table 2 shows ICV, structural connectivity measures and working memory performance outcomes of the included participants at pre-training and post-training. On average, the Cogmed group had a larger ICV than the placebo group at pre-training. Values for structural connectivity measures were similar between the Cogmed and placebo groups at pre-training and post-training. On average, the Cogmed group had lower working memory scores at pre-training compared with the placebo group.

Effect of Cogmed training on structural connectivity

There was little evidence for differences in the change in structural connectivity measures from pre-training to post-training between the Cogmed and placebo groups. An exception was the raw density measure, where there was some evidence that the Cogmed group had a greater increase from pre-training to post-training than the placebo group (Table 3). Results were similar after adjusting for baseline general cognitive ability, social risk and birth weight (Supplementary Table 2), and after excluding the participants who completed fewer than the recommended minimum of 20 training sessions (Supplementary Table 3).

Associations between changes in structural connectivity and working memory

There was little evidence for associations between changes in structural connectivity measures and changes in working memory performance scores pre-training to post-training, and little evidence that these associations varied between the groups (Figure 2). Results were similar after adjusting for baseline general cognitive ability, social risk and

birth weight (Supplementary Figure 1), and after excluding the participants who completed fewer than the recommended minimum of 20 training sessions (Supplementary Figure 2).

DISCUSSION

The current study found generally little evidence that Cogmed working memory training compared with a placebo program was associated with changes in the brain structural connectome in EP/ELBW children. Furthermore, we found little evidence that changes in structural connectivity from pre-training to two weeks post-training were associated with changes in working memory performance following either Cogmed or placebo training.

Changes observed from pre-training to post-training in the majority of the structural connectivity measures were similar for the Cogmed and placebo groups, suggesting that Cogmed does not have strong training-specific effects on structural connectivity networks in EP/ELBW children. The only evidence for an effect of Cogmed on whole-brain connectivity was in relation to the raw density measure, which increased following training in the Cogmed group but not in the placebo group. The magnitude of change in raw density was comparable with the difference in raw density between very preterm (<30 weeks) and full-term 7-year-olds previously reported in a separate study by our group (Thompson et al., 2016). An increase in raw density across the whole brain may reflect improved capacity of the white matter fibre bundles to transmit information between brain regions (R.E. Smith et al., 2020). Interestingly, this measure reflects the density of connections, whereas the other measures reflect the topology rather than density of the connectome. Therefore, additional studies on connectome density may be worthwhile. However, we acknowledge this finding may have occurred by chance, given the large number of comparisons performed in this study, and requires confirmation in future studies.

Our results are largely consistent with previous reports from the IMPRINT trial, which found little evidence for Cogmed-specific effects on cognitive outcomes (Anderson et al., 2018b), voxel-wise white matter microstructure (Kelly et al., 2020) and resting-state functional connectivity networks (Tseng et al., 2019). Despite the largely null findings from our trial, previous studies have reported that Cogmed is associated with enhanced brain activity and

connectivity in typically developing 8- to 11-year-olds based on magnetoencephalography (MEG) (Astle, Barnes, Baker, Colclough, & Woolrich, 2015; Barnes, Nobre, Woolrich, Baker, & Astle, 2016). A recent study also found that Cogmed was associated with greater increases in fractional anisotropy in the left superior longitudinal fasciculus, right uncinate fasciculus and left cingulum than a placebo program in survivors of neonatal critical illness at age 8-12 years (Schiller et al., 2019). Additionally, a previous study based on a similar graph theoretical analysis of structural connectivity found that Cogmed was associated with increased global efficiency within a frontoparietal attention network compared with a placebo program in healthy young adults aged 26 years (Caeyenberghs et al., 2016). This finding was observed when graph network edges were weighted by intrinsic longitudinal relaxation rate (R_1) derived from the multicomponent driven equilibrium single pulse observation of T(1)/T(2) (mcDESPOT) protocol, but not when edges were weighted by diffusion tensor imaging metrics, Composite Hindered and Restricted Model of Diffusion (CHARMED) metrics, or the number of streamlines (Caeyenberghs et al., 2016). The mcDESPOT metrics are thought to provide increased sensitivity to myelin compared with other MRI measures (Deoni, Rutt, Arun, Pierpaoli, & Jones, 2008), and thus future studies could incorporate MRI sequences sensitised to myelin to explore if working memory training programs alter the myelin properties of the structural connectome in EP/ELBW children. Regardless, the discrepancies in findings observed across trials highlight that previous positive results may not be readily generalisable to all populations.

We found little evidence that changes in structural connectivity metrics were related to changes in working memory performance from pre-training to two weeks post-training in EP/LBW children, or that these relationships differed between the Cogmed and placebo groups. This is not surprising given the limited differences in structural connectivity changes between groups discussed above, and the lack of training effect on working memory performance in the IMPRINT trial previously reported (Anderson et al., 2018b). Indeed, in a previous structural connectivity study in healthy adults, no associations were found between changes in global efficiency and changes in cognitive performance scores (including working memory) following Cogmed (Caeyenberghs et al., 2016). In contrast, there was some evidence for associations between changes in global efficiency of the R_1-weighted networks and changes in performance on the Cogmed training activities,

however the evidence for these correlations was relatively weak and did not survive correction for multiple comparisons (Caeyenberghs et al., 2016). Thus, our findings appear largely congruent with this prior study. It is important to acknowledge that in our previous study of functional connectivity networks in the IMPRINT trial, we found that increased functional connectivity in the precuneus network was associated with increased working memory performance scores in the Cogmed but not placebo group, suggesting that changes in functional connectivity may support working memory performance following Cogmed in EP/ELBW children (Tseng et al., 2019). Similar findings were not apparent based on the structural connectivity metrics utilised in the current study, highlighting the importance of examining both structural and functional connectivity. Further multi-modal studies may be beneficial to clarify the relationship between structural and functional connectivity following cognitive training.

Strengths of the current study include the use of a randomised controlled design which included an active control group, and the large number of working memory outcomes. Use of advanced diffusion MRI and graph theoretical analyses enabled us to examine effects of Cogmed on whole-brain network connectivity thought to give rise to cognition, instead of isolated brain regions (Bressler & Menon, 2010). The number of participants included in the current study was similar to or larger than previous related studies (Astle et al., 2015; Barnes et al., 2016; Caeyenberghs et al., 2016; Schiller et al., 2019). Despite this, we acknowledge the relatively small neuroimaging sample limited our statistical power, and in particular our study was likely underpowered to identify interactions within the statistical models (Altman & Bland, 2003). While a small number of participants did not complete the minimum recommended 20 training sessions, results remained similar after excluding these participants, suggesting lower training duration did not contribute to the results. There was also some difference in baseline working memory performance between the Cogmed and placebo groups, however adjusting for this difference did not affect the overall conclusions of our study.

Conclusions

This study provides little evidence that Cogmed is associated with training-specific changes to the brain structural connectome in EP/ELBW children, except potentially for the density

of connections. Thus, there is currently limited evidence that Cogmed training results in changes to brain structure in EP/ELBW children compared with a placebo program. Further research using large sample sizes and randomised controlled trial designs are needed to validate this finding.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR'S CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization,* C.K., K.L., L.P., E.J., M.S., C.N., G.R., L.D., M.L.S., D.T. and P.A.; *Investigation and Formal Analysis*, C.K., R.H., K.L., L.P., E.J., C.A. and R.B.; *Writing - Original Draft and Visualization*, C.K. and R.H.; *Writing - Review & Editing*, C.K., R.H., K.L., L.P., E.J., M.S., C.A., R.B., C.N., G.R., L.D., M.L.S., D.T. and P.A.; *Funding Acquisition and Resources*, K.L., C.N., G.R., L.D., M.L.S., D.T. and P.A.

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DATA ACCESSIBILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

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FIGURE LEGENDS

Figure 1. Participant flowchart. MRI, magnetic resonance imaging.

Figure 2. Relationships between changes in structural connectivity measures and changes in working memory performance from pre-training to post-training in the Cogmed and placebo groups. CI, confidence interval.

Table 1. Clinical and demographic characteristics of the participants.

	Cogmed group ***n*** **= 28**	**Placebo group** ***n*** **= 27**
Gestational age at birth (weeks), M (SD)	27.0 (2.2)	26.6 (1.5)
Birth weight (g), M (SD)	834 (152)	885 (216)
Male, *n* (%)	12 (43)	12 (44)
Multiple birth, *n* (%)	2 (7)	7 (26)
Bronchopulmonary dysplasia, *n* (%)	16 (57)	13 (48)
Proven necrotising enterocolitis, *n* (%)	2 (7)	4 (15)
Intraventricular haemorrhage grade 3/4, *n* (%)	3 (11)	2 (7)
Cystic periventricular leukomalacia, *n* (%)	0 (0)[†]	1 (4)[‡]
Age (years), M (SD)	7.8 (0.4)[‡]	7.8 (0.4)[§]
Social risk[¶], M (SD)	2.2 (1.4)	3.1 (2.5)
Higher social risk[¶], *n* (%)	21 (75)	19 (70)
General cognitive ability[¶], M (SD)	97 (11)	102 (14)
Number of completed training sessions, M (SD, min-max)	20 (7, 3-25)	21 (7, 2-25)
Completed ≥20 training sessions, *n* (%)	20 (71)	22 (81)

M, mean; SD, standard deviation. [†]based on n = 27. [‡]based on n = 26. [§]based on n = 25. [¶]Social risk was assessed using a previously described social risk index (Anderson et al., 2018b; Roberts et al., 2008; Roberts, Lim, Doyle, & Anderson, 2011). General cognitive ability was assessed using the General Conceptual Ability composite score from the Differential Ability Scales- 2nd edition (Elliott, 2007).

Table 2. Structural connectivity and working memory performance at pre-training and post-training for the Cogmed and placebo groups.

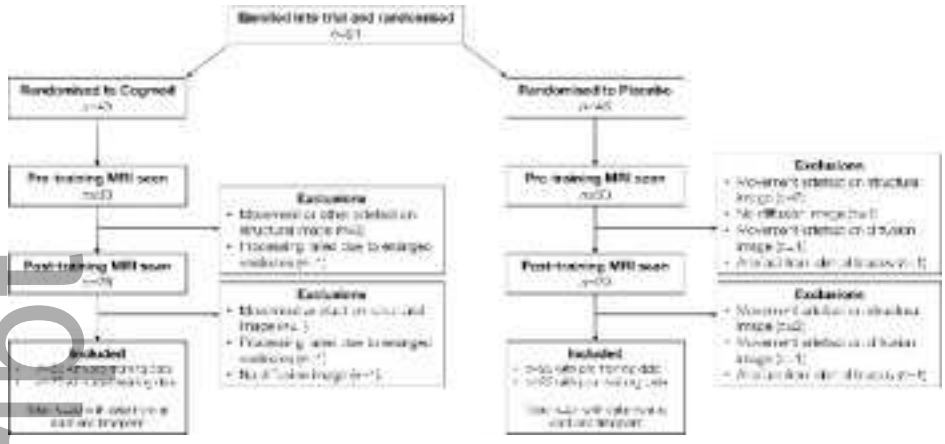
	Cogmed (*n* = 28)		Placebo (*n* = 27)	
	Pre-training	**Post-training**	**Pre-training**	**Post-training**
	M (SD)	**M (SD)**	**M (SD)**	**M (SD)**
Intracranial volume (cm^3)	1376 (161)[‡]	1391 (192)[§]	1345 (128)[‡]	1359 (141)[‡]
Structural connectivity				
Raw density	0.48 (0.05)[‡]	0.49 (0.05)[§]	0.51 (0.06)[‡]	0.50 (0.06)[‡]
Global efficiency	0.02 (0.005)[‡]	0.02 (0.005)[§]	0.02 (0.007)[‡]	0.02 (0.006)[‡]
Local efficiency	0.03 (0.007)[‡]	0.03 (0.007)[§]	0.03 (0.009)[‡]	0.03 (0.008)[‡]
Small worldness	1.65 (0.15)[‡]	1.60 (0.16)[§]	1.61 (0.17)[‡]	1.62 (0.17)[‡]
Characteristic path length	72.37 (17.70)[‡]	71.37 (19.14)[§]	76.66 (18.89)[‡]	71.28 (16.97)[‡]
Average clustering coefficient	0.01 (0.002)[‡]	0.01 (0.003)[§]	0.01 (0.002)[‡]	0.01 (0.002)[‡]
Modularity	0.33 (0.02)[‡]	0.34 (0.02)[§]	0.34 (0.02)[‡]	0.34 (0.02)[‡]
Working memory[¶]				
Backward digit recall	8.7 (2.5)[†]	11.0 (3.9)[‡]	9.3 (2.9)[†]	12.2 (3.9)[‡]
Mister X	7.8 (3.2)[†]	9.5 (3.6)[‡]	8.6 (3.9)[‡]	9.1 (3.5)[‡]
Backward block recall	11.6 (5.3)[†]	16.0 (4.9)[‡]	13.1 (5.0)[†]	14.5 (4.9)[†]
Digit recall	24.1 (3.7)	26.5 (3.9)[‡]	25.3 (4.5)	27.4 (5.5)[†]
Block recall	20.6 (4.6)	24.6 (4.9)[‡]	21.5 (3.7)	25.3 (3.9)[†]

M, mean; SD, standard deviation; [†]one participant had incomplete data; [‡]two participants had incomplete data; [§]three participants had incomplete data; [¶]for all working memory measures, raw scores are presented.

Table 3. Changes from pre-training to post-training in structural connectivity measures in the Cogmed and placebo groups.

Structural connectivity measure	Cogmed β (95% CI), *p*	Placebo β (95% CI), *p*	Interaction *p*
Raw density	.015 (.004, .026), 0.006	-.006 (-.017, .005), 0.32	0.008
Global efficiency	-.0004 (-.0018, .0011), 0.61	.0011 (-.0003, .0026), 0.12	0.14
Local efficiency	-.0006 (-.0026, .0014), 0.56	.0017 (-.0003, .0037), 0.11	0.12
Small worldness	-.053 (-.109, .004), 0.07	.006 (-.051, .063), 0.84	0.15
Characteristic path length	.105 (-5.869, 6.079), 0.97	-4.599 (-10.600, 1.403), 0.13	0.28
Average clustering coef.	.0006 (-.0002, .0014), 0.15	-.0008 (-.0016, .0000005), 0.05	0.02
Modularity	.00444 (-.00008, .00897), 0.05	.00085 (-.00370, .00540), 0.71	0.27

CI, confidence interval.



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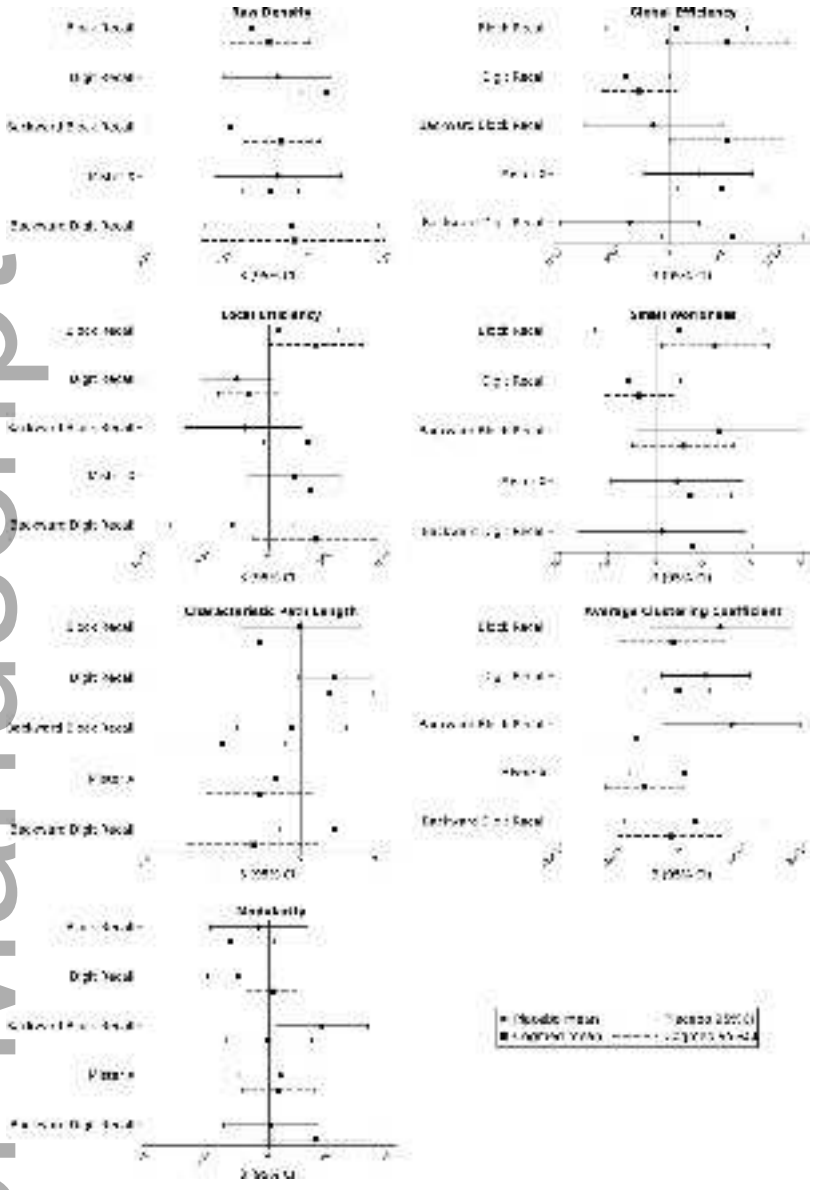

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