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Working-memory training following neonatal critical illness: a Randomized Controlled Trial

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Key words: neurodevelopmental disorders, neuropsychology; extracorporeal membrane oxygenation; hernias, diaphragmatic, congenital; cognitive remediation; memory.

Word count: 2956

Abstract

Objective To test the immediate and long-term effectiveness of Cogmed Working-Memory Training (CWMT) following ECMO and/or CDH.

Design A nationwide randomized controlled trial assessing neuropsychological outcome immediately and one year post-CWMT, conducted between October 2014-June 2017. Researchers involved in the follow-up assessments were blinded to group allocation.

Setting Erasmus MC-Sophia Children's Hospital, Rotterdam and Radboud University Medical Center, Nijmegen, the Netherlands.

Patients Eligible participants were neonatal ECMO and/or CDH survivors (8-12 years) with an IQ $\geq$ 80 and a *z*-score $\leq$ -1.5 on at least one (working)memory test at first assessment.

Interventions CWMT, comprising 25 sessions of 45 minutes for five consecutive weeks at home.

Measurements and Main Results Participants were randomized to CWMT (n = 19) or no intervention (n = 24) (two dropped out after T0). Verbal working-memory (estimated coefficient = 0.87; p = .002) and visuospatial working-memory (estimated coefficient = 0.96, p = .003) had significantly improved in the CWMT group at T1, but was similar between groups at T2 (verbal, p = .902; visuospatial, p = .416). Improvements were found at T2 on long-term visuospatial memory following CWMT (estimated coefficient = 0.95, p = .003). Greater improvements in this domain at T2 following CWMT were associated with better self-rated school functioning (r = .541, p = .031) and parent-rated attention (r = .672, p = .006).

Conclusions Working-memory improvements after CWMT disappeared one year post-training in neonatal ECMO and/or CDH survivors. Gains in visuospatial memory persisted one year post-intervention. CWMT may be beneficial for survivors with visuospatial memory deficits.

Trial Registration NTR4571: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4571.

Introduction

Growing up after neonatal critical illness has long-term neurodevelopmental consequences(1-7). Specifically, children treated with neonatal extracorporeal membrane oxygenation (ECMO) and/or with congenital diaphragmatic hernia (CDH) are at risk of specific (working)memory and attention deficits at school-age, despite average intelligence(1,3,8). These deficits become more evident as children mature, suggesting they 'grow into deficit'(9). This mechanism – where subtle brain injuries acquired in early life become evident only later in life when higher cognitive functioning is required – has recently been described by our group across survivors of neonatal critical illness(10). As more educational problems occur following neonatal critical illness than in the general population(4,11), it is imperative to find intervention strategies to prevent or diminish impaired outcome.

Working-memory, one of the fundamental building blocks for higher cognitive functioning, is highly associated with academic performance(12) and may be at risk of impairment following neonatal ECMO(1,13). Training programs to improve cognitive functioning have received increasing attention over the years, and are based on the idea that repetitive mental exercise of one cognitive task results in improved functioning that may generalize to other tasks with similar underlying skills. A widely evaluated cognitive training for children with working-memory problems is Cogmed Working-Memory Training (CWMT)(14). Near-transfer effects, i.e. improvements on trained and untrained working-memory tasks, as well as far-transfer effects to non-trained cognitive functions have been found immediately after CWMT(15,16). However, whether effects persist beyond six months post intervention remains largely unknown(17,18).

In this single-blind RCT, the immediate and long-term effectiveness of CWMT on (working)memory in school-age (8-12 years) survivors of neonatal ECMO and/or CDH are studied. We hypothesized that CWMT improved (working)memory and attention immediately after training. Furthermore, we hypothesized that these improvements persisted 12 months post- training.

Materials and methods

Design and setting

This RCT, conducted between October 2014 and June 2017, compared CWMT to no training in school-age neonatal ECMO and/or CDH survivors (NTR4571). Children born between February 2002 and December 2007 who were treated in either of the two referral centers for neonatal ECMO and CDH treatment in the Netherlands (Erasmus MC, Rotterdam or the Radboudumc, Nijmegen) were recruited. As we have previously shown similar long-term cognitive outcome in CDH patients irrespective of ECMO treatment, CDH patients treated without ECMO were also recruited(2,8). ECMO had been applied using the entry criteria described by Stolar et al.(19), which did not change over time. The study took place at the Erasmus MC-Sophia Children's Hospital. Ethical approval was granted by our institution's Review Board (MEC-2014-001).

Eligibility and Recruitment

Eligible participants were: neonatal ECMO and/or CDH survivors between 8-12 years at first assessment, IQ ≥ 80, and a *z*-score ≤ -1.5 on at least one (working)memory test.(20) Children were recruited in two ways: 1) children who underwent neuropsychological assessment as part of the structured follow-up program in Rotterdam(21,22) and met the inclusion criteria were referred to our study or, 2) potentially eligible children received information by mail about the trial and were invited to contact our center. Written informed consent from all parents and children ≥12 years old was obtained. Exclusion criteria were: usage of psychopharmaceutic drugs (e.g. methylphenidate) and/or genetic syndromes that affect neuropsychological functioning. All children had sufficient knowledge of the Dutch language to perform the assessments.

Eligible children were randomized into either the CWMT group or the control group by an independent researcher uninvolved with the neuropsychological assessments. Randomization was performed by drawing from sealed, opaque envelopes containing a paper with either 'intervention' or 'no intervention'. The psychologists who conducted the neuropsychological assessments were blinded to group allocation.

Intervention

The CWMT^{RM} version for 7-17-year-old children was used. Children trained at home for 45 minutes a day, five days a week, for five consecutive weeks, after which the training was completed as per manufacturer's instructions(14). Task level adapted automatically to ensure the child was continuously performing at its' maximum ability. As part of the program, children were supervised by a certified CWMT coach, who provided weekly support to the family by phone and e-mail, and closely monitored the child's performance via online access.

Children in the control group did not receive any training.

Outcome measures

After baseline assessment (T0), neuropsychological assessments were repeated in all participants one week (T1) and one year (T2) post-intervention (Figure 1). The primary outcome measure was verbal working-memory(23), assessed using the WISC-III-NL Digit Span(24), at T1. For all secondary outcome measures, please refer to Supplemental Digital Content (SDC) 1 and 2.

Sample size calculation

The power calculation was based on the expected difference between the CWMT group and control group on verbal working-memory, the primary outcome measure. Based on previous

findings on the effect of CWMT on verbal working-memory in children with working-memory problems(23,25,26), we expected a difference of 0.8 SD between groups (considered a large effect according to Cohen's guidelines(27)). We assumed that baseline scores would show a correlation of 50% with scores at T1. We calculated that a sample size of 25 children per group would be needed (power of 90%, alpha of .05)(28).

Statistical analysis

Clinical and demographic characteristics and neuropsychological outcome at baseline were compared between groups using independent samples t-tests and ANCOVA (normally distributed variables), Mann-Whitney U tests or Fisher's exact tests (non-normally distributed continuous or categorical variables).

All analyses were based on the intention-to-treat principle. Outcome scores were converted to z-scores (individual score minus population mean divided by population SD). Scores were inverted where appropriate so that a higher score always equated with better performance. To assess outcome after CWMT at T1 and T2, we estimated linear mixed models. This method accounts for within-subject correlations and allows for missing values in the dependent variable. Based on the Akaike information criterion, a random intercept was included in the mixed models to account for the within-subject correlations. P-values for the fixed effects were calculated using t-tests with the Satterthwaite approximation method. Performance at baseline was constrained to be equal. Neuropsychological outcome was the dependent variable, and group and time-point as well as the group*time-point interaction term were independent variables. For analyses with the secondary neuropsychological outcome measures (all but verbal working-memory at T1), the False Discovery Rate (FDR)-correction(29) was used to correct for multiple testing. It was applied once for each set of tests in the same neuropsychological domain (e.g. once for the analyses done with tests measuring attention). Additionally, linear mixed models were estimated with the self- and proxy-rated outcomes as dependent variables.

Finally, if any sustained improvements were found on the neuropsychological outcome measures following CWMT at T2, we assessed whether these were associated with subjective improvements scored by parents, teachers or children on EF, working-memory, attention, self-esteem or school functioning. We conducted Pearson correlation analyses between the change-score from T0 to T2 on neuropsychological outcome and these self- and proxy-reported outcomes at T2 in the CWMT group. In secondary analyses, no correction for multiple testing was applied.

Statistical analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY) and R Statistical Software version 3.1.3 (R Core Team, 2014)(lme4 and lmerTest packages). Results of the linear mixed models were summarized using the estimated marginal means, which are the predicted values of the dependent variable adjusted for the effects of the independent variables. These can be interpreted as z-scores. For all analyses, a two-sided (FDR-corrected) p-value <.05 was considered statistically significant.

Results

Of 217 invited children, 54 declined to participate and 68 did not respond. Fifty assessed children were excluded because they did not meet the inclusion criteria and two dropped out after randomization, leaving 43 participants. Of these, 19 were assigned to the CWMT group and 24 to the control group (Figure 2). Age, ethnicity, gender, IQ, education type, or clinical characteristics, such as ECMO treatment, were similar between groups (Table 1). See Figure 3 for baseline neuropsychological outcome.

All children in the CWMT group completed 25 sessions, except one who completed 20 sessions. Sensitivity analyses were performed without this child's data. As the results did not change, the child was not excluded from the analyses.

Primary outcome measure

The CWMT group improved significantly on verbal working-memory at T1 compared to controls (estimated coefficient = 0.87; $p = .002$) (SDC3, Figure 4).

Secondary outcome measures

Working-memory

Verbal working-memory was similar between groups at T2 (estimated coefficient = -0.04, $p = .902$) (SDC3, Figure 4A). Additional analyses were performed to evaluate the Digit Span Forward (DSF), i.e. short-term memory, and Digit Span Backward (DSB), i.e. working-memory, separately(24). Performance on the DSF and DSB improved significantly at T1 in the CWMT group compared to the control group (forward: estimated coefficient = 0.93, $p = .028$; backward: estimated coefficient = 1.13, $p = .033$), whereas no group differences were found at T2 (forward: estimated coefficient = -0.08, $p = .860$; backward: estimated coefficient = 0.38, $p = .497$).

The CWMT group improved significantly on visual working-memory compared to the control group at T1 (estimated coefficient = 0.96, $p = .003$). However, this difference disappeared at T2 (estimated coefficient = 0.29, $p = .416$) (SDC3, Figure 4A). An improvement in Spatial Span Forward was found in the CWMT group at T1 compared to controls (estimated coefficient = 1.12, $p < .001$), but not at T2 (estimated coefficient = -0.15, $p = .613$). Spatial Span Backward did not differ between the CWMT group and controls (T1: estimated coefficient = 0.43, $p = .146$; T2: estimated coefficient = 0.61, $p = .056$).

Memory

The CWMT group improved on short-term visuospatial memory at T1 and T2 compared to the control group, but this difference did not reach significance. Long-term visuospatial memory improved significantly in the CWMT compared to the control group at T2 (estimated coefficient = 0.95, $p = .003$) (SDC3, Figure 4A).

Verbal memory did not change (SDC3).

Other neuropsychological outcomes

Attention, processing speed, EF and visuospatial processing were similar between groups at T1 and T2 (SDC3).

Proxy- and self-reported outcomes

Parents, but not teachers, of the CWMT group scored EF at T2 higher than the control group (estimated coefficient = 0.57, $p = .034$). Parent- and teacher-rated working-memory did not differ between groups (Figure 4B, SDC4).

Parents and teachers scored the child's behavior within the average range in both groups at all time-points (SDC4). Parents, but not teachers, of the CWMT group reported fewer problems with attention and hyperactivity at T2 compared to controls (estimated coefficient = 0.58, p = .042)(SDC4).

Children in the CWMT group reported better quality of life at T2 than the control group (estimated coefficient = 0.92, p = .034). Parents did not report changes in (psychosocial) quality of life following CWMT (SDC4).

Children in the CWMT group reported better school functioning at T2 than controls, but this difference did not reach significance. Proxy-reported school functioning was similar in both groups (SDC4).

Neuropsychological improvement and subjective outcome following CWMT

Larger gains in long-term visuospatial memory from T0 to T2 were associated with higher scores on school functioning scored by children in the CWMT group at T2 (r = .541, p = .031), and better parent-reported attention and hyperactivity at T2 (r = .672, p = .006) (Figure 3B). No other associations were found between visuospatial memory improvement and the subjective outcomes (not shown).

Discussion

This nationwide single-blind randomized controlled trial confirmed our hypothesis by showing that school-age neonatal ECMO and/or CDH survivors who completed CWMT significantly improved on working-memory immediately post-intervention. However, this improvement did not persist one year post-intervention. We found positive far-transfer effects of CWMT to long-term visuospatial memory, persisting one year post-intervention. These children reported better school functioning and their parents reported fewer problems with inattention and hyperactivity. As over half of our cohort had visuospatial memory deficits at baseline, these improvements following CWMT are highly relevant for this particular population.

Our findings of improved verbal and visuospatial working-memory immediately after CWMT are in line with the effects demonstrated in other groups(30-33). The ability to memorize digits for a short period of time and manipulate them are directly trained in CWMT(31). However, after one year, working-memory performance had returned to baseline. This suggests that active training of working-memory is needed to maintain improved functioning in these domains. A period of retraining after CWMT completion may lead to more sustained effects, but this remains speculative. Although studies with follow-up assessments more than six months post-intervention are scarce, gains in working-memory performance have been found to persist seven months(30) and one year post-training(25). The inconsistency in results may be due to differences in population and the type of neuropsychological deficits that exists between populations. For example, working-memory was within the average range in our population at baseline, in contrast to the children with working-memory deficits studied in the two other long-term studies(25,30).

Short- and long-term verbal and visuospatial memory are at major risk of impairment following neonatal ECMO and/or CDH(1,3). In this school-age cohort, more than half of the children had such memory deficits at baseline. However, short- and long-term verbal memory did not change following CWMT. CWMT consists of mostly visual and visuospatial training tasks, and as such may not target verbal (working-)memory enough to result in far-transfer effects(31). In line with this, children in the CWMT group did show sustained improvement on long-term visuospatial memory one year after the intervention, resulting in average performance at this time. Visuospatial memory is important for everyday life and gains in this domain are therefore of great significance.

Greater sustained improvements in the CWMT group in long-term visuospatial memory were associated with better self-reported school functioning and less proxy-reported problems with attention at T2. These findings suggest that the improvements on visuospatial memory extend to daily life. However, these results should be interpreted with caution due to the small sample size in combination with the number of analyses. The generalizability of cognitive improvements to everyday life and school performance has received considerable attention over the last few years. Studies reported both improved attention in daily life following CWMT(34) and no benefits to educational performance(35). In our study, teachers did not report any improvements following CWMT. However, they did not report any problems at baseline either. Future studies that include objective measures of academic performance such as reading or mathematical ability are needed in both preschool and school-age neonatal ECMO and/or CDH survivors following CWMT to get a better impression of its impact on school functioning and daily life.

Attention and (working)memory share similar pathways in the brain(36). In addition to (working)memory, attention may also improve through CWMT. Sustained attention deficits have been previously found following neonatal ECMO and/or CDH(1,3), and were confirmed

in this cohort. Although we found faster processing speed following CWMT at T2, significance disappeared after multiple testing correction. Selective and sustained attention did not improve post-CWMT. Neuroimaging studies in children with ADHD or childhood cancer, found improvements in attention immediately post-CWMT to be associated with fronto-parietal networks(32,37-39). However, attention deficits following neonatal ECMO and/or CDH were found to be associated with global white matter microstructure and cingulum bundle alterations(3,5). CWMT therefore may not target the networks responsible for attention deficits in this population. Our group is currently working on studying the effectiveness of CWMT following neonatal ECMO and/or CDH using advanced neuroimaging techniques. Such findings could enhance our understanding of how CWMT affects the brain in these survivors.

This is the first study investigating the effectiveness of CWMT following neonatal ECMO and/or CDH, demonstrating high feasibility of such a training in this group. However, our study has some limitations. First, we used a non-active control group for ethical considerations against subjecting children to an intensive training without potential benefits, which limits our ability to attribute our findings to the specific characteristics of the CWMT training. The self- and proxy-rated outcomes should therefore be interpreted with caution. Nonetheless, various studies have found improved outcome following CWMT when compared to a non-adaptive training program which also included weekly phone calls from a certified Cogmed training coach (25,31,34,40). Second, our sample size was smaller than anticipated. We did not extend our inclusion time because we did not want our control group to wait longer than needed to complete CWMT if it was proven to be beneficial. Finally, our primary outcome measure was based on initial reports of neuropsychological outcome in the study population that showed working-memory problems(2,7,11) and on previous studies on CWMT(23,25,26). However, ongoing research testing all major neuropsychological domains demonstrated primarily short- and long-term memory problems in these children(8). Given these new insights, a different primary outcome measure than working-memory would have been more appropriate for this population.

Conclusions

We found improved working-memory immediately after CWMT in school-age neonatal ECMO and/or CDH survivors, but this did not sustain until one year post-training. Sustained far-transfer effects on long-term visuospatial memory were found following CWMT. Given the high risk of visuospatial memory deficits in these children and the importance of memory in daily life, CWMT shows clinical utility for children with visuospatial memory deficits. Future studies with advanced neuroimaging techniques and objective measures of academic performance are needed to further delineate the effectiveness of CWMT in neonatal ECMO and/or CDH survivors.

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Figure Legends

Fig. 1 Trial outline

For short descriptions of the tests and questionnaires used, please refer to Supplemental Digital Content 2. *IQ > 80 and a *z*-score ≤ -1.5(20) on one or more memory tests. Abbreviations: CWMT, Cogmed Working Memory Training.

Figure 2. CONSORT flow diagram

T1 refers to the first follow-up assessment immediately after the intervention, T2 refers to the assessment one year after the intervention. Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder.

Fig. 3 Neuropsychological outcome at baseline for the CWMT group and the control group

Mean z-score is given per group. Scores of the CWMT group are presented in blue, scores of the control group are presented in black. Independent samples T-test was used to identify differences between the groups. *****Significant difference between the groups. Abbreviations: CWMT, Cogmed Working Memory Training; RAVLT, Rey Auditory Learning Test; RCFT, Rey Complex Figure Test; DCT, Dot Cancellation Test; TMT, Trail Making Test; STROOP, Stroop Color Word Test.

Fig. 4 Neuropsychological outcome immediately and one year after CWMT in ECMO and/or CDH survivors

Blue lines represent the CWMT group, black lines represent the control group. Panel A shows verbal working-memory, visuospatial working-memory, and visuospatial memory at baseline (T0), immediately after (T1) and one year after CWMT (T2). A red dot represents a significant group by time effect, showing a significant improvement in the CWMT group compared to the control group at that time-point. Panel B shows the significant correlations between the change in z-scores from T0 to T2 in long-term visuospatial memory and z-scores on the self- and parent-reported outcomes on school functioning and attention in the CWMT group at T2. Abbreviations: CWMT, Cogmed Working Memory Training; ECMO, extracorporeal membrane oxygenation; CDH, congenital diaphragmatic hernia.

Tables

Table 1. Study population characteristics

Characteristics	All (n = 43)	Controls (n = 24)	CWMT (n = 19)	*P*-value
a) Demographic				
Age (years)	10 ± 2	10 ± 2	10 ± 1	.275
Gender				.812
Male	24 (56%)	13 (54%)	11 (58%)	
Ethnicity				.127
Dutch	37 (86%)	19 (79%)	18 (95%)	
Maternal education level[a]				.407
Low	7 (16%)	3 (13%)	4 (21%)	
Moderate	13 (30%)	7 (29%)	6 (32%)	
High	23 (54%)	14 (58%)	9 (47%)	
Type of education child				.953
Regular	27 (63%)	14 (58%)	13 (68%)	
Regular with help	13 (30%)	9 (38%)	4 (21%)	
Special education	3 (7%)	1 (4%)	2 (11%)	
IQ	100 ± 12	98 ± 12	101 ± 12	.359
b) Clinical				
Birthweight (grams)	3596 ± 479	3474 ± 338	3772 ± 605	.765
Gestational age (weeks)	40 ± 1	40 ± 2	41 ±1	.492

Mechanical vent. (days)	11 (9-17)	12 (9-17)	10 (9-17)	.677
CLD presence	6 (15%)	3 (13%)	3 (19%)	.423
Abnormal CUS				.969
Yes	3 (9%)	2 (9%)	1 (9%)	
No	29 (91%)	19 (91%)	10 (91%)	
Unknown[b]	11	3	8	
CDH-non-ECMO	12 (28%)	6 (50%)	6 (50%)	.646
ECMO treatment[c]	31 (72%)	18 (75%)	13 (68%)	.643
Type of ECMO				.357
VA	21 (66%)	10 (56%)	11 (84%)	
VV	9 (31%)	8 (44%)	1 (8%)	
VV conversion to VA	1 (3%)	0 (0%)	1 (8%)	
Age start ECMO (days)	2 (1-3)	2 (1-4)	1 (1-2)	.077
Hours on ECMO	110 (90-182)	119 (87-196)	104 (90-182)	.824

N (%), mean ± SD or median (interquartile range) is reported where appropriate for the group as a whole ('All' in column 1), the control group (Controls in column 2) and the CWMT group (CWMT in column 3) separately. Dutch refers to children with two native Dutch parents. [a]Based on the highest level of education completed by the mother(41).

[b]In CDH-non-ECMO patients, cranial ultrasounds were not routinely performed in our centers.

[c]Diagnoses underlying ECMO treatment were congenital diaphragmatic hernia (n=2), meconium aspiration syndrome (n=22), persistent pulmonary hypertension of the newborn (n = 4), infant respiratory distress syndrome (n = 2), and cardiac anomaly (n=1).

Abbreviations: CWMT, Cogmed Working Memory Training; IQ, Intelligence Quotient; CLD, chronic lung disease; CUS, cranial ultrasound; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous

Supplementary Material

Supplemental Digital Content 1. Outcome measures

Overview of outcome measures assessed at the different time points of the study. T0 is the baseline assessment, T1 is six weeks after baseline, and T2 is 12 months after baseline. The primary outcome measure was working-memory assessed by Digit Span. Abbreviations: WISC-III-NL, Wechsler Intelligence Scale for Children; WNV, Wechsler Non Verbal Scale of Ability; RAVLT, Rey Auditory Learning Test; RCFT, Rey Complex Figure Test; DCT, Dot Cancellation Test; TMT, Trail Making Test; BADS-C-NL, Behavioural Assessment of the Dysexecutive Syndrome.

Supplemental Digital Content 2. Descriptions of the neuropsychological tests.
Brief descriptions of the neuropsychological tests used.

Supplemental Digital Content 3. Neuropsychological outcome immediately and one year after CWMT in neonatal ECMO and/or CDH survivors
Results of linear mixed model analyses showing the effect of CWMT on neuropsychological outcome at T1 and T2. All estimated coefficients are reported as z-scores. The control group was used as the reference group and the baseline assessment T0 as the reference time-point. FDR-correction(26) was applied to correct for multiple testing. FDR-correction was applied once for each set of tests in the same neuropsychological domain (i.e. once for the tests measuring attention). An **FDR-corrected *p*-value** <.05 is considered to be statistically significant.
Abbreviations: CWMT, Cogmed Working Memory Training; ECMO, extracorporeal membrane oxygenation; CDH, congenital diaphragmatic hernia; T1, six weeks after baseline; T2, 12 months after baseline; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; DCT, Dot Cancellation Test; TMT, Trail Making Test; BADS-C-NL, Behavioural Assessment of the Dysexecutive Syndrome.

Supplemental Digital Content 4. Proxy- and self-reported outcomes immediately and one year after CWMT in neonatal ECMO and/or CDH survivors
Results of the linear mixed model analyses showing the effect of CWMT on proxy- and self-reported outcomes at T1, as well as at T2. The control group was used as the reference group and the baseline assessment T0 as the reference time-point. P value <.05 is considered to be statistically significant. Abbreviations: CWMT, Cogmed Working Memory Training; ECMO, extracorporeal membrane oxygenation; CDH, congenital diaphragmatic hernia; T1, six weeks after baseline; T2, 12 months after baseline; BRIEF, Behaviour Rating Inventory of Executive Functioning; PedsQL, Paediatric Quality of Life Inventory; SDQ, Strengths and Difficulties Questionnaire; CHQ, Child Health Questionnaire.