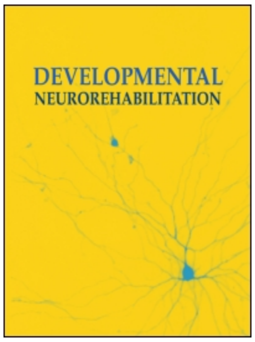

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Specific Effects of Individualized Cognitive Training in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): The Role of Pre-Training Cognitive Impairment and Individual Training Performance

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ABSTRACT

Objective: We investigated the impact of the pre-training neuropsychological (NP) impairment and of the training progress on the NP and behavioural outcome after computerized cognitive training (CogT) in children with ADHD.
Method: Thirty-one participants underwent individualized CogT (focussing on one or two cognitive domains: working memory, inhibition, attention) over 12 weeks. NP tests and behaviour ratings served as outcome measures.
Results: After CogT, significant improvements emerged according to parents' ratings, but only on very few NP test measures. Children with milder/no pre-training NP impairment showed larger improvements on behavioural ratings than more impaired children. A steeper training performance slope was related to better behavioural outcomes.
Conclusion: We find partial support for specific effects of CogT, but the assumption that an individually tailored selection of training tasks would be particularly beneficial for children with ADHD with NP deficits was not confirmed.
Trial registration number: NCT02358941.

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ADHD; child; cognitive intervention; plasticity; executive functions

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood, with an estimated worldwide prevalence rate of approximately 5.8%.[1] The disorder is characterized by persistent symptoms of inattention, overactivity, and/or impulsiveness.[2] Boys are more frequently affected than girls (gender ratio 7:1 to 2:1).[3] Stimulant medication is widely used as a treatment for ADHD.[4] However, there is an ample need for effective alternative or supplementary non-pharmacological intervention methods, as parents may have reservations about pharmacotherapy, and undesired side effects are common.[5]

Computerized training of cognitive functions has garnered intense interest as a non-pharmacological intervention for ADHD in recent years. The rationale for process-based cognitive training (CogT) in ADHD lies in both neuropsychological (NP) and neurobiological models of the disorder.[6,7] ADHD has repeatedly been associated with NP impairment[8,9] and neurobiological abnormalities.[10,11] Through mechanisms of brain plasticity, CogT is thought to strengthen the deficient cognitive functions that are assumed to mediate ADHD behaviour, which may lead to an alleviation of ADHD symptom severity.[7,12] Computerized CogT was shown to improve performance in untrained cognitive tasks (see refs.[13–17]) and to reduce symptoms of ADHD (see refs.[18–20]) However, recent meta-analyses have challenged the usefulness of CogT for ADHD, as probably blinded measures and active control group trials have not provided sufficient evidence of significant symptom reduction and clinical relevance of improvements.[5,21] Moreover, evidence for the generalization of training effects to everyday situations is particularly limited.[12,22]

Several authors have argued that it would be beneficial to identify subgroups which would benefit most from CogT.[7,23,24] One potential reason for the findings of low efficacy in meta-analyses lies in the fact that trained ADHD samples were not selected according to whether they had the specific NP deficit at which the CogT was aimed.[21] This observation is pivotal considering that no more than half of the children with ADHD-combined type can be reasonably classified as 'impaired' in NP tests.[25,26] Moreover, a possible lack of room for improvement or the targeting of 'wrong' NP deficits might also be responsible for the small effects of CogT.[21] This notion was further underpinned by the finding that the training of multiple cognitive domains was superior in reducing ADHD symptoms to the training of an individual cognitive function (i.e. working memory).[21] The large interindividual heterogeneity in the NP profiles of patients with ADHD[27-29] suggests that tailoring the training contents to

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individual needs may be particularly beneficial.[14,30] Two studies in adults reported a more pronounced training response of initially poorer performers to working memory training.[31,32] Hence, one might also expect children with ADHD and with NP deficits in the trained area to benefit to a greater extent from CogT than neuropsychologically unimpaired children. Furthermore, if ADHD symptoms are mediated by NP deficits, then larger training-induced improvements of neuropsychological functions should also lead to larger clinical benefits.

Facilitating Far Transfer

'Far transfer' has been described as transfer to tasks that are related to the trained task but that are not located in the same cognitive function. An improvement in the same type of task, in contrast, would be described as 'near transfer' (e.g. performance in different working memory tasks would be improved after working memory training).[23] In the ADHD literature, far transfer is extended to behavioural measures such as behavioural ratings of ADHD symptom severity, academic functioning, and behavioural observation.[12,22] Critical aspects that might affect successful transfer include motivation[33,34], personalized feedback[35], metacognitive skills[36], adequate self-evaluation[37], and expectations about the malleability of cognition.[38] Cognitive-behavioural therapeutic procedures provide a means to target some of these aspects and thus increase the likelihood of successful transfer.

Specificity of Training Effects

The amount of training performance gain in the trained task might further moderate training and transfer effects. Several studies reported that participants who reached larger training performance gains during cognitive training showed more pronounced improvement in a transfer tasks after training.[32,39–41] In ADHD samples, post-training teacher ratings were influenced by performance in a working memory training task.[42] A recent study found that children with ADHD with steeper learning curves in working memory training showed larger benefits in working memory transfer measures.[43] These findings indicate a direct relation between successful learning and the supposed underlying plastic changes of cognitive functions with treatment outcome. Such specific effects of CogT are also corroborated by studies comparing adaptive training with non-adaptive training methods.[14,18] However, inconsistent findings (e.g. refs.[13,42]) and motivational issues inherent in undemanding control training paradigms suggest that more research is needed to examine the specificity of CogT.

Stability of NP Parameters in ADHD

For the analysis of near-transfer effects, NP test measures need to be sufficiently reliable to yield a good estimation of the true performance. However, the small number of studies that have investigated the test-retest reliability of neurocognitive tests in ADHD point in the opposite direction. For the Stop Signal task and the Conners' Continuous Performance task (CPT), acceptable test-retest reliability over one-week intervals was reported in children with ADHD for measures of inhibitory control errors and reaction time, but coefficients were near zero for omission errors.[44] In typically developing children, only CPT reaction time yielded an acceptable level of test-retest reliability over an interval of six months, while all others reliability coefficients were low.[45] Only moderate test-retest reliability coefficients were reported for Go Nogo task measures[46] and for a battery of standardized attention tests (Test of Attentional Performance Battery; TAP) in samples of typically developing children.[47,48]

For the evaluation of intervention effects, repeated assessments of cognition are usually conducted, and both the temporal stability of the used measures and the role of practice effects need to be considered.[45,49] For this purpose, a dual baseline model has been suggested to assess cognitive change in children.[50] This design requires two NP assessments prior to the beginning of an intervention, allowing the stability of cognitive test performance to be examined and thus providing a better estimation of the true pre-training cognitive impairment.[49]

The Present Study

In the present study, we investigated the effects of an individualized PC-supported CogT for children with ADHD on NP test performances and on ADHD symptoms as rated by parents and teachers. A dual baseline design with a waiting period of approximately 10 to 12 weeks prior to treatment was used. This enabled the evaluation of test-retest reliability and an estimation of the true pre-training NP performance by averaging both pre-training baseline scores.

The following hypotheses guided our research with regard to waiting time effects and general outcome:

(1) With regard to the dual baseline assessment of NP performances, we expected at best moderate stability coefficients over the waiting time, due to the known fluctuations of executive function test performance in ADHD **(1a)**. After completion of the training, we expected significant improvements on NP test performance **(1b)** and on behavioural rating scales **(1c)** compared to the averaged pre-training NP test performance and behavioural rating.

Regarding the specificity of treatment effects, we investigated the following hypotheses:

(2) We assumed that participants with more severe NP impairment would benefit from individualized training to a greater extent than less impaired participants, both with respect to NP tests **(2a)** and behavioural ratings **(2b)**.
(3) We hypothesized that larger training performance gains would be associated with greater treatment response, i.e. larger improvements on NP tests **(3a)** and behavioural ratings **(3b)**.
(4) We assumed that clinical responders (i.e. children who show considerable improvements on parent- and teacher-rated behavioural scales after training) would be more impaired in the NP test battery before training **(4a)**, that they would show a larger training performance gain within the training tasks **(4b)**, and that they would

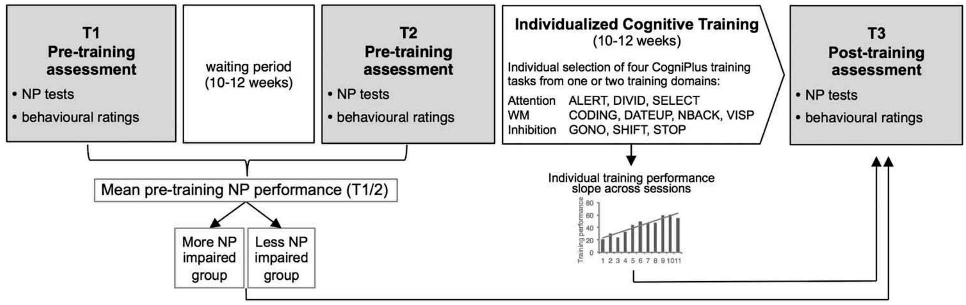


Figure 1. Study design. The intervention took place between T2 and T3 assessment and was individualized with regard to training domains and tasks. The main outcome variables were the NP test performance scores and the behavioural ratings that were collected at all three assessment times. NP = neuropsychological; WM = working memory.

show larger improvements in NP test performances after training **(4c)** than clinical non-responders (i.e. children who show negligible improvements on parent- and teacher-rated behavioural scales after training).

The operationalization of these research questions within the design of the present study is shown in Figure 1.

Methods

Participants

A total of 31 children and adolescents aged between 8 and 14 years participated in the study (see Table 1 for demographic data). To be included in the study, participants had to present clinically relevant symptoms of ADHD with or without hyperactivity (based on the Conners-3 DSM-IV ADHD indices; German version; see ref.[51]) Exclusion criteria were severe comorbidities, neurological disturbances, and IQ below 80. Children who had been under constant stimulant medication (only methylphenidate, MPH) for at least three months before entering the study were allowed to participate if a) ADHD symptoms were still present and b) medication was kept stable throughout the study period. Children taking medication other than MPH were excluded from the study. During the waiting and training period, children continued to take their medication as usual. Medication was only interrupted for NP testing, at least 24 hours prior to assessments (i.e. T1, T2, and T3).

The present analysis is part of a larger study, in which two interventions, CogT and neurofeedback training, were compared. Results of this comparison and more details on the recruitment of participants are reported elsewhere.[52] Parents and children gave written consent to participate. The study was approved by the local ethics committee. Clinical trial registration number NCT02358941.

Procedure

For screening, the Development and Wellbeing Assessment (DAWBA; see ref.[53]) was administered to parents and a short form of the WISC-IV (see ref.[54]) was conducted with the children. At baseline (T1), questionnaire data were obtained and the first NP assessment was administered. After T1, a waiting period of approximately three months was scheduled. The waiting period was followed by assessment T2, at which questionnaires, the NP assessment, and parent or teacher interviews on individual problems and goals (goal attainment) were conducted. Thereafter, the CogT was delivered in 30 sessions, each lasting for 45 to 60 minutes, over 10 to 12 weeks. Training was conducted either in a separate room at the participant's school (*n* = 13) or at an outpatient clinic (*n* = 18). After the completion of the training

Table 1. Sample characteristics.

	Total *n* = 31	More impaired subgroup[a] (*n* = 16)	Less impaired subgroup[a] (*n* = 15)	Group comparison[b] *p*
Age (years) *M (SD)*	10.52 (1.98)	10.50 (1.75)	10.53 (2.26)	.964
Range	8–14	8–14	8–13	
Gender				
Male *n (%)*	21 (67.7)	13 (81.25)	8 (53.33)	.097
IQ (estimated) *M (SD)*	99.94 (9.01)	97.13 (9.32)	102.93 (7.88)	.072
Medicated *n (%)*	10 (32.26)	5 (31.25)	5 (33.33)	.901
Conners-3 parent (T1)				
DSM-IV IN T *M (SD)*	66.32 (6.67)	64.31 (7.44)	68.47 (5.15)	.083
DSM-IV HI T *M (SD)*	65.55 (7.04)	65.44 (7.52)	65.67 (6.76)	.930
Conners-3 teacher (T1)				
DSM-IV IN T *M (SD)*	67.42 (4.54)	67.00 (5.29)	67.87 (3.72)	.604
DSM-IV HI T *M (SD)*	62.90 (8.26)	64.31 (7.67)	61.40 (8.85)	.335
Comorbidity				
Disruptive behaviour disorder *n (%)*	9 (29.03)	3 (18.75)	6 (40.00)	.206
Anxiety disorder *n (%)*	1 (3.23)	1 (6.25)	0 (0.00)	.325

[a]Group categorization based on the mean global NP composite score of T1 and T2. [b] Independent t-tests (for age, IQ, Conners-3) and chi-square tests (for gender, medication, comorbidity) were computed to compare groups. IN = inattention; HI = hyperactivity/impulsivity; T = T-score.

course, questionnaires and the NP assessment were again administered (T3). See Figure 1 for an overview of the study design.

Treatment Outcome Measures

NP Performance Scores

The NP assessment included 12 tests (with 22 individual test scores). The tests were administered in the same order at each assessment time. The sustained attention task took place at the end of the assessment. All children underwent the subtest 'Alertness' (tonic and phasic) of the Test for Attentional Performance (TAP, see ref.[55]) Children over the age of 10 years further underwent the subtests 'Distractibility', 'Divided Attention', 'Flexibility', 'Go Nogo', 'Sustained Attention', and 'Working Memory' of the TAP. Younger participants underwent the same subtests (except for 'Working Memory') in the TAP version for children (KiTAP, see ref.[56]) Both TAP and KiTAP are well-established tests used for clinical and research purposes with ADHD (for a description of KiTAP tasks, see refs.[57–59]; for a description of TAP tasks, see refs.[17,60,61]) The D2 paper-pencil test was conducted to assess selective attention.[62] The Digit Span subtest of the WISC-IV was used to assess auditory short-term memory and working memory. The Corsi Block Tapping Test and the Stop Signal Test were administered within the Vienna Test System to assess spatial working memory capacity and response inhibition, respectively.[63,64]

Behavioural Rating Outcome Measures

The parent- and teacher-rated Conners-3 ADHD DSM-IV symptom scales of inattention and hyperactivity/impulsivity (German version; see ref.[51]) and the Behaviour Rating Inventory of Executive Function (BRIEF; German version; see ref.[65]) indices of behavioural regulation and metacognition served as outcome measures.

Individualized Computerized Cognitive Training

The children performed selected training tasks of the computerized NP training program CogniPlus, which aim at improving specific components of attention, inhibition, and working memory.[66] Four out of 10 CogniPlus tasks were selected for each participant, based on their aggregated T1 and T2 NP test profiles and on interview data (see Table 2(a) for the step-by-step procedure). For the training of *attentional functions*, there were three possible CogniPlus tasks: ALERT for the training of alertness, SELECT for the training of selective attention, and DIVID for the training of divided attention. Four tasks were available for the training of *working memory*: VISP for the training of visuospatial working memory, NBACK for the training of working memory capacity, DATEUP for the training of updating of visual information, and CODING for the training of visuospatial coding. The training task DATEUP is described by way of example in Table 3(a). Three subtasks of the CogniPlus training programme HIBIT were available for the training of *inhibitory processes*: Go Nogo, Stop Signal, and Behavioural Shift. All training tasks had adaptive difficulty levels. The efficacy of CogniPlus has not yet been investigated in ADHD participants, but its precursor AixTent was shown to positively affect some near-transfer outcome measures in children with ADHD.[17]

Performance Feedback System and Training Performance Slope

The individualized CogT was supplemented with several therapeutic elements encompassing transfer and feedback components as indicated in Table 2(b). A newly developed electronic point reward system represented a pivotal feedback component. It informed participants consistently about their training performance and enabled a visual display of progression over time. The points of the performance feedback system also served as a measure of training performance gain across sessions (learning slope). This aimed to bear analogy with the analysis of learning in the neurofeedback treatment group (not reported here).[67] For the calculation of the points, the level reached, the number of impulsivity errors, the duration of the training block, and the difficulty level of the supplemental task were entered into the system (see formula and example in Table 3(b)). In the formula, the CogniPlus level reached had the highest weighting, while errors, duration and supplemental task difficulty contributed only minor proportions to the points. In this respect, it was ensured that the points would not automatically increase with progression of the training. This formula was used in order to compensate to some degree for the increased number of errors that were likely to occur at an advanced level of difficulty with longer duration of training blocks and supplemental transfer components. Children were thus encouraged to work at their performance limit, which is considered a prerequisite for plastic change. A maximum of 120 points was possible for each training task. The points for the level reached were computed as a percentage of the maximum accessible level (e.g. 50 points were given when the mean task level was reached). This ensured that points were comparable between tasks, which all had different numbers of levels (e.g. ALERT had 18 levels in total, CODING had 21).

Statistical Analysis

The statistical analysis was performed using IBM SPSS version 23 and RStudio version 0.99.903. All effects were reported as significant if $p < .05$.

Sample Characteristics

The sample characteristics (age, estimated IQ, initial Conners-3 scores) of the more and less NP impaired groups derived by median split (see procedure below) were compared using two-sided independent t-tests. Gender, medication, and comorbidity were compared using chi-square tests.

NP Performance Scores

Normed scores of NP performances were used for the analysis (e.g. T-values), as the children underwent different though equivalent test versions depending on their age (TAP vs. KiTAP). Four tests were not normed for children or not for the full age range (i.e. Sustained Attention, Working Memory, Corsi, Stop Signal Task). For these tests, raw or percentage scores were used. A global composite score of NP impairment was determined for each participant at each assessment time

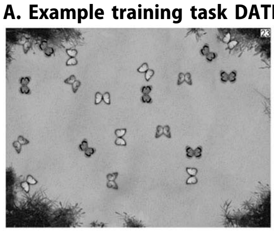
Table 2. Overview of the training components.

Training components	Description
A.Steps for the individualization of the CogT	
1. Pre-selection of training focus	• The individual training focus (one or two training domains, e.g. attention and inhibition training) was determined based on an evaluation of aggregated T1 and T2 results (questionnaires, test results, parent/teacher interviews)
2. Calibration training	• Each pre-selected training task was tested in a short 'calibration' phase to determine the individual starting level and the fit to the difficulties
3. Final selection of training tasks	• Four final training tasks were selected with the goals to (a) match deficits, (b) be perceived as challenging by the participants, and (c) offer enough room for improvement
B.Transfer-facilitating instruments	
1. Goal attainment	• Assessment of the participants' training goals and subsequent mental contrasting
2. Diary	• Self-report of everyday difficulties to establish problem awareness
3. Self-evaluation of behaviour with feedback	• Self-rating of behaviour on a visual analogue scale (e.g. 'how often did you move?') and comparison with the trainer's rating of behaviour with the goal to improve the accuracy of self-evaluation
4. Supplemental tasks	• Addition of supplemental tasks to the training to increase difficulty and to maintain motivation (e.g. adding visual or auditory distractors to the training environment) with adaptive level of difficulty (3 levels)
5. Implementation intention	• Formulation of if-then plans to help the participants to remember to implement their training skills in everyday life (e.g. 'whenever I am getting tired doing math homework, I will refocus as in the 'tunnel task')
6. Transfer cards	• Memory aid to facilitate the implementation of training contents in everyday life

See ref. [90] for details on mental contrasting and implementation intentions.

Table 3. Example description of the CogniPlus task DATEUP and the performance feedback system.

A. Example training task DATEUP



- Different-coloured butterflies change positions from time to time in a natural scene, the programme stops at irregular intervals.
- Depending on the level, one of three different questions is asked: e.g. which butterfly was the last but one to change position (N-Back task)? In what order did the last three butterflies change position (Running task)? Which butterfly of each colour changed its position last (Keep track task)?
- DATEUP has 25 levels with increasing difficulty: The number of butterflies that must be updated increases (from 1 to 6). The type of task (N-Back, Running, Keep track) changes after two consecutive levels and is varied in the last 8 levels.
- The level increases after 10 trials with more than 70% correct responses; it decreases with less than 30% correct responses.

B. Performance feedback system

Points =	100 * reached level / maximum level	- errors+ time bonus[a] + transfer bonus[b]	Example: A training block of 20 min DATEUP with final level 15, and no supplemental task resulted in 65 performance feedback points.

[a]20 min = 5 bonus points
[b]depending on the difficulty level of the supplemental task (level 1 = 5 bonus points, level 2 = 10 bonus points, level 3 = 15 bonus points)

based on the percentage of normed test measures in which he or she scored below a clinical cut-off (i.e. T < 40).

Temporal Stability of NP Performance across the Waiting Period

To assess the mean retest stability of NP performance, bivariate Pearson correlation coefficients of each variable were transformed by Fisher's z, then averaged and back transformed into r_{tt}.[68]

Mixed Model Analysis of the Association between Pre-Training NP Impairment and NP Test Scores

In separate linear mixed models, the mean T1/2 and the T3 values of each NP performance measure were entered as the dependent variables. The mean of T1 and T2 was selected as an estimate of each subject's true pre-training performance.[69] In the mixed models, selected predictors were time, a categorical variable for the impairment group (the less impaired group vs. the more impaired group; determined by median splits on the mean T1/2 performance of each score), and the time by impairment interaction. Random effects were fitted for the subjects. Time effects indicated whether there occurred a significant change over treatment time (from the mean of T1/2 to T3). Post-hoc Tukey contrasts were calculated to follow up on significant time by impairment group interactions (lsmeans package; see ref.[70]) For 22 NP test scores, the Bonferroni correction yielded an adjusted alpha-error level of $p = .002$.

Mixed Model Analysis of the Association between Pre-Training NP Impairment and Behavioural Rating Outcomes

In separate linear mixed models, the mean T1/2 and the T3 values of each behavioural rating scale were entered as the dependent variables. Predictors were time, a categorical variable distinguishing the generally less impaired from the generally more impaired group (based on the mean T1/2 global NP composite score by median split), and the time by impairment group interaction. Random effects were fitted for the subjects. Time effects indicated whether there occurred a significant change over treatment time (from the mean of T1/2 to T3). Post-hoc Tukey contrasts were calculated to follow up on significant time by impairment group interactions (lsmeans package; see ref.[70]) For four behavioural rating scales, the Bonferroni correction yielded an adjusted alpha-error level of $p = .01$.

Training Performance Slopes

The training performance gain was operationalized as each subject's random slope of the performance points across training sessions. The lme4 package was used for the extraction of random slopes corrected for age and IQ.[71] Slopes were generated for the point mean of all four training tasks a child performed (general training performance gain), and in addition for attention, working memory, and inhibition training tasks separately. A total of $n = 27$ participants performed at least one attention training task, $n = 28$ participants performed at least on working memory task, and $n = 17$ participants performed at least one inhibition training task.

Correlation Analysis of the Association between Training Performance Slopes and NP Test Scores and Behavioural Rating Outcomes

The association between training performance slopes and outcomes was analysed using bivariate Pearson correlations between difference scores of NP test scores (T3 – meanT1/2) and the training performance slopes, and between differences scores of behavioural rating scale scores (T3 – meanT1/2) and the training performance slopes.

Clinical Responders

The percentage of children who improved to a reliable degree on the Conners-3 scales from the mean T1/T2 to T3 was calculated based on the Reliable Change Index (RCI)[72] scores reported in the original Conners third edition.[72,73] The BRIEF RCI responder rates were calculated using test-retest reliability coefficients of the German BRIEF[65] in the RCI formula.[72] In total, a clinically reliable improvement was possible on eight scales (two BRIEF indices and two Conners-3 ADHD DSM-IV scales rated by parents and teachers). Children who showed a clinically reliable improvement on three or more of these scales were classified as global clinical responders; the remaining children were classified as global clinical non-responders. The groups were compared with respect to the variables of interest using two-sided independent t-tests.

Results

Temporal Stability of NP Performance across the Waiting Period

Table 4 displays the descriptive statistics for test scores of T1 and T2 (waiting time interval in days $M = 71.94$, $SD = 18.43$) and the respective Pearson correlations. The correlation coefficients ranged between $r = .12$ (Go Nogo) and $r = .79$ (Corsi). The mean correlation coefficient r_{tt} for all NP measures was $r_{tt} = .52$.

Treatment Time Effects on NP Test Scores (T1/2 – T3)

Table 5 displays the descriptive statistics and the treatment time effects from mean T1/2 to T3 for all 22 NP test variables and the composite score. A significant improvement over treatment time was found on the tonic Alertness RT SD, D2 total score, Divided Attention commission and omission errors, Flexibility errors and RT median, and Corsi. The D2 improvement was the only one to survive Bonferroni correction.

Treatment Time Effects on Behavioural Ratings (T1/2 – T3)

Three out of four parent-rated outcome variables (DSM-IV inattention, DSM-IV hyperactivity/impulsivity, and BRIEF behavioural regulation index) improved significantly over treatment time and survived Bonferroni correction (see Table 5). Treatment time effects were not significant for teacher-rated outcomes (all $p > .05$).

Association between Pre-Training NP Impairment and NP Test Scores

Table 5 displays the interactions of time by pre-training impairment (less vs. more impaired) for the NP test scores. Significant interactions emerged in six out of 22 variables: Tonic Alertness RT SD, Sustained Attention commission and omission errors, Distractibility commission errors, Divided Attention omission errors, and Flexibility errors. None of these interactions survived Bonferroni correction. Post-hoc Tukey contrasts revealed that the number of omission errors in the Sustained Attention task deteriorated in the initially less impaired group ($b = -17.03$, $t(29) = -3.29$, $p = .003$) but remained stable in the initially more impaired group ($b = -1.51$, $t(29) = -0.36$, $p = .984$). No further significant within-group contrast emerged. The interactions are depicted in Figure 2.

Association between Pre-Training NP Impairment and Behavioural Rating Outcomes

Table 5 shows the interactions of time by pre-training NP impairment for the parent and teacher behavioural ratings. For parent-rated BRIEF metacognition index, the interaction reached significance and is depicted in Figure 2. Post-hoc Tukey contrasts indicated that the initially less NP impaired group improved significantly over treatment time ($b = 18.68$, $t(27) = 4.61$, $p < .001$), while the more NP impaired group showed no change over treatment time in metacognition ($b = 6.66$, $t(27) = 1.70$, $p = .344$).

Training Performance

The mean of the total performance points of the last five training sessions ($M = 73.9$, $SD = 15$) was significantly higher than the mean of the first five training sessions ($M = 56.5$, $SD = 10.4$; $t(30) = -10.25$, $p < .001$), indicating a significant training performance gain. The same applied to the separate analyses of the three training domains (all $p < .05$). The mean of the programme levels of the last five training sessions ($M = 60.4$, $SD = 13.6$) was significantly higher than the mean of the levels of the first five training sessions ($M = 51.\ 3$, $SD = 10.8$; $t(30) = -6.32$, $p < .001$). The learning slopes extracted from the performance points were highly correlated with the slopes extracted from the programme levels ($r = .93$, $p < .001$).

Table 4. Descriptive statistics for T1 and T2 scores and stability coefficients for the NP test scores.

		T1	T2	T1-T2 stability	
Test name	Variables	*M (SD)*	*M (SD)*	*r*	*p*
Alertness phasic	RT median T	46.2 (7.5)	44.4 (7.4)	.51	**.002**
	RT SD T	48.9 (10.9)	44.8 (11.0)	.25	.092
Alertness tonic	RT median T	47.2 (8.6)	45.0 (8.7)	.32	**.042**
	RT SD T	41.3 (10.8)	38.3 (9.9)	.59	**<.001**
Sustained Attention	Commission%	4.1 (4.3)	3.9 (5.4)	.43	**.008**
	Omission%	30.9 (16.1)	36.2 (20.1)	.36	**.023**
Distractibility	Commission T	49.5 (10.8)	54.6 (10.4)	.58	**<.001**
	Omission T	53.8 (15.8)	54.5 (14.8)	.59	**<.001**
D2	Total score	94.0 (12.6)	99.2 (14.2)	.78	**<.001**
Divided attention	Commission T	50.3 (8.9)	50.3 (7.1)	.32	**.044**
	Omission T	53.8 (9.3)	54.3 (9.5)	.25	.096
Flexibility	Errors T	44.3 (11.6)	47.3 (11.2)	.39	**.015**
	RT median T	48.5 (14.2)	53.4 (11.8)	.57	**<.001**
	RT SD T	45.9 (11.5)	49.7 (10.2)	.56	**.001**
Working Memory	Commission raw	3.8 (4.0)	2.9 (3.5)	.53	**.005**
	Omission raw	6.1 (3.3)	5.9 (3.1)	.67	**<.001**
Digit span	Standard score	9.3 (1.5)	8.4 (1.6)	.49	**.003**
Corsi	Sum correct raw	6.0 (2.4)	7.1 (3.1)	.79	**<.001**
Go Nogo	Commission T	53.0 (11.5)	56.2 (8.6)	.12	.269
	Median T	47.5 (10.6)	42.4 (10.9)	.29	.055
Stop Signal	Commission raw	20.9 (8.3)	21.1 (8.6)	.75	**<.001**
	SS RT raw	0.39 (0.1)	0.43 (0.2)	.71	**<.001**
Global NP composite		25.4 (14.7)	24.7 (13.7)	.38	**.017**

raw = raw score; RT SD = standard deviation of reaction time; SS RT = Stop Signal reaction time; T = T-score; % = percentage of errors.

Table 5. Descriptive statistics for mean T1/2 and T3 scores, time effects and time by pre-training impairment (less vs. more impaired) interactions for all outcome variables.

			T1/2	T3	Time	Time x pre-training impairment
			M (SD)	*M (SD)*	*F*	*b (SE)*
NP test scores						
Alertness phasic		RT median T	45.2 (6.5)	46.4 (8.3)	1.41	−1.25 (2.19)
		RT SD T	46.8 (8.6)	48.2 (9.9)	2.70	-3.20 (2.57)
Alertness tonic		RT median T	46.0 (7.1)	45.7 (9.5)	0.21	1.31 (2.62)
		RT SD T	39.8 (9.1)	41.0 (10.9)	**7.11***	**-10.38 (3.39)****
Sustained Attention		Commission%	4.0 (4.1)	3.4 (3.1)	4.03	**3.10 (1.51)***
		Omission%	33.6 (15.0)	42.6 (20.0)	0.13	**15.52 (6.05)***
Distractibility		Commission T	52.1 (9.4)	52.6 (9.9)	3.50	**−7.39 (3.15)***
		Omission T	54.1 (13.6)	50.4 (16.8)	0.97	-2.70 (3.60)
D2		Total score	96.3 (12.8)	104.1 (12.6)	**19.50*****	−1.41 (2.79)
Divided attention		Commission T	50.3 (6.5)	53.3 (8.6)	**5.96***	−4.39 (3.05)
		Omission T	54.4 (8.0)	54.4 (9.1)	**4.77***	**-10.40 (3.33)****
Flexibility		Errors T	45.8 (9.5)	48.1 (11.8)	**6.01***	**−8.83 (3.87)***
		RT median T	51.0 (11.5)	56.6 (12.9)	**8.83***	-5.80 (0.16)
		RT SD T	47.8 (9.6)	51.5 (13.8)	4.01	-7.60 (5.34)
Working Memory		Commission raw	3.4 (3.3)	3.3 (3.3)	1.09	1.96 (1.46)
		Omission raw	6.0 (2.9)	6.7 (3.0)	0.00	1.50 (0.97)
Digit span		Standard score	8.9 (1.4)	9.8 (2.7)	1.54	0.51 (0.80)
Corsi		Sum correct raw	6.6 (2.6)	7.4 (3.0)	**4.86***	−1.23 (0.92)
Go Nogo		Commission T	54.6 (7.6)	52.7 (9.3)	0.07	−2.83 (2.59)
		Median T	45.0 (8.6)	45.4 (10.1)	1.65	-5.30 (3.32)
Stop Signal		Commission raw	21.0 (7.9)	21.5 (9.4)	1.04	4.56 (2.33)
		SS RT raw	0.41 (0.1)	0.40 (0.2)	2.88	0.07 (0.05)
Global NP composite			25.0 (11.8)	22.3 (14.2)	1.53	1.84 (4.20)
Behavioural ratings (raw scores)						
Conners-3	*Parent*	DSM-IV inattention	19.2 (5.8)	12.9 (6.8)	**12.68****	−2.38 (2.09)
		DSM-IV hyperact./imp.	16.4 (6.2)	11.5 (7.3)	**13.16****	0.07 (1.97)
	Teacher	DSM-IV inattention	19.3 (3.8)	16.5 (6.4)	0.94	−2.47 (2.35)
		DSM-IV hyperact./imp.	15.8 (8.7)	14.4 (8.9)	0.83	-0.29 (2.02)
BRIEF	*Parent*	Behavioural Regulation	52.3 (11.6)	46.1 (13.0)	**10.29****	0.99 (3.04)
		Metacognition	101.4 (13.8)	89.7 (20.3)	2.88	**-12.03 (5.64)***
	Teacher	Behavioural Regulation	52.7 (10.8)	49.2 (12.8)	1.91	−0.29 (3.54)
		Metacognition	97.1 (11.8)	89.5 (16.0)	1.38	-6.79 (5.32)

Note. BRIEF = Behaviour Rating Inventory of Executive Function; raw = raw score; RT SD = standard deviation of reaction time; SS RT = Stop Signal reaction time; T = T-score; % = percentage of errors. Classification into the less impaired and the more impaired group was based on median splits on the mean T1/2 performance of each score. For behavioural ratings, the classification into the generally less impaired and the generally more impaired group was based on a median split on the mean T1/2 of the global NP composite score. * $p < .05$, ** $p < .01$.

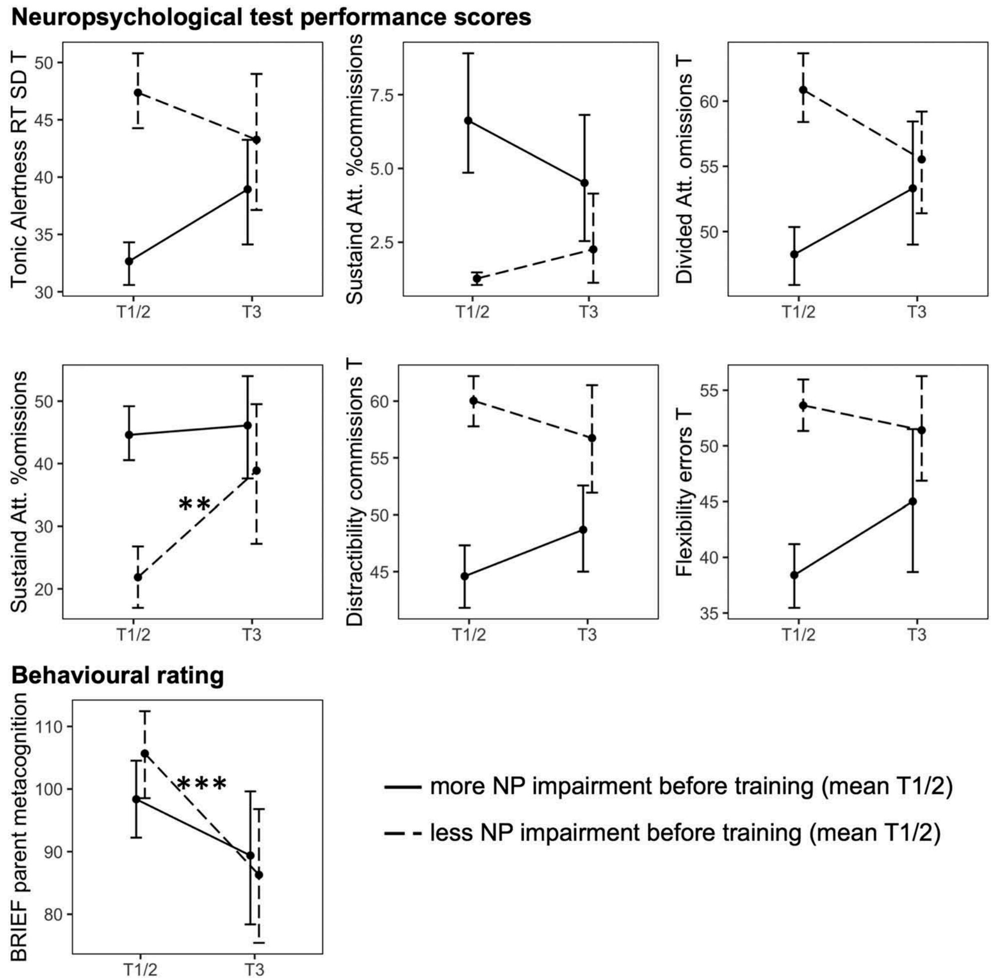


Figure 2. Significant interactions between time and pre-training impairment (more vs. less impaired) on NP test performance scores and behavioural ratings. Att. = Attention; BRIEF = Behaviour Rating Inventory of Executive Function; NP = neuropsychological. The significant within-group Tukey contrasts are labelled with asterisks: ** $p < .01$, *** $p < .001$.

Figure 3 shows the mean progression of training performance points and levels across training sessions.

Association between Training Performance and NP Test Scores

Correlations between changes in NP test scores and training performance slopes are shown in Table 6. Ten significant correlations emerged ($r = .32$ to .50), which indicated that the larger the training performance gain (i.e. a steeper slope), the greater was the improvement in the respective NP test. In total, four tests of the battery showed such associations: Sustained Attention, Distractibility, Go Nogo, and the Stop Signal task. Another correlation showed the opposite relation: Between the inhibition training performance slope and the Digit Span performance change, a significant correlation of $r = -.48$ emerged.

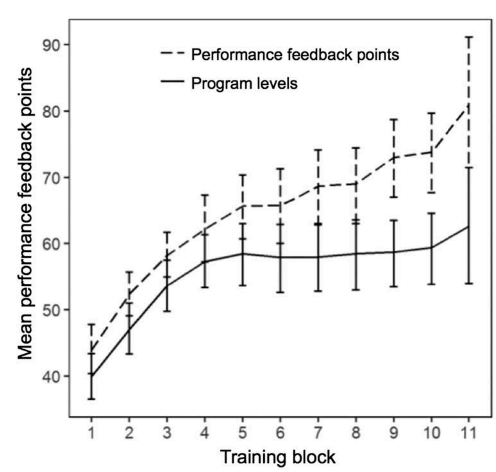


Figure 3. Group means of performance points and programme levels across sessions with 95% confidence intervals. In order to be able to compare and average the programme levels, they were transformed into percentage terms of the maximum level of each training task. The individual slopes of the performance feedback points were used for further analyses.

Association between Training Performance and Behavioural Rating Outcomes

Correlation analyses (Table 6) revealed five significant, medium to large correlations ($r = .34 - r = .48$) between changed behavioural ratings of ADHD symptoms (Conners-3 parent and teacher) and training performance gain. The correlations with BRIEF scores did not reach significance, however, the parent-rated metacognition score and the teacher-rated

Table 6. Bivariate correlations between changes in outcome variables and training performance slopes.

Change scores (T3 – meanT1/2)			General training performance n = 31	AT training performance n = 27	WM training performance n = 28	IH training performance n = 17
NP test scores						
Alertness phasic		RT median T	–.10	–.21	–.10	–.11
		RT SD T	–.06	–.15	–.02	–.01
Alertness tonic		RT median T	.07	–.17	.02	.13
		RT SD T	.07	.10	.01	.02
Sustained Attention		Commission%	–.22	–.27°	–.16	.17
		Omission%	**–.38***	–.22	**–.35***	–.18
Distractibility		Commission T	–.03	.31°	–.14	–.05
		Omission T	**.42***	.17	**.42***	.19
D2		Total score	–.03	.01	.16	–.07
Divided Attention		Commission T	.20	–.05	.25	.21
		Omission T	.28°	.27°	.13	.13
Flexibility		Errors T	.29°	.02	.26°	.13
		RT median T	.08	.23	.02	.12
		RT SD T	–.15	.09	–.14	–.11
Working Memory		Commission raw	.11	.06	.18	–.24
		Omission raw	.01	–.04	.11	.02
Digit Span		Standard score	–.01	.27°	–.14	**–.48***
Corsi		Sum correct raw	–.11	.22	–.14	–.16
Go Nogo		Commission T	.14	**.35***	.01	.36°
		RT median T	**.32***	.18	.31°	.06
Stop Signal		Commission raw	–.23	**–.42***	–.22	.02
		SS RT raw	**–.42****	**–.50****	**–.42***	–.33°
Global NP composite			–.29°	–.06	–.24	–.17
Behavioural ratings						
Conners-3	Parent	DSM-IV inattention	–.16	–.27°	–.11	–.07
		DSM-IV hyperact./imp.	**–.34***	–.11	–.29°	**–.48***
	Teacher	DSM-IV inattention	–.25°	**–.41***	**–.35***	–.08
		DSM-IV hyperact./imp.	–.24	–.17	**–.47****	.04
BRIEF	Parent	Behavioural Regulation	.13	–.18	.14	–.20
		Metacognition	–.22	–.14	–.29°	–.38°
	Teacher	Behavioural Regulation	–.07	–.07	–.31°	.08
		Metacognition	.06	–.10	–.13	–.13

AT = attention; BRIEF = Behaviour Rating Inventory of Executive Function; IH = inhibition; raw = raw score; RT SD = standard deviation of reaction time; SS RT = Stop Signal Reaction Time; T = T-score; WM = working memory; % = percentage of errors. * p (one-sided) < .05, ** p (one-sided) < .01, ° p (one-sided) < .10.

behavioural regulation score reached correlations with training performance slopes of r > .30. The directions of all correlations indicated that a larger training performance gain was associated with a more pronounced symptom reduction in the respective scales.

Clinical Responders

The RCI calculations revealed the following percentage scores of participants with significant clinical improvements: Parent-rated inattentive symptoms improved in 45.2% of the children, and hyperactive-impulsive symptoms improved in 41.9% of the children. Teacher-rated inattentive symptoms improved in 25.8% of the children, and hyperactive-impulsive symptoms improved in 16.1% of the children. Both BRIEF indices improved in 41.4% of the participants according to parents. According to teachers, the metacognition index improved in 61.3% of the participants and the behavioural regulation index improved in 29% of the participants. Three subjects (9.7%) had no clinically reliable improvement on any of these scales.

Group comparisons between global clinical responders (i.e. those with a reliable improvement on at least three rating scale indices, n = 17) and non-responders (n = 14) regarding the variables of pre-training NP test performance, training performance gain, and NP test performance improvement (on the NP composite score) are displayed in Table 7. Two significant differences emerged: Global clinical responders were significantly less NP impaired before training and they showed a significantly steeper training performance slope in working memory tasks compared to global clinical non-responders.

Discussion

The main goals of this study were to evaluate the influence of pre-training NP performance and training performance gain on treatment response to individualized CogT for ADHD. The dual-baseline design enabled the analysis of the stability of impairment.

Temporal Stability of NP Performance across the Waiting Period

The mean stability of test performance over a time period of approximately 10 weeks without intervention was moderate (mean r = .52), as expected. The test scores for Sustained Attention, Divided Attention, Digit Span, and Go Nogo were particularly unstable (r < .50). Only the test scores for the Corsi block tapping, the Stop Signal task and the D2 were tolerably stable (r > .70). Moderate retest-reliability and performance fluctuations in executive function and attention

Table 7. Comparison of global clinical responders and non-responders.

	Global non-responders (n = 14)	Global responders (n = 17)	Group comparison (two-sided[a])
	M (SD)	M (SD)	p
Global NP composite (mean T1/2)	30.46 (10.36)	20.58 (11.29)	**.018**
General training performance slope	−.33 (1.08)	.27 (1.12)	.142
AT training slope, n = 27 (Global responders: n = 15)	−.37 (1.41)	.30 (1.31)	.213
WM training slope, n = 28 (Global responders: n = 15)	−.69 (1.47)	.59 (1.61)	**.038**
IH training slope, n = 17 (Global responders: n = 8)	−.15 (2.50)	.17 (2.61)	.797
Change (T3 − T1/2) in global NP composite	−4.02 (7.68)	−1.65 (14.08)	.556

[a]Independent samples t-tests; AT = attention; IH = inhibition; WM = working memory.

tests have been reported before and possible reasons may be, besides measurement error[45,74,75], repetition effects[46,50], motivational fluctuations, and fatigue.[76–78] The results emphasize the utility of dual-baseline assessments in children with ADHD, as the validity of a single assessment to establish impairment profiles appears to be insufficient.

Treatment Effects on NP Tests

We found one robust significant improvement over treatment time on the D2 task. This improvement might, at least to some degree, reflect practice effects. Other significant improvements – Alertness, Divided Attention, Flexibility, and Corsi test performance – did not survive correction for multiple testing. Overall, the NP treatment response was poorer than expected. This is striking, because the most recent meta-analysis implied a considerable preponderance of effects on NP measures over far-transfer effects after CogT.[21] Several reasons may have impeded better NP outcomes. First, the generally low stability of NP impairment in ADHD made it difficult to define a valid treatment focus for several children. Second, each subject received a tailored set of training tasks, which could have prevented general treatment effects on the group level. Third, a motivational decline at T3 assessment – at least in a part of the sample – might have masked treatment effects in our design with an initial waiting phase. Fourth, the training tasks used may not be adequately designed to bring about lasting improvements in cognitive performance in children with ADHD. Finally, we cannot rule out that a longer duration of training would have been necessary to achieve better outcomes in children with distinct NP impairment.

Treatment Effects on Behavioural Ratings

Significant reductions in parent-rated ADHD symptoms and BRIEF executive impairment were found. The results support the positive effects of the training, with 42% to 45% of participants showing a clinically significant improvement in ADHD symptoms according to parents (as assessed by RCI). Clinical responder rates were comparable to a recent study of CogT in ADHD which applied computerized training of different executive functions.[79] These far-transfer effects on parent ratings stand in contrast to studies that failed to find significant parent-rated improvement after CogT.[80–83] This may indicate that the individually adapted task selection, the supplemental exercises, and the incentives of our CogT were successful in promoting far transfer to the home context.

Association between Pre-Training NP Impairment and NP Test Scores

We expected subjects with more pronounced pre-training NP impairment to show better treatment response than less NP impaired subjects. The NP measures showed little evidence to support this hypothesis. Although six significant interactions with pre-training impairment emerged (Alertness RT SD, Sustained Attention commission and omission errors, Distractibility commission errors, Divided Attention omission errors, Flexibility errors), these could not be plausibly discerned from mere regression to the mean effects.[69,84] As Figure 2 shows, the significant interactions seem to be driven by a deteriorated performance of the less impaired and an improved performance of the more impaired participants. Post-hoc Tukey contrasts however, did not reveal the expected preponderance of improvement in the more NP impaired group. Only one significant contrast emerged, which indicated that less impaired participants showed a significant deterioration in sustained attention from pre- to post-training. Additionally, none of the interactions survived correction for multiple comparisons.

Association between Pre-Training NP Impairment and Behavioural Rating Outcomes

With regard to behavioural ratings, the results suggested the opposite pattern to what we have expected. Less NP impairment seemed predictive of more behavioural improvement: Only the less NP impaired group showed a significant within-group improvement in parent-rated executive functions (BRIEF metacognition index) after training (following up the significant time by group interaction), and global clinical responders performed significantly better in NP tests before training than non-responders. Thus, instead of the hypothesized impairment-specific effect, a magnification effect might have been present.[33,85] Good initial performance on NP tests might be a result of past plasticity, which in turn enabled the better performers to benefit from adaptive practice to a greater extent than poorer performers.[85] This inverse relation calls into question the rationale for cognitive training for ADHD, as it suggests that the effects of CogT are mainly unspecific to underlying NP dysfunctions. However, it remains uncertain whether a placebo effect may have been particularly pronounced in the children with less NP impairment, or whether the present sample may simply not have included enough participants with actual cognitive impairment. The median split approach most likely also categorized some children without impairment or with mainly motivational issues into the more impaired group, which could have biased the results. We must also consider the possibility that in developmental disorders, CogT facilitates cognitive processes through mechanisms other than inducing neural plasticity of the targeted domain. The developing brain presumably reacts differently to CogT than the mature brain, and the disordered brain may be even more distinctively affected. CogT might be effective in ADHD by strengthening the more flexible use of brain functions and facilitating compensatory cognitive strategies instead of structural changes.[6] Such training mechanisms would not benefit particularly those participants with a specific NP deficit in the targeted domain. This might also shed a different light on findings suggesting that combined NP training tasks seem to lead to better outcomes than isolated domain-specific training tasks[21]: not because an impaired domain had been incidentally trained, but because several non-impaired domains might have been strengthened by the training. However, a more fine-grained categorization with larger samples and neuroimaging approaches will help to resolve these issues in the future.

Association between Individual Training Performance and NP Test Scores

The children showed significant performance increases in the training tasks over time (i.e. significant learning occurred). We found that individual differences in training performance slopes were significantly associated with changes in NP test scores over training. This is in line with the literature on working memory training in healthy children[41] and children with ADHD.[43] We found small to medium correlations (r = .26 to .50) between the learning slopes and pre- to post-training changes in 12 out of 22 NP test scores (55%). Domain-specific relations were scarce, i.e. the training performance slope extracted specifically for working memory training tasks was not specifically associated with improved performance in working memory tests of the comprehensive NP test battery. This could indicate that practice with the training tasks transferred to other domains, partly also because an overlap in underlying functions exists between training tasks and added transfer elements. Nevertheless, the associations suggest a specific effect of CogT on NP test performance. That is, post-training test performance did not merely result from unspecific effects induced by the training regimen or by the repetition of tests, but were significantly affected by the participants' performance within the training tasks.

Association between Individual Training Performance and Behavioural Rating Outcomes

The training performance slopes were further correlated with pre- to post-training changes in six out of eight behavioural rating outcomes (75%) with mostly medium to large coefficients (r = .27 to .48). Congruent with the underlying constructs, the attention training performance gain predicted teacher-rated improvement in inattention (r = −.41), and the inhibition training performance predicted parent-rated improvement in hyperactivity/impulsivity (r = −.48). The working memory training performance gain was correlated with improved teacher ratings of ADHD symptoms (r = −.35 and r = −.47) and BRIEF behavioural regulation (r = −.31). Smaller correlations emerged between the working memory training performance slope and parent-rated hyperactivity/impulsivity (r = −.29) and BRIEF metacognition (r = −.29). The results indicate that the more successfully the trained functions were improved, the greater the reduction in behavioural problems. Hence, the clinical treatment response may be specifically dependent on the supposed underlying plastic changes of the trained functions.

Overall, the working memory training performance slope showed more associations with behavioural outcomes than the performance slopes of attention and inhibition training. In particular, the working memory training slope differentiated significantly between global clinical responders and non-responders. Improvement in working memory training tasks thus seemed to have a specific effect on behaviour and clinically relevant impairment. Potentially, successful far transfer requires improved working memory functioning. However, the performance in specific working memory tests did not improve as a function of working memory training gain. The improvements in behavioural ratings therefore did not reflect the change in an underlying test construct of working memory. This also relates to the common finding of generally low correlations between NP test performance and ADHD symptom or executive function ratings.[86,87]

Alternatively, the learning slope may reflect a process other than that of the plastic enhancement of the trained cognitive function. It is conceivable that particularly those children who were more able to recruit cognitive resources to cope with the increasing cognitive load of the tasks (i.e. who had fewer problems regulating effort[88]) may have shown a steeper learning slope. Compared to the attention and inhibition training tasks, the working memory training tasks were less dependent on fast motor responses and more dependent on paying close attention and carefully selecting responses. This could have particularly differentiated the children's ability to mobilize cognitive resources.

Our findings clearly weaken the concept that children with more severe and circumscribed NP impairment and consequently with more room for improvement would show larger training gain and a larger treatment response. Instead, initially higher cognitive ability might have been a prerequisite for better learning and clinically relevant transfer.

Limitations

In this study, we analysed specific effects by relating treatment outcomes to pre-training parameters and cross-session learning. The generalizability of these results is limited due to the lack of a placebo control group with non-adaptive training and/or no additional therapeutic components (results with regard to a randomized control training are presented in ref. 48). Moreover, most results must be regarded as exploratory in nature, as only a few effects survived correction for multiple comparisons. The sample size was rather small, which prevented deeper analyses of group characteristics, e.g. effects of gender, age etc. Although the groups of more and less NP impaired children appeared to be equal with regard to most descriptive variables (see Table 1), this did not fully apply to the gender distribution. Seven out of 10 girls were in the less NP impaired group, which is in line with the finding that girls with ADHD show fewer problems with impulsivity than boys.[89] More research is required to study possible gender-related impacts on effects of CogT. Furthermore, we acknowledge that by averaging the two pre-training assessments of behavioural ratings for analyses, the effects of waiting-time-specific processes on informant ratings were ignored. This was purposefully done to enhance the comparability of the results with pre-training NP test scores, although we were well aware that these may be subject to distinct effects between assessments (i.e. practice, fatigue etc.). In-depth analyses of waiting-time effects of these data are reported elsewhere.[52]

Conclusion

This study provided valuable insight into the mechanisms of CogT by investigating possible predictors of treatment response. The results implied that NP impairment was not a necessary condition for the success of individualized CogT. Given the direct relations between training performance slopes and NP and behavioural improvements, we suggest that participants of CogT should be motivated to work at their performance limit and to increase their performance day by day. More research is needed to investigate what facilitates children with ADHD to adapt to the increasing cognitive demand of training tasks and how this ability could be promoted. The role of motivation in CogT should also be elucidated.

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Disclosure of interest

The authors report no conflict of interest.

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