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Originalartikel

Long-term Effects of a Multimodal Behavioural ADHD Training: a fMRI Study

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Abstract: Several studies have demonstrated that behavioural therapy oriented interventions exert a positive influence on the clinical course of the attention-deficit hyperactivity disorder (ADHD). However, the long-term effects of the behavioral treatment in ADHD, especially those on neuronal mechanisms underlying this disorder, have been studied insufficiently. Functional MRI (Go-NoGo paradigm) was carried out in 9 children with ADHD before and 1.5 years after a response cost and token-based training. In the follow-up, patients were still characterized by a significant increase in activation in the anterior cingulate and in the precentral gyrus compared with recordings done before the training. It seems likely that the behavioural training elicits stable neuronal changes in children with ADHD which correspond with an improvement of neuropsychological functioning and clinical symptoms.

Keywords: Attention deficit/hyperactivity disorder, Summercamp, behavior therapy, functional magnetic resonance imaging, impulse control

Langzeiteffekte eines multimodalen verhaltenstherapeutischen ADHS-Trainings: fMRT-Studie

Zusammenfassung: Obwohl die Effektivität verhaltenstherapeutischer Interventionen bei Kindern mit Aufmerksamkeitsdefizit/Hyperaktivitätsstörung (ADHS) in früheren Studien ausführlich untersucht wurde, sind die Langzeiteffekte verhaltenstherapeutischer Programme bei ADHS, besonders auf neuronale Mechanismen dieser Erkrankung, nicht ausreichend erforscht. In dieser Studie, funktionelle Magnetresonanztomographie (Go-NoGo-Paradigma) wurde bei 9 Kindern mit ADHS vor und 1,5 Jahre nach einem intensiven Response-cost-Training durchgeführt. In der Katamnese zeigten die Patienten eine signifikant stärkere Aktivierung im anterioren Gyrus cinguli und in dem präzentralen Gyrus verglichen mit den Daten vor dem Training. Das Trainingsprogramm scheint langfristige neuronale Veränderungen im Netzwerk der Impulskontrolle bei Kindern mit ADHS verursacht zu haben, korrespondierend mit der signifikanten Besserung im klinischen Verlauf der Störung sowie neuropsychologischen Funktionsniveau der Patienten.

Schlüsselwörter: Aufmerksamkeitsdefizit/Hyperaktivitätsstörung, Summercamp, Verhaltenstherapie, funktionelle Magnetresonanztomographie, Impulskontrolle

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate levels of hyperactivity, impulsivity, and inattention (American Psychiatric Association, 1994). Although the course of ADHD may vary among individuals, research indicates that it is a chronic disorder typically characterized by behavioral and cognitive manifestations during the preschool years. Children and adolescents with ADHD have higher than average risk for academic, behavioral, and social difficulties (Gawrilow, Schmitt & Rauch, 2011;

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Hasselhorn & Hartmann 2011; Petermann & Jäncke, 2012; Schmidt & Petermann, 2009; Witthöft, Koglin & Petermann 2010). ADHD is commonly treated with psychostimulant medication. However, frequent side effects, insufficient duration of action for the most long-acting stimulants, and unsufficient evidence for long-term effect of psychostimulants on children's behavior, brain maturation and prognosis of the disorder limit the value of medication for the treatment of ADHD (Daly, Creed, Xanthopoulos & Brown, 2007; Gilsbach, Günther & Konrad, 2011). In addition to pharmacological treatment options, different behavioral training programmes have been developed. Especially the combination of psychostimulant medication and behavioral interventions may improve long-term prognosis. The multimodal treatment was shown to be more effective than stimulant treatment alone for specific functional impairments such as conduct and emotional problems, oppositional behavior, poor social skills, disruptive behavior, and poor academic achievement (Fabiano et al., 2008; Hodgson, Hutchinson & Denson, in press). It is worthwhile to emphasize that the behavioral therapy has been proven to be effective not only immediately after the treatment, but also in the long-term follow-up (Daly et al., 2007, see results of the Multimodal Treatment Study MTA in Swanson et al., 2008). It can be suggested that this psychotherapeutic intervention influences the central nervous system which undergoes dynamic modifications in structure and function based on learning. Thus, the long-term effects of behavioral therapy may be associated with long-lasting changes in the neuronal plasticity and in the activity in neuronal networks underlying key symptoms of ADHD.

Recently, significant positive long-term effects of the response cost and token (RCT) approach within the scope of the ADHD Summercamp training have been demonstrated in children with ADHD in two multicenter studies (Gerber-von Müller et al., 2009; Gerber, Gerber-von Müller, Petermann, Niederberger & Siniatchin, 2012; Toussaint et al., 2011; Schmidt et al., 2012). The RCT is a classical behavioral intervention based on explicit contingency management. The approach provides rewards or incentives for verifiable, targeted behaviors (Gerber-von Müller et al., 2009; Langberg, Epstein & Graham, 2008). There is increasing evidence that the RCT approach is effective in the treatment of ADHD. In previous studies, RCT treatment programs were able to reduce symptoms of ADHD and improve neuropsychological performance (Northup et al., 1999; Pelham, Greiner & Gnagy, 1997; Reitman, Hupp. O'Callaghan, Gulley & Northup, 2001; Tamm & Carlson, 2007). The clinical and neuropsychological effects of the RCT approach were associated with activity changes in neuronal networks underlying symptoms of ADHD (Siniatchkin et al., 2012). Immediately after the training, ADHD patients demonstrated a significant increase in haemodynamic changes in the dorsolateral prefrontal cortex (DLPFC), dorsal part of the anterior cingulate cortex (ACC), parietal cortex and caudate nucleus during a behavioral inhibition task (Go-NoGo paradigm). The clinical improvement and enhancement of executive functions correlated with an increase in cortical activation in the DLPFC and ACC. Whether the long-term effects of the RCT approach are associated with long-term functional changes in the described networks of the impulse control has not been investigated yet.

Here the long-term effects of the RCT approach on neuronal networks of response inhibition were investigated before and 1.5 years after the Summercamp training in children with ADHD using the same Go-NoGo experimental design (see Siniatchkin et al., 2012). In order to exclude repetition effects, healthy control children were investigated twice with the same time interval between the first and second recording similar to ADHD children.

Methods and Materials

Participants

Nineteen children with ADHD and fifteen healthy children were recruited for fMRI recordings which were planed before (T1) and after (T2) a behavioural ADHD Summercamp training. The complete datasets for both time periods were obtained in 12 children with ADHD and 11 healthy children. The results of the comparison T1 vs. T2 were published elsewhere (Siniatchkin et al., 2012). 9 children with ADHD ($9.8 + 1.54$ years, 2 girls, $IQ = 97.2 + 10.2$) and 7 healthy, sex- and age-matched children ($10.4 + 0.79$ years, 2 girls) were reinvestigated (T3) 18 Months after the end of the ADHD Summercamp training or after the comparable time period for healthy controls. 3 children of 12 from the ADHD group did not participate because of compliance problems, it was no differences in clinical improvement between these children and the patient participated in the study. Patients with ADHD and healthy children did not differ according to any of demographic variables.

Patients were recruited from the outpatient unit of the Institute of Medical Psychology and Medical Sociology, University of Kiel. The inclusion criteria consisted of (I) diagnosis of ADHD without comorbidity with conduct disorders or tic disorders which was made by an experienced neuropediatrician and confirmed by a child and adolescent psychiatrist (last author), (II) no other neuropsychiatric problems (Child Behavior Checklist $T < 70$ on the anxiety/depression scale) or somatic disorders, (III) sufficient compliance of the child and his/her family, (IV) normal school achievement, (V) no MRI exclusion criteria (i. e. ferromagnetic body objects, pregnancy or a history of claustrophobia). According to DSM IV, all ADHD children met criteria of composite or hyperactive-impulsive type (314.01, ICD-10 diagnosis: F90.0). The diagnosis of ADHD was supported by the parents' version of a German adaptive Diagnostic Checklist, DCL-HKS (Döpfner & Lehmkuhl, 2000, mean sum score: $33.4 + 16.1$). The number of items from this questionnaire equates to the number of DSM-IV items and also provides a severity score for each ADHD symptom. Patients who received stimulant treat-

ment (n = 4) discontinued their medication at least 24 hours before all fMRI recordings. Moreover, none of the children took any medication during the whole time of the RCT training (the treatment with stimulants was stopped immediately before the RTC training). No other psychiatric comorbidity was found in ADHD children. Healthy children were recruited using advertisements in a local newspaper. The children were from the same local schools as those with ADHD, had normal school achievement and did not meet MRI exclusion criteria. All subjects had normal or corrected to normal vision and were right-handed. None presented with any neurological symptoms during neurological examination before MRI sessions, all children were normally developed and had normal structural MRI. None of them took any additional medication nor presented with any history of developmental disorders or language problems. All of participants were German native speakers.

All participants and their parents were instructed about the study, and written informed consent according to the Declaration of Helsinki was obtained. The study was approved by the local Ethic Committee.

Procedure

ADHD children attended the intensive multimodal summer camp behavioral treatment program which lasted 10 consecutive days (approx. 100 hours) and included attention training as well as social skills training, which was conducted in a playful manner, and sports (for a detailed description see Gerber et al., 2012; Toussaint et al., 2011; Schmidt et al., 2012). Using an intensive response cost token system, the children received contingent points for adhering to the specific rules during all daily activities (attention tasks, school tests, sports, lunches). Failure to comply with the rules resulted in points being removed. Before (T1), immediately (T2) and 1.5 years (T3) after the training, ADHD children were subjected to clinical evaluation, neuropsychological testing and fMRI recordings. Healthy children were also investigated twice with the same time interval between both fMRI sessions in order to rule out repetition effects on fMRI changes. No intervention was performed in healthy children between recordings. All fMRI measurements were carried out in the afternoon; all neuropsychological assessments were performed at the morning.

Assessment of clinical efficacy

The clinical improvement of ADHD was assessed using German adaptive Diagnostic Checklist, DCL-HKS (Döpfner & Lehmkuhl, 2000). This questionnaire provides scores for the main symptoms of ADHD: inattentiveness, impulsiveness and hyperactivity (internal consistency: Cronbachs Alpha = .80, see Görtz, Döpfner, Nowak, Bonus & Lehmkuhl, 2002) and was filled out by parents before and immediately after the training. To assess neuropsychological improvement, a child-adapted version of the Trail Making Test (TMT) was carried out before and after the RCT training (Broshek & Jeffrey, 2000). The clinical efficacy of the training was statistically characterized for comparison between T1 and T3 using Wilcoxon tests and a significance level of $p < 0.05$. Because of exploratory nature of the study, no Bonferroni alpha adjustment was performed.

fMRI paradigm

The Go/No-go task used in this study was adapted from Suskauer et al. (2008). Every fMRI session started with a detailed and completely standardized instruction concerning the procedure. The children participated in a short training session outside the scanner which was finished only if a child completely understood the task and made no errors in 10 consecutive trials. Trials consisted of green (Go, n = 260) and red (No-go, n = 40) flying monsters which appeared pseudorandomly on a monitor inside the scanner (IFIS stimulation system; screen-eye distance ca. 15 cm, luminance comparable to that of a standard computer monitors) for 300 ms with an interstimulus interval of 1,500 ms (see Figure 1). Children were instructed to use the right index finger to push a mouse button as quickly as possible if green but not red monsters appeared. Participants completed a short practice block (20 Go and 8 No-go trials) followed by four runs, each consisting of a total of 75 stimuli and lasting approximately 5 minutes. Rest periods in which a crosshair remained on the screen for 20 sec occurred at the end of each run. Stimulus presentation and response logging were completed using E-prime (Psychology Software Tools, Pittsburg, PA).

Behavioural measurements during the fMRI session

Neuropsychological effects of the treatment were assessed for the following dependent variables from the Go/No-go task: reaction time (ms), reaction time variability, omission errors (number of Go trials which were ignored) and false alarms (number of No-go trials which prompted a reaction). Each participants' reaction time variability was measured using the coefficient of variation (CV) calculated as [(standard deviation of Go reaction time)/(mean Go reaction time)] (Suskauer et al., 2008). All behavioral measurements were carried out between T1 and T3 using Wilcoxon tests; the significance level was kept at $p < 0.05$. All statistical analyses were performed using SPSS Version 17.0.

fMRI data acquisition and analysis

BOLD-sensitive MRI was performed with a 3-Tesla MR scanner (Philips Achieva, Philips, Best, The Netherlands) and a standard, 8-channel SENSE head coil. A single-shot T2*-weighted gradient-echo planar imaging sequence was used (TR = 2500 ms, TE = 35 ms, 30 slices, 64 x 64 matrix, slice thickness = 3.5 mm, FOV = 200 mm, flip angle = 90^0, interleaved order), allowing "whole-brain" (i.e. including cerebellum and midbrain) volume acquisition (event-related design). An anatomical MRI for superimposition with functional images was acquired using a high-resolution, whole-head, T1-weighted, 3-D MPR sequence (1 mm slice thickness, 208 x 208 matrix, 150 slices, FOV = 208 mm, TE = 3.6 ms, TR = 7.8 ms, flip angle = 8^0, NSA = 2).

The fMRI data were analyzed using SPM5 software (Wellcome Department of Imaging Neurosciences, UCL, UK, http://www.fil.ion.ucl.ac.uk/spm). The first five images were discarded to ensure steady-state longitudinal magnetization. All volumes were realigned to the first volume, slice-time corrected and spatially normalized to the template of the Montreal Neurological Institute (MNI; voxel size 3 x 3 x 3 mm). Images were then smoothed with a 3-D isotropic Gaussian kernel (8 mm full-width-half-maximum) and high-pass filtered at a cut-off of 128 s. The preprocessed fMRI time series were statistically analyzed at an individual level using General Linear Model. Each event (Go or No-go) was represented as a stick function, convolved with a canonical hemodynamic response function as used in SPM5 (Friston, Holmes & Worsley, 1995). In each individual, one-tailed t-tests were applied to test for regional event-related BOLD signal increases. At the voxel level, the significance level was set at $p < 0.05$ after correction for multiple comparisons across the whole brain using the family-wise error (FWE) correction method as used in SPM5 (Friston et al., 1995). The following contrasts were used: (I) Go trials, (II) No-go trials, (III) six realignment parameters for possible movement effects as a contrast of no interest. Trials with omission errors or false alarms were disregarded because of a low statistical power and were modelled as a regressor of no interest. Our preliminary analyses of these trials did not reveal any significant results.

Using the estimated parameter obtained by single-subject analyses, we performed a second-level random effect group analysis using firstly a two-factor ANOVA with time point (measurement 1 and measurement 3) as the within-subject factor and group (patients versus controls) as the between-subjects factor and than the post hoc t-tests to test for typical effects at the population level (see Freyer et al., 2011, and Huyser, Veltman, Wolters, de Haan & Boer, 2011). The threshold was set at $p < 0.001$ (uncorrected). The resulting statistical maps were displayed in MNI space. Because we were interested in the effect of RCT training on response inhibition, only No-go trials were analyzed. For No-go trials, the following comparisons were carried out using t-tests: (I) Measurement 1 vs. Measurement 2 in healthy control subjects; (II) Measurement before RCT treatment vs. Measurement 1.5 years after RCT treatment in ADHD patients. The labels of activated regions were defined using the Anatomy toolbox for SPM (Eickhoff et al., 2005).

Results

Clinical and neuropsychological effects

Figure 1 demonstrates long-term changes of clinical and neuropsychological measures in the sample of children with ADHD who was included into the fMRI study. Results of the whole sample are published elsewhere (Schmidt et al., 2012). There were trends for reduction of the inattention score ($z = -1.61$; $p = 0.11$) and ADHD sum score ($z = -1.54$; $p = 0.12$) given by the parents indicating long-term clinical effects of the RCT approach in the 1.5 years follow-up. The clinical improvements were associated with positive neuropsychological changes. There was a significant reduction of the processing speed in the TMT part B ($z = 2.0$; $p = 0.036$) 1.5 years after the RCT training compared with the parameters obtained before the training.

In the Go-NoGo task performed in the MR scanner, there was a significant reduction of the reaction time in both groups of healthy subjects (mean + SD for T1:373.6 + 39.4 ms and for T3: 347.2 + 30.1 ms, diff. $z = -2.19$; $p = 0.028$) and ADHD patients (mean + SD for T1:388.2 + 39.4 ms and for T3: 349.8 + 32.2 ms, diff. $z = -2.54$; $p = 0.011$). Again, the number of omission errors demonstrated a significant reduction over time also in both groups (healthy subjects: mean + SD for T1:27.2 + 21 ms and for T3: 12.6 + 11.7 ms, diff. $z = -2.2$; $p = 0.028$, and ADHD patients: mean + SD for T1:32.6 + 18.8 ms and for T3: 21.5 + 17.2 ms, diff. $z = -1.9$; $p = 0.05$). However, the groups did not differ significantly according to changes in the standard deviation of the reaction time, coefficient of variability, and false alarms.

Results of the functional neuroimaging

In healthy subjects, the comparison of both measurements 1 and 3 (in the time before RCT training done in ADHD children and 1.5 years after the training) did not reveal significant haemodynamic changes. In children with ADHD, the comparison of recordings before and 1.5 years after the RCT training described significant differences between conditions in the dorsal part of the anterior cingulate gyrus and in the left precentral gyrus: there was an increase in BOLD response in this structures 1.5 years after the RCT training (figure 2, table 1).

Discussion

The patients demonstrated more pronounced activation of the dorsal part of the anterior cingulate cortex as well as in the left precentral gyrus even 1.5 years after the ADHD

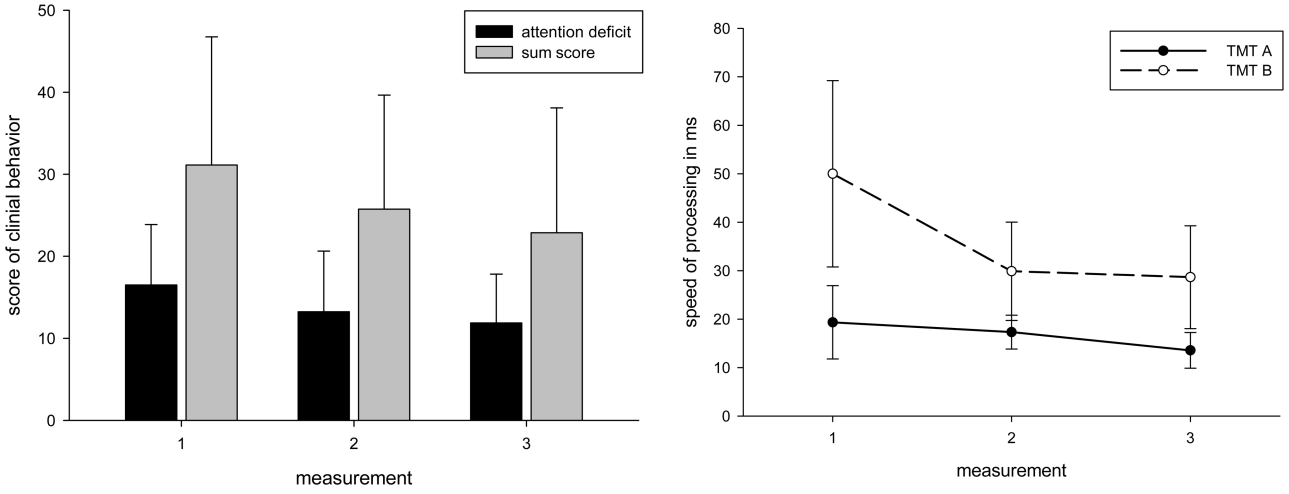

Figure 1. Changes of clinical and neuropsychological parameters during the 1.5 years follow-up in children with ADHD (measured at T1, T2 and T3 time points).

Table 1
Results of functional MRI for No-go condition (MNI coordinates, maximal t-values and cluster sizes) in ADHD patients. The comparison between recordings done after the RCT training and before the training ($p < 0.001$ uncorrected)

Brain area	x	y	z	Max. t-value	Cluster size
Anterior cingulate	–14	–15	41	4.04	22
Precentral gyrus left	–18	–24	54	3.99	45

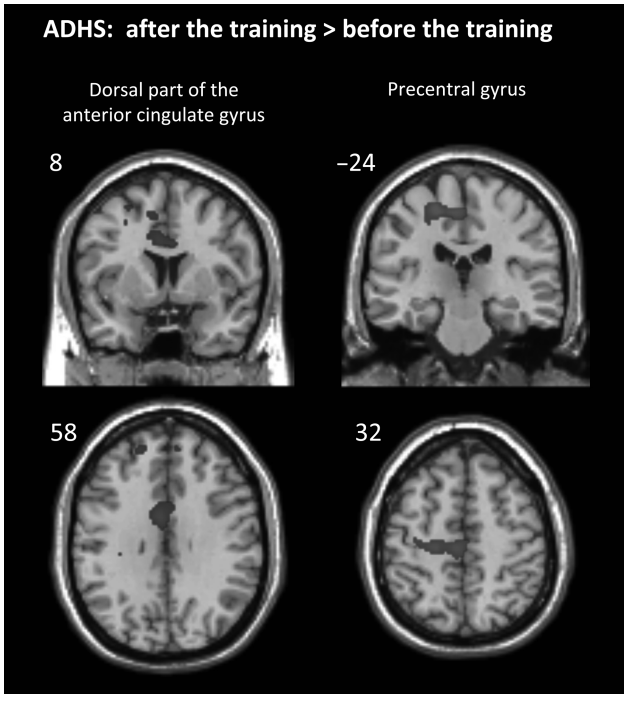

Figure 2. Long-term changes in the neuronal network of response inhibition after RCT training in children with ADHD.

Summercamp. It seems likely that the behavioural training favours stable neuronal changes in children with ADHD which correspond with an improvement in neuropsychological functioning and clinical symptoms.

Clinical and neuropsychological long-term effect of the RCT approach

The study supports previously published results of long-term clinical and neuropsychological effects of the RCT training performed in a larger group of children with ADHD in the small selected sample of patients with ADHD who underwent fMRI recordings. In the first study, Gerber-von Müller and co-authors (2009) demonstrated a significant reduction of ADHD symptoms as revealed by a teacher-form of the DCL-HKS questionnaire in 37 affected children. The effect was significant and even more prominent 2 years later in the RCT training group, but disappeared in the control group of ADHD children who were involved into a community care programme based on a standard parental counselling (Gerber-von Müller et al., 2009). Six months after the RCT training the children were still characterized by a significant improvement in attention, response inhibition, cognitive flexibility and working memory, and demonstrated a lower response and performance variability (Gerber et al., 2012). In the second study, clinical course of ADHD and neuropsychological function-

ing were investigated in a larger sample of patients (n = 43) immediately, 6 months and 1 year after the RCT training (Toussaint et al., 2011; Schmidt et al., 2012). This study revealed a prominent clinical improvement and positive changes in attention and executive functions, especially in response inhibition, stimulus monitoring and cognitive flexibility, which still lasted or became even more pronounced during the follow-up. Results which were obtained in our sample correspond with previously published studies of our group and of other authors (Carlson & Tamm, 2000; Reitman et al., 2001) and confirm them even after the longer (1.5 years) follow-up period. Moreover, the sample of subjects in this study seems to be representative for the whole large sample which has been published elsewhere (Toussaint et al., 2011; Schmidt et al., 2012). It can be speculated that the long-term effects of the RCT training on activity in neuronal networks of response inhibition shown for the selected patient group in this study, may be expected also for other children from the larger sample who took part in the same RCT training and demonstrated a comparable clinical and neuropsychological improvement which was observed on the clinical and neuropsychological levels, although the effects are considerably weaker as in larger samples of patients. The weak effect may be explained by an insufficient statistical power. The same could be true for changes over time of reaction time, response variability, omission errors and false alarms obtained during Go-NoGo recording inside the scanner. In the small sample of patients it was impossible to replicate results of our previous study which demonstrated significant changes of the response variability in children with ADHD after the RCT training (Siniatchkin et al., 2012). In this study, the reaction time and the number of omission errors demonstrated a reduction in the follow-up in both ADHD patients and healthy subjects. It seems likely that the described changes of these parameters can be attributed to repetition effects. However, despite of few changes in response inhibition over time shown on the behavioural level, patients with ADHD were characterized by an improved pattern of activation after 1.5 years follow-up.

Long-term changes in neuronal network of response inhibition

One and half years after the RCT training, children with ADHD still demonstrated an increase in activation in the dorsal part of the anterior cingulate cortex and the precentral gyrus. These haemodynamic changes can not be attributed to the repetition effect because the described increase in activity was not observed in healthy subjects.

A significant BOLD signal increase in the dorsolateral prefrontal cortex (DLPFC), parietal cortex, and ACC during response inhibition was found immediately after the training compared with network activation before the training (Siniatchkin et al., 2012). The activation in the ACC preserved even after 1.5 years follow-up. It was shown immediately after the training, that the most pronounced haemodynamic changes as relieved by a significant ANOVA interaction GROUP x TIME and the higher correlations between the changes in clinical symptoms of ADHD as well as response variability and changes in BOLD signal after the training were found in the ACC. Our study provides an additional support for the role of the ACC as a key structure in the neuronal network of response inhibition which is deficient in ADHD. Low activation in ACC has been repeatedly shown in a large number of neuroimaging studies performed in patients with ADHD (Rubia et al., 1999; Tamm, Menon, Ringel & Reiss, 2004; Booth et al., 2005; Durston, Mulder, Casey, Ziermans & van Engeland, 2006; Smith, Taylor, Brammer, Toone & Rubia, 2006). Increase of activity in ACC was observed in ADHD patients under successful stimulant treatment (Vaidya et al., 1998; Dodds et al., 2008; Rubia et al., 2009) and after behavioural interventions (Levesque, Beauregard & Mensour, 2006; Beauregard & Levesque, 2006). Moreover, the activity in ACC has been shown to be associated with response variability in healthy subjects and ADHD patients: the less is the activity in ACC, the more pronounced is the response variability (Rubia, Smith, Brammer & Taylor, 2007). Since subjects with ADHD are characterised by a higher response and performance variability as healthy individuals (Klein, Wendling, Huettner, Ruder & Peper, 2006; Uebel et al., 2010) which improves after a successful treatment (Siniatchkin et al., 2012), the more clear long-term effect of the treatment on neuronal activity during response inhibition would be expected in the ACC – as confirmed by our study. Interestingly, previous studies failed to show this long-term effect on ACC activity after 1 year of the methylphenidate treatment despite of the improvement of the structural brain maturation (rev. in Gilsbach et al., 2011).

Additionally, a significant increase in activation 1.5 years after the RCT training in ADHD children was observed in the precentral gyrus – in the brain region of the left primary motor region (area of fit and hand). It is worthwhile to note that all subjects in this study were right handed and pressed the button with the right hand. So, more activation in the left primary motor cortex after the RCT training in children with ADHD may demonstrate a greater involvement of the motor cortex in the regulation of motor activity. Noteworthy, the activation was observed during the NoGo condition. It seems likely that not only the premotor and prefrontal cortex are involved into the active inhibition, the activity in the motor cortex is an important premise for the successful inhibition (Jaffard et al., 2008). The activity in the premotor/motor cortex is also associated with the response variability in healthy subjects and ADHD patients (Suskauer et al., 2008). Especially in ADHD, the activation in the premotor/motor cortex is negatively correlated with the response variability. The response variability did not change over time in our small sample of ADHD patients. Therefore, we were unable to replicate results of Suskauer et al. (2008). However, our study may provide an additional evidence for the significance of motor cortex in the impulse control in ADHD

patients. This significance was proven in several studies using transcranial magnetic stimulation (Moll, Heinrich, Trott, Wirth & Rothenberger, 2000; Gilbert, Isaacs, Augusta, Macnell & Mostofsky, 2011), measures of electrophysiological activity in the motor cortex (Banaschewski et al., 2008; Bender et al., in press) and in fMRI studies (Suskauer et al., 2008; Epstein, 2009): all of them have demonstrated a deficient function in the motor cortex associated with ADHD. It can be suggested that the improved executive control after the RCT training caused more efficient activation of the motor cortex during response inhibition and, in such a particular way, contributed to clinical efficacy of the training even 1.5 years after the Summercamp.

Limitations of the study

Although this is the first study which demonstrates long-term effects of a behavioral training programme on neuronal activity in ADHD, the results of the study have to be interpreted with caution because of a number of limitations. First of all, the very small number of patients represents the most restricting aspect which may have influenced the statistical power of analyses applied for fMRI, clinical and neuropsychological data. Because of this limitation, the appropriate correction for multiple comparisons was impossible. Therefore, the study may be treated only as an exploratory in nature. Moreover, the type II statistical error (false negative results because of low statistical power) can not be excluded, so other long-term changes in neuronal function after behavioural treatment in ADHD may be expected. To overcome this limitation in the future, replication studies are needed with substantially larger sample sizes. Because the RCT training can be performed only annually (long German school vacation) and is very demanding (7 psychologists working continuously with 10 children in each run), multicenter studies are needed to prove the effect of RCT training on clinical efficacy and neuronal networks in ADHD appropriately. The further limitation is related to possible differences between the groups according to IQ. The group of ADHD patients was characterized by normal intelligence. However, healthy children were not tested in this study. The effect of cognitive abilities on the results presented is unlikely, since the healthy children were recruited from the same school as ADHD patients and presented with similar scholar achievement. However, effect of IQ can not be excluded completely. The third limitation is related to the control conditions. In order to show strictly whether the RCT training exerted a specific effect on neuronal networks responsible for response inhibition in ADHD, another treatment options such as placebo, or another psychotherapeutic technique, for example community based standard interventions should be applied as a control condition. The non-specific long-term effects in neuronal networks in ADHD can not be excluded at the moment. And finally, stimulants have been shown to influence the same neuronal networks as described in this study (Vaidya et al., 1998). The long-term effect of medication which has been given to all patients during the observed 1.5 years follow-up, can not be completely ruled out, although the medication was withdrawn 24 h before the fMRI recording and the immediate short-term effects could be excluded.

Despite of limitations, however, this study demonstrates the long-term effect of behavioral intervention on clinical course, neuropsychological functioning and for the first time on neuronal networks of response inhibition in children with ADHD. Further studies are needed to support the findings presented here.

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