

**Aus dem Institut für Medizinische Psychologie
der Universität Tübingen**

Direktor: Professor Dr. N. Birbaumer

**Long term effects after feedback of slow cortical potentials
and of Theta / Beta - amplitudes in children with
Attention Deficit Hyperactivity Disorder (ADHD)**

**Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin**

**der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen**

vorgelegt von

Cihan Gani

aus

Berlin

2009

**Aus dem Institut für Medizinische Psychologie
der Universität Tübingen**

Direktor: Professor Dr. N. Birbaumer

**Long term effects after feedback of slow cortical potentials
and of Theta / Beta - amplitudes in children with
Attention Deficit Hyperactivity Disorder (ADHD)**

**Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin**

**der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen**

vorgelegt von

Cihan Gani

aus

Berlin

2009

Dekan:

Professor Dr. I. B. Autenrieth

1. Berichterstatter:

Professor Dr. N. Birbaumer

2. Berichterstatter:

Frau Professor Dr. I. Krägeloh-Mann

Im Andenken an

**Prof. Dr. Sedat Ersoy
Herbert Simpfendörfer**

Table of contents

1. Introduction	6
2. Methods	
2.1. Study design and participants	9
2.2. Neurofeedback sessions in the 2-year follow up	12
2.3. Data analysis	16
3. Results	
3.1. Participants	19
3.2. Regulation of SCPs	23
3.3. Regulation of Theta / Beta ratios	25
3.4. Behavior	27
3.5. Attention	31
4. Discussion	34
5. References	38
6. Curriculum Vitae	42

1. Introduction

Though stimulant medication is regarded as the most effective therapy for attention deficit hyperactivity disorder (ADHD), till recently there were no studies demonstrating evidence for long-term benefits from pharmacotherapy (Goldman et al., 1998). Children, who discontinued medication, experience a considerable loss of improvement at follow-up. Only lately the “3- year follow-up of the NIMH MTA Study” (Jensen et al., 2007) showed that early advantages of medication management compared with behavioral therapy and community care were no longer present at 3- year follow-up. In addition, a large number of non-responders - approximately 25% (DuPaul GJ, 1998) - and side effects of stimulant medication, such as several vegetative complaints (Schachter et al., 2001) and reduced growth (Swanson et al., 2007) have led to an increased demand for alternative therapy options.

Neurofeedback has been used as a treatment for attention deficit hyperactivity disorder since the 1970s when scientist recognized, that children with seizure disorders improved at school when they were treated with neurofeedback (Lubar and Shouse, 1976). In the beginning neurofeedback was dismissed as poorly researched and overly hyped, yet several studies have shown that after neurofeedback behavioral problems, attention, academic performance, and social behavior are improved (Lubar and Lubar, 1984).

Neurofeedback protocols mainly aim at two different electrophysiological patterns. Children with ADHD show increased Theta and decreased Beta activity in their spontaneous EEG (Monastra et al., 1999) and event- related potentials in children with ADHD are characterized by decreased amplitudes and prolonged latencies compared to healthy children (Johnstone et al., 2001).

Although several studies had shown that feedback of EEG frequencies leads to improvement of symptoms, neurofeedback has not been acknowledged because of methodological shortcomings (e.g. no randomization, no EEG data, no controls, no follow-up (Ramirez et al., 2001)). Since 2002 this has changed to the better. Two controlled studies showed that neurofeedback of spontaneous EEG activity (e.g. theta and beta) leads to the same improvements in behavior and academic performance as medication (Fuchs et al., 2003) and that improvement after a therapy combining medication, parental counseling and individual school counseling endured after washout of medication only if neurofeedback had been added (Monastra et al., 2002).

Self regulation training of slow cortical potentials aims at the deviant latencies and amplitudes of event related potentials. Slow cortical potentials (SCPs) are a special type of event related potentials reflecting the excitation threshold of the upper cortical layer. They are slow direct current shifts. SCP shifts in the electrical negative direction reflect a reduction of the excitation threshold while shifts in the electrical positive direction reflect an increase of the excitation threshold (Rockstroh, 1989). Children with attentional problems have an impaired ability to regulate their SCPs (Rockstroh, 1990). There is only a small number of studies aiming at self-regulation of SCPs (Heinrich et al., 2004), (Strehl et al., 2006). Heinrich et al showed a reduction of ADHD symptoms by 25 % after training of slow cortical potentials with neurofeedback (Heinrich et al., 2004). Drechsler et al showed that children with a diagnosis of ADHD who underwent neurofeedback training of slow cortical potentials improved more than children who had participated in cognitive behavior group therapy (Drechsler et al., 2007).

Yet the vast majority of studies so far has examined self-regulation training of electroencephalogram (EEG) frequency bands. In most cases the training rationale with ADHD patients was to decrease activity in the Theta band and to increase activity in the Beta band. In a randomized study neurofeedback of Theta/Beta Frequencies or SCPs, Leins et al treated children between 8 and 13

years with either with a Theta / Beta or a SCP protocol (Leins et al., 2007). They demonstrated that children gained the ability to self regulate cortical activity. Moreover patients improved significantly in attention and IQ, as well as in behavior. The results remained constant six months after the end of training. For the current study the same population was re-invited for the 2 year follow-up. We present the first randomized long-term follow-up study, providing EEG data from neurofeedback sessions 2 years after the end of treatment. Furthermore behavioral ratings have been assessed and associated with the EEG data.

The goal of the 2 year follow-up is to determine a) whether patients kept the ability to self regulate cortical activation, b) whether improvements in attention and behavior remained stable and c) whether the different treatments lead to differences in the stability of cortical self regulation and clinical effects.

2. Methods

2.1. Study Design and Participants

Figure 1 shows the schedule of the whole study and the number of children participating at each assessment point. 23 children participated in the 2 years follow-up assessment, 11 out of the SCP-Group and 12 of the Theta/Beta group. For our study the assessment points “screening”, “end of treatment” and “2 year follow-up” were included. Detailed comparisons between screening, end of treatment and six month follow-up have been reported by Strehl et al and Leins et al. Due to the unequal times of data analysis in Stehl et al and Leins et al, sample sizes in those articles might deviate from the ones given in Figure 1 (Strehl et al., 2006; Leins et al., 2007).

Participants were recruited from the outpatient clinic for psychotherapy at the University of Tübingen and from local psychiatric practitioners and psychotherapists. Approval was obtained from the local ethics committee of the faculty of medicine according to the convention of Helsinki.

Each child met DSM-IV criteria for ADHD inattentive, hyperactivity or combined type and was aged between 8 and 13. Children with a Full-Scale IQ of <80 or additional neurological conditions were excluded. After parents and children had signed written informed consent, children were randomly assigned to treatment. Children were matched according to age, sex, IQ, diagnosis and medication. Parents and children were blinded according to group assignment (Theta/Beta or SCP Feedback).

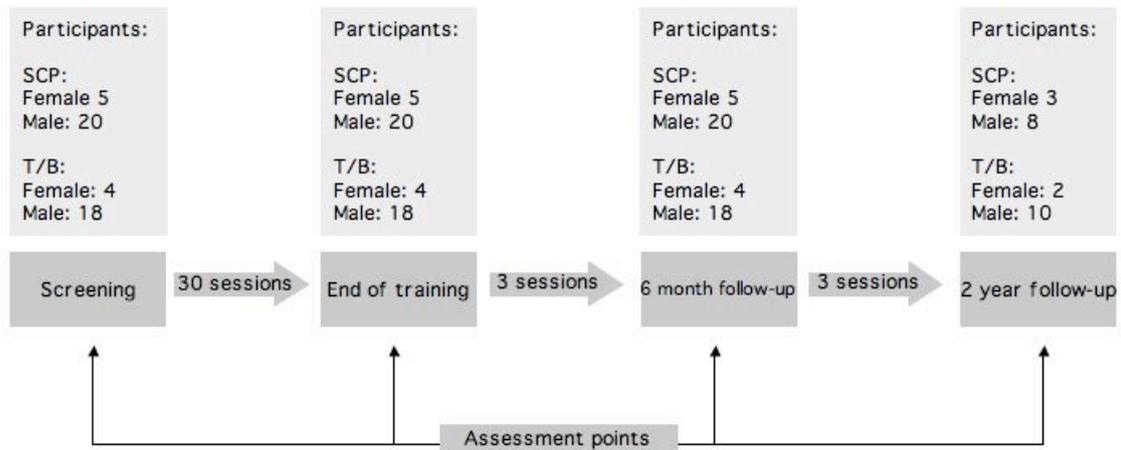


Figure 1. Study design and schedule (SCP = Slow cortical potentials. T/B = Theta/Beta ratio.) Note: Only patients who completed the first 30 sessions are included in the graph. Drop-out rate between “Screening” and “End of training”: 2 in the SCP and 3 in the Theta/Beta group.

In order to evaluate long-term outcome, self regulation skills, behavioral symptoms and variables of attention were assessed as follows:

- 3 sessions EEG Feedback
- DSM IV questionnaire for parents
- Eyberg Child Behavior Inventory (Eyberg, 1999)
- Conners' Rating Scale (Translated into German) (Conners CK, 1997)
- Testbatterie zur Aufmerksamkeitsprüfung, Version 1.7 (Zimmermann and Fimm, 2002)

At preceding assessment points following instruments had been used in addition:

- Kindl-Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents, parents' and children's version (Ravens-Sieberer, 2003)
- German Version of Wechsler Intelligence Scale for Children: Hamburg-Wechsler-Intelligenztest für Kinder (Tewes, 1999)
- DSM-IV – questionnaire for teachers to assess DSM-IV-criteria for ADHD.

Because of possible practice effects the Intelligence Scale was not applied at the 2 year follow-up. As most children's teachers had changed between screening and 2 year follow-up, and because parents did not want to involve school any more (especially if symptoms had vanished), it was decided to do without teachers' ratings.

Parents whose children did not participate at the 2 year follow-up were interviewed by telephone and were asked for their reasons to decline the invitation.

2.2. Neurofeedback sessions in the 2-year follow-up

Setting, instruments and trainer were identical in both groups. The only but fundamental difference between both groups consisted in the feedback signal. Although detailed descriptions have been given elsewhere (Strehl et al., 2006), (Leins et al., 2007) basic information about the two different training modalities will be repeated here.

Training of slow cortical potentials

Slow cortical potentials can be observed with a latency of about 500ms after stimulus onset and may endure several seconds. They reflect the excitability of brain areas. Electrically negative SCPs decrease the excitation threshold while positive SCPs increase this threshold. It is assumed that developing self regulation skills will help to improve the symptoms of hypoarousal in children with ADHD.

Children were seated in an armchair in front of a 17" monitor in a distance of approximately 50 inches. Electrodes were affixed on Cz, and on both mastoids, with a 10 k Ω resistance between Cz and the mastoids. EEG signals were amplified using an EEG 8 (Contact Precision Instruments, Cambridge, MA) amplifier with a time constant of 16s and a low frequency filter of 40 Hz. EEG signals were digitized with a sampling rate of 256 Hz. The slow-wave amplitude just before the beginning of the active phase of a trial was taken as baseline and set to zero. For online and offline correction of eye movements a vertical electrooculogram was recorded with electrodes fixed above and below the left eye.

During the active phase the slow-wave amplitude was calculated every 62.5 milliseconds as the average of the preceding 500 milliseconds. The difference between every 500 millisecond amplitude in the active phase and the amplitude

during the baseline corresponded to the position of the feedback signal, a yellow “ball”.

The patients saw two rectangles, one on the top and one on the bottom of the screen. A highlighted upper rectangle indicated that a SCP shift in the electrical negative direction was demanded; a highlighted lower rectangle indicated that a positive SCP shift was required (see Figure 2 for a picture of the screen).

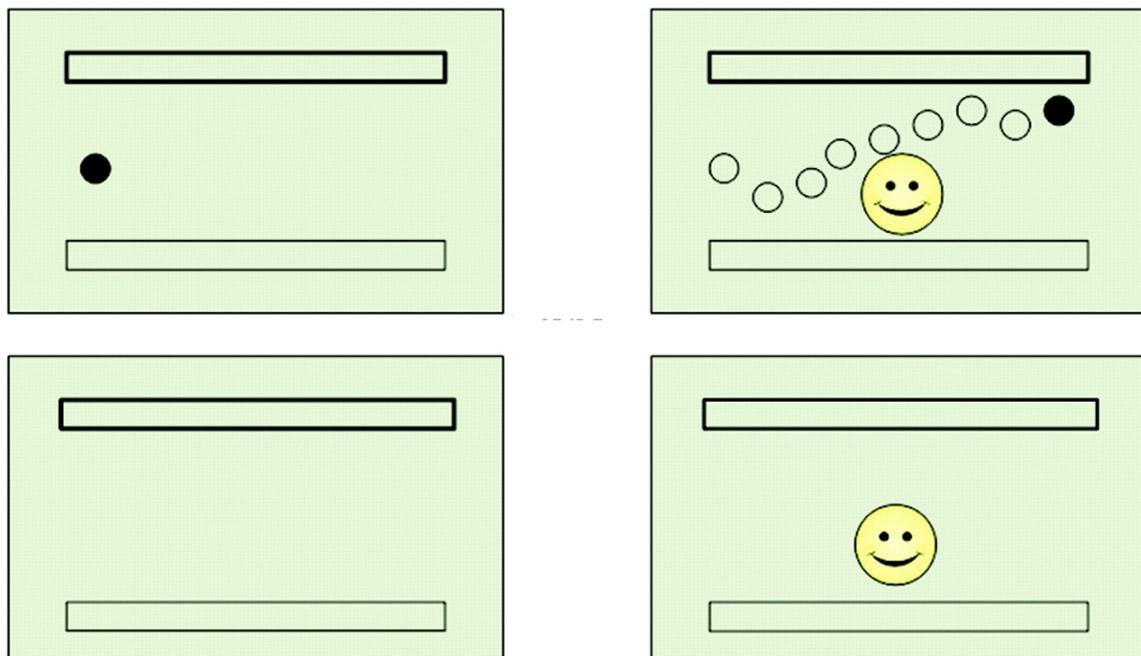


Figure 2. Screens: The upper screens depict the beginning (left) and at the end (right) of a trial. The lower screens indicate a transfer trial at the beginning (left) and at the end (right) of a trial (Figure taken from Strehl et al., 2006)

Each session consisted of 3 to 5 runs, each run included 39 trials. The ratio between negativity and positivity tasks was 3:1. Each trial consisted of a 2 second passive phase, followed by a 6 second active phase. Visual feedback was given by a round yellow circle (“ball” with a 1 inch diameter) that moved upwards (negativity – so called activation) or downwards (positivity – so called deactivation) proportionally to the cortical shift. The ball moved from left to right with a constant velocity and up and down dependent of the amplitude of the

cortical shifts. After successful trials a smiley face appeared on the screen. Furthermore, auditory feedback was given by piano tones with high frequency (negativation) and low frequency (positivation). A harmonious jingle at the end of a trial signaled success. Depending from the number of correct results children received a voucher of a certain amount. This voucher could be exchanged in a local toyshop. The value was a minimum of 3 € and a maximum of 10 € for all sessions.

In order to facilitate practice of self regulation in daily life transfer trials were inserted (see lower panel of Figure 2). No auditory or visual feedback was given during the active phase, only the appearance of the smiley face and the jingle at the end of a trial delivered information about success.

During the sessions the trainer sat next door and observed the EEG online on a monitor and the child on a second monitor. Intervention was possible by a two-way intercom or by joining the child.

Training of Theta/Beta ratio

Number of runs and sessions, relation of tasks (activation / deactivation), conditions (feedback / transfer) as well as the depiction of the feedback signal on the screen and reinforcement was identical to the SCP-training. Different from the SCP protocol, electrodes were fixed at Cz, and additionally at C3f, which is halfway between C3 and F3 and C4f, which is halfway between C4 and F4. Electrodes on both mastoids were used as reference.

The feedback signal was calculated online as the averaged Theta/Beta ratio measured the averaged activity at C3f and C4f minus the averaged ratio measured at the mastoids. Theta range was between 3 and 7 Hz and Beta range was between 12 and 20 Hz. Baseline phase was expanded to 2 seconds and feedback phase to 7.5 seconds, as Theta and Beta frequencies show greater oscillations than SCP. An 8 second “pre-baseline” was measured at the

beginning of each training session. Integration of the Theta/Beta ratio measured during the pre-baseline and the Theta/Beta ratio measured prior to the first trial delivered an “overall-baseline”, which acted as a reference for the first trial. This reference was corrected online by each new trial-baseline-ratio during the training session.

So called “activation tasks” demanded a decrease of the Theta/Beta ratio, which could be reached by either decreasing Theta and / or increasing Beta. So called “deactivation tasks” demanded an increase of the Theta/Beta ratio. The movement of the ball in the vertical direction reflected the current Theta/Beta ratio. An increasing ratio resulted in a ball movement downwards, a decreasing ratio in a movement upwards. A trial was rated as correct when in comparison to the overall-baseline-ratio the averaged ratio was lower in “activation tasks” and higher in “deactivation tasks”.

	SCP group	T/B group
Feedback signal	< 1 Hz	Theta (3-7 Hz) / Beta (7-20Hz)
Electrodes	Cz, mastoids	Cz, C3f, C4f, mastoids
Baseline phase	2 seconds	Continuous integration of 8 seconds pre-baseline (taken before each session) and 2 seconds (taken before each trial)
Feedback phase	6 seconds	7.5 seconds
Window of Feedback phase considered for analysis	3-6 seconds	3-7.5 seconds

Table 1: Differences between SCP and T/B protocols

2.3. Data analysis

As can be seen from Figure 1 the design of the whole study contained 4 assessment points. Since 6 month-follow-up data are published elsewhere (Leins et al., 2007), here we compare data from screening, end of training and 2 year follow-up.

EEG Data

According to our goal to determine long-term effects of SCP- and Theta/Beta-Feedback as a therapy for children with ADHD we investigated whether

- a) subjects of both groups were still able to differentiate between activation and deactivation tasks at 2-year follow-up
- b) the difference between activation and deactivation tasks changed with time (“screening” = sessions 2 + 3; “end of treatment” = sessions 29 + 30, “2 year follow-up” = sessions 35 + 36)

Sessions 1 and 34 were discarded as habituation sessions.

SCP - Group

For each child mean SCP amplitudes were calculated for both tasks (positivity / negativity) and conditions (feedback / transfer) after testing for normal distribution with the Kolmogorov-Smirnov-Test for each of the three assessment points “screening”, “end of treatment” and “2 year follow-up”).

The differences of SCP amplitudes between both tasks were analyzed for both conditions and each assessment point by an independent samples t-test. An analysis of variance (ANOVA) with repeated measures (time x condition x task) was performed in order to evaluate changes between assessment points. Bonferroni-corrected post hoc paired samples tests were performed in case of a

significant result in the ANOVA. The ANOVA was corrected with Greenhouse-Geisser.

Theta / Beta - Group

The difference between the Theta/Beta ratio during the baseline phase and the ratio during the active phase was calculated for each subject, for both conditions (feedback/transfer), both tasks (activation/deactivation) and each assessment point (“screening”, “end of treatment” and “2 year follow-up”).

After testing for normal distribution with the Kolmogorov-Smirnov-Test the difference between the Theta/Beta ratio during activation and deactivation tasks was analyzed separately for feedback und transfer tasks for each assessment point with a one samples t- test.

In order to assess possible changes of the Theta/Beta ratios an ANOVA with repeated measures (“screening”, “end of treatment” and “2 year follow-up”) was performed for both conditions and task (activation/deactivation). Bonferroni corrected post hoc paired samples test were applied if significant changes with time were found.

Psychometric test data

After testing for normal distribution, test data and questionnaires were analyzed by a mixed design ANOVA with repeated measures factors and the group factor SCP vs Theta / Beta in order to examine the effects of time (“screening”, “end of treatment” and “2 year follow-up”). In case of a significant result in the ANOVA post hoc paired samples tests were performed.

Effect sizes

Cohen's d (Cohen, 1988) was used in order to assess effect sizes for each significant result after correction with Bonferroni. Cohen's d is equal to the differences between the means $M1 - M2$, divided by the pooled standard deviation $s_{\text{pooled}} = \sqrt{[(s_1^2 + s_2^2) / 2]}$

3. Results

3.1. Participants

Groups had been matched for age and IQ. See Table 2 and Table 3 for demographic data and diagnosis. A comparison between the participants at 2-year follow-up still yielded no significant difference regarding to IQ and age.

In order to avoid biasing of our data we contacted those parents and children who did not participate at the follow-up and asked for their reasons. In most cases lack of time was given as a reason. Full time education was introduced in many schools in Germany at this time.

As can be seen in Table 4 there was no significant difference regarding age and IQ between children who participated in the 2 year follow-up and those who did not. Yet in the Theta/Beta group a significant difference in diagnosis at the 6 month follow-up could be observed. Pearson's χ^2 test showed that children who did not participate in the 2 year follow-up had a significantly higher rate of ADHD diagnosis than children who participated.

SCP	Code	Age	Sex	Med (mg)		IQ	Diagnosis Screening		Diagnosis 2 year follow up	
				Screening	Follow up		Hyperactivity	Inattention	Hyperactivity	Inattention
	12	8	m	0	0	85	y	y	n	n
	13	9	m	40	40	123	y	y	y	y
	19	8	f	0	0	98	y	y	y	y
	23	8	m	0	0	89	y	y	y	n
	24	8	f	0	0	126	y	y	y	y
	26	9	m	0	0	116	y	y	n	n
	30	9	m	25	20	120	y	y	n	n
	31	8	m	0	0	101	y	y	n	n
	32	9	m	15	0	111	n	y	n	y
	35	10	m	0	0	113	y	y	n	n
	40	9	m	0	0	98	n	y	n	y

Table 2: Description of the sample (SCP group) before the beginning of treatment and at 2 year follow-up (y = diagnosis, n = no diagnosis)

Theta/Beta				Med (mg)	IQ	Diagnosis Screening	Diagnosis 2 year follow up
2	10	m	10	0	79	y	n
6	9	m	15	10	112	y	n
7	8	m	0	0	99	n	y
8	8	m	20	5	95	y	n
25	8	m	0	0	98	y	n
47	8	m	0	0	100	y	y
49	8	m	0	0	109	y	y
58	8	m	0	0	101	y	n
60	8	f	0	0	105	y	n
61	12	m	0	0	92	y	n
67	10	f	20	20	85	y	y
69	8	m	0	0	93	y	n

Table 3: Description of the sample (Theta/Beta group) before the beginning of treatment and at 2 year follow-up (y = diagnosis, n = no diagnosis).

	SCP group			Theta/Beta group		
	Participants	Non-Participants	p	Participants	Non-Participants	p
IQ (mean)	107,27	98,64	0,076	97,33	100,1	0,49
Age (mean)	8,64	9,86	0,056	8,75	9,7	0,11
Diagnosis						
<i>session 2+3</i>						
Combined	9	11	0,84	7	9	0,096
Inattentive	2	3	0,84	4	1	0,19
Hyperactive	0	0		1	0	0,35
<i>6 month follow-up</i>						
Combined	3	7	0,24	2	7	0,011
Inattentive	4	4	0,67	3	1	0,36
Hyperactive	2	2	0,79	1	0	0,35
No diagnosis	2	1	0,39	6	2	0,14

Table 4: Comparison of participating and non-participating children at 2 year follow-up.

3.2. Regulation of SCPs

SCP amplitudes were distributed normally (Kolmogorow-Smirnov). Differences between activation and deactivation tasks in the feedback condition were close to significance only at the end of treatment ($t_{10} = -2,220$, $p = 0.051$, $ES = 0.39$). The difference was not significant at other assessment points. No significant difference could be observed in the transfer condition.

In the feedback condition the difference between activation and deactivation tasks increased significantly with time ($F_{2,20} = 13.226$, $p = 0.03$). In the transfer condition the increase was close to significance ($F_{2,20} = 3.02$, $p = 0.079$). Yet an F-value which is higher than “1” indicates that the p-value might become significant in a larger sample. A significant interaction between time x task (positivity / negativity) could be observed for the feedback condition ($F_{2,40} = 4.38$, $p = 0.032$) but not for the transfer condition. In the feedback condition post hoc paired samples tests revealed a significant increase of the difference between SCP amplitudes in activation and deactivation tasks between screening and end of treatment ($t_{10} = 4.22$, $p = 0.006$, $ES = 0.53$). Between screening and 2-year follow-up the increase of this difference was close to significance ($t_{10} = 2,789$, $p = 0.057$, $ES = 0.40$). At 2-year follow-up a significant decrease of the difference between SCP amplitudes in activation and deactivation tasks in the feedback condition compared to end of treatment could be observed ($t_{10} = -4.494$, $p = 0.003$, $ES = 0.21$).

As can be seen in Figure 3 (upper panel) SCP amplitudes in activation tasks (feedback) increased significantly between screening and end of treatment ($t_{10} = 3,039$, $p = 0.036$, $ES = 0.47$). Between end of treatment and 2-year follow-up the mean amplitudes in negativity tasks did not change significantly.

As shown in Figure 3 (both panels), in the transfer condition children were able to produce positive shifts in positivity tasks for the first time at 2 year follow-up, while in the feedback condition they already had this skill at the end of training. Yet at following assessment points this ability was no longer present.

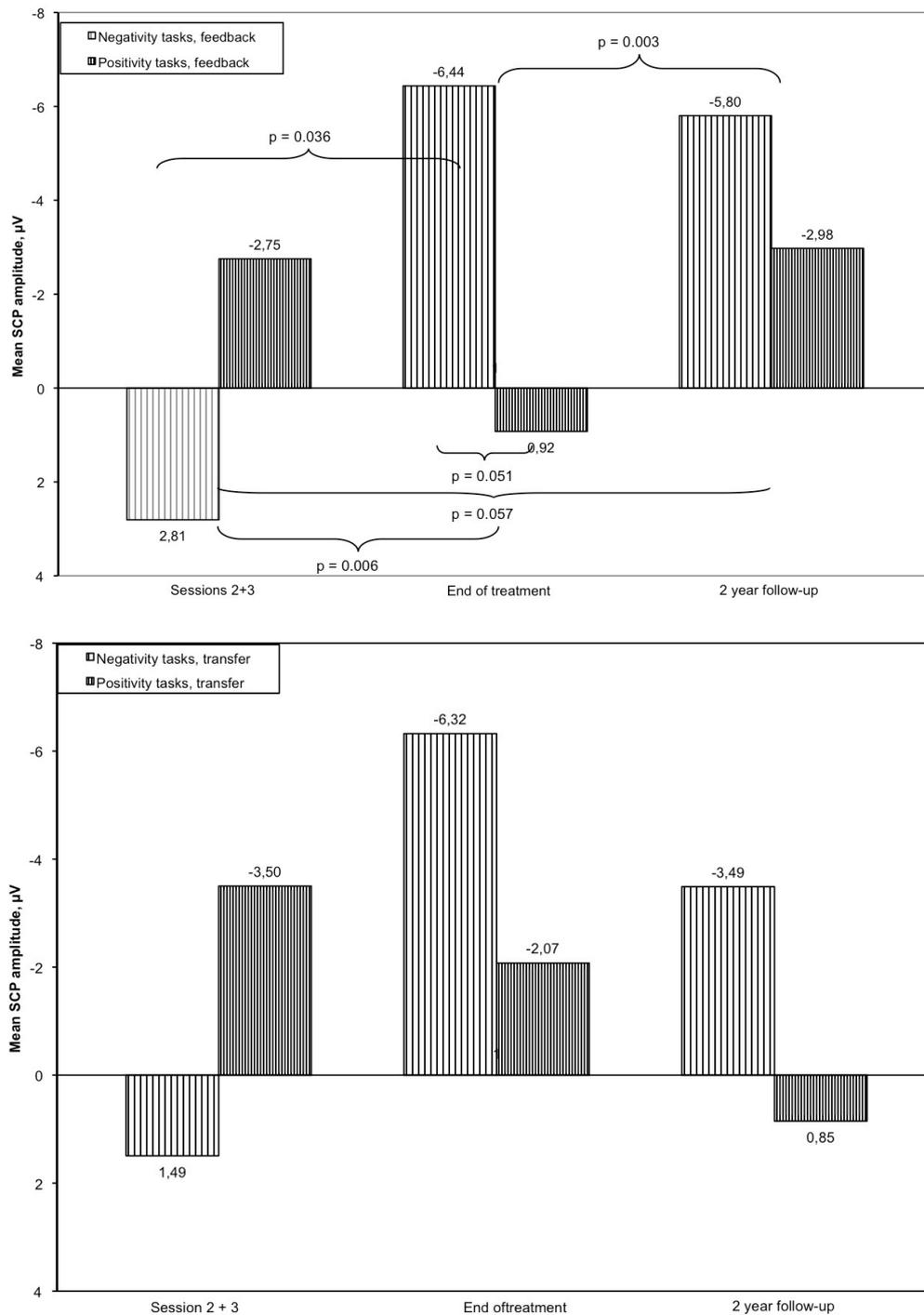


Figure 3. Upper panel: Mean amplitudes in negativity and positivity trials in the feedback condition during screening, end of treatment and 2 year follow-up. Lower panel: Mean amplitudes in negativity and positivity trials in the transfer condition during screening, end of treatment and 2 year follow-up.

3.3. Self regulation of Theta/Beta ratios

Theta/Beta ratios were distributed normally (Kolmogorow-Smirnov).

Differences between activation and deactivation tasks in the feedback condition (Figure 4, upper panel) were close to significance at the end of treatment ($t_{11} = -2,127$, $p = 0.057$, $ES = 0.45$). The difference between activation and deactivation tasks did not change significantly with time neither in the transfer ($F_{2, 22} = 0.22$, $p = 0.71$) nor in the feedback ($F_{2, 22} = 0.20$, $p = 0.69$) condition.

The increase of the Theta/Beta ratio (see Figure 5, lower panel) in deactivation tasks between screening and 2-year follow-up was close to significance in the transfer condition ($t_{11} = -2.536$, $p = 0.084$, $ES = 0.31$).

No further significant changes between any of the assessment points could be observed.

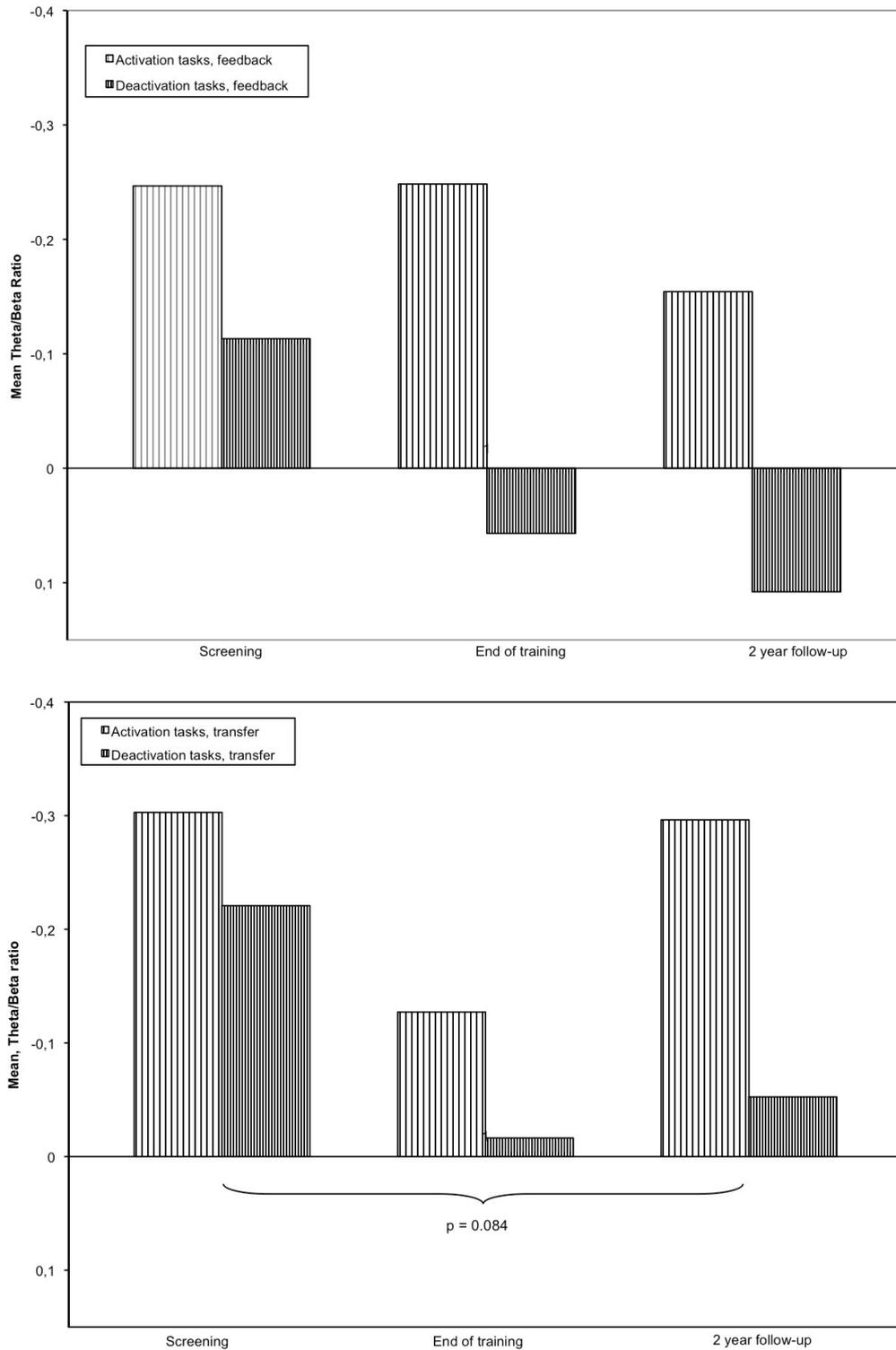


Figure 4. Upper panel: Mean Theta / Beta ratios in activation and deactivation tasks in the feedback condition during screening, end of treatment and 2 year follow-up. Lower panel: Mean Theta / Beta ratios in activation and deactivation tasks in the transfer condition during screening, end of treatment and 2 year follow-up.

3.4. Behavior

Parental ratings

The number of DSM IV criteria for both inattention ($F_{2, 40} = 16.40, p=0.00$) and hyperactivity ($F_{2, 40} = 14.59, p=0.00$) decreased significantly over time. Interaction of group x time and differences between groups did not reach significance.

As shown in Figure 5, post hoc Wilcoxon Signed ranks tests revealed significant changes for both groups. In the SCP group a significant decrease of the number of DSM IV criteria for inattention could be observed between screening and 2 year follow-up ($Z = -2.530, p = 0.033, ES = 0.51$). The decrease of the number of DSM IV criteria from screening to 2 year follow-up for hyperactivity in the SCP group after Bonferroni correction was close to significance ($Z = -2.203, p = 0.084, ES = 0.55$). In the Theta/Beta group a significant decrease of DSM IV criteria could be observed for both hyperactivity ($Z = -2.825, p = 0.015, ES = 0.53$) and inattention ($Z=-2.593, \text{asyp. sig} = 0.033, Z = 0.39$) between screening and 2 year follow-up.

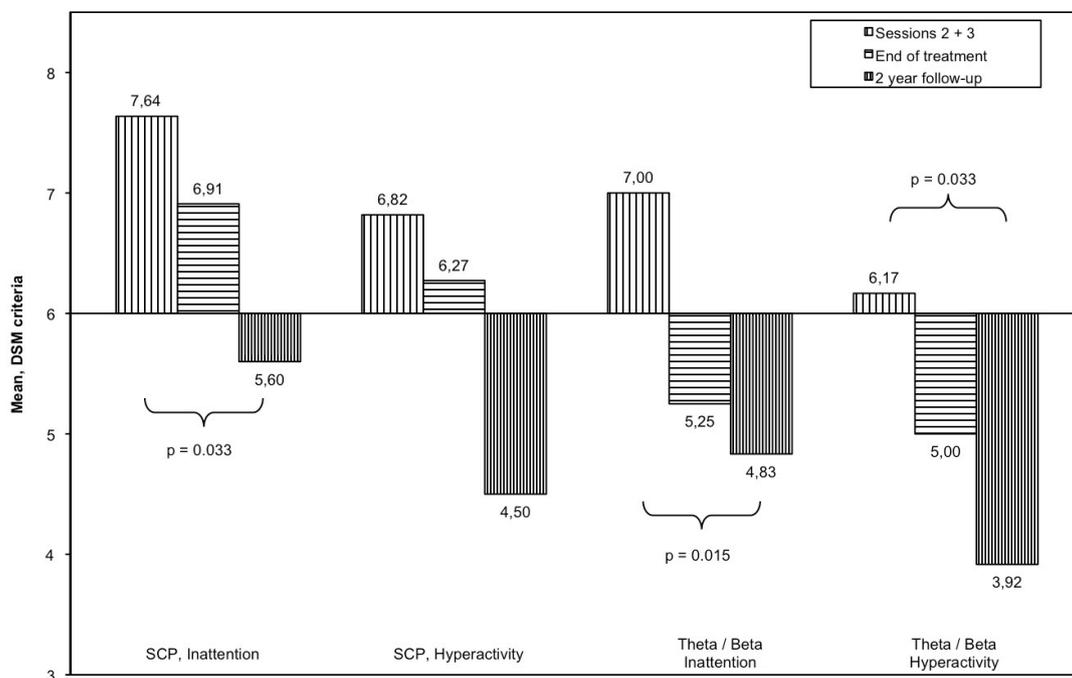


Figure 5: DSM IV criteria, parents' ratings. Scores below 6 are normal.

Group-means for hyperactivity and inattention in both groups were below the cut-off-value of 6. In the SCP group only 3 out of 11 children still had a diagnosis of combined ADHD at 2 year follow-up, 5 no longer had a diagnosis of ADHD at all. In the Theta/Beta group only 3 children still had a diagnosis of combined ADHD, 6 did not meet DSM criteria anymore. See Table 5 for further details.

Group	Screening		End of Training		2 year follow-up	
	SCP	Theta/Beta	SCP	Theta/Beta	SCP	Theta/Beta
Patients	25	22	25	22	11	12
Male	20	18	20	18	8	10
Female	5	4	5	4	3	2
Diagnosis, n						
ADHD	20	16	17	7	3	3
ADD, predominantly inattentive type	5	5	5	5	2	2
ADHD, predominantly hyperactive type	0	1	2	4	1	1
No Diagnosis of ADHD	0	0	1	6	5	6
Medication (Ritalin, 18-60mg)	7	5	7	5	2	3

Table 5: Development of diagnosis assessed by DSM-IV questionnaire.

In both groups Fisher's exact test showed that the changes of diagnosis from screening to 2-year follow-up are significant (SCP- group: $p=0.006$, Theta/Beta group: 0.03)

Frequency of problems at home and impact of problems at home were assessed by the Eyberg questionnaire. A general linear model showed a significant change for both frequency of problems ($F_{2,40} = 22.27$, $p = 0.00$) and impact of problems ($F_{2,40} = 12.436$, $p = 0.00$). No significant time x group interaction could be observed. Post hoc paired samples tests revealed a significant decrease of frequency of problems in the SCP group between screening and 2 year follow-up ($t_9 = 5.349$, $p = 0.00$ ES = 0.59) and also for

impact of problems ($t_9 = 4.263$, $p = 0.006$, $ES = 0.34$). In the Theta/Beta group post hoc samples test also showed a significant improvement for frequency of problems between screening and 2 year follow-up ($t_{11} = 4.195$, $p = 0.003$, $ES = 0.46$) and also between end of treatment and 2 year follow-up ($t_{11} = 3.252$, $p = 0.024$, $ES = 0.23$) The impact of problems decreased significantly in the Theta/Beta group between screening and 2 year follow-up ($t_{11} = 3.593$, $p = 0.012$, $ES = 0.45$). At 2 year follow-up means for frequency of problem in both groups were below the cut-off value of 126 for the first time (see Figure 6).

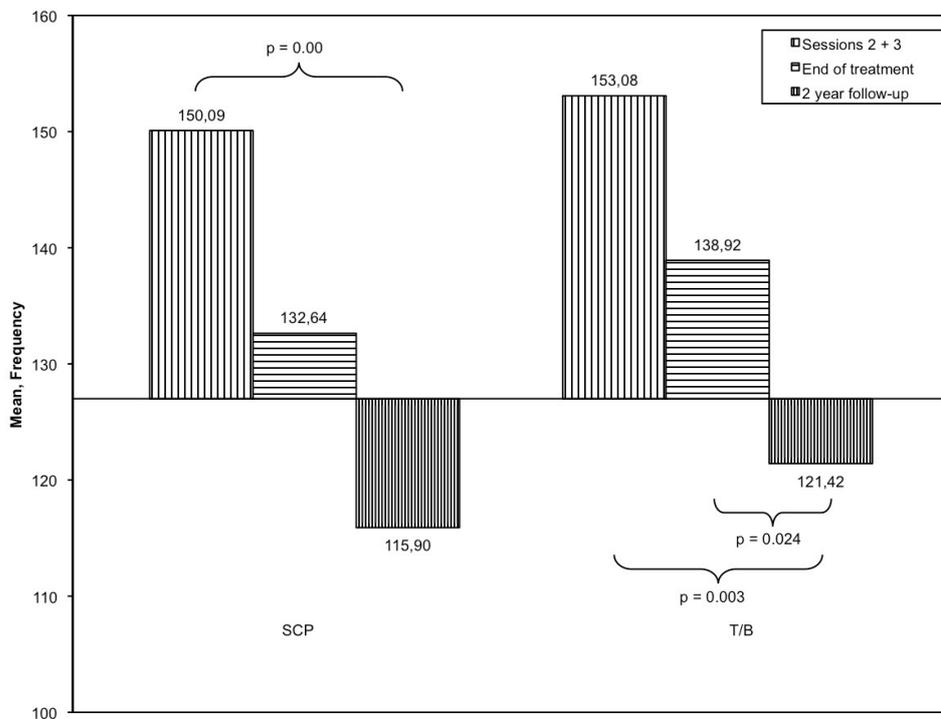


Figure 6. Frequency of problems, parents' ratings (Eyberg questionnaire); Scores below 127 are considered as normal.

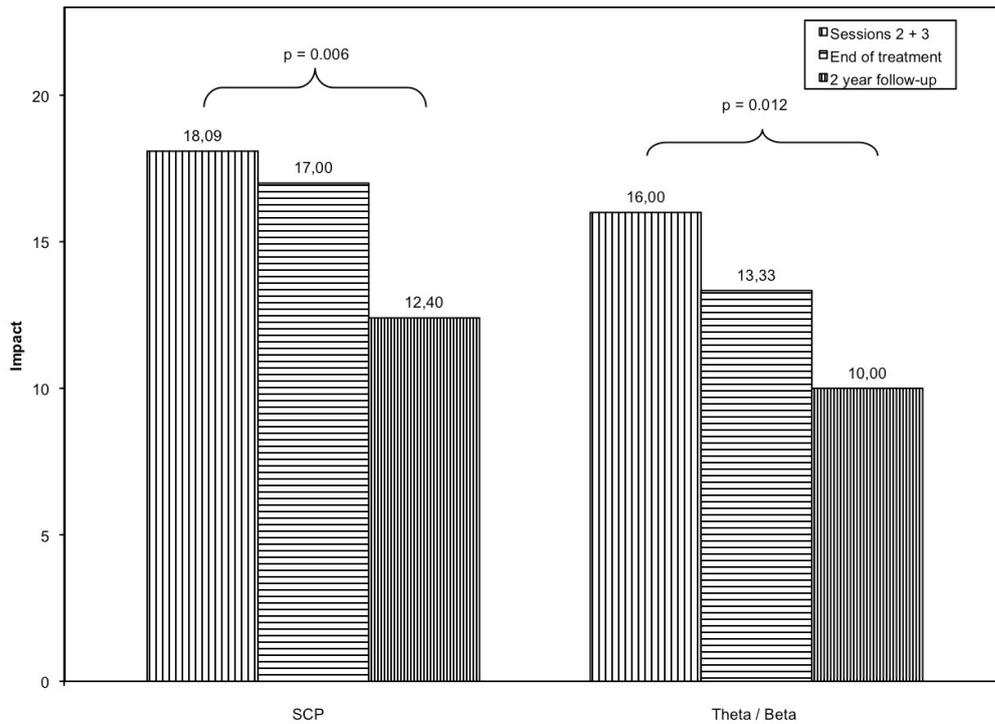


Figure 7. Impact of problems, parents' ratings (Eyberg questionnaire); Scores below 45 are considered as normal.

By using Connors rating scale parents rated their children's behavior three days in succession at each assessment point. The changes over time were significant ($F_{2, 40} = 8.277, p=0.01$). No time x group interaction could be observed. There was no significant difference between the groups. Post hoc tests showed a significant improvement for the SCP group between screening and 2 year follow-up ($t_9 = 5.142, p = 0.003, ES = 0.65$). As shown in Figure 8, mean values in both groups were below the cut-off value of 15 at 2 year follow-up.

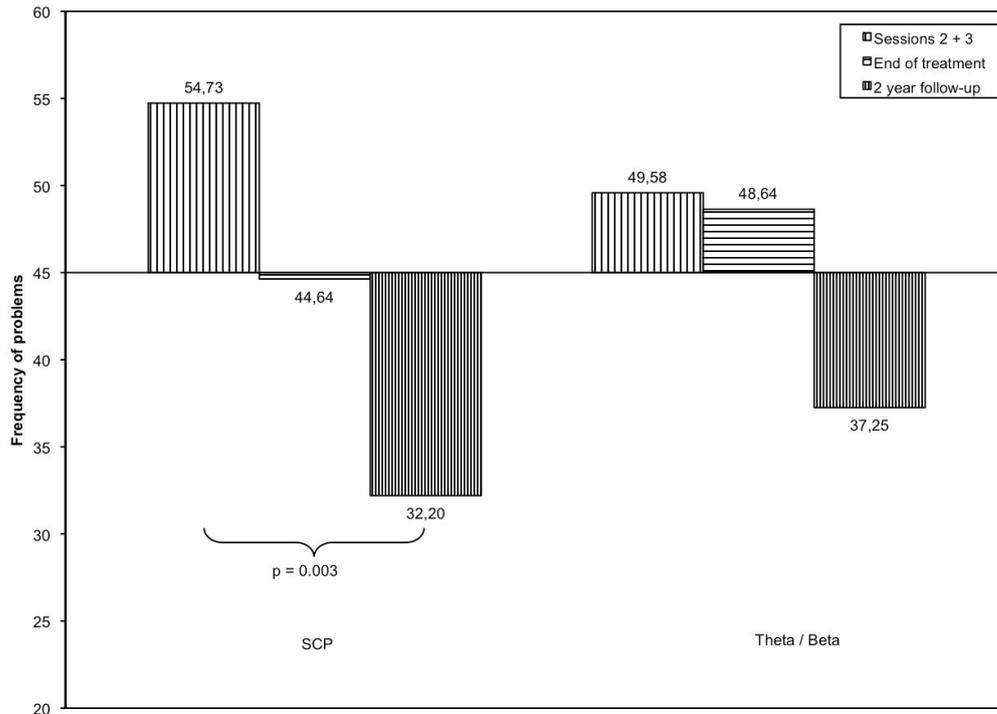


Figure 8. Frequency of problems, parents' ratings (Connors questionnaire); Scores below 15 are considered as normal.

3.5. Attention

The “Testbatterie zur Aufmerksamkeitsprüfung” (Zimmermann and Fimm, 2002) was used in order to assess attention. Seven subtests evaluated percent ranges for speed, omissions and commissions. Single test results were aggregated to the number of results with a below-average achievement (below 25th percentile) and to the number of results with an above-average achievement (above 75th percentile). There was a significant decrease by time for below achievements ($F_{2, 40} = 28.399$, $p = 0.00$) and a significant increase for above achievements ($F_{2, 40} = 26.349$, $p = 0.00$). No significant difference between both groups could be observed neither for above nor for below achievements.

In the SCP-group post-hoc paired samples tests showed a significant decrease of below-average achievements between screening and 2 year follow-up ($t_{10} = 7.717$, $p = 0.00$, $ES = 0.54$) and between end of treatment and

2 year follow-up ($t_{10} = 4.404$, $p = 0.003$, $ES = 0.225$). A significant increase of above-average achievements between screening and 2 year follow-up could be shown, too ($t_{10} = -6.328$, $p = 0.00$, $ES = 0.58$).

In the Theta / Beta group children showed significantly more above-average achievements ($t_{10} = -4.755$, $p = 0.003$, $ES = 0.39$) at 2 year follow-up compared to screening. Reduction of below-average achievements between screening and 2 year follow-up was close to significance ($t_{10} = 2.593$, $p = 0.081$, $ES = 0.22$). In addition a significant increase of above-average achievements between end of treatment and 2 year follow-up ($t_{10} = -3.758$, $p = 0.012$, $ES = 0.25$) could be observed (see Figure 9).

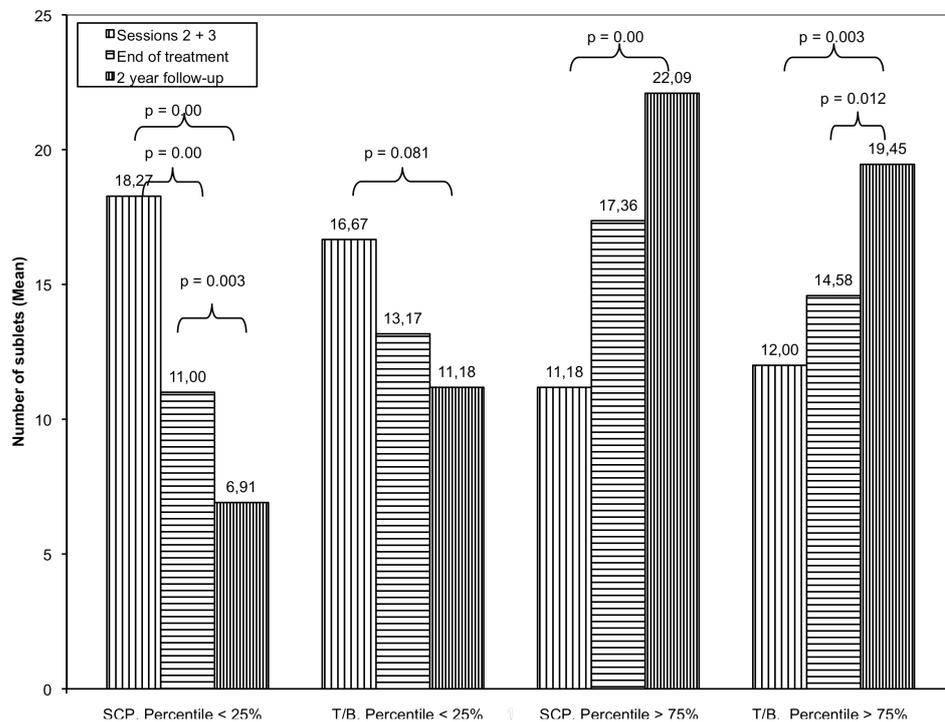


Figure 9: Comparison of performance in the TAP (Test of attention).

		SCP Group			p / ES		
		Screening	End of Training	2 year follow up	[scr - end]	[end - 2yfu]	[scr - 2yfu]
DSM	<i>Inattention</i>	7.64 ± 1.12	6.91 ± 1.81	5.60 ± 2.11	ns	ns	0.033 / 0.51
	<i>Hyperactivity</i>	6.82 ± 1.94	6.27 ± 2.00	4.50 ± 1.50	ns	ns	0.084 / 0.55
Eyberg	<i>Impact</i>	18.09 ± 7.06	17.00 ± 7.82	12.40 ± 8.43	ns	ns	0.006 / 0.34
	<i>Frequency</i>	150.09 ± 24.87	132.64 ± 32.22	115.90 ± 20.97	0.057 / 0.29	ns	0.000 / 0.59
Connors		54.72 ± 13.60	44.63 ± 23.01	32.20 ± 12.91	ns	ns	0.003 / 0.65
TAP	<i>Above achievements</i>	11.18 ± 6.97	17.36 ± 10.22	22.09 ± 8.11	0.057 / 0.33	ns	0.000 / 0.58
	<i>Below achievements</i>	18.27 ± 9.86	11.00 ± 9.97	6.91 ± 7.57	0.000 / 0.34	0.003 / 0.225	0.000 / 0.54
Theta/Beta Group							
		Screening	End of Training	2 year follow up	[scr - end]	[end - 2yfu]	[scr - 2yfu]
DSM	<i>Inattention</i>	7.00 ± 1.28	5.25 ± 1.91	4.83 ± 2.04	0.018 / 0.47	ns	0.015 / 0.53
	<i>Hyperactivity</i>	6.17 ± 2.37	5.00 ± 2.56	3.92 ± 2.88	0.051 / 0.256	ns	0.033 / 0.39
Eyberg	<i>Impact</i>	16.00 ± 5.11	13.33 ± 6.62	10.00 ± 6.58	ns	ns	0.012 / 0.45
	<i>Frequency</i>	153.08 ± 26.71	138.92 ± 39.09	121.42 ± 32.85	ns	0.024 / 0.23	0.003 / 0.46
Connors		49.54 ± 18.12	48.63 ± 20.19	37.25 ± 19.81	ns	ns	ns
TAP	<i>Above achievements</i>	12.00 ± 8.75	14.58 ± 10.02	19.45 ± 8.51	ns	0.012 / 0.25	0.003 / 0.39
	<i>Below achievements</i>	16.67 ± 12.81	13.17 ± 11.93	11.18 ± 10.70	ns	ns	0.081 / 0.22

Table 6. Synopsis of means and p-values in behaviour and attention. (scr = screening prior to the first sessions, end = end of training, 2yfu = 2 year follow-up)

4. Discussion

For the first time long-term data after a neurofeedback training of Theta/Beta frequency bands and SCPs is reported. While cortical self regulation as well as improvements in behavior (parents' and teachers' rating), attention and IQ have been shown to be stable six months after the end of training (Strehl et al., 2006), (Leins et al., 2007), we here present data two years after the end of treatment. The stability of self regulation of EEG as well as of concomitant changes in target behavior and attention have been analyzed. In both groups self regulation skills and clinical outcome are stable at 2 year follow-up.. In some cases even an additional improvement at 2 year follow-up could be observed.

EEG self regulation skills showed a mixed pattern regarding groups and conditions. In the SCP group children gained and kept the ability to generate negative potential shifts and in the transfer condition they continuously improved their ability to produce shifts in the positive direction. A similar observation could be made in the Theta/Beta group (feedback condition) where children continuously improved their ability to produce shifts in the positive direction (i.e. enlarging the Theta/Beta ratio = "deactivation"). Strehl et al. already showed that children are able to regulate their SCPs at the end of treatment, i.e. to differentiate between positivity and negativity tasks, and that this skill remained stable for at least six months (Strehl et al., 2006). At 2 year follow-up this significant difference between positivity and negativity tasks in the SCP-amplitudes could no longer be observed. Yet it should be pointed out that in the feedback condition this effect was caused by a decrease of the mean SCP amplitude in positivity tasks, while the mean amplitude in negativity tasks did not change significantly (see Fig. 3). As the skill to produce positive shifts does not seem to be as important in regard to abolishment of symptoms, we are not expecting a negative influence on the clinical outcome. In the transfer condition Leins et al. had shown that at six month follow-up children were able to produce positive SCP-shifts in positivity tasks for the first time since the beginning of treatment (Leins et al., 2007). At 2 year follow-up this skill still is present. Though there is no significant

difference between positivity and negativity tasks in the transfer condition it can be seen in Fig. 3 that children were still able to produce the required shifts, i.e. to produce positive shifts in positivity tasks and negative shifts in negativity tasks.

Participants in the Theta/Beta group were able to decrease the Theta/Beta ratio in activation tasks ever since the beginning of treatment. The ability to increase the Theta/Beta ratio in deactivation tasks improved continuously over time. At 2 year follow-up, patients are - as at the end of treatment - still able to decrease the Theta/Beta ratio in activation tasks and increase the Theta/Beta ratio in deactivation tasks. In transfer tasks, patients were not able to produce a positive Theta/Beta ratio at any time of assessment, yet the difference between Theta/Beta ratio in activation and deactivation tasks has nearly doubled from the end of treatment until 2 year follow-up.

Though mean SCP-amplitudes and mean Theta/Beta ratios indicate that children are still able to self regulate cortical potentials, many results especially in the Theta/Beta group do not reach statistical significance. This may be due to the small number of patients participating at the study. The decreasing number of participants in long-term follow-up studies is a well-known problem.

Parents reported a reduction of behavioral problems. In each of the three questionnaires children remained below the cut-off values. Some of these values have been reached for the first time. In the SCP group effect sizes of these changes were mostly medium, while in the Theta/Beta Group small effect sizes could be observed. Test results of attention testing also showed further improvements again with medium effect sizes in the SCP group and small effect sizes in the Theta/Beta group (see Table 5 for a synopsis of all questionnaires and tests results).

Neither psychometric data nor neurofeedback data support a significant difference between both training protocols. Being asked about their experience, many children from the SCP-group reported, that in the first trials

of each session it took them pretty long to find adequate strategies to control the cursor. This subjective report is reflected by Figure 3 and Figure 4: While children in the SCP group were not able to respond with appropriate shifts neither in positivity nor negativity tasks during the first sessions, children in the Theta/Beta group were able to decrease the Theta/Beta ratio in activation tasks from the beginning.

As can be seen from EEG training data improvements in attention and behavior do not reliably match with the improvements regarding self regulation of brain activity in both groups. Especially in the Theta/Beta group significant results in EEG data are very rare. Due to the absence of a control group there is currently no proof that self-regulation training of frequency bands or SCPs leads to improved behavior. In the preceding study Strehl et al. had used Pearson's χ^2 test to show a statistical correlation between self-regulation skills of SCPs and clinical outcome (Strehl et al., 2006). Unfortunately this analysis cannot be applied at this 2 year follow-up due to the small number of participants.

How to explain the good clinical outcome given the low number of significant results in EEG training data in the Theta /Beta group? The most obvious explanation is that non-specific factors might contribute to the outcome. Goth determined predictors for clinical outcome and acquisition of self-regulation skills in children undergoing treatment with training of SCPs or Theta / Beta bands (Goth, 2006). While in the SCP group the acquisition of self-regulation skills at six months follow-up could be shown to be a predictor for a good clinical outcome, factors not related to the neurofeedback training (e.g. IQ and psychological wellbeing) were detected in Theta/Beta group.

Another important question cannot be answered by our data: 'Would the symptoms have improved without any treatment, too? Would an improvement just be the normal course of the disease?' Several studies already addressed this question. Barkley et al. showed that approximately 80% of treated adolescents with a diagnosis of ADHD still had significant ADHD symptoms at 8 year follow-up (Barkley et al., 1990). Biedermann et al reported that a

decline in hyperactivity symptoms in untreated children with ADHD correlates with age, while inattentive symptoms do not (Biederman et al., 2000). Our study showed a continuous improvement in both hyperactivity and inattentive symptoms, which indicates that there is an association between training of self regulation skills and clinical outcome.

The heterogeneity of the samples in both groups regarding age, IQ, diagnosis and gender is a major limitation of the study. Though both groups were matched for age and IQ, there are obvious differences between both samples. Moreover biasing of the data in the Theta/Beta ratio group cannot be ruled out, as children who participated in the 2 year follow-up had shown greater improvement in their behaviour at preceding assessment points than children who did not participate at the 2 year follow-up.

In the NIMH MTA study Jensen et al showed that early advantages of medication treatment compared with combined treatment (medication and behavior therapy), community care and behavior therapy were no longer present at 3 year follow-up. Instead the treatment modalities applied in the study did not differ significantly in terms of reduction of ADHD symptoms. Although the ADHD score in all groups was below baseline levels at any point of follow-up, at 3 year follow-up children in the medication and in the combined group had lost some of the gain that had been observed at 14 month follow-up. In contrast to the results of the NIMH MTA study, in our study children still improved although treatment was terminated 2 years ago.

The present study has shown that children improve in behavior and attention after being treated with neurofeedback and that these effects are stable or even more improved two years after the last training session had taken place. At 2 year follow-up approximately half of the children in both groups do no longer meet the diagnostic criteria for ADHD at all. The long-term effects of neurofeedback can be considered as a major advantage of this treatment compared with pharmacological treatment. Future studies involving blind control groups should prove a causal relationship between neurofeedback treatment and clinical outcome.

5. References

Barkley, R. A., M. Fischer, et al. (1990). The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 29(4): 546-57.

Biederman, J., E. Mick, et al. (2000). Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry* 157(5): 816-8.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ.

Conners CK (1997). *Conners' Rating Scale-Revised: Technical Manual*. North Tonawande, NY, Multi-Health Systems.

Drechsler, R., M. Straub, et al. (2007). 1Controlled evaluation of a neurofeedback training of slow cortical potentials in children with Attention Deficit/Hyperactivity Disorder (ADHD). *Behav Brain Funct* 3: 35.

DuPaul GJ, B. R., Connor DF (1998). *Stimulants. Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*. R. Barkley. New York, NY, Guilford Press 510-551.

Eyberg, S., Pincus D. *Eyberg Child Behavior Inventory and Sutter-Eyberg Student Behavior Inventory-Revised* (1999). *Eyberg Child Behavior Inventory and Sutter-Eyberg Student Behavior Inventory-Revised*. Odessa, FL, Psychological Assessment Resources.

Fuchs, T., N. Birbaumer, et al. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. *Appl Psychophysiol Biofeedback* 28(1): 1-12.

Goldman, L. S., M. Genel, et al. (1998). *Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents*. Council on Scientific Affairs, American Medical Association. *Jama* 279(14): 1100-7.

Goth, G. (2006). *Neurofeedbacktherapie bei Kindern mit ADHS: Prädiktoren für den Erwerb kortikaler Selbstkontrolle und die klinische Verbesserung*. Unpublished doctoral Thesis: 65.

Heinrich, H., H. Gevensleben, et al. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. *Biol Psychiatry* 55(7): 772-5.

Jensen, P. S., L. E. Arnold, et al. (2007). 3-year follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry* 46(8): 989-1002.

Johnstone, S. J., R. J. Barry, et al. (2001). Topographic distribution and developmental timecourse of auditory event-related potentials in two subtypes of attention-deficit hyperactivity disorder. *Int J Psychophysiol* 42(1): 73-94.

Leins, U., G. Goth, et al. (2007). Neurofeedback for children with ADHD: a comparison of SCP and Theta/Beta protocols. *Appl Psychophysiol Biofeedback* 32(2): 73-88.

Lubar, J. F. and M. N. Shouse (1976). EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): a preliminary report. *Biofeedback Self Regul* 1(3): 293-306.

Lubar, J. O. and J. F. Lubar (1984). Electroencephalographic biofeedback of SMR and beta for treatment of attention deficit disorders in a clinical setting. *Biofeedback Self Regul* 9(1): 1-23.

Monastra, V. J., J. F. Lubar, et al. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: an initial validation study. *Neuropsychology* 13(3): 424-33.

Monastra, V. J., D. M. Monastra, et al. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Appl Psychophysiol Biofeedback* 27(4): 231-49.

Ramirez, P. M., D. Desantis, et al. (2001). EEG biofeedback treatment of ADD. A viable alternative to traditional medical intervention? *Ann N Y Acad Sci* 931: 342-58.

Ravens-Sieberer, U. (2003). The KINDL Questionnaire for Measuring Health Related Quality of Life in Children and Adolescents-Revised Version. *Assessment of Quality of Life and Well-being*: 184-188.

Rockstroh, B., Elbert, T., Canavan, A., Lutzenberger, W., Birbaumer, N. (1989). *Slow cortical potentials and behavior*. Baltimore, München, Wien, Urban & Schwarzenberg.

Rockstroh, B., Elbert, T., Lutzenberger, W., & Birbaumer, N. (1990). *Biofeedback: Evaluation and therapy in children with attentional dysfunctions*. *Brain and behavior in child psychiatry*. A. Rothenberger. Berlin, Springer: 345-355.

Schachter, H. M., B. Pham, et al. (2001). How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *Cmaj* 165(11): 1475-88.

Strehl, U., U. Leins, et al. (2006). Self-regulation of slow cortical potentials: a new treatment for children with attention-deficit/hyperactivity disorder. *Pediatrics* 118(5): e1530-40.

Swanson, J. M., G. R. Elliott, et al. (2007). Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. *J Am Acad Child Adolesc Psychiatry* 46(8): 1015-27.

Tewes, U. R., P. Schallberger, U. (1999). Hamburg Wechsler Intelligenztest für Kinder - Dritte Auflage (Hawik III).

Zimmermann, P. and B. Fimm (2002). Testbatterie zur Aufmerksamkeitsprüfung (TAP) Version 1.7.

Danksagung

Mein aufrichtiger Dank gebührt Frau PD Dr. Ute Strehl für die hervorragende Betreuung meiner Arbeit, für das Heranführen an das wissenschaftliche Publizieren und für all die Ratschläge und Hilfestellungen im Institut und weit darüber hinaus.

Des weiteren danke ich Herrn Prof. Dr. Birbaumer, der in mir das Interesse für die Neurowissenschaften geweckt hat, Frau Sonja Kaller für die Einarbeitung in Labor und Arbeitsplatz, sowie all den ehemaligen Doktoranden, die mit mir freundlicherweise ihre Erfahrungen geteilt haben und stets bei Fragen zur Verfügung standen.

Herrn Prof. Kotchubey danke ich für die freundliche und wertvolle Durchsicht meiner Statistiken.

Zu guter Letzt gebührt meine Wertschätzung allen Mitarbeitern des Instituts für Medizinische Psychologie, die mir stets hilfreich zur Seite standen.

Curriculum vitae

Name: Cihan Gani
Born: 09 February 1983 in Berlin

Education:

1989 - 1993: Schiller Grundschule Esslingen a.N.
1993 - 1995: Mörike-Gymnasium Esslingen a.N.
1995 - 2002: Theodor-Heuss-Gymnasium Esslingen a.N.
Degree: Abitur

Medical studies:

2003 - 2009: Eberhard-Karls-University, Tübingen
2007 - 2008: Brown University, Providence, Rhode Island, USA
2005: Erster Abschnitt Staatsexamen, Degree: "Good"
2005 - 2008: Doctoral Thesis, "Long term effects after feedback of slow cortical potentials and of Theta / Beta-amplitudes in children with Attention Deficit Hyperactivity Disorder (ADHD)"
2008: United States Medical Licensing Exam, Step 1. Score: "240/99"
2009: United States Medical Licensing Exam,
Step 2 CK. Score: "225/93"
Step 2 CS. Passed
5. Nov 09 Ärztliche Prüfung (2. Staatsexamen), Degree: "Good"

Clinical electives:

03/16/2006-04/14/2006 Cardiology, Esslingen Hospital
08/21/2006-08/25/2006 Radiology, „Diagnostikzentrum Esslingen“
09/11/2006-10/08/2006 Neurology, Beaumont Hospital Dublin, Ireland
02/26/2007-03/26/2007 Gynecology & Obstetrics, Ingolstadt Hospital
03/27/2007-04/17/2007 Emergency Medicine, Ingolstadt Hospital
07/30/2007-08/10/2007 Surgery, Ruit Hospital
08/27/2007-09/21/2007 Endocrinology, Rhode Island Hospital, USA
10/01/2007-10/26/2007 Emergency Medicine, Rhode Island Hospital, USA
10/29/2007-11/23/2007 Hematology, The Miriam Hospital, Providence, USA
11/26/2007-12/21/2007 Gastroenterology, Rhode Island Hospital, USA
01/22/2007-01/25/2007 Medicine/ICU, The Miriam Hospital, Providence, USA
01/28/2007-02/08/2007 Radiology, Rhode Island Hospital, Providence, USA
02/11/2007-02/22/2007 Ophthalmology, Providence, USA

Final year "PJ":

08/25/2008-12/14/2008 Surgery, University Hospital of Tübingen
12/15/2008-04/05/2009 Radiation Oncology, University Hospital of Tübingen
04/06/2009-07/26/2009 Internal Medicine, NIH, Bethesda MD, USA
Internal Medicine, University Hospital of Tübingen