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Effect of EEG Biofeedback on Cognitive Flexibility in Children with Attention Deficit Hyperactivity Disorder With and Without Epilepsy

Sophia Bakhtadze¹ · Maia Beridze² · Nana Geladze¹ · Nana Khachapuridze¹ · Natan Bornstein³

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Abstract Attention deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders in school-aged children. Symptoms consistent with ADHD have been observed in 8–77 % of children with epilepsy. Researchers have been motivated to search for alternative forms of treatment because 30 % of patients with ADHD cannot be treated by psychostimulants. Several studies support the use of a multimodal treatment approach that includes neurofeedback (NF) for the long-term management of ADHD. These studies have shown that NF provides a sustained effect, even without concurrent treatment with stimulants. We aimed to assess cognitive flexibility in ADHD children with and without temporal lobe epilepsy (TLE), and to evaluate the effects of NF on cognitive flexibility in these groups of children. We prospectively evaluated 69 patients with ADHD aged 9–12 years. The control group was 26 ADHD children without TLE who received no treatment. The first experimental group comprised 18 children with ADHD. The second experimental group comprised 25 age-matched ADHD children with TLE. This group was further divided in two subgroups. One subgroup comprised those with mesial temporal lobe epilepsy (16 patients, 9 with hippocampal sclerosis and 7 with hippocampal atrophy), and

the other with lateral temporal lobe epilepsy (9 patients, 5 with temporal lobe dysplasia, 3 with temporal lobe cysts, and 1 with a temporal lobe cavernoma). We treated their ADHD by conducting 30 sessions of EEG NF. Reaction time and error rates on the Trail Making Test Part B were compared before and after treatment, and significant differences were found for all groups of patients except those who had mesial temporal lobe epilepsy with hippocampal atrophy. Our results demonstrate that in most cases, NF can be considered an alternative treatment option for ADHD children even if they have TLE. Additional studies are needed to confirm our results.

Keywords Attention deficit hyperactivity disorder · Lateral temporal lobe epilepsy · Mesial temporal lobe epilepsy · Neurofeedback

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders in school-aged children, with a prevalence of 3–7 % (Swanson et al. 1998). The core clinical signs of ADHD include inattention, restlessness, and impulsivity (Taylor 2007). ADHD is sometimes accompanied by other conditions, including epilepsy. Symptoms consistent with ADHD have been observed in 8–77 % of children with epilepsy, depending on the sample studied and the criteria used for the diagnosis of ADHD (Dunn et al. 2003). A possible explanation for this association is that ADHD symptoms might be mediated by decreased metabolic activity in several brain areas, especially the frontal lobes. Genetic and environmental risk factors for epilepsy may also increase the likelihood of developing ADHD. In children with poorly controlled

✉ Sophia Bakhtadze
sophiabakhtadze@yahoo.com

¹ Department of Child Neurology, G. Zhvania Academic Clinic of Paediatrics, Tbilisi State Medical University, 21 Lubliana Str, 0159 Tbilisi, Georgia

² Department of Neuromedicine, Tbilisi State Medical University, Tbilisi, Georgia

³ Department of Neurology, Tel Aviv Sourasky Medical Center, Tel-Aviv University, Tel Aviv, Israel

epilepsy, seizure activity itself can produce an impairment of attention that can be improved by treatment with antiepileptic drugs (Gonzalez-Heydrich et al. 2007). Abnormal signaling in parallel networks connecting the prefrontal cortex and limbic system with the thalamus may account for both epilepsy and ADHD (Gonzalez-Heydrich et al. 2007). Additionally, the prevalence of epileptiform EEG abnormalities in children with ADHD is higher than in normal children (Holtmann et al. 2003). Thus, the existence of an epileptic focus (e.g., in the temporal lobe) may reflect underlying structural damage that could also be responsible for producing ADHD symptoms, such as executive impairment, which is one of the most important cognitive disorders affecting children with ADHD (Millichap 2010).

Two of the most important and directly connected behavioral components of executive attention are being mentally flexible and organizing one's behavior to solve problems. Executive attention requires activation of frontal cortex in the brain (Posner and DiGirolamo 1998). In contrast, the role of the temporal lobes, the primary brain region related to epilepsy (temporal lobe epilepsy; TLE), in executive attention remains ambiguous. However, some studies have demonstrated that frontal lobe dysfunction characterized by executive malfunctioning can also occur in patients with TLE (Igarashi et al. 2002). Children with frontal lobe dysfunction exhibit poor executive attention, whereas in those with TLE, memory impairments are relatively more severe. Investigating executive attention in children with TLE is important because problems in shifting attention, and thus cognitive flexibility, may be under-recognized in these children.

Cognitive flexibility is one of the most important components of executive function, and it should be evaluated in children with ADHD both with and without comorbid conditions, including epilepsy. Not only should cognitive flexibility be assessed in ADHD children with TLE, but strategies to mitigate problems with executive attention in these children should also be considered. The efficacy of methylphenidate (MPH) is proven in children with ADHD (Aacap Official Action 2002). In ADHD patients with TLE, the use of MPH is controversial because stimulants are believed to decrease the seizure threshold. Although several studies have shown that stimulants do not exacerbate well-controlled epilepsy, the data on seizure risk in non-epileptic children treated with stimulants are limited (Hemmer et al. 2003). The deleterious effect of antiepileptic drugs (AEDs) on cognition has been confirmed in multiple clinical trials. However, while it is clear that AEDs may contribute to the cognitive deficits observed in patients with epilepsy, there have been few systematic studies on the effects of AEDs on specific cognitive domains, including attention (Shannon and Love

2005). Thus, the search for treatment options that improve executive attention in children who have both TLE and ADHD is relevant for clinicians.

Researchers have been motivated to search for alternative forms of treatment because 30 % of patients with ADHD cannot be treated by psychostimulants (Arns et al. 2009). The efficacy of EEG biofeedback (neurofeedback; NF) for improving executive attention has been demonstrated in children with ADHD. Several studies support the use of a multimodal treatment approach that includes NF for the long-term management of ADHD. These studies have shown that NF provides a sustained effect, even without concurrent stimulant treatment (Dalley 2004; Kropotov 2009; Levesque and Beaugard 2011; Yucha and Gilbert 2004). Moreover, NF is recommended for use in epilepsy to reduce seizure frequency (Monderer et al. 2002; Yucha and Gilbert 2004) and has been used successfully in the treatment of refractory epilepsy (Uhlmann and Frsöcher 2001). However, these benefits of NF require further confirmation.

Thus, we aimed to assess the efficacy of NF on cognitive flexibility in ADHD children with and without TLE.

Subjects and Methods

Subjects

Children who met the DSM-IV diagnostic criteria for ADHD were included in the study (American Academy of Pediatrics 2000). ADHD was diagnosed by both an experienced, board-certified neurologist and a pediatric neurologist based on neuropsychological and neurological examinations and on a detailed caregiver interview involving the use of the Conners' parent rating scale (Conners et al. 1998). We prospectively evaluated 69 patients with ADHD aged 9–12 years. Twenty-six of the ADHD children who did not have TLE formed the control group and did not receive any treatment. NF treatment was administered to two experimental groups of ADHD children, one without TLE (18 children; ADHD-1) and one with TLE (25 age-matched children; ADHD-2). The second group was further divided into those with mesial temporal lobe epilepsy (MTLE, also known as limbic epilepsy) or lateral temporal lobe epilepsy (LTLE, also known as neocortical epilepsy) according to their International League Against Epilepsy (ILAE) Task Force TLE classifications (Panayiotopoulos 2007). The MTLE subgroup was further divided into 16 patients with hippocampal sclerosis and 9 with hippocampal atrophy (MTLE-scl and MTLE-atr groups, respectively). The LTLE subgroup contained nine patients, five with temporal lobe dysplasia, three with temporal lobe cysts, and one with

a temporal lobe cavernoma. Thus, we analyzed five groups of patients: controls, ADHD-1, LTLE, MTLE-scl, and MTLE-atr, with the latter three being part of the ADHD-2 group of patients who also had epilepsy.

Methods

Written, informed consent was obtained from the parents or guardians of all children. The study protocol was approved by the Biomedical Research Ethics Committee of Tbilisi State Medical University in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki. An EEG investigation was performed and digitally recorded in all children. A diagnosis of TLE was made based on clinical manifestations and ictal and interictal EEG examinations. These examinations are not routinely performed in the context of ADHD but were done to select an appropriate NF training session. The cohort of TLE patients with left-sided changes on the EEG were selected for inclusion in this study because the left hemisphere is extremely sensitive to the Trail Making Test (TMT) (Faber 2005), which was used for part of the neuropsychological assessment (see below). The assessment, including IQ testing using the Wechsler Intelligence Scale for Children-Revised (WISC-R), was conducted in all groups of children. Children with $IQ > 70$ were included in the study, while those with lower IQ scores were excluded.

The neuropsychological assessment was conducted using the TMT adapted for Georgian children in the age range of our patients. The TMT is commonly used to measure frontal lobe function (Zakzanis et al. 2005), and in particular cognitive flexibility. This test contains two subtests: Subtests A and B (Franzen et al. 1996). Both parts of the TMT consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1–25, and the patient is asked to draw lines that connect the numbers in ascending order. In Part B, the circles include both numbers (1–13) and letters (A–L). As in Part A, the patient draws lines to connect the circles in an ascending pattern but with the added task of alternating between the numbers and letters. The patient is instructed to connect the circles as quickly as possible without lifting the pen or pencil from the paper. The key measures are the time needed to connect the “trail” and the number of errors. To assess cognitive flexibility, we used the TMT-B. The results of all subtests were recorded in the form of scores that represent a range of reaction times (RTs) necessary for performing each task. The number of errors (ERs) on each subtest was also recorded (Table 1). The TMT-B was carried out twice: before and after NF therapy in the ADHD-1 and ADHD-2 groups, and on the first day of assessment and after a 40-day interval for the control group. This amount of time

has been shown to be required for NF training. Improvements in performance and speed, which are common among ADHD patients, were assessed in the second session.

We adopted criteria for cognitive flexibility based on TMT-B results obtained from a normal, school-aged population of children. Cognitive flexibility is considered in the normal range when a child’s RT for the TMT-B is between 14–28 s (corresponding to scores of 8–10). Impairment is considered mild when a child’s RT is between 29–42 s (scores of 5–7), moderate when between 43–56 s (scores of 3–4), and severe when longer than 57 s (scores of 0–2) (Buck et al. 2008).

NF sessions were carried out using a psychophysiological training complex “Rehacor”, RF in the ADHD-1 and ADHD-2 groups, as previously described (Lubar and Lubar 1984). NF sessions were held over a period of 6 weeks, with five training sessions per week (total, 30 sessions). Training was divided in two phases, with 15 sessions in each phase. In the first phase, children were trained to enhance the amplitude of sensorimotor rhythms (SMR; 12–15 Hz) and decrease the amplitude of theta activity (4–7 Hz). Beta/theta training was conducted during the second phase. In this training, children were instructed to decrease the amplitude of theta waves (4–7 Hz) and increase the amplitudes of their beta-1 waves (15–18 Hz). During the first phase, EEG was recorded at the Cz electrode, with the reference placed on the left earlobe and the ground electrode on the right earlobe. During the second phase, EEG was recorded from Fz-Pz derivations in accordance with a recommended protocol (Lubar and Lubar 1984), with the same reference and ground electrode placements. SMR enhancement is known to reduce hyperactivity as well as seizure frequency (Monderer et al. 2002; Sterman and Egner 2006). Beta/theta training is conducted based on evidence that suppressing theta activity diminishes problems maintaining attention (Lubar and Shouse 1976). During the training sessions, children played games on a computer monitor and interacted with both visual and acoustic stimuli. In the game, an object (eagle, balloon, etc.) rose higher and increased speed against a landscape as the child made correct changes to one of the desired control parameters. If the parameter changed in the wrong direction, the object descended, and when influenced by a head wind, drifted back to starting point. The purpose was to fly the maximum distance marked on the map. Successful training was determined as a 3 % change in the controlled parameter in the correct direction over the course of training. Positive reinforcement in the form of an acoustic signal was given when a patient successfully changed the controlled parameter more than one standard deviation from baseline levels during the session. Depending on training performance, audio feedback of

Table 1 The five groups, their mean ages, and their mean performance on the TMT-B (reaction time scores and error rates) before and after treatment

	Age (years)	TMT-B			
		Reaction time (scores)		Error rate	
		Before treatment (mean \pm SE)	After treatment (mean \pm SE)	Before treatment (mean \pm SE)	After treatment (mean \pm SE)
Control N = 26	8.61 \pm 0.26	4.42 \pm 0.25	7.08 \pm 0.20	12.58 \pm 0.36	7.65 \pm 0.24
ADHD-1 N = 18	9.61 \pm 0.14	4.77 \pm 0.23	5.77 \pm 0.30	13.00 \pm 0.33	12.00 \pm 0.30
ADHD-2 ADHD + LTLE N = 9	10.33 \pm 0.16	4.33 \pm 0.40	7.55 \pm 0.50	12.66 \pm 0.33	8.44 \pm 0.38
ADHD-2 MTLE with hippocampal sclerosis N = 9	9.89 \pm 0.21	3.33 \pm 0.33	6.00 \pm 0.33	11.77 \pm 0.43	7.89 \pm 0.76
ADHD-2 ADHD + MTLE with hippocampal atrophy N = 7	10.29 \pm 0.24	2.57 \pm 0.36	3.42 \pm 0.20	16.85 \pm 0.73	16.42 \pm 0.68

“Poor”, “Good”, or “Very Good” was delivered to the patient via earphones.

SMR training included the following phases: measuring the baseline of the controlled parameter (120 s), instruction #1 (8 s), training 31 (120 s), instruction #2 (10 s), relaxation (60 s), instruction #3 (9 s), training #2 (180 s), instruction #4 (10 s), and measuring final state of the controlled parameter (60 s). In the second phase of the study, beta/theta training included the following phases: measuring the baseline of the controlled parameter (50 s), instruction #1 (8 s), training #1 (155 s), instruction #2 (8 s), relaxation (105 s), instruction #3 (8 s), training #2 (230 s), instruction #4 (8 s), and measuring the final state of the controlled parameter (160 s).

Correlation with Clinical Variables

For inclusion in the ADHD-1 group, we selected only those patients with combined-type ADHD, which is defined by both inattentiveness and hyperactivity. For study subjects with TLE (the ADHD-2 group), clinical variables examined included the seizure focus (mesial temporal lobe or lateral temporal lobe), changes in MRI findings (hippocampal sclerosis or hippocampal atrophy), and laterality (left-sided changes in the EEG). Etiology, age of onset, duration of epilepsy, seizure type, presence of secondary generalization, frequency of seizures, and history of previous neurological insult were not taken into consideration.

Statistical Analysis

Statistical analyses of TMT-B results, which provide a direct measure of cognitive flexibility, were conducted by an independent statistician from Tbilisi State Medical University (TSMU). The data were analyzed by one-way ANOVA and with the Kruskal-Wallis test. A 5 group \times 2 conditions repeated-measures ANOVA was used to determine the effect of treatment on TMT-B performance. Wilcoxon matched-pairs test was conducted to observe the effect of treatment in all groups.

Results

The study groups, their mean ages, and mean performances on the TMT-B (RTs and ERs), are shown in Table 1. The differences in mean RT and ER between groups and their changes after treatment are shown in Fig. 1. Both RTs and ERs differed significantly between groups, and both groups exhibited a significant treatment effect. If differences between groups are reflected in different initial RTs and the effect of treatment by the changes in ER, we can hypothesize that effect of treatment differed between the ADHD-1 and ADHD-2 groups.

The effect of treatment on TMT-B performance, as measured by RTs and ERs before and after treatment were entered separately in a 5 (groups) \times 2 (conditions; before

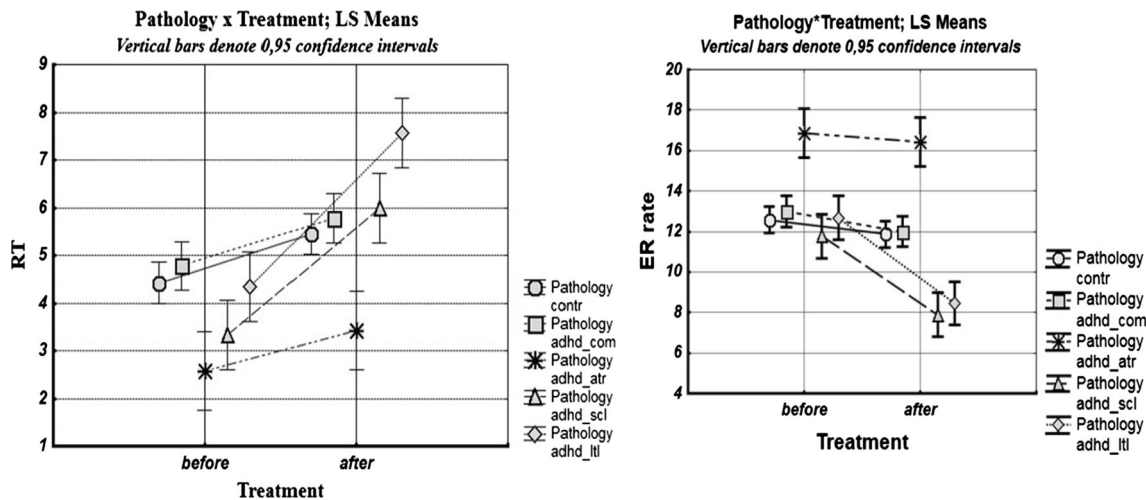


Fig. 1 Differences in mean reaction time (RT) scores and error rate (ER) between groups and their changes after treatment

treatment vs. after treatment) repeated-measures ANOVA (Fig. 2; Table 2). According to Table 2, the null hypothesis states that the mean RTs and ERs of the five different groups are equal. Because the *p* value was <0.001, which is less than the significance level of 0.05, we can reject the null hypothesis and conclude that some of the groups have different mean scores, and therefore the treatment was effective for some groups. Thus ANOVA revealed significant effects of treatment on both RT and ER in all children in the ADHD-2 group, except those with atrophy compared with ADHD-1.

Table 3 shows the results of the one-way ANOVA and Kruskal-Wallis H tests that compared the RTs and ERs of those children for whom treatment showed significant improvement on attention parameters (ADHD-1, LTLE, and MTLE-scl). Both tests show statistically significant differences in RT and ER rates between groups (ADHD-1 vs. LTLE and MTLE-scl). While results were significant

for both RT and ER after treatment, only those for RT were significant before treatment. These data suggest that all children in the ADHD-2 group respond to NF except those with hippocampal atrophy.

Table 4 and Figs. 3 and 4 show the results from a Wilcoxon matched pairs test of RT scores and ER grouping by pathology. Results indicate that post-test scores are statistically significantly higher than pre-test scores (*p* < 0.01) for each group, except for the ADHD-2, MTLE-atr group.

Discussion

Our results show that children with ADHD and TLE exhibited problems with shifting attention. A complex anatomical and functional network is known to connect the temporal and frontal lobes and that because of this

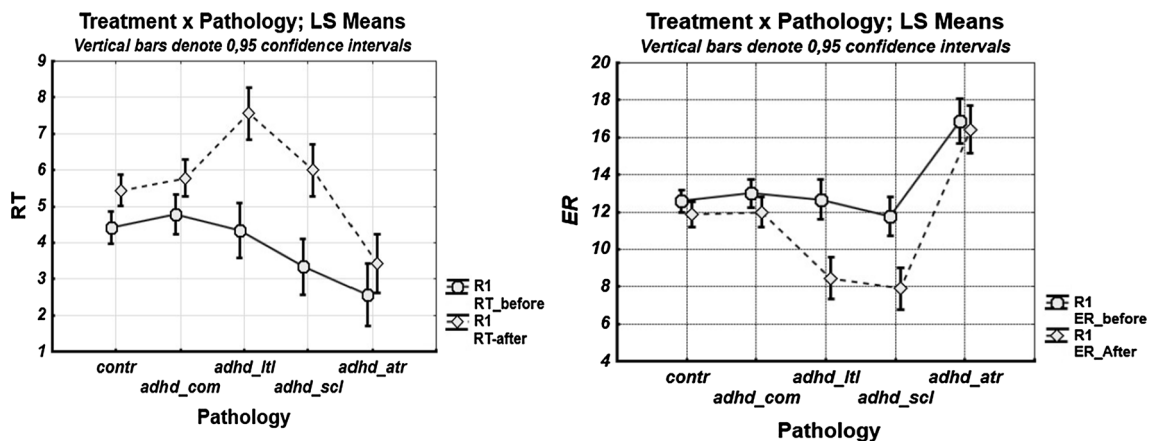


Fig. 2 Repeated measures ANOVA. The interactions among 5 groups × 2 conditions (before treatment and after treatment) were analyzed

Table 2 ANOVA results showing the effect of treatment on performance of the TMT-B, as measured by reaction time and error rate

Reaction time scores	Degree of freedom	F	<i>p</i>	Partial eta-squared
Effect treatment × pathology	4	11.514	<i>p</i> < 0.001	0.418
ER effect treatment × pathology	4	37.349	<i>p</i> < 0.001	0.700

The interactions among 5 groups × 2 conditions (before treatment and after treatment) were analyzed

Table 3 Comparison of reaction time and error rate between the ADHD-1 group and some of the ADHD-2 group (LTLE and MTLE with hippocampal sclerosis)

ADHD-1 versus LTLE + MTLE with hippocampal sclerosis	TMT-B			
	Reaction time		Error rate	
	Before treatment	After treatment	Before treatment	After treatment
One-way ANOVA	$F_{1,34} = 6.5, p = 0.015$	$F_{1,34} = 4.6, p = 0.038$	$F_{1,34} = 3.1, p = 0.085$	$F_{1,34} = 60.4, p < 0.0001$
Kruskal-Wallis H test	$H = 5.56, df = 1, p = 0.018$	$H = 3.38, df = 1, p = 0.05$	$H = 2.82, df = 1, p = 0.093$	$H = 24.58, df = 1, p < 0.0001$

Table 4 Wilcoxon Matched Pairs Test of reaction time and error rate, grouped by pathology

Wilcoxon matched pairs test				
Pathology	Pair of variables			
	RT scores before and RT scores after		ER before and ER after	
	Z	<i>p</i> value	Z	<i>p</i> value
Controls	3.72	<i>p</i> < 0.01	3.01	<i>p</i> < 0.01
ADHD-1	3.18	<i>p</i> < 0.01	3.51	<i>p</i> < 0.01
ADHD-2	2.67	<i>p</i> = 0.01	2.67	<i>p</i> < 0.01
ADHD + LTLE				
ADHD-2	2.52	<i>p</i> = 0.01	2.67	<i>p</i> < 0.01
MTLE with hippocampal sclerosis				
ADHD-2	1.81	<i>p</i> = 0.07	1.57	<i>p</i> = 0.12
ADHD + MTLE with hippocampal atrophy				

network, the temporal epileptogenic zone is able to affect the frontal and prefrontal regions responsible for attention (Hermann et al. 2002). In line with these observations, recent functional neuroimaging studies have demonstrated decreased metabolism in the prefrontal regions of patients with TLE, especially in patients with mesial temporal lobe lesions (Takaya et al. 2006). This finding may explain why children with mesial temporal lobe lesions were found to exhibit more severe impairment in the ability to shift attention compared with children with lateral temporal lobe lesions. Several clinical studies have also demonstrated roles for the hippocampus and the amygdala in attention-processing. Plessen et al. (2006) showed that connectivity between prefrontal regions and the hippocampus and the

amygdala regulate a variety of attention, memory, and emotional processes implicated in the pathophysiology of ADHD. These authors also detected larger hippocampal volumes in children with ADHD and reported that among children with hippocampal dysfunction, larger hippocampal volumes tended to accompany less severe ADHD symptoms. This is in accordance with our findings demonstrating severe problems related to cognitive flexibility in ADHD children with MTLE that included hippocampal atrophy compared with those who had MTLE that included hippocampal sclerosis.

The significant impairment in attentional shifting in ADHD children with MTLE caused by hippocampal atrophy can be explained by another finding reported by

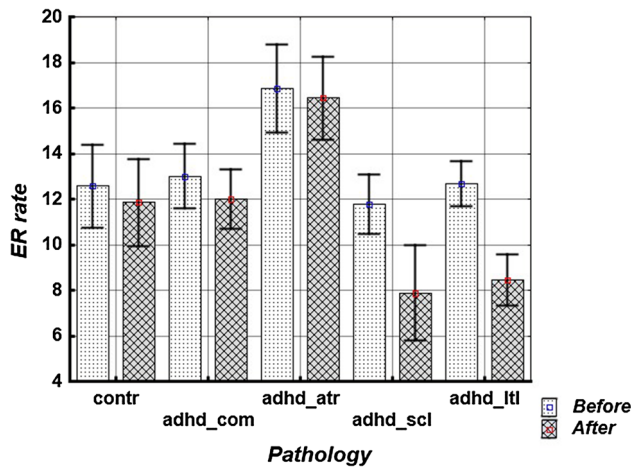


Fig. 3 Mean ER grouped by pathology, before and after treatment. Error bars denote the standard deviation

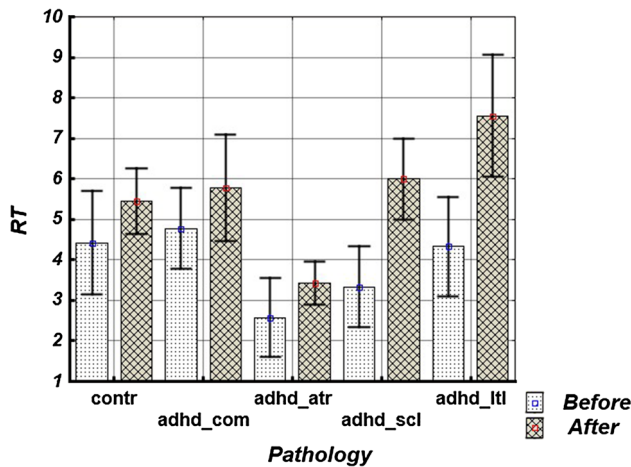


Fig. 4 Mean RT scores grouped by pathology, before and after treatment. Error bars denote the standard deviation

Cormack et al. (2005). The authors found that these children had reduced grey-matter density ipsilateral to the seizure focus in the hippocampus, in lateral temporal lobe and extra-hippocampal regions, including the thalamus, cerebellum, frontal cortex, and parietal opercular cortex. The authors suggest that these altered grey-matter densities could reflect structural changes resulting from the disruption of cortical development caused by recurrent seizures and a loss of functional input from the sclerotic or atrophic hippocampus. This finding demonstrates that the changes in these patients were more than functional and intermittent, and could potentially explain our finding that the performance of MTLE children with atrophy was worse than that of MTLE children with sclerosis. The poorer performance that we observed in MTLE children with atrophy might have resulted from a substantial loss of functional input from an atrophic hippocampus, which was

greater than the loss of functional input from a sclerotic hippocampus.

NF is known to have an effect on neural networks that support attention, executive functions, and motor regulation. These complex networks consist of several parallel networks, including the corticostriatal, cortico-pallidal, and cortico-cerebellar networks. In the corticostriatal circuit, the caudate nucleus receives projections from the extrastriate cortex, lateral parietal, lateral frontal, and temporal cortices. The cortico-pallidal projections arise in premotor cortex and primary somatosensory and motor cortices. The fronto-cerebellar circuit connects frontal cortical areas with the cerebellum. The latter is topologically connected to distinct sensorimotor regions via the pons and the thalamus (Makris et al. 2009). Although the thalamic pacemaker generates different brain rhythms depending on which cortical loops are being activated, changes in cortical loops can modify the firing rate of the pacemaker neurons and hence alter their firing patterns (Lubar 1997). Thus, NF treatment could potentially influence central and frontal loops, which in turn are linked to other brain regions, including not only the thalamus, which regulates EEG activity during NF training, but also temporal regions. This potential influence on neural circuits may explain why training was successful in the ADHD-1 and ADHD-2 groups, except for those ADHD-2 children who had MTLE with hippocampal atrophy. We suggest that the poor response observed in these children may be because the severity of lesions in the structural and functional connections between their atrophic hippocampus and other structures of the brain were worse than those in children with hippocampal sclerosis.

According to our results, problems in shifting attention also improved in the control group without any NF, although the effect was less prominent. Because repeated use of instruments like the TMT can cause practice effects that often obscure detection of meaningful intraindividual cognitive changes in serial assessment (Buck et al. 2008), this result can be considered as a false positive. In conclusion, our findings demonstrate that disorders of cognitive flexibility occur not only in children with ADHD but also in children with ADHD+TLE. The efficacy of NF is clear for all ADHD children tested, except in those who had MTLE with hippocampal atrophy. Thus, non-pharmacological therapy shows promise for the treatment of ADHD even when it occurs with epilepsy, provided that epilepsy-related damage to the hippocampus is not too severe. Additionally, NF therapy can be used to correct attentional problems, which are frequently associated with epilepsy. The limitation of this study is that our sample size was too small to prove beyond a doubt the benefit of NF for reducing cognitive flexibility disorders in ADHD children with or without TLE. Larger follow-up studies are

necessary to determine the consistency with which improvement in cognitive flexibility is found in these children.

Conclusions

Problems shifting attention occur in all children with ADHD. Those who also have TLE experience additional executive malfunction, especially those with mesial temporal lobe lesions. Among TLE children with these lesions, disturbances in shifting attention are more prominent in those with hippocampal atrophy than in those with hippocampal sclerosis. NF has the potential to be a successful treatment approach for children with ADHD, even those with TLE, as long as the TLE is not accompanied with pronounced executive impairment that resulted from extensive hippocampal atrophy.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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