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ATTENTION IMPAIRMENT REHABILITATION WITH COMPUTER-BASED FORAMENREHAB PROGRAM IN 8- TO 12-YEAR-OLD CHILDREN WITH EPILEPSY

Master's Thesis

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Running head: ***Attention rehabilitation in children with epilepsy***

Tartu 2015

Abstract

Epilepsy is a common neurological disorder in children and is frequently accompanied with attention impairment. Attention is a key component in cognitive functioning. Using modern cognitive neurorehabilitation methods is crucial in remediation. Still, few systematically controlled rehabilitation techniques for children exist. The main aim of the study was to design and test the effectiveness of a computer-based rehabilitation method in attention impairment rehabilitation for children with epilepsy.

17 children with epilepsy aged 8-12 years received neurorehabilitation during 5 weeks (10 sessions) with the Attention module of ForamenRehab computer-program. 12 age equivalent children with epilepsy in waiting-list group participated in assessments with baseline tasks before and after the five-week-period with no active training. All patients participated in the follow-up assessment after 1.31 years. Also, 19 healthy children participated in the first assessment.

At baseline level, all patients showed worse results in attention compared to healthy peers. After the intervention, study group patients showed significantly improved performance in complex attention and tracking components. Follow-up assessment revealed long-term effects of rehabilitation in study group that exceeded the normal developmental change in waiting-list group. Parents' and children's feedback indicated positive generalized effect of training and confirmed the positive effect of rehabilitation. In conclusion, attention rehabilitation with ForamenRehab is effective for children with epilepsy. Rehabilitation should focus on training specific components of attention and follow individual-based rehabilitation process.

Keywords: epilepsy, attention impairment, cognitive rehabilitation, computer-based rehabilitation in children, ForamenRehab program

Tähelepanu rehabilitatsioon ForamenRehab arvutiprogrammiga 8-12 aasta vanustel epilepsiaga lastel

Kokkuvõte

Epilepsia on lastel sagedasti esinev neuroloogiline haigus, millega kaasnevad tihti tähelepanu probleemid. Tähelepanu on kognitiivse võimekuse põhifunktsioone. Kaasaegsete kognitiivse neurorehabilitatiooni meetodite kasutamine on paranemise protsessis ülioluline. Siiski leidub väga vähe süstemaatiliselt kontrollitud tõenduspõhiseid laste rehailitatsiooni tehnikaid. Antud uuringu peamine eesmärk oli kujundada ja testida arvutipõhise rehabilitatsiooniprogrammi efektiivsust epilepsiaga laste tähelepanufunktsiooni ravis.

17 epilepsia diagnoosiga 8-12 aasta vanust last osales rehabilitatsioonis, mis kestis viis nädalat (10 treeningut) ning viidi läbi ForamenRehab arvutiprogrammi Tähelepanu mooduliga. 12 sama vana epilepsia diagnoosiga last kuulusid ootelehe kontrollgruppi, kes osalesid baastaseme ülesannete testimisel enne ja pärast viienädalast sekkumiseta perioodi. Kõik patsiendid osalesid järeltestimisel 1.31 aastat hiljem. Lisaks osales esimesel baastasemete testimisel kontrollgrupp, kuhu kuulusid 19 tervet last.

Tulemustest selgus, et esimesel testimisel oli patsientide tähelepanufunktsiooni tase erinevate komponentide osas oluliselt madalam võrreldes tervete lastega. Treeningu järgselt paranesid uuringugrupi tulemused oluliselt tähelepanu jagamise ning seiramise komponentides. Järeltestimise tulemusena tuli esile ka treeningu positiivne kaugmõju, kuna treeninggrupi sooritus ületas ootelehe kontrollgrupi tulemusi ka 1,31 aasta möödudes. Lapsevanemate ja lastepoolne tagasiside kinnitas treeningu positiivset mõju. Antud tulemustest võib järeldada, et ForamenRehab on efektiivne meetod epilepsiaga laste tähelepanuhäirete ravis. Rehabilitatsioon peaks keskenduma spetsiifiliste tähelepanu alakomponentide individuaalsele treenimisele.

1. INTRODUCTION

1.1. Attention

As one of the key components of cognitive functioning, attention has been described as the processes that enable a person to concentrate on specific cognitive tasks and ignore others (Loring and Meador, 1999). Sohlberg and Mateer (1989) stated that attention is a multidimensional cognitive process that affects other dimensions of cognition - learning, memory, communication, problem solving, and perception. Based on diverse theoretical backgrounds, different models of attention components have been developed. Sohlberg & Mateer (2001; Sohlberg, 2013) have differentiated at least four categories of models for attention. These are clinical models, factor analytic models, cognitive processing models and neuroanatomic models. The current study is based on a clinical model of attention developed by Sohlberg and Mateer (2001/1989/1987), by which the attention function consists of five components: focused, sustained, selective, alternating and divided attention. *Focused attention* is the person's ability to respond to specific visual, auditory, or tactile stimuli. *Sustained attention* (sometimes regarded to as *vigilance*) is the capability to maintain attention on a task for long periods. It also involves other aspects of the attentional process, including effort and motivation (Wood, 1988). *Selective attention* is known as the capacity to focus on important stimuli, while ignoring irrelevant information. Thereby, selecting among many available stimuli (e.g., listening to a specific voice in a room with many people talking at the same time) (Pashler, 1999). A person with deficits in this attention component would be easily distracted by irrelevant stimuli, including both external and internal distractions (like worry or rumination) (Sohlberg & Mateer, 2001). *Alternating attention* refers to a mental flexibility of shifting the focus of attention and moving between tasks, therefore choosing the information to be proceeded (Sohlberg & Mateer, 2001). *Divided attention* is the ability to attend to competing stimuli simultaneously (Styles, 2005). Two or more behavioural responses could be required to divide attention, e.g., driving while listening to the radio (Sohlberg & Mateer, 2001). Wood (1988) stresses that divided attention is the attentional capacity as well as the focusing of attention for recognizing important cues. Also, *tracking function* of attention has been described in literature, which could be comprehended as part of complex attention and where attention is needed while doing some other mental task (e.g., digit span backwards in a task concept) (Lezak, 2004).

1.2. Epilepsy and attention impairment

Impairments of attention accompany various disorders, e.g., epilepsy (Guzeva, Belash, Guzeva, Guzeva, & Anastazi., 2009), traumatic brain injury (TBI) (Laatsch et al., 2007; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2007; Levin et al., 2007; Max et al., 2004), schizophrenia (Cornblatt & Keilp, 1994), brain tumours (Brière, Scott, McNall-Knapp, & Adams, 2008). Epilepsy is one of the most common neurological disorders in children and adolescents. The incidence rate of epilepsy in Estonia is up to 45: 100 000 (Beilmann et al., 1999).

It is widely known that epileptic seizures affect the functioning of the central nervous system. Among other cognitive deficits, children with epilepsy have been found to show clearly expressed dysfunctions in attention components (Engle & Smith, 2010; Hermann, 2006; Kolk, Beilmann, Tomberg, Napa, & Talvik, 2001; Kolk, Talvik, & Laine, 2004; Dunn, Austin, Harezlak, & Ambrosius, 2003; Fastenau, Dunn, & Austin, 2006; Austin et al., 2001). Impairments in overall attention (Rathouz et al., 2014; Engle & Smith, 2010; Kolk et al., 2001; Glügönen et al., 2000), sustained attention (Baglietto et al., 2001; Semrun-Clikeman & Wical, 1999, Picirilli et al. 1994), selective attention (Kolk et al., 2001) and altertness (Bennet-Levi & Stores, 1984) have been described. Both modalities, visual and auditory attention, have been found to be affected (Massa et al., 2001; Aldenkamp et al., 2000; Metz-Lutz et al., 1999). Also, deficits in phonological, visuo-perceptual and memory skills have been reported in children with epilepsy (Kolk et al., 2001/2004). Furthermore, in a recent study by Rathouz et al. (2014) they showed that cognitive deficits in children with epilepsy, that are present at baseline assessment, are maintained at least up to 5–6 years. This constitutes as a prevalent problem in the educational quality of these children as with impaired attention they may be less able to learn and acquire new skills from their environment. Besides, attention impairment is closely linked to impairments in other cognitive functions (e.g., working memory and executive functions) (Lenartowicz, 2014; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011; O'Brien, Dowell, Mostofsky, Denckla, & Mahone, 2010; Biederman et al., 2004; Russell & D'Hollosy, 1992). Attention is crucial for learning and thus impairments in this function have been found to contribute to major negative influence on academic and social competences (Genizi, Shamay-Tsoory, Shahar, Yaniv, & Aharon-Perez, 2012; Danckaerts et al., 2010; Fastenau, Shen, Dunn, & Austin, 2008; Nixon, 2001; Mayes, Calhoun, & Crowell, 2000; Kinsella, 1998). Sustained problems with cognitive functioning also impact children's future employment (Chamberlain, 1995).

1.3. Brain plasticity and cognitive rehabilitation

Plasticity is the "capacity of a system to respond to normal or aberrant developmental or lesion-induced changes in the internal or external environments by adopting new, stable, developmentally appropriate phenotypes and/or restoring old phenotypes" (Dennis et al., 2013). Neuroplasticity is known as the ability of the nervous system to change its structure and function during the processes that underlie learning and memory (Johnston, 2009). Initially, the basis for impairments in patients with epilepsy has been found in decreased functional connectivity and reorganization of brain functions which influence cognitive abilities, including attention (Datta et al., 2013; Zhang et al., 2009; Pitkänen & Sutula, 2002). The purpose of neuroplasticity is to adjust with environmental changes and recover impaired functions after brain lesion. During learning processes, specific activated neurons change the strength of their connections when responding to the presented stimuli and neural networks make adaptations which include increases in dendritic complexity (Dennis et al., 2013). By training specific cognitive functions the neural paths for these abilities are activated. Studies using functional magnetic resonance imaging (fMRI) or electroencephalogram (EEG) recordings to assess the effect of cognitive trainings in patients with acquired brain injury (ABI) have found support for this mechanism. Research in patients with multiple sclerosis has demonstrated that intensive attention rehabilitation improved the overall cognitive functioning and affected neural plasticity as increased brain activity was seen in fMRI (Cerasa et al., 2013; Filippi et al., 2012). In a study with adult TBI patients significant EEG changes were found following attention skills training with the Captain's Log computer-program (Stathopoulou & Lubar, 2004). Kim et al. (2009) also studied TBI patients and found that after training the improved performance of attention tasks was accompanied by changes in attentional network activation. Kolb et al. (2010) stated that animal studies have demonstrated identifiable systems which underlie the beneficial effects of rehabilitation. Gordon & Maggio (2012) conclude in their review that multidisciplinary studies using neurophysiology and magnetic resonance imaging are needed in the evidence research of rehabilitation for paediatric ABI. Furthermore, normally developing children also have been found to show a more adult-like pattern in EEG compared to controls after attention training (Rueda et al., 2005). The authors conclude that the data suggest "the executive attention network appears to develop under strong genetic control, but is subject to educational interventions during development".

One suitable intervention method to facilitate cognitive remediation is cognitive rehabilitation (CR). The aim of CR is to improve a person's functioning in their everyday life by increasing the abilities to do what they need and like, but find difficult or impossible due to their cognitive disability (Sarajuuri & Koskinen, 2006; Ylvisaker, 1998). CR has previously been shown to have positive effect in improving cognitive functions, including attention, for patients with various types of acquired brain injuries - TBI (Cicerone et al., 2005), brain tumor (Gehring et al., 2011), multiple sclerosis (Cerasa et al.; 2012), ADHD (Shalev, Tsal, & Mevorach, 2007), malaria (Bangirana et al., 2009/2011) and epilepsy (Engelberts et al., 2002). Langenbahn, Ashman, Cantor, & Trott (2013) thoroughly reviewed articles about attention rehabilitation in patients with epilepsy and concluded that CR together with teaching strategy use is the effective solution.

However for children, very few modern neurocognitive rehabilitation techniques exist and most of the available methods used are designed for adults. Different studies and reviews have pointed out the need for further more accurate and systematically controlled research in paediatric cognitive rehabilitation (Ross, Dorris, & McMillan, 2011; Slomine & Locascio, 2009; Limond & Leeke, 2005; Van't Hooft, Andersson, Sejersen, Bartfai, & Von Wendt, 2003; Butler & Copeland, 2002; Prigatano, 2000; Warschausky, Kewman, & Kay, 1999). The field of neuropsychological rehabilitation needs guidelines and underlying principles to organize the work of clinicians (Backeljauw & Kurowski, 2014; Prigatano, 2000). Thus, finding new methods for intervention is significant for these children, their families, schools and the whole society.

Five approaches in rehabilitation have been previously reported to manage difficulties in attention – attention process training working with specific components of attention (e.g. sustained attention, divided attention), environmental supports, self-regulatory strategies, use of external aids and psychosocial support (Sohlberg & Mateer, 1989/2001). These are often used simultaneously during the rehabilitation process.

Based on the clinical model of attention components by Sohlberg and Mateer (as mentioned before), they created the fundamental Attention Process Training (APT), which is a therapeutic program for direct training of different attention processes or components (Sohlberg & Mateer, 1987/1989; Sohlberg, Johnson, Paule, Raskin, & Mateer, 1994). It is a hierarchical, multilevel treatment to remediate attention deficits in brain-injured persons. The APT is an effective technique exactly due to neuroplasticity and has been found to be effective by various studies (Rabiner, Murray, Skinner, & Malone, 2010; Galbiati et al. 2009; Sohlberg et al., 2000). Also, studies have shown that APT has a generalized positive effect as, besides attention, it improves memory, learning, aspects of executive control and other untrained abilities (Rabipour & Raz, 2012; Jaeggi et al., 2010; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Sturm, Willmes, Orgass, & Hartje, 1997; Neimann, Ruff, & Baser, 1990; Ruff, Baser, & Johnson, 1989; Mateer & Sohlberg, 1988). Also, evidence shows that attention training can improve children's overall attention and concentration skills outside the training environment, as in the classroom and home settings (Rabiner et al., 2010; Shalev et al., 2007). Therefore, one important aspect of the training is to follow the generalization of improvement beyond the clinical setting of rehabilitation.

1.4. Attention rehabilitation in children

CR in children with attention impairments is nowadays mainly developed as computer-based interventions. This type of rehabilitation is efficient, because there is a possibility of making the programs more and more interesting and, therefore, attractive to children. We cannot forbid children from using computers on daily basis, but we should instead use the positive educational influence that computers may provide (Žumárová, 2015).

Previous studies have either evaluated the efficacy of a specific intervention for attention remediation or incorporated different cognitive domains, including attention. The most effective method is found to be attention training separately from other cognitive domains. In a recent review by Backeljauw and Kurowski (2014) they found that the best practice is intensive attentional training as demonstrated in the Galbiati study (Galbiati et al. 2009).

A thorough review by Cicerone et al. (2011) about recent studies with children with TBI and stroke found significant positive evidence for rehabilitation of cognitive functions, including attention. Together with their previous reviews the authors have examined 370 intervention studies. On this comprehensive basis they implicated that the training should be addressed to specific attention functions and teaching strategies for contributing to generalization. Backeljauw and Kurowski (2014) also concluded that the reviewed ABI studies demonstrated similar positive effect as TBI studies and the described results may be generalized to both TBI and other ABI groups. This means that the attention training programs that are at first developed for a single ABI diagnosis may be afterwards effectively expanded into the rehabilitation of different ABI diagnosis.

Various studies have described specific computer-based rehabilitation designs for attention impairment in children with ABI. African children surviving cerebral malaria (Bangirana et al., 2009/2011) and children with HIV (Boivin et al., 2010) were trained with Captain's Log cognitive training software configured for attention and memory skills. Results showed immediate benefit on these specific neuropsychological functions. The same program has also been found to elicit positive outcome in attention with survivors of childhood cancer (Hardy, Willard, & Bonner, 2011). Lee, Harn, Sohlberg, & Wade (2012) presented outcome data from three pilot participants with TBI who completed an intervention with computerized Attention Improvement Management (AIM) program. After training, the participants showed clinically meaningful improvements on attention outcome measures and also generalization of metacognitive strategies, trained within the program, to contexts outside of therapy. Galbiati et al. (2009) also trained children with TBI and found attention-specific neuropsychological training to significantly improve attention performance. In addition, this also positively affected children's adaptive skills. In a pilot study by Luton, Reed-Knight, Loiselle, O'Toole, & Blount (2011) used a short version of the Cognitive Remediation Programme (CRP) with 6-15 year-old children diagnosed with neurological disorders and attention problems. Children completed a six-module programme after which they showed improved attention measured both by parents' reports and children's performance on tasks. Significant improvement in attention functions after computerized training has also been shown in children with foetal alcohol spectrum disorders (Pei & Kerns, 2012; Kerns, MacSween, Vander Wekken, & Gruppuso, 2010).

Attention remediation training has also been successfully used in children with attention deficit hyperactivity disorder (ADHD) (Sohrabi, 2013; Rabiner et al., 2010; Shalev et al., 2007). A study with ADHD children by Shalev and colleagues (2007) reported an eight-week intervention with the Computerized progressive attentional training (CPAT) program where parents reported a significant decline in children's inattentive symptoms. Also, the children improved in reading comprehension and speed of copying passages in academic performance. Rabiner and colleagues (2010) conducted a study for students in first grade with attention difficulties evaluating the impact of two computer-based interventions - Computerized Attention Training (CAT) and Computer Assisted Instruction (CAI). Results showed that teachers rated a moderate decline in attention problems for all children who completed either intervention. Gains in reading fluency and in teacher ratings of academic performance were reported for students receiving CAI. Also, positive effect of computer-based neuropsychological training has been reported by Amonn, Frölich, Breuer, Banaschewski, & Doepfner (2013) in their study with children with ADHD aged 6 to 13 years. Specific training for 12 to 15 weekly sessions focusing on attentional dysfunction resulted in significant improvement in the trained parameters and symptoms of inattention and deportment.

Also, different reviews and meta-analyses have stressed the positive effect of attention training in children with ABI (Cernich, Kurtz, Mordecai, & Ryan, 2010; Rohling, Faust, Beverly, & Demakis, 2009) and importance of guidance in developing strategies (Cicerone et al. 2011; Slomine & Locascio, 2009).

As for epilepsy, very few studies have investigated the effects of cognitive rehabilitation programs for accompanied attention impairments. The amount of research is yet modest compared to other ABI diagnoses and has mostly been conducted with adult patients with epilepsy. In a study in adults with focal seizures, Engelberts and colleagues (2002) used two training methods for attention rehabilitation – the Retraining Method and the Compensation Method – and found both to be effective in improving the patients' neuropsychological outcomes. Gupta and Naorem (2003) stated that after a 6-week specific cognitive training (including for attention deficits) that used both paper and pencil tasks and real life activities for patients with epilepsy, overall improvement in cognitive performance occurred. Also, the authors noted the importance of identifying and targeting specific cognitive deficits. However, in children with epilepsy the research about attention training is still extremely limited and requires further development.

Ross and colleagues (2011) concluded in their review that there still exists a necessity for good intervention designs in CR of children with brain injuries. The following studies should also take into account the school and home environments. As well as consider the needs and abilities of each child. Karch, Albers, Renner, Lichtenauer, & von Kries (2013) concluded in their meta-analyses that positive training effect has only been proved with individual training programs and guidance. Thus, this kind of approach should be most effective. They also emphasized good compliance showing that children accept computer-based trainings lasting for many weeks.

Still, there is a lack of modern neurorehabilitation possibilities for children with epilepsy and the need to utilize new neurorehabilitation programs. Also, the necessity for systematic evidence-based recommendations exists. In my seminar paper (Saard, 2012) the current ForamenRehab software was tested with healthy control children and it was established that the program is suitable for children aged 9 – 12 years.

The main aim of the current research was to test the effectiveness of a computer-based rehabilitation method with the Attention module of ForamenRehab program in attention impairment rehabilitation for children with epilepsy aged 8-12 years.

The specific aims were:

1. to create an individual-based intervention design with strict protocol and optimal difficulty levels for attention impairment rehabilitation in 8- to 12-year-old children;
2. to examine the attention profiles of children with epilepsy and compare the results with healthy age equivalent children;
3. to examine the rehabilitation effect on specific attention components to discover the optimal duration for training;
4. to measure long-term rehabilitation effect in follow-up assessments;
5. to provide clinical implications for computer-based attention rehabilitation in children with acquired brain injury.

2. METHODS

2.1. Participants

2.1.1. Study group

The current study has been carried out between May 2012 until March 2015 in the Department of Neurology and Neurorehabilitation in the Children's Clinic of Tartu University Hospital.

17 children aged 8-12 years (mean age 10.07 yrs.; SD=1.150) with attention impairment and diagnosis of epilepsy have participated in the intervention. There were 12 boys and 5 girls in the intervention group (see Table 1 for further details). The age group was chosen due to the methodological considerations: 1) the children were required to have sufficient reading and basic mathematical skills; 2) keeping the age range and developmental level of the children comparable.

Participants were chosen according to the following inclusion criteria:

1. Previously diagnosed epilepsy (ICD-10 G40.0-G40.1), diagnosis confirmed by child neurologist;
2. Mild to moderate attention impairment stated by parents and teachers and affirmed by certified clinical neuropsychologist on the basis of neuropsychological assessment. The assessment included attention subtests from the NEPSY test battery (Visual Attention, Auditory Attention and Response Set, Design Fluency, Knock and Tap);

3. Fluency in Estonian (first spoken language);
4. Age between 8-12 years;
5. Parental written consent and child's verbal agreement to participate in the intervention.

Table 1

Study group characteristics

Pt	Age at intervention (yrs)	Sex	Age at epilepsy onset (yrs)	Duration of epilepsy (yrs)	Specification (EEG)	AED medication
P1	10.75	M	8.75	2.00	Spike-wave activity CT sin	LEV
P2	11.08	F	10.08	1.00	Spike-wave activity T>C sin	OXC
P3	10.33	F	8.75	1.58	Spike-wave activity TC sin	VPA
P4	9.67	M	9.50	0.17*	Bilateral spike-wave activity, C region	OXC
P5	10.50	M	6.58	3.92	Spike-wave activity CT dex	VPA
P6	10.42	F	7.42	3.00	Slow bioelectrical activity and spike-wave activity in sleep T3	CBZ
P7	9.33	M	6.42	2.91	Bilateral spike-wave activity S>T	VPA
P8	11.33	M	7.92	3.41	Spike-wave activity CT dex	OXC
P9	9.75	M	6.50	3.25	Spike-wave activity in T region	VPA
P10	8.42	M	6.58	1.84	Spike-wave activity CT sin	VPA
P11	11.58	F	11.50	0.08*	Slow bioelectrical activity and spike-wave activity in sleep CT sin	OXC
P12	8.17	M	8.08	0.09*	Bilateral spike-wave activity, O region	OXC
P13	11.08	M	10.92	0.16*	Spike-wave activity in sleep T>C	OXC
P14	9.33	M	6.67	2.66	Spike-wave activity PT>T, slow bioelectrical activity dex	VPA
P15	11.25	F	6.17	5.08	Slow bioelectrical activity and spike-wave activity sin	CBZ, LEV
P16	8.08	M	6.33	1.75	Spike-wave activity in PC sin	VPA
P17	8.08	M	5.25	2.83	Spike-wave activity in sleep FT sin	VPA

Pt – patient, M – male, F – female, EEG – electroencephalography, O – occipital, T – temporal, C - central, FT – frontotemporal, CT – centrotemporal, PT – parietotemporal, AED – antiepileptic drug, OXC – oxcarbazepine, VPA – valproate, LEV – levetiracetam, CBZ – carbamazepine

* newly diagnosed epilepsy

Exclusion criteria included other documented diseases involving the central nervous system (e.g., stroke, tumors, encephalitis, cerebral palsy), psychiatric co-morbidity (e.g., ADHD, anxiety disorder, mental retardation [ICD-10 F70-F79]), and treatment with any psychotropic medication other than antiepileptic drugs during the rehabilitation period.

2.1.2. Control groups

Two control groups were included in the study – waiting-list control group and healthy children's control group.

1. The waiting-list control group was composed of 12 children with epilepsy aged 8-12 years (mean age 10.13 yrs; SD=1.907) with attention impairment. There were 9 boys and 3 girls in the group (see Table 2 for further details). The inclusion and exclusion criteria were the same as for the intervention group. The study group and waiting-list group did not differ significantly regarding the age at epilepsy onset.

Table 2
Waiting-list control group characteristics

Pt	**Age at intervention (yrs)**	**Sex**	**Age at epilepsy onset (yrs)**	**Duration of epilepsy (yrs)**	**Specification (EEG)**	**AED medication**
P1	8.92	M	6.25	2.67	Spike-wave activity C>TP sin	Diazepam
P2	9.58	M	9.58	0*	Slow bioelectrical activity sin, Spike-way activity TC sin	LEV
P3	12.99	F	8.58	4.84	Spike-way activity C sin>dex	CBZ
P4	12.50	M	7.00	5.5	Slow bioelectrical activity	CLZ
P5	12.42	M	12.42	0*	Spike-wave activity in sleep, C region	VPA
P6	9.17	M	6.75	2.42	Spike-way activity C3	OXC
P7	12.25	M	7.17	5.08	No interictal epileptical activity	CBZ
P8	8.83	F	8.83	0*	Slow bioelectrical activity and spike-wave activity TO sin	VPA
P9	9.08	M	7.25	1.83	Spike-wave activity in sleep O>T	LEV, VPA
P10	8.75	F	8.75	0*	Spike-way activity CT sin>dex	VPA
P11	9.50	M	8.25	1.25	Spike-way activity PC>T sin, in sleep bilateral sin>dex	VPA
P12	8.42	M	8.42	0*	Spike-way activity CT dex	VPA

Pt – patient, M – male, F – female, EEG – electroencephalography, O – occipital, T – temporal, C - central, FT – frontotemporal, CT – centrotemporal, PT – parietotemporal, AED – antiepileptic drug, OXC – oxcarbazepine, VPA – valproate, LEV – levetiracetam, CBZ – carbamazepine, CBZ - Clonazepam
* newly diagnosed epilepsy

2. To assess the baseline levels of attention tasks and obtain the results of the normal population the healthy children's control group was composed of 19 healthy age equivalent children aged 8-12 years. There were 11 boys and 8 girls in the control group. The children were recruited from an ordinary school in Tartu and attended 2nd to 5th grades. Parental written consent and child's verbal consent to participate in the study were received. Children

with any known neurologic or psychiatric diagnosis were excluded from the control group. The three groups did not differ significantly in terms of age and sex.

2.2. Rehabilitation software

The FORAMENRehab Cognitive Rehabilitation Software® (FORAMENRehab) was used in the study. FORAMENRehab is a tool for cognitive rehabilitation that was developed in year 2000 by Koskinen and Sarajuuri (2002) in Finland. Due to variability of the tasks, the software can be used for children with acquired or developmental disorders. In a present study, the Attention module was implemented. Different components of attention function were assessed and trained with the module. The tasks were divided into four categories or components (see Table 3).

Table 3
Four components of attention

Attention component	Cognitive processes involved
1. Focused	Attention activation, simple visual or auditory reaction; selective attention and reaction inhibition
2. Sustained	To keep attention, finding relevant stimuli, processing speed, correctness
3. Complex	Dividing and shifting attention, cognitive flexibility, working memory, word recognition, comparison with existing knowledge
4. Tracking	Sustained attention, attention activation, auditory / visual dividing of attention, executive function

The exercises are playful and last from 1 to 4 minutes (with the exception of a sustained attention task which can take up to 20 minutes). The menu structure, toolbar and icons of the software are illustrative; each task has a clear written instruction as well as a model animation. The parameters of each task are adjustable. The results are given both in numerical tables and graphs. Several outcomes are recorded for every application: solving and/or reaction time, number of correct responses and subcategories of mistakes (omission errors, premature responses, commission errors, and total number of errors – sum of omission and commission errors). As a result, different aspects of attention components can be investigated separately and the records may be analyzed in detail.

In each task application the user can read the task instructions, modify task parameters, look at the model performance (animation), perform the task and view results.

2.3. Rehabilitation procedure

The rehabilitation of the patients took place during a 5-week period, twice a week. 13 meetings were conducted altogether: the first baseline assessment, 10 active trainings, and the second assessment with baseline tasks (primary outcome) on the twelfth meeting. Also a final follow-up assessment with baseline tasks or the secondary outcome was conducted 1.31 years (SD=0.398) after the training period (third assessment with baseline tasks). For now, 10 children from the study group and 9 children from the waiting-list group have participated in the final follow-up and were included in this study.

Trainings occurred in an outpatient setting in a private room in the Children's Clinic. The time for each individual session varied between 30-40 minutes.

At the first meeting the intervention methods and goals were introduced to the patient. Thereafter, the first performance on the baseline tasks was conducted to assess the child's current profile of attention components. Before starting with each task a model animation of the upcoming exercise was shown and instructions were given to the participant. The training sessions started on the second meeting. Throughout, the therapist did not only introduce the tasks, but also motivated and guided the child individually in order to help him/her to cope better with new complicated situations and to apply the learned techniques in everyday life.

A strict protocol for the procedure of our intervention was created. For assessing the effectiveness of the neurorehabilitation, the baseline tasks were tested once more at the last meeting of the six-week period and finally 1.31 years later to reveal sustained long-term effects of rehabilitation.

The generalized effect of the APT was evaluated by parents' and children's questionnaires about the perceived attention, behavior and school performance before and after the intervention, in addition to objective baseline assessments.

2.4. Rehabilitation designs for FORAMENRehab software

Two different intervention designs were used in the process of conducting the intervention and evaluating the appropriateness of the FORAMENRehab computer program. The established intervention designs differed on the structure and complexness of the baseline assessment tasks. Also, the difficulty levels of tasks in the training protocol were different. Based on the results of the first design the intervention protocol were modified to better differentiate children's baseline impairment profiles, more accurately measure the rehabilitation effect and facilitate the progress on difficulty levels during training. The new procedure protocol for the intervention was created (see Figure 1). The results of the current paper are based on the new design.

Meeting no. 1	2	3	4	5	6	7	8	9	10	11	12		13 Follow-up
Baseline assessment 1	**Interventional trainings**										**Baseline assessment 2**	⟶	**Baseline assessment 3**
	1	2	3	4	5	6	7	8	9	10			

Figure 1
Design of the intervention

In the baseline assessment all four components of attention were represented. Two to three tasks from each component were chosen. For trainings other tasks under the same attention components were used, divided into three difficulty levels: easy (I), medium (II) and difficult (III) (see Table 4 for detailed description of difficulty levels). Some tasks were divided into two difficulty levels as there were no easy or difficult settings for children.

Table 4
Difficulty levels in tasks under four attention components and the affected attention functions

Easy	**Medium**	**Difficult**	**Affected attention functions**
Focused attention			
Visual Reaction Time	Visual Reaction Time; Auditory Warning Visual Choice Reaction Time	Visual Multiple Choice Reaction Time	Attention activation, alertness and selectivity: simple visual or auditory reaction (intrinsic vigilance); tasks with warning (phasic activation of attention) or with distracting stimuli (selective attention and reaction inhibition).
Auditory Reaction Time	Auditory Reaction Time; Visual Warning Auditory Choice Reaction Time	Auditory Multiple Choice Reaction Time	
Sustained attention			
Easy	**Medium**	**Difficult**	**Affected attention functions**
Single Figure Search with letter, number, symbol I, symbol II, or picture (easy level)	(medium level)	(difficult level)	Continuous attention, high ratio of relevant stimuli.
Series Search with letter, number, figure, or symbol series (easy level)	(medium level)	(difficult level)	
Paced Search with Single Target (target length – 2 characters)	(target length – 4 characters; target shifting interval – faster)	(target length – 7 characters)	
-	Repeated pairs search with symbols	Repeated pairs search with letters	Continuous attention, high ratio of disturbing stimuli.
Complex attention			
Easy	**Medium**	**Difficult**	**Affected attention functions**
Paced Search with Dual Targets (target length – 2 characters; speed – 1,5s; direction - right)	(target length – 3 characters; faster stimulus interval; direction - left)	(faster stimulus interval)	Dual tasks: dividing and shifting attention, cognitive flexibility. Single addition: dividing attention, working memory.
Addition; Single Number (series length – 4 digits; speed – 1.5s)	(series length – 6-8 digits; faster stimulus interval)	Addition; Dual Numbers	Single word recognition: continuous attention, comparison with existing knowledge.
Word Recognition; Single Target	Word recognition; Dual Targets	Simultaneous Word Recognition and Mental Arithmetic	
Tracking			
Easy	**Medium**	**Difficult**	**Affected attention functions**
Tracking task			Continuous attention, attention activation.
PASAT; Visual presentation	PASAT; Visual presentation (faster stimulus interval)	-	Visual dividing of attention, executive function of working memory.

The development on difficulty levels of tasks was individual-based and depended on the child’s personal improvement. If the child was flawless on the task, he/she advanced to the next level of the same attention component at the next training session. If the child’s response was incorrect, he/she had to perform the same task level at least 80-90% correctly (depending on the task) for three meetings consecutively until advancing to the next difficulty level. This affirmed that the child had acquired the requested abilities. Thus, the training procedure followed a strict protocol, but at the same time took into account the children’s current capabilities. Also, the rate of advancement on levels could be different in various attention functions.

All 17 children attended all 10 sessions of the training – therefore, compliance with the intervention was 100%.

2.5. Testing of the controls

The children in the waiting-list group participated in three assessments with baseline tasks – the first assessment, primary outcome assessment and follow-up or secondary outcome assessment. During the five-week period between the first and the second assessment (while the intervention group participated in trainings), the waiting-list group received no intervention. One-time testing of healthy control children took place in their school setting. All children completed the baseline assessment with the FORAMENRehab Attention module. One meeting lasted about 40 minutes.

2.6. Data analysis

Statistical data analysis was performed with the R version 3.1.2. For some of the figures also the SAS 9.2 was used. Kolmogorov-Smirnov criterion was used for the assessment of normality. Wilcoxon-Mann-Whitney test was used to compare study group and controls on each of the attention variables. For each task, different components of performance were evaluated if possible (correct responses, omission and commission errors, total number of mistakes, reaction time, and processing speed). Wilcoxon signed-rank test was mainly used to compare the baseline performance to primary (immediate intervention effect) and secondary outcomes within study group and waiting-list control group. For comparing proportions (qualitative variables) the McNemar’s test was used. The confidence level was set to $p<0.05$. Effect sizes for non-normal distributions (Cliff’s Delta) were also calculated.

The study was approved by The Research Ethics Committee of the University of Tartu.

3. RESULTS

3.1. Differences in attention profiles in children with epilepsy and healthy children

Comparison of performances on the baseline assessment between children with epilepsy (including study group and waiting-list control group) and healthy children was conducted.

1) Focused Attention. The Visual Choice Reaction Time and Auditory Choice Reaction Time tasks were used as measurements of focused attention and analyzed with the Wilcoxon-Mann-Whitney test. Results showed that there were no statistically significant differences in the visual or auditory reaction times or the percent of correct responses between the children with epilepsy and their healthy peers. Although, trend showed a quicker reaction time to visual stimuli in healthy children (see Table 5 for further details). Figure 2 shows visual and auditory reaction times at the first assessment with baseline tasks in epilepsy group and healthy children's control group.

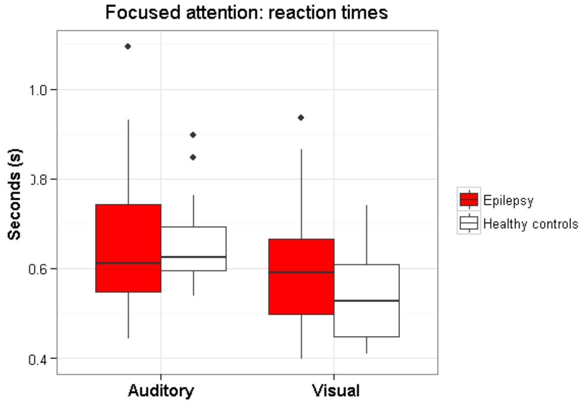

Figure 2
Auditory and visual reaction times at the first assessment with baseline tasks in epilepsy group and healthy children's control group

We also compared the visual reaction time to auditory reaction time within the epilepsy group and healthy children's group separately. The results of Wilcoxon signed-rank test showed that there were statistically significant differences between visual and auditory reaction times both in children with epilepsy (p=0.0069) and healthy children's group (p=0.0003). Therefore, children in our study reacted quicker to visual stimuli compared to auditory stimuli.

Linear regression model equation showed the visual and auditory reaction times to be associated with each other as children with faster reaction to visual stimuli also tended to have faster auditory reactions. Visual and auditory reaction times were significantly correlated for the epilepsy group (r=0.6552, p<0.0001) and healthy children's group (r=0.4945, p=0.0314). Figure 3 shows the association between visual and auditory reaction times for both groups.

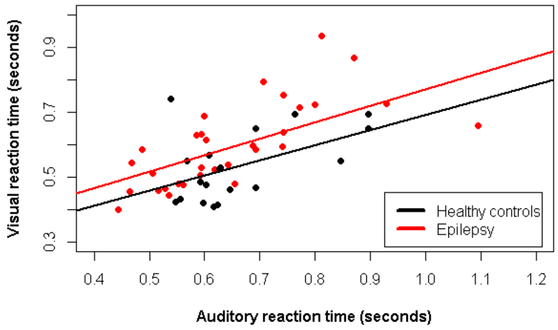

Figure 3
Scatter plot of visual and auditory reaction times with regression lines for children with epilepsy (Pearson's correlation r= 0.6552, p<0.0001) and for healthy control children (r=0.4945, p=0.0314)

Table 5
Comparison of performances on first baseline assessment between patients and healthy control children

Parameters of ForamenRehab Attention tasks *First baseline assessment (B1)*	Patients Median (Lower and Upper Quartiles)[a]	Controls Median (Lower and Upper Quartiles)	d[b]	Sig. P
Focused attention				
Visual reaction time (s)	0.59 (0.49…0.67)	0.53 (0.43…0.65)	0.29	0.082
Auditory reaction time (s)	0.61 (0.54…0.74)	0.62 (0.59…0.69)	-0.08	0.626
Sustained attention				
Correct responses in picture search (%)	97.44 (94.87…98.72)	98.72 (96.15…100.00)	-0.32	0.040*
Omission errors in picture search[c] (%)	2.56 (0.00…3.85)	1.28 (0.00…3.85)	0.24	0.178
Processing speed in picture search (s)	205.00 (160.50…244.00)	159.00 (140.00…215.00)	0.38	0.026*
Processing speed in numbers search (s)	709.00 (597.00…886.00)	603.00 (393.00…747.00)	0.36	0.042*
Complex attention				
Correct responses in paced search (%)	31.80 (16.15…46.06)	55.88 (38.89…74.19)	-0.57	<.001*
Omission errors in paced search (%)	68.20 (53.94…83.85)	44.12 (25.81…61.11)	0.57	<.001*
Total errors in paced search[d] (nr)	32.00 (26.00…35.00)	22.00 (12.00…27.00)	0.58	<.001*
Correct responses in word recognition (%)	41.67 (25.00…66.66)	80.13 (50.00…90.91)	-0.66	0.0001*
Omission errors in word recognition (%)	58.33 (33.33…75.00)	19.87 (9.09…50.00)	0.66	0.0001*
Commission errors in word recognition[e] (nr)	1.00 (1.00…2.00)	2.00 (1.00…3.00)	-0.16	0.335
Correct responses in addition (%)	30.00 (15.00…65.00)	80.00 (70.00…90.00)	-0.77	<.0001*
Tracking				
Correct responses in PASAT (%)	22.50 (10.00…30.00)	65.00 (45.00…95.00)	-0.82	<.0001*
Omission errors in PASAT (%)	50.00 (27.50…65.00)	17.50 (5.00…20.00)	0.63	0.0003*
Commission errors in PASAT (%)	22.50 (15.00…47.50)	12.50 (0.00…30.00)	0.43	0.013*
Commission errors in tracking task (nr)	1.0 (0.00…2.00)	0.00 (0.00…0.00)	0.40	0.013*

a Median (Lower 25%ile and Upper 75%ile)
b Effect size index Cliff's delta
c Omission errors – missed responses to target stimuli
d Total errors – sum of omission and commission errors
e Commission errors - responses to nontarget stimuli
* P<0.05

2) Sustained Attention. The Picture Search and Repeated Pairs of Numbers Search tasks were used to assess the baseline performance. The Wilcoxon-Mann-Whitney test revealed that in the Picture Search the children with epilepsy had a significantly worse overall performance compared to healthy peers as they demonstrated slower processing speed and lower percent of correct responses (see Table 5). There was no difference in omission errors between the two groups. In the more complex task with targeting numbers the results also showed that children with epilepsy had a significantly slower processing speed than healthy children (see Table 5). In more detailed analyses, for distinguishing processing speed from mistakes (as children with faster processing speed could have made lots of mistakes), the processing speed in children with only a 100% correct performance was compared. Statistically significant difference still existed between children with epilepsy and healthy children as patients presented with slower processing speed (p=0.0086). Therefore, slower processing speed for children with epilepsy was found in both modalities - targeting pictures and the more complex and longer task involving processing of numbers (see Figure 4 and 5 for visualization).

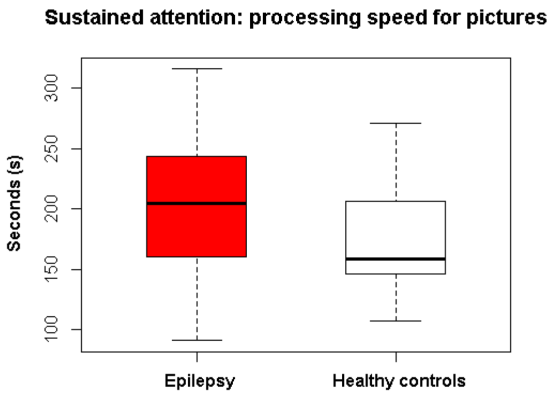

Figure 4
Baseline scores of processing speed in sustained attention with pictures at baseline assessment in epilepsy group and healthy children's control group

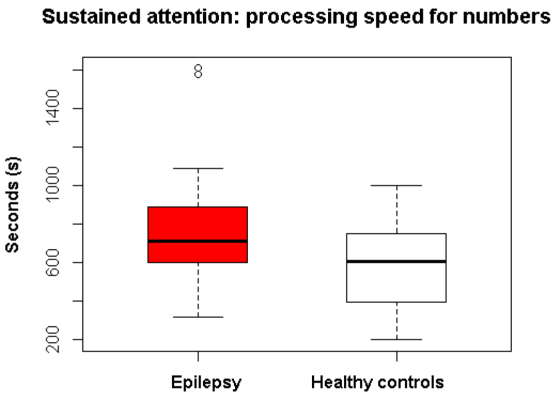

Figure 5
Baseline scores of processing speed in sustained attention with numbers at baseline assessment in epilepsy group and healthy children's control group

3) Complex Attention. Three different tasks were used to assess this component - Paced Search with Dual Targets, Word Recognition with Dual Targets and Addition. In Paced Search the patients performed significantly worse than healthy children in each aspect of the task: they gave significantly less correct responses, and had more omission errors and total errors (sum of omission and commission errors) (see Table 5). In Word Recognition the patients' groups also had significantly lower results compared to healthy children: they gave less correct responses and had more omission errors (see Table 5). In Addition the children with epilepsy also had significantly less correct responses than healthy control group (see Table 5). Figure 6 shows the percent of correct responses in all three tasks under complex attention component in both groups at the first baseline assessment.

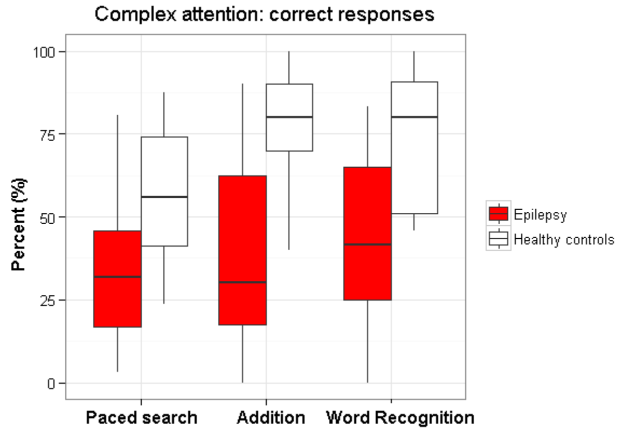

Figure 6
Percent of correct responses in three complex attention tasks at baseline assessment in epilepsy group and healthy children's control group

4*) Tracking*. The baseline assessment included two tasks from the tracking component: Paced Auditory Serial Addition Test (PASAT) and Tracking task. In the PASAT the patients' group had significantly worse results in every aspect of the test compared to healthy controls: they had less correct responses and more commission and omission errors (see Figure 7 and Table 5 for further details).

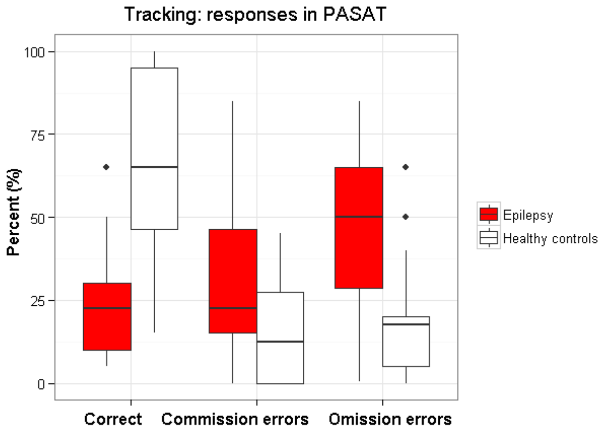

Figure 7
Responses in PASAT under tracking component at baseline assessment in epilepsy group and healthy children's control group

In Tracking task, the percent of commission errors was significantly higher for children with epilepsy compared to healthy controls (Table 5).

3.2. Primary outcome in comparison of the baseline scores before and after the intervention period

3.2.1. Immediate rehabilitation effect (primary outcome) on specific components of attention in study group

Noticeable improvements were seen for study group after the intervention. At first there were no significant differences in performances on baseline levels between study and waiting-list groups in any of the tasks under attention components (p>0.05). Wilcoxon signed-rank sum test showed that immediately after the intervention the study group had significantly improved in complex attention and tracking components compared to baseline performance (for further details see Table 6).

Table 6

Primary outcome of attention function training

Parameters of ForamenRehab Attention tasks *Study Group*	B1 Mean (95%CI)[a]	B2 Mean (95%CI)	d[b]	Sig P
Focused attention				
Visual reaction time (s)	0.64 (0.57…0.71)	0.67 (0.58…0.76)	-0.06	0.818
Auditory reaction time (s)	0.66 (0.59…0.73)	0.67 (0.58…0.75)	0.18	0.517
Sustained attention				
Correct responses in picture search (%)	96.15 (93.59…100.00)*	98.72 (96.15…100.00)*	0.12	0.210
Omission errors in picture search[c] (%)	3.85 (0.00… 6.41)*	1.28 (0.00…3.85)*	-0.06	0.247
Processing speed in picture search (s)	185.71 (165.54…205.87)	210.94 (161.77…260.12)	-0.06	0.480
Processing speed in numbers search (s)	738.94 (588.32…889.56)	854.65 (675.19…1034.10)	0.29	0.225
Complex attention				
Correct responses in paced search (%)	33.26 (24.32…42.21)	57.86 (46.71…69.02)	0.76	0.0003**
Omission errors in paced search (%)	66.74 (57.79…75.68)	41.99 (30.96…53.03)	-0.76	0.0003**
Total errors in paced search[d] (nr)	32.19 (27.37…37.00)	18.35 (13.51…23.20)	-0.75	0.0008**
Correct responses in word recognition (%)	43.85 (29.40…58.30)	61.22 (48.03…74.41)	0.47	0.007**
Omission errors in word recognition (%)	56.15 (41.70…70.60)	38.78 (25.59…51.97)	-0.47	0.007**
Commission errors in word recognition[e] (nr)	2.00 (1.00…2.00)*	1.00 (0.00…2.00)*	-0.38	0.071
Correct responses in addition (%)	41.77 (26.75…56.78)	63.53 (49.57…77.49)	0.59	0.001**
Tracking				
Correct responses in PASAT (%)	25.88 (17.79…33.97)	55.29 (38.70…71.89)	0.00	0.004**
Omission errors in PASAT (%)	36.80 (23.97…49.62)	29.70 (15.70…43.71)	-0.35	0.455
Commission errors in PASAT (%)	20.00 (15.00…60.00)*	10.00 (5.00…20.00)*	-0.52	0.006**
Commission errors in tracking task (nr)	1.00 (0.00…2.00)*	1.00 (1.00…2.00)*	0.12	0.954

a Mean score (95% confidence intervals for Mean)
b Effect size index Cliff's delta
c Omission errors – missed responses to target stimuli
d Total errors – omission and commission errors
e Commission errors - responses to nontarget stimuli
* Median score (Lower 25%ile and Upper 75%ile), *non-normal distribution*
**P<0.05

After the training the assessment showed that the study group patients performed significantly better in Paced Search with Dual Targets (complex attention): they gave more correct responses, had less omission errors and less total errors compared to the first assessment. In Word Recognition with Dual Targets (complex attention) the study patients had significantly more correct responses and less omission errors. In this task most of the epilepsy children had some commission errors in baseline as well as in primary outcome assessment. Thus, for more distinctive examination we divided the groups into two by the number of commission errors where the cut-off point was 6 errors. McNemar's test showed a significant overall improvement: 86.7% of children belonged to the group with greater number of mistakes at baseline assessment, but only 26.67 percent at primary outcome assessment ($p<0.05$). In Addition (complex attention) the intervention group gave significantly more correct responses after the rehabilitation (see Table 6). Figure 8 shows the percent of correct responses for each task under complex attention in the baseline, primary and secondary outcome assessments.

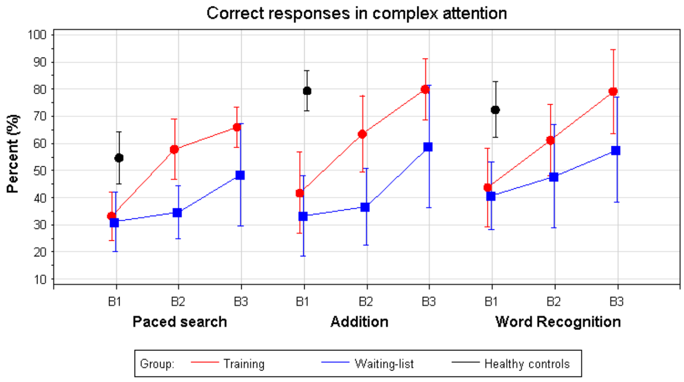

Figure 8
Percent of correct responses in three complex attention tasks at three assessment points (B1-baseline, B2-primary outcome, B3-secondary outcome) in study and control groups

Also, the study group patients had improved significantly after training in the PASAT (tracking component): they gave more correct responses and had less commissions. Figure 9 shows the percent of correct responses for each aspect of PASAT in the baseline, primary and secondary outcomes.

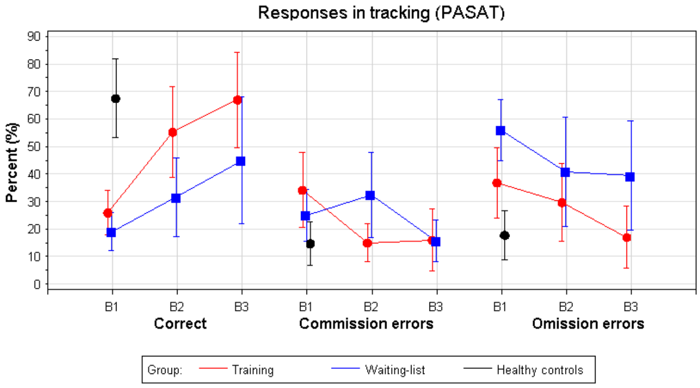

Figure 9
Percent of correct responses, commission and omission errors in PASAT under tracking component at three assessment points (B1-baseline, B2-primary outcome, B3-secondary outcome) in study and control groups

No statistically significant dynamic changes were revealed in focused attention for reaction times (Figure 10) and in sustained attention for processing speed (Figure 11).

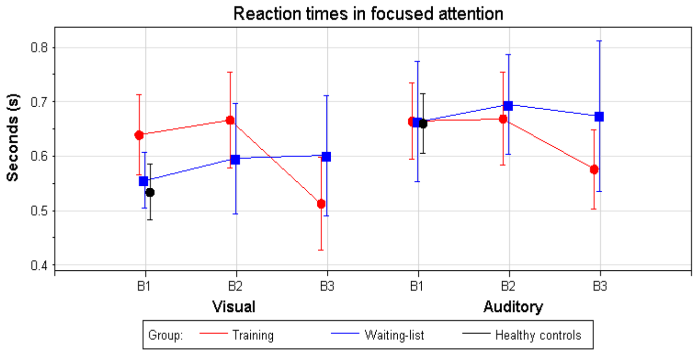

Figure 10
Visual and auditory reaction times in focused attention at three assessment points (B1-baseline, B2-primary outcome, B3-secondary outcome) in study and control groups

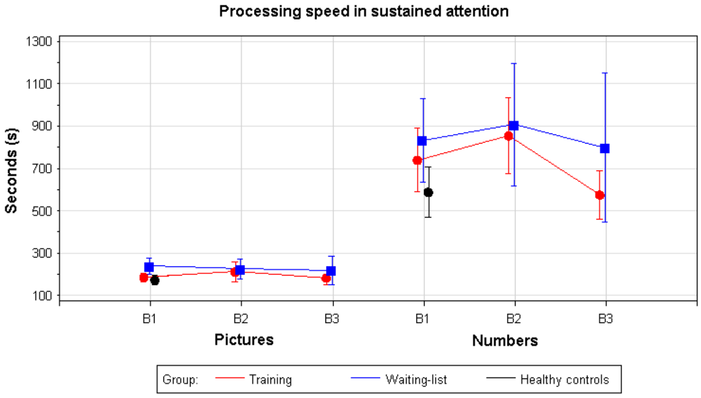

Figure 11
Processing speed in two tasks under sustained attention at three assessment points (B1-baseline, B2-primary outcome, B3-secondary outcome) in study and control groups

3.2.2. Second assessment with baseline tasks in waiting-list control group

After the 5-week period without intervention, the waiting-list control group had significant differences between the first and second assessment with baseline tasks in only two aspects of one complex attention task: in Paced Search they had higher percent of correct responses [Mean1=31.12 (95%CI=20.16…42.08); Mean2=34.67 (95%CI=24.90…44.43); d=0.67, p=0.026] and lower percent of omissions [Mean1= 68.88 (95%CI=57.92…79.84); Mean2=65.33 (95%CI=55.57…75.10); d=-0.67, p=0.026]. For visualized comparison with study group see Figures 8-11.

3.3. Patients' improvement during rehabilitation process

We also examined the study group children′s individual improvement during the rehabilitation process and advancement on reaching higher difficulty levels. Slower rehabilitation effect out of the four attention components occurred in two: *complex attention* and *tracking* - where children's average attained level at the end of the training was only 1.55 (95%CI: 1.36…1.74) out of the maximal 4 and 1.31 of the maximal 3 respectively (see Table 7 for further details).

For assessing the difficulty of tasks the average number of trainings needed on first the difficulty level before progressing onto the second level was measured in each task (see Table 8).

Table 7

Average attained difficulty levels at the end of intervention in four attention components

Attention component	Nr of task	Mean level	95% confidence interval	
Focused attention	1	3.88	3.69	4.06
	2	4	-	
Sustained attention	1	3.31	2.94	3.69
	2	3	2.81	3.19
	3	3.56	3.23	3.9
Complex attention	1	1.19*	0.97	1.4
	2	1.62*	1.3	1.95
	3	1.88*	1.61	2.14
Tracking	1	1.31*	0.99	1.63

* tasks with slower progress

Table 8

Average number of trainings attended before moving from first difficulty level to second level

Attention component	Nr of task	Mean sessions	95% confidence interval	
Focused attention	1	1.75	1.22	2.28
	2	1.56	1.01	2.11
Sustained attention	1	2.12	1.51	2.74
	2	1.38	0.99	1.76
	3	1.62	1.2	2.05
Complex attention	1	7.69*	6.56	8.82
	2	5.81*	4.46	7.16
	3	4.62*	3.37	5.88
Tracking	1	5.62*	4.69	6.56

* tasks with slower progress

All children had positive individual progress throughout the intervention as they gradually reached higher difficulty levels. Still, the speed of progress was different by child.
At the end of training, children with faster progress had attained approximately 1.5-2 times higher difficulty levels compared to the children with slower progress (see Figure 12).

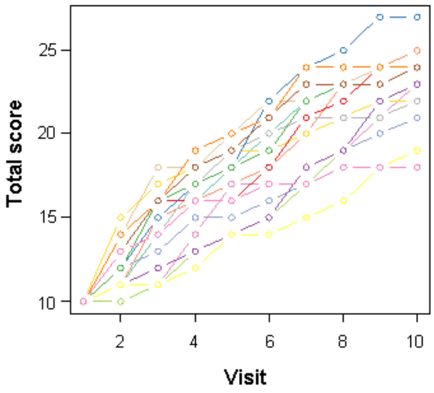

Figure 12

Children's individual progress trajectories for 10 training sessions (summary score per visit)

3.4. Follow-up or secondary outcome

In the follow-up assessment 1.31 years later - secondary outcome - the study group showed significant positive long-term effect of intervention (see details in Table 9). In *focused attention* the reaction time to visual stimuli was significantly faster compared to the first baseline performance. In *sustained attention* the study group patients demonstrated faster processing speed in targeting numbers. Also, improvements existed in all *complex attention* tasks: they had a higher percent of correct responses, less omission errors and lower percent of total errors. In *tracking component* they had significantly more correct responses and trend for less commission errors. It is noteworthy that the waiting-list group performed significantly better compared to baseline performance level only in two aspects of *complex attention* tasks. In Paced Search they had a higher percent of correct responses [Mean1= 31.12 (95%CI=20.16…42.08); Mean3=48.58 (95%CI=29.76…67.40); d=0.56, p=0.039] and lower percent of omissions [Mean1= 68.88 (95%CI=57.92…79.84); Mean3=51.42 (95%CI=32.60…70.25); d=-0.56, p=0.039]. In Addition they had more correct responses [Mean1=33.33 (95%CI=18.44…48.23); Mean3=58.89 (95%CI=36.33…81.45); d=0.8, p=0.008]. Figures 8-11 show long-term results for both groups and the comparison with primary and secondary outcome on baseline tasks.

Table 9

Study group's first baseline performance and secondary outcome

Parameters of ForamenRehab Attention tasks *Study Group*	B1 Mean (95%CI)[a]	B3 Mean (95%CI)	d[b]	Sig P
Focused attention				
Visual reaction time (s)	0.64 (0.57…0.71)	0.51 (0.43…0.60)	-0.8	0.009*
Auditory reaction time (s)	0.66 (0.59…0.73)	0.58 (0.50…0.65)	-0.2	0.193
Sustained attention				
Correct responses in picture search (%)	96.15 (93.59…100.00)*	99.36 (97.44…100.00)*	0.4	0.672
Omission errors in picture search[c] (%)	3.85 (0.00… 6.41)*	0.64 (0.00…2.56)*	-0.4	0.195
Processing speed in picture search (s)	185.71 (165.54…205.87)	182.10 (148.09…216.11)	-0.1	0.672
Processing speed in numbers search (s)	738.94 (588.32…889.56)	575.00 (459.70…690.30)	-0.8	0.037*
Complex attention				
Correct responses in paced search (%)	33.26 (24.32…42.21)	66.07 (58.69…73.44)	0.9	0.002*
Omission errors in paced search (%)	66.74 (57.79…75.68)	33.94 (26.56…41.31)	-0.9	0.004*
Total errors in paced search[d] (nr)	32.19 (27.37…37.00)	17.67 (13.60…21.73)	-1	0.008*
Correct responses in word recognition (%)	43.85 (29.40…58.30)	79.24 (63.74…94.73)	1	0.002*
Omission errors in word recognition (%)	56.15 (41.70…70.60)	20.76 (5.27…36.26)	-1	0.002*
Commission errors in word recognition[e] (nr)	2.00 (1.00…2.00)*	0.00 (0.00…2.00)*	-0.5	0.156
Correct responses in addition (%)	41.77 (26.75…56.78)	80.00 (68.82…91.18)	0.8	0.008*
Tracking				
Correct responses in PASAT (%)	25.88 (17.79…33.97)	67.00 (49.71…84.29)	1	0.002*
Omission errors in PASAT (%)	36.80 (23.97…49.62)	17.00 (5.66…28.34)	-0.5	0.219
Commission errors in PASAT (%)	20.00 (15.00…60.00)*	10.00 (0.00…30.00)*	-0.6	0.072
Commission errors in tracking task (nr)	1.00 (0.00…2.00)*	0.50 (0.00…1.00)*	0.3	1.000

a Mean score (95% confidence intervals for Mean)
b Effect size index Cliff's delta
c Omission errors – missed responses to target stimuli
d Total errors – omission and commission errors
e Commission errors - responses to nontarget stimuli
* Median score (Lower 25%ile and Upper 75%ile), *not normally distributed*
**P<0.05

3.5. Generalized effect of attention rehabilitation

Subjective feedback from parents about the intervention suggested positive behavioral change in children. As a manifestation of generalized effect the parents stated that their children were less distracted and more prone to social communication. Also, according to the parents' reports reading, writing, mathematics, and visuomotor skills had improved. Children stated improved concentration skills and better functioning in school tasks.

4. DISCUSSION

This research has been conducted to test a modern computer-based intervention method for children with attention impairment and examine the rehabilitation effect on different attention components.

Effective computer-based rehabilitation method for children and an individual-based intervention protocol was designed

In the beginning of the research project the Attention module of the ForamenRehab software for rehabilitation of children was adapted and a first rehabilitation design was created. After the first results modifications for more complicated baseline levels were made. The new rehabilitation design better describes the children's outcome and facilitates progress. The current study has demonstrated that the computer-based intervention program is a suitable method for children with epilepsy. The rehabilitation design successfully endorsed continuous progress during the intervention process in different attention components. One of the strengths of this method is that it is tailored to follow each individual's abilities and attention impairment profile. Amonn et al. (2013) has stated that for proving clinical value the cognitive training programs should "focus more strongly on individually existing neuropsychological deficits". However, the strict training protocol developed in the current study also allows to observe progress for each individual child, children's overall progress within attention components separately and to compare outcomes between children.

The rehabilitation of children is different from adults' interventions as children do not enter the process by their own initiation. Therefore, they need continuous guidance and motivation throughout the rehabilitation period. According to Cicerone et al. (2000) *active therapist involvement* enhances the overall effectiveness of rehabilitation. Our design involves a therapist for helping to make individual plans by following each child's progress and to follow the training protocol. The therapist motivates the child and supports the use of acquired skills in everyday life situations. Charvátová et al. (2007) have pointed out that children do not make a strict distinction between games, work, leisure and educational activities, but the crucial characteristics are motivation, competitiveness, emotions, and natural curiosity. This assures our view about the importance of the therapist in the rehabilitation process. Children with epilepsy have also previously shown improved behavioural performance when presented with rewards which could significantly benefit in cognitive remediation programs (Triplett et al., 2014). Our study implies that guided intervention is especially valuable in children with attention impairment as they need continuous extraneous help in directing attention to tasks.

Besides, an important part is also the therapist-guided metacognitive study-experience for children, which teaches different learning and solving strategies. That leads the child to become more aware of different options and to learn to compensate for cognitive weaknesses. Therefore, it could help them to become more independent in the learning process. Our experience showed that if the child understands the solution process by using a specific strategy, he/she gets a successful experience and gains motivation and self-confidence. This is a valuable additional gain to the intervention as children with epilepsy have been reported to perceive stigma associated with the "need for information and support" (Austin, Perkins, & Dunn, 2014) and present with emotional problems (Borgatti et al., 2003).

The Neuropsychology Task Force of the International League Against Epilepsy (ILAE) has stated the importance of providing the patients' families with implications of assessment results and clinical recommendations of what can be done for cognitive improvement (Wilson et al., 2015). In our study the parents received personal feedback about their child's attention profile, progress throughout the training and suggestions for future training possibilities at home (e.g., via the Internet). Also, they were provided with additional advice for supporting the general learning abilities and considering their child's individual differences.

Characteristics of attention function impairment in children with epilepsy compared to healthy children

In order to illustrate the attention impairment profiles, additionally to neuropsychological assessment, the baseline tasks of the FORAMENRehab Attention module were used. Our results demonstrated that the baseline assessment successfully differentiate children with epilepsy from their healthy peers as their performance levels were significantly lower in three out of the four measured attention components. Notably, an efficient rehabilitation design should focus on specific components of the impaired attention function. Therefore, the three attention components: sustained, complex and tracking, need selective and longer training.

In *sustained attention* children with epilepsy were distinguished from their healthy peers in targeting significantly less stimuli and showing slower processing speed in tasks with numerous different pictures or numbers as stimuli. Difficulties in sustained attention (Semrud-Clikeman & Wical, 1999) and slower processing speed (Borgatti et al., 2003) in children with epilepsy have been reported before. The processing speed differed significantly between patients and healthy children also when we only included children with same performance levels regarding correct choices. This was important to be analyzed separately as some children with visible concentration problems rushed through tasks, quit prematurely, and although gaining faster processing speed, also made more mistakes.

Children with epilepsy performed remarkably worse than healthy children also in *complex attention* component. Same results - a distinctive part of attention impairment in difficulties dividing attention between two or more stimuli at the same time - has been previously reported (Ceminara et al., 2013; Ceminara et al., 2010). Under complex attention, significant deficits also existed in tasks that demanded reading and calculation skills that besides require working memory involvement. Similar difficulties also existed at school for these children, as was reported by the parents. Impairments in working memory have been previously described for children with epilepsy (Sherman, Brooks, Fay-McClymont, & MacAllister, 2012). Furthermore, previous studies have proved them to have lower results in verbal learning (Giordani et al., 2006) and they present with specific learning difficulties (Pavlou &

Gkampeta, 2011; Piccinelli et al., 2008), which affect activities that require reading, writing or mathematical skills. Overall lower educational outcome and need for special education for children with epilepsy have been reported over time (Pastor, Reuben, Kobau, Helmers, & Lukacs, 2015; Berg et al., 2005; Sillanpää, 1992; Ross, Peckham, West, & Butler, 1980).

In the current study, patients were also worse in *tracking* component compared to healthy peers. Therefore, in tasks that require continuous tracking of stimuli, they detect less correct stimuli and commit or react to wrong stimuli more often. They would therefore have problems with tasks requiring intact working memory that enables prolonged information processing and takes into account the data acquired moments before, but could be omitted by these children. In general our data confirms the previous findings (Cerminara et al., 2013; Mitchell, Zhou, Chavez, & Guzman, 1992) that children with epilepsy make more omission errors.

In *focused attention* the results showed possible modality based difficulties in children with epilepsy as they had a trend for slower reaction time to visual stimuli, but no differences in auditory stimuli, compared to healthy children. However, the results might have been in part affected by a better distinctive quality of the visual task compared to auditory. Still, impairments in tasks in visual reaction have been also reported earlier (Kolk et al., 2001; Massa et al., 2001). Yet some studies have found no difference between children with epilepsy and healthy peers regarding reaction time in focused attention (Ceminara et al., 2013; Ceminara et al., 2010). Overall, this suggests that if the children with epilepsy attend to the task in hand, their reaction to sounds, at least, would be as quick as their healthy peers’, but the key is to get them to focus. This is also where the help of the therapist is crucial, because staying focused on a task is impaired in these children (Semrud-Clikeman & Wical, 1999).

The additional finding about the positive association between the two modalities – visual and auditory reactions - shows that the reaction time itself is a multisensory unitary quality of the nervous system with both reactions influenced by similar factors. Colonius and Diedrich (2010) stated in their study that the theory of optimal time window of visual–auditory integration could be “extended to reaction times collected under the focused attention paradigm”. This could mean that if children with epilepsy have an impairment in one of the modalities (in our case implications to visual), they could have difficulties integrating information from two modalities into one whole picture. Taking together, what we hear is influenced by what we see, as is stated in the McGurk effect (McGurk & MacDonald, 1976), and therefore focusing attention to visual and auditory stimuli simultaneously is important in perception. It is also noteworthy that the reaction to auditory stimuli was generally slower than reaction to visual stimuli in both groups which may suggest developmentally quicker processing of visual information for healthy children as well as children with epilepsy. But this should also be further investigated as again the results might have been affected by the different difficulty levels of the tasks. Various previous studies have found different results in comparing visual to auditory reaction time. Some suggest that in healthy children the visual reaction is typically quicker than auditory (Yagi, Coburn, Estes, & Arruda, 1999), yet others claim the opposite (Shelton & Kumar, 2010; Thompson et al., 1992).

Effects of rehabilitation in study group

The effect of the rehabilitation was studied by comparing the performances on baseline tasks before and after the intervention period. After active training for five weeks, the study group children’s performance improved significantly in two attention components: complex attention and tracking tasks showed significant improvement in various aspects. Van’t Hooft et al. (2007) have previously also described positive change in children after rehabilitation in complex tasks of attention, in contrast to the simpler reaction time tests. Better outcome in complex attention could show improved abilities to focus on task, and divide and shift attention between stimuli. Significantly less commission errors may suggest improvement also in impulse control and behaviour regulation, as commissions in tasks have been described to indicate impulsivity by rapid, but incorrect responses (Halperin, Wolf, Greenblatt, & Young, 1991). Also, tracking component of attention or tracking the processes of a task improved during the training, and therefore the ability to simultaneously process the information received little time ago and at the moment was positively affected.

In focused attention no significant change was discovered when measuring visual and auditory reaction times. Similar results have also been reported before by Van’t Hooft et al. (2007) and Cicerone (2002). Also, this was a probable result as significant differences did not exist already before the training in comparison with healthy children (especially in auditory reactions). And as the authors before (Van’t Hooft et al., 2007), we also believe that although the training might not improve reaction times, it still provides the children with valuable solution techniques and strategies.

Furthermore, by measuring children’s individual progress on difficulty levels, distinctive differences in the more complicated attention components were revealed. At the end of the rehabilitation the study group had attained lower difficulty levels in complex attention and tracking components compared to focused and sustained attention. Although the comparison with baseline tasks showed significant improvements in these particular attention components: complex attention and tracking, prolonged training may lead to more effective remediation where children would reach even higher levels. However, in sustained attention components patients showed worse results at baseline compared to controls and no significant changes after training. Still, they had positive progress during training which means that the duration of the intervention should be longer for also the sustained attention component.

The positive rehabilitation effect in intervention group was further confirmed in comparison with the waiting-list group who demonstrated very little changes between the two baseline performances. Furthermore, the follow-up assessment after 1.31 years showed sustained positive long-term effect of rehabilitation in study group, in contrast to the children in waiting-list group who demonstrated remarkably less positive dynamics over time. This emphasizes the effectiveness of intervention and diminishes the chance of positive outcome solely due to normal developmental processes. The sustained positive effect based on objective measures was thereafter conclusively confirmed by parents as they reported noticeable positive changes in children's every-day life situations. The generalized effect of rehabilitation manifested in children's behavior and overall performance in school.

A valuable part is also that the family became aware of the children's cognitive strenghts and weaknesses and the importance of cognitive rehabilitation. In the end, full compliance and positive feedback from children showed that the computer-based neurorehabilitation is pleasing for children and enhances long-lasting involvement.

Clinical implications for rehabilitation

Developing an intervention design with a specific protocol and well-defined instructions for therapists is recommended. Otherwise, the results may be influenced by different information the children recieve for guidance. In a review by Sohlberg, Ehlhardt & Kennedy (2005) the importance of giving systematic instructions in cognitive rehabilitation is emphasized. These should consist of "simple, consistent instructional wording and scripts to reduce confusion and focus learner on relevant content".

Also, based on qualitative feedback we noted that an important task for a therapist is to find specific motifs for each individual child. E.g., for best cooperation some children preferred joking, some needed little brakes after a while and others hoped for frequent appraisal and endorsement. Yet some children also required more specific boundries to follow. In some cases children preferred the therapist to be of the same gender as them. After all, individual approach in motivating was essential for enhancing positive intervention effect and for seeing the best possible improvement levels.

Furthermore, it was noticable that the children’s motivation was also influenced by their parents’ attitude towards regular training. Educating parents about the importance and outcome of rehabilitation facilitates cooperation and compliance.

Limitations and future directions

The study also has several limitations. For one, the study group was composed of children who lived in Tartu city or near Tartu, which means that the group was not completely randomly chosen. Secondly, the diagnosis of the children was known to the therapist so this was not a blinded study. Thirdly, typically to intervention studies, the sample size was relatively small, but it should be noted that the trainings were time-consuming. Still, if the study group had been larger, more significant findings might have been revealed in all attention components. Therefore, it is recommended to continue the research with a larger sample size.

5. CONCLUSIONS

Our multifaceted neurorehabilitation design with FORAMENRehab is effective for children. Training specific components improved attention function in children with epilepsy. Significant improvement was seen in complex attention and tracking components. Furthermore, long-term positive effects also persisted in these domains. The present computer program is a modern and suitable method for children with epilepsy. The intervention design combines principles of holistic rehabilitation, modern computer-assisted neurocognitive rehabilitation and individual approach. It holds practical future benefits as an effective intervention is a prerequisite for out-patient trainings in clinical settings. Intervention effectiveness is best described with positive results from assessments with baseline tasks and development on task levels. Hence, outcome assessment methods should be used simultaneously to examine the rehabilitation effect. Individual improvement is important to follow as complicated tasks relate with slower progress and thus need longer training period (at least 10 sessions). Therefore, the personalized approach and importance of considering individual differences are fundamental in paediatric neurorehabilitation. We recommend the computer-assisted ForamenRehab in attention impairment intervention for supporting the basic learning skills for children with acquired brain injury and cognitive impairments.

Acknowledgements

This study was supported by the Estonian Science Foundation (GARLA 9016) and by the Estonian Ministry of Education and Research TARLA 2695.

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Lihtlitsents lõputöö reprodutseerimiseks ja lõputöö üldsusele kättesaadavaks tegemiseks

Mina, Marianne Saard

(sünnikuupäev: 21.02.1989)

1. annan Tartu Ülikoolile tasuta loa (lihtlitsentsi) enda loodud teose ATTENTION IMPAIRMENT REHABILITATION WITH COMPUTER-BASED FORAMENREHAB PROGRAM IN 8- TO 12-YEAR-OLD CHILDREN WITH EPILEPSY, mille juhendaja on Anneli Kolk,

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