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Rehabilitation of visuospatial deficits using computer-based FORAMENRehab program in children with epilepsy

Master's Thesis

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

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Abstract

Children with epilepsy have shown deficits in attention and visuospatial functions, which could disrupt their normal life. For example, visuospatial functions have been found to predict achievements in mathematics. Very few systematically controlled evidence-based neurorehabilitation treatments for children exist at the moment. Using modern cognitive rehabilitation methods in children is important for their development and remediation. The aim of the current study was to test the effectiveness of computer-based rehabilitation program in the treatment of visuospatial deficit for children with epilepsy.

58 children aged 8-12 participated in the study: 17 children diagnosed with epilepsy were in the training group, 22 children in the waiting-list control group and 19 healthy controls. The training group received guided visuospatial functions training using the FORAMENRehab software. Trainings took place twice a week for a 5-week period. Baseline assessments were carried out before and immediately after the intervention and a follow-up assessment 1.31 years after.

Remarkable improvements were observed in the training group following intervention. The training group showed positive immediate rehabilitation effect in 3 out of 4 visuospatial components: *visual organization*, *visual attention* and *visuospatial perception*. Furthermore, a positive long-term rehabilitation effect in the training group was observed in all 4 of the visuospatial components. The general ability of the children improved, even though some of the visuospatial components showed no significant improvements after intervention. This positive generalized effect of the intervention was confirmed by the parents' and children's qualitative feedback with some of the learned skills transferring to the everyday life of the children. 100% compliance further confirms the motivation of the children to participate in the study and the effectiveness of the FORAMENRehab software for neurorehabilitation.

***Keywords*: epilepsy, visuospatial deficits, cognitive rehabilitation in children, computer-based rehabilitation, FORAMENRehab**

Visuaal-ruumiliste defitsiitide rehabilitatsioon FORAMENRehab arvutiprogrammiga epilepsiaga lastel

Kokkuvõte

Epilepsiaga lastel kaasnevad haigusega sageli tähelepanu ja visuaalruumiliste funktsioonide defitsiit, mis võib hakata nende elu häirima. Näiteks on leitud, et head visuaalruumilised funktsioonid ennustavad edukust matemaatikas. Hetkel leidub veel vähe lastele mõeldud süstemaatiliselt kontrollitud tõenduspõhiseid neurorehabilitatsiooni tehnikaid. Nimelt kaasaegsete kognitiivsete sekkumismeetodite kasutamine on arengu ja paranemise protsessis tähtsal kohal. Uuringu eesmärk oli testida arvutipõhise rehabilitatsiooniprogrammi efektiivsust visuaalruumiliste funktsioonide ravis epilepsiaga lastel.

58 last vanuses 8-12 osalesid uuringus: 17 epilepsia diagnoosiga last treeninggrupis, 22 ootelehe kontrollgrupis ja 19 tervet kontrolli. Treeninggrupp läbis juhendatud visuaal-ruumiliste funktsioonide treeningu kasutades FORAMENRehab tarkvara. Treeningud toimusid kaks korda nädalas 5-nädala jooksul. Tulemusi hinnati enne ja pärast rehabilitatsiooniperioodi ning 1,31 aastat pärast sekkumist.

Treeninggrupis oli näha märkimisväärselt paremaid sooritusi pärast sekkumist. Kohe pärast sekkumist oli positiivseid muutuseid näha kolmes visuaal-ruumiliste funktsioonide komponentides: *visuaal-konstruktiivsetes võimetes, visuaalses tähelepanus* ning *nägemis-ruumitajus*. 1,31 aastat pärast sekkumise lõppu oli näha olulist paranemist kõigis neljas visuaal-ruumilise funktsiooni valdkonnas: *visuaalse materjali äratundmises*, *visuaal-konstruktiivsetes võimetes*, *visuaalses tähelepanus* ja *nägemis-ruumitajus*.

Neurorehabilitatsioon FORAMENRehab tarkvaraga on epilepsiaga lastel efektiivne ja huvitav, mida tõestab ka 100%-line ravisoostumus. Visuaal-ruumiliste võimete treeningu tulemusel paranesid treenitavatel ka teised kognitiivsed funktsioonid ja õpitud oskused kandusid edasi igapäevaellu. Generaliseerunud e. üldefekti hindasime ning see kinnitus laste ja vanemate positiivse tagasiside põhjal.

Märksõnad: **epilepsia, visuaal-ruumilised defitsiidid, kognitiivne rehabilitatsioon lastel, arvutipõhine rehabilitatsioon, FORAMENRehab**

1. INTRODUCTION

1.1. Visuospatial functions

Van der Ham & Borst (2011) have stated that the ability of the visual system to process spatial relations between objects or parts of an object is imperative in the processing of visual information. Currently, there is no general agreement between researchers on the definition of visuospatial functions, although it is agreed that they are an important element of intellectual ability and that these functions involve multiple processes (Linn & Petersen, 1985; Uttal et al. 2013). Linn & Petersen (1985) posited that visuospatial functions are skills in representing, transforming, generating and recalling information that is symbolic and nonlinguistic. According to Linn & Petersen (1985) there are three categories of visuospatial abilities: spatial perception, mental rotation and spatial visualization. Spatial perception is the ability to determine spatial relationships with respect to the orientation of their own bodies, while ignoring distracting information. Mental rotation is the ability to rapidly and accurately rotate a two or three dimensional figure and spatial visualization is the ability to manipulate complex spatially presented information with multiple solution strategies (Linn & Petersen, 1985).

Visual information, which originates from specific locations in space, gives us the possibility to assign meaning to objects and also allows us to direct our movements to the objects in space (Kolb & Whishaw, 2003). Furthermore, objects have a location that is relative to an individual, which is called egocentric space, and a location that is relative to one another, which is called allocentric space (Kolb & Whishaw, 2003).

Uttal et al. (2013) have proposed a classification system for visuospatial skills that makes use of two fundamental distinctions: distinction between intrinsic and extrinsic information and distinction between static and dynamic tasks (Newcombe & Shipley 2015; Uttal et al., 2013). Uttal et al. (2013) have described intrinsic information (within object) as something one would think about when defining an object: the specification of the parts and the relation between the parts defines a particular object. The same authors describe extrinsic information (between objects) as the relation among objects in a group, relative to one another or to an overall framework. For example, intrinsic information is the spatial information that allows us to distinguish between categories of objects and the extrinsic information is the spatial relations among those objects and the relations of each object to the wider world (Uttal et al., 2013).

The second distinction proposed by Uttal et al. (2013) is the distinction between static and dynamic tasks. When the information is about objects that are fixed, then it is static information. But objects can be moved or they can change their intrinsic specification when they are folded or rotated in place. Also, movement can change the object’s position with regard to other surrounding objects and overall spatial frameworks (Uttal et al., 2013).

Visuospatial functions could also include visual recognition, visual organization, visual attention and visuospatial perception. Visual recognition is the ability to recognize faces, objects or categories and to respond to visual information (Kolb & Whishaw, 2003). Visual organization or visuospatial constructive cognition has been defined as the ability to see an object or a picture as a sum of parts and then to construct a duplicate of the original from these parts (Mervis, Robinson & Pani, 1999). Visual attention has been described as the privileged processing of information coming from a certain area of the visual field (Cave & Bichot, 1999). Visuospatial perception is defined by Donnon, DesCôteaux & Violato (2005) as the ability to represent physical environment in one's mind and the movements to be performed in that environment.

Because there is no general agreement on the definition of visuospatial functions, it is only possible to fit the tasks used in this thesis to a previous framework. According to the intrinsic-extrinsic and static-dynamic framework (Uttal et al., 2013), the tasks in the FORAMENRehab visuospatial module would consist of 1 task that is mostly intrinsic-dynamic (Cubes), 3 tasks that are mostly extrinsic-static (Line Orientation Judgement; Construction, Spatial Attention) and 2 tasks that are mostly extrinsic-dynamic (Geometric Pattern Recognition, Circle Following, Maze).

There are many reasons why the research of visuospatial functions in children are important. For example, such skills as visual-motor abilities, visuospatial organizational skill, visual discrimination, and the ability to integrate perceptual and motor processes are all recquired if a young child wishes to learn to count or to perform simple arithmetic calculations (Assel, Landry, Swank, Smith, & Steelman, 2003). Moreover, visuospatial skills have been found to predict achievements in mathematics (Assel et al., 2003; Carlson, Rowe & Curby, 2013). A study carried out on first grade students found a strong relationship between academic performance in math, reading, writing and skills such as visual-motor integration, visual perception, hand control and overall motor proficiency (Pienaar, Barhorst & Twisk, 2014). In addition, research by Simms, Clayton, Cragg, Gilmore & Johnson (2016) found that visuospatial skills and visuomotor integration were significantly correlated with number line estimation tasks, which has a significant relationship between mathematical achievement. Lastly, Wai, Lubinski and Benbow (2009) conducted a longitudinal study and found that spatial skills predict achievement in the STEM (science, technology, engineering and mathematics) domains.

1.2. Epilepsy and visuospatial functions

Epilepsy is a brain disorder characterized by recurrent and unpredictable interruptions of normal brain function, which are called epileptic seizures (Fisher et al., 2005). Epilepsy can be classified as generalized epileptic seizures or focal epileptic seizures (Berg et al., 2010). Generalized epileptic seizures have been conceptualized as originating from bilaterally distributed networks, which can include cortical and subcortical structures. Focal epileptic seizures are conceptualized as originating within networks that are limited to one hemisphere (Berg et al., 2010). Chung, Hsieh, Lai, & Huang (2014) have stated that epilepsy is a common and serious neurological disorder worldwide, with an estimated prevalence rate of 0.5-1% in the general population. The incidence of childhood epilepsy in Estonia is 45: 100 000 (Beilmann et al., 1999).

Cognitive deficits in children diagnosed with epilepsy are present early in the course of the disorder including at the time of diagnosis and at the beginning of treatment (Rathouz et al., 2014). Some of the reported cognitive deficits in children with epilepsy include attention impairments (Bender et al., 2007; Kolk, Beilmann, Tomberg, Napa & Talvik, 2001; Rathouz et al., 2014; Zilli, Zanini, Conte, Borgatti & Urgesi, 2015), impairments in executive functions (Bender et al., 2007; Zilli et al., 2015) and in social perception (Genizi, Shamay-Tsoory, Shahar, Yaniv & Aharon-Perez, 2012; Zilli et al., 2015). Rathouz et al. (2014) reported in their study that cognitive deficits in children with epilepsy remain stable up to 6 years without evidence of progressive worsening or recovery. It is necessary to rehabilitate these deficits early on, because cognitive deficits caused by epilepsy increase the clinical burden and also impair the patients' quality of life (Farina, Raglio & Giovagnoli, 2015).

There have been studies that have assessed visuospatial skills in children with epilepsy and the findings have not been consistent. For example, Bender et al. (2007) conducted a study where they measured neuropsychologic functioning of children with epilepsy. They found that as a group, children with epilepsy were impaired in attention, executive functioning, and sensorimotor abilities, whereas memory skills were less compromised and visuospatial abilities were comparable to non-neurologically impaired peers (Bender et al., 2007). In contrast, Riva, Saletti, Nichelli & Bulgheroni (2002) assessed the neuropsychologic performance in children with frontal lobe epilepsy and found that patients with left side focus had deficits in categorization, verbal long-term memory and visuospatial analysis. In addition, Parisi et al. (2012) assessed neuropsychological impairment in patients affected by epilepsy and also in patients affected by both epilepsy and migraine. They found that children diagnosed with epilepsy, with and without migraine, had deficits in visual-spatial analysis and visual attention (Parisi et al., 2012). In addition, it has been found that children with newly diagnosed partial epilepsy prior to medication develop deficits in attention, short-term memory and visuo-perceptual functions (Kolk, Beilmann, Tomberg, Napa & Talvik, 2001). Finally, Danielsson & Petermann (2009) found deficits in spatial perception and visual-constructive skills in children with rolandic epilepsy. These findings are not enough to make generalizations about visuospatial deficits in children with epilepsy, but they do point out that these deficits have been reported.

1.3. Cognitive Rehabilitation

Impairments in the developing brain often cause subsequent cognitive and behavioral problems and the children's cognitive deficit could expand in the course of the time. This could disrupt the development of other cognitive functions and social competences, which is why it is necessary to rehabilitate these disorders. In these scenarios, the most fitting treatment method would be neuropsychological rehabilitation. Cognitive rehabilitation is a concept, that refers to planned systematic therapeutic approaches to improve information processing (Cope, 1995). Cognitive rehabilitation is a system of activities with the aim to compensate impaired functions by incorporating individual and context-related demand (Farina, Raglio & Giovagnoli, 2015). Besides focusing on specific cognitive gains, the generalization to other cognitive functions is also another important goal of cognitive rehabilitation (Farina, Raglio & Giovagnoli, 2015).

Sarajuuri & Koskinen (2006) have stated that cognitive rehabilitation may have numerous approaches that include: restoring impaired functions by restoration training; enhancing preserved but weakened functions; compensatory strategies that are not good for remediation; using external compensatory devices; helping the patient understand and become aware of his or her strengths and weaknesses. Despite the approach, the aim of cognitive rehabilitation is to improve the everyday functioning of the patient's life (Sarajuuri & Koskinen, 2006).
A recent systematic review examined cognitive rehabilitation after Traumatic Brain Injury (TBI) or stroke (Cicerone et al., 2011). 112 studies from 2003 to 2008 were examined and it

was concluded that there is sufficient evidence to support interventions for attention, memory, social communication skills, executive functions and for comprehensive-holistic neuropsychologic rehabilitation after TBI. Moreover, visuospatial rehabilitation after right hemisphere stroke has been found to be useful (Cicerone et al., 2011). In addition, cognitive rehabilitation has also shown positive results in patients with multiple sclerosis (Hanssen, Beiske, Landrø, Hofoss & Hessen, 2016), HIV (Livelli et al., 2015) and in cancer survivors (Cherrier et al., 2013).

Many studies involving adults with epilepsy have been carried out to analyze the efficacy of cognitive rehabilitation. Engelberts et al. (2002) conducted a randomized-controlled trial to assess the cognitive rehabilitation program for patients with focal seizures and attention impairments. Fifty patients were randomly assigned to the Retraining Method, the Compensation Method or the waiting-list control condition. In the Retraining Method, patients had to rehearse their responses and task difficulty automatically increased when the patient's performance improved and in the Compensation Method, patients were taught compensatory strategies. The authors found that both Retraining and Compensation groups had a positive effect in such neuropsychological outcomes as attention and memory (Engelberts et al., 2002). Helmstaedter, Kurthen, Lux, Reuber & Elger (2008) studied the effects of cognitive rehabilitation on memory outcome in patients who had temporal lobe surgery. They found that rehabilitation had a positive effect on verbal memory. Radford, Lah, Thayer & Miller (2011) found that the objective and subjective memory outcome measures all showed improvements in both training groups after a 6-week, group-based, cognitive rehabilitation training program in patients with epilepsy. Koorenhof, Baxendale, Smith & Thompson (2012) reported improvements in verbal memory after a memory rehabilitation program on patients who underwent surgery for left temporal lobe epilepsy. Although most of these reported studies focused on the rehabilitation of memory, these results suggest that cognitive rehabilitation has been found to have a positive effect on adult patients with epilepsy.

One of the goals of holistic neuropsychological rehabilitation programs is to help children understand the nature of their problems and to help them cope with these problems (Koskinen & Sarajuuri, 2006). Many of the cognitive rehabilitation approaches existing today are designed for adults, but relatively few studies have been designed for children. There have been studies that have shown a positive effect in the cognitive rehabilitation of attention and memory in children with acquired brain injury (ABI) compared to controls (van't Hooft et al., 2005). It has been pointed out by several authors that well-controlled studies are needed in paediatric cognitive rehabilitation (Limond & Leeke, 2005; Shaw, 2014; Slomine & Locascio, 2009). It is important to point out that research concerning the cognitive rehabilitation of deficits in visuospatial functions in adults or children diagnosed with epilepsy has not been previously carried out.

1.4. Computer-based cognitive rehabilitation

Chen, Thomas, Glueckauf & Bracy (1997) propose a view that there are two categories of cognitive rehabilitation techniques used in modern neurorehabilitation treatment: traditional and computer-assisted. Traditional methods use cognitive strategies to treat deficits in different functions, whereas computer-assisted techniques use similar neuropsychologial processes but use computerized exercises to train attention and skills such as executive, perceptual motor and problem-solving skills with programs that resemble games (Chen, Thomas, Glueckauf & Bracy, 1997).

It has been found that computer-based neuropsychological assessments have a few advantages over traditional paper-and-pencil tests. Witt, Alpherts & Helmstaedter (2013) brought out a few benefits of administering computerized tests on patients with epilepsy. For instance, computerized tests have the advantage of being personalized for each patient separately and since patients advance on each task individually, the difficulties on each task could be set according to the patients' performance. In addition to these advantages stated above, Witt, Alpherts & Helmstaedter (2013) pointed out that computerized tests are appropriate for examining almost all of the cognitive domains the traditional tests are examining. This includes the domains of attention and decision making, visual perception, language or motor dominance, visuospatial orientation and navigation, learning, memory and social cognition. The authors also mention that only a small number of neuropsychological computer tests have been used in patients with epilepsy (Witt, Alpherts & Helmstaedter, 2013).

Computer-based cognitive rehabilitation in patients with epilepsy could have the same advantages as found in computer-based neuropsychological assessment. Previous research about computer-based cognitive neurorehabilitation has found to improve executive functions in patients diagnosed with Alzheimer's disease (Cipriani, Bianchetti & Trabucchi, 2006). Moreover, computer-based cognitive training had a positive effect on neuropsychological outcomes in African children with cerebral malaria (Bangirana et al., 2009). Lastly, neurocognitive benefit was found after a computer-based cognitive rehabilitation therapy in African children with HIV (Boivin et al., 2010).

Epilepsy is a continuous process in children that is in constant change due to the maturation of the central nervous system, which is why rehabilitation provides a framework for a dynamic treatment plan that addresses the changing needs of the child with epilepsy (Marks, Hernandez & Gabriel, 2003). However, very few studies exist about the efficacy of computer-based cognitive rehabilitation in children with epilepsy. As an example, Blocher, Fujikawa, Sung, Jackson & Jones (2013) found computer-assisted cognitive behavioral intervention to be effective in allieviating anxiety in children with epilepsy.

There have been a few computer-based cognitive rehabilitation programs to treat visuospatial deficits in different patient populations. Kang et al. (2009) used interactive computer-based program in the treatment of visuospatial deficit in patients with stroke and they found that the scores of the visual perception task increased significantly after treatment, however there were no significant differences between the experimental group and control group. Furthermore, computer-based cognitive rehabilitation has been used to treat visuospatial deficits in patients with visual neglect (Kerkhoff, 1998).

Many authors have expressed the need for randomized controlled studies in the field of children's rehabilitation and the need to continue to investigate the efficacy of cognitive rehabilitation for children (Laatsch et al., 2007; Limond & Leeke, 2005; Slomine & Locascio, 2009; Tal & Tirosh, 2013). Furthermore, Chung, Hsieh, Lai, & Huang (2014) pointed out the need for additional controlled studies of cognitive rehabilitation in patients with epilepsy. Taken together, there is a need for modern cognitive rehabilitation techniques for children that are individualized, computer-based, therapist guided, motivating and interesting.
Previously, the visuospatial functions module of FORAMENRehab computer-based cognitive rehabilitation program was tested in healthy controls to examine, which base level exercises would be suitable for children (Siimon, 2012).

The main aim of the current study was to test the effectiveness of computer-based rehabilitation program in the treatment of visuospatial deficit for children with epilepsy aged 8-12.
The specific aims of the study are:

1. To test the effectiveness of the novel computer-based intervention method – visuospatial module of FORAMENRehab program – in the treatment of visuospatial deficit in children aged 8-12 diagnosed with epilepsy.

2. To compare the results with children who have the same visuospatial deficit profile but did not receive a treatment with the FORAMENRehab program (waiting-list patients).
3. To create individual-based intervention design with optimal difficulty levels and duration of the intervention.
4. To measure long-term rehabilitation effect in follow-up assessments
5. To provide clinical implications for computer-based visuospatial functions rehabilitation in children with epilepsy

2. METHODS

2.1. Participants

2.1.1. Study group

This study was conducted in the Department of Neurology and Neurorehabilitation in the Children's Clinic of Tartu University Hospital. 17 children (*M*=9.95, *SD*=1.212) with partial epilepsy (PE) and previously diagnosed visuospatial deficits participated in the intervention (see Table 1 for further details).

Patients in the intervention group received individual attention and visuospatial training using FORAMENRehab software. The 8-12-years old age group was chosen for the reason that the children were required to have sufficient reading skills and basic mathematical skills. Furthermore, the age group was chosen to keep the children's age range and developmental level comparable.

The following inclusion criteria was used to choose the participants:

1) Previously diagnosed epilepsy confirmed by child neurologist.
2) Previously diagnosed cognitive impairment confirmed by neuropsychologist.
3) Fluency in Estonian
4) Children's age between 8-12
5) Written consent from the parent and child's verbal agreement to participate in the study.

The following exclusion criteria was used to exclude the participants:

1) Previously diagnosed other diseases involving the central nervous system.
2) Psychiatric co-morbidity and treatment with any psychotropic medication other than antiepileptic drugs during the rehabilitation period.

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 spikewave 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 spikewave 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 spikewave 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

2.1.2. Control group

The current study consisted of two control groups: the waiting-list control group and healthy control group. The waiting-list control group consisted of 22 children (*M*=10.29, *SD*=1.85) with visuospatial impairment and diagnosed with PE, including 15 boys and 7 girls (see Table 2 for further details). The waiting-list control group were offered the training, but for several reasons could not participate. For example, many of the children lived outside of Tartu and it was not possible for them to attend the training sessions twice a week. The inclusion and the exclusion criteria was the same for the waiting-list control group as for the study group. The age of epilepsy onset did not differ significantly between the training group and waiting-list control group (see Table 1 and Table 2).

The healthy control group consisted of 19 age equivalent children, of which 8 were girls and 11 boys. They were recruited from regular schools in Tartu. Written consent from the parent and child's verbal agreement to participate in the study was taken before the beginning of the study. Children with any psychiatric disorders or any diseases involving the central nervous system were excluded from the healthy control group. There were no significant differences between the three groups in terms of sex and age.

Table 2

Waiting-list control group characteristics

Pt	Age at intervention (years)	Sex	Age at epilepsy onset (yrs)	Duration of epilepsy (years)	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-wave activity TC sin	LEV
P3	12.99	F	8.58	4.84	Spike-wave 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-wave 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-wave activity CT sin>dex	VPA
P11	9.50	M	8.25	1.25	Spike-wave activity PC>T sin, in sleep bilateral sin>dex	VPA
P12	8.42	M	8.42	0*	Spike-wave activity CT dex	VPA
P13	7.83	F	7.62	0.21*	Bilateral spike-wave activity T>0	OXC
P14	12.08	M	12.06	0.02*	Spike-wave activity T>P, in sleep T>P, FT	VPA
P15	11.83	M	9.97	1.86	Spike-wave activity OT dex>sin	OXC
P16	8.75	F	6.39	2.36	Bilateral spike-wave activity CT sin	VPA
P17	12.89	F	7.08	5.81	Spike-wave activity CT bilateral dex>sin	VPA
P18	11.12	M	9.51	1.61	Bilateral spike-wave activity sin>dex	VPA
P19	12.00	F	11.24	0.76*	Bilateral spike-wave activity dex>sin	VPA
P20	8.90	M	9.62	0*	Spike-wave activity T sin	OXC
P21	8.00	M	6.92	1.08	Spike-wave activity C dex	VPA
P22	12.81	M	1.75	11.06	Spike-wave activity F dex	LEV, 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

2.2. Rehabilitation software

The study used computer-based ForamenRehab Cognitive Rehabilitation Software (Sarajuuri & Koskinen, 2006). The software consists of four modules: attention, executive functions and problem solving; memory and visuospatial perception. For this Master's thesis the visuospatial functions module was used that was previously translated to Estonian and adapted for Estonian patients (Cognuse LLC, 2009) and for children by author. For example, the adaptation process included working out the exact wording suitable for children and choosing suitable difficulty levels. The visuospatial module consists of visual recognition, visual organization, visual attention and visuospatial perception components.

Most of the exercises in the visuospatial perception module take up to 5 minutes to complete and the longest exercise up to 20 minutes. All of the difficulty levels of the exercises are adjustable and the difficulty levels are kept the same for all three assessment points. The outcomes measured include: time taken to solve a task; number of tasks completed in a given time; percentage of correct responses; degrees of deviation from a given horizontal line and percentage of wrong moves and navigation errors in a task. A brief description of the baseline tasks measured at three assessment points is below:

Visual Recognition. The Circle Following task requires the participant to hold their gaze and maintain the direction of the movement. This exercise requires the participant to keep a dot inside a circle using the computer mouse. This task examines the eye-hand coordination of the patient. The Line Orientation Judgement task requires the participant to determine and to replicate the inclination of a line inside a circle. This task examines spatial awareness and executive functions.

Visual Organization. In the Geometric Pattern Recognition task, the participant is shown a fragment of an object inside a small window and is required to recognize and pick the object from a set of different objects. This task examines the visual attention, memory and construction abilities of the patient.

Visual Attention. In the Spatial Attention task, a small dot appears briefly in a matrix and the participant has to point out which row and column the small dot appeared in. This exercise examines the reaction time, visual attention and the visual field of the patient.

Visuospatial Perception. In the Cubes task, the participant has to count all the cubes shown in an image, including the ones which are not directly visible. This task examines the mathematical and construction abilities of the patient. The Construction task requires the participant to use small blocks of different shapes to recreate the same pattern as shown. This task is used to assess visual construction abilities, attention and executive functions of the patient. The Maze task requires the participant to move through a maze as quickly as possible and make as little navigation errors and collisions against the maze wall (wrong moves) as possible. This task is used to assess the visual-spatial relations and planning skills.

2.3. Procedure

2.3.1. Baseline assessments

During the baseline assessments, the participants were first instructed how to complete any given task before the exercises started and they were also shown an animation of the exercise if they did not understand the instructions. A protocol for administering the exercises was developed prior to the start of the study and all of the baseline assessments were carried out with minimal interference by the instructors.

The participants in the training group came to the Children's Clinic for a total of 13 appointments (see Table 3). The first session was baseline assessment and the next 10 sessions were rehabilitation sessions taking place twice a week during a 5-week period. The second baseline assessment or primary outcome assessment was conducted on the 12th session, taking place 6 weeks after the first assessment. The third baseline assessment or secondary outcome assessment was conducted 1.31 years (*SD*=0.398) after the intervention. Currently, 13 patients from the training group have participated in the follow-up and were included in this study.

Table 3

Design of the intervention

Meeting no.	1	2 3 4 5 6 7 8 9 10 11	12	13
Training group	I Baseline assessment	10 active training sessions (5-week period)	II Baseline assessment	III Baseline assessment (1.31 years after)
Waiting-list group	I Baseline assessment	No rehabilitation treatment for 5 weeks	II Baseline assessment	III Baseline assessment (1.31 years after)
Healthy controls group	I Baseline assessment			

The participants of the waiting-list control group were assessed 3 times during the baseline assessments. They did not receive any rehabilitation treatment during the 5-week period between the first and the second baseline assessments and no rehabilitation treatment afterwards. 10 patients in the waiting-list control group have taken part in the follow-up assessment after the intervention, and were included in this study.

The baseline assessment of the healthy children's group was carried out only once in their school setting in order to compare the baseline levels of visuospatial tasks with the study group and the waiting-list control group.

We also measured generalized effect of the study with subjective measures: qualitative feedback from the children and a questionnaire for the parents about the child's general functioning, school performance and behavior. Individual progress during training was measured with the average difficulty level reached during the end of intervention and average sessions required to advance from the first to the second difficulty level.

2.3.2. Rehabilitation

The rehabilitation sessions for the study group consisted of 10 active training sessions, taking place twice a week for a 5-week period. Usually, the training sessions lasted for 30 minutes and 6-7 visuospatial tasks were completed during this time. All of the visuospatial modules were covered for each rehabilitation session, but the exercises differed from the baseline assessment tasks.

A protocol was established how the participants could advance on each task to reach higher levels. If the participants completed the task without any mistakes, they advanced automatically to the next level starting at the next session. If the participants' correct responses were below 80% of the tasks answers, then they were required to complete 80-90% of an exercise for three consecutive sessions to reach a new difficulty level. Each of the exercises had three difficulty levels: easy, medium and difficult. During the rehabilitation sessions, the participants were encouraged to keep solving the exercises until all of them were completed. They were instructed to be as thorough as possible and they were told in some tasks that the solving time was measured as well. In addition to the briefing on how to complete each task, the participants were also instructed how to reach higher levels. The advancement on each exercises' difficulty levels was individual-based and determined by the children's personal improvement. Compliance was 100% - all of the 17 training group patients attended all 10 of the active training sessions.

The author's contribution to this research project includes: working out the method of the study; data collection and analysis; carrying out the training sessions and assessments. This study was approved by the Research Ethics Committee of the University of Tartu.

2.4. Data analysis

The statistical analysis was performed using the statistical package SAS Version 9.2 and the R version 2.15.2. Statistical comparisons between non-normally distributed continuous variables were performed with Wilcoxon-Mann-Whitey test. Kolmogorov-Smirnov criterion was used for the assessment of normality. Differences at baseline assessments between patients receiving the training, waiting-list controls and healthy control groups were studied with Kruskal-Wallis test and pairwise comparison with Wilcoxon-Mann-Whitney test.

Repeated Measures ANOVA was conducted to assess whether longitudinal changes in groups were significantly different. Wilcoxon signed-rank test was used to detect differences in time within groups. Continuous outcome variables were log-transformed when necessary to satisfy model assumptions.

We controlled the false discovery rate (FDR) to be lower than 5% by using linear step-up procedure (Benjamini & Hochberg, 1995) for multiple t-tests. Only p-values that are below the adjusted FDR significance threshold are therefore significant and marked as such (***) in the tables.

3. RESULTS

3.1. Characteristics of visuospatial components in the first baseline assessment between training group, waiting-list control group and healthy controls

The comparison of performances on the first baseline assessment was carried out to describe the differences between the training group, waiting-list control group and healthy controls.

Visual Recognition. Visual recognition component was measured with the Circle Following task and the Line Orientation Judgement task. The Kruskal-Wallis test showed no significant differences between the training group, waiting-list control group and healthy controls in the Circle Following task (p=0.1061) (see Table 4 for further details). Pairwise comparisons were conducted using the Wilcoxon-Mann-Whitney test, which showed that the waiting-list control group had significantly lower scores compared to the healthy control group (p=0.0470). No significant differences existed between the healthy control group and training group (p=0.1626) or between the training and the waiting-list control group (p=0.3958) in the Circle Following Task (see Table 4).

The Kruskal-Wallis test showed significant differences between the training group, waiting-list control group and healthy controls in the Line Orientation Judgement task (p<.0001). Both, the training group and the waiting-list control group performed significantly worse compared to the healthy control group (p=0.0003 and p<.0001, respectively) (see Table 4 and Figure 1).

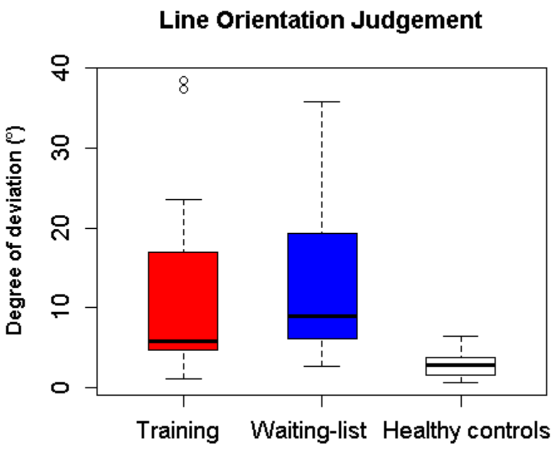

Figure 1. Degree of deviation in a visual recognition task at first baseline assessment between training group, waiting-list control group and healthy control group.

Table 4

Comparison of performances on the first baseline assessment between the training group, waiting-list control group and healthy controls.

Tasks in the FORAMENRehab Visuospatial module	Training group	Waiting-list group	Healthy control group	Training vs Waiting-list vs Healthy	Training vs Healthy	Waiting-list vs Healthy	Training vs Waiting-list
First baseline assessment (B1)	Median (Lower and Upper Quartiles)[a]	Median (Lower and Upper Quartiles)[a]	Median (Lower and Upper Quartiles)[a]	*p*	*p*	*p*	*p*
Visual recognition							
Circle Following (%)	30.81 (21.69...57.44)	28.89 (16.18...39.85)	71.58 (50.10…93.07)	0.1061	0.1626	0.0470	0.3958
Line Orientation Judgement (°)	5.83 (4.75...16.92)	8.92 (6.13...21.58)	2.92 (1.67...3.75)	<.0001	0.0003**	<.0001**	0.2999
Visual organization							
Geometric Pattern Recognition (nr)	14.35 (13.34...15.36)*	14.60 (13.63...15.57)*	14.06 (12.90...15.22)*	0.7865	0.8473	0.5050	0.6741
Geometric Pattern Recognition (%)	61.54 (53.33…71.43)	64.10 (51.67...73.61)	73.33 (71.43...81.82)	0.0140	0.0101**	0.0134**	0.9029
Visual attention							
Spatial Attention (%)	80.00(50.00...90.00)	70.00 (67.50...81.67)	95.00 (90.00...100.00)	<.0001	0.0003**	<.0001**	0.8055
Spatial Attention (s)[b]	8.50 (7.00...14.86)	8.82 (6.74...11.97)	6.15 (5.04...7.47)	0.0015	0.0034**	0.0010**	0.7722
Visuospatial perception							
Cubes (%)	20.00 (0.00...40.00)	20.00 (0.00...50.00)	80.00 (40.00...80.00)	0.0006	0.0007**	0.0011**	0.6585
Cubes (s)[b]	37.43 (30.04...44.81)*	38.67 (31.46...42.87)	48.15 (25.56...61.40)	0.6087	0.4694	0.3370	0.9393
Construction (%)	66.67 (33.33...100.00)	66.67 (33.33...100.00)	100.00 (100.00...100.00)	0.0007	0.0005**	0.0008**	0.6382
Construction (s)[b]	243.17 (148.31...311.24)	221.93 (160.25...321.04)	103.16 (74.00...198.50)	0.0027	0.0030**	0.0030**	0.9878
Maze (nr)	6.00 (4.00...9.00)	6.00 (2.50...16.50)	1.00 (1.00...3.00)	0.0002	0.0002**	0.0008**	0.8306
Maze (%)	32.87 (27.62...36.96)	24.62 (11.98...38.48)	8.53 (0.45...12.11)	<.0001	<.0001**	0.0008**	0.2171
Maze (s)[b]	54.83 (46.16...84.60)	63.18 (56.87...75.81)	42.46 (37.37…51.35)	0.0004	0.0047**	0.0001**	0.4929

[a]Median (Lower 25%ile and Upper 75%ile)

[b]seconds

* - Mean (95%CI)

** We controlled the FDR to be lower than 5% by using linear step-up procedure (Benjamini and Hochberg 1995) for multiple t-tests.

Visual Organization. Visual organization was measured with the Geometric Pattern Recognition task. The Kruskal-Wallis test showed no significant differences between the training group, waiting-list control group and healthy controls in the number of solved exercises in the Geometric Pattern Recognition task (p=0.7865). Pairwise comparisons showed no significant differences between the healthy control group and training group (p=0.8473), healthy control group and waiting-list control group (p=0.5050) nor training group and waiting-list control group (p=0.6741) (see Table 4).

There were statistically significant differences between the training group, waiting-list control group and healthy controls in the percent of correct responses in the Geometric Pattern Recognition task (p=0.0140). The Wilcoxon-Mann-Whitney test was used for pairwise comparisons, which showed significant differences between the healthy control group and training group (p=0.0101) and between the healthy controls and waiting-list group (p=0.0134) (see Figure 2 and Table 4).

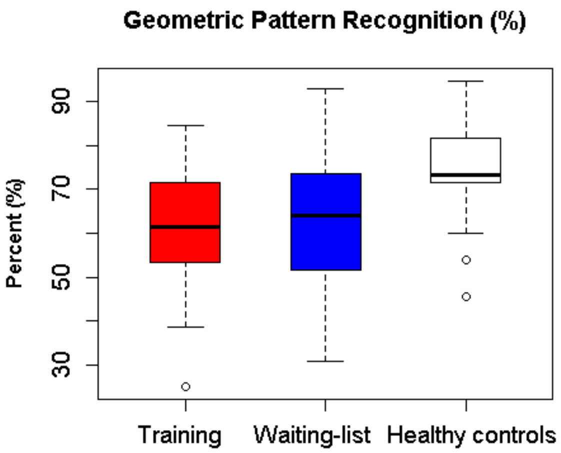

Figure 2. Percent of correct responses in a visual organization task at first baseline assessment between training group, waiting-list control group and healthy control group.

Visual Attention. Visual attention was measured with the Spatial Attention task. The Kruskal-Wallis test showed statistically significant differences between the training group, waiting-list control group and healthy controls in the percent of correct responses in the task (p<.0001). Both the training group and the waiting-list control group performed significantly worse compared to the healthy control group (p=0.0003 and p<.0001, respectively) (see Figure 3 and Table 4).

The Kruskal-Wallis test also showed statistically significant differences between the training group, waiting-list control group and healthy controls in the reaction time in the Spatial

Attention task (*p*=0.0015). The healthy control group was significantly quicker in the reaction time compared to the training group (*p*=0.0034) and the waiting-list control group (*p*=0.0010) (see Figure 4 and Table 4).

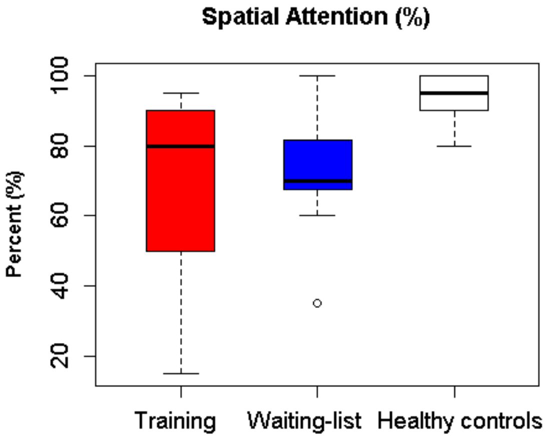

Figure 3. Percent of correct responses in a visual attention task at first baseline assessment between training group, waiting-list group and healthy control group.

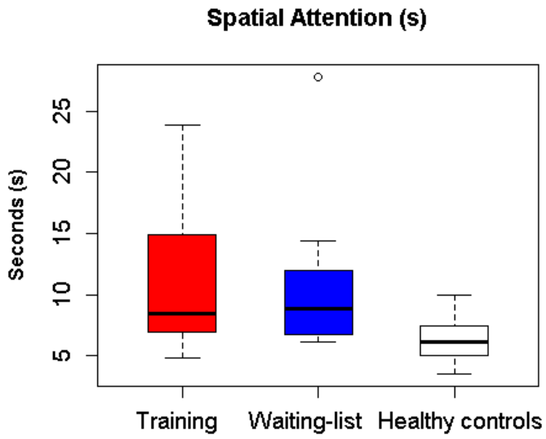

Figure 4. Reaction times in a visual attention task at first baseline assessment between training group, waiting-list control group and healthy control group.

Visuospatial Perception. Visuospatial perception was measured using the Cubes, the Construction and the Maze tasks. The Kruskal-Wallis test showed statistically significant differences between the training group, waiting-list control group and healthy controls in the percent of correct responses in the Cubes task (*p*=0.0006). The healthy control group gave significantly more correct responses compared to the training group (*p*=0.0007) and compared to the waiting-list control group (*p*=0.0011) (see Figure 5 and Table 4).

There were no significant differences between the training group, waiting-list control group and healthy controls in the reaction time of the Cubes task (*p*=0.6087). Pairwise comparison showed that compared to the healthy control group, there were no significant differences between the performances of the training group and waiting-list control group (*p*=0.4694 and *p*=0.3370, respectively) (see Table 4).

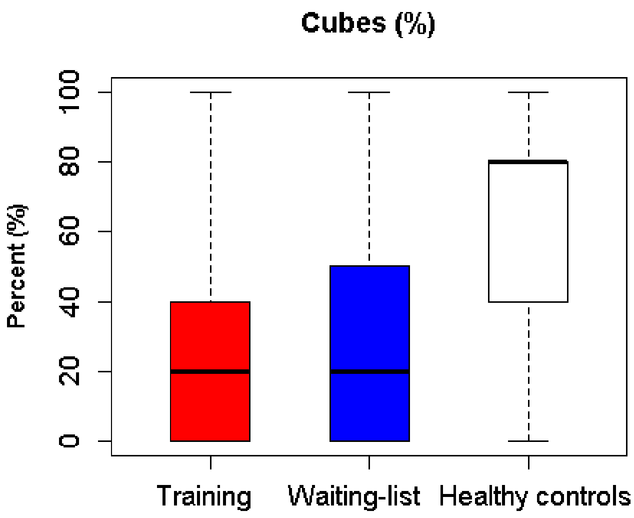

Figure 5. Percent of correct responses in a visuospatial perception task at first baseline assessment between training group, waiting-list control group and healthy control.

The Kruskal-Wallis test also showed statistically significant differences between the groups in the percent of correct responses in the Construction task (*p*=0.0007). The healthy control group gave significantly more correct responses compared to the training group (*p*=0.0005) and compared to the waiting-list control group (*p*=0.0008) (see Figure 6 and Table 4).

The Kruskal-Wallis test showed statistically significant differences between the training group, waiting-list control group and healthy controls in the reaction time of the Construction task (*p*=0.0027). The healthy control group was significantly quicker in the task compared to the training group (*p*=0.0030) and compared to the waiting-list control group (*p*=0.0030) (see Figure 7 and Table 4).

Statistically significant differences between the training group, waiting-list control group and healthy control group were found with the Kruskal-Wallis test in the amount of wrong moves in the Maze task (*p*=0.0002). Furthermore, the Wilcoxon-Mann-Whitney test showed significant differences between the healthy control group and training group (*p*=0.0002) and between the healthy control group and waiting-list control group (*p*=0.0008) (see Table 4).

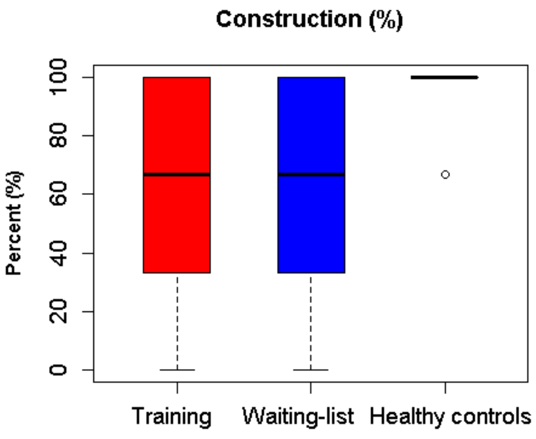

Figure 6. Percent of correct responses in a visuospatial perception task at first baseline assessment between training group, waiting-list control group and healthy control group.

Figure 7. Reaction times in a visuospatial perception task at first baseline assessment between training group, waiting-list control group and healthy control group.

Significant differences between the training group, waiting-list control group and healthy control group were also found in the percent of navigation errors in the Maze task (p<.0001). Both the training group and the waiting-list control group performed significantly worse compared to the healthy control group (p<.0001 and p=0.0008, respectively) (see Figure 8 and Table 4).

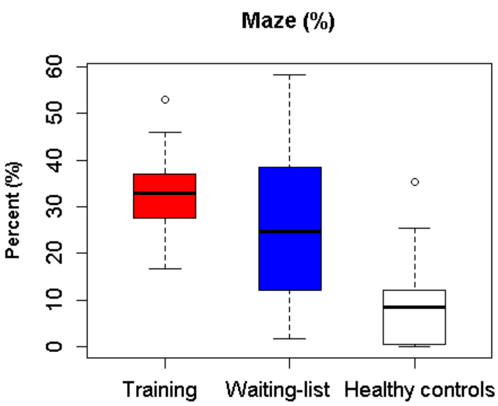

Figure 8. Percent of navigation errors in a visuospatial perception task at first baseline assessment between training group, waiting-list control group and healthy control group.

The solving time in the Maze task was statistically different in the training group, waiting-list control group and healthy control group (p=0.0004). The healthy control group performed better in the Maze task compared to the training group (*p*=0.0047) and compared to the waiting-list control group (*p*=0.0001) (see Figure 9 and Table 4).

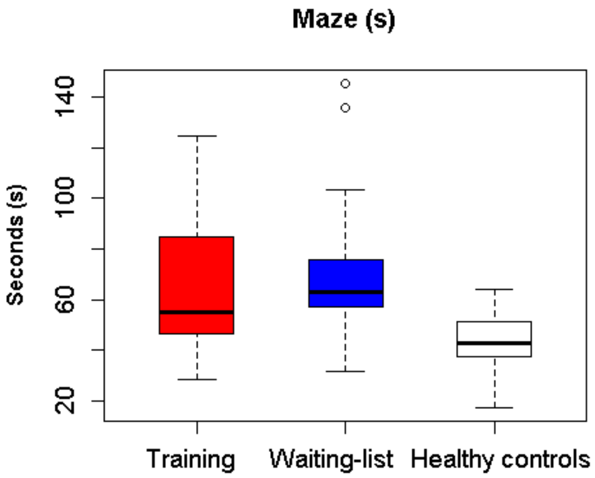

Figure 9. Solving speed in the visuospatial perception task at first baseline assessment between training group, waiting-list control group and healthy control group.

3.2. Patients' individual improvement during the rehabilitation

Individual improvement in the training group during the intervention was measured by the mean achieved difficulty levels by the end of intervention in each of the 4 visuospatial components (see Table 5). Furthermore, the progress on reaching higher difficulty levels was also examined by measuring the average number of sessions needed to move to second difficulty level in the tasks (see Table 5). Most of the tasks had a maximum difficulty level of 4 with the exception of 4 tasks that had 3 difficulty levels (see Table 5). Slower rehabilitation effect occured in 2 visual recognition tasks and in 2 visuospatial perception tasks.

All children in the training group showed positive individual advancement on the visuospatial tasks. Figure 10 shows that all children in the training group had individually different progress trajectories. The difference between the reached difficulty levels at the end of the intervention is up to 2 times higher for the children with the quickest improvements compared to the children with the slowest improvements.

Table 5
Average achieved difficulty levels at the end of intervention and average number of completed sessions before moving from first to second difficulty level in 4 visuospatial components.

Visuospatial component	Nr of task	Mean level	Mean sessions
		Mean (95%CI)	Mean (95%CI)
Visual recognition	1	1.56 (1.29...1.84)*	4.69 (3.3...6.07)
	2	1.81 (1.33...2.3)	5.06 (3.99...6.14)
	3	2.19 (1.74...2.63)*	2.38 (1.35...3.4)
Visual organization	1	3.25 (2.84...3.66)	1.62 (1.08...2.17)
	2	3.12 (2.55...3.7)	1.5 (1.02...1.98)
Visual attention	1	3.31 (2.89...3.74)	2 (1.25...2.75)
Visuospatial perception	1	1.38 (0.99...1.76)	6.25 (5.35...7.15)
	2	2.12 (1.7...2.55)*	3 (2.13...3.87)
	3	3.31 (2.81...3.82)	1.88 (1.26...2.49)
	4	1.62 (1.3...1.95)*	3.94 (3.04...4.84)
	5	1.25 (1.01...1.49)	3.94 (2.98...4.9)

* Tasks with a maximum difficulty level of 3

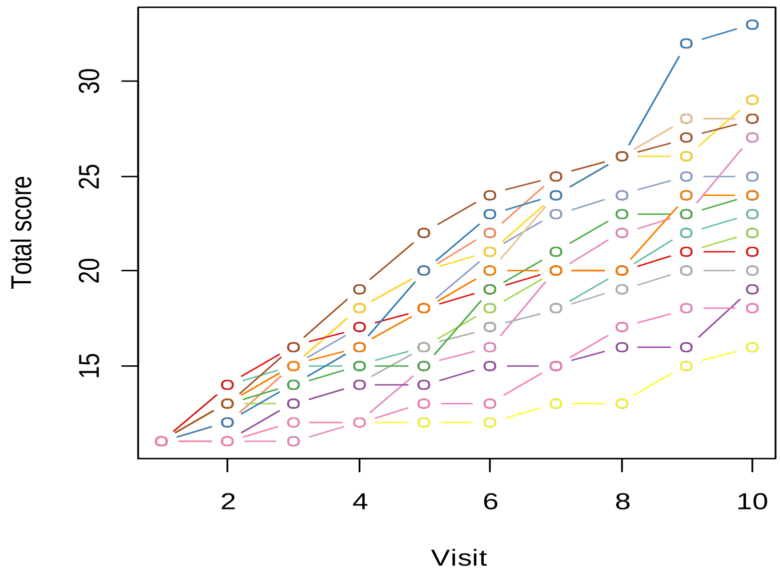

Figure 10. Children's individual progress trajectories for 10 training sessions (total score per visit).

3.3. Comparison of performances between training group and waiting-list control group on the immediate and long-term rehabilitation effect

The comparison of performances on the baseline assessment, the primary outcome assessment and secondary outcome assessment (long-term follow-up) was carried out to see the differences between the training group and the waiting-list control group.

Visual Recognition. The Circle Following task was excluded from the comparison due to a recording error in the software: it did not record the results of some participants in the primary outcome assessment and secondary outcome assessment. Repeated Measures ANOVA was conducted to assess whether longitudinal changes (comparing differences at three assessment points) in groups were significantly different. Wilcoxon signed-rank test was used to detect differences in time within groups. There were no statistically significant longitudinal change, when comparing differences at three assessment points in Line Orientation Judgement task between training group and waiting-list control group (p= 0.2807). In the follow-up assessment 1.31 years later, which is the secondary outcome, the training group showed positive long-term rehabilitation effect on the Line Orientation Judgement task (p=0.0007). The degree of deviation from a given horizontal line in the Line Orientation task was smaller in the secondary outcome compared to the first baseline assessment in the training group (see Table 6).

Visual Organization. There were no statistically significant longitudinal changes, when comparing differences at three assessment points in the amount of solved Geometric Pattern Recognition tasks between training group and waiting-list control group (p= 0.2249). However, there was a significant positive immediate rehabilitation effect in the training group (p=0.0371). This means that immediately after the intervention, the training group had quicker solving time compared to the first baseline assessment (see Table 6).

There were no statistically significant longitudinal changes in the percent of correct responses in the Geometric Pattern Recognition task between training group and waiting-list control group (p= 0.0867). However, the training group showed a positive immediate rehabilitation effect (p= 0.0327) and a positive long-term rehabilitation effect (p= 0.0002). The waiting-list control group improved their performance only on the secondary outcome (p= 0.0020) compared to the first baseline assessment (see Figure 11 and Table 6).

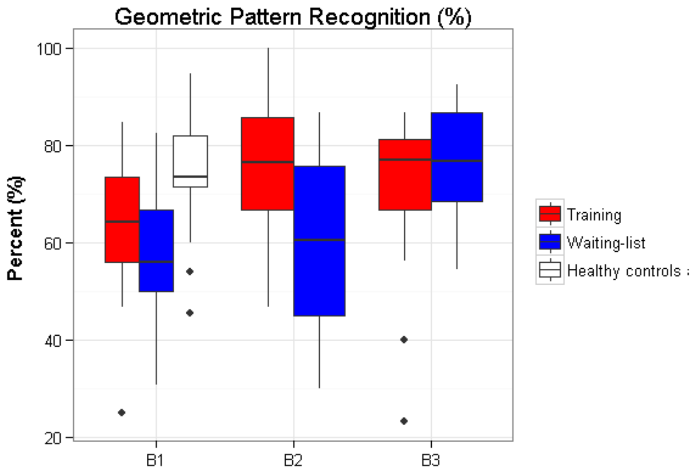

Figure 11. Longitudinal change in the percent of correct answers in a visual organization task between training group, waiting-list group and healthy control group at three assessment points (B1 – baseline, B2 – primary outcome, B3- secondary outcome).

Visual Attention. There was a significant longitudinal change, when comparing differences at three assessment points in the percent of correct responses in the Spatial Attention task between training group and waiting-list control group (p= 0.0223). Compared to the first baseline assessment, the training group significantly improved their performance on the primary outcome (p=0.0054) and secondary outcome assessments (p=0.0059), while the waiting-list control group performed better only on the secondary outcome assessment (p=0.0313) (see Figure 12 and Table 6).

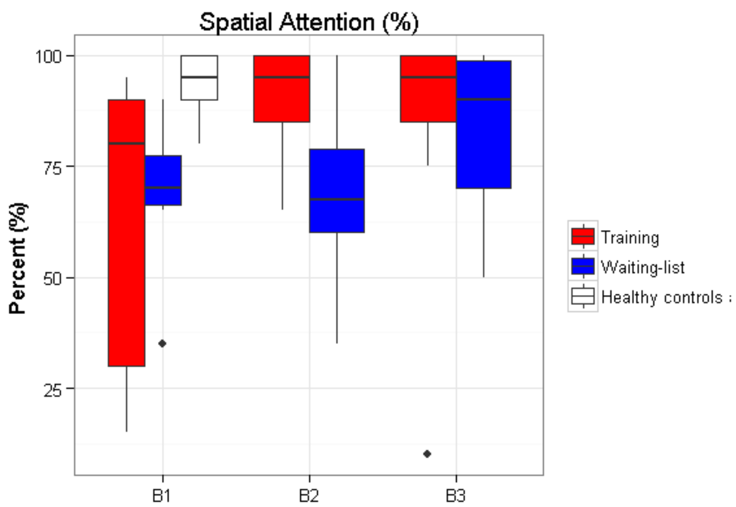

Figure 12. Longitudinal change in the percent of correct responses in a visual attention task between training group, waiting-list group and healthy control group at three assessment points (B1 – baseline, B2 – primary outcome, B3- secondary outcome).

Table 6

Comparison of performances in time within training group and waiting-list control group (three assessment points)

Tasks of the FORAMENREHAB Visuospatial module		Training group	Waiting-list group	B1 vs B2	B1 vs B3	B2 vs B3
		Mean (95% CI)[b]	Mean (95% CI)	*p*	*p*	*p*
Visual recognition	B1[a]	9.38 (4.98...17.65)**	13.26 (6.11...28.78)**	n. s.	Training=0.0007***	n. s.
Line Orientation Judgement (degree of deviation)	B2	3.83(1.67...8.80)**	10.76 (4.90...23.61)**			
	B3	2.67 (1.42...5.0298)**	5.63 (3.02...10.49)**			
Visual organization	B1	14.23 (13.07...15.39)	13.80 (12.34...15.26)	Training=0.0371	n. s.	n. s.
Geometric Pattern Recognition (number of solved tasks)	B2	15.62 (14.61...16.62)	14.00 (11.57...16.43)			
	B3	14.31 (12.97...15.65)	15.10 (13.58...16.62)			
	B1	64.29 (56.00...73.33)*	55.83 (50.00...66.67)*	Training=0.0327	Training= 0.0002***	n. s.
Geometric Pattern Recognition (percent of correct answers)	B2	76.47 (66.67...85.57)*	60.48 (44.44...78.57)*		Waiting= 0.0020***	
	B3	76.92 (66.67...81.25)*	76.79 (66.67...88.89)*			
Visual attention	B1	80.00 (45.00...90.00)*	70.00 (65.00...80.00)*	Training= 0.0054***	Training= 0.0059***	n. s.
Spatial Attention (percent of correct answers)	B2	95.00 (85.00...100.00)*	67.50 (60.00...80.00)*		Waiting= 0.0313	
	B3	97.50 (85.00...100.00)*	90 (65.00...100.00)*			
	B1	9.38 (7.03...12.51)**	9.76 (7.63...12.49)**	Training=0.0005***	Training=0.0134***	n. s.
Spatial Attention (reaction time)	B2	5.67 (4.72...6.80)**	9.11 (7.15...11.60)**			
	B3	6.53 (5.56...7.68)**	7.51 (5.85...9.65)**			
Visuospatial perception	B1	24.62 (9.69...39.54)	26.00 (9.41...42.59)	Training=0.0469	n. s.	n. s.
Cubes (percent of correct answers)	B2	36.92 (17.28...56.56)	62.00 (39.18...84.82)			
	B3	43.08 (24.07...62.09)	48.00 (29.90...66.10)			
	B1	33.66 (24.30...39.03)*	41.27 (32.49...41.92)*	n. s.	n. s.	n. s.
Cubes (reaction time)	B2	26.86 (23.06...35.72)*	39.85 (30.22...46.05)*			
	B3	26.51 (24.02...35.76)*	36.62 (29.27...47.52)*			
	B1	50.00 (0.00...83.34)*	66.67 (66.67...100.00)*	Training=0.0098***	Training=0.0313***	n. s.
Construction (percent of correct answers)	B2	100.00 (83.34...100.00)*	83.34 (33.33...100.00)*			
	B3	83.34 (66.67...100.00)*	100.00 (66.67...100.00)*			

Table 6 continued

Tasks of the FORAMENREHAB Visuospatial module		Training group	Waiting-list control group	B1 vs B2	B1 vs B3	B2 vs B3
		Mean (95% CI)	Mean (95% CI)	*p*	*p*	*p*
	B1	243.59 (166.21...320.96)	218.95 (153.71...284.19)	Waiting=0.0234	Training=0.0479	n. s.
Construction (reaction time)	B2	195.58 (126.72...264.45)	193.87 (126.38...261.37)*			
	B3	159.97 (110.52...209.41)	174.06 (116.32...231.79)*			
	B1	7.04 (4.82...10.26)**	7.85 (2.93...21.01)**	n. s.	n. s.	Waiting=0.0391
Maze (amount of wrong moves)	B2	4.15 (1.54...11.20)**	8.22 (3.83...17.69)**			
	B3	4.25 (1.63...11.07)**	3.29 (1.87...5.79)**			
	B1	30.59 (25.79...36.29)**	23.96 (15.53...36.99)**	n. s.	Training=0.0105***	n. s.
Maze (percent of navigation errors)	B2	12.31 (5.61...27.02)**	27.99 (18.74...41.80)**			
	B3	8.62 (3.58...20.80)**	12.62 (5.67...28.07)**			
	B1	61.30 (48.38...77.67)**	72.21 (57.68...90.41)**	n. s.	Waiting=0.0371	n. s.
Maze (speed of solving)	B2	55.92 (43.77...71.45)**	74.46 (57.83...95.87)**			
	B3	52.60 (39.69...69.71)**	52.44 (36.96...74.40)**			

[a] B1 – first baseline assessment, B2 – primary outcome assessment, B3 – secondary outcome assessment (follow-up)

[b] Mean score (95% confidence intervals for Mean)

* - Median (Lower 25%ile and Upper 75%ile)

** - Geometric Mean (95%CI)

*** We controlled the FDR to be lower than 5% by using linear step-up procedure (Benjamini and Hochberg 1995) for multiple t-tests.

n. s. – not significant

There was a statistically significant longitudinal change in the reaction time of the Spatial Attention task between training group and waiting-list control group (*p*=0.0085). The training group showed a positive immediate intervention effect (*p*=0.0005) and positive long-term rehabilitation effect (*p*=0.0134) (see Figure 13 and Table 6).

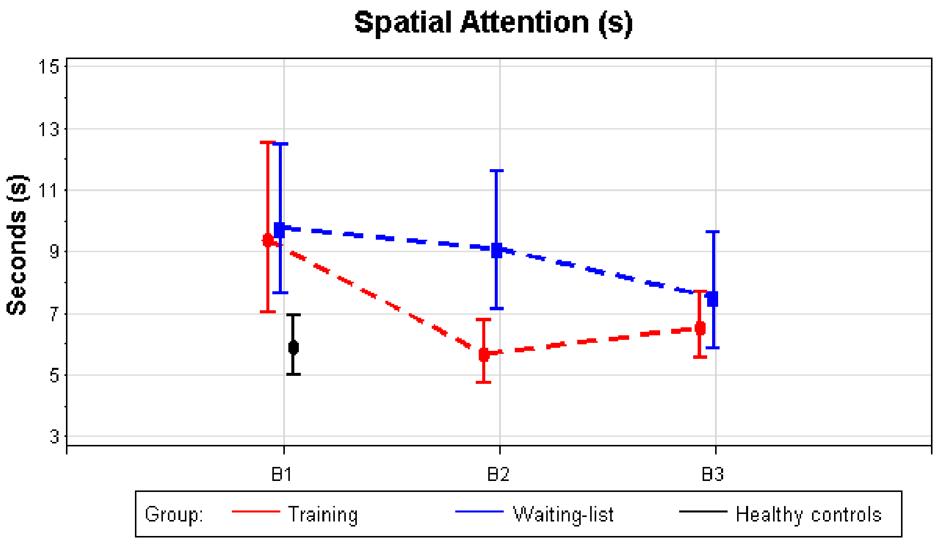

Figure 13. Longitudinal change in the reaction time of a visual attention task between training group, waiting-list group and healthy control group at three assessment points (B1 – baseline, B2 – primary outcome, B3- secondary outcome).

Visuospatial Perception. There was no statistically significant longitudinal change in the percent of correct responses in the Cubes task (*p*= 0.2929) or the reaction time of the Cubes task (*p*= 0.9541) between the training group and the waiting-list control group. However, the training group showed a positive immediate intervention effect in the Cubes task (*p*=0.0469), giving more correct responses in the primary outcome assessment compared to the first baseline assessment (see Table 6).

There was a statistically significant longitudinal change in the percent of correct responses in the Construction task between the training group and waiting-list control group (*p*=0.009). Compared to the first baseline assessment, the training group gave more correct responses in the primary outcome assessment (*p*=0.0098) and secondary outcome assessment (*p*=0.0313), showing positive immediate and long-term intervention effect (see Table 6).

There was no significant longitudinal change in the reaction time of the Construction task between the training and the waiting-list control group (*p*=0.9195). However, compared to the first baseline assessment, the waiting-list control group significantly improved their reaction time on the primary outcome assessment (*p*=0.0234) and the training group improved their reaction time on the secondary outcome assessment (*p*=0.0479) (see Table 6).

There were no significant longitudinal change in the amount of wrong moves in the Maze task (p=0.5718) and no significant longitudinal change in the amount of navigation errors in the Maze task (p=0.1233) between the training group and waiting-list controls. However, the training group showed a long-term intervention effect by decreasing their navigation errors in the Maze task in the secondary outcome assessment (p=0.0105), when compared with the first baseline assessment (see Table 6).

There were no significant longitudinal change in the speed of solving the Maze task between the training group and waiting-list control group (p=0.4771). The waiting-list control group improved their solving time in the secondary outcome assessment (p=0.0371) compared to the first baseline assessment (see Table 6).

3.4. Generalized effect

Generalized effect was measured with subjective measures before and 1.31 years after the intervention during the secondary follow-up assessment. For the parents' feedback we created a questionnaire measuring concentration and general functioning of the children, including information about behaviour and school performance. In addition, we collected qualitative feedback from the children.

Parents´ feedback showed positive behavioural change: children were less distracted and they were more prone to social communication. Furthermore, the skills in reading, writing, mathematics and visuomotor functions improved. Children declared better functioning in school tasks and improved concentration skills. Children reported the preference of the visuospatial perception module tasks: the Maze task and the Construction task.

4. DISCUSSION

The main aim of the current study was to test the effectiveness of a computer-based rehabilitation program in the treatment of visuospatial deficit for children with epilepsy aged 8-12 years.

4.1. Comparison of the visuospatial function profiles between the training group, waiting-list control group and healthy control group

In the *visual recognition component,* on baseline level the first task, which additionally measured eye-hand coordination, showed no differences between the training group and healthy controls, although a marginal difference between the waiting-list group and healthy controls was observed. Similar results have been reported before by Hernandez et al. (2002), who found deficits in motor coordination in children with frontal lobe epilepsy. Deficits in the task measuring visual recognition ability with additional spatial awareness and executive functions in children with epilepsy (training group and waiting-list control group) were observed as well. Previously, deficits in executive functions in children with epilepsy have also been reported (Zilli et al., 2015).

Results from the baseline assessment imply that even though children in the training group and waiting-list control group were as quick as healthy control group in solving time in the *visual organization* component, they gave significantly less correct answers, indicating deficits in children with epilepsy. More specifically, visual attention, visuospatial memory and construction abilities were measured. Our results are in line with Danielsson & Petermann (2009) who found deficits in visual-constructive skills in children with rolandic epilepsy and with Deonna et al. (2000) who reported deficits in visuospatial memory and visuospatial organization in children with benign partial epilepsy.

Children diagnosed with epilepsy showed deficits in the *visual attention* components: they gave less correct answers and had slower processing speed than their healthy peers. Deficits in visual attention have been reported before in children with benign epilepsy of childhood with centro-temporal spikes (BECTS) and in children with BECTS and migraine (Parisi et al., 2012).

Children with epilepsy also showed deficits in *visuospatial perception* component before the intervention. Even though their reaction time did not differ significantly from the healthy controls, they gave significantly less correct answers compared to the control group. In one task, children with epilepsy performed significantly worse in all subcomponents: in the amount of wrong moves, percent of navigation errors and in the time taken to complete the task. Visual construction abilities, attention and executive functions were also part of the measured functions. Deficits in visual construction skills (Danielsson & Petermann, 2009) attention (Bender et al., 2007) and executive functions (Bender et al., 2007; Rathouz et al., 2014) have been reported before in children with epilepsy.

To sum up, in the first baseline assessment before the intervention, children diagnosed with epilepsy in the training and waiting-list group showed significant deficits in all 4 of the visuospatial function components compared to the healthy control group. These results show that the baseline assessment with the FORAMENRehab program successfully distinguished children diagnosed with epilepsy from the healthy controls. Moreover, the training group and waiting-list control group did not differ significantly from each other in any of the tasks assessed at baseline, suggesting no differences in visuospatial functions between these two groups before intervention.

4.2. Immediate rehabilitation effect (primary outcome)

The immediate rehabilitation effect of the intervention was examined by comparing the results in baseline tasks before and after the intervention. After the five-week training period, the training group showed an immediate rehabilitation effect in 3 out of 4 visuospatial function components: *visual organization*, *visual attention* and *visuospatial perception*.
At the same time, no significant improvements were observed in *visual recognition*. No significant immediate rehabilitation effect was observed in this component, however trend showed better improvements in the primary outcome in the training group compared to the waiting-list group. This could indicate the need for longer rehabilitation.
Following the intervention, a positive immediate rehabilitation effect in all of the parameters of *visual organization* and *visual attention* was observed, which could signify the suitability of these tasks in rehabilitation.
In *visuospatial perception*, the amount of correct responses improved. However, no significant improvements in the reaction time were observed in children with epilepsy. This could mean that the rehabilitation helped the children find better strategies to solve tasks, even though reaction times did not improve during training. The waiting-list control group improved their performance only on the reaction time in one component task compared to the first baseline assessment. This result gives further confirmation of the positive immediate effect of the rehabilitation, since it points out that the improvements for the training group were not explained by the normal developmental processes alone.

4.3. Individual improvement

Individual improvements in the training group during the rehabilitation were observed by determining the average difficulty levels achieved at the end of intervention. Also, the average number of sessions needed to advance from the first to the second difficulty level was measured.
The slowest advancement was in 2 out of 3 *visual recognition* tasks and in 3 out of 5 *visuospatial perception* tasks. In contrast, higher difficulty levels were achieved in all *visual organization* and *visual attention* tasks. More specifically, the first two tasks in the *visual recognition* component required more than 4 sessions to advance from the first difficulty level to the second. This suggests that these tasks were quite difficult and require more training for the positive immediate rehabilitation effect to appear.
In contrast, easier was *visual organization*, where children on average achieved high difficulty

levels by the end of intervention and less than 2 sessions were required to advance to the second difficulty level. Moreover, the average achieved level of *visual attention* was one of the highest - only 2 sessions were required to advance to the second level. However, both of these findings demonstrated positive immediate rehabilitation effect in the primary outcome with baseline assessment tasks.

Tasks in the *visuospatial perception* component differed from one another in terms of difficulty: children achieved higher difficulty levels only in 2 tasks out of 5. Some of the tasks could have been easier: one task required on average 6.25 out of 10 training sessions to reach the second difficulty level and another task required on average almost 4 sessions out of 10 to reach the second difficulty level. Also, the average achieved difficulty level in the Maze task was 1.62 out of 3 and it took on average 3.94 sessions to advance to the second difficulty level, indicating high difficulty of this task. This could explain why no significant improvements were found in any of the parameters of the Maze task in the training group immediately after the intervention.

In sum, children with better progress in the intervention reached 1.5-2 times higher difficulty levels compared to the children with slower progress. Specific cognitive components that require longer training on easier levels are *visual recognition* and *visuospatial perception*. Results from the individual improvement trajectories point out the need for individualized approach which takes each child’s progress into consideration.

4.4. Long-term rehabilitation effect in follow-up assessments

The long-term rehabilitation effect of the intervention was examined by comparing the results in baseline tasks before and 1.31 years after the intervention.

In *visual recognition*, a positive long-term rehabilitation effect was observed, even though no immediate rehabilitation effect was found. This may suggest that the positive effects of the intervention were observable not immediately following the intervention, but more than a year later: since the waiting-list control group did not show any improvements in the secondary outcome and the results cannot be explained by normal developmental processes alone.

In *visual organization*, even though there was a positive immediate rehabilitation effect, the amount of solved exercises (or the solving time) did not improve significantly in the secondary outcome assessment. The percent of correct answers improved in the secondary outcome, showing positive long-term rehabilitation effect. This could indicate that the strategies learned during active training were maintained, but regular training is required to keep up the speed of solving the tasks.

Positive immediate and long-term rehabilitation effect in all parameters of the *visual attention* were observed. However, the waiting-list control group also improved in the number of correct responses, indicating normal developmental processes as a possible cause, but not in the reaction time during the secondary outcome.

In *visuospatial perception,* none of the parameters demonstrated significant improvement over time in one task, despite an observed positive immediate rehabilitation effect (higher percent of correct responses). These results suggest that children should continue regular training in order to maintain the positive effect of the rehabilitation.

Still, positive long-term effect was observed in another task in the percent of correct answers and reaction time and also in the percent of navigation errors. As mentioned above, the lack of positive immediate and long-term rehabilitation effect in different parameters could be due to the high difficulty levels of some tasks. This also shows that different tasks should be used when measuring components so that various parameters of a function could be observed.

To sum up, the training group showed a preserved positive long-term rehabilitation effect in all 4 of the visuospatial function components. In contrast, the waiting-list control group improved only in the percent of correct answers on two tasks, and in the solving in one task. We believe that the normal developmental processes are not the main cause of the immediate and long-term effects in the training group since there was a noticeable difference in improvements between the two groups. Taken together, all the results from the study suggest that a successful rehabilitation effect in children's individual improvements was achieved in *visual organization* and *visual attention* as these components had tasks with easier difficulty levels. *Visual recognition* and *visuospatial perception* need further active training sessions or in some cases easier levels for a more successful rehabilitation.

4.5. Effectiveness of the computer-based intervention in the treatment of visuospatial perception deficit in children aged 8-12 diagnosed with epilepsy

Altogether, we found that the FORAMENRehab computer-based rehabilitation program is suitable for children diagnosed with epilepsy. Children were captivated by the intervention and this was supported by the full compliance and positive feedback from both the children and their parents.

Amonn, Frölich, Breuer, Banaschewski & Doepfner (2013) have stated that cognitive training programs should focus more strongly on specific neuropsychological deficits. We agree that for an effective rehabilitation, it is important to focus on specific deficits in visuospatial components. A therapist must be present to guide the child during all of the training sessions.

From our experience, the children require active guidance to effectively learn the strategies used to complete the exercises. Furthermore, in some instances the children need to be motivated to finish the tasks that are more time consuming and require more sustained attention.

As pointed out by van't Hooft et al. (2007), involving the parents in the intervention procedures gives them a better comprehension of the rehabilitation strategies and outcome. Personalized feedback for the parents was provided after the first baseline assessment to educate them about the child's specific deficits in visuospatial components. Also, feedback was provided after the primary and secondary outcome assessments to inform them about the child's progress and give necessary guidelines for future.

The aim of cognitive rehabilitation is to improve the everyday functioning of the patient's life (Sarajuuri & Koskinen, 2006). Even though no significant improvement was observed in some parameters of the visuospatial components after the intervention, the general ability of the children improved. This positive generalized effect was confirmed by parental and children's feedback, who reported improved functions in everyday life: better functioning in school tasks and positive behavioral change.

4.6. Clinical implications for computer-based visuospatial function rehabilitation in children with epilepsy and the role of therapist

Specific instructions for therapists in the rehabilitation program are required to make sure the results are not influenced by different information the child receives during training. The success of cooperation depends also on the therapist's ability to adapt his or hers instructions to the needs of the child in training: some children require enthusiastic praises, some children like jokes, other children prefer the therapist to be the same gender as them. Nonetheless, each child needed continuous motivation by the therapist. We agree with Amonn et al. (2013) who have previously stated that providing frequent and immediate feedback and reinforcement to the child is crucial in computer-based training methods. Furthermore, we found that the children's motivation was influenced by the parents' motivation, which is why it is necesarry to educate the parents about the importance of the rehabilitation in order to improve cooperation and compliance. Slomine & Locascio (2009) have pointed out that educating and involving the parent in the rehabilitation setting helps to allievate the cognitive and behavioral problems of the children. We have created a strict rehabiliation protocol and specific baselevels for the rehabilitation of visuospatial function, which could be used in the future for stationary treatment of patients in the Children's Clinic or outpatients in rehabilitation centers or even in school settings. Furthermore, this rehabilitation program could be adapted to be used on children diagnosed with different acquired brain injuries, such as traumatic brain injury. The 100% compliance further confirms the motivation of the children to participate in the study and the effectiveness of the FORAMENRehab software for chilren's neurorehabilitation.

4.7. Limitations

The study involved children who lived near to Tartu, but in the future it would be advised to include children from all over Estonia. Due to the time consuming nature of the intervention, only a small sample was used. In addition, the diagnosis of the child was known to the therapist. This could have influenced the non-verbal communication of the therapists or the way therapists provided instructions.

5. CONCLUSIONS

Neurorehabilitation with the computer-based FORAMENRehab software is effective for children with epilepsy. Before the intervention, children with epilepsy showed cognitive deficits in all of the visuospatial components compared to the healthy controls. However, the children who received the intervention showed positive immediate rehabilitation effect after the intervention in 3 out of 4 visuospatial components: *visual organization, visual attention and visuospatial perception*. Furthermore, a positive long-term rehabilitation effect in the training group was observed in all 4 visuospatial components. In contrast, the waiting-list control group improved only on some parameters of the visuospatial components, ruling out the possibility of positive outcomes only due to normal developmental processes. At least 10 intervention sessions are needed to notice substantial improvements in visuospatial components. Altogether, the general ability of the study group children improved, even though some of the visuospatial components showed no significant improvements after intervention. This positive generalized effect of the intervention was confirmed by the parent's and children's qualitative feedback with some of the learned skills transferring to everyday life. The 100% compliance and the positive results show that modern neurocognitive rehabilitation is an efficient way to guide children towards their full potential.

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