

# **Neurocognitive Functioning of Preschool Children with 'Epilepsy Only'**

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*Abstract*

*Purpose* There are only few studies concerning cognitive functioning of small children with 'epilepsy only'. The aim of this study was to describe neurocognitive functioning of 3-6 year old children with 'epilepsy only', i.e. children with epilepsy but without any associated neurological disorder or chronic illness.

*Methods* The intellectual (IQ) and neurocognitive functioning of the children with 'epilepsy only' (n=13) was compared with that of matched healthy controls (n=13). The Wechsler's Primary and Preschool Scale of Intelligence-Revised (WPPSI-R) and the Developmental Neuropsychological Assessment (NEPSY) were administered. Neurocognitive functions of Attention, Language, Sensomotor, Visuospatial and Memory were included in the assessment.

*Results* There were statistically significant differences between the study and the control group in Verbal IQ and Full scale IQ, but no difference between the two groups was found in Performance IQ. VIQ of children with 'epilepsy only' differed also statistically significantly from WPPSI-R normative data, but no differences between PIQ or FIQ and normative data were found. Children with 'epilepsy only' had subtle neurocognitive difficulties in verbal short-term memory ( $p < .01$ ) and attention ( $p < .05$ ) compared to healthy children.

*Conclusions* The intellectual functioning of children with 'epilepsy only' was comparable to healthy controls. However, children with early onset (i.e. before or during preschool age) 'epilepsy only' seem to have difficulties in general language development and special impairments in verbal short-term memory and attention skills compared to healthy preschool children. Psychological screening and detailed neuropsychological assessment are suggested for clinical practice.

Keywords: 'epilepsy only', neurocognitive function, preschool children

## INTRODUCTION

Epilepsy is one of the most common neurological disorders in childhood. Epilepsy is defined as a chronic condition characterized by a tendency towards recurrent seizures (Anderson, Northam, Hendy, & Wrennall, 2001). Seizures and epilepsies are classified according to International League Against Epilepsy (ILAE) as generalized and focal (Engel, 2001). Generalized seizures are more commonly observed among children, whereas focal seizures are predominant in adolescents and adults (Pellock, 2004). Idiopathic epilepsies are age-dependent and assumed to have a genetic etiology (Hommet, Sauerwein, De Toffol, & Lassonde, 2006). The prevalence of active epilepsy in children is estimated at between 3 and 11 per 1000 children (Larsson & Eeg-Olofsson, 2006) and in Finland 2 – 4 per 1000 in children under 16 years of age (Eriksson & Koivikko, 1997; Sillanpää, Jalava, Kaleva, & Shinnar, 1998).

The developing, immature brain is more epileptogenic than the mature brain (Moshé, 1987, 1993). Therefore, the incidence of epilepsy is highest during the first year of life and the incidence rate declines with increasing age during childhood (Anderson et al., 2001; Hauser & Annegers, 1993). Early childhood years are an important phase of brain development for neuron and synapse selection and reorganization (Aylward, 1997). During middle childhood significant changes happen in myelination of axonal tracts, synaptic densities, concentrations of neurotransmitters and degree glucose uptake (Kagan & Herschkowitz, 2005). Electroencephalography (EEG) studies show that there are cyclical growth spurts within the central nervous system (CNS), which begin at 12 – 18 months of age and last for 2 – 4 years (Anderson et al., 2001). During sensitive period the CNS is highly susceptible to the effects of damage or harmful internal or external conditions (Aylward, 1997). Any interruption (e.g. the presence of an active epileptic focus) during a critical period of the CNS development may divert the expected developmental course and interfere with the normal maturation of cognitive functions (Anderson et al., 2001; Elger, Helmstaedter, & Kurthen, 2004; Hommet et al., 2006).

Animal and clinical studies demonstrate that early seizures may profoundly influence the brain development and increase the later vulnerability of the matured brain to the effects of seizures (Holmes, 2004; Squier, Salisbury, & Sisodiya, 2003). Seizures and antiepileptic drugs (AED) may have age-dependent outcome on development and behavior (Moshé, 1993, 2000). Particularly early onset and refractory epilepsy with recurrent seizures affects cognitive development (Elger et al., 2004; Kobayashi

et al., 2001; Leonard & George, 1999; Mangano, Fontana, & Cusumano, 2005). In addition to permanent deficits, early seizures may change the developing neural circuits (Motamedi & Meador, 2003). Especially, epilepsies with onset in the first year of life have poor prognosis for cognitive outcome (Battaglia et al., 1999). Mandelbaum and Burack (1997) concluded that later, school-aged onset epilepsy has a better prognosis because of the skills and knowledge acquired prior to the onset of epileptic seizures and initiation of antiepileptic medication. On the other hand, early onset epilepsy can also induce processes of functional reorganization and behavioral compensation (Elger et al., 2004). Also, normal development before onset of epilepsy is regarded as an indicator for favourable cognitive outcome (Battaglia et al., 1999). On the other hand, Vanderlinden and Lagae (2004) demonstrated that some preschool children with idiopathic epilepsy become developmentally delayed because of the poor seizure control and despite the normal development before the seizure onset. Further, Smith, Elliot and Lach (2002) demonstrated that even children with relatively short seizure history may show considerable neurocognitive impairments.

In addition to age at seizure onset, other epilepsy related factors are also associated with cognitive functions. In school-aged children with epilepsy, seizure type, frequency and duration of seizures, antiepileptic drugs (AEDs) and their side-effects are associated with neurocognitive and learning problems (Aldenkamp, Overweg-Plandsoen, & Diepman, 1999; Leonard & George, 1999). Some (Bailet & Turk, 2000) have found no relation between age at the onset of seizures, seizure type or frequency and neurocognitive functions. The severity of epilepsy (i.e. seizure frequency) is regarded the dominant factor associated with lower intellectual functioning in children with partial or generalized epilepsy (Tromp et al., 2003). In addition, an early onset and a burden of anticonvulsive therapy are associated with poorer intellectual capacity (Elger et al., 2004; Nolan et al., 2003). Duration of epilepsy has been found to relate with intelligence (Smith et al., 2002). However, there is also evidence that even relatively short seizure history could be associated with considerable impairment in neurocognitive functioning (Smith et al., 2002). Deficits have also been reported with newly diagnosed epilepsies (Austin et al., 2002; Kolk, Beilmann, Tomberg, Napa, & Talvik, 2001; Oostrom, Smeets-Schouten, Kruitwagen, Peters, & Jennekens-Schinkel, 2003), although the impairments do not necessarily persist (Oostrom, Schouten, Kruitwagen, Peters, & Jennekens-Schinkel, 2002). Also, Lindgren et al. (2004) indicated that after active phase of idiopathic epilepsy cognitive development in children resembles that of healthy children.

Developmental problems are more common in children with symptomatic epilepsy than in children with idiopathic or cryptogenic epilepsy (Rodin, 1989; Svoboda, 2004). In most idiopathic, uncomplicated epilepsies cognition is mildly impaired or within normal range (Elger et al., 2004; Hommet et al., 2006; Motamedi & Meador, 2003; Rodin, 1989). Children with partial or convulsive seizures have been found to have a better cognitive performance compared to children with generalized seizures (Dodrill, 2004; Mandelbaum & Burack, 1997). Prior to antiepileptic medication children with generalized or absence seizures seem to be at greater risk of having cognitive impairments (Mandelbaum & Burack, 1997).

Normal development and average intellectual functioning are associated with idiopathic epilepsies (Mandelbaum & Burack, 1997; Motamedi & Meador, 2003). In spite of the benign medical prognosis, various neurocognitive deficits have been reported in children with idiopathic epilepsies. Mental slowing, impairments in attention and memory are quite typical in children with epilepsy (Aldenkamp et al., 1999). Slower reaction times (Aldenkamp & Arends, 2004; Kolk et al., 2001; Leonard & George, 1999; Suurmeijer, Reuvekamp, & Aldenkamp, 2001), overall attention problems (Gülgönen, Demirbilek, Korkmaz, Dervent, & Townes, 2000; Kolk et al., 2001; Oostrom, Teeseling, Smeets-Schouten, Peters, & Jennekens-Schinkel, 2005) and specific deficits in visual and verbal attention (Henkin et al., 2005; Williams, Griebel, & Dykman, 1998) have frequently been reported in school-aged children with idiopathic epilepsy or ‘epilepsy only’. Aldenkamp et al. (2001) also found problems with alertness. Reported attention problems are more often inattentive than impulsive type, although attention-deficit-hyperactivity disorder (ADHD) is also associated with epilepsy (Hiemenz, Hynd, & Jimenez, 1999; Leonard & George, 1999; Williams, Schulz, & Griebel, 2001). In addition, various memory problems have been reported; impairments in short-term memory (Bailet & Turk, 2000; Kolk et al., 2001; Oostrom et al., 2005; Suurmeijer et al., 2001), verbal (Gülgönen et al., 2000; Henkin et al., 2005), both in visual and nonverbal memory (Gülgönen et al., 2000; Pavone et al., 2001) and generalized memory problems (Northcott et al., 2005) have been demonstrated.

When language functions have been studied, deficits in word fluency (Henkin et al., 2005), auditory perception and lexical skills (Kolk et al., 2001), phonological processing (Northcott et al., 2005) and speech production and comprehension (Cohen & Le Normand, 1998; Kolk et al., 2001) have been reported. Specific neurocognitive impairment in school-aged children with epilepsy also include deficits in visuomotor coordination (Hiemenz et al., 1999; Leonard & George, 1999), controlled fine motor responses (Henkin et al., 2005), psychomotor speed (Bailet & Turk, 2000), visuooperceptual

abilities (Kolk et al., 2001), and severe non-verbal problems (Høie et al., 2005). Though there are a lot of studies showing different kinds of neurocognitive impairments in children with epilepsy, there are also opposite results. For example, Pavone et al. (2001) found intact verbal memory and language functions. Also, Boelen et al. (2005) reported the overall psychomotor development comparable to controls.

This inconsistency of findings demonstrates that there exists no single pattern of neuropsychological impairment in idiopathic epilepsy (Deonna, Zesiger, Davidoff, Maeder, & Roulet, 2000; Seidenberg, 1989) or in childhood epilepsy in general (Williams et al., 1998). Instead, a more diffuse neuropsychological profile with benign childhood epilepsy (Germanó et al., 2005; Williams et al., 1998) has been suggested. There is also a lack of consistency in the literature between neurocognitive functioning and seizure related factors (Fastenau et al., 2004). It is clear, that the association between epilepsy and comorbid neurocognitive deficits is complex and direct causality has not been demonstrated. Family related factors (i.e. disorganized/unsupportive home environments) have been found to further affect the neuropsychological deficits (e.g. Fastenau et al., 2004). As Nolan et al. (2003) point out, the majority of studies have been conducted in school-aged children. Studies of the impact of early onset seizures and subsequent development are relatively scarce.

The purpose of the present study was to describe the intellectual and neuropsychological functioning of preschool children with 'epilepsy only'. The term preschool refers to children from three to six years of age. In this study children with epilepsy but without any associated neurological disorder or chronic illnesses are referred as 'epilepsy only' (Sillanpää, 1992), i.e. children with seemingly age appropriate neurological and social development. The neurocognitive functioning of the 'epilepsy only' children was compared with that of matched healthy controls. Two primary research questions were 1) Do the preschool children with 'epilepsy only' differ from healthy controls in their intellectual functioning and 2) Do the preschool children with 'epilepsy only' differ from healthy controls with respect to neurocognitive functions? Also, the associations between intellectual, neurocognitive variables and epilepsy related factors (e.g. epilepsy type and onset of seizures) were studied. On the basis of previous studies conducted on school aged children with idiopathic epilepsy or 'epilepsy only', it was hypothesized first that the intellectual functioning of the study group were within normal range and no statistical difference between the study and the control group existed. Second assumption was that if any neurocognitive deficits were to be found, they would demonstrate a diffuse pattern with various

impairments in attention, memory and / or visuomotor speed as in school aged children with epilepsy (Aldenkamp et al., 1999).

This research was made in collaboration with Department of Psychology at University of Tampere, Paediatric Neurology Unit of Tampere University Hospital and Paediatric Research Centre at University of Tampere. The study was approved by the ethical committee of Tampere University Hospital.

## **METHODS**

### **Participants**

The data consisted of population-based cohort of preschool children with active epilepsy (N=58) that were identified from the Paediatric Neurology Unit at Tampere University Hospital, Finland. All the patients who were 3 – 6 years old with epilepsy at point prevalence day (September 30, 2004) participated in the study. The inclusion criteria were diagnosed epilepsy, no other neurological disorders or developmental delay assessed by standardized psychological tests (IQ > 75 was required), MRI within normal range, age between 3 and 6 years 11 months. Exclusion criteria were any associated major neurological disorder identifiable from previous medical records or reported by parents or caregivers. Total of 26 children were excluded on the basis of IQ < 75 and/or other associated neurological disorders (e.g. cerebral palsy). Of the original cohort (N=58) total of 55 % (n=32) children had ‘epilepsy only’. Of these ‘epilepsy only’ children, 41 % (n=13) parents gave their written consent for participation to the study. There were no differences between participants and non-participants on IQ-scores or epilepsy related factors. Non-participants were, however, significantly older than participants; their mean age was 72 months compared to 58 months of the study group ( $t(23) = -3.40$ ,  $p < .01$ ).

Intelligence tests and neuropsychological assessments were made to 13 children with epilepsy on the basis of informed consent obtained from their parents. Two children failed to complete the full neuropsychological assessment due to oppositional behavior and/or other behavioral problems. Also, the other child had fluctuating, occasionally high seizure frequency. Therefore, the number of participants in the study group varies between 11 and 13 depending upon subtest in question. Neuropsychological assessments took place at Tampere University Hospital, Department of Psychology in University of Tampere or at the day-care centre.

**Healthy controls** were age and gender matched healthy volunteers with the same exclusion criteria as the study group; no chronic illness or neurological disorder. These children were from two day-care centres at Lempäälä Municipality, near Tampere. The managers of the day-care centres were asked to exclude those children who had some chronic illness or developmental problems (e.g. specific language impairment, mental retardation, autism) or who needed special assistance or special education based on medical and/or developmental reason. Total of 23 parents gave their written consent to participate of those healthy children who were included as potential controls. Of these volunteers, 13 children were matched according to age ( $\pm$  3 months) and gender with the study children. Neuropsychological assessments took place at the day care centres.

### **Medical and background data**

Medical data including demographic factors, duration of epilepsy, seizure and epilepsy type, seizure control during the time of the study, electroencephalographic recordings (EEG), imaging of the brain with 1,5T magnetic resonance imaging (MRI), current AEDs and most recent AED levels were analyzed retrospectively from children's medical records. Also results of previous psychological evaluations made according to clinical practice during earlier routine visits to the paediatric neurology unit were reviewed. Additional data was collected by using background information questionnaire which included variables concerning children's medical and non-medical every-day living (e.g. need for day-care, therapies, play and seizure related variables).

### **Intellectual and neuropsychological assessment methods**

All the subjects and the controls were assessed by clinical neuropsychologists and using the same standardized tests. The Weschler's Primary and Prescool Scale of Intelligence, WPPSI-R (Weschler, 1995) was used to assess intellectual functioning. Scores for Full Scale Intelligence Quotient (FIQ), for Verbal Intelligence Quotient (VIQ) and for Performance Intelligence Quotient (PIQ) were estimated on the basis of following subtests: Information, Similarities, Arithmetic, Picture Completion, Block Design and Object Assembly.

Neurocognitive functions were assessed by the NEPSY-test, the Developmental Neuropsychological Assessment (Korkman, Kirk, & Kemp, 1997). NEPSY-test consists of five domains: Attention and Executive Function, Language Function, Sensomotor Function, Visuospatial Function and Memory and Learning Function. Ten subtests (two per each function) were selected to obtain the core assessment of



the neurocognitive development i.e. a brief overview of the five complex, cognitive domains mentioned. From the suggested subtests for core assessment those ten that were recommended for ages 3 – 4 and for ages 5 – 6 were chosen (Korkman et al., 1997). For the Attention and Executive Function subtests Visual attention and Statue, for the Language Function subtests Comprehension of Instructions and Phonological Processing, for the Sensomotor Function subtests Visuomotor Precision and Imitating Hand Positions, for the Visuospatial Function subtests Blocks and Copying and for the Memory and Learning Function subtests Sentence Repetition and Narrative Memory were administered. Thus, the neuropsychological assessment consisted total of 16 subtests and the assessment takes two to three sessions (á 45 minutes).

### **Statistical analysis**

Statistical analyses were made by the SPSS (version 12.0). For the comparison of the intellectual functioning of the study and the control group, Full Scale IQ, Verbal IQ and Performance IQ were calculated. Standard scores and z-scores for age groups were used in the analysis of the group differences. Continuous and normally distributed variables were compared with ANOVA. Normality was tested with Shapiro-Wilk and homogeneity of variances was tested with Levene's test. IQs were also compared against the normative data of WPPSI-R test by using Student's t-test. Spearman's rho was used to explore the linkage between epilepsy related factors and neurocognitive variables. P-values less than .05 were considered statistically significant. Clinically significant neurocognitive impairment was considered to exist when a child scores two standard deviations below the neuropsychological test mean (i.e. standard score <4) (Korkman, 2000; Lezak, 1995).

## **RESULTS**

### **Data**

The data consisted of thirteen children (six boys and seven girls) with 'epilepsy only' and their matched controls. The study and the control group had a comparable social status. Mean age was 4 years 10 months (i.e. 58,0 months, SD=10,84) in study group and 5 years (i.e. 60,7 months, SD=10,09) in the control group. In the 'epilepsy only' group (n=13) the age at the onset of epilepsy varied between 6 and 64 months, mean age at the onset was 2 years 4 months. Six children were under 24 months and 7 children between 25-72 months at the onset of epilepsy. Focal epilepsy (FE) was diagnosed in 6 children and generalized epilepsy (GE) in 7 children. MRIs were normal with all children, and EEGs were consistent with the clinical seizure and epilepsy diagnosis. Nine children were on AED

monotherapy, three children on polytherapy and one child had no AED. Valproate was the most common AED used (n=10). Seizure control was good (i.e. seizure remission of at least 1 year at the time of the study) in four children, partial (i.e. seizures less than once a month) in six children and poor (i.e. monthly seizures) in three children. Clinical characteristics of the study group are presented in the Table 1. All the children in the ‘epilepsy only’ group had received special day care services based on the diagnosis of epilepsy, but none in the control group. In Tampere University Hospital District, the special day-care services are commonly available for children with chronic illnesses. Eight children in the study group have received therapies at some point during their lives. Speech therapy was ongoing therapy in three children, occupational therapy in two children and physiotherapy in one child. One child had three simultaneous therapies. In the control group only one child had speech therapy and other have not received any therapies.

Table 1 here

Clinical characteristics of the study group

### **Intellectual functioning**

IQ-scores were at the lower end of the normal distribution with the 'epilepsy only' group and at the upper end with the controls. Verbal intelligence quotient (VIQ) was 92,5 (SD=10,5) in epilepsy group and 113,0 (SD=10,2) in controls, Performance intelligence quotient (PIQ) was 99,4 (SD=13,3) and 108,6 (SD=14,4) with controls and Full scale intelligence quotient (FIQ) was 94,6 (SD=12,2) and 112,8 (SD=13,0) with controls. VIQ and FIQ differed significantly between the study and control groups (VIQ  $F_{1, 24}=25,4$ ,  $p=.000$  and FIQ  $F_{1, 24}=13,5$ ,  $p=.001$  respectively), but no differences between the two groups was found in PIQ ( $F_{1, 24}=2,9$ ,  $p=.104$ ). VIQ of children with 'epilepsy only' differed also statistically significantly from WPPSI-R norms ( $t(12)=-2,58$ ,  $p=.02$ ), but no differences between PIQ or FIQ and norms were found. VIQ were more discrepant from PIQ (i.e. VIQ scores lower than 1 SD, -15 IQ-points from PIQ) in the study group ( $F_{1, 24}=4,43$ ,  $p=.05$ ) compared to controls. There were six children in the study group with VIQ over 1 SD lower than PIQ, but none in the control group.

### **Neurocognitive functioning**

All the NEPSY subtest-scores in the study group were within -2 standard deviations (SD) compared to the norms and within 1 SD in the control group (Table 2). The study group performed better than controls in three subtests: Phonological processing, Visuomotor precision and Block construction, although the difference was not significant. Children with epilepsy had lower scores on several NEPSY subtests compared to scores of the healthy controls (Table 2). Children with epilepsy had mild difficulties (standard scores below 1 SD, i.e. standard score  $< 7$ ) in Comprehension of instructions, Repetition of sentences and Imitating hand positions. The study group performed weaker than healthy controls in the subtests Repetition of sentences ( $F_{1, 22}=10,70$ ,  $p=.003$ ), Comprehension of instructions ( $F_{1, 24}=7,83$ ,  $p=.01$ ) and Visual attention ( $F_{1, 23}=5,01$ ,  $p=.035$ ). However, no clinically significant neurocognitive impairments (i.e. subtest scores 2 SD below the neuropsychological test mean, standard score  $< 4$ ) (Korkman et al. 1997; Lezak 1995) existed in children with epilepsy. The variances of visuospatial and visuomotor subtests within both the study and the control groups were large and no differences between the two groups were found. Detailed performances in the IQ-test and neurocognitive domains of the study group are presented in Table 3.

Table 2 here  
The standard scores of the NEPSY subtests

Table 3 here  
Intellectual and neurocognitive data of the study group

The mean z-scores for the main neurocognitive domains were calculated from the domain subtests in NEPSY-test. Statistically significant differences between the groups were found in Attention ( $F_{1, 22} = 5,85$ ,  $p = .024$ ) and Verbal short-term memory ( $F_{1, 22} = 8,53$ ,  $p = .008$ ) (see Figure 1).

Figure 1 here  
Mean z-scores of the study and the control group for neurocognitive domains of the NEPSY-test

When studying the associations between intellectual functioning and epilepsy related variables, there were no differences between generalized (GE n=7) and focal (FE n=6) epilepsy types (GE/FE: VIQ= 92,3 / 92,3, PIQ=101,3 / 97,2, FIQ=95,6 / 93,5). Correlations between seizure control and neurocognitive variables were not statistically significant. None of the epilepsy related factors were correlating with VIQ, PIQ or FIQ, except secondary seizures that were associated with FIQ ( $\rho = -.59$ ,  $p = .03$ ). There were three epilepsy related variables: age at the onset of seizures, initiation of AEDs and total number of seizures that were associated with the neurocognitive domains. The age at the onset of seizures were associated with Attention ( $\rho = .91$ ,  $p < .001$ ) and Verbal short-term memory ( $\rho = .73$ ,  $p = .02$ ). Initiation time of AEDs were associated with Attention ( $\rho = .81$ ,  $p < .01$ ), Visuospatial ( $\rho = .62$ ,  $p = .04$ ) and Verbal memory ( $\rho = .66$ ,  $p = .03$ ) domains, and also total number of seizures correlated with Visuospatial domain ( $\rho = .59$ ,  $p = .05$ ).

## DISCUSSION

The aim of this study was to describe the intellectual and neurocognitive functioning of children with ‘epilepsy only’ in early childhood and to compare them with the functioning of healthy controls. Idiopathic epilepsy or ‘epilepsy only’ is regarded having a good medical prognosis and the intellectual functioning of school aged children is generally within normal limits (Bailet & Turk, 2000; Mandelbaum & Burack, 1997). Also, normal development before seizure onset predicts a good cognitive outcome (Battaglia et al., 1999). Therefore, the intellectual functioning of children with ‘epilepsy only’ was expected to be normal. In this study, the intellectual functioning of the ‘epilepsy only’ children were indeed within the normal range but differed from that of matched healthy controls. This difference compared to healthy children was against expectations.

Based on the previous studies, some diffuse problems in attention, visuomotor speed and / or memory functions were assumed to found. With respect to neurocognitive domains, some functions of the ‘epilepsy only’ children were normal. In addition to performance IQ, visuospatial and sensomotor functions were intact and no differences were found compared to these functions of controls. The overall psychomotor development has been indicated to be comparable to controls (Boelen, Nieuwenhuis, Steenbeek, Veldwijk, Ven-Verest et al., 2005), although previously, also deficits in visuomotor coordination (Hiemenz et al., 1999; Leonard & George, 1999), psychomotor speed (Bailet & Turk, 2000; Boelen, Nieuwenhuis, Steenbeek, Veldwijk, Ven-Verest et al., 2005) and visuoperceptual abilities (Høie et al., 2005; Kolk et al., 2001), have also been reported in school-aged

children with epilepsy. In this study, one sensomotor subtest, Imitation of hand positions, was found to be problematic, because both the study group and the healthy children performed at the lower end of norms. Korkman (2000; Korkman et al., 1997) has pointed out, that the reliability of sensomotor subtests may be weaker in younger children. This unreliability may reflect individual maturation and differentiation of sensomotor skills also in healthy children.

Attention skills of preschool children with ‘epilepsy only’ may be considered moderately affected compared to healthy controls. This result is concordant with previous studies of attention problems with school-aged children with idiopathic epilepsy or ‘epilepsy only’ (Gülgönen et al., 2000; Kolk et al., 2001). Attention deficits have been associated with both absence and generalized tonic-clonic seizures (Henkin et al., 2005), but attention problems do not necessarily persist (Oostrom et al., 2002). In addition to attention, the study group in this study differed from controls with respect to verbal short-term memory. Various memory problems, including short-term memory problems (Nolan et al., 2004; Northcott et al., 2005) have been demonstrated before. However, the neurocognitive impairments found in attention and in verbal short-term memory were not clinically significant, if the clinical significance is defined as a performance lower than two standard deviations from the norms.

Contrary to previous research and preliminary expectations, language was mostly affected in preschool children with ‘epilepsy only’. There was a difference between ‘epilepsy only’ children and controls in Verbal IQ and Comprehension of instructions. At the individual level, there were some children ( $n=6$ ) in the study group with Verbal IQ significantly lower than the Performance IQ, which may be regarded as clinically significant indicator for language difficulties (Lezak, 1995). In addition, verbal short-term memory difficulty found in this study could be explained with primary impairment in receptive language, because pure memory deficits are rarely seen in young children (Aylward, 1997) and verbal memory deficits in children are often associated with language impairments (see for overview Baddeley, 2003). Further, one could also argue that memory functions during early childhood are yet to be matured and differentiated as a specialized function (Gathercole, 1998; Tideman & Gustafsson, 2004).

The association between epileptic activity and language development have been suggested before (Monjauze, Tuller, Hommet, Barthez, & Khomsi, 2005; Svoboda, 2004), and language development may be adversely affected by epileptic activity (Gordon, 2000). On the other hand, according to study by Pavone et al. (2001) verbal memory and language capacity should be intact in idiopathic generalized

epilepsy. Language deficits and attention problems have been also met in benign epilepsy (Hommet et al., 2006). Language deficits in auditory perception, lexical skills and comprehension of speech have also been reported in children with new onset partial epilepsy (Kolk et al., 2001). Cohen and Le Normand (1998) found also deficits in linguistic comprehension and production in their longitudinal study of children with early onset simple partial seizures focusing on the left hemisphere. However, even the delay in speech comprehension persisted for years, it reached normal levels by the age of seven. Instead, problems in linguistic production persisted longer. In this study, there were only four children with good seizure control. Therefore, the deficits found in language may also be an indication of active epilepsy possibly disappearing after remission as some have found to be typical pattern in some benign childhood epilepsies (Lindgren et al., 2004; Northcott et al., 2006; Svoboda, 2004). Although, some researches (Pavone et al., 2001) has not found any association between the duration of remission and cognitive impairment. Early childhood is a critical period of language acquisition and establishment. Therefore, it is possible that electrophysiological epileptic activity, seizures and / or antiepileptic medication at that time may interfere especially with language development, which is active at that age period. Gordon (2000) emphasized the importance of the association between epileptic activity and language especially in small children, but not all the studies (Monjauze et al., 2005) found correlation between the age at the seizure onset and language performance. Alternative explanation may be an undetermined maturation defect of the brain as suggested by Doose and Baier (1989).

With respect to seizure type, Mandelbaum and Burack (1997) found that children with partial (or focal) seizures performed better than children with generalized seizures on cognitive functioning. In this study, possibly due to a small sample size, no difference was found in cognitive functioning between focal and generalized seizures. In the correlation analysis, only few epilepsy related factors associated with neurocognitive domains of attention, verbal short-term memory and visuospatial functions.

The benefits of this study are the narrow age group, consistent and widely used psychological testing measures and the use of matched control group. Usually, in order to obtain sufficient data (i.e. patients), studies have gathered patients from wider age group (e.g. children from 3 to 16 years of age). Neuropsychological assessments with standardized tests are also time-consuming and require trained neuropsychologist. Therefore the total number of the participants remains often quite small in clinical studies. Also, the results of the present study are based on a limited number of participants. However, there were no differences on overall intellectual functioning between participating and non-

participating children with ‘epilepsy only’. Therefore, the study group may be considered to be a fairly representative sample of neurocognitive functioning of preschool children with ‘epilepsy only’. Nevertheless, due to the small sample size, the results may be best seen as preliminary. Partly missing detailed neuropsychological data in two subjects may also affect the overall findings.

The developmental changes in cognitive processes during childhood have not been fully studied, although there is consensus that developmental changes may occur in the level and also in the structure of performance (Korkman et al., 1997). Studies focusing on early childhood or preschool years are mostly lagging. Some studies do exist (e.g. Battaglia et al., 1999), but the focus on these studies has been on medical aspects and remission of seizures rather than on the psychological outcome. Some studies with neuropsychological assessments have been conducted (e.g. Chaix et al., 2003; Mangano et al., 2005). Still, further studies with detailed neuropsychological assessments and follow-up time are needed to obtain more insight to the developmental course of ‘epilepsy only’ children. Studies at the level of overall intellectual functioning (IQ) do not suffice anymore. It seems unlikely, that there is a specific pattern of neuropsychological impairment in idiopathic epilepsy (Deonna et al., 2000; Seidenberg, 1989). Rather, a more diffuse neuropsychological profile with idiopathic childhood epilepsy (Germanó et al., 2005; Williams et al., 1998) has been suggested. This may partly reflect the inconsistency of the results concerning the association between neurocognitive functioning and seizure related factors. Previously, lower intellectual functioning was associated with childhood epilepsy, but the studies were based on heterogeneous groups. Later, the overall cognitive development with uncomplicated childhood epilepsy was regarded normal, but there are increasing number of studies demonstrating a subtle, but identifiable neurocognitive problems with benign epilepsies. Today, subtle neurocognitive difficulties may be regarded as quite common in children with idiopathic epilepsy despite the good cognitive overall capacity. Still, there is no consensus about the association between epilepsy related factors and neurocognitive deficits.

In summary, neurocognitive deficits found in this study were subtle and their clinical significance for further development of these preschool children is difficult to determine. However, it is also important to notice that these subtle neurocognitive impairments are not necessarily socially disabling cognitive deficits (Elger et al., 2004), but definite answers would require a long-term follow-up study. In Finland, multi-center studies are needed in order to obtain sufficient data. Because of developmental risks found in this study, psychological screening and detailed neuropsychological assessment are suggested in clinical practice. Buelow and McNelis (2002) have also suggested that neuropsychological assessment



should be considered in the initial evaluation of children with epilepsy. So far, it is unclear whether the mild neurocognitive deficits during the development persist or whether they resolve after seizure remission. Lindgren et al. (2004) suggested the importance of maturational factors in the development of cognitive functions. Therefore, the follow up of children with early onset 'epilepsy only' is crucial as a standard procedure.

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## Appendix 1

Table 1 Clinical characteristics of the study group

Subject number	Gender, age	Epilepsy type	Age at onset	EEG	AED	Seizure control*
1	Boy, 4 yrs, 8 months	G40.3 CAE <sup>1</sup>	3 yrs	Generalised epileptiform abnormality	Valproate	Poor
2	Girl, 6 yrs, 10 months	G40.3CAE <sup>1</sup>	3 yrs, 9 months	Generalised epileptiform abnormality	Valproate	Partial
3	Boy, 5 yrs, 9 months	G40.3 GE <sup>2</sup>	3 yrs, 8 months	Generalised epileptiform abnormality	Lamotrigine	Good
4	Girl, 3 yrs, 7 months	G40.4 GE <sup>2</sup>	2 yrs, 11 months	Normal	Levetiracetam, valproate, fenobarbital	Partial
5	Boy, 6 yrs, 3 months	G40.3 GE <sup>2</sup>	2 yrs, 1 month	Generalised epileptiform abnormality	Oxcarbazepine, Valproate	Partial
6	Boy, 3 yrs, 11 months	G40.3 GE <sup>2</sup>	1 yr, 11 months	Focal epileptiform abnormality	Valproate	Partial
7	Boy, 5 yrs, 3 months	G40.3 GE <sup>2</sup>	1 yr, 9 months	Normal	Valproate	Good
8	Boy, 5 yrs, 6 months	G40.2 FE <sup>3</sup>	5 yrs, 4 months	Focal epileptiform abnormality	Oxcarbazepine	Partial
9	Girl, 4 yrs, 2 months	G40.2 FE <sup>3</sup>	2 yrs, 11 months	Abnormality of background activity	Valproate	Poor
10	Girl, 6 yrs, 3 months	G40.2 FE <sup>3</sup>	6 months	Abnormality of background activity	no AED	Good
11	Girl, 4 yrs, 4 months	G40.2 FE <sup>3</sup>	6 months	Abnormality of background activity	Valproate	Poor
12	Girl, 5 yrs, 6 months	G40.29 FE <sup>3</sup>	9 months	Generalised epileptiform abnormality	Topiramate, valproate	Good
13	Girl, 3 yrs, 9 months	G40.2 FE <sup>3</sup>	1 yrs, 1 month	Generalised epileptiform abnormality	Valproate	Partial

<sup>1</sup> Childhood absence epilepsy, <sup>2</sup> Generalized epilepsy, <sup>3</sup> Focal epilepsy

\* Seizure control: Good: seizure remission > 1 year, Partial: seizures < 1 per month, Poor: seizures > 1 per month

## Appendix 2

Table 2 The standard scores of the NEPSY subtests

NEPSY subtest	Group Study (n=13) M	SD	Control (n=13) M	SD	F	p-value
Visual attention <sup>1</sup>	10,17	4,53	13,62	3,10	F(1,23)=5,01	.035*
Statue <sup>2</sup>	7,09	3,24	8,77	3,94	F(1,22)=1,27	.272
Phonological processing <sup>2</sup>	9,33	1,97	9,00	1,41	F(1,23)=0,24	.629
Comprehension of instructions	6,77	2,71	9,62	2,47	F(1,24)=7,83	.010**
Imitating hand positions <sup>1</sup>	6,36	3,08	7,31	2,43	F(1,22)=0,71	.410
Visuomotor precision <sup>1</sup>	9,00	3,82	8,85	3,81	F(1,22)=0,01	.922
Copying	8,69	4,98	9,08	3,15	F(1,24)=0,06	.816
Block construction <sup>1</sup>	11,00	3,38	10,77	2,35	F(1,22)=0,04	.846
Narrative memory <sup>1</sup>	9,09	2,59	10,92	2,66	F(1,22)=2,90	.103
Repetition of sentences <sup>1</sup>	5,55	3,14	9,46	2,73	F(1,22)=10,70	.003**

\*p< .05, \*\*p< .01

<sup>1</sup> n=11, <sup>2</sup> n=12

## Appendix 3

Table 3 Intellectual and neurocognitive data of the study group

Subject number	Gender, age	VIQ*	PIQ**	FIQ** *	Attention z-score	Language z-score	Sensomotor z-score	Visuospatial z-score	Verbal memory z-score
1	Boy, 4 yrs 8 months	104	122	116	,33	-,50	-,33	1,83	,17
2	Girl, 6 yrs, 10 months	111	110	112	-,50	-,33	-,17	1,00	-,67
3	Boy, 5 yrs, 9 months	100	98	98	<sup>1</sup>	-,83	<sup>1</sup>	<sup>1(2)</sup>	<sup>1</sup>
4	Girl, 3 yrs, 7 months	83	83	78	,00	-,83	-,67	-,33	,00
5	Boy, 6 yrs, 3 months	77	96	83	-,1,50	-,1,67	-,2,00	-,67	-,1,67
6	Boy, 3 yrs, 11 months	96	107	101	1,17	-,50	-,1,00	,00	-,2,00
7	Boy, 5 yrs, 3 months	77	93	81	-,1,67	-,50	-,1,33	-,33	-,1,67
8	Boy, 5 yrs, 6 months	84	104	93	-,83	-,67	,17	-,33	-,1,50
9	Girl, 4 yrs, 2 months	96	104	100	-,1,00	-,1,33	-,1,83	-,1,50	-,1,50
10	Girl, 6 yrs, 3 months	102	91	96	,17	,17	,00	2,17	,50
11	Girl, 4 yrs, 4 months	93	110	101	-,33	,17	-,67	,67	-,83
12	Girl, 5 yrs, 6 months	93	70	77	-,17	-,33	-,67	-,1,00	-,67
13	Girl, 3 yrs, 9 months	86	104	94	<sup>1(3)</sup>	<sup>1(3)</sup>	<sup>1</sup>	<sup>1(3)</sup>	<sup>1</sup>

\* Verbal Intelligence Quotient

\*\* Performance Intelligence Quotient

\*\*\* Full Scale Intelligence Quotient

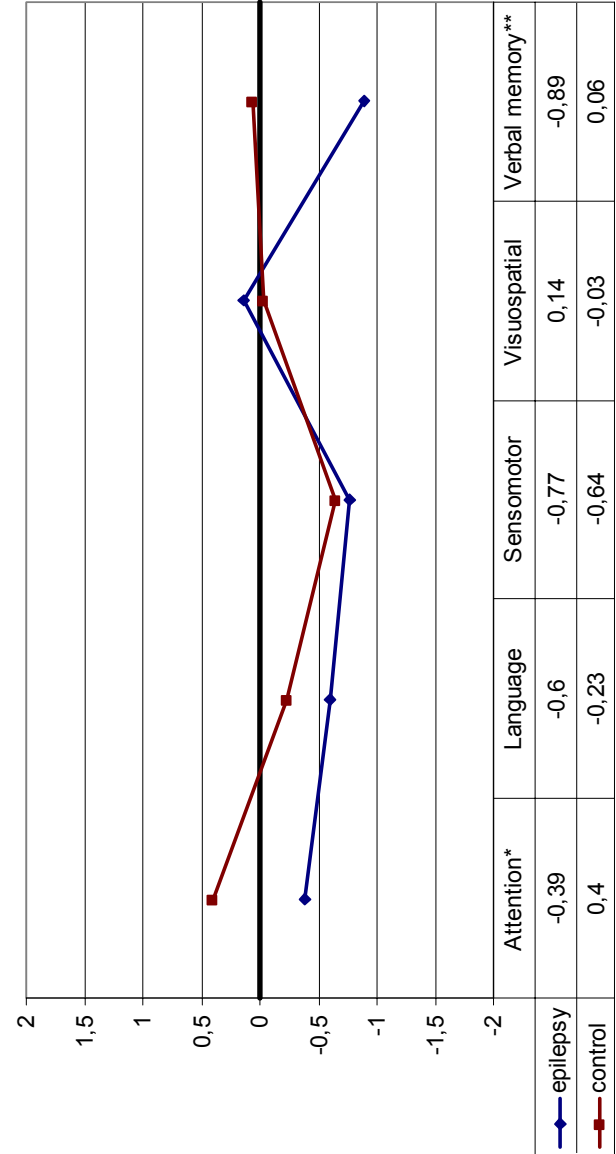
<sup>1</sup> Missing data in either a single subtest or both subtests required for domain score

(<sup>2</sup>) The subject was able to complete Copying (-1,94).

(<sup>3</sup>) The subject was able to complete Statue (-1,11), Comprehension of instructions (-1,94) and Copying (-2,22).



Appendix 4



\*p< .05, \*\*p< .01

Figure 1 Mean z-scores of the study and the control group for neurocognitive domains of the NEPSY-test