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COGNITIVE PROFILE AND ITS CHANGES IN CHILDREN WITH NEONATAL AND CHILDHOOD STROKE

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Running head: Cognitive outcome in pediatric stroke

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ABSTRACT

This study assesses the cognitive outcome of children with stroke and differences in profiles related to stroke onset (neonatal vs childhood insult) and other clinical variables. 21 children with neonatal and 10 children with childhood stroke were assessed with NEPSY test battery. Data of prospective assessment of 20 children are included to estimate the developmental change in cognitive functions. Children with neonatal stroke showed significant deficits in various domains, including sensorimotor, visuospatial, language, memory and attentional skills. Children with childhood stroke had deficits in sensorimotor, memory and attentional skills. Stroke type (ischemic vs hemorrhagic) had most consistent effect on cognitive profile but this depended on stroke onset. According to prospective data cognitive abilities had a small improvement in long-term. The speed of change was not consistently affected by different clinical measures in both groups.

Keywords: cognitive outcome, development, neonatal stroke, childhood stroke, neuropsychological assessment

KOKKUVÕTE

Kognitiivne profiil ja selle muutused lastel neonataalse ja lapseea insuldi korral

Selle uuringu eesmärgiks on hinnata kognitiivse arengu kaugtulemusi ajuinsuldiga lastel ning kahjustuse tekkeaja (neonataalne vs lapseea insult) ja teiste kliiniliste muutujate mõju kognitiivsele profiilile. Hinnatud on 21 last neonataalse ja 10 last lapseea insuldiga, kasutades NEPSY testipatareid. Lisatud on prospektiivse uuringu andmed 20 lapse kohta, et hinnata arengulisi muutusi kognitiivsetes funktsioonides. Neonataalse insuldiga lapsed said oluliselt kehvemad tulemused mitmetes funktsioonides, sh sensomotoorsetes, visuaal-ruumilistes, keele, mälu ja tähelepanuülesannetes. Lapseea insuldiga lapsed said kehvemad tulemused sensomotoorsetes, mälu- ja tähelepanuülesannetes. Insuldi tüüp (isheemiline vs hemorraagiline) mõjutas kognitiivset profiili kõige enam, sõltudes kahjustuse tekkeajast. Prospektiivse uuringu andmetel paranesid kognitiivsed võimed vähesel määral. Muutuste kiirus polnud mõlemas grupis süstemaatiliselt mõjutatud erinevate kliiniliste näitajate poolt.

Märksõnad: kognitiivsed kaugtulemused, areng, neonataalne insult, lapseea insult, neuropsühholoogiline hindamine.

INTRODUCTION

A vascular event causing acute focal neurological symptoms that last for more than 24 hours is referred to as a stroke or insult. Recent estimation from Estonia gives an overall incidence rate of 188 cases per 100 000 persons annually in adult population (Vibo, Kõrv, & Roose, 2005). It is the third most common cause of death and leading cause of disability in older generation.

Three pathological types have been differentiated: ischemic stroke, caused by thrombotic or embolic clottings (about 80% of the cases); primary intracerebral hemorrhage, caused by bleeding inside the brain (about 15% of the cases); and subarachnoid hemorrhage where bleeding occurs in the subarachnoid space (about 5% of cases). The neurological signs and symptoms inculde weakness of limb, speech disorders, impaired sensation, vision disorders, and others (Warlow, Sudlow, Dennis, Wardlaw, & Sandercock, 2003). Diagnosis is reliably confirmed with imaging methods, especially magnetic resonance imaging (Grunwald & Reith, 2002).

When stroke occurs, then the lack of blood supply leaves underlying nerves in shortage of oxygen and nutritients, and cascade of neurobiological events even after some minutes of ischemia can finally lead to cell death and infarction in the associated tissue. Damaged nerve cells are eventually replaced by scar tissue and cerebrospinal fluid. Bleeding in case of hemorrhage causes hematoma that by its mass effect hinders the blood supply to adjacent tissue. That in turn will further lead to ischemic damage and the end-state of ischemia and hemorrhage is the same. Hemorrhagic damage is still somewhat more diffuse and may not be so well focalized to the supply area of one blood vessel, as in ischemic damage (Dirnagl, Iadecola, & Moskowitz, 1999).

The process of necrosis and removal of dead cells from the lesion site is completed in a few weeks, after which imaging usually reveals a porencephalic cyst mirroring the structural change. This focal damage left by the insult corresponds to the functional damage observed in stroke survivors. For the most part, functions associated with the affected area are impaired. The focal nature of the damage and its sudden onset makes insults the best model for assessing the brain and behavior relations for

neuropsychology (Damasio & Damasio, 1989). The damage is usually restricted to the supply area of one blood vessel and sudden onset does not leave time for compensatory neuronal mechanisms development to manage the damage.

Stroke is commonly considered to be an illness associated with advancing age and suspecting it in children might seem peculiar. However children with symptoms related to one-sided neurological lesion have been described a long time ago. The first description associating these signs in children with vascular incidence is assigned to Sigmund Freud (Rothman, 2002). Children too can be subject to one-sided weakness of limbs or have a slow developmental rate of motor skills and language acquisition, suggesting that these conditions can be regarded as a counterpart to the adult stroke. The nature and structural damage of stroke in children is similar to adult cases – typically a porencephalic cyst is left. However the context of lesions ocurring in children and in adults is essentially different. The nervous system of an adult patient is well formed and static, but child's brain develops significantly until at least the third year of life, when major structural units and associations are formed. Stroke in children interferes with nervous system development by inactivating affected areas from further development. Children undergo drastic changes in cognitive development whereby their skills and functional proficiency increases markedly. Adults, in contrast, slowly decline in their ability levels. Stroke sets different demands to the neurocognitive system – in children to manage both the development and the impairment; in adults to recover the previous level of performance.

As strokes in children occur in the context of a developing nervous system they provide a good model for research on the establishment of brain and behaviour relations. According to a common belief in neuropsychology brain is modular by structure and the principles of functioning (Ellis & Young, 1988). Our cognitive apparatus is organized into different modules that have distinct representations and can be dissociated from others by impairment. Adult neuropsychology offers an ample number of cases where after the brain lesion the patient displays a cognitive decline in some separate skills or processes, while leaving others intact.

In the normal adult brain cognitive functions are allocated to their designated place in the cortex. Functional differences on the most general level are seen between the two hemispheres by movement lateralization and thereby hand preference has been used

as an index of the specialization of the hemispheres. Right-handed individuals are left-hemisphere dominant and therefore other highly skilled movements – namely speaking and language – are also lateralized to that side. This channeling is achieved via interplay with other functions that come to be canalized likewise. Concisely stated, the left hemisphere mediates verbal abilities and is involved with processing of symbolic information at a local level; the right hemisphere is specialized to nonverbal abilities, visuospacial functions and information processing on a global level (Kolb & Wishaw, 2003).

Although brain is partitioned into a number of separate functional areas, these operate in a nicely orchestrated way and the whole brain is needed for efficient cognitive functioning. The specialization of each brain area will be wired in during the course of development, and as this is an ongoing process starting with birth, the establishment of functional lateralization and localization can continue via alternate routes if something hinders the normal developmental course. This is the case seen in early focal damage. Therefore brain insult in children provides a good opportunity to investigate whether different cognitive processes or modules are innately partialized to distinct brain areas (if same relations observed in adult patients with focal damage also hold for children).

BRAIN INSULTS IN CHILDREN

Cerebrovascular event occurring from 28 weeks of gestation to 7 days of life is termed as perinatal stroke; an event occurring until 28 days of life is termed as neonatal stroke. Some researchers also discriminate prenatal or fetal stroke occurring between 14 weeks of gestation and the onset of labor but usually pre-, peri- or neonatal stroke are not differentiated in research. These cases are all referred to as neonatal stroke or insult in this thesis. If insult occurs between 28 days and18 years of life it is termed as pediatric or childhood (acquired) stroke. Neonatal and childhood stroke differ in terms of incidence, etiological causes and risk factors, and outcome, therefore it is appropriate to regard them separately.

Neonatal stroke

The incidence of neonatal stroke is reported between 24.7 to 28.6 cases per 100 000 births (deVeber, 2002; Lynch, Hirtz, DeVeber, & Nelson, 2002), risk of recurrence is about 10%, including transient ischemic attacks (deVeber, MacGregor, Curtis, & Mayank, 2000). Ischemic insults are more common, but the index between ischemic and hemorrhagic events is rather similar in contrast with adults (ischemic 55.1%, hemorragic 44.9%; Schoenberg, Mellinger, & Schoenberg, 1978).

The first signs of stroke are usually seizures (mostly focal) or other nonspecific signs are present, like apnoea, muscular hypotony, and lethargy or depressed level of alertness. Recognition rests chiefly on neuroimaging evidence. Many children receive brain imaging for some other reason that reveals structural changes of insult (Nelson & Lynch, 2004). Stroke can also be diagnosed in utero with ultrasonography or fetal magnetic resonance imaging (Özduman et al., 2004). Hemiparesis that is typical for the lesion usually does not occur before the beginning of voluntary movement approximately at the age of six months. In many children insult is diagnosed retrospectively when hemiparesis is present or when their motor development is asymmetric or lags behind. Similarly, seizure disorder can appear later (Nelson & Lynch, 2004). Thus the majority of signs referring to damage are unspecific. Hemiparesis in children is typically caused by cerebrovascular disorders but can occur for other reasons (for example cerebral dysgenesis, or in cases of acquired damage from tumor or demyelinating conditions; Oskoui & Shevell, 2005).

The majority of lesions are located in the supply area of the medial cerebral artery on the left hemisphere, producing right-sided hemiparesis (Nelson & Lynch 2004; Raz et al., 1994). A number of reasons have proposed to explain this asymmetry. This may reflect hemodynamic differences between the left and right carotid arteries or differences in vasculature, whereby the aortic arc may make the left carotid circulation more vulnerable to emboli (Raz et al., 1994; Trauner, Chase, Walker, & Wulfeck, 1993). Another possible explanation may be related to differences in maturation. The left hemisphere is more immature at birth and therefore more vulnerable to early damage (Goodman, 1994).

Various risk factors are implicated on the etiology of stroke in neonates. The commonest causes are different cardiac pathologies but blood and metabolic disorders are also prevailing. Stroke can be effected by infectious disorders (both central nervous system or systemic), vasculopathies and a host of mother-related factors (placental disorders, trauma, substance abuse) (Nelson & Lynch, 2004). Many affected children have multiple risk factors present (Lanthier, Carmant, David, Larbrisseau, & de Veber, 2000).

Neonatal insult can co-occur with a more general hypoxia or birth asphyxia. The type of damage caused by hypoxia is nevertheless different from ischemic damage. Hypoxia leads to more diffuse damage that potentiates the risk of further adverse lesions. Hypoxic damage is selectively tuned to white matter and spares cortical areas. Hypoxic-ischemic encephalopathy amplifies the possibility of intraventricular and cerebral hemorrhages that are nevertheless in most cases asymmetrically converged to one hemisphere, thus creating a “focal” effect. This type of damage is commonly found in preterm babies (Back, 2006; Inder & Volpe, 2000).

Childhood stroke

Incidence of childhood stroke is reported in the range of 2.6-3.1 cases per 100 000 children (Kirkham, 1999; Lynch et al., 2002). Certain temporality trends have been observed in incidence. Stroke is more common in children under 2 years of age and progressively decreases until adolescence (Kleindorfer et al., 2006; Noce, Fábio, Siqueira Neto, Santos, & Funayama, 2004). The risk of recurrence depends on the etiology and ranges between 6.6 (Sträter et al., 2002) to 22% (Chabrier, Husson, Lasjaunias, Landrieu, & Tardieu, 2000). The index of ischemic and hemorrhagic insults is similar to neonatal stroke and is more even than in adults (Schoenberg et al., 1978; Kleindrofer et al., 2006). This can be explained with the differences in the risk factors, because traditional risks for the ischemic stroke have not yet appeared in children.

The clinical picture differs by age and depends also on the type of damage. Motor symptoms are notable but stroke can be indicated by seizures, change in consciousness or mental status, and also by sensory or speech disorders (deVeber, 2002; Nicolaides &

Appleton, 1996). First signs in childhood stroke can be rather general, like headache or vomiting (Lynch 2004). Diagnosing can be complicated, because children may not notice some pathologic signs or do not know how to complain about them (Gabis, Yangala, & Lenn, 2002). Although left-hemisphere lesions involving the territory of medial cerebral artery are more prevalent, the difference is not as uneven as in neonatal stroke. One large population-based study (Sträter et al., 2002) reported that 47% of strokes occur in the territory of left medial cerebral artery, 23% occur in the territory of right medial cerebral artery, and fewer in other locations.

The most common etiologic risk factor is cardiac pathology but hematologic or metabolic disorders are also common, including coagulation abnormalties and sickle cell disease. Sickle cell disease has a very high recurrence risk (up to 67%) and a very high risk for “silent strokes” where overt neurological clinical symptoms are absent but imaging gives evidence of infarction (Bernaudin et al., 2000; Hoppe, 2004). Other risk factors for childhood stroke involve vascular disorders, including the moyamoya disease, but also vascular malformations. Stroke can also result from infections, trauma and some other more uncommon factors (Daseking, Heubrock, Hetzel, & Petermann, 2003; Kirkham, Prengler, Hewes, & Ganesan, 2000; Lynch, 2004). Multiple risk factors can coexist and thereby potentiate the probabilty of insult. The possible causal reason stays unknown in about 8.3 (Wraige et al., 2003) to 22% of cases (Bowen, Burak, & Barron, 2005; Noce et al., 2004).

PROGNOSIS AND OUTCOME

Prognosis is generally considered to be better in neonatal insult. Approximately 20% of children with childhood stroke die either directly by the stroke or by causes related to the stroke (Lanthier et al., 2000). Mortality in neonatal stroke is estimated to be around 3-5% (Nelson & Lynch, 2004), autopsy studies give the same proportion (Barmada, Moossy, & Schuman, 1979). Mortality is significantly higher in hemorrhage. In a recent report by Futagi et al. (2006), the death rate of infants with intraventricular hemorrhage was found to be 33.8%. Also in childhood stroke the mortality rate of hemorrhagic events is higher (29% as compared to 16% in ischemic stroke; Lanthier et al., 2004).

In general, the results of outcome studies are difficult to generalize, because of differences in sampling (e.g. whether deaths are included as a poor outcome or not), differences in assessment methods (chart reviews, parent's ratings or clinical assessment), the length of follow-up period, and so forth. These factors all have an impact on the general outcome of the prognosis.

The most notable residual impairments after insult are motor difficulties – hemiparesis in different degrees. In cases of neonatal insult this may mean a delay in the progress of motor development but some reports conclude otherwise (Jan & Camfield, 1998; Trauner et al., 1993; Wulfeck, Trauner, & Tallal, 1991). Still, the same reports note residual hemiparesis in up to 72% of children studied (Trauner et al., 1993). This does not mean significant activity limitation, as these children have been found to master independent walking.

In comparison with childhood stroke the motor outcome of neonatal insult is better but significant weaknesses may appear later when children become older. In acquired stroke a majority of children are found to have persistent neurological deficits. Bowen et al. (2005) found that 77% of children had residual neurological impairment that ranges from moderate to severe in 44% of the cases. Similar results have been reported in other studies. Chabier et al. (2000) noted that 27% of children recovered while 44% had an unfavorable outcome. Prognosis is also related to stroke type and is better in cases of hemorrhage when deaths are excluded. Lanthier et al. (2000) reported that among

children with ischemic insult, 49% had persistent neurological deficits, in contrast with 33% of children who had hemorrhage. In spite of this, ¾ of stroke survivors are independent in the activities of daily living and fare quite well (Hurvitz, Beale, Ried, & Nelson, 1999).

The manifestation of epilepsy after stroke is much more common in children than in adults (Ganesan et al., 2000). The danger of epilepsy remains high even late after the event due to the structural change in nerve tissue that is liable to aberrant electric discharges. Epilepsy again exacerbates recovery, as it has a detrimental effect on subsequent development or functional improvement (Golomb et al., 2006). Seizures in neonatal stroke are reported in 50% of children (Trauner et al., 1993; Wulfeck et al., 1991); in cases of childhood stroke the rate of recurrent seizures is estimated at about 29-39% (Giroud et al., 1997). Seizures are more common in ischemic insults (Lanthier et al., 2000), and some studies of hemorrhagic stroke estimate the occurrence of seizures to be around 10% (Al-Jarallah, Al-Rifai, Riela, & Roach, 2000; Futagi et al., 2006).

It has been noted that a significant portion of children with stroke later develop psychiatric disorders, and that stroke has a long-term effect on the social life of these children. By parental estimation, about half of the children have psychiatric problems after stroke, individual assessment gives an even higher rate (Goodman & Graham, 1996). Children are more impaired and socially withdrawn and this leads to a lower self-esteem. Emotional and conduct disorders are common. Brain injury in children is related to difficulties in self-organization, concentration and attentional monitoring, and therefore it is not surprising that the rate of attention deficit hyperactivity disorder (ADHD) is very high (up to 57% have ADHD traits or lifetime history of ADHD) among children with childhood stroke (Max et al., 2003). The development of behavioral problems is not associated with lateralization or lesion localization in frontal areas, as might be expected from data of adults (Goodman & Yude, 1997; Trauner, Nass, & Ballantyne, 2001). The behavioral problems seem to be more mediated by intelligence. A lowered intelligence level makes these children more vulnerable psychiatrically (Goodman & Graham, 1996). Social isolation can be a secondary result to hemiparesis, whereby affected children are marginalized and under pressure by peers (Blom et al., 2003).

The general outcome is modified by the localization of the lesion. The majority of studies report a better outcome in those children who have damage in subcortical structures than damages that involve cortical areas (Steinlin, Roellin, & Schroth, 2004). In neonates, insults that involve parenchyma tend to have a worse outcome in comparison with non-parenchymal lesions (Vollmer et al., 2006). Claeys et al. (1983) found that isolated unilateral ventricular dilatation, reflecting periventricular white matter damage was associated with a mild handicap, normal intelligence and no epilepsy, which they called a "benign variety of congenital hemiparesis" (p. 451). Lesions that involve cortical areas give more neurocognitive after-effects. Similarly, lesions in basal ganglia are considered to have a more favorable course (Garg & DeMyer, 1995) but some reports state otherwise (Ganesan, Ng, Chong, Kirkham, & Connelly, 1999). A better prognosis of subcortical damage may instead reflect a smaller lesion in size and the better outcome is just a side-effect. Some reports have found that lesion size has an influence (Ganesan et al., 1999; Gordon, Ganesan, Towell, & Kirkham, 2002), others have found no notable difference (deVeber et al., 2000).

Boys have been found to be at a cognitive disadvantage after early brain damage (Raz et al., 1995) and this might result from their maturational lag. Accelerated cerebral maturation may provide girls with an edge in the acquisition of cognitive function. Also cognitive functions in females are also more symmetrically represented, making it easier to shift the function to the undamaged hemisphere to overcome injury.

COGNITIVE OUTCOME

Reports on cognitive outcome have given very varied results. Some studies note very favorable outcome, especially in the neonatal population (Jan & Camfiled, 1998; Trauner et al., 1993; Wulfeck et al., 1991), others have been more reserved (Vollmer et al., 2006). Sreenan et al. (2000) have indicated cognitive impairment in up to 41.3% of children. Futagi et al. (2006) report that in cases of hemorrhage 11.3% of infants have later borderline intelligence and 10.2% are mentally retarded.

General intellectual abilities of children with childhood stroke are close to the mean reference value of the standardization sample, however more children fall in the bottom half of the distribution (Ganesan et al., 2000). Intellectual outcome is complicated by epilepsy (De Schryver, Kappelle, Jennekens-Schinkel, & Peters, 2000). In spite of an average intellectual performance, children may still have subtle cognitive deficits. They proceed in academic advancement at suboptimal level. Hurvitz et al. (1999) found that about half of the children studied needed support services and assistance to meet the educational demands. Subtle neuropsychological problems like difficulties in attention, concentration and processing speed have been found to impede academic achievement (Steinlin et al., 2004). Aram & Ekelman (1988) in their study of academic achievement found that although the prognosis for scholastic aptitude and achievement in lesioned children was favorable, their performance was poor in writing (for both left- and right-sided lesion), reading and math (in right-sided lesion only). Subcortical damage had a more unfavorable effect for children with left-sided lesion but in children with right-sided lesion the subcortical damage was associated with a better performance.

Previous studies in Estonia have shown that children with early-onset hemiparesis and unilateral brain damage are compromised in various cognitive domains, including language, visuospatial abilities, attention and memory, and sensorimotor functions (Kolk, Beilmann, Tomberg, Napa, & Talvik, 2001; Kolk & Talvik, 2000; 2002; Pedjak, 2004). Differences between neonatal and childhood stroke groups have found to be negligible and effects of laterality have found to reflect the adult pattern of cognitive deficits (Kolk & Talvik, 2000).

General intelligence

Very different patterns of effect have emerged. Some studies state that the effect on intelligence is mild or only slightly directed to lower levels (Aram & Eisele, 1994; Blom et al., 2003; De Schryver et al., 2000; Ganesan et al., 2000; Kuroda, et al., 2004; Nass, deCoudres Peterson, & Koch, 1989). This is considered as a proof of the brain's remarkable ability to overcome early injury. Some studies report a notably worse outcome in children who have the damage very early, particularly in the neonatal period (Hebb, 1942; 1949; Montour-Proulx et al., 2004; Riva & Cazzaniga, 1986; Woods, 1980). This is considered as an indication that the brain needs previous "wiring" to find ways for compensation and although motor functions and language can recover to a large extent, the higher cognitive functions are more dependent on the total amount of cortical tissue left intact (Montour-Proulx et al., 2004). Others have reported an U-shaped curve where children have a worse recovery if damage occurs between 6 months to 5 years (Goodman & Yude, 1996; Hetherington, Tuff, Anderson, Miles, & deVeber, 2005). This is critical a time of synaptogenesis and skill development and a lesion obtained in this period is thought to alter these processes significantly, resulting in an unfavorable outcome. In the neonatal period the lesion is conquered, because plasticity for recovery coincides with plasticity for development. Also a reversed U-shaped curve has been proposed when the best outcome is expected if the insult occurs between 5-9 years of age (McFie, 1961; Pavlovic, et al., 2006). However, this can partially confirm the U-shaped curve, as the time scales do not conflict. Insults at the neonatal age are thought to alter the course of the brain's development so that networks for higher cognitive functions do not develop. In adolescence the recovery is also reduced because by that time the brain no longer has an excess of free synaptic connections (Pavlovic et al., 2006).

Adult unilateral damage leads to a characteristic pattern of intelligence scale difference where left-sided damage leads to a more marked decrease in verbal abilities and right-sided damage depresses nonverbal or performance intelligence more. This characteristic verbal/performance IQ split is not expected to occur in children before 2 to 5 years of age because skills are established well enough by that time to be affected differently (Aram & Ekelman, 1988; Goodman & Yude, 1996; Hogan, Kirkham, & Isaacs, 2000; McFie, 1961). Still, some studies report the split even in neonatal insult

(Montour-Proulx et al., 2004; Raz et al., 1994). Intellectual outcome in the early age depends more on the side of the lesion, because hemispheres may differ in their abilities to compensate damage due to their different functional roles. Left-sided damage is said to influence both verbal and performance IQ, because these functions are delegated to the intact right hemisphere and compete for representation that downscales both. Right-sided damage has an influence on performance IQ only, because language development in intact left hemisphere is prioritized and therefore only nonverbal abilities suffer (Ballantyne, Scarvie, & Trauner, 1994; Riva & Cazzaniga, 1986). Exactly the opposite is proposed by other studies where early damage in the right hemisphere affects both IQ scores, but left-sided damage preserves verbal abilities by relocating them to the intact right hemisphere that leads to a decline in nonverbal abilities only (Nass et al., 1989; Woods, 1980).

Age at testing than lesion onset may be a more important factor to consider, because the more time has passed since insult onset, the longer the recovery period has been. Alternatively, the impact of damage may appear later, when the compromised cognitive system is not able to manage the more complex skill development. Support has been gathered for both possibilities. Aram and Eisele (1994) noted a relative stability in intelligence levels of children with early damage, and only right-lesioned children had a tendency to decrease in verbal IQ over time. Muter et al. (1997) obtained similar results and no significant hemisphere difference emerged in their study. Again, oppsing results have been published. Banich et al. (1994) in a cross-sectional study noticed a significant decline in the intellectual level over time, starting at 6-8 years of age. This was later confirmed by Levine et al. (2005), suggesting that the damaged brain can reorganize functions at an earlier age but not support the later-developing higher cognitive functions. The drop in IQ was associated with lesion size and previous IQ level. Smaller lesions were associated with a higher previous level but it was directed to a greater decline later.

To conclude, research in this matter has been quite inconclusive.

Language

Language has received the most attention in the research of focal damage effects in children. Earlier studies stressed the fact that neonatal damage does not result in

aphasia that is characteristic to similar damage in adults (Alajouanine & Lhermitte, 1965; Basser, 1962; Vargha-Khadem, O'Gorman, & Watters, 1985), creating an opinion of a good prognosis after early insult. Later studies have not been so optimistic and note developmental delays in the language acquisition (Bates et al., 1997; Dall'Oglio, Bates, Volterra, Di Capua, & Pezzini, 1994; Rankin, Aram, & Horwitz, 1981; Reilly, 2000; Vicari et al., 2000). However, the picture emerging from studies of early language development is somewhat different from expectancies based on adult studies. Developmental delay is not related to the side of the lesion or is even more pronounced on the receptive speech after a right-sided lesion (Bates, et al., 1997; Eisele & Aram, 1993; Reilly, 2000). On the basis of adult data one would expect difficulties in comprehension after left posterior damage, yet damage to this area was associated with more preserved comprehension abilities in early development. Expressive speech development was found to be more associated with the left hemisphere, as it was more delayed after a left hemisphere lesion. This delay appeared in syntactic and semantic development as children started to speak and combine words, although they comprehend and know the meaning of words. This was more the case after left-sided posterior lesions, yet based on adult data, one would expect this difficulty after anterior damage in the left hemisphere. It seems that these children have difficulties in translating the meaning of words to an expression. Syntactic and semantic development is not so much affected after the right-sided lesion but they are less expressive using gestures (Chilosi et al., 2000).

These differences in lexical, grammatical and semantic abilities resolve by the age of 5 years and children with an early lesion seem to acquire relative competency in language after that age since their performance by that age is quite similar to control groups, although the obtained level may still be suboptimal (Chapman, Max, Gamino, McGlothlin, & Cliff, 2003; Reilly, Bates, & Marchman, 1998; Reilly, Losh, Bellugi, & Wulfeck, 2004). Errors may emerge in more demanding situations and affected children are more reluctant to use speech while it is still developmentally compromised. Drawbacks are evident in narrative speech, as the children use more simple sentences, convey less details and essential information, and more poorly organize their utterances to connected speech patterns (Aram, Ekelman, & Whitaker, 1986; Chapman et al., 2003; Reilly et al., 1998). The pragmatic aspects of language are similarly affected, children are

poorer to presuppose the truth and make correct inferences from spoken sentences, more so after a left-sided lesion (Eisele, Lust, & Aram, 1998). Left sided lesions are also associated with more difficulties in naming and they need more time to access lexical and semantic categories (Aram, Ekelman, & Whitaker, 1987). Some other complex aspects of language, like idiom comprehension, do not seem to be affected (Kempler, Van Lancker, Marchman, & Bates, 1999). The development of reading and writing is commonly unaffected (Aram, Gillespie, & Yamashita, 1990). In general, late effects are more associated with left-sided damage and hint to an early specialization of language abilities in the left hemisphere. Language may be effectively reorganized but subtle deficits remain.

When stroke occurs after language is acquired, the resulting deficits are more similar to aphasic symptoms seen in adults (Alajouanine & Lhermitte, 1965; Aram, Rose, Rekate, & Whitaker, 1983; Gout et al., 2005; Martins, 2000). The initial presentation is mutism and a reduction of expressive activities. Spontaneous speech is lacking and after some days children can recover some individual words. Emerging speech can be dysarthric and is severely anomic while comprehension stays intact. Descriptions of fluent aphasia in children are rare. Prognosis is relatively good but the outcome is believed to be better in older children. In younger children the aphasic syndrome may interfere with reading and writing acquisition (Pitchford, 2000).

Visuospatial functions

Deficits in visuospatial processing in neonatal stroke are found to be more salient and persistent than language deficiencies, and spatial functions are not so easy to reorganize after right-hemisphere damage. Extensive lesions in the right hemisphere can give rise to visual problems on the analysis of different aspects of visual information that is similar to adult damage (Ahmed & Dutton, 1996). Visual attention and orientation are disturbed both in neonatal (Bava, Ballantyne, May, & Trauner, 2005; Trauner, 2003) and childhood insults (Schatz, Craft, Koby, & DeBaun, 2004). Processing is affected on the visual field contralateral to the lesion side, and asymmetires in visual processing and tracking are quite persistent in younger children (Trauner, 2003).

Visual-spatial skills are similarly multicomponential like language and both hemispheres have their contribution. Therefore skills are affected irrespective of the lesion side but this is expressed in a different way. However, the pattern of damage is more akin to the picture seen in adult unilateral lesion, when compared with language disturbances. After damage to the left hemisphere, subjects rely more on the general configuration and discard specific elements, they have more difficulties in local level processing. After right-sided damage, subjects evince problems in the analysis of general configuration, they concentrate on individual aspects and are unable to integrate the spatial array. (Stiles & Thal, 1993). Thus tasks requiring the analysis and synthesis of visual information have different error patterns depending on the involved hemisphere. In one study using block design (Schatz, Ballantyne, & Trauner, 2000) children with early onset lesion to the left hemisphere made more local level errors and confused details but children with the right hemisphere damage were guided by details and made mistakes in general configuration. These side-specific differences are also confirmed by studies of drawing development (Akshoomoff, Feroleto, Doyle, & Stiles, 2002; Stiles, Trauner, Engel, & Nass, 1997; Stiles-Davis, Janowsky, Engel, & Nass, 1988). Children with right-sided lesions are more delayed in development of copying and free drawing. Hildren with left hemisphere damage draw organized and coherent figures while right-lesioned children ignore spatial relations between individual details. They can analyse their drawings but are unable to produce a higher order organization. The ability to draw improves over time and by 6-7 years of age both groups have obtained the necessary graphic formulas to represent objects. However, this improvement is only relative and deficiencies emerge under a higher processing load. It is evidenced when children are asked to draw impossible figures. Children with left-hemisphere damage, just as normal children, were able to generate alternative spatial configurations and used configurational distortion. Children with right-sided injury had difficulties in spatial reorganization. They have fewer strategies for drawing and try to retain the graphic formula or change it to some other formula available to them (Stiles & Thal, 1993; Stiles et al., 1997). Both groups persist in using more immature strategies for drawing even when they are older (Akshoomoff et al., 2002). The processing deficits after childhood stroke are more

marked after right-sided lesion and significantly improve after left-hemisphere injury (Schatz et al., 2004):

Attention and executive functions

More than half of the children with stroke have attentional disorders (Max et al., 2003), but only few studies specifically address the development and status of attentional functions in children with stroke. Attention is a “diffuse” ability depending on large neural networks. Lesions caused by stroke typically involve these networks and the specific attentional processes involved depend on the lesion localization (Max et al., 2004). Generally alertness and sensory orientation are more affected than executive control. Also the processing speed of children with childhood stroke is limited and they are slower in divided attention tasks (Block, Nanson, & Lowry, 1999). Lower information processing speed affects other functions as well.

Inhibitory control is deficient after early bilateral damage (Christ, White, Brunstrom, & Abrams, 2003). Some other papers report that impulsivity and a reckless answering style that confounds test performance is more common after right hemisphere insult (Aram & Ekelman, 1987; Aram et al., 1987). This is more true after earlier lesions and in younger children.

Differences in executive functions are not so evident. Children with frontal lesion are poorer at strategy application, rule following and self-monitoring but planning and problem solving abilities are reduced in other pathologies as well (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Jacobs & Anderson, 2002). Not much is known about executive functions in children with stroke. Deficiencies in these skills are more evident after bilateral damage, as both hemispheres mediate various aspects of executive functions (Anderson et al., 2002).

Memory

Memory disorders have been regarded as one of the most important and most persistent sequelae after stroke, in children and in adults (Mosch, Max & Tranel, 2005). Memory is not a unitary construct but includes a host of different processes and

components that each can be dissociated from others. Some memory processes are more persistent to damage than others. Short-term memory is reported to be rather preserved after childhood stroke (Pitchford, 2000; Vargha-Khadem et al., 1985), just as working memory, although it can be compromised in some patients with anterior lesions (White, Salorio, Schatz, & DeBaun, 2000). Studies of other childhood disorders report preserved implicit memory (Yeates & Enrile, 2005). Implicit memory assumes full competence very early in the development and does not seem to be affected even by neonatal lesions. Children show intact conceptual and perceptual priming, and procedural learning even if explicit memory is disturbed.

Ability to remember is related to other cognitive functions, mostly to comprehension and attention, and is therefore not differentially affected by lesion localization (Block et al., 1999; Lansing et al., 2004). Verbal memory is attenuated while children with stroke do not use effective organizing strategies and semantic clustering to aid memorizing and recall (Lansing et al., 2004). Deficits in visual memory show more side- and coding-specific effects whereby left-lesioned children are better to recall integrated whole, omiting details, and right-lesioned children rely more on part-by-part memorizing and not recall the general outline (Akshoomoff et al., 2002). These indications are more striking in younger children as they are more deficient in encoding and also recognition accuracy (Lansing et al., 2004), and even if improvement is made this can be due to an increase in processing capacity – children may still use more immature strategies to remember information (Akshoomoff et al., 2002). Memory disorders after stroke seem to be quite persistent and do not recover over time; although progress is made, children with insult still lag behind their age-mates on acquisition and recall (Gupta, MacWhinney, Feldman, & Sacco, 2003).

THEORETICAL ACCOUNTS OF COGNITIVE OUTCOME

Two opposing views have been entertained to explain the results and differences related to the age at injury and the side of injury. On the one hand the proponents of

plasticity propose that the immature brain of neonates and infants is in advance in terms of recovery compared to the injuries of toddlers or older children. The development of the nervous system is prolonged to postnatal years that provide biological potential for plasticity to overcome the effects of injury. Dendritic growth, formation of synapses and myelination occur mainly postnatally that enables rerouting of connections, whereby functional associations are established with brain regions not usually connected with the functions they serve after reorganization. The brain is considered to be equipotential at birth, so in theory brain regions are essentially indifferent to functions and every area can assume whatever function it "desires" (Lenneberg, 1967).

Proof of plasticity is supported by some case studies demonstrating normal or favorable developmental and cognitive outcome after perinatal lesion (Golomb, Carvalho, & Garg, 2005; Ingram, Levin, Guinto, & Eisenberg, 1994). The fact that children after left hemisphere lesion at a very early age do not show aphasic syndrome has also been perceived as evidence of the brain's remarkable reorganization (Alajouanine & Lhermitte, 1965; Basser, 1962). Imaging studies reveal that cognitive functions can be served by areas that are usually hired for other functions. After early damage to the left hemisphere language will be processed by homologous areas in the right hemisphere. This interhemispheric reorganization occurs in lesions before 5 years of age. Injuries after that age lead to more intrahemispheric reorganization, recruiting adjacent areas in the same hemisphere (Jacola et al., 2006; Müller, Rothermel, Behen, Muzik, Chakraborty, & Chugani, 1999; Tierney, Varga, Hosey, Grafman, & Baun, 2001). Therefore immature brain allows greater variability to reroute functions. The disadvantage of older children comes from the fact that their brain is more mature and functional associations are more in place. This limits the possibilities of plasticity to respond to the injury.

Further evidence for plasticity and equipotentiality comes from hemispherectomy studies where the cortex and large areas of one hemisphere are removed for therapeutic purposes of intractable seizures. The results of these operations are found to be quite propitious (Devlin et al., 2003; Pulsifer, Brandt, Salorio, Vining, Carson, & Freeman, 2004). The results are even better in operations of younger children and it shows that all functions can be reorganized to only one side of the brain. Functions can be already reorganized before the operation and hence the removal of the hemisphere does not leave

any dramatic sequelae. It can even improve functional status by releasing the remaining hemisphere from the adverse influence of the affected hemisphere (Krynauw, 1950).

On the other hand accounts of early vulnerability propose that earlier damage leads to more pronounced deficiencies while different brain areas are at least to a certain extent committed to subserve certain functions. The associations may not be rigidly determined but depend on environmental input that helps to focalize these pre-attuned associations. Plasticity may not be the same for all functions and both hemispheres. Visuospatial functions are believed to be phylogenetically older and develop earlier, therefore they are more affected after early damage (Stiles & Thal, 1993). Also the symptomatic picture in visuospatial functions is more similar to adult damage as these skills mature earlier. The neural basis and developmental period for skill establishment may be more limited and therefore plasticity for these functions is more restricted. Linguistic processing develops later and the brain has more time to respond to early damage. In language functions the symptomatic picture seen in children after early injury is not similar to the characteristic pattern of adult damage. One explanation of this proposes that brain areas that serve the function during development may not be the same areas serving this function later (Bates et al., 1997). Early left-sided damage may not show language deficit as left hemisphere is not yet actively mediating this function but certain aspects of language reveal deficits later when activation of affected left hemisphere areas is needed. Early right-sided damage may show more deficiencies in language in short-term but these are lost when language related activation switches over to the unaffected hemisphere.

Since every brain area has its own ultimate aim, the developmental re-routing compromises not only the function associated with the injured area, but also other functions related to areas where affected functions will be reorganized. Early left- and right-sided damages do not show much difference in terms of language function since it is preserved after left-sided damage by hiring right hemisphere areas to serve language. However this reorganization comes with a price of compressing visuospatial skills. This preferred development of language at the expense of nonverbal skills is termed as crowding (Milner, 1974; Teuber, 1974) and it is evidenced by (in)equalities of verbal/performance IQ scale scores after left-sided damage (Ballantyne et al., 1994; Nass

et al., 1989; Riva & Cazzaniga, 1986; Woods, 1980). Same does not hold for early right-sided lesion since language is not crowded out by visuospatial skills. This may be because left hemisphere may be less “crowdable”, and respective right hemisphere functions may be more devoted to the right side and less reorganizable. Also language that is prioritized during development may not be associated with the left hemisphere in the beginning. Later lesions in the left hemisphere do not create this pattern of crowding and reveal a functonal split between verbal and nonverbal abilities common to the adult insult.

Another possibility is that the development in younger children is more bilaterally distributed and modular complexes of the adult cognitive system will be worked in by ongoing selective activation. Associations between function and certain brain area are built in step-by-step as activation becomes more lateralized during development, depending on the task at hand (Stiles et al., 2003). After neonatal damage functions do not reorganize but fail to establish the expected pattern of selective activation in the course of development. A short-term favorable outcome after early damage ensues from the possibility that function can be served with unilateral activation but modular order within functional domain remains unestablished. This will later interfere with cognitive maturation. Therefore possibilities for reorganization may be greater for later insults as the activation patterns can be re-oriented.

The accounts of plasticity may be shortsighted if one considers the long-term effects of damage. Some studies show developmental slowing or intellectual arrest after the age of 8-9 years after early damage (Banich et al., 1994; Levine et al., 2005). Cognitive functions are not isolated in the course of development but later competence and more complex skills build up on the basis of previously established abilities. The true effects of early damage can then be revealed only later when cognitive demands are higher. Brain plasticity may be effective to reorganize simple functions but not more complex ones that require higher processing demands. Therefore placticity associated with earlier damage will not work for the children but against them in the long run. One recent study has also proposed that the outcome of children is not particularly better than the outcome of adults. Mosch et al. (2005) in their matched lesion analysis study found

that in general children do not have an edge in improvement after injury. The chronic outcomes of children and adults with similar lesions were strikingly alike.

To sum-up, the departure point between different accounts is whether brain areas are believed to be equipotential or specialized at birth. This determines the outcome and group differences between neonatal and later damage, and also differences between the left and right hemisphere compensation after early damage. Both views have gained some credit but more researchers are now turned to the early vulnerability accounts since studies stress more function-specific disparities and long-term effects in the cognitive outcome.

THE AIMS OF THIS STUDY

On the basis of previous studies it was expected that the cognitive outcome of children with stroke is more in line with the early vulnerability hypothesis, showing more compromised results in neonatal stroke. If early specialization applies, the cognitive profile of affected children should show focalized effects similar to those observed in adults. Handedness contralateral to lesion side should show more diffuse cognitive deficits as it is related to more intrahemispheric reorganization. Epilepsy is expected to depress cognitive functions more. Sex related effects should be minimal.

The aims of this study are:

1) to investigate the cognitive outcome of children with neonatal and childhood stroke
2) to investigate the associations of cognitive outcome with different clinical measures, including lesion laterality, handedness, hemiparesis severity, stroke type (hemorragic vs ischemic), cortical vs subcortical damage, epilepsy, and sex.
3) during prospective study to investigate the cognitive change of children after a 2-year period.
4) to investigate the associations of cognitive change with different clinical measures noted above.

METHOD

Subjects

The study I included 31 children with hemiparesis resulting from unilateral stroke, 21 with neonatal and 10 with childhood event. The following inclusion criteria were used for patient selection: (1) congenital or acquired hemiparesis and/or focal seizures, (2) computed tomography or magnetic resonance imaging revealing an acute or remote ischemic or hemorrhagic (subarachnoid, intraparencymal or intraventricular hemorrhage) stroke, (3) gestational age at least 32 weeks, (4) no other documented diseases with central nervous system involvement before the diagnosis of the stroke, (5) use of Estonian language as mother tongue. Data of subjects is presented in table 1.

The age span at testing ranged from 3 to 12 years with a mean age of 7.29 years (6.86 years for neonatal and 8.21 years for childhood stroke). In childhood stroke cases, the vascular event occurred at a mean age of 5.49 years. There were 17 boys (11 with neonatal and 6 with childhood stroke) and 14 girls (10 with neonatal and 4 with acquired stroke). The left hemisphere was involved in 25 children and the right hemisphere in 6.

Data of lesion localization was obtained from imaging. Data for one child was unavailable (N4) and her laterality was determined by hemiparesis. The signal abnormalities were classified as cerebral cortex (according to lobes), basal ganglia, posterior limb of internal capsule, and periventricular white matter involvement. Imaging revealed no apparent lesion in one child (N11), whose laterality was determined by hemiparesis. In most of the cases the vascular territory of the medial cerebral artery was involved. Stroke was ischemic in 20 children and hemorrhagic in 8, data was unavailable for three children. Hemiparesis severity was assessed according to the hand function and ranged from 0 (no impairment present) to 3 (minimal finger movements).

Table 1. Sample characteristics.

Patient	Sex	Age at onset	Age at test	Hemipare-sis severity	Handedness	Lesion side	Imaging findings	Epilepsy
					Neonatal stroke			
N1	F	0-0	4-7	1	Left	Left	F,P, capsula externa	No
N2	M	0-0	7-4	2	Left	Left	F,T,P	Yes
N3	M	0-0	6-9	2	Left	Left	F,P, periventricular, cella media	No
N4	F	0-0	5-2	2	Right	Left	No data	No
N5	M	0-0	3-4	1	Left (mixed)	Left	F	No
N6	F	0-0	8-9	2	Left	Left	F	Yes
N7	F	0-0	4-3	0	Right (mixed)	Left	F	Yes
N8	M	0-0	3-0	2	Left	Left	Periventricular	No
N9	F	0-0	9-0	1	Left	Left	Hippocampus	Yes
N10	M	0-0	9-6	1	Left (mixed)	Left	BG	No
N11	F	0-0	6-1	1	Left	Left	Normal	No
N12	F	0-0	5-8	3	Left	Left	T,P,F	Yes
N13	F	0-0	6-6	2	Right (mixed)	Left	F,P	Yes
N14	F	0-0	7-2	2	Left	Left	P	No
N15	M	0-0	5-11	3	Left	Left	T,P, BG	No
N16	M	0-0	11-7	3	Left	Left	F,P,BG	No
N17	M	0-0	8-5	2	Left	Left	Periventricular	Yes
N18	M	0-0	12-9	2	Left	Left	Periventricular	Yes
N19	M	0-0	8-0	0	Right	Right	Periventricular	No
N20	F	0-0	5-4	1	Right	Right	F	Yes
N21	M	0-0	4-9	3	Right	Right	Periventricular	No
					Childhood stroke			
C1	F	0-1	5-3	1	Left	Left	T	Yes
C2	M	2-6	6-7	1	Right	Left	BG	No
C3	F	4-9	7-4	2	Left	Left	Cerebral peduncule, thalamus	No
C4	F	5-5	5-8	2	Left	Left	BG, periventricular	No
C5	M	10-0	11-2	2	Right	Left	BG, IC	No
C6	M	4-8	11-8	2	Left	Left	BG, IC	Yes
C7	M	2-0	10-0	2	Left	Left	BG,IC	Yes
C8	M	10-4	10-4	2	Right	Right	T	No
C9	F	9-0	9-5	2	Right	Right	F,P	No
C10	M	4-8	4-8	1	Left	Right	BG, caudate nucleus	No

Imaging: F – frontal, P – parietal, T – temporal, BG – basal ganglia, IC – internal capsule.

21 children preferred their left and 10 prefered their right hand during testing. Four children were initially ambidextrous. All of them were later retested (see below) and two were later found to use their left hand more while the other two used their right hand, although their preference was more mixed than certain. Their handedness was decided by their later hand use. Altogether 12 children had seizures and received antiepileptic medication (8 monotherapy, 4 polytherapy). Three children receiving polytherapy had poor compliance with treatment.

The control group was composed of 31 age and sex matched children drawn from regular public kindergartens and schools in Tartu. The mean age for control children was 7.34 years and none of them had any known neurological or psychiatric complaints.

The study was approved by the Medical Research Ethics Committee of Tartu University and informed consent was obtained from the parents for participation in the study.

In Study II 20 children were retested after a mean interval of 2.29 years (neonatal stroke 2.32 years, childhood stroke 2.23 years, range 1.00-4.25 years). There were 13 children with neonatal stroke (mean age 8.34 years) and 7 children with childhood stroke (mean age 10.05 years). Data of subjects is presented in table 1, included are cases N1-N8, N10-N14 from the neonatal group, and C1-C3, C5, C8-C10 from the childhood group. From those for whom retest data was unavailable three children were unresponsive to contacting, one was out of the test's age range and too little time had passed from the initial testing of seven children. At least one year was required before retesting to avoid possible practice effects.

Procedure

All children were individually tested with NEPSY (Korkmann, Kirk, & Kemp, 1997). The test has been adapted to Estonian by Kolk and used for assessment of hemiparetic children in Estonia in previous studies (Kolk, et al., 2001; Kolk & Talvik, 2000; 2002; Pedjak, 2004). This is a comprehensive neuropsychological battery aimed at the complex assessment of children between the ages of 3 to 12 years. The test battery is

based on Luria's diagnostic principles (Korkman, 1999) but incorporates also other testing techniques. Altogether 30 different subtests are included, subtests selection depends on the child's age according to manual. All tasks are conceptually organized into five separate domains: attention and executive functions (6 subtests), language (8 subtests), sensorimotor functions (5 subtests), visual-spatial functions (5 subtests), and memory and learning (6 subtests). Scores usually denote the number of correct answers, but some tasks are time constrained and error scored. Short subtest descriptions and further details of scoring procedures used are provided in Appendix A. NEPSY has been shown to be a valid instrument for differential diagnosis and syndrome analysis in children with neurological and developmental conditions (Ahmad & Warriner, 2001; Schmitt & Wodrich, 2004).

This study includes some test protocols reported in a previous study by Pedjak (2004). This was done to add more children for retesting since the focalized unilateral damage in children is quite rare and the population is small. Occasionally some subtests were not completed by all children due to time constraints or refusal by a child. These protocols were not excluded from analysis to include the maximum number of subjects.

Statistical analysis

The raw scores of subtests were standardized into z-scores to make the scales comparable. Group differences were tested using Fisher's Exact Test with categorical variables. Effect sizes and corresponding overlap percentages were computed and compared according to the formula and tables by Cohen (1969) and Zakzanis (2001). Effect sizes for neonatal and childhood groups were computed separately, comparing their mean and standard deviation with the whole control group mean test values and standard deviations in both instances.

In Study I both stroke groups were compared to control children with analysis of covariance (ANCOVA) using age as covariate and NEPSY subtest scores as dependent variable. Possible effect of different clinical variables to lesion onset time (neonatal versus childhood) was assessed with 2 by 2 ANCOVA including laterality (left- or right-sided lesion), handedness, hemiparesis severity (rescored as mild (0,1) and moderate-to-

severe (2,3)), stroke type (hemorrhagic versus ischemic), cortical or subcortical involvement, epilepsy, and sex as other grouping variables. Post-hoc analysis was performed by inspecting 95% confidence intervals.

Some subtests did not meet the normality assumption and simple transformations of these scales were not effective in establishing normal distribution. With this restriction in mind we still proceeded with the analysis of covariance as F-tests have been shown to be rather insensitive to normality and quite “conservative” (not to increase the Type I error; Kerlinger & Lee, 2000). Also to depart from original data with more complex transformations was not an objective.

In Study II the long-term effects were assessed with the Wilcoxon matched pairs test. To assess the effect of change between groups a score difference was computed by subtracting the subtest scores of Study II from the corresponding scores of Study I. This score difference was assessed with the Mann-Whitney U-test and ANCOVA using the intertest interval as covariate. The effect of the aforementioned clinical variables on score difference was tested with 2 by 2 ANCOVA using intertest interval as covariate and difference score as dependent variable. Again not all subtest met the normality assumption but the analysis proceeded like mentioned above.

RESULTS

Study I

As the age at testing significantly influenced the results in all subtests it was treated as a covariate. Control group outperformed both groups of children with stroke in most tests. Subtest mean values, standard deviations and corresponding effect sizes are provided in table 2. Effect sizes considered to be “large” are marked in bold. However, none met the more stringent criteria set by Zakzanis (2001), who proposed that magnitude of 3.0 should be considered a clinical marker criteria (corresponding to 7.2% of overlap between groups). When comparing neonatal group with control subjects the biggest effect size was 1.90 for Manual motor sequences (corresponding to 20.6%

overlap). In general the sizes for sensorimotor and visual domain were greater. For the childhood stroke group fewer effect sizes were of consequence, the most emerging was for subtest Speeded naming – correct 1.87 (corresponding to 21.6% overlap). Again effect sizes in sensorimotor domain prevailed as “large”.

Table 2. Mean z-scores, standard deviation and effect size values.

	Control		Neonatal			Childhood		
	M	SD	M	SD	d	M	SD	d
Attention and executive functions								
Tower	0.22	0.64	-0.34	1.34	0.56	0.06	1.00	0.20
Auditory attention	0.27	0.72	-0.38	1.10	0.75	-0.23	1.42	0.54
Visual attention – time	0.37	0.81	-0.40	0.93	**0.89**	-0.34	1.34	0.75
Visual attention – correct	0.48	0.50	-0.54	0.97	**1.41**	-0.40	1.53	**1.06**
Statue	0.26	0.77	-0.23	1.09	0.53	-0.39	1.37	0.71
Design fluency	0.18	1.04	-0.36	0.70	0.58	0.03	1.28	0.14
Knock and tap	0.31	0.50	-0.44	1.52	0.76	-0.19	0.82	**0.85**
Language								
Phonological processing	0.24	0.80	-0.38	0.99	0.70	0.04	1.37	0.20
Comprehension of instructions	0.43	0.70	-0.59	1.06	**1.19**	-0.10	1.08	0.66
Speeded naming – time	0.24	0.70	-0.14	1.03	0.45	-0.57	1.62	**0.84**
Speeded naming – correct	0.42	0.41	-0.45	1.41	**0.97**	-0.61	0.92	**1.87**
Repetition of nonsense words	0.30	0.53	-0.40	1.23	0.79	-0.09	1.32	0.48
Verbal fluency – semantic	0.43	0.81	-0.60	0.95	**1.18**	-0.14	1.05	0.65
Verbal fluency – phonemic	0.40	0.93	-0.67	0.90	**1.16**	-0.13	0.86	0.58
Oromotor sequences	0.31	0.64	-0.52	1.25	**0.91**	-0.00	1.14	0.40
Sentence comprehension	0.19	0.78	-0.35	1.09	0.60	-0.00	1.35	0.21
Sensorimotor functions								
Fingertip tapping	0.49	0.33	-0.53	1.27	**1.20**	-0.38	1.08	**1.53**
Imitating hand positions	0.57	0.68	-0.72	0.92	**1.64**	-0.26	0.97	**1.10**
Visuomotor prescision – time	0.13	0.83	-0.24	0.97	0.42	0.11	1.48	0.02
Visuomotor prescision – mistakes	0.45	0.50	-0.42	1.05	**1.14**	-0.51	1.45	**1.16**
Manual motor sequences	0.50	0.62	-0.92	0.95	**1.90**	-0.15	1.05	**0.94**
Finger discrimination	0.53	0.57	-0.77	1.03	**1.64**	-0.03	1.00	**0.82**

Table 2 (continued).

	Control		Neonatal			Childhood		
	M	SD	M	SD	d	M	SD	d
Visual-spatial functions								
Design copying	0.36	0.80	-0.54	0.97	**1.04**	-0.03	1.20	0.42
Arrows	0.37	0.79	-0.61	1.07	**1.08**	0.12	0.91	0.31
Block construction	0.29	0.81	-0.45	1.04	**0.81**	0.05	1.19	0.26
Route finding	0.25	1.05	-0.66	0.80	**0.95**	0.58	0.50	0.35
Picture perception	-0.13	1.00	-0.09	1.03	0.03	0.59	0.78	0.75
Memory and learning								
Memory for faces	0.42	0.74	-0.41	1.15	**0.88**	-0.31	0.92	**0.93**
Memory for names	0.15	0.92	-0.31	1.09	0.47	0.18	0.99	0.03
Narrative memory	0.26	0.80	-0.22	1.16	0.51	-0.40	1.12	0.75
Sentence repetition	0.49	0.61	-0.64	0.96	**1.46**	-0.26	1.33	**0.91**
List learning	0.30	0.82	-0.38	1.22	0.69	-0.22	0.95	0.61
Picture recognition	0.39	0.72	-0.36	1.24	0.78	-0.36	0.78	**1.03**

Effect sizes in bold are considered to be “large”.

Both groups were compared with control group mean subtest scores. In attention and executive functions domain following subtests were significantly different between groups: Auditory attention $F(2,42)= 5.11$, $p<.010$, Visual attention – time $F(2,57)= 4.86$, $p<.011$, and Visual attention – correct $F(2,75)= 9.61$, $p<.000$. Inspection of 95% confidence intervals demonstated that neonatal and childhood stroke groups both were more incorrect in auditory and visual attention, and neonatal group was more slower in visual attention than other groups. Subtest results are presented in figure 1.

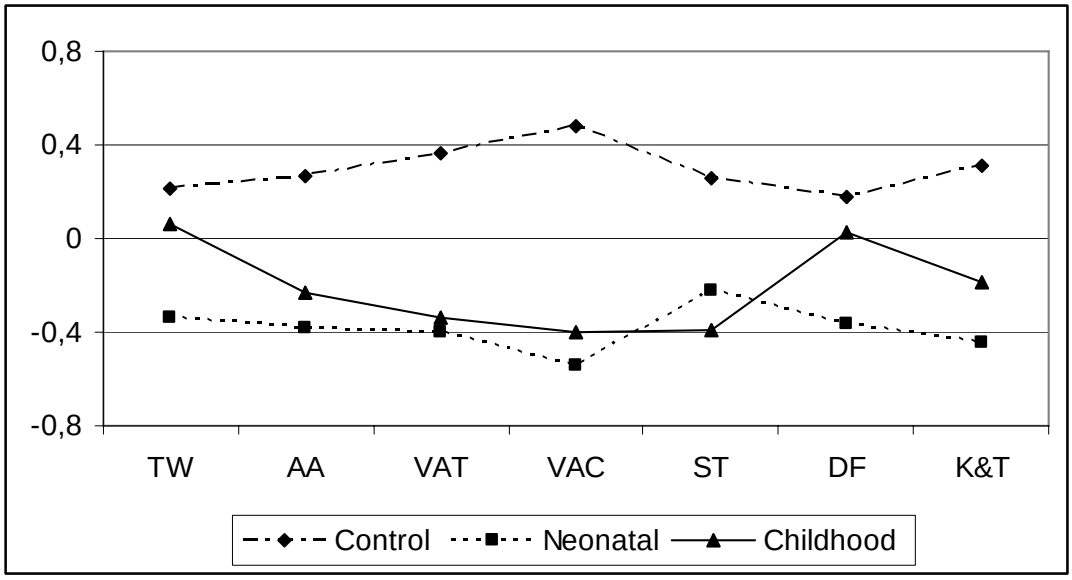

Figure 1. Auditory and executive function domain mean results. TW – Tower, AA – Auditory attention, VAT – Visual attention – time, VAC – Visual attention – correct, ST – Statue, DF – Design fluency, K&T – Knock and tap.

In language domain following subtests were significantly different between groups: Phonological processing $F(2,58)= 6.09$, $p<.004$, Comprehension of instructions $F(2,58)= 14.71$, $p<.000$, Speeded naming – time $F(2,42)= 4.53$, $p<.016$, Speeded naming – correct $F(2,42)= 6.75$, $p<.003$, Verbal fluency – semantic $F(2,57)= 12.5$, $p<.000$, Verbal fluency – phonemic $F(2,24)= 4.60$, $p<.020$, and Oromotor sequences $F(2,53)= 6.57$, $p<.003$. Inspection of 95% confidence intervals showed that neonatal group performed significantly worse than controls on most of these subtests, except Speeded naming – time where childhood stroke group had a poorer performance. Children with childhood stroke performed similar to neonatal stroke children, except on phonemic fluency where their results were very varied. Subtest results are presented in figure 2.

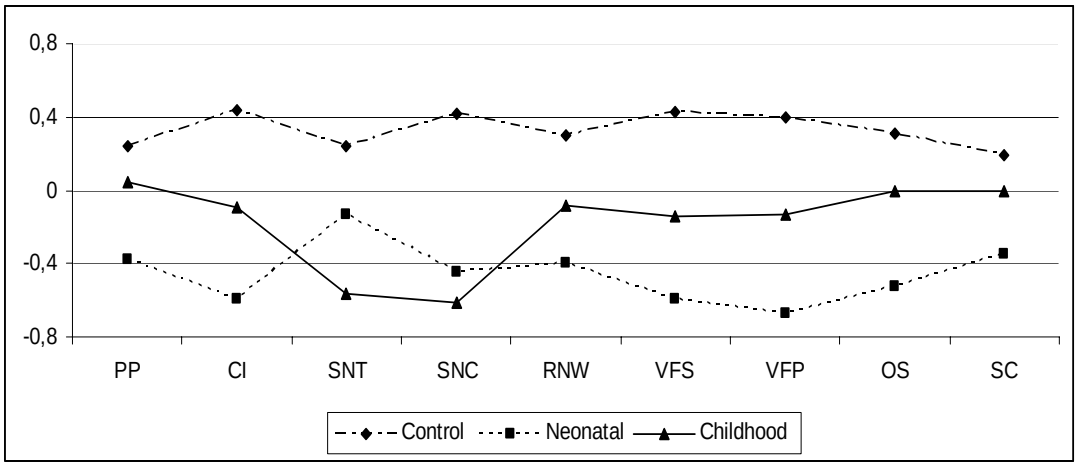

Figure 2. Language domain mean results. PP – Phonological processing, CI – Comprehension of instructions, SNT – Speeded naming – time, STC – Speeded naming – correct, RNW – Repetition of nonsense words, VFS – Verbal fluency – semantic, VFP – Verbal fluency – phonemic, OS – Oromotor sequences, SC – Sentence comprehension.

Sensorimotor domain subtests were particularly difficult to master for both stroke groups because most of these tasks require the use of their hemiparetic hand. Groups differed in Fingertip tapping $F(2,46)= 7.82$, $p<.001$, Imitating hand positions $F(2,58)= 26.05$, $p<.000$, Visuomotor speed – mistakes $F(2,58)= 8.95$, $p<.000$, Manual motor sequences $F(2,48)= 24.1$, $p<.000$, and Finger discrimination $F(2,45)= 14.18$, $p<.000$. In most of the tests control children were better than both stroke groups, who performed equally poor, except in Finger discrimination where childhood stroke group confidence intervals were just in between neonatal and control group and significantly overlapped. Subtest results are presented in figure 3.

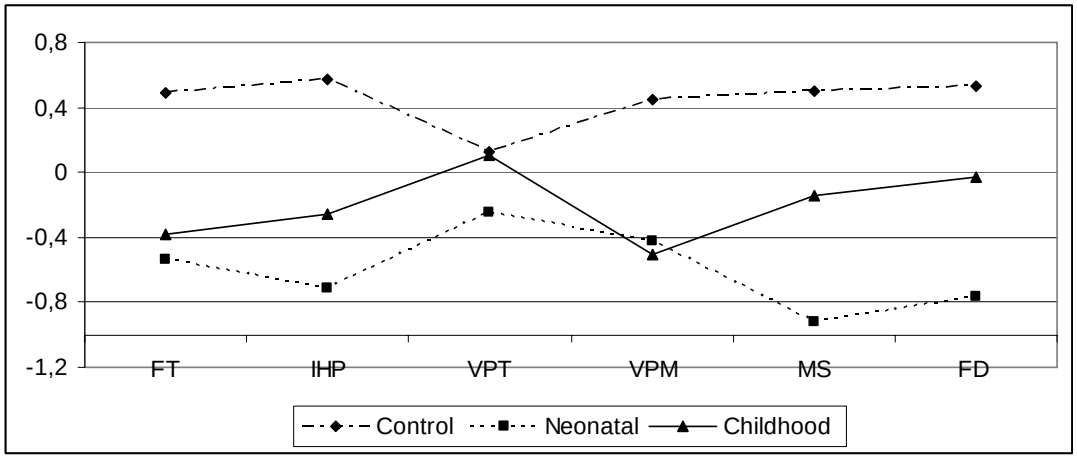

Figure 3. Sensorimotor domain mean results. FT – Fingertip tapping, IHP – Imitating hand positions, VPT – Visuomotor prescision – time, VPM – Visuomotor prescision – mistakes, MS – Manual motor sequences, FD – Finger discrimination.

Tasks in visual-spatial domain were also fairly difficult for stroke groups. Significantly lower scores were obtained in Design copying $F(2,57)= 13.29$, $p<.000$, Arrows $F(2,47)= 7.73$, $p<.001$, and Block construction $F(2,58)= 7.61$, $p<.001$. Neonatal stroke children had significantly more complications in Arrows and Block construction than childhood stroke and control groups. In a curious way childhood stroke children outperformed even controls in Route finding and Picture perception due to one control child who fell at the bottom with these tasks. Results are presented in figure 4.

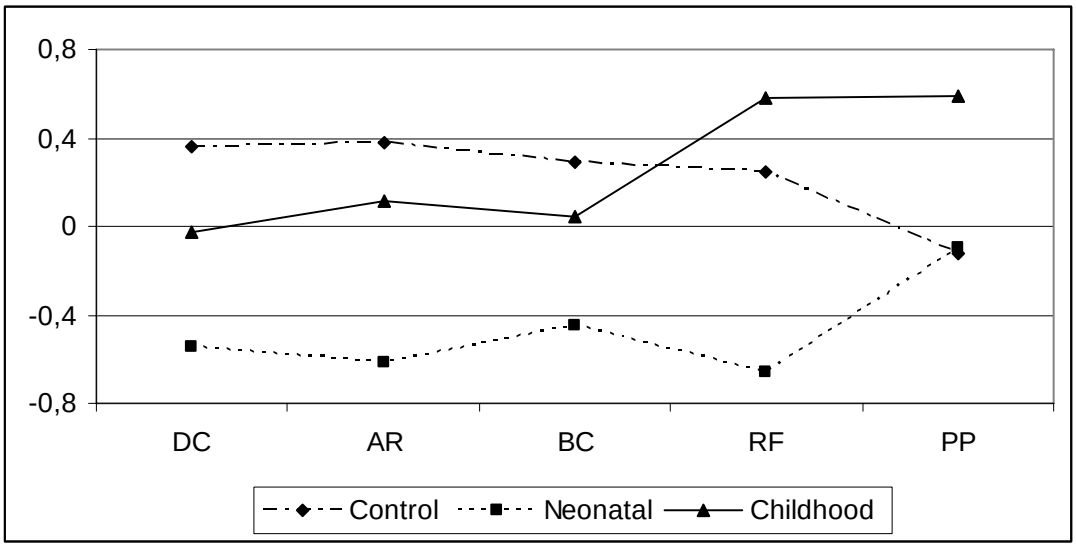

Figure 4. Visual-spatial domain mean results. DC – Design copying, AR – Arrows, BC – Block construction, RF – Route finding, PP – Picture perception.

In learning and memory domain both stroke groups were poorer in Memory for faces $F(2,49)= 5.14$, $p<.009$, and Sentence repetition $F(2,56)=18.18$, $p<.000$. Also the results of Narrative memory were significantly different $F(2,56)= 4.74$, $p<.012$, but this task was more difficult for childhood stroke group as evidenced by confidence intervals. Memory for names was equally tasking for control children as well. Subtest results are presented in figure 5.

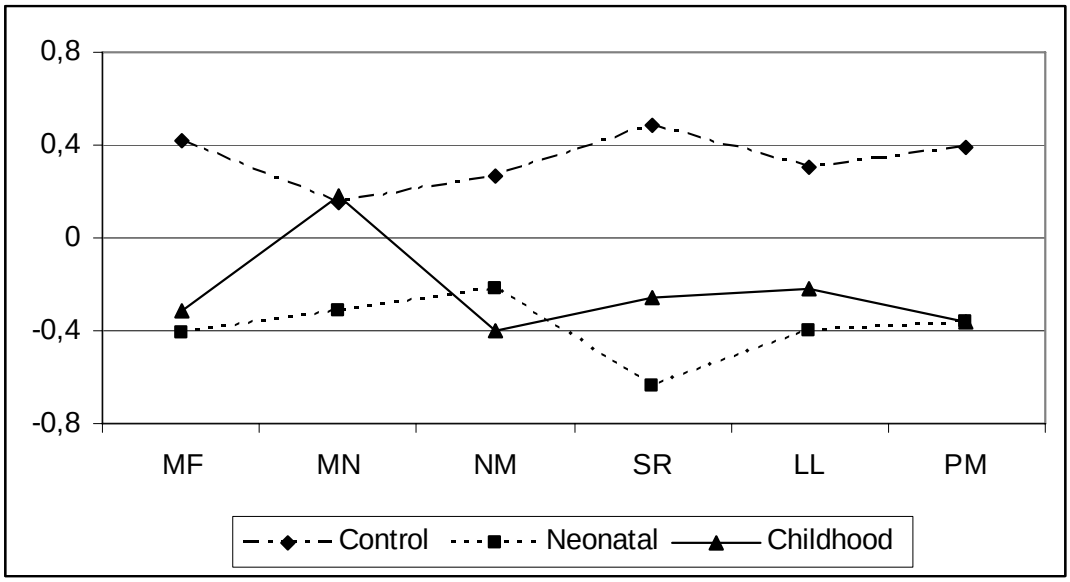

Figure 5. Learning and memory domain mean results. MF – Memory for faces, MN – Memory for names, NM – Narrative memory, SR – Sentence repetition, LL – List learning, PM – Picture memory.

We were then interested in differences between neonatal versus childhood stroke and possible effect of various clinical measures on NEPSY subtest scores. A 2 (neonatal versus childhood stroke) by 2 (some other clinical variable) ANCOVAs were conducted with NEPSY subtest scores as dependent measure. Although the groups were of unequal size they did not differ in relative proportion of other subject variables (laterality, handedness, hemiparesis severity, stroke type, cortical vs subcortical damage, epilepsy, sex – Fisher's exact test $p>.1$).

Laterality had a very moderate effect on cognitive performance in both groups. In general those who had a right hemisphere lesion fared better. Significant difference was observed in Visuomotor prescision – time $F(1,26)= 7.20$, $p<.012$, Copying $F(1,25)= 5.16$, $p<.032$, Block design $F(1,26)= 16.87$, $p<.000$, and Sentence repetition $F(1,24)= 5.23$, $p<.031$. In all cases children with right hemisphere damage performed better than children with left hemisphere injury. Most of these tasks are nonverbal and are considered to be functionally associated with right hemisphere. Some verbal subtests (Speeded naming – time, Repetition of nonsense words) showed a similar trend but failed to meet significance.

Handedness has been considered to be another token of hemispheric dominance and laterality. Handedness effect was observed in subtests Repetition of nonsense words $F(1,21)= 11.50$, $p<.003$, Fingertip tapping $F(1,20)= 6.32$, $p<.021$, Imitating hand positions $F(1,26)= 5.43$, $p<.028$, and Block construction $F(1,26)= 4.72$, $p<.039$. In all cases right-handed children outperformed those, who were forced to use their left hand. Tendency was stronger in children with neonatal stroke. In some subtests this same trend did not reach significance (Oromotor sequences $F(1,21)= 4.13$, $p< .055$, Knock and tap $F(1,17)= 3.90$, p.065).

The effect of hemiparesis severity was observable in interaction with lesion onset time. Children with neonatal stroke had better performance in Phonological processing $F(1,26)= 4.24$, $p<.050$, and Sentence repetition $F(1,24)= 4.55$, $p<.043$ associated with mild hemiparesis, while the opposite was true for children with childhood stroke who had better performance on those tests when hemiparesis was moderate-to-severe. This same patter was consistent in some other subtests where interaction failed to meet significance (Finger discrimination $F(1,19)= 4.00$, $p<060$, Narrative memory $F(1,24)= 4.01$, $p<.057$, Visual attention – time $F(1,25)= 3.82$, $p<.062$, and Speeded naming – time $F(1,16)=3.95$, $p<.064$). The performance level in tests of sensorimotor domain was very variable.

Type of stroke had more contiguous effect on test results. (Cases whom the stroke type was not known were dropped from this analysis.) In general, children with ischemic stroke fared better. This was more true for tests of memory and verbal content, namely in Comprehension of instructions $F(1,23)=4.56$, $p<.043$, Memory for names $F(1,17)= 9.08$, $p<.008$, and Narrative memory $F(1,21)= 6.67$, $p<.017$. In many tests this effect apperad in interaction with lesion onset where children with neonatal stroke had better outcome after ischemic damage in comparison with cases of hemorrhagic insult but in childhood stroke reverse pattern was noted. This was again related with tasks of memory and language domain but also in some attention tests: Picture memory $F(1,19)=4.44$, $p<.049$, Narrative memory, $F(1,21)=6.95$, $p<.015$, Memory for faces $F(1,20)= 8.34$, $p<.009$, Repetition of nonsense words $F(1,18)=4.63$, $p<.045$, Speeded naming – time $F(1,14)= 17.25$, $p<.001$, Knock and tap $F(1,15)= 9.05$, $p<.009$, Auditory attention $F(1,14)= 8.57$, $p<.011$, and Tower $F(1,18)= 4.75$, $p<.043$. In many other tests this pattern was observable as trend not

reaching significance (Visual attention – time, Statue, Phonological processing, Oromotor sequences, Finger tapping, Finger discrimination, and Sentence repetition).

The effects of cortical versus subcortical damage was again apparent in interaction with onset time. (Cases with missing values were excluded from this analysis.) Results of Block construction were notably better in those children, who had lesion in cortical areas $F(1,23)= 4.31$, $p<.049$, but this was more observable in interaction $F(1,23)= 10.37$, $p<.004$. This association was stronger in children with childhood damage while difference was not marked in neonatal stroke. Same type of interaction between lesion in cortical areas and acquired stroke emerged in tests of Visuomotor processing – time $F(1,23)= 5.77$, $p<.025$, and Phonological processing $F(1,23)= 5.01$, $p<.035$, while Sentence repetition showed a trend ($F(1,21)= 3.88$, $p<.062$). Children with neonatal insult had no apparent difference between cortical versus subcortical damage.

Epilepsy had only minor effect on test performance. Subjects without epilepsy had better results in Route finding $F(1,10)= 5.10$, $p<.047$. Again interaction effect emerged with onset time in subtests Visual attention – time $F(1,25)=5.31$, $p<.030$, Design fluency $F(1,15)= 9.21$, $p<.008$, Verbal fluency – phonemic $F(1,8)= 10.86$, $p<.011$, and List learning $F(1,9)=9.74$, $p<.013$. In all tasks children with neonatal stroke fared better when epilepsy was not present, but in childhood stroke this trend was not observed.

Sex had only small effect on cognitive test scores. Boys had more correct answers in Visual attention subtest $F(1,25)= 7.68$, $p<.010$, and had more correct repetitions of nonsense words $F(1,21)= 4.35$, $p<.049$. Interaction was observed in number of mistakes in Visuomotor prescision subtest $F(1,26)= 7.92$, $p<009$ where girls with childhood stroke were significantly better than boys but this trend was not so apparent in neonatal cases.

Study II

A further aim was to observe the changes in cognitive profile in our subjects. Therefore 20 children were retested with the same instrument after a mean intertest interval of 2.29 years. To compare the change in test scores only results of those subjects with retest data were used in data analysis. Raw scores were standardized to z-scores and test results were compared with the Wilcoxon matched pairs test to determine the change within groups. Only very few test scores changed significantly. Children with neonatal

stroke had a higher score after second testing in Route finding Z=2.02, p<.043, while trend for important change was observed in Fingertip tapping Z=1.86, p<.062, and Knock and tap Z=1.82, p<.069. For childhood stroke subjects the subtests Block construction Z=2.37, p<.018, and Picture memory Z=1.99, p<046 showed significant improvement.

To determine the score changes between groups score differences were calculated by subtraction and results were compared with the Mann-Whitney U-test. Only Block construction scores reached statistical significance U=2.20, p<.028. As these results may have been confounded by age the difference between groups was rechecked with ANCOVA using intertest interval as covariate. Significant change appeared in subtests Fingertip tapping F(1,12)= 4.75, p<.050, and Block construction F(1,17)= 6.22, p<.023. This change was in favor of neonatal stroke group. It is also interesting to note that intertest interval as covariate showed significance in only some subtests, that mostly tap linguistic abilities (Phonological processing, Comprehension of instructions, Sentence comprehension, Sentence repetition, Imitating hand positions, Design copying).

The possible effect of different clinical measures on the score change was analysed with ANCOVA using intertest interval as covariate and score differences as dependent variable. None of the neonatal children with right hemisphere lesion had a retest therefore it was not possible to perform 2 (onset time) by 2 (lateralization) ANCOVA and laterality effect was compared separately. Only the score change for Arrows was different F(1,13)= 6.49, p<.024. Children with left-sided lesion improved more on this subtest. These results are only tentative due to unequal number of right- and left-sided cases included in retest (Fisher's exact test p<.030). Although the group sizes were not balanced the groups did not differ in relative proportion of other subject variables (handedness, hemiparesis severity, stroke type, cortical vs subcortical damage, epilepsy, sex – Fisher's exact test p>.1).

The effect of handedness appeared more in interaction with onset time in some visuomotor and attention tests. Interaction emerged in subtests Visual attention – time F(1,13)= 6.19, p<.027, Auditory attention F(1,7)= 9.08, p<020, Sentence comprehension F(1,12)= 8.11, p<.015, and nearly reached significance in Picture perception F(1,14)= 4.28, p<057, and Block design F(1,15)= 3.87, p<.068. Right-handed children with neonatal stroke experienced more gain while left-handed children with childhood stroke

improve more on the same tasks. Severity of hemiparesis had only minor effect on cognitive functions. Interaction with onset time emerged in semantic verbal fluency $F(1,15)= 6.23$, $p<.025$ where children with neonatal stroke who have mild hemiparesis gain more, but in childhood stroke this gain is associated with moderate-to severe hemiparesis. Interaction with onset time was nearly significant in Sentence repetition $F(1,13)= 4.25$, $p<.060$, and Arrows $F(1,11)= 3.96$, $p<.072$. The main effect of severity failed to meet significance in Oromotor sequences $F(1,10)= 4.70$, $p<.055$, and Design copying $F(1,14)= 3.35$, $p<.088$, where children with mild hemiparesis tend to have higher gain.

The effect of lesion localization in cortical or subcortical areas to cognitive outcome did not show any systematic improvement. Cortical damage was associated with more change in Route finding $F(1,3)= 10.83$, $p<046$, and Memory for names $F(1,7)= 22.37$, $p<.002$. On the other hand subcortical damage was associated with more improvement in Block construction $F(1,12)= 8.21$, $p<.014$, and Auditory attention $F(1,5)= 8.02$, $p<.037$. Some effects were observed in terms of interaction with onset time. In Memory for names the change associated with cortical damage was more marked in children with childhood stroke $F(1,7)= 7.05$, $p<.033$. In Arrows bigger change was seen in neonatal stroke children with cortical lesion and childhood stroke children with subcortical lesion $F(1,8)= 6.53$, $p<.034$. Similar pattern emerged in Phonological processing but did not reach significance $F(1,12)= 4.66$, $p<.052$.

Stroke type was associated with more gain in Fingertip tapping $F(1,8)= 5.66$, $p<.045$ in favor of hemorrhagic stroke. Interaction between stroke type and onset time was observed in Memory for faces $F(1,11)= 6.79$, $p<.024$, Speeded naming – time $F(1,6)= 15.47$, $p<.008$, and Visuomotor prescision – time $F(1,13)= 6.24$, $p<.027$ where higher gain in hemorrhagic stroke was notable in neonatal insults but childhood stroke subjects did not show marked difference between types.

Epilepsy had only few effects. Children with epilepsy gained more in Design copying $F(1,14)= 4.94$, $p<.043$, and interaction was evident in Imitating hand positions $F(1,15)= 9.58$, $p<.007$ where children with childhood stroke and epilepsy improved more while no apparent effect emerged for children with no epilepsy present.

In terms of sex effects boys tend to become faster in Visual attention $F(1,13)= 6.72$, $p<.022$, while girls become more accurate in the same subtest $F(1,13)= 6.63$, $p<.023$. Interaction between sex and onset time emerged in Tower $F(1,11)= 6.02$, $p<.032$ where girls with neonatal and boys with childhood stroke improve more, and semantic verbal fluency $F(1,15)= 8.12$, $p<.012$ where girls with childhood stroke improve more but no notable effect was present for neonatal stroke.

DISCUSSION

In general children with neonatal stroke had a poorer outcome than children with childhood stroke. Their deficits were spanned over several functional domains and their subtest mean scores tended to be lower than in the childhood stroke group.

Both patient groups had lower levels of sensorimotor functions that is associated with hemiparesis, especially in fine-motor skills. This refers to lower plasticity of the motor system in overcoming the impact of damage. Only motor speed was retained in a test of eye-hand coordination but at the expense of accuracy. Tactual sensation is more preserved in childhood stroke. The variability of results in sensorimotor tests was very large. Even mild hemiparesis results in deficiencies in more skilled movements. Cognitive outcome was not directly associated with motor outcome, although neonatal group showed a trend of fewer cognitive sequelae after mild hemiparesis.

Auditory and visual attention were affected in both groups in comparing with control subjects. Children with childhood stroke seem to be somewhat more impulsive and made more mistakes in several tests. Some earlier studies have stated that children become more impulsive after right-sided injury (Aram & Ekelman, 1987; Aram et al., 1987). This was not apparent in the current study.

Executive functions did not reveal a large difference from controls. Usually lesions caused by stroke in children do not involve prefrontal areas and executive functions associated with this brain region are not significantly affected. Executive functions have also more protracted course of development (Anderson et al., 2002;

Jacobs & Anderson, 2002) and even normal children may not perform some more complex tasks at the optimal level. It is possible that deficiencies in these skills appear later when full competence is obtained.

Verbal functions were more affected in children with neonatal stroke. Difficulties in language tasks in the childhood stroke group were the most apparent when children were required to use and switch verbal tokens according to a visual display. They were slower and also made more mistakes in this test in comparison with neonatal and control group. It can be concluded that language disturbances after childhood insults were mild and deficits appear in more demanding conditions. Also their ability to retain verbal information was poorer in the test of narrative memory. A majority of children with childhood stroke had damage in subcortical areas that may have preserved their language function, although deficits in language are likely to follow even after subcortical damage (Aram et al., 1983; Gout et al., 2005). In contrast children with neonatal stroke had more marked problems in comprehension and word-finding.

Visuospatial functions were not impaired in the childhood stroke sample. Recent studies also report good recovery of spatial skills in childhood stroke after left-sided lesion (Schatz et al., 2004). Children with neonatal stroke had more marked shortcomings in visuospatial tests, involving both perception and constructive skills. More involvement of visuospatial functions in neonatal insult was also evidenced in the effect size analysis, although the effect sizes can not be very large due to the variability of the functional level within the wide age-range in this study.

Short-term memory was more affected than verbal and associative learning. Previous reports have shown more spared short-term memory skills (Vargha-Khadem et al., 1985; White et al., 2000). It is possible that the task used in this study (asking children to repeat complex sentences of increasing length) was more demanding to children as they had difficulties in using verbal tokens in a speeded setting and finding necessary words. Deficits in learning and memory were apparent in verbal and visual modality. Earlier studies have also stated that deficiencies in memory acquisition and recall are important sequelae after stroke in children (Block et al., 1999; Lansing et al., 2004; Mosch et al., 2005).

Laterality effects were in favor of the right-sided lesion since children with right-sided damage had a better outcome. These were more evident in visuospatial skills. Although laterality effects were not seen in interaction with lesion onset the findings may be heavily influenced by the performance of neonatal group as their level of visuospatial skills was lower and this group also has a smaller percentage of right-lesioned subjects. Children with neonatal stroke also had a lower ability level in verbal subtests that shows functional dependency between these cognitive skills in those children. This can be explained with the crowding hypothesis, proposing that language is spared after left-sided damage by reorganizing it to right hemisphere that interferes with its dominant functions (Milner, 1974; Teuber, 1974). This is also affirmed by data from previous research referring to lowered performance level of nonverbal abilities after left-sided damage in neonatal stroke (Ballantyne et al., 1994; Muter et al., 1997; Nass et al., 1989; Riva & Cazzaniga, 1986; Woods, 1980). Similar functional dependency between verbal and visual skills was not seen after left-sided childhood damage. Their visual skills were spared and although some children had difficulties in constructional tasks these result more from hemiparesis than domain-specific deficits.

A more drastic influence of the left-sided injury can be inferred from handedness-related effects, where right-handed subjects outperformed left-handed subjects on some sensorimotor, verbal and visual subtests. Left-handedness associated with hemiparesis can be considered as “pathological” left-handedness, forced by the inability to use the right hand in spite of dominant disposition. These cases may involve larger lesions that need greater reorganization. However, these results must be considered with caution; precise effects of laterality remained unraveled because too few children with right-hemisphere damage were examined to make more definite conclusions on the general ability level. Some previous research has shown adult-like effects after early damage (Kolk & Talvik, 2000; Montour-Proulx et al., 2004; Raz et al., 1994) and studies also show marked visuospatial deficits after early right-sided damage (Akshoomoff et al., 2002; Schatz et al., 2000; Stiles & Thal, 1993). It is possible that with inclusion of further cases and a more balanced number of left- and right-lesioned subjects the profile would reveal a more adult-like pattern. Precise effects of inter- or intrahemispheric reorganization as reflected by handedness were also unrevealed. Nearly all subjects with

left-hemisphere injury in neonatal group were left-handed, that shows interhemispheric transfer. Of the three left-lesioned children who preferred their right hand two were initially ambidextrous, that is their handedness was not clearly established.

Epilepsy only had a minor effect on overall performance that was not predicted by some earlier research (Kolk et al., 2001; Steinlin et al., 2004). Epilepsy effects were more apparent in children with neonatal stroke in tasks of fluency and learning. Still some children with epilepsy had a more reduced performance level on various tests. Although in majority of cases the seizures were well controlled the deficits in cognitive functions were more marked in those who had poor compliance with treatment. Sex also had a nonsignificant effect on the overall performance. This was evident in scores of some subtests and it can be concluded that plasticity and functional recovery in general is the same for both girls and boys.

The most consistent relationship with cognitive outcome was associated with the stroke type. This was more expressed in language and memory skills. Children with neonatal stroke had a better performance after ischemic insult in these tests while in cases of childhood stroke the better outcome was associated with hemorrhagic insults. This effect may be explained by differences in lesion localization and size. Hemorrhagic strokes in neonates have more general brain damage effect as larger areas are impaired and lesions typically concentrate to the periventricular region involving more white matter damage. Therefore the functional effects of these injuries may be broader if damage involves cortical tracts (Futagi et al., 2006). Childhood hemorrhagic strokes occur more in the subdural space and bleedings are more intraparenchymal. These may not leave so evident structural damage (Al-Jarallah et al., 2000; Lynch, 2004). Therefore the recovery may be better after hemorrhagic damage than after ischemia. Other studies have provided somewhat discordant findings in this question. Papers on childhood stroke are in accordance with results of this study showing better outcome after hemorrhage (Blom et al., 2003). In neonatal stroke the outcome is reported to be better after subcortical damage (Claeys et al., 1983; Steinlin et al., 2004) that is a typical finding after hemorrhage in this group. However, these studies do not differentiate the type of stroke and subcortical damages may result from ischemic lesions as well. Futagi et al. (2006) in a recent population-based study gives a more pessimistic view. The outcome after

hemorrhage in neonates was associated with more severe lesion and unfavorable outcome.

Prospective analysis of long-term outcome revealed no significant change in recovery of cognitive functions. Marked improvement between two testing sessions was noted in only some subtests and the pattern was not uniform in both stroke groups, but it was more apparent in visuospatial tasks. Developmental change as indexed by intertest interval effects was notable in several language tasks but also in motor proficiency and copying. Small improvement was noted in raw scores of nearly all of the tests for both stroke groups and none of the tests showed a large and significant score decline. Nevertheless these gains were rather modest. All children were retested after an interval of at least one year to avoid the practice effect and the increase of scores should reflect developmental change.

We were interested if developmental change is related to different clinical measures (lesion laterality, handedness, hemiparesis severity, stroke type, cortical or subcortical involvement, epilepsy, and sex). The influence of these subject variables seem to be more casual than concise and the improvement was not generally accelerated in some groups. Most effects appeared via interaction and since only few children were included the effects may be heavily disturbed by a combination of the small sample size and a large variablity of test scores. In general small developmental improvement in cognitive functions appeared in both groups. Score changes were fairly even in left- and right-lesioned subjects. Handedness effects were observed in interaction, whereby improvement differences favored right-handed subjects in neonatal group and left-handed subjects in childhood stroke group on some language and attention tests. Improvement in cognitive functions was not accelerated in less severe hemiparesis. Cortical or subcortical lesion localization had differential effect depending on task and lesion onset. The type of stroke did not had a general differentiating effect but children in neonatal group with hemorrhagic lesion tended to make more gains. Children with epilepsy made more improvement in some language and motor tests. The range of improvement was different for boys and girls in some attention and executive tasks. More complex analysis with combining these variables was not possible due to small number of subjects and unbalanced groups. It can be concluded that the speed of improvement depends more on

the subject with different clinical factors also playing their role. Improvement can be accelerated in some tests or domains. A general finding was that those who had a lower score on the first testing made a more marked improvement in raw score points. They had simply more to gain. Still this finding was not observed in all domains and in some subtests lower scores did not direct to more improvement. Parents of children also received rehabilitation guidelines to improve the affected functions of their child. However it is not known how systematically they assisted their child to use these guidelines and whether the suggested strategies generalized over different tasks.

According to data of this study cognitive deficits seem to persist over time. Some other previous studies have also shown no apparent change in cognitive functions in the long-term (Banich et al., 1994; Levine et al., 2005). Children seem to resign from the usual speed of development and make fewer gains when they get older. This developmental arrest was associated with lesion size, but the vantage of smaller lesions is downgraded by time. Lesion laterality or the child's seizure status did not have an impact (Levine et al., 2005).

This arrested development may stem from different reasons in neonatal and childhood stroke groups. In children with neonatal stroke the development seems to be capacity-bound. The development proceeds quite fairly until about 6 years of age when it starts to level off. Later development demands for more complex cognitive skills that are challenging for children with stroke after that age. This in turn leads to developmental slowing. Development itself is not a unitary linear skill perfecting. Normal children make a developmental leap at the ages of 5-8 years when they obtain relative competency in the majority of cognitive functions. Developmental curve after that age becomes more flat (Korkman, Kemp, & Kirk, 2001). The mean age at the time of stroke for childhood stroke group was 5.49 years. In the light of normal developmental course insults in this period may seem especially undesirable since the relative competency in different functions is not yet gained. Children who encounter the insult after 8-10 years of age have already mastered cognitive skills at the expected range and the developmental course is "flatlined".

However it must be reminded that as a group, the children included in this study cannot be regarded as having retarded development. A majority of them attained regular

kindergartens or schools and only some needed educational assistance. They were making reasonable academic progress at the time of the study by parental estimation, although this data was not available for all children.

This study has some important limitations. The scheme of data analysis may not be the most correct one since the analysis of covariance was used is spite of the fact that not all of the subtests met the normality assumption and simple transformations were unable to improve the situation. Since age is the most important predictor of cognitive abilities and the sample included children from a large age range (3-12 years) it was important to override the age effects. Another possibility would have been to transform scores to scaled scores standardized for age. Unfortunately a large normative data pool of Estonian children is lacking. An option would have been to convert scores by using Finnish normative data as reference (Korkman et al., 1997). Standardization according to norms from other cultures has been used previously in some studies (e.g. Mulenga, Ahonen, & Aro, 2001) but the authors warn against possible flaws due to cultural and educational differences between countries that may induce systematic errors.

We decided to use the raw score data since a further aim was a prospective study of long-term change. Results would be more straightforward and interpretable by using raw score data in this analysis. Likewise it would have been useful to standardize data to age-scaled scores that would create a context of normative expectation. This can be a following advance of this study.

An additional limitation was the small number of subjects and unequal groups. Still the study includes most of the known children with unilateral brain injury available for studying. Brain insults in children are quite unusual and due to this the study groups cannot be significantly increased. However, increasing the sample does not decrease the large variability of lesion variables. Children with childhood stroke differ from neonatal stroke survivors in terms of insult onset. Since children can experience childhood stroke at any time, they differ in terms of the previous period of normal development. Many children in Study I were tested quite soon after the insult and acute effects may have influenced the results. However their performance was not systematically downscaled. It can be also revealed by the fact that the change in the performance level was not notable in the childhood insult either. Children included in the study are not homogenous in terms

of lesion localization. The results may be confounded by lesion size, although it has been shown not to have a large effect on the cognitive outcome. In the current study the grading of lesion size was unavailable but it is desirable to assess also the possible effect of lesion size on different cognitive subtest scores.

CONCLUSIONS

This study assessed the cognitive outcome of children with stroke. The results were in line with early vulnerability hypothesis. Children with neonatal damage had more adverse effects; they had lower ability level in tests of sensorimotor functions, visuospatial skills, language, memory and learning, and attention. Children with childhood stroke had milder deficits, these were more notable in domains of sensorimotor functions, memory and learning, and attention. Executive functions were spared in both groups. Subjects with left hemisphere lesion had a more unfavorable outcome but precise effects of laterality remained unrevealed. From different clinical measures the stroke type had most consistent effect on tests of memory and language. Prospective study showed small improvements in raw scores of nearly all tests but these were not highly significant in various cognitive domains. The speed of change was similar in both stroke groups and was not systematically affected by different clinical measures. Stroke leads to only small developmental gains in both neonatal and childhood insults.

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APPENDIX A

NEPSY subtest descriptions (Kemp, Korkman, & Kirk, 2001; Korkman, Kirk, & Kemp, 1997) and scoring procedures used.

Attention and executive functions domain

(1) Tower – This is a Tower of London type of task to assess rule-based problem solving, where child is expected to match the position of balls on the pegs according to model presented in certain number of moves within time limit. Score is number of correct solutions.

(2) Auditory attention and response set – This subtest assesses selective and complex auditory attention, where child is presented with words on the audiotape and asked to react with correct selection of stimuli in part A and shifting the set in part B. Score is number of correct reactions given.

(3) Visual attention – This subtest assesses the speed and accuracy of focused and dividedd attention in visual domain. Child is expected to carry out a search of targets from the response sheet within time limit. Score is product of correct targets found and time spent on task. As speed and accuracy of response have a quite different meaning on the overall performance, the speed and accuracy were scored separately. The speed score was further reversed by subtracting the time spent on task from the maximum time allowed, to make the meaning of score comparable to other scores.

(4) Statue – This subtest measures motor persistence and the ability to inhibit motor response. Child is asked to stay in a designated position with eyes closed and ignore the external distractors. Score is number of time intervals achieved.

(5) Design fluency – This subtest assesses nonverbal fluency by asking child to generate as many unique designs in the matrix of dots within time limit. Score is number of unique designs.

(6) Knock and tap – This is a go/no-go task where child is required to switch motor response in response to examiner’s presentation. Score is number of correct responses.

Language domain

(1) Body part naming – This is a task of auditory comprehension where child is asked to identify body parts from a picture of a child. Score is number of correct identifications. This subtest is exclusive to 3-4 year olds and it was later dropped from the analysis due to small number of children assessed.

(2) Phonological processing – This subtest assesses phonemic awareness, where child is asked to match word segment with pictude or modify word segments to generate a new word. Score is number of correct answers.

(3) Comprehension of instructions – This is a verbal comprehension task that requires the child to respond to oral directions realted to visual stimulus plate. Score is number of correct answers.

(4) Speeded naming – This subtest measures rapid access to and production of langauge labels for visually presented stimuli within time limit. Score is a product of correct labels and time spent on task. As speed and accuracy of response have a quite different meaning on the overall performance, the speed and accuracy were scored separately. The speed score was further reversed by subtracting the time spent on task from the maximum time allowed, to make the meaning of score comparable to other scores.

(5) Repetitions of nonsense words – This subtest measures decoding of nonsense words presented on the audiotape that child is asked to repeat. Score is number of correct repetitions.

(6) Verbal fluency – This task assesses the ability to generate words within specific semantic and phonemic categories. Score is number of words generated within time limit. Here the semantic and phonemic fluency are scored separately.

(7) Oromotor sequences – This subtest assesses the ability to repeat difficult auditory sequences without mistakes. Score is number of correct repetitions.

(8) Sentence comprehension – This is a verbal comprehension task where child is asked to respond to difficult questions and sentences. Score is number of correct responses.

Sensorimotor domain

(1) Fingertip tapping – This subtest assesses finger dexterity, fine motor speed, and motor programming for both hands. Score is time spent to generate expected number of fingertip tappings.

(2) Imitating hand positions – This subtest assesses visuospatial analysis and motor programming by asking child to imitate a hamd position presented by examiner for both hands. Score is number of correct imitations.

(3) Visuomotor precision – This task measures graphomotor speed and accuracy for dominant hand asking child to follow a route with pencil within time limit. Score is a product of mistakes and time spent on task. As speed and accuracy of response have a quite different meaning on the overall performance, the speed and accuracy were scored separately. The speed score was further reversed by subtracting the time spent on task from the maximum time allowed, to make the meaning of score comparable to other scores. The accuracy score measured in mistakes was reversed by changing the sign, to make the meaning of score comparable to other scores.

(4) Manual motor sequences – This subtest asesses motor programming and bimanual motor coordination where child is asked to repeat multistep hand sequences presented by examiner. Score is number of correct repetitions.

(5) Finger discrimination – This subtest assesses tactile perception by asking child to identify fingers by touch on both hands. Score is number of correct identifications.

Visual-spatial domain

(1) Design copying – This is a two-dimensional construction task where child is asked to reproduce geometric designs of increasing complexity. Score is the accuracy of reproductions computed for each design by set criteria.

(2) Arrows – This subtest assesses the judgement of line and angle orientation by asking child to identify arrows pointing directly to target from number of distractors. Score is number of correct identifications.

(3) Block construction – This is a three-dimensional construction task where child is asked to copy a design presented by examiner. Score is number of correct constructions.

(4) Route finding – This is a subtest of visuo-spatial analysis and orientation where child is asked to transfer a route from a simple schematic map to a more complex one. Score is number of correct answers.

(5) Picture perception – This is a object identification task where child is asked to identify objects from blurry and unclear pictures. Score is number of correct identifications.

Memory and learning domain

(1) Memory for faces – This is a test of immediate and delayed facial recognition where child is asked to identify faces after brief presentation. Score is number of correct identifications for both trials

(2) Memory for names – This is an evaluation of name learning with immediate and delayed recall trials where child is asked to learn the names of line drawings of children. Score is number of correct identifications across trials.

(3) Narrative memory – This is a measure of story memory with free and cued recall conditions. Score is number of story units remembered.

(4) Sentence repetition – This is a short-term verbal memory task where child is asked to repeat sentences of increasing length. Score is number of correct repetitions.

(5) List learning – This is a verbal learning and memory test where child is asked to remember words from a list presented across trials with delayed recall of the same list. Score is number of remembered words across trials.

(5) Picture recognition – This subtest assesses the recent memory for pictures of object presented previously on a Picture perception task from an array of pictures. Score is number of correct answers.