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COGNITIVE REHABILITATION IN CHILDREN WITH ACQUIRED BRAIN INJURIES

Ingrid Hagberg-van't Hooft

Karolinska Institutetet
Department of Women and Child Health,
Astrid Lindgren Children's Hospital

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Vad rätt du tänkt
Vad du i kärlek vill
Vad skönt du drömt
Kan ej av tiden härjas
Det är en skörd som undan
Honom bärgas
Ty den hör evighetens rike till

Till Ferdinand, Frederik och Gustav

ABSTRACT

The concept acquired brain injury (ABI) refers to conditions arising postnatally owing to trauma, infections, vascular catastrophes or malignancies. It has been reported that up to 50% of children with ABI have cognitive sequelae, as brain injury during development not only disrupts established functions, but also affects functions that are still to emerge.

Deficits in attention, memory and executive functions are the most common cognitive dysfunctions after ABI and may have a major negative influence on academic and social adjustment. Neuropsychological measures can assess these dysfunctions and shortcomings in academic and social life, but there is a great need for new efficacious cognitive treatment programmes.

The main aims of this thesis were to evaluate the direct and maintained effects of a specific programme for cognitive training in children, and to evaluate whether the effects of training are transferred to the children's daily life.

In **Study I** a computerized measure of attention and impulsivity, the Gordon Diagnostic System (GDS) was validated. The GDS was used on a sample (N=71) of Swedish children from the greater Stockholm area fulfilling the criteria for Attention Deficit Hyperactivity Disorder (ADHD) according to the Diagnostic and Statistical Manual for Mental Disorders DSM-IV. The Children with ADHD had significantly lower scores of correct responses on the GDS as compared to controls (N=88). These scores were also strongly associated with age.

In **Study II** the feasibility of a cognitive training programme, the Amsterdam memory and attention training for children (Amat-c) was tested on children with traumatic brain injuries (TBI).The results on several neuropsychological tests improved. Parents' and teachers' ratings indicated that the children learned strategies enabling them to improve their school achievement and their self-image. The Amat-c method was modified to take into account the experience gained from the preliminary results before launching a randomized controlled study, which formed Study III.

In **Study III** the immediate effects of the Amat-c programme were evaluated. The training group (N=18) as compared to controls (N=20) showed a significant improvement on complex neuropsychological tests of attention and memory. Less effect was observed on more simple tests of reaction time.

In **Study IV** the persistence of training induced effects was examined 6 months after completion of the intervention, and an investigation whether demographic and clinical variables influenced outcome. The essential finding was that the significant improvement in complex attention and memory tasks reported in Study III persisted 6 months after completion of the training. No significant influence of demographic or clinical variables on outcome could be detected. This result provided support for the robustness of the training programme as well as for its external validity.

In **Study V** the possible transfer of the previous positive treatment, on the children's daily life was evaluated using behaviour rating scales for the parents, teachers and children. Teachers, in particular observed a significant improvement in school performance as well as on attention and executive functions. Parents and children described a similar trend. Less effect was observed on social behaviour.

Summary: The Gordon Diagnostic System is an objective measure to assess attention problems in children across ages. The Amat-c cognitive training method improved complex attention and memory functions in children with ABI. The gains are maintained for at least 6 months following completion of the programme. Children learn to develop strategies and deal appropriately with a task, but do not improve speed of performance. The training effects seem to transfer to behavioural aspects like school performance, attention and executive functions, but less obviously to social behaviour.

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I. El-Sayed E, **van’t Hooft I**, Fried I, Larsson J-O, Malmberg, K, Rydelius P-A.

Measurements of Attention Deficits and Impulsivity: a Swedish study of the Gordon Diagnostic System. *Acta Paediatrica,* 1999, 88, pp 1262-1268

II. **van´t Hooft I**, Andersson K, Sejersen T, Bartfai A, von Wendt L.

Attention and Memory Training in Children with Acquired Brain Injuries.

Acta Paediatrica, 2003, 92, pp 935-940

III. **van´t Hooft I**, Andersson K, Bergman B, Sejersen T, von Wendt L, Bartfai A.

Beneficial Effects from a Cognitive Training Programme on Children with Acquired Brain Injuries Demonstrated in a Controlled Study. *Brain Injury in press*

IV. **van´t Hooft I**, Andersson K, Bergman B, Sejersen T, von Wendt L, Bartfai A.

A Randomized Controlled Trial on Children with Acquired Brain Injury reveals Sustained Favourable Effects of Cognitive Training. *Submitted to Pediatric Rehabilitation*

V.**van´t Hooft I**, Brodin U, Sejersen T, von Wendt L, Bartfai A.

Measuring Effects on Behaviour after Cognitive Training in Children with Acquired Brain Injuries. *Manuscript under preparation*

ABBREVIATIONS AND TERMS

ABI	**Acquired Brain Injury**
ADHD	**Attention Deficit Hyperactivity Disorder**
ALL	**Acute Lymphatic Leukaemia**
AMAT-c	**Amsterdam Memory and Attention Training for Children**
CE	**Errors of Commission**
CR	**Correct Responses**
CRP	**Cognitive Remediation Program**
CNS	**Central Nervous System**
DSM-IV	**Diagnostic Statistical Manual for Mental Disorders**
GDS	**Gordon Diagnostic System**
IQ	**Intelligence Quotient**
RBMT	**Rivermead Behavioural Memory Test**
RCFT	**Rey-Osterrieth Complex Figure Test**
ROC	**Receiver operating characteristics**
TMT	**Trail Making Test**
TBI	**Traumatic Brain Injury**

1. GENERAL INTRODUCTION

One of the "major tasks" of the developing child is to acquire an enormous quantity of new information and a large number of new skills. The interruption of development caused by an acquired brain injury (ABI) in childhood may have devastating intellectual and socio-emotional consequences (Koskeniemi et al. 1995, Taylor and Alden 1997, Eslinger and Biddle 2000, Ewing-Cobbs et al. 2004).

There has been a longstanding, widely held belief, that damage to the brain early in life leads to a better outcome than damage received later in life because of, children's higher brain plasticity and greater possibilities for brain reorganization (Kennard 1942). This opinion has in the last decades been modified. Brain injury in children not only disrupts established functions but it may also affect functions that are in the process of developing or that have yet to emerge. Children who appear to have fully recovered from brain injury may, over time, demonstrate deterioration in cognitive, socio emotional and behavioural functioning (Anderson et al. 1997, Anderson et al. 2000, Ewing-Cobbs et al. 1985, Benz et al. 1996).

Valid neuropsychological assessment methods and evidence based cognitive rehabilitation programmes especially designed for children are needed if one is to be able to evaluate the eventual consequences, influence children's recovery and prevent secondary effects after ABI.

1.1Acquired brain injuries

Epidemiology

The concept acquired brain injuries (ABI) in children is defined as an injury to the central nervous system (CNS) occurring during development, after the post neonatal period. The most common cause of an ABI is trauma. While most of these injuries are mild, with few sequelae, children sustaining moderate to severe traumatic brain injury (TBI) may suffer permanent cognitive and behavioural impairment. Other, non-traumatic causes for injury to the brain during childhood are infections, brain tumours, vascular catastrophes, anoxia, and other conditions affecting the central nervous system (CNS).

Traumatic brain injury

TBI is the most common cause of death in children and adolescence (case fatality rate ranging from 3 to 14 per 100 cases) and the incidence of children and adolescence being hospitalized for TBI is 180/100.000 (Kraus 1995). In Sweden 7200 children and adolescents (age 0-19 years) are hospitalised every year because of head trauma (SBU 2000).

Emanuelson (1997) reported that 12 children/ 100.000 inhabitants have contusion-level brain injury (concussions excluded) every year. Concussion is characterized by transient loss of consciousness (<30 minutes) with loss of awareness immediately following a head injury. Contusion often includes a loss of consciousness from 30 minutes and longer. Typical locations for contusions are the frontal poles, the sub-frontal cortex and the anterior temporal lobes. However, the most common subgroup consists of children with mild or minor head injury equivalent to concussion, which accounts for at least 90% of all head traumas (Kraus 1994, Emanuelson 1997, Hawley 2004). Swedish data report an incidence of mild traumatic brain injury varying from to 468/100.000 in the age group 0-17 years (Dahl et al. 2003), to 1000/100.000 (Falk et al. 2005).

The severity of traumatic brain injury (TBI) is graded according to the Glasgow Coma Scale into three groups of severity: *mild TBI* (corresponding to a GCS 13-15), Lack of Consciousness (LOC<30 minutes) and Post Traumatic Amnesia (PTA< 1 hour), *moderate TBI* with a GCS of 8-12, LOC variable ranging from 30 minutes to 24 hours, and a PTA of 1-24 hours; and *severe TBI with a GCS* below 8, LOC of 6 hrs to one week, and PTA of 1-7 days or more than 7 days.

Non- traumatic brain injuries

<u>Malignancies</u>

In industrialized countries the inclusive annual incidence rates for paediatric malignancies vary from 110 to 150 cases per million children under 15 years of age (Stiller and Draper 1998). The most frequently occurring malignant diseases in childhood are leukaemias, constituting 1/3 of all cases of malignancies in children younger than 15 years of age. The second most common such malignant disease is brain tumour, accounting for 1/4 of all paediatric cases (American Cancer Society 1997). Astrocytomas and primitive neuroectodermal tumour (PNET)/medulloblastomas, comprising about 50% and 20% respectively, of primary brain tumours, are the most common histological subgroups (Parkin et al. 1988).

Although the mortality rate has decreased the prevalence of Acute Lymphatic Leukaemia (ALL) and brain tumours have according to some studies, been reported to be increasing (Bleyer et al. 1997, McNeil et al. 2002, Ries et al. 1999). A trend for an increasing incidence of childhood astrocytomas have been revealed in several international registers (Blair and Birch 1994, Bunin et al. 1996, Gurney et al. 1996, Hjalmars et al. 1999). The cause for this trend is not known, but improvements and changes in diagnostic methods are often considered the most likely explanation. In a study of the Nordic countries Hjalgrim et al. (2003) reported that the incidence of ALL during the last 20 years has been stable.

<u>CNS Infections</u>

Meningitis is a relatively common childhood disorder characterized by inflammation of the meningeal membranes. It has been reported that viral meningitis occurs annually in 14/100.000/year in the 1-19 year-old age group (Khetsuriani et al. 2003). Bacterial meningitis has an annual incidence rate varying from 27 to 69/100.000 in the paediatric age group (Feigin and Pearlman 1998).

Encephalitis occurs when a virus or another micro organism invades the brain, resulting in acute inflammation of cerebral tissue possibly associated with neuronal damage or death (Toltiz 1995). A more delayed, post-infectious demyelination of white matter may also occur.

The mortality rate is 5 % for most forms of encephalitis (Toltzis 1995). Herpes simplex virus induced type I encephalitis is one of the most common forms; it causes impairments in 1-2/100.000, and is responsible for 5-10% of the 20.000 cases of encephalitis per year in the U.S. (Gordon et al. 1990).

Stroke

Stroke is the common expression for brain infarction and intracerebral bleeding. The incidence rate for lethal and non-lethal intracerebral haemorrhage and subarachnoidal haemorrhage in children under the age of 15 years has been estimated to 1.5/100.000 (Broderick et al. 1993).

Hypoxia/Anoxia

Hypoxia refers to oxygen deprivation within the brain (Adams, Victor 1993). Hypoxic episodes may occur as a result of respiratory or cardiac failure. Near drowning has been reported to occur in about 18.4/100.000 in children below 5 years of age in a study representing the populations from the U.S.A. (Ellis and Trent, 1985). The incidence of other, more rare conditions, such as suffocation, choking and strangulation causing lethal anoxic brain injury was reported to be and 0.7/100.000 in the age group below 15 years (Nixon et al. 1995).

1.2 COGNITIVE CONSEQUENCES OF ACQUIRED BRAIN INJURY

Children with ABI frequently make a good physical recovery, and may appear outwardly to have made a full recovery. The expectations of their abilities and behaviours are often determined by this relatively healthy appearance, despite the fact that they may exhibit persisting significant cognitive and behavioural disabilities (Johnson 1992).

Research evaluating paediatric brain injury emphasises the importance of certain risk factors that are related to the *nature of the injury* and the age of the person afflicted at the time at which the injury occurred. Thus, for example, children with focal brain injuries may go on to acquire many age appropriate abilities, and may be free from the deficits that are observed following similar injuries in adulthood (Taylor and Alden 1997). However, there is evidence to suggest that there may be a "crowding effect" in these cases, thus, where one region of the brain, needs to take on functions usually subsumed by another part, this may result in a general decrease in neuro-behavioural function (Anderson et al. 1997, Kolb 1995). On the other hand, children sustaining a generalized cerebral insult have been shown to undergo a slower recovery and to have poorer outcomes than adults with similar insults (Anderson and Moore 1995, Anderson and Taylor 1997, Gronwall et al. 1997, Taylor and Alden 1997). Thus, the *age at the time of injury* plays a role. The earlier the injury the smaller the store of learned knowledge and skills, and the greater the likelihood of global impairment (Dennis 1999, Temple 1997). The timing of the CNS insult is particularly important in the immature brain. If the insult occurs during a sensitive or critical developmental period specific structures or functions may be disrupted (Anderson 2003). Indeed, the timing of the insult, the nature of the injury, the stage of skills development and the social context of the child interact to determine the outcome for the child (Eslinger et al. 1999, Ylvisaker and Feeney 2002). This interaction between development and brain injury is sometimes referred to as *"growing into deficits"* (Mateer et al 1999). Furthermore, the *preinjury cognitive profile* of the child, the *psycho-*

social context and family function are known to play an important role for recovery following ABI in children (Anderson 2001).

Cognitive consequences of traumatic brain injuries

Up to 50% of the children with moderate to severe traumatic brain injury (TBI) are reported to have cognitive sequelae (Anderson et al. 2000, Brown et al. 1981, Klonoff et al. 1995) while mild TBI seems to have less impact on intellectual skills, also in the acute recovery phase (Anderson 2003).

Deficits in attention, memory and executive functions are the most common cognitive dysfunctions in children with TBI (Beers 1992, Donders 1993, Ewing-Cobbs et al. 1985, Hawley et al. 2004, Kaufman et al. 1993, Klonoff et al. 1995) and may contribute to academic failure (Catroppa and Anderson 2000, Goldstein and Levin 1985) In addition to which increased problems in behaviour, and psychiatric disturbances after TBI are often found (Cattelani et al. 1998, Perrott et al. 1991).

Cognitive consequences of malignancy

Of those children who are diagnosed with *cancer* up to 80 % are cured of their illness, but 50 % are at risk of acquiring cognitive dysfunctions (Fletcher and Copeland, 1988, Armstrong et al. 1995, Parker et al. 1997, Mulhern et al.1992, Mulhern et al. 2004). Late neurocognitive effects are defined as those occurring after the successful completion of medical therapy, usually two or more years after the time at which the diagnosis was made. It is generally assumed that late effects are chronic, if not progressive in their course (Mulhern and Butler 2004, Dennis et al.1996). The late neurocognitive core deficits, evident after cancer treatment in childhood are slow processing speed, and problems with attention, memory, and executive functions (Mulhern and Butler 2004). Children surviving brain tumours are at risk of severe deficits due in particular to the continued use of cranial radiation therapy (CRT) (Butler and Copeland 1993, Ris and Noll 1994, Mulhern et al. 2004). Preliminary results suggest a reduction in the development of normal appearing white matter among patients with brain tumour resection followed by CRT with or without chemotherapy (Mulhern et al. 1999).

Cognitive consequences of CNS infections

Approximately every third child with a CNS infection may exhibit neurological sequelae or cognitive impairment (Toltzis 1995).

As far as the cognitive consequences of *encephalitis* are concerned, the limited empirical evidence to date suggests that subsequent to encephalitis, children generally function within the average range, but obtain lower scores than controls, on tests of general intelligence (Rantala et al. 1991).

A large-scale prospective cohort study of *bacterial meningitis* survivors in Australia (Anderson and Taylor 1999, Grimwood et al. 1995, 1996) showed that subtle neuro-developmental anomalies increased with the length of time. Twelve years following illness the post-meningitic group was at greater risk of impairment in intellectual, academic and executive ability (Anderson et al. 2004).

Cognitive consequences of stroke

The sequelae remaining after stroke in childhood are highly variable. In a Danish study by Engberg and Teasdale (1997), for example, the rate of disabling sequelae after cerebral haemorrhage was (17%) in girls and (22 %) in boys, whereas Max et al. (2004) found that children showed significantly more attention dysfunction (46%) after stroke, which was significantly higher than for children with orthopedic problems (17%). The attention dysfunction was independent of lesion volume or site. The specific attention related core symptoms were inattention and apathy (Max et al. 2004). Furthermore, Chapman (2003) found a significant poorer outcome after stroke on language discourse for those afflicted with a lesion at an early age, as compared to later age at stroke. These findings alter the previously existing belief in optimistic language outcomes after childhood stroke (Feldman 1992). However, no site or size of lesion effects common to adult stroke has been identified in children.

Cognitive consequences of anoxia/hypoxia

In a review of 55 articles from 1966-2000 relating to cognitive behavioural and academic outcomes in children up to 14 years of age who had been exposed to chronic or intermittent hypoxia 78.2% reported an adverse effect. Of the 37 controlled studies 83.8% showed an adverse effect on cognition (Bass et al. 2004).

1.3 COGNITIVE FUNCTIONS

The development of cognitive functions during childhood is characterized by maturation in a number of different areas such as, attention, memory and executive functions. These functions are often considered to be separate domains, although they actually overlap and interact in complex ways that make it difficult to discuss one process without referring to some of the others (Sohlberg and Mateer 2001). The neural circuitry sub-serving attention, memory and executive functions is widely shared and are particularly vulnerable to disruption following ABI in both children and adults (Finlayson and Garner 1994, Sohlberg and Mateer 2001).

Attention

As Parasuraman (2000) points out “Attention is not a single entity, but the name given to a finite set of brain processes that can interact mutually, and with other brain processes, in the performance of different perceptual, cognitive and motor tasks”. Aspects of attention are mediated by diverse brain regions, which are linked by neural networks, or functional systems. These regions progressively mature during development, influencing the attention related capacities in children. Over the past two decades numerous models of attention related systems have been proposed (Mirsky et al. 1991, Posner and Peterson 1990, 1992, Sturm et al. 1997). Regardless of the theoretical model adopted, most models describe attention as an integrated system, both cognitively and physiologically, involving a number of separate, but interrelated components. These components include 1) the ability to sustain attention over time (vigilance), 2) the ability to attend to stimuli selectively, 3) the ability to alternate or switch attention to stimuli or tasks and 4) the ability to divide attention to maintain more than one ongoing process. Sohlberg and Mateer (1989) developed a model of attention in which attention was considered to be a multidimensional cognitive capacity, which directly affects new learning, memory, communication, problem solving, perception and most of the other dimensions of cognition. Attention was here considered to be a hierarchical function, where lower levels of attention included basic functions such as focusing attention (with no competing stimuli) and sustaining attention over time. Higher levels of attention, such as selective attention, and alternating or dividing attention, required lower levels of attention to be intact. It has been hypothesised that these higher orders of attention are not only dependent on the underlying functions but also involve the ability to disengage attention and inhibit response. These higher orders of attention are dependent on the frontal regions of the brain and overlap with some abilities that have been termed executive functions.

This model by Sohlberg and Mateer has served as the theoretical base for the Amat-c cognitive training programme (Hendriks, 1996), evaluated in the work conducted for this thesis.

A more recent complex, hierarchical and comparable theory on attention was proposed by Fuster (2004). This theory encompasses an interaction between *perceptual attention*, *working memory and executive attention*. *Perceptual attention* is the selective processing of sensory stimuli as a function of their physical context. The selectivity takes place at all stages of sensory processing and is enhanced by neural influences that run in two directions *bottom-up* and *top-down* control of attention. The *bottom- up control* derives largely from the physical properties of the stimuli and the physiological properties of the sensory systems. The *top-down control,* in contrast, is the modulation exerted by higher cortices upon the responses of perceptual cognitive networks to sensory stimuli. In the execution of perceptually guided tasks the control comes from the prefrontal cortex. Fuster, assigns *working memory* the role of attention focused on the internal representations of the cognitive content recently activated for the performance of executive functions.

Finally, the highest level of *executive attentional control* depending on the highest and most integrative stage in the hierarchy of cortical regions is that performed by the prefrontal cortex.

These theories of Sohlberg and Mateer (1989) and Fuster (2004) both aim at an integrative and hierarchical model where attention overlaps with memory and executive functions.

Developmental research demonstrates that young children have a limited attentional capacity, reflecting the immaturity of the underlying neural substrates, for example unmyelinated axons and developing frontal lobes (McKay et al. 1994, Ruff and Rothbarth 1996). The development of attention is characterized by a systematic increase in a child's ability to override innate response tendencies, and replace them with more appropriate ones, in situations where it is advantageous to do so. These increases in attentional capacity depend on the ability to transmit information both within the cortex and via sub cortical-cortical connections. It is argued that the development of these neural networks occur in a set order, and within a set time frame, with the posterior-anterior neural network progressively maturing but not being fully developed until late childhood (Klingberg et al. 1999). The developmental differences may be relevant to the pattern of impairment seen after ABI during development, where skills established early on are more consolidated and therefore less vulnerable, whilst less developed skills are at greater risk of impairment (Catroppa and Anderson, 2005).

Memory

Memory is the capacity to retain information about oneself and one's environment, the ability to store the mental traces of experience, of past events, and of learned facts.

Memory also includes the knowledge that we acquire, retrieve and utilize functions e.g. motor skills, perceptual and emotional knowledge without conscious awareness.

Many models have been proposed to explain the process, by which information is registered, encoded, stored and retrieved (McCarthy and Warrington 1990, Squire 1987, Tulving 1995). The major components in these models are the *sensory stores*, where information enters the system via the sense organs and is held, for a brief duration. *Short- term memory* associated with retention over seconds to minutes and the concept of *working memory* a temporary storing of information used to guide future actions and to the active maintenance of information relevant to an ongoing behaviour, as well as *long -term memory* in days or years (Gazzaniga 2003). Memory is fundamentally an associative function (Fuster 2004). According to the theory of Fuster (2004) memory consists of the joint activation of the neural components of a large cognitive network of perceptual and executive memory. These are represented in overlapping networks of the neo-cortex in the occipital, temporal, parietal, and frontal lobes, seem to be hierarchically organized by their content, and have been shown to play an important role in the formations of memory structures (Fuster 2004, Kandel 2000). Consequently, the networks of a memory can span wide cortical territories, from sensory cortex (perceptual memory) to the highest conceptual cortex (executive memory) (See Color Plate 1). The sub-cortical limbic structure (hippocampus) and cerebellum have a consolidating and mediating function on these networks. During development are in particular, the white matter and the frontal lobes, progressively maturing and not fully developed until late childhood (Rakic 1995, Dennis et al. 2000, Kandel 2000, Klingberg et al. 1999, Stuss and Anderson 2004).

(Color Plate 1 from Fuster (2004) with permission)

The basic biophysical process at the root of memory formation is the modulation of transmission of information across synapses, the neural elements anatomically associating cells with one another (Hebb 1949, Kandel 2000). Attention, rehearsal, repetition, and practice are functions that strengthen the synapses of the memory networks of the cortex.

The consolidation or encoding of a memory on cell level consists of synaptic modulation under the assistance of these cognitive functions. According to Fuster (2004) the solidity of a memory and its resistance to loss by cortical injury is depending on two structural factors: the strength of its synaptic connections, and the hierarchical ranking of its content. The greater the consolidation of a memory, the greater its resistance to injury. Accordingly there is an inverse relationship between the hierarchical rank of memory content and the vulnerability to cortical injury. The lower the memory in hierarchy, the more vulnerable it is to injury, the higher the memory the more resistant it is. By gaining width of distribution memories gain solidity.

These principles are of importance for understanding the cognitive consequences after ABI and for developing cognitive training programmes. The nature of a memory deficit is critically dependent on which regions of the brain are damaged and the extent to which they are uniquely involved in one system or more generally involved in multiple systems. The possibilities for rehabilitation will be dependent on what components of a system are damaged, how complete the damage is, and the extent to which other systems is preserved (Glisky, 2002).

Executive functions

Executive function (EF) may be described as the central executive component of the information- processing system- the component that directs attention, monitors activity, and coordinates and integrates information and activity. Stuss (1992) provides an integrated model of executive function, including a set of associated skills that allow the individual to develop goals, hold them in active memory, monitor performance and control for interference in order to achieve those goals. This very broad definition may be operationalized to include three separable, but integrated components: (1) attentional control: selective and sustained attention (2) cognitive flexibility: working memory, attentional shift, self-monitoring, and conceptual transfer; (3) goal setting: initiating, planning, problem solving and strategic behaviour.

The neural correlates of these executive functions of behaviour are supposed to be mediated by the anterior association areas in the prefrontal cortex (Kandel 2000). There is a growing body of research that describes progressive improvement of executive functions through childhood, parallel to growth spurts in frontal lobe development (Yakovlev and Lecours 1967, Giedd et al 1999, Stuss and Anderson 2004). Executive functions are by developmental psychologists often described as self regulation: setting and managing goals, planning, organizing, initiating, inhibiting, self monitoring and controlling attention and memory (Ylvisaker 2002). In educational and cognitive psychology, the term metacognition is also commonly used to refer to self-regulation of learning (Ylvisaker 2002). Children with executive impairments often have greater difficulty in learning and regulating their social behaviour in school than their psychometrical testing predicts (Eslinger 1997).

The interaction between attention, memory and executive function are most evident in the context of ABI and commonly targeted in neurorehabilitation programs where the ability of self-regulation is a functional goal.

1.3. PLASTICITY VERSUS VULNERABILITY

Environmental and other events can alter the organization of the normal and the injured brain, a property of the brain referred to as *plasticity* (Kolb, 2003*)*. Neuroimaging studies have suggested that the damaged brain may undergo reorganization following injury, and animal research has demonstrated plasticity in both the neocortex and hippocampus that appears to be stimulated by functional exercises and enriched environments associated with behavioural changes (Kandel 2000, Kolb 2003). In children the concept of plasticity needs to be considered in the light of the vulnerability of the still developing immature brain. Plasticity and early vulnerability theories represent counteracting mechanisms. It could be possible that different structures sub-serve emerging skills versus established ones. If an area is functionally immature at the time of injury, deficits may not be observable until the function that is assumed to depend on that particular damaged region is expected to develop (Anderson et al. 1999). In children, brain regions are not yet as dedicated to certain functions as they are in adults. Despite high plasticity this leads to greater vulnerability when injured. With diffuse, widespread, or bilateral injury, the mechanisms for plasticity may not be available (Kolb 1995). It is also possible that the significant deficits associated with early brain injury are related to the rapid development of many important skills during childhood. Ewing-Cobbs and co-workers (2003) have suggested that these skills are more vulnerable when a brain injury occurs at some ages than others because rates of skill acquisition vary with age. Early injury may disrupt the acquisition of basic competencies that provide the necessary foundations for later development.

As a child moves through later childhood and adolescence, the nature of impairment comes to resemble the adult picture more closely, reflecting the more mature CNS, and the associated reduction in plasticity/flexibility for recovery and reorganization (Anderson 2003).

One of the challenges is, that if neural circuits are more plastic at young age, the rehabilitation conducted on children with ABI should be designed to facilitate these plastic changes. In principle, there are two ways the brain might undergo plastic changes supporting recovery. Firstly, through the reorganization of remaining circuits, indicating that the nervous system can "do more with less". Secondly, through the application of different treatments that facilitates formation of new, functionally adequate synaptic connections (Kolb 2004).

A challenge for future rehabilitators will be the identification of cognitive training or behavioural therapy methods that would influence development and reparative processes in the injured brain (Ponsford 2004, Prigatano 1999, Sohlberg and Mateer 2001).

1.4. NEUROPSYCHOLOGICAL ASSESSMENTS IN CHILDREN

The primary goals of neuropsychological assessments in children are to provide information about the integrity of the central nervous system (CNS) (Lezak 2004).

A more specific goal is to detect the neuro-behavioural strength and weaknesses of a particular child in order to contribute to appropriate rehabilitation and management interventions. Another ongoing aim is to evaluate the efficacy of treatment and rehabilitation interventions (Anderson 2001). Neuropsychological assessment includes tests of cognitive and intellectual functioning involving different aspects of attention, perception, visuo-constructional, memory and executive functions (Lezak 2004). There are important developmental issues, which need to be considered when assessing the consequences of an injury on the developing brain. It is important to distinguish between a brain-injury induced deficit (meaning a persistent impairment) and a *delay* or *lag* in development (which entails the supposition that a child may eventually "catch up") resultant from brain injury. A brain injury may affect the onset of a skill, the order of emergence of a skill, the manner in which a skill develops and/or the degree of development of a skill. It is likely that the capacity for functional compensation may vary across brain regions and cognitive domains, and that damage to multiple systems may interact to produce greater disability.

It is particularly important to assess abilities often, as skills during development change rapidly and there are important interactions between development and injury effects.

To follow the development of these cognitive capacities it is important to have test devices that are standardized, have the capacity to measure changes over time, and can be combined with other psychometric assessments.

There were no available standardized and validated tests for specific measuring of attentional capacities across ages in Sweden when embarking on the series of studies presented here.

The GDS is a computerized test device that had been standardized (Gordon 1988) in the U.S. among 1400 normal American children between the ages of 4-16 years of age. This test is easy administered and can be connected to computer. For the work presented in this thesis, the GDS was tested on Swedish children before being used as an objective instrument evaluating the effect of cognitive training.

1.5. ECOLOGICAL VALIDITY

The role of neuropsychological testing has changed with the development of brain-imaging techniques because they allow physicians to gather more precise information about lesion, location and type of brain pathology (Long and Kibby 1995).

The focus of neuropsychology today are moving away from diagnostic questions to questions about the patients' everyday cognitive abilities and disabilities and to evaluate the effects of rehabilitation programs (Sbordone 1997, Wilson 1993). The tests, however, have not changed accordingly. The same tests that were developed to answer diagnostic questions are now used to answer questions about functioning in the real world. It is important to demonstrate that neuropsychological tests have ecological validity. Two approaches to address the problem of the ecological validity of tests have been identified. The first concerns the degree to which the cognitive demands of a test theoretically resemble the cognitive demands in the every day environment (Franzen and Wilhelm 1996). The other approach used in ecological validity research refers to the degree to which existing tests are empirically related to measures of every day functioning (Franzen and Wilhelm, 1996). This type of research involves the use of statistical techniques to relate performance in traditional tests to measures of real- world functioning, such as questionnaires, or clinical ratings. As it is known that there is an interaction between cognitive deficits and the environment to produce behaviour, both need to be assessed if ecological validity is to be demonstrated (Goldstein 1995).

1.6. NEUROPSYCHOLOGICAL REHABILITATION

It is of importance to emphasise the fact that brain injury affects cognitive, social, behavioural, and emotional functioning. As each of these domains interacts with others, they need to be considered simultaneously (Sohlberg and Mateer 2001). The goals of neuropsychological rehabilitation are to promote recovery and to work with the injured child and his/her family to compensate for residual deficits, to understand and treat cognitive and behavioural impairments, to recognize the role of these impairments in functional disabilities and to monitor the impact on the role of the family and other socio-emotional factors (Prigatano 1999, Wilson 2003, Ylvisaker 1998). Working with the emotional reactions to frustration and loss is another integral part of effective treatment (Prigatano 1999, Sohlberg and Mateer 2001). Parents play a key role in the rehabilitation process and educating parents is an essential component of any rehabilitation program (Wilson 2003).

As for adults neuropsychological rehabilitation in children is a multidisciplinary teamwork.

The team involves physicians, neuropsychologists, physiotherapists, occupational therapists, speech therapists, play therapists, special educators and social workers. These provide a range of specialist interventions. The families of the children also provide an active and important role during rehabilitation.

1.7. COGNITIVE REHABILITATION

Cognitive remediation, rehabilitation and retraining are all terms that refer to systematic therapeutic efforts designed to improve cognitive functions (Cope, 1995, Carney 1999, Cicerone 2000, Sohlberg & Mateer 2001, Ponsford 2004). Cognitive rehabilitation may involve *internally focused* interventions meaning the direct process-specific training of a function, e.g. like attention and/or memory training as well as learning compensatory techniques. Another aspect of internally focused interventions often included in cognitive rehabilitation programs involves facilitation of insight and self-awareness with regard to cognitive abilities, which includes instruction in the use of meta-cognitive strategies.

Externally focused interventions, on the other hand, involve adapting to environmental demands, making environmental modifications and the use of specialised teaching strategies.

Reviews of a large number of studies on the effectiveness of cognitive rehabilitation for adults after stroke or TBI provided support for several forms of cognitive rehabilitation. For example, a specific positive effect for attention training in the post-acute phase of rehabilitation, and for compensatory memory training in mild memory impairments has been found beneficial (Cappa et al. 1999, Cicerone et al. 2000).

The few existing studies on cognitive rehabilitation of children are based on small samples and frequently include no control conditions (Mateer et al. 1999). Moreover, currently available training methods for children are often versions of material designed for adults (Warschausky et al. 1999). The Attention Process Training (APT) materials, based on the hierarchical model of attention from Sohlberg and Mateer, is one such method developed for adults (Sohlberg and Mateer 2001). Thomson (1995) reported notable gains in several psychometric measures of attention when using APT in a preliminary study on children with TBI. Kerns et al. (1999) evaluated a more child-oriented version of this programme, called "Pay Attention," and revealed that there was significant improvement in children with ADHD

Klingberg et al. (2002) showed enhanced performance in a controlled study on children with ADHD with a computerized child directed process specific training for working memory. Butler and Copeland (2002) reported positive effects with their broader cognitive remediation program in a pilot study on children surviving cancer.

The Amsterdam Memory and Attention Training method for working with children (Amat-c) is a cognitive training programme developed by Hendriks and co workers (Hendriks, 1996) for children who had survived cancer. This training programme consists of both internally and externally interventions of cognitive rehabilitation. Following adaptations and modifications this training programme is evaluated in the present thesis. A more detailed description of this method will follow on pages 32-34.

2. AIMS

The overall aim of this thesis was to apply a test of sustained attention and impulse control on a Swedish population, assess cognitive functions and to evaluate the effectiveness of a cognitive training programme on children with acquired brain injuries. The more specific aims can be summarised as follows:

- To test the computerized measure known as the Gordon Diagnostic System (GDS) of attention and impulsivity on Swedish children using a group of children with ADHD and a control group to provide a comparison.

- To test the feasibility of a cognitive training programme on children with traumatic brain injuries (TBI).

- To evaluate the effectiveness after 17 weeks of cognitive training on children with ABI in a randomized controlled study using a neuropsychological test battery consisting of the GDS.

- To investigate the consistency of the training effect, as well as to identify factors that might influence outcome at the follow up, conducted 6 months after the completed training.

- To evaluate the transfer of the training effects on behaviour using behavioural rating scales for parents, children and teachers.

3. MATERIAL

3.1 Subjects

Study 1. In total 71 children participated in Study I. They had a mean age of 10.5 years and were referred from a central hospital unit (Astrid Lindgren Children's Hospital), from one outpatient unit and from a specialized local team in the greater Stockholm area; they fulfilled the ADHD criteria according to DSM- IV. A control group of 88 children, with a mean age of 10.2 years was recruited from normal schools and in the same areas as the clinical sample.

Study II. Three children participated in Study II. They were children with TBI who had been followed at the Neuropaediatric Unit of the Astrid Lindgren Children´s Hospital. See Table I

Table 1 Essential clinical features of 3 subjects in Study I

Subjects	**Patient 1**	**Patient 2**	**Patient 3**
Gender	**boy**	**boy**	**girl**
Age at injury/illness	**7.1 years**	**7.1 years**	**13.1 years**
Glasgow coma scale	**3**	**-**	**11**
Diagnosis/ Type of damage	**Penetrating object right hemisphere**	**Intracerebral bleeding left temporal lobe**	**Multiple contusions**
Age at start of training	**10.2 years**	**12.10 years**	**16.10 years**

The children who participated in **Studies III, IV, V** consisted of a sample of children followed at the Neuropaediatric or the Oncology department of Astrid Lindgren Children's Hospital, Folke Bernadotte/ Academic Hospital of Uppsala or Lund University Hospital. The criteria for inclusion were: age> 9 years, ABI, 1-5 years having elapsed since the time of the injury (TBI) or since the end of treatment (brain tumours), IQ>70, performing 20% 1 SD or more below the age-appropriate average in the neuropsychological test battery of attention and memory functions.

Exclusion criteria were not speaking Swedish as the native language and pre-injury Neuropsychiatric diagnosis.

All eligible children from the participating clinical units who fulfilled the inclusion criteria's were invited to participate in the study. Of the 53 eligible children, the parents of 40 gave their consent to their child to participate. Two children with brain tumours elapsed into malignancy.

Table 2. Clinical data of the children in the training and control group in Studies III, IV, and V

	Training group n=18	**Control group n=20**
Mean age, at time of injury or diagnosis of disease (age in years and range)	**11.7 (2.3)**	**12.05 (2.6)**
Mean time to have elapsed since injury or termination of treatment (years)	**2.2 (1.0)**	**2.6 (1.2)**
Boys/girls	**12/6**	**10/10**
Diagnosis		
Tbi[a](GCS[b] >8)	**7**	**6**
Tbi (GCS<8)	**5**	**3**
Encephalitis	**1**	**1**
Anoxia	**1**	**0**
Brain malignancies	**4**	**10**
Irradiation therapy	**4**	**6**
Chemotherapy	**4**	**6**
Pretest IQ	**95**	**94**
Attention factor	**82**	**82**

a) Tbi= Traumatic brain injury b) GCS= Glasgow Coma Scale

2. 2 Methods

Gordon Diagnostic Systems

The Gordon Diagnostic System is a computerized test that was developed to measure impulse control, attention, vigilance and distractibility (Gordon, 1983). It was standardized in 1988 on American children. Two specific subtests were used in the **Study I**, the *Vigilance Test* and the *Delay Task* to measure the ability to sustain attention over time, self-regulation, and inhibition, the ability to estimate time as well as the capacity to develop strategy and readiness to respond to stimuli. In **Studies III and IV,** only the Vigilance Test was administered.

Cognitive training method

The intervention programme (Amat-c) was developed by Hendriks and coworkers (1996) at the Emma Ziekenhuis, Amsterdam Medical Center in the Netherlands. This programme is based on a modified model from Sohlberg and Mateer (1989), which differentiates attention on three levels: sustained attention, selective attention and mental tracking. In the same way, Hendriks et al. (1996) differentiated the memory processes on three levels corresponding to; the sensory register, the short-term or working memory and the long-term memory. The interaction between attention and memory is most evident at the level of mental tracking. Mental tracking (Lezak 2004) is defined as "the ability to co-ordinate and integrate sustained and selective attention, as well as to divide, alternate and shift attention".

The Amat-c method involves a combination of daily practice and games on the one hand, and exercises in specific attention and memory techniques on the other. Additional behaviour modification techniques are incorporated in the programme. These techniques focus on learning strategies for use in daily life and in the accomplishment of school tasks. Skills for enhancing both visual and auditory modalities are trained. Daily exercises of 30 minutes during 17 weeks; gradually increase in terms of the level of difficulty according to the three phases mentioned below. Children perform the exercises with a coach (teacher or parent) at school or at home. Written instructions and a diary complement the exercises. Once a week the child and his/her coach are seen at the hospital for feedback and reinforcement. This session provides the opportunity to give therapeutic intervention beyond that encompassed by the specific training tasks, enabling the child to share his/her cognitive, emotional and behavioural experiences. There are two versions of the Amat-c method, one for children between 8 and 12 years of age and one for adolescents aged 13 or older.

First phase: training sustained attention

The training techniques in this phase include only one or two auditory or visual stimuli, with only one response alternative. One example of this technique is 'listening to the ticking of a clock', or listening to the radio and registering sounds, it is intended to train the ability to focusing attention consciously. The results are registered in the diary. This diary can then provide the basis for discussion during the weekly therapeutic session at the hospital. This first phase of learning to focus attention step by step and to inhibit impulses also simultaneously acts as a time for establishing an alliance between trainer and child.

Second phase: training selective attention

During the second phase of the programme, responses have to be further inhibited or activated. Distracting stimuli are introduced that have to be distinguished from the relevant stimuli. The second part of the selective attention phase trains the child's ability to divide his or her attention between different stimuli and alternate activation of responses. The differences between relevant and irrelevant stimuli have a higher level of complexity in this phase.

One example of an exercise in this phase is the letter maze. The child has to track down specific words one by one: find one word, cross it through and ignore all the other words or combinations of letters. After the exercise, the child is asked to write down all the different ways in which he/she found the words, to increase the awareness of meta-cognitive strategies.

Third phase: training mental tracking

The third and final phase of the training is a combination of mental tracking and training of internal compensatory strategies for semantic and episodic memory. The overlapping functions of attention and memory are especially clear in this phase and are trained in combination. This phase includes verbal, visual and spatial memory exercises, starting with simple encoding techniques, such as repetition, and then progressing into semantic encoding strategies and finally combining all the techniques and strategies. The children's capacity for retrieval is trained by association, recognition, free recall, cued recall, as well as recall with vanishing cues. The exercises are mixed with interactive games that include incidental learning, visual imagery and semantic processing. Several stimuli patterns are processed sequentially. The children consciously learn to organise encoding in order to improve retrieval by using different conceptual search strategies. In addition to memory techniques, they learn step- wise strategies how to deal with new information and with situations demanding self- regulation i.e. executive functions.

Methods of evaluation

<u>Neuropsychological test batteries</u>

The effect of training was assessed with neuropsychological test batteries.

The tests described below were performed before the training commenced, directly after the training had been completed (within 2 weeks), and then 6 months later.

Neuropsychological test battery for Study II

The feasibility of the cognitive training method in Study II was evaluated using eleven neuropsychological tests. This particular test battery was selected specifically to replicate the Dutch study (Hendriks 1996).

1. *Sustained attention* was assessed by the Bourdon-Vos (Vos 1988) and Visual and Auditive Reaction Time Tests (Alphers and Aldenkamp 1992).

2. *Selective attention* was assessed with the Stroop-Color and Word Test (Hammes 1978), the Binary Choice Test (Alphers and Aldenkamp 1992), the Coding (Wechsler 1991), and the Trail Making Test A and B (König 1993).

3. *Mental tracking and memory functions* were investigated with the Digit Span Test (Wechsler 1991), the 15-Word Test (König 1993), the Seashore Rhythm Test (Alphers and Aldenkamp 1992) and the Rivermead Behavioural Memory Test (Wilson 1991).

4. General intellectual ability was assessed using the Wechsler Intelligence Scales for children (Wechsler 1991), but this was only assessed before the intervention and 6 months after completion of the cognitive training which formed the basis for Study III.

Neuropsychological test batteries Study III, and IV

Based on the results from the pilot study, Study I, we excluded the Bourdon-Vos Test and the Seashore Rhythms Test. The test battery then used in Studies III and IV was extended to include the Gordon Diagnostic System (GDS) and the Rey-Osterrieth Complex Figure Test (RCFT).

1. *Sustained attention* was assessed by the Visual and Auditory Reaction Time Tests *(*Alphers and Aldenkamp 1992) and the GDS (Gordon 1988, El Sayed et al. 1999).

The Visual and Auditory Reaction Time Tests are computerised tests for simple auditory or visual stimuli. The stimulus exposure lasts until a push-button response is given. The inter-stimulus interval is varied at random from 2.5 to 4 seconds. The scores calculated represented the total time (in ms) for the identification tasks to be completed, and thus higher scores indicate impaired performance.

The GDS is a computerized test including different attention requiring tasks. In this study the Vigilance Test based upon continuous performance paradigm was used. The child is shown a series of digits and told to respond only when a particular combination of numbers appear. Digits appear for 200 milliseconds and are presented at a rate of one per second over a period of 9 minutes. Correct responses and errors of commission are registered.

2. *Selective attention* was assessed with the Stroop-Colour and Word Test (Hammes 1978) the Binary Choice Test, (Alphers and Aldenkamp 1992) the Coding (Wechsler 1991) and the Trail Making Test (Reitan 1986, König 1993). The Stroop Test consists of three stimuli cards on which colour -related words are written first in black, and then as signs in different colours and lastly in words describing colours printed with ink in a colour that is incongruent with the word. Stroop scores were calculated as the number of correct words given, where higher scores indicate better performance. The Binary Choice Test is a computerised Choice Reaction Time Test. Either a red or a green half square-inch block is displayed in a random sequence in either the left or the right half of the screen. The child is asked to push one of two buttons on either side of the keyboard, corresponding to the position of the coloured block on the screen. The results are expressed as the number of correct responses and higher scores indicate better performance.

The Coding test is administered according to the WISC-III manual. The Trail Making Test (TMT) includes two parts, A and B. Results are expressed in terms of the time taken for completion (sec). Lower scores indicate better performance.

3. *Memory functions* were investigated with the Digit Span Test (Wechsler 1991), the 15-Word Test (König 1993), the Rey-Osterrieth Complex Figure recall (Spreen and Strauss 1991), and the Rivermead Behavioural Memory Test (Wilson 1991).

Scores for the Digit Span were calculated as described in the WISC-III manual (Wechsler 1991). In the 15 Word Test simple unrelated words were presented five times. The task was, after each presentation, to repeat as many words as possible in a free recall condition after each presentation. The score was the total number of immediately recalled words. There was also a delayed free recall after 40 minutes. A separate score was calculated for the total number of words remembered during the delayed recall.

In the RCFT recall condition the children have to reproduce a complex geometrical design 30 minutes after copying it and without prior warning that they will be asked to do this. The accuracy score is the number of remembered elements remembered and reflects the amount of information retained over the time.

The Rivermead Behavioural Memory Test (RBMT) includes mostly practical tasks, such as remembering a name associated with a photograph, remembering where a hidden item is, remembering an appointment and a story, face and picture recognition, remembering a new route, both immediately and after a 10 minutes delay, delivering a message during the route recall task, orientation in both time and space, and knowing the date. The total memory score is the sum of the test scores. Higher values indicate better performance.

General intellectual ability was assessed using the Wechsler Intelligence Scales for Children (Wechsler 1991) before the intervention, and then at the follow-up (6 months after the training was completed).

Behavioural Rating Scales

In the **Study II** we used the same rating scale as in the Dutch study (Hendriks 1996); namely the Deasey-Spinetta Behaviour Rating Scale, (Deasey and Spinetta 1981) pre and post training. The questionnaire consists of 38 items, for assessing learning ability (11 items), social behaviour (12 items) and emotional behaviour (15 items). The yes/no answers were coded for positive/negative behaviour respectively (yes=1, no=0).

To evaluate the children and parents view of this method, we developed seven open questions. The aim was to find out how the method was perceived and what effect they thought it had on the children's attention and memory performance. Parents and children answered the questions separately. They recounted what the children and the parents experienced using the method, whether the exercises were easy, whether it was possible to integrate the training into daily life and whether the training had an effect on concentration, memory or other aspects of behaviour. There were three alternative answers coded as very good =2, relatively good =1 and not at all good =0. Both very good and relatively good were regarded as positive answers.

In **Study V** we applied a reduced version of the Anser System (Levin 1992), the Ansula Behaviour Rating Scale: again this was conducted before training, directly after completion of training and then 6 months after the training had been completed training. This instrument consists of questions regarding school performance, attention, executive functions and social behaviour. The questions asked of parents and teachers are identical, with 23 items assessing school performance, 25 items focusing on attention and executive functions and 29 items on social behaviour. The answers are rated on a scale from 1 to 4, where the lower numbers represent negative answers and higher numbers positive ones. An additional simplified form of the questionnaire was specifically developed for the children consisting of 23 items concerning school performance, attention and executive functions. The questionnaires were answered at home or at school and were sent to the authors by mail.

Procedure

In **Study I** all children were tested with the Vigilance Test and the Delay Task of the GDS. In **Study II** 3 children with TBI were tested with the neuropsychological test battery before and after 20 weeks of interactive cognitive training. This training started in September 1999 and was completed in January 2000. Questionnaires about the method and the effect that it had on the children's behaviour were answered before and after the training by parents, teachers and the children separately. In **Study III** parents were informed about two different interactive activities to be performed at home or at school. And it was explained that we were planning to evaluate whether these interactive activities could have an influence on their children's attention and memory capacities. The parents were told that instructions for one activity would be given by the authors (BB, IvH, and KA), but that the other activity would be freely chosen by the child and the person (parent or teacher) who would "coach" this joint activity. The prerequisite was that the freely chosen activity should be interactive; that is, no television or computer games were acceptable. The free activities could, for example, consist of playing interactive games or doing sports.

The parents, teachers and children were not made aware that one of these activities was a treatment method. After parents' consent was obtained, the children were randomized to one group or the other.

Children who were assigned to the group which received instructions from the authors (BB, IvH, and KA) henceforth referred to as the treatment group, registered daily their activities in a diary. Once a week at a one hour session, they visited the hospital together with their "coaches" to get support, feed back and to receive new instructions. During this session also matters relating to problems arising in everyday life could be discussed. The children in the group with the freely chosen interactive activities, which will be referred to as the control group, registered their activities in a diary like the others and sent it back by mail every week. This group was also contacted by telephone each week Before and after treatment the children were tested with the neuropsychological test battery and parents, teachers and children answered the behavioural rating scales (Levin 1992), about attentional capacities, memory and executive functions as well as school and social behaviour. Same coworkers did not perform the neuropsychological evaluation and the cognitive training. The first training group (Study II) started in autumn 1999 and the last training group (Study III) finished in June 2003.

In **Study IV** the children were reassessed 6 months after completing their training with the neuropsychological battery. Parents, teachers and children again answered the same questions relating to the behavioural rating scale. In **Study V** these behavioural rating scales were retrospectively analyzed using an alternative mixed statistical model to measure relative effect.

The Karolinska Institute Ethical Committee approved of the studies.

Statistical analysis

Study I The Student t-test was used to compare the control and clinical samples with the Gordon standardization group. Categorical variables were analysed with the chi-square test for contingency tables and the Fisher's exact test. Correlation coefficients were calculated and multiple regression analyses were performed with the Gordon Test results as the dependent variable, and with gender, sample group and age as independent variables. We also calculated the area under the receiver operating characteristics (ROC) curve for the predictive accuracy of the Gordon Test results concerning the clinical sample regarded as positive cases and the control sample as the negative cases.

Study II In this pilot study with such a reduced number of children (N=3) and the absence of control conditions we only used descriptive statistics**.**

Study III The differences in the test results before and after training were compared between the two groups using the Mann-Whitney non-parametric test, because of the non- normal distribution and heterogeneous variances. Explorative regression analysis was performed to evaluate potentially important influences from other variables.

Study IV An ANOVA model was used to evaluate the change in the test results of the two groups after training and at the 6 months follow up. Even if the variables were not strictly normally distributed, it was considered that the ANOVA gave reasonable results, as non-parametric procedures are not easily applied to this design. Extra caution was therefore taken in the interpretation of p-values just below the 5% significance level. A regression analysis, similar to the one used in Study III, was performed.

Study V. A mixed effect model approach with group specific variances was found to be appropriate (Brown and Prescott 1999, SAS 1999). A two factor model including interaction was considered with treatment as the, ‘between-subjects factor’, and time (directly after treatment and at 6 months follow up) as the ‘within-subjects factor’. The residuals from the models were inspected and found to be at least roughly symmetric and normally distributed.

Owing to problematic randomization we were forced to restrict the analyses of the outcome variables to intervals where both groups were reasonably represented at baseline. In this respect, the analysis became conservative due to the low number of children and the shorter pre-treatment intervals of the sum score.

An alternative, unbiased estimate of the relative effect of treatment on behaviour was created to fulfil the following requirements:

a. If the treatment has no effect, the expected mean value of the effect variable should be zero (unbiased).

b. The possible outcome space should be the same for all subjects in the sample; however, the outcome probabilities might differ between subjects.

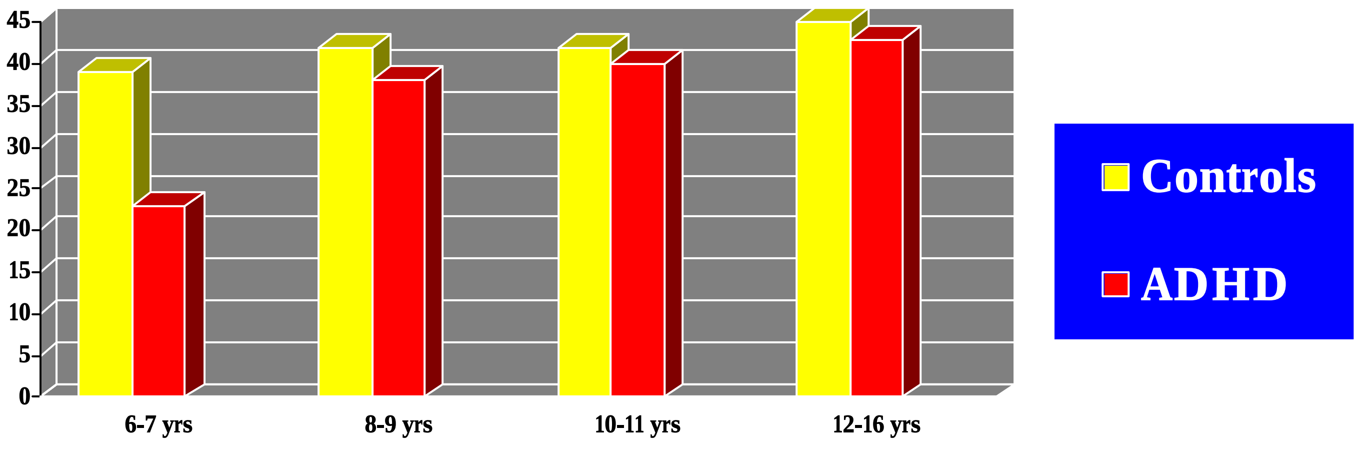
Thus, the relative effect is calculated towards the lower sum score limit when a decrease is observed (as is commonly done), and towards the upper sum score limit when an increase is observed. In such a way, the relative change will be in the range [-100%, 100], and a ‘no treatment effect’ will have an expectation of zero. Furthermore, unreasonably large effects arising from low baseline values can thus be avoided and (the usually strong) dependence on the baseline value can be made almost negligible.

4. RESULTS

Study I Measurements of attention deficits and impulsivity: a Swedish study of the Gordon Diagnostic System

The children with ADHD had significantly lower scores on the Delay Task of the GDS, than the controls and the American standardization group from the Gordon study. The ADHD group also had a significantly higher number of errors of commissions as compared to the controls and the standardization group. In addition, the ADHD group showed significant lower number of correct responses on the Vigilance task, than the control group and the standardization group (Figure 1). The GDS scores were not associated with gender, but were strongly associated with age. The conclusions from this study were that this tool was valid for use on Swedish children and could be applied in studies assessing children's ability to focus attention over time as well as to evaluate the effect of interventions.

Figure 1. Number of correct responses on the Vigilance Test (GDS) for children with ADHD (N=71) and for controls (N=88)



***p>.001 **p<.01 **p<.01 *p<.05

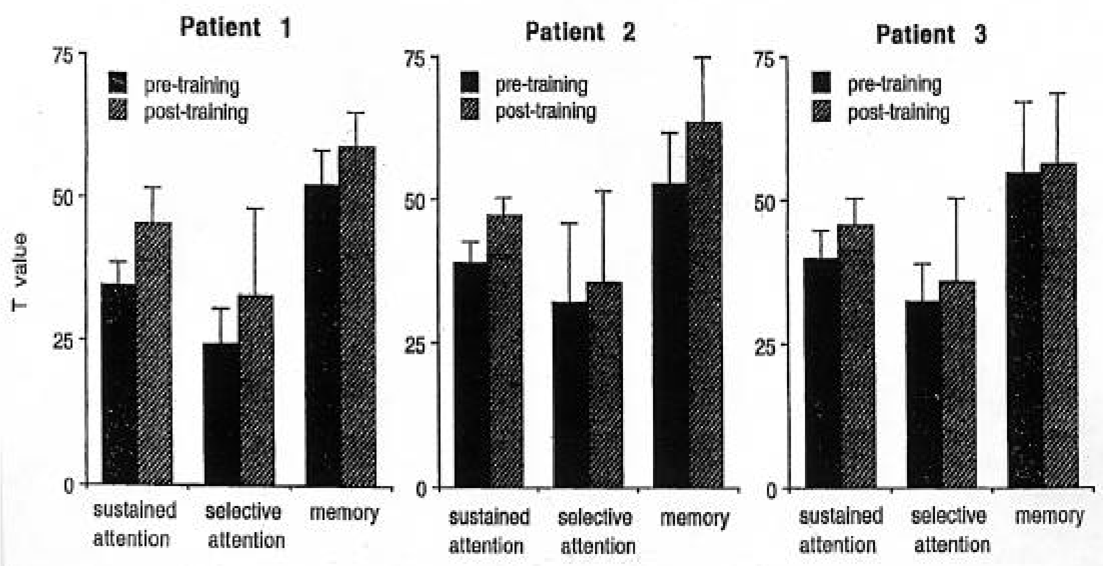
Study II Attention and memory training in children with acquired brain injuries

All three children and their "coaches" completed the training without interruptions. The results showed an improvement in the neuropsychological tests of sustained and selective attention as well as in memory after training. Figure 2 describes the age-corrected composite scores for sustained, selective attention and memory for each child before and after training. Questionnaires filled in by parents and teachers indicated that, using the Amat-c method, the children were able to learn strategies that improved their school achievement and their self-image. On the basis of these results, and the seven open questions answered by the "coaches" about how the method was perceived, the programme was modified. These modifications made were:

1) The training period was reduced from 20 to 17 weeks to fit in with the Swedish school year 2) The level of difficulty was individualized to adapt the training to the children's different levels of performance 3) A reward system was introduced to improve motivation and

4) The aim of exercises was clarified and the sequence of time visualized.

Figure 2. Neuropsychological performance in age corrected composite scores



Raw scores for neuropsychological tests of sustained, selective attention as well as memory were transformed into age-related T-scores. Mean =50 SD =10.

Results are presented as mean T-scores for each case

Study III- Beneficial effects of a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study

The treatment group (N=18) and controls (N=20) were assessed before and after training with the modified version of the Amat-c method. Directly after the cognitive training had been completed, more complex neuropsychological tests of sustained attention, selective attention (Figure 3), and memory-related performance (Figure 4) demonstrated that significant improvements had been made in the training group as compared to controls. This indicated that the training programme had an effect on complex attention and memory functions (Table 3). Explorative regression analysis revealed that diagnosis partly might account for someinfluence. However, further analysis with stratified Mann-Whitney test for diagnosis, showed that the statistically significant treatment effect was confirmed.

Figure 3. Change in performance on Trail making Test B after training

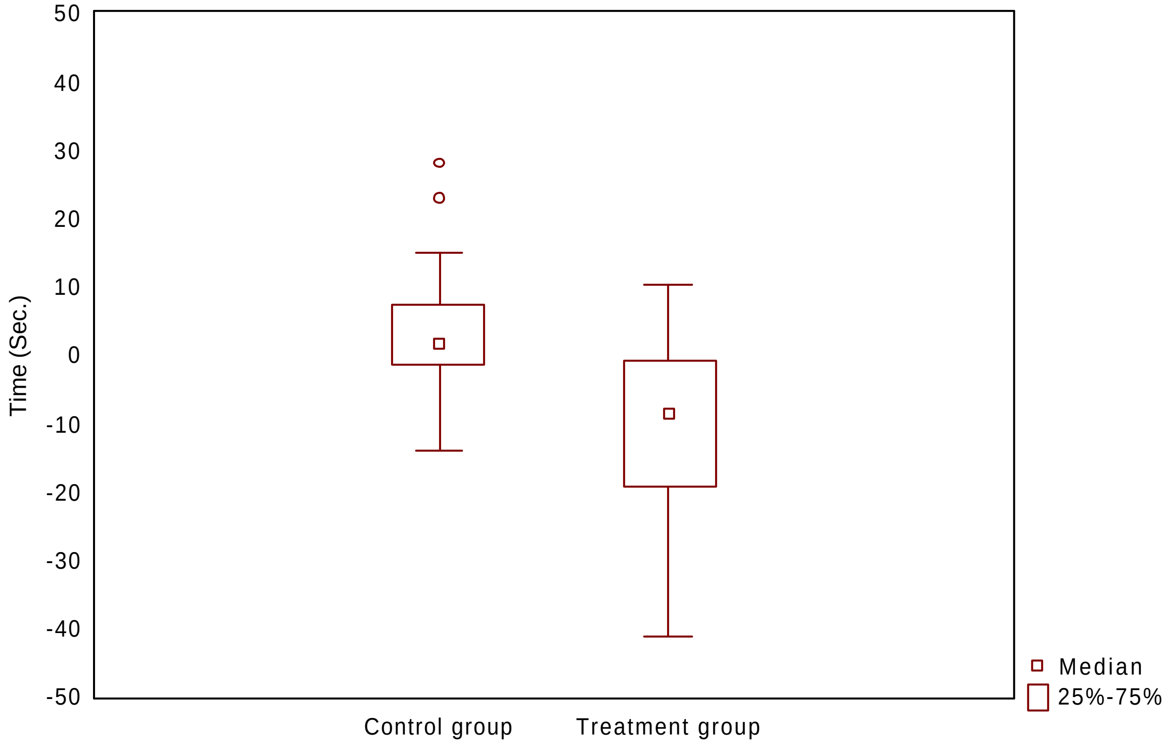
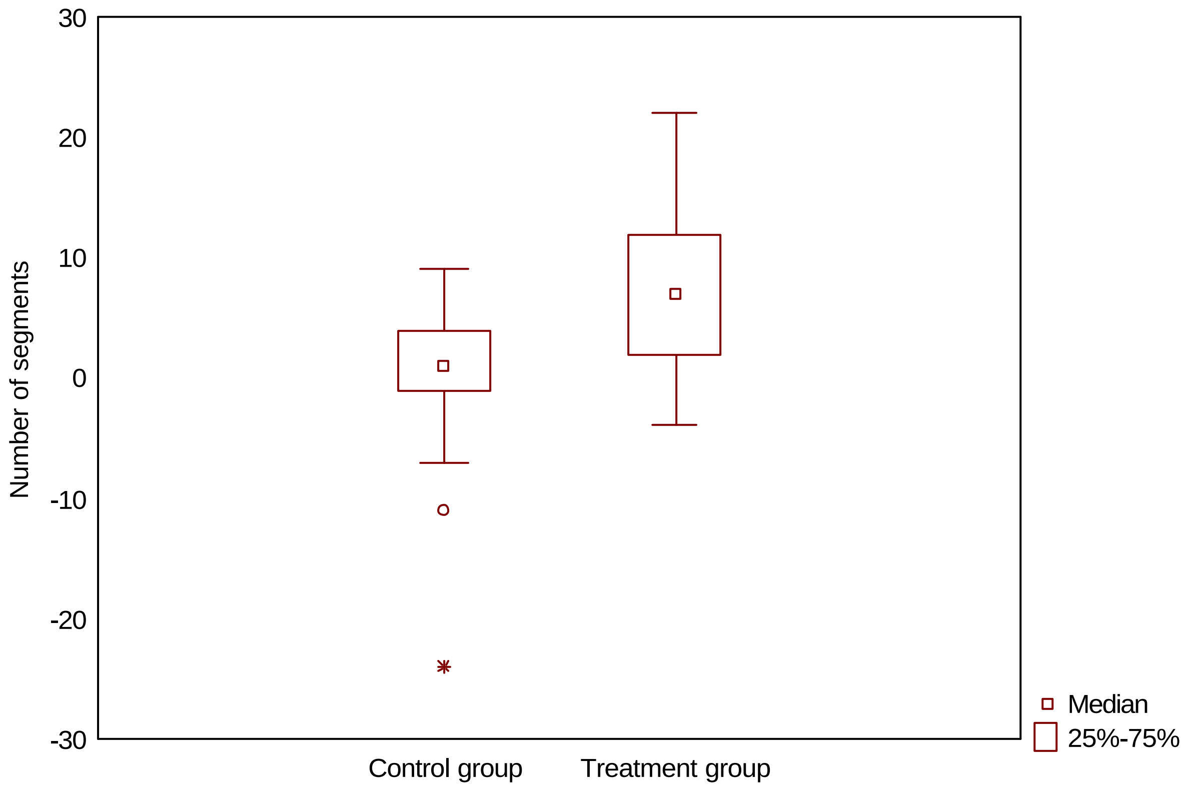


Figure 4. Change of number of recalled segments on the RCFT after training



Study IV A randomized controlled trial on children with acquired brain injury reveals sustained favorable effects of cognitive training

The children were assessed 6 months after they had completed their training with a new investigation that used the same test battery as had been used before and immediately after training.

The training group exhibited significantly more persistent improvement with respect to attention and memory-related tasks in comparison to the control group (see Figures 4 and 5). In addition, the earlier results that no effect had been made on simple Reaction Time Tests were confirmed (Table 3). Results obtained with the WISC-III one year after the start of training showed a significant improvement in the treatment group in comparison to the controls on the freedom of distractibility factor and the verbal comprehension factor (Table 4).

Table 3 Neuropsychological performance pre, and post training and at 6 months follow up

TEST	Treatment group (n=18)			Control group (n=20)			
TEST	PRE-TRAINING	POST TRAINING	POST 6 MONTHS	PRE TRAINING	POST TRAINING	POST 6 MONTHS	p<.05
Aud RT[a]	359 (319-442)	340 (313-442)	319 (293-363)	400 (347-356)	350 (304-397)	348 (299-405)	ns
Vis RT	368 (350-454)	354 (324-405)	375 (347-419)	400 (373-356)	373 (334-397)	370 (347-419)	ns
Gordon corr [b]	39 (35-43)	43 (40-45)	45 (42-45)	42 (39-43)	43 (41-44)	43 (41-49)	.<.001
Gordon com [c]	5 (2-7)	3 (1-6)	1 (1-5)	3 (0-6)	2 (1-4)	2 (1-6)	.04
Binary time	426 (335-482)	359 (304-458)	375 (337-426)	429 (379-480)	412 (335-457)	403 (371-433)	ns
Binary corr	53 (42-58)	57 (55-60)	57 (55-58)	55 (54-58)	56 (51-58)	57 (55-58)	.002
TMT A(s)[d]	40 (28-60)	29 (24-41)	34 (28-41)	31 (27-37)	32 (25-46)	36 (28-48)	ns
TMT B(s)	110 (88-139)	72 (58-89)	70 (58-87)	89 (67-137)	88 (58-119)	90 (65-110)	.03
Stroop 1	53 (41-70)	68 (54-81)	76 (60-83)	71 (60-90)	73 (57-90)	80 (71-92)	ns
Stroop 2	45 (37-52)	53 (41-63)	51 (44-61)	45 (36-56)	50 (41-56)	55 (43-58)	ns
Stroop 3	24 (20-40)	32 (25-45)	32 (27-46)	27 (18-34)	26 (20-38)	31 (21-40)	.004
Coding	38.5 (29-43)	41 (34-54)	44 (38-53)	43 (32-49)	39 (29-51)	44 (34--56)	.009
Digit span	11.5 (8-13)	14 (12-15)	13 (11-16	10 (9.-12	11 (9-13)	11 9-13)	ns
15 word	36 (32-47)	45 (39-55)	48 (45-60)	43 (35-50)	46 (41-50)	48 (44-54)	.005
15 w recall	9 (7-11)	11 (8-14)	13 (11-14)	9 (7.5-11)	10 (8-12)	10. (9-13)	.01
RCFTrecall[e]	11 (9-22)	18 (15-26)	22 (17-27)	19 (10-22)	16 (10-25)	17 (12-22)	<.001
Rivermead	52 (47-57)	64 (60-66)	65 (59-72)	60 (52-62)	58 (51-62)	53 (49-59)	<.001

a) Reaction Time b) Gordon correct responses c) Gordon commission errors d) Trail Making Test and e) Rey-Osterrieth Complex Figure Test

Figure 5. Performance on the Digit Span Test
pre, post and post 6 months after training

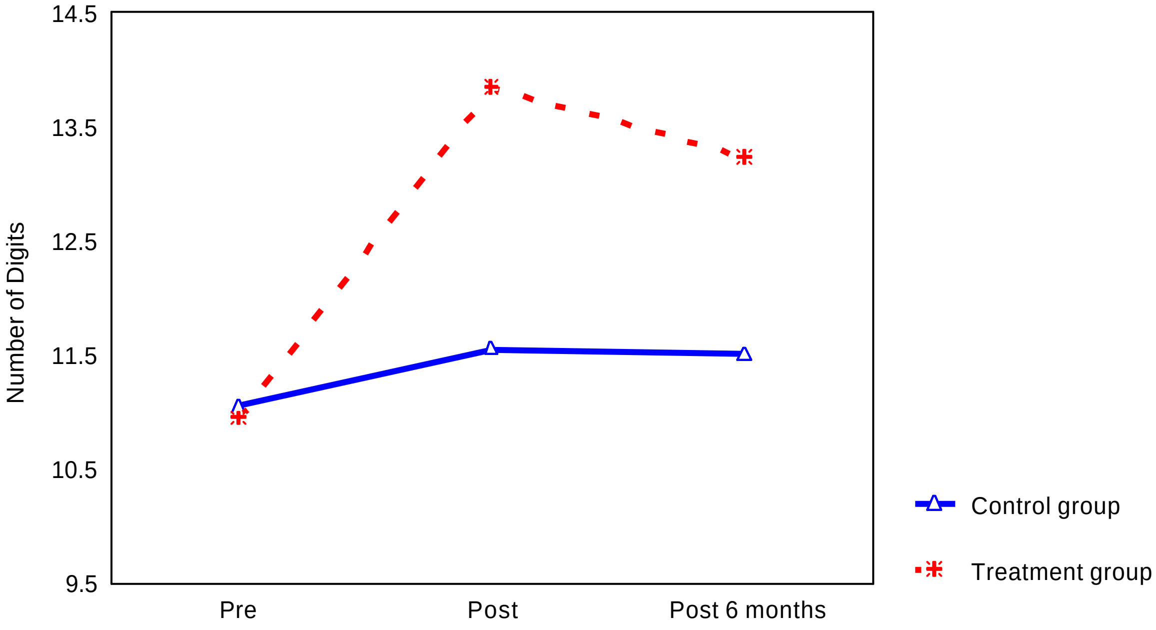


Figure 6. Preformance on the Rivermead Behavioural Memory Test
pre, post and post 6 months after training

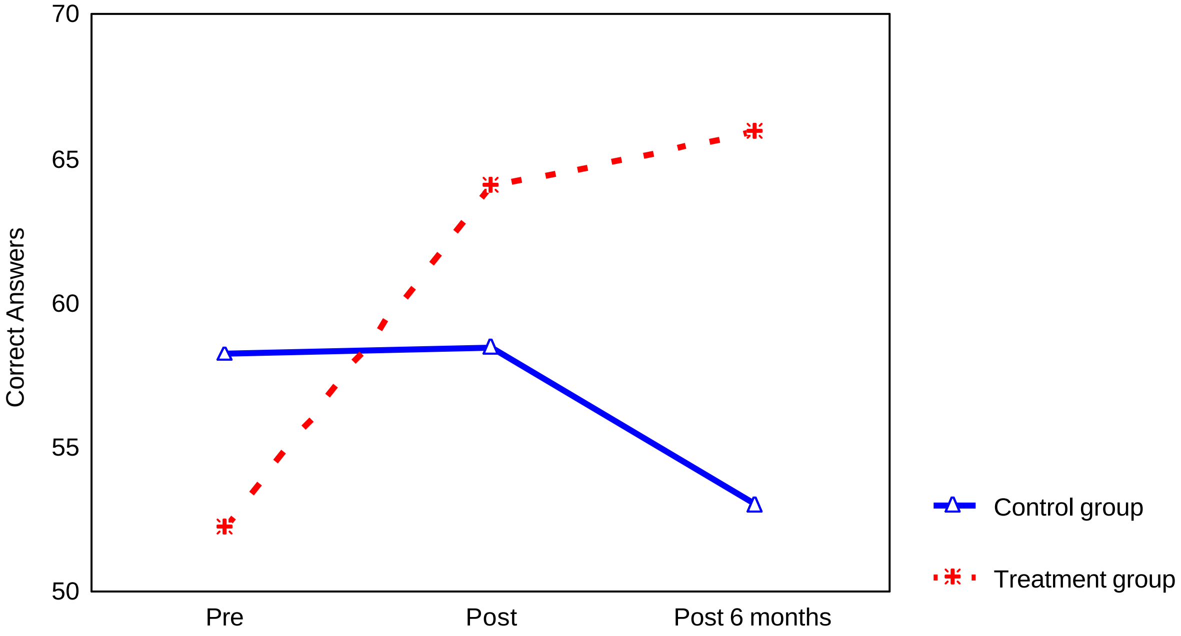


Table 4. Intellectual performance before training and one year after start of training.

	Treatment Group		Control group		
TEST	PRE TRAINING	POST TRAINING	PRE TRAINING	POST TRAINING	P- LEVEL
Full IQ Wisc-III	95 (80-104)	101 (88-109)	95 (84-99.5)	93.5 88-105.5)	P=.46
Verbal factor	101(85-111)	108(92-114)	100 (94-105)	97 (90-110)	P=.03*
Perceptual organization	96 (86-107)	103 (97_112)	98 (92-105)	100 (91-112)	P= .49
Attention factor	82(75-97)	91 (88-100)	82 (75-91)	87(75-92)	P=.05*
Speed of processing	80 (62-88)	90 (71-103)	85 (68-95)	89 (78-97)	P=.25

Study V. Measuring effects on behaviour after cognitive training in children with acquired brain injuries

The teachers of children in the training group described significant improvements in school performance (17.9 %), expressed as simple sum scores, directly after training, as compared to the control group (1.3%). The teachers also described attention and executive functions as being markedly improved in the training group (15 %) whereas the controls showed a slight decrease (-4.5%) (Figure 7). Answers about social behaviour showed a slightly positive change (5.4 %) However, Figure 7 shows that children in the training group initially had lower ratings, which were controlled for with a more restricted analysis. The unbiased, restricted analysis confirmed the systematic difference between the training and the control group for school performance, attention and executive functions, although just indicated for social behaviour (Table 5). The trends revealed by parents (Table 6) and the children's observations showed the same trend but without reaching the level of significance.

Table 5. Estimates (restricted) of relative training effect in % based on teacher's ratings

		After training			6 mo follow-up			
Questions	Group	mean	SE	*n*	mean	SE	*n*	*p*
School perfor-mance (> 42)[a]	training	12.3	4.6	13	17.3	4.4	15	.012
	control	1.3	3.3	19	1.8	3.5	17	
Attention and executive functions (45–65)	training	15.7	6.7	7	16.5	6.4[b]	8	.001
	control	-2.0	3.0	9	-3.5	3.0	9	
Social behaviour (> 65)	training	5.4	4.1	9	1.8	3.8	11	.100
	control	-1.6	1.9	17	-3.4	2.0	15	

[a)]Numbers in this column are sum score limits before training.
[b]One extreme value (outlier) was deleted because it had a large Cook's distance. This deletion does not affect the *p* value but yields a more reliable estimate of the training effect.

Teachers' ratings (sum scores) of school performance before training, immediately after training, and at 6 month follow-up

Fig. 7

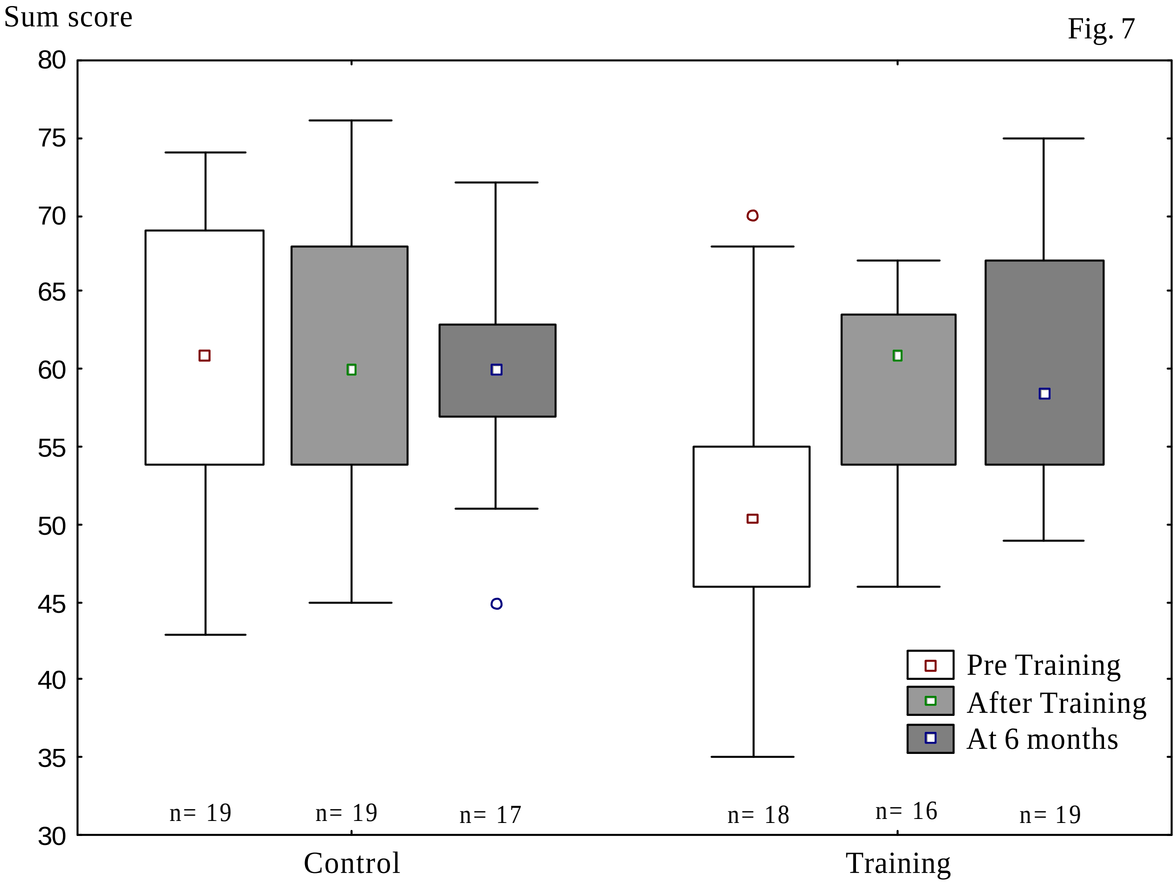


Table 6. Estimates (restricted) of relative training effect in % based on parents' ratings

		After training			6 m follow-up			
Questions	Group	mean	SE	*n*	mean	SE	*n*	*p*
School perfor	training	6.1	5.0	12	8.1	4.8	13	.41
mance (45–75)[a]	control	1.5	4.2	19	3.4	4.3	18	
Attention and	training	-5.6	6.4	9	-4.5	6.1	10	> .50
executive func-	control	-3.6	2.9	20	-3.6	3.0	18	
tions (> 45)								
Social behaviour	training	5.6	3.2	13	7.0	3.1	14	.11
(> 60)	control	0.1	2.5	20	0.7	2.5	18	

a) Numbers in this column are sum score limits before training

5. GENERAL DISCUSSION

The main results of the present set of studies were that the GDS test of sustained attention (vigilance) and impulse control (delay task) could differentiate between a clinical sample of children with ADHD and controls, and that the performance was strongly associated with age. Furthermore, it was shown in a randomized controlled study that cognitive training with the Amat-c method significantly improved complex attention and memory functions in children with ABI. These effects had been maintained 6 months after completed training. In contrast, no influence was found of the training on simple reaction time tests. According to the teacher's ratings, a significant positive change was observed in attention and executive functions as well as in school performance after training. Parents and children described the same finding.

Thus, the overall main result is that this broad based cognitive training programme, specifically designed for children, has an impact on their complex attention and memory functions and that this improvement transfers to school performance.

Ideally, all children in Study III should have been recruited and followed at the same clinic and by the same investigators. However, to achieve sufficient statistical power and be able to compare two groups on repeated neuropsychological measures, it was necessary to have 20 children in each group. This in order to fulfill the criteria for 85% power and an effect-size of 1.00, with a significance level of .05. Despite the considerable size of the greater Stockholm area (1.8 millions), this was not possible. The study was, therefore, expanded to include children from the Children's Clinic of Lund University Hospital and Folke Bernadotte Hemmet, Uppsala University Hospital. This expansion only necessitated having one additional instructor (BB) who instructed the children in both Uppsala and Lund. The "coach" during the training could be a parent or a teacher, and the person selected was not consistently either the teacher or a parent throughout the group, but varied from child to child according to what was possible. From the overall results it can be concluded that the consistence of coaches was not of crucial importance. The Amat-c method seems to tolerate this inconsistency in the coaches as long as the method is followed according to the instructions given in the manual.

The series of studies presented here focused on the rehabilitation of cognitive impairments in children with ABI irrespective of etiological subgroups within ABI. The inclusion criteria's of the children were therefore primarily based on their cognitive profiles of performance on the neuropsychological test battery. Including clinical and neuroimaging data into this process would not improve the reliability as the correlation between neuroimaging findings and cognitive performance has been shown to be modest (Emanuelsson 1997). The few earlier published studies in children with ABI have focused on the process specific training within the concept of cognitive rehabilitation (Thomson 1995, Kerns and Thomson 1998). Although this approach is generally effective in improving the child's performance on tasks similar to the training exercises, limited generalization to dissimilar tasks and everyday life functioning has been a problem (Butler and Copeland 2002). Pilot data from a more holistic approach of cognitive training, the cognitive remediation programme (CRP) reported positive effects on children surviving cancer, where strategy acquisition seemed to normalize sustained attention in many subjects (Butler and Copeland 2002). Butler (1998) concluded in an earlier case report that increased effort needed to be directed towards generalization strategies in order to achieve maximal treatment gains. The broader CRP programme consists of massed practice with hierarchical attention exercises supplemented with meta-cognitive strategies and cognitive behavioural interventions (Butler and Copeland 2002). Equally to the CRP, the Amat-c method consists of hierarchical graded attention and memory exercises, as well as meta-cognitive strategies, but in contrast to the CRP the Amat-c is not specifically designed to improve processing speed. Accordingly, less effect was seen on tasks that demanded processing speed, implying that the Amat-c does not train speed of performance, but the ability to develop strategies and deal correctly with a task. A similar trend has been reported in studies on cognitive rehabilitation in adults with TBI (Cicerone 2002, Ponsford and Kinsella 1988), and epilepsies (Engelberts et al 2002).

The results suggest that attention could be brought under some degree of voluntary control by self-instructional procedures. Metacognitive strategies that is teaching children to monitor their own thinking, have received some of the strongest support in improving attentional processes in brain injured children (Brett and Laatsch 1998). One of the crucial questions concerning cognitive training is if there is maintenance and transfer of effects on daily life?

Six months following completion of the training with Amat-c, the treatment group demonstrated significantly larger and more consistent gains in complex attention as well as on memory tasks. To our knowledge this is the first randomized controlled study and follow up after systematic cognitive rehabilitation training in children with ABI demonstrating direct and maintained positive influence on complex attention and memory tasks, as well as transfer to school behaviour, attention and executive functions.

Some of the exercises within the Amat-c training programme can be transferred to and used in situations outside the training session. In fact this is encouraged during the weekly session at the hospital, with the goal that the children should become aware of new ways how to deal with their disabilities and improve self-regulation. It is a challenge for rehabilitation specialists to find everyday routines, which can be used as effective generalization tasks.

In addition, the education and support provided by the daily contact with the chosen educators, which is required, so that they can be effective facilitators for the training of cognitive functions in real life is another important aspect.

Teachers described a significant change in the training group, in school behaviour, attention and executive functions after cognitive training, indicating a possible transfer effect. The strategies contained in the Amat-c method are directed at how to deal with homework, how to focus and remember information, how to compensate disabilities and foster self-regulation. Wehmeyer et al. (2000) observed that few teachers have training in facilitating self-regulation in their pupils. Bronson, (2000) highlighted the value of adult-child routines of guided joint participation in childhood and of collaborative problem solving. He argues that school-age children benefit from routines in which the self-regulatory aspects of academic and daily tasks are made explicit. These include setting goals, creating a plan, executing in strategic behaviour and evaluating the outcome.

Parents and children reported the same trend of improved school behaviour, attention and executive functions in the training group. Parents of children with acquired brain injuries can also become effective deliverers of appropriately contextualized rehabilitation services in their home environment. This was demonstrated in a randomized controlled study conducted by Braga in Brazil (2000). Those children who were served indirectly by rehabilitation specialists by means of the training given to their parents had better cognitive and physical outcomes than those served directly by specialists in clinical settings. Butler (2002) also stresses the importance of providing parents with additional problem solving and advocacy skills to further strengthen the effectiveness of cognitive intervention.The Amat-c programme is a “team” approach which involves children, parents and teachers and has, therefore, the potential to be an important instrument for parents and teachers dealing with children who need to train their attention and memory functions.

Conclusions and future research

In summary, although, based on relatively small samples, the studies presented in this thesis suggest that there is a direct potential benefit in children with ABI from cognitive training on their cognitive functions as well as a maintained effect 6 months after completion of the training. The combination of hierarchical practice to retrain a dysfunction, and the adoption of learning skills and strategy acquisition, as well as the individual's weekly contact with a professional and the active involvement of the parents and teachers all contribute to the rehabilitative benefit. In addition, this effect transfers to behaviour at school, and to attention-related and executive functions.

A next step to validate the theoretical and practical consequence of these studies could be to test the Amat-c method in larger groups of children from multiple rehabilitation units. Questions that remain, concern the optimal length of training, the ideal mode of administration (individual or group), the timing (acute or post acute phase) the possibility of avoiding the need to travel great distances between the homes of the children and their families and rehabilitation units (using the internet). Since many children with ABI over time show behavioural dysfunctions and no effect from this training method was found on social measures, the Amat-c method could possibly be complemented by a cognitive behavioural modification approach. Furthermore, it could be of interest to evaluate this cognitive programme on other diagnostic groups with developmental disturbances.

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