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**Longitudinal development of hand
function in children with unilateral
cerebral palsy and its relation to
brain lesion and treatment**

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Longitudinal development of hand function in children with unilateral cerebral palsy and its relation to brain lesion and treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my family

Ad astra per aspera
“Mot stjärnorna genom svårigheter”
- Latinskt ordspråk

ABSTRACT

The overall aim of this thesis was to describe the development of hand function in children with unilateral spastic cerebral palsy (CP), and to investigate its relation to brain lesion and treatment. Effective hand use is necessary for task performance and independence in everyday activities. Due to a lesion in the developing brain, children with unilateral CP have difficulties in using the arm and hand on one side of the body, and this motor impairment negatively influences their independence in everyday activities. Therefore, exploration of hand function in children with unilateral CP is essential.

Development of hand function during childhood and adolescence was investigated in studies I and IV, using the Assisting Hand Assessment (AHA) and three other measures of hand function. In study IV, results from 96 children studied at age 18 months to 12 years showed improved use of the affected hand over time, but to a varying extent. The development was rapid at early age, and slowed down and levelled out to a stable performance as the child grew older. Different developmental patterns were found, based on children's ability. Children with a higher AHA score at 18 months or on a higher MACS level had a faster increase to a higher level. In study I, change in hand function over time in 11 adolescents with unilateral CP 10–21 years of age was investigated. The hand function was found mainly to remain stable during adolescence. Only grip strength increased with age.

Factors assumed to influence development as well as response to training were investigated in studies II and III. In study II, the relation between response to constraint-induced movement therapy (CIMT) and corticomotor organization and brain lesion characteristics was investigated in 16 children aged 10–16 years. The children were evaluated using different measures of hand function, and by transcranial magnetic stimulation to explore the type of corticomotor projections as well as by structural magnetic resonance imaging to describe characteristics of the brain lesion. The results showed that improvement after CIMT was possible irrespective of the type of corticomotor projection and characteristics of the brain lesion. In study III, a possible effect of CIMT in infants below one year of age (baby-CIMT) was explored by using a retrospective design. Use of the affected hand, measured by the AHA at age two, was investigated in a group of 72 children where some had participated in a baby-CIMT programme and others had not. A more favourable use of the affected hand at age two was found in children who had received training before one year of age.

The overall clinical implications of this thesis are that children with unilateral CP increase the use of the affected hand in bimanual activities at an early age and thereafter function at a stable level. The AHA measure at 18 months can be used to predict the future use of the affected hand. CIMT can be offered to children regardless of their underlying pathophysiology, and when adjusted for infants it seems to be an applicable model for improving hand function at young age.

LIST OF SCIENTIFIC PUBLICATIONS

The thesis is based on the following four articles. They will be referred to in the text by their Roman numerals.

- I. **Nordstrand, L.** and A. C. Eliasson (2013). "Six years after a modified constraint induced movement therapy (CIMT) program--what happens when the children have become young adults?" *Physical and Occupational Therapy in Pediatrics* 33(2): 163-169.
- II. Islam, M., **Nordstrand, L.**, Holmstrom, L., Kits, A., Forssberg, H., and Eliasson, A. C. (2014). "Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics?" *Developmental Medicine and Child Neurology* 56(3): 252-258
- III. **Nordstrand, L.**, Holmefur, M., Kits, A., and Eliasson, A. C. "Improvements in bimanual hand function after baby-CIMT in two-year old children with unilateral cerebral palsy: a retrospective study" (Submitted)
- IV. **Nordstrand, L.**, Eliasson, A. C., and Holmefur, M. "Longitudinal development of hand function in children with unilateral cerebral palsy aged 18 months to 12 years of age" (Submitted)

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LIST OF ABBREVIATIONS

AHA	The Assisting Hand Assessment
AIC	Akaike's Information Criteria
ANOVA	Analysis of variance
CIMT	Constraint-Induced Movement Therapy
CP	Cerebral Palsy
CT	Computer Tomography
GMFCS	Gross Motor Function Classification System
ICF	International Classification of Functioning, Disability and Health
JTHFT	Jebsen-Taylor Hand Function Test
MACS	Manual Ability Classification System
MRI	Magnetic Resonance Imaging
MUUL	Melbourne Assessment of Unilateral Upper Limb function
PEO model	Person-Environment-Occupation performance model
TMS	Transcranial Magnetic Stimulation
WMDI	White Matter Damage of Immaturity

1. INTRODUCTION

Effective use of the hands is essential for the performance of everyday tasks. Humans engage in numerous occupations and activities throughout an ordinary day and throughout life, and a large number of new activities are learned and included in our repertoire. Most of these require the use of the hands, unimanually or bimanually.

Unilateral cerebral palsy (CP) is caused by a lesion to the immature brain, resulting in motor impairment of one side of the body (Bax et al., 2006; Cans et al., 2007). Children with unilateral CP have, to varying degree, difficulties in using the affected arm and hand. This asymmetry in hand function influences the ability to use the two hands together in a smooth way.

Studying the development of hand function in children with unilateral CP is crucial for prognostic and predictive purposes. One of the questions parents of children who are early diagnosed with cerebral palsy ask is what to expect throughout childhood, adolescence and adulthood (Novak, 2014). Investigating the development in hand function in a long-term perspective both in children and adolescents helps clinicians to answer this question more reliably. In studies I and IV of the thesis, the perspective of long-term development has been explored.

Furthermore, parents and clinicians wish to know what interventions are most suitable for the child (Novak, 2014) and when in a lifetime perspective different interventions should be administered. One of the interventions shown to improve motor function in children and adolescents with unilateral CP is constraint-induced movement therapy (CIMT) (Eliasson et al., 2014a; Hoare et al., 2007; Novak et al., 2013; Sakzewski et al., 2014). However, individual variation in training response has been noticed. Different factors have been investigated when trying to identify which children benefit best from the intervention. In study II, training response to CIMT in relation to brain lesion characteristics and corticomotor projections has been explored. As mentioned, CIMT has shown a positive effect on motor function, but the intervention has mainly been conducted involving children 2 years of age or older. In study III, the possible impact on hand function of CIMT administered in the first year of a child's life one year later has been investigated.

1.1 HAND USE IN EVERYDAY LIFE

Our hands are the tools we commonly use in work- and school-related activities as well as in self-care and play. Specific aspects of the hand function, such as the ability to grasp, bimanual hand use, in-hand manipulation, etc. are reported to be necessary for increased independence with increasing age in activities of daily living (Exner, 2005). These aspects are affected, to various degrees, in children with unilateral CP, resulting in a negative influence on their independence in everyday activities. An activity such as zipping a jacket, which requires good fine motor performance is often difficult for children with unilateral CP (Dellatolas et al., 2005; Ohrvall et al., 2010; Skold et al., 2004; Skold et al., 2007). The close relationship between accurate hand function and performance in everyday life makes the exploration of hand function in children with CP essential.

Performance of everyday tasks is the dynamic interaction between the person, the task and the environment as visualized in the person-environment-occupation performance (PEO) model (Law et al., 1996). Optimal occupational performance occurs when there is a balance between these factors. The dynamic interaction between personal, environmental and occupational factors indicates that a change in one dimension automatically affects the others (Christiansen et al, 2011; Law et al., 1996). In this way, intervention aiming at improving function (person dimension) will have an influence on occupational performance and probably also on the other dimensions (environment and occupation dimensions). Hand function can be assumed to relate mainly to the person dimension which constitutes functions of body and mind as well as spiritual qualities.

The interaction between health conditions and function is described in the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2007). This model is wide-spread in the health-care system around the world. The ICF describes functioning as composing of body functions and body structures, activity and participation. Furthermore, functioning is related to contextual factors. Hand-related categories can be found within all components of functioning, described for example by “control of voluntary movement” (body function), “fine hand use” and “self-care” (activity and participation) (World Health Organization, 2007). In this way, limitations in hand function among children with unilateral CP impact on a number of components of function and daily life.

In this thesis, different aspects of hand function have been studied. Some relate to body function (grip strength and quality of movements) and others to activity and participation (use of the affected hand). Even though environmental factors are known to influence performance, no further investigation of this construct has been conducted in the thesis, but it needs to be taken into consideration when interpreting the results of the studies.

1.2 CEREBRAL PALSY

Cerebral palsy is caused by a lesion in the developing brain. It is the most common cause of physical impairments in children in the western world (McIntyre et al., 2011). In Sweden, the prevalence is reported to be approximately 2/1,000 live births ("CPUP Annual Report 2014 ", 2014; Himmelmann et al., 2010; Himmelmann & Uvebrant, 2014).

1.2.1 Definition

The definition of CP, used today, was constructed in a consensus discussion at the International Workshop on Definition and Classification of Cerebral Palsy in July 2004 (Rosenbaum et al., 2007):

“Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.” (from Rosenbaum et al. (2007))

Cerebral palsy is described as causing activity limitation, affecting the person’s everyday life. Furthermore, the definition describes that, in addition to the motor problems, other functions are also often affected. CP is commonly not diagnosed until a later age (McIntyre et al., 2011; Novak, 2014; Smithers-Sheedy et al., 2014). However, signs usually present during the first months of a child’s life (Chen et al., 2013; Cioni et al., 2000; Guzzetta et al., 2003; Guzzetta et al., 2010).

1.2.2 Aetiology

A large number of risk factors for the clinical diagnosis of CP have been reported. Maternal factors, such as infection during pregnancy or a diagnosis of epilepsy or intellectual disability, have been found to increase the risk of CP in the child. Also, twin births and some genetic disorders are reported to result in an increased risk of CP (Bax et al., 2006; Himmelmann, et al., 2011; O’Callaghan et al., 2011). Other risk factors related to the child have been identified. Preterm birth is one of these. A younger gestational age is related to increasing prevalence of CP (Bax et al., 2006; Himpens et al., 2008; McIntyre et al., 2013; O’Callaghan et al., 2011). For children born before week 28, the prevalence is 56–74/1,000 compared to 2–2.5/1,000 in the total population (Himmelmann et al., 2010; Himmelmann & Uvebrant, 2014; McIntyre et al., 2013). Also, infection in the new-born child, intrapartum hypoxic event, low birth weight and neonatal stroke have been reported to increase the risk of a CP diagnosis (Bax et al., 2006; Dahlseng et al., 2013; Himmelmann et al., 2011; McIntyre et al., 2013; O’Callaghan et al., 2011; Wu et al., 2006a). Even though these individual factors have been identified, an increased risk of developing CP is assumed to be the combination of multiple factors.

1.2.3 Brain lesion characteristics

As mentioned earlier, CP is caused by a lesion in the immature brain. Specific structures of the brain are more sensitive to insults during certain periods of maturation. Injuries occurring early in pregnancy, during the first and second trimester, often result in maldevelopment. Approximately 15% of children with unilateral spastic CP present with maldevelopment (Krageloh-Mann & Cans, 2009). In the late second and early third trimester, the white matter are reported to be more vulnerable to lesions. In unilateral spastic CP, periventricular white matter injury is reported to be the underlying lesion in 12–45% of the children (Bax et al., 2006; Himmelmann et al., 2010; Krageloh-Mann & Cans, 2009; Wu et al., 2006b). Cortical and subcortical grey matter structures are more sensitive to lesions occurring late in the pregnancy, around the time of birth. Grey matter lesions are reported to be the underlying cause in 31–42% of the cases of unilateral CP (Bax et al., 2006; Himmelmann et al., 2010; Krageloh-Mann & Cans, 2009; O'Shea, 2008). Abnormal neuroimaging findings has been reported in ~85% of the children with CP when using conventional structural magnetic resonance imaging (MRI) as the evaluation method. As a result, in ~15% of children with CP the underlying lesion is classified as normal or unspecified (Bax et al., 2006; Krageloh-Mann & Cans, 2009; Krageloh-Mann & Horber, 2007).

1.2.4 Classification

Cerebral palsy is broadly categorized into three subtypes, based on the main motor symptom; spastic, dyskinetic and ataxic CP (Bax et al., 2006; Cans et al., 2007; Surveillance of Cerebral Palsy in Europe (SCPE), 2000). Spastic CP is the most common subtype, affecting 70–80% of the CP population. It can be either bilateral or unilateral. Dyskinetic CP and ataxic CP are less common, occurring in approximately 15% and 5% respectively of the total population with CP (Himmelmann et al., 2010; Himmelmann & Uvebrant, 2014; Jones et al., 2007).

The motor function in children with CP is commonly described using the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997; Palisano et al., 2006; Palisano et al., 2008) and the Manual Ability Classification System (MACS) (Eliasson et al., 2006a; Öhrvall, et al., 2014). GMFCS describes the gross motor function of children with CP on a five-level scale. Children at level I walk without restriction, whereas children at level V have severely limited self-mobility even with the use of assistive technology (Palisano et al., 1997; Palisano et al., 2008).

MACS describes how children with CP handle objects in everyday life, relating to the child's typical performance (Eliasson et al., 2006a). It consists of five levels of ability, where level I indicates independence in handling objects in everyday life with only minor difficulty, whereas children at level V need assistance in handling all objects in everyday activities (Table 1) (Eliasson et al., 2006a). MACS is valid for use in children of 4–18 years of age with cerebral palsy. It has been found to be stable over time in this age range (Öhrvall et al., 2014).

Table 1. Description of each of the five levels of Manual Ability Classification System (MACS).

MACS level	Description*
I	Handles objects easily and successfully
II	Handles most objects but with somewhat reduced quality and/or speed of achievement
III	Handles objects with difficulty; needs help to prepare and/or modify activities
IV	Handles a limited selection of easily managed objects in adapted situations
V	Does not handle objects and has severely limited ability to perform even simple actions

* Adjusted from the original description of the five levels on MACS (Eliasson et al., 2006a), collected from www.macs.nu

1.3 UNILATERAL SPASTIC CP

In this thesis, the focus is on studying hand function in unilateral spastic CP. Unilateral spastic CP accounts for approximately 30% of the whole population of CP (Arner et al., 2008; Hagberg et al., 2001; Himmelmann et al., 2010; Krageloh-Mann & Cans, 2009). Unilateral CP is, as mentioned, characterized by motor impairment of one side of the body. Children with unilateral spastic CP mostly present with a gross and fine motor function corresponding to levels I–III on GMFCS and MACS (Arner et al., 2008; Himmelmann et al., 2006). There is a small predominance of right-side involvement (53%) and a small difference in gender distribution, where CP is somewhat more common in boys (~60%) (Himmelmann et al., 2006; Himmelmann & Uvebrant, 2014; Jarvis et al., 2005; O’Callaghan et al., 2011). The motor problems in unilateral CP are in varying degrees accompanied by additional impairments, such as epilepsy (~25%), attention deficits and intellectual disability (20–30%) (Bottcher et al., 2010; Forsman & Eliasson, 2015; Himmelmann et al., 2006; Novak et al., 2012). Children with unilateral CP present, in varying degrees, also with other additional problems such as communication problems (20–30%), visual impairment (5–31%), hearing impairments (10–40%), pain (50–75%), sleeping disturbances (20%–40%) and nutritional problems (up to 30%) (Bax et al., 2006; Newman et al., 2006; Novak et al., 2012; Pruitt & Tsai, 2009). All the above-mentioned additional difficulties are assumed to affect hand function and performance. However, the main focus in this thesis is to evaluate aspects of affected hand use in everyday activities.

1.3.1 Cortical control of voluntary movements

When investigating hand function in children with a brain lesion, it is important to know how the cortical control of voluntary movements typically occurs. The system responsible for motor function has its primary location in the primary motor area (M1) placed anterior to the central sulcus. However, other regions are also important for a well-functioning motor system. These include the premotor areas, basal ganglia, thalamus, midbrain, cerebellum and the spinal cord. The corticospinal tract, described in more detail in the chapter below, connects the components

of the motor system. Movement commands are initiated in the motor cortex (M1 and premotor areas) and projects by electrical signals through the corticospinal tract to the ventral horn in the spinal cord. The motor system works in close relation with the sensory system. The primary somatosensory area (S1) is located posterior to the central sulcus. Also, the thalamus, one of the central nuclei, is important in the sensorimotor control of movements. The thalamus serves as a relay station, regulating which inputs from the sensory system to proceed to the cerebral cortex. The basal ganglia and cerebellum are important for movement quality, enhancing smooth and well-timed hand and finger movements (Kandel et al., 2000; Martin, 2005; Prodoehl et al., 2009).

1.3.2 Corticomotor re-organization

The cortical control of hand and arm movements occurs through electrical signals sent in the corticospinal fibres. The typical pattern of cortical control is through contralateral projections of the corticospinal fibres, i.e. the right hemisphere controls the left hand and vice versa (Eyre et al., 2001; Martin, 2005). There are however, a small number of fibres that project uncrossed, i.e. ipsilateral projections, the right hemisphere has connection to the right hand. The corticospinal fibres develop rapidly during pregnancy and the first two years of life. Migration of the corticospinal axons from the cortex to the grey matter in the spinal cord is reported to occur before week 24 of gestation. Dendritic growth accelerates in the third trimester of pregnancy and remains active during the first year of life. From term until age 1–2 years, a rapid myelination of the corticospinal axons occurs (de Graaf-Peters & Hadders-Algra, 2006; Eyre, 2003; Martin, 2005). In infants, enlarged bilateral projections are seen, from each hemisphere (Eyre, 2007; Martin, 2005). However, the ipsilateral projections withdraw during the first two years, so that a primarily contralateral projection pattern is established. This process seems to be activity-dependent (de Graaf-Peters & Hadders-Algra, 2006; Eyre, 2007; Eyre et al., 2001; Martin et al., 2004; Martin et al., 2007).

In lesions in the developing brain, remaining ipsilateral projections may persist to a larger extent (Figure 1) (Carr, 1996; Eyre, 2007; Eyre et al., 2007). This has, however, only been found to be the case in unilateral lesions (Eyre et al., 2007). The re-organization has been suggested to relate to different characteristics of the brain lesion (Holmstrom et al., 2010; Staudt et al., 2004; Staudt et al., 2002). The few studies conducted suggest that lesion size as well as location have an influence. For example, smaller lesions were found to relate more often to a typical pattern of organization, i.e. contralateral projections (Figure 1), whereas larger lesions and those involving the subcortical grey matter were reported to be more related to ipsilateral projections. The timing of the lesion seems to have a smaller influence, since ipsilateral projections has been found over different lesion types (Holmstrom et al., 2010; Staudt et al., 2004; Staudt et al., 2002). The relation between brain lesion and re-organization of the corticomotor projections needs further investigation.

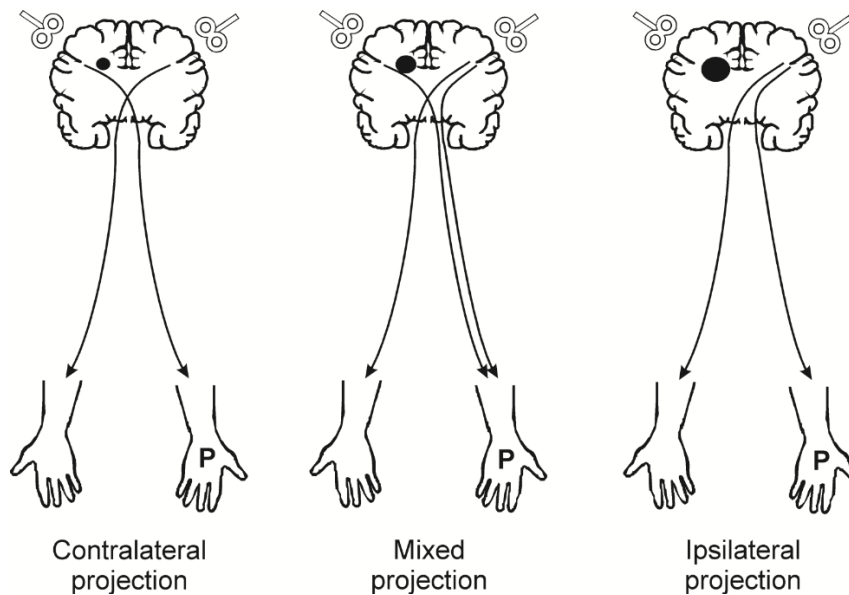


Figure 1. Schematic drawing of the organization of corticomotor projections in relation to brain lesion. On the left, the typical pattern i.e. contralateral projection is seen. In some brain lesions affecting the motor system, the ipsilateral projections from the “healthy” hemisphere remain to a larger extent in addition to the typical contralateral projections, a mixed projection pattern. Large lesions often result in a complete loss of motor control from the damaged hemisphere. In those cases, the ipsilateral projections from the healthy hemisphere take over the control of the affected hand, an ipsilateral pattern.

1.4 HAND FUNCTION IN CHILDREN WITH UNILATERAL CP

Children with unilateral spastic CP have varying ability to use their affected hand due to the motor impairment on one side of their body. The ability varies from good ability, only showing some clumsiness in high precision tasks, to not using the arm and hand at all. Common features of impaired hand function are muscle weakness (Duque et al., 2003; Klingels et al., 2012; Mackenzie et al., 2009; Smits-Engelsman et al., 2004; Vaz et al., 2006), decreased range of motion (ROM) and increased muscle tone (Arner et al., 2008; Klingels et al., 2012; Vaz et al., 2006).

Children with unilateral CP have one well-functioning and one more affected hand. In tasks that require the use of both hands, most children with unilateral CP initiate their more affected hand but often in a less effective way (Krumlinde-Sundholm et al., 2007; Skold et al., 2007). Difficulties in grasping and regulating the grip force in the affected hand are common among children with unilateral CP (Dellatolas et al., 2005; Forsberg et al., 1999; Islam et al., 2011; Mackenzie et al., 2009). Children with unilateral CP present with a sequential rather than a smooth force regulation found in typically developing children (Eliasson et al., 1995; Forsberg et al., 1991; Forsberg et al., 1999; Forsberg et al., 1992). They also use a larger safety margin in applied grip force than typically developing children (Eliasson, 2006). This means that a greater grip force is applied, increasing the risk of breaking fragile objects. Fine motor speed and dexterity is often also affected (Duque et al., 2003; Sakzewski et al., 2010). Children with unilateral CP present to a varying degree with decreased quality of upper limb movements on

the affected side. This influences their performance in, for example, reaching for, grasping and releasing objects (Hadders-Algra, 2013; Klingels et al., 2012; Law et al., 2008; Mackey et al., 2014; Sakzewski et al., 2010). The quality of movements has been found to relate to level of manual ability, where children with a high level of manual ability (MACS I) had a better quality of movements (Mackey et al., 2014).

1.4.1 Influence of lesion characteristics and corticomotor re-organization

The pattern of corticomotor projections as well as the timing, size and location of the underlying brain lesion have been shown to relate to the severity of hand motor impairments. Primarily ipsilateral projections are reported to relate to poorer function and less use of the affected hand (Eyre et al., 2007; Holmstrom et al., 2010; Staudt et al., 2002; Thickbroom et al., 2001; van der Aa et al., 2013). The ipsilateral projection pattern is also suggested to relate to poorer response to intensive training (Kuhnke et al., 2008). Regarding the influence of brain lesion characteristics, children with periventricular white matter lesions have been found to have less impact on their hand function than children with cortical/subcortical lesions (Feys et al., 2010; Holmstrom et al., 2010; Mackey et al., 2014; Staudt et al., 2000). It is reported that smaller lesions relate to a more favourable hand function than those of larger extent (Holmstrom et al., 2010; Staudt et al., 2000). The lesion type has also been found to predict different developmental patterns of hand use in children with unilateral CP. A more favourable development was found among children with primary white matter damage compared to a cortical grey matter lesion. The extent of volume reduction of basal ganglia and thalamus was also related to different patterns of development of hand function (Holmefur et al., 2013).

1.4.2 Development during childhood and adolescence

Just as in typically developing children, children with unilateral CP are expected to learn new skills due to development and maturation. Some studies have investigated the development of hand function in a long-term perspective among children with unilateral CP (Eliasson et al., 2006b; Fedrizzi et al., 2003; Hanna et al., 2003; Holmefur et al., 2010; Pagliano et al., 2001). The majority of studies report improved function with age, at least for some aspects of hand function. However, the studies have used different methods and measures to describe hand function development, which makes conclusions difficult.

Previous investigations of the development of hand function during childhood showed a rapid increase in function during the first years of life with a decreasing rate with age (Hanna et al., 2003; Holmefur et al., 2010). However, differences in development pattern were found, based on the severity of the children's hand function (Hanna et al., 2003; Holmefur et al., 2010). In Holmefur et al. (2010), the use of the affected hand was followed over time in children aged 1-8 years with unilateral CP, using the Assisting Hand Assessment (AHA). The effect of severity on development was investigated by grouping the children according to their MACS level (I-III) and 18-months AHA measure. The children were divided into two groups based on their AHA-score at 18 months, high – “children who mostly use a grip for holding objects” and low – “children who mostly do not hold objects with their affected hand” (Holmefur et al., 2010). Distinct differences in development patterns were found between the two groups. Children with better ability showed a more rapid increase to a higher level. This was also found when children were grouped by their MACS level (Holmefur et al., 2010). Differences in development pattern based on severity of hand function were also investigated in Hanna et al. (2003). They used the

Peabody Developmental Motor Scales and the Quality of Upper Extremity Skills Test (QUEST) to explore the development of general hand function and quality of movements of the upper extremity in children with CP from 16 months to 5 years of age. They found a more favourable development in children with a milder impairment. Among children with more severe impairment, a so called ‘peak and decline’ pattern was found when using QUEST as the evaluation measure (Hanna et al., 2003). A peak and decline pattern means that the child’s function first increased but, after reaching a maximum, started to decrease. This pattern was not observed for general hand function evaluated with the Peabody Developmental Motor Scales, indicating that a possible worsening in function at an older age might relate to which aspect of hand function is investigated. Studies using other evaluation measures have not reported a decline in function at an older age (Eliasson et al., 2006a; Fedrizzi et al., 2003; Holmefur et al., 2010; Pagliano et al., 2001). However, mainly children in preschool and early school age have been investigated.

Three studies have included children of older age (Eliasson et al., 2006b; Fedrizzi et al., 2003; Pagliano et al., 2001). In two of the studies, some individual improvement was reported from before 4 years to after 11 years of age. However, at a group level both hand grip and spontaneous use of the affected hand was shown to be unchanged (Fedrizzi et al., 2003; Pagliano et al., 2001). The most recent study of development in adolescence explored the change in fine motor speed and dexterity as well as precision grip control from age 6–8 years to 19–21 years. Improved function for both parameters was found (Eliasson et al., 2006b). However, when in the age range this improvement occurred is unclear. The different results imply a need to investigate the development of hand function further. In studies I and IV of this thesis, development during childhood and adolescence (age 1–21 years) has been investigated for different aspects of hand function.

1.5 INTERVENTION FOR IMPROVING HAND FUNCTION

Several different approaches to improve hand function in children with unilateral CP are reported to be used in clinical work. They aim at improving different aspects of hand function with the common goal of enabling a greater independence in activities of importance for the child and the family. The intervention which this thesis focus on is constraint-induced movement therapy (CIMT).

CIMT is an intensive hand motor training for individuals with a unilateral impairment of the upper extremities. The key elements of CIMT are 1) intensive structured training, and 2) restraint of the less-affected hand (Eliasson et al., 2014a; Taub et al., 1994). CIMT was developed from the phenomenon of ‘learned non-use’, which is defined as a “lack of use of the involved limb ... as a result of initial unsuccessful attempts to use it” (Taub 1980, in Charles and Gordon (2005)). The original model of CIMT developed for adults with stroke has been adjusted to better fit children. A wide variety of models for the paediatric population have been reported (Eliasson et al., 2014a). The adaptations regard both the type of restraint, the extent of training and the training characteristics.

Different models of CIMT conducted in various contexts have been reported. The different models can be categorized as “short-length, high duration or long-length, low-duration”. In

short-length models, CIMT is administered over a period of 2–4 weeks, whereas in long-length models the period of training ranges from 5 to 10 weeks. Both models include a wide variety of therapy dosage (8–126 hours) (Sakzewski et al., 2014). The optimal dosage has been discussed, but no conclusion have been reported. Training has mostly been conducted in hospital or clinical settings, but also in the child's home, at school or in community leisure environments. After education and supervision, parents have been reported to be effective providers of CIMT. Individualized therapy or CIMT provided in groups of children has been presented. In most studies investigating the effect of CIMT, a removable restraint, such as a glove, mitt, sling or splint has been used (Eliasson et al., 2014a; Sakzewski et al., 2014). These types of restraints have predominantly been worn only during training. Some studies have used non-removable casting, increasing the unstructured training of the affected hand.

Regardless of the modifications made, CIMT has been shown to be effective in improving hand function in children with unilateral CP of different ages (Chen et al., 2014; Eliasson et al., 2014a; Gordon et al., 2006; Hoare et al., 2007; Novak et al., 2013; Sakzewski et al., 2014). The gains in function seen after CIMT have been found to transfer to improvements in bimanual performance, measured with the AHA, and to effects in everyday life activities. Despite being shown to be effective on a group level, individual variation in training response to CIMT is probable, indicated by the large standard deviations reported in the majority of studies. The usual time of follow up after CIMT is 6 months, where most studies report on sustained effect (Case-Smith et al., 2012; Eliasson et al., 2014a; Lin et al., 2011; Sakzewski et al., 2011b). Some studies have increased the time of follow up to 12 months after intervention (Charles & Gordon, 2007; Sakzewski et al., 2011a; Taub et al., 2011). In two of them, a sustained effect was seen (Charles & Gordon, 2007; Sakzewski et al., 2011a). Investigating the effect over even longer follow-up periods is of interest, but holds some limitations (Eliasson et al., 2014a). In study I of the thesis, hand function was investigated 6 years after a CIMT-program for adolescents with unilateral CP.

1.5.1 Training response to Constraint-Induced Movement Therapy

Several factors have been investigated with the purpose of evaluating which children benefit the best from CIMT (Chen et al., 2014; Eliasson et al., 2014a; Gordon et al., 2006; Kuhnke et al., 2008; Sakzewski et al., 2011c). Potential predictors of outcome after CIMT have been suggested to be age at training, sex, affected hand, baseline upper-extremity motor capacity and characteristics of the underlying brain lesion. However, it has not been possible to draw any conclusions based on the rather small number of studies directly investigating the question of best responders to CIMT. One study investigated the relation between training response to CIMT and characteristics of the underlying brain lesion and the type of corticomotor organization (Kuhnke et al., 2008). They found that individuals with cortical/subcortical lesions and a typical contralateral corticomotor projection pattern responded better to the training than did individuals with periventricular white matter lesions and an ipsilateral projection pattern. Individuals with the latter lesion characteristics even showed a slower performance after the training (Kuhnke et al., 2008). Based on this, one can speculate on whether CIMT is an optimal intervention for children with a re-organized corticomotor pattern i.e. ipsilateral projections. It would be of great clinical importance to clarify the training response in relation to type of corticomotor projection. In the thesis, this was addressed in study II.

1.5.2 Constraint-Induced Movement Therapy in infants

For infants at risk of developing unilateral CP, there are only a few interventions for improving hand function, and their effect is unclear (Blauw-Hospers et al., 2007; Spittle et al., 2012). CIMT as an intervention for infants has only been investigated in some case studies (Coker et al., 2009; Cope et al., 2008; Lowes et al., 2014). Due to the lack of assessments sensitive to measuring change in hand function after intervention in such young children (Krumlinde-Sundholm et al., 2015), the evaluation of the effect is difficult. Friel et al. (2012) administered a CIMT-like intervention in kittens of different ages with the intention of testing the hypothesis of better effect of early onset of training than training at older age. Only the group which had early CIMT showed improved motor function, even though restoration of the motor system was found in all kittens (Friel et al., 2012; Friel et al., 2014; Martin et al., 2011). From the rationale of increased possibilities of plastic changes in the young brain, a modified version of CIMT (baby-CIMT), adjusted to the young age of the children, was developed some years ago (Eliasson et al., 2014b). In study III of the thesis, the possible effect of baby-CIMT in the first year of life on hand function at two years of age was investigated.

2. AIM

The overall purpose of this thesis was to describe the development of hand function in children with unilateral spastic cerebral palsy and to investigate its relation to brain lesion and treatment. This has been explored in four studies with the following specific aims.

Study I

The aim was to investigate the hand function in adolescents and young adults with unilateral CP across a 6-year time frame.

Study II

The aim was to explore individual variation in outcome of hand function after constraint-induced movement therapy (CIMT) in relation to the organization of corticomotor projection and brain lesion characteristics in participants with unilateral CP.

Study III

The aim was to explore the impact of a baby-CIMT programme on children's hand function at two years of age.

Study IV

The aim was to describe the development of hand function, particularly the use of the affected hand in bimanual tasks, among children with unilateral CP age 18 months to 12 years.

3. METHOD

3.1 STUDY OUTLINE

Included in this thesis are studies conducted with a number of different designs depending on the aim of the study. In all the studies, children's hand function was assessed. The Assisting Hand Assessment (AHA) was used in all the studies. It measures how effectively children with unilateral impairment use their affected hand in bimanual tasks. More information on AHA and the other measurements of hand function is found in Chapter 3.5.1. A summary of the methods of each study is given in Table 1.

Table 1. Overview of the method in each of the studies included in the thesis

Study	Design	Participants	Measurements	Statistical analysis
I	Descriptive	n=11 median age 18y 1mo (range 15y 5mo – 21y 7mo), MACS I (n=1), MACS II (n=10)	<i>Hand function</i> AHA JTHFT MUUL Grippit dynamometer	- Friedman ANOVA - Wilcoxon matched-pairs signed-rank test
II	Descriptive	n=16, mean age 13y (range 10-16y), MACS I (n=1), MACS II (n=15)	<i>Hand function</i> AHA JTHFT MUUL <i>Neuroimaging</i> MRI <i>Neurophysiology</i> TMS	- Wilcoxon matched-pairs signed-rank test - Mann-Whitney U test - Spearman's rho
III	Retrospective explorative	n=72, mean age 21mo (range 18-27mo) 31 children had participated in a baby-CIMT programme	<i>Hand function</i> AHA <i>Neuroimaging</i> MRI CT	- Mann-Whitney U test - Pearson's Chi ² -test - Binary logistic regression
IV	Prospective longitudinal	n=96, median age 24mo at inclusion (followed between 18mo-12y) MACS I (n=28) MACS II (n=45) MACS III (n=16)	<i>Hand function</i> AHA	- Non-linear mixed effects model

AHA = Assisting Hand Assessment, CIMT = Constraint-Induced Movement Therapy, CT = Computer Tomography, JTHFT = Jebsen-Taylor Hand Function Test, MACS = Manual Ability Classification System, MRI = Magnetic Resonance Imaging, MUUL = Melbourne assessment of Unilateral Upper Limb function, TMS = Transcranial Magnetic Stimulation

3.2 PARTICIPANTS

Children and adolescents with spastic unilateral CP were included in the studies. Some participants have been included in more than one of the studies (Table 2). The children investigated ranged in age from 1 to 21 years, covering a large part of the participants' childhood and adolescence. The age range of children in each study is presented in Table 1, above.

Table 2. Distribution of participants over the four studies

	Study I	Study II	Study III	Study IV
Study I (n=11)	11			
Study II (n=16)	10	16		
Study III (n=72)	0	1	72	
Study IV (n=96)	4	6	53	96

3.2.1 Study I

The study included adolescents from a CIMT day camp in 2005. Out of the 16 participants at the day camp, 11 adolescents agreed to participate in a follow-up assessment of their hand function six years after the camp. No inclusion criteria other than willingness to participate in the follow up were defined. The participants were at a median age of 18 years and 1 month (range 15y 5mo – 21y 7mo) at the time of the 6 year assessment. Four were female; the left hand was affected in three of the participants and three of them had decreased sensation of the affected hand. All but one were classified as MACS level II, representing a moderate hand function. The final participant was classified as MACS level I.

3.2.2 Study II

Participants from two CIMT day camps, one in 2005 (n=10) and one in 2011 (n=6) were included in the study. The study included 16 children, of whom eight were female and nine had right-side involvement. The mean age at training was 13 years (SD 2y, range 10–16y). Fifteen children were classified as MACS level II and one as MACS level I. Ten children out of the total 26 from the two day camps did not take part in the study due to declined participation (n=6), epilepsy (n=2) and personal reason (n=2). Three of the participants included did not participate in the TMS investigation, and for two participants MRI data were missing.

3.2.3 Study III

A convenience sample of 72 children was included in the study based on the following criteria; 1) an AHA already conducted at approximately age 2 years, 2) information regarding participation or not in a CIMT-program in the first year of life (baby-CIMT), and 3) a diagnosis of unilateral CP. The children had been assessed with AHA at an average age of 21 months (range 18–27mo). Thirty-one of the children had participated in a baby-CIMT programme and 41 had not. Thirty-four children were females and 27 had a left-side involvement. The average gestational age of the children was week 37 (range week 25–43). For 50 of the children, information from neuroimaging was available.

3.2.4 Study IV

The study included a convenience sample of 96 children. Inclusion criteria were: a diagnosis of spastic unilateral CP, age 10 or younger at recruitment and willingness to participate in at least three data collection points during a minimum of 12 months. The children were recruited at an age of 17–127 months (median 24mo). The majority of the children were recruited from the Stockholm habilitation services. Twenty-seven of the children were born preterm (before week 37). Forty-three were females and 60 had a right-side involvement. The children varied in ability level; 28 children were classified as MACS level I, 45 as level II and 16 as level III. A majority of the children had received CIMT and/or medical treatment with botulinum toxin injections or surgery of the upper limb as part of regular services.

3.3 DATA COLLECTION

Data were collected using different methods and instruments. The hand function was investigated from different perspectives covering the use of the affected hand in bimanual tasks (AHA), fine motor speed and dexterity (JTHFT), movement quality of the upper limb (MUUL) and grip strength (Gripping). Brain lesion characteristics were investigated in two ways, using neuroimaging (MRI or CT) and neurophysiological investigation (TMS). Some instruments have been used in more than one study (Table 3). A more detailed description of the measurements is presented in Chapter 3.5.

Table 3. Overview of the measurements used in the studies of the thesis

<i>Measurements</i>	<i>Study I</i>	<i>Study II</i>	<i>Study III</i>	<i>Study IV</i>
Assisting Hand Assessment (AHA)	x	x	x	x
Jebsen-Taylor Hand Function Test (JTHFT)	x	x		
Melbourne assessment of Unilateral Upper Limb function (MUUL)	x	x		
Gripping dynamometer	x			
Magnetic resonance imaging (MRI)		x	x	
Computer tomography (CT)			x	
Transcranial Magnetic Stimulation (TMS)		x		

3.3.1 Study I

Four aspects of hand function were evaluated for the participants in study I. The fine motor speed and dexterity (JTFHT), use of the affected hand in bimanual task (AHA), movement quality of the upper limb (MUUL) and grip strength (Gripping dynamometer) was measured for all participants. All assessments were administered and analysed by an occupational therapist not involved in the day camp. The adolescents were assessed three times in 2005 and one time in 2011. The same measurements (JTHFT, AHA, MUUL and Gripping dynamometer) were administered on every test occasion.

3.3.2 Study II

Hand function of the participants in study II was assessed twice, prior to and after the day camp, using JTHFT, AHA and MUUL. An occupational therapist not involved in the day camp and unaware of the participant's individual goals with the training conducted the assessments. In addition to the hand function measurements, 12 of the children were investigated with transcranial magnetic stimulation (TMS, Chapter 3.5.2). The aim of the TMS-investigation was to determine the corticomotor projection pattern of the participants. Prior to the investigation, the participants were screened for eligibility, with children diagnosed with epilepsy or those who had any metal implants (including braces) being excluded from the TMS investigation. Structural magnetic resonance imaging (MRI, Chapter 3.5.2) was also collected for participants eligible for the investigation. For participants with no prior MRI or an MRI before age 6 years, new neuroimaging was conducted at the MR-centre at Karolinska University Hospital by researchers involved in the study. The TMS and new MRI-investigations were administered after the day camps had ended.

3.3.3 Study III

In this study, earlier administered AHA-assessments at before 28 months of age were collected and compiled. Children were screened for participation in a baby-CIMT programme or not. Data for the no baby-CIMT group were mainly taken from other projects conducted before baby-CIMT was introduced as an early intervention programme in the Stockholm region. Children in the baby-CIMT group were recruited to the intervention from a follow-up programme after preterm birth or neonatal stroke or from the Karolinska University Hospital, due to asymmetric hand function. Their AHA-assessment at 18 months was administered as part of ongoing projects. Information on the child's brain lesion was collected from earlier administered MRI or CT-scans, conducted as part of clinical work. For statistical purposes, the children were grouped according to their AHA measure at 18 months, into four clinically relevant functional levels (Chapter 3.5.1)

3.3.4 Study IV

The AHA was also used in study IV. Children were assessed with the AHA at regular intervals in the age 18 months to 12 years, according to a standardized protocol (see article IV). Some individual variation in the interval of data collection was seen. The AHA was conducted by researchers linked to the study or by occupational therapists at the child's local habilitation centre. The AHA was analysed by experienced AHA raters. For statistical purposes the children were grouped according to their MACS level as well as their AHA level at 18 months, using the four functional levels defined in study III (Chapter 3.5.1).

3.4 INTERVENTION

3.4.1 Constraint-Induced Movement Therapy (CIMT)

CIMT is, as described in the background, an intensive hand training where the affected hand is engaged in intense practice while the less-affected hand is restrained. In this thesis, two types of CIMT have been used, CIMT day camp (studies I and II) and baby-CIMT (study III).

The CIMT day camp lasted for two weeks where participants were involved in intensive practice of the affected hand for 7 hours/day for a total of 63 hours (Eliasson et al., 2009). The less-affected hand was restrained by a stiff glove during the training. The children were involved with leisure activities and an important aspect of the camp was that it should be enjoyable for the participants. Before the camp the child had formulated individual goals for which the training was adjusted. The camp leaders were physiotherapists and occupational therapists working at the Stockholm habilitation services and volunteers with experience from a CIMT day camp. For participation in the day camp, children had to have the ability to lift a 500 gram bottle with the affected hand and had to be motivated for the intense practice.

The baby-CIMT consisted of intense practice of the affected hand for 30 minutes per day, 6 days a week, in two six weeks periods with six weeks in between, in total 36 hours (Eliasson et al., 2014b). The child's less-affected hand was restrained with a soft restraint (a sock or regular glove) during the training. Parents of the children conducted the training at home with weekly guidance from an occupational therapist. The training was built upon the child's individual needs and goals and could, for example, include play stimulating supination of the forearm. As with the training at the day camp, the practice in baby-CIMT should be enjoyable for the child. Children were offered to participate in baby-CIMT on the criteria: a clear asymmetric hand function and that the family was prepared to undergo the intense training.

3.4.2 Usual care in the hospital and at local habilitation services

All children in studies I, III and IV received care from the hospital and local habilitation services as part of clinical practice during the study period. According to the regional healthcare programme for children and young people with cerebral palsy (Stockholms Läns Landsting, 2014) interventions are multi-professional. This programme works as guidelines on when in a life time perspective different interventions should be offered. Interventions focused on motor function are described in four topics: 1) medical treatment, 2) surgery, 3) training where the child is an active participant and 4) adjustments of the environment. The focus of treatment varies with the child's age. The common focus of care in the first year of life is on following the development of motor function and early detection of any atypical pattern or delay in motor functions. As the child grows, the need of orthosis, medical treatment, specialized motor interventions as well as assistive devices and/or adjustments in the environment is monitored. The frequency of specialized interventions varies considerably. A minority of children undergo surgery of the hand and arm, usually after the age of 10 years (Stockholms Läns Landsting, 2014). The most common form of care from hospital and local habilitation services is counselling from the professions included in the child's care (occupational therapists, physiotherapist, speech and language therapists etc.). It is usually offered throughout the child's life with a frequency commonly of 1–2 times/month.

Since this thesis includes children born 1990–2011 and some children live outside Stockholm County, the interventions included in the usual care from hospital and local habilitation services may differ from those described above. However, all children are assumed, to a varying degree, to have received counselling and been followed up by occupational therapists or physiotherapists.

3.5 MEASUREMENTS

Both clinical assessments of hand function, neuroimaging and neurophysiological measures have been used in the studies, to various extents (Table 3).

3.5.1 Clinical measurements of hand function

The clinical assessments investigated four different aspects of hand function; use of the affected hand in bimanual tasks (AHA), fine motor speed and dexterity (JTFHT), quality of upper limb movements (MUUL) and grip strength (Grippit).

3.5.1.1 *The Assisting Hand Assessment (AHA)*

The AHA has been used in all four studies. It was developed with the aim of investigating how effectively the affected hand is used in bimanual activities in individuals with a unilateral impairment (Holmefur et al., 2009; Holmefur et al., 2007; Krumlinde-Sundholm, 2012; Krumlinde-Sundholm et al., 2007). The children's AHA is conducted in two different ways depending on the child's age. Children aged 18 months–5 years play freely with pre-selected toys presented by the examiner in a standardized manner. Older children (6–12 years) play a board game including the same toys in another context suitable for the children's age. A version for adolescents and young adults with unilateral CP is under construction, but a research version of the AHA for this age group is available and has been used in studies I and II. The research version consists of the task of unwrapping and wrapping a gift. The adolescent is asked to do as he/she usually does when wrapping gifts at home. The adolescent is encouraged to perform the task to its end. The play, board game and gift wrapping is videotaped for later scoring of 22 items on a four point scale. Children's performance was in this thesis scored according to AHA 4.4. A score of 1 generally means "does not do", i.e. does not use the affected hand, and 4 means "effective", i.e. the affected hand is used well in bimanual tasks. The total raw score is converted by means of a Rasch-analysis to interval scale AHA-units (0–100) where a higher score indicates a better use of the affected hand in bimanual tasks. The smallest detectable difference (SDD) has been calculated to 5 AHA units (Holmefur et al., 2009; Krumlinde-Sundholm, 2012).

For statistical purpose in studies III and IV, the AHA-score at 18 months was used to group children into four clinically relevant functional levels (AHA levels). The cut-off values were determined in a consensus discussion by an expert group consisting of experienced occupational therapists and AHA raters. Findings from an earlier study on the development of hand function (Holmefur et al., 2010) guided the cut-off between moderate and low functional levels. The cut-off differentiates between children who actively use grasp and those who do not. The other cut-off values were decided based on clinically meaningful difference in performance on AHA. The performance for children at each functional level is described below.

- *High functional level* (63–100 AHA units): These children used both hands together in play, spontaneously holding objects in the affected hand with a stable or nearly stable grasp.

- *Moderate functional level* (39–62 AHA units): These children often but not always used the affected hand spontaneously. They grasped toys only from the well-functioning hand. The grasp was unstable and a number of objects slipped.
- *Low functional level* (21–38 AHA units): These children commonly used one hand only and needed help to perform bimanual play. They held only a few objects in the affected hand, objects that they had placed there.
- *Very low functional level* (0–20 AHA units): These children consistently used one hand only and needed help to perform bimanual play. At best, they could only hold objects in the affected hand that were placed there by someone else, not initiating purposeful movements with the affected hand.

3.5.1.2 *Jebesen-Taylor Hand Function Test (JTHFT)*

The JTHFT examines the speed and dexterity in seven quantitative time-based fine motor tasks (Taylor et al., 1973). One of the tasks, the writing task, was excluded when JTHFT was used in this thesis. The participant sits at a table and is instructed to perform the task at hand as rapidly and as accurately as possible. Two trials of each task were recorded. If the participant was not able to finish the task before the maximum time, here set to 120 seconds, the task was stopped and the participant received a time of 120s on that task. The time on each task was added together to a total time of maximum 720 seconds. A smallest detectable difference for JTHFT has not been established (Gilmore et al., 2010a; Klingels et al., 2011).

3.5.1.3 *Melbourne assessment of Unilateral Upper Limb function (MUUL)*

The MUUL measures the quality of upper limb movements in 16 unimanual tasks, including reach, grasp, release, manipulation and functional tasks like, bringing a biscuit to the mouth, etc. (Randall et al., 2001). It is a standardized, criterion-based test where the scoring is done from the video-recording of the session. The final result is presented as a percentage of total possible points. A high percentage indicates a good quality of movements. The smallest detectable difference is reported to be 9% (Gilmore et al., 2010a; Klingels et al., 2008).

3.5.1.4 *Gripping dynamometer*

The Gripping dynamometer is used to assess the grip strength of children and adults with different impairments (Hager-Ross & Rosblad, 2002; Nordenskiöld & Grimby, 1993). It consists of a force handle placed vertically on a board. The handle is moveable sideways to allow a comfortable position for the participant. The participant is instructed to squeeze the handle as hard as possible for 10 seconds. The device records the maximum, mean and endurance, and present these in Newtons on a screen. After a rest of 60 seconds, the next trial starts with the same instructions. Three trials on each hand were recorded. Norm values have been presented for children 4–16 years and for adults 20–69 years (Hager-Ross & Rosblad, 2002; Nordenskiöld & Grimby, 1993). No reports of a smallest detectable difference in relation to intervention are available.

3.5.2 **Neuroimaging and neurophysiological assessment**

Neuroimaging techniques were used in both study II and III so as to explore the influence of brain lesion characteristics. In study II, both magnetic resonance imaging (MRI) conducted as part of clinical work and as administered by the authors of the study was included. Study II

also included investigation with transcranial magnetic stimulation (TMS) for determining the pattern of corticomotor projection. In study III, neuroimaging administered with MRI or computer tomography (CT) as part of clinical work was used. MRI and TMS are described in more detailed below.

3.5.2.1 *Magnetic Resonance Imaging (MRI)*

Conventional structural MRI has been used in study II and III. The MRI investigations were performed on either a 3T or 1.5T scanner, and the investigation included T1 and T2 sequences. The images were visually analysed by two experienced neuroradiologists on a protocol developed earlier by a consensus group and used in previous publications (Holmefur et al., 2013; Holmstrom et al., 2010). The findings were grouped according to the basic pattern of brain damage as follows: white matter damage of immaturity (WMDI), focal infarct or maldevelopment (Krageloh-Mann, 2004). The lesion was also classified according to the location (unilateral or bilateral), severity of white matter reduction and involvement (i.e. volume reduction) of cerebral nuclei. In study III, only the basic pattern of damage was used in the statistical analysis. It was categorized as either WMDI, focal infarct or other (including maldevelopment as well as normal findings).

3.5.2.2 *Transcranial Magnetic Stimulation (TMS)*

TMS is a non-invasive method where a magnetic pulse generates an electrical response in the stimulated area in the cortex (Barker et al., 1985; Ziemann, 2011). The electrical response, if large enough and if stimulation of the motor cortex occurs, can be read as a motor-evoked potential (MEP) by surface electrodes placed on the targeted muscle. Single-pulse TMS, used in study II, was conducted by a Magpro X-100 stimulator and a figure-of-eight coil (Model C-B60, Medtronic Inc., Minneapolis, MN, USA). MEPs were recorded simultaneously on both hands by surface electrodes placed on the abductor pollicis brevis and the first dorsal interosseous. A previously developed protocol was used to reliably establish the type of corticomotor projection pattern with as few stimulations as possible (Holmstrom et al., 2010). An absence of response was confirmed when 100% stimulator output could not generate any MEPs in any of the muscles. The corticomotor projection pattern was categorized depending on the stimulation response as contralateral, mixed or ipsilateral (see Chapter 1.3.2).

3.6 STATISTICAL ANALYSIS

Several different statistical methods have been used to analyse the data in the four studies. The statistical method was chosen based on the aim of the study as well as sample size and the data fulfilling the assumptions for parametric tests or not. In studies I and II, non-parametric tests have been used due to the small sample size and non-normalized data. In study III, non-parametric tests were used for comparison of demographical data of the baby-CIMT and no baby-CIMT groups. The identification of a possible effect of baby-CIMT was done using a parametric binary logistic regression. Data in study IV were analysed by a non-linear mixed effects model. Additional analysis has also been conducted (see Chapter 3.6.3). A p-value <0.05 was thought to be statistically significant for all the tests conducted.

3.6.1 Exploration of change over time

3.6.1.1 *Wilcoxon matched-pairs signed-rank test and Friedman two-way ANOVA*

Wilcoxon matched-pairs signed-rank test was used in studies I and II with the aim of detecting change between two test occasions. In study I, median performance for each of the hand function tests was calculated on a group level on each occasion. To explore possible changes in hand function in a 6 years perspective, the Wilcoxon matched-pairs signed-rank test was used comparing performance on the first and last occasion. In addition, Friedman two-way ANOVA was used to detect differences in performance between the four data points. The Wilcoxon test was also used in study II in order to explore the effect of the training on a group level, comparing performance on each assessment prior to and after the two week CIMT day camp.

3.6.1.2 *Non-linear mixed effects model*

Non-linear mixed effects model was used in study IV to statistically describe the development pattern of children over different levels of ability. The children were grouped according to their MACS level as well as their AHA measure at 18 months, using the four functional levels describe in Chapter 3.5.1.1. Two models were applied to the data, a stable limit and a peak and decline model. Both models assume a rapid increase in function in early years. For the stable limit model, this is followed by a stable level of ability. In the peak and decline model, instead a decrease and later a plateau follows after the child has reached its highest performance. The formula for each model can be found in article IV (at the end of this thesis). Akaikes Information Criteria (AIC) values of the two models were compared for each subgroup (MACS and AHA levels) so as to establish which model best fitted the data. Limit and rate of development were presented and an age-90 was calculated to more easily interpret the rate of development in the stable limit model. Age-90 represents the age at which children reach 90% of their estimated limit. The limit of development will also be termed as the children's final performance on AHA. Developmental curves were produced for each subgroup (MACS and AHA levels). Comparison between the levels within the two subgroups was conducted to detect possible different development patterns.

3.6.2 Comparison between groups

3.6.2.1 *Mann-Whitney U test*

Mann-Whitney U test was used to detect any differences in demographic data between the baby-CIMT and no baby-CIMT group in study III. It was further used in study II for comparison of training response between subgroups of brain lesion characteristics, investigated with MRI. The subgroups are presented in Chapter 3.5.2.1.

3.6.2.2 *Pearson's Chi²-test*

Differences in demographic data between the groups in study III (i.e. baby-CIMT and no baby-CIMT) was further investigated using the Pearson's Chi²-test. The variables investigated with this statistical test were gender, presence of MRI and affected side (right or left hand).

3.6.2.3 Spearman's rho

In study II, Spearman's rho was used to investigate the relation in training response, on a group level, over the different tests (AHA, JTHFT and MUUL). Training response was described as change in the percentage of baseline performance of each test.

3.6.2.4 Binary logistic regression

To explore the possible effect of baby-CIMT on future hand function, in study III, binary logistic regression was carried out. Two outcomes were investigated: high function versus lower function and very low function versus higher function. In the binary logistic regression, a possible effect of the basic pattern of brain lesion was controlled for.

3.6.3 Additional analysis

In addition to the statistical test used in study I, the ratio between grip strength in the affected and the less-affected hand for each data point was calculated. For study II, individual training response was calculated for each test and described as a percentage of baseline performance. This information was used to describe individual training response within each corticomotor projection pattern in relation to the smallest detectable difference (SDD) of each of the clinical assessments. See Chapter 3.5.1 for information on the SDD of each test. In study III, a visual inspection of the proportional distribution over the four AHA levels was conducted in order to detect differences between the baby-CIMT and no baby-CIMT groups.

3.7 ETHICAL CONSIDERATIONS

Studies I, II and III were approved by the Stockholm Regional Ethical Review Board and study IV by the Ethical Review Board at Karolinska Hospital in Stockholm. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki. Participants and guardians (where appropriate) were given both oral and written information on the studies and on what was expected of them. Written consent was obtained from the participants or guardians, for younger children. Participation in the studies was voluntary, and the participant could at any time withdraw participation without giving any explanation.

Extra attention should be paid to the ethical consideration regarding MRI and TMS investigations in children and adolescents in study II. MRI is commonly used as part of clinical practice in children with cerebral palsy or other diagnosis requiring this investigation. The MRI and TMS investigations conducted in study II were administered at the Karolinska University Hospital by persons with experience of those investigations in children. The children and adolescents were thoroughly informed of the MRI and TMS procedure prior to the investigation. They had the opportunity to visit the scanner before the MRI-session in order to get used to the equipment and environment. One of the researchers was sitting by the participant during the whole session, to observe any discomfort or other possible risks. At any discomfort, the researcher by the participant tried to calm him/her down and if necessary the scanning was paused or aborted. TMS is used in clinical practice with adults. It has, however, been used in children with unilateral CP in one previous study by our research group with no reported adverse events (Holmstrom et al., 2010). The participants could chose to watch a movie during

the investigation. During the session, one of the researchers paid extra attention to the participant's reaction to the investigation. At signs of discomfort, the investigation was paused and, if necessary, ended. Precaution was taken prior to the MRI and TMS investigation by screening the participants for eligibility according to a safety check-list.

4. SUMMARY OF RESULTS

A summary of the findings of the four studies included in the thesis is presented below in two main topics; development of hand function (studies I and IV) and training response in relation to brain lesion and age (studies II and III). The main findings in each topic are presented at the end of each section.

4.1 DEVELOPMENT OF HAND FUNCTION

4.1.1 Development during childhood

The development during childhood, 18 months to 12 years, was described based on analysis of 702 AHA data points (study IV). On a group level, the children showed a rapid increase in function during their early years followed by a stable level until age 12. The development was further explored by comparing development patterns for children with different abilities (described by AHA and MACS levels). This revealed a significantly higher developmental rate and final performance on AHA in children with higher ability, indicating a more favourable development pattern.

The limit of development on AHA differed between levels when grouping the children using their AHA results at 18 months (Figure 2, Table 4). Children with a high function reached a significantly higher performance than children with a moderate function ($p < 0.001$). A difference was also found between children with moderate and low function ($p < 0.001$). Low and very low levels presented with similar final performance on AHA ($p = 0.230$) but still lower than for the other two levels (Figure 2, Table 4).

Table 4. Developmental limit and rate on the Assisting Hand Assessment (AHA), interpreted as final performance and age-90, for each of the levels in the two subgroups

	Final performance on AHA, mean AHA units	Age-90, months
AHA levels		
<i>High</i>	82	29
<i>Moderate</i>	65	32
<i>Low</i>	54	46
<i>Very Low</i>	50	100
MACS levels		
<i>I</i>	77	33
<i>II</i>	59	38
<i>III</i>	50	56

Significant difference in final AHA performance was seen for high compared to moderate and moderate compared to low AHA level as well as between all MACS levels. Developmental rate, interpreted as age-90, differed significantly between AHA levels moderate – low and low – very low and between MACS levels II and III.

Developmental rate differed between all AHA levels except for high compared to moderate function. This indicates a similar development pattern among children who use active grasp (high and moderate AHA level), though with a higher final performance in high functioning children. Another way of describing the developmental rate is by the children's age-90, i.e. the age at which children in the different levels reached 90% of their limit of development (a stable level). This occurred at different ages for the different levels. Children with a very low function needed distinctly longer time to reach 90% of their limit compared to children with better initial ability (Figure 2, Table 4).

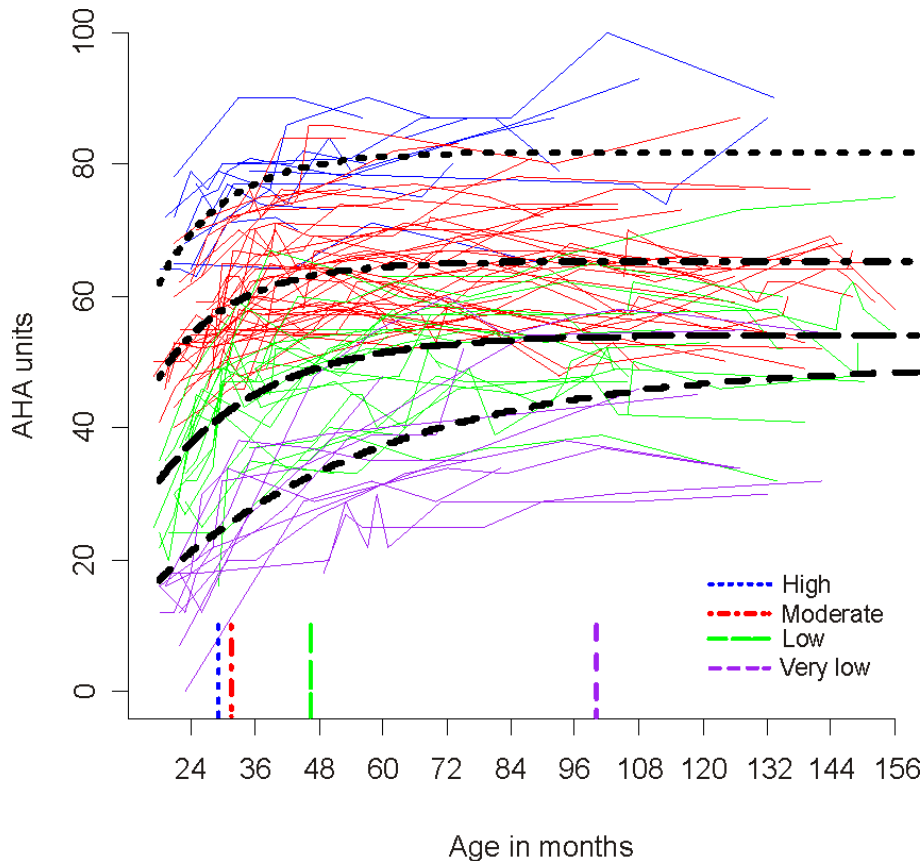


Figure 2. Development of use of the affected hand, measured with the Assisting Hand Assessment (AHA) for children (n=96) when grouped according to the four AHA levels; high, moderate, low and very low. The children's individual performance (solid, coloured lines) as well as average performance for each AHA level (black, dotted lines), in the age range 18 months to 12 years (i.e. 156 months, x-axis), is presented. The vertical lines indicate the age at which the children in the different levels reached 90% of their limit of development on AHA (age-90).

Differences in the limit of development on AHA were also found when grouping the children based on their MACS level ($p < 0.05$, Table 4). A higher MACS level (i.e. better manual ability) was associated with a higher final performance (Figure 3). The rate of development was found to differ between the two lower levels (MACS II and III, $p = 0.048$), whereas the two highest levels (MACS I and II) showed a similar rate ($p = 0.148$). The children reached a stable level of performance in the age range 33 to 56 months (Table 4). Children with a better manual ability (MACS level I and II) had a faster increase in function than children with poorer ability (MACS level III, Figure 3).

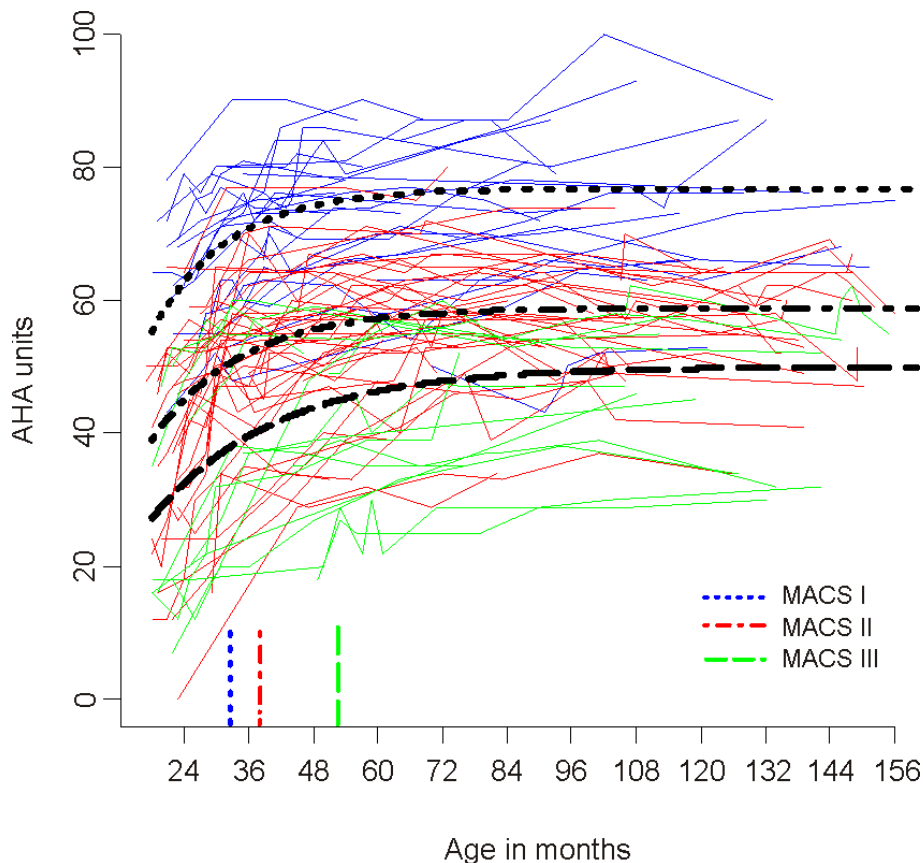


Figure 3. Development of use of the affected hand from 18 months to 12 years for children ($n=89$) divided into levels of the Manual Ability Classification System (MACS). Assisting Hand Assessment (AHA) units, range 0–100, are presented on the y-axis and the age in months on the x-axis. Solid, coloured lines represent the development trajectory for each child and the black, dotted lines are average development of children in the different MACS levels. The vertical lines indicate the age at which the children in the three MACS levels reached 90% of their final performance (age-90).

4.1.2 Development during adolescence

Development during adolescence was explored by measures of hand function on four occasions during a 6-year period in 11 adolescents with unilateral CP 16–21 years of age at last occasion (study I). Over the 6-year period, a stable level of performance on AHA was found (62–63 AHA units, $p = 0.72$). The fine motor speed and dexterity also showed a stable level in the 6-year time frame (123–117 seconds, $p = 0.80$). The adolescents showed an increase in grip

strength for both the less-affected (94.4%, $p=0.008$) as well as the affected hand (+80.9%, $p=0.02$, Figure 4). The proportional increase was similar for the two hands, indicated by a stable ratio between the hands (see Article I). The data on the quality of movements of the affected limb showed a small decrease in the older ages (-6%), although it was not a statistically significant decline ($p=0.15$). Nor did it exceed the smallest detectable difference ($\pm 9\%$). Study I also aimed to describe the long term effect after a CIMT day camp. Participants were assessed prior to, and 2 weeks, 6 months and 6 years after the camp. The participants only showed improved performance on the JTHFT (baseline – 2 weeks after the camp) and for grip strength (baseline – 6 years after the camp). The improvement on JTHFT directly after the camp (123–109 seconds, $p=0.021$) was not sustained at the 6 months follow-up. Grip strength did not improve directly after the camp, but from a 6-year perspective, indicating that the improvement is probably due to development rather than as an effect of the intervention.

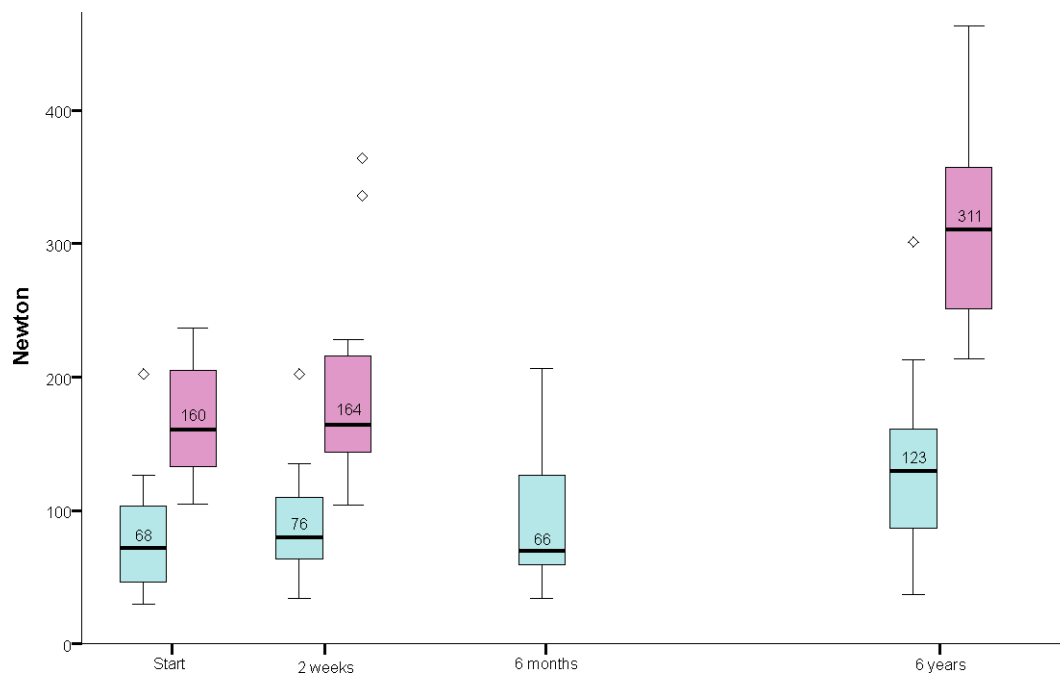


Figure 4. Change in grip strength, measured with the Grippit dynamometer, in a 6-year time frame, presented for the affected (turquoise) and the less-affected (pink) hand. Median value for the group ($n=11$) is reported as Newton (y-axis) for each test occasion (x-axis). Grip strength of the less-affected hand at 6 months was not measured. A significant increase of grip strength was seen for both the less-affected ($p=0.008$) and the affected hand ($p=0.02$) from baseline to the 6-year assessment.

4.1.3 Summary of findings on development of hand function

Findings from the two studies (I and IV) allow a description of the development from early age to young adulthood. The main findings were that use of the affected hand increased rapidly at a younger age. During older school age and adolescence, a stable level of performance was found for use of the affected hand and fine motor speed and dexterity. Even though a stable level of performance mainly was seen in older age, children can still learn new skills and can improve their function by intervention, as indicated by the significant improvement in speed

and dexterity in adolescents after the day camp. An increase in grip strength during adolescence was seen for both hands.

The other main finding was that children with different initial abilities differed in developmental rate and limit on AHA. This means that the course of development can be predicted, based on the child's use of the affected hand at 18 months. Performance on AHA at 18 months can thus be used to predict future use of the affected hand in bimanual tasks, enabling clinicians to give parents more reliable information on what to expect.

4.2 CIMT IN RELATION TO BRAIN LESION AND AGE

4.2.1 Training response in relation to brain lesion characteristics

Individual outcome after a CIMT day camp was investigated in 16 children age 10–16 years (study II). Training response was explored in relation to brain lesion characteristics and corticomotor projection patterns. Individual variations in training response to CIMT were found among the participants in the study (JTHFT -12 to $+54\%$, AHA -3 to $+7$ units and MUUL -3 to $+7\%$). Improved hand function after CIMT was found for children regardless of type of corticomotor projection and underlying brain lesion characteristics. On JTHFT improvement was seen among participants within all corticomotor projection patterns; i.e. contralateral, mixed and ipsilateral (Figure 5). Minor improvements were seen on the AHA and MUUL. Only 5 participants improved more than the smallest detectable difference (SDD) on AHA (5 AHA units) and none for the MUUL (SDD = 9%). The children with a change exceeding the SDD on AHA had ipsilateral or mixed pattern.

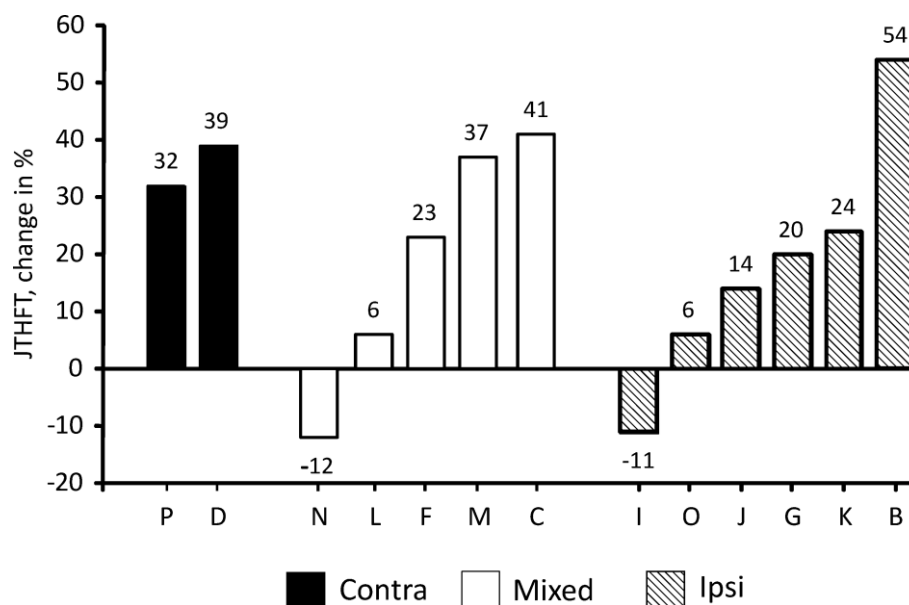


Figure 5. Percentage improvement on Jebsen-Taylor Hand Function Test (JTHFT) for participants with different corticomotor projection patterns. Letters on the x-axis represent each investigated participant (n=13). The figure shows that improvement after constraint-induced movement therapy is not dependent on the type of corticomotor projection. The figure is collected from Islam et al. (2014), p. 5 (Developmental Medicine and Child Neurology).

Improvements on one test were not automatically related to improvements on the other tests, as indicated by the low correlations between training responses for each test (see Article II). This means that children respond differently to CIMT on different aspects of hand function.

4.2.2 Training response in relation to age at intervention

Performance on AHA at two years of age was explored for 72 children, of whom 31 had participated in a baby-CIMT programme within their first year of life (study III). Children who had participated in baby-CIMT had a more favourable use of their affected hand at age two than did children who had not participated in baby-CIMT. Analysis of the distribution over the four AHA levels revealed a higher proportion of children with high functional level in the baby-CIMT group (36%) compared to the no baby-CIMT group (12%, Figure 6). The proportion of children with a very low function, an ineffective use of the affected hand, was at age two in the baby-CIMT group 16% and in the no baby-CIMT group 27%.

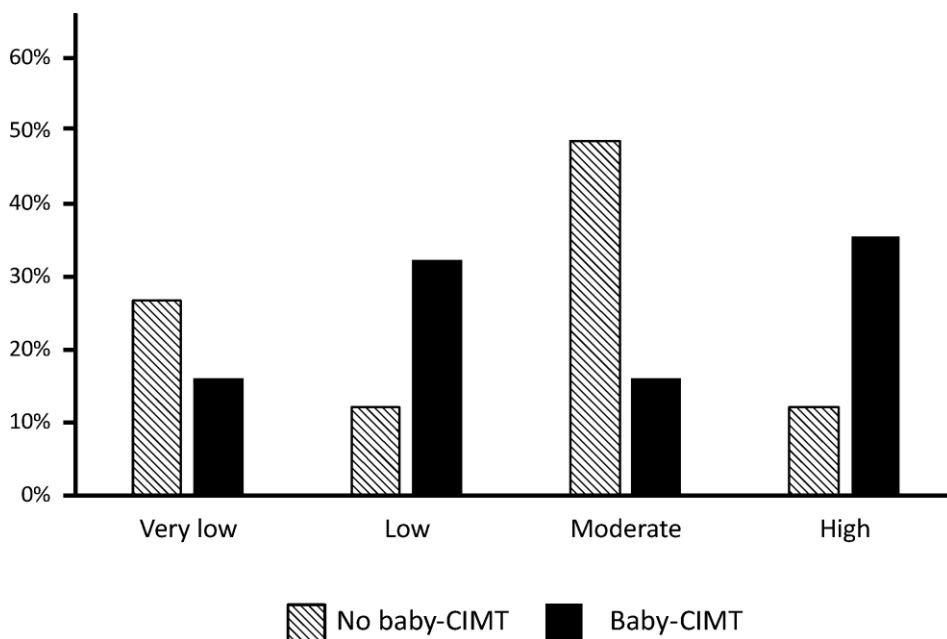


Figure 6. Difference in proportional distribution of children at each functional level between the baby-CIMT and no baby-CIMT groups.

The logistic regression, controlling for differences in basic pattern of brain lesion between the groups, supported the findings of better use of the affected hand among children with baby-CIMT, at least among high performing children. Children who had participated in baby-CIMT were 6 times more likely to have a high functional level compared to children without baby-CIMT ($p=0.001$). The odds of having a very low function were not significantly different between the baby-CIMT and no baby-CIMT groups ($p=0.084$), despite the differences observed on visual inspection of the proportional distribution (Figure 6). In analysis of the odds of having very low function, the brain lesion seemed to “over rule” the effect of the intervention. Children who presented with white matter damage of immaturity (WMDI) were less likely, than children with focal infarct to have a very low function ($p=0.038$), indicating a lower risk of performing poorly.

4.2.3 Summary of findings for CIMT in relation to brain lesion and age

Findings from studies II and III give insight on outcome after CIMT in relation to brain lesion and age. The main finding was that individual improvement is possible regardless of underlying brain lesion characteristics and type of corticomotor projection (study II). This indicates that training response is multifactorial, not only explained by brain lesion characteristics or type of corticomotor projection.

The second main finding were that children who had participated in baby-CIMT had a more favourable hand function at age two than children with no baby-CIMT (study III). This means that CIMT adjusted for infants is a possible treatment for improving hand function in children with risk of developing unilateral CP.

5. DISCUSSION

This thesis has explored the development of hand function in children and adolescents with unilateral cerebral palsy. Furthermore, the relation between brain lesion characteristics and treatment was investigated as well as the possible effect of treatment administered at an early age. Some important findings have emerged from the studies included in the thesis. These findings will be discussed here in relation to current knowledge, clinical relevance and the need for further research.

5.1 CHANGE IN HAND FUNCTION OVER TIME

5.1.1 Development to a stable level of performance

Children were found to increase their use of the affected hand over time, with a rapid increase in early years which slowed down and levelled out with age (study IV). The result is of clinical relevance, indicating that children with unilateral CP already early in life have a well-established way of using the affected hand. This information can be used by clinicians in their communication with parents, but also provides a reference when evaluating interventions aimed at improving the use of the affected arm and hand in a long-term perspective. The pattern of an increased function followed by a mainly stable level of performance is in agreement with recently conducted studies on fine and gross motor development (Holmefur et al., 2010; Smits et al., 2013). However, it partly contradicts the findings in Hanna et al. (2003). They found a reduced function in older age when using QUEST to evaluate the development of hand function. However, QUEST measures a different aspect of hand function than what was investigated in study IV, namely the quality of movements. In the small sample of adolescents investigated in study I, a stable performance on AHA and in fine motor speed and dexterity was found over a 6-year period from early adolescence to young adulthood. In Eliasson et al. (2006b), an increased fine motor speed and dexterity was found in the period 6–8 to 19–21 years. The somewhat different findings might indicate that development of this aspect of hand function mainly occurs before the teenage years. Grip strength increased during adolescence in both the affected as well as the less-affected hand. This pattern of increased grip strength is in accordance with typical development, where a rapid increase in grip strength occurs in adolescence (De Smet & Vercammen, 2001; Hager-Ross & Rosblad, 2002). The pattern of development during adolescence, described by findings from study I, should be interpreted with caution due to the small sample of participants. Continuous investigation of development of different aspects of hand function in a long-term perspective during childhood and adolescence is needed in order to confirm the findings presented in this thesis.

The increased performance in AHA with age, found in study IV, probably relates in part to increased cognitive abilities. Children learn as they grow older how to use their affected arm/hand in a more effective way. Also, the increased input from the environment might partly explain the rapid increase in AHA at early age. As the child grows, an enlarged environmental stimulus occurs, the child starts preschool and takes part in play in the playground.

The finding in study I, of a similar increase in grip strength in the affected and the less-affected hand, was somewhat surprising. Grip strength, which is classified as a body function in ICF, is influenced by factors at a body structure level such as forearm muscle characteristics and hand size (Hager-Ross & Rosblad, 2002; Neu et al., 2002). In children with unilateral CP those factors are known to be impaired in the affected hand (Demir et al., 2006; Vaz et al., 2006). Based on this, one might have expected a smaller increase in grip strength in the affected than in the less-affected hand. The change over time in quality of movements, investigated in study I, might be influenced by the development of contractures, to various degrees. It is, therefore, of great importance to know more about the growth of limbs and the development of contractures for children with CP and to relate this to the development hand function.

5.1.2 Prediction of development using AHA-score at 18 months

In study IV, it was possible to identify different development patterns based on the child's ability, using MACS level and AHA-score at 18 months. Children reached a stable level of function at various ages based on their ability level. The differences in pattern based on ability are in accordance with findings in a previous study by Holmefur et al. (2010). However, children in our study in general reached their stable level at an earlier age than children in the previous study, both when grouping the children by MACS level and AHA-score at 18 months. In our study it was possible to describe the children's performance at 18 months using four functional levels (AHA levels), compared to the two group division presented in Holmefur et al. (2010). This enabled a more differentiated description of development patterns for children with various abilities. Compared to the previous study (Holmefur et al., 2010), the most prominent difference applies to children with lower ability, who did not use grasp at 18 months. These children, in Holmefur et al. (2010), presented with a stable level at 87 months of age which can be compared to age 46 months for children with low AHA level and age 100 months for children with very low AHA level in our study.

Children with a better ability in general reached a higher limit of development. It should be noted that children "started off" with different ability, so the differences in final performance might not be that surprising. Based on this, a rather interesting finding was seen for children with very low function. They needed, as mentioned, a longer time to reach a stable level; however, they developed to the same limit as children with low function, who initially had better use of their affected hand. The reason for this pattern of development needs to be further investigated. Characteristics of the underlying brain lesion might influence the development. From a previous study, it is known that specific characteristics of the brain lesion relate to different patterns of development of hand function (Holmefur et al., 2013). A more favourable development was found among children with primary white matter damage compared to a cortical grey matter lesion affecting the media cerebri artery territory. Differences were also found based on the degree of involvement of cerebral nuclei (Holmefur et al., 2013). These findings highlights the need of exploring the possible impact of characteristics of the underlying brain lesion also in our sample of children.

Taken together, the findings of different development patterns for children with different AHA-score at 18 months indicate that these AHA levels can be used to predict future function. It means that clinicians, by conducting an AHA at an early age in children with unilateral CP, can acquire a picture of the child's expected development, which can be used in the

communication with parents. Over the studies, children in various ages (1–21 years) have been included. This has provided information on development in a long-term perspective, throughout childhood and adolescence. It has been stated that parents early in their child's life have questions on expected future function (Novak, 2014). Findings from study IV give insights into what could be an expected development of use of the affected hand for children with different abilities. For families with a child with unilateral CP, this information might help in giving realistic expectations of their child's ability in bimanual activities.

5.2 TRAINING RESPONSE TO CIMT

5.2.1 CIMT, corticomotor organization and brain lesion characteristics

Findings from study II showed that children could improve from CIMT regardless of their pattern of corticomotor projection and the characteristics of the brain lesion. This is important from a clinical perspective. Children with cortical/subcortical or larger lesions or ipsilateral corticomotor projections are assumed to have a more impaired function but our findings indicate that children with these lesion characteristics can still benefit from intervention. One other study investigating the relation between the outcome after CIMT and corticomotor projections and characteristics of the brain lesion came to a somewhat different conclusion (Kuhnke et al., 2008). They found participants with an ipsilateral projection to present with a slower performance after CIMT. The different findings between the studies might be due to the use of different assessments for evaluating the training response, but also due to differences in the samples investigated. The study by Kuhnke et al. (2008) included participants with specific combinations of basic pattern of brain lesion and type of corticomotor projection pattern. Individuals with cortical/subcortical lesion and contralateral projection pattern were compared to those with unilateral periventricular lesion and ipsilateral projection pattern. In our study participants were recruited with the main aim to participate in the training, i.e. the recruitment criteria did not specify any basic pattern of brain lesion or corticomotor projection. Children in our study were also younger at time of training than in the study by Kuhnke et al. (2008). Based on these differences and the small sample size in both studies, the influence of corticomotor projection patterns and brain lesion characteristics on training response has to be further investigated.

5.2.2 CIMT and age at administration

Age as a factor possibly influencing outcome after CIMT has been investigated in some studies (Chen et al., 2014b; Gordon et al., 2006; Sakzewski et al., 2011c). Of these, two came to the conclusion that an older age at training was related to better response (Chen et al., 2014b; Sakzewski et al., 2011c), whereas the third study found that children could benefit from CIMT regardless of age at training (4-8 versus 9-13 years) (Gordon et al., 2006). Our findings in study III, showing a probably positive effect of early administered CIMT, support the assumption that CIMT can be effective regardless of age. The findings from study III add to the knowledge on the effect of early training (Blauw-Hospers et al., 2007; Spittle et al., 2012). However, few children have as yet been included in early hand function intervention, and the studies have used different evaluation measures and study designs (Coker et al., 2009; Cope et al., 2008; Lowes et al., 2014). Continuous exploration of the effect of early hand function intervention is

essential. Whether an earlier start of CIMT, during the period of most rapid maturation of the corticomotor system, will result in a better effect than intervention later in life remains to be answered. It is possible that intervention early in life will have the potential to influence the development of the corticomotor system towards a more favourable pattern, and thereby have a long-term effect (Basu, 2014). The possibility to identify children early who are likely to develop CP is also important from the perspective of administering and evaluating early intervention (Jones et al., 2007; Novak, 2014).

In study III, investigating the effect of baby-CIMT, the possible confounding effect of brain lesion was controlled for. Somewhat different results were found for a high compared to very low function. Visual analysis of the proportional distribution was in favour of the baby-CIMT group at both these functional levels. But when controlling for the basic pattern of brain damage, a positive effect of baby-CIMT was only seen for children with high function. The reasons for this are not clear. It was not possible to control for any other characteristics of the brain lesion. Such an analysis might possibly reveal a different influence of the brain lesion on the effect of early intervention. Characteristics of the brain lesion in relation to CIMT administered in both infants and older children have to be further investigated so as to clarify the possible impact on training response.

5.2.3 Training response relates to multiple factors

Findings from study II indicate that training response to CIMT depends on numerous factors. Besides brain lesion characteristics, the pattern of corticomotor projection and age, already discussed, the child's motivation for the training is assumed to be of importance (Gilmore, et al., 2010b). Children also have different skills and experiences when entering the intervention and have varying contextual support during the training, which might influence the outcome. Further, cognitive ability are assumed to influence the outcome after CIMT (Eliasson et al., 2014a). However, the findings in study III indicate that improvement after CIMT is possible even when the cognitive abilities assumed to be needed for participation are not yet developed. However, it should be noted that the intervention was adapted to the young age of the child. The knowledge of primary predictors of positive change is still limited (Eliasson et al., 2014a).

Children with unilateral CP may have impairments additional to the motor problem. In the studies for this thesis, children were reported to have additional difficulties to various degrees. Sensory deficits were reported in some participants in study I. Sensory deficits have been found to relate to poorer fine motor dexterity (Krumlinde-Sundholm & Eliasson, 2002). This might also have implications for response to training regarding fine motor speed and dexterity. No exploration of training response in relation to sensory deficits was conducted in this thesis. However, findings from one previous study found visual-motor ability to relate to response to a home-based CIMT programme (Chen et al., 2014b). Further research is needed to identify which children benefit best from the intervention, and how factors within the person as well as environmental factors influence the effect of training.

5.3 HAND FUNCTION AND EVERYDAY LIFE PERFORMANCE

The increased use of the affected hand with age found in study IV does probably improve the child's performance in everyday tasks. Also improvement in JTHFT and in grip strength found in studies I and II of this thesis might result in better occupational performance. Occupational performance is a combination of personal factors, the task at hand and the environment in which the task is performed (see Chapter 1.1). James et al. (2015) investigated the relation between activities of daily living and upper limb function in children with unilateral CP. They found performance on AHA to be correlated with AMPS motor skills, i.e. the actions a person performs in order to move him/herself or task objects. A better AHA score indicated better AMPS performance (James et al., 2015). Also, the speed and dexterity, grip strength and stereognosi have been found to be important for execution of everyday task (Arnould et al., 2014; Arnould et al., 2007; James et al., 2015; Klingels et al., 2012). It is important to notice from findings of previous studies that performance in everyday task only to 46–66% is explained by the above mentioned hand function aspects (Arnould et al., 2014; Arnould et al., 2007; James et al., 2015; Klingels et al., 2012). This indicates that other factors also influence occupational performance, in accordance with the PEO model (Law et al., 1996). Further studies are needed to clarify the relation between improvements in hand function and possible improvements in occupational performance.

5.4 METHODOLOGICAL CONSIDERATIONS

Both studies I and II, investigating changes in a 6-year perspective, as well as training response in relation to brain lesion characteristics and corticomotor projections, included quite a small sample of children. The small sample size might influence the trustworthiness of the results. Further, the small sample size makes findings from the two studies hard to generalize to the whole population of children and adolescents with unilateral CP. This highlights the need of future studies of a larger group of children so as to confirm the results of the studies. Children in both studies were also quite homogeneous, all but one presenting with MACS level II. All studies included a convenience sample of children with unilateral spastic CP, which might induce a risk of bias.

The retrospective design in study III might not be assumed to be the optimal design when evaluating the effect of an intervention. However, in the light of the lack of valid assessments evaluating change in hand function in infants (Krumlinde-Sundholm et al., 2015) the design can be seen as a strength. The design allowed for the use of an assessment validated for children with unilateral CP at this age. Another strength of the design was that only children with a confirmed diagnosis were included in the study. Retrospective designs do not include a baseline measure per se. The children were selected on criteria not including any specification on degree of severity, gender, birth weight, etc.; therefore the sample can be assumed to be randomly selected. This reduces the risk of systematic inclusion bias. Matching of the children was not possible due to the small sample and uncertainty of what factors to match the children on.

In many of the studies, non-parametric statistical methods have been used, mostly due to the small sample sizes. In study I, the possible bias of the small sample was addressed by using the

median value, instead of mean value, in the statistical analysis of change over time. In study II, the data were mainly analysed visually based on few participants in each subgroup. This allowed for a description of individual training response, but lowers the possibility of coming to any conclusions about the effect of the investigated factors on a group level. In study III, investigating the possible effect of baby-CIMT, logistic regression was used to be able to control for any confounding effect of basic pattern of brain lesion. However, for only 50 of the 72 participants in study III, information regarding the brain lesion was available. One can argue that the logistic regression should only have been conducted using children for which neuroimaging information was present. However, by doing this the results would probably be biased, since all the children with high functional level in the no baby-CIMT group would have been excluded. Therefore, multiple imputation was used so as also to be able to include children where information on the brain lesion was not available.

Neuroimaging used in study II and III was visually analysed by experienced neuroradiologists on a previously established protocol. Different characteristics of the brain lesion were identified and classified. Reliable determination of the basic pattern of damage is possible by using only visual analysis. However, for analysis of other characteristic this is probably not sensitive enough method. More advanced methods such as diffusion tensor imaging would probably give better information on, for example, white matter integrity (Holmstrom et al., 2011). In the studies of the thesis, the neuroimaging used was mainly conducted as part of clinical work, including mostly structural MRI sequences administered at different ages of the children. Future studies including more structured and detailed information from neuroimaging data are needed.

Finally, when analysing the data in study III and IV, exploring the possible effect of baby-CIMT as well as longitudinal development of use of the affected hand, the AHA results of the children at 18 months, grouped into four functional levels, were used. It should be stated that the AHA levels are only relevant to the children included in the studies. Further research is needed to clarify whether this division is also useful for other children with unilateral CP.

6. CONCLUSIONS AND CLINICAL IMPLICATION

The studies included in this thesis have contributed to the knowledge of the development of hand function during childhood and adolescence in children with unilateral CP. The studies have further provided information on the relation of training response and brain lesion characteristics, and the effect of both early and later CIMT programme. The findings are of high clinical relevance enabling the provision of prognostic information to parents and clinicians regarding the child's hand function in a life time perspective.

The development of the use of the affected hand was found to differ for children with different AHA-score at 18 months. Thereby, the child's AHA measure at 18 months can be used for the prediction of future hand function. The pattern of development was characterized by a rapid increase of use of the affected hand during the early years which slowed down and levelled out as the children grew older. An investigation of development in a small sample of adolescents and young adults indicated that the hand function was kept stable during adolescence. Interestingly, the grip strength increased by age in both the affected and non-affected hand. Although a general stable level seems to be present at an older age, it is important to notice that children can still learn new skills important to them in daily life and take advantage of intervention.

Factors such as brain lesion characteristics and pattern of corticomotor projection have previously been found to influence the child's hand function. However, our findings show that there were still possibilities for children with different brain lesion characteristic and corticomotor projection patterns to improve their hand function by training. This indicates that training response is probably multifactorial, and not explained by single factors. The findings further indicate that CIMT can be offered to children with unilateral CP irrespective of their underlying pathophysiology.

CIMT in infants was found to be an applicable intervention model for improving hand function. Children who had participated in a baby-CIMT programme within their first year of life were more likely to have a favourable hand function at age two years. The findings indicate that CIMT, when adjusted to the young age of the participants, can be offered to children younger than one year of age.

7. FUTURE RESEARCH

From the studies of this thesis, new research questions have taken shape. Regarding development of hand function, further investigation over a longer time frame, especially during adolescence, is needed. When conducting these studies, investigation of more than one aspect of hand function is suggested to be included, since different aspects seem to develop somewhat differently. Development of hand function is probably influenced by other factors, for example, development of grip strength is related to the growth of the upper limb. The quality of movements is assumed to be affected by decreased ROM and the development of contractures. Brain lesion has also been found to influence the development of hand function. Therefore, it is of great importance to investigate the development of hand function in relation to those factors.

It is still not clarified which factors influence the outcome after CIMT but the training response is most likely multifactorial. Even though we did not find any relation between individual training response and specific brain lesion characteristics or corticomotor projection pattern, these factors probably have an influence. At what age CIMT is administered might be another factor influencing training response. Further investigation is needed of whether early intervention is more efficient than intervention administered at older age. Also, exploration of the relation between the early onset of CIMT and the development of the corticomotor system is essential.

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